First Edition

Malaysian Guideline *for* Safety Reporting of Investigational Products

National Pharmaceutical Control Bureau
Ministry of Health Malaysia

MALAYSIAN GUIDELINE FOR SAFETY REPORTING OF INVESTIGATIONAL PRODUCTS

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This Guideline is adapted from ICH Harmonised Tripartite Guideline E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

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FOREWORD

As Malaysia is increasingly involved in clinical trials, it is of utmost importance that the safety information generated from these trials be reported in a timely fashion to the regulatory authority. This is because the safety information of medicinal products in development is very limited and prompt reporting of such information is paramount to ensure the safety of clinical trial subjects as it enables action to be taken on any important safety data detected. Ultimately, the responsibility for the on-going safety evaluation of the medicinal product during the drug development cycle falls on the sponsors.

This guideline is developed to expand the scope and coverage of safety information reporting to the regulatory authority stated in the *Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption 5th Edition* and is adapted from the *ICH Harmonised Tripartite Guideline E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* for use in Malaysia. This document will supersede the requirements stated in the *Guidelines for Application of Clinical Trial Import Licence and Clinical Trial Exemption 5th Edition.* All parties involved in conducting clinical trials in Malaysia are required to understand and adhere to the requirements of this guideline.

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TABLE OF CONTENTS

GLOSSARY

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 as ADR. 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 to a marketed medicinal products, ADR is a response to a drug which is noxious and unintended 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 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 exemption issued under regulation 15 (5), Control of Drugs and Cosmetics Regulations 1984 by Director of Pharmaceutical Services which exempts a person who wishes to manufacture product(s) solely for the purpose of producing samples for clinical trials from the provisions of regulation 7 (1) or regulation 18A of Control of Drugs and Cosmetics Regulations 1984.

Clinical Trial Import Licence (CTIL)
A license, in Form 4 in the Schedule of the Control of Drugs and Cosmetics Regulations 1984, issued by Director of Pharmaceutical Services under regulation 12 (1) (c) of the same Regulations which authorises 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.

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

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.

Drug Control Authority (DCA)
A body set up under the Control of Drugs and Cosmetics Regulations 1984 and as such its responsibility, role and mandate are defined by law.

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.

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 is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable 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 IEC may differ among countries, but should allow the IEC to act in agreement with GCP as described in this guideline.

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.

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.

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; or
b. A drug to be used as an ingredient for a preparation for a medicinal purpose.

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.

Registered (Approved) Product
Product being approved by the DCA.

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

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

1.0 INTRODUCTION

1.1 Purpose

This document is established to provide guidance for the industry on the reporting of safety information arising from clinical trials requiring the Clinical Trial Import Licence (CTIL) and/or Clinical Trial Exemption (CTX) in Malaysia to the National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia.

1.2 Scope

This guideline will cover the following areas involving safety information reporting.

- Definitions and terminology associated with clinical safety experience
- Standards for expedited reporting
  - Elements to be reported
  - Reporting timeframes
  - What, when and how to report
  - Managing blinded therapy
- Reporting process in Malaysia
- Documentation requirements for expedited report submission

However, Post Marketing Study, usually Phase IV study, which does not require CTIL and/or CTX (e.g. observational or non interventional study), the reporting requirement of safety information from this kind of study is out of scope of this guideline.

2.0 DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

2.1 Basic Terms

Definitions for the terms “adverse event (or experience)”, “adverse reaction” and “unexpected adverse reaction” have previously been agreed to by consensus of more than 30 Collaborating Centres of the WHO International Drug Monitoring Centre (Uppsala, Sweden). [*Edwards, I.R., et al, Harmonisation in Pharmacovigilance. Drug Safety 10(2): 93-102, 1994*.] Although those definitions can pertain to situations involving clinical investigations, some minor modifications are necessary, especially to accommodate the pre-approval drug development environment.

The following definitions, with input from the WHO Collaborative Centre, have been agreed:

a. Adverse Event (or Experience)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

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

b. 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.

c. 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 medicinal product).

2.2 Serious Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g. change in dose, population, needed monitoring or consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators.

Therefore, special medical or administrative criteria are needed to define reactions that, either due to their nature ("serious") or due to the significant, unexpected information they provide, justify expedited reporting.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

> *The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.*

The following definition is extracted from the *Malaysian Guideline for Good Clinical Practice, 3rd Edition,* Item 1.56:

> *A serious adverse event (SAE) or serious adverse drug reaction (Serious ADR) is 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.*

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may

jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered “serious”.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

2.3 Expectedness of an Adverse Drug Reaction

The purpose of expedited reporting is to make regulators, investigators and other appropriate people aware of new, important information on serious reactions. Therefore, such reporting will generally involve events previously unobserved or undocumented and a guideline is needed on how to define an event as “unexpected” or “expected” (expected/unexpected from the perspective of previously observed, not on the basis of what might be anticipated from the pharmacological properties of a medicinal product).

As stated in the definition (Section 2.1 c.), an "unexpected" adverse reaction is one, the nature or severity of which is not consistent with information in the relevant source document(s). Until source documents are amended, expedited reporting is required for additional occurrences of the reaction.

The following documents or circumstances will be used to determine whether an adverse event/reaction is expected:

a. For a medicinal product not yet approved for marketing in Malaysia, the sponsor's Investigator's Brochure will serve as the source document,
b. Product Information Leaflet for a medicinal product registered with the Drug Control Authority, Malaysia and
c. Reports, which add significant information on specificity or severity of a known and already documented serious ADR, constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered “unexpected”. Specific examples would be (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

3.0 STANDARDS FOR EXPEDITED REPORTING

3.1 What Should Be Reported

3.1.1 Single Cases of Serious, Unexpected ADRs

All adverse drug reactions (ADRs) that are both serious and unexpected are subjected to expedited reporting. This applies to reports from all clinical trials at Malaysia that require CTIL and/or CTX.

Information obtained by a sponsor or manufacturer on serious, unexpected reports should be submitted on an expedited basis to the NPCB if the minimum criteria for expedited reporting are met (Appendix B).

Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate. Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not. Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subjected to expedited reporting.

Causality assessment is required for clinical investigation cases. All cases judged by either the reporting health care professional or the sponsor as having a reasonable suspected causal relationship to the medicinal product qualify as ADRs.

Many terms and scales are in use to describe the degree of causality (attributability) between a medicinal product and an event, such as certainly, definitely, probably, possibly or likely related or not related. Phrases such as "plausible relationship", "suspected causality" or "causal relationship cannot be ruled out" are also invoked to describe cause and effect. However, there is currently no standard international nomenclature. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

3.1.2 Other Observations

There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgement should be applied for

each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:

3.1.2.1 For an "expected", serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

3.1.2.2 A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.

3.1.2.3 A major safety finding from a newly completed animal study (such as carcinogenicity).

3.2 When to Start and End Reporting

The reporting of serious, unexpected adverse drug reactions shall commence from the date of notification of CTIL and/or CTX approval from NPCB for the product used in the trial in Malaysia. The reporting of safety information to NPCB shall continue till all trial sites in Malaysia are closed.

3.3 Reporting Timeframes

3.3.1 Fatal or Life-Threatening Unexpected ADRs

Certain ADRs may be sufficiently alarming so as to require very rapid notification to regulators in countries where the medicinal product or indication, formulation or population for the medicinal product are still not approved for marketing, because such reports may lead to consideration of suspension of, or other limitations to, a clinical investigations program. Fatal or life-threatening, unexpected ADRs occurring in clinical investigations qualify for very rapid reporting.

The NPCB should be notified as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by a report as complete as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal

products. Follow-up information should be actively sought and follow-up reports should be submitted to the NPCB when it becomes available.

3.3.2 All Other Serious, Unexpected ADRs

Serious, unexpected ADRs that are not fatal or life-threatening must be notified to the NPCB as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting. Follow-up information should be actively sought and follow-up reports should be submitted to the NPCB when it becomes available.

3.3.3 Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required timeframes for reporting outlined above. Nevertheless, for regulatory purposes, initial reports should be submitted within the prescribed time as long as the following minimum criteria are met:

a. An identifiable patient,
b. A suspect medicinal product,
c. An identifiable reporting source,
d. An event or outcome that can be identified as serious and unexpected, and
e. In clinical investigation cases, there is a reasonable suspected causal relationship.

3.4 How to Report

The CIOMS-I form (Appendix A) 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 B, when available, be included in any expedited report (although some items may not be relevant depending on the circumstances).

Please refer to Appendix C for a summary of the safety reporting requirements for clinical trials to the Centre for Investigational New Product, NPCB.

The expedited safety reports should be submitted to the Centre for Investigational New Product electronically via e-mail to:

mysusar@bpfk.gov.my

Expedited report submissions should be accompanied with a cover letter (Appendix D) and should be standardised as follows:

- A cover letter, either in email body or company letterhead, is required for each submission.
- The format of the expedited report(s) attached to the email should be in a PDF file.
- All expedited report(s) from the same clinical trial protocol to be submitted under the same cover letter.
- All expedited safety report(s) should be compiled and separated into two PDF files according to local and foreign sources of the report(s).

All efforts should be made to submit the expedited reports to the NPCB via email. In the event that the electronic submission infrastructure unavailable for maintenance, the expedited safety report(s) may be submitted in hardcopy to:

Deputy Director,
Centre for Investigational New Product,
National Pharmaceutical Control Bureau,
Ministry of Health Malaysia,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor Darul Ehsan,
Malaysia.
(Attention: IP Safety Monitoring Section)

An acknowledgement of receipt will be sent by email for electronic submissions. As for expedited safety reports sent in printed copy, an acknowledgement of receipt will be provided upon submission.

3.5 Managing Blinded Therapy Cases

When the sponsor and investigator are blinded to individual patient treatment (as in a double-blind study), the occurrence of a serious event requires a decision on whether to open (break) the code for the specific patient. If the investigator breaks the blind, then it is assumed the sponsor will also know the assigned treatment for that patient. Although it is advantageous to retain the blind for all patients prior to final study analysis, when a serious adverse reaction is judged reportable on an expedited basis, it is recommended that the blind be broken only for that specific patient by the sponsor

even if the investigator has not broken the blind. It is also recommended that, when possible and appropriate, the blind be maintained for those persons, such as biometrics personnel, responsible for analysis and interpretation of results at the study's conclusion.

There are several disadvantages in maintaining the blind under the circumstances described which outweigh the advantages. By retaining the blind, placebo and comparator (usually a marketed product) cases are filed unnecessarily. When the blind is eventually opened, which may be many weeks or months after reporting to regulators, it must be ensured that company and regulatory databases are revised. If the event is serious, new and possibly related to the medicinal product, then if the Investigator's Brochure is updated, notifying relevant parties of the new information in a blinded fashion is inappropriate and possibly misleading. Moreover, breaking the blind for a single patient usually has little or no significant implications for the conduct of the clinical investigation or on the analysis of the final clinical investigation data.

However, when a fatal or other "serious" outcome is the primary efficacy endpoint in a clinical investigation, the integrity of the clinical investigation may be compromised if the blind is broken. Under these and similar circumstances, it may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subjected to routine expedited reporting. In such cases, a written request for NPCB’s agreement shall be made together with application for CTIL and/or CTX for the clinical trial concerned.

3.6 Miscellaneous Issues

3.6.1 Reactions Associated with Active Comparator or Placebo Treatment

SUSAR associated with active comparator or placebo shall not be reported to NPCB. However, it is the sponsor's responsibility to decide whether active comparator drug reactions should be reported to the other manufacturer and/or directly to appropriate regulatory agencies including NPCB. Sponsors must report such events to either the manufacturer of the active control or to appropriate regulatory agencies and ethics committee. Events associated with placebo will usually not satisfy the criteria for an ADR and, therefore, for expedited reporting.

3.6.2 Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occurred after the patient had completed a clinical study (including any protocol-required post-treatment follow-up) will possibly be reported by an investigator to the sponsor. Such cases should be regarded for expedited reporting purposes as though they were study reports. Therefore, a causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

3.6.3 Compassionate Use Programme

The compassionate use programme in Malaysia is available as an extension to an approved clinical trial protocol. Through this programme, only subjects enrolled in the approved clinical trial is allowed to continue the use of the unregistered medicinal product with the approval of the DCA.

As the compassionate use programme is an extension of a completed clinical trial and subjects will be provided with continued treatment with the unregistered product, all serious, unexpected adverse drug reactions should be reported to the Centre for Investigational New Product (Refer Section 3.1).

In the event that the product to be used by the subjects of the completed clinical trial is registered with the DCA and commercially available, all suspected local adverse reactions should be reported to the Pharmacovigilance / ADR / MADRAC Unit, Centre for Post Registration of Products in accordance with their established procedures.

Meanwhile, for named patient programs involving compassionate use of unregistered product and which fall under the following applications where CTIL and/or CTX are not applicable, any SUSAR arisen should be reported to the Pharmacovigilance / ADR / MADRAC Unit, Centre for Post Registration of Products in accordance with their established procedures.

- *Pengecualian untuk Mengimport / Mengilang Keluaran Tidak Berdaftar bagi Tujuan Merawat Penyakit yang Mengancam Nyawa*
- *Permohonan Memperolehi & Menggunakan Ubat yang Memerlukan Kelulusan Khas KPK Malaysia / Pengarah Kanan Perkhidmatan Farmasi*

3.6.4 Safety Information other than SUSAR Report

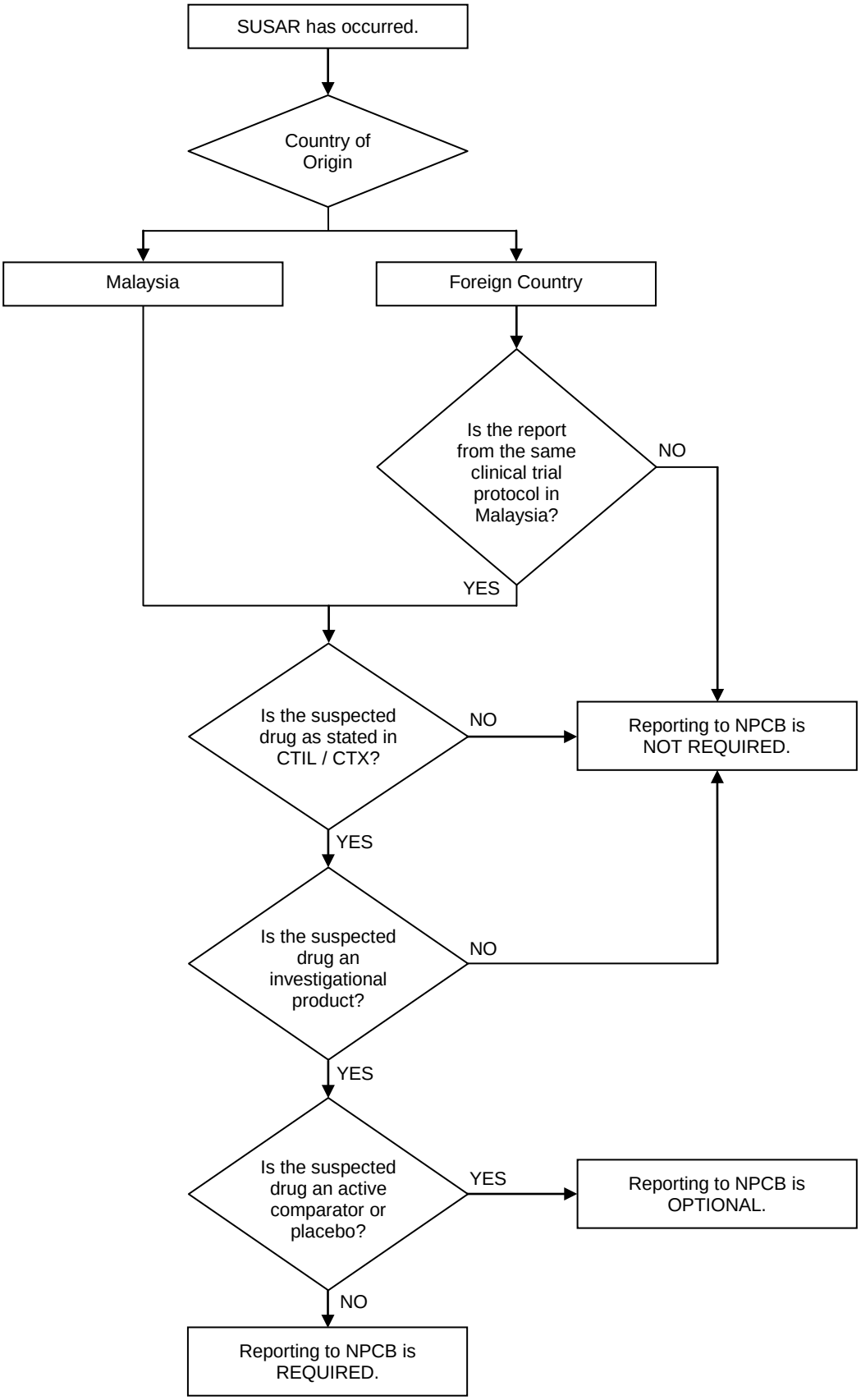
The following safety reports are not mandatory to be reported to NPCB. However, the submission of these reports is encouraged.

- 6 Monthly SUSAR Line Listing
- Annual Safety Report
- Periodic Safety Update Report
- Developmental Safety Update Report

3.7 Informing Investigators and Independent Ethics Committees/Institutional Review Boards of New Safety Information

All SUSARs/SAE should be informed promptly to the relevant ethics committee within the timeframe according to the requirement of the individual ethics committee as stipulated in Section 3.3 of this guideline.

Figure 1: Process of Qualifying SUSAR Reporting to NPCB



APPENDIX A

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITALS (First, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTOIN
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (Include generic name)		20. DID REACION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION? ☐ YES ☐ NO ☐ 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)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

APPENDIX B

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

APPENDIX C

REPORTING REQUIREMENTS AND TIMELINE TO CENTRE FOR INVESTIGATIONAL NEW PRODUCT

Nature of Report		Report? (Y/N)	Timeframe of Report	Preferred Form	Content of Submission	Responsibility for Reporting
Clinical trial is not conducted in Malaysia.		NO	Not Applicable			
Suspected drug is known to be active comparator, placebo or drug other than the investigational product.		NO				
Serious Adverse Events (not drug related)		NO				
Suspected Expected Serious Adverse Reaction		NO				
For clinical trial conducted in Malaysia requiring CTIL/CTX	Suspected Unexpected Serious Adverse Reaction Death/Life Threatening Event	YES	• Initial report as soon as possible but no later than 7 calendar days, followed by as complete a report as possible within additional 8 calendar days. • Follow-up information should be actively sought and submitted as it becomes available.	CIOMS-I	Where applicable: Cover letter Sponsor's comment	Sponsor
	Suspected Unexpected Serious Adverse Reaction Non-fatal/Non-Life Threatening Event	YES	• Initial report as soon as possible but no 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 comment	Sponsor

APPENDIX D

LETTERHEAD

<Insert date>

Deputy Director,
Centre for Investigational New Product,
National Pharmaceutical Control Bureau,
Ministry of Health,
Lot 36, Jalan Universiti,
46200 Petaling Jaya,
Selangor Darul Ehsan,
Malaysia.
[Attn: IP Safety Monitoring Section]

Dear Sir/Madam,

SUBMISSION OF SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) REPORT(S)

Study Drug:	
Study/Protocol ID/No.:	
Study Title:	

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

No.	CIOMS No.	SUSARs	Country of Origin	Report Type (Initial/Follow up)	Date of SUSAR	Date of Report
1						
2						
3						
4						
5						

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

Thank you.

Yours Sincerely,

<Signature>

<Insert Name and Designation>