

# MedDRA<sup>®</sup> TERM SELECTION: POINTS TO CONSIDER

ICH-Endorsed Guide for MedDRA Users

***Release 4.2***  
***Based on MedDRA Version 14.1***

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## Table of Contents

|  |    |
|--|----|
| <b>Section 1 – INTRODUCTION</b> .....  | 1  |
| 1.1 – Objectives of this Document.....   | 1  |
| 1.2 – Uses of MedDRA.....  | 1  |
| 1.3 – How to Use this Document.....  | 2  |
| 1.4 – Preferred Option.....  | 2  |
| 1.5 – MedDRA Browsing Tools .....  | 2  |
| <b>Section 2 – GENERAL TERM SELECTION PRINCIPLES</b> .....                             | 2  |
| 2.1 – Quality of Source Data .....   | 2  |
| 2.2 – Quality Assurance .....  | 2  |
| 2.3 – Do Not Alter MedDRA .....  | 3  |
| 2.4 – Always Select a Lowest Level Term.....   | 3  |
| 2.5 – Select Only Current Lowest Level Terms .....                                     | 5  |
| 2.6 – When to Request a Term .....   | 5  |
| 2.7 – Use of Medical Judgment in Term Selection .....                                  | 5  |
| 2.8 – Selecting More than One Term .....   | 5  |
| 2.9 – Check the Hierarchy.....   | 6  |
| 2.10 – Select Terms for All Reported Information, Do Not Add Information .....         | 6  |
| <b>Section 3 – TERM SELECTION POINTS</b> .....   | 6  |
| 3.1 – Definitive and Provisional Diagnoses with or without Signs and<br>Symptoms ..... | 6  |
| 3.2 – Death and Other Patient Outcomes .....   | 9  |
| 3.2.1 Death with ARs/AEs.....  | 9  |
| 3.2.2 Death as the only reported information .....                                     | 10 |
| 3.2.3 Death terms that add important clinical information .....                        | 10 |
| 3.2.4 Other patient outcomes (non-fatal) .....   | 10 |
| 3.3 – Suicide and Self-Harm.....   | 11 |
| 3.3.1 If overdose is reported .....  | 11 |
| 3.3.2 If self-injury is reported.....  | 11 |
| 3.3.3 Fatal suicide attempt.....   | 12 |
| 3.4 – Conflicting/Ambiguous/Vague Information.....                                     | 12 |
| 3.4.1 Conflicting information .....  | 12 |
| 3.4.2 Ambiguous information .....  | 12 |
| 3.4.3 Vague information.....   | 13 |
| 3.5 – Combination Terms .....  | 13 |
| 3.5.1 Diagnosis and sign/symptom .....   | 13 |
| 3.5.2 One reported condition is more specific than the other.....                      | 14 |
| 3.5.3 A MedDRA combination term is available.....                                      | 14 |
| 3.5.4 When to “split” into more than one MedDRA term .....                             | 14 |
| 3.5.5 Event reported with pre-existing condition .....                                 | 15 |
| 3.6 – Age vs. Event Specificity .....  | 16 |
| 3.6.1 MedDRA term includes age and event information.....                              | 16 |
| 3.6.2 No available MedDRA term includes both age and event information<br>.....        | 16 |
| 3.7 – Body Site vs. Event Specificity .....  | 16 |
| 3.7.1 MedDRA term includes body site and event information .....                       | 16 |

|   |    |
|---|----|
| 3.7.2 No available MedDRA term includes both body site and event information.....     | 17 |
| 3.7.3 Event occurring at multiple body sites .....                                    | 17 |
| 3.8 – Location Specific vs. Microorganism Specific Infection .....                    | 18 |
| 3.8.1 MedDRA term includes microorganism and anatomic location.....                   | 18 |
| 3.8.2 No available MedDRA term includes both microorganism and anatomic location..... | 18 |
| 3.9 – Modification of Pre-existing Conditions .....                                   | 19 |
| 3.10 – Exposures During Pregnancy and Breast Feeding.....                             | 20 |
| 3.10.1 Events in the mother.....  | 20 |
| 3.10.2 Events in the child or fetus.....  | 21 |
| 3.11 – Congenital Terms .....   | 21 |
| 3.11.1 Condition described as congenital .....  | 22 |
| 3.11.2 Condition not congenital/not present at birth.....                             | 22 |
| 3.12 – Neoplasms .....  | 22 |
| 3.12.1 Do not infer malignancy .....  | 23 |
| 3.13 – Medical and Surgical Procedures.....   | 23 |
| 3.13.1 Only the procedure is reported .....   | 23 |
| 3.13.2 Procedure and diagnosis are reported.....                                      | 23 |
| 3.14 – Investigations .....   | 24 |
| 3.14.1 Results of investigations as ARs/AEs .....                                     | 24 |
| 3.14.2 Investigation results consistent with diagnosis.....                           | 25 |
| 3.14.3 Investigation results not consistent with diagnosis.....                       | 25 |
| 3.14.4 Grouped investigation result terms .....                                       | 26 |
| 3.14.5 Investigation terms without qualifiers .....                                   | 26 |
| 3.15 – Medication/Administration Errors and Accidental Exposures .....                | 27 |
| 3.15.1 Medication error reported with clinical consequences .....                     | 27 |
| 3.15.2 Medication error reported without clinical consequences.....                   | 27 |
| 3.15.3 Accidental exposures.....  | 28 |
| 3.15.4 Medication errors in the context of labeled interactions .....                 | 28 |
| 3.15.5 Do not infer a medication error .....  | 29 |
| 3.16 – Transmission of Infectious Agent via Medicinal Product .....                   | 30 |
| 3.17 – Overdose, Toxicity and Poisoning.....  | 30 |
| 3.17.1 Overdose reported with clinical consequences.....                              | 31 |
| 3.17.2 Overdose reported without clinical consequences.....                           | 31 |
| 3.18 – Device-related Terms .....   | 31 |
| 3.18.1 Device-related event reported with clinical consequences.....                  | 31 |
| 3.18.2 Device-related event reported without clinical consequences.....               | 32 |
| 3.19 – Drug Interactions .....  | 32 |
| 3.19.1 Reporter specifically states an interaction.....                               | 32 |
| 3.19.2 Reporter does not specifically state an interaction.....                       | 32 |
| 3.20 – No Adverse Effect and “Normal” Terms.....                                      | 33 |
| 3.20.1 No adverse effect.....   | 33 |
| 3.20.2 Use of “normal” terms .....  | 33 |
| 3.21 – Unexpected Therapeutic Effect .....  | 33 |
| 3.22 – Modification of Effect .....   | 34 |

|                  |   |           |
|------------------|---|-----------|
| 3.22.1           | Lack of effect .....  | 34        |
| 3.22.2           | Do not infer lack of effect .....                                     | 34        |
| 3.22.3           | Increased, decreased and prolonged effect .....                       | 34        |
| 3.23             | – Social Circumstances .....  | 35        |
| 3.23.1           | Use of terms in this SOC .....  | 35        |
| 3.23.2           | Illegal acts of crime or abuse .....                                  | 36        |
| 3.24             | – Medical and Social History .....                                    | 36        |
| 3.25             | – Indication for Product Use .....                                    | 37        |
| 3.25.1           | Medical conditions .....  | 37        |
| 3.25.2           | Prevention and prophylaxis .....                                      | 37        |
| 3.25.3           | Procedures and diagnostic tests as indications .....                  | 38        |
| 3.25.4           | Supplementation and replacement therapies .....                       | 38        |
| 3.25.5           | Indication not reported .....   | 39        |
| 3.26             | – Off Label Use .....   | 39        |
| 3.26.1           | Off label use when reported as an indication .....                    | 39        |
| 3.26.2           | Off label use when reported with an AR/AE .....                       | 40        |
| 3.27             | – Product Quality Issues .....  | 40        |
| 3.27.1           | Product quality issue reported with clinical consequences .....       | 40        |
| 3.27.2           | Product quality issue reported without clinical<br>consequences ..... | 41        |
| 3.27.3           | Product quality issue vs. medication error .....                      | 41        |
| <b>Section 4</b> | <b>– APPENDIX</b> .....   | <b>42</b> |
| 4.1              | – Versioning .....  | 42        |
| 4.1.1            | Versioning methodologies .....  | 42        |
| 4.1.2            | Timing of version implementation .....                                | 43        |
| 4.2              | – Links and References .....  | 43        |
| 4.3              | Membership of the ICH Points to Consider Working Group .....          | 44        |
| 4.3.1            | Current members of the ICH Points to Consider Working Group .....     | 44        |
| 4.3.2            | Former members of the ICH Points to Consider Working Group .....      | 45        |

## Section 1 – INTRODUCTION

The **Medical Dictionary for Regulatory Activities** terminology (MedDRA) was designed for sharing regulatory information for human medical products. However, unless users achieve consistency in how they assign terms to verbatim reports of symptoms, signs, diseases, etc., use of MedDRA cannot have the desired harmonizing effect in the exchange of coded data.

This *MedDRA Term Selection: Points to Consider* (MTS:PTC) document is an ICH-endorsed guide for MedDRA users. It is updated in step with new MedDRA versions and is a companion document to MedDRA. It was developed and is maintained by a working group charged by the ICH Steering Committee. The working group consists of regulatory and industry representatives of the European Union, Japan and the United States, as well as representatives from the Canadian regulatory authority, the MedDRA Maintenance and Support Services Organization (MSSO) and the Japanese Maintenance Organization (JMO). (See Appendix, Section 4.3 for list of members).

### 1.1 – Objectives of this Document

The objective of the MTS:PTC document is to promote **accurate** and **consistent** term selection.

Organizations are encouraged to document their term selection methods and quality assurance procedures in organization-specific coding guidelines which should be consistent with the MTS:PTC.

Consistent term selection promotes medical accuracy for sharing MedDRA-coded data and facilitates a common understanding of shared data among academic, commercial and regulatory entities. The MTS:PTC could also be used by healthcare professional, researchers, and other parties outside of the regulated biopharmaceutical industry.

The document provides term selection advice for business purposes and regulatory requirements. There may be examples that do not reflect practices and requirements in all regions. This document does not specify regulatory reporting requirements, nor does it address database issues. As experience with MedDRA increases, and as MedDRA changes, there will be revisions to this document.

### 1.2 – Uses of MedDRA

Term selection for adverse reactions/adverse events (ARs/AEs), device-related events, product quality issues, medication errors, medical history, social history, investigations, and indications is addressed in this MTS:PTC document.

MedDRA's structure allows for aggregation of those reported terms in medically meaningful groupings to facilitate analysis of safety data. MedDRA can also be

used to list AR/AE data in reports (tables, line listings, etc), compute frequencies of similar ARs/AEs, and capture and analyze related data such as product indications, investigations, and medical and social history.

### **1.3 – How to Use this Document**

The MTS:PTC document does not address every potential term selection situation. Medical judgment and common sense should also be applied.

This document is not a substitute for MedDRA training. It is essential for users to have knowledge of MedDRA's structure and content. For optimal MedDRA term selection, one should also refer to the MedDRA Introductory Guide (See Appendix, Section 4.2).

### **1.4 – Preferred Option**

In some cases, where there is more than one option for selecting terms, a “preferred option” is identified in this document. **Designation of a “preferred option” does not limit MedDRA users to applying that option.** An organization should be consistent in the option that they choose to use.

### **1.5 – MedDRA Browsing Tools**

The MSSO and JMO provide two browsers (a desktop browser and a Web-based browser) that allow for searching and viewing the terminology (See Appendix, Section 4.2). Users may find these browsers useful aids in term selection.

## **Section 2 – GENERAL TERM SELECTION PRINCIPLES**

### **2.1 – Quality of Source Data**

The quality of the original reported information directly impacts the quality of data output. Clarification should be obtained for data that are ambiguous, confusing or unintelligible. If clarification cannot be obtained, refer to Section 3.4.

### **2.2 – Quality Assurance**

To promote consistency, organizations should document their term selection methods and quality assurance procedures in coding guidelines consistent with this MTS:PTC document.

Clear initial data can be promoted through careful design of data collection forms, and training of individuals in data collections and follow-up (e.g., investigators, drug sales representatives).

Term selection should be reviewed by a qualified individual, i.e., a person with medical background or training who has also received MedDRA training.

Human oversight of term selection performed by IT tools (such as an autoencoder) is needed to assure that the end result fully reflects the reported information and makes medical sense.

### 2.3 – Do Not Alter MedDRA

MedDRA is a **standardized** terminology with a pre-defined term hierarchy that should not be altered. Users must not make *ad hoc* structural alterations to MedDRA, including changing the primary SOC allocation; doing so would compromise the integrity of this standard. If terms are found to be incorrectly placed in the MedDRA hierarchy, a change request should be submitted to the MSSO.

#### Example

| <b>Change Request to Re-Assign Primary SOC</b>  |
|---|
| <p>In a previous version of MedDRA, PT <i>Factor VIII deficiency</i> was incorrectly assigned to primary SOC <i>Blood and lymphatic system disorders</i>. By means of a Change Request, the PT was re-assigned to primary SOC <i>Congenital, familial and genetic disorders</i> (making SOC <i>Blood and lymphatic system disorders</i> its secondary SOC assignment)</p> |

### 2.4 – Always Select a Lowest Level Term

MedDRA Lowest Level Term(s) (LLT) that **most accurately reflects the reported verbatim information** should be selected.

The degree of specificity of some MedDRA LLTs may be challenging for term selection. Here are some tips for specific instances:

- *A single letter difference in a reported verbatim text can impact the meaning of the word and consequently the term selection*

#### Example

| <b>Reported</b> | <b>LLT Selected</b>          |
|-----------------|------------------------------|
| Lip sore        | Lip sore (PT Lip pain)       |
| Lip sores       | Sores lip (PT Cheilitis)     |
| Sore gums       | Sore gums (PT Gingival pain) |
| Sores gum       | Sores gum (PT Gingivitis)    |

- *Gender specific terms*

MedDRA generally excludes terms with demographic descriptors (age, gender, etc.), but some terms with gender qualifiers are included if the gender renders the concept unique.

### Example

| <b>Distinct Gender Specific Terms</b>   |
|---|
| In MedDRA, there are separate LLTs/PTs for <i>Infertility</i> , <i>Infertility female</i> and <i>Infertility male</i> |

Organization specific coding guidelines should address instances when it is important to capture gender specific concepts.

MedDRA users should also consider the impact of gender-specific terms when comparing current data to data coded with a legacy terminology in which such gender-specificity may not have been available.

### Example

| <b>Gender Specificity - Legacy Terms vs. MedDRA</b>   |
|---|
| Consider the impact of selecting gender-specific MedDRA terms for breast cancer (e.g., LLT <i>Breast cancer female</i> ) when comparing data coded in a legacy terminology with only a single "Breast cancer" term. |

- *Postoperative and post procedural terms*

MedDRA contains some "postoperative" and "post procedural" terms. Select the most specific term available.

### Example

| <b>Reported</b>                     | <b>LLT Selected</b>    |
|-------------------------------------|------------------------|
| Bleeding after surgery              | Bleeding postoperative |
| Sepsis occurred after the procedure | Post procedural sepsis |

- *Newly added terms*

More specific LLTs may be available in a new version of MedDRA. See Appendix, Section 4.2.

## 2.5 – Select Only Current Lowest Level Terms

Non-current LLTs should not be used for term selection.

## 2.6 – When to Request a Term

Do not address deficiencies in MedDRA with organization-specific solutions. If there is no MedDRA term available to adequately reflect the reported information, submit a change request to MSSO.

Example

| Change Request for a New Term  |
|--|
| LLT <i>HBV coinfection</i> was added to MedDRA following a user's request. |

## 2.7 – Use of Medical Judgment in Term Selection

If an exact match cannot be found, **medical judgment** should be used to adequately represent the medical concept with an existing MedDRA term.

Example

| Reported     | LLT Selected  | Comment   |
|--------------|---------------|---|
| Brittle hair | Hair breakage | There is no MedDRA term for "brittle hair".<br>LLT <i>Hair breakage</i> more accurately reflects the reported concept than the less specific LLT <i>Hair disorder</i> |

## 2.8 – Selecting More than One Term

When a specific medical concept is not represented by a **single** MedDRA term, consider requesting a new term through the change request process (See Section 2.6). While waiting for the new term, select one or more existing terms using a consistent approach with careful consideration of the impact on data retrieval, analysis and reporting.

In some cases, it may be appropriate to select more than one MedDRA LLT to represent the reported information. If only one term is selected, specificity may be lost; on the other hand, selecting more than one term may lead to redundant counts. Established procedures should be documented.

## Example

| <b>More Than One LLT Selected</b>   |
|---|
| There is no single MedDRA term for "metastatic gingival cancer". Therefore, the options are:<br>1. Select LLT <i>Gingival cancer</i> OR LLT <i>Metastatic carcinoma</i><br>2. Select LLT <i>Gingival cancer</i> AND LLT <i>Metastatic carcinoma</i> |

### 2.9 – Check the Hierarchy

When considering selecting an LLT, check the hierarchy above the LLT (PT level and further up the hierarchy to HLT, HLGT and SOC) to ensure the placement accurately reflects the meaning of the reported term.

### 2.10 – Select Terms for All Reported Information, Do Not Add Information

Select terms for every AR/AE reported, regardless of causal association. In addition, select terms for device-related events, product quality issues, medication errors, medical history, social history, investigations, and indications as appropriate.

If a diagnosis is reported with characteristic signs and symptoms, the **preferred option** is to select a term for the diagnosis only (see Section 3.1 for details and examples).

When selecting terms, no reported information should be excluded from the term selection process; similarly, do not add information by selecting a term for a diagnosis if only signs or symptoms are reported.

## Example

| <b>Reported</b>   | <b>LLT Selected</b>     | <b>Comment</b>  |
|---|-------------------------|---|
| Abdominal pain, increased serum amylase, and increased serum lipase | Abdominal pain          | It is <b>inappropriate</b> to assign an LLT for diagnosis of "pancreatitis" |
|   | Serum amylase increased |   |
|   | Lipase increased        |   |

## Section 3 – TERM SELECTION POINTS

### 3.1 – Definitive and Provisional Diagnoses with or without Signs and Symptoms

The table below provides term selection options for definitive and provisional diagnoses with or without signs/symptoms reported. Examples are listed below the table.

A provisional diagnosis may be described as “suspicion of”, “probable”, “presumed”, likely”, “rule out”, “questionable”, “differential”, etc.

The **preferred option** for a single or multiple provisional diagnosis(es) is to select a term(s) for the diagnosis(es) *and* terms for signs and symptoms. This is because a provisional diagnosis may change while signs/symptoms do not.

| <b>SINGLE DIAGNOSIS</b>  |  |
|--|--|
| <b>DEFINITIVE DIAGNOSIS</b>  | <b>PROVISIONAL DIAGNOSIS</b>   |
| <p><b>Single definitive diagnosis without signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• Diagnosis (only possible option)</li> </ul>  | <p><b>Single provisional diagnosis without signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• Provisional diagnosis (only possible option)</li> </ul>   |
| <p><b>Single definitive diagnosis with signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• <b>Preferred:</b> Diagnosis only</li> <li>• <b>Alternate:</b> Diagnosis and signs/symptoms</li> </ul> <p><i>Note: Always include signs/symptoms not associated with diagnosis</i></p> <p style="text-align: center;"><b>EXAMPLE 1</b></p> | <p><b>Single provisional diagnosis with signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• <b>Preferred:</b> Provisional diagnosis and signs/symptoms</li> <li>• <b>Alternate:</b> Signs/symptoms only</li> </ul> <p><i>Note: Always include signs/symptoms not associated with diagnosis</i></p> <p style="text-align: center;"><b>EXAMPLE 2</b></p> |
| <b>MULTIPLE DIAGNOSES</b>  |  |
| <b>DEFINITIVE DIAGNOSES</b>  | <b>PROVISIONAL DIAGNOSES</b>   |
| <p><b>Multiple definitive diagnoses without signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• Multiple diagnoses (only possible option)</li> </ul>   | <p><b>Multiple provisional diagnoses without signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• Multiple provisional diagnoses (only possible option)</li> </ul>  |

|   |   |
|---|---|
| <p><b>Multiple definitive diagnoses with signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• <b>Preferred:</b> Multiple diagnoses only</li> <li>• <b>Alternate:</b> Diagnoses and signs/symptoms</li> </ul> <p><i>Note: Always include signs/symptoms not associated with diagnosis</i></p> <p><b>EXAMPLE 3</b></p> | <p><b>Multiple provisional diagnoses with signs/symptoms</b></p> <ul style="list-style-type: none"> <li>• <b>Preferred:</b> Multiple provisional diagnoses and signs/symptoms</li> <li>• <b>Alternate:</b> Signs/symptoms only</li> </ul> <p><i>Note: Always include signs/symptoms not associated with diagnosis</i></p> <p><b>EXAMPLE 4</b></p> |
|---|---|

| Example | Reported  | LLT Selected  | Preferred Option |
|---------|---|---|------------------|
| 1       | Anaphylactic reaction, rash, dyspnea, hypotension, and laryngospasm   | Anaphylactic reaction   | ✓                |
|         |   | Anaphylactic reaction<br>Rash<br>Dyspnea<br>Hypotension<br>Laryngospasm               |                  |
| 2       | Possible myocardial infarction with chest pain, dyspnea, diaphoresis  | Myocardial infarction<br>Chest pain<br>Dyspnea<br>Diaphoresis                         | ✓                |
|         |   | Chest pain<br>Dyspnea<br>Diaphoresis  |                  |
| 3       | Pulmonary embolism, myocardial infarction, and congestive heart failure with chest pain, cyanosis, shortness of breath, and | Pulmonary embolism<br>Myocardial infarction<br>Congestive heart failure               | ✓                |
|         |   | Pulmonary embolism<br>Myocardial infarction<br>Congestive heart failure<br>Chest pain |                  |

| Example  | Reported   | LLT Selected   | Preferred Option |
|--|--|--|------------------|
|  | blood pressure decreased   | Cyanosis<br>Shortness of breath<br>Blood pressure decreased  |                  |
| 4  | Chest pain, cyanosis, shortness of breath, and blood pressure decreased. Differential diagnosis includes pulmonary embolism, myocardial infarction, and congestive heart failure | Pulmonary embolism<br>Myocardial infarction<br>Congestive heart failure<br>Chest pain<br>Cyanosis<br>Shortness of breath<br>Blood pressure decreased | ✓                |
|  |  | Chest pain<br>Cyanosis<br>Shortness of breath<br>Blood pressure decreased  |                  |
| <b>Always include signs/symptoms not associated with diagnosis</b> | Myocardial infarction, chest pain, dyspnea, diaphoresis, ECG changes and jaundice  | Myocardial infarction<br>Jaundice (note that jaundice is not typically associated with myocardial infarction)  |                  |

### 3.2 – Death and Other Patient Outcomes

Death, disability, and hospitalization are considered **outcomes** in the context of safety reporting and not usually considered ARs/AEs. Outcomes are typically recorded in a separate manner (data field) from AR/AE information. A term for the outcome should be selected if it is the only information reported or provides significant clinical information.

(For reports of suicide and self-harm, see Section 3.3).

#### 3.2.1 Death with ARs/AEs

Death is an outcome and not usually considered an AR/AE. If ARs/AEs are reported along with death, select terms for the ARs/AEs. Record the fatal outcome in an appropriate data field.

Example

| Reported  | LLT Selected  | Comment                    |
|---|---|----------------------------|
| Death due to myocardial infarction                              | Myocardial infarction                                     | Record death as an outcome |
| Constipation, ruptured bowel, peritonitis, sepsis; patient died | Constipation<br>Perforated bowel<br>Peritonitis<br>Sepsis |                            |

### 3.2.2 Death as the only reported information

If the only information reported is death, select the most specific death term available. Circumstances of death should not be inferred but recorded only if stated by the reporter.

Death terms in MedDRA are linked to HLGT *Fatal outcomes*.

Example

| Reported  | LLT Selected                     |
|---|----------------------------------|
| Patient was found dead  | Found dead                       |
| Patient died in childbirth                                    | Maternal death during childbirth |
| The autopsy report stated that the cause of death was natural | Death from natural causes        |

### 3.2.3 Death terms that add important clinical information

Death terms that add important clinical information should be selected along with any reported ARs/AEs.

Example

| Reported  | LLT Selected                 |
|---|------------------------------|
| Patient experienced a rash and had sudden cardiac death | Rash<br>Sudden cardiac death |

### 3.2.4 Other patient outcomes (non-fatal)

Hospitalization, disability and other patient outcomes are not generally considered ARs/AEs.

## Example

| Reported  | LLT Selected             | Comment                              |
|---|--------------------------|--------------------------------------|
| Hospitalisation due to congestive heart failure | Congestive heart failure | Record hospitalisation as an outcome |

If the only information reported is the patient outcome, select the most specific term available.

## Example

| Reported                 | LLT Selected    |
|--------------------------|-----------------|
| Patient was hospitalised | Hospitalisation |

### 3.3 – Suicide and Self-Harm

Accurate and consistent term selection for reports of suicide attempts, completed suicides and self-harm is necessary for data retrieval and analysis. If the motive for reported injury is not clear, seek clarification from the source.

#### 3.3.1 If overdose is reported

Do not assume that an overdose – including an intentional overdose – is a suicide attempt. Select only the appropriate overdose term (See Section 3.17).

#### 3.3.2 If self-injury is reported

For reports of self-injury that do not mention suicide or suicide attempt, select only the appropriate self-injury term.

## Example

| Reported                        | LLT Selected              | Comment   |
|---------------------------------|---------------------------|---|
| Self slashing                   | Self inflicted laceration | LLT <i>Self inflicted laceration</i> is linked to PT <i>Intentional self-injury</i> |
| Cut her own wrists              |                           |   |
| Cut wrists in a suicide attempt | Suicide attempt           | In addition, LLT <i>Self inflicted laceration</i> can be selected                   |

### 3.3.3 Fatal suicide attempt

If a suicide attempt is fatal, select the term that reflects the outcome instead of the attempt only.

Example

| Reported                          | LLT Selected      | Comment                    |
|-----------------------------------|-------------------|----------------------------|
| Suicide attempt resulted in death | Completed suicide | Record death as an outcome |

### 3.4 – Conflicting/Ambiguous/Vague Information

When conflicting, ambiguous or vague information is reported, term selection to support appropriate data retrieval may be difficult. When this occurs, attempt to obtain more specific information. If clarification cannot be achieved, select terms as illustrated in the examples below (Sections 3.4.1 through 3.4.3).

#### 3.4.1 Conflicting information

Example

| Reported   | LLT Selected             | Comment  |
|--|--------------------------|--|
| Hyperkalemia with a serum potassium of 1.6 mEq/L | Serum potassium abnormal | LLT <i>Serum potassium abnormal</i> covers both of the reported concepts (note: serum potassium of 1.6 mEq/L is a <b>low</b> result, not high) |

#### 3.4.2 Ambiguous information

Example

| Reported | LLT Selected | Comment   |
|----------|--------------|---|
| GU pain  | Pain         | "GU" could be either "genito-urinary" or "gastric ulcer". Since "pain" is definite, |

| Reported | LLT Selected | Comment                |
|----------|--------------|------------------------|
|          |              | <i>select LLT Pain</i> |

### 3.4.3 Vague information

For information that is vague, attempt to obtain more specific information. If clarification cannot be achieved, select an LLT that reflects the non-specific nature of the reported event.

Example

| Reported   | LLT Selected      | Comment   |
|------------|-------------------|---|
| Congestion | Unevaluable event | "Congestion" reported alone is vague; this can refer to multiple organs and physiologic processes |

### 3.5 – Combination Terms

A **combination term** in MedDRA is a single medical concept combined with additional medical wording that provides important information on pathophysiology or etiology. A combination term is an internationally recognized distinct and robust medical concept as illustrated in the examples below.

Example

| MedDRA Combination Terms   |
|--|
| PT Diabetic retinopathy<br>PT Hypertensive cardiomegaly<br>PT Eosinophilic pneumonia |

A combination term may be selected for certain reported ARs/AEs (e.g., a condition "due to" another condition), keeping the following points in mind (NOTE: medical judgment should be applied):

#### 3.5.1 Diagnosis and sign/symptom

If a diagnosis and its characteristic signs or symptoms are reported, select a term for the diagnosis (See Section 3.1). A MedDRA combination term is not needed in this instance.

**Example**

| Reported                                | LLT Selected          |
|---|-----------------------|
| Chest pain due to myocardial infarction | Myocardial infarction |

**3.5.2 One reported condition is more specific than the other**

If two conditions are reported in combination, and one is more specific than the other, select a term for the more specific condition.

**Example**

| Reported                                       | LLT Selected        |
|--|---------------------|
| Hepatic function disorder<br>(acute hepatitis) | Hepatitis acute     |
| Arrhythmia due to atrial fibrillation          | Atrial fibrillation |

**3.5.3 A MedDRA combination term is available**

If two conditions are reported in combination, and a single MedDRA combination term is available to represent them, select that term.

**Example**

| Reported                    | LLT Selected         |
|-----------------------------|----------------------|
| Retinopathy due to diabetes | Diabetic retinopathy |
| Rash with itching           | Itchy rash           |

**3.5.4 When to “split” into more than one MedDRA term**

If “splitting” the reported ARs/AEs provides more clinical information, select more than one MedDRA term.

**Example**

| Reported | LLT Selected |
|----------|--------------|
|----------|--------------|

| Reported                   | LLT Selected           |
|----------------------------|------------------------|
| Diarrhea and vomiting      | Diarrhea<br>Vomiting   |
| Wrist fracture due to fall | Wrist fracture<br>Fall |

Exercise medical judgment so that information is not lost when “splitting” a reported term. Always check the MedDRA hierarchy above the selected term to be sure it is appropriate for the reported information.

#### Example

| Reported                       | LLT Selected                      | Comment   |
|--------------------------------|-----------------------------------|---|
| Hematoma due to an animal bite | Animal bite<br>Traumatic hematoma | <i>LLT Traumatic hematoma is more appropriate than LLT Hematoma (LLT Traumatic hematoma links to HLT Non-site specific injuries NEC and HLT Haemorrhages NEC while LLT Hematoma links only to HLT Haemorrhages NEC)</i> |

### 3.5.5 Event reported with pre-existing condition

If an event is reported along with a pre-existing condition **that has not changed**, and if there is not an appropriate combination term in MedDRA, select a term for the event only. (See Section 3.9 for pre-existing conditions that have changed).

#### Example

| Reported                                       | LLT Selected        | Comment   |
|--|---------------------|---|
| Shortness of breath due to pre-existing cancer | Shortness of breath | In this instance, “shortness of breath” is the event; “cancer” is the pre-existing condition that has not changed |

### 3.6 – Age vs. Event Specificity

#### 3.6.1 MedDRA term includes age and event information

Example

| Reported              | LLT Selected      |
|-----------------------|-------------------|
| Jaundice in a newborn | Jaundice neonatal |

#### 3.6.2 No available MedDRA term includes both age and event information

The **preferred option** is to select a term for the **event** and record the age in the appropriate demographic field.

Alternatively, select terms (more than one) that together reflect both the age of the patient and the event.

Example

| Reported                  | LLT Selected | Preferred Option | Comment   |
|---------------------------|--------------|------------------|---|
| Pancreatitis in a newborn | Pancreatitis | ✓                | Record patient age in a demographic field                 |
|                           | Pancreatitis |                  | In addition, LLT <i>Neonatal disorder</i> can be selected |

### 3.7 – Body Site vs. Event Specificity

#### 3.7.1 MedDRA term includes body site and event information

Example

| Reported          | LLT Selected |
|-------------------|--------------|
| Skin rash on face | Rash on face |

### 3.7.2 No available MedDRA term includes both body site and event information

Select a term for the **event**, rather than a term that reflects a non-specific condition at the body site; in other words, the **event** information generally has priority.

Example

| Reported           | LLT Selected | Comment   |
|--------------------|--------------|---|
| Skin rash on chest | Skin rash    | In this instance, there is no available term for a skin rash on the chest |

However, medical judgment is required, and sometimes, the body site information should have priority as in the example below.

Example

| Reported                   | LLT Selected            | Comment  |
|----------------------------|-------------------------|--|
| Cyanosis at injection site | Injection site reaction | Cyanosis implies a generalized disorder. In this example, selecting LLT <i>Cyanosis</i> would result in loss of important medical information and miscommunication |

### 3.7.3 Event occurring at multiple body sites

If an event is reported to occur at more than one body site, and if all of those LLTs link to the same PT, then select a single LLT that most accurately reflects the event; in other words, the **event** information has priority.

Example

| Reported                   | LLT Selected | Comment  |
|----------------------------|--------------|--|
| Skin rash on face and neck | Skin rash    | LLT <i>Rash on face</i> and LLT <i>Neck rash</i> both link to PT <i>Rash</i> |

| Reported                 | LLT Selected          | Comment   |
|--------------------------|-----------------------|---|
| Oedema of hands and feet | Oedema of extremities | LLT <i>Oedema hands</i> and LLT <i>Oedematous feet</i> both link to PT <i>Oedema peripheral</i> . However, LLT <i>Oedema of extremities</i> most accurately reflects the event in a single term |

### 3.8 – Location Specific vs. Microorganism Specific Infection

#### 3.8.1 MedDRA term includes microorganism and anatomic location

Example

| Reported               | LLT Selected           | Comment  |
|------------------------|------------------------|--|
| Pneumococcal pneumonia | Pneumococcal pneumonia | In this example, the implied anatomic location is the lung |

#### 3.8.2 No available MedDRA term includes both microorganism and anatomic location

The **preferred** option is to select a term that best represents the **microorganism specific infection**.

Alternatively, select a term that reflects the anatomic location **or** select more than one term that together reflect both the microorganism specific infection and the anatomic location.

Each organization should consider their specific products and select the location of infection if that is the most appropriate option.

Example

| Reported                         | LLT Selected         | Preferred Option | Comment                           |
|----------------------------------|----------------------|------------------|-----------------------------------|
| Respiratory chlamydial infection | Chlamydial infection | ✓                | Represents microorganism specific |

| Reported | LLT Selected                                  | Preferred Option | Comment   |
|----------|---|------------------|---|
|          |   |                  | infection   |
|          | Respiratory infection                         |                  | Represents location-specific infection  |
|          | Chlamydial infection<br>Respiratory infection |                  | Represents both microorganism specific infection <b>and</b> anatomic location |

### 3.9 – Modification of Pre-existing Conditions

Pre-existing conditions that have changed may be considered ARs/AEs, especially if the condition has worsened or progressed. (See Section 3.5.5 for pre-existing conditions that have not changed, and Section 3.21 for an unexpected improvement of a pre-existing condition).

| Ways That Pre-existing Conditions May Be Modified             |
|---|
| Aggravated, exacerbated, worsened<br>Recurrent<br>Progressive |

Select a term that most accurately reflects the modified condition (if such term exists).

#### Example

| Reported                          | LLT Selected                 |
|-----------------------------------|------------------------------|
| Exacerbation of myasthenia gravis | Myasthenia gravis aggravated |

If no such term exists, consider these options (Note: keep in mind possible database limitations):

- Option 1: Select a term for the pre-existing condition and record the modification in a consistent, documented way (narrative, check box on data collection form, etc.)

- Option 2: Select a term for the pre-existing condition **and** a second term for the modification of the condition (e.g., LLT *Condition aggravated*, LLT *Disease progression*)

### Example

| Options  | Reported                         | LLT Selected                             | Comment   |
|----------|----------------------------------|--|---|
| Option 1 | Halitosis worsened               | Halitosis                                | Record "worsened" in a consistent, documented way (e.g., check box on data collection form) |
| Option 2 | Progression of Addison's disease | Addison's disease<br>Disease progression | Use 2 terms to record pre-existing condition and modification                               |
|          | Jaundice aggravated              | Jaundice<br>Condition aggravated         |   |

## 3.10 – Exposures During Pregnancy and Breast Feeding

To select the most appropriate term (or terms), first determine if the subject/patient who experienced the event is the mother or the child/fetus.

### 3.10.1 Events in the mother

- Patient became pregnant while receiving product

Pregnancy is not normally considered an adverse event, but organizations may wish to record this information in their databases.

### Example

| Reported                      | LLT Selected                   | Comment   |
|-------------------------------|--------------------------------|---|
| Pregnancy (no adverse effect) | Pregnancy<br>No adverse effect | Select LLT <i>No adverse effect</i> (in addition to LLT <i>Pregnancy</i> ) if no adverse event has occurred. (See Section 3.20) |
| Pregnancy (outcome unknown)   | Pregnancy                      | Select LLT <i>Pregnancy</i> <b>only</b> if neither outcome  |

| Reported | LLT Selected | Comment                       |
|----------|--------------|-------------------------------|
|          |              | nor occurrence of AE is known |

- Pregnant patient receiving medication experienced adverse event

Example

| Reported  | LLT Selected                                    | Comment   |
|---|---|---|
| Pregnant patient receiving drug X experienced a pruritic rash | Drug exposure during pregnancy<br>Pruritic rash | LLT <i>Pregnancy</i> should also be selected for medical history, concomitant medical condition |

### 3.10.2 Events in the child or fetus

Select terms for both the type of exposure and any adverse event(s).

Example

| Setting/Patient   | Reported   | LLT Selected  |
|---|--|---|
| Child/fetus with AE; exposed <i>in utero</i> ; <b>mother</b> took product | Pregnant woman taking drug X had fetal tachycardia noted on routine examination  | Fetal tachycardia<br>Drug exposure in utero<br><b>OR</b> Drug exposure during pregnancy       |
| Child/fetus with AE; exposed <i>in utero</i> ; <b>father</b> took product | Baby born with cleft palate; father had been taking drug X at time of conception | Cleft palate<br>Paternal drug exposure  |
| Child with AE; exposed to product via breast milk                         | Mother exposed to drug X; nursing newborn experienced vomiting                   | Vomiting neonatal<br>Drug exposure via breast milk (See Section 3.15.3, Accidental exposures) |

### 3.11 – Congenital Terms

“Congenital” = any condition present at birth, whether genetically inherited or occurring *in utero*. (MedDRA Introductory Guide, Version 14.1; see Appendix, Section 4.2 for a link to the MedDRA Introductory Guide).

### 3.11.1 Condition described as congenital

Select terms from SOC *Congenital, familial and genetic disorders* when the reporter describes the condition as congenital or when medical judgment establishes that the condition was present at the time of birth.

Example

| Reported                      | LLT Selected             |
|-------------------------------|--------------------------|
| Congenital heart disease      | Heart disease congenital |
| Child born with heart disease |                          |

### 3.11.2 Condition not congenital/not present at birth

If the condition is not described as congenital or present at birth, select the non-qualified term for the condition; if a non-qualified term is not available, select the “acquired” term for the condition.

Example

| Reported        | LLT Selected             | Comment   |
|-----------------|--------------------------|---|
| Night blindness | Night blindness          | LLT/PT <i>Night blindness</i> (links to primary SOC <i>Eye disorders</i> ). Do not assume the condition is congenital (LLT/PT <i>Congenital night blindness</i> ) |
| Cholangiectasis | Cholangiectasis acquired |   |

### 3.12 – Neoplasms

Due to the large number of neoplasm types, specific guidance cannot be provided for all situations. The MedDRA Introductory Guide describes the use and placement of neoplasm terms and related terms in MedDRA.

Keep in mind the following points:

| Neoplasms Terms in MedDRA  |
|--|
| <p>“Cancer” and “carcinoma” are synonyms (Appendix B of Introductory Guide)</p> <p>“Tumo(u)r” terms refer to neoplasia</p> <p>“Lump” and “mass” terms are <u>not</u> neoplasia</p> |

If the type of neoplasia is not clear, seek clarification from the reporter. Consult medical experts when selecting terms for difficult or unusual neoplasms.

### 3.12.1 Do not infer malignancy

Select a malignancy term only if malignancy is stated by the reporter. Reports of “tumo(u)r” events should not be assigned a “cancer”, “carcinoma” or another malignant term unless it is clear that malignancy is present.

Example

| Reported                 | LLT Selected            |
|--------------------------|-------------------------|
| Tumour growing on skin   | Skin tumour             |
| Cancer growing on tongue | Malignant tongue cancer |

### 3.13 – Medical and Surgical Procedures

Terms in SOC *Surgical and medical procedures* are generally not appropriate for ARs/AEs. Terms in this SOC are not multi-axial. Be aware of the impact of these terms on data retrieval, analysis and reporting.

Keep in mind the following points:

#### 3.13.1 Only the procedure is reported

If only a procedure is reported, select a term for the procedure.

Example

| Reported                               | LLT Selected         |
|--|----------------------|
| Patient had transfusion of platelets   | Platelet transfusion |
| Patient had tonsillectomy in childhood | Tonsillectomy        |

#### 3.13.2 Procedure and diagnosis are reported

If a procedure is reported with a diagnosis, the **preferred option** is to select terms for both the procedure and diagnosis. Alternatively, select a term only for the diagnosis.

Example

| Reported                                  | LLT Selected                          | Preferred Option | Comment   |
|---|---------------------------------------|------------------|---|
| Liver transplantation due to liver injury | Liver injury<br>Liver transplantation | ✓                | Selecting term for the procedure may indicate severity of the condition |
|   | Liver injury                          |                  |   |

### 3.14 – Investigations

SOC *Investigations* includes test names with qualifiers (e.g., increased, decreased, abnormal, normal) and without qualifiers. Corresponding medical conditions (such as “hyper-” and “hypo-” terms) are in other “disorder” SOC (e.g., SOC *Metabolism and nutrition disorders*).

SOC *Investigations* is not multi-axial; always consider the terms in this SOC for data retrieval.

#### 3.14.1 Results of investigations as ARs/AEs

Keep in mind the following points when selecting terms for results of investigations:

- Selecting terms for a medical condition vs. an investigation result

Example

| Reported          | LLT Selected      | Comment  |
|-------------------|-------------------|--|
| Hypoglycemia      | Hypoglycemia      | LLT <i>Hypoglycemia</i> links to SOC <i>Metabolism and nutrition disorders</i> |
| Decreased glucose | Glucose decreased | LLT <i>Glucose decreased</i> links to SOC <i>Investigations</i>                |

- Unambiguous investigation result

Example

| Reported         | LLT Selected | Comment                                      |
|------------------|--------------|--|
| Glucose 40 mg/dL | Glucose low  | Glucose is clearly below the reference range |

- Ambiguous investigation result

Example

| Reported           | LLT Selected     | Comment  |
|--------------------|------------------|--|
| His glucose was 40 | Glucose abnormal | In this example, no units have been reported. Select LLT <i>Glucose abnormal</i> if clarification cannot be obtained |

### 3.14.2 Investigation results consistent with diagnosis

When investigation results are reported with a diagnosis, select only a term for the diagnosis **if investigation results are consistent with the diagnosis**.

Example

| Reported   | LLT Selected | Comment  |
|--|--------------|--|
| Elevated potassium, K 7.0 mmol/L, and hyperkalemia | Hyperkalemia | It is not necessary to select LLT <i>Potassium increased</i> |

### 3.14.3 Investigation results not consistent with diagnosis

When investigation results are reported with a diagnosis, select a term for the diagnosis **and also** select terms for any investigation results that are **not** consistent with the diagnosis.

Example

| Reported  | LLT Selected                            | Comment   |
|---|---|---|
| Alopecia, rash, and elevated potassium 7.0 mmol/L | Alopecia<br>Rash<br>Potassium increased | Elevated potassium is not consistent with the diagnoses of alopecia |

| Reported | LLT Selected | Comment   |
|----------|--------------|---|
|          |              | and rash. Terms for all concepts should be selected |

### 3.14.4 Grouped investigation result terms

Select a term for each investigation result as reported; do not “lump” together separate investigation results under an inclusive term **unless reported as such**.

Example

| Reported  | LLT Selected  | Comment  |
|---|---|--|
| Abnormalities of liver function tests   | Abnormal liver function tests   |  |
| Increased alkaline phosphatase, increased SGPT, increased SGOT and elevated LDH | Alkaline phosphatase increased<br>SGPT increased<br>SGOT increased<br>LDH increased | Select four individual terms for the investigation results. A single term such as LLT <i>Liver function tests abnormal</i> should <b>not</b> be selected |

### 3.14.5 Investigation terms without qualifiers

Terms in SOC *Investigations without qualifiers* may be used to record test names when entering diagnostic test data (such as in E2B field B.3.1c).

Example

| Information/Reported (Verbatim) | LLT Selected for Test Name | Comment  |
|---------------------------------|----------------------------|--|
| Cardiac output measured         | Cardiac output             |  |
| Increased blood sugar           | Blood glucose              | LLT <i>Blood glucose increased</i> should <b>not</b> be selected as it is both a test name and a result* |

\* Enter a qualifier (e.g., “increased”) or a numeric result (if available) into the “Result” data field of the E2B format.

### 3.15 – Medication/Administration Errors and Accidental Exposures

Reports of medication errors may or may not include information about clinical consequences.

Appendix B of the MedDRA Introductory Guide contains descriptions of the interpretation and use of certain medication error terms (e.g., “Dispensing error”).

#### 3.15.1 Medication error reported with clinical consequences

If a medication error is reported with clinical consequences, select terms for both the medication error and the clinical consequences.

Example

| Reported   | LLT Selected   |
|--|--|
| Patient was administered wrong drug and experienced hypotension                                | Wrong drug administered<br>Hypotension                 |
| Because of similar sounding drug names, the patient took the wrong drug and experienced a rash | Drug name confusion<br>Wrong drug administered<br>Rash |

#### 3.15.2 Medication error reported without clinical consequences

Medication errors without clinical consequences are not ARs/AEs. However, it is important to record the occurrence or **potential** occurrence of a medication error. Select a term that is closest to the description of medication error reported.

Also, if specifically reported that no adverse effect has occurred, it is acceptable to select LLT *No adverse effect*.

Example

| Reported  | LLT Selected   | Comment          |
|---|--|------------------|
| Medication was given intravenously instead of intramuscularly                         | Intramuscular formulation administered by other route                      |                  |
| Medication was given intravenously instead of intramuscularly <b>without sequelae</b> | Intramuscular formulation administered by other route<br>No adverse effect | See Section 3.20 |
| Patient was dispensed the   | Intercepted drug   |                  |

| Reported   | LLT Selected   | Comment   |
|--|--|---|
| wrong drug strength. The error was detected prior to patient administration  | dispensing error   |   |
| Pharmacist notices that the names of two drugs are similar and is concerned that this may result in a medication error | Circumstance or information capable of leading to medication error | LLT <i>Drug name confusion</i> could be an optional additional term to select (for tracking purposes). Note: this example is a potential medication error |

### 3.15.3 Accidental exposures

The same principles apply to accidental exposures.

Example

| Reported  | LLT Selected   |
|---|--|
| Nurse splashed injectable drug in her own eye resulting in excessive tearing    | Inadvertent exposure to drug<br>Excess tears           |
| Child accidentally took grandmother's pills and experienced projectile vomiting | Accidental drug intake by child<br>Vomiting projectile |

### 3.15.4 Medication errors in the context of labeled interactions

If the label describes **known effects** when the product is co-administered with specific drugs, with specific foods, or to patients with specific disease states, then select a medication error term for the type of interaction, such as those listed below:

| Medication Error Terms - Labeled Interactions      |
|--|
| Labelled drug-drug interaction medication error    |
| Labelled drug-food interaction medication error    |
| Labelled drug-disease interaction medication error |
| Documented hypersensitivity to administered drug   |

Example

| Reported  | LLT Selected                              | Comment                                    |
|---|---|--|
| Patient became pregnant whilst taking an antifungal | Labelled drug-drug interaction medication | Interaction must be stated in product data |

| Reported   | LLT Selected  | Comment  |
|--|---|--|
| drug and an oral contraceptive   | error<br>Pregnancy on oral contraceptive              | sheet (See also Section 3.19)                              |
| Patient drank grapefruit juice whilst taking a calcium channel blocker                   | Labelled drug-food interaction<br>medication error    | Product is labeled for grapefruit juice interaction        |
| Patient with renal failure is prescribed a drug that is contraindicated in renal failure | Labelled drug-disease interaction<br>medication error |  |
| Patient is administered a sulfonamide-based drug   | Documented hypersensitivity to administered drug      | Medical file clearly indicates patient has a sulfa allergy |

### 3.15.5 Do not infer a medication error

Do not infer that a medication error has occurred unless specific information is provided. This includes inferring that extra dosing, overdose, or underdose has occurred. (See Section 3.17)

#### Example

| Reported   | LLT Selected   | Comment  |
|--|--|--|
| Antibiotic was prescribed for a week, and the patient stopped treatment after 2 days because of bitter taste | Prescribed dosing duration not completed<br>Taste bitter | LLT <i>Taste bitter</i> represents a sensory perception issue. LLT <i>Medication after taste</i> refers to a product quality issue |
| Incorrect dosing by patient  | Incorrect dose administered                              | Do not select <i>Extra dose administered</i> or <i>Overdose</i> based on this information alone                                    |
| Patient took only half the prescribed dose   | Underdose  |  |

### 3.16 – Transmission of Infectious Agent via Medicinal Product

If a report of transmission of an infectious agent via medicinal product is received, select a term for the transmission. If the infection is identified, select a second term for the specific infection.

#### Example

| Reported   | LLT Selected  |
|--|---|
| Patient received a nasal spray product and later developed a severe nasal infection with <i>Burkholderia cepacia</i> . Cultures of unopened containers of the nasal spray grew <i>B. cepacia</i> | Transmission of an infectious agent via a medicinal product<br>Burkholderia cepacia infection |
| Patient received a blood transfusion and developed Hepatitis C   | Transfusion-transmitted infectious disease<br>Hepatitis C                                     |

Medical judgment should be used if the reporter does not explicitly state transmission of an infectious agent via medicinal product but this could be implied by other data within the case. In this instance, select LLT *Suspected transmission of an infectious agent via a medicinal product*. The same LLT should be used in the E2B field for the sender’s diagnosis (B.5.3).

### 3.17 – Overdose, Toxicity and Poisoning

Overdose terms are grouped under HLT *Overdoses*. Toxicity and poisoning terms are grouped under HLT *Poisoning and toxicity*. For more information, refer to the MedDRA Introductory Guide, v14.1. (See Appendix, Section 4.2 for a link to the MedDRA Introductory Guide).

If overdose, poisoning or toxicity is explicitly reported, select the appropriate term.

#### Example

| Reported   | LLT Selected                               |
|--|--|
| Overdose of pills  | Overdose                                   |
| A child was accidentally poisoned when she ingested a chemical cleaning product                          | Accidental poisoning<br>Chemical poisoning |
| Patient intentionally took many more than the prescribed number of pills to treat a very severe headache | Intentional overdose                       |

### 3.17.1 Overdose reported with clinical consequences

Select terms for overdose and for clinical consequences reported in association with an overdose.

Example

| Reported                               | LLT Selected              |
|--|---------------------------|
| Stomach upset from study drug overdose | Stomach upset<br>Overdose |

### 3.17.2 Overdose reported without clinical consequences

If an overdose report specifically states that there were no clinical consequences, select LLT *Overdose* and the additional LLT *No adverse effect* can be selected. (See Section 3.20).

Example

| Reported  | LLT Selected                  | Comment   |
|---|-------------------------------|---|
| Patient received an overdose of medicine without any adverse consequences | Overdose<br>No adverse effect | LLT <i>No adverse effect</i> can also be selected |

## 3.18 – Device-related Terms

### 3.18.1 Device-related event reported with clinical consequences

If available, select a term that reflects both the device-related event and the clinical consequence, if so reported.

Example

| Reported  | LLT Selected               |
|---|----------------------------|
| Patient with a vascular implant developed an infection of the implant | Vascular implant infection |
| Patient noted the prosthesis caused pain                              | Medical device pain        |

If there is no single MedDRA term reflecting the device-related event and the clinical consequence, select separate terms for both.

### Example

| Reported   | LLT Selected                                  |
|--|---|
| Ventricular tachycardia due to malfunction of device | Device malfunction<br>Ventricular tachycardia |
| Partial denture fractured leading to tooth pain      | Dental prosthesis breakage<br>Tooth pain      |

### 3.18.2 Device-related event reported without clinical consequences

If a device-related event is reported in the absence of clinical consequences, select the appropriate term.

### Example

| Reported                      | LLT Selected    |
|-------------------------------|-----------------|
| Medical device breakage       | Device breakage |
| My patch is leaking on my arm | Leaking patch   |

### 3.19 – Drug Interactions

This term includes reactions between drugs and other drugs, food, devices and alcohol. In this document, “drug” includes biologic products.

Labeled drug interactions may be medication errors. (See Section 3.15.4).

#### 3.19.1 Reporter specifically states an interaction

Select an interaction term and additional term(s) for any reported medical event.

### Example

| Reported   | LLT Selected                           |
|--|--|
| Torsade de pointes with suspected drug interaction   | Drug interaction<br>Torsade de pointes |
| Patient drank cranberry juice which interacted with anticoagulant drug causing an INR increase | Food interaction<br>INR increased      |

#### 3.19.2 Reporter does not specifically state an interaction

Two products may be used together, but if the reporter does not specifically state that an interaction has occurred, select terms only for the medical events reported.

Example

| Reported  | LLT Selected                        |
|---|-------------------------------------|
| Patient was started on an anti-seizure medication and a heart medication and developed syncope  | Syncope                             |
| Patient was already on an anti-seizure medication and was started on a heart medication, and anti-seizure medication levels increased | Anticonvulsant drug level increased |

**3.20 – No Adverse Effect and “Normal” Terms**

**3.20.1 No adverse effect**

LLT *No adverse effect* can be used when absence of an AR/AE is specifically reported, despite exposure to a product (See Sections 3.15.2 and 3.17.2).

Some organizations may want to record LLT *No adverse effect* for administrative purposes (e.g., pregnancy registries, overdose and medication error reports).

**3.20.2 Use of “normal” terms**

Terms for normal states and outcomes can be used as needed.

| Examples of Terms for “Normal” States and Outcomes      |
|---|
| Sinus rhythm<br>Normal baby<br>Normal electrocardiogram |

**3.21 – Unexpected Therapeutic Effect**

Some organizations may want to record LLT *Unexpected therapeutic effect* for reports of a beneficial effect of a product apart from the reason it had been given. (Such effects are not usually considered ARs/AEs).

Example

| Reported | LLT Selected |
|----------|--------------|
|----------|--------------|

| Reported   | LLT Selected   |
|--|--|
| A bald patient was pleased that he grew hair while using a product | Hair growth increased<br>Unexpected therapeutic effect |

### 3.22 – Modification of Effect

It is important to record modification of effect (e.g., increased, prolonged) although it is not always an AR/AE.

#### 3.22.1 Lack of effect

The **preferred option** is to select only the “lack of effect” term even if consequences are also reported. However, terms may also be selected for events associated with the lack of effect.

Example

| Reported  | LLT Selected                 | Preferred Option |
|---|------------------------------|------------------|
| Patient took drug for a headache, and her headache didn't go away | Drug ineffective             | ✓                |
|   | Drug ineffective<br>Headache |                  |
| Antibiotic didn't work  | Lack of drug effect          | ✓                |

#### 3.22.2 Do not infer lack of effect

Example

| Reported                               | LLT Selected | Comment   |
|--|--------------|---|
| AIDS patient taking anti-HIV drug died | Death        | Do not assume lack of effect in this instance. Select only a term for death (See Section 3.2) |

#### 3.22.3 Increased, decreased and prolonged effect

Example

| Reported                                 | LLT Selected          |
|--|-----------------------|
| Patient had increased effect from drug A | Increased drug effect |

| Reported                                 | LLT Selected          |
|--|-----------------------|
| Patient had decreased effect from drug A | Drug effect decreased |
| Patient had prolonged effect from drug A | Drug effect prolonged |

### 3.23 – Social Circumstances

#### 3.23.1 Use of terms in this SOC

Terms in SOC *Social circumstances* represent social factors and may be suitable to record social and medical history data. Such terms are not generally suitable for recording ARs/AEs; however, in certain instances, terms in SOC *Social circumstances* are the only available terms for recording ARs/AEs or may add valuable clinical information.

#### Example

| Reported                                | LLT Selected             |
|---|--------------------------|
| Patient's ability to drive was impaired | Impaired driving ability |

Terms in SOC *Social circumstances* are not multi-axial and, unlike terms in other “disorder” SOC in MedDRA (e.g., SOC *Gastrointestinal disorders*), they generally refer to a **person**, not to a medical condition.

Be aware of the impact that terms in SOC *Social circumstances* may have on data retrieval, analysis and reporting as illustrated in the table below:

| Term in SOC <i>Social circumstances</i> (“person”) | Similar term in “Disorder” SOC (“condition”) |
|--|--|
| Alcoholic  | Alcoholism                                   |
| Drug abuser  | Drug abuse                                   |
| Drug addict  | Drug addiction                               |
| Glue sniffer                                       | Glue sniffing                                |
| Smoker   | Nicotine dependence                          |

Note that “abuse” terms not associated with drugs/substances are in this SOC\*, regardless of whether they refer to the person or to the condition, as illustrated in the table below:

| LLT          | PT          |
|--------------|-------------|
| Child abuse  | Child abuse |
| Child abuser |             |

| LLT          | PT          |
|--------------|-------------|
| Elder abuse  | Elder abuse |
| Elder abuser |             |

(See Section 3.23.2 concerning illegal/criminal acts).

### 3.23.2 Illegal acts of crime or abuse

Terms for illegal acts of crime and abuse (excluding those related to drug/substance abuse) are in SOC *Social circumstances*, such as LLT *Physical assault*.

LLTs representing the **perpetrator** are linked to PTs describing the unlawful act committed. PTs representing the **victim** of unlawful acts generally begin with “*Victim of...*”.

Example

| Reported  | LLT Selected                    | Comment  |
|---|---------------------------------|--|
| Patient's history indicates that patient is a known sexual offender | Sexual offender                 | <b>Perpetrator;</b> LLT <i>Sexual offender</i> links to PT <i>Sexual abuse</i> in SOC <i>Social circumstances</i>                      |
| Patient was a childhood sexual assault victim                       | Childhood sexual assault victim | <b>Victim;</b> LLT <i>Childhood sexual assault victim</i> links to PT <i>Victim of sexual abuse</i> in SOC <i>Social circumstances</i> |

### 3.24 – Medical and Social History

Example

| Reported   | LLT Selected                                |
|--|---|
| History of gastrointestinal bleed and hysterectomy         | Gastrointestinal bleed<br>Hysterectomy      |
| Patient is a cigarette smoker with coronary artery disease | Cigarette smoker<br>Coronary artery disease |

### 3.25 – Indication for Product Use

Indications can be reported as medical conditions, prophylaxis of conditions, replacement therapies, procedures (such as anesthesia induction) and verbatim terms such as “anti-hypertension”. Terms from almost any MedDRA SOC – including SOC *Investigations* – may be selected to record indications.

#### 3.25.1 Medical conditions

Example

| Reported                       | LLT Selected  |
|--------------------------------|---------------|
| Hypertension                   | Hypertension  |
| Anti-hypertensive              |               |
| Chemotherapy for breast cancer | Breast cancer |

If the only information reported is the type of therapy, select the most specific term.

Example

| Reported                      | LLT Selected |
|-------------------------------|--------------|
| Patient received chemotherapy | Chemotherapy |

It may not be clear if the reported indication is a medical condition or a desired outcome of therapy. The term selected in either case may be the same.

Example

| Reported          | LLT Selected      | Comment  |
|-------------------|-------------------|--|
| Weight loss       | Weight loss       | Unclear if the purpose is to induce weight loss or to treat an underweight patient |
| Immunosuppression | Immunosuppression | Unclear if the purpose is to induce or to treat immunosuppression                  |

#### 3.25.2 Prevention and prophylaxis

When an indication for prevention or prophylaxis is reported, select the specific MedDRA term, if it exists. (Note: the words “prevention” and “prophylaxis” are synonymous in the context of MedDRA).

### Example

| Reported                  | LLT Selected           |
|---------------------------|------------------------|
| Prophylaxis of arrhythmia | Arrhythmia prophylaxis |
| Prevention of migraine    | Migraine prophylaxis   |

If there is no MedDRA term containing “prevention” or “prophylaxis”, choose one of the following options (Note: the **preferred option** is to select a general prevention/ prophylaxis term **and** a term for the condition):

### Example

| Reported                     | LLT Selected                 | Preferred Option | Comment  |
|------------------------------|------------------------------|------------------|--|
| Prevention of hepatotoxicity | Prevention<br>Hepatotoxicity | ✓                | Select the closest term for both concepts      |
|                              | Hepatotoxicity               |                  | Select a term for the condition                |
|                              | Prevention                   |                  | Select the closest prevention/prophylaxis term |

### 3.25.3 Procedures and diagnostic tests as indications

Select the appropriate term if the product is indicated for performing a procedure or a diagnostic test.

### Example

| Reported                              | LLT Selected            |
|---------------------------------------|-------------------------|
| Induction of anesthesia               | Induction of anesthesia |
| Contrast agent for angiogram          | Angiogram               |
| Contrast agent for coronary angiogram | Coronary angiogram      |

### 3.25.4 Supplementation and replacement therapies

Terms for supplemental and replacement therapies are in SOC *Surgical and medical procedures*. (See Section 3.13). If the product indication is for supplementation or replacement therapy, select the closest term.

Example

| Reported                         | LLT Selected                 |
|----------------------------------|------------------------------|
| Testosterone replacement therapy | Androgen replacement therapy |
| Prenatal vitamin                 | Vitamin supplementation      |

### 3.25.5 Indication not reported

If clarification cannot be obtained, select LLT *Drug use for unknown indication*.

Example

| Reported                                    | LLT Selected                    |
|---|---------------------------------|
| Aspirin was taken for an unknown indication | Drug use for unknown indication |

### 3.26 – Off Label Use

#### 3.26.1 Off label use when reported as an indication

“Off label use” refers to use of a product for an indication for which it is not labeled.

If a medical condition is reported as an indication along with “off label use”, the **preferred option** is to select a term for the medical condition for the “indications” field. Alternatively, select terms for the medical condition /indication and LLT *Off label use*. Select LLT *Off label use* alone **only** if it is the only information available.

Example

| Reported                            | LLT Selected                  | Preferred Option |
|-------------------------------------|-------------------------------|------------------|
| Hypertension; this is off label use | Hypertension                  | ✓                |
|                                     | Hypertension<br>Off label use |                  |

Example

| Reported      | LLT Selected  |
|---------------|---------------|
| Off label use | Off label use |

### 3.26.2 Off label use when reported with an AR/AE

If an AR/AE occurs as a result of off label use, the **preferred option** is to select a term for the AR/AE; alternatively, select LLT *Off label use* and a term for the AR/AE.

#### Example

| Reported   | LLT Selected            | Preferred Option |
|--|-------------------------|------------------|
| Patient was administered a drug off label for pulmonary hypertension and suffered a stroke | Stroke                  | ✓                |
|  | Stroke<br>Off label use |                  |

### 3.27 – Product Quality Issues

It is important to recognize product quality issues as they may have implications for patient safety. They may be reported in the context of adverse events or as part of a product quality monitoring system.

Product quality issues are defined as abnormalities that may be introduced during the manufacturing/labeling, packaging, shipping, handling or storage of the products. They may occur with or without clinical consequences. Such concepts may pose a challenge for term selection.

Familiarity with HLGT *Product quality issues* (in SOC *General disorders and administration site conditions*) is essential for term selection. Under this HLGT are categories of specific product quality issues such as HLT *Product packaging issues*, *Product physical issues*, etc. Navigating down to the appropriate LLTs from the MedDRA hierarchy is the optimal approach for term selection.

Explanations of the interpretations and uses of certain product quality issue terms (e.g., “Product coating incomplete”) are found in The MedDRA Introductory Guide (Appendix B, MedDRA Concept Descriptions).

#### 3.27.1 Product quality issue reported with clinical consequences

If a product quality issue results in clinical consequences, term(s) for the product quality issue and the clinical consequences should be selected.

#### Example

| Reported | LLT Selected |
|----------|--------------|
|----------|--------------|

| Reported  | LLT Selected  |
|---|---|
| New bottle of drug tablets have unusual chemical smell that made me nauseous                        | Product odor abnormal<br>Nauseous                             |
| I switched from one brand to another of my blood pressure medication, and I developed smelly breath | Product substitution issue<br>brand to brand<br>Smelly breath |

### 3.27.2 Product quality issue reported without clinical consequences

It is important to capture the occurrence of product quality issues even in the absence of clinical consequences.

#### Example

| Reported   | LLT Selected                        |
|--|-------------------------------------|
| Sterile lumbar puncture kit received in broken packaging (sterility compromised) | Product sterile packaging disrupted |

### 3.27.3 Product quality issue vs. medication error

It is important to distinguish between a product quality issue and a medication error.

Product quality issues are defined as abnormalities that may be introduced during the manufacturing/labeling, packaging, shipping, handling or storage of the products. They may occur with or without clinical consequences.

Medication errors are defined as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in control of the health care professional, patient or consumer.

Explanations of the interpretations of product quality issue terms are found in the MedDRA Introductory Guide (Appendix B, MedDRA Concept Descriptions).

#### Example

| Reported   | LLT Selected                                       | Comment               |
|--|--|-----------------------|
| Pharmacist dispensing Drug A inadvertently attached a product label for Drug B | Wrong label placed on medication during dispensing | Medication error      |
| The drug store clerk noted   | Product label                                      | Product quality issue |

| Reported   | LLT Selected     | Comment |
|--|------------------|---------|
| that the wrong product label was attached to some bottles in a shipment of mouthwash | on wrong product |         |

## Section 4 – APPENDIX

### 4.1 – Versioning

#### 4.1.1 Versioning methodologies

Each organization should have a versioning strategy that should be documented. The versioning strategy may differ between safety databases and clinical trial databases. For example, there may be no need to update clinical trial data from older trials if the data are not presently used or will not be used in the future. On the other hand, postmarketing safety data may be required to be reported in the current (or near-current) version of MedDRA, and version update recommendations then apply.

Users should choose the most optimal approach based on their organization's characteristics. The optional methods described below can be used to document the extent to which an organization has applied a new version of MedDRA. These methods should not be interpreted as regulatory requirements but may be used to communicate effectively between and within organizations.

The table below summarizes the types of versioning methods.

| Method | Description   | Resource Intensity | Data Accuracy |
|--------|---|--------------------|---------------|
| 1      | Begin to use new version for coding new data; no recoding of existing data  | Least              | Least         |
| 2      | Identify verbatim terms linked to non-current LLTs and recode existing data   | ↓                  | ↓             |
| 3      | Identify verbatim terms linked to non-current LLTs and recode existing data and<br>Recode verbatim terms to new LLTs that are direct or lexical matches |                    |               |
| 4      | Identify verbatim terms linked to non-current   | Most               | Most          |

| Method | Description   | Resource Intensity | Data Accuracy |
|--------|---|--------------------|---------------|
|        | <p>LLTs and recode existing data<br/>and<br/>Recode verbatim terms to new LLTs that are<br/>direct or lexical matches<br/>and<br/>Recode verbatim terms to new LLTs that are more<br/>accurate concepts</p> |                    |               |

This list may not be inclusive; other versioning methods may be used. Depending on how MedDRA data are stored in the database, additional steps may be needed to ensure consistency in data retrieval and reporting, including medical review of the data after the version method has been applied.

Note that Method 4 is the most resource intense and Method 1 is the least. There are additional points to consider: recoding to LLTs that are new direct matches or more accurate concepts (Method 4) provides the most accurate data compared to the other methods.

#### 4.1.2 Timing of version implementation

For single case reporting, the sender and receiver of the data need to be in synchrony regarding MedDRA versions. There are MSSO recommendations for the timing of the implementation of a new MedDRA release for both individual case safety reporting and clinical trial data (See Appendix, Section 4.2).

| <b>Date of New Reporting Version for Individual Case Safety Reporting</b>  |
|--|
| <p>A new release version of MedDRA should become the reporting version on the first Monday of the second month after it is released. To synchronize this event over the three ICH regions, the MSSO recommends midnight GMT, Sunday to Monday, for the switchover. For example :</p> <ul style="list-style-type: none"> <li>• 1 March - MedDRA X.0 released</li> <li>• First Monday of May - MedDRA X.0 becomes the reporting version</li> <li>• 1 September - MedDRA X.1 released</li> <li>• First Monday of November - MedDRA X.1 becomes the reporting version</li> </ul> |

#### 4.2 – Links and References

| Document | Link |
|----------|------|
|----------|------|

| Document   | Link  |
|--|---|
| MedDRA Introductory Guide                                  | <a href="http://meddramsso.com/files_acrobat/intguide_14_1_English_update.pdf">http://meddramsso.com/files_acrobat/intguide_14_1_English_update.pdf</a> |
| MedDRA Change Request Information document                 | <a href="http://meddramsso.com/subscriber_download_change_request.asp">http://meddramsso.com/subscriber_download_change_request.asp</a>                 |
| MedDRA Web-based Browser                                   | <a href="https://meddramsso.com/subscriber_download_tools_wbb.asp">https://meddramsso.com/subscriber_download_tools_wbb.asp</a>                         |
| MedDRA Desktop Browser                                     | <a href="https://meddramsso.com/subscriber_download_tools_browser.asp">https://meddramsso.com/subscriber_download_tools_browser.asp</a>                 |
| MedDRA Version Report (lists all changes in new version) * | <a href="https://meddramsso.com/secure/subscriber_download_translations.asp">https://meddramsso.com/secure/subscriber_download_translations.asp</a>     |
| MSSO's Recommendations for Single Case Reporting           | <a href="http://meddramsso.com/files_acrobat/VCGuide_semiannual.pdf">http://meddramsso.com/files_acrobat/VCGuide_semiannual.pdf</a>                     |
| MSSO's Recommendations for Clinical Trial Versioning       | <a href="http://meddramsso.com/files_acrobat/clinicaltrialversioning.pdf">http://meddramsso.com/files_acrobat/clinicaltrialversioning.pdf</a>           |

\* Requires user ID and password to access

### 4.3 Membership of the ICH Points to Consider Working Group

#### 4.3.1 Current members of the ICH Points to Consider Working Group

| Affiliation   | Member            |
|---|-------------------|
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|   | Carmen Kreft Jais |
| European Federation of Pharmaceutical Industries Associations | Hilary Vass**     |
|   | Christina Winter* |
| Health Canada   | Alison Langevin   |

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|  | Lynn Macdonald      |
| Japanese Maintenance Organization                    | Osamu Handa         |
|  | Kazuyuki Sekiguchi  |
|  | Reiji Tezuka        |
| Japan Pharmaceutical Manufacturers Association       | Yo Tanaka           |
| MedDRA MSSO  | Patricia Mozzicato  |
| Ministry of Health, Labour and Welfare               | Izumi Oba           |
|  | Daisuke Tanaka      |
| Pharmaceutical Research and Manufacturers of America | Susan M. Lorenski   |
|  | JoAnn Medbery       |
| US Food and Drug Administration                      | John (Jake) Kelsey* |
|  | Toni Piazza-Hepp    |
|  | Sonja Brajovic      |

\* Current co-Rapporteurs

\*\* Acting Rapporteur for June 2010 meeting of Working Group

#### 4.3.2 Former members of the ICH Points to Consider Working Group

| <b>Affiliation</b>  | <b>Member</b>  |
|---|--|
| Commission of the European Communities                        | Dolores Montero  |
| European Federation of Pharmaceutical Industries Associations | Barry Hammond†; Reinhard Fescharek†  |
| Health Canada   | Heather Morrison; Michelle Séguin;<br>Heather Sutcliffe; Bill Wilson   |
| Japanese Maintenance Organization                             | Akemi Ishikawa; Yasuo Sakurai; Yuki Tada   |
| Japan Pharmaceutical Manufacturers Association                | Takayoshi Ichikawa; Akemi Ishikawa;<br>Satoru Mori; Yasuo Sakurai;<br>Kunikazu Yokoi   |
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| Ministry of Health, Labour and Welfare                        | Tamaki Fushimi; Wakako Horiki;<br>Kazuhiro Kemmotsu; Tatsuo Kishi; Chie Kojima;<br>Emiko Kondo; Kemji Kuramochi;<br>Tetsuya Kusakabe; Kaori Nomura;<br>Yoshihiko Sano; Kenichi Tamiya; Takashi |

| Affiliation   | Member   |
|---|--|
|   | Yasukawa; Manabu Yamamoto;<br>Nobuhiro Yamamoto        |
| Pharmaceutical Research and<br>Manufacturers of America | David Goldsmith; Sidney Kahn;<br>Margaret M. Westland† |
| US Food and Drug Administration                         | Miles Braun; Andrea Feight; Brad Leissa                |

† Former Rapporteur