Good Clinical Practice for Proprietary Chinese Medicines

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Chapter 1  General Principles

1. These guidelines are formulated with reference to internationally recognized principles, in order to provide assurance that the trial process is standardized; the results are scientific and reliable; and that the rights and safety of trial subjects are protected. The guidelines should be adopted as guiding principles by those conducting the clinical trial for proprietary Chinese medicines.

2. The guidelines serve as the standard requirement for the process of a clinical trial, including protocol designing, organizing, conducting, monitoring, auditing, recording, analyzing and reporting.

3. The guidelines are applied at all phases of the clinical trial, which include human bioavailability study or bioequivalence study.

4. For the general organization chart of the personnel involved in a clinical trial, please refer to Annex I.

Chapter 2  Preparations and prerequisites for clinical trial

5. All researches involving human subjects should be conducted in accordance with the principles of the Declaration of Helsinki, i.e. justice, respect for patients’ rights, maximizing the benefits, and minimizing the harm to the trial subject(s). All individuals involved in conducting a trial must fully understand and comply with such principles.

6. The clinical trial should be scientifically justified. Prior to the planning of any trial involving human subjects, the objective, the problems to be solved, the anticipated benefits and foreseeable risks to the subjects and the public, should be considered. The anticipated benefits should out-weight the possible risks. The clinical trial method chosen must conform to accepted scientific and ethical standards.

7. Investigational products for clinical trial should be prepared and supplied by the sponsor. Before the clinical trial, the sponsor is responsible for providing the pre-clinical information on the investigational product, and the information should conform to the requirements of the clinical trial at respective phases. The sponsor is also responsible for providing information on efficacy and safety of the investigational product obtained in previously-completed, and ongoing, clinical trial in other regions. Investigational products should be manufactured, handled, and stored in accordance with the applicable Good Manufacturing Practice (GMP) and they should be used in accordance with the approved protocol.

8. The facilities and conditions of the clinical trial institutions need to conform to the requirements by which a clinical trial can be conducted safely and efficiently. All investigators should have the professional expertise, qualification and competence to undertake such a trial. Prior to the beginning of the trial, the investigator and the sponsor should reach a written agreement on the protocol, monitoring and auditing of the trial, standard operating procedures, and allocation of trial-related responsibilities, etc.
9. Clinical trial should be conducted in compliance with the protocol with prior approval from the Ethics Committee.

10. A qualified physician, or a registered Chinese medicine practitioner, should be responsible for medical decisions of the trial subjects.

11. The information and records that can be used to identify subjects should be protected and privacy and confidentiality rules should be respected in accordance with the applicable regulatory requirements.

12. All clinical trial information should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

Chapter 3 Protection of Trial Subject’s Rights

13. The personal rights of the trial subjects should be fully protected during the process of the clinical trial. Special attention should be paid to trial that involves vulnerable subjects; and the scientific integrity and credibility of the trial should be ensured. The rights, safety and well-being of the trial subjects should prevail over any other interests of science and society. Ethics Committee and the informed consent form are major measures to safeguard the rights of the subjects.

14. To ensure the rights, safety and well-being of the trial subjects during the clinical trial, and to provide public reassurance, an independent Ethics Committee should be established within the institution and made known to the regulatory authorities.

15. The Ethics Committee should include at least one medical professional, a non-medical or non-scientific person, a legal expert and a person who is independent of the institution. The Ethics Committee should consist of at least five members including both genders, who collectively have the qualification and experience to review and evaluate the medical aspects, scientific and ethical integrity of the proposed trial. A list of Ethics Committee members and their qualifications should be maintained. The composition and work of the Ethics Committee should not be influenced by those involved in the trial.

16. Prior to the beginning of the trial, the protocol should have obtained approval from Ethics Committee. Any amendments to the protocol during the trial should be made with the Ethics Committee’s approval, unless they are adopted by the investigator to eliminate immediate hazards to the subjects or they involve only logistical or administrative aspects of the trial. Any serious adverse events should be reported to the Ethics Committee immediately.

17. The Ethics Committee should obtain the following documents:

   Trial protocol/amendments, written informed consent form and its updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisement), written information provided for the subjects, investigator’s brochure, available safety information, information about payments and compensation available to subjects, the investigator’s current curriculum vitae and/or documentation evidencing qualifications, and any other documents that the Ethics Committee may need to fulfil its responsibilities.

18. The decision of the Ethics Committee in respect of a clinical trial should be made by vote
after discussion, while members involving in the clinical trial should not vote. A quorum must be present in order for the Ethics Committee to reach a decision specified in the written operating procedures. When required, non-member experts or the investigator may be invited to attend the meeting and provide information, but they cannot vote. The Ethics Committee should establish its working procedures. Minutes of all of its meetings and resolutions should be retained for a period of 5 years after completion of the trial.

19. When reviewing a clinical trial protocol, the Ethics Committee should consider the following to ensure that the trial subjects’ rights are protected:

(1) The acceptability of the investigator, in terms of his/her qualification, experience, availability for the duration of the study; and the conformity of the supporting staff and available facilities to the requirements of the trial. The investigator should provide a current curriculum vitae, and proof of relevant qualifications.

(2) The consideration of ethical principles in the trial protocol, including the objective of the study, potential risks and benefits for the subjects and others, and the scientific efficiency of the study design.

(3) The means by which subjects will be recruited; the completeness and understandability of the information given to the subject (or his family, guardian, legally acceptable representative) regarding the study; and the appropriateness of the method of obtaining the informed consent form.

(4) Provision of treatment and/or indemnity in case of death or other loss, or injury to a subject if attributable to the trial.

(5) The acceptability of the proposed amendment to the protocol.

(6) The Ethics Committee should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to subjects, but at least once per year.

(7) The appropriateness of the amount and form of payment to the subjects, to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject. The Ethics Committee should ensure that information regarding payment to subjects is set forth in the written informed consent form and or other written information to be provided to subjects.

20. Upon receipt of an application, the Ethics Committee should in due course review a proposed clinical trial in a meeting. After that, the Ethics Committee should issue a written opinion and enclose the list of attendance with individual signatures and their professional status. The opinion of the Ethics Committee can be one of the following:

(1) approval/favourable opinion

(2) modification required prior to its approval/favourable opinion

(3) disapproval/negative opinion

(4) termination or suspension of the approved trial.

21. The investigator or his/her designated representative must explain to the subject the following details of a clinical trial:
1. That the subject’s participation in the trial is voluntary and that the subject may refuse to participate or withdrawn from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

2. The subject must be made aware that his/her participation in the trial and his/her personal data will be kept confidential. However, the Ethics Committee, the regulatory authorities or the sponsor may be granted access to such information in accordance with required procedures.

3. The objective, process and duration of the trial, testing procedure and any expected benefit and risk/inconvenience to the subject should be explained. Also, the subject should be informed that he/she may be assigned to various treatment groups.

4. The subject should be given ample time and opportunity to decide whether or not to participate in the trial. If the subject is incapable of giving consent, an introduction and explanation of the trial should be given to the subject’s legally acceptable representative. Language and words used in the informed consent process should be understandable to the subject or the subject’s legally acceptable representative. The subject may have access to information related to him/her at any time during the trial. The subject or the subject’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject’s willingness to continue participation in the trial.

5. The compensation and treatment available to the subject in the event of trial-related injury.

6. The subject’s responsibilities.

7. The anticipated prorated payment to the subject and the anticipated expenses to the subject for participating in the trial.

8. The records that identify the subject will be kept confidential. If the results of the trial are published, the subject’s identity will remain confidential.

9. The person to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.

10. The foreseeable circumstances and/or reasons under which the subject’s participation may be terminated.

11. The approximate number of subjects.

22. The informed consent form should be obtained after thorough and comprehensive explanation of the trial.

   1. The informed consent form should be signed and dated by the subject or the subject’s legally acceptable representative, and by the investigator who conduct the informed consent discussion. Prior to participation in the trial, the subject or the subject’s legally acceptable representative should receive a copy of the signed and dated informed consent form, together with any other information provided to the subjects.

   2. Inclusion of subject under disability in a trial may be acceptable if the Ethics Committee approves in principle and the investigator believes that participation offer a prospect of benefit to the subject. In this case, the subject’s legally
acceptable representative should sign and date the informed consent form.

(3) If a subject or the subject’s legally acceptable representative is unable to read, an impartial witness should be present throughout the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subject, is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s representative has orally consented to the subject’s participation in the trial and if capable, has signed and personally dated the informed consent form, the witness should also sign and personally date the informed consent form. By signing the consent form, the witness attests that the information in the consent form and other written information has been accurately explained to, and understood by, the subject or the subject’s legally acceptable representative, and that informed consent was freely given by the subject or by the subject’s legally acceptable representative.

(4) In principle, children cannot be included as subjects unless the proposed indication of the investigational product is for children only. It will then be necessary to obtain the informed consent form signed by the legally acceptable guardian of the child. Assent should be obtained when the child is fully capable of making decision on his/her participation.

(5) In an emergency situation when prior consent of the subject or the subject’s legally acceptable representative is not possible, and when there is no proven effective treatment for the disease while the investigational product has the potential to save the subject’s life, the subject could be enrolled into the trial if such enrollment method has been clearly stated in the trial protocol and other relevant documents and has been prior approval granted by the Ethics Committee. The investigator should, as soon as possible after the administration of investigational product, inform the subject or the subject’s legally acceptable representative about the trial and seek his/her consent to continue. The investigator should simultaneously report the situation to the Ethics Committee.

(6) The written informed consent form should be revised whenever important new information becomes available. The revised informed consent form should have obtained the approval of the Ethics Committee before use and the investigator should obtain the subject’s consent again.

Chapter 4  Clinical Trial Protocol

23. Clinical trial protocol should be formulated before the trial. The protocol agreed and signed by both the investigator and the sponsor should only be implemented after obtaining approval from the Ethics Committee.

24. The clinical trial protocol should include the following:

(1) Title of the trial, protocol identifying number and date. Any amendment should also bear the amendment number and date.

(2) Objective and background of the trial. A summary of findings from nonclinical studies that have clinical significance, and the findings from clinical trials that are relevant to the trial. Any known or potential risk and benefits, if any, to human subjects and possible variations for the investigational product in different races.
(3) Name and address of the sponsor. Address and telephone number of the trial site. Name, title and address of the investigator(s). Name, title and address of the medical expert on the sponsor’s side. Name and address of the clinical laboratory and other medical and/or technical departments.

(4) A statement that the trial will be conducted in compliance with the protocol, the GCP and other applicable regulatory requirements.

(5) Description of the design of the trial, method of randomization and level of blinding.

(6) The subject inclusion criteria, exclusion criteria and withdrawal criteria, description of the process of recruitment and the method of allocation of trial subjects.

(7) The number of subjects planned to be enrolled to meet the trial objective, as calculated by statistical methods.

(8) Treatment to be administered to the subject, including the name, dose form, dosage, route and method of administration, dosing schedule, treatment period of the investigational product, requirement of concomitant medication/treatment, and descriptions on the packaging and labeling of the investigational product.

(9) The name(s) and frequency of the intended clinical and laboratory examination(s) and, where technically feasible, the pharmacokinetic analysis to be carried out, etc.

(10) The systems of receipt and usage recording, dispensing, distribution and storage condition of the investigational product.

(11) Clinical observation, follow-up procedures and measures for monitoring the compliance of the subject.

(12) Criteria for suspension or termination of the clinical trial; instructions on completing the clinical trial.

(13) Specification of efficacy parameters, including methods and timing for assessing, recording and analyzing of such parameters.

(14) Specification of safety parameters, including methods and timing for assessing, recording and analyzing of such parameters.

(15) The expected duration of subject participation.

(16) Primary and secondary endpoints to be measured during the trial.

(17) Maintenance of the subject identification codes, randomization list and case report form.

(18) The requirements of recording adverse events, method of reporting serious adverse events. The type and duration of the follow-up of subjects after adverse events.

(19) Maintenance of trial treatment randomization code, and procedures for breaking codes and emergency unblinding.

(20) The description of the statistical analysis plan, the definition and choice of the data set of the statistical analysis, and the timing of any planned interim analysis. The level of significance to be used in the statistical analysis, and procedures for
handling of missing, unused, and spurious data.

(21) Policy for data management and data tracing.

(22) A statement specifying that the investigator will permit trial-related monitoring, audits, Ethics Committee review, and regulatory inspections; and that the investigator will provide them with direct access to source data/documents.

(23) Quality control and quality assurance of the clinical trial.

(24) Trial-related ethics.

(25) Anticipated progress and completion date of the clinical trial.

(26) Follow-up and medical care after completion of the trial.

(27) Statements regarding responsibilities for each party and other relevant regulations.

(28) List of references.

25. Amendments can be made to the protocol in accordance with prescribed procedures, if they are necessary during the trial.

Chapter 5 Responsibilities of the Investigator

26. The investigator, who is responsible for the clinical trial, should possess the following:

(1) Qualification to practise medicine in a legally approved medical institution.

(2) Good knowledge and experience in the field required by the protocol.

(3) Experience in trial research methods or receive scientific support from an experienced colleague.

(4) Familiarity with available relevant information and literature provided by the sponsor.

(5) Availability of adequate human resources and facilities needed for the conduct of the trial.

(6) Awareness of, and compliance with, the GCP, local laws, regulations, and ethical requirements.

27. The investigator must read carefully and be familiar with the contents of the protocol, and must conduct the trial in compliance with the protocol which has been agreed to by the sponsor (and regulatory authorities if necessary) and approved by the Ethics Committee. The investigator and the sponsor must sign the protocol, or an alternative contract to confirm agreement.

28. The investigator must be thoroughly familiar with the nature, function, effects and safety of the investigational product (including relevant pre-clinical data of the investigational product). The investigator should also be aware of all new information on the investigational product which may become available during the course of the clinical trial. If such new information relates to the consent of the subject, the investigator should amend the informed consent form and other written information provided for the subject.
Amended informed consent form, and other written information intended to be provided to the subject, should be approved by the Ethics Committee before use.

29. Before initiating a trial, the investigator should have approval from the Ethics Committee.

30. The investigator should provide the Ethics Committee with a copy of the current investigator’s brochure as part of the investigator’s written application to the Ethics Committee.

31. The investigator must conduct the trial in an institution with adequate medical facilities, laboratory equipment and staff. The institution should have facilities to deal with emergency, so as to ensure the safety of subjects and accurate conduct of trial. The laboratory results must be accurate and reliable.

32. The investigator should obtain permission from the hospital or the institution where he/she works to ensure that he/she has sufficient time to conduct and complete the trial within the period defined in the protocol. The investigator should provide adequate information to all persons assisting in the trial on the trial-related requirements and their duties. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects.

33. The investigator should fully inform the subject of all the pertinent aspects of the trial which are approved by the Ethics Committee, and should obtain the subject’s informed consent form. Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or continue to participate in a trial.

34. The investigator, or a person designated by the investigator, should explain the correct use of the investigational product to each subject, and should check regularly that each subject is following the instructions properly.

35. The investigator should be responsible for trial-related medical decisions and should ensure that adequate medical care is provided to a subject for any adverse events happened during the trial.

36. The investigator is obliged to take appropriate measures to ensure the safety of subjects and such measures should be documented. In case of serious adverse events during the course of the trial, the investigator should promptly arrange treatment for the subject. At the same time, the investigator should report to the regulatory authorities, to the sponsor and to the Ethics Committee, and should date and sign that report.

37. The investigator should follow the trial randomization procedures (if any), and should ensure that the randomization code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document, and explain to the sponsor, any premature unblinding of the investigational product.

38. The investigator should ensure that data is recorded in the medical record and in the case report form in a true, accurate, complete, timely and lawful manner.

39. The investigator should permit monitoring and auditing by monitor and auditor who are sent by the sponsor, and auditing and inspection by the regulatory authorities, to ensure the quality of the trial.

40. The investigator should negotiate with the sponsor the cost of the clinical trial, and this should be documented in the contract.
41. The investigator should submit a written summary of the trial status to the Ethics Committee annually, or upon the Ethics Committee’s request. Upon completion of the trial, the investigator must submit a final report, which is signed and dated by the investigator, to the sponsor.

42. If a clinical trial is suspended or terminated, the investigator must inform the subjects, the sponsor, the Ethics Committee and the regulatory authority(ies) with explanation.

**Chapter 6 Responsibilities of the Sponsor**

43. The sponsor is responsible for initiating, applying for, organizing and monitoring a clinical trial, and for providing funds. The sponsor should submit an application for clinical trial to the regulatory authorities in accordance with applicable regulatory requirements. The sponsor may transfer some of the sponsor’s trial-related duties and functions to a contract research organization (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should establish quality assurance and quality control systems. Any trial-related duty and function that is transferred to, and assumed by, a CRO should be specified in writing. Any trial-related duties and functions not specifically transferred to, and assumed by, a CRO are retained by the sponsor. All references to a sponsor in this guide also apply to a CRO.

44. The sponsor should select the clinical trial institution and investigator with recognized qualifications, to ensure the completion of the trial.

45. The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial-related medical questions.

46. The sponsor may consider establishing an independent data monitoring committee (IDMC) to assess the progress of the clinical trial regularly.

47. The sponsor is responsible for providing an up-to-date investigator’s brochure with available chemical, pharmaceutical, toxicological, pharmacological and clinical data (including data from previous and ongoing trials) regarding the investigational product.

48. The sponsor should provide sufficient time for the investigator to review the protocol and the information provided.

49. With the approval of the regulatory authorities and the Ethics Committee, the sponsor may start to organize the clinical trial according to the protocol.

50. The sponsor should design the clinical trial protocol jointly with the investigator with specification on the duties and responsibilities of each party, including implementing, data management, statistical analysis, result reporting and way of publication, etc. Both parties should sign the mutually agreed protocol and contract.

51. When planning the trial, the sponsor should ensure that sufficient safety and efficacy data from both the non-clinical studies and the clinical trials are available to support human exposure by the route, at the dosages, and for the duration to be studied.

52. The sponsor should obtain the investigator’s agreement:

   (1) to conduct the clinical trial in compliance with GCP, with the applicable regulatory requirements and with the protocol agreed by the sponsor and approved by the
Ethics Committee;

(2) to comply with procedures for data recording/reporting;

(3) to permit monitoring, auditing and inspection.

53. The sponsor should ensure timely delivery of investigational new products, reference standards, comparators or placebos which are fully characterized, properly coded, and affixed with special labels. The sponsor should also ensure that those products have reached quality standards. The investigational product should be packed and stored in accordance with the protocol. The sponsor should establish management and recording system for the investigational product. These should include the procedures and recording of the transport, receipt, dispensing and destruction of investigational product, and return and disposal of unused investigational products. The sponsor should determine the storage temperature, storage conditions and storage time for the investigational product. The sponsor should also ensure that the investigator follows the written operating procedures for handling the investigational product.

54. The sponsor should take steps to ensure that the investigational product is stable over the period of use and should maintain sufficient quantities of the investigational product used in the trial to reconfirm its specification, whenever necessary. The sponsor should maintain records of the batch sample analyses and, of the characteristics of the investigational product.

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

56. The sponsor should ensure that the trial is adequately monitored. In general, on-site monitoring should be conducted before, during and after the trial. The qualified monitors appointed by the sponsor and accepted by the investigator should conduct the monitoring of the ongoing clinical trial and write-up the monitoring report after each site visit.

57. The sponsor should ensure that it is specified in the protocol or other written agreements that the investigator should provide direct access to source data/document for trial-related monitoring, auditing, Ethics Committee review, or regulatory inspections.

58. The sponsor should setup quality control and quality assurance systems for the clinical trial; the sponsor may perform audits as part of quality assurance.

59. The sponsor must investigate promptly, together with the investigator, all serious adverse events, and take appropriate measures to ensure the safety and rights of the trial subjects; and report to the regulatory authorities and the Ethics Committee immediately. Other investigators engaging in clinical trials of the same investigational product should also be informed.

60. If the sponsor suspends or terminates a clinical trial, the sponsor should inform the investigator, the Ethics Committee and the regulatory authority(ies) with explanation.

61. The sponsor is responsible for submitting the final report of the trial to the regulatory authorities.

62. The sponsor should provide insurance for the trial subjects, and should be responsible for the treatment cost and compensation for subjects in the event of trial-related injury or death. The sponsor should also indemnify (legal and financial coverage) the investigator,
except for claims that arising from malpractice and/or negligence.

63. The financial aspects of the trial should be documented in the agreement between the sponsor and the investigator.

64. Noncompliance with the protocol, and/or applicable regulatory requirement(s) by an investigator should lead to prompt action by the sponsor to secure compliance. If the noncompliance is serious and/or persistent, the sponsor should terminate the investigator’s participation in the trial and report this to the regulatory authority(ies).

Chapter 7  Responsibilities of the Monitor

65. The purposes of trial monitoring are to ensure that the rights of the subject are protected, the data are accurately and completely recorded and reported, and that the trial is conducted in compliance with the approved protocol, with the GCP, and with the applicable regulatory requirements.

66. The monitor serves as the principal communication link between the sponsor and the investigator and is appointed by the sponsor. The number of monitors and the frequency of monitoring depend on the complexity of the clinical trial and the number of institutions involved. The monitor should have adequate medical, pharmaceutical or relevant professional qualifications, and should be properly trained. The monitor should be familiar with the relevant drug regulations, the pre-clinical and clinical findings of the investigational product, as well as with the trial protocol and other relevant documentation.

67. The monitor should follow the standard operating procedures to ensure that the clinical trial is conducted in compliance with the protocol. The duties include:

   (1) To make sure that the trial sites are in appropriate situation, including staff allocation and training, laboratory conditions and facilities are suitable to perform the test, the participating staffs are familiar with the requirements of the protocol before starting the trial.

   (2) To verify the implementation of the trial protocol by the investigator. To ensure that the investigator receives the investigator’s brochure before the trial; to confirm that all informed consent forms were obtained before each subject’s participation; to be aware of the subjects’ recruitment rate; and to confirm that only eligible subjects are enrolled.

   (3) To ensure that all data are fully recorded and reported, and that all case report forms are accurately filled out in accordance with the source documents. Any error or omission should be corrected or specified, and signed and dated by the investigator. Any dose and/or therapy modification, concomitant medication, intercurrent illnesses, visits that the subjects fail to make, examinations that are not performed, etc., should be confirmed and recorded. To verify that all withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the case report forms.

   (4) To confirm that all adverse events are recorded and all serious adverse events are reported and recorded within the specified time period.
To ensure that the supply, storage, dispensing and return of the investigational product are in accordance with applicable regulatory requirements and corresponding records are made.

To assist the investigator in carrying out any necessary notification and application, and to report the trial data and results to the sponsor.

To document any follow-ups that is missing, any tests that are not conducted, and any examinations that are not performed by the investigator. To verify whether the errors or omissions are corrected by the investigator.

To confirm that the investigator is maintaining the essential documents (please refer to Appendix II).

To verify that the investigator and the investigator’s trial staff are performing the specified trial functions, in accordance with the protocol, and any other written agreement between the sponsor and the investigator, and have not delegated these functions to unauthorized individuals.

To submit a written report to the sponsor after each site-visit. The report should include the date, time, name of the monitor, the significant findings and name of the investigator contacted.

Chapter 8 Records and reports

68. The medical record is the source document of the clinical trial and should be kept intact. The data of the case report form should be originated from, and be consistent with, the source documents. Any observations and examination results of the trial should be recorded timely, accurately, completely, legibly and truly into the medical record and the case report form. If it is necessary to make corrections of mistakes, it should be made in a way not obscure the original entry, and should be signed and dated by the person correcting them.

69. Laboratory values with normal reference ranges should be recorded on the case report form or be attached to it. Values outside a clinically accepted reference range, or values that differ significantly from previous values, must be verified. Units of measurement must always be stated.

70. In order to protect the privacy of the trial subject, the name of the subject on the case report form should be abbreviated. The investigator should keep the subject identification code and verification record.

71. Contents of the final report of the clinical trial should be consistent with the requirements of the trial protocol, including:

(1) The actual case number of each treatment group by randomization, and the withdrawal and dropout of cases, with explanations.

(2) A comparison of the baseline features between different groups to confirm comparability.

(3) A statistical significance analysis and a clinical significance analysis should be done for all efficacy assessment parameters. The interpretation of the statistical
analysis results should focus on their clinical significance.

(4) Safety evaluations should include statistical analysis on clinical adverse events and laboratory abnormalities. Detailed description and assessment of serious adverse events should be provided.

(5) When assessing efficacy in a multicentre trial, consideration should be given to the divergence of different centers and its influence.

(6) A brief description and discussion should be provided on the efficacy and safety of the investigational product, and the relationship between risks and benefits.

72. The essential documents of the clinical trial should be retained (Appendix II) and managed according to regulatory requirements. The investigator should retain the essential documents of the clinical trial for at least 5 years after completion of the clinical trial. The sponsor should retain the information of the clinical trial for at least 5 years after the approval of marketing.

Chapter 9 Data management and statistical analysis

73. The aim of data management is to assure that the data collected are promptly, completely and accurately entered into the record. All steps involved in data management should be documented, to enable the examination of the data quality and study performance of the trial. Appropriate procedures should be followed to ensure the confidentiality of the data base, including maintenance and supporting procedures of the computer data base.

74. The allocation of trial subjects should follow the trial randomization procedure. The treatment code for each subject should be kept by the sponsor and the investigator. In case of a blinded trial, the protocol must state the conditions under which the code is allowed to be broken and by whom, and immediate access to the information must be allowed in an emergency. In an emergency, access to the treatment schedule of one trial subject at a time is permitted, but this must be justified and documented in the case report form.

75. The procedures of statistical analysis, and the presentation of results of the clinical trial data, should adopt a standardized statistical method. Qualified biostatistical expertise is necessary throughout the entire clinical trial. The clinical trial protocol should include a statistical analysis plan, which is verified and detailed before the analysis. If an interim analysis is planned, explanation and operating procedures should be provided. When estimating the treatment effect, consideration should be given to the confidence intervals and results from the hypothesis testing. The statistical analysis data set chosen should be stated. An account must be made of missing, unused or spurious data. The statistical report of the clinical trial should be consistent with the final report of the clinical trial.

76. When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

   (1) Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).

   (2) Maintain standard operating procedures for using these systems.

   (3) Ensure that the systems are designed to permit data changes in such a way that the
data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).

(4) Maintain a security system which prohibits unauthorized access to the data.

(5) Maintain a list of individuals who are authorized to make data changes.

(6) Maintain adequate backup of the data.

(7) Safeguard the blinding, if any. (e.g. maintain the blinding during data entry and processing).

77. If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

Chapter 10 Management of investigational product

78. The investigational product used in the clinical trial should not be sold in the market without approval.

79. The sponsor is responsible for the proper packaging and labeling of the investigational product used in the clinical trial, and stating that the product is for clinical trial use only. In the double-blinded trial, all features, including appearance, packaging, labeling, etc, of the investigational new drugs, comparators or placebos should be indistinguishable from each other. However, in case of medical emergency, rapid identification of the product is permitted without any undetectable break of the blinding.

80. The record of the usage of the investigational product should include information on quantity, transportation, delivery, receipt, dispensing, return and destruction of the remaining product, after administration.

81. The investigator is responsible for the use of the investigational product. The investigator should ensure that all investigational products are only used for subjects included in the trial; that the dosage and method of use should comply with the trial protocol; and that the remaining investigational product is returned to the sponsor. These processes should be handled, and recorded, by a designated person. The investigator should not give the investigational product to anyone who is not participating in the clinical trial.

82. The supply, usage and storage of the investigational product, and the handling procedures of the remaining product, should be under inspection of relevant individuals.

Chapter 11 Quality assurance

83. To ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the GCP, a planned and systematic quality assurance programs should be established. The sponsor and investigator should fulfill their duties, strictly comply with the trial protocol, and adopt the standard operating procedures to ensure implementation of quality control and quality assurance systems in the clinical trial.

84. All observations and findings in the clinical trial should be verified. Quality control procedures must be applied to each stage of data handling, to ensure that all data are
complete, accurate, true and reliable.

85. The regulatory authorities or the sponsor may appoint an auditor to conduct a systematic evaluation to determine whether the trial is implemented in accordance with the trial protocol, and whether the reported data are consistent with the records at the trial sites (i.e. whether the data recorded in the case report forms are the same as those in the medical records or other original records). An audit should be conducted by individuals not directly involved in the clinical trial. The auditor should report any fraud or forgery found in the trial.

86. If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

(1) The purpose of a sponsor’s audit, which is independent of, and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, standard operating procedures and the GCP, etc.

(2) The sponsor should appoint individuals, who are independent of the clinical trial, to conduct audits. The auditors should be qualified by training and experience.

(3) The sponsor should ensure that the auditing of clinical trials is conducted in accordance with the sponsor’s written procedures on what to audit, how to audit, the frequency of audits, and the content of audit reports.

(4) The sponsor’s audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities; the number of subjects in the trial; the type and complexity of the trial, and the level of risks to the subjects, etc.

(5) The observations and findings of the auditor(s) should be documented.

(6) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis, when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(7) When required by applicable law or regulation, the sponsor should provide an audit certificate.

87. Regulatory authorities should conduct inspection on the respective responsibilities and implementation status of the investigator and sponsor in the trial. All the data (including medical records) of the institutions and laboratories participating in the trial should be available for inspection by the regulatory authorities.

Chapter 12 Multicentre trial

88. A multicentre trial is conducted by several investigators at different locations, or sites, following the same protocol. The principal investigator should be the person with overall responsibility for the multicentre trials, and he/she should be the coordinating investigator for different trial centers.

89. Consideration should be given to the following items, in planning and implementing a
multicentre trial:

1. The protocol and its attachments, which are discussed and agreed by the sponsor and the investigators from each center, should be executed only upon prior approval by the Ethics Committee.

2. The investigators’ meetings should be held at the beginning and the mid-term of the clinical trial.

3. The sample size, and the allocation of samples among different centers, should comply with the requirements of the statistical analysis.

4. Similar measures for the management of the investigational products, including the dispensing and storage, should be taken at different centers.

5. The investigators that are involved in the trial should be trained according to the same protocol.

6. Standardized evaluation methods should be formulated. The laboratory and clinical evaluation method adopted by different centers should have unified quality control. The laboratory testing may be conducted by a centralized laboratory, if available.

7. Data management and data analysis should be centralized. Standard procedures of data transmission, management, verification and enquiry should also be set up.

8. The compliance with the protocol by the investigators at different centers should be ensured, including termination of their participation in the trial in case of non-compliance.

90. A multicentre trial requires a management system, the scale of which depends on the number of participating centers, the requirements of trial and knowledge of the investigational product. The coordinating investigator should be responsible for the implementation of the entire trial.

Chapter 13 Investigator’s Brochure

91. The Investigator’s Brochure (IB) is a compilation of the clinical and non-clinical data on the investigational product. Its purpose is to provide the investigators and others involved in the trial with 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/interval, methods of administration; and safety monitoring procedures. The IB also provides insight to support the clinical management of the trial subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that would enable a physician, a registered Chinese medicine practitioner, or a potential investigator to understand it and to make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically-qualified person should generally participate in the editing of an IB, and the contents of the IB should be approved by representatives of the disciplines that generated the described data.

92. This guideline describes the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. When the
investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary.

93. Where permitted by the regulatory authorities, a product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that may be of importance to the investigator.

94. If a marketed product is being studied for a new use (i.e. a new indication), an IB specific to that new use should be prepared.

95. The IB should be reviewed at least annually, and revised as necessary, in compliance with a sponsor’s written procedures. More frequent revision may be appropriate, depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, the Ethics Committee and/or regulatory authorities before it is included in a revised IB.

96. Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigators and that the investigators are responsible for providing the up-to-date IB to the responsible Ethics Committee. In an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer.

97. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where the preparation of a formal IB is impractical, the sponsor-investigator should provide an expanded background information section in the trial protocol, containing the minimum current information required, as described in this guide.

98. General Considerations:

The IB should include:

(1) **Table of contents**: This should provide the sponsor’s name, the identity of each investigational product (i.e., research number, drug or approved general name, and trade name desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition its supersedes, be provided. An example is given in Annex 2.

(2) **Confidentiality Statement**: The sponsor may wish to include a statement instructing the investigator/recipient to treat the IB as a confidential document for the sole information and use of the investigator’s team and the Ethics Committee.

99. Contents of the Investigator’s Brochure The IB should contain the following sections, each with literature references where appropriate:

(1) **Table of contents**: An example of the Table of Contents is given in Annex 3.

(2) **Summary**: A brief summary (preferably not exceeding two pages) should be given, highlighting the significant clinical and non-clinical information available that is relevant to the stage of clinical development of the investigational product.

(3) **Introduction**: A brief introductory statement should be provided, containing: the drug name (and general and trade name when approved) of the investigational
product; the rationale for performing research with the investigational product; and the anticipated therapeutic indication. Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

(4) **Physico-chemical and Pharmaceutical Properties and Formulation** : A brief summary should be given on the relevant physico-chemical and pharmaceutical properties of the investigational product. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation to be used, including excipients, should be provided and justified, if clinically relevant. Instructions for the storage and handling of the dosage form should also be given.

(5) **Non-clinical studies**:

**Introduction**:

The results of all relevant non-clinical pharmacology and toxicology studies should be provided in summary form. Where technically feasible, the results of pharmacokinetic and investigational product metabolism studies should also be provided. This summary should address the methodology used, the results, and provide a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans. If possible, the following information should be provided:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g. milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible, to enhance the clarity of the presentation. The following sections should review the most important findings from the studies, including the dose response of 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 reviewed). 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 a mg/kg basis.

(a) Non-clinical Pharmacology
A summary of the pharmacological aspects of the investigational product and, where possible, 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 actions other than the intended therapeutic effects).

(b) Pharmacokinetics and Product Metabolism in Animals (where technically feasible)
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 in different animal species should be described under the following headings:
- Single dose
- Repeated dose
- Carcinogenicity (where appropriate)
- Special toxicological studies (e.g. irritancy and sensitization) (where appropriate)
- Reproductive toxicity (where appropriate)
- Genotoxicity (mutagenicity) (where appropriate)

(6) Effects in Humans

Introduction:
A thorough discussion of the known effects of the investigational product in humans should be provided, including information on pharmacodynamics, dose response, safety, efficacy and other pharmacological activities (where technically feasible, information on pharmacokinetics and metabolism should also be included). Where possible, a summary of each completed clinical trial should be provided. Information should also be provided about the results of any use of the investigational product other than those discovered in clinical trials, such as from experience during marketing.

(a) Pharmacokinetics and Metabolism of Investigational Product in Humans (where technically feasible)
A summary of information on the pharmacokinetics of the investigational product should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, absorption, plasma protein
binding, distribution, and elimination)
- Bioavailability of the investigational product (absolute and/or relative) using a reference dosage form
- Population subgroups (e.g. gender, age and impaired organ function)
- Interactions (e.g. product-product interactions and effects of food)
- Other pharmacokinetic data (e.g. results of population studies performed within clinical trial)

(b) Safety and Efficacy
A summary of information should be provided about the investigational product’s (including metabolites, where appropriate) safety, pharmacodynamics, efficacy and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be reviewed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials, by indications in subgroups, may provide a clear presentation of the data. Table summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/indications across indications, or subgroups, should be evaluated. The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experience with the product under investigation, and with related products. A description should also be provided of the precautions to be taken or special monitoring to be done, as part of the investigational use of the product.

(c) Marketing Experience
The IB should identify those 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, route of administration, and adverse product reaction). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

(7) 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 product, wherever possible. In this way, the 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. If possible, the published reports on related products should be reviewed. This could help the investigator to anticipate 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 physico-chemical, pharmaceutical, pharmacological, toxicological and clinical information on the investigational product. Guidance should also be provided to the investigator on the recognition
and treatment of possible overdose and adverse drug reactions, based on previous human experience, and on the pharmacology of the investigational product.
Annex 1

Organizational Chart of the Personnel Involved in a Clinical Trial

**Audit**
- A systematic examination conducted by personnel not directly involved in the trial to determine whether the implementation, data recording and its analysis are in accordance with the trial protocol and the Good Clinical Practice.

**Sponsor**
- An individual, company, institution or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

**Monitor**
- A person, who possesses relevant knowledge, appointed by and responsible to the sponsor for monitoring and reporting the progress of the trial and verification of data.

**Ethics Committee**
- An independent body whose responsibility is to confirm that the trial protocol and its attachments are ethical, and to provide public assurance that the trial subject’s safety, health and rights are protected.

**Investigator**
- A person who is responsible for the conduct and the quality of the trial, and the safety and rights of the trial subjects.
Annex 2

Title Page of the Investigator’s Brochure (Example)

Sponsor’s name

Product:

1. Research Number:
2. Drug Name, General Name (if approved)
3. Trade Name(s) (if desired by the sponsor)

Investigator’s Brochure

Edition Number:
Release Date:

Replaces Previous Edition Number: (if applicable)
Date:
Annex 3

Table of Contents of Investigator’s Brochure (Example)

- Confidentiality Statement (optional)
- Signature page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Pharmaceutical Properties and Formulation
5. Nonclinical Studies
6. Effects in Humans
7. Summary of Data and Guidance for the Investigator

NB: References on 
1. Publications
2. Reports

These references should be found at the end of each chapter
Appendices (if any)
Appendix I

Glossary

1. **Adverse Drug Reaction (ADR):**
A noxious and unintended response to a pharmaceutical product occurs at doses normally used in man which also implies a causal relationship between the product and the adverse event. In the clinical experience with a new pharmaceutical product or its new usage, particularly as the therapeutic dose may not be established, all noxious and unintended responses to a pharmaceutical product, and having a possible causal relationship with the treatment, should be considered as adverse drug reaction.

2. **Adverse Event:**
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal (investigational) product.

3. **Applicable Regulatory Requirement**:
Any law or regulation addressing the conduct of clinical trials of investigational products.

4. **Approval (in relation to Ethics Committee):**
The affirmative decision of the Ethics Committee that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the Ethics Committee, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

5. **Audit:**
A systematic examination conducted by personnel not directly involved in the trial to determine whether the implementation, data recording and its analysis are in accordance with the trial protocol, Good Clinical Practice (GCP) and applicable regulatory requirement.

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

7. **Audit Report:**
A written evaluation by the sponsor’s auditor of the results of the audit.

8. **Audit Trail:**
Documentation that allows reconstruction of the course of events.

9. **Blinding/Masking:**
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment. Single-blinding usually refers to the subject being unaware, and double-blinding usually refers to the subject, investigator, monitor and, in some cases, data analyst being unaware of the treatment assignment.
10. **Case Report Form:**
A document which is designed according to the protocol to record data on each subject during the course of the trial.

11. **Clinical Trial:**
Any systematic investigation in human bodies (patients or healthy volunteers) intended to verify and discover the effects, adverse reactions and/or absorption, distribution, metabolism, and excretion of an investigational product with the objective of ascertaining its safety and efficacy.

12. **Comparator (product):**
An investigational or marketed product (i.e. active control), or placebo, used as a reference in a clinical trial.

13. **Compliance (in relation to trials):**
Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

14. **Contract:**
A written, dated and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

15. **Contract Research Organization (CRO):**
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor’s trial-related duties and functions.

16. **Coordinating Investigator:**
An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

17. **Direct Access:**
Permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical trial. Any party (e.g. domestic and foreign regulatory authorities, sponsor’s monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement, to maintain the confidentiality of the subjects’ identities and sponsor’s proprietary information.

18. **Documentation:**
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

19. **Essential Documents:**
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.
20. Ethics Committee:

An independent body constituted of medical, legal and non-medical members, whose responsibility is to verify that the trial protocol and its attachments are ethical, and to provide public assurance that the trial subject’s safety, well-being and rights are protected. Ethics Committee should be constituted and operated so that their task can be executed free from bias, or from any influence of those who are organizing and conducting the trial.

21. Good Clinical Practice for Proprietary Chinese Medicines (GCP):

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are protected.

22. Impartial Witness:

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, and who attends the informed consent process if the subject or the subject’s legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

23. Independent Data-Monitoring Committee (IDMC):

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

24. Informed Consent:

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

25. Informed Consent Form:

A documentation that proves a subject participating in a particular trial on a voluntary basis. The investigator needs to explain to the subject the nature, aim, potential risks and hazards of the trial, other available treatment methods and the subject’s rights and responsibilities as prescribed in the Declaration of Helsinki. Informed consent is obtained only after the subject fully understands the explanations.

26. Inspection:

The act by a regulatory authority of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CRO) facilities.

27. Institution:

Any public or private entity or agency, or medical or dental facility, where clinical trials are conducted.

28. Interim Clinical Trial/Study Report:
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

29. **Investigator:**
A person responsible for the conduct and quality of the trial, and the safety and rights of the trial subjects. The investigator must undergo the verification of his/her qualifications and he/she should possess trial-related professional expertise, qualifications and competence. In a multicentre trial, a principal investigator is responsible for the conduct of the whole trial, and serves as the coordinator among various trial centres.

30. **Investigator’s Brochure:**
A compilation of the clinical and nonclinical data on the investigational product which is relevant to the study of the investigational product in human subjects.

31. **Investigational Product:**
Any product being tested, or used as a comparator or placebo in a clinical trial.

32. **Legally Acceptable Representative:**
An individual or juridical or other body authorized under the applicable law to consent, on behalf of a prospective subject, to the subject’s participation in the clinical trial.

33. **Monitor:**
A person, who possesses relevant knowledge, appointed by and responsible to the sponsor for the monitoring and reporting of the progress of the trial and for verification of the data, to ensure that the trial is conducted in accordance with the protocol, standard operating procedures (SOPs), Good Clinical Practice (GCP) and other applicable regulatory requirements.

34. **Monitoring Report:**
A written report from the monitor to the sponsor, after each site visit and/or other trial-related communication, according to the sponsor’s SOPs.

35. **Multicentre Trial:**
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

36. **Protocol:**
A document that describes the background, rationale, objective, design, methodology and organization of a trial, including statistical considerations, and the conditions under which it is to be performed and completed. The protocol must be signed and dated by the principal investigator, the institution involved and the sponsor.

37. **Protocol Amendment:**
A written description of a change to, or formal clarification, of a protocol.

38. **Quality Control (QC):**
The operational techniques and procedures to ensure that the requirements for quality of the
trial-related activities have been fulfilled.

39. **Randomization:**

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce any possible bias.

40. **Regulatory Authorities:**

Bodies having the power to regulate. Regulatory authorities include those review submitted clinical data and those conduct inspections.

41. **Serious Adverse Event (SAE):**

Any occurrence during a clinical trial that requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, life-threatening consequences, death or congenital anomaly.

42. **Source Data:**

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

43. **Source Documents:**

Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories, and at medico-technical departments, involved in the clinical trial).

44. **Sponsor:**

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

45. **Sponsor-Investigator:**

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

46. **Standard Operating Procedures (SOPs):**

Standardized and detailed written instructions to achieve effective implementation and completion of a specific function in a clinical trial.

47. **Subject/Trial Subject:**

An individual who participate in a clinical trial, either as a recipient of the investigational product or as a control.

48. **Subject Identification Code:**
A unique identifier assigned by the investigator to each trial subject to protect the subject’s identity and used in lieu of the subject’s name when the investigator reports adverse events and/or other trial related data.

49. Trial Site:
The location where trial-related activities are actually conducted.

50. Unexpected Adverse Drug Reaction:
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator’s Brochure for an unapproved investigational product or package insert/summary of product of characteristics for an approved product).

51. Vulnerable Subjects:
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified 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, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects included patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors and those incapable of giving consent.
**Documentation retained for clinical trial**

**I. Before the Clinical Phase of the Trial Commences**

<table>
<thead>
<tr>
<th>Documents retained for the clinical trial</th>
<th>Investigator</th>
<th>Sponsor</th>
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<tbody>
<tr>
<td>1. Investigator’s brochure</td>
<td>retained</td>
<td>retained</td>
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<tr>
<td>2. Trial protocol and amendments (signed) original</td>
<td>retained</td>
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</tr>
<tr>
<td>3. Case report form (sample)</td>
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<tr>
<td>4. Informed consent form and other written information provided for the subject</td>
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<td>5. Financial aspects of the trial</td>
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<td>6. Insurance statement (where required)</td>
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<td>7. Multilateral agreements (signed) (the investigator, sponsor, CRO)</td>
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<td>8. Written approval of the EC (including the protocol and its amendments, case report form (if applicable), informed consent form, other written information provided for the subject and compensation to the subject (if any))</td>
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<tr>
<td>9. Composition of Ethics Committee</td>
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<td>10. Application form for clinical trial</td>
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<td>11. Pre-clinical laboratory data</td>
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<td>12. Written approval of the regulatory authorities in respect of the protocol</td>
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<td>13. Curriculum vitae of investigator(s) and/or other relevant documents</td>
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<td>14. Normal ranges for trial-related laboratory tests</td>
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<tr>
<td>15. Quality control verification for medical/laboratory operation</td>
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<td>16. Label of the investigational product</td>
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<tr>
<td>17. Instructions for handling of investigational product and trial-related materials</td>
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<td>18. Shipment record for the investigational product and trial-related materials</td>
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### Documents retained for the clinical trial

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<td>19.</td>
<td>Certificate of analysis of the investigational product</td>
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<td>20.</td>
<td>Decoding procedures for blinded trial</td>
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<tr>
<td>21.</td>
<td>Master randomization list</td>
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<tr>
<td>22.</td>
<td>Trial monitoring report (before the trial and when the trial commences)</td>
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#### II. During the Clinical Phase of the Trial

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<td>23.</td>
<td>Updates of the Investigator’s Brochure</td>
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<td>24.</td>
<td>Any revision of other documents (the protocol, case report form, informed consent form, written notification)</td>
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<tr>
<td>25.</td>
<td>Written approval of the EC in respect of updates of the above information (dated)</td>
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<tr>
<td>26.</td>
<td>Written approval of the regulatory authority in respect of amendments to the protocol</td>
<td>Retained if necessary</td>
</tr>
<tr>
<td>27.</td>
<td>Curriculum vitae of new investigator(s)</td>
<td>retained</td>
</tr>
<tr>
<td>28.</td>
<td>Updates to normal range of medical, laboratory and technical procedures</td>
<td>retained</td>
</tr>
<tr>
<td>29.</td>
<td>Updates of medical or laboratory procedures</td>
<td>retained</td>
</tr>
<tr>
<td>30.</td>
<td>Documentation of investigational product and trial-related material shipment</td>
<td>retained</td>
</tr>
<tr>
<td>31.</td>
<td>Certificate of analysis for new batches of investigational product</td>
<td>original retained</td>
</tr>
<tr>
<td>32.</td>
<td>Monitoring visit report</td>
<td>original retained</td>
</tr>
<tr>
<td>33.</td>
<td>Relevant communication other than site visit</td>
<td>retained</td>
</tr>
<tr>
<td>34.</td>
<td>Signed informed consent form</td>
<td>original retained</td>
</tr>
<tr>
<td>35.</td>
<td>Source documents</td>
<td>original retained</td>
</tr>
<tr>
<td>36.</td>
<td>Case report form (completed, signed and dated)</td>
<td>copy retained</td>
</tr>
<tr>
<td>37.</td>
<td>Documentation of case report form correction</td>
<td>copy retained</td>
</tr>
<tr>
<td>38.</td>
<td>Report of serious adverse event prepared by the investigator to the sponsor</td>
<td>original retained</td>
</tr>
<tr>
<td>Documents retained for the clinical trial</td>
<td>Investigator</td>
<td>Sponsor</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------------------------------</td>
<td>--------------</td>
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</tr>
<tr>
<td>39. Report of unexpected serious adverse event prepared by the sponsor to the regulatory authority and Ethics Committee</td>
<td>retained</td>
<td>original retained</td>
</tr>
<tr>
<td>40. Notification by sponsor to investigator of safety information</td>
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</tr>
<tr>
<td>41. Interim or annual report of the clinical trial</td>
<td>retained</td>
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</tr>
<tr>
<td>42. Subject identification list</td>
<td>original</td>
<td>retained</td>
</tr>
<tr>
<td>43. Subject screening and enrollment logs</td>
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<td>retained</td>
</tr>
<tr>
<td>44. Investigational product accountability at the site</td>
<td>retained</td>
<td>retained</td>
</tr>
<tr>
<td>45. Signature specimen of the investigators</td>
<td>retained</td>
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</tr>
<tr>
<td>46. Records of retaining samples of body fluid and tissue</td>
<td>retained</td>
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### III. After completion or termination of the trial

<table>
<thead>
<tr>
<th>Documents retained for the clinical trial</th>
<th>Investigator</th>
<th>Sponsor</th>
</tr>
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<tbody>
<tr>
<td>47. Investigational product accountability at site</td>
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<td>retained</td>
</tr>
<tr>
<td>48. Documentation of investigational product destruction</td>
<td>retained</td>
<td>retained</td>
</tr>
<tr>
<td>49. Completed subject identification list</td>
<td>retained</td>
<td>retained</td>
</tr>
<tr>
<td>50. Audit certificate (if necessary)</td>
<td>retained</td>
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<tr>
<td>51. Final trial close-out monitoring report</td>
<td>original</td>
<td>retained</td>
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<tr>
<td>52. Treatment allocation and decoding documentation</td>
<td>original</td>
<td>retained</td>
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<tr>
<td>53. Report of trial completion by the investigator (to the Ethics Committee and regulatory authority)</td>
<td>original</td>
<td>retained</td>
</tr>
<tr>
<td>54. Final Report</td>
<td>retained</td>
<td>original retained</td>
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</table>