

Good Clinical Practice for Proprietary Chinese Medicines

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Good Clinical Practice (GCP) for Proprietary Chinese Medicines

Chapter 1 General Principles

1. These guidelines are formulated with reference to internationally recognized principles, 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 guideline should be adopted as guiding principles by those conducting the clinical trial for proprietary Chinese medicines.
2. The guideline is the standard requirement for the process of a clinical trial, including protocol designing, organizing, conducting, monitoring, auditing, recording, analyzing and reporting.
3. The guideline is 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 (Appendix 1), 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 of the subjects and the public, respectively, should be considered. The anticipated benefits should out-weigh 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, the monitoring and auditing of the trial, the standard operating procedures, and the allocation of trial-related responsibilities, etc.
9. Clinical trial should be conducted in compliance with the protocol that has received the prior approval of the Ethics Committee.
10. The medical decisions made on behalf of subjects should always be the responsibility of a qualified physician, or a registered Chinese medicine practitioner.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules 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 trials that involve vulnerable subjects; and the scientific integrity and credibility of the trial should be ensured. The rights, safety and well-being of the trial subject 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 subject.
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 of each gender, 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 receive approval from Ethics Committee. During the trial, any amendments to the protocol 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 needed by the Ethics Committee to fulfill 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. The Ethics Committee should make its decision at a formal meeting with at least a quorum, as 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. All of its meetings and resolutions should have written records and those records 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 help to ensure that the patient's 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 relevant documentations to prove his/her 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, of 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 the ongoing trial at intervals according to the degree of risk to subjects, but at least once a 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 hold a meeting to discuss the protocol. 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) The subject's participation in the trial is voluntary and that the subject may refuse to participate in, or withdrawn from, the trial at any time without penalty or loss of benefits to which the subject is 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 scrutinized 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 consider whether he/she is willing to participate in the trial. For the subject who is unable to provide informed consent, an introduction and explanation of the trial should be given to the subject's legally acceptable representative. The process of obtaining informed consent should be conducted in a language and words that are understood by the subject or the subject's legally acceptable representative. During the trial, the

subject may have access to any information related to him/her at any time. The subject and/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 his/her 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, plus any other written information provided to the subjects.
 - (2) If the subject is incapable of giving personal consent, the inclusion of such a patient in a trial may be acceptable, provided that the Ethics Committee approves in principle and the investigator thinks that participation will be in the interests of 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. Consent of the child is also required when he is able to make a decision to participate or not, in the trial.
- (5) In emergency situation when prior consent of the subject or the subject's legally acceptable representative is not possible, but there is no proven effective treatment for the disease and the investigational product has the potential to save the subject's life, the subject could also be enrolled into the trial, provided that the enrollment method has been stated in the trial protocol and other relevant documents clearly with prior approval by the Ethics Committee. After administering the investigational product, the investigator should inform the subject or the subject's legally acceptable representative about the trial as soon as possible and seek his/her consent to continue it. 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 receive 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 which is agreed and signed by both the investigator and the sponsor should be implemented only after receiving 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 in order to meet the trial objective 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) Items that are intended for clinical and laboratory examination, frequency of those examinations 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's participation.
- (16) Primary and secondary endpoints to be measured during the trial.

- (17) Maintenance procedures of the subject identification codes, randomization list and case report form.
 - (18) The requirements of recording adverse events, and method of reporting serious adverse events. The way and time of follow-up visit.
 - (19) The establishment and maintenance of the trial randomization code, and how, and by whom, it can be broken in case of emergency.
 - (20) The description of the statistical analysis plan, the definition 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 analysis. Procedures for accounting for missing, unused, and spurious data.
 - (21) Regulations for data management and data tracing.
 - (22) A statement specifying that the investigator will permit trial-related monitoring, audit, Ethics Committee review, and regulatory inspection; 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 Responsibility 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) Access to human and other resources 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 strictly comply with the protocol which agreed by the sponsor (and regulatory authorities if necessary) and approved by the Ethics Committee. The investigator must sign the protocol, or an alternative contract, with the sponsor 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 which may become available concerning the product 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 current copy of the 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 good 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 on the trial-related requirements and the duties of all persons assisting in the trial. The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects.
33. The investigator should inform the subject fully 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 to be suspended or terminated, the investigator must inform the subject, the sponsor, the Ethics Committee and the regulatory authorities with explanation.

Chapter 6 The 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 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. Before suspension or termination of any clinical trial by the sponsor, the sponsor should inform the investigator, the Ethics Committee and the regulatory authorities with reasons.
 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. If the investigator does not comply with the approved protocol and applicable regulatory requirements in conducting the clinical trial, the sponsor should point out the problem and request correction. If the situation is serious and/or

persistent, the sponsor should terminate the participation of the investigator in the trial and report this to the regulatory authorities.

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 staff are familiar with the requirements of the protocol before starting the trial.
 - (2) To oversee 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 recorded and reported completely, and that all case report forms are accurately completed and are consistent 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, dropouts or missed of examinations should be confirmed and recorded. To verify that all withdrawals and dropouts of enrolled subjects should be 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.
 - (5) 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.

- (6) To assist the investigator in carrying out any necessary notification and application, and to report the trial data and results to the sponsor.
- (7) To document any follow-ups that are 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.
- (8) To confirm that the investigator is maintaining the essential documents (please refer to Appendix III)
- (9) To verify that the investigator and the investigator's trial staff, are performing the designated duties in accordance with the protocol, and with the agreement between the sponsor and the investigator, and that they have not delegated these duties to any unauthorized individuals.
- (10) 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, the corrections should not obscure the original entry, and should be signed and dated by the correcting person.
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 confirm with the list.
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 the 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) The safety assessment should include reasonable statistical analyses on clinical adverse events and laboratory indicators. Detailed description and assessment of serious adverse events should be provided.
 - (5) When assessing efficacy in a multi-centre 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 III) 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 the electronic trial data handling and/or remote electronic trial data systems, the sponsor should:
 - (1) Ensure and document the electronic data processing system conforms to the requirements for completeness, accuracy, reliability and consistent intended performance (i.e. validation), as set by the sponsor.
 - (2) Maintain standard operating procedures for using this system.
 - (3) Ensure that correction of data is permitted in such a way that all data changes are documented, and there is no deletion of entered data (i.e. to retain an audit trail, data trail and 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) Establish measures to safeguard the blinding (e.g. maintain blinding method during the data entry and processing), if any.
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 used only 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 participated 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 the examination of the individuals concerned.

Chapter 11 Quality assurance

83. To ensure that the trial is performed and the data are generated, documented and reported in accordance with the GCP, a planned and systematic quality assurance action should be established. The sponsor and investigator should fulfill their duties respectively, and should strictly comply with the trial protocol, and adopt the standard operating procedures, to ensure the 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. Complete, accurate, true and reliable.
86. The regulatory authorities or the sponsor may appoint an auditor to conduct a systematic evaluation to determine whether the trial implementation is 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 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.
87. If or when the sponsor performs audits, as part of the quality assurance, he/she should consider:
 - (1) The purpose of the sponsor's audit, which is independent of, and separate from routine monitoring or quality control functions, is to evaluate the compliance of the trial with the protocol, standard operating procedures and the GCP.
 - (2) The sponsor should appoint individuals, who are independent of the clinical trial, to conduct audits. Such individuals should be qualified by training and experience.
 - (3) The sponsor should ensure that the auditing of the clinical trial is conducted in accordance with the sponsor's written audit procedures on whom to audit, how to audit, the frequency of audits, and what to audit.
 - (4) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to be submitted to the 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 auditors should be documented.
 - (6) To preserve the independence and value of the audit function, the regulatory authorities should not routinely request the audit reports. Regulatory authorities 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 regulations, the sponsor should provide an audit certificate.
88. 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 Multi-centre trial

89. A multi-centre 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 multi-centre trials, and he/she should be the coordinating investigator for different trial centers.
90. Consideration should be given to the following items, in planning and implementing a multi-centre 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.
91. A management system should be established in consideration of the number of participating centers, the requirements of trial and the extent of knowledge on the investigational product. The coordinating investigator should be responsible for the implementation of the entire trial.

Chapter 13 Investigator's Brochure

92. 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.
93. 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.
94. 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.
95. 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.
96. 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.

97. 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.
98. 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.

99. General Considerations:

The IB should include:

- (1) *Title Page* : 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 Appendix 2.
- (2) *Confidentiality Statement* : The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the Ethics Committee.

100. 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 Appendix 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 of 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.

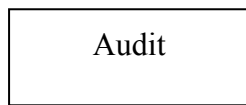
(7) Summary of Data and guidance for the investigator

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.

Organizational Chart of the Personnel Involved in a Clinical Trial

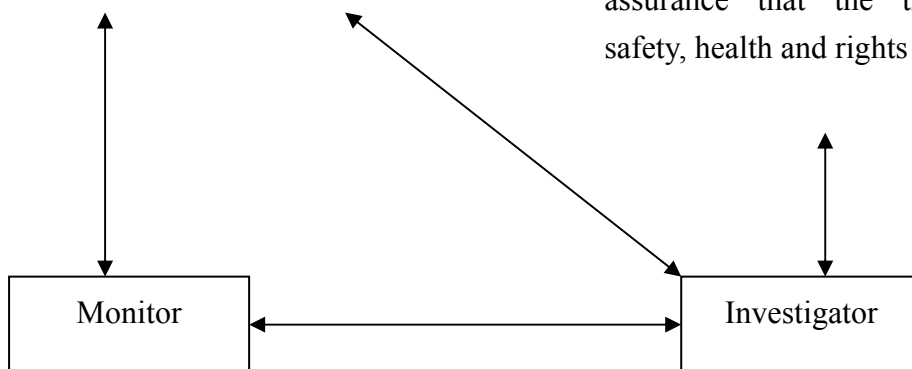


A systematic examination conducted by personnel not directly involved in the trial to determine whether the implementation, data recording and its analysis are in accordance with the trial protocol and the Good Clinical Practice.



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

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.



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.

A person who is responsible for the conduct and the quality of the trial, and the safety and rights of the trial subjects.

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:

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)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

18th WMA General Assembly Helsinki, Finland, June 1964

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September, 1989

48th WMA General Assembly, Somerset West Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research, which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research

on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research, which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case, the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the

best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods does not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

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 investigator 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, signed and dated agreement between two or more involved parties that sets out the 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 participating in a multicentre trial at different centres.

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 the 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 electrodiagrams) 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 confirm 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. Final Report:

A detailed conclusion of the trial after its completion, which includes description of experimental methods and materials, a presentation and evaluation of the results, statistical analyses and a critical, ethical, statistical and clinical appraisal.

22. 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.

23. 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.

24. 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.

25. 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.

26. 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 may be obtained only after the subject fully understands the explanations.

27. 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.

28. Institution:

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

29. Interim Clinical Trial/Study Report:

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

30. 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.

31. 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.

32. Investigational Product:

A product used as a reference, or comparator, or placebo, in a clinical trial.

33. 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.

34. 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.

35. 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.

36. 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.

37. Pharmaceutical Product:

A material, with indication, usage and dosage, used in prevention, treatment and diagnosis of disease with a view to adjusting functions of the human body.

38. 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.

39. Protocol Amendment:

A written description of a change to, or formal clarification, of a protocol.

40. Quality Control (QC):

The operational techniques and procedures to ensure that the requirements for quality of the trial-related activities have been fulfilled.

41. 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.

42. Regulatory Authorities:

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

43. 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.

44. 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.

45. 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).

46. Sponsor:

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

47. 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.

48. Standard Operating Procedures (SOPs):

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

49. Subject/Trial Subject:

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

50. 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.

51. Trial Site:

The location where trial-related activities are actually conducted.

52. 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).

53. 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 hierarchy 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

Documents retained for the clinical trial		Investigator	Sponsor
1.	Investigator's brochure	retained	retained
2.	Trial protocol and amendments (signed)	original retained	retained
3.	Case report form (sample)	retained	Retained
4.	Informed consent form and other written information provided for the subject	original retained	retained
5.	Financial aspects of the trial	retained	retained
6.	Insurance statement (where required)	retained	retained
7.	Multilateral agreements (signed) (the investigator, sponsor, CRO)	retained	retained
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))	original retained	retained
9.	Composition of Ethics Committee	original retained	retained
10.	Application form for clinical trial		original retained
11.	Pre-clinical laboratory data		original retained
12.	Written approval of the regulatory authorities in respect of the protocol	retained	original retained
13.	Curriculum vitae and/or other relevant documents	retained	original retained
14.	Normal ranges for trial-related laboratory tests	retained	retained
15.	Quality control verification for medical/laboratory operation	original retained	retained
16.	Label of the investigational product		original retained

17.	Instructions for handling of investigational product and trial-related materials	retained	retained
18.	Shipment record for the investigational product and trial-related materials	retained	retained
19.	Certificate of analysis of the investigational product		original retained
20.	Decoding procedures for blinded trial		original retained
21.	Master randomization list		original retained
22.	Trial monitoring report (before the trial and when the trial commences)		original retained

II. During the Clinical Phase of the Trial

Documents retained for clinical trial		Investigator	Sponsor
23.	Updates of the Investigator's Brochure	retained	retained
24.	Any revision of other documents (the protocol, case report form, informed consent form, written notification)	retained	retained
25.	Written approval of the EC in respect of updates of the above information (dated)	original retained	retained
26.	Written approval of the regulatory authority in respect of amendments to the protocol	Retained if necessary	original retained
27.	Curriculum vitae for new investigator	retained	original retained
28.	Updates to normal range of medical, laboratory and technical procedures	retained	retained
29.	Updates of medical or laboratory procedures	original retained	retained
30.	Documentation of investigational product and trial-related material shipment	retained	retained
31.	Certificate of analysis for new batches of investigational product		original retained
32.	Monitoring visit report		original retained
33.	Relevant communication other than site visit	retained	retained
34.	Signed informed consent form	original retained	
35.	Source documents	original retained	
36.	Case report form (completed, signed and dated)	copy retained	original retained

37.	Documentation of case report form correction	copy retained	original retained
38.	Report of serious adverse event prepared by the investigator to the sponsor	original retained	retained
39.	Report of unexpected serious adverse event prepared by the sponsor to the regulatory authority and Ethics Committee	retained	original retained
40.	Notification by sponsor to investigator of safety information	retained	retained
41.	Interim or annual report of the clinical trial	retained	retained
42.	Subject identification list	original retained	
43.	Subject screening and enrollment logs	retained	retained
44.	Investigational product accountability at the site	retained	retained
45.	Signature specimen of the investigators	retained	retained
46.	Records of retaining samples of body fluid and tissue	retained	retained

III. After completion or termination of the trial

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