

**MedDRA[®] DATA
RETRIEVAL AND PRESENTATION:
POINTS TO CONSIDER**

*Release 2.0
Based on MedDRA Version 12.0*

**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 process². 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, Sections 6.1 and 6.2, for working group members.)

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 *Introductory Guide*, Version 12.0. 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, this document addresses data retrieval in a broader context.

The examples contained in this document are based on MedDRA Version 12.0 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.

Figures referenced in the text are found in the Appendix, Section 6.3.

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

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

- To capture and present product indications, investigations, medical history and social history data

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*, the *Introductory Guide for Standardised MedDRA Queries (SMQs)*, 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 Documentation of Data Retrieval and Presentation Practices

Organizations are encouraged to document their term selection conventions, data retrieval and output strategies (including SMQs and other queries), and quality assurance procedures. These organization-specific guidelines should be consistent with the Points to Consider documents and should include the:

- MedDRA version used for the search
- Search strategy methods in sufficient detail to be reproducible
- Version update process(es)
- Processes for creation and maintenance of customized MedDRA queries

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	<i>Cardiac arrhythmias</i>
HLT	<i>Cardiac conduction disorders</i>
HLT	<i>Rate and rhythm disorders NEC</i>
HLT	<i>Supraventricular arrhythmias</i>
HLT	<i>Ventricular arrhythmias and cardiac arrest</i>

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	<i>Vascular tests NEC (incl blood pressure)</i>
PT	<i>Blood pressure</i>
PT	<i>Blood pressure abnormal</i>
PT	<i>Blood pressure decreased</i>
PT	<i>Blood pressure increased</i>

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. Figure 1 illustrates how data coded to a single PT from another terminology may be expressed by several PTs in MedDRA.

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 MedDRA *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 SOC's 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 SOC's address anatomical locations and etiology, as well as purposes or other concepts; therefore, data might reside in SOC's 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 in Figure 2, 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*.

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 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 11.1, *Nephritis interstitial* was a PT and in Version 12.0 it was “demoted” to an LLT.

As noted in the table in Figure 3, the original query was done in MedDRA Version 11.1 in which there was a PT *Nephritis interstitial*. If the query had been re-run in MedDRA Version 12.0, these events would not have been found at the PT level because in MedDRA Version 12.0, PT *Nephritis interstitial* was demoted to an LLT under PT *Tubulointerstitial nephritis*.

In MedDRA Version 11.1, the primary SOC assignment for PT *Peripheral coldness* was SOC *General disorders and administration site conditions* and the secondary SOC assignment was SOC *Vascular disorders*. In Version 12.0, the primary SOC assignment was changed to SOC *Vascular disorders* and the secondary SOC assignment to SOC *General disorders and administration site conditions*. If one were able to retrieve PTs only under their primary SOC assignment, this term will seem to have “disappeared” from SOC *General disorders and administration site conditions*.

The terms used for queries should be in the same MedDRA version as the data being queried; keep in mind that stored data for an organization may also be in more than one version of MedDRA. For example, new terms might have been included in a query built on MedDRA Version 12.0 that might not be present in stored data coded in MedDRA Version 11.1; this could lead to search results that are incomplete.

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 GENERAL 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.

3.1.2 Patient sub-populations

On the MSSO and JMO Web sites, there are pediatric and gender-specific adverse event term lists (http://meddramsso.com/MSSOWeb/document_library/PediatricGenderTermLists.htm). These may aid in the retrieval of data that are gender-specific or age-specific for the pediatric population. However, it is necessary to refer to individual database fields for demographics.

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	<i>Chest discomfort</i>
PT	<i>Chest pain</i>
PT	<i>Oedema peripheral</i>
PT	<i>Sudden death</i>
PT	<i>Localised oedema</i>
PT	<i>Oedema due to cardiac disease</i>
PT	<i>Peripheral oedema neonatal</i>
PT	<i>Cardiac death</i>

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 HLT 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 HLTs, 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 (HLT and HLT) and PTs for more complex data. Figure 4 provides an example of such an output.

The Internationally Agreed Order of SOCs was developed to facilitate consistency irrespective of language or alphabet (see Figure 5). 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.

Graphical display might facilitate understanding by the viewer. This can include histograms, bar charts, pie charts, etc. Figures 6 and 7 are examples of such displays.

Figures 8a and 8b display data 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.

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.

Figure 9 is an example of such a display.

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.

Figure 10 displays a potential approach for focused searches.

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). See also Figure 11.

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*

Benefits:

The multi-axial links enhance the value of the grouping terms. In other words, this method overcomes the limitations described under Section 3.2.1.

Limitations:

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

4 STANDARDISED MedDRA QUERIES

4.1 Introduction

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

SMQs are a joint effort of the Council for International Organizations of Medical Sciences (CIOMS) SMQ Working Group 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.

It is essential for the MedDRA user to 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.

4.2 SMQ Benefits

As with all MedDRA-based queries, users of SMQs should be aware of several factors that may influence data retrieval including database characteristics, data conversion processes, coding conventions, and MedDRA versioning. For more details, see Section 3.1.

SMQ benefits include:

- Application across multiple therapeutic areas
- Validated reusable programming
- Standardized communication of safety information

- Consistent data retrieval
- Maintenance by MSSO/JMO

4.3 SMQ Limitations

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

4.4 SMQ Modifications

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

4.5 SMQs and MedDRA Version Changes

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

As with all searches of MedDRA-related data, it is important to document the MedDRA and SMQ versions used.

Changes to SMQs that can occur with each MedDRA version include (but are not limited to) the following:

- Addition of PTs
- Inactivation of a PT (i.e., a PT is effectively “removed” from an SMQ)
- Change of term scope (e.g., a narrow term becomes a broad term)
- Restructuring of an SMQ (e.g., change in the hierarchical position of an SMQ)
- Creation of a new SMQ

For a full description of the types of changes that can occur to SMQs, please reference the MedDRA “Change Request Information” document (http://meddramsso.com/MSSOWeb/mssosubs/coresubs/6282_120_changereq_in fo.pdf; note that subscriber’s user ID and password are required). Changes introduced with each new version are documented in the “What’s New” document for each MedDRA version. (The cumulative changes are contained within the ascii files in the fields called “Term_addition_version” and “Term_last_modified_version”).

The MedDRA version of the SMQ and 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:

PT *Basal ganglia infarction* was added to SMQ *Ischaemic cerebrovascular conditions* in MedDRA Version 12.0. Using the Version 11.1 of this SMQ – which does not contain this PT – would fail to identify cases coded to this term in a database using MedDRA Version 12.0.

For further details, see Section 2.5.

4.6 SMQs – Impact of MedDRA Legacy Data Conversion

The method of conversion of data coded in other terminologies (e.g., COSTART) also impacts the application and output of SMQs. See Section 2.1.2, *Impact of data conversion method on data retrieval*.

4.7 SMQ Change Requests

Users are encouraged to submit Change Requests to MSSO/JMO as needed to improve the utility of SMQs. A rationale (and possibly testing data) for a submitted Change Request must be provided. The MSSO may require more time to evaluate SMQ Change Requests than regular MedDRA Change Requests.

Before submitting an SMQ Change Request, users should review the SMQ documentation for inclusion and exclusion criteria of the SMQ.

4.8 SMQ Technical Tools

The MSSO browser allows for searching and viewing the contents of SMQs and includes additional details such as the SMQ description (definition) and development notes. An Excel spreadsheet containing the terms in each SMQ is available from the MSSO and JMO (<http://meddramsso.com/MSSOWeb/SMQ/index.htm>; link “Production SMQ Spreadsheet”). This spreadsheet allows a user to readily transfer SMQ terms to query tools. File specifications related to SMQs are found in “MedDRA ASCII and Consecutive Files Documentation” supplied with each MedDRA version.

To assist organizations with SMQ usage, some SMQ system tools that provide technical support are referenced on the MSSO Web site (<http://meddramsso.com/MSSOWeb/meddra/tools.htm>).

4.9 SMQ Applications

SMQs were developed to address the high granularity and unique features of MedDRA and to maximize 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). It is good practice to define and document criteria for evaluation of 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 (see Section 4.10.1).

4.9.1 Clinical trials

SMQs may be applied in the clinical trial setting – particularly for aggregate data – where the safety profile has yet to be fully established. Here, most if not all available SMQs may be employed, 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.

Example:

When developing a data analysis plan for a targeted safety study, one may consider employing the narrow terms of an SMQ to aggregate events of interest.

4.9.2 Postmarketing

In the post marketing setting, SMQs can be used in a variety of ways as described below.

4.9.2.1 Suspected or known safety issue

A specific SMQ or a selection of SMQs may be utilized to retrieve relevant cases for subsequent medical review.

Example:

A company suspects an emerging signal of pancreatitis for a new HIV product. SMQ *Acute pancreatitis* can be applied to their data.

4.9.2.2 Signal detection

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

4.9.2.3 Single case alert

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

Example:

A medical issue of interest needs to be communicated to a regulatory authority as part of an agreed risk management plan. The SMQ narrow search or more specific levels of a hierarchical SMQ may be applied to identify potential cases of interest.

4.9.2.4 Periodic reporting

SMQs may assist in aggregating 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.

4.10 SMQ Search Options

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

Some SMQs are hierarchical (i.e., include one or more sub-searches). Other SMQs employ algorithms, and in one case (SMQ *Systemic lupus erythematosus*), assign weightings to particular signs, symptoms and/or laboratory results to help in identifying cases.

4.10.1 Narrow and broad searches

Most SMQs have “narrow” and “broad” subsets of PTs. The “narrow” terms have a greater likelihood of identifying only events of interest (high specificity), while the “broad” terms are intended to identify additional possible events (high sensitivity). Some events retrieved by broad search terms may, upon further review, not relate to the condition of interest. The user can select the scope of search (narrow or broad) that is most applicable to the question that is being asked.

When a compound is in early phase development or has only recently been marketed, it may be advisable to apply a broad search.

Example:

If evaluating an emerging signal of lactic acidosis using SMQ *Lactic acidosis*, narrow terms may be applied to identify events where the

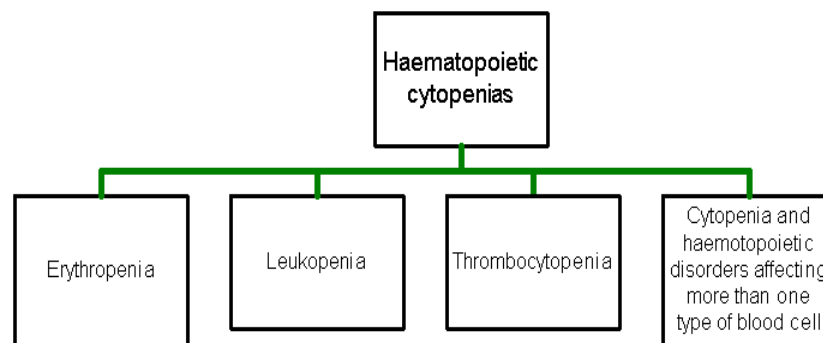
specific diagnosis has been reported; however, events of reported signs and symptoms would not be retrieved. If there is further need or concern to find cases where no specific diagnosis (but mainly signs and symptoms) have been reported, then a broad search (i.e., narrow + broad search terms) should be applied.

4.10.2 Hierarchical SMQs

A number of SMQs have a hierarchical structure (one or more level of sub-searches of increasing specificity). The user can select the search that is most applicable to the question that is being asked or a combination of sub-search SMQs as needed.

The SMQ Introductory Guide has explanatory notes to guide the user in the appropriate use of each hierarchical SMQ.

An example of a hierarchical SMQ is illustrated below (SMQ *Haematopoietic cytopenias*).



Example:

The medical condition of interest is thrombocytopenia. SMQ *Haematopoietic cytopenias* may be too inclusive as sub-searches for decreases of other hematopoietic cell lines (e.g., SMQ *Leukopenia*) are included. A user may wish to select only the sub-search SMQ *Thrombocytopenia* in this instance.

4.10.3 Algorithmic SMQs

An algorithm provides for a combination of terms which – if retrieved in a single case – are more likely to identify a case of interest than isolated broad search terms (see table below). The broad terms of algorithmic SMQs are subdivided into categories that could be groupings of organ-specific signs or symptoms, laboratory terms, etc. (Note: the broad search categories are labeled as B, C, etc.). Using an algorithm may thus reduce the amount of “noise” (i.e., non-relevant cases).

Using an algorithmic SMQ without employing the algorithm (i.e., simply applying the narrow and broad searches) will yield different results from those obtained using the algorithm.

Example of an algorithmic SMQ (SMQ Anaphylactic reaction)

Category B – Upper airway/Respiratory	Category C – Angioedema/Urticaria, etc.	Category D – Cardiovascular/Hypotension
<i>Acute respiratory failure</i>	<i>Allergic oedema</i>	<i>Blood pressure decreased</i>
<i>Asthma</i>	<i>Angioedema</i>	<i>Blood pressure diastolic decreased</i>
<i>Bronchial oedema</i>	<i>Erythema</i>	<i>Blood pressure systolic decreased</i>

Algorithm:

- Case = A (Narrow terms – not included in table)
- Or Term from Category B **and** term from Category C
- Or Term from **either** Category B or Category C **plus** Term from Category D

SMQ *Systemic lupus erythematosus* is an algorithmic SMQ that also assigns weightings to various MedDRA terms (e.g., PT *Pleural effusion* = 3), and a total weighting score of greater than 6 would suggest a case.

Note: Not all software tools will support algorithmic SMQs.

4.11 SMQ vs. MedDRA Grouping Terms

Data retrieved using MedDRA grouping terms (HLTs, HLGTS) may differ from those retrieved using a related SMQ.

Example:

Cardiac arrhythmia is a suspected issue (e.g., by review of a primary SOC output of all data). If events retrieved by using HLGTS *Cardiac arrhythmias* are compared to those retrieved by SMQ *Cardiac arrhythmias*, more events may be retrieved by the SMQ because it includes additional terms found in other SOC such as SOC *Investigations*.

5 CUSTOMIZED SEARCHES

MedDRA allows a variety of searching options as described above. However, there will be situations where a customized search is required.

5.1 Modified SMQs

Do not modify the term content or structure of the SMQ unless there is a compelling reason to do so since altering it in any way makes it non-standard (see Section 4.1).

5.1.1 “Modified MedDRA query based on an SMQ”

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 is the responsibility of the organization that created it.

5.1.2 Examples of modified MedDRA queries based on SMQs:

5.1.2.1 Additional PTs are needed

Example:

A product being investigated for possible lack of efficacy is a combination of a drug and a device. SMQ *Lack of efficacy/effect* does not include PT *Device failure*. When documenting a search, indicate that PT *Device failure* has been added.

Example:

A product is being investigated for a possibly safety signal of dementia, and the user wishes to use SMQ *Dementia*. For this particular product, addition of PT *Disturbance in attention* may be needed.

5.1.2.2 Some PTs may be excluded

Example:

An antipsychotic product is being investigated for potential QT prolongation and also has a well-described association with hypotension and fainting. When using SMQ *Torsade de pointes/QT prolongation* (broad search), the user may wish to exclude PT *Syncope* to prevent excess “noise” in data retrieval.

5.1.2.3 Changing the scope (“narrow” or “broad”) of an SMQ term

Example:

A product is being investigated for severe cutaneous adverse reactions including a potential for DRESS syndrome, and a specific (“narrow”) search result is desired. The SMQ for severe cutaneous adverse reactions (SCAR) does not include DRESS syndrome as part of the narrow search although it is represented in the broad search as an LLT linked to PT *Drug rash with eosinophilia and systemic symptoms*. For this query, include PT *Drug rash with eosinophilia and*

systemic symptoms with the narrow search terms.

5.2 Ad hoc Queries

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:
 - Have medical knowledge
 - Know the structure and characteristics of MedDRA (e.g., hierarchy, multi-axiality) 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, 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 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 (e.g., terms at the LLT and PT levels initially)
 - A “top-down” survey (i.e., starting at the SOC level and drilling down through the hierarchy)
- Consider looking at secondary links for multi-axial terms as additional relevant query terms may be found. For example, PT *Dyspnoea* can be found with other respiratory symptom PTs in its primary SOC (SOC *Respiratory, thoracic and mediastinal disorders*), and it can also be found with related cardiac symptom PTs in its secondary SOC *Cardiac disorders*.
- Include grouping terms (i.e., HLTs, HLGTS) when possible (remembering the caveats described in Section 2.4.1).
- 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 the query.
- Consider saving the *ad hoc* query for future use; maintenance is necessary for MedDRA version changes

- An *ad hoc* query that may be useful to other MedDRA users can be submitted to the MSSO (via a change request) for possible development as an SMQ.

6.0 APPENDICES

6.1 Current Members of the ICH *Points to Consider* Working Group:

Co-Rapporteurs:

John (Jake) Kelsey
Christina Winter

Japan:

Ministry of Health, Labour and Welfare:
Wakako Horiki
Yoshihiko Sano
Japan Pharmaceutical Manufacturers Association
Yo Tanaka
Japanese Maintenance Organization
Reiji Tezuka
Yasuo Sakurai
Osamu Handa

European Union:

Commission of the European Communities
Morell David
Carmen Kreft-Jais
European Federation of Pharmaceutical Industries Associations
Hilary Vass
Christina Winter

Canada:

Health Canada
Alison Langevin
Michelle Séguin

United States:

US Food and Drug Administration
John (Jake) Kelsey
Toni Piazza-Hepp
Pharmaceutical Research and Manufacturers of America
Susan M. Lorenski
JoAnn Medbery
MedDRA MSSO
Patricia Mozzicato

6.2 Past Members/Affiliations of the ICH *Points to Consider* Working Group:

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Ministry of Health, Labour and Welfare

Tamaki Fushimi

Kazuhiro Kemmotsu

Tatsuo Kishi

Chie Kojima

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Kaori Nomura

Kenichi Tamiya

Manabu Yamamoto

Nobuhiro Yamamoto

Takashi Yasukawa

Japan Pharmaceutical Manufacturers Association

Takayoshi Ichikawa

Akemi Ishikawa

Satoru Mori

Yasuo Sakurai

Kunikazu Yokoi

Japanese Maintenance Organization

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Canada:

Health Canada

Lynn Macdonald

Heather Morrison

Heather Sutcliffe

Bill Wilson

European Union:

Commission of the European Communities

Dolores Montero

European Federation of Pharmaceutical Industries Associations

Barry Hammond – past *Rapporteur*

Reinhard Fescharek – past *Rapporteur*

United States:

US Food and Drug Administration

Miles Braun

Brad Leissa

Andrea Feight

Pharmaceutical Research and Manufacturers of America

David Goldsmith

Sidney Kahn
Margaret M. Westland – past *Rapporteur*
MedDRA MSSO
JoAnn Medbery

6.3 Figures

OTHER TERMINOLOGY PREFERRED TERMS	NO. OF EVENTS	MEDDRA VERSION 12.0 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

Figure 1 – How data coded to a single PT from another terminology may be expressed by several PTs in MedDRA

	OTHER TERMINOLOGY		MedDRA Version 12.0	
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)				

Figure 2 – Multiple MedDRA terms may be used to code similar medical conditions included in a “disorder SOC”; associated laboratory findings are in SOC Investigations

MedDRA Version 11.1	Number of Events at PT Level
Nephritis interstitial (PT)	15
Tubulointerstitial nephritis	5
MedDRA Version 12.0	
Nephritis interstitial (no longer a PT)	0
Tubulointerstitial nephritis	20

Figure 3 – In MedDRA Version 11.1, Nephritis interstitial was a PT and in Version 12.0 it was demoted to an LLT

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

Figure 4 – Primary SOC output listing - example

MedDRA Version 12.0 English Alphabetical Order	MedDRA Version 12.0 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

Figure 5 – The alphabetical SOC order (in English) and the Internationally Agreed Order of SOCs

Figure 1
Relative frequency of events per primary SOC

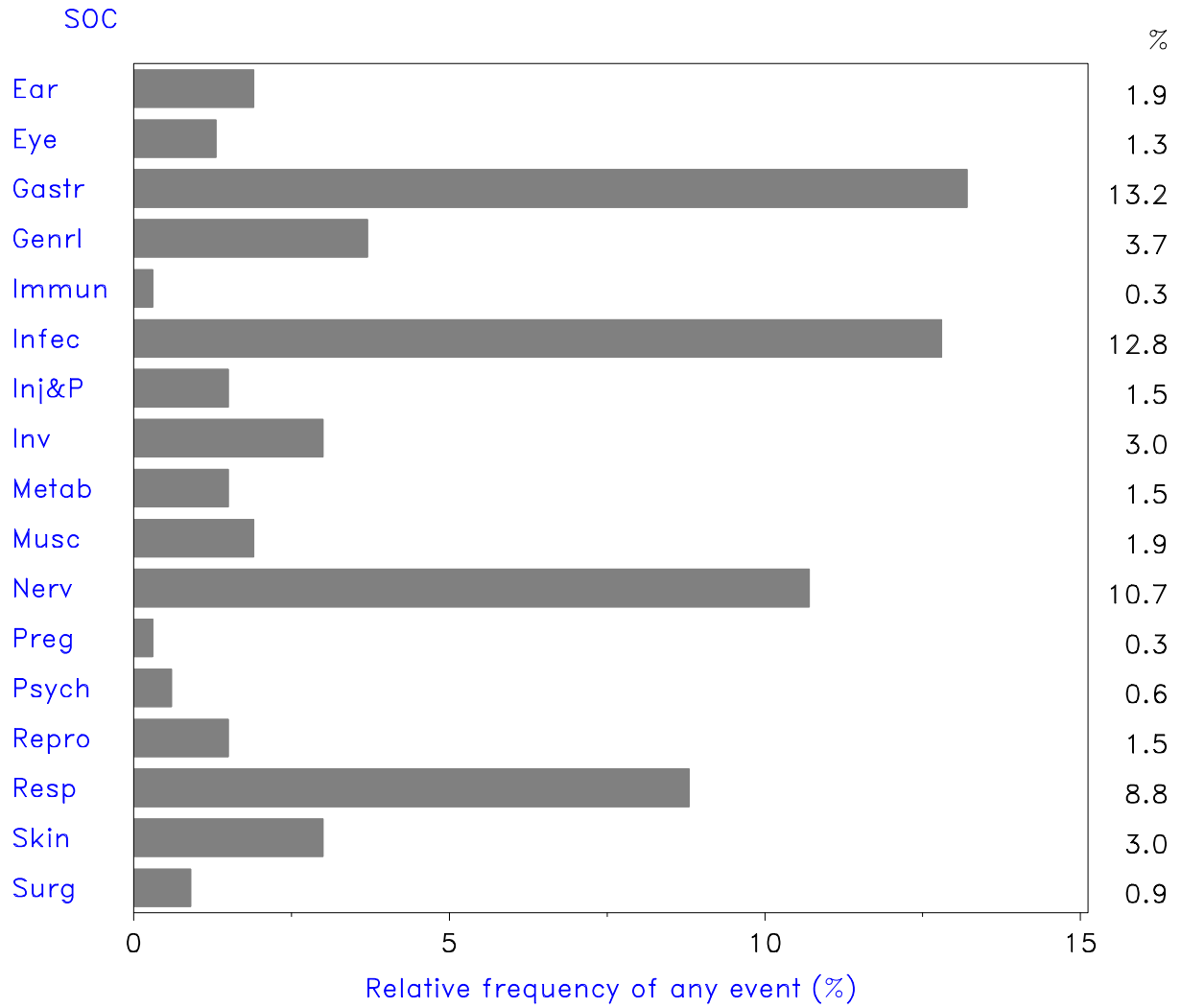


Figure 6 – Example of a graphical display (frequency by primary SOC)

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

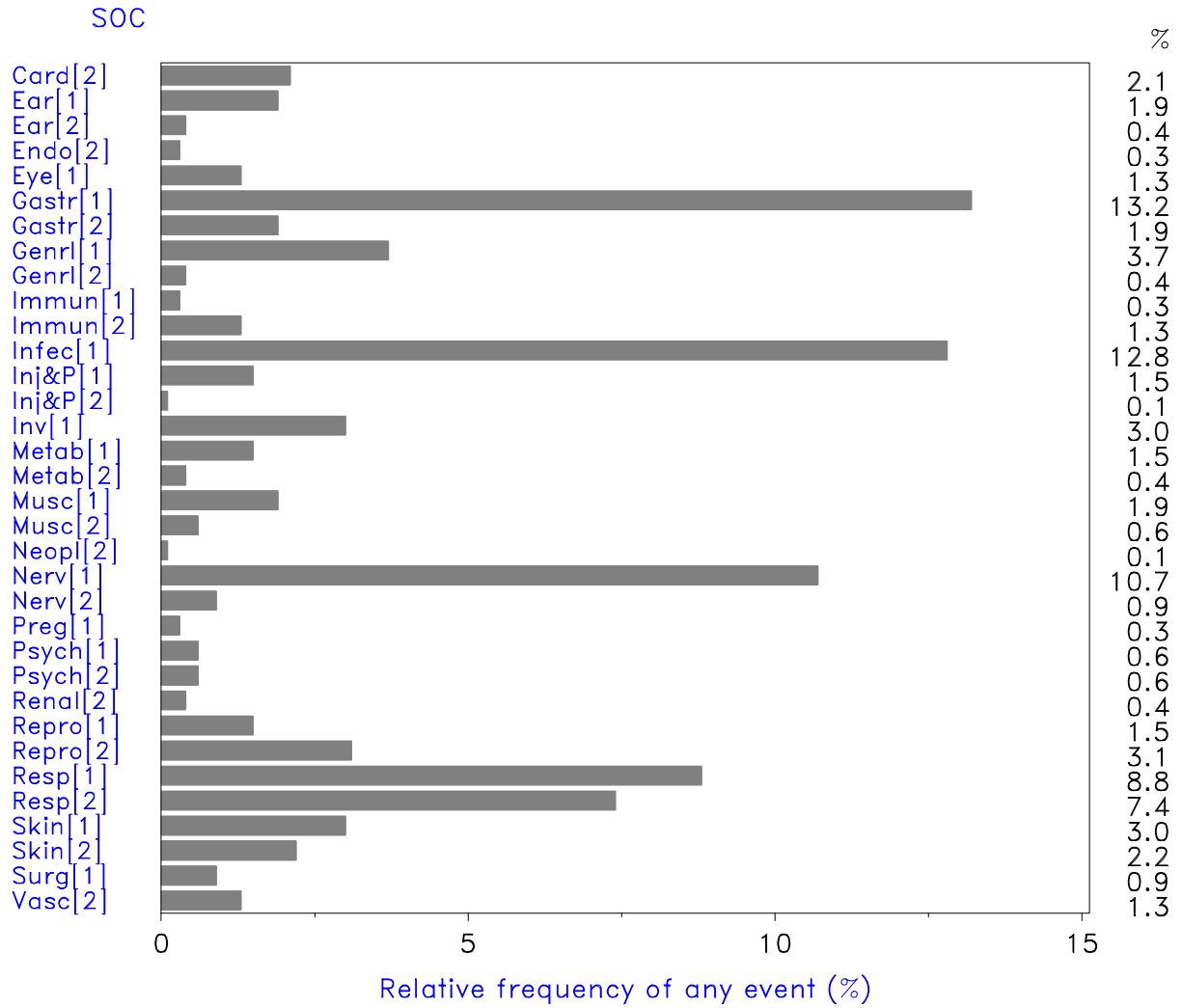


Figure 7 – Example of a graphical display (frequency by primary and secondary SOC)

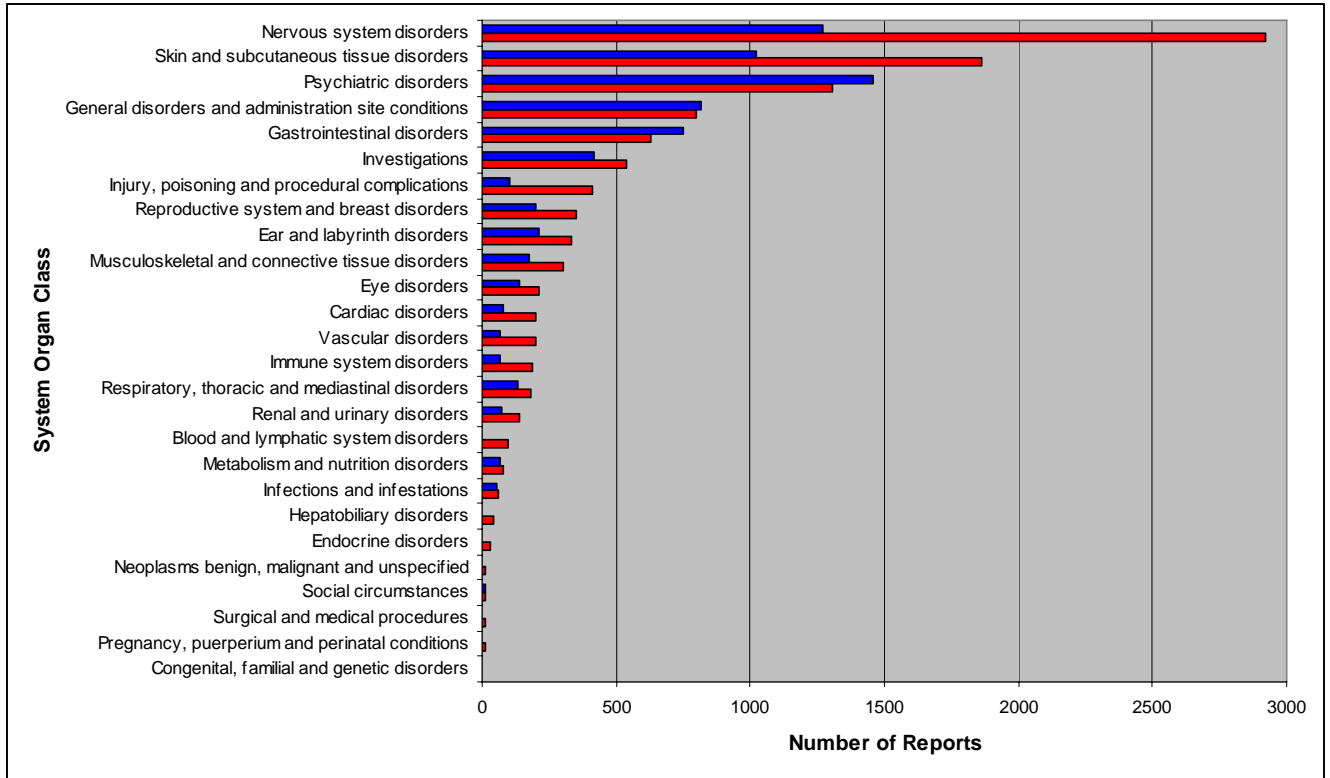


Figure 8a – The upper bar of each pair represents numbers of reports from Consumers (blue) and the lower bar reports from Health Care Professionals (red) (Population 1)

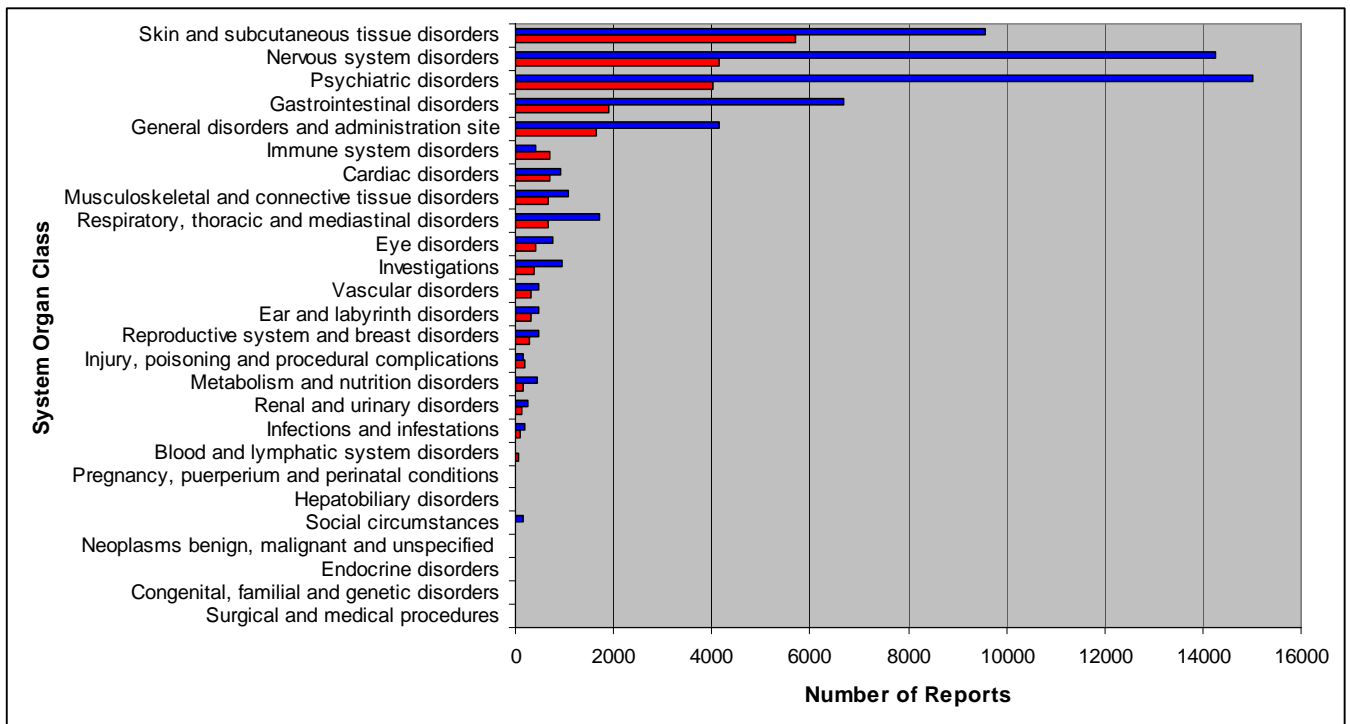


Figure 8b – The upper bar of each pair represents numbers of reports from Consumers (blue) and the lower bar reports from Health Care Professionals (red) (Population 2)

Most Frequent On-Therapy Adverse Events
 PTs sorted by relative risk

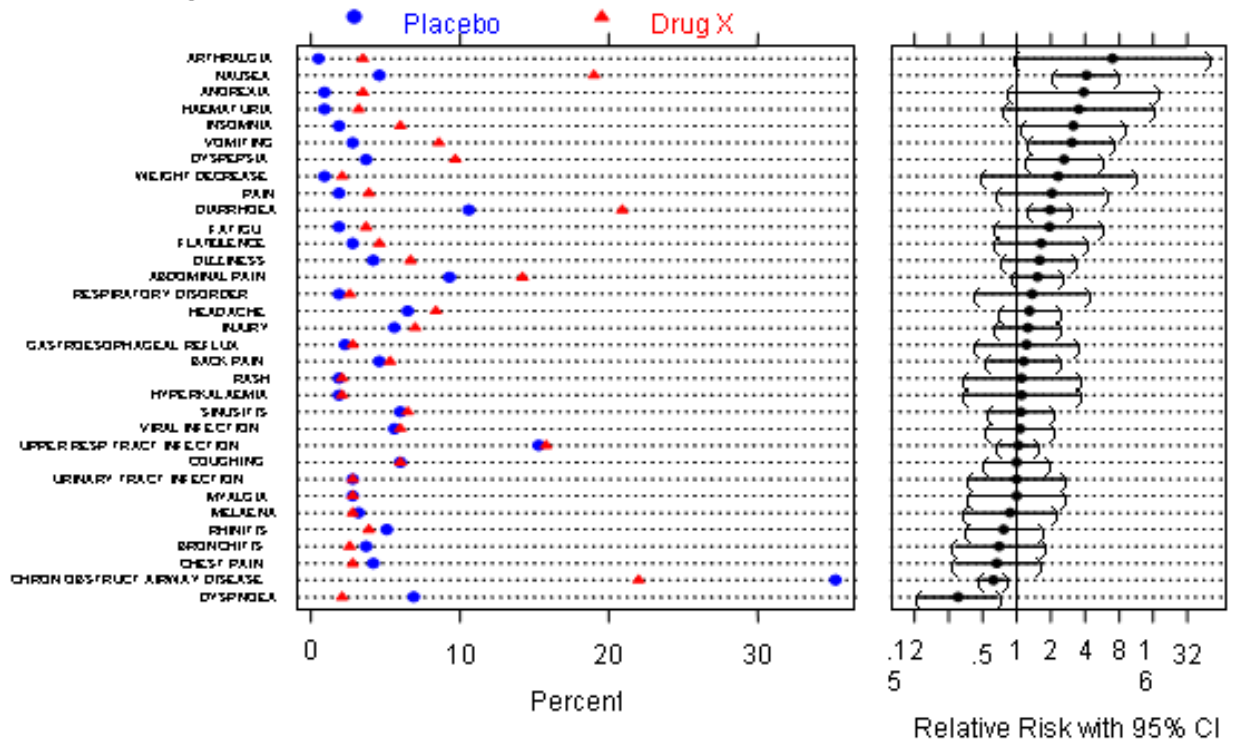


Figure 9 – For a small dataset, a display of PTs may be adequate

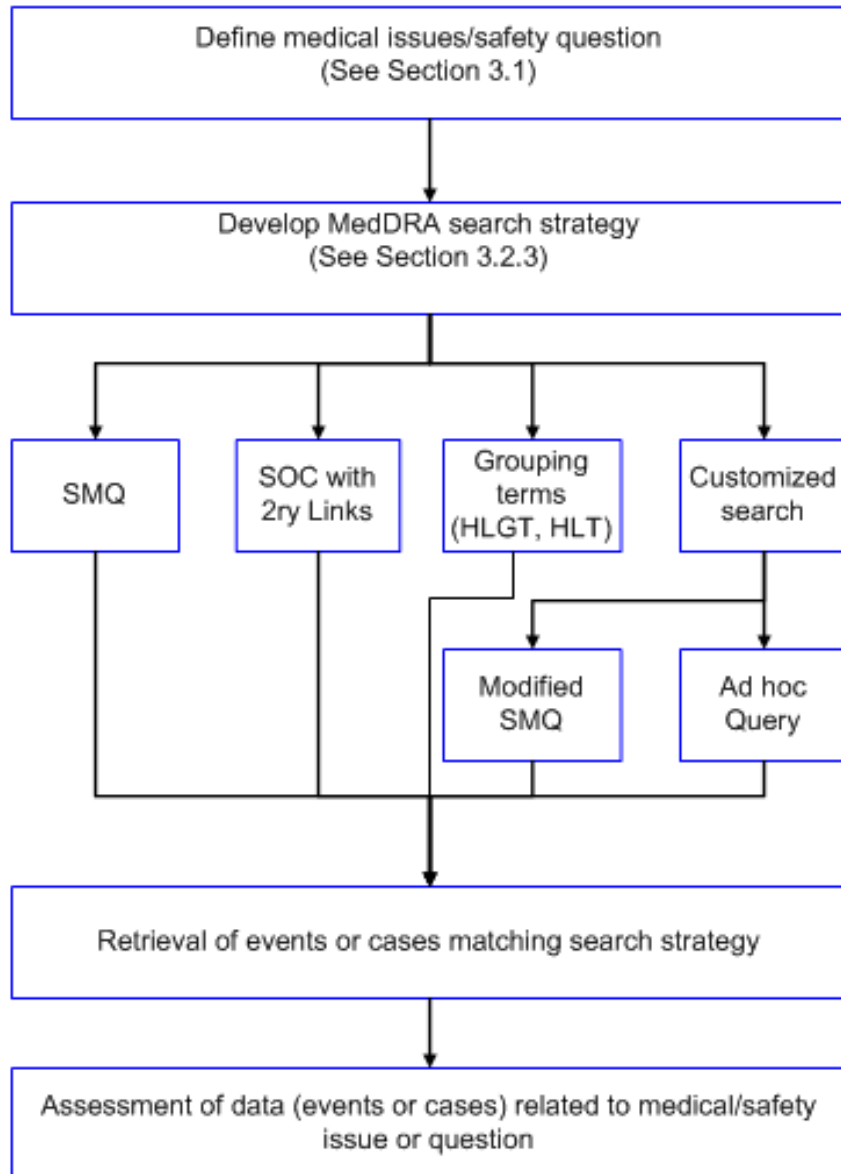


Figure 10 – Potential approach for focused searches

**Incidence of treatment-emergent adverse events coded by MedDRA 12.0
Population: Patients Valid for Safety**

System Organ Class		Active		Control	
	High Level Term	(N=21)		(N=19)	
	Preferred Term				
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.

Figure 11 – Primary and secondary SOC output