

**MedDRA™ TERM SELECTION:
POINTS TO CONSIDER**

Release 2.0

ICH-Endorsed Guide for MedDRA Users

**Application to Adverse Drug Reactions
and Adverse Events**

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1.0 INTRODUCTION

A great deal of time, resources, and expertise has been invested in developing an improved standard international medical terminology. The Medical Dictionary for Regulatory Activities (MedDRA)¹ was designed for the specific use of sharing regulatory information for human medical products. However, unless users can achieve a certain amount of consistency in the way they assign particular terms to particular symptoms, signs, diseases, etc., the new terminology will yield little improvement over the divergent practices of the past.

The objective of this “Points to Consider” Document is to promote medical accuracy and consistency when using MedDRA to share clinical safety data worldwide. This will in turn facilitate a common understanding of safety data shared across and/or between academic, commercial and regulatory entities. It could also be used by healthcare professionals, researchers and other interested parties outside of the regulated pharmaceutical/biological industry. It is expected that as the usage of and experience with MedDRA increases, there will be additions and perhaps changes in these points to consider.

1.1 Purposes of Using MedDRA

To aggregate reported terms in medically meaningful groupings for the purpose of reviewing and/or analyzing safety data

To facilitate identification of common data sets for evaluation of clinical and safety information

To facilitate consistent retrieval of specific cases or medical conditions from a database

To improve consistency in comparing and understanding “safety signals” and aggregated clinical data

To facilitate electronic data interchange of clinical safety information

To report adverse reaction/adverse event (ADR/AE)² terms via individual case safety reports

To include ADR/AEs in tables, analyses, and line listings for reports

To identify frequency of medically similar ADR/AEs

¹ MedDRA refers to all sequential and translated versions of the terminology, which are maintained by either the Maintenance and Support Services Organization (MSSO) or the Japanese Maintenance Organization (JMO).

² For ADR/AE definitions, refer to ICH Guidelines and CIOMS publications.

1.2 Background

This Points to Consider has been prepared to help all MedDRA users to begin on common ground, as the terminology itself does not contain specific guidelines for its use; it provides a framework to foster consistent use of a standard terminology for data in-put and retrieval. The end result allows for medically meaningful review and analysis of safety data.

For optimal MedDRA term selection, it is suggested that the reader also refer to the MedDRA Introductory Guide, which is provided with each MedDRA subscription.

This Points to Consider document is an ICH-endorsed guide for MedDRA users that is designed to be a living, companion document to the MedDRA Terminology. It was developed by a working group to the MedDRA MSSO Management Board consisting of regulatory and industry representatives of the European Union, Japan and the United States, as well as representatives from Canada, the MedDRA Maintenance and Support Services Organization (MSSO), and Japanese Maintenance Organization (JMO).

Specific examples contained in this document are based on MedDRA version 3.2, and subsequent changes to the terminology may render the examples outdated. However, the principles illustrated should remain valid.

1.3 Scope of the Points to Consider

The current document focuses on term selection for data entry of ADR/AEs.

2.0 GENERAL PRINCIPLES

2.1 Level of term selection

Select the lowest level term that most accurately reflects the initial reporter's words.

2.2 Choice of term

2.2.1 It is not appropriate to address deficiencies in MedDRA by developing organization-specific solutions. If the medical concept reported is not adequately represented in the latest version of MedDRA, the appropriate solution is to submit a change request to the MSSO.

Example: The term "HIV viral load increased" was added to MedDRA following a user's request.

2.2.2 Medical judgment should be used if an exact match cannot be found, but the medical concept can be adequately represented by an existing term.

Example: If “brittle hair” is reported, “Hair texture abnormal” more accurately reflects the medical concept than the less-specific term “Hair disorder NOS.”

2.2.3 In situations where a specific medical concept is not represented by a **single** MedDRA term, a new term should be requested from the MSSO. While awaiting the addition of the new term, it is appropriate to select one or more existing terms. A consistent approach should be used. The impact on data retrieval, analysis, and reporting should be carefully considered.

Example: If “metastatic colon cancer” were not represented in MedDRA by a single term, it would be appropriate to select “Colon cancer NOS” or “Metastases NOS” or both “Colon cancer NOS” and “Metastases NOS”.

If just one term is selected, specificity will be lost, whereas the selection of two terms may lead to redundant counts.

2.3 Do not subtract or add information

2.3.1 Do not omit reported information

Terms should be selected for every ADR/AE reported, regardless of perceived relationship to the drug product. No reported medical concept should be excluded from the term selection process.

2.3.2 Do not add information

No new medical concepts are to be added. Neither a diagnosis nor a mechanism of action is to be derived or inferred from reported signs or symptoms.

Example: If abdominal pain, increased serum amylase, and increased serum lipase are reported, it is inappropriate to assign a diagnosis of “pancreatitis”.

2.3.3 Diagnosis reported with signs and symptoms

If both a diagnosis and its characteristic signs and symptoms are provided by the reporter, one may select terms for both, but it is sufficient to select a term for the diagnosis and not for the signs and symptoms. However, terms should also be selected for signs or symptoms that are not generally recognized as part of that diagnosis.

Example: If “anaphylactic reaction” is reported with rash, dyspnea, hypotension, and laryngospasm, selecting “anaphylactic reaction” alone is appropriate.

Example: If “myocardial infarction” is reported with “chest pain, dyspnea, diaphoresis, ECG changes, and jaundice”, it would be appropriate to select terms for both “myocardial infarction” and “jaundice”.

2.4 Quality Assurance

Tools such as auto-encoders may be helpful, but human intervention is necessary to assure the end result fully reflects the original information and makes medical sense.

To promote consistent term selection, organizations are encouraged to document their term selection strategies, methods, and quality assurance procedures, which should be consistent with the “MedDRA Rules and conventions” described in the MedDRA Introductory Guide.

The MedDRA terminology is multi-axial and more complex than common terminologies previously used. Therefore, term selection should be reviewed by a qualified individual, a person with medical background and/or training and who is also trained in the use of MedDRA.

The assignment of terms across SOCs is pre-determined within the terminology and should not be altered by users. If MedDRA users believe that term(s) are inappropriately placed in the hierarchy, they should inform the MSSO by the usual change request process.

Example: In a previous version of MedDRA it was found that the Primary SOC for the term “Factor VIII deficiency” was “Blood and lymphatic system disorders”. It was corrected by making “Congenital and familial/genetic disorders” the primary SOC and “Blood and lymphatic system disorders” the secondary SOC.

2.5 Terms can be selected in any language for which MedDRA is maintained

2.6 Quality of source data

Since the quality of the information originally reported is reflected in the quality of data output, it is strongly encouraged that clarification of data that are ambiguous, confusing or unintelligible be obtained for optimal term selection. If clarification cannot be obtained, refer to Term Selection Points: Conflicting/ambiguous/vague information (section 3.3).

Data clarity can be promoted through careful design of data collection forms and training of individuals involved in the data collection process, e.g., clinical investigators/monitors, medical product sales representatives and others.

3.0 TERM SELECTION POINTS

3.1 Provisional diagnoses

3.1.1 If only a single provisional diagnosis e.g. “suspicion of”, “probable”, “presumed”, “likely”, “questionable”, etc. is provided, in the absence of additional clinical information, it should be managed as if a confirmed diagnosis. However, in some regions, provisional diagnoses are not encountered.

Example: If “possible myocardial infarction” is the only information reported, select “Myocardial infarction”.

3.1.2 If both a provisional diagnosis and its characteristic signs and symptoms are provided by the reporter, one may select terms for both, but it is sufficient to select a term for the provisional diagnosis and not for the signs and symptoms. However, terms should also be selected for signs or symptoms that are not generally recognized as part of that provisional diagnosis.

Example: If “chest pain, dyspnea, diaphoresis, and jaundice (possible myocardial infarction)” is reported, it would be appropriate to select terms for both “myocardial infarction” and “jaundice”.

3.1.3 If there are multiple provisional diagnoses without signs and symptoms, select terms for each provisional diagnosis.

Example: If a differential diagnosis that includes pulmonary embolism, myocardial infarction, and congestive heart failure is reported, select terms for each provisional diagnosis.

3.1.4 If multiple provisional diagnoses are reported together with signs and symptoms, it is sufficient to select terms for only the signs and symptoms.

Example: If a differential diagnosis that includes pulmonary embolism, myocardial infarction, and congestive heart failure is reported along with chest pain, cyanosis, shortness of breath, and hypotension, select “Chest pain”, “Cyanosis”, “Shortness of breath”, and “Hypotension NOS”. It is also acceptable to select terms for each provisional diagnosis, in addition to the signs and symptoms.

3.2 Death

3.2.1 Death is an outcome and not usually considered to be an ADR/AE. When an ADR/AE is reported in association with a fatal outcome, select a term for the ADR/AE, and capture death as the outcome.

Example: If “death due to myocardial infarction” is reported, select “Myocardial infarction” and capture death as the outcome.

3.2.2 If multiple ADR/AEs are reported in association with a fatal outcome, select MedDRA terms for each reported event.

Example: If “constipation, ruptured bowel, peritonitis, sepsis, and patient died” are reported, select “Constipation”, “Perforated bowel”, “Peritonitis”, and “Sepsis”, and capture death as the outcome.

3.2.3 If the only information reported is death, then the most specific death term available should be selected.

Example: If a reporter states only that “a patient was found dead”, select “Found dead”.

3.3 Conflicting/ambiguous/vague information

When conflicting, ambiguous, or vague information is provided, it can be difficult to select a term that will lead to appropriate data retrieval. In such circumstances, attempts should be made to obtain more specific information. (See *General Principles: Quality of Source Data*.)

If clarification attempts have failed, the examples below may be helpful:

3.3.1 Conflicting information:

Example: If only “hyperkalemia with a serum potassium of 1.6 mEq/L” is reported, select “Potassium abnormal”, because this single term conveys both medical concepts.

3.3.2 Ambiguous information:

Example: If “GU pain” is reported, “GU” could refer to either “genito-urinary” or “gastric ulcer”. However, since pain was reported, select “Pain”.

3.3.3 Vague information:

Example: If the only information reported is “patient experienced every listed adverse event”, and attempts to obtain more specific information are unsuccessful, it is appropriate to select “Unevaluable reaction”.

3.4 Combination terms

When combination terms are reported, apply medical judgment. If splitting provides more clinical information, it is appropriate to select more than one term.

Example: If “diarrhea and vomiting” is reported, select both terms “Diarrhea” and “Vomiting”.

Example: If “retinopathy due to diabetes” is reported, select “Diabetic retinopathy”.

Example: If “wrist fracture due to fall” is reported, select both terms “Wrist fracture” and “Fall”.

3.5 Pre-existing medical conditions

Pre-existing medical conditions that have not changed are not classified as ADR/AEs.

3.5.1 It is important to capture the concept that a pre-existing condition was modified, such as aggravated, exacerbated, worsened, intermittent, recurrent, progressive, or improved. If a pre-existing medical condition is modified, select the specific MedDRA term, provided that it exists.

Example: If “exacerbation of myasthenia gravis” is reported, select “Myasthenia gravis aggravated”.

3.5.2 In the absence of such a term, the following options are appropriate:

3.5.2.1 Request a new term from the MSSO by the usual change request process. In general the MSSO will not add such terms unless there is clearly demonstrated medical significance, as stated in the MedDRA Introductory Guide, version 3.2.

3.5.2.2 Select a term for the condition and capture the modification in a consistent, documented way without selecting an additional MedDRA term.

Example: If “halitosis worsened” is reported, select “Halitosis” only.

3.5.2.3 Select a term for the condition and an additional term to describe the modification of the condition, such as “*Condition aggravated*”, “*Disease progression NOS*”, etc.

Example: If “progression of Alzheimer’s disease” is reported, select “Alzheimer’s disease” and “Disease progression NOS”.

3.6 Congenital terms

The definition of “congenital” for MedDRA is “any condition present at birth, whether genetically inherited or acquired in utero” (MedDRA Introductory Guide).

3.6.1 Use terms from the “Congenital and familial/genetic disorders” SOC when the condition is described as congenital by the reporter or when medical judgment establishes that the condition was present in the child at the time of birth.

Example: If either “congenital heart disease” or “child born with heart disease” is reported, select “Congenital heart disease NOS”.

3.7 Medical/Surgical Procedures

Medical/Surgical Procedures are not usually considered ADR/AEs. However, in the following situations, it may be appropriate to select procedure terms.

3.7.1 The procedure represents the only information provided.

Example: If “patient had gallbladder surgery” is the only information reported, select “Gallbladder operation NOS”.

3.7.2 If a procedure is reported in combination with a diagnosis, it is sufficient to select a term for the ADR/AE alone. It is also acceptable to select a term for the procedure in addition to a term for the diagnosis.

Example: If “liver transplantation due to liver failure” is reported, select either “Liver failure” alone or both “Liver failure” and “Liver transplant”.

Example: If “surgery for bleeding gastric ulcer” is reported, select either “Bleeding gastric ulcer” alone or both “Bleeding gastric ulcer” and “Gastric operation NOS”.

3.8 Investigations

The “Investigations” SOC includes only test names and their qualifiers (e.g., increased, decreased, abnormal, normal). Corresponding medical conditions, such as “hyper“ and “hypo“ terms, are represented in other “disorder” SOCs. By design, the terms in the “Investigations” SOC are not multi-axial. Therefore, for data retrieval, the “Investigations” SOC must always be considered, in addition to the specific “disorder” SOC(s).

3.8.1 The results of investigations may or may not represent ADR/AEs. When selecting terms for results of investigations, the following points may be helpful.

3.8.1.1 Medical conditions versus laboratory results.

Example: If “hypoglycemia” is reported, select “Hypoglycemia”.

(Note: “Hypoglycemia” maps to the Metabolism and nutrition disorders SOC.)

Example: If “decreased glucose” is reported, select “Glucose decreased”.

(Note: “Decreased glucose” maps to the Investigations SOC)

3.8.1.2 Unambiguous laboratory results

Example: If a value is reported that is clearly below the reference range, e.g., glucose 40 mg/dL, select “Glucose low”.

3.8.1.3 Ambiguous laboratory results

Example: If “his glucose was 40” is reported without units, and additional clarification cannot be obtained, select “Glucose abnormal”.

3.8.2 It is not necessary to select terms for each diagnostic result that is consistent with the clinical diagnosis provided by the reporter.

Example: If “elevated potassium, K 7.0 mmol/L and hyperkalemia” are reported, it is sufficient to select “Hyperkalemia” alone.

3.8.3 Nonspecific investigation terms should only be used when more specific result terms are not available.

Example: If “abnormal liver function tests” is reported, select “Abnormal liver function tests”.

Example: If “increased alkaline phosphatase, increased SGPT, increased SGOT, and elevated LDH ” is reported, select the four corresponding individual terms. Do not combine the four terms by selecting a single term, such as “Liver function tests raised”.

3.9 Medication/administration errors and accidental exposures

3.9.1 Medication errors in the absence of clinical consequences are not ADR/AEs, however, it is important to capture the occurrence of a medication error. Select the closest term available, e.g. “Drug maladministration” or “Medication error”. It is acceptable to select the additional term “No adverse effect”, if specifically so reported.

Example: If “medication was given intravenously instead of intramuscularly” is reported, select “Wrong route of administration”.

3.9.2 The same principle applies to accidental exposures.

Example: If “nurse splashed an injectable drug in her eye” is reported, select “Inadvertent exposure to drug”.

3.10 Overdose/Toxicity/Poisonings

3.10.1 Overdose, toxicity, and poisoning are three different concepts in MedDRA and should not be considered synonymous. If overdose, toxicity, or poisoning, are not explicitly reported, it may not be appropriate to select these terms.

Example: If report of “overdose of pills”, select “Overdose”

3.10.2 Select terms for signs and/or symptoms reported in association with an overdose. It is acceptable to select the additional term “No adverse effect”, if specifically so reported.

3.11 Drug interactions

This term includes drug/drug³, drug/food, drug/device, and drug/alcohol interactions. With respect to interactions, MedDRA does not include specific product names.

When the reporter specifically states that an interaction occurred, select an appropriate interaction term.

3.12 No adverse effect

The term “No adverse effect” could be used when no ADR/AE occurred, despite exposure to a product. It may be appropriate to use this term to maintain records for administrative purposes, e.g. for pregnancy registries, overdoses, and medication errors.

It is appropriate to use this term if the reporter specifically states that no adverse event occurred.

3.13 Unexpected therapeutic effect

Unexpected therapeutic effects are not usually considered ADR/AEs. Reports occasionally describe the beneficial effect of a drug aside from the use for which it had been given.

Example: If “a bald patient was pleased that he grew hair while on an antihypertensive” is reported, the term “Benefit unexpected” may be appropriate. In addition, a term may be selected for hair growth.

3.14 Modification of effect

Modifications of effect are not always considered ADR/AEs; however, it is important to capture the information, and in certain situations, lack of effect is a reportable event. MedDRA contains many terms that describe modifications of effect. Select the closest term(s) available to capture the reported medical concept(s), unless this information is captured by another means.

3.14.1 Lack of effect

It is appropriate to use this group of terms when:

3.14.1.1 The reporter specifically states that the drug was ineffective (or did not work, or similar wording);

Example: If “antibiotic didn’t work” is reported, select “Lack of drug effect”.

Example: If “patient took drug, her headache didn’t go away, drug is ineffective”, is reported, select “Drug ineffective”.

³ In this document, the term “drug” includes biological products

3.14.1.2 The information reported clearly communicates that the expected effect. was not obtained;

Example: If “patient developed measles despite measles vaccination” is reported, select “Vaccination failure” and “Measles”.

Example: If “an epileptic patient took an anti-convulsant, but the seizures continued unchanged”, select “Lack of drug effect”.

3.14.1.3 In some situations it is not appropriate to infer a lack of effect.

Example: If “AIDS patient taking anti-HIV drug died” is reported, do not assume “Lack of drug effect”; select a term for death, as described in section 3.2 of this document.

3.14.2 Increased, Decreased, and Prolonged effects

It is appropriate to use this group of terms when the reporter specifically identifies a modification of effect.

Example: If “patient had increased effect from drug A” is reported, select “Increased drug effect”.

Example: If “patient had decreased effect from drug A” is reported, select “Drug effect decreased”.

Example: If “patient had prolonged effect from drug A” is reported, select “Drug effect prolonged”.

3.15 Social Circumstances

The terms in the “Social Circumstances SOC” are not multi-axial in MedDRA. The SOC contains terms reflecting clinical conditions that are exact word matches to ADR/AE terms. Users should be aware of the impact that use of these terms will have on data retrieval, data analysis, and reporting. The following examples are illustrative:

Social Circumstances SOC	“Disorder” SOC
Blind	Blindness
Deaf	Deafness
Paralyzed	Paralysis
Drug addict	Drug addiction