

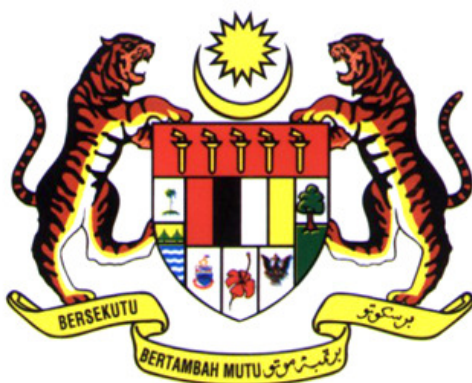


GUIDELINES FOR APPLICATION OF CLINICAL TRIAL IMPORT LICENCE AND CLINICAL TRIAL EXEMPTION IN MALAYSIA

**National Pharmaceutical Control Bureau
Ministry of Health
Malaysia**

Fifth Edition

June 2009



Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption in Malaysia

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FOREWORD

Since the last update of the Guidelines for the Application of Clinical Trial Import License (CTIL) and Clinical Trial Exemption (CTX) in Malaysia in 2004, there has been significant changes in regulatory environment for clinical trial. Thus, it is timely and appropriate to streamline the existing guidelines in accordance with the current needs, regulatory requirements and international standards.

The significant changes in this guideline amongst others include changes in the format of the guidelines, application forms for CTIL and CTX, reporting of serious adverse events, pharmaceutical data requirements for herbal products (Annex B1), responsibility of license holders, conditions for CTIL / CTX, labelling requirements, guidance for the application of variation, processing fee for CTIL renewal and product accountability and disposal. The updated guidelines shall assist sponsors, contract research organisations (CROs), local investigators and others in their applications for CTIL/ CTX. Adherence to these updated guidelines will facilitate the CTIL/ CTX applications leading to timely approval by the Drug Control Authority.

I would like to take this opportunity to extend my deepest appreciation to all the committee members who have contributed in one way or another to making this 5th edition of the guidelines (June 2009) a reality. It is my hope that with these guidelines will further contribute towards strengthening and promoting Malaysia as a clinical trial hub in this region.

Selvaraja Seerangam

Director of Pharmacy Regulatory
National Pharmaceutical Control Bureau
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June 2009

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GLOSSARY

Accuracy

The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

This is sometimes termed trueness.

Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. The relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function.

Adverse Event (AE)

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 (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

CIOMS Form

A form for reporting ADR according to The Council of International Organisation for Medical Science.

Clinical Trial Exemption (CTX)

An approval by the DCA authorising the applicant to manufacture any local product for the purpose of clinical trial.

Clinical Trial Import Licence (CTIL)

A license in Form 4 in the schedule of The Control of Drugs and Cosmetics Regulations of 1984, authorising the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial/Study Report

A written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

Comparator (Product)

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

Contract

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

Contract Research Organisation (CRO)

A person or an organisation (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Controlled Product

Scheduled Poisons and Psychotropic substances.

Detection Limit

The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

Drug Control Authority (DCA)

A regulatory authority established for the purpose of regulating the Control of Drugs and Cosmetics Regulations, 1984.

Drug

Includes any substance, product or article intended to be used or capable, or purported or claimed to be capable, of being used on humans or any animal, whether internally or externally, for medicinal purposes.

Good Clinical Practice (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.

Herbal/ Animal Medicinal Products

Plant/animal-derived materials or products with therapeutic or other human health benefits which contain either raw or processed ingredients from one or more plants/animals.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

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.

Inspection

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

Institution (medical)

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

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non-scientific members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Interim Clinical Trial/Study Report

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

Investigational Product

A pharmaceutical form of an active ingredient including herbal/ animal medicinal products or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

Linearity

The linearity of an analytical procedure is its ability (within a give range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

Manufacture

All operations of purchase of materials and products, production, quality control, release, storage, shipment (from storage related to manufacturing site) of finished products, and related controls.

Manufacturer

A company that carries out at least one step of production as well as the final release of the finished product.

Medicinal Purpose

Any of the following purposes;

- a. Alleviating, treating, curing or preventing a disease or a pathological condition or symptoms of a disease;
- b. Diagnosing a disease or ascertaining the existence, degree or extent of a physiological or pathological condition;
- c. Contraception;
- d. Inducing anaesthesia;
- e. Maintaining, modifying, preventing, restoring or interfering with, the normal operation of a physiological function;
- f. Controlling body weight
- g. General maintenance or promotion of health or well-being.

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.

Poison

Means any substance specified by name in the first column of the Poisons List and includes any preparation, solution, compound, mixture or natural substance containing such substance, other than an exempted preparation or an article or preparation included for the time being in the Second Schedule.

Product

- a. a drug in a dosage unit or otherwise, for use wholly or mainly by being administered to one or more human beings or animals for a medicinal purpose;”
- b. a drug to be used as an ingredient for a preparation for a medicinal purpose; or
- c. a cosmetic

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Quantitation Limit

The quantitation limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/ or degradation products.

Registered (=Approved) Product

Product being approved by the DCA

Repeatability

Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

Reproducibility

Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardisation of methodology)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Specificity

Specificity is the ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: to ensure the identity of an analyte.

Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, i.e. related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency):

To provide an exact result which allows an accurate statement on the content or potency of the analyte in a sample.

Sponsor

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

Trial Site

The location(s) where trial-related activities are actually conducted.

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 characteristics for an authorised product).

Unregistered Product

Any product which is not registered in Malaysia by the DCA.

SECTION I

1. INTRODUCTION

The guidelines outlined in this booklet are primarily drawn in accordance to the legal requirement of the Control of Drugs and Cosmetics Regulations 1984, Sale of Drug Act 1952 and Poisons Regulation (Psychotropic Substances) 1989 where controlled substances are involved.

2. PRODUCTS THAT REQUIRE CLINICAL TRIAL IMPORT LICENCE (CTIL) / CLINICAL TRIAL EXEMPTION (CTX)

Prior to importation/manufacturing product locally, the Principal Investigator or sponsor is required to apply for CTIL/CTX from the Drug Control Authority (DCA). The following products will require a CTIL/CTX:

- 2.1 Products including placebo which are not registered with the DCA and are intended to be imported for clinical trial purpose.
- 2.2 A product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for unapproved indication or when use to gain further information about an approved use.
- 2.3 An unregistered product manufactured locally for the purpose of the clinical trial.

3. APPLICATION FORMALITIES FOR CTIL/CTX

3.1 Who can apply for CTIL/CTX?

- 3.1.1 Any Principal Investigator (PI)
- 3.1.2 An authorised person from a locally registered pharmaceutical company (sponsor) with a permanent address in Malaysia.

Note:

- Application for CTIL/CTX containing a 'poison/ drug' should be made by a License A holder.
- The holder of a CTIL/CTX for a particular product need not necessarily conduct the clinical trial himself or herself.

3.2 Responsibility of the Applicant

3.2.1 The applicant shall be responsible for the product and all information supplied in support of his/her CTIL/CTX application for his/her product. He/ She shall be responsible for updating any information relevant to the product or application.

3.2.2 In case where the applicant is not the manufacturer and where secrecy considerations prevent disclosure of certain information to the applicant, such information may be furnished to the DCA through the applicant in a sealed envelope marked 'CONFIDENTIAL'.

3.2.3 Any person who knowingly supplies any false or misleading information in connection with his/ her application for CTIL/CTX commits an offence under the Control of Drugs and Cosmetics Regulations 1984.

3.3 Where to Apply

CTIL or CTX application should be submitted to:

Senior Principal Assistant Director
Clinical Research and Compliance Section
National Pharmaceutical Control Bureau
Ministry of Health, Malaysia
Lot 36, Jalan Universiti,
46200 Petaling Jaya.

3.4 Documents required in a new application for CTIL/CTX

3.4.1	<p>A complete application form signed by the applicant</p> <p>Application form for</p> <ul style="list-style-type: none"> • Clinical Trial Import Licence (Current Borang BPfK 442) or • Clinical Trial Exemption (Current Borang BPfK 443) <p>Note:</p> <ul style="list-style-type: none"> ▪ These application forms can be downloaded from our website: http://www.bpfk.gov.my.
3.4.2	Two copies of Application Submission Form, 'Borang Penyerahan Permohonan' (current Borang BPfK 001)
3.4.3	Two copies of Submission Checklist, 'Senerai Semak untuk Penyerahan Permohonan Lesen Mengimport/Permit Bagi Percubaan Klinikal' (current Borang BPfK 002)
3.4.4	<p>Processing Fee</p> <p>Please refer to Section 3.6.</p>
3.4.5	A copy of Company Registration Certificate
3.4.6	A copy of License A of the applicant (in case where a product containing a poison/ drug)
3.4.7	<p>Letter of Authorisation</p> <p>Note:</p> <ul style="list-style-type: none"> • Letter of Authorisation/ Agreement should be submitted to DCA in cases where; <ul style="list-style-type: none"> ○ Sponsor or a PI decide to use a service of CRO for the conduct of a clinical trial; or ○ The applicant is not the Sponsor or product owner. • Structure for Letter of Authorisation can be found in Appendix E.

3.4.8	<p>Approval Letter by Ethics Committee of the Institution(s) where the clinical trial is to be conducted.</p> <p>Note:</p> <ul style="list-style-type: none"> ▪ Ethics Committee of the Institution(s) must be registered with the DCA. ▪ The PI or sponsor is allowed to submit parallel applications to the DCA and the IEC. ▪ However, approval letter by the IEC should be submitted to the DCA as soon as possible when available. A CTIL/CTX will not be issued prior to IEC approval.
3.4.9	<p>Current copy of certificate of Good Manufacturing Practices (GMP) or a statement on GMP from the manufacturer and repacker.</p> <p>Note:</p> <ul style="list-style-type: none"> • Certificate of GMP must be issued by authority recognised by the DCA i.e. the authorities listed in the WHO 'Certificate Scheme on The Quality of Pharmaceutical Product Moving In International Commerce'. • Statement on GMP can be issued by the Quality Assurance department where the product is manufactured. • For local product, the manufacturing license is required. <p><i>For comparator product, the following is required:</i></p> <ul style="list-style-type: none"> • Certificate of GMP. If GMP certificate is not available, one of the following documents can be submitted: <ul style="list-style-type: none"> ▪ Approval letter from the regulatory authority ▪ Annual Registration of Drug Establishment ▪ Package Insert <p><i>For repacked product:</i></p> <ul style="list-style-type: none"> • certificate of GMP • If certificate of GMP is not available, statement of GMP must be submitted by repacker.

3.4.10	Study Protocol and amendments (Annex A) signed by PI
	Structure for Annex A can be found in Appendix A
3.4.11	Informed Consent form (Initial version only)
3.4.12	Pharmaceutical Data (Annex B) Note: <ul style="list-style-type: none"> ▪ Certificate of Analysis (CoA) of the recent, representative batch for the product. ▪ A sample of the label(s) for the imported products. ▪ Applicant must ensure labels of the products for clinical trial meet the Labelling Requirements, which can be found in Appendix D. ▪ Structure for Annex B can be found in Appendix B
3.4.13	Investigator Brochure (Annex C) Note: <ul style="list-style-type: none"> • Product particulars, data and supporting documentation sufficient to establish safety, efficacy and quality of Investigator Brochure (IB). • Structure for Annex C can be found in Appendix C.

The license holder shall inform the DCA of any changes in information, or any information received by him that casts doubt on the continued validity of the data which was submitted with or in connection with the application for the CTIL/ CTX.

3.5 Product Particulars, Data and Supporting Documents

No.	Particular	Notes
3.5.1	Annexes	<p>All applications for CTIL/CTX must be accompanied with the product particulars and data necessary for the evaluation of the product</p> <p>The product particulars and data shall be presented with supporting documentation in the form of Annexes (Please refer to Appendix A, B and C for the Structure of the respective Annexes).</p>
3.5.2	Presentation	<p>i. Compilation</p> <p>A content page should be provided.</p> <p>Each Annex shall be original copy and compiled with a label in a well-presented orderly manner.</p> <p>ii. Pages</p> <p>Every page of documents should be well annotated and numbered sequentially with separate series for each Annex.</p> <p>Drawings, tables, graphs etc must be appropriately captioned and referenced.</p> <p>iii. Binding</p> <p>Each copy of Annex shall be clearly separated.</p> <p>iv. Paper size</p> <p>A4 size paper.</p>
3.5.3	Language	<p>Application form, current Borang BPFK 442 and Borang BPFK 443 must be written in Bahasa Melayu or English.</p> <p>All other data, supporting documents, labels and package inserts can be in Bahasa Melayu or English.</p> <p>In cases where supporting documents is not originally in Bahasa Melayu or English, a copy of the document in its original language, accompanied by authenticated translation in Bahasa Melayu or English shall be submitted.</p>

3.6 Processing Fee

3.6.1 CTIL Application or Renewal

Every application for CTIL and CTIL renewal shall be accompanied with a processing fee. The fee is RM 500 per product.

3.6.2 CTX Application

Application for Clinical Trial Exemption is free of charge.

3.6.3 Mode of payment

The processing fee shall be paid in the form of bank draft/money order/postal order payable to '**Biro Pengawalan Farmaseutikal Kebangsaan**'.

Note: Foreign currencies are not acceptable.

The processing fee is not refundable

4.0 Processing of Application

Application for CTIL/ CTX shall essentially be complete in the first instances based on the Submission Checklist, which includes:

- i. Current application form, Borang BPFK 442 or Borang BPFK 443 duly completed and signed by the applicant
- ii. Study protocol and/or amendments (Annex A)
- iii. GMP certificate or statement for the manufacturers/ repacker
- iv. Pharmaceutical data (Annex B)
- v. Investigator's Brochure (Annex C)
- vi. Correct processing fee
- vii. 2 copies of the Application Submission Form (current Borang BPFK 001)
- viii. 2 copies of the Submission Checklist (current Borang BPFK 002)

Incomplete application will be rejected within 1 week of the submission date.

5.0 Decisions of the DCA

- The applicant shall be informed in writing of the decisions of the DCA.
- The DCA reserves the right to terminate the license if the licensee does not comply to regulatory requirements as specified in the Control of Drugs and Cosmetics Regulation 1984, Malaysian Good Clinical Practice Guidelines and CTIL/CTX Guidelines.

6.0 Guidance for the Application of Variation

Application of Variation includes: additional quantity of study medication(s), additional trial site(s), additional new product, additional manufacturer/ repacker, additional port of entry, change of applicant, extension of product's shelf life and new protocol.

Please include the following documents in every application of variation:

- a. A new application form using current **Borang 442**
- b. **Copies of CTILs** pertaining to the products

Following are the additional documents to be included for the application of variation:

No.	Variation Application	Documents Required
1	Additional Investigative Site	<ul style="list-style-type: none">• Study protocol signature page by the new site Principal Investigator• IEC Approval Letter
2	Change of Applicant	<ul style="list-style-type: none">• Applicant of the same company<ol style="list-style-type: none">a. Cover letterb. License A• Applicant of different company<ol style="list-style-type: none">a. Cover Letterb. License Ac. Company registration certificated. Letter of Authorisation

No.	Variation Application	Documents Required
3	Additional strength	<ul style="list-style-type: none"> Documents requirement as per application for a new product
4	Extension of Shelf life	<ul style="list-style-type: none"> Stability data / CoA Memo to confirm extension followed by CoA
5	Additional or New Manufacturer/ Repacker	<ul style="list-style-type: none"> GMP Certificate or Statement of GMP compliant
6	New Protocol	<ul style="list-style-type: none"> Annex A Study protocol signature page by the site Principal Investigator IEC Approval letter
7	CTIL Renewal	<ul style="list-style-type: none"> Processing Fee <p>Please refer to section 3.6 for more information.</p>

7.0 Conditions for CTIL/CTX

The license holder shall submit to the DCA a copy of endorsed CTIL/CTX (including Borang A) and/or evidence of delivery to the approved investigator(s)/ Trial centre(s) on importation and supply of each consignment of the product at the end of each study.

Product shall only be supplied to the investigator(s) at the trial centre(s) named in the application for the CTIL/CTX for the purpose and use as stated in the said application. No change in investigator, trial centre or trial protocol shall be made without notification to the DCA.

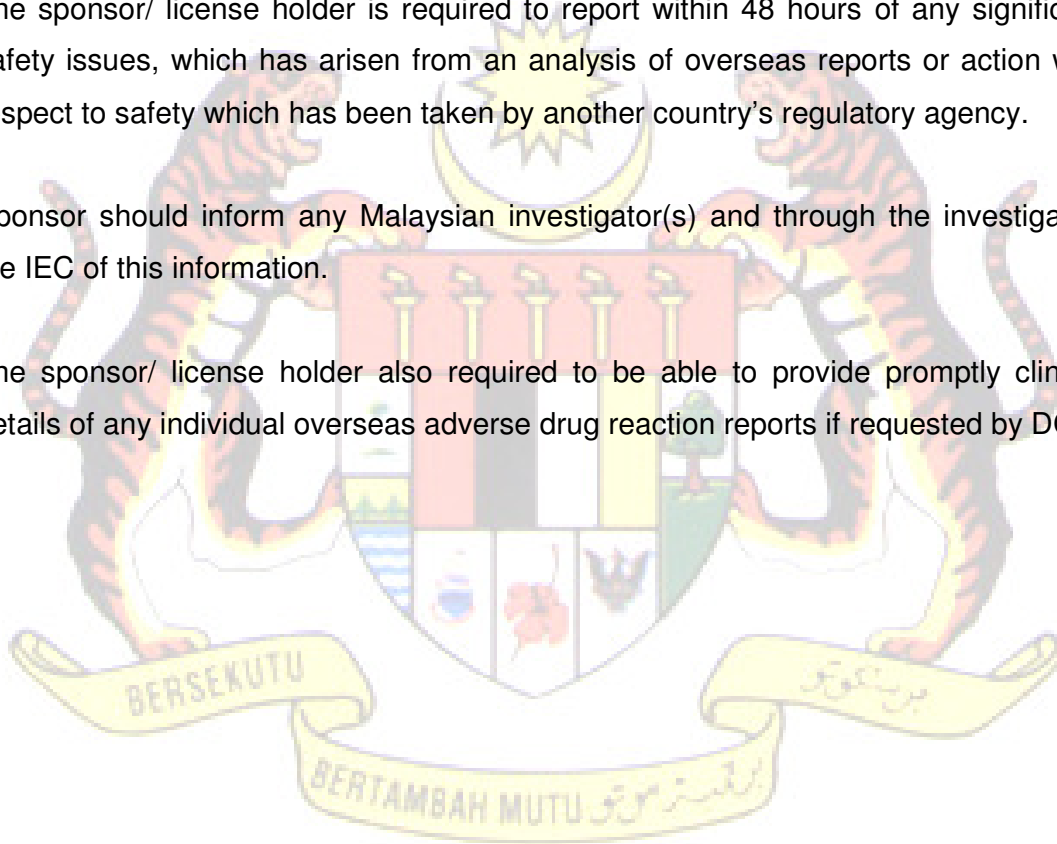
The license holder shall ensure that adequate precautions are taken for all study medication(s) such as storage in securely locked cabinet, access to which is limited to prevent theft or illegal distribution.

8.0 Safety Decision Arising from Report Analysis / by Other Regulatory Authority

The sponsor/ license holder is required to report within 48 hours of any significant safety issues, which has arisen from an analysis of overseas reports or action with respect to safety which has been taken by another country's regulatory agency.

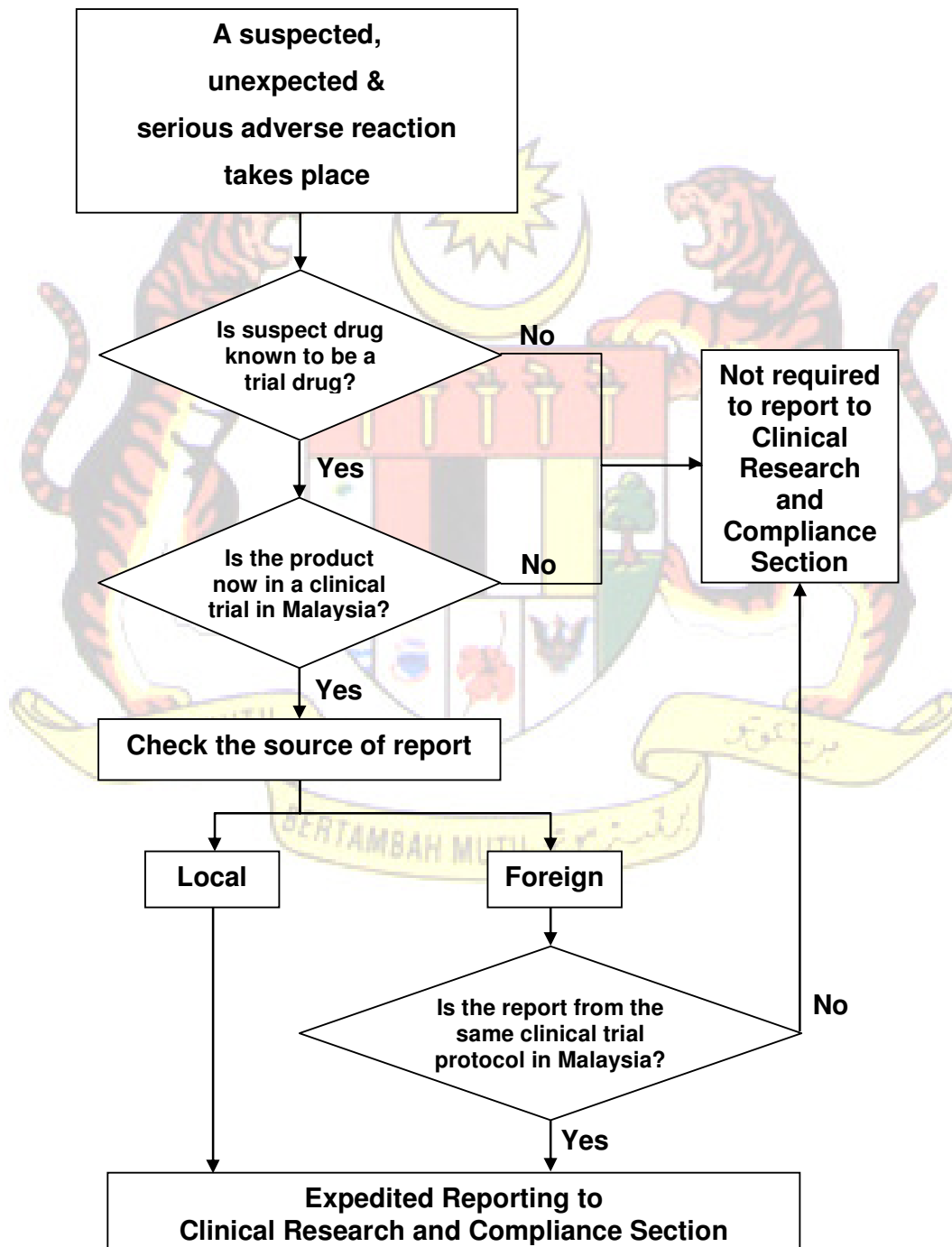
Sponsor should inform any Malaysian investigator(s) and through the investigator, the IEC of this information.

The sponsor/ license holder also required to be able to provide promptly clinical details of any individual overseas adverse drug reaction reports if requested by DCA.



9.0 Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

9.1 Flow Chart of Safety Reporting Process Arising for Drugs involved in Clinical Trial Malaysia



9.2 How to Report

The CIOMS-I form (Appendix H) is a widely accepted standard for expedited adverse reaction reporting. However, no matter what the form or format used, it is important that certain data elements described in Appendix I, when available, be included in any expedited report (although some items may not be relevant depending on the circumstances).

Please refer to Appendix J for a summary of the safety reporting requirements for clinical drug trials to the Clinical Research and Compliance Section.

The expedited safety reports should be submitted to the Clinical Research and Compliance Section in printed copy or via e-mail to saeclinicaltrial@bpfk.gov.my with effect from June 2009.

Sample of cover letter for submission of the expedited safety reports in Appendix K is preferable, and should be standardised as follows:

- A cover letter is required for each submission.
- Only expedited safety report(s) from a same clinical trial protocol to be submitted with a cover letter.

In addition, reports for electronic submission should be compiled as following:

- The file type of the expedited safety report(s) attached to the email should be a *PDF* file.
- All cases of expedited safety report(s) can be compiled in a *PDF* file, however the reports should be separated accordingly to local and foreign expedited safety reports in two different *PDF* files.

For expedited safety reports sent in printed copy, an acknowledgement of receipt shall be made upon submission, whereas for expedited safety reports sent by email, an acknowledgement of receipt will be sent by email.

10.0 Reporting Change of information

10.1 Supplementary Data/New Information Updates

Any new information available for the product, which involves adverse events, changes in formulation, manufacturer for the active ingredients or finished products, Investigator's Brochure updates and change in PI must be reported to the DCA.

The DCA must be immediately informed after IEC approval should there be changes to the following:

- Protocol amendments
- Additional Trial Sites

The DCA may request for further supplementary data or documentation when appropriate.

11.0 Interim Report

In cases of trials lasting for more than six months, an interim report shall be submitted at six-monthly intervals. The interim report shall include briefly number of patients treated, number of Serious Adverse Events (SAE) reported, number of discontinued patients post-randomisation and the reason of discontinuation, progress of trial and any findings obtained up to the time of the report.

Please refer to Appendix F for the format of an Interim Report.

12.0 Discontinuation of Trial

The license holder shall inform the DCA of any decision to discontinue the trial to which the license related and shall state the reason for the decision.

The license holder should return the CTIL/ CTX as soon as possible.

13.0 Trial Termination

13.1 End of Study Summary Report

- The CTIL or CTX license holder shall submit an End of Study Summary Report pertaining to the sites conducting the trial to the DCA, **within 3 months from the Last Patient Out (LPO) / Last Patient Last Visit (LPLV)**.
- In cases of a multi-centre trials and the study is completed at different time frame for each site, an End of Study Summary Report should be submitted within 3 months from site closure.
- Please refer to Appendix F for the format of an End of Study Summary Report.

13.2 Final Study Report

- The DCA shall be informed on the trial findings shall be submitted **within 1 year after the completion of the whole trial** or within 1 year from frozen file or data lock date for International multi-centre studies.
- The DCA shall be informed of any possible delay in submission of the report particularly where the delay is unavoidable as in multi-centre studies.
- Please refer to Appendix G for the structure of a Final Study Report.

13.3 Drug Accountability Report and Disposal

- A product Accountability/ Disposal report shall be submitted to DCA **within 3 months** from the site closure.
- The report should include:
 - Original or copy of CTIL/CTX
 - Borang A for the relevant site
 - Date(s) and quantity received for each product.
 - Balance of the study medication(s)
 - Letter for additional quantity
- **Disposal**
 - Confirmation on the appropriate local drug supplies disposal, and/or return to the used/ unused drug supplies to country of origin or regional depot.
 - For local disposal, all investigative products should be disposed by the authorised bodies/ authority and documented.

14. Archiving

It is responsibility of the investigator and the sponsor to archive safely all the documents related to the trial.

15. INSPECTION/AUDIT BY THE REGULATORY AUTHORITY

An inspection/auditing of clinical trial site may be conducted by the regulatory authority. The aim is to evaluate the acceptability of clinical data submitted to the DCA, and to ensure that legislation, Good Clinical Practice (GCP) principles and the Declaration of Helsinki are complied with. The authorised officer of the regulatory authority may contact the PI or sponsor for the date of inspection when required.



SECTION II: **GUIDELINES ON ANNEXES**

INTRODUCTION

1. Section II comprises recommended formats for Annexes A, B and C.
2. Details of particulars and supporting documentations should be enclosed as specified.

Failure to enclose necessary details and supporting documents may result in delay in the processing, or rejection of an application.

3. Headings set out for each Annex are minimum general requirements. These may not be applicable in all circumstances, neither are they exhaustive.

Interpretation of these guidelines should be flexible and related to the nature and proposed use of the product.

4. Where a heading is not applicable or information is not available, indicate clearly in the appropriate sections.
5. Data in addition to those specified in the guidelines may be submitted to support the application for import licence for clinical trial / clinical trial exemption. Such data must be presented in a well compiled manner, with a summary of the particulars.
6. These guidelines do not preclude any other information required by the Drug Control Authority (DCA). Such additional information should be supplied to the DCA on request.

Appendix A

ANNEX A: FORMAT FOR CLINICAL STUDY PROTOCOL

Note: The protocol should contain the following particulars, where applicable.

1. Name and Dosage form of Product

- State the **name or code number** under which the product will be imported and known during the trial or study
- State clearly the **pharmaceutical dosage form** of the product e.g. tablet, capsule, injection, etc

* A separate application is required for each trial.

2. Title of the Trial

3. Objective(s) of the Trial

- State the specific objective(s) and rationale of study or trial

4. Description of the Trial Design

- State
 - **Type** of the trial, e.g. controlled, open-labelled
 - **Trial design**, e.g. parallel group, cross-over technique
 - **Blinding technique**, e.g. double-blind, single-blind
 - **Randomisation** method and procedure
- State **total number of subjects** involved to achieve the trial objective(s) based on statistical consideration (sufficient to allow drop-out, variability effect, etc.)

5. Description of trial Subjects

- **Inclusion and exclusion criteria** of potential trial subjects and process of recruitment types, methods and allocation time of subjects.

Appendix A

6. Treatment profile

- State the **dose**: including justification for route of administration, dosage, dosage interval and treatment period for pharmaceutical product being tested and the product being used as a control.
- State previous treatment, **concomitant treatment** may be permitted or give, or subsequent therapy, if any.
- **Washout period**, where applicable.

7. Study Parameters

- **Indices, variables**, etc. that were selected for measuring parameter under study (effect, reactions etc.)
- **Methods of measurements & assessment of observations** including details of measuring techniques, assessment, qualification of response, clinical and laboratory tests, pharmacokinetic analysis, etc.
- **Rationale** for choice of indices, variables and their methods determination specificity, sensitivity and the precision of the method selected.

8. Operational Aspects

- Information on the establishment of the trial code where it will be kept and when, how by whom it can be broken in the event of an emergency.
- Measures to be implemented to ensure the safe handling and storage of pharmaceutical products.

9. Adverse Event

- Methods of recording and reporting adverse events/ reactions, provisions for dealing with complications.

10. Evaluation of Results

- Description of methodology on evaluation of results, (e.g. statistical method) and on the report on patients/ subjects withdrawn from the trial.

11. Name of the Principal Investigator

- Designation of Principal Investigator

Appendix B

ANNEX B: FORMAT FOR PHARMACEUTICAL DATA ON DOSAGE FORM

Note: This is the recommended format for Annex B for individual drug. Spacing should be adjusted by applicant where necessary. Extension sheets for details and supporting documents should be numbered and referenced appropriately.

Product:

Ref:

1. Finished Product

- Description (Physical Characteristics)
- Composition (Complete Formula)
 - Active Ingredient(s)
 - Name of Active Ingredient(s)
 - Other Ingredient(s), e.g. adjuncts, excipients, preservative, colour, flavor, etc.
 - Name of other ingredient(s)
 - Packing/Pack Size (brief)

2. Manufacture of Product

Note: If desired, enclosed in sealed envelope marked 'CONFIDENTIAL'.

- Complete Batch Manufacturing Master Formula
 - Name of Ingredients (Active and otherwise)
- Manufacturing Process
 - Brief Description and Principles

3. Quality Control

- State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.
- If quality control tests are done by an external laboratory, state
 - Name and address of the laboratory
 - Tests done by the external laboratory
 - Reasons why the tests are not done by the manufacturer

Appendix B

- Specifications for Ingredients, Active and otherwise

Example:

Name of Ingredients	Specifications (State whether derived from B.P or U.S.P or Manufacturer's)	Source (Manufacturer & Country of Origin)
---------------------	---	--

- In-process Quality Control
 - Tests performed during manufacturing process and sampling protocols.

Example:

Tests	Stages at which test is done	Frequency of Sampling	Quantity of sample taken each time
<ul style="list-style-type: none"> • Finished Product Quality Control <ul style="list-style-type: none"> ○ Tests and Specification Limits (Check and Release Specifications) 	Acceptance Limits	Release for Test Method and Limit (B.P/ U.S.P/ Manufacturers/ etc)	Test
<ul style="list-style-type: none"> ○ Certificate of Analysis (CoA) must be certified by Quality Assurance Manager. CoA for the recent batch should be submitted (minimum of 1 batch) 			

4. Stability of Product

- **Storage condition** to be included on the label
- **Proposed Shelf life**
 - In the events if the extension of shelf life for clinical trial materials is required, industry will provide supportive data in the form of retest results will be considered.
- **Stability Studies**
 - Completed stability studies/ accelerated stability studies (Summary of stability studies, characteristic and degradation products monitored results and conclusions of completed stability studies).
 - Stability studies results of at least one batch are required.

Appendix B

- On-going/ Proposed Stability Studies
 - Outline of on-going or proposed stability studies

*Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

5. Containers/ Packaging

- **Immediate containers/ packaging**
 - Type
 - Material
 - Capacity, where applicable
 - Closure and liner (type and material), where applicable
- **Other container(s)/ packaging(s)**
- **Dose-measuring device/ applicators/ administration set/ etc., if any**
 - Description/ Type
 - Material
 - Capacity, where applicable
- **Packaging inclusions (desiccant, filler, etc), if any**
 - Description and compositions
- Is there any known interaction between the product and packaging material?
[Yes /No]

6. Labelling

- Please refer to Appendix D
- Samples or proposed drafts of the following are required to be submitted:
 - Label(s) for immediate package/container of product
 - Label(s) for outer package/container of product
 - Original Package insert(s) for comparator drug

Appendix B1

ANNEX B1: FORMAT FOR QUALITY DATA ON HERBAL PRODUCTS

Note: This is the recommended format for Annex B1 for clinical trials involving herbal products with therapeutic claims. Spacing should be adjusted by applicant where necessary. Extension sheets for details and supporting documents should be numbered and referenced appropriately.

Product:

Ref:

1. Finished Product

- Description (Physical Characteristics)
- Composition (Complete Formula)
 - Active Ingredient(s)/ Standardised Extract(s)
 - Name of Active Ingredient(s) / Standardised Extract(s)
 - Other Ingredient(s), e.g. adjuncts, excipients, preservative, colour, flavor, etc.
 - Name of other ingredient(s)
 - Packing/Pack Size (brief)

2. Standardisation Of Extract

For Example:

The extract is standardised to contain:

- X% of compound A (assayed by e.g. HPLC, UV Spectrophotometry etc.)
- Y% of compound B (assayed by e.g. HPLC, UV Spectrophotometry etc.)

3. Manufacture of Product

Note: If desired, enclosed in sealed envelope marked 'CONFIDENTIAL'.

- Complete Batch Manufacturing Master Formula
 - Name of Ingredients (Active and otherwise)
- Manufacturing Process
 - Brief Description and Principles

Appendix B1

4. Quality Control

- State whether quality control is done in part or solely by the manufacturer's own quality control department or an external laboratory.
- If quality control tests are done by an external laboratory, state
 - Name and address of the laboratory
 - Tests done by the external laboratory
 - Reasons why the tests are not done by the manufacturer

4.1 Specifications of the Standardised Extracts

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers/ etc)
▪ Appearance		
▪ Qualitative Assay: <ul style="list-style-type: none"> ○ Chemical fingerprint 		
▪ Quantitative Assay		
▪ Loss on drying/Moisture		
▪ Solubility		
▪ Microbial limits <ul style="list-style-type: none"> ○ Total bacterial count ○ Yeast and mould ○ Salmonella ○ <i>E. coli</i> 		
▪ Heavy metal limits <ul style="list-style-type: none"> ○ Arsenic ○ Mercury ○ Lead ○ Cadmium 		
▪ Other Tests (if applicable)		

Certificate of Analysis for The Standardised Extracts need to be attached (**minimum of 1 batch**).

4.2 Method of Identification of Marker Compounds in the Standardised Extracts

4.3 Method of Analysis of Marker Compounds in the Standardised Extracts

- Both of the method used for identification and analysis need to be explained.

Appendix B1

4.4 Finished Product Quality Control

- Tests and Specification Limits (Check and Release Specifications)

Test/Criteria	Acceptance Limits/Specifications	Methodology (Manufacturers/ etc)
▪ Appearance (e.g. capsules/tablets)		
▪ Appearance of content		
▪ Quantitative Assay		
▪ Microbial limits <ul style="list-style-type: none"> ○ Total bacterial count ○ Yeast and mould ○ Salmonella ○ <i>E. coli</i> 		
▪ Heavy metal limits <ul style="list-style-type: none"> ○ Arsenic ○ Mercury ○ Lead ○ Cadmium 		
▪ Uniformity of Weight		
▪ Disintegration/Dissolution test		

- Certificate of Analysis (CoA) must be certified by Quality Assurance Manager. CoA for the recent batch should be submitted (**minimum of 1 batch**)

4.5 Validation of Analytical Method (Quantitative Assay of the Finished Product)

- Validation Reports need to be submitted
 - Contents of Validation Reports :
 - Introduction
 - Specificity
 - Repeatability
 - Reproducibility
 - Linearity
 - Accuracy
 - Detection Limit
 - Quantitation Limit
 - Conclusions

Appendix B1

5. Stability of Product

- **Storage condition** to be included on the label
- **Proposed Shelf life**
 - In the events if the extension of shelf life for clinical trial materials is required, industry will provide supportive data in the form of retest results will be considered.
 - **Stability Studies***Completed stability studies/ accelerated stability studies
(summary of stability studies, characteristic and degradation products monitored, results and conclusions of completed stability studies).
 - Stability studies results of at least one batch is required.
 - On-going/ Proposed Stability Studies
- Outline of on-going or proposed stability studies

*Stability studies must be carried out in accordance to ASEAN/ ICH Stability Studies Guidelines.

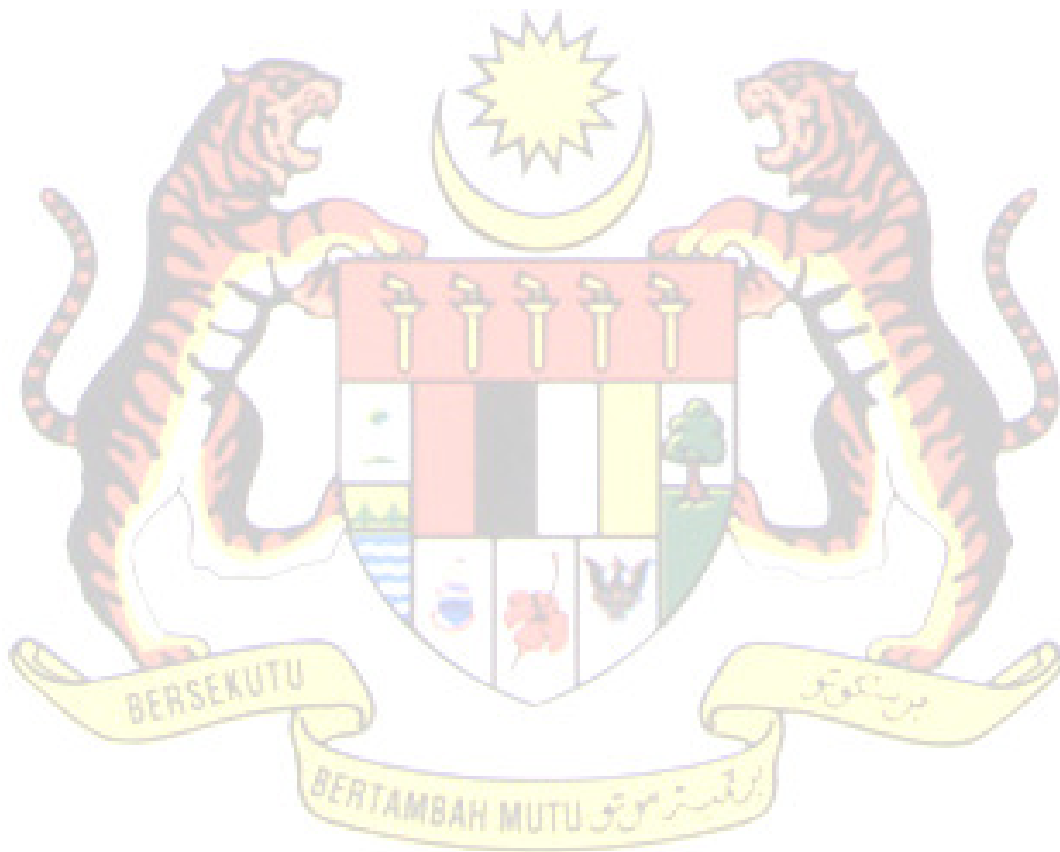
6. Containers/ Packaging

- **Immediate containers/ packaging**
 - Type
 - Material
 - Capacity, where applicable
 - Closure and liner (type and material), where applicable
- **Other container(s)/ packaging(s)**
- **Dose-measuring device/ applicators/ administration set/ etc., if any**
 - Description/ Type
 - Material
 - Capacity, where applicable
- **Packaging inclusions (desiccant, filler, etc), if any**
 - Description and compositions
- Is there any known interaction between the product and packaging material?
[Yes /No]

Appendix B1

7. Labelling

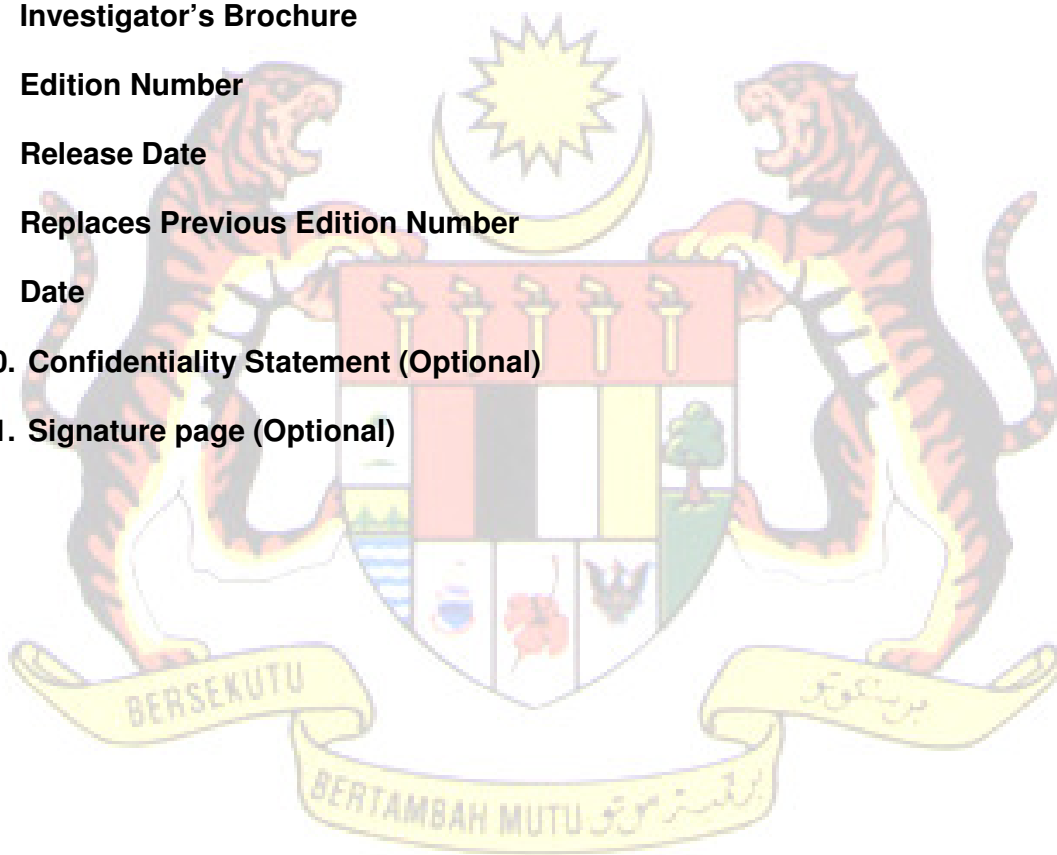
- Please refer to Appendix D
- Samples or proposed drafts of the following are required to be submitted:
 - Label(s) for immediate package/container of product
 - Label(s) for outer package/container of product
 - Original Package insert(s) for comparator product



Appendix C

ANNEX C: FORMAT FOR INVESTIGATOR'S BROCHURE

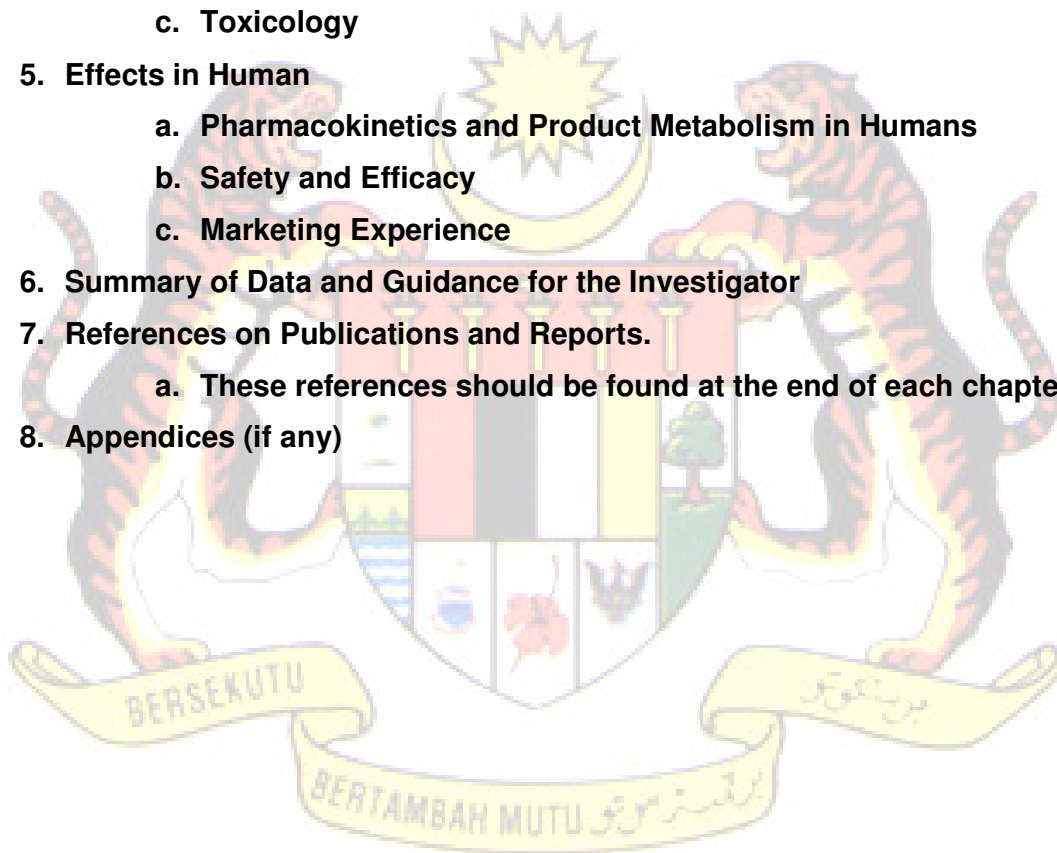
1. Title Page
2. Sponsor's Name
3. Product Name(s) – Chemical, Generic (if approved)
4. Trade Name(s) – if legally permissible and desired by the sponsor)
5. Investigator's Brochure
6. Edition Number
7. Release Date
8. Replaces Previous Edition Number
9. Date
10. Confidentiality Statement (Optional)
11. Signature page (Optional)



Appendix C

Investigator's Brochure Table of Contents

1. Summary
2. Introduction
3. Physical, Chemical and Pharmaceutical Properties Formulation
4. Non-clinical Studies
 - a. Non-clinical Pharmacology
 - b. Pharmacokinetics and Product Metabolism in Animals
 - c. Toxicology
5. Effects in Human
 - a. Pharmacokinetics and Product Metabolism in Humans
 - b. Safety and Efficacy
 - c. Marketing Experience
6. Summary of Data and Guidance for the Investigator
7. References on Publications and Reports.
 - a. These references should be found at the end of each chapter.
8. Appendices (if any)



Appendix D

LABELLING REQUIREMENTS FOR UNIT CARTON, INNER AND BLISTER/ STRIPS

The following information should present on the label of the products for clinical trial:

Parameters	Unit Carton/ Patient Kit	Inner Labels	Blister/ Strips
Study No./ Protocol	√	√	√
Visit	√**	√**	√**
Patient No./ Patient Initials	√	√*	√
Product Name/ Code	√	√	√
Dosage Form	√**	√**	NA
Name of Active Substance(s)	√**	√**	√**
Strength of Active Substance(s)	√**	√**	√**
Instruction for use	√	√*	√
Batch number	√	√	√
Expiry Date /Retest date	√	√	√
For Clinical Trial Use Only	√	√*	√
Name and address of manufacturer/ final release/ Product Owner (corporate address)/ Sponsor	√	√**	√**
Route of Administration	√	√	√
Storage Condition	√	√	NA
Pack Sizes	√	√*	NA
Sources of gelatin capsule (Porcine/ Bovine)	√**	√**	√**
Keep Out of Reach of Children	√	√**	√**

Please take note that if the product is supplied without an outer carton, the information that is required on the outer carton should be stated on the inner label.

NA Not Applicable

* Exempted for small label such as ampoule and vial

** Optional

Appendix E

**STRUCTURE OF
LETTER OF AUTHORISATION**

LETTER OF AUTHORISATION

Date:

.....
(Company's Name)

a company operating under the laws of, located in do
hereby authorise

Local Company's Name and Address

Tel no.:

Facsimile no.:

to represent us in Malaysia for the application of the Clinical Trial Import
Licence for :-

Title of the Clinical Trial :

Protocol No :

Release Date :

..... (Local company's name and address) is authorised to be the
Clinical Trial Import Licence Holder and will be responsible for all matters
pertaining to the Clinical Trial Import Licence for the above mentioned study
protocol.

Yours faithfully,

.....
(Responsible Signatures)

APPENDIX F

STRUCTURE OF INTERIM REPORT & END OF STUDY SUMMARY REPORT

Date:

Senior Principal Assistant Director
Clinical Research and Compliance Section
National Pharmaceutical Control Bureau
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor Darul Ehsan.

Dear <Insert Name>,

INTERIM/ END OF STUDY SUMMARY REPORT (whichever applicable)
<Title of the trial>, <Protocol Number>, <Name of trial site>, <Name of PI>

The following is a summary of the <Trial Title> trial conducted in <insert institution name>;

First Patient In (FPI): <insert date>

Last Patient In (LPI): <insert date>

Last Patient Out (LPO): <insert date>

Number of patients screened: <insert number>

Number of patients randomized: <insert number>

Number of patients discontinued: <insert number>

Reason of discontinuation: <List of individual discontinued patient>

Number of patients completed study: <insert number>

Number of Serious Adverse Events (SAEs): <insert number>

Number of patients reach study Endpoints: <insert number- if applicable, if not, to be removed>

Last batch of drug supplies collected back from site: <insert date>

Last batch of drug supplies sent back to <originating site> for destruction <insert date>

(Note: if drug are destruct locally, replace this with relevant information)

Thank you.

Best Regards,

<Insert Clinical Research Associate's Name>
Clinical Research Associate

APPENDIX G

**FORMAT FOR CLINICAL STUDY REPORTS
(ICH TOPIC E3, STRUCTURE & CONTENT FOR CLINICAL STUDY
REPORTS CPMP/ICH/137/95)**

(Please refer to Malaysia Good Clinical Practice Guidelines, Section 5.22)

- 1. Title page**
- 2. Synopsis**
- 3. Table of Contents for the Individual Study Report**
- 4. List of Abbreviations and Definition of Terms**
- 5. Ethics**
- 6. Investigators and Study Administrative Structure**
- 7. Introduction**
- 8. Study Objectives**
- 9. Investigational Plan**
- 10. Study Patients**
- 11. Efficacy Evaluation**
- 12. Safety Evaluation**
- 13. Discussion and Overall Conclusions**
- 14. Tables, Figures and Graphs referred to but not included in the text**
- 15. Reference List**
- 16. Appendices**

APPENDIX H

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT												

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
7 + 13. DESCRIBE REACTION(S) (including relevant tests/lab data)										<input type="checkbox"/> PATIENT DIED <input type="checkbox"/> INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION <input type="checkbox"/> INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY <input type="checkbox"/> LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUG? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)		
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)		
From/To Dates	Type of History/Notes	Description

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE <input type="checkbox"/> STUDY <input type="checkbox"/> LITERATURE <input type="checkbox"/> HEALTH <input type="checkbox"/> LITERATURE PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE <input type="checkbox"/> INITIAL <input type="checkbox"/> FOLLOW UP	

APPENDIX I

DATA ELEMENTS FOR INCLUSION IN EXPEDITED REPORTS OF SERIOUS ADVERSE DRUG REACTIONS

The following list of items has its foundation in several established precedents, including those of CIOMS-I, the WHO International Drug Monitoring Centre, and various regulatory authority forms and guidelines. Some items may not be relevant depending on the circumstances. The minimum information required for expedited reporting purposes is: an identifiable patient, the name of a suspect medicinal product, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected and for which, in clinical investigation cases, there is a reasonable suspected causal relationship. Attempts should be made to obtain follow-up information on as many other listed items pertinent to the case.

1. Patient Details

- Initials
- Other relevant identifier (clinical investigation number, for example)
- Gender
- Age and/or date of birth
- Weight and Height

2. Suspected Medicinal Product(s)

- Brand name as reported
- International Non-Proprietary Name (INN)
- Batch number
- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify Units - e.g., mg, ml, mg/kg)
- Route of administration
- Starting date and time of day
- Stopping date and time, or duration of treatment

3. Other Treatment(s)

For concomitant medicinal products (including non-prescription/OTC medicinal products) and non-medicinal product therapies, provide the same information as for the suspected product.

4. Details of Suspected Adverse Drug Reaction(s)

Full description of reaction(s) including body site and severity, as well as the criterion (or criteria) for regarding the report as serious should be given. In addition to a description of the reported signs and symptoms, whenever possible, attempts should be made to establish a specific diagnosis for the reaction.

- Start date (and time) of onset of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Setting (e.g., hospital, out-patient clinic, home, nursing home)

Outcome: information on recovery and any sequelae; what specific tests and/or treatment may have been required and their results; for a fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction should be provided. Any autopsy or other post-mortem findings (including a coroner's report) should also be provided when available. Other information: anything relevant to facilitate assessment of the case, such as medical history including allergy, drug or alcohol abuse; family history; findings from special investigations.

5. Details on Reporter of Event (Suspected ADR)

- Name and Address
- Contact number
- Profession (specialty)

6. Administrative and Sponsor/Company Details

- Source of report
- Date event report was first received by sponsor/manufacture
- Country in which event occurred
- Type of report filed to authorities: initial or follow-up (first, second, etc.)
- Name and address of sponsor/manufacture/company
- Name, address, telephone number, and Fax number of contact person in reporting company or institution
- Sponsor/ manufacture's identification number for the case (this number must be the same for the initial and follow-up reports on the same case).

Appendix J

**SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS REPORTING
REQUIREMENTS AND TIMELINES TO THE CLINICAL RESEARCH AND
COMPLIANCE SECTION**

Nature of Report		Report ? (Y/N)	Timeframe of Report	Form Preferred	Content of Submission	Responsibility for Reporting to CRACS
Clinical trial not conducted in Malaysia		NO	Not Applicable			
Suspect drug is known to be other than trial drug (e.g. Other treatments, placebo or comparator drug)		NO	Not Applicable			
Serious Adverse Events and Not drug related		NO	Not Applicable			
Suspected Expected Serious Adverse Reactions		NO	Not Applicable			
For clinical trials conducted in Malaysia and other multi-centres overseas	Suspected unexpected Serious Adverse Reactions	YES	<u>Expedited Reporting:</u> Initial report as soon as possible but not later than 7 calendar days Follow by as complete a report as possible within 8 additional calendar days	CIOMS-I	Where applicable: Cover Letter Sponsor's comments	Sponsor
	Death / Life Threatening Events					
	Suspected unexpected Serious Adverse Reactions	YES	<u>Expedited Reporting:</u> Initial report: as soon as possible but not later than 15 calendar days Follow-up information should be actively sought and submitted as it becomes available	CIOMS-I	Where applicable: Cover Letter Sponsor's comments	Sponsor
	Non Fatal/ Non Life Threatening Events					

Appendix K

SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS REPORT

LETTERHEAD

<insert date>

Senior Principal Assistant Director,
Clinical Research and Compliance Section,
Centre for Compliance and Licensing,
National Pharmaceutical Control Bureau,
Ministry of Health,
Lot 36, Jalan University,
46200 Petaling Jaya,
Selangor.

Dear <Insert Name>,

Submission of Clinical Drug Trial Suspected Unexpected Serious Adverse Reactions (SUSARs) Report(s)

Study Drug:

Study/Protocol ID/No.:

Study Title:

Location of Event:

☐

Local

☐

Foreign

With reference to the above matter, we would like to submit the following SUSARs report(s) for DCA to review:

No	SUSARs	Country	Type of Report (Initial/Follow up)	Date of SUSARs	Date of Report

Please find the enclosed copy of the SUSARs Report(s).

Thank you.

Yours Sincerely,

<Insert Name and Designation>

APPENDIX L

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

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
53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.
3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
4. The Declaration of Geneva of the WMA 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 in the patient's best interest when providing medical care."
5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.
6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.
7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. 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 adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially

information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.

- 16.** Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.
- 17.** Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
- 18.** Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
- 19.** Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
- 20.** Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
- 21.** Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
- 22.** Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
- 23.** Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
- 24.** In medical research involving competent human subjects, 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, and any other relevant aspects of the study. The potential subject must be

informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

- 25.** For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
- 26.** When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
- 27.** For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.
- 28.** When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
- 29.** Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
- 30.** Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for

the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

- 31.** The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
- 32.** The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:
 - The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
 - Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.
- 33.** At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
- 34.** The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
- 35.** In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.