MedDRA® DATA RETRIEVAL AND PRESENTATION: POINTS TO CONSIDER

ICH-Endorsed Guide for MedDRA Users on Data Output

Condensed Version

2018

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INTRODUCTION

The **Med**ical **D**ictionary for **R**egulatory **A**ctivities terminology (MedDRA) was designed for sharing regulatory information for human medical products. In order for MedDRA to harmonise the exchange of coded data, users should be consistent in the assignment of terms to verbatim reports of symptoms, signs, diseases, etc.

MedDRA is a large terminology with very specific ("granular") terms called Lowest Level Terms (LLTs) that serve to accurately record the reporter's words (verbatim term). LLTs are generally synonyms linked to their parent terms known as Preferred Terms (PTs).PTs are also relatively specific and large in number.

While a highly granular terminology such as MedDRA reduces the need for interpretation at data entry, it impacts the processes of data retrieval, sorting and presentation necessary for support of drug development, pharmacovigilance and risk management. The hierarchical structure of MedDRA facilitates data retrieval by providing grouping terms (High Level Terms [HLTs] and High Level Group Terms [HLGTs]) that aggregate the very specific terms used for coding into broader medical categories. MedDRA's multiaxiality (assignment of a PT to more than one System Organ Class [SOC]) allows flexibility in data retrieval via primary and secondary paths. Whilst grouping terms and multiaxiality permit a reasonable first approach to data retrieval, the complexity of MedDRA requires guidance to optimise the results.

This condensed *Data Retrieval and Presentation: Points to Consider* (DRP:PTC) document is an ICH-endorsed guide for MedDRA users. Its focus is on the fundamental principles of data retrieval; for more detailed information and examples of different data retrieval and presentation options, users should refer to the full DRP:PTC document. The full DRP:PTC is available in English and Japanese, is updated in step with new MedDRA versions and is a companion document to MedDRA. In contrast, this condensed DRP:PTC is not updated with each MedDRA release.

Both the full and condensed DRP:PTC documents were developed and are maintained by a working group charged by the ICH Management Committee. The working group consists of representatives of ICH regulatory and industry members, the World Health Organization, the MedDRA Maintenance and Support Services Organization (MSSO) and the Japanese Maintenance Organization (JMO).

The principles described in this document are most effective when used in conjunction with the principles described in the *MedDRA Term Selection: Points to Consider* document for data entry (coding). This condensed DRP:PTC document summarizes data retrieval and presentation options for either industry or regulatory purposes. Although MedDRA includes some data retrieval tools, this document addresses data retrieval in a broader context.

Examples shown in this document are intended to facilitate reader understanding and are **not** intended to imply regulatory requirements.

Objectives of this Document

The objective of this condensed DRP:PTC document is to demonstrate how data retrieval options impact the accuracy and consistency of data output. For example, certain drugs or therapeutic areas may need a customised approach for data output. Options for data input described in the *MedDRA Term Selection: Points to Consider* document – or in organisation-specific coding guidelines – should also be taken into consideration.

Organisations are encouraged to document their data retrieval and output strategies, methods and quality assurance procedures in organisation-specific guidelines which should be consistent with this condensed DRP:PTC document.

Reasons to Use MedDRA

MedDRA is used to report adverse reaction/adverse event (AR/AE) terms in individual case reports – both on paper or electronically. Its 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 AR/AEs, and capture and analyse related data such as product indications, investigations, and medical and social history.

How to Use this Document

This condensed DRP:PTC document addresses fundamental data retrieval principles and provides a framework to foster **consistent** use of MedDRA for data analysis and presentation for medically meaningful review and analysis of clinical data. The full DRP:PTC document provides more detailed information, including examples and figures illustrating data retrieval and presentation options.

The principles described in this document apply to all data encoded with MedDRA with a focus on aggregated data. This document does not address the use of MedDRA for single case reporting, labeling, medical evaluation and statistical methodology.

This document highlights the impact of MedDRA's structure, rules and conventions on data output. It is not intended to communicate specific regulatory reporting requirements or address specific database issues. The condensed and full DRP:PTC documents cannot address every situation, therefore, medical judgment should always be applied.

The document is not a substitute for MedDRA training. It is essential for users to have knowledge of MedDRA's structure and content. For optimal use of MedDRA, one should refer to the full DRP:PTC document, the MedDRA *Introductory Guide*, the *Introductory Guide for Standardised MedDRA Queries (SMQs)*, and the *MedDRA Term Selection: Points to Consider* document.

Users may also wish to refer to the CIOMS report "Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA" for additional information about the purpose and appropriate use of SMQs in safety surveillance activities. Please refer to the CIOMS website for more information on

the second edition (2016) of this report, also known as the “Red Book”. See Appendix, Section 6.1, Links and References.

GENERAL PRINCIPLES

Quality of Source Data

High quality data output occurs when the quality of the information originally reported is maintained with consistent and appropriate term selection. Organisations should pursue continuous oversight of data quality. Data quality issues are also addressed in the *MedDRA Term Selection: Points to Consider* document.

Data conversion considerations

Give special consideration to the method used to convert data from other terminologies into MedDRA. The methods used can impact retrieval and presentation strategies.

- Method 1 – Data converted from legacy terminology terms to MedDRA

- Results will reflect the specificity of the previous terminology
- The benefits of the greater specificity of MedDRA are not attained

Example

Reported	Legacy Term	MedDRA Term
Gastrointestinal ischaemia	Gastrointestinal Disorder	Gastrointestinal disorder

- Method 2 – Data converted from the original reported terms (verbatim terms) to MedDRA terms

Example

Reported	Legacy Term	MedDRA Term
Gastrointestinal ischaemia	Gastrointestinal Disorder	Gastrointestinal ischaemia

Document the data conversion method used, including the date of the conversion and the MedDRA version used.

Impact of data conversion method

Combining the two conversion methods described above can affect interpretation of data output.

Example

Data Output with Combined Data Conversion Methods
If data have been converted directly from legacy terminology terms to MedDRA terms (Method 1), and if newly acquired data are coded directly from reported terms to MedDRA, the resulting differences in specificity could make interpretation difficult.

When designing a search strategy, it may be useful to examine the **reported terms** for data converted using Method 1. If the search has been based on specific MedDRA terms, data previously coded to non-specific terms may be otherwise overlooked.

Example

Impact of Method 1 Conversion on Search Strategy
If searching with MedDRA PT *Gastrointestinal ischaemia*, cases of gastrointestinal ischaemia coded with the legacy term *Gastrointestinal disorder* would be missed. In this case, it would be important to know the date of the legacy data conversion and the MedDRA version used.

To conduct a search requiring this level of detail, it might be necessary to review or recode from the reported terms. For legacy data, this information might be found in fields other than those for ARs/AEs.

Documentation of Data Retrieval and Presentation Practices

It is important to document MedDRA term selection conventions, data retrieval and output strategies (including SMQs and other queries) and quality assurance procedures. Organisation-specific strategies should be consistent with the *Points to Consider* documents and should include:

- MedDRA version used for the search
- Search strategy methods (sufficiently detailed to be reproducible)
- Version update processes
- Processes for creating and maintaining customized MedDRA queries

Do Not Alter MedDRA

MedDRA is a **standardised** 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.

Organisation-Specific Data Characteristics

Although MedDRA is a standardised terminology, different organisations have implemented it in various ways. It is important to understand organisation-specific data characteristics and implementation strategies.

- Database structure (how the MedDRA hierarchy is stored and used)
- Data storage (e.g., level of term, synonym/reported term)
- Data conversion from other terminologies (if applicable)
- Coding practices over time
- Limitations or restrictions such as inability to display secondary SOC links
- Term selection principles used
    - Selecting more than one term when coding a medical condition increases counts of terms.
    - Selecting a diagnosis term only (and not terms for signs and symptoms) reduces the counts of terms.
    - The adverse event profile resulting when both diagnosis and signs/symptoms terms are coded may appear different than when the diagnosis only is coded. Always consider the organisation's coding conventions when using or comparing data from other databases (e.g., co-developing or co-marketing partners, regulatory authorities).

Characteristics of MedDRA that Impact Data Retrieval and Analysis

MedDRA's structure, rules and conventions are detailed in the MedDRA *Introductory Guide.*

Keep the following MedDRA characteristics in mind for data retrieval and presentation:

Grouping terms (HLTs and HLGTs)

The HLT and HLGT levels are an additional tool for data analysis and retrieval as they provide clinically relevant groupings of terms.

Example

Cardiac Arrhythmias
HLGT *Cardiac arrhythmias*
HLT *Cardiac conduction disorders*
HLT *Rate and rhythm disorders NEC*
HLT *Supraventricular arrhythmias*
HLT *Ventricular arrhythmias and cardiac arrest*

Example as of MedDRA Version 19.0

Review terms within the HLGT or HLT of interest to be sure that all terms therein are suited for the purpose of the output.

Granularity

MedDRA PTs are more specific ("granular") than comparable terms in other terminologies. Related events that may have been represented by a single term in another terminology may be represented by more than one MedDRA PTs. The potential impact of this on signal detection should be kept in mind.

Multiaxiality

Multiaxiality means that a PT may exist in more than one SOC. This allows terms to be grouped in different, but medically appropriate, ways (e.g., by aetiology or organ system). Each PT is assigned one primary SOC; all other SOC assignments for that PT are called "secondary". Having a single primary SOC prevents double counting of events when outputting data from all SOCs.

Primary SOC assignment rules

Primary SOC assignment rules are described in the MedDRA *Introductory Guide*. Because these rules allow for terms related to a particular medical condition to be in more than one SOC, users should be familiar with the general structure and content of all MedDRA SOCs to be sure that data are not overlooked.

PTs relating to diseases or signs and symptoms are assigned to the prime manifestation site SOC with the following exceptions:

- Terms for congenital and hereditary anomalies are assigned to SOC *Congenital, familial and genetic disorders* as the primary SOC.
- Terms for neoplasms are assigned to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as primary SOC. This does not apply to cyst and polyp terms which have as their primary SOC the manifestation site SOC.
- Terms for infections are assigned to SOC *Infections and infestations* as the primary SOC.

If a PT links to more than one of these three "exceptions" SOCs, the following priority is used to determine the primary SOC:

- SOC *Congenital, familial and genetic disorders*
- SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
- SOC *Infections and infestations*

Non multiaxial SOCs

Terms in the following three SOCs do not have multiaxial links:

SOC *Investigations*

SOC *Surgical and medical procedures*

SOC *Social circumstances*

This is important when designing queries and other retrieval strategies because one cannot rely on multiaxiality to locate all terms of interest in MedDRA.

Example

Terms for Test Results in SOC *Investigations*
When querying a database for events or cases of hepatic abnormalities, data coded to PTs in SOC *Hepatobiliary disorders* is a logical starting point. Additionally, data coded to terms in SOC *Investigations* – such as PT *Liver function test abnormal* – and data coded to terms in SOC *Surgical and medical procedures* - such as PT *Liver transplant* – could also be of interest. Neither of these PTs has a link to SOC *Hepatobiliary disorders.* **Failure to consider data coded in the non multiaxial SOCs could lead to incomplete analysis.**

MedDRA Versioning

MedDRA is updated twice yearly. Version "X.0" contains both simple and complex changes; version "X.1" contains only simple changes.

Organisations should be aware of the types of MedDRA changes for their possible impact on data output.

Both simple and complex changes impact retrieval and presentation strategies. Users should read the documentation provided with each MedDRA release, especially the *What's New* document. The MSSO and JMO provide tools to assist the user in comparing the changes between MedDRA versions. The Version Report (provided by the MSSO and JMO) is a spreadsheet listing all changes between the current version of MedDRA and the one previous to it; this spreadsheet is provided with each new release of MedDRA. The MSSO also provides the MedDRA Version Analysis Tool (MVAT) that facilitates identification and understanding of the impact of changes between any two MedDRA versions, including non-consecutive ones. Organisations should plan and document their strategy for handling MedDRA version updates. When planning or performing data retrieval and presentation, the MedDRA version used should be documented.

Keep in mind that MedDRA changes may impact previous data retrieval approaches and results, including event frequencies.

Example

Impact of Version Changes – Change of Primary SOC Assignment
PT *Intra-abdominal haematoma* had a primary link to SOC *Vascular disorders* and a secondary link to SOC *Gastrointestinal disorders* in MedDRA Version 18.0. In Version

Impact of Version Changes – Change of Primary SOC Assignment
18.1, the primary SOC assignment was changed to SOC *Gastrointestinal disorders* and the secondary assignment to SOC *Vascular disorders*. In a primary SOC output of data, PT *Intra-abdominal haematoma* will seem to have “disappeared” from SOC *Vascular disorders*.

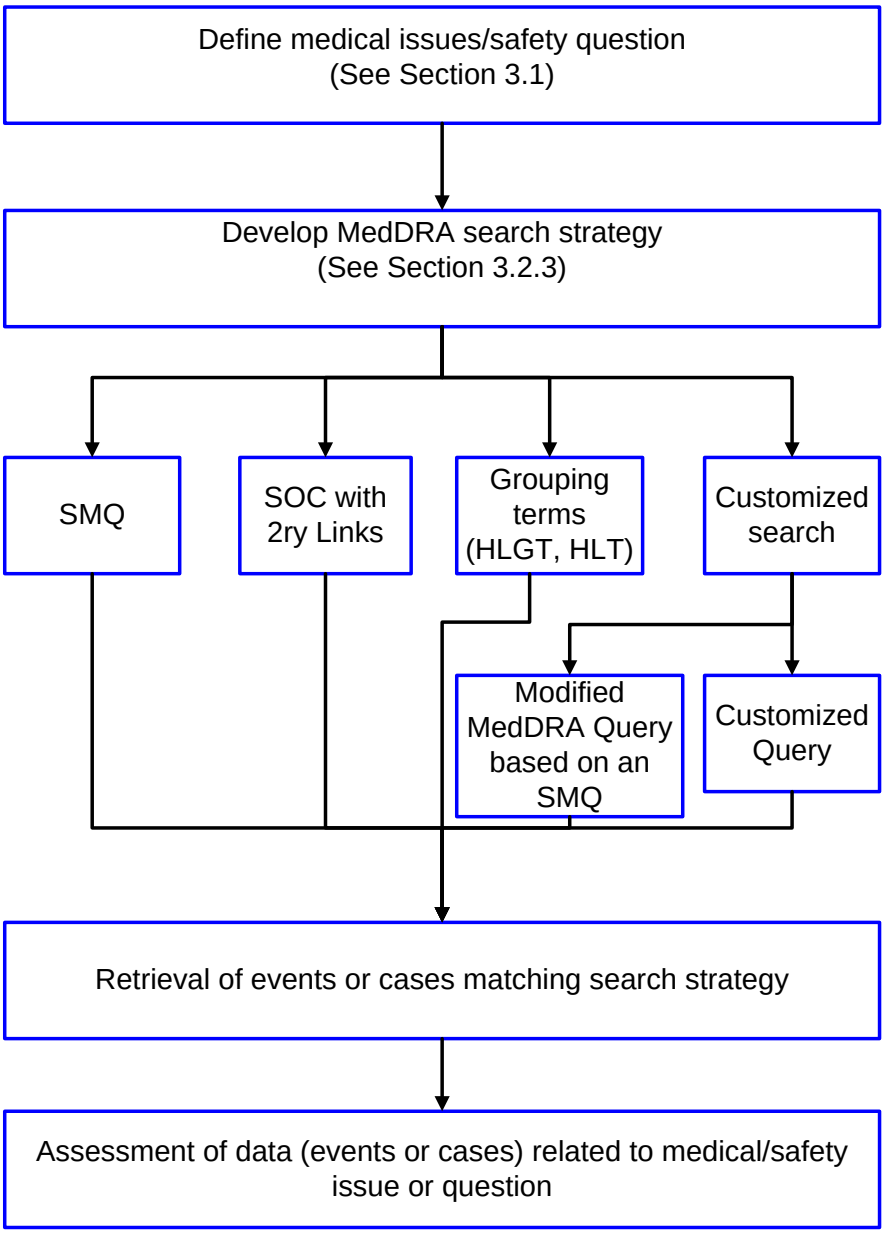
Example as of MedDRA Version 18.0 and 18.1

Terms used to construct queries should be in the same MedDRA version as the data being queried. Advice on how an organisation should handle new MedDRA versions is not within the scope of this document (see condensed *MedDRA Term Selection: Points to Consider,* Appendix 4.1). Refer also to the MedDRA website for the MedDRA Best Practices for more information on versioning options for clinical trial and post-marketing data (see Appendix, Section 6.1).

GENERAL QUERIES AND RETRIEVAL

General Principles

Data retrieval is performed for summary and analysis of clinical trial data, pharmacovigilance, medical information questions and for a number of other purposes. The search strategies, methods and tools used to retrieve data might differ based on the intended use of the output. A general approach for data retrieval is outlined in the chart below.



Overall Presentation of Safety Profiles

The aims of an overall safety profile presentation are to:

- Highlight distribution of ARs/AEs
- Identify areas for in depth analysis

Present the data in a way that allows for easy recognition of patterns of terms potentially related to the relevant medical conditions. There are various ways to do this ranging from a full listing of terms to sophisticated statistical approaches such as data mining techniques (for reference, see ICH E2E: Pharmacovigilance Planning Document on the ICH website).

Overview by primary System Organ Class

This overview is recommended as a first step in data retrieval and for planning of further analysis.

Display of all data ensures that all events will be seen and may be useful to identify data clusters by SOC. The primary SOC view can be used for standard tables and line listings (clinical trials and post-marketing data) and for cumulative summaries (post-marketing data. Depending on the reason for the output, it might be beneficial to use the primary SOC and PT display; for large datasets, display by SOC **and** by grouping terms (HLGTs and HLTs) may be preferable.

The Internationally Agreed Order of SOCs was developed for consistency irrespective of language or alphabet (see the MedDRA *Introductory Guide* and MedDRA ASCII files). The SOC order was based upon the relative importance of each SOC in AR/AE reports. Use of the Internationally Agreed Order may be applicable to certain regulatory functions, e.g., the Summary of Product Characteristics guideline.

Focused searches

Focused searches may be useful for further investigation of medical concepts of interest.

Below are listed options for focused search approaches. The order of applying these approaches may depend on resources, expertise, systems or other factors.

Focused searches by secondary SOC assignments

This focused search augments the Overview by Primary System Organ Class (see Section 3.2.1) by addressing secondary SOC assignments, thus providing a more comprehensive view of the data and taking advantage of MedDRA's multiaxiality.

The method used for a focused search by secondary SOC assignment may depend on the database characteristics of the organisation and may require programming to include the secondary SOC assignments in the display. It should be noted that this method of display of PTs by both primary and secondary SOC assignments could lead to double counting of cases/events.

Example

Programming a List of PTs in Primary and Secondary SOC Locations

Programming a List of PTs in Primary and Secondary SOC Locations
SOC *Eye disorders* HLGT *Vision disorders* HLT *Visual pathway disorders* PT *Chiasma syndrome* **PT *Optic nerve compression* (primary SOC location)** **PT *Optic nerve disorder* (primary SOC location)** **PT *Optic neuropathy* (primary SOC location)** **PT *Toxic optic neuropathy* (primary SOC location)** PT *Visual cortex atrophy* PT *Visual pathway disorder* **3 of 7 PTs are primary to SOC *Nervous system disorders*** ***Example as of MedDRA Version 19.0***

STANDARDISED MedDRA QUERIES

Introduction

Standardised MedDRA Queries (SMQs) were created to standardise identification and retrieval of safety data.

SMQs are a joint effort of the Council for International Organizations of Medical Sciences (CIOMS) and ICH (including MSSO and JMO) representing both industry and regulatory authorities. An SMQ is a grouping of terms from one or more SOCs that relate to a defined medical condition or area of interest. The terms included relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. that are associated with the medical condition or area of interest.

Users should carefully read the *Introductory Guide for Standardised MedDRA Queries (SMQs)* before applying an SMQ to fully understand the scope of the SMQ and to properly apply search options such as algorithms and weightings.

SMQ Benefits

- Application across multiple therapeutic areas
- Validated reusable search logic
- Standardised communication of safety information
- Consistent data retrieval
- Maintenance by MSSO and JMO

SMQ Limitations

- SMQs do not cover all medical topics or safety issues
- SMQs evolve and undergo further refinement even though they have been tested during development

SMQ Modifications and Organisation-Constructed Queries

If any modifications are made to term content or structure of an SMQ, it can no longer be called an "SMQ" but it should instead be referred to as a "modified MedDRA query based on an SMQ". See Section 5.1 for further details on SMQ modification.

Under no circumstances should a query constructed for the specific need of an organisation be called an "SMQ" by its originator. This is to ensure that there is no confusion with the ICH-endorsed SMQs applied by other MedDRA users. Any alternate name for the organisation-constructed query is acceptable as long as it could not be potentially confused with an ICH-endorsed SMQ.

SMQs and MedDRA Version Changes

Each SMQ relates to a specific MedDRA version. SMQs are part of each new MedDRA release, are maintained by MSSO and JMO, and correspond to the terms present in that version of MedDRA.

The MedDRA version of the SMQ and the coded data being searched should be the same because mismatches could produce unexpected results. For example, if an SMQ from an older version of MedDRA is applied to data coded in a more recent version, data coded to terms that are not present in the older SMQ would not be retrieved.

Example

Consequence of Version Mismatch of Coded Data and SMQ
PT *End stage renal disease* was added to SMQ *Chronic kidney disease* in MedDRA Version 19.0. Using Version 18.1 of this SMQ – which does not contain this PT – would fail to identify cases coded to this term in a database using MedDRA Version 19.0.

Example as of MedDRA Versions 18.1 and 19.0

SMQ Technical Tools

The MSSO browsers (both the Desktop and Web-Based browsers) allow for searching and viewing the contents of SMQs and they include additional details such as the SMQ description (definition) and development notes. An Excel spreadsheet containing the terms in each production SMQ is available from MSSO and JMO. This spreadsheet allows a user to transfer SMQ terms to query tools.

SMQ Applications

SMQs were developed to address the high granularity and unique features of MedDRA and to maximise the likelihood that all terms related to a specific medical condition of interest are identified.

The user should first review the list of available SMQs to determine which of them may be applicable to the question being asked. If an SMQ seems applicable, the user should check the documentation in the SMQ Introductory Guide to understand the purpose and definition of the SMQ. The user may also wish to review the term contents of the SMQ.

Following application of the selected SMQ on coded data, search results (i.e., retrieved data) should then be evaluated against the question originally posed. The search output alone may not be sufficient for data assessment (e.g., frequency of a condition). Define and document criteria for case evaluation.

Generally, more cases/events will be retrieved than will eventually be subjected to analysis due to “noise”. This is a more significant consideration for “broad” searches but in principle also applies to “narrow” searches

Clinical trials

SMQs may be applied in the clinical trial setting – especially for aggregate data – where the safety profile has yet to be fully established. In this instance, most (if not all) available SMQs may be used, possibly on a routine basis.

Alternatively, a user can apply an SMQ (or SMQs) that relates to a previously identified area of interest (e.g., from pre-clinical data or class effect) for further evaluation.

Post-marketing

A specific SMQ or a selection of SMQs may be used to retrieve relevant cases for subsequent medical review in a focused search of potential safety issues

The entire set of SMQs may be used on the database for signal detection. The user may wish to use the narrow terms or more specific levels of hierarchical SMQs (i.e., a sub-search SMQ) to minimise dilution of the signal.

SMQs may also be used to create a “watch list” of single case alerts (e.g., an automated notification system) to alert the user of incoming cases needing urgent review.

In addition, SMQs may help aggregate relevant cases for ongoing review of specific safety issues in periodic safety reports. SMQs may also be used for other routine reviews of aggregate data (e.g., reports of lack of efficacy) in the context of a periodic report.

SMQ Search Options

Some SMQs have options that may be used to refine a particular search. The most common option is use of narrow and broad search terms. By definition, a broad search includes both narrow and broad terms.

Some SMQs are hierarchical (i.e., contain one or more sub-searches). Other SMQs use algorithms, and in one case (SMQ *Systemic lupus erythematosus*), weightings are assigned to particular terms for signs, symptoms and laboratory results to help identify cases.

CUSTOMISED SEARCHES

Modified MedDRA Query Based on an SMQ

Do not modify the term content or structure of an SMQ unless there is a compelling reason to do so since altering it in any way makes it non-standard. If an SMQ is modified in any way, it should be referred to as a **"modified MedDRA query based on an SMQ"**. All modifications to the original SMQ should be documented.

If a modified MedDRA query based on an SMQ is to be used on an ongoing basis, version updates and maintenance of the query are the responsibility of the organisation that created it.

Customised Queries

Consider these points when constructing a customised query for MedDRA-coded data:

- Those responsible for constructing a customised query should:
    - Have medical knowledge
    - Know the structure and characteristics of MedDRA (e.g., hierarchy, multiaxiality) and the general content of MedDRA groupings (SOCs, HLGTs, and HLTs)
    - Understand the characteristics and structure of the data
- The specificity of the search should be defined.
- Initial focus should be on SOCs related to the condition of interest. For example, a customised search for a renal condition should start with SOC *Renal and urinary disorders*.
- The non multiaxial SOCs (SOC *Investigations*, SOC *Surgical and medical procedures* and SOC *Social circumstances*) should always be reviewed. Also, it may be useful to review terms in other SOCs that are not organ systems (e.g., SOC *General disorders and administration site conditions*, SOC *Injury, poisoning and procedural complications* and SOC *Pregnancy, puerperium and perinatal conditions*).
- It may be useful to identify relevant query terms by the following approaches:
    - A "bottom-up" survey of MedDRA (terms at the LLT and PT levels initially)
    - A "top-down" survey of MedDRA (starting at the SOC level and drilling down through the hierarchy)
- Consider looking at secondary links for multiaxial terms since additional relevant query terms could be found. For example, PT *Dyspnoea* can be found with other respiratory symptoms PTs in its primary SOC *Respiratory, thoracic and mediastinal disorders*, and it can also be found with related cardiac symptoms in its secondary SOC *Cardiac disorders*.

- Include grouping terms (HLGTs, HLTs) when possible
- In general, queries should be built on PTs and grouping terms. Unless very specific concepts (e.g., bacterial species) are needed, avoid using LLTs to build queries.
- Consider saving the customised query for future use; maintenance is necessary for MedDRA version changes.
- A customised query that may be useful to other MedDRA users can be submitted to the MSSO as a Change request for possible development as an SMQ.

APPENDIX

Links and References

The following documents and tools can be found on the MedDRA website: (www.meddra.org). Documents are available in all supported MedDRA languages except where noted.

- MedDRA Term Selection: Points to Consider document (full version available in English and Japanese)
- MedDRA Data Retrieval and Presentation: Points to Consider document (full version available in English and Japanese)
- Condensed MedDRA Term Selection: Points to Consider document
- MedDRA Introductory Guide
- Introductory Guide for Standardised MedDRA Queries (SMQs)
- MedDRA Change Request Information document (English)
- MedDRA Web-Based Browser *
- MedDRA Desktop Browser
- MedDRA Version Report (lists all changes in new version) *
- MedDRA Version Analysis Tool (compares any two versions) *
- MedDRA Best Practices
- Transition Date for the Next MedDRA Version

- Production SMQ spreadsheet*
- List of system tools that support SMQs

* Requires user ID and password to access

The following document can be found on the ICH website (www.ich.org):

- ICH E2E: Pharmacovigilance Planning

The following report can be found on the CIOMS website (www.cioms.ch)

- Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA. Second edition.