HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

EXPEDITED SAFETY REPORTING REQUIREMENTS FOR CLINICAL TRIALS

GN-CT-10 Rev. No. 003

This guidance also outlines the expedited safety reporting requirements for therapeutic products, cell, tissue and gene therapy products and medicinal products used in other clinical research not regulated under the Health Products (Clinical Trials) Regulations and the Medicines (Clinical Trials Regulations).

HSA Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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SUMMARY OF AMENDMENTS

- Administrative changes due to HSA re-organisation

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1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to industry on the expedited reporting of unexpected, serious adverse drug reactions (USADR) related to therapeutic products (TP)[1], cell, tissue and gene therapy products (CTGTP)[1] and medicinal products (MP)[2] used in clinical research, including clinical trials requiring a Clinical Trials Authorisation (CTA), Clinical Trials Notification (CTN) or Clinical Trials Certificate (CTC) (referred to as "regulated clinical trials" in this guidance; see Section 1.3).

1.2. Background

When a TP/CTGTP/MP is under clinical development, there is limited safety information surrounding its use. This is especially so in the early stages of clinical trials and before any marketing experience is available. It is important to obtain timely and pertinent safety information in order to have a broader picture of the clinical safety surrounding a TP/CTGTP/MP, and if necessary, to take action on important clinical safety information arising during clinical development. The sponsor is ultimately responsible for the ongoing safety evaluation of the TP/CTGTP/MP, and timely communication of safety information to relevant stakeholders including regulators, institutional review boards and other investigators.

In Singapore, sponsors are required, under the Health Products (Clinical Trials) Regulations and the Medicines (Clinical Trials) Regulations, to report USADR to HSA as soon as possible and in any case, no later than timelines stipulated in the regulations. Similar provisions are in the Health Products (Clinical Research Materials) Regulations and the Medicines (Medicinal Products as Clinical Research Materials) Regulations. This means that sponsors of any clinical

[1] Therapeutic Product and CTGTP are defined in the First Schedule to the Health Products Act.

[2] Medicinal Product is defined in the Medicines Act.

research, including regulated clinical trials, have an obligation to report to HSA, all USADRs related to TP, CTGTP and MP used in the clinical research.

This guidance is adapted from the ICH Harmonised Tripartite Guideline E2A – Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, which has been developed by the appropriate ICH Expert Working Group and subjected to consultation by the regulatory parties, in accordance with the ICH Process. It serves to clarify the local regulatory requirements in relation to the ICH Harmonised Tripartite Guideline E2A.

1.3. Scope

This guidance applies to the following types of clinical research conducted in Singapore, which involves the use of TP/CTGTP/MP:

(a) Regulated Clinical Trials

(i) Clinical trials on TP or Class 2 CTGTP[3] that are subject to the requirements for a Clinical Trials Authorisation (CTA) or Clinical Trials Notification (CTN)

(ii) Clinical trials on MP that are subject to the requirements for a Clinical Trial Certificate (CTC)

(b) Other clinical research involving the use of TP/CTGTP/MP

These include, but are not limited to, the following:

(i) observational clinical trials of TP, Class 2 CTGTP or MP;

[3] Class 1 and Class 2 CTGTP are defined in the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

- Class 1 CTGTP means a CTGTP that —
  (a) is the result of only minimal manipulation of human cell or tissue;
  (b) is intended for homologous use;
  (c) is not combined or used with a therapeutic product or a medical device; and
  (d) is assigned by HSA as a Class 1 CTGTP due to a lower health risk to a user of the product.
- Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.

(ii) clinical studies in which TP or MP are used for a known effect, and are not the subject of investigation for potential efficacy, safety, pharmacokinetics etc.

This guidance addresses the type of documents to be submitted, the timelines and the requirements for reporting of safety information in clinical research involving the use of TP/CTGTP/MP. It covers the following:

⇒ Definitions and terminology associated with clinical safety experience
⇒ Standards for expedited reporting: what to report and how to report
⇒ Timelines for expedited reporting
⇒ Minimum data set for reporting
⇒ Managing blinded therapy cases

This guidance does not cover safety reporting relating to TP/CTGTP/MP that *do not* have any ongoing clinical trials or other clinical research in Singapore.

2. DEFINITIONS AND TERMINOLOGY ASSOCIATED WITH CLINICAL SAFETY EXPERIENCE

2.1. Adverse Event (AE)

Any untoward medical occurrence in a trial participant administered a TP/CTGTP/MP 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, for example), symptom, or disease temporally associated with the use of a TP/CTGTP/MP, whether or not considered related to the TP/CTGTP/MP.

2.2. Adverse Drug Reaction (ADR)

Any untoward and unintended response in a trial participant to a TP/CTGTP/MP which is related to any dose of the TP/CTGTP/MP administered to that trial participant. In other words, a causal relationship between a TP/CTGTP/MP and an

adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

2.3. Unexpected Adverse Drug Reaction

An adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved TP/CTGTP/MP, local product information leaflet or Investigator's Brochure for a TP/CTGTP/MP that has been approved for marketing).

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 TP/CTGTP/MP).

As stated in the definition, an "unexpected" adverse reaction is one where 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) The Investigator's Brochure will serve as the source document for a TP/CTGTP/MP that is not yet approved for marketing in Singapore;
(b) The local product information leaflet or the Investigator's Brochure for a TP/CTGTP/MP that has been approved for marketing in Singapore;
(c) Reports which add significant information on specificity or severity of a known, 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 acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis; or hepatitis with a first report of fulminant hepatitis.

2.4. Serious Adverse Event or Adverse Drug Reaction

A serious adverse event or adverse drug reaction is any untoward medical occurrence that at any dose:

(a) results in death,
(b) is life-threatening*,
(c) requires inpatient hospitalisation or prolongation of existing hospitalisation,
(d) results in persistent or significant disability/incapacity, or
(e) 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 were more severe*.

Seriousness of an Adverse Event or Adverse Drug Reaction

During clinical investigations, adverse events may occur which, if suspected to be TP/CTGTP/MP-related (adverse drug reactions), might be significant enough to lead to important changes in the way the TP/CTGTP/MP is developed (e.g., change in dose, population, needed monitoring, 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 the Investigational Medicines and Non-Clinical Assessments Division (IMNAD).

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

As stated in the definition, a "serious" adverse event/ reaction is one where the patient/event outcome or action criterion is associated with events that pose a threat to a patient's life or functioning. 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.

Additionally, 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.

2.5. Unexpected Serious Adverse Drug Reaction (USADR)

A serious adverse drug reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved TP/CTGTP/MP, local product information leaflet or Investigator's Brochure for a TP/CTGTP/MP that has been approved for marketing).

3. STANDARDS FOR EXPEDITED REPORTING

3.1. What Should Be Reported

3.1.1. Single Cases of USADR

All USADR for pre-marketed TP/CTGTP/MP (i.e., locally unregistered) and marketed TP/CTGTP/MP (i.e., locally registered) involved in ongoing clinical research in Singapore are subjected to expedited reporting. Such expedited safety reports should be sent to the Investigational Medicines and Non-Clinical Assessments Division (IMNAD) when the minimum criteria for expedited reporting are met (refer to Section 3.2.3). The source of these expedited safety reports should always be specified.

An "investigational product" (IP) is defined as a TP/CTGTP/MP or a placebo that is to be tested or used as a reference in a clinical trial.

(a) Locally <u>unregistered</u> TP/CTGTP/MP used as investigational product

Clinical trials involving locally unregistered TP/CTGTP/MP as investigational product usually require a Clinical Trial Authorisation (CTA) or a Clinical Trial Certificate (CTC). All USADR on locally unregistered TP/CTGTP/MP involved in such clinical trials are subject to expedited reporting.

Safety reports from the following sources should be submitted:

- Any type of clinical investigation, independent of design or purpose (including other protocols with the same investigational TP/CTGTP/MP);
- Cases not reported directly to a sponsor or manufacturer, for example, those found in regulatory authority-generated ADR registries;
- Overseas spontaneous reports. Please refer to Section 3.2.3 to ensure that the minimum criteria are met for regulatory reporting.

(b) Locally registered TP/CTGTP/MP used as investigational product

For regulated clinical trials on locally registered TP/CTGTP/MP:

- If the locally registered TP/CTGTP/MP is used as a test product, *local and overseas* reports of USADR arising from that same clinical trial protocol conducted in Singapore should be submitted.
- If the locally registered TP/CTGTP/MP is used as a reference (i.e., comparator), only *local* reports of USADR arising from that same clinical trial protocol should be submitted.

Any additional information may be requested as needed.

For other clinical research involving the use of locally registered TP/CTGTP/MP as investigational product (e.g., observational clinical trials of TP/CTGTP/MP), only local reports of USADR arising from that same clinical trial protocol conducted in Singapore should be submitted.

(c) TP/MP used as auxiliary product

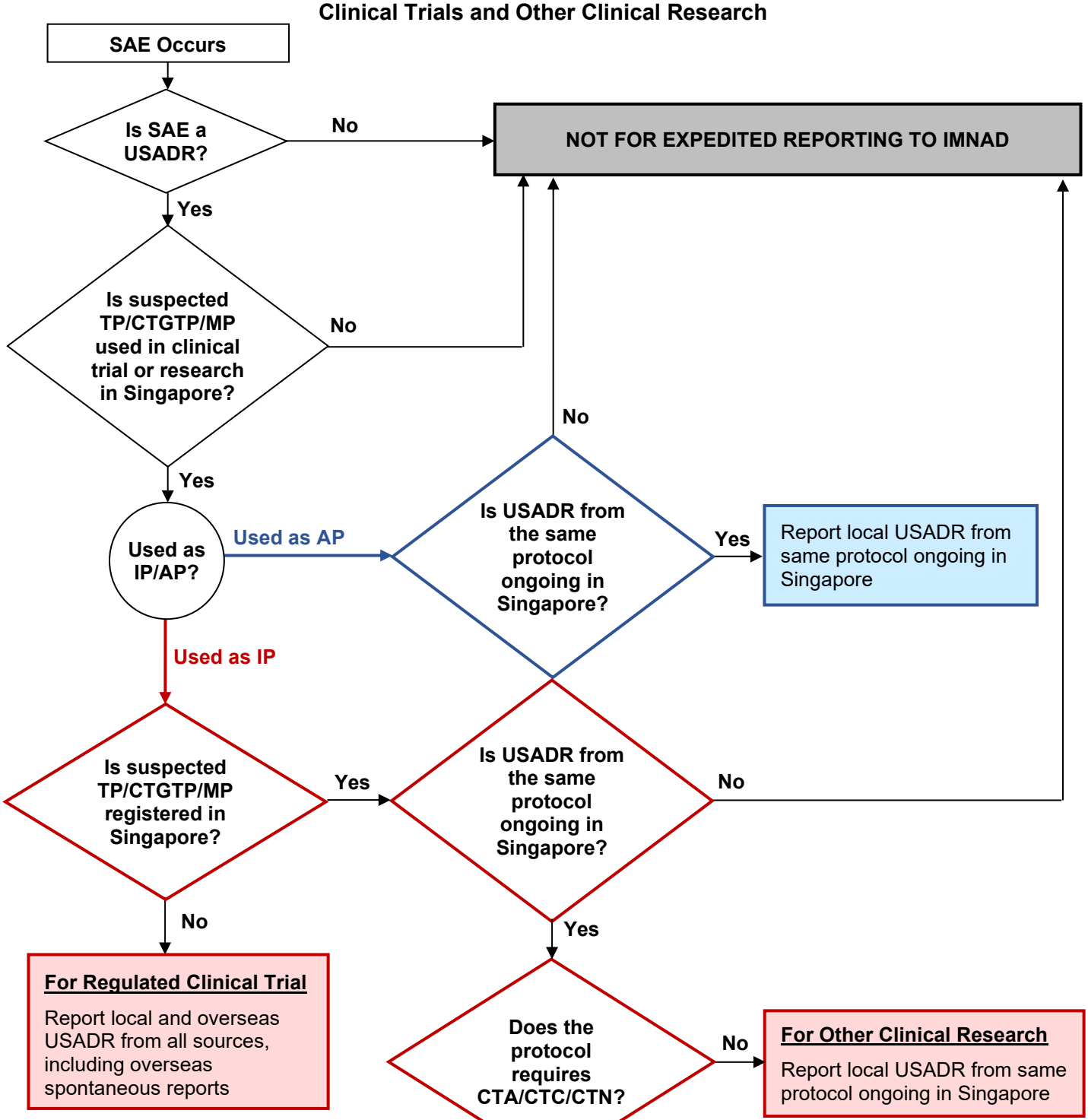
An "auxiliary product" (AP) is defined as a TP/MP used for the needs of a clinical trial as described in the protocol, but not as an investigational product.

For regulated clinical trials and other clinical research, sponsors should submit to HSA all local USADR that are related to the use of the auxiliary TP/MP in that research protocol. This is regardless of the registration status of the auxiliary TP/MP.

Figure 1 is a flow chart of the overall safety reporting decision process for SAEs arising from the use of TP/CTGTP/MP as investigational product or TP/MP as auxiliary product in clinical trials and other clinical research.

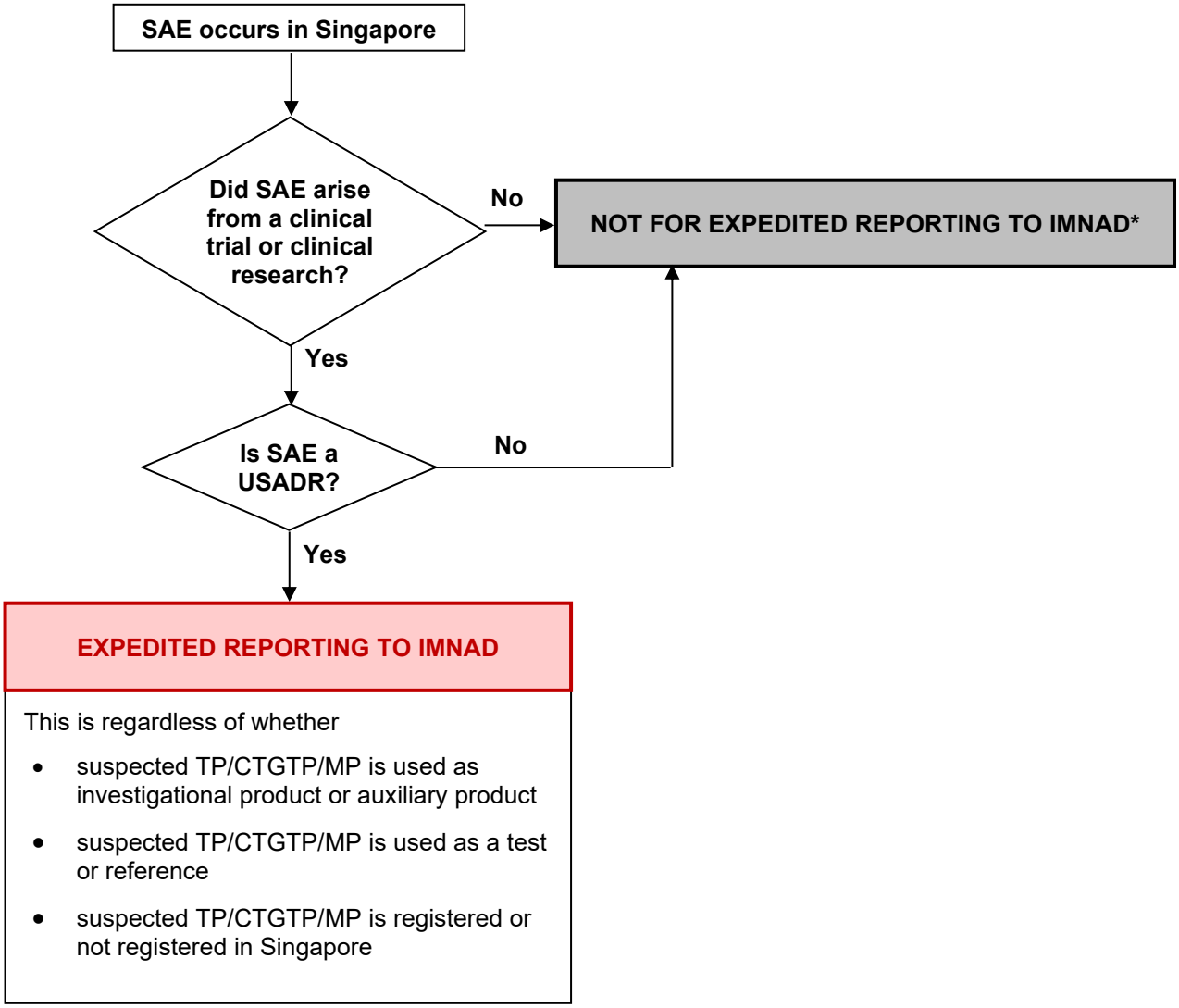
Figure 2 (2a and 2b) shows a breakdown of the safety reporting decision process for a local SAE and an overseas SAE.

Figure 1. Safety Reporting Decision Process for TP/CTGTP/MP used in Clinical Trials and Other Clinical Research



Legend
SAE: Serious Adverse Event
USADR: Unexpected Serious Adverse Drug Reaction
TP/CTGTP/MP: Therapeutic Product / Cell, Tissue and Gene Therapy Product / Medicinal Product
IP/AP: Investigational / Auxiliary Product
IMNAD: Investigational Medicines and Non-Clinical Assessments Division

Figure 2a. Safety Reporting Decision Process for Local SAEs



Legend

SAE: Serious Adverse Event

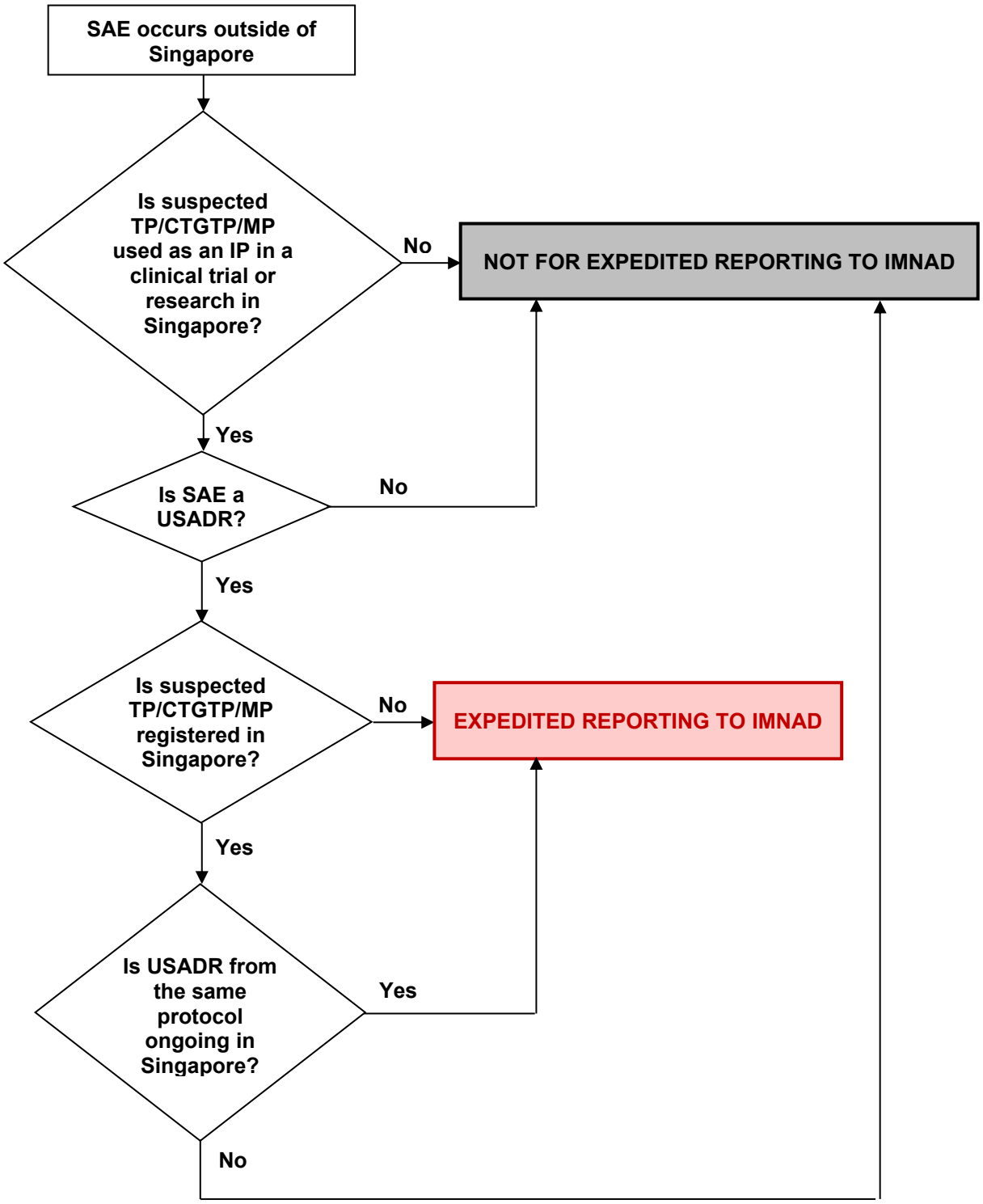
USADR: Unexpected Serious Adverse Drug Reaction

TP/CTGTP/MP: Therapeutic Product / Cell, Tissue and Gene Therapy Product / Medicinal Product

IMNAD: Investigational Medicines and Non-Clinical Assessments Division

**Note: For local SAEs not reportable to the Investigational Medicines and Non-Clinical Assessments Division (IMNAD), please refer to HSA website to determine if the SAEs are reportable as part of post-marketing vigilance requirements.*

Figure 2b. Safety Reporting Decision Process for Overseas SAEs



Legend

SAE: Serious Adverse Event

USADR: Unexpected Serious Adverse Drug Reaction

TP/CTGTP/MP: Therapeutic Product / Cell, Tissue and Gene Therapy Product / Medicinal Product

IMNAD: Investigational Medicines and Non-Clinical Assessments Division

It should be noted that expedited reporting in the following situations would ordinarily not be required:

- Adverse events or adverse drug reactions which are serious but expected
- Serious adverse events from clinical investigations that are considered not related to study product, whether expected or not
- Non-serious adverse drug reactions, whether expected or not
- Adverse events associated with placebo

3.1.1.1. Causality Assessment

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 TP/CTGTP/MP qualify as ADRs.

Adverse event reports associated with marketed TP/CTGTP/MP (spontaneous reports) usually imply causality. However, for the purposes of regulatory reporting, if a spontaneous report initially lacks sufficient detail to permit rational assessment of causality by the healthcare professional or sponsor, the report (even if serious in nature), may be submitted to HSA only after proper causality assessment has been made by a healthcare professional or the sponsor based on updated information.

Many terms and scales are in use to describe the degree of causality (attributability) between a TP/CTGTP/MP 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 the Investigational Medicines and Non-Clinical Assessments Division; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a TP/CTGTP/MP or that would be sufficient to consider changes in TP/CTGTP/MP administration or in the overall conduct of a clinical investigation represent such situations.

Examples include:

(a) For an “expected,” serious ADR, an increase in the rate of occurrence which is judged to be clinically important.

(b) A significant hazard to the patient population, such as lack of efficacy with a TP/CTGTP/MP used in treating life-threatening disease.

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

3.2. Reporting Time Frames

3.2.1. Fatal or Life-Threatening USADR

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

The Investigational Medicines and Non-Clinical Assessments Division 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 as complete a report as possible within 8 additional calendar days. This report may include an assessment of the importance and implication of the findings, including relevant

previous experience with the same or similar TP/CTGTP/MP. Subsequent follow-up reports should be submitted as it becomes available.

3.2.2. All Other USADR

USADRs that are not fatal or life-threatening must be filed 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 reports should be submitted as it becomes available.

3.2.3. Minimum Criteria for Reporting

Information for final description and evaluation of a case report may not be available within the required time frames for reporting outlined above.

Nevertheless, for regulatory purposes, initial reports should be submitted as soon as possible and within the prescribed time, as long as the following minimum criteria are met:

- An identifiable patient;
- A suspect TP/CTGTP/MP;
- An identifiable reporting source;
- Event or outcome that can be identified as serious and unexpected;
- There is a reasonable suspected causal relationship.

Follow-up information should be actively sought and submitted as it becomes available.

3.3. How To Report

The CIOMS-I form (Appendix 1) is a widely accepted standard for expedited adverse event reporting. However, no matter what the form or format used, it is important that certain data elements described in Appendix 2, when available, be included in any expedited report (although some items may not be relevant depending on the circumstances).

It is recommended that the description for the USADRs be reported using MedDRA (**Med**ical **D**ictionary for **R**egulatory **A**ctivities), which is a standardised medical terminology developed by ICH to classify adverse event information associated with the use of biopharmaceuticals and other medical products.

All reports must be sent to the Investigational Medicines and Non-Clinical Assessments Division, and other official parties requiring them (e.g., Investigators and Institutional Review Boards). Please refer to Appendix 3 for a summary of the safety reporting requirements for clinical trials of TP/CTGTP/MP.

For regulated trials, the expedited safety reports should be submitted through the Expedited Safety Reporting (ESR) online module in Pharmaceutical Regulatory Information System (PRISM).

For other clinical research, the expedited safety reports should be submitted via email to HSA_CT_SAE@hsa.gov.sg.

4. 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 to 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 TP/CTGTP/MP, 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.

For events where the treatment blind has been broken for submission to the European Medicines Agency (EMEA) or other national authorities, this information should be submitted through the online ESR form.

For events where the treatment blind has been broken and reveals placebo, and no expedited report has been filed to the Investigational Medicines and Non-Clinical Assessments Division (IMNAD) yet, expedited safety reporting is not required. On the other hand, if a report has already been submitted and subsequently, the blind is broken, the IMNAD must be updated on this new information by sending the safety report and highlighting this information for the database to be updated.

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 the IMNAD in advance concerning serious events that would be treated as disease-related and not subjected to routine expedited reporting.

5. MISCELLANEOUS ISSUES

5.1. Products with More Than One Presentation or Use

To avoid ambiguities and uncertainties, an ADR that qualifies for expedited reporting with one presentation of a product (e.g., a dosage form, formulation, delivery system) or product use (e.g., for an indication or population), should be reported or referenced to regulatory filings across other product presentations and uses.

It is not uncommon that more than one dosage form, formulation, or delivery system (oral, IM, IV, topical, etc.) of the pharmacologically active compound(s) is under study or marketed; for these different presentations there may be some marked differences in the clinical safety profile. The same may apply for a given product used in different indications or populations (single dose vs. chronic administration, for example). Thus, “expectedness” may be product or product-use specific, and separate Investigator’s Brochures may be used accordingly. However, such documents are expected to cover ADR information that applies to all affected product presentations and uses. When relevant, separate discussions of pertinent product-specific or use-specific safety information will also be included.

It is recommended that any ADRs that qualify for expedited reporting observed with one product dosage form or use be cross referenced to regulatory records for all other dosage forms and uses for that product. This may result in a certain amount of over-reporting or unnecessary reporting in obvious situations (for example, a report of phlebitis on IV injection sent to authorities in a country where only an oral dosage form is studied or marketed). However, underreporting is completely avoided.

5.2. Post-study Events

Although such information is not routinely sought or collected by the sponsor, serious adverse events that occur after the patient has 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, causality assessment and determination of expectedness are needed for a decision on whether or not expedited reporting is required.

6. INFORMING INVESTIGATORS AND ETHICS COMMITTEES (EC) / INSTITUTIONAL REVIEW BOARDS (IRB) OF NEW SAFETY INFORMATION

In general, the sponsor of a study should amend the Investigator's Brochure as needed, so as to keep the description of safety information updated. Sponsors should refer to the current safety reporting requirements of the IRB.

7. FREQUENTLY ASKED QUESTIONS (FAQs)

7.1. What are the regulatory requirements for safety reporting of registered TP/CTGTP/MP used in regulated clinical trials?

Registered TP/CTGTP/MP may be used in clinical trials in one of the following ways:

- As the investigational product being tested;
- As the reference or comparator product; or
- As an auxiliary product

For registered TP/CTGTP/MP in general, reports of USADR arising from protocols ongoing in Singapore should be reported to HSA. The following table summarises the types of report (local or overseas) that should be submitted to HSA:

	Local Reports from protocols ongoing in Singapore	**Overseas Reports from protocols ongoing in Singapore**
Investigational TP/CTGTP/MP (Test)	✓	✓
Investigational TP/CTGTP/MP (Comparator/Reference)	✓	✗
Auxiliary TP/MP	✓	✗

7.2. When should the sponsor start or stop submitting USADR to HSA?

Submission of USADR should start immediately upon clinical trial authorisation, acceptance of notification or issuance of a clinical trial certificate.

However, should any new safety concern surface from individual reports or aggregate analysis of USADR during the clinical trial application review period, the local sponsor should ensure that the new safety information is promptly communicated to HSA by email so that the information can be considered in the benefit-risk assessment of the clinical trial.

Submission of USADR reports may stop when Last Patient Last Visit (LPLV) is achieved in Singapore, unless otherwise indicated in the protocol. However, the local sponsor should inform HSA of any new safety information that emerges thereafter, particularly if the information were of relevance or potential significance to previously-treated trial participants.

7.3. Does the sponsor need to submit safety reports from Named Patient Programme or for compassionate use of unregistered TP?

If the compassionate use programme takes the form of a long-term clinical trial extension protocol for which a CTA or CTC has been granted, USADR should be submitted to the Investigational Medicines and Non-Clinical Assessments Division, in accordance with clinical trial regulations and guidance.

All local reports of serious adverse drug reactions (regardless of expectedness) arising from the use of unregistered drugs in other types of compassionate use programmes (i.e., those without a CTA or CTC) should be submitted to the Vigilance & Compliance Division of HSA. Please refer to HSA website for more details on adverse event reporting of therapeutic products.

7.4. Does the sponsor need to submit periodic line listings, Development Safety Update Reports (DSUR), annual or periodic safety reports to HSA?

There is currently no requirement for submission of such reports. These reports may be submitted to HSA at the sponsor's discretion.

HSA may also request for these reports to be submitted when deemed necessary.

7.5. If the serious adverse event was causally related to a study procedure in a clinical trial, is there a need to report this event?

In general, procedure-related serious adverse events need not be reported to HSA.

However, if the procedure involves the use of a TP, CTGTP, MP or medical device that might have contributed to the adverse event which has the potential to affect the safety and welfare of other trial participants, and preventive actions can be taken at local trial sites to prevent a similar occurrence, HSA should be informed by email since such an event might warrant a protocol or informed consent form amendment.

7.6. Are the any instances whereby serious and expected reactions are to be reported to HSA?

Expected reactions can be reported when the information may materially influence

a) the benefit-risk assessment of a product, or
b) the overall conduct of a clinical trial

An increase in the rate of occurrence of a serious and expected adverse drug reaction, which is judged to be clinically important, would fit these criteria.

7.7. When does the reporting timeline for submission of USADR start?

The reporting timeline starts upon first receipt by the sponsor, regardless of physical location.

7.8. Can the sponsor do a batch submission of USADR?

The regulations require sponsors to submit the USADR reports to HSA as soon as possible (i.e., without undue delay). Therefore, batch reporting is generally not

encouraged and should be considered only if the sponsor is able to ensure that the legal obligation is not compromised.

7.9. Who should assume responsibility when the sponsor company does not have a local party performing safety reporting submissions?

All clinical trials conducted in Singapore require a local sponsor. The local sponsor assumes responsibility for ensuring that safety reporting in clinical trials is in accordance with local regulatory requirements.

Although the function of safety reporting submissions may be contractually delegated to a contract research organisation, the local sponsor assumes overall responsibility for ensuring that safety reporting submissions are performed in accordance with local regulatory requirements.

7.10. How can one gain access to the Expedited Safety Reports (ESR) module in PRISM?

The CRIS administrator of your company must assign either drafter or submitter rights for the ESR module to you. Please note that if drafter role was assigned, the CRIS administrator will need to map the required clinical trials to the drafter for access, via the CRIS module. The PRISM ESR module can be accessed via HSA website.

7.11. In cases where safety reporting is done by the pharmacovigilance department of the sponsor company located overseas, can the reporting be done via ESR module in PRISM?

The overseas staff may gain access to ESR module by applying for HSA PIN. Please note that HSA PIN holders can only perform drafting; final submission must

still be performed by a Corppass holder. Information on how to apply for HSA PIN is available at HSA website.

7.12. If the local sponsor outsources the safety reporting to a Clinical Research Organization (CRO), how may the CRO use the online ESR module?

The local sponsor may provide drafter rights for ESR module to the CRO, who would then be able to draft ESR applications. The drafter may then notify the local sponsor to proceed with the submission.

Please note that the implication of providing submitter rights to a CRO is that the CRO will be able to view and access all clinical trial applications filed under the sponsor company.

8. REFERENCES

(i) Health Products (Clinical Trials) Regulations
(ii) Medicines (Clinical Trials) Regulations
(iii) Health Products (Clinical Research Materials) Regulations
(iv) Medicines (Medicinal Products as Clinical Research Materials) Regulations
(v) ICH Harmonised Tripartite Guideline E2A - Clinical Safety Data Management: Definitions And Standards For Expedited Reporting

9. APPENDICES

9.1. Appendix 1: CIOMS-I Format

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (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 REACTION
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										☐ 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 REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ 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, allergics, 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	

9.2. Appendix 2: 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 TP/CTGTP/MP, an identifiable reporting source, and an event or outcome that can be identified as serious and unexpected, and for which 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

Height

2. Suspected TP/CTGTP/MP(s)

Brand name as reported

International Non-Proprietary Name (INN)

Batch number

Indication(s) for which suspect TP/CTGTP/MP 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 TP/MP (including non-prescription/OTC TP/MP) and non-TP/MP 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

Address

Telephone number

Profession (specialty)

6. Administrative and Sponsor/Company Details

Source of report: spontaneous, clinical investigation (to provide details), literature, or other

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

HSA-HPRG clinical trial application/reference number

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).

The information provided in this Appendix is only a summary. Please read the entire guidance.

9.3. Appendix 3: Summary of Expedited Reporting Requirements (Clinical Trials)

Investigational TP/CTGTP/MP

Locally unregistered: Local and overseas USADRs, including those from other sources using the same TP/CTGTP/MP

Locally registered:

- Regulated clinical trials: (Used as test product) Local and overseas USADRs arising from the protocol ongoing in Singapore
  (Used as reference or comparator) Local USADRs arising from the protocol ongoing in Singapore
- Other clinical research: Local USADRs arising from the protocol ongoing in Singapore

Auxiliary TP/MP

Local USADRs arising from the protocol ongoing in Singapore

Nature of Report	Expedited Reporting?	Timeframe of Report	Preferred Format	Other Documents	Party Responsible for Reporting to CTB
Serious and Unrelated	**NO**	Not Applicable			
Serious, Related, and Expected	**NO**	Not Applicable			
Serious, Related, and Unexpected (i) Death * / Life-threatening events	**YES**	• Initial report by 7 calendar days • Follow-up report as complete as possible within 8 additional calendar days • Subsequent follow-up reports: As they become available	CIOMS-I	Where applicable: • Dear Healthcare Professional Letter • Company's comments	Sponsor
(ii) All other events		• Initial report: 15 calendar days • Follow-up reports: As they become available			

** Note: The investigator should supply HSA as well as the IRB and Sponsor with any additional requested information.*

HEALTH SCIENCES AUTHORITY

Applied Sciences Group
Blood Services Group
Enforcement Group
Integrated Health Regulation Group

www.hsa.gov.sg

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