MINISTRITY OF HEALTH

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CIRCULAR
Guidelines for Clinical trials on Drugs

Based on the Law on Pharmacy of 14.6.2005 and Decree No. 79/2006/ND-CP dated 09/08/2006 guiding implementation of some provisions of the Law on Pharmacy;
Pursuant to Decree No. 188/2007/ND-CP dated 27/12/2007 of the Government regulating functions, duties, powers and organizational structure of Ministry of Health,
The Ministry of Health provides the following guidelines for clinical practice for trials on Drugs:

Chapter I
GENERAL PROVISIONS

Article 1. Scope

This Circular provides guidelines for drugs subject to clinical trials, drugs exempt from full clinical trials, drugs exempt from some phases of clinical trials, conditions applying to the conduct for clinical trials; registration, review and approval of clinical trials, phases of clinical trials, rights and obligations of related parties and the supervision, inspection, evaluation for acceptability of clinical trials in Vietnam for research purposes and the marketing authorization of pharmaceuticals, biologics, vaccines and oriental medicines, drugs made of medicinal materials, used in the diagnosis, treatment and prevention of disease in humans (hereafter referred to as Drugs)

Article 2. Interpretation of terms

In this Circular, the following terms are construed as follows:

1. Reference country is any country among the UK, France, Germany, USA, Japan, Australia, Canada or the European Medicines Agency (EMA).

2. A multi-center clinical trial is a trial conducted in two or more research centers to ensure the inclusiveness of participants and demographic, anthropologic diversity.

3. Agencies, organizations, individuals having the candidate drugs are agencies, organizations and individuals with a mandate for research, production, import, export, distribution of medicines which are in need to undertake clinical trials on their drugs.

4. Host institutions (in receipt of the trials) are medical establishments with a mandate for scientific research, with functionally qualified personnel, premises, facilities and equipments to carry out clinical trials and which are appraised, authorized by the Ministry of Health to do so.

5. Trial subjects are patients or healthy individuals who participate voluntarily in clinical trials.

6. Clinical Research Organization (Contract Research Organization CRO) is an organization with legal status, with appropriately qualified personnel meeting Ministry of Health's requirements, is independent from the Agencies, organizations, individuals owing the candidate drug(s), which is contracted by the latter to perform trial-related duties the like of writing research protocol, trial monitoring, data analysis.

7. Site Management Organization (SMO) is an organization with legal status, functionally qualified in accordance with Ministry of Health's requirements, is independent from Agencies, organizations, individuals having the candidate drug(s) or the Host institution, which is contracted by either of the latter two entities to perform duties in support of the management of the trial site.

8. Foreign clinical data are methods and results of clinical studies which have been undertaken abroad.

9. Ethnic factors are factors related to large population with common genetic characteristics, culture, traditions and environment.

10. International regulations for clinical trial on drugs recognized by the Health Ministry are guidelines for good practices for clinical trials of jurisdictions party to the The *International Conference on Harmonisation* (*ICH*) and Guidelines for good clinical practice for trials on pharmaceutical products (Good Clinical Practice - GCP) of the World Health Organization (WHO).

Article 3. Principles of clinical trials

1. Clinical trials shall be conducted in accordance with the provisions of this Circular, regulatory requirements on science and technology, good clinical practice for trials on drugs and international treaties to which Vietnam is a signatory.

2. Selection of trial subjects shall be in compliance with ethical principles for biomedical research.

Article 4. Prohibited Acts

1. Conduct clinical trials without Ministry of Health's authorization.

2. Unilaterally amend, supplement the content of drug dossiers, research protocols after they have been approved by Ministry of Health.

3. Use the drug(s) under clinical trials for other purposes.

4. Coerce subjects into participating in trials or withhold information from, or not provide information as required to trial subjects.

Chapter II
DRUGS SUBJECT TO CLINICAL TRIALS, DRUGS EXEMPT FROM FULL CLINICAL TRIALS AND DRUGS EXEMPT FROM SOME PHASES OF CLINICAL TRIALS

Article 5. Drugs which are subject to full clinical trials

1. Pharmaceutical products, biomedical products:

a) Pharmaceuticals that contain a new active ingredient or products with new combination of a marketed ingredient.
b) Newly developed biologics or biologics with a new combination of a marketed ingredient.

c) Pharmaceuticals, biologics which have been legally marketed but for a period of less than 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory).

d) Pharmaceuticals, biologics for which a clinical trial has been conducted before the effective date of this Circular but which has not met the requirements of Ministry of Health's good practice for clinical trials or those of international guidelines on good clinical practice for trials on medicines recognized by Ministry of Health.

2. Vaccines:

a) Newly developed vaccines, manufactured and put to use for the first time.

b) Foreign vaccines which have been legally marketed but for a period of less than 5 years in the country of origin (or a reference country if provided for under international treaties to which Vietnam is a signatory).

c) Vaccines for which a clinical trials has been conducted before the effective date of this Circular but which has not met the requirements of Ministry of Health's good practice for clinical trials or those of international guidelines on good clinical practice for trials on medicines recognized by Ministry of Health.

3. Oriental medicines or drugs made from medicinal materials:

a) Drugs containing new ingredients which are first used in humans.

b) Drugs for which a clinical trial has been conducted before the effective date of this Circular but which has not met the requirements of Ministry of Health's good practice for clinical trials or those of international guidelines on good clinical practice for trials on medicines recognized by Ministry of Health.

Article 6. Drugs which are exempt from clinical trials

1. Pharmaceutical products, biological products

a) Pharmaceutical drugs with non-proprietary name (Generic drugs).

b) Foreign drugs for which a registration number for marketing in Vietnam has not been granted but which have been legally marketed for at least 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority, for the same route of administration, formulation and indications with those intended for use in Vietnam.

c) Foreign drugs for which a registration number for marketing in Vietnam has been granted, but have undergone modifications or supplementations in relation to indications, route of administration, dosage forms identical with those of the same drugs which have been legally marketed in the country of origin

for at least 5 years (or a reference country if provided for by international treaties to which Vietnam is a signatory).

2. Vaccines:

a) Foreign vaccines with a valid registration number for marketing in Vietnam, which are imported into Vietnam for the final step of labeling, packaging.

b) Re-registration of vaccines in Vietnam due to expiry of existing marketing registration number without the vaccines undergoing any modification.

3. Oriental medicines, drugs made of medicinal materials:

a) Oriental prescriptions which have been recognized by the Health Ministry.

b) Oriental medicines, drugs made from foreign medicinal materials for which a registration number for marketing in Vietnam has not been granted but which have been legally marketed for at least 05 years in the country of origin (or reference country if provided for under international treaties of which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority for the same route of administration, formulation and indications with those intended for use in Vietnam.

Article 7. Drugs which are exempt from some phases of clinical trials

1. Pharmaceutical products, biological products:
Foreign drugs for which a registration number for marketing in Vietnam has been granted but have undergone modifications or supplementations in relation to indications, route administration, dosage forms different from those of the same drugs which have been legally marketed for at least 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory). These drugs are subject to:

a) Clinical trials for the assessment of safety;
b) Clinical trials for the assessment of effectiveness if this has not been performed before or if the assessment has been performed but it failed to meet the requirements of Ministry of Health's good practice for clinical trials or those of international guidelines for good clinical practice for trials on medicines recognized by Ministry of Health.

2. Vaccines:

Clinical trials for the assessment of safety shall be conducted for:

a) Foreign vaccines for which a registration number for marketing in Vietnam has not been granted, which have been legally marketed for at least 05 years in the country of origin (or reference country if provided for under international treaties to which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority for the same route of administration, formulation and indications as those intended for use in Vietnam.

b) Vaccines manufactured in Vietnam from imported semi-finished products with components having been legally marketed for at least 5 years in the country of origin (or a country of reference if provided for under international treaties to which Vietnam is a signatory).

c) Vaccines for which a registration number for marketing in Vietnam has been granted but which have undergone modifications or supplementations in relation to excipients, preservatives, changes in production facilities (no change in production processes).

Clinical trials for the assessment of safety and immunogenicity in phase 3 shall be conducted for:

a) Foreign vaccines which have been legally marketed for at least 5 years in the country of origin (or a reference country if provided for under international treaties to which Vietnam is a signatory) for which manufacturing technology is transferred to Vietnam.

b) Vaccines manufactured in Vietnam from imported intermediates with components having been legally marketed for at least 5 years in the country of origin (or a country of reference if provided for under international treaties of which Vietnam is a signatory).

a) Vaccines for which a registration number for marketing in Vietnam has been granted but which have undergone modifications or supplementations in relation to manufacturing process, dosage forms, indications, target population (age, sex, race), route of administration, dosage, vaccination schedule.

3. Oriental medicines, drugs made from medicinal materials:

Clinical trials for the assessment of safety shall be conducted for:

Drugs for which a registration number for marketing in Vietnam has been granted and other oriental prescriptions recognized by the Ministry of Health but which have undergone modifications or supplementations in relation to indications, route of administration, formulation, dosage forms different from those of the same drugs which have been legally marketed for at least 05 years in the country of origin (or reference country if provided for in international treaties to which Vietnam is a signatory).

Article 8. Clinical trials in special cases involving health security emergencies

Minister of Ministry of Health with advice from the Advisory Council for Marketing Licensing and the Ministry of Health Biomedical research Ethics Committee shall consider and grant exemption from clinical trials for the following cases:

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1. Drugs for use in special cases relating to emergency health security including:

a) Pharmaceuticals, biologics, vaccines which have been legally marketed but for a period of less than 5 years in the country of origin (or a reference country if provided for under international treaties to which Vietnam is a signatory), for which clinical trial data from multicenter trial conducted in Vietnam and Asia is available, of which safety and effectiveness have been proven by trial results for the same formulation, indications, route of administration with those in use in the respective country.

b) Pharmaceuticals, oriental medicines or drugs from medicinal materials which meet special therapeutic demands, which are listed in the list of rare drugs published by Ministry of Health, with particular dosage forms not yet manufacturable domestically, for which no substitute is available, without which patients' life would be compromised, for which a registration number for marketing in Vietnam has not been

granted, which have been legally marketed in the country of origin but for a period of less than 5 years (or country of reference if provided for under international treaties to which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority for the same route of administration, formulation and indications as those intended for use in Vietnam.
c) Vaccines for use in the prevention of emerging infectious diseases of yet to be known pathogen or deadly highly infectious diseases capable of rapid and wide scale spread with high mortality rate, for which a registration number for marketing in Vietnam has not been granted, which have been legally marketed in the country of origin but for a period of less than 5 years (or a reference country if provided for under international treaties to which Vietnam is a signatory) and which have been certified as safe and effective by the respective country's competent authority for the same route of administration, formulation and indications as those intended for use in Vietnam.

2.. Drugs which are products resulted from research projects, research grants of ministerial equivalent or higher level, which were conducted prior to the effective date of this Circular in strict compliance with provisions of this Circular and guidelines on good clinical practice for trials, which have been evaluated for acceptability and authorized for marketing by the ministerial equivalent or higher level council of science and technology.

Chapter III
CONDITIONS FOR CLINICAL TRIALS

Article 9. Conditions which apply to investigational drugs (*)

(*) translator note:– not clear whether "Thuốc thử trên lâm sàng" covers all investigational drugs used inthe trial only the candidate drug.

Investigational Drugs shall meet the following requirements:

1. Pre-clinical studies on the drugs have been conducted, for which safety has been proven and documented making the drugs eligible for progressing to the next trial phase.

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2. Formulation, dosage forms and manufacturing process of the drugs have been stabilized.

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3. Availability of results of previous phases of the clinical trial on the drugs if the application is for the authorization to progress to the next phase.

4. Meeting quality standards as stated in the dossier for the registration of clinical trials.

5. Investigational Drugs shall be clearly labeled with the wordings "Products for clinical trials. Use for other purposes is prohibited"

Article 10. Conditions which apply to the clinical trial dossier

Dossier for registration of clinical trial shall be in Vietnamese (01 original, legally signed, sealed and 03

copies), comprising of:

1. Application for authorization to conduct a clinical trial by the agencies, organizations, individuals having the candidate drug(s) (Appendix 1 attached to this Circular).

2. Investigator's brochure in Vietnamese or in English accompanied by a summary in Vietnamese (Appendix 2 of this Circular).

3. Application requesting for review, approval of the trial protocol by the Host institution (Appendix 3 of this Circular).

4. Agreement between Agencies, organizations, individuals having the candidate drugs and the Host institution and Agreement between Agencies, organizations, individuals having the candidate drugs and the Contract research organization, the Site management organization, if applicable (Appendix 4 of this Circular).

5. Explanatory Notes to the trial protocol (Appendix 5 of this Circular).

6. Professional Curriculum Vitae and Certificate of good practice on clinical trial of the Principal investigator/Chief researcher issued by Ministry of Health or other agencies recognized by Ministry of Health.

7. Clinical trial Information sheet and the Informed Consent form (Appendix 6 of Circular).

8. Minutes of the local (Host institution) Biomedical research Ethics committee's opinion on the scientific aspects and ethical considerations of the clinical trials.

9. Written confirmation of participation by the participating research institutions in case of multi-center trials conducted in Vietnam.

10. Notice by the people's committee of provinces, cities reporting to central government, accepting to participate in the clinical trials which take place in their respective localities.

11. Documentation on the investigational drugs(s) comprising of:

a) Documentation on investigational drugs: composition, formulation, manufacture processes, quality standards, drug testing slips (for pharmaceutical drugs, oriental medicines or drugs from medicinal materials: testing slips by the central testing agency or manufacturers meeting good manufacturing practice standards (GMP); for vaccines: quality certificate by national quality control agency or ex-factory delivery certificate by respective national drug regulatory agency for imported vaccine lots, biologics).

b) Documentation of pre-clinical studies of investigational drug on pharmacology, toxicology, safety and proposed dosage, route and method of administration.

c) Documentation of the preceding phases of the clinical trials (if application is for the authorization to progress to the next phase of the trials)

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12. For investigational drugs which are candidate of safety assessment, clinical trial phase 4: A certified copy of the certificate of pharmaceutical product (CPP) or free sale certificate (FSC) and certificate of good manufacturing practice (GMP) of the respective state regulatory authority.

13. Labels of investigational drugs as stipulated in Clause 6 Article 9 of this Circular and photographs of the drug samples.

Article 11. Conditions which apply to Host institutions, the Principal investigator and participating investigators

1. Host Institutions shall satisfy the standards of good clinical practice for trials on pharmaceutical products (GCP), be independent financially and with respect to personnel from Individuals, organizations having the candidate drugs and shall undertake to carry out the trials free from any conflict of interests.

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2. The Principal investigator shall be qualified with in depth technical knowledge, clinically experienced, operationally competent to ensure compliance with the principles of good clinical practice, be thoroughly familiar with the requirements of clinical trials, be capable of implementing the trial as per the approved protocol in full and to schedule, be GCP certified by the Ministry of Health or organizations recognized by the Ministry of Health.

3. The participating investigators shall have appropriate expertise, be trained on the subject matter and skills necessary for the conduct of the trials, be GCP certified by Ministry of Health or other organizations recognized by Ministry of Health.

Article 12. Conditions for trial subjects

1. Trial subjects shall be volunteers meeting the needs of the trial, shall sign an informed consent with the Host institution, except when s/he is restricted in his or her civil act capacity, has lost his or her civil act capacity or is without civil act capacity.

2. Where the trial subject is under 18 years old, is restricted in his or her civil act capacity, has lost his or her civil act capacity or is without civil act capacity, consent shall be obtained from the representative in accordance with the law.

3. Where trial subject is a woman who is pregnant or breast-feeding, the rationale for the selection of the subject shall be given in the Investigator's Brochure, be approved by Minister of Health with due consideration given to the opinion of the Ministry of Health Ethics Committee for Biomedical research on the scientific and ethical nature of the selection.

Article 13. Conditions which apply to funding of clinical trials

1. Funding shall be sufficient to cover all trial related activities (including budget lines for studies, management fee, supervision, inspection) shall be provided by the Agencies, organizations, individuals having the candidate drugs through contractual agreements between the latter and the Host institution.

2. For drugs which are object of government funded programs, research grants under collaboration with national or foreign entities, the Lead researcher and Host institutions shall budget for the clinical trials as part of the total grant allocated.

3. The Host institution and the Principal investigator shall be responsible for managing their allocated budget to ensure expenditures are appropriate and to cost norms in accordance with relevant regulatory requirements or contractual terms between two parties.

Chapter IV
REGISTRATION, REVIEW AND AUTHORIZATION FOR CLINICAL TRIALS

Article 14. Registration for clinical trials

1. The Agencies, organizations, individuals having the candidate drugs shall submit to the Ministry of Health a registration dossier comprising of documents stipulated in Clause 1, Clause 2, Article 10 of this Circular.

2 Within 15 working days from the date of receipt of registration, Ministry of Health shall give written notice to the Agencies, organizations, individuals having the drug(s) regarding required next steps.

Article 15. Formulating the Trial Protocol

Based on Ministry of Health's written authorization, the Agencies, organizations, individuals having the candidate drugs in conjunction with the Principal investigator and the Host institution shall prepare the Trial Protocol as follows:

1. The Agencies, organizations, individuals having the candidate drugs shall provide the Principal investigator and the Host institution with documents specified in paragraphs 1, 2, 7, 11, 12 and 13, Article 10 of this Circular.

2. The Principal investigator, in conjunction with the Agencies, organizations, individuals having the candidate drugs and members of the research group, shall formulate the Trial Protocol, ensure the dossier's completeness as stipulated by Article 10 of the Circular this.

Article 16. Application for Authorization to conduct clinical trials

1. A clinical trial dossier as stipulated in Article 10 of this Circular shall be sent to Ministry of Health which serves as the basis for the review, consideration and authorization.

2. Dossiers received at the Health Ministry before the 20th of each month shall be evaluated in the same month. Dossiers submitted after this timeline shall be evaluated in the following month.

3. Information regarding registration, preparation and submission of application can be accessed via the Ministry of Health electronic portal www.iecmoh.vn or the Ministry of Health Biomedical research Ethics Committee's web site www.iecmoh.vn.

Article 17. Review and Authorization of clinical trials

1. Review the clinical trial dossier
Within 30 working days from the date of receipt of a complete dossier as stipulated in Article 10 of this Circular, Ministry of Health shall convene a Biomedical research Ethics Committee meeting.

2. Notice of results
Within 15 working days from the date the results of the Biomedical research Ethics committee's review become available, Department of Science and Training shall finalize the dossier and give written notice of results to the Agencies, organizations, individuals having the candidate drugs, the Host institution.

3. Authorization
Within 15 working days after notification of results and completion of supplementary documents (if any), Department of Science and Training shall compile the dossier and submit to Minister of Health for authorization.

Chapter V
PHASES OF CLINICAL TRIAL ON DRUGS AND THE CONDUCT OF CLINICAL TRIALS

Article 18. Phases of clinical trials on pharmaceutical products, biological products

Phase 1:
a) Is the first phase of trials on of a new active ingredient or new formulations in humans (usually done in healthy volunteers).

b) Purpose of phase 1 trials: to establish a preliminary assessment of safety and a first outline of pharmacokinetic and pharmacodynamic profile of the active ingredient in humans.

c) Sample size: shall be considered carefully based on results of preclinical studies, sample size of 10-30 subjects.

Phase 2:
a) Is the phase with trials conducted on a limited number of patients.

b) Purpose of phase 2: to evaluate the therapeutic activity and to assess safety of the active ingredient in patients, to determine the appropriate dose ranges and regimens in order to provide an optimal therapeutic plan for clinical trial.

c) Sample size: a minimum of 50 subjects.

Phase 3:
a) Is the phase with trials conducted in larger number of patients. The conditions under which these trials are carried out should be close to normal conditions. These are often multicenter trials, of randomized, controlled design.

b) Purpose of phase 3: to determine the stability of the formulation, the short and long term safety, effectiveness of the active ingredient, to assess the overall therapeutic value, to investigate any frequent adverse reactions and explore any special features of the products.

c) Sample size: A minimum of 200 subjects.

Phase 4:

a) These are clinical studies performed after the drugs have been marketed. Study designs may vary but the same scientific and ethical standards as in pre-marketing phase shall apply. Purpose of phase 4: clinical trials at this phase are conducted on the basis of product characteristics under which the marketing authorization was granted and normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies.

c) Sample size: a minimum of 1,000 subjects.

Article 19. Phases of clinical trials on vaccines

1. Phase 1:
a) Is the first phase of small scale trials for the preliminary assessment of new vaccine's safety through information collected on tolerability of the vaccine. Phase 1 is usually performed on adult healthy volunteers, at low risk of infection and complications before it being administered on target recipients.
b) Phase 1 studies are usually open label, non-randomized with a placebo controlled group, can be done on different age and population groups to determine dose range, safety, vaccination schedule, method of delivery .

c) Live attenuated vaccine (virus or bacteria) capable of infecting recipients or contacts should be closely monitored on dosage, clinical signs of infection, immune response (immediate, early and late). Phase 1 trials can provide preliminary information on distribution, reversibility of toxic effects, communicability and the genetic stability of the vaccine strains.

d) Sample size: shall be considered carefully based on results of pre-clinical studies, sample size of 30-50 subjects.

2. Phase 2:

a) Is conducted after completion of phase 1 with results approved by the Ministry of Health Biomedical research Ethics Committee. Phase 2 trials aim to demonstrate the immunogenicity of the active ingredients, the safety of the vaccines tested on target population, to evaluate the immune response related to age, race, sex. These trials are of randomized controlled design.

b) For live attenuated vaccines, in addition to the monitoring of parameters specified in phase 1 trials, the presence and existence of antibody titer should be noted: neutralizing antibodies or cross agglutination antibodies or cell-mediated immunity and interactions impacting the immune system (e.g., interactions with pre-existing antibodies, other drugs concurrently taken).

c) Sample size: a minimum 200 subjects.

3. Phase 3:

a) Phase 3 trials are done on a large scale, multi-center to evaluate the protective effectiveness and safety of the immunogen of the vaccine in the target recipient.

b) Sample size: a minimum of 500 subjects.

4. Phase 4:

a) Phase 4 studies are conducted after the vaccines have been licensed for marketing. Phase 4 is considered as post licensing surveillance or post licensing studies with the purpose of determining adverse effects and monitoring the protective effectiveness after the vaccines have been used as per indications widely on in the community. Phase 4 can be performed to assess:

- The optimized conditions for the use of vaccines (optimal age for vaccination, concomitant use with other vaccines and other conditions).
- Protective effectiveness for at risk groups (elderly, immune compromised patients, people with certain diseases).
- Sustainability of effectiveness and long-term safety.

b) Sample size: a minimum of 10,000 subjects.

Article 20. Phases for clinical trials on oriental medicines, drugs made of medicinal materials

1. Phase 1:

a) Trials are often conducted on volunteers who meet the clinical trials' criteria for the purpose of determining safe dose range (highest strength dose is the dose that should cause no serious side effects), specifically:

b) The starting dose administered must be equal to 1/3 - 1/5 of the dose predicted by preclinical studies. Multiple smaller doses may be administered in the interval between the starting and the highest strength dose. This phase ends once the safe dose has been determined.

c) Sample size: shall be considered carefully based on results of pre-clinical studies, sample size of 10-30 subjects.

2.Phase 2:
a) These trials are to evaluate the safety and efficacy of the drugs and should be of randomized controlled design with a minimum of 25 subjects in each group.

b) Therapeutic dose: doses used in this phase must be based on phase 1 studies' results.
c) Sample size: a minimum of 50 subjects.

3. Phase 3:
a) To validate the safety and effectiveness in extended conditions. Study subjects were assigned by randomized controlled or self controlled method.
b) Sample size: a minimum of 100 patients.

4. Phase 4:

a) Provisions for Pharmaceutical drugs apply.
b) Sample size: a minimum of 200 patients.

Article 21. Multicenter clinical trials

1. When conducting trials at different sites, the Host institution shall establish a joint steering committee comprising of one Principal investigator and principal investigators from other branches (?) and representatives of lead research institutions (?) in order to reach agreements on the trial's objectives, content, evaluation criteria, plans and timelines.

2. For supranational clinical trials of which Vietnam is a participant, procedures shall be in strict compliance with provisions of this Circular. Objectives and contents of the trials conducted in Vietnam, joint study activities conducted in conjunction with other countries shall be detailed in the trial protocol.

Article 22. Objectives, contents and sample size

Minister of Health shall decide on specific objectives, content, sample size for clinical trials as stipulated in Article 18, 19, 20 and 21 of this Circular based on the advice of the Ethics Committee for biomedical research specific to each dossier, trial protocol.

Article 23. Handling adverse events during the clinical trial

Procedures for handling untoward events in the course of the trials are as follows:

1. In case a serious adverse event occurs threatening the life of trial subject(s) the Investigator and Host institution shall discontinue the trial on the subject immediately, take rescue actions, overcome and resolve the consequences, document the events, and expedite reporting to local Ethics committee, Ministry of Health Ethics committee, Department of Science and Training.

2. In case of trials causing injury to or compromising the subjects' health, the Principal investigator shall suspend the trial for the treatment of the subject's condition and monitor its development and make judgment as to continue or discontinue the clinical trial.

3. In the occurrence of untoward events which were anticipated and for which measures to overcome have been effectively adopted, the clinical trials shall continue.

Article 24. Information and data collection

1. Information which is derived from the course of the trials shall be recorded in the case report form (CRFs). Case report form shall be considered as source documents, be kept and archived in accordance with applicable regulatory requirements, and forms the basis for monitoring, evaluation for acceptability of the trials' results.

2. Relevant documentation necessary for clinical assessments (lab tests' results, diagnostic images, prescriptions) shall be copied from the original, clearly marked with the full name of the cross checking person (?), and its source, and shall be managed, stored in accordance with applicable regulatory requirements.

Article 25. Data processing

1. The trial data shall be processed using biostatistical methods and by an agency, organization which is independent from the Host institution to ensure objectivity, integrity and reliability.

2. Results of statistical analysis shall be clearly presented to facilitate the interpretation of differences in clinical outcomes; the evaluation of therapeutic value shall be based on confidence intervals and results obtained from statistical analysis. The final report of the clinical trials shall be consistent with the results of statistical analysis.

Article 26. Archiving of clinical trial records

1. Data, source documents, lab test results, diagnostic images, trial-related documentation gathered, minutes of committee meetings, monitoring records, progress reports, registration documents and other documents related to the clinical trial shall be preserved, retained at the research facilities for at least 15 years from the date of completion of the trials.

2. The Principal investigator shall be responsible for the whole process of preserving and archiving of documentation pertinent to the clinical trials and for making them available upon request of the inspection, supervision teams and competent regulatory agencies.

Article 27. Reports of the clinical trial results

1. Reports of the clinical trial results shall be made in compliance with the prescribed template (Appendix 7, of this Circular), containing full information on the drugs, describing the research methods, the trials' processes, data analysis, results evaluation, in comparison with the trial objectives and purposes, providing accurate conclusions, unbiased and objective. Contents of the report must be consistent with the trial objectives and contents outlined in the approved trial protocol.

2. The Principal investigator shall be responsible for the scientific soundness, accuracy and integrity of

data, findings, observations and other contents of the report.

Article 28. Management of investigational drugs

1. The export, import of investigational drugs shall be in compliance with current regulations on importation and exportation of drugs.

2. The management of investigational drugs shall be conducted in accordance with current regulatory requirements from sampling, quality testing, packaging, transportation, delivery, storage, labeling to distribution.

3. A journal shall be maintained to track the use of investigational drugs, along with information on drugs quantity, quality.

4. Unfinished drugs and drugs in storage shall be managed stringently, kept separated and preserved in accordance with relevant regulatory requirements. Unused drugs shall be handed over to the Agencies, individuals having the candidate drugs.

5. Minutes of disposition shall be prepared for drugs which do not meet quality standards in accordance with Ministry of Health's requirements.

6. Drugs samples (03 smallest packaged units) shall be preserved at the Host institutions' site for a minimum 3 years (36 months) from the termination of the trials.

Chapter VI
RIGHTS AND OBLIGATIONS OF TRIAL SUBJECTS, INDIVIDUALS (?) HAVING THE CANDIDATE DRUGS AND HOST INSTITUTIONS

Article 29. Rights of Trial subjects

1. Be provided with complete and truthful information before the trial about the trial process and possible associated risks that may occur.

2. Be compensated by the Agencies, organizations, individuals having the candidate drugs for any damages suffered, if these are caused by the trial.

3. Have confidentiality of pertinent personal information safeguarded.

4. Bear no liability when unilaterally withdraw him/herself from participating in the trials.

5. File complaints, denunciations against the Organizations, individuals having the candidate drugs and Host institution for their acts of law infringement.

6. Be provided with medical care during the trials in accordance with the approved trial protocol.

Article 30. Rights of Agencies, organizations, individuals having the candidate drug(s)

1. Select and propose entities meeting the trial requirements with respect to premises, facilities and qualified personnel for the conduct of the clinical trial.

2. Have ownership of all the trial results on the drug(s).

3. Have the right to terminate the trial if the Host institution is in serious breach of the trial protocol.

Article 31. Obligations of agencies, organizations and individuals having the candidate drug(s)

1. Apply and be granted with an Authorization by the Ministry of Health before initiating the trials.

2. Compensate trial subjects for damages suffered if these are caused by adverse events during the trial in accordance with relevant regulatory requirements.

3. Sign contract with the Host institution or the clinical research organization (if any) for the conduct of clinical trials

4. Be responsible before law for the safety and quality of drugs supplied by them.

Article 32. Rights of Host institutions

1. Be supplied by Agencies, organizations and individuals having the candidate drugs with investigational drugs and funding for the conduct of clinical trials in accordance with the law.

2. Be allowed to make use of the trial results in accordance with agreements with the Agencies, organizations, individuals having the candidate drugs.

Article 33. Obligations of Host institutions

1. Comply with the standards of Good clinical practice for trials on drugs, submit to Ministry of Health reports on trial progress, results and ad hoc reports as need be.

2. Sign contracts for the conduct of the clinical trial with Agencies, organizations, individuals having the candidate drugs and Trial subjects.

3. Continue to monitor trial subjects' health conditions as agreed in the contract and outlined in the trial protocol.

Chapter VII
SUPERVISION AND INSPECTION FOR QUALITY ASSURANCE OF CLINICAL TRIALS

Article 34. Supervision of the conduct of clinical trials

1. Supervision and inspection shall be performed to ensure the protection of rights, interests and well being of trial subjects, the complete, accurate, timely recording of trials' data in accordance with the approved trial protocol.

2. Ministry of Health shall establish supervision team for periodic inspections and ad hoc inspection in specific cases.

3. Competent state authorities, Agencies, organizations, individuals having the candidate drug(s), Clinical research organizations (CRO) or Site management organizations (SMO) with written approval by the Ministry of Health, may assign personnel for the monitoring, supervision of the clinical trial process in a systematic manner. Person(s) assigned to the supervision function shall not be member of the research team, shall adhere strictly to requirements on confidentiality of trial data and information pertinent to the trial subjects and be responsible before law for his/her performance.

4. The Principal investigator and participating investigators shall be responsible for the facilitation of inspectors' direct access to trial data when required.

5. The supervision, inspection teams shall be responsible for the inspection, documentation, recommendation to competent state authorities for the latter to take appropriate action in accordance with the law.

Article 35. Ensuring credibility of the clinical trial results

1. To ensure the clinical trial's credibility of trials, analysis, findings and conclusions shall derive from raw data. All clinical data and lab test values shall be verified at every phase of the trials.

2. When necessary the evaluation board of different levels may invite expert evaluator for the evaluation of results, data verification, inspection of trial products or establish Data and Safety Monitoring Board (DSMB) as required by regulatory agencies.

Chapter VIII
FINAL EVALUATION OF THE CLINICAL TRIAL RESUTLS

Article 36. Procedures for evaluation for acceptability of clinical trial results

1. Final evaluation for acceptability of clinical trial results shall be performed in accordance with the relevant regulatory requirements on acceptability evaluation for science and technology research projects and good clinical practice for trials on drugs.

2. The evaluation shall be conducted at two levels: the local level and Ministry of Health level. At the end of the trials, the Principal investigator shall be responsible to report to the Host institution for the latter to conduct the local level evaluation and compile a final report to Ministry of Health for the acceptability evaluation at ministerial level.

Article 37. Dossier for the Ministry of Health's acceptability evaluation

Dossier for the ministerial acceptability evaluation (01 original, legally signed, and 03 copies), including:

1. Official note from the Host institution requesting the ministerial acceptability evaluation.

2. Copy of the approved trial protocol.

3. Decision of approval of the trial protocol.

4. Decision for the establishment of the local acceptability evaluation board.

5. Minutes of the local acceptability evaluation board meeting.

6. Full-text report of the clinical trial results in accordance with regulatory requirements with possible supplementary documents as deemed appropriate.

Article 38. Completion of clinical trials

1. Within 30 working days from the date of receipt of the complete dossier requesting for the acceptability evaluation, Ministry of Health shall convene an acceptability evaluation board meeting in accordance with relevant regulatory requirements.

2. Clinical trials shall only be deemed complete after the final report of the trials has been evaluated for acceptability and any supplementary documents submitted by the Principal investigator at the request of the Board's member have been accepted.

3. Data and results of the clinical trials shall only be published after approval by Ministry of Health Biormedical research Ethics committee.

Chapter IX

IMPLEMENTATION

Article 39. Responsibility for implementation

The Department of Science and Training shall lead and coordinate with the relevant departments, divisions to

1. Receive and review registration dossiers, provide guidance to Organizations, individuals having the candidate drugs for the implementation of this Circular in compliance with its provisions and those of other relevant regulations.

2. Conduct appraisal of the conditions for clinical trials applied for in the dossiers, personnel's technical qualifications, premises and facilities and the legality of the Host institutions, the Contract research organizations, Site management organizations and report to the Ministry's leadership for the granting of an authorization for the conduct of the clinical trials.

3. Organize Ministry of Health Biomedical research Ethics committee meetings to review the trial protocols, consider the ethical aspects of the studies and in the relevant science, evaluate the trial result for acceptability and submit its recommendations to the Ministry leadership for approval.

4. Provide supervision, conduct periodic or ad hoc inspection of the trial processes.

5. Disseminate the contents of this Circular, provide implementation guidance to pertinent agencies, organizations, individuals, ensure their compliance with guidelines of good clinical practice for trials and ethical standards in biomedical research.

Article 40. Transitional provisions

Dossiers for the registration of clinical trials on drugs submitted before the effective date of this Circular shall be reviewed and evaluated in accordance with the "Regulations on clinical trials" issued by Decision No. 01/2007/QD -BYT dated 11/01/2007 of the Minister of Health.

Article 41. Effective date

1. This Circular shall take effect from the date of 20th March 2012.

2. Decision 01/2007/QD-BYT dated 11 January 2007 for the promulgation of the "Regulations on clinical trials" shall be rescinded from the effective date of this Circular.

Should issues arise during the implementation process please report promptly to the Ministry of Health for revision, supplementation as appropriate./.

MINISTER OF HEALTH

NGUYEN THI KIM TIENG

Recipients:
- The Government Office (Official Gazette, Electronic Portal CP);
- Ministries, ministerial-level agencies;
- Ministry of Justice (Bureau of Inspection of legal documents);
- Ministry of Science and Technology (Legal Department);
- Deputy Ministers of Health;
- People's Committees of provinces and cities under central authority;
- Departments of Health of the provinces and cities under central authority;
- Hospitals under the Ministry of Health, Medical facilities of Ministries and line agencies;
- Departments, Divisions, General departments, Office of the Ministry, the Inspectorate of the Ministry - Ministry of Health;
- Ministry of Health Electronic Portal;
- For file: VT, PC, K2DT. ¬