1. INTRODUCTION

Good Clinical Practices (GCP) are an ethical and scientific quality standard for designing, conducting, recording and reporting clinical trials conducted on human beings, which are based on current provisions of the Declaration of Helsinki.

Good Clinical Practices provide public assurance that the rights, safety, well-being and privacy of volunteers are protected and data obtained from the trial are safe.

Good Clinical Practice Guidelines aim to provide a single standard to facilitate mutual acceptance of clinical data internationally.

GCP Guidelines provide guidance on collection of clinical data to be submitted to the General Directorate of Health Services and the relevant ethics committees and describe the principles and details of clinical trials on Traditional and Complementary Medicine Practices (GETAT) conducted or planned to be conducted in Turkey.

2. DEFINITIONS

2.1. Adverse Event: Whether there is a causality relationship with the treatment administered or not, all undesirable medical conditions that are seen in the volunteer participating in the clinical trial. Whether it is accepted or not, adverse event includes any unfavorable and unintended finding, symptom or disease including an abnormal laboratory finding temporarily associated with the use of an investigational product.

2.2. Adverse Reaction: All undesirable and unintended responses seen in the volunteer participating in the clinical trial. In the pre-registration clinical trials with GETAT product, especially as the therapeutic dose(s) may not be determined yet, all adverse events which are found to have a logical causal relationship with any dose including the status of the medicinal product are considered adverse reactions. The term of "logical causal relationship" is used to state the presence of evidence or an opinion to suggest a causal relationship. With respect to the licensed products, adverse reaction refers a response which is noxious and unintended and which occurs at doses normally used in human beings for prophylaxis, diagnosis, or treatment of disease or for modification of physiological function.

2.3. Investigator: A person taking part in clinical trial under the supervision of the principal investigator.

2.4. Investigator's Brochure: Documents about clinical and non-clinical data regarding the product or practice that is being researched.

2.5. Trial Protocol: Documents that define the objective, design, methodology, statistical methods and organization of clinical trials in a detailed way.

2.6. Trial Protocol Amendment: A document which describes trial protocol amendments.

2.7. Investigational Product: A pharmaceutical form of an active substance or placebo which is being tested or used as a reference in clinical trials.

2.8. Independent Data Monitoring Committee (Data Monitoring Group or Data Safety Monitoring Committee): A committee which comprises independent experts who are not involved in the trial and who assess the progress, safety data and if needed critical efficacy endpoints of clinical trials and recommend to the sponsor whether to continue, modify or terminate a trial.

2.9. Unexpected Adverse Reaction: All kinds of adverse reactions the nature, severity and result of which are inconsistent with the reference safety information.

2.10. Informed Consent Form (ICF): A document that proves in writing the consent received by providing detailed and comprehensible information about the trial.

2.11. Serious Adverse Event or Reaction: Adverse event or reaction that causes death, life-critical situation, hospitalization, longer hospital stay, permanent or critical disability or invalidity, congenital anomaly or defect.

2.12. Double Dummy: It is a blinding method used to mask products administered to study groups in blinded trials, where an investigational product is compared with its two different pharmaceutical forms. To illustrate, one study group is administered a placebo tablet and an ampoule containing active substance whereas the other group is administered a tablet containing active substance and a placebo ampoule.

2.13. Multicenter Clinical Trials: A clinical trial that is conducted in more than one center in line with a single protocol and thus encompasses more than one principal investigator.

2.14. Inspection: The act by the Institution of conducting a review of the places where clinical trials are conducted, the sites owned by the sponsor or the contract research organization, the trial documents and records, quality assurance regulations and all other general directorates, boards and institutions involved in the trial, including the ethics committee, in terms of compliance with the relevant legislation, with or without prior notice.

2.15. Inspection Report: The report produced by the relevant health authority at the end of the inspection.

2.16. Sponsor: An individual, General Directorate or organization that is responsible for initiating, conducting or financing the clinical trials.

2.17. Direct Access: Permission to examine, analyze, verify and reproduce any records and reports for evaluation of a clinical trial. All parties with direct access, i.e. the Ministry of Health and its affiliated institutions, the General Directorate of Health Services, the relevant health authorities and those who make examinations, should take all reasonable precautions within the constraints of the applicable legislation to maintain the confidentiality of volunteers' identities or the sponsor's proprietary information.

2.18. Documentation: All documents in any form including written, electronic, magnetic records and scans, x-rays and electrocardiograms that describe and record the methods, conduction and/or results of a trial, the factors affecting a trial, and the actions taken.

2.19. Ethics Committee: Independent committees to be approved by the General Directorate of Health Services, which are established to provide scientific and ethical opinions about consents to be received from volunteers and methods and documents to be used in informing the volunteers as well as other trial-related matters with a view to protecting rights, safety and well-being of volunteers.

2.20. Vulnerable Subjects: Individuals whose willingness to volunteer in clinical trials may be unduly influenced by the expectation, whether accepted or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure such as medical, pharmacy, dentistry and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, soldiers and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons and patients in emergency situations, children and those incapable of giving consent.

2.21. Essential Documents: Documents which individually and collectively permit evaluation of conduct of a trial and the quality of data produced.

2.22. Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a volunteer's identity.

2.23. Volunteer: A sick or healthy person that will take part in clinical trials by providing their own written consent or that of their legal representative.

2.24. Volunteer Code: A code assigned by the principal investigator or other investigators to each volunteer to keep the volunteer's identity confidential and used in lieu of the volunteer's name when the investigator reports adverse events or other trial-related data.

2.25. Responsible Person for Administrative Affairs: A person preferably with a specialty or doctoral degree who is responsible for ensuring coordination about trial-related administrative issues in a multicenter trial while the trial is being conducted among principal investigators and ethics committee, sponsor or legal representative of the sponsor and between them and the General Directorate of Health Services if necessary.

2.26. Good Clinical Practices (GCP): Rules including the regulations on design, conduct, monitoring, budgeting, assessment and reporting of the clinical trials; protection of all rights and physical integrity of volunteers as well as the confidentiality and reliability of the trial data with a view to ensuring the trial is conducted as per international scientific and ethical standards, which are required to be complied by the participants.

2.27. Permission (Permission of the General Directorate): Affirmative decision of the General Directorate as to the fact that the trial can be conducted in relevant sites in line with good clinical practices and limits set forth as per the applicable legislation.

2.28. Monitoring: The act of overseeing the progress of a clinical trial and of ensuring that it is conducted in accordance with the Trial Protocol, Standard Operating Procedures (SOP), good clinical practices and the applicable legislation.

2.29. Monitoring Report: A written report which is prepared following each site visit or communication with the relevant parties based on standard operation procedure of the sponsor and which is submitted by the monitor to the sponsor.

2.30. Quality Assurance: All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented, recorded and reported in compliance with the Good Clinical Practices and the applicable legislation.

2.31. Quality Control: Operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

2.32. Legal Representative: A person who is authorized to give consent for the volunteer taking part in clinical trials on behalf of the potential volunteer in line with the legislation in force.

2.33. Comparator: A product or placebo used as a reference in clinical trials.

2.34. Source Documents: Certified copies or original documents of hospital records, laboratory notes, annotations, volunteers' diaries or evaluation checklists, drug delivery records, recorded data obtained from automated instruments, copies certified after verified as being true, complete and accurate, photographic negatives, microfilms, x-rays, and records kept at laboratories and medico-technical departments involved in the clinical trials.

2.35. Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in clinical trials. Source data are contained in source documents.

2.36. Clinical Trial: A study conducted on human beings, which intends to discover or verify clinical or pharmacological effects of one or more investigational product(s) or GETAT method(s), to define adverse events or reactions, and to study their safety and efficacy.

2.37. Interim Clinical Trial Report: A report of intermediate results and their evaluation based on analyses performed in the course of a trial.

2.38. Clinical Trial Report: A written description of a trial conducted on volunteers with a therapeutic, prophylactic or diagnostic purpose, in which the clinical and statistical descriptions, presentations, and analyses are fully integrated into a single report.

2.39. Non-Clinical Study: Biomedical studies which are not conducted on human volunteers.

2.40. Coordinator: A physician or dentist with a specialty or doctoral degree who is responsible for ensuring coordination among the principal investigators and the ethics committee, the sponsor or the legal representative of the sponsor in a multicenter trial and between them and the General Directorate of Health Services if necessary.
2.41. Blinding (Masking): A procedure in which one or more parties to the trial such as the principal investigator or other investigators, volunteers or monitor are kept unaware of the assigned treatment. Single-blind usually refers to the procedure in which the volunteer is not informed about treatment while double-blind refers to the procedure in which the volunteer, the principal investigator or other investigators, the monitor, and, in some cases, data analysts are not informed about the treatment assignment.
2.42. Site Organization Management Service: Overall services provided by a contract research organization, independent of the sponsor, to the trial sites with a view to carrying out such trial procedures as organizing trial files, preparing volunteers for visit, etc. in parallel with the principal investigator's demand.
2.43. Case Report Form (CRF): A printed, optical, or electronic document designed to record data pertaining to each volunteer and the other information as defined by the trial protocol.
2.44. Approval (Approval of the Ethics Committee): Affirmative decision of the ethics committee as to the fact that the trial can be conducted in the relevant sites within the limits set forth in the applicable legislation and good clinical practices.
2.45. Primary Endpoint: The most important endpoint in the trial, which provides primary data.
2.46. Randomization (Random Assignment): The process of assigning volunteers to treatment or control groups with equal probability so as to reduce bias.
2.47. Site Coordinator: Qualified persons assigned, independently of the sponsor, in a trial site to carry out such trial procedures as organizing trial files, preparing volunteers for visit, etc. in parallel with the principal investigator's demand.
2.48. Secondary Endpoint: An endpoint which is less important than the primary endpoint in a trial.
2.49. Endpoint: It can be defined as a variable which is one of the main fields of interest of the trial. This variable may be related to efficiency and safety. Endpoint may be used as a synonym of efficiency variability and safety variability; however, it may not be used as a synonym of demographic variability.
2.50. Principal Investigator: A physician or dentist responsible for conducting the trial, who has a certificate in the relevant field.
2.51. Contract: A written, dated and signed agreement between two or more involved parties which sets out any arrangement on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The trial protocol may serve as the basis of a contract.
2.52. Contract Research Organization (CRO): An independent organization which operates in line with good clinical practices and to which the sponsor has transferred all or some of its trial-related duties and authorities with a written contract.
2.53. Standard Operating Procedures (SOP): Detailed, written instructions to provide complementary guidance and support to the relevant regulations and Good Clinical Practices.
2.54. Impartial Witness: A person, who is independent of the trial and not a part of the trial team, who should not be influenced by people involved with the trial, who attends the informed consent process if the volunteer or the volunteer's legal representative is illiterate,

and who reads the informed consent form and any other written information supplied to the volunteer.

2.55. Compliance: Adherence to all the trial-related requirements, good clinical practices and the applicable legislation.

2.56. Sub-investigator: Any individual member of the trial team designated and supervised by the investigator at a trial site to carry out critical trial-related methods or to make important trial-related decisions.

2.57. Audit: A systematic and independent examination of the trial-related activities and documents to determine whether the trial-related activities are conducted, and the data are recorded, analyzed and accurately reported according to the trial protocol, the sponsor's standard operating procedures, the good clinical practices and the applicable legislation.

2.58. Audit Trail: Documentation that shows the course of events.

2.59. Audit Certificate: A declaration of confirmation by the auditor that an audit has taken place.

2.60. Audit Report: A written evaluation by the auditor of the results of the audit.

3. BASIC PRINCIPLES OF GOOD CLINICAL PRACTICES

3.1. Clinical trials should be conducted in accordance with the good clinical practices, the applicable legislation and ethical principles that are based on current provisions of the Declaration of Helsinki.

3.2. Before a clinical trial is initiated, any probable risks should be weighed against the anticipated benefit for the volunteer and the society. A clinical trial can be initiated and continued only if the anticipated benefits outweigh any probable risks.

3.3. The rights, safety, and well-being of the volunteers are the most important considerations. Scientific benefits and public interest expected of the trial cannot prevail over the rights, safety and well-being of the volunteers.

3.4. The available non-clinical and clinical information on an investigational product should be adequate to support the clinical trials.

3.5. Clinical trials should be in compliance with scientific rules and be described by a scientifically valid, clear and detailed protocol.

3.6. Clinical trials should be conducted in compliance with the approved trial protocol.

3.7. Medical care given to and medical decisions made on behalf of volunteers should always be under the responsibility of physicians or dentists with necessary professional qualifications.

3.8. Each individual involved in conducting the trial should be qualified by education, training and experience to perform her/his relevant tasks.

3.9. Before a clinical trial commences, informed consent of the volunteer is received to make sure the volunteer will be included in the trial of their own free will in compliance with the applicable legislation.

3.10. Clinical trial-related information should be recorded, processed and kept in a way to ensure it is properly reported, construed and verified.

3.11. All records related to the volunteer's identity should be protected in a way to follow the principle of privacy and confidentiality in parallel with the provisions of the applicable legislation.

3.12. Investigational products should be manufactured, handled, and stored in accordance with the applicable good manufacturing practices. These products should be used in accordance with the approved trial protocol.

3.13. Quality systems that assure the quality of every aspect of the trial should be implemented.
3.14. It is mandatory to take out insurance for bloodletting procedure provided that it is conducted by a professional with necessary professional qualifications. However, amount of blood to be taken and frequency of bloodletting should be approved by the ethics committee.

4. ETHICS COMMITTEE

4.1. The ethics committee should have the required qualifications to review and evaluate scientific, medical and ethical aspects of the proposed trial.
4.2. Pursuant to the applicable legislation, the ethics committee should consist of minimum seven and maximum fifteen members among whom there are one non-healthcare professional and one lawyer and most of whom are healthcare professionals with doctoral degree or medical specialty.
4.3. Members of the ethics committee who are healthcare professionals are supposed to receive basic trainings on good clinical practices and clinical trials carried out as per the applicable legislation before they join the ethics committee and to receive certificate of training in this respect. Members of the ethics committee who are not healthcare professionals are obliged to receive basic trainings on good clinical practices and clinical trials carried out as per the applicable legislation within the shortest time period after they are assigned in the ethics committee.
4.4. The ethics committee should be established with an equal gender distribution if possible.
4.5. The ethics committee should protect the rights, safety and well-being of volunteers and give significant consideration to the trials in which vulnerable subjects will take part.
4.6. The ethics committee should give due consideration to ensuring that documents and information required to be submitted in clinical trial applications are complete and in compliance with the applicable legislation.
4.7. The ethics committee should examine the proposed clinical trial application within the time period set forth in the applicable legislation and convey its decision to applicant.
4.8. When conveying its decision, the ethics committee should pay attention to following issues, the decision should be in compliance with the format specified in the web site of the General Directorate of Health Services, and the committee should document them in writing:
4.8.1. Title of the trial,
4.8.2. List of documents reviewed if available, including date and version number,
4.8.3. A list of members of the ethics committee where specialties of the members are specified,
4.8.4. Affirmative decision and its date if an affirmative decision is taken,
4.8.5. Non-affirmative decision, its justification and date if a non-affirmative decision is taken,
4.8.6. If a previously given affirmative decision is cancelled or temporarily suspended, justification and date for the same.
4.9. The ethics committee should examine the qualifications of the principal investigator and of the other investigators, the coordinator and the responsible person for administrative affairs if required for the proposed trial, as documented by a current curriculum vitae or by any other relevant documentation the ethics committee requests.
4.10. The ethics committee may request further information than is given in the Informed Consent Form if it considers it will make significant contribution to the rights, safety and well-being of volunteers.

4.11. When a non-therapeutic trial is to be carried out with the consent of the volunteer's legal representative, the ethics committee should give due consideration to ensuring that the proposed trial protocol or other documents adequately satisfy the relevant ethical concerns and comply with the applicable legislation for such trial.

4.12. Where the protocol indicates that it is not possible to receive the prior consent of the volunteer or the volunteer's legal representative in case the trial necessitates to take emergency actions and the volunteer is unconscious and her/his legal representative or relative is not available to get consent at the time of intervention required, the ethics committee should determine whether the proposed trial protocol or other documents adequately satisfy the relevant ethical concerns and comply with the applicable legislation for such trial.

4.13. The ethics committee should review both the amount and method of expenditures such as transportation and food expenditures, which may arise from the volunteers' participation in the trial, so as to ensure that they neither pose problems of coercion or negative influence on volunteers. Payments to a volunteer should not wholly depend on completion of the trials by the volunteer.

4.14. The ethics committee may request information regarding the way payment will be distributed to the volunteers.

4.15. The ethics committee should make sure that information on expenditures such as transportation and food expenditures are included in the Informed Consent Form and other written instruments to be provided to the volunteers.

4.16. The ethics committee should review and evaluate the ongoing clinical trials based on information and documents such as annual report forms at regular intervals, but not less than once a year, taking into consideration the degree of risk on volunteers.

4.17. The ethics committee performs review of clinical trial applications when the application is submitted and also throughout the trial period.

4.18. Members of the ethics committee are obligated to follow the principle of confidentiality regarding any information conveyed to them.

4.19. It is forbidden that members of the ethics committee disclose any and all types of trial-related documents and information provided to them. Such documents and information can be submitted to the legally authorized persons and institutions only if requested by them.

4.20. Members of the ethics committee will begin performing their duties after signing a non-disclosure agreement and commitment letter to be prepared and published on the web site by the General Directorate of Health Services. Such documents are annually renewed and submitted to the General Directorate of Health Services in case there is any change in declaration given.

4.21. Standard operating procedures of the ethics committee are determined by the General Directorate and published on the web site of the General Directorate. The ethics committee conducts its duties within the framework of the specified standards.

4.22. The ethics committee should carry out its activities in compliance with the applicable legislation, good clinical practices and standard operating procedures and keep written records of all activities carried out.

4.23. The ethics committee may receive written opinion of those who are competent in the examined topic or may invite them as a counselor to the meeting, if needed. These specialists are obliged to sign a non-disclosure agreement and commitment letter published on the web site of the General Directorate of Health Services.

4.24. Only members who participate in the ethics committee reviews and discussions should vote, provide their opinions or give recommendations.

4.25. A member of the ethics committee who is independent of the clinical trial team or the sponsor can vote or provide opinion on trial-related matters. A member of the ethics committee who is associated with or takes part in the trial which is being inspected may not participate in discussions and voting in the ethics committee of this trial and sign the ethics committee decision.
4.26. The coordinator, the responsible person for administrative affairs, the responsible investigator, the investigator, the sponsor or the legal representative of the sponsor may be invited to the ethics committee meeting to provide information on any aspect of the trial. The coordinator, the responsible person for administrative affairs, the principal investigator, the investigator, the sponsor or the legal representative of the sponsor may not participate in voting or deliberations of the ethics committee.
4.27. A current list including names and qualifications of the members of the ethics committee should be kept.
4.28. Names and qualifications of the members of the ethics committee may be conveyed to the relevant parties when necessary.
4.29. Members of the ethics committee convene with at least two-third of the total number of members and make a decision with simple majority of the total number of members.
4.30. The term of office of the ethics committee members is two years and the members may be re-elected.
4.31. The membership of those who do not participate in three meetings in a row or five meetings at intervals without any excuse during their membership is automatically annulled. A new member with the same qualifications is selected to replace those who complete their term of office or whose membership is annulled.

5. THE PRINCIPAL INVESTIGATOR AND THE INVESTIGATOR

5.1. The coordinator, the responsible person for administrative affairs, the principal investigator and other investigators should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial.
5.2. The curriculum vitae of the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators should comply with the form published on the web site of the General Directorate of Health Services and should be up-to-date and signed. These qualifications should be confirmed and certified upon request by the General Directorate of Health Services, the ethics committee or the sponsor.
5.3. A physician or dentist who has completed her/his education in the relevant field and is responsible for conducting the trial can perform her/his duties as the principal investigator. The principal investigator is supposed to have a doctoral degree or specialty in medicine.
5.4. The Coordinator, the responsible person for administrative affairs, the principal investigator and other investigators should have adequate and detailed information on the investigational products described in the current trial protocol and Investigator's Brochure and in other information sources provided by the sponsor.
5.5 The coordinator, the responsible person for administrative affairs, the principal investigator and other investigators should be informed about and should comply with the good clinical practices, the current provisions of the Declaration of Helsinki and the applicable legislation.
5.6. The coordinator, the responsible person for administrative affairs, the principal investigator and other investigators are obliged to permit monitoring and auditing by the ethics committee and/or the sponsor, and inspection by the General Directorate of Health

Services or other relevant health authorities in all respects including investigation site, trial documentation.

5.7. Provided that the General Directorate of Health Services and the ethics committee are notified, the principal investigator may delegate a trial nurse, a site coordinator, a sub-investigator or a qualified person to help conduct of the trial in parallel with the applicable legislation, and should keep records of those delegations. The General Directorate of Health Services may cancel this delegation, providing justification.

5.8. The principal investigator should have adequate number of qualified personnel and adequate facilities to conduct the trial in a proper and safe manner within the foreseen time period.

5.9. The principal investigator inspects trial team members delegated in accordance with the applicable legislation who assume trial-related duties.

5.10. In case services are provided by a team to carry out trial-related duties, the principal investigator should make sure that the team is suitably qualified to conduct the same and should adopt procedures which will provide integrity of data obtained and duties carried out with respect to the trial.

5.11. The Coordinator, the responsible person for administrative affairs and the principal investigator should have sufficient time to properly perform and complete the trial within the specified time period. The coordinator, the responsible person for administrative affairs, the principal investigator and other investigators may perform a certain number of studies at the same time in accordance with the nature of the trial provided that a reasonable justification is given. However, the General Directorate of Health Services or the ethics committee may impose restrictions provided that a justification is given.

5.12. The principal investigator demonstrates a potential for recruiting the required number of volunteers with suitable qualifications within the recruitment period.

5.13. The Coordinator, the responsible person for administrative affairs and the principal investigator ensure that the trial team is adequately informed about the trial protocol, the investigational products and the trial-related matters.

5.14. A qualified physician or dentist, who acts as the principal investigator or sub-investigator, is responsible for all trial-related medical or dental decisions.

5.15. During and following a volunteer's participation in the trial, the principal investigator or sub-investigator and the trial site ensure that the volunteer is provided with adequate medical care in case of any adverse events, including clinically significant laboratory values, related to the trial.

5.16. The principal investigator or sub-investigator informs a volunteer when medical care is needed for other illnesses of which the principal investigator or sub-investigator becomes aware, occurring during or after a clinical trial, in addition to an ongoing disease.

5.17. It is recommended that the principal investigator or sub-investigator inform the relevant physician about the volunteer's participation in the trial if the volunteer has a primary physician and if the volunteer agrees the primary physician is informed.

5.18. The volunteer is not obliged to give her/his reasons for withdrawing prematurely from the trial. However, the principal investigator or sub-investigator may make a reasonable effort to understand the reasons, while fully respecting the volunteer's rights.

5.19. Before the trial commences; the coordinator, the responsible person for administrative affairs and the principal investigator are supposed to receive the approval of the ethics committee and permission of the General Directorate of Health Services for the trial requiring the Ministerial permission.

5.20. The principal investigator or sub-investigator conducts the trial in compliance with the trial protocol approved by the ethics committee. For a trial requiring the permission according to the relevant legislation, the trial should be conducted in compliance with the protocol permitted by the General Directorate of Health Services.
5.21. The coordinator, the responsible person for administrative affairs or the principal investigator and the sponsor sign the trial protocol to confirm agreement.
5.22. The coordinator, the responsible person for administrative affairs or the principal investigator may not amend the trial protocol without review and written approval of the ethics committee; for the trial requiring permission according to the relevant legislation, they may not amend the protocol without the permission of the General Directorate of Health Services. However, the ethics committee and the General Directorate of Health Services are informed about the matter and provided with justifications as soon as possible in case of any deviation from or changes in the protocol aiming to eliminate an immediate threat.
5.23. The coordinator, the responsible person for administrative affairs, the principal investigator or other investigators document and explain any deviation from the approved protocol, providing its justifications. Deviations from the protocol are notified if requested by the ethics committee and the General Directorate of Health Services.
5.24. The principal investigator in each trial site where trial is conducted is liable to accept, preserve and distribute products in accordance with written requests or trial protocol, to perform stock control for them, to keep records, and to conduct transactions for the remaining products.
5.25. A person who is designated by the principal investigator keeps records of the investigational product inventory at the site, its use by volunteers, its return to the sponsor, or alternative disposition of unused products. These records include dates, quantities, batch/serial numbers, expiration dates and the code numbers assigned to the investigational products and the volunteers.
5.26. The person who is designated by the principal investigator should ensure that the investigational products are stored in accordance with the applicable legislation.
5.27. The principal investigator or sub-investigator keeps records evidencing that the volunteers are provided with products specified in the trial protocol and ensures that all investigational products are in line with consumed amounts.
5.28. The principal investigator or sub-investigator ensures that the investigational products are used only in accordance with the approved trial protocol.
5.29. The principal investigator or sub-investigator or eligible person designated by the principal investigator explains the correct use of the investigational products and checks, at intervals appropriate for the trial, whether volunteers are following the instructions properly.
5.30. The principal investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the trial protocol. If the trial is blinded, the principal investigator should promptly document and explain to the sponsor reasons of any premature unblinding of the investigational product.
5.31. In obtaining and documenting informed consent, the principal investigator or a sub-investigator should comply with the applicable legislation and the ethical principles.
5.32. Prior to the beginning of the trial, the coordinator, the responsible person for administrative affairs and the principal investigator should ensure that the informed consent of each volunteer is obtained.
5.33. The principal investigator should retain a copy of the original signed informed consent forms.

5.34. The principal investigator should ensure all data to be submitted to the sponsor in the Case Report Forms and in all required reports are communicated in an accurate, complete and timely manner.
5.35. Data reported in the Case Report Form, which are derived from source documents, should be consistent with the source documents. Any discrepancies should be explained.
5.36. Any change in or correction to a case report form should be dated, initialed, and explained if necessary. This should not prevent the original data entry and should apply to both written and electronic changes. The sponsor should provide guidance to the principal investigator or the principal investigators' designated sub-investigator on making such corrections. The sponsor should have written procedures to assure that changes or corrections in case report forms are required to be documented and that such changes are necessarily approved by the principal investigator or the sub-investigator. The principal investigator retains records of the changes and corrections.
5.37. The coordinator or the principal investigator should keep sensitive and accurate source information and trial records including observations on volunteers involved in the trial at the site. Source data should be attributable, legible, original, accurate and complete. Any change in source data should be traceable, should not obscure the original entry, and should be explained if necessary.
5.38. The principal investigator should maintain the trial documents in accordance with the applicable legislation and take measures to prevent accidental or premature destruction of these documents.
5.39. Documents related to the trial should be retained for minimum fourteen years following the end of the trial at all trial sites. However, these documents may be retained for a longer period if required by an agreement with the sponsor. It is the responsibility of the sponsor to inform the principal investigator as to when these documents no longer need to be retained.
5.40. The financial aspects of the trial are documented in an agreement between the sponsor and the principal investigator. This agreement is also made between the coordinator or the responsible person for administrative affairs when necessary.
5.41. Upon request the coordinator, the responsible person for administrative affairs or the principal investigator allows the monitors', the auditors', the ethics committee's, or the General Directorate of Health Services' or other relevant health authorities' direct access to all requested trial-related records.
5.42. The coordinator, the responsible person for administrative affairs or the principal investigator submits written summaries of the trial status to the institution conducting the trial, the ethics committee and the General Directorate of Health Services at least annually, or more frequently, if requested by the ethics committee and the General Directorate of Health Services.
5.43. The coordinator, the responsible person for administrative affairs or the principal investigator promptly provides written reports to the sponsor, the ethics committee and the General Directorate of Health Services on any changes significantly affecting conduct of the trial or increasing the risk to volunteers.
5.44. The coordinator, the responsible person for administrative affairs or the principal investigator informs all relevant parties when new information is obtained which may adversely affect the health of volunteers or conduct of the trial.
5.45. The principal investigator or sub-investigator should respect the time periods for safety notifications of the trial described in applicable legislation and should meet her/his obligations.

5.46. All serious adverse events should be immediately reported by the principal investigator or an investigator designated by the principal investigator except for those which do not need immediate reporting according to the trial protocol or other documents. The immediate reports are followed by detailed, written reports. The immediate and follow-up reports identify volunteers by a single code number assigned to them. Volunteers' names, personal identification numbers or addresses should not be used.
5.47. Adverse events or laboratory abnormalities identified in the trial protocol as critical in terms of safety evaluations should be reported to the sponsor by the principal investigator or designated investigator according to the reporting requirements and within time periods specified in the trial protocol.
5.48. For reported deaths, the principal investigator submits autopsy reports and other medical reports upon request by the General Directorate of Health Services or the ethics committee.
5.49. If the trial is prematurely terminated or suspended for any reason, the principal investigator promptly informs the volunteers and ensures appropriate treatment and follow-up for them.
5.50. If the principal investigator terminates or suspends a trial without obtaining prior approval of the sponsor, the principal investigator informs the institution conducting the trial, the sponsor and the ethics committee, and provides the General Directorate of Health Services, the sponsor and the ethics committee with a detailed written explanation of the termination or suspension.
5.51. If the sponsor, the ethics committee or the General Directorate of Health Services terminates or suspends a trial, the coordinator, the responsible person for administrative affairs or the principal investigator informs the institution conducting the trial, providing justifications.
5.52. The principal investigator should make sure that the institution conducting the trial, the ethics committee and the General Directorate of Health Services are notified after the trial is completed.
5.53. All references to the principal investigator in these guidelines also apply to the coordinator.

6. SPONSOR

6.1. The sponsor is responsible for developing written standard operating procedures and for implementing and maintaining quality assurance and quality control systems to ensure that trials are conducted and data are generated, documented and reported in compliance with the trial protocol, current provisions of the Declaration of Helsinki, principles of the good clinical practices, and the applicable legislation.
6.2. The sponsor is responsible for ensuring agreement between all involved parties to ensure direct access to all trial-related sites, source data and documents for the purpose of monitoring and auditing by the sponsor, and inspection by the General Directorate of Health Services and other relevant health authorities.
6.3. The sponsor should ensure it is specified in the protocol and other written agreements that the investigator will allow monitoring, auditing and inspection related to the trial by allowing direct access to the source data.
6.4. The sponsor should apply quality control to each step of data processing to ensure reliability and proper processing of all data.

6.5. The sponsor implements a system to manage quality throughout the design, conduct, recording, evaluation, reporting and archiving of clinical trials.
6.6. The sponsor focuses on trial activities essential to ensuring volunteer protection and the reliability of trial results. Quality management includes clinical trial protocols, data collection tools and procedures, and collection of information required to make a decision.
6.7. Methods used to assure and control the quality of the trial should be proportionate to the risks inherent in the trial and the importance of the information collected. The sponsor ensures that all aspects of the trial are operationally feasible and avoids unnecessary complexity, procedures and data collection. Protocols, case report forms, and other operational documents should be clear, concise and consistent.
6.8. All agreements between the sponsor and the principal investigator or any other parties involved with the clinical trial should be made in writing as part of the trial protocol or in a separate agreement.
6.9. The sponsor may transfer any or all of the sponsor's trial-related duties and functions to a contract research organization. The sponsor is responsible for selection of the contract research organization. However, the ultimate responsibility for the quality and accuracy of the trial data always resides with the sponsor. The contract research organization implements systems related to quality assurance and quality control.
6.10. Any trial-related duty and function that is transferred to and assumed by a contract research organization is specified in writing.
6.11. The sponsor ensures supervision of trial-related duties and functions carried out on behalf of the sponsor.
6.12. The responsibility for any trial-related duty, except for those specifically transferred to and assumed by a contract research organization, resides with the sponsor.
6.13. All references to a sponsor in these guidelines also apply to a contract research organization to the extent that a contract research organization has assumed the trial-related duties and functions of a sponsor.
6.14. The sponsor should utilize qualified individuals throughout all stages of the trial process, from design of the trial protocol and case report forms and planning of the analyses to analysis and preparation of interim and final clinical trial reports.
6.15. The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions or problems. If necessary, consultants may be appointed for this purpose.
6.16. The sponsor should utilize appropriately qualified individuals to supervise conduct of the trial, to process and verify data, to conduct the statistical analyses, and to prepare the trial reports.
6.17. The sponsor may establish an independent data monitoring committee to assess the progress of a clinical trial including the safety data and the critical efficacy endpoints at intervals and to recommend to the sponsor whether to continue, modify or stop a trial. The independent data monitoring committee should have written operating procedures and keep written records of all meetings conducted.
6.18. When necessary, the ethics committee or the General Directorate of Health Services may request the sponsor to establish an independent data monitoring committee.
6.19. When using electronic trial data processing or remote electronic trial data systems, the sponsor:
6.19.1. Ensures and documents that the electronic data processing systems conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent validation,

6.19.2. Prepares standard operating procedures related to use of these systems,
6.19.3. Ensures that the systems are designed to permit data changes in such a way that the data changes are documented and that data -such as audit trail, data trail or edit trail which are entered to the system- are not deleted.
6.19.4. Maintains a security system that prevents unauthorized access to the data,
6.19.5. Keeps a list of the individuals who are authorized to make data changes,
6.19.6. Allows and maintains adequate backup of the data,
6.19.7. Allows comparison of the original data and observations with the processed data if data are transformed during processing,
6.19.8. Safeguards the blinding if any.
6.20. The sponsor should use a volunteer code that allows identification of all the data reported for each volunteer.
6.21. The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents.
6.22. The sponsor should retain all sponsor-specific essential documents in compliance with the applicable legislation of the countries where the product is approved or where the sponsor intends to apply for approval.
6.23. If the sponsor ceases a part of or whole clinical development process of an investigational product, the sponsor should maintain all sponsor-specific essential documents for at least 5 years after formal termination.
6.24. If the sponsor ceases a part of or whole clinical development process of an investigational product, the sponsor notifies all the trial investigators, the ethics committee and the General Directorate of Health Services and provides justification for it.
6.25. Any transfer of ownership of the data is reported to the ethics committee and the General Directorate of Health Services and its justification is provided.
6.26. The sponsor informs the principal investigator in writing of the need for record retention or notifies the principal investigator in writing when the trial-related records are no longer needed.
6.27. The sponsor is responsible for selecting the principal investigators and other investigators and investigational sites.
6.28. The sponsor is also responsible for selection of the coordinator and the responsible person for administrative affairs for multicenter trials.
6.29. Before entering an agreement with the coordinator, the responsible person for administrative affairs or other investigators to conduct a trial, the sponsor provides them with the trial protocol and an up-to-date Investigator's Brochure and provides sufficient time to review them.
6.30. The sponsor makes sure that the coordinator, the responsible person for administrative affairs or other investigators make an agreement with the sponsor, and signs the trial protocol or an alternative document together with the coordinator, the responsible person for administrative affairs or other investigators in a way to satisfy the following conditions:
6.30.1. To carry out the trial in compliance with good clinical practices, the applicable legislation, and the trial protocol which is agreed by the sponsor, approved by the ethics committee and permitted by the General Directorate of Health Services,
6.30.2. To comply with procedures for data recording or reporting,
6.30.3. To allow monitoring, auditing and inspection,
6.30.4. To retain the trial-related essential documents for a period and under the circumstances specified in the relevant legislation until the sponsor informs the principal investigator that these documents are no longer needed.

6.31. Before a clinical trial commences, the sponsor defines and implements all trial-related duties and functions.
6.32. If required by the applicable legislation, the sponsor provides insurances with legal and financial coverage or indemnifies the principal investigator and other investigators against claims/needs arising from the trial.
6.33. The sponsor specifies in writing the treatment expenses of events, such as the trial-related injuries which may result from complications arising from the trial, in compliance with the applicable legislation.
6.34. When volunteers receive compensation due to problems arising from the trial, the method and manner of compensation are required to comply with the applicable legislation.
6.35. The financial aspects of the trial are documented in an agreement between the sponsor and the investigator. This agreement is also made between the coordinator or the responsible person for administrative affairs when necessary.
6.36. Before initiating the clinical trial, the sponsor submits any required applications to the General Directorate of Health Services in accordance with the format published on the web site of the General Directorate of Health Services for review, acceptance or permission to begin the trials. Any notification should be dated and contain sufficient information to identify the protocol.
6.37. The sponsor is responsible for notifying, during the first application of the clinical trial, the ethics committee and the General Directorate Health Services the number of volunteers planned to be enrolled to the trial from our country as well as the total number of volunteers. When total number of the volunteers specified in the clinical trial application cannot be achieved, the number of volunteers planned to be enrolled to the trial from our country can be increased, which requires to receive the approval of the ethics committee and the permission of the General Directorate of Health Services as well as submission of up-to-date documents such as current insurance and budget together with a justification.
6.38. In multicenter trials, the investigative sites should be notified by the sponsor that the trial is to be performed at these sites. This notification includes the approval of the ethics committee, the permission of the General Directorate of Health Services, summary of the trial protocol, the informed consent form and biological material transfer form, if any.
6.39. When planning trials, the sponsor should ensure that sufficient safety and efficacy data to be obtained from preclinical trials or clinical trials for investigational products are available to support the route, the dosages, the duration, and the trial population to be studied.
6.40. The sponsor updates the Investigator's Brochure as significant new information becomes available.
6.41. The sponsor should make sure that the investigational product is suitable for trial phase, is manufactured in accordance with the applicable good manufacturing practices, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with the applicable legislation.
6.42. The sponsor provides acceptable storage conditions, storage times, environment and procedures required to prepare the investigational products, and devices for product infusion, if any. The sponsor informs all relevant parties.
6.43. The sponsor should ensure that the investigational products are packaged in a way to prevent contamination and unacceptable deterioration during transport and storage.
6.44. In blinded trials, the coding system for the investigational products should include a mechanism that permits rapid identification of the product in case of a medical emergency, but does not permit breaks of the blinding.

6.45. If significant formulation changes are made in the investigational or comparator product during the course of clinical trial, the results of any additional studies of the product (e.g. stability, dissolution rate, bioavailability, etc.) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be made available by the sponsor prior to the use of the new formulation in clinical trials.

6.46. The sponsor is responsible for supplying investigational products to the principal investigator and investigative sites.

6.47. The sponsor should not supply the investigational product to an investigative site until the sponsor obtains approval from the ethics committee and permission from the General Directorate of Health Services.

6.48. The Sponsor is liable to store, distribute and deliver investigational products to the investigative sites in accordance with their features after they are manufactured or imported, to maintain these conditions after they are delivered to the investigative sites, to ensure that unused products are recalled from the investigative sites and returned or properly destroyed, and to ensure that the above-stated processes are recorded.

6.49. The sponsor should ensure that written procedures include instructions that the principal investigator and those who are designated by the principal investigator should follow to process and store investigational products, as well as documentation of the same. The said procedures should ensure that investigational products are safely received, processed, stored, that they are given to the volunteers, that unused products are recalled from volunteers and returned to the sponsor, or that they are disposed of or destroyed in an alternative method which is permitted by the sponsor and complies with the applicable legislation.

6.50. The sponsor is liable to ensure timely delivery of investigational products to the investigators.

6.51. The sponsor is liable to maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

6.52. The sponsor maintains a system for the disposition of unused investigational products and for the documentation of this disposition.

6.53. The sponsor takes measures to ensure that the investigational products are stable over the period of use.

6.54. The sponsor maintains sufficient quantities of the investigational products used in the trials to reconfirm specifications when necessary and keeps records of sample analyses and characteristics. As the responsibility rests with the manufacturing company for maintaining sufficient quantities of the investigational products (including products of comparative arm) marketed or available in the market in our country for serial sample analysis pursuant to the applicable legislation, the sponsor conducting the clinical trial may not be held responsible.

6.55. To the extent stability permits, the samples are retained in a site in Turkey or abroad until the analyses of the trial data are complete or for a period required by the licensing requirements in force (whichever represents a longer period of time) pursuant to the applicable legislation.

6.56. The sponsor should ensure that it is specified in the protocol or other written agreement that the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators provide direct access to source data or source documents for trial-related monitoring, audits, review by the ethics committee, inspection by the General Directorate of Health Services and of other relevant health authorities.

6.57. The sponsor should make sure that each volunteer has consented, in writing, to direct access to her/his original medical records for trial-related monitoring, audit, review and inspection.
6.58. The sponsor is responsible for continuous safety evaluation of the investigational products.
6.59. The sponsor informs the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators, investigative sites, the ethics committee and the General Directorate of Health Services of findings that could affect adversely the safety of volunteers and conduct of the trial, or change the affirmative decision to continue the trial.
6.60. The sponsor expedites the reporting process of both serious and unexpected adverse reactions to the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators and, when required, to the ethics committee and the General Directorate of Health Services.
6.61. The sponsor submits all safety updates and periodic reports to the General Directorate of Health Services in accordance with the applicable legislation.
6.62. The sponsor makes sure that the trial is appropriately monitored.
6.63. The sponsor monitors the trial with a view to ensuring that the rights and well-being of volunteers are protected, the reported trial data are accurate, complete, and verifiable from source documents, conduct of the trial is in compliance with the currently approved trial protocol, the good clinical practices and the applicable legislation.
6.64. The sponsor may conduct an audit separately and independently of the routine monitoring and quality control functions. It aims to assess whether conduct of the trial is in compliance with the trial protocol, standard operating procedures, the good clinical practices and the applicable legislation.
6.65. The sponsor selects officers to conduct the audit who are independent of the clinical trial and data collection systems.
6.66. The sponsor should ensure that the auditors are trained and experienced enough to appropriately conduct the audit. It is necessary to document qualifications of auditors.
6.67. The sponsor is expected to have written methods for audits of clinical trials and systems, which indicate how and how often an issue will be audited as well as format and content of audit reports. The audit reports submitted to the General Directorate of Health Services or the relevant health authorities contain information on significance of the trial, number of volunteers in the trial, type of the trial and the level of complexity as well as the level of risk on the volunteers and the specified outcomes of the risk. Moreover, observations and findings by the auditors should be documented. The General Directorate of Health Services or the relevant health authorities should not routinely request audit reports in order to protect independence and value of the audit procedure. If there are serious violations of good clinical practices or during a legal condition or investigation, the General Directorate of Health Services or the relevant health authorities may access the case-based audit report during the audit.
6.68. The sponsor immediately takes necessary measures to eliminate non-compliance if personnel of the sponsor, the coordinator, the responsible person for administrative affairs, the principal investigator or other investigators or those who take part in the trial do not follow the protocol, standard operating procedures, the good clinical practices and/or the applicable legislation.
6.69. If serious or repetitive non-compliance by the coordinator, the responsible person for administrative affairs, the principal investigator or other investigators or those who take part

in the trial is detected following a monitoring or an audit, the sponsor terminates their participation in the trial and immediately informs the General Directorate of Health Services thereof.

6.70. In case a trial is prematurely terminated or suspended, the sponsor notifies the principal investigators, the ethics committee and the General Directorate of Health Services of the termination and suspension and its justification.

6.71. The sponsor is responsible for producing trial reports and submitting them to the ethics committee and the General Directorate of Health Services when the trial is completed or prematurely terminated.

6.72. In multicenter trials, the sponsor is responsible for designing the case report forms in such a way that they include all necessary data for all investigational sites and for submitting the additional case report forms designed to collect additional data to the investigators collecting additional data.

6.73. Responsibilities of the coordinator, the principal investigators, sub-investigators and those who take part in the trial are documented by the sponsor before the conduct of a trial.

6.74. The Coordinator, the principal investigators and sub-investigators are informed by the sponsor that they should follow uniform standards specified to act in accordance with the protocol and evaluate clinical and laboratory findings and that they should fill in the case report forms. The required records are kept.

6.75. The sponsor ensures communication between the principal investigator, the coordinator, the responsible person for administrative affairs, sub-investigators and those who take part in the trial.

6.76. The sponsor makes sure that the trial is appropriately monitored.

6.77. Responsibilities of monitors and the relevant parties taking part in the trial with respect to the use of computer-aided systems should be clear and the sponsor should train the users on the use of these systems.

6.78. The sponsor provides data integrity including any data which clarify the context, content and structure of data when there is any alteration in the computer-aided systems such as software updates or data transfers.

6.79. The sponsor develops a systematic, prioritized and risk-oriented approach to monitor clinical trials.

7. QUALITY MANAGEMENT

7.1. All parties taking part in the trial team are responsible for building and implementing a quality management system within the scope of the duties and authorities specifies in these Guidelines.

7.2. The quality management system should use a risk-based approach as described below:

7.2.1. During protocol development, the sponsor should identify those processes and data that are critical to ensure volunteer protection and the reliability of trial results.

7.2.2. Risks to critical working processes and data should be determined. Risks should be assessed at both the system level (standard operating procedures, computer-aided systems, personnel, etc.) and clinical trial level (investigational product, trial design, data collection, and recording).

7.2.3. Risks identified should be assessed taking into consideration the followings:

7.2.3.1. The likelihood of errors occurring considering current risk controls,

7.2.3.2. The impact of such errors on volunteer protection and data integrity,

7.2.3.3. The extent to which such errors would be detectable.

7.2.4. The sponsor should decide which risks to reduce and/or which risks to accept. The sponsor may take part in risk reduction activities, protocol design and implementation, monitoring plans, agreements between parties defining roles and responsibilities, systematic measures to ensure adherence to standard operating procedures, and training in processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact safety of volunteers or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

7.2.5. Quality management activities should be documented and communicated to those who are involved in or affected by such activities, to facilitate risk review and continual improvement during clinical trial.

7.2.6. The sponsor should periodically review risk control measures to ascertain whether the implemented quality management activities remain effective and relevant, taking into account emerging knowledge and experience.

7.2.7. The sponsor describes the quality management approach implemented in the trial and summarizes important deviations from the predefined quality tolerance limits.

8. MONITOR AND MONITORING ACTIVITY

8.1. Monitors are appointed by the sponsor.

8.2. Monitors should be appropriately trained on good clinical practices and clinical trials and should have the scientific or clinical knowledge needed to monitor the trial properly.

8.3. The qualifications of the monitor should be documented.

8.4. Monitors should be thoroughly familiar with the investigational products, the protocol, written informed consent form and any other written information to be provided to volunteers, the sponsor's SOPs, GCP, and the applicable legislation.

8.5. When determining the extent of monitoring, the sponsor should take into considerations the objective, design, size, complexity, blinding, and endpoints of the trial.

8.6. In general there is a need for on-site monitoring before, during, and after the trial.

8.7. In accordance with the sponsor's requirements, the monitors carry out the following activities when relevant and necessary to the trial and the trial site:

8.7.1. Acting as the main line of communication between the sponsor and the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators,

8.7.2. Verifying that the principal investigator and the sub-investigator have adequate qualifications and resources and remain adequate throughout the trial period and that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period,

8.7.3. Verifying that the principal investigator and other investigators follow the approved protocol and all approved amendments, if any,

8.7.4. Verifying that written informed consent is obtained before each volunteer's participation in the trial,

8.7.5. Ensuring that the principal investigator and other investigators receive the current Investigator's Brochure, all documents, and all trial supplies which are needed to conduct the trial properly and to comply with the applicable legislation,

8.7.6. Verifying that the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators fulfill all obligations set forth in the protocol

and any other written agreement between the sponsor and the principal investigator, and have not delegated these obligations to unauthorized individuals,

8.7.7. Ensuring that the investigator and the sub-investigators are enrolling only eligible volunteers,

8.7.8. Making sure of the volunteer recruitment date,

8.7.9. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained,

8.7.10. Verifying that the responsible investigator and sub-investigators provide all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

8.7.11. Checking the accuracy and completeness of CRF entries, source data and other trial-related records against each other.

8.7.12. For the investigational products, verifying:

8.7.12.1. That storage times and conditions are acceptable,

8.7.12.2. That investigational products are sufficient throughout the trial,

8.7.12.3. That the investigational products are supplied only to volunteers, who are eligible to receive them, in doses and for durations specified in the protocol,

8.7.12.4. That volunteers are provided with necessary instruction on how to use, handle, store, and return the investigational products properly,

8.7.12.5. That the receipt, use, and return of the investigational products at the trial sites are controlled and documented properly.

8.7.12.6. That arrangements related to unused investigational products at the trial sites comply with the applicable legislation.

8.8. The monitor specifically should verify that:

8.8.1. The data required by the protocol are reported accurately in CRFs and are consistent with the source documents,

8.8.2. Any dose and/or therapy modifications are well documented for each trial volunteer,

8.8.3. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol in CRFs,

8.8.4. Visits that the volunteers fail to make, tests that are not conducted, and examinations that are not performed are clearly reported in CRFs,

8.8.5. All withdrawals and dropouts of enrolled volunteers from the trial are reported and explained in CRFs.

8.8.6. The principal investigator and sub-investigators are informed of any CRF entry error, omission, or illegibility.

8.8.7. Appropriate corrections, additions or deletions are made, dated, explained (if necessary), and are initialled by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator.

8.8.8. Safety notifications are properly reported to the General Directorate of Health Services, the ethics committee and the sponsor as specified in the applicable legislation,

8.8.9. The principal investigator is maintaining the essential documents,

8.8.10. Deviations from or violations of the protocol, SOPs, GCP, and the provisions of the applicable legislation are communicated to the investigator and appropriate actions are taken to prevent their recurrence.

8.9. The monitor should follow the sponsor's established written SOPs, the applicable legislation, and the procedures that are specified by the sponsor for monitoring a specific trial.

8.10. The monitor submits a written report to the sponsor after each trial site visit or trial-related communication. The reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted. Also, the reports should include a summary of the monitor's review and the monitor's statements concerning the significant findings, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.
8.11. The review and follow-up of the monitoring report are documented by the sponsor's designated representative.

9. TRIAL PROTOCOL AND PROTOCOL AMENDMENTS

The contents of a trial protocol should generally include the following topics. However, site-specific information may be provided on separate protocol pages, or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.
9.1. Protocol title, protocol identifying number, and date.
9.2. Any amendment(s) should also bear the amendment number(s) and date(s).
9.3. Name and address of the sponsor and the monitor (if other than the sponsor).
9.4. Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.
9.5. Name, title, address, and telephone number(s) of the sponsor's medical expert, or the dentist when appropriate, for the trial.
9.6. Name and title of the investigators who are responsible for conducting the trial and the address and telephone numbers of the trial sites.
9.7. Name, title, address, and telephone number of the qualified physician or the dentist who is responsible for all trial-site related medical or dental decisions.
9.8. Addresses of the clinical laboratories and other medical departments or institutions involved in the trial.
9.9. Name and description of investigational products, if applicable.
9.10. A summary of findings of non-clinical studies, of findings that potentially have clinical significance, and of findings of clinical trials that are relevant to the trial. **9.11** A summary of the known and potential risks and benefits to volunteers.
9.12. Description of and justification for the administration method, the route of administration, dosage, dosage regimen, and treatment periods,
9.13. A statement that the trial will be conducted in compliance with the trial protocol, Good Clinical Practices and the applicable legislation.
9.14. Description of the population to be studied.
9.15. References to literature and data that are relevant to the trial and that provide background for the trial.
9.16. A detailed description of the objectives and the purpose of the trial.
9.17. Trial design. The scientific integrity of the trial and the credibility of the data obtained from the trial depend substantially on the trial design. A description of the trial design should include:
9.17.1. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
9.17.2. A description of the type and design of trial to be conducted and a schematic diagram of trial design, procedures and stages.
9.17.3. A description of the measures taken to minimize or avoid bias.

9.17.4. A description of the trial treatments and the dosage and dosage regimen, if any, of the investigational products.
9.17.5. A description of the dosage form, packaging, and labeling of the investigational products.
9.17.6. The expected duration of volunteer participation, and a description of all trial periods, including follow-up, if any.
9.17.7. A description of the "stopping rules" or "discontinuation criteria" for a part of the trial or for the entire trial for individual volunteers.
9.17.8. Accountability procedures for the investigational products and the placebos, if any.
9.17.9. Maintenance of trial treatment randomization codes and procedures for breaking codes.
9.17.10. The identification of any data to be recorded directly on CRFs (i.e. no prior written or electronic record of data) and to be considered to be source data.
9.18. Volunteer inclusion criteria.
9.19. Volunteer exclusion criteria.
9.20. Volunteer withdrawal criteria and procedures specifying:
9.20.1. When and how to withdraw or remove volunteers from the trial,
9.20.2. The type and timing of the data to be collected for volunteers withdrawn or removed.
9.20.3. Whether and how volunteers are to be replaced.
9.20.4. The follow-up of volunteers withdrawn or removed from the trial.
9.21. Treatments to be administered including the name of all products, doses, the dosage schedule, the route of administration, and the treatment periods including the follow-up periods for volunteers for each investigational product treatment/trial treatment group/arm of the trial.
9.22. Medications/treatments permitted (including rescue medication) and not permitted before or during the trial.
9.23. Procedures for monitoring volunteer compliance.
9.24. Specification of the efficacy parameters.
9.25. Methods and timing for assessing, recording, and analyzing the efficacy parameters.
9.26. Assessment of safety:
9.26.1. Specification of safety parameters,
9.26.2. Methods and timing for assessing, recording, and analyzing the safety parameters,
9.26.3. Procedures for submitting reports of and for recording the adverse event and intercurrent illnesses,
9.26.4. The method and duration of the follow-up of volunteers after adverse events.
9.27. Statistics:
9.27.1. A description of the statistical methods to be employed, including timing of any planned interim analyses,
9.27.2. The number of volunteers planned to be enrolled,
9.27.3. In multicenter trials, the numbers of enrolled volunteers projected for each trial site,
9.27.4. Reason for choice of sample size, including evaluations on the power of the trial and clinical justification,
9.27.5. The level of significance to be used,
9.27.6. Criteria for the termination of the trial,
9.27.7. Procedure for accounting for missing, unused, and spurious data,
9.27.8. Procedures for reporting any deviations from the original statistical plan (any deviations from the original statistical plan should be described and justified in protocol or in the final report, as appropriate),

9.27.9. Selection of volunteers to be included in the analyses (all eligible volunteers, all evaluable volunteers, all randomized volunteers, volunteers who have received the investigational product).
9.28. Specifications of persons, the General Directorate or institutions authorized to directly access to source data,
9.29. Description of the ethical assessments related to the trial.
9.30. Processing and recording the data,
9.31. Information on finance and insurance, if not addressed in a separate agreement,
9.32. Publication policy, if not addressed in a separate agreement,
9.33. Specification of arrangements allowing volunteers to access the interventions, which are found to be useful during the trial, after the trial.

10. INFORMED CONSENT FORM

10.1. When the informed consent is obtained from the volunteers and it is documented, the Good Clinical Practices and the ethical principles based on current provisions of the Declaration of Helsinki are followed.
10.2. The approval of the ethics committee and the permission of the General Directorate of Health Services should be obtained prior to conducting the trial for the written informed consent form given to the volunteers participating in the trial.
10.3. The written informed consent form to be provided to the volunteers should be reviewed in the light of new information obtained, with respect to the consent given by the volunteer. Before any revised informed consent form is used, the approval of the ethics committee and the permission of the General Directorate of Health Services are obtained. The volunteer or the legal representative of the volunteer should be immediately informed when new information is obtained, which may possibly influence the will of the volunteer to continue the trial. It should be necessarily documented that such information is shared.
10.4. The principal investigator or any person from the trial staff should not either force or improperly influence the volunteer to participate in a trial or continue an existing trial.
10.5. Neither verbal information nor written documents pertaining to the trial, including the written informed consent form, may include any provision or statement which voids the legal rights of the volunteer or the legal representative. Moreover, they may not include any provision or statement which may release the principal investigator, any person from the trial staff, any institution, the sponsor or their representatives from any obligations arising from their own negligence, either.
10.6. The volunteer or the legal representatives is informed about all aspects of the trial.
10.7. The verbal and written words and the language of the documents related to the trial, including the written informed consent form, should be clear, understandable and free of technical terms such that they should be satisfactorily understood by the volunteer or the legal representative or the impartial witness.
10.8. When the written informed consent is obtained, the volunteer and the legal representative should be allowed sufficient time to ask questions about details of the trial and make decisions on whether to participate in the trial. All questions about the trial should be answered by the qualified person providing the information to the satisfaction of the volunteer or the legal representative.
10.9. Before the volunteer takes part in the trial, the written informed consent should be personally signed and dated by the investigator, who is a qualified physician or dentist, conducts the informed consent interviews and is a member of the trial team, and when necessary, by the legal representative and impartial witness with their own handwriting.

Each page of the written informed consent form should be initialled by the volunteer or, when necessary, the legal representative and the impartial witness.

10.10. If the volunteer or the legal representative is illiterate, or if the volunteer is visually impaired, the entirety of the written informed consent interview should be made in the presence of an impartial witness, who is not a member of trial staff. After the written informed consent form and other written explanations, required to be given to the volunteer, are read and explained to the volunteer or the legal representative and the volunteer or the legal representative gives verbal consent about the participation in the trial and the said persons sign the approval form, if possible; the impartial witness should sign and date the written informed consent form. Signing the written informed consent, the witness testifies and confirms that information in the written informed consent form and other written explanations are clearly instructed to the volunteer or the legal representative, they are understood by the volunteer or the legal representative, and the informed consent is given with the free will of the volunteer or the legal representative.

10.11. The informed consent interview, the written informed consent form given to the volunteers as well as other written information should include explanations for at least the following issues:

10.11.1. The trial is an investigational study,

10.11.2. The purpose of the trial,

10.11.3. The possibility that volunteers can be randomized to trial groups for treatments to be administered in the trial.

10.11.4. All methods to be followed or administered to the volunteers including invasive methods to be performed during the trial,

10.11.5. Responsibilities of the volunteer,

10.11.6. Experimental parts of the trial,

10.11.7. The anticipated risks and discomforts the volunteer will be exposed to (if the trial is conducted on pregnant or puerperal women, the risks and discomforts to the embryo, fetus or infant),

10.11.8. The volunteer is informed about the possibility that there may be no clinical benefit for the volunteer in relation with benefits which are reasonably anticipated from the trial,

10.11.9. The alternative methods which may be possibly applied to the volunteer, or the treatment schedule and their possible risks and benefits,

10.11.10. In case of injury related to the trial, the indemnity/the treatment to be paid/provided to the volunteer,

10.11.11. The information on payments to be made to the volunteers for expenditures such as transportation and food expenditures,

10.11.12. The fact that the volunteer's participation in the trial is voluntary and the volunteer may refuse participation in and may withdraw from the trial at any time without any penalty or sanction and without losing any rights,

10.11.13. That the monitors, auditors, the ethics committee, the General Directorate of Health Services and other relevant health authorities will have direct access to the original medical records of the volunteer but such information will be kept confidential and that the volunteer or the legal representative allows the said access by signing the written informed consent form,

10.11.14. Pursuant to the applicable legislation, the records directly identifying the volunteer will be kept confidential, they will not publicly disclosed and the identity of the volunteer will be still kept confidential even if results of the trial are published,

10.11.15. The volunteer or the legal representative will be informed in timely manner when new information is obtained in relation to the trial, which may possibly influence the will of the volunteer to continue the trial.
10.11.16. Persons as well as 24 (twenty four) hour available phone numbers of such persons whom the volunteer can contact to have further information on the trial, the volunteer's own rights or any adverse event related to the trial,
10.11.17. Conditions or reasons requiring the termination of the volunteers' participation in the trial,
10.11.18. The approximate number of volunteers involved in the trial,
10.11.19. Number of volunteers expected to participate in the trial,
10.12. Prior to participation in the trial, the volunteer or the legal representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the volunteers. During a volunteer's participation in the trial, the volunteer or the legal representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to volunteers. Both the principal investigator and the volunteer are supposed to have one copy of these informed consent forms.
10.13. In case of a clinical trial where the volunteer can only be enrolled in the trial with the consent of her/his legal representative, the volunteer should be informed about the trial to the extent compatible with the volunteer's understanding and, if capable, the volunteer should personally give consent and sign and date the written informed consent form.
10.14. Except as described in Article 10.15, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the volunteer) should be conducted on volunteers who personally give consent and who sign and date the written informed consent form.
10.15. Non-therapeutic trials may be conducted on volunteers with the consent of a legal representative provided that the following conditions are fulfilled:
10.15.1. The objectives of the trial cannot be met by means of a trial conducted on volunteers who can give informed consent personally.
10.15.2. The foreseeable risks to the volunteers are low,
10.15.3. The negative impact on the volunteer's well-being is minimized and low,
10.15.4. The trial is not prohibited by law,
10.15.5. The approval of the ethics committee is expressly sought on the inclusion of such volunteers and the written approval/favorable opinion covers this aspect, such trials, unless an exception is justified, should be conducted on patients having a disease or condition for which the investigational product is intended. Volunteers participating in these trials should be closely monitored and should be withdrawn if they appear to be unduly distressed.
10.16. In emergency situations where it is not possible to receive prior consent of the volunteer, the consent of the volunteer's legal representative, if any, should be requested with a view to protecting rights, safety and well-being of the volunteers and ensuring compliance with the applicable legislation, When the volunteer's legal representative is not available, the requirements set forth in the protocol for which the prior approval of the ethics committee and the prior permission of the General Directorate of Health Services are received for the volunteer's participation in the trial should be followed. The volunteer or the volunteer's legal representative should be informed about the trial as soon as possible, and the volunteer's or the legal representative's written consent to continue or to withdraw from the trial with their own free will should be requested.
10.17. With respect to the clinical trials which will be conducted on children; if child is able to express her/his consent, the consent of child as well as the consent of her/his parents or

her/his guardian -if s/he is under custody- is obtained in writing after s/he is informed as per the applicable legislation.

10.18. The legal representatives, if any, or relatives if there is no legal representative, of the individuals who are in intensive care and unconscious are informed and their written consent is obtained in accordance with applicable legislation. If none of them are available, the patient can be involved in the trial under the responsibility of the investigator who is the principal investigator or who is a doctor or dentist.

10.19. The approval of the ethics committee and the permission of General Directorate of Health Services are obtained for the written information and documents other than the informed consent form to be given to the volunteers participating in the trial.

10.20. Patient cards and patient diaries which are used in ongoing and permitted trials can be changed provided that the General Directorate of Health Services and the ethics committee are informed. However, the General Directorate of Health Services or the ethics committee may request revision, providing justification.

11. INVESTIGATOR'S BROCHURE

11.1. The Investigator's Brochure is a compilation of the clinical and non-clinical data on the investigational products. These guidelines provide guidance on the minimum information that should be included in the investigator's brochures and provide recommendations on the design.

11.2. The purpose of the Investigator's Brochure is to provide the principal investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency or interval, methods of administration, and safety monitoring procedures.

11.3. The Investigator's Brochure also provides insight to support the clinical management of the volunteers during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or a potential investigator, to understand it and make her/his own unbiased risk-benefit assessment of the appropriateness of the trial.

11.4. A medically qualified person may generally participate in editing process of an Investigator's Brochure, but this should be approved by the disciplines generating the described data.

11.5. It is expected that the type and extent of information available will vary with the stage of development of the investigational product.

11.6. If the investigational product is licensed in our country, an extensive Investigator's Brochure may not be necessary. Where permitted by the General Directorate of Health Services, a basic product information brochure may be an appropriate alternative to the summary of product characteristics, user instructions or labeling, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the principal investigator. If a licensed product is being studied for a new use, an Investigator's Brochure specific to that new use should be prepared.

11.7. The Investigator's Brochure should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision or renewal may be appropriate depending on the stage of development and the generation of relevant new information. However, this new information should be communicated to the ethics committees for approval. If it requires an amendment in the informed consent form or the trial protocol, it is required to receive the permission of the General Directorate of Health Services in addition to the approval of the ethics committee.

11.8. The sponsor is responsible for ensuring that an up-to-date Investigator's Brochure is made available to the principal investigator. In the case of an investigator-sponsored trial, the investigator should determine whether an investigator's brochure is provided by the commercial manufacturer. If the Investigator's Brochure is provided by the investigator, s/he should provide the necessary information to the trial personnel.

11.9. The Investigator's Brochure should include a title page and a confidentiality statement. Accordingly:

11.9.1. Title page: This should provide the sponsor's name, the identity of each investigational product (i.e., trial number, chemical or approved generic name and trade name(s) where legally permissible and desired by the sponsor). It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided.

11.9.2. Confidentiality Statement: The sponsor may wish to make a statement suggesting that the Investigator's Brochure is a confidential document for the sole information and use of the trial team, the ethics committee and the General Directorate of Health Services.

11.10. The Investigator's Brochure should contain the following sections, each with literature references where appropriate:

11.10.1. Table of Contents: An example of the Table of Contents is given in Article 11.12.

11.10.2. Summary: A short summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information available that is relevant to the stage of clinical development of the investigational product.

11.10.3. Introduction: A brief introductory statement should be provided which contains the chemical name (and generic and trade names when approved) of the investigational products, all active ingredients, the investigational products' pharmacological class and its expected position within this class (e.g. advantages), the rationale for conducting trials with the investigational products, and the anticipated prophylactic, therapeutic or diagnostic indications. Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

11.10.4. Physical, Chemical, and Pharmaceutical Properties and Formulation: A description of the investigational product substances (including the chemical or structural formulas) should be provided, and a brief summary of the relevant physical, chemical and pharmaceutical properties should be given. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulations to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage forms should also be given. Any structural similarities to other known compounds should be mentioned.

11.10.5. Non-clinical Studies: The results of all relevant non-clinical pharmacological (pharmacodynamics, pharmacokinetics), toxicological and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic effects as well as the possible unfavorable and unintended effects in humans. The information provided should include the followings, as appropriate, if known/available:

11.10.5.1. Animal species tested,
11.10.5.2. Number and sex of animals in each group,
11.10.5.3. Unit dose (e.g., mg/kg, ml/kg),
11.10.5.4. Dose interval,

11.10.5.5. Route of administration,
11.10.5.6. Duration of dosing,
11.10.5.7. Information on systemic distribution,
11.10.5.8. Duration of post-exposure follow-up,
11.10.5.9. Findings, including the following aspects:
11.10.5.9.1. Nature and frequency of pharmacological or toxicological effects,
11.10.5.9.2. Severity or intensity of pharmacological or toxicological effects,
11.10.5.9.3. Time-to-onset of effects,
11.10.5.9.4. Reversibility of effects,
11.10.5.9.5. Duration of effects,
11.10.5.9.6. Dose-response relationship.

Table format or lists should be used whenever possible to ensure the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose-response relationship of the observed effects, the relevance to humans, and any aspects to be studied in humans.

If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on an mg/kg basis.

a) Non-clinical Pharmacology: A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological effects other than the intended therapeutic effects).

b) Pharmacokinetic Properties and Product Metabolism in Animals: A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

c) Toxicology: A summary of the toxicological effects found in relevant studies conducted on different animal species should be described under headings of single dose, repeated dose, special studies (e.g., irritancy and sensitization), reproductive toxicity, genotoxicity, mutagenicity and carcinogenicity.

11.10.6. Effects on Human Beings: A thorough discussion of the known effects of the investigational products on humans should be provided, including information on pharmacokinetic properties, metabolism, pharmacodynamic properties, dose-response relationship, safety, efficacy and other pharmacological properties. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational products other than those obtained from clinical trials (such as from experience during marketing).

11.10.7. Pharmacokinetic Properties and Product Metabolism in Humans: A summary of information on the pharmacokinetics of the investigational products should be presented, including the followings, if available:

11.10.7.1. Pharmacokinetic properties (including metabolism, as appropriate, and absorption, plasma protein binding, and elimination),

11.10.7.2. Bioavailability of the investigational product (absolute, where possible, or relative) using a reference dosage form,
11.10.7.3. Population subgroups (e.g., gender, age, and impaired organ function),
11.10.7.4. Interactions (e.g., product-product interactions and interaction with food),
11.10.7.5. Other pharmacokinetic data,
11.10.8. Safety and Efficacy: A summary of information should be provided about the investigational products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose-response relationship that are obtained from previous trials conducted on the volunteers. The relevance of this information should be discussed. In cases where many clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups provides a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all indications studied) should be provided. Differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed. The Investigator's Brochure should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the investigational product and with other products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the products.
11.10.9. *Marketing Experience:* The Investigator's Brochure should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g., formulations, dosages, routes of administration, and adverse product reactions). The Brochure should also identify all the countries where the investigational product did not receive approval/license for marketing or was withdrawn from marketing/license.
11.10.10. Summary of Data and Guidance for the Investigator: This section should provide an overall discussion of the non-clinical and clinical data, and should summarize the information from various sources on different aspects of the investigational products, wherever possible. Thus, the principal investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. Where appropriate, the published reports on the relevant products should be discussed. This could help the principal investigator or sub-investigators to forecast adverse drug reactions or other problems in clinical trials. The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational products. The investigator should also be provided guidance on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.
11.11. Examples of the title page of the Investigator's Brochure are as follows:

Name of the sponsor
Product
Trial Number
Names: chemical name, generic name (if approved)
Commercial names (if legally permitted and requested by the sponsor)
Issue Number of the Investigator's Brochure
Issue Date of the Investigator's Brochure
The previous Issue Number and Date replaced by the Investigator's Brochure

11.12. An example of the Table of Contents of the Investigator's Brochure is as follows:

Confidentiality statement (optional)
Signature page (optional)
Table of Contents
Summary
Introduction
Physical, chemical and pharmaceutical properties and formulation
Non-clinical studies
Non-clinical pharmacology
Pharmacokinetic properties and product metabolism in animals
Toxicology
Effects on human beings
Pharmacokinetic properties and product metabolism in humans
Safety and efficacy
Marketing experience
Summary of data and guidance for the investigator
References to publications and reports: These references should be included at the end of each section.
Annexes (if available).

12. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

12.1. Essential Documents are those documents which individually and collectively permit evaluation of conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the principal investigator and other investigators, the sponsor and the monitor with the standards of good clinical practices and with all requirements of the applicable legislation.

12.2. Submission of these documents to the relevant authorities in a timely manner can assist the successful management of a trial by the coordinator, the responsible person for administrative affairs, the principal investigator, other investigators, the sponsor and the monitor.

12.3. These documents are also audited within the scope of the sponsor's independent audit function and inspected by the General Directorate of Health Services as part of the process to confirm the validity of the trial conducted and the integrity of data collected.

12.4. Documents to be prepared are grouped in three sections according to the stage of the trial during which they will normally be generated: Before the clinical phase of the trial commences, During the clinical performance of the trial, After the completion or termination of the trial.

12.5. A description of the purpose of each document is given. It is specified whether they should be filed in either the principal investigator' or the sponsor' files, or both. Some of the documents can be combined provided that the individual elements are readily identifiable.

12.6. Trial master files should be prepared at the beginning of the trial and kept by both the principal investigator and the sponsor. A final close-out of a trial can only be done when the monitor has reviewed both the principal investigator's and the sponsor's files and confirmed that all necessary documents are in the appropriate files.

12.7. Any or all of the documents addressed in these guidelines should be subject to, and therefore available for, audit by the sponsor's auditor and inspection by the General Directorate of Health Services or the relevant health authority.

12.8. The sponsor and the principal investigator should keep a record of the location(s) of the relevant essential documents. Archiving systems should ensure document identification, search and retrieval.
12.9. Individual trials may require additional documents which are not specifically stated in essential document list based on the activities carried out. The sponsor or the principal investigator should include them as a part of the trial master file.
12.10. The sponsor should ensure that the principal investigator has control of and continuous access to CRF data reported to the sponsor. The sponsor should not have exclusive control of those data. When a copy is used to replace an original document, the copy should fulfill the requirements for certified copies.
12.11. Before the clinical phase of the trial commences, at least the following documents should be generated and should be in file before the trial formally starts.
12.11.1. The Investigator's Brochure to document that relevant and current information about the investigational product is provided to the investigator,
12.11.2. Signed protocol and amendments, if any, and CRF (this may be draft CRF, however, the approval of the ethics committee should be received until the first volunteer is enrolled to the trial) to document the investigator and sponsor agreement to the protocol/amendment(s) and CRF,
12.11.3. Informed consent form to document the informed consent; any other information to document that volunteers will be given appropriate written information to support their ability to give fully informed consent; and advertisement for volunteer recruitment, if any, to document that recruitment measures are appropriate and not coercive,
12.11.4. Financial aspects of the trial,
12.11.5. Insurance coverage when required,
12.11.6. Signed agreement between involved parties,
12.11.7. Approval of the ethics committee,
12.11.8. Permission of the General Directorate of Health Services specified when required as per the applicable legislation,
12.11.9. The curriculum vitae of the coordinator, the responsible person for administrative affairs, the principal investigator and other investigators,
12.11.10. Normal values or rates for tests specified in the trial protocol, and laboratory-related documents, if any,
12.11.11. The investigational product’s label prepared in accordance with the applicable legislation,
12.11.12. Instructions for handling of the investigational products, if not included in the protocol or the Investigator’s Brochure, to document instructions needed to ensure proper storage, packaging, dispensing and disposition of the investigational products and trial-related materials,
12.11.13. Shipping records for the investigational products and trial-related materials to document shipment dates, batch numbers and method of shipment of the investigational products and trial-related materials,
12.11.14. Certificate(s) of analysis of the investigational product(s) shipped,
12.11.15. Unblinding methods in blinded trials,
12.11.16. Randomization list,
12.11.17. Pre-trial monitoring report to document that the site is suitable for the trial,
12.12. In addition to having on file the above documents, the followings should be added to the files during the clinical phase of the trial as evidence that all new relevant information is documented as it becomes available:

12.12.1. The Investigator's Brochure updates,
12.12.2. Amendments to the protocol, the informed consent form, CRF, etc. during the course of the trial,
12.12.3. The approval of the ethics committee and the permission of the General Directorate of Health Services for the amendments, when necessary,
12.12.4. Amendments by the coordinator, the responsible person for administrative affairs, the principal investigator or other investigators,
12.12.5. Changes in normal values or rates for tests specified in the trial protocol, and in laboratory-related documents, if any,
12.12.6. Monitoring reports,
12.12.7. Other important communication notes other than visits to the investigational sites (phone call notes, meeting notes, etc.),
12.12.8. Signed informed consent forms and source documents which are prepared as per the applicable legislation,
12.12.9. Signed, dated and completed CRF,
12.12.10. Corrections in CRF,
12.12.11. Safety notifications,
12.12.12. Volunteer screening log,
12.12.13. Volunteer identification code list,
12.12.14. Relevant records to document that the investigational products are used in compliance with the trial protocol,
12.12.15. Signature page to document signatures and initials of those who are authorized to make entries or corrections in CRF,
12.13. After completion or termination of the trial, all of the documents specified in Article 12.11 and 12.12 should be in the file together with the followings:
12.13.1. Records retained in the investigational site in relation with the investigational product and account details on use,
12.13.2. Documents on the disposal of the investigational products in compliance with the applicable legislation,
12.13.3. Completed volunteer identification code list,
12.13.4. Final trial close-out monitoring report,
12.13.5. Documents of audits and inspections, if any,
12.13.6. In case of unblinding, the relevant documents,
12.13.7. Final report to be submitted to the ethics committee and the General Directorate of Health Services,
12.13.8. Clinical trial report.

13. OTHER PROVISIONS

13.1. When an extension is made on insurance documents, which are previously approved by the ethics committee and permitted by the General Directorate of Health Services, without amending any insurance condition, it is sufficient to inform the ethics committee and the General Directorate of Health Services.
13.2. A trial nurse, a site coordinator, a sub-investigator, a monitor, a pharmacist or a qualified person may be delegated to help conduct of the trial provided that the General Directorate of Health Services and the ethics committee are notified. However, the General Directorate of Health Services or the ethics committee may cancel this delegation, providing justification.

13.3. The principal investigator involved in the trials that has previously received the approval of the ethics committee and the permission of the General Directorate of Health Services can be changed provided that the General Directorate of Health Services and the ethics committee are informed. However, the General Directorate of Health Services or the ethics committee may cancel this delegation, providing justification.
13.4. With regard to international multicenter clinical trials, it is sufficient to inform the ethics committee about changes in documents such as the Investigator's Brochure, the protocol and the informed consent form which will not be applied in our country and do not include information about safety notifications.
13.5. At the first application to receive the approval of the ethics committee and the permission of the General Directorate of Health Services with a view to conducting a clinical trial, CRF should be submitted and the required approval and permission should be obtained. On the other hand, it is sufficient to inform the ethics committee for further changes in CRF.
13.6. For some technical changes (changes in a CRF version approved by the ethics committee and the General Directorate of Health Services which facilitate answering the data in the CRF, insert automatic queries in case of incorrect data entry, or do not alter the quality or quantity of data such as interface modifications in the program used) which do not affect the validation of electronic CRFs, it is sufficient to inform the ethics committee.
13.7. It is sufficient to have a single ethics committee decision in multicenter clinical trials. The said ethics committee decision is taken by the ethics committee where the center is located.

14. ENTRY INTO FORCE

These Guidelines enter into force on the date of approval.