MedDRA® DATA RETRIEVAL AND PRESENTATION: POINTS TO CONSIDER

Release 1.4
Based on MedDRA Version 10.1

ICH-Endorsed Guide for MedDRA Users on Data Output

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1 INTRODUCTION

The Medical Dictionary for Regulatory Activities (MedDRA)[1] was designed for the specific use of sharing regulatory information for human medical products. However, unless consistency can be achieved in the selection of terms for reported symptoms, signs, and diseases, etc. or in the methods used to retrieve data for evaluation, the terminology will yield little improvement over the divergent practices of the past.

The MedDRA terminology was developed as a medically validated medical terminology for use throughout the regulatory process[2]. MedDRA has a large number of very specific terms called Lowest Level Terms (LLTs) in order to accurately capture the reporter's words (verbatim term). This large number of LLTs results in a correspondingly large number of Preferred Terms (PTs), a concept that is sometimes referred to as "granularity" and/or "specificity."

A highly granular terminology minimizes the need for interpretation at data entry. However, classification of data received is only one part of the data management process which attempts to retrieve, sort and present data in the most understandable and reproducible way for the benefit of drug development, pharmacovigilance and risk management. Therefore, the developers of the terminology designed a structure that facilitates data retrieval in the form of grouping terms called High Level Terms (HLT) and High Level Group Terms (HLGT), which group very specific terms used for coding into broader medical concepts. Moreover, MedDRA's feature of multi-axiality, in which PTs can be assigned to more than one System Organ Class (SOC), allows flexibility in data retrieval via primary or secondary paths. While these features of MedDRA allow a reasonable "first approach" to data retrieval, the complexity of MedDRA calls for guidance to optimize the results. *The MedDRA Data Retrieval and Presentation: Points to Consider* document is an ICH-endorsed guide for MedDRA users. It is designed to be updated based on MedDRA changes, and is a companion document to the MedDRA terminology. The principles described in this document are most effective when the user has followed the principles of the *MedDRA Term Selection: Points to Consider* document for data entry (i.e., coding).

This document was developed and is maintained by a working group charged by the ICH Steering Committee. Members of the working group include 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). (See Appendix 1 for working group members.)

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[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] From MedDRA 10.1 Introductory Guide. The MedDRA *Introductory Guide* can be found at the following link (Note: MedDRA user ID and password are required): http://www.meddramsso.com/translations/translationdownloads.htm

This document is intended to provide data retrieval and presentation options for either industry or regulatory purposes. Although MedDRA includes some data retrieval tools – including Standardised MedDRA Queries (SMQs) – this document addresses data retrieval in a broader context.

The examples contained in this document are based on MedDRA Version 10.1 and are intended to facilitate reader comprehension. The examples presented are not intended to imply regulatory requirements. This document reflects a broad range of experience. It is expected that as experience with data retrieval and presentation of MedDRA-encoded data increases, there will be additions and perhaps changes to this document.

1.1 Objective

The objective of the *MedDRA Data Retrieval and Presentation: Points to Consider* document is to promote understanding of the impact of the various options for data retrieval on the accuracy and consistency of the output. For example, certain drugs and/or therapeutic areas might need a customized approach for data output. One should take into consideration the options for data input that are described in the *MedDRA Term Selection: Points to Consider* document or in company specific coding practices.

For reproducibility and understanding, organizations are encouraged to document their data retrieval and output strategies, methods and quality assurance procedures in organization–specific guidelines, which should be consistent with this document.

1.2 Applications of MedDRA

- To aggregate reported terms in medically meaningful groupings for the purpose of reviewing, analyzing and/or summarizing 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 drug reaction/adverse event (ADR/AE)[3] terms via individual case safety reports
- To report ADR/AEs in tables, analyses, and line listings
- To identify frequency of medically similar ADR/AEs
- To capture and present product indications, investigations, medical history and social history data

[3] For ADR/AE definitions, refer to ICH Guidelines and CIOMS publications.

1.3 Background

This *Points to Consider* document has been prepared to help all MedDRA users begin on common ground, as the MedDRA terminology itself does not contain specific guidelines for its use. The document provides a framework to foster consistent use of MedDRA for data retrieval and presentation, with the goal of allowing medically meaningful review and analysis of clinical data.

The intent of this document is to describe the features of MedDRA and to highlight the impact of the structure, rules and conventions of MedDRA on data output. It is written to address principles only. The examples and options for use that are provided are not intended to communicate specific regulatory reporting requirements or address database issues. As this document cannot address every situation, medical judgment should always be applied.

This document is not a substitute for MedDRA training. It is considered essential that users have knowledge of the complexity and content of MedDRA. The reader should also refer to the MedDRA *Introductory Guide* and the *MedDRA Term Selection: Points to Consider* document.

1.4 Scope

The principles described in this document apply to all data encoded with MedDRA. The focus is on aggregated data. This document does not address the use of MedDRA for:

- Single case reporting
- Labeling
- Medical evaluation
- Statistical methodology

2 GENERAL PRINCIPLES

2.1 Quality of Source Data

High quality data output is dependent upon maintaining the quality of the information originally reported by using consistent and appropriate term selection. Organizations are encouraged to pursue continuous oversight of data quality. Data quality issues are also addressed in *MedDRA Term Selection: Points to Consider*.

2.1.1 Data conversion considerations

Special consideration should be given to the methodology used for the conversion of data from other terminologies into MedDRA. The method(s) used for conversion of data can impact retrieval and presentation strategies.

Method 1 – Data are converted from legacy terms to MedDRA

- Results will reflect the specificity of the previous terminology.

- There is no benefit gained from the greater specificity of MedDRA.

Example:

Reported term: Bowel ischaemia
Legacy term: Gastrointestinal Disorder
MedDRA term: Gastrointestinal disorder

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

Example:

Reported term: Bowel ischaemia
Legacy term: Gastrointestinal Disorder
MedDRA term: Bowel ischaemia

It is important to document the data conversion method(s) that was (were) used, including the date(s) of conversion.

2.1.2 Impact of data conversion method on data retrieval

- Interpretation of the data output can be affected if the two methods described above are combined. For example, if legacy data have been converted directly from legacy terms to MedDRA terms (Method 1) and newly acquired data are coded from reported terms in MedDRA, the difference in resulting specificities could make interpretation difficult.
- When designing a search strategy, it might be appropriate to look at the reported terms for data converted using Method 1 because, if the query is based on specific MedDRA terms, the cases previously coded to a non-specific term might be overlooked. For example, if searching on *bowel ischaemia,* cases of bowel ischemia that had been coded under the legacy term *gastrointestinal disorder* would be missed. In this example, it would be critical to have knowledge of the date of legacy data conversion.

Should there be a need to conduct a search requiring this level of detail, it might be necessary to review or re-code from the reported term data. For legacy data, this information may be found in data fields other than ADRs/AEs.

2.2 Quality Assurance of the Process of Data Retrieval and Presentation

Careful documentation of the coding conventions used for data entry is essential for understanding and reproducing results. Organizations are encouraged to document their data retrieval and presentation strategies, methods, and quality assurance procedures in organization-specific guidelines, which should be consistent with this document. The version of MedDRA in which the data are being retrieved should be specified.

The MedDRA terminology is multi-axial and more complex than common terminologies previously used. Therefore, an individual with a medical background who is also trained in the use of MedDRA should review the data

retrieval and presentation strategy.

MedDRA is a standardized terminology and the assignment of terms across SOCs is pre-determined within the terminology; therefore, users should not alter it in any way. If users believe that terms are inappropriately placed in the hierarchy, they should inform the MedDRA MSSO via the change request process.

2.3 Organization-Specific Data Characteristics

Although MedDRA is intended to be a standardized terminology, there are variations in the way that implementation has been conducted. It is important to understand the organization-specific characteristics of both the data and the implementation strategies.

Each organization should have access to a MedDRA specialist who can provide expert advice on MedDRA and has knowledge of the following characteristics of the database:

- Database structure (i.e., how hierarchy is stored and used)
- Data storage (e.g., level of term, synonym/reported term)
- Data migration from other terminologies to MedDRA
- Coding practices over time. For example, MedDRA users should consider the impact of gender-specific terms when comparing MedDRA coded data to data coded with older terminologies which may not have had corresponding gender-specific terms. If the organization's prior terminology had only a single term for "breast cancer", consider the impact of selecting gender-specific terms for breast cancer for current data.
- Limitations/restrictions. For example, one should not assume that secondary PTs will be seen when searching using a specific HLT; this is only the case if the database configuration allows for output by secondary path.

Knowledge of term selection principles used by an organization for coding is also critical. The following term selection points (which are discussed in detail in *MedDRA Term Selection: Points to Consider* document) illustrate some of the factors to keep in mind when planning retrieval and presentation of data:

- Selecting more than one term when coding a medical condition increases counts of terms.
- Conversely, selecting a diagnosis term only (without also selecting terms for signs and symptoms) reduces the counts of terms.

This is very important to consider when reviewing adverse event profiles. The profile obtained when both diagnosis and signs and symptoms have been coded will appear very different than the profile obtained when only a diagnosis has been coded. An organization's coding conventions should always be considered whenever the data from other databases (e.g., co-developing or co-marketing partners, regulators) are used and/or compared.

2.4 Characteristics of MedDRA that Impact Data Retrieval and Presentation

The structure, rules and conventions of MedDRA are detailed in the MedDRA *Introductory Guide*. The following characteristics of MedDRA need to be kept in mind for data retrieval and presentation:

2.4.1 Grouping Terms - HLGTs and HLTs

The hierarchy of MedDRA, in particular the HLGT and HLT levels, should be viewed as an additional tool to aid in data retrieval and presentation, as it provides clinically relevant groupings of terms.

Example:

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

2.4.1.1 Review of terms under a group term

Users should review the terms within the HLGT or HLT of interest to ensure that all terms are suited for the purpose of the output. Note in the example below that terms describing changes in blood pressure in both "directions" are grouped under a common HLT.

Example:

HLT *Vascular tests NEC (incl blood pressure)*
PT *Blood pressure*
PT *Blood pressure abnormal*
PT *Blood pressure decreased*
PT *Blood pressure increased*

This HLT also includes many other PTs for parameters such as pulmonary arterial pressure, vascular resistance, hemodynamic tests, etc.

2.4.2 Granularity

Unique medical concepts (PTs) in MedDRA are considerably more specific (i.e., "granular") than terms on a comparable level of hierarchy in other terminologies. The following table illustrates how data coded to a single PT from another terminology may be expressed by several PTs in MedDRA.

OTHER TERMINOLOGY PREFERRED TERMS	NO. OF EVENTS	MEDDRA VERSION 10.1 PREFERRED TERMS	NO. OF EVENTS
Infection	15	Upper respiratory tract infection	7
		Nasopharyngitis	2
		Infection	1
		Lower respiratory tract infection	4
		Skin infection	1
Abdominal pain	9	Abdominal pain	4
		Abdominal pain upper	3
		Abdominal tenderness	2
Accidental injury	4	Injury	1
		Skin laceration	1
		Joint sprain	1
		Back injury	1

As a consequence of this specificity, related events that might have been represented by a single term in other terminologies might now be represented among more than one MedDRA PT. Among other things, this can compromise signal detection.

2.4.3 Multi-axiality

MedDRA is a multi-axial terminology, which means that a PT may be assigned to more than one SOC. Multi-axiality allows terms to be grouped in different ways (e.g., by etiology or body system/site). Each PT is assigned to one primary SOC; assignments of that PT to other SOCs are considered secondary. Assignment of a single primary SOC prevents multiple counting.

All possible secondary SOC assignments for any given concept may not exist in MedDRA. However, MedDRA is an evolving terminology and new or revised SOC assignments can be created in the future as a result of the change request process.

2.4.3.1 Primary SOC assignment rules

MedDRA users should be aware of primary SOC assignment rules that are described in the *Introductory Guide*. These rules affect the way terms are placed in the terminology and determine their data display by SOC. Because MedDRA placement rules allow for terms related to a particular medical condition to reside in more than one SOC, users should be familiar with the general content and structure of all MedDRA SOCs to ensure that data are not overlooked.

Example:

All terms reflecting congenital events are primary to the SOC *Congenital, familial and genetic disorders.*

Example:

The primary assignment for PT *Enterocolitis infectious* is SOC *Infections and infestations* (with a secondary assignment to SOC *Gastrointestinal disorders*) whereas the primary assignment for PT *Enterocolitis* is SOC

Gastrointestinal disorders.

2.4.3.2 Non multi-axial SOCs

Users should also be aware that the following three SOCs do not have multi-axial assignments for any of their terms (i.e., terms assigned to these SOCs do not appear in any other SOC):

SOC *Investigations*

SOC *Surgical and medical procedures*

SOC *Social circumstances*

When designing retrieval strategies, terms in these SOCs need to be considered.

2.4.3.3 Clinically related PTs

Clinically related PTs in MedDRA might be overlooked or not recognized as belonging together as they might exist in different locations within a single SOC or within more than one SOC (see Section 2.4.3).

Example:

HLGT *Epidermal and dermal conditions*
HLT *Bullous conditions*
PT *Stevens-Johnson syndrome*
PT *Toxic epidermal necrolysis*
HLT *Exfoliative conditions*
PT *Dermatitis exfoliative*
PT *Dermatitis exfoliative generalised*
PT *Nikolsky's sign*
PT *Skin exfoliation*

Hence, the overall frequency of a medical concept might be underestimated if the above points are not taken into consideration, possibly impacting the interpretation of the data (see Section 3.2).

Example:

PT *Thrombocytopenia* is in SOC *Blood and lymphatic system disorders*
PT *Platelet count decreased* is in SOC *Investigations*

MedDRA's 26 SOCs address anatomical locations and etiology, as well as purposes or other concepts; therefore, data might reside in SOCs that are not anticipated by the user. Thus, the impact of multi-axiality on frequencies of the medical condition of interest should be considered.

Example:

PT *Post procedural haemorrhage* has the primary SOC assignment of SOC *Injury, poisoning and procedural complications*
PT *Chest pain* has the primary SOC assignment of SOC *General disorders and administration site conditions*

Example:

For hepatic abnormality, SOC *Investigations* should be searched (in addition to SOC *Hepatobiliary disorders*) to identify related laboratory test terms. Furthermore, SOC *Surgical and medical procedures* should be searched for related terms such as PT *Liver transplant*.

2.4.3.4 Test results

Test results are not linked via multi-axiality to a corresponding medical condition. For example, PT *Blood glucose increased* is in SOC *Investigations* (its only SOC assignment) but PT *Hyperglycaemia* is in SOC *Metabolism and nutrition disorders* and has no link to SOC *Investigations.* Tables or other views of the data need to take into account the impact of SOC *Investigations*. As illustrated in the table below, multiple MedDRA terms might be used to code very similar medical conditions and might be included in a "disorder SOC" while its associated laboratory finding is displayed in SOC *Investigations*.

	OTHER TERMINOLOGY		MedDRA Version 10.1	
Reported Event (% subjects)	**Coded Term (% subjects)**	**Body System/SOC (% subjects)**	**PT (% subjects)**	**SOC (% subjects)**
Hyperglycaemia (4.1)	Hyperglycemia (10.5)	Metabolism & nutritional disorders (10.5)	Hyperglycaemia (4.1)	Metabolism & nutrition disorders (4.1)
Increased blood sugar (2.7)				
Glucose increased (2.2)			Blood glucose increased (6.4)	Investigations (6.4)
Blood glucose high (1.0)				
Increasing glucoses (0.5)				

Thus, multi-axiality can have a significant impact on frequencies of the medical condition of interest and should be considered for any search.

2.5 Standardised MedDRA Queries[4]

Standardised MedDRA Queries (SMQs) are a joint effort of the Council for International Organizations of Medical Sciences (CIOMS) SMQ Working Group and ICH (MSSO/JMO). SMQs are groupings of terms from one or more SOCs that relate to a defined medical condition or area of interest. The terms included could 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.

More information on SMQs can be found in the documentation listed in the footnote.[4]

[4] http://www.cioms.ch/frame_meddra_queries_oct_2004.htm Contains an introduction to SMQs but the full publication is available only as a paper copy.
http://www.cioms.ch/frame_whats_new.htm Contains the minutes of the meetings.
Publication = SMQs: Development and Rational use of Standardised MedDRA Queries (SMQs)
Introductory Guide for Standardised MedDRA (SMQs) – MedDRA Version 10.1

Characteristics of SMQs include:

- SMQs are developed from a case definition of a medical condition.
- SMQs can contain grouping terms (HLTs and HLGTs) as well as PTs.
- Development of SMQs is focused on highly relevant drug safety topics.
- SMQs can have usage options such as “narrow” and “broad” sub-searches, hierarchical relationships between related SMQs and algorithmic design.

2.6 MedDRA Versioning

The MedDRA terminology is updated twice per year. Version “X.0” contains both simple and complex changes. Version “X.1” contains simple changes only.

“Simple” changes include:

- Adding a PT (new medical concept)
- Moving an existing PT from one HLT to another
- Demoting a PT to the LLT level
- Adding or removing a link to an existing PT
- Adding an LLT
- Moving an existing LLT from one PT to another
- Promoting an LLT to the PT level
- Making a current LLT non-current or a non-current LLT current
- Changing the primary SOC allocation
- Changes to SMQs

“Complex” changes include:

- Adding or changing multi-axial links
- Adding new grouping terms
- Merging existing grouping terms
- Restructuring a SOC

Both simple changes and complex changes impact retrieval and presentation strategies. Users should read the documentation provided with each MedDRA release, especially the *What's New* document and the MedDRA version reports (provided by the MSSO and JMO) that list the changes in detail.

It is recommended that organizations plan and document their strategy for handling MedDRA version updates. When planning or performing data retrieval and presentation, the version of MedDRA used should be documented.

Keep in mind the above changes may impact previous data retrieval approaches and results, including event frequencies. For example, in MedDRA Version 10.0, *Electrocardiogram QT corrected interval prolonged* was a PT and in Version 10.1 it was "demoted" to an LLT.

Example:

MedDRA Version 10.0	**Number of Events at PT Level**
Electrocardiogram QT corrected interval prolonged (PT)	15
Electrocardiogram QT prolonged	5
MedDRA Version 10.1	**Number of Events at PT Level**
Electrocardiogram QT corrected interval prolonged (no longer a PT)	0
Electrocardiogram QT prolonged	20

As noted in the table above, the original query was done in MedDRA Version 10.0 in which there was a PT *Electrocardiogram QT corrected interval prolonged*. If the query had been re-run in MedDRA Version 10.1, these events would not have been found at the PT level because in MedDRA Version 10.1, PT *Electrocardiogram QT corrected interval prolonged* was demoted to an LLT under PT *Electrocardiogram QT prolonged.*

In MedDRA Version 10.0, the primary SOC assignment for PT *Retinal scar* was SOC *Eye disorders*; in Version 10.1, the primary SOC assignment was changed to SOC *Injury, poisoning and procedural complications* and the secondary SOC assignment to SOC *Eye disorders.* If one were able to retrieve PTs only under their primary SOC assignment, this term will seem to have "disappeared" from SOC *Eye disorders.*

The terms used for queries should be in the same MedDRA version as the data being queried. For example, new terms might have been included in a query built on MedDRA Version 10.1 that might not be represented in stored data

coded in MedDRA Version 9.1; this could lead to search results that are incomplete. On the other hand, a search built on an earlier MedDRA version (e.g., from a closed study), might not detect all of the relevant data in an integrated safety summary (ISS) coded in a later version of MedDRA. Any queries stored in an organization's system should be updated to the appropriate version of MedDRA prior to use on new data.

Organizations are encouraged to screen these types of changes for possible impact on data output.

Information on how to handle MedDRA version updates is out of the scope of this document. Some organizations may have in their databases multiple studies coded with different versions of MedDRA; this may affect aggregation of data (e.g., ISS). Users are encouraged to refer to MSSO documents on versioning options for clinical trial and postmarketing data (www.meddramsso.com) for more information.

3 QUERIES and RETRIEVAL

3.1 General Principles

Data retrieval is performed for summary and analysis of clinical trial data, pharmacovigilance, medical information queries and for a number of other purposes. The search strategies, methods and tools applied to retrieve the data might be different depending on the intended use of the output.

The user should be aware of particular database characteristics, organization-specific data entry conventions, data sources, and the size of the database. In addition, archives of previously used searches might be available, particularly for pharmacovigilance purposes; with updating, these may be suitable for reuse. The user should be aware of the version of MedDRA used in coding all data.

Prior to data retrieval, one may be aware of safety issues that require further investigation. Information from pre-clinical studies, clinical trials, post-marketing surveillance, similar products (class effects) and regulatory queries can be useful in identifying areas of possible focus. Understanding gained might affect the strategy for aggregation of search terms, the methods used and the way data should best be displayed.

In presenting adverse events, it is important to display and to group related events (i.e., events that represent the same condition of interest) so that the true occurrence rate of an event is not obscured. Search strategies should be documented. The search output alone may not be sufficient for data assessment (e.g., frequency of a condition). Search results (i.e., retrieved data) should then be evaluated against the question originally posed.

Capturing related adverse events into categories can be challenging. A search that is defined with parameters that are too narrow might exclude events of potential relevance, whereas parameters that are too broad might make it difficult to identify a trend or signal. The grouping of terms that describes a

potential effect or medical condition, whether or not it can be regarded as a syndrome, requires medical judgment and the results of the analysis should be carefully interpreted. For complex queries, it is advisable to create a data analysis plan including definition(s) of the medical condition(s) of interest. It may be advisable to have an interdisciplinary discussion so that the most suitable tools and methods relevant to the query are identified.

The following are examples of the types of searches for which these principles might apply:

- Overview of safety profile in a summary report, Periodic Safety Update Report (PSUR), ISS, etc.
- Comparison of the frequency of ADR/AE (reporting rates for spontaneous reports or incidence for studies)
- Analysis of a specific safety concern
- Identification of patient subpopulations at risk (e.g., searching medical history information)

3.1.1 Graphical displays

Graphical displays can be very useful, especially when dealing with large sets of data. Such displays can allow quick visual representation of potential signals. Organizations are encouraged to utilize graphs to display data. Simple displays such as histograms, bar charts, and pie charts can be useful as well as more complex, statistically driven displays (e.g., output of data mining algorithm). Examples of such types of displays are presented in various sections of this document.

3.2 Overall Presentation of Safety Profiles

The aim of an overall presentation of the safety profile is to highlight the distribution of ADR/AEs and to identify areas where more in depth analysis should be conducted. The data should be presented in a way that allows ready recognition of patterns of terms potentially associated with relevant medical conditions. There are various ways to accomplish 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 at www.ich.org).

Historically, the standard approach has been to present data by "Body System" or "System Organ Class" and “Preferred Term” corresponding to SOCs and PTs in MedDRA. However, due to the unique characteristics of MedDRA previously described (granularity, multi-axiality, etc.), this type of presentation alone might not optimally represent the frequency of events and can even be misleading. For example, if a number of reports describe a similar medical condition, they could be represented under:

- Many specific PTs, thereby diluting the signal
- Different group terms
- Different SOCs
- SOCs where the user would not expect them intuitively (e.g., SOC *General disorders and administration site conditions,* SOC *Pregnancy, puerperium and perinatal conditions,* SOC *Injury, poisoning and procedural complications,* SOC *Infections and infestations*)

Example:

The following PTs have as their primary SOC assignment SOC *General disorders and administration site conditions* and their secondary assignment SOC *Cardiac disorders*.

PT *Chest discomfort*
PT *Chest pain*
PT *Oedema peripheral*
PT *Sudden death*
PT *Localised oedema*
PT *Oedema due to cardiac disease*
PT *Peripheral oedema neonatal*
PT *Cardiac death*

3.2.1 Overview by Primary System Organ Class

In this section, the objectives, methods, benefits and limitations of this approach are described.

As a first look, one should display all data. This assures that all events will be seen, and the overview might be useful in identifying clusters per SOC. If the hierarchy is displayed as well, clustering may occur in an HLGT or HLT. For a small dataset, this display by primary SOC might be all that is required.

Objectives:

- To display all the data in the entire MedDRA structure
- To include all events (as this approach is all-inclusive, no events are omitted)

It is recommended that this overview be undertaken as the first step in data retrieval and for planning further analyses.

Method:

The primary SOC view of the data including HLGTs, HLTs, and PTs can be used for standard tables (clinical trial and postmarketing data) and cumulative summaries (postmarketing data). Line listings (both clinical and post-marketing data) can also be displayed by primary SOC and PT. It

might be sufficient to use the primary SOC and PT display only for small data sets, but it might be preferable to display data by SOC as well as by grouping terms (HLGTs and HLTs) and PTs for more complex data.

The Internationally Agreed Order of SOCs was developed to facilitate consistency irrespective of language or alphabet. The order of the SOCs was based upon the relative importance of each SOC in ADR/AE reports. Use of the Internationally Agreed Order may be applicable to certain regulatory functions e.g., the SPC guideline and PSUR (see the MedDRA *Introductory Guide* and MedDRA ASCII files). Organizations exchanging data should agree on the order of SOCs when preparing data for presentation.

MedDRA Version 10.1English Alphabetical Order	**MedDRA Version 10.1 Internationally Agreed Order**
Blood and lymphatic system disorders	Infections and infestations
Cardiac disorders	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Congenital, familial and genetic disorders	Blood and lymphatic system disorders
Ear and labyrinth disorders	Immune system disorders
Endocrine disorders	Endocrine disorders
Eye disorders	Metabolism and nutrition disorders
Gastrointestinal disorders	Psychiatric disorders
General disorders and administration site conditions	Nervous system disorders
Hepatobiliary disorders	Eye disorders
Immune system disorders	Ear and labyrinth disorders
Infections and infestations	Cardiac disorders
Injury, poisoning and procedural complications	Vascular disorders
Investigations	Respiratory, thoracic and mediastinal disorders
Metabolism and nutrition disorders	Gastrointestinal disorders
Musculoskeletal and connective tissue disorders	Hepatobiliary disorders
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin and subcutaneous tissue disorders
Nervous system disorders	Musculoskeletal and connective tissue disorders
Pregnancy, puerperium and perinatal conditions	Renal and urinary disorders
Psychiatric disorders	Pregnancy, puerperium and perinatal conditions
Renal and urinary disorders	Reproductive system and breast disorders
Reproductive system and breast disorders	Congenital, familial and genetic disorders
Respiratory, thoracic and mediastinal disorders	General disorders and administration site conditions
Skin and subcutaneous tissue disorders	Investigations
Social circumstances	Injury, poisoning and procedural complications
Surgical and medical procedures	Surgical and medical procedures
Vascular disorders	Social circumstances

Graphical display might facilitate understanding by the viewer. This can include histograms, bar charts, pie charts, etc.

Example:

Primary SOC Output Listing

SOC *Cardiac disorders*	22
HLGT *Cardiac arrhythmias*	
HLT *Supraventricular arrhythmias*	
PT *Atrial tachycardia*	22
LLT *Paroxysmal atrial tachycardia*	9
LLT *Tachycardia atrial*	10
LLT *Tachycardia paroxysmal atrial*	3
SOC *Investigations*	10
HLGT *Enzyme investigations NEC*	
HLT *Skeletal and cardiac muscle analyses*	
PT *Blood creatine phosphokinase MB increased*	10
LLT *Blood creatine phosphokinase MB increased*	2
LLT *CPK-MB increased*	2
LLT *Plasma creatine phosphokinase MB increased*	5
LLT *Serum creatine phosphokinase MB increased*	1

Example:

Graphical presentations of MedDRA-coded data

Author
16NOV2005

Figure 1
Relative frequency of events per primary SOC

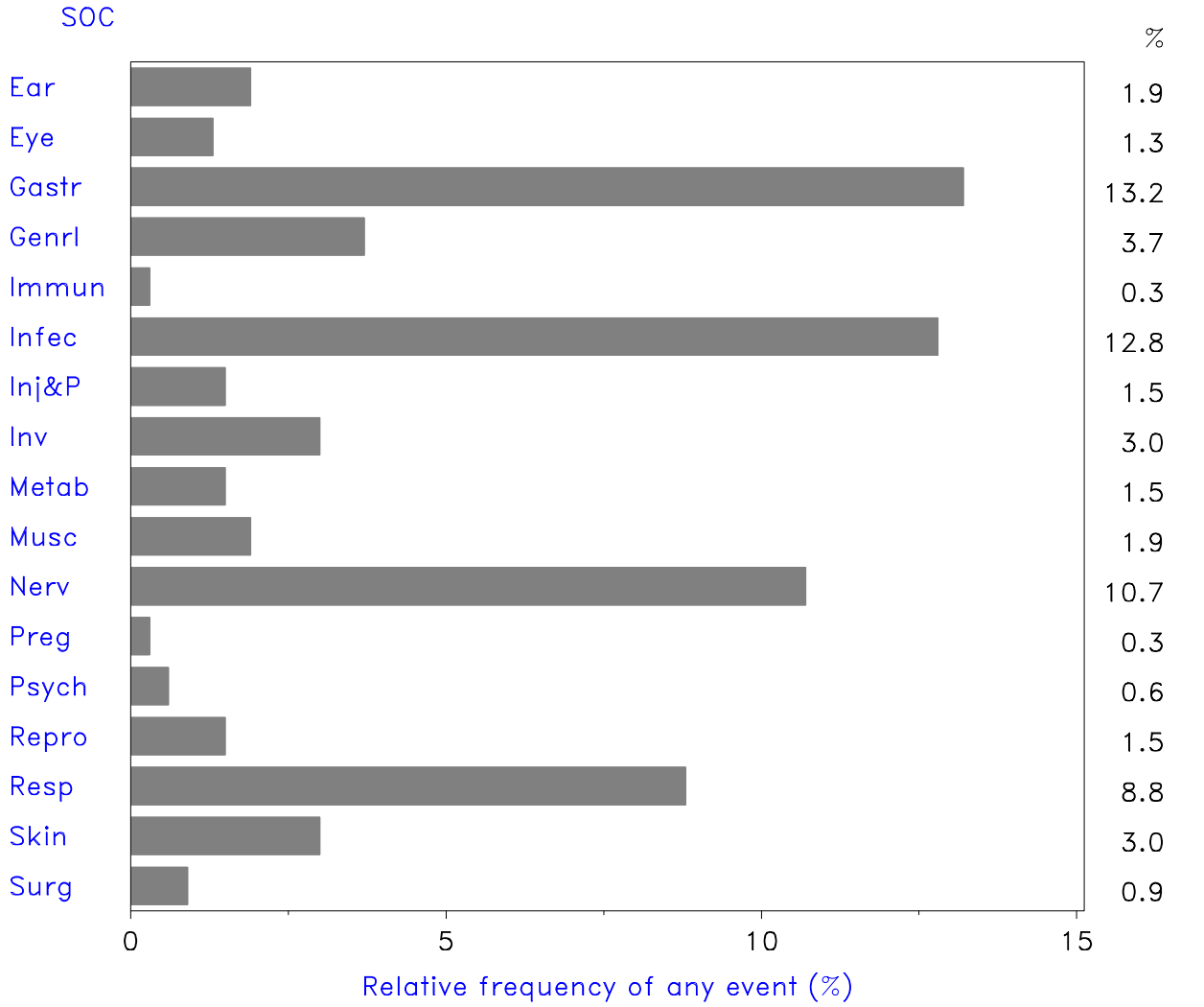

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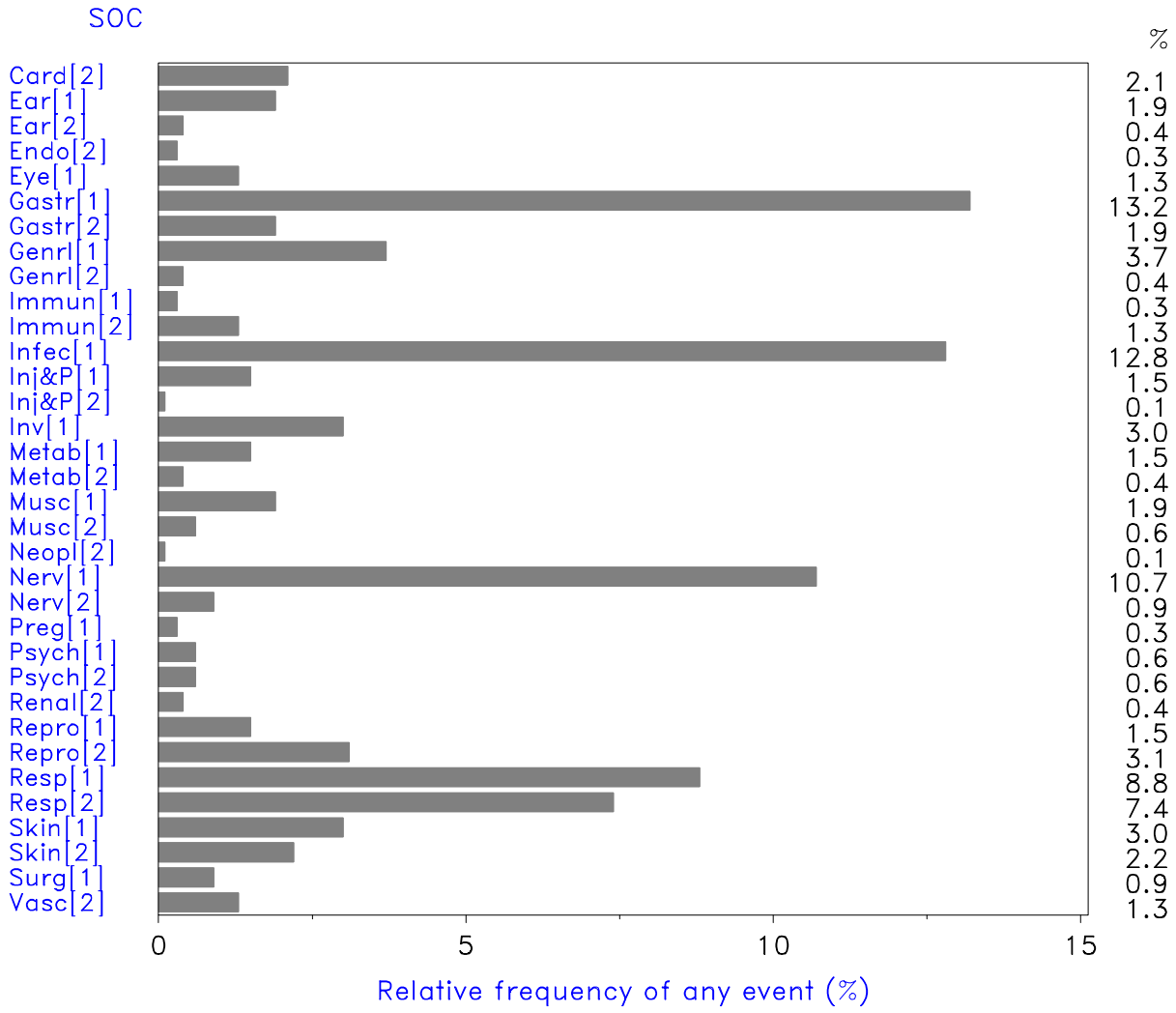
Figure 2
Relative frequency of events per primary [1] and per secondary [2] SOC

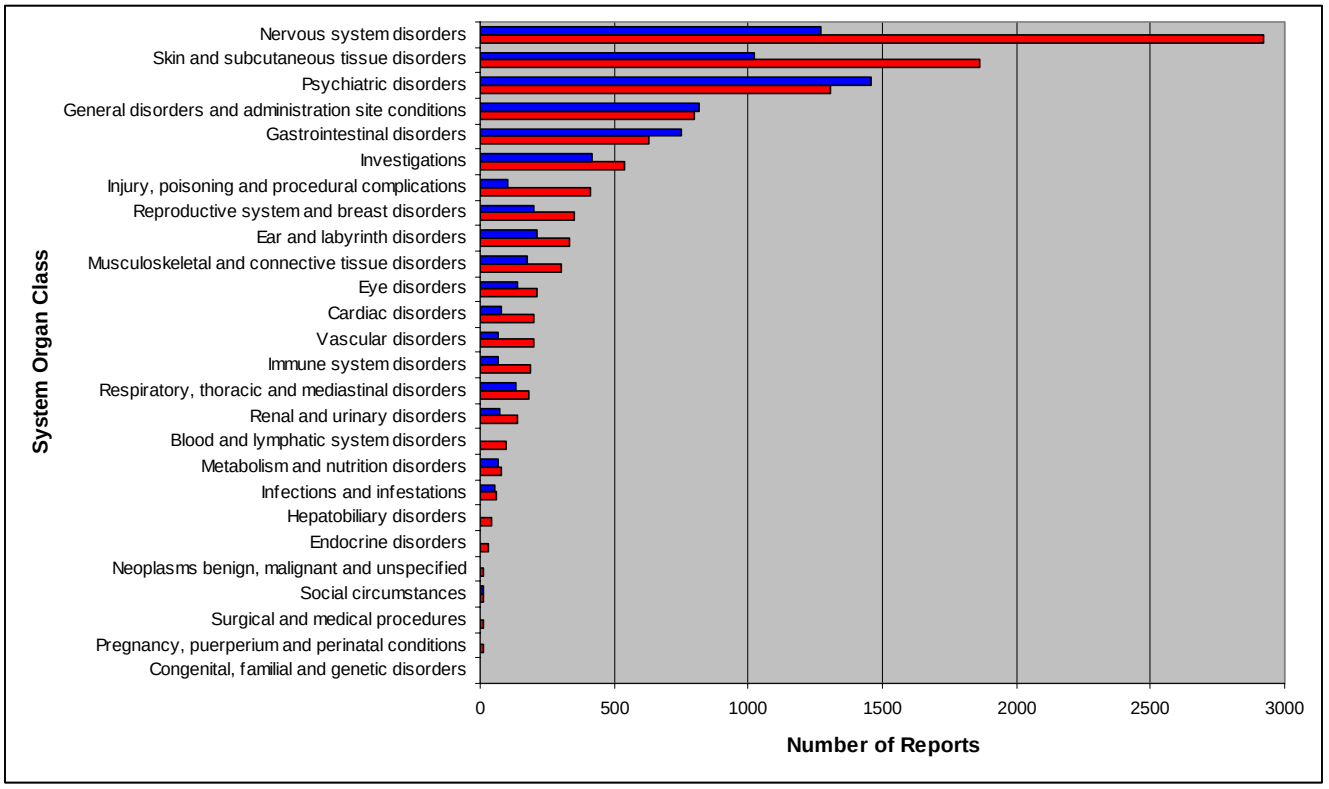


Example:

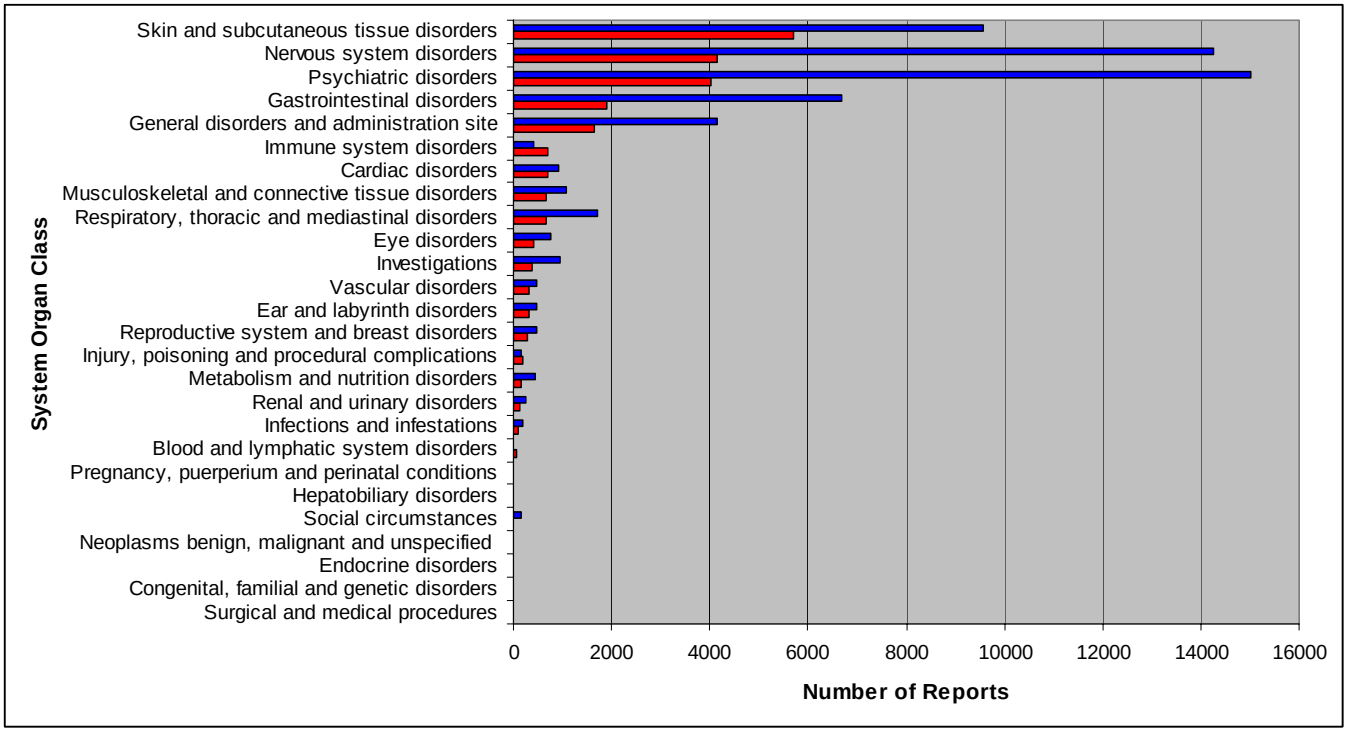
Graphical display by Primary SOC

The displays below are for one compound, in two patient populations. Within each patient population, the reports are split by SOC and by reporter. The upper bar of each pair represents numbers of reports from Consumers (blue) and the lower bar reports from Health Care Professionals (red). If further detail is required, adverse events may be displayed by PT with decreasing frequency.

Patient population 1



Patient population 2



Benefits:

- Provides a broad overview of the distribution of data and helps to identify areas of special interest that might call for more in-depth analysis.
- Grouping terms help to aggregate related PTs to facilitate the identification of medical conditions of interest. An individual PT will be displayed only once, preventing over counting of terms.
- The primary SOC overview might be the only form of analysis appropriate for a small dataset.

In-depth analysis will require medical expertise in order to define terms that should be aggregated.

Limitations:

- Because it is based on primary PT-to-SOC assignment, there might be incomplete groupings of terms that relate to a particular medical condition/syndrome because they might be distributed among different SOCs.
- Due to certain MedDRA rules, events might not be found where the

user expects them to be.

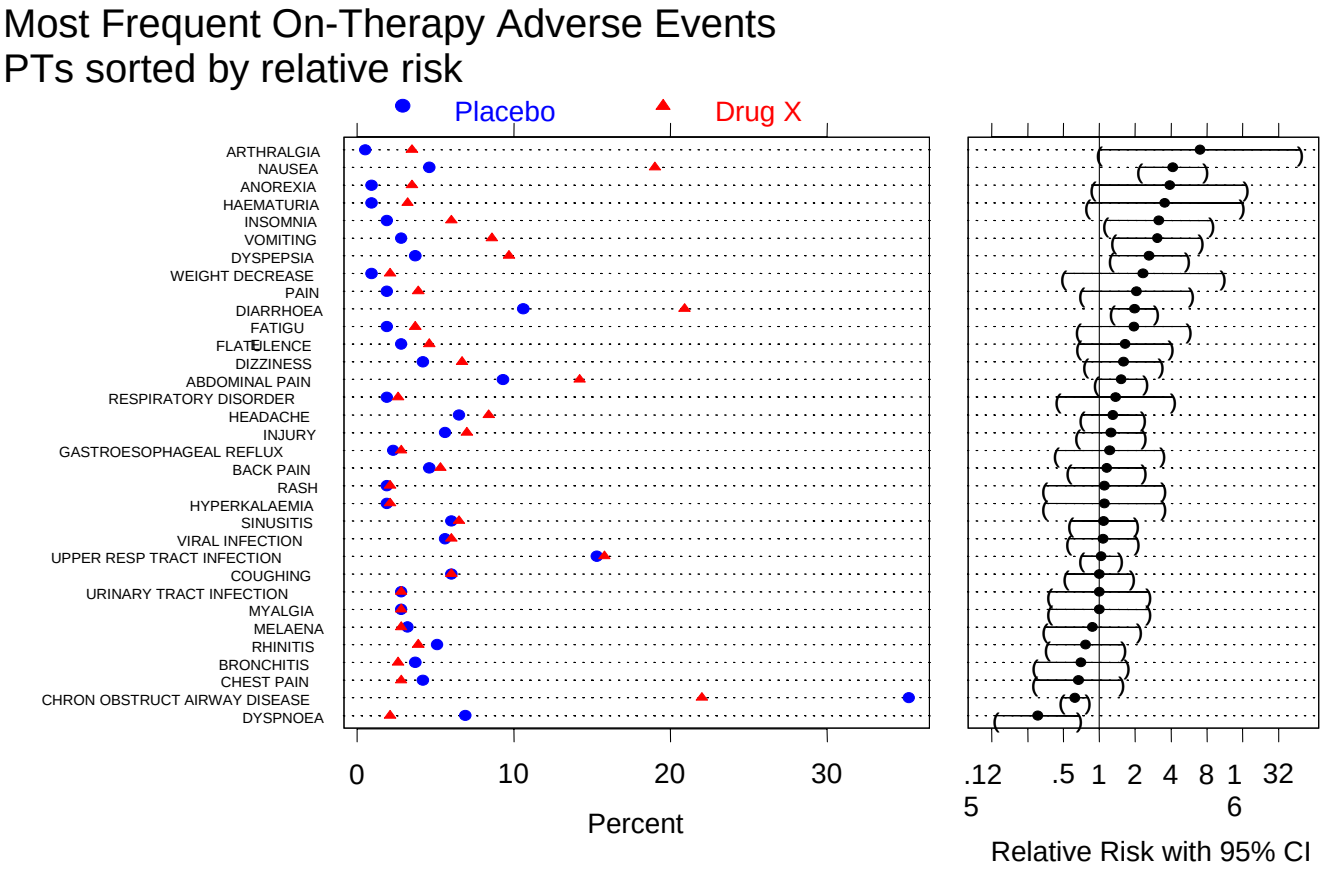
- Potential for a very lengthy output when applied to large data sets

3.2.2 Overall Presentations of Small Datasets

When the safety profile is limited to a relatively small list of PTs (e.g., early in clinical development), a display of these PTs may be adequate.

The following is an example of such a display:

Example:



3.2.3 Focused Searches

Focused searches may be useful when further investigating medical concepts of interest. For example, a focused search may be used to determine the number of cases or events of interest (e.g., in response to a regulatory query).

In this section, the objectives, methods, benefits and limitations of this approach are described.

Objectives:

In certain situations such as those listed below [Note: this list is not all inclusive], users might wish to design a specific search in addition to the Overview by Primary System Organ Class (see Section 3.2.1).

- Further examination of clusters seen in Primary SOC output
- Previously identified safety concerns (e.g., known class effects, results from toxicology and animal studies, etc.)
- Monitoring events of special interest
- Responding to regulatory and other queries

The following describe options for focused search approaches. The order of application of these approaches may be dependent on resources, expertise, systems or other factors.

3.2.3.1 Focused search by secondary SOC assignments

This focused search augments the "Overview by Primary System Organ Class" (see Section 3.2.1) by capturing the secondary SOC assignments. This provides a more comprehensive "view" and takes full advantage of the multi-axial features of MedDRA (i.e., the medical interrelatedness of terms).

Method:

- Query the SOC, HLGT or HLT to include both primary and secondary SOC assignments in display.
- If the database does not allow automated output by secondary SOC, then the query should be performed using available processes (e.g., programming a list of all individual PTs in the primary and secondary SOC locations).

Example:

SOC *Eye disorders*
HLGT *Vision disorders*
HLT *Visual field disorders*
PT *Hemianopia*
PT *Hemianopia heteronymous*
PT *Hemianopia homonymous*
PT *Scotoma* (primary SOC location)
PT *Tunnel vision*
PT *Uhthoff's phenomenon* (primary SOC location)
PT *Visual field defect*

5 of 7 PTs are primary to SOC *Nervous system disorders*

Example:

Incidence of treatment-emergent adverse events coded by MedDRA 10.1
Population: Patients Valid for Safety

System Organ Class / High Level Term / Preferred Term	Active (N=21)		Control (N=19)	
Any System Organ Class				
Any High Level Term				
Any event	3	14.3%	1	5.3%
Cardiac disorders				
Any High Level Term				
Any event	2	9.5%	1	5.3%
Ventricular arrhythmias and cardiac arrest				
Any event	2	9.5%	1	5.3%
[2] Sudden death	2	9.5%	1	5.3%
General disorders and administration site conditions				
Any High Level Term				
Any event	3	14.3%	1	5.3%
Any primary path	2	9.5%	1	5.3%
Death and sudden death				
Any event	2	9.5%	1	5.3%
Any primary path	2	9.5%	1	5.3%
[1] Sudden death	2	9.5%	1	5.3%
Febrile disorders				
Any event	2	9.5%	0	0.0%
[2] Postoperative fever	2	9.5%	0	0.0%
Injury, poisoning and procedural complications				
Any High Level Term				
Any event	2	9.5%	0	0.0%
Any primary path	2	9.5%	0	0.0%
Non-site specific procedural complications				
Any event	2	9.5%	0	0.0%
Any primary path	2	9.5%	0	0.0%
[1] Postoperative fever	2	9.5%	0	0.0%

Note: Sorted first by System Organ Class (alphab. order), then by High Level Term (alphab. order), then by Preferred Term (alphab. order).
Note: The table presents MedDRA terms of all paths.
Note: [1] means primary path, [2] means secondary path.

Benefits:

The multi-axial links enhance the value of the grouping terms. In other words, this method overcomes the limitations described under Section 2.4.1.

Limitations:

- Covers only conditions that are represented in one SOC or HLGT/HLT.
- Using this method, displaying PTs by primary and secondary SOC assignment could lead to double counting of terms.

3.2.3.2 Search by Standardised MedDRA Queries (SMQs)

- If an SMQ has been developed that is relevant to the search, it should be used.
- More than fifty SMQs are currently in production. If an available SMQ is relevant to the search, it may be used. Do not modify the term content or structure of the SMQ unless there is a compelling reason to do so since altering it makes it non-standard. If altering an SMQ is absolutely necessary, document the changes made.
- It is essential for the MedDRA user to carefully read the SMQ Introductory Guide before applying an SMQ in order to fully understand the scope of the SMQ and to properly apply algorithms (an optional feature).
- It is recommended that the user decide initially whether a broad or a narrow search or specific sub-search is needed and to document the choice.
- It is good practice to define adjudication rules for cases identified by an SMQ. 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".
- The search output alone may not be sufficient for data assessment (e.g., frequency of a condition). Search results (i.e., retrieved data) should then be evaluated against the question originally posed.
- For SMQs which contain HLGTs and or HLTs it is also important to verify whether the database structure will allow for retrieval of only primary PTs under the included HLTs or whether also secondary PTs will be retrieved (see also Section 2.3)

3.2.3.3 Search by *ad hoc* queries

Although the number of SMQs will steadily increase, there will always be a need for organization specific or project specific (i.e., *ad hoc*) searches.

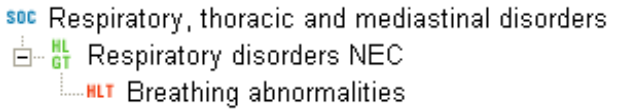
Users that have created an *ad hoc* query that may be broadly applicable are encouraged to send the aggregated terms to the MSSO (via a change request) for consideration for development as an SMQ.

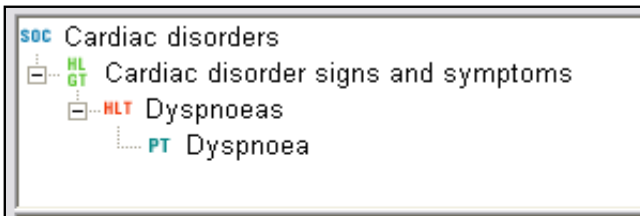
There are a number of points to consider when constructing an *ad hoc* query for MedDRA-coded data:

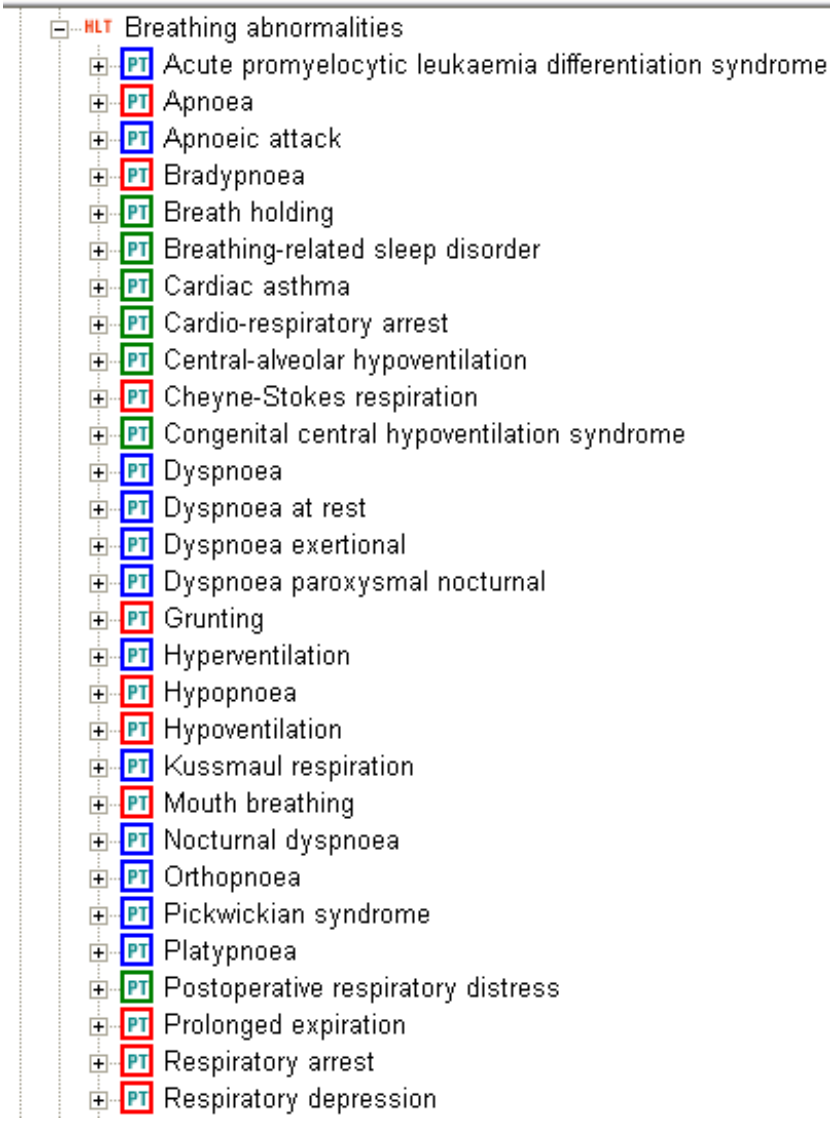
- Those responsible for constructing an *ad hoc* query should be familiar with:
  - Medicine
  - The structure and characteristics of MedDRA (e.g., hierarchy, multi-axiality) and the general content of MedDRA groupings (SOCs, HLGTs and HLTs)
- Data characteristics and structure
- The scope of the search should be defined, i.e., will it be "broad" or "narrow" in focus?
- Initial focus should be on SOCs related to the condition of interest. For example, an *ad hoc* query for a renal condition should start with SOC *Renal and urinary disorders.*
- The non multi-axial SOCs should always be reviewed (SOC *Investigations*, SOC *Surgical and medical procedures* and SOC *Social circumstances*). In addition, it may be useful to review for relevant terms other SOCs that do not represent 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 terms by a "bottom-up" survey of MedDRA (e.g., finding relevant terms at the LLT and PT levels initially) combined with a "top-down" approach (i.e., starting at the SOC level and drilling down through the hierarchy).
- When possible, consider using multi-axial links that lead to other SOCs as additional relevant query terms may be found there. In another SOC, the same PT may be placed in another context which may help identify additional relevant terms. (See example of PT *Dyspnoea* below).
- Include grouping terms when possible (remembering the caveats described in Section 2.4.1).
- In general, queries should be built on PTs and groupings (i.e., HLTs, HLGTs and SOCs). Unless very specific concepts (e.g., bacterial species) are needed, avoid using LLTs to build the query.
- Consider saving the ad hoc query for future use.
- Account for version changes in stored ad hoc queries.

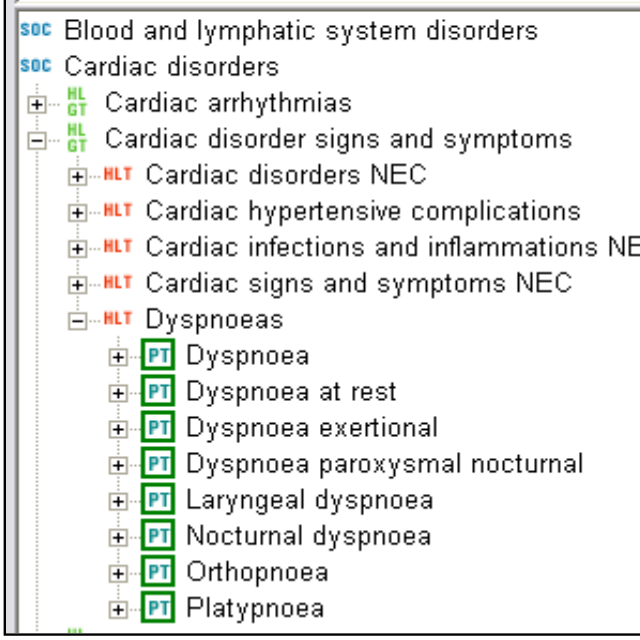
For information regarding principles used to construct SMQs including testing for sensitivity and specificity, refer to "SMQs DEVELOPMENT AND RATIONAL USE OF STANDARDISED MedDRA QUERIES (SMQs), CIOMS, Geneva 2004."

Example:


SOC Respiratory, thoracic and mediastinal disorders
HLGT Respiratory disorders NEC
HLT Breathing abnormalities


SOC Cardiac disorders
HLGT Cardiac disorder signs and symptoms
HLT Dyspnoeas
PT Dyspnoea


HLT Breathing abnormalities
PT Acute promyelocytic leukaemia differentiation syndrome
PT Apnoea
PT Apnoeic attack
PT Bradypnoea
PT Breath holding
PT Breathing-related sleep disorder
PT Cardiac asthma
PT Cardio-respiratory arrest
PT Central-alveolar hypoventilation
PT Cheyne-Stokes respiration
PT Congenital central hypoventilation syndrome
PT Dyspnoea
PT Dyspnoea at rest
PT Dyspnoea exertional
PT Dyspnoea paroxysmal nocturnal
PT Grunting
PT Hyperventilation
PT Hypopnoea
PT Hypoventilation
PT Kussmaul respiration
PT Mouth breathing
PT Nocturnal dyspnoea
PT Orthopnoea
PT Pickwickian syndrome
PT Platypnoea
PT Postoperative respiratory distress
PT Prolonged expiration
PT Respiratory arrest
PT Respiratory depression


SOC Blood and lymphatic system disorders
SOC Cardiac disorders
HLGT Cardiac arrhythmias
HLGT Cardiac disorder signs and symptoms
HLT Cardiac disorders NEC
HLT Cardiac hypertensive complications
HLT Cardiac infections and inflammations NE
HLT Cardiac signs and symptoms NEC
HLT Dyspnoeas
PT Dyspnoea
PT Dyspnoea at rest
PT Dyspnoea exertional
PT Dyspnoea paroxysmal nocturnal
PT Laryngeal dyspnoea
PT Nocturnal dyspnoea
PT Orthopnoea
PT Platypnoea

4.0 Appendices:

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- Tetsuya Kusakabe

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- Morell David
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