Introductory Guide for Standardised MedDRA Queries (SMQs) Version 23.0

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Acknowledgements

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Notice to Readers

The *Introductory Guide for Standardised MedDRA Queries (SMQs),* prepared in English, is intended only for use with the English version of MedDRA and its version-specific SMQs. It is included with each MedDRA release, and is also accessible on the MedDRA website under Support Documentation. In addition to the English version, editions of the *Introductory Guide for Standardised MedDRA Queries (SMQs)* have been developed in other languages and are included with the respective MedDRA version release translations.

Please note that SMQs do not cover all medical topics or safety issues. Also, the content of an SMQ may change subsequent to implementation, because all SMQs are subject to ongoing refinement with the successive versions of MedDRA.

If any modifications are made to term content or structure of an SMQ by a subscriber or user, it can no longer be called an "SMQ" but it should instead be referred to as a "modified MedDRA query based on an SMQ". **Under no circumstances should a query constructed for the specific need of an organization be called an "SMQ" by its originator.** This is to ensure that there is no confusion with the ICH-endorsed SMQs applied by other MedDRA users. Any alternate name for the organization-constructed query is acceptable as long as it could not be potentially confused with an ICH-endorsed SMQ.

Throughout this *Introductory Guide for Standardised MedDRA Queries*, there are occasional references to "Phase II testing." Earlier in the development of SMQs, there was a period of time when the queries were provided to MedDRA subscribers for pre-production testing and feedback; this was called "Phase II." As of July 2006, Phase II has been eliminated.

This document includes a number of website citations and hyperlinks in the lists of references for individual SMQs, and in other sections. Note that some web sites may no longer be active, or may have changed, but they remain included in their original format for historical purposes.

One new SMQ has been added in MedDRA Version 23.0, *Opportunisitc infections (SMQ)*, which is described in Section 2.72 of this *Introductory Guide for Standardised MedDRA Queries*.

1. INTRODUCTION

1.1 Definition of a Standardised MedDRA Query

Standardised MedDRA Queries (SMQs) are groupings of MedDRA terms, ordinarily at the Preferred Term (PT) level that relate to a defined medical condition or area of interest. SMQs are intended to aid in the identification and retrieval of potentially relevant individual case safety reports. The included terms may relate to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc. The only Lowest Level Terms (LLTs) represented in an SMQ are those that link to a PT used in the SMQ; all others are excluded.

1.2 Background

SMQs arose out of a recognized need of the MedDRA user community for standard tools to assist in the identification and retrieval of safety data. The original MedDRA Special Search Categories (SSCs) were intended for a similar purpose, but after several years of MedDRA use, the biopharmaceutical community (regulators and industry) concluded that these tools did not adequately address the need. In response, the MedDRA Maintenance and Support Services Organization (MSSO), in early 2002, began to develop MedDRA Analytical Groupings (MAGs). MAGs were defined as collections of terms from any level of the MedDRA hierarchy (except, in general, LLTs) and from any, several, or all MedDRA SOCs that relate to the medical condition or area of interest defined by the name of the MAG, including signs, symptoms, physical findings, laboratory and other physiologic test data, and associated social circumstances related to the medical condition or area of interest.

At the same time that MAGs were being developed at the MSSO, an independent initiative by the Council for International Organizations of Medical Sciences (CIOMS) was started to address the need for special queries/groupings using MedDRA-coded data; their groupings were called Standardised Search Queries (SSQs). It was clear that the concepts of MAGs and SSQs were quite similar to one another and were both intended to fulfill the perceived need for a retrieval tool to accompany MedDRA. Thus, CIOMS and the MSSO agreed that it was in the user community's best interest for the CIOMS Working Group and the MSSO to combine their efforts in developing this tool. To recognize the joint effort, the former "MAG" and "SSQ" designations were dropped, and an agreement on a name for these new standard groupings was reached. Since May 2003, the joint efforts of the CIOMS Working Group and MSSO have been designated Standardised MedDRA Queries (SMQs). In November 2003, the ICH MedDRA Management Committee endorsed the cooperative effort, and the ICH process was adopted for the development of SMQs.

The CIOMS Working Group is composed of senior scientists from several drug regulatory authorities, international pharmaceutical companies, the MSSO, the Japanese Maintenance Organization (JMO), the World Health Organization, and other institutions.

1.3 Development of SMQs

A focus of the early phase of SMQ development was to identify which areas of interest were candidates for development. Close to 100 possible topics were initially identified.

The definitions, inclusion and exclusion criteria, hierarchy (if applicable), and algorithm (if applicable) for each SMQ are included in this Introductory Guide. Much of this information was derived from the anonymized SMQ CIOMS Working Group detailed documentation and can be found at https://www.meddra.org/software-packages. The general methodological approach to the development and use of SMQs was published in a document published by CIOMS *Development and Rational Use of Standardised MedDRA Queries (SMQs): Retrieving Adverse Drug Reactions with MedDRA*. The reader is referred to the CIOMS Web site for further information: http://www.cioms.ch/.

1.4 Design Concepts for SMQ Content

SMQs may have a mixture of very specific terms and less specific terms that are consistent with a description of the overall clinical syndrome associated with a particular adverse event and drug exposure. Some SMQs are a straightforward collection of terms; others have been designed to accommodate combinations of terms from more than one group (see 1.4.2 Algorithm, below). To address these varied aspects, SMQs may have certain specific design features:

1.4.1 Narrow and Broad Scope

This approach accommodates those instances in which a user may need to identify cases that are highly likely to represent the condition of interest (a “narrow” scope) and those instances in which a user seeks to identify all possible cases, including some that may prove to be of little or no interest on closer inspection (a “broad” scope). Thus, a “narrow” search yields “specificity” while the “broad” search yields “sensitivity.” A “broad” search includes both the “narrow” terms and the additional “broad” terms, often of a less-specific nature.

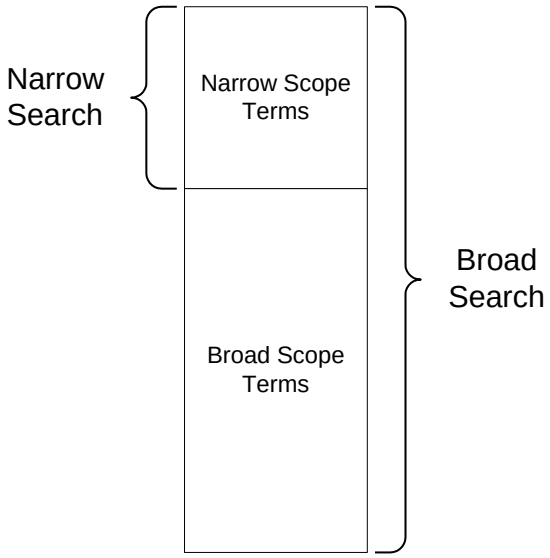

Figure 1-1. Narrow Search vs. Broad Search

1.4.2 Algorithm

In addition to narrow and broad searches, for some SMQs an algorithmic search approach is available. This is a combination of search terms from various sub-categories of the broad search terms to further refine the identification of cases of interest compared to the broad search category. Algorithmic search methodology yields greater sensitivity compared to the narrow search and greater specificity compared to the broad search. A typical example is *Acute pancreatitis (SMQ)* where the broad search terms are grouped into two categories: Category B is a list of laboratory values and Category C is a list of signs and symptoms. The algorithm for *Acute pancreatitis (SMQ)* defines a case of interest as a record coded with either at least one term of Category A (narrow scope), or coded with a combination of at least one term of Category B AND one term of Category C.

Use of an algorithm is not required in order to be able to retrieve cases of interest using a particular SMQ. Application of the algorithm may be most helpful when it is expected that a large number of cases will be retrieved by broad scope terms; the algorithm may reduce the need for manual sorting for cases of interest.

1.4.3 Category

For those SMQs that are algorithmic, the broad search terms are divided into various categories so that a defined combination of terms may be applied. In algorithmic SMQs, narrow search terms are always Category A, and broad search terms are always Categories B, C, D, etc. For example, in *Acute pancreatitis (SMQ)*, the broad search terms are grouped into two categories: Category B is a list of laboratory values and

Category C is a list of signs and symptoms. The algorithm for *Acute pancreatitis (SMQ)* defines a case of interest as a record coded with one of the Category A (narrow scope) terms OR a record coded with one of the Category B AND one of the Category C terms.

1.4.4 Weight

SMQ term weight may also be used with an algorithm. A term weight indicates the relevancy of each category within the algorithm. For example, terms in *Systemic lupus erythematosus (SMQ)* are grouped into 9 categories with Category A being the narrow scope terms and Categories B through I being the broad scope terms. Each broad scope Category is assigned a weight from 1 to 3. Based on the algorithm for *Systemic lupus erythematosus (SMQ)*, a case of interest is a record coded with one of the Category A (narrow scope) terms OR a record with various broad search categories terms with a sum of the category weights greater than 6.

1.4.5 Hierarchy

Some SMQs are a series of queries related to one another in a hierarchical relationship similar to the hierarchical structure of MedDRA itself. These consist of one or more subordinate SMQs that could be combined to create a superordinate, more inclusive SMQ. In some hierarchical SMQs, there are no separate “narrow” and “broad” categories within the subordinate SMQs (sub-SMQs). A specific term may be included in more than one of the sub-SMQs in a hierarchical SMQ provided that the term is of the same scope – narrow or broad – in each sub-SMQ.

The hierarchy provides flexibility for the user. For example, a user may wish to apply the entire scope of the SMQ topic (e.g., the entire *Hepatic disorders (SMQ)* including all sub-SMQs) to retrieve all cases related to hepatic disorders in a database. A user may also elect to apply a single sub-SMQ of *Hepatic disorders (SMQ)* (e.g., *Pregnancy-related hepatic disorders (SMQ)*) or combinations of more than one sub-SMQ in the hierarchy based on the user’s need.

1.4.6 PT/LLT

In SMQ_Content file, PTs (level 4) are **not** duplicated at the LLT level (level 5). Users can conduct a search with only PTs if the data are stored at the PT level. Users can also conduct a search with both PTs and LLTs if the data are stored at the LLT level because in MedDRA, all PTs are duplicated at the LLT level.

1.4.7 Term Status

Each SMQ – including its sub-ordinate PTs/LLTs – has an assigned status. The status can be either “active” or “inactive.”

An active SMQ is the one that is currently maintained by the MSSO. An inactive SMQ is no longer maintained although it is included in and distributed with the SMQ ASCII

files for at least one release. An SMQ may be made inactive if it has been found to not be useful to users, becomes outdated, or is found to be otherwise problematic.

PTs and LLTs that have been made inactive remain in their SMQ and are never deleted. An "inactive" status could be assigned for the following circumstances:

- A PT that is included in error or is no longer part of the SMQ (e.g., due to a change of an SMQ's inclusion or exclusion criteria)
- An LLT that is moved to a PT that is not part of the SMQ

  When applying an SMQ for data retrieval, **inactive** LLTs and PTs should be removed from the search.

1.5 Notes on SMQ Implementation and the Expectation of Query Result

The various design features described in sections 1.4.1 – 1.4.5 have impacts on the SMQ implementation and ultimate query results. The following sections explain options of SMQ implementation and usage.

1.5.1 Performing Searches without Using SMQ Special Features

The special features (narrow *vs.* broad searches, algorithmic search, and hierarchies) are intended to improve the quality of query result by increasing the specificity and reducing the noise level. It should be noted that they are optional, which means that users could use an SMQ as a list of MedDRA terms without any special features.

1.5.2 Performing Searches Using SMQ Special Features

1.5.2.1 Narrow and Broad

Based on the specificity, the user may perform:

- A narrow search for specificity of case retrieval: only narrow terms are applied in the query

OR

- A broad search for sensitivity of case retrieval: both narrow and broad terms are applied in the query

Although most SMQs have both narrow and broad scope terms, some SMQs have only narrow terms or only broad terms, which impact the SMQ programming outputs as follows:

- SMQs with both narrow and broad terms: The results for narrow search and broad search are different. Broad search results include those cases retrieved by narrow terms and additional ones retrieved by broad terms.
- SMQs with only narrow terms: The retrieved cases from narrow search and broad search are the same because there are no additional broad terms in the SMQ.

- SMQs with only broad terms: The narrow search returns null result (or zero case) because there are no narrow terms. Only broad search retrieves cases.

1.5.2.2 Algorithm Search Option

An algorithmic SMQ is designed to reduce the “noise” level among broad terms. Not all SMQs have an algorithm. For those SMQs that do have an algorithm, each algorithm is unique and needs to be implemented individually. For detailed information, see the “Algorithm” section under a particular algorithmic SMQ.

1.5.2.3 Hierarchy Search Option

In most hierarchical SMQs, the sub-SMQs as well as the superordinate SMQ are independent search queries. User may take any of the sub-SMQ or the superordinate SMQ and obtain all relevant MedDRA terms related to that sub-topic or super-topic. However, a few hierarchical SMQs have unique features related to the sub-SMQs in the way that narrow and broad searches are utilized. These unique SMQs are listed below:

- *Biliary disorders (SMQ)*
- *Cardiac arrhythmias (SMQ)*
- *Embolic and thrombotic events (SMQ)*
- *Hepatic disorders (SMQ)*

For detailed information on how these unique hierarchical SMQs should be implemented or used, please refer to the particular session of that SMQ.

2. INDIVIDUAL SMQs

2.1 Accidents and injuries (SMQ)

(Production Release September 2007)

2.1.1 Definition

- Accidents and injuries have been associated with use of medications
  - Particularly older psychotropic medications
  - Especially patients with pre-existing high risk levels and/or continuing mental problems
  - In a study of falls in elderly, use of certain drugs (benzodiazepines, phenothiazines, and antidepressants) was an independent risk factor
  - Study on risk of accidental injury and benzodiazepines also confirmed an increased risk, especially in patients who had recently filled their prescription
- "Accident" defined as "an unplanned or unintended but sometimes predictable event leading to injury, *e.g.,* in traffic, industry, or a domestic setting, or such an event developing in the course of a disease."
- In medicine, the term "injury" can have a very broad meaning.
  - For the purpose of this SMQ, a more narrow definition is used, i.e., "to injure" is "to wound, hurt or harm"
- Focus of this SMQ is not on "metabolic" injury (toxicity, etc.), but on personal injury or accident to the individual as a result of altered perception, consciousness, attention, behavior, etc. (see NOTE below)

2.1.2 Inclusion/Exclusion Criteria

- Included:
  - Terms that relate to definition, i.e., terms for accident, injury, burns, trauma, fall, fracture, wound, crush, contusion, etc.
  - PT *Wound* but not terms for complications of wound such as PT *Wound infection*
  - PT *Snake bite* and other animal and human "bite" terms (**except** arthropod bites and stings)
  - Relevant "foreign body" terms (e.g., PT *Foreign body in eye*) but not "sensation of foreign body" terms such as PT *Foreign body sensation in eyes*
  - Procedure terms that could only relate to trauma, e.g., PT *Limb reattachment surgery*
- Excluded:

- Terms that refer to risk factors for accident or injury (e.g., PT *Sudden onset of sleep*)
- Terms related to poisoning/toxicities and radiation associated accidents and injuries (e.g., PT *Pulmonary radiation injury*)
- Terms for device and procedural complications
- Terms for repetitive motion injuries (e.g., PT *Iliotibial band syndrome*)
- Terms for tissue trophic consequences of injury (e.g., PT *Myositis ossificans*, PT *Eschar*)
- Terms for arthropod, bites and stings
- Terms for birth trauma (e.g., PT *Perinatal brain damage*); this includes the maternal complication of laceration of cervix
- Terms for self-injury (e.g., PT *Intentional self-injury*)
- Terms for medication errors, iatrogenic injuries, and overdoses (e.g., PT *Product prescribing error*, PT *Iatrogenic injury*)
- Terms for victims of crimes and abuse (e.g., PT *Victim of child abuse*)
- "Removal of foreign body" terms (e.g., PT *Removal of foreign body from external ear*)

NOTE: Several specific terms pertaining to hemorrhage and hematoma were originally included in this SMQ because they were found to be useful in the identification of cases relevant to *Accidents and injuries (SMQ)*. However, these conditions may result from multiple etiologies, including, but not limited to injury. In addition to the selected hemorrhage terms in this SMQ, this note is included to remind the user that *Haemorrhages (SMQ)* may also be useful in identifying potential reports of accidents and injuries

NOTE: Currently, many MedDRA PTs (e.g., PT *Gallbladder injury*) have dual links to groupings in SOC *Injury, poisoning and procedural complications* and groupings in "disorder" SOCs, implying that the terms can represent either metabolic or traumatic injury. This needs to be borne in mind when reviewing cases retrieved by this SMQ.

NOTE: Users should consider including cases coded to LLT *Loss of teeth due to accident, extraction, or local periodontal disease;* to LLT *Injury asphyxiation*; and to LLT *Accidental needle stick* – these terms are not currently linked to an included PT in this SMQ but may retrieve cases of interest.

2.1.3 Notes on Implementation and/or Expectation of Query Results

Accidents and injuries (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.1.4 List of References for *Accidents and injuries (SMQ)*

- Wadsworth, EJK, Moss, SC, Simpson, SA, and Smith, AP. Psychotropic medication use and accidents, injuries and cognitive failures. Hum Psychopharmacol Clin Exp 2005; 20: 391-400.
- Tinetti, ME, Speechley, M, and Ginter, SF. Risk factors for falls among elderly persons living in the community. N Engl J Med 1988; 319(26): 1701-1707.
- Oster, G, Huse, DM, Adams, SF, Imbimbo, J, and Russell, MW. Benzodiazepine tranquilizers and the risk of accidental injury. Am J Public Health 1990; 80: 1467-1470.
- Stedman's Medical Dictionary, 27th edition, 2000.

2.2 Acute central respiratory depression (SMQ)

(Production Release September 2007)

NOTE: The original CIOMS WG documentation sometimes refers to this SMQ as "Central respiratory depression"; it was subsequently renamed to *Acute central respiratory depression (SMQ)*.

2.2.1 Definition

- Acute central respiratory depression is a form of respiratory failure
- Respiratory failure is defined as impairment of gas exchange between ambient air and circulating blood
  - Problems in intrapulmonary gas exchange lead to hypoxemia
  - Problems in the movement of gases cause hypercapnia
- Depression of the respiratory center with resulting respiratory acidosis may occur:
  - Acutely with general anesthetics, sedatives, and head trauma
  - Chronically with sedatives, alcohol, intracranial tumors, and syndromes of sleep-disordered breathing, including the primary alveolar and obesity-hypoventilation syndromes
- Acute hypoxemia may cause cardiac arrhythmia and coma. Alteration of consciousness is typical, confusion is common
- Acute hypercapnia may cause:
  - Subtle personality changes and headache through to marked confusion and narcosis
  - Cerebral vasodilatation and increased CSF pressure
  - Acidemia which, when severe, contributes to pulmonary arteriolar vasoconstriction, systemic vascular dilatation, reduced myocardial contractility, hyperkalemia, hypotension, and cardiac irritability
- Central respiratory depression mainly occurs in neonates of prematurity or in sleep apnea
  - Apnea of prematurity may be caused by CNS immaturity (central) or airway obstruction
  - Central sleep apnea (CSA) has two categories:
    - Hypercapnia with decreased ventilatory drive or a decreased ability to breathe. Causes include central lesions, such as brain stem infarctions, encephalitis, Arnold-Chiari malformation.
    - Eucapnia or hypocapnia with increased ventilatory drive but sleep-induced apnea and periodic breathing. Cheyne-Stokes breathing is a discrete

pattern of this form of CSA. Causes include heart failure, high altitude, pain, anxiety. (Cheyne-Stokes respiration is also seen in opiate associated respiratory depression).

2.2.2 Inclusion/Exclusion Criteria

- Included:
  - Relevant investigation terms containing the word “abnormal”, such as those under HLT *Blood gas and acid base analyses*, included in broad search
  - Broad “umbrella” terms such as PT *Respiratory failure* included in narrow search
  - Other potential umbrella terms such as PT *Respiratory acidosis* included in broad search
  - Terms indicating neonatal events (e.g., PT *Neonatal respiratory depression*)
  - Signs and symptoms like PT *Respiratory arrest,* PT *Cardio-respiratory arrest* included in broad search although pre-production testing indicated that these two PTs might create “noise”
- Excluded:
  - PTs containing the word “normal” (e.g., PT *Blood gases normal*)
  - Terms without a qualifier (e.g., PT *PO2,* PT *Carbon dioxide*)
  - PTs that indicate an etiology rather than that potentially drug-induced, e.g., PT *Cardiac asthma* or PT *Pickwickian syndrome*
  - PT *Anxiety* due to high “noise” level
  - Non-specific symptoms related to respiratory acidosis/failure such as peripheral arterial vasodilatation, central vasoconstriction and pulmonary edema
  - Known causes of respiratory depression due to high “noise” level

NOTE: The terms in *Acute central respiratory depression (SMQ)* were updated in Version 18.0 on the basis of new testing results. The original testing of *Acute central respiratory depression (SMQ)* was performed with MedDRA 10.1. During a subsequent initiative to broaden the scope of this SMQ to include terms for both chronic and non-central causes, re-testing was performed using the PTs from the existing *Acute central respiratory depression (SMQ)* and a set of new PT proposals for the broader *Respiratory failure (SMQ)* which was in development. Upon review of the test results, this initiative was not pursued, because it was determined that the specificity of the SMQ would have been diminished, and excessive “noise” complicated retrieval of cases specific to centrally acting drugs potentially associated with acute central respiratory depression. Consequently, *Respiratory failure (SMQ)* was developed as an

additional stand-alone SMQ. As a result of this testing, 28 term modifications to *Acute central respiratory depression (SMQ)* were included in the MedDRA Version 18.0 release. For detailed information, please refer to the original documentation for *Acute central respiratory depression (SMQ)*, to which the most recent re-test results have been added.

2.2.3 Notes on Implementation and/or Expectation of Query Results

Acute central respiratory depression (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.2.4 List of References for *Acute central respiratory depression (SMQ)*

- The Merck Manual accessed online on 12 January 2006. http://www.merck.com/mmpe/sec06/ch065/ch065c.html?qt=acute%20respiratory&alt=sh
- Harrison's Principles of Internal Medicine, accessed online on 12 January 2006.

2.3 Acute pancreatitis (SMQ)

(Production Release November 2005)

2.3.1 Definition

- Drug-induced pancreatitis is usually an acute condition. If clinically suspected, it should always be confirmed by biochemical investigations
- Definition of acute pancreatitis:
  - An inflammatory disease of the pancreas characterized by upper abdominal pain and vomiting; in severe cases – abdominal guarding, rigidity, rebound tenderness and diminution or loss of bowel sounds
  - Almost always accompanied by increased pancreatic enzymes – amylase and lipase – in the blood and urine
  - Other signs/findings are icterus, increased alkaline phosphatase and/or bilirubin, ileus, ascites, hyperglycemia, hypocalcemia and leukocytosis
  - Cullen's sign is sometimes associated with severe necrotizing pancreatitis
- Severe attacks may lead to shock with renal and pulmonary insufficiency, which may be fatal

2.3.2 Inclusion/Exclusion Criteria

- Included:
  - PTs with the word "pancreatitis" (other than those indicative of chronic conditions)
  - PTs indicative of pancreatic dysfunction (such as pancreatorenal syndrome)
  - PT *Cullen's sign*
  - Terms for laboratory values (abnormal/increased values) and signs and symptoms relevant for pancreatitis per definition
  - Terms for typical complications, e.g. PT *Pancreatic pseudocyst*
- Excluded:
  - Terms for chronic pancreatitis
  - Terms representing forms of pancreatitis not considered drug-related (e.g. PT *Pancreatitis mumps*, PT *Cytomegalovirus pancreatitis*)

2.3.3 Algorithm

To apply the algorithm for this SMQ, a report is considered a relevant case for further review if:

- it includes a term from Category A

OR

- it includes at least one term from Category B (the list of laboratory values) and at least one term from Category C (the list of signs and symptoms)

2.3.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Acute pancreatitis (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow and broad searches (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Acute pancreatitis (SMQ)* is A or (B and C). Cases filtered by the algorithm can be listed for output.

2.3.5 List of References for *Acute pancreatitis (SMQ)*

- Anonymous. Pancreatitis. Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use. Bankowski Z, Bruppacher R, Crusius I et al (Eds). Council for International Organizations of Medical Sciences: Geneva, 1999, pp 53-54.
- Berardi RR and Montgomery PA. Pancreatitis. Pharmacotherapy: A Pathophysiologic Approach (5th Ed). DiPiro JT, Talbert RL, Yee GC et al (Eds). McGraw-Hill: New York, NY. 1999. pp 701-715.
- Greenberger NJ, Toskes PP, and Isselbacher KJ. Acute and chronic pancreatitis. Harrison's Principles of Internal Medicine (14th Ed). Fauci AS, Braunwald E, Isselbacher KJ et al (Eds). McGraw-Hill: New York, NY. 1998. pp 1741-1752.

2.4 Acute renal failure (SMQ)

(Production Release April 2005)

2.4.1 Definition

Acute renal failure (ARF) is a syndrome characterized by:

- A relatively rapid decline in renal function that leads to the accumulation of water, crystalloid solutes, and nitrogenous metabolites in the body.
- Other clinical features include: increase in serum creatinine and urea nitrogen levels (azotemia) greater than 0.5 and 10 mg per deciliter, respectively; oliguria; and changes in the rate of urine flow.

ARF may present with a *de novo* onset in individuals whose baseline renal function was within normal limits. Additionally, ARF may consist of acute exacerbation of pre-existing chronic renal insufficiency.

2.4.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow scope: diagnoses and symptoms that are unique or directly lead to acute renal failure are included. For example, PT *Acute kidney injury* (diagnosis) and PT *Anuria* (symptom).
  - Broad scope: These terms have the potential of identifying positive cases.
    - Test results that are closely related to acute renal failure, such as PT *Blood urea increased* (test result).
    - Key pathological changes of ARF, such as acute tubular necrosis
    - Prominent drug-induced etiologies of ARF, such as interstitial nephritis
  - Some commonly reported reactions identified in drug-induced acute renal failure, such as terms for acute tubular necrosis, pre-renal failure, vascular nephropathy, and tubular obstruction.
  - Renal dialysis PTs from SOC Surgical and medical procedures, e.g., dialysis, hemodialysis, and peritoneal dialysis
- Excluded:
  - Normal and unspecified investigational terms (e.g., PT *Blood creatinine*), except for PT *Fractional excretion of sodium* (please refer to note below)
  - PTs referring to chronic renal failure (e.g., PT *Chronic kidney disease*)
  - Electrolyte imbalances (i.e., terms for hyperkalemia, hyponatremia, and blood potassium increased): case evaluations in Phase I testing revealed that these electrolyte imbalances were not specific enough for ARF to identify representative cases.

- Terms representing prerenal etiologies (e.g., PT *Renal vein occlusion*, PT *Cardiac failure*, PT *Hepatic cirrhosis,* etc.) or terms suggestive of a non-drug-induced renal failure (e.g., PT *Glomerulonephritis acute*, etc.)
- PT *Nephritic syndrome* because it is commonly caused by infection or other non-drug related events.
- This SMQ is focused on the acute phase, i.e., sudden, reversible failure of kidney function. Terms for prolonged reactions are excluded, such as focal glomerulosclerosis, which occurs when scar tissue forms in some of the glomeruli of the kidney; proliferative glomerulonephritis, and rapidly progressive glomerulonephritis that include conditions in which progressive loss of kidney function occurs over weeks to months.

NOTE: In Version 18.0, in accordance with recent International Society of Nephrology classifications and terminology, LLT *Acute kidney injury* was swapped with PT *Renal failure acute*, resulting in new PT *Acute kidney injury*; and LLT *Chronic kidney disease* was switched with PT *Renal failure chronic*, resulting in new PT *Chronic kidney disease*.

NOTE: In Version 18.0, PT *Fractional excretion of sodium* was added as a broad scope term to *Acute renal failure (SMQ)*, as an exception to the exclusion criterion "Normal and unspecified investigational terms." Fractional excretion of sodium assessment is useful in the evaluation of acute renal failure to determine whether renal failure is due to pre-renal, post-renal, or intrinsic renal pathology. PT *Fractional excretion of sodium* is thus of potential relevance for inclusion in this SMQ for the identification of cases of acute renal failure.

2.4.3 Notes on Implementation and/or Expectation of Query Results

Acute renal failure (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.4.4 List of References for *Acute renal failure (SMQ)*

- *The Merck Manual*, 17th Edition.
- *Cecil Textbook of Medicine*, 19th Edition.
- *Harrison's Principles of Internal Medicine*, 13th Edition.

2.5 Agranulocytosis (SMQ)

(Revised September 2019; Original Production Release November 2005)

2.5.1 Definition

- Agranulocytosis can occur as a reaction to a wide variety of toxic agents (including drugs)
- Life-threatening due to increased susceptibility to infection
- Overall annual incidence less than 1:100,000 in the general population
- Severe neutropenia (< 0.5 x 10^9/l of circulating granulocytes) associated with the sudden onset of signs and symptoms of bacterial infection such as:
  - Fever, malaise and prostration
  - Oropharyngeal or anorectal lesions

2.5.2 Inclusion/Exclusion Criteria

- Included:
  - All MedDRA terms with the word “agranulocytosis”
  - Terms representing serious disorders affecting white blood cells
  - “Combination” terms of white blood cell disorders and infections/fever (e.g., PT *Febrile neutropenia*)
  - Terms representing decreases in neutrophils/granulocytes without specific mention of the severity of the decrease are included as broad scope terms (e.g., PT *Neutropenia*, PT *Granulocyte count decreased*)
  - Terms representing typical mucosal and tonsillar lesions
- Excluded:
  - Non-specific terms representing general signs and symptoms of agranulocytosis (e.g., arthralgia, fever, chills, swelling of cervical lymph nodes, malaise, and prostration)

NOTE: If possible, full blood counts and repeated white blood cell counts should be reported, sought for in follow up, and coded. Concerning database queries with broad search terms, additionally coded data on hematological values help to find relevant cases more easily. In case laboratory values are not coded in a database, individual review is then needed to decide upon relevance in the context of agranulocytosis.

NOTE: The terms in *Agranulocytosis (SMQ)* were updated in MedDRA Version 22.1 based on a review by experts from regulatory authorities and industry. *Sepsis (SMQ)* was created as an additional stand-alone SMQ and the relevant sepsis terms in

Agranulocytosis (SMQ) were made inactive. Terms representing decreases in neutrophils/granulocytes without specific mention of the severity of the decrease were added as broad scope terms to *Agranulocytosis (SMQ)*, e.g., PT *Neutropenia*, PT *Granulocyte count decreased*. It may be necessary to combine *Agranulocytosis (SMQ)*, *Sepsis (SMQ)*, and *Toxic-septic shock conditions (SMQ)* to perform a comprehensive search.

2.5.3 Notes on Implementation and/or Expectation of Query Results

Agranulocytosis (SMQ) has features of narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.5.4 List of References for *Agranulocytosis (SMQ)*

- Reporting Adverse Drug Reactions, Definitions and Criteria for Their Use, CIOMS, Geneva, 1999.
- Harrison's Principles of Internal Medicine, 15th edition, Eugene Braunwald [et al.], McGraw-Hill, 2001.

2.6 Anaphylactic reaction (SMQ)

(Production Release November 2005)

2.6.1 Definition

- An acute systemic reaction characterized by pruritus, generalized flush, urticaria, respiratory distress and vascular collapse
- Occurs in a previously sensitized person upon re-exposure to the sensitizing antigen
- Other signs and symptoms: agitation, palpitation, parasthesias, wheezing, angioedema, coughing, sneezing and difficulty breathing due to laryngeal spasm or bronchospasm
  - Less frequent clinical presentations: seizures, vomiting, abdominal cramps and incontinence

2.6.2 Inclusion/Exclusion Criteria

- Included:
  - Any terms, at the PT level, representing events which may be noted during anaphylaxis
  - In a spreadsheet format, the testing pharmaceutical company's list and the testing regulator's list were positioned alongside the MedDRA SSC list for anaphylaxis, and this three-column table was then systematically reviewed top-down. Unanimous agreement for/against inclusion of each term was achieved by the group
- Excluded:
  - Terms for signs and symptoms that do not fall within the three defined categories (Upper Airway/Respiratory, Angioedema/Urticaria/Pruritus/Flush, and Cardiovascular/Hypotension) in the broad search are excluded.

NOTE: There are two SMQs related to anaphylaxis: *Anaphylactic reaction (SMQ)* and *Anaphylactic/anaphylactoid shock conditions (SMQ)*. The two SMQs have different focuses. *Anaphylactic/anaphylactoid shock conditions (SMQ)* is specific for more severe anaphylactic manifestations, i.e. those that result in shock, and not less severe ones such as rash. *Anaphylactic reaction (SMQ)* widens the search beyond shock conditions by including such terms as PT *Type I hypersensitivity*.

2.6.3 Algorithm

The SMQ *Anaphylactic reaction* consists of three parts:

- A **narrow search** containing PTs that represent core anaphylactic reaction terms

- A **broad search** that contains additional terms that are added to those included in the narrow search. These additional terms are signs and symptoms possibly indicative of anaphylactic reaction;
- An **algorithmic approach** which combines a number of anaphylactic reaction symptoms in order to increase specificity. A case must include either:
  - A narrow term or a term from Category A;
  - A term from Category B - (Upper Airway/Respiratory) AND a term from Category C - (Angioedema/Urticaria/Pruritus/Flush);
  - A term from Category D - (Cardiovascular/Hypotension) AND [a term from Category B - (Upper Airway/Respiratory) OR a term from Category C - (Angioedema/Urticaria/ Pruritus/Flush)]

2.6.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Anaphylactic reaction (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Anaphylactic reaction (SMQ)* is A or (B and C) or (D and (B or C)). Cases filtered by the algorithm can be listed for output.

2.6.5 List of References for *Anaphylactic reaction (SMQ)*

- The Merck Manual. 15th edition. Merck, Sharp & Dohme Research Laboratories. (1987): 306-7.

2.7 Angioedema (SMQ)

(Production Release November 2005)

2.7.1 Definition

- Urticaria (CIOMS definition):
  - Many possible causes (e.g., insect stings, food and drugs)
  - Characterized by multiple transient wheals, usually with itching; individual lesions may come and go but are of short duration
- Angioedema (also called Quincke's oedema or angioneurotic oedema):
  - Similar to urticaria but involving the deeper dermal, submucosal and subcutaneous tissues
  - Sometimes associated with severe respiratory distress due to edema of the upper airway
  - Edema results from dilatation and increased permeability of the capillaries
- Urticaria and angioedema may appear separately or together as cutaneous manifestations of localized nonpitting edema
  - Similar process may occur at mucosal surfaces of the upper respiratory or gastrointestinal tract
  - Angioedema of the upper respiratory tract may be life-threatening due to laryngeal obstruction
- Urticaria and/or angioedema are classified as:
  - IgE-dependent, e.g., specific antigen sensitivity to pollens, food, drugs, etc. fungi, molds, Hymenoptera venom, etc.
  - Complement-mediated (hereditary type 1 and 2; acquired type 1 and 2, necrotizing vasculitis, serum sickness, etc.)
  - Non-immunologic (opiates, antibiotics, radiocontrast media, aspirin, azo dyes, etc.)
  - Idiopathic

2.7.2 Inclusion/Exclusion Criteria

- Included:
  - Terms containing the words "angioedema" or "angioneurotic oedema"
  - All PTs linked to HLT *Angioedemas*. This includes PT *Hereditary angioedema* which -- although initially considered for exclusion -- is listed as a narrow search term for optional use.

- PTs indicating similar conditions, edema, or swelling affecting the face, upper respiratory tract, and other parts of the body, including the gastrointestinal tract
- All PTs containing the word “urticaria” that link to HLT *Urticarias* (such as PT *Urticaria*, PT *Urticaria chronic*, PT *Idiopathic urticaria*, etc.) and which do not indicate a relationship to the application site (such as PT *Application site urticaria*) or a non-drug related cause (such as PT *Solar urticaria*)
- PT *Allergic oedema*

- Excluded:
  - Terms indicating a relation to an injection/infusion/application of a drug such as infusion site swelling, infusion site edema, etc.
  - Urticaria pigmentosa, as this condition is cutaneous mastocytosis
  - Nausea and vomiting (non-specific symptoms that would create too much “noise” relative to signal)

2.7.3 Notes on Implementation and/or Expectation of Query Results

Angioedema (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.7.4 List of References for *Angioedema (SMQ)*

- Bankowski Z, Bruppacher R, Crusius I et al. Reporting adverse drug reactions, definition of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS) 1999 pp 12 -13.
- Dorland’s Illustrated Medical Dictionary, 28th Edition 1994 p78.
- Braunwald E, Fauci A and Kasper D. Harrison’s Principles of Internal Medicine, 15th Edition, 2001 p 341 and pp 1917-1918.
- Beers M and Berkow R. The Merck Manual of diagnosis and therapy, 17th edition, dated 1999 pp 1054-56.

2.8 Anticholinergic syndrome (SMQ)

(Production Release September 2006)

2.8.1 Definition

- Anticholinergic syndrome is a confusional state with characteristic features related to dysfunction of the autonomic parasympathetic (cholinergic) nervous system.
- The presence of fixed and dilated pupils is essential.
- Anticholinergic compounds (muscarinic receptor antagonists) inhibit the actions of acetylcholine at receptors on neurons, ganglions, autonomic effector sites innervated by postganglionic cholinergic nerves and also at sites lacking cholinergic innervation.
- Clinical picture described as “hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hatter”.
- Symptoms classified into systemic and CNS manifestations.
  - Systemic (peripheral) symptoms: blurred vision, photophobia, nonreactive mydriasis, loss of accommodation response, flushed and dry skin, dry mouth, tachycardia, hypertension and fever. Gastrointestinal and urinary motility are frequently reduced.
  - Central Anticholinergic Syndrome is an acute psychosis-like picture characterized by delirium, agitation, disorientation, and visual hallucinations. Ataxia, choreoathetosis, myoclonus and seizures may also occur without peripheral symptoms.

2.8.2 Inclusion/Exclusion Criteria

- Included
  - PTs related to anticholinergic syndrome and its major manifestations as described above
  - This SMQ is focused on the acute anticholinergic syndrome
- Excluded
  - No specific terms excluded

2.8.3 Algorithm

The categories are defined as following:

- Category A (narrow scope): Cases encoding to PT *Anticholinergic syndrome*
- Category B (broad scope): Nervous system-related PTs
- Category C (broad scope): Psychiatric-related PTs

- Category D (broad scope): Other relevant anticholinergic syndrome-related PTs

The algorithmic approach is as follows: Cases to be selected for further review would include any cases reporting the PT listed for Category A or any case reporting some combination of at least one PT from each of the three groups of PTs listed as Categories B, C, and D.
Note: Some reporters included only terms from the SOC *Psychiatric disorders*; other reporters included only non-CNS related terms. If it is considered important to identify these cases, then a non-algorithmic approach should be taken for the broad search; however, this approach may identify a large number of irrelevant cases.

The CIOMS WG for SMQs reviewed phase II feedback on this SMQ at their May 2006 meeting. A MedDRA subscriber had commented that PT *Hypertension* is not included in this SMQ. The leader of the development team for this SMQ indicated that inclusion of PT *Hypertension* had been considered, but that it was felt to be non-specific and likely to lead to retrieval of many non-relevant cases. In addition, the team reviewed all cases in a regulatory database for a strong positive control test product for this SMQ and found only a single case that reported hypertension.

2.8.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Anticholinergic syndrome (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow and broad searches (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Anticholinergic syndrome (SMQ)* is A or (B and C and D). Cases filtered by the algorithm can be listed for output.

2.8.5 List of References for *Anticholinergic syndrome (SMQ)*

- Bankowski Z, Bruppacher R, Crusius I et al. Reporting adverse drug reactions, definition of 1. Terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS), 1999. Pages 24-25.
- Heller Brown J, Taylor P. Muscarinic receptor agonists and antagonists. In: Hardman JG, Limbird LE, Molinoff PB, Ruddon RW eds. *Goodman and Gilman: The Pharmacological Basis of Therapeutics.* New York, NY: McGraw Hill; 1996:141-160.
- Watemberg NM et al. Central Anticholinergic Syndrome on Therapeutic Doses of Cyproheptadine. Pediatrics. 103(1):158-60, Jan 1999.

2.9 Arthritis (SMQ)

(Production Release September 2013)

2.9.1 Definition

- SMQ *Arthritis* is intended to identify potential cases of arthritis and worsened arthritis that may be drug related

- Arthritis = inflammation of one or more joints, resulting in:
  - Redness
  - Warmth
  - Pain
  - Swelling
  - Stiffness
  - Limited movement

- Numerous types of arthritis exist, including:
  - Osteoarthritis (degenerative joint disease)
  - Infective arthritis
  - Rheumatoid arthritis
  - Psoriatic arthritis
  - Related autoimmune diseases

- Pain caused by intra-articular disorders may be secondary to:
  - Inflammatory arthritis (e.g., infection, RA, crystal deposition)
  - Noninflammatory process (e.g., osteoarthritis)

- Inflammatory arthritis may involve:
  - Peripheral joints only (e.g., hands, knees, feet); or
  - Both peripheral and axial joints (e.g., sacroiliac, apophyseal, discovertebral, costovertebral)

- Peripheral oligoarticular and polyarticular arthritis have specific likely causes such as:
  - Juvenile idiopathic arthritis
  - Lyme disease arthritis

- Acute polyarticular arthritis:
  - Most often due to infection (usually viral), or flare of a rheumatic disease

- Chronic polyarticular arthritis:
  - In adults:
    - Most often due to rheumatoid arthritis (inflammatory), or osteoarthritis (noninflammatory)

- In children:
  - Most often due to juvenile idiopathic arthritis

- In many patients, arthritis is often transient, resolving without diagnosis, or may not fulfill criteria for a defined rheumatic disease

2.9.2 Inclusion/Exclusion criteria

- Included:
  - Terms for various forms of arthritis including infective, reactive and rheumatic disorders
  - Terms for signs and symptoms of joint inflammations, e.g., PT *Joint stiffness*
  - Terms for relevant investigations and procedures that help to identify and treat arthritis and common complications
  - Terms for systemic autoimmune diseases for which joint inflammation is part of the concept, e.g., PT *SLE arthritis*
  - Terms for diseases that can mimic arthritis because of similar characteristics, e.g., PT *Plica syndrome*
  - Terms for genetic syndromes affecting joints e.g., PT *Pyogenic sterile arthritis pyoderma gangrenosum and acne syndrome*

- Excluded:
  - Terms for non-drug etiologies that are not always associated with arthritis, e.g., PT *Behcet's syndrome*
  - Terms for organ abnormalities of rheumatoid diseases in which the arthritic component is not the focus. e.g., PT *Rheumatoid lung*
  - Causative terms, e.g., PT *Femoroacetabular impingement*
  - Terms for non-specific and broad concepts that contribute to “noise” in data output, e.g., PT *Pain in extremity*, PT *Bone scan abnormal*

2.9.3 List of References for *Arthritis (SMQ)*

- Polyarticular joint pain. *The Merck Manual for Health Professionals*, http://www.merckmanuals.com/professional/musculoskeletal_and_connective_tissue_disorders/symptoms_of_joint_disorders/polyarticular_joint_pain.html

2.10 Asthma/bronchospasm (SMQ)

(Production Release November 2005)

2.10.1 Definition

- Asthma:
  - A chronic inflammatory disorder of the airways in which mast cells, eosinophils and T lymphocytes play a role
  - The inflammation causes an increased airway responsiveness to a variety of stimuli leading to bronchospasm/bronchoconstriction
  - Clinically characterized by recurrent, generally short-lived episodes (especially at night or in early morning) of wheezing, breathlessness, chest tightness, and cough
  - Characteristic of these episodes is variable airflow limitation; this may resolve or partly reversed either spontaneously or with treatment
- Bronchospasm/bronchoconstriction:
  - Airflow limitation due to contraction of bronchial smooth muscle; an improvement in airflow in response to bronchodilators is essential for the diagnosis
  - Bronchospasm, along with airway inflammation, is a contributing factor to airway limitation in asthmatics
  - “Aggravated bronchospasm/bronchoconstriction” and “paradoxical bronchospasm” are terms used when there is an unexpected episode of bronchospasm/bronchoconstriction with inhalation aerosol treatment of lung disorders; its causes can be either the inhalation procedure or irritation due to the aerosol (active or inactive ingredients)

2.10.2 Inclusion/Exclusion Criteria

- Included:
  - Terms describing various forms of asthma/bronchospasm (excluding PT *Cardiac asthma*)
  - Terms representing the various signs and symptoms, mainly of a respiratory nature
  - Supporting investigations terms such as PT *Charcot-Leyden crystals*; additional investigation terms representative of pulmonary function test abnormalities (e.g., PT *Forced expiratory volume decreased*)

- Excluded:
  - Related infectious disorders (e.g., PT *Bronchopulmonary aspergillosis allergic*)
  - Treatment and/or prophylaxis-related terms (e.g., PT *Asthma prophylaxis*)
  - Various respiratory signs and symptoms considered too non-specific to add value in case identification (e.g., PT *Dyspnoea*, PT *Chest discomfort*, PT *Rhonchi*, PT *Respiratory distress*, and PT *Total lung capacity increased*)

2.10.3 Notes on Implementation and/or Expectation of Query Results

Asthma/bronchospasm (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.10.4 List of References for *Asthma/bronchospasm (SMQ)*

- CIOMS publication, “Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use”, pp 89 – 90, 1999.
- The Merck Manual, Seventeenth Edition, pp 556 – 568, 1999.
- “Harrison’s Principles of Internal Medicine”, 14th edition, pp 1419 – 1426, 1998.

2.11 Biliary disorders (SMQ)

(Production Release September 2007)

2.11.1 Definition

- SMQ developed to detect all types of disorders related to the biliary tract (treatment-associated or as medical history)
- Concerns all types of gallbladder and bile duct disorders.
- Includes neoplasms and congenital disorders related to biliary tract

2.11.2 Inclusion/Exclusion Criteria

- Included:
  - SMQ *Biliary disorders* covers all types of conditions related to biliary disorders including:
    - Neoplasms
    - Congenital disorders
    - Investigations
    - Signs and symptoms of biliary disorders
  - Sub-SMQ *Functional, inflammatory and gallstone related biliary disorders*
    - All functional, inflammatory and gallstone related biliary disorders
  - Sub-SMQ *Biliary system related investigations, signs and symptoms*
    - Investigations
    - Signs and symptoms
  - Sub-SMQ *Gallbladder related disorders*
    - Specific disorders of the gallbladder
  - Sub-SMQ *Biliary tract disorders*
    - Specific disorders of the bile duct
  - Sub-SMQ *Infectious biliary disorders*
    - Infections of the biliary tract
    - Inflammatory conditions which are possibly the result of infection
  - Sub-SMQ *Gallstone related disorders*
    - Conditions related to gallstones
  - Sub-SMQ *Biliary neoplasms*
    - Biliary neoplasms (benign and malignant)

- Sub-SMQ *Biliary neoplasms malignant and unspecified*
  - Malignant biliary neoplasms
  - Biliary neoplasms unspecified as benign or malignant
- Sub-SMQ *Biliary neoplasms benign (incl cysts and polyps)*
  - Benign biliary neoplasms
- SMQ *Congenital biliary disorders*
  - Congenital disorders of biliary system

- Excluded:
  - Non-specific laboratory test results (*e.g.*, PT *Hepatic enzyme increased,* PT *Gamma-glutamyltransferase abnormal*, PT *Gamma-glutamyltransferase increased*)
  - LLT *Pancreatitis due to gallstones* is excluded because it is linked to PT *Pancreatitis* which is not included in the SMQ (see NOTE below)
  - Sub-SMQ *Functional, inflammatory and gallstone related biliary disorders*
    - Neoplasms
    - Congenital disorders

NOTE: In MedDRA v16.0, Level 3 SMQ *Bile duct related disorders* was renamed to SMQ *Biliary tract disorders* because some of the included "biliary" terms are not bile duct-specific. Also, Level 3 SMQ *Site unspecified biliary disorders* was merged under the renamed SMQ *Biliary tract disorders* (please refer to the v16.0 *Version Report* for a listing of the impacted terms); therefore, SMQ *Site unspecified biliary disorders* no longer exists

NOTE: If the user requires a complete search of all biliary tract and liver-related investigation terms, use of SMQ *Liver related investigations, signs and symptoms* (sub-search SMQ of SMQ *Hepatic disorders*) together with SMQ *Biliary system related investigations, signs and symptoms* is recommended.

NOTE: LLT *Pancreatitis due to gallstones* links to PT *Pancreatitis* which is not included in SMQ *Biliary disorders.* Inclusion of this LLT in a search may, however, be considered by the user.

NOTE: Sub-search SMQ *Biliary system related investigations, signs and symptoms* is called SMQ *Bile system related investigations, signs and symptoms* in the CIOMS WG original documentation.

NOTE: In Version 14.0, two new sub-SMQs have been added to existing sub-SMQ *Biliary neoplasms malignant and unspecified* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: In Version 12.1, sub-SMQ *Biliary neoplasms benign* was renamed sub-SMQ *Biliary neoplasms benign (incl cysts and polyps)*

NOTE: In Version 12.1, sub-SMQ *Biliary system related investigations, signs and symptoms* was modified in scope to include both broad and narrow search terms, from formerly narrow terms only.

NOTE: In Version 12.1, sub-search SMQ *Biliary system related investigations, signs and symptoms* was modified to have both broad and narrow scope terms, from formerly having narrow terms only. Other than the hierarchy structure, the implementation for this sub-search SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1).

2.11.3 Hierarchy Structure

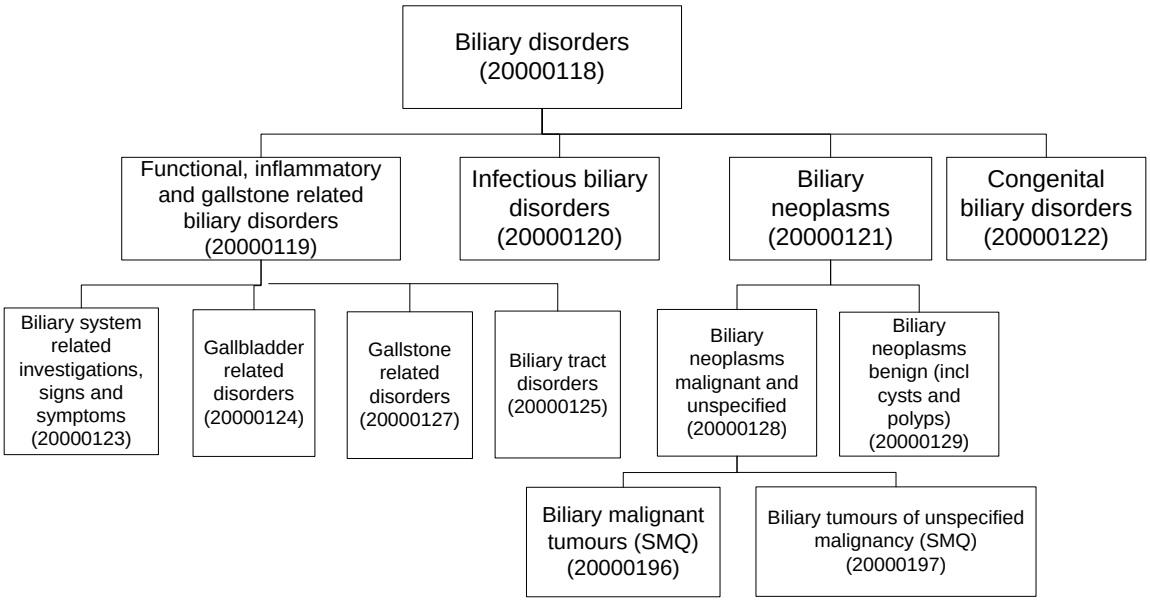

Figure 2-1. Hierarchy Structure of *Biliary disorders (SMQ)*

2.11.4 Notes on Implementation and/or Expectation of Query Results

Biliary disorders (SMQ) is a hierarchical SMQ with only narrow search terms for eleven of the twelve sub-SMQs (Sub-SMQ *Biliary system related investigations, signs and symptoms* includes both broad and narrow terms). Therefore, for eleven of the sub-SMQs, narrow search and broad search return the same result for superordinate and subordinate SMQs. Other than the hierarchy structure, the implementation is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

Because terms for investigations, signs and symptoms are grouped in sub-SMQ *Biliary system related investigations, signs and symptoms (SMQ)*, subordinate SMQs of *Biliary disorders (SMQ)* are not independent queries. For example, to find relevant cases of "gallstone related disorders", those retrieved by sub-SMQ *Gallstone related disorders (SMQ)* may not be sufficient. Cases retrieved by terms for relevant signs and symptoms, such as PT *Jaundice*, and those for laboratory result terms, such as bilirubin test terms (located in sub-SMQ *Biliary system related investigations, signs and symptoms (SMQ)*) may need to be included to get a complete set of relevant cases. Therefore, some level of manual intervention is required when applying subordinate SMQs. Medical judgment may need to be applied.

2.11.5 List of References for *Biliary disorders (SMQ)*

- Harrison's Principles of Internal Medicine 16th ed, Mc Graw Hill, 2005, pp 1880-1891.

2.12 Breast neoplasms, malignant and unspecified (SMQ)

(Production Release September 2008)

2.12.1 Definition

- Developed to detect all malignant and unspecified tumors related to breast
- Covers all malignant and unspecified neoplasms related to breast and in addition:
  - Malignancy related conditions
  - Malignancy related therapeutic and diagnostic procedures
  - Tumor markers specific for this organ

2.12.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for malignant or unspecified neoplasms with a clear reference to breast
  - Terms for conditions related to malignant or unspecified neoplasms of breast, including:
    - Procedures
    - Investigations
    - Tumor markers
    - Signs and symptoms pointing to such disorders
  - Male versions of breast neoplasm terms
  - PT *Phyllodes tumour ,* (denotes a rare, predominantly benign tumor which can be malignant)
- Excluded:
  - Terms for malignant or unspecified neoplasms without a clear reference to breast
  - Terms for unspecified site malignancy related therapeutic and diagnostic procedures and tumor markers
  - Terms for metastases to breast
  - PT *Metastases to reproductive organ*
  - PT *Breast operation* as it is not a malignancy specific therapeutic procedure. (This term may, however, be added if a very broad search is required).

NOTE: In Version 14.0, two new sub-SMQs have been added to *Breast neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: For searches of non-specific malignancy related conditions and malignancy related therapeutic and diagnostic procedures, it is recommended to use the respective lower level sub-SMQ of *Malignancies (SMQ)*.

NOTE: PT *Breast operation* is excluded from this SMQ but may be added if a very broad search is required.

2.12.3 Hierarchy Structure

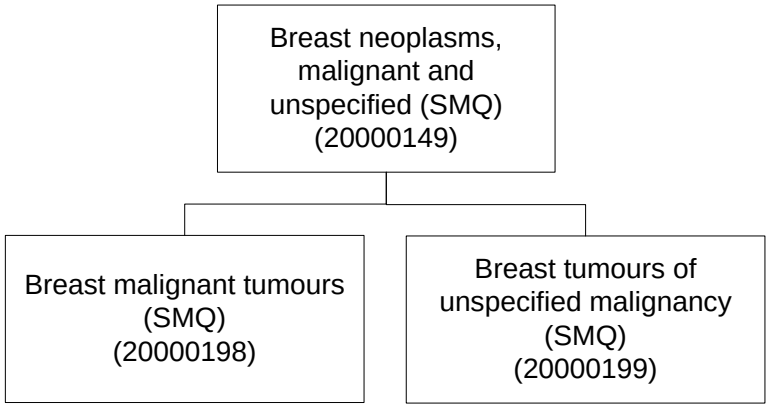

Figure 2-2. Hierarchy Structure of *Breast neoplasms, malignant and unspecified (SMQ)*

2.12.4 Notes on Implementation and/or Expectation of Query Results

Breast neoplasms, malignant and unspecified (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.12.5 List of References for *Breast neoplasms, malignant and unspecified (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H, Veronesi, U., Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://egtm.web.med.uni-muenchen.de.

2.13 Cardiac arrhythmias (SMQ)

(Production Release September 2006)

2.13.1 Definition

- Arrhythmia is any disorder of the formation or conduction of the cardiac impulse.
- Arrhythmia may be primary, due to electrophysiological disorder, or secondary, caused by hemodynamic or other abnormalities.
- Arrhythmias are divided into two main groups:
  - Bradyarrhythmias
  - Tachyarrhythmias

2.13.2 Inclusion/Exclusion Criteria

- Included
  - All types of conditions which are related to cardiac arrhythmias, including conduction disturbances and repolarization defects. It includes appropriate ECG, investigations and heart rate terms
- Excluded
  - Cardiac pacemaker related procedures and investigations and heart rate related terms referring to normal values or not stating an abnormality (e.g. PT *Heart rate normal* and PT *Heart rate*)

NOTE: *Torsade de pointes/QT prolongation (SMQ)* is a separate level 1 SMQ. For the analysis of all cardiac arrhythmia cases, it is recommended to include *Torsade de pointes/QT prolongation (SMQ)* in the search.

NOTE: In Version 12.1, the following sub-SMQs were modified in scope to include both broad and narrow search terms (formerly included only broad terms):

Arrhythmia related investigations, signs and symptoms (SMQ)
Congenital and neonatal arrhythmias (SMQ)
Supraventricular tachyarrhythmias (SMQ)
Ventricular tachyarrhythmias (SMQ)

NOTE: In Version 12.1, the following sub-SMQs were modified in scope to include only narrow search terms (formerly included only broad terms):

Bradyarrhythmia terms, nonspecific (SMQ)
Cardiac arrhythmia terms, nonspecific (SMQ)
Conduction defects (SMQ)
Disorders of sinus node function (SMQ)
Tachyarrhythmia terms, nonspecific (SMQ)

2.13.3 Hierarchy Structure

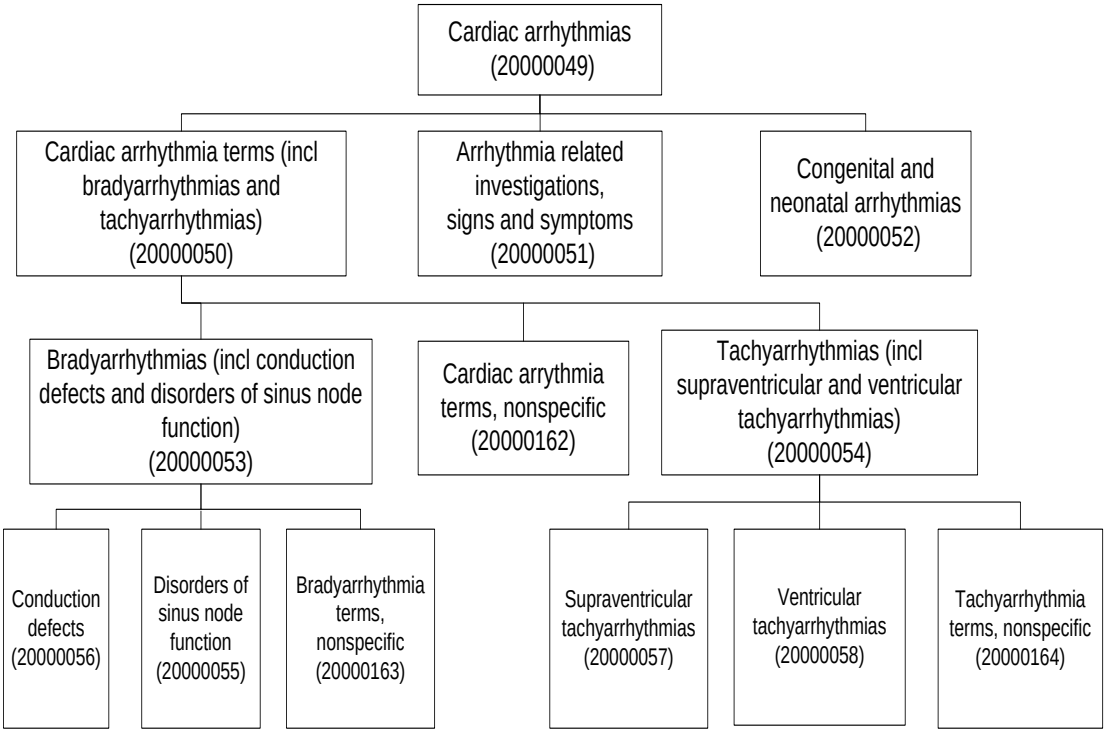

Figure 2-3. Hierarchy Structure of *Cardiac arrhythmias (SMQ)*

In Version 12.0, per user's request, *Cardiac arrhythmia terms, nonspecific (SMQ)* was added at level 3 to group the PTs that have been linked to *Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)* but did not belong to any of its sub-SMQs. Unlike other level 3 sub-SMQs (e.g., *Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)*), *Cardiac arrhythmia terms, nonspecific (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic - Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ).

For the same purpose, *Bradyarrhythmia terms, nonspecific (SMQ)* was added at level 4 to group the PTs that had been linked to *Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)* and *Tachyarrhythmia terms, nonspecific (SMQ)* was added at level 4 to group PTs that had been linked to *Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)*. Both *Bradyarrhythmia terms, nonspecific (SMQ)* and *Tachyarrhythmia terms, nonspecific (SMQ)* are not standalone SMQ topics. They should only be used as part of their superordinate SMQ topics.

2.13.4 Notes on Implementation and/or Expectation of Query Results

Cardiac arrhythmias (SMQ) is a hierarchical SMQ with both broad and narrow search terms.

The following seven sub-SMQs have both Broad and Narrow Search Terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

- *Arrhythmia related investigations, signs and symptoms (SMQ)*
- *Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)*
- *Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)*
- *Congenital and neonatal arrhythmias (SMQ)*
- *Supraventricular tachyarrhythmias (SMQ)*
- *Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)*
- *Ventricular tachyarrhythmias (SMQ)*

The following five sub-SMQs *h*ave only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

- *Bradyarrhythmia terms, nonspecific (SMQ)*
- *Cardiac arrhythmia terms, nonspecific (SMQ)*
- *Conduction defects (SMQ)*
- *Disorders of sinus node function (SMQ)*
- *Tachyarrhythmia terms, nonspecific (SMQ)*

Because terms for supporting investigations, signs and symptoms are grouped in sub-SMQ *Arrhythmia related investigations, signs and symptoms (SMQ)*, subordinate SMQs of *Cardiac arrhythmias (SMQ)*, which contain only diagnosis and pathognomonic sign, symptom, or investigation result terms, are not independent queries. For example, to find relevant cases of “conduction defects,” those retrieved by sub-SMQ *Conduction defects (SMQ)* may not be sufficient. Cases retrieved by terms for supporting investigation results, such as ECG test terms (located in sub-SMQ *Arrhythmia related investigations, signs and symptoms (SMQ)*) may need to be included to get a complete set of relevant cases. Similar to *Biliary disorders (SMQ)*, some level of manual intervention is required when applying subordinate SMQs. Medical judgment may need to be applied.

2.13.5 List of References for *Cardiac arrhythmias (SMQ)*

- Harrison’s Textbook of Internal Medicine.

2.14 Cardiac failure (SMQ)

(Production Release March 2007)

2.14.1 Definition

- A condition in which the heart is unable to pump an adequate amount of blood to meet metabolic and physiological needs of body
- Classified on basis of severity according to criteria set by New York Heart Association (NYHA)
  - Classes I to IV starting from no limitation of physical activity to slight or marked limitation, up to the inability to carry out any physical activity without discomfort
- Clinical findings vary but include: dependent edema, raised jugular venous pressure, hepatomegaly, pulmonary congestion/edema, tachycardia, cardiomegaly, and dyspnea
- Cardiac ejection fraction is less than 35%.

2.14.2 Inclusion/Exclusion Criteria

This SMQ does not make a distinction between left and right ventricular failure.

- Included:
  - Narrow scope:
    - Terms describing existing cardiac failure in its various forms with or without right/left ventricular specified
    - A small number of terms for symptoms, signs, investigational findings, and procedures that are pathognomonic of the condition
  - Broad scope:
    - Signs, symptoms or investigational findings highly suggestive of current or past evidence for this condition
    - Cardiac cirrhosis
- Excluded:
  - Causality terms of cardiac failure, such as ventricular tachyarrhythmia or myocardial infarction
  - Signs and symptoms that may result from cardiac failure, but are shared with so many other etiologies that they would merely serve to add noise or confusion to the search (e.g., dyspnea other than paroxysmal nocturnal dyspnea and orthopnea)
  - General effects of cardiac failure on the liver and kidney

2.14.3 Algorithm

The CIOMS Working Group discussed in detail whether an algorithm could be applied to this SMQ based on the definition of cardiac failure provided. Such an algorithm, however, has not been tested by the CIOMS Working Group. Therefore, the Working Group is requesting users to comment on the practical relevance of an algorithm approach. Such an algorithm could involve broad terms as follows: one edema term, one dyspnea term plus one clinical/sign/symptom or investigation, making up three terms in total.

2.14.4 Notes on Implementation and/or Expectation of Query Results

Cardiac failure (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.14.5 List of References for *Cardiac failure (SMQ)*

- Council for International Organisations of Medical Sciences (CIOMS). Reporting Adverse Drug Reactions. Definition of terms and criteria for their use. 1999: p 64-65.

2.15 Cardiomyopathy (SMQ)

(Production Release September 2008)

2.15.1 Definition

- Cardiomyopathy: general diagnostic term designating
  - Primary non-inflammatory disease of heart muscle
  - Often of obscure or unknown etiology
  - Not the result of:
    - Ischemia
    - Hypertension
    - Congenital anomaly
    - Valvular disease
    - Pericardial disease
  - Usually subdivided into the following forms:
    - Dilated
    - Hypertrophic
    - Restrictive
- According to World Health Organization (WHO):
  - Only those disorders in which pathological process involves only myocardium
  - Cause is unknown
  - Not part of a disease affecting other organs
  - Also called “primary cardiomyopathy”

2.15.2 Inclusion/Exclusion Criteria

- Included:
  - PTs containing "cardiomyopathy" or "myocarditis"
  - Cardiomyopathy-related PTs linked to HLGT *Myocardial disorders*
  - Terms for hypertensive cardiomyopathy (e.g., PT *Hypertensive cardiomyopathy*) and its associated findings (e.g., PT *Ventricular hypertrophy*)
  - Terms for inflammatory conditions that may result in cardiomyopathy (e.g., PT *Cardiac sarcoidosis*)

  - Terms for ischemic conditions that may result in cardiomyopathy (e.g., PT *Ischaemic cardiomyopathy*)
  - PTs for secondary forms of cardiomyopathy
  - PTs for metabolic influences that may lead to cardiomyopathy (e.g., PT *Cardiomyopathy alcoholic*)
  - Cardiomyopathy-related PTs linked to HLGT *Cardiac and vascular investigations (excl enzyme tests)*
  - PTs *Heart and lung transplant,* PT *Heart transplant,* and PT *Ventricular assist device insertion* (linked to HLT *Cardiac therapeutic procedures NEC*)
  - Postural hypotension terms
  - Cardiac biopsy terms
- Excluded:
  - Terms for coronary heart diseases
  - Terms for valvular diseases
  - Terms for pericardial diseases
  - Terms for epicardial diseases
  - Terms for endocardial diseases
  - PT *Myectomy* (linked to HLT *Muscle therapeutic procedures*)
  - All congenital terms, e.g., PT *Arrhythmogenic right ventricular dysplasia,* PT *Congenital cardiovascular anomaly,* PT *Heart disease congenital,* PT *Uhl's anomaly*, etc.
  - Terms for laboratory findings and test results (e.g. PT *Atrial natriuretic peptide increased*) that are not specific for heart failure

NOTE: The narrow search is very specific, and cardiomyopathy – seen from the reporting and adverse event coding perspective – does not have very specific signs or symptoms. PT *Dyspnoea* might create substantial "noise" in retrieval of cases and therefore may be excluded from a query.

In testing, most cases were retrieved by the broad search terms of *Cardiac failure (SMQ)* (and were not also retrieved by narrow search terms).

Users may also consider the broad search terms from *Cardiac failure (SMQ)* as a more comprehensive list of heart failure signs and symptoms which may be of additional potential relevance to the identification of cases of cardiomyopathy.

2.15.3 Notes on Implementation and/or Expectation of Query Results

Cardiomyopathy (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.15.4 List of References for *Cardiomyopathy (SMQ)*

- Dorland's Illustrated Medical Dictionary, Saunders, Philadelphia, 2000.
- Towbin JA, Lipshultz SE.: Genetics of neonatal cardiomyopathy. Curr Opin Cardiol. 1999 May;14(3):250-62.

2.16 Central nervous system vascular disorders (SMQ)

[Production Release September 2006;
Renamed in March 2015 from former name:
Cerebrovascular disorders (SMQ)]

2.16.1 Definition

- Concerns central nervous system hemorrhages and cerebrovascular accidents
  - Divided into the two main groups of ischemic and hemorrhagic central nervous system vascular disorders
  - Additional small group contains terms not covered by these main groups

2.16.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for conditions related to cerebrovascular disorders irrespective of cause and irrespective of acuteness or chronicity
  - Congenital cerebrovascular disorder terms
  - Cerebrovascular disorder terms related to infections
  - Terms describing cerebrovascular procedures
- Excluded:
  - Cerebrovascular disorder terms clearly related to accidents and injuries, e.g. PT *Traumatic intracranial haemorrhage*

NOTE: For searches related to retinal vascular pathology, subscribers have several available options including *Retinal disorders (SMQ)*, *Embolic and thrombotic events (SMQ)* as well as the creation of a modified MedDRA query based on an SMQ.

NOTE: The CIOMS WG for SMQs reviewed phase II feedback on this SMQ at their May 2006 meeting. A MedDRA subscriber had recommended the addition of several signs and symptoms terms that were already present in the broad search. In addition, a term for memory impairment was suggested, but the WG agreed not to include such a term as it was felt to be non-specific.

NOTE: The terms in *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* reflect the most common and classic signs and symptoms of cerebrovascular accidents.

2.16.3 Hierarchy Structure

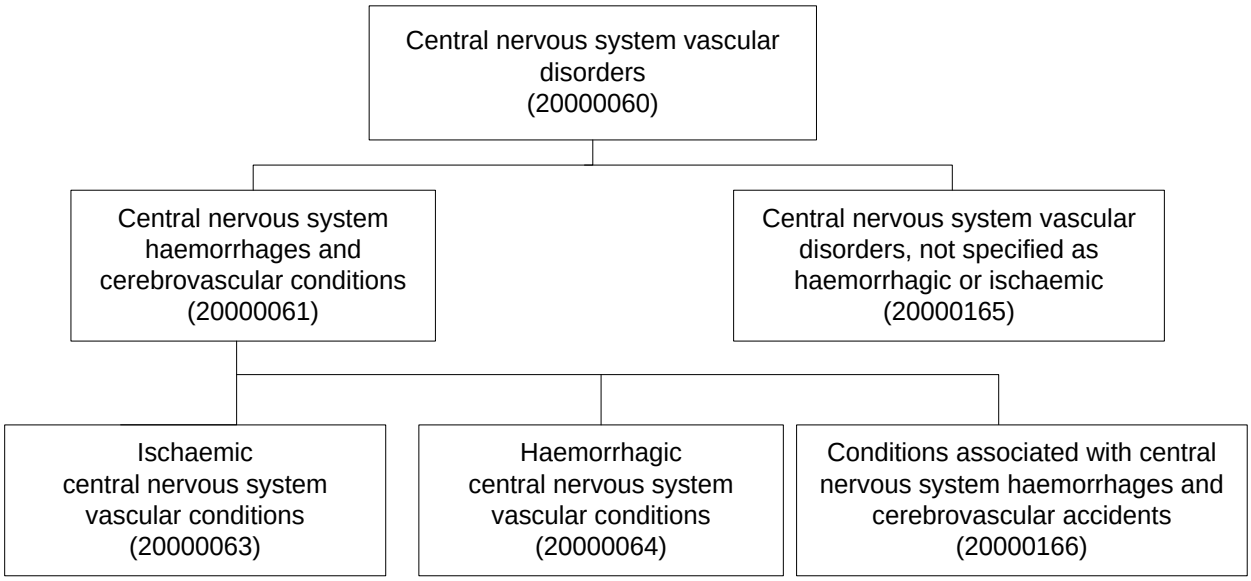

Figure 2-4. Hierarchy Structure of *Central nervous system vascular disorders (SMQ)*

NOTE**:** Four SMQs were renamed in MedDRA Version 18.0 to more precisely represent that the respective SMQ terms may pertain to both the brain and the spinal cord of the central nervous system:

Previous SMQ Name	New SMQ Name
Cerebrovascular disorders (SMQ)	*Central nervous system vascular disorders (SMQ)*
Cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ)	*Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ)*
Ischaemic cerebrovascular conditions (SMQ)	*Ischaemic central nervous system vascular conditions (SMQ)*
Haemorrhagic cerebrovascular conditions (SMQ)	*Haemorrhagic central nervous system vascular conditions (SMQ)*

Table 2-1. Modifications of sub-SMQ names under *Central nervous system vascular disorders (SMQ)* in V. 18.0

Level 2 SMQ *Central nervous system haemorrhages and cerebrovascular conditions (SMQ)* is divided into “narrow” and “broad” terms. The “narrow” group is divided into two Level 3 SMQs, namely, *Ischaemic central nervous system vascular conditions (SMQ)* and *Haemorrhagic central nervous system vascular conditions (SMQ)*.

In Version 12.0, per user’s request, *Cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ)* was added at level 2 to group the PTs that had been linked to *Cerebrovascular disorders (SMQ)* but did not belong to the level 2 sub-SMQ *Central nervous system haemorrhages and cerebrovascular conditions (SMQ)*. Unlike *Central nervous system haemorrhages and cerebrovascular conditions (SMQ)*, *Cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic - *Cerebrovascular disorders (SMQ)*.

For the same purpose, *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* was added at level 3 to group the broad terms that had been linked to *Central nervous system haemorrhages and cerebrovascular conditions (SMQ)*. *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic.

NOTE: Prior to Version 16.1, the terms in *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* were broad scope only. In Version 16.1, the terms included in *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* have been reclassified to be either broad or narrow in scope.

NOTE: The names of the sub-SMQs in the CIOMS WG documentation differ from this bulleted summary as follows:

CIOMS WG Document	Introductory Guide for Standardised MedDRA Queries (SMQs)
SMQ *1.2 Other cerebrovascular disorders*	This sub-SMQ has been removed. All sub-ordinate PTs, formerly in SMQ *1.2 Other cerebrovascular disorders (SMQ)* are linked to the level 2 sub-SMQ *Cerebrovascular disorders, not specified as haemorrhagic or ischaemic (SMQ).*

SMQ *1.1.1 Narrow search central nervous system haemorrhages and cerebrovascular accidents*	SMQ *Central nervous system haemorrhages and cerebrovascular conditions (SMQ)* [NOTE: This is a hierarchical SMQ which includes the following three subordinate SMQs: *Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)* with narrow and broad terms; *Haemorrhagic central nervous system vascular conditions (SMQ)* and *Ischaemic central nervous system vascular conditions (SMQ)*with only narrow terms each.
SMQ *1.1.2 Broad search central nervous system haemorrhages and cerebrovascular accidents*	
SMQ *1.2.1 Narrow search other cerebrovascular disorders*	Merged into the level 1 SMQ
SMQ *1.2.2 Broad search other cerebrovascular disorders*	Merged into the level 1 SMQ

Table 2-2. Link Table between CIOMS WG Document and SMQ Introductory Guide for *Central nervous system vascular disorders (SMQ)*

2.16.4 Notes on Implementation and/or Expectation of Query Results

Central nervous system vascular disorders (SMQ) is a hierarchical SMQ with both narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.16.5 List of References for *Central nervous system vascular disorders (SMQ)*

- The Merck Manual (Seventeenth Edition), 1999.

2.17 Chronic kidney disease (SMQ)

(Production Release March 2013)

2.17.1 Definition

- Chronic kidney disease (CKD) = heterogeneous disorders affecting kidney structure and function
- Variable presentation related to cause, pathology, severity and rate of progression
- Symptoms include: anorexia, nausea, vomiting, stomatitis, dysgeusia, nocturia, lassitude, fatigue, pruritus, decreased mental acuity, muscle twitches and cramps, water retention, undernutrition, gastrointestinal ulceration and bleeding, peripheral neuropathies, and seizures
- Diagnosis is based on laboratory testing of renal function and sometimes renal biopsy
- Treatment directed at the underlying condition but includes fluid and electrolyte management, erythropoietin for anemia, dialysis or transplantation
- CKD may result from a number of causes including:
  - Vascular disease:
    - Renal artery stenosis
    - C-ANCA-positive, P-ANCA-positive and ANCA-negative vasculitides
    - Atheroemboli
    - Hypertensive nephrosclerosis
    - Renal vein thrombosis
  - Primary glomerular disease:
    - Membranous nephropathy
    - Immunoglobulin A (IgA) nephropathy
    - Focal and segmental glomerulosclerosis
    - Minimal change disease
    - Membranoproliferative glomerulonephritis
    - Rapidly progressive (crescentic) glomerulonephritis
  - Secondary glomerular disease:
    - Diabetes mellitus
    - Systemic lupus erythematosus
    - Rheumatoid arthritis
    - Mixed connective tissue disease

- Scleroderma
- Goodpasture syndrome
- Wegener granulomatosis
- Mixed cryoglobulinemia
- Postinfectious glomerulonephritis
- Endocarditis
- Hepatitis B and C
- Syphilis
- Human immunodeficiency virus (HIV)
- Parasitic infection
- Heroin use
- Gold
- Penicillamine
- Amyloidosis
- Light chain deposition disease
- Neoplasia
- Thrombotic thrombocytopenic purpura
- Hemolytic-uremic syndrome
- Henoch- Schönlein purpura
- Alport syndrome
- Reflux nephropathy

– Tubulointerstitial disease:
  - Drugs (e.g., sulfa, allopurinol)
  - Infection (viral, bacterial, parasitic)
  - Sjögren syndrome
  - Chronic hypokalemia and chronic hypercalcemia
  - Sarcoidosis
  - Multiple myeloma cast nephropathy
  - Heavy metals
  - Radiation nephritis
  - Polycystic kidneys
  - Cystinosis

  - Urinary tract obstruction:
    - Urolithiasis
    - Benign prostatic hypertrophy
    - Tumors
    - Retroperitoneal fibrosis
    - Urethral stricture
    - Neurogenic bladder
- Markers of kidney damage in addition to proteinuria include:
  - Urine sediment abnormalities
  - Abnormalities on imaging studies
- Two major outcomes of CKD include:
  - Loss of kidney function leading to failure
  - Development of cardiovascular disease
- High blood pressure is both a cause and a complication of CKD and is associated with a faster loss of kidney function and development of cardiovascular disease
- Additional complications include:
  - Anemia
  - Malnutrition
  - Bone disease and disorders of calcium and phosphorus metabolism
  - Neuropathies
- Criteria for CKD established by the National Kidney Foundation:
  - Kidney damage for ≥3 months (structural or functional abnormalities) with or without decreased glomerular filtration rate manifested by either:
    - Pathological abnormalities; or
    - Markers of kidney damage (urine or blood abnormalities, or abnormalities in imaging tests)
  - Glomerular filtration rate <60 mL/min/1.73m^2 for ≥3 months, with or without kidney damage

- Five stages of CKD are defined as follows:

Stage	Description	GFR (mL/min/1.73m)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with normal or ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney failure	<15 (or dialysis)

Table 2-3. Five Stages of Chronic kidney disease

2.17.2 Inclusion/Exclusion criteria

- Included:
  - Terms related to the definition including signs and symptoms and long term consequences of CKD (e.g., PT *Chronic kidney disease*, PT *Chronic kidney disease-mineral and bone disorder*, and PT *Oedema due to renal disease*)
  - Terms for pertinent laboratory tests including those qualified with “abnormal” (e.g., PT *Glomerular filtration rate abnormal*)
  - Terms for therapeutic procedures associated with CKD (e.g., PT *Peritoneal dialysis*)
- Excluded:
  - Terms for underlying causes or risk factors for development of CKD (e.g., PT *Diabetes mellitus*)
    - Exceptions are nephropathies and other etiologic terms related directly to renal disease (e.g., included are terms such as PT *Diabetic nephropathy,* but not PT *Diabetes mellitus*)
    - PT *Hypertension* – along with several other terms that proved noisy on testing – is excluded (see the CIOMS SMQ Working Group’s original documentation for details)
  - Terms for nonspecific symptoms likely to return considerable of “noise” (e.g., PT *Nausea*, PT *Fatigue*)
  - Congenital and neonatal terms
  - Renal transplant complications and rejection terms, except PT *Chronic allograft nephropathy*

NOTE: In Version 18.0, in accordance with recent International Society of Nephrology classification and terminology, LLT *Chronic kidney disease* was swapped with PT *Renal failure chronic*, resulting in new PT *Chronic kidney disease.*

NOTE: After testing of candidate SMQ *Chronic kidney disease* in both regulatory and company databases, several additional "untested" PTs were added to the term list of the SMQ based on medical judgment. Please see the original CIOMS SMQ Working Group documentation for additional details.

2.17.3 List of References for *Chronic kidney disease (SMQ)*

- Levey AS, Coresh J. Chronic kidney disease. The Lancet published online August 15, 2011. DOI:10.1016/S0140-6736(11)60178-5
- Merck Manuals Online Medical Library for Health Professionals, Chronic Kidney Disease, accessed 2011-09-26: http://www.merckmanuals.com/professional/genitourinary_disorders/renal_failure/chronic_kidney_disease.html
- Verrelli, M. et al Chronic renal failure. eMedicine, accessed 2011-09-26: http://emedicine.medscape.com/article/238798-overview
- Harrison's On-line (Harrison's Principles of Internal Medicine, 17e), Ch. 280, Chronic Kidney Disease, accessed 2011-09-26 http://accessmedicine.com/content.aspx?aID=9130075&searchStr=kidney+failure%2c+chronic#9130075
- K/DOQI *Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification*. Am J Kidney Dis 39:S1-S266, 2002 (suppl 1)

2.18 Conjunctival disorders (SMQ)

(Production Release September 2009)

2.18.1 Definition

- Conjunctiva: mucous membrane investing
  - Anterior surface of eye (bulbar conjunctiva)
  - Posterior surface of eyelids (palpebral conjunctiva)
- Disorders that affect conjunctiva:
  - Acute conjunctivitis (viral, bacterial, inclusion, seasonal/allergic)
  - Chronic conjunctivitis (trachoma, perennial allergic, vernal keratoconjunctivitis)
- Trauma (subconjunctival hemorrhage, foreign bodies, lacerations)
  - Degenerative conditions (Cogan's senile plaque, pinguecula, pterygium, concretions, retention cysts)
  - Blistering mucocutaneous diseases (cicatrical pemphigoid, Stevens-Johnson syndrome)
  - Pigmented lesions
  - Tumors
- Symptoms vary according to underlying problem; some common features are:
  - Complaints of a red eye
  - Epiphora (excess tears)
    - Irritation, such as a foreign body sensation, due to presence of follicles or papillae
    - Itching – hallmark of allergic conjunctivitis but may also occur in blepharitis or keratoconjunctivitis sicca
    - Pain – generally mild. In absence of trauma, significant pain is unusual
    - Complaints of a discharge

2.18.2 Inclusion/Exclusion criteria

- Included:
  - Terms for irritation, inflammation, degeneration, deposit, and other non-traumatic and non-infectious conjunctival conditions
  - Terms for investigations related to conjunctiva (e.g., PT *Biopsy conjunctiva abnormal*)
  - Terms for conjunctiva procedures (e.g., PT *Conjunctivoplasty*)

  - Terms for conjunctival neoplasms (e.g., PT *Benign neoplasm of conjunctiva*)
  - PT *Allergic keratitis* because LLT *Allergic keratoconjunctivitis* is linked to this PT and would likely retrieve relevant cases
  - Terms where the origin of the event could be either infectious or non-infectious (see Exclusion criteria regarding exceptions) (e.g., PT *Conjunctival cyst*)
- Excluded:
  - Terms for signs and symptoms of conjunctival disorders that could be shared with other eye disorders
  - Terms for known causes of or syndromes associated with conjunctival disorders (e.g., PT *Pemphigoid*)
  - Terms that clearly indicate infections of conjunctiva (e.g., PT *Conjunctivitis bacterial*)
  - Terms related to conjunctival trauma (e.g., PT *Chemical burns of eye*) except if the term may relate directly to application of an eye product (e.g., PT *Conjunctival abrasion*)
  - Congenital terms
  - Scleral terms

2.18.3 Notes on Implementation and/or Expectation of Query Results

Conjunctival disorders (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.18.4 List of References for *Conjunctival disorders (SMQ)*

- Scott, O. Conjunctival problems. Patient UK, http://www.patient.co.uk/showdoc/40025324/, May 2008.
- Conjunctival disorders. Merck Manual, 17th edition, pp 710 – 717, 1999.
- Stedman's Medical Dictionary, 27th Edition.

2.19 Convulsions (SMQ)

(Production Release March 2007)

2.19.1 Definition

- Seizure: paroxysmal event due to abnormal, excessive, hypersynchronous discharges from an aggregate of central nervous system (CNS) neurons
  - Manifestations range from dramatic convulsive activity to experiential phenomena not readily discernible by an observer.
- Epilepsy: recurrent seizures due to a chronic, underlying process; not a single disease entity
- Convulsions are the motor component of cerebral seizures.
  - Characterized by contractions of skeletal muscles, appearing abruptly and involuntarily
  - Contractions may be tonic or clonic and they may be focal or generalized
- International Classification of Epileptic Seizures (1981):
  - Partial seizures
    - Simple partial seizures (with motor, sensory, autonomic, or psychic signs)
    - Complex partial seizures
    - Partial seizures with secondary generalization
  - Primarily generalized seizures
    - Absence (petit mal)
    - Tonic clonic (grand mal)
    - Tonic
    - Atonic
    - Myoclonic
  - Unclassified seizures
    - Neonatal seizure
    - Infantile spasms

2.19.2 Inclusion/Exclusion Criteria

- Included:
  - PTs containing the words “convulsions”, “epilepsy” or “ictus”; irrespective of whether the form of seizure involved muscular movement (e.g. PT *Petit mal epilepsy)*

- Terms indicative for complications after convulsions (e.g. PT *Postictal paralysis*)
- Relevant supporting terms from SOC *Investigations* containing the word “abnormal” in the broad search
- Terms representing various signs and symptoms of convulsive events (e.g. PT *Tongue biting*)
- Congenital and genetic disorders if convulsions are a primary presenting component of the disease or syndrome (e.g. PT *Baltic myoclonic epilepsy*)
- Treatment and/or prophylaxis related terms (e.g. PT *Seizure prophylaxis*)
- Diagnoses which are difficult to distinguish from seizures (e.g. PT *Narcolepsy*)

- Excluded:
  - Terms for SOC *Investigations* with the qualifier “normal” and those with no qualifier
  - PTs describing “incontinence” were non-specific and retrieved irrelevant cases
  - PTs *Loss of consciousness* and PT *Depressed level of consciousness* contributed considerable “noise”
  - PTs that only described movement without mentioning seizure (e.g. PT *Myoclonus)*

2.19.3 Notes on Implementation and/or Expectation of Query Results

Convulsions (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.19.4 List of References for *Convulsions (SMQ)*

- Harrison’s online, Chapter 348, accessed on 29 May 2005 http://accessmedicine.com/public/about_am.aspx
- Bankowski Z, Bruppacher R, Crusius I et al. Reporting adverse drug reactions, definition of 1. Terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS), 1999. Pages 24-25.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Epilepsia 22:489-501, 1981.

2.20 Corneal disorders (SMQ)

(Production Release March 2009)

2.20.1 Definition

- Corneal disorders grouped into:
  - Refractive errors due to irregular curvature (myopia, hyperopia, and astigmatism)
  - External eye conditions affecting cornea (allergies, conjunctivitis, Sjogren's syndrome)
  - Corneal disorders:
    - Corneal infections
    - Corneal dystrophies
    - Pterygium
    - Drug associated conditions such as Stevens-Johnson syndrome
- SMQ defined to include corneal disorders with associated specific and selected non specific signs and symptoms involving one or more layers of cornea
  - Epithelium
  - Bowman's membrane
  - Stroma
  - Descemet's membrane
  - Endothelium

2.20.2 Inclusion/Exclusion Criteria

- Included:
  - All terms involving the cornea
- Excluded:
  - Congenital corneal disorders
  - Infections involving cornea
  - Physical injuries involving cornea

NOTE: Non specific terms such as PT *Blindness*, PT *Visual impairment*, and PT *Visual acuity reduced* were removed after testing because they contributed considerable noise. PT *Stevens-Johnson syndrome* was also removed after testing because it represents a broader disorder and eye involvement occurs only in some cases.

2.20.3 Notes on Implementation and/or Expectation of Query Results

Corneal disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.20.4 List of References for *Corneal disorders (SMQ)*

- Anon. Facts about the Cornea and Corneal Disease. National Institutes of Health, National Eye Institute. December 2007. (http://www.nei.nih.gov/health/cornealdisease/index.asp#0/)
- Hollander DA; Aldave AJ Drug-induced corneal complications. Curr Opin Ophthalmol 2004 Dec;15(6):541-8.
- Dart J. Corneal toxicity: the epithelium and stroma in iatrogenic and factitious disease. Eye 2003 Nov; 17 (8):886-92.

2.21 Dehydration (SMQ)

(Production Release March 2018)

2.21.1 Definition

- Dehydration is a deficiency of body water.
  - Dehydration occurs with deficient intake of water or, more commonly, when excessive amounts of water and sodium are lost by the kidneys, the gastrointestinal tract or the skin. Water depletion may affect extracellular or intracellular volume, or both. Dehydration may be the consequence of abnormality of water intake (hypothalamic malfunction) or renal water wasting (diabetes insipidus). Hypernatremia (Na > 145 mmol/l) is common. When both water and sodium are depleted, tachycardia, hypotension, and weight loss are common.

- Clinical findings can vary with the severity of the dehydration.
  - Mild dehydration is characterized by an alert level of consciousness, capillary refill of 2 seconds or less and normal mucous membranes, tears, respiratory rate/pattern, blood pressure, pulse, skin turgor and appearance of both the eyes and fontanelles. Heart rate is slightly increased and urine output is decreased.
  - In moderate dehydration, the patient is lethargic, capillary refill is between 2 and 4 seconds, mucous membranes are dry, tears are decreased, the respiratory rate/pattern and heart rate are increased, blood pressure is normal (although orthostasis is present), pulse is thready, skin turgor is slow to recover, open fontanelles are depressed, eyes are sunken and oliguria is present.
  - A patient with severe dehydration is obtunded, has capillary refill greater than 4 seconds, extremities are cool to touch, mucous membranes are parched or cracked, tears are absent, the respiratory rate/pattern is increased and hyperpnea is present, heart rate is very increased, blood pressure is decreased, pulse is faint or impalpable, skin turgor testing displays persistent tenting, open fontanelles are sunken, eyes are very sunken and oliguria/anuria is present.

2.21.2 Inclusion/Exclusion Criteria

- **Included:**
  - Terms for signs and symptoms of mild to moderate dehydration (e.g., PT *Thirst*, PT *Hypohidrosis*, PT *Skin turgor decreased*, PT *Urine output decreased*, PT *Dry mouth*, etc.)
  - Terms for laboratory values that are more specific markers for dehydration (e.g., PT *Blood urea nitrogen/creatinine ratio increased*, PT *Blood sodium*

increased, PT *Urine osmolarity increased*, PT *Specific gravity urine increased*, etc.)

- All PTs from HLT *Total fluid volume decreased* except PT *Shock haemorrhagic*

- **Excluded**:
  - Symptoms of hypernatremia (e.g., Lethargy, Irritability, Confusional state, Asthenia, Hyperreflexia, etc.)
  - Non-specific terms related to fluid imbalance and electrolyte imbalance that could create too much “noise” relative to signal.
  - Laboratory analysis for electrolytes (other than increased sodium), hematologic parameters.
  - PT *Shock haemorrhagic* is excluded

2.21.3 Notes on Implementation and/or Expectation of Query Results

Dehydration (SMQ) has both narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.21.4 List of References for *Dehydration (SMQ)*

- Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use; 1999. ISBN 92 9036 071 2
  MedScape: Drugs and Disease: Dehydration, updated 2016-11-27, accessed 2017-08-29
  http://emedicine.medscape.com/article/906999-overview?src=refgatesrc1

2.22 Dementia (SMQ)

(Production Release March 2007)

2.22.1 Definition

- Dementia is defined as deterioration or loss of cognitive functions that impairs activities of daily living (ADLs).
- Numerous known causes:
  - Metabolic-toxic (e.g., vitamin B12 deficiency)
  - Structural (e.g., Alzheimer's disease)
  - Infectious (e.g., HIV-related)
- Drug-associated (generally reversible) includes anticholinergics, sedatives and barbiturates
- Other forms of dementia:
  - Alzheimer's disease (characterized by amyloid plaques and neurofibrillary tangles in the central nervous system)
  - Vascular dementia (10% to 20% of cases); may co-exist with Alzheimer's disease
  - Some medications (e.g., sleeping pills, anticholinergics, H2 blockers) are known to exacerbate dementia of other etiologies.
- Additional definitions from multiple references:
  - Progressive loss of cognitive and intellectual function; disorientation, impaired memory, judgment, and intellect, and a shallow labile affect
  - Deterioration in cognitive abilities; impairs previously successful performance of ADLs. Judgment, comprehension, orientation, learning, calculation, problem solving, mood and behavior may be affected. Deficits in *executive function* – mental activity involved in planning, initiating and regulating behavior
  - Cognitive impairment (memory, orientation, language), loss of functional autonomy, neuropsychiatric signs/symptoms (agitation, apathy, delusions, aggressiveness)
- Modified DSM-IV criteria for **dementia**:
  - Memory impairment
  - One or more of the following cognitive disturbances:
    - Aphasia
    - Apraxia
    - Agnosia

- Disturbance in executive functioning
- Impairment of social or occupational functioning

- Modified DSM-IV criteria for **Alzheimer's disease**:
  - Exclusion of other causes
  - Loss of neurons in cerebral cortex subcortical structures
  - Memory loss, inability to learn new information, language problems (especially word finding), mood swings, personality changes, problems performing ADLs, diminished abstract thinking, diminished judgment, irritability, hostility, agitation, aphasia, visuospatial difficulties, strange behavior, emotional lability, behavioral disorganization, confusion, "sundowning".

2.22.2 Inclusion/Exclusion Criteria

- Included:
  - Terms that relate to the general definition of dementia (as described above)
  - Alzheimer's disease terms (because of the possibility that the reporter assumes that dementia is Alzheimer's and reports it as such)
  - Vascular dementia
  - Although testing results for Amnesia and hallucination terms did not show useful, CIOMS WG decided to keep these terms in the SMQ. Specifically, PT *Amnestic disorder* has been added
  - PT *Delusion* and PT *Delusional disorder, unspecified type* are included in this SMQ. For other more specific types of delusional disorders, one may refer to the *Psychosis and psychotic disorders (SMQ)*.
- Excluded:
  - Other specific diseases manifesting with dementia (e.g., normal pressure hydrocephalus)
  - Pseudodementia
  - Three PTs – *Disturbance in attention*, *Insomnia*, and *Irritability* – were initially included but were subsequently removed based on testing results.

NOTE: In v15.0, new PT *Substance-induced psychotic disorder* was added, and several LLTs that were previously subordinate to PT *Psychotic disorder* (such as: LLT *Drug psychoses, other*; LLT *Unspecified drug psychosis*; LLT *Steroid psychosis*) were moved to this new PT. Accordingly, these LLTs are no longer included in *Dementia (SMQ)*, although PT *Psychotic disorder* remains a broad scope term in this SMQ. It was

judged that the concepts represented by PT *Substance-induced psychotic disorder* do not have a robust relevance to the identification of reports of dementia. PT *Substance-induced psychotic disorder* may be electively included in a query by the user if relevant to the product or to the patient population being studied.

NOTE: In Version 13.1, *Dementia (SMQ)* was modified in scope to include both narrow and broad search terms. This SMQ formerly included only broad terms.

2.22.3 Notes on Implementation and/or Expectation of Query Results

Dementia (SMQ) has both narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.22.4 List of References for *Dementia (SMQ)*

- Stedman's Medical Dictionary, 27th Edition, 2000.
- Harrison's Principles of Internal Medicine, 14th Edition, 1998, pp 142 – 149.
- The Merck Manual 17th edition, 1999, pp 1393 – 1400.
- Fago, JP. Dementia: Causes, Evaluation, and Management. Hospital Practice. www.hosppract.com/.

2.23 Demyelination (SMQ)

(Production Release September 2008)

2.23.1 Definition

- Group of diseases of nervous system with damage and destruction of myelin sheaths surrounding nerve fibers
- Axons may be damaged as well
- Mechanism of myelin damage may be different in various diseases
- Impairs conduction of signals in affected nerves
- Causes impairment in sensation, movement, cognition, or other functions
- Most common demyelinating disease is multiple sclerosis
- Other examples include central pontine myelinolysis, progressive multifocal leukoencephalopathy, and subacute combined degeneration of spinal cord
- Demyelination: loss of myelin with preservation of the axons or fiber tracts
  - Central demyelination occurs within central nervous system (e.g., multiple sclerosis)
  - Peripheral demyelination affects peripheral nervous system (e.g., Guillain-Barre syndrome)
  - Other causes:
    - Genetic
    - Autoimmune reaction
    - Immunological disorders
    - Nutritional or metabolic disorder
    - Toxins (including some used in therapy such as anti-mitotic agents and radiotherapy)
    - Unknown

2.23.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for peripheral and central demyelinating diseases (e.g., PT *Multiple sclerosis,* PT *Guillain-Barre syndrome,* and PT *MELAS syndrome*)
  - Terms containing the root “demyel” (e.g., PT *Demyelinating polyneuropathy* and PT *Chronic inflammatory demyelinating polyradiculoneuropathy*)
  - Terms for cranial nerve disorders specific to demyelinating disorders (e.g., PT *Optic neuritis*)

- Terms for encephalomyelitis and leukoencephalopathies related to demyelination (e.g., PT *Acute haemorrhagic leukoencephalitis* and PT *Progressive multifocal leukoencephalopathy*)
- Terms for very specific signs or symptoms that are **not** included in SMQ *Peripheral neuropathy* or SMQ *Guillain-Barre syndrome* are included in broad terms (see NOTE below) (e.g., PT *Lhermitte's sign* and PT *Saccadic eye movement*)
- PT *Trigeminal neuralgia* is included in broad terms due to possible association with multiple sclerosis or other demyelinating conditions
- Terms representing a disability scale which is highly specific for MS (e.g., PT *Expanded disability status scale score increased*)

- Excluded:
  - Congenital terms
  - Terms for dysmyelinating diseases
  - Terms for causes of demyelination (e.g., PT *Alcoholism,* PT *Vitamin B12 deficiency*)
  - Terms for signs and symptoms that are already included in SMQ *Peripheral neuropathy* or SMQ *Guillain-Barre syndrome* (e.g., PT *Paraesthesia,* PT *Areflexia,* PT *Muscular weakness*)
  - Terms for signs and symptoms that are very non-specific or represent advanced demyelination (e.g., PT *Dizziness,* PT *Fatigue,* PT *Anal incontinence* and PT *Muscle spasticity*)
  - Investigational test terms, in general, are excluded with the exception of very specific diagnostic and prognostic concepts (e.g., PT *Expanded disability status scale score increased*)
  - Terms for non-specific neuropathies and cranial nerve disorders
  - HIV terms
  - The following PTs: PT *Polyneuropathy in malignant disease*, PT *Plasma cell myeloma*, PT *POEMS syndrome*, PT *Lyme disease,* PT *Waldenstrom's macroglobulinaemia*, and PT *Optic neuritis meningococcal*

NOTE: If searching for a *de novo* signal of demyelination, it is recommended to use the narrow and broad terms in this SMQ and also SMQ *Peripheral neuropathy* and SMQ *Guillain-Barre syndrome*. Broad terms for signs and symptoms of demyelinating diseases were excluded because they are in SMQ *Peripheral neuropathy* and SMQ *Guillain-Barre syndrome.* Some broad terms were also excluded as being too non-specific, related to advanced demyelination, or because of poor performance in SMQ

testing. These excluded terms (see Tables 1 and 2 in the original CIOMS WG documentation) may be included in a search at the user's discretion.

2.23.3 Notes on Implementation and/or Expectation of Query Results

Demyelination (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.23.4 List of References for *Demyelination (SMQ)*

- http://www.uvm.edu/~jkessler/NP/neumyshe.htm#anchor4438902.
- Gale Encyclopedia of Neurological Disorders. 2005. The Gale Group, Inc.
- Stedman's Medical Dictionary 26th ed.
- Demyelinating Diseases. Walter R. Timperley, M.D. Lecture. 2000. http://www.dokkyomed.ac.jp/dep-k/cli-path/a-super/super-demyeli.html

2.24 Depression and suicide/self-injury (SMQ)

(Production Release March 2006)

2.24.1 Definition

- Depression is a morbid mental state dominated by a lowering of mood
  - Often includes a variety of associated symptoms, particularly anxiety, agitation, feelings of unworthiness, suicidal ideas, alteration of appetite and sexual function, psychomotor retardation, sleep disturbance, and various somatic signs and symptoms
- Etiology is complex and is thought to reflect changes in brain neurotransmitters, particularly norepinephrine, serotonin, and dopamine
- May follow a severe psychosocial stressor
- Often associated with chronic medical conditions (such as diabetes, myocardial infarction, carcinomas, stroke)
- Associated with a variety of medications (such as antihypertensive drugs, oral contraceptives, and corticosteroids)
- Patients also frequently develop other psychiatric conditions, most notable anxiety or panic disorders, and alcohol or substance abuse
- Thoughts of death, suicidal ideation, and suicide attempts are frequent complications of depression
- Diagnostic criteria as described in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*)© of depression-related disorders include the presence of depressed mood or markedly diminished interest or pleasure in all, or almost all, activities for most of the day, nearly every day

2.24.2 Inclusion/Exclusion Criteria

- Included:
  - Relevant PTs selected by comparing the *DSM-IV* diagnostic criteria for Major Depressive Episode, Major Depressive Disorder, Minor Depressive Disorder, Dysthymic Disorder, and Substance-Induced Mood Disorder.
  - PTs related to depression or depression-related symptoms, depressed or altered mood, feelings of guilt or despair, psychomotor retardation or agitation, specific depression-related sleep disturbances, substance abuse, suicide, and psychiatric therapies suggestive of depression.
  - PT *Intentional overdose* and PT *Poisoning deliberate* are included in the narrow search of the *Suicide/self-injury (SMQ)* because their LLTs are suggestive of suicide or self-injury.

- The insomnia-related PTs, PT *Terminal insomnia,* PT *Initial insomnia*, and PT *Middle insomnia* are somewhat more specific to the type of insomnia often reported in depressed patients and they were included in the SMQ.
- As the result of the 18-24 month review of this SMQ by the CIOMS WG team, abuse and dependence concepts are included as broad scope terms for the level 1 SMQ Depression and suicide/self-injury.

- Excluded:
  - PTs for anxiety not associated with depression, agitation, restlessness, fatigue, or weight changes
  - PT *Insomnia* because it only creates “noise” based on Phase I testing

2.24.3 Hierarchy Structure

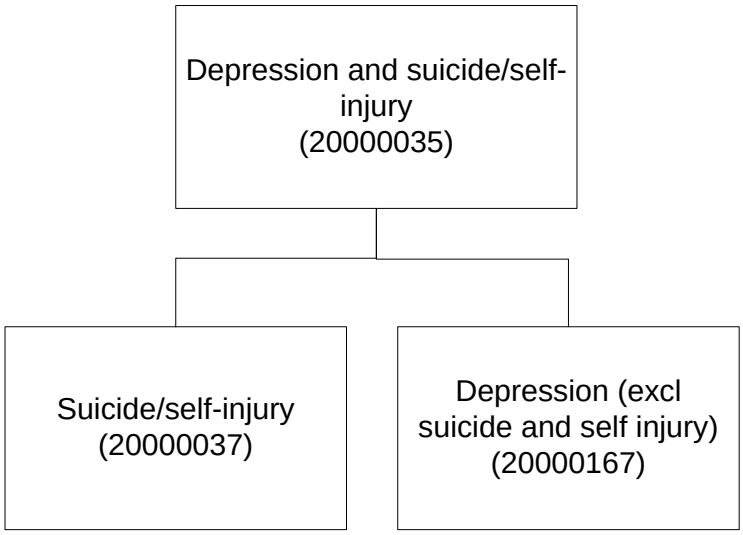

Figure 2-5. Hierarchy Structure of *Depression and suicide/self-injury (SMQ)*

This SMQ has a two-level hierarchy consisting of a comprehensive search of depression (first level) terms and a sub-SMQ specific for suicide and self-injury (second level):

- *Depression and suicide/self-injury (SMQ)*: including depression specific terms, which are grouped under *Depression (excl suicide and self injury) (SMQ)*, and all terms under *Suicide/self-injury (SMQ)*.
- *Suicide/self-injury (SMQ)*: only narrow search is proposed as separate narrow and broad searches were determined not necessary by the SMQ Working Group.

In Version 12.0, per user's request, *Depression (excl suicide and self injury) (SMQ)* was added at level 2 to group the PTs that had been linked to *Depression and suicide/self-injury (SMQ)* but did not belong to the level 2 sub-SMQ *Suicide/self-injury (SMQ)*. Unlike *Suicide/self-injury (SMQ)*, *Depression (excl suicide and self injury) (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic - *Depression and suicide/self-injury (SMQ)*.

2.24.4 Notes on Implementation and/or Expectation of Query Results

Depression and suicide/self-injury (SMQ) is a hierarchical SMQ. The parent SMQ (*Depression and suicide/self-injury (SMQ)*) has both narrow and broad search terms. However the sub-SMQ (*Suicide/self-injury (SMQ)*) has only narrow search terms. Thus, the sub-SMQ's narrow and broad searches would return the same result. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.24.5 List of References for *Depression and suicide/self-injury (SMQ)*

- Definitions and basic requirements for the use of terms for reporting adverse drug reactions (IV). Pharmacoepidemiology and Drug Safety 1993; 2:149-153.
- Depression. Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use. Bankowski Z, Bruppacher R, Crusius I et al (Eds). Council for International Organizations of Medical Sciences: Geneva, 1999, pg. 43.
- Kando JC, Wells BG, and Hayes PE. Depressive disorders. Pharmacotherapy: A Pathophysiologic Approach (5th Ed). DiPiro JT, Talbert RL, Yee GC et al (Eds). McGraw-Hill: New York, 2002, pg. 1243-1264.
- Major depressive episode. Diagnostic and Statistical Manual of Mental Disorders (4th Ed). American Psychiatric Association: Washington DC, 1994, pg. 320-327.
- Major depressive disorder. Diagnostic and Statistical Manual of Mental Disorders (4th Ed). American Psychiatric Association: Washington DC, 1994, pg. 370-375.
- Substance-induced mood disorder. Diagnostic and Statistical Manual of Mental Disorders (4th Ed). American Psychiatric Association: Washington DC, 1994, pg. 370-375.
- Dysthymic disorder. Diagnostic and Statistical Manual of Mental Disorders (4th Ed). American Psychiatric Association: Washington DC, 1994, pg. 345-350.

- Minor depressive disorder. Diagnostic and Statistical Manual of Mental Disorders (4th Ed). American Psychiatric Association: Washington DC, 1994, pg. 719-721.

2.25 Drug abuse, dependence and withdrawal (SMQ)

(Production Release September 2007)

2.25.1 Definition

- Drug abuse:
  - Habitual use of drugs:
    - Not needed for therapeutic purposes (e.g., to alter mood)
    - To effect a body function unnecessarily (e.g., laxative)
    - Non-medical use of drugs
  - Prevalence of cocaine, other psychostimulant abuse appears to be increasing in some metropolitan areas
  - Initiation and persistence of drug abuse determined by complex interaction of:
    - Pharmacologic properties and relative availability of the drug, the personality and expectation of the user, and the environmental context in which the drug is used
  - Polydrug abuse is increasingly common
  - May be an acute or a chronic intoxication
  - Symptoms vary according to pharmacologic properties, dose, and regular use of drug
- Withdrawal:
  - Abrupt cessation of use in a habituated person
  - A substance specific syndrome follows cessation or reduction in intake of a psychoactive substance previously used regularly
  - Withdrawal symptoms vary according to psychoactive substance used:
    - Generally “opposite” the acute effects of drug
    - Include nonspecific symptoms e.g., nausea, diarrhea or obstipation, profuse sweating, increase in respiratory rate, tachycardia
    - Common symptoms include anxiety, restlessness, irritability, insomnia, impaired attention

2.25.2 Inclusion/Exclusion Criteria

- Included:
  - Drug abuse/dependence:

    - All relevant terms referring to drug "abuse," "intentional misuse," "illicit drug," or "dependence" included as narrow terms
    - Terms observed with abuse but which also occur without abuse (e.g. , "increased tolerance" or "overdose" or "drug level increased" or "drug toxicity") included as broad terms
    - Terms indicating neonatal events
  - Withdrawal:
    - All terms containing "drug withdrawal" included as narrow terms
    - Terms only containing "withdrawal" or "rebound" included as broad terms
    - Terms indicating neonatal events

NOTE: Between the original version of this SMQ (based on MedDRA Version 9.1) and MedDRA Version 10.0, originally included PT *Rebound hypertension* was demoted to an LLT linked to PT *Hypertension*. Because PT *Hypertension* is non-specific and has linked LLTs unrelated to drug withdrawal, PT *Hypertension* has not been added to this SMQ. When applying this SMQ, users should keep in mind that there may be cases of interest linked to LLT *Rebound hypertension.*

- Excluded:
  - Drug abuse/dependence:
    - Terms for symptoms of drug abuse or drug intoxication
    - Terms for laboratory values indicating increased level of specific drugs due to the fact that some such terms (e.g., PT *Analgesic drug level above therapeutic*) were initially included and tested but were subsequently deleted following discussion by CIOMS WG team.
  - Terms related to alcohol and nicotine abuse
  - Medication error/maladministration terms are generally excluded except for terms related to inappropriate use of medication, such as incorrect site, incorrect route, as they may signify drug abuse.
  - Withdrawal:
    - Terms for symptoms of drug withdrawal (too nonspecific and create too much "noise")
    - Terms related to alcohol and nicotine withdrawal
    - Terms for "withdrawal" that do not fit the definition for this SMQ, i.e., drugs that are neither psychoactive, nor used habitually.

2.25.3 Hierarchy Structure

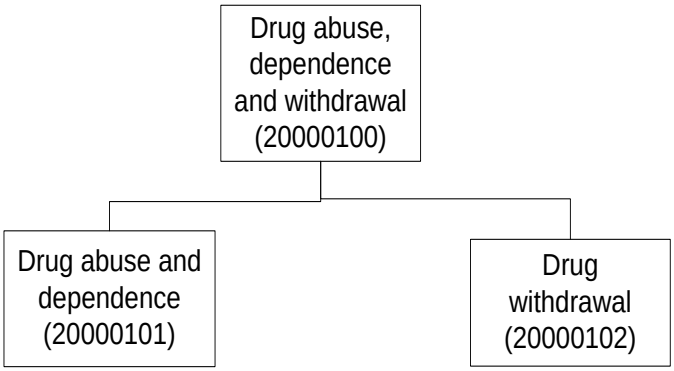

Figure 2-6. Hierarchy Structure of *Drug abuse, dependence and withdrawal (SMQ)*

NOTE: (added in Version 17.1) This SMQ does not contain signs and symptoms often associated with drug abuse and dependence, including neurological signs and symptoms like dizziness, disturbances in consciousness, anxiety symptoms, and perception disturbances such as hallucinations, etc., which are mostly found in SOC *Nervous system disorders* and SOC *Psychiatric disorders*. These types of terms were not added to the SMQ due to their potential to introduce “noise”, and because, depending on the drug in question, the manifestations of drug abuse and dependence may vary significantly. Nevertheless, they should be taken into account if deemed appropriate for a particular search.

NOTE: In Version 16.0, Level 2 SMQ *Drug abuse* was renamed to SMQ *Drug abuse and dependence*.

NOTE: The original CIOMS WG documentation refers to this SMQ as SMQ *Drug abuse and withdrawal*. It also refers to sub-SMQ *Drug withdrawal* as SMQ *Withdrawal*.

2.25.4 Notes on Implementation and/or Expectation of Query Results

Drug abuse, dependence and withdrawal (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.25.5 List of References for *Drug abuse, dependence and withdrawal (SMQ)*

- Stedman's Medical dictionary 5th Edition, Lippincott, Williams & Wilkins, 2005.
- Harrison's Principles of internal Medicine, 16th Edition, McGraw Hill, 2005.
- Huang B, Dawson DA, Stinson FS, Hasin DS, Ruan WJ, Saha TD, Smith SM, Goldstein RB, Grant BF. Prevalence, correlates, and comorbidity of nonmedical prescription drug use and drug use disorders in the United States: Results of the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry 2006 Jul;67(7):1062-73.
- Isaacson JH, Hopper JA, Alford DP, Parran T. Prescription drug use and abuse. Risk factors, red flags, and prevention strategies. Postgrad Med 2005. Jul;118(1):19-26
- Haydon E, Rehm J, Fischer B, Monga N, Adlaf E. Prescription drug abuse in Canada and the diversion of prescription drugs into the illicit drug market. Can J Public Health 2005 Nov-Dec;96(6):459-61.
- Woody GE, Senay EC, Geller A, Adams EH, Inciardi JA, Schnoll S AU - Munoz A TI - An independent assessment of MEDWatch reporting for abuse/dependence and withdrawal from Ultram (tramadol hydrochloride). Drug Alcohol Depend 2003 Nov 24;72(2):163-8.
- Brady KT, Lydiard RB, Brady JV. Assessing abuse liability in clinical trials. Drug Alcohol Depend 2003 Jun 5;70(3 Suppl):S87-95.
- Johnson MD, Heriza TJ, St Dennis C. How to spot illicit drug abuse in your patients. Postgrad Med 1999 Oct 1;106(4):199-200.
- Widlitz M, Marin DB. Substance abuse in older adults. An overview. Geriatrics 2002 Dec;57(12):29-34.

2.26 Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)

(Production Release March 2016)

2.26.1 Definition

- Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe, potentially life-threatening, delayed-onset drug reaction characterized by skin eruption, fever, hematologic abnormalities (eosinophilia, atypical lymphocytes), lymphadenopathy, and internal organ involvement. Although initially reported with antiepileptic medications, the syndrome has also been reported with other medications. It is associated with a highly variable clinical presentation, with patients exhibiting a wide array of symptoms. As a result, there is a lack of standardization of both the diagnostic criteria and the nomenclature.

- Determining the true incidence of DRESS has proven difficult, but estimates range from 1:1000 to 1:10000.

- The precise pathogenic mechanisms of DRESS are unknown; however, it is thought to be the result of a combination of genetic and immunologic factors. The medical literature provides a number of hypotheses.
  - Detoxification defects in the drug metabolism pathway may result in toxic metabolite formation and lead to an immune response.
  - Drugs metabolized by slow acetylation may lead to an accumulation of lymphotoxic metabolites.
  - Drug-mediated release of cytokines may play a role in the immune mechanisms for DRESS; for example, interleukin-5 release may activate eosinophils.
  - Drug-mediated reactivation of herpes virus (HHV-6, HHV-7, Epstein-Barr) may induce or amplify the immune reaction.
  - In recent years, certain HLA alleles have been found to be associated with specific drugs causing DRESS. In some cases, the HLA allele appears to predict the particular manifestations that the patient experiences.

- A number of drugs have been reported in association with DRESS, including:
  - allopurinol
  - carbamazepine
  - dapsone
  - lamotrigine
  - mexiletine
  - minocycline
  - nevirapine
  - oxcarbazepine
  - phenobarbital
  - phenytoin

- sulfasalazine
- telepravir
- vancomycin

Other drugs with fewer literature reports of DRESS include (not a comprehensive list): amoxicillin/clavulanic acid, amitriptyline, atorvastatin, aspirin, captopril, cefadroxil, celecoxib, chlorambucil, clomipramine, codeine phosphate, cotrimoxazole/cefixime, cyanamide, efalizumab, esomeprazole, hydroxychloroquine, ibuprofen, imatinib, olanzapine, phenylbutazone, quinine and thiamine, salazosulfapyridine, sodium meglumine ioxitalamate, sodium valproate/ethosuximide, spironolactone, streptomycin, strontium ranelate, sulfamethoxazole, tribenoside, and zonisamide.

- DRESS is diagnosed on the basis of clinical presentation as described above. There is no “gold standard” for diagnosis of DRESS; however, several groups have proposed diagnostic criteria which were considered in the term selection for *Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)*.

- Descriptions of the following diagnostic criteria are included in the original documentation for this SMQ: Phenotype Standardization Project (PSP);RegiSCAR; and the Japanese consensus group.

- Treatment includes:
  - Stopping the offending medication and providing supportive care
  - Systemic steroids may be used to manage cutaneous manifestations and internal organ involvement

- DRESS is associated with a mortality rate of up to 10%. Early recognition and drug withdrawal are critical in improving outcomes and preventing fatalities.

- The differential diagnosis for DRESS includes (but is not limited to):
  - connective tissues diseases
  - idiopathic hypereosinophilia
  - hypereosinophilic syndrome
  - angioimmunoblastic lymphadenopathy
  - Stevens-Johnson syndrome
  - toxic epidermal necrolysis
  - acute generalized exanthematous pustulosis
  - Kawasaki disease
  - serum sickness
  - lymphoma
  - pseudolymphoma
  - various acute viral infections (e.g., Epstein-Barr, hepatitis, influenza, cytomegalovirus, and human immunodeficiency virus).

- Selection criteria for cases of DRESS
  - Included:
    Cases that report:
    - Onset of symptoms within three months of starting therapy with a drug, **AND**
    - Evidence of involvement of the skin and/or an extracutaneous organ system, **AND**
    - At least two of the following:
      Fever
      Eosinophilia (and/or atypical lymphocytes)
      Lymphadenopathy

  - Excluded:
    Cases are excluded that:
    - Did not report a temporal relationship between suspect drug and reaction; note: this may include cases in which the multiple signs & symptoms associated with DRESS did not occur within one month of each other (e.g. skin eruption followed by lymphadenopathy and fever 6 months later)
    - Did not meet the inclusion criteria above
    - Reported a condition listed in the differential diagnosis section, or cases that described another more likely diagnosis
    - Are categorized as “toxic drug-induced exanthema.” These include cases in which patients have an exanthem and fever, but other manifestations have not been detected because laboratory tests were either not performed or could not be done.

2.26.2 Inclusion/Exclusion Criteria

- Included
  - Terms directly referring to DRESS syndrome, e.g., PT *Drug reaction with eosinophilia and systemic symptoms* and PT *Pseudolymphoma* (included as narrow scope terms, Category A)
  - Terms related to skin manifestations and systemic involvement/internal organ damage commonly seen in DRESS cases, including corresponding investigation terms, e.g., PT *Dermatitis exfoliative*, PT *Hepatic failure*, PT *Hepatic enzyme increased* (included as broad scope terms, category B)
  - Other relevant terms related to mucocutaneous involvement commonly seen in DRESS cases, e.g., PT *Mucocutaneous rash*, PT *Mucosal ulceration* (included as broad scope terms, category B)
  - Terms related to viral reactivation, e.g., PT *Cytomegalovirus infection* (included as broad scope terms, category B)
  - Terms related to general hypersensitivity, e.g., PT *Drug hypersensitivity* (included as broad scope terms, category B)
  - Terms related to fever, e.g., PT *Hyperpyrexia* (included as broad scope terms, category C)

- Terms related to lymphadenopathy (included as broad scope terms, category D)
- Terms related to hematologic abnormalities commonly seen in DRESS cases, e.g., PT *Eosinophilia* (included as broad scope terms, category E)

- Excluded
  - Congenital terms
  - Unqualified investigation terms
  - Infectious etiologies
  - Terms related to "site" conditions, e.g., PT *Administration site lymphadenopathy*

2.26.3 Algorithm

The categories are defined as follows:

Category A- Narrow search terms
Category B- Terms related to organ damage, including skin involvement, viral reactivation, general hypersensitivity
Category C- Terms related to fever
Category D- Terms related to lymphadenopathy
Category E- Terms related to hematologic abnormalities commonly seen in DRESS cases

A report is considered a relevant case for further review if it includes:

A term from Category A (Narrow terms)
OR
At least one term from Category B and a term from two of the three categories C, D, E

In summary: A or (B and C and D) or (B and C and E) or (B and D and E)

2.26.4 Notes on Implementation and/or Expectation of Query Results

Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ) is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. Use of the broad search for this SMQ is only meaningful if applied with an algorithm. This SMQ is intended to identify relevant cases for further medical review, which may then apply a scoring method in the evaluation of retrieved cases. Users should consider using the RegiSCAR criteria for DRESS to score cases for inclusion; however, information provided in spontaneous postmarketing reports is generally limited and it may prove

difficult to apply these criteria, thus potentially resulting in the exclusion of relevant cases.

PT *Acute generalised exanthematous pustulosis,* PT *Stevens-Johnson syndrome,* PT *Toxic epidermal necrolysis*, PT *Hypersensitivity*, *and* PT *Drug hypersensitivity* were found in testing to retrieve cases of interest in older data, but were less useful for more recent data. The final decision was made to keep these PTs in Category B (skin/organ involvement). When searching older data for DRESS, it is recommended to simultaneously use *Severe cutaneous adverse reactions (SMQ)*, *Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)*, PT *Drug hypersensitivity,* and PT *Hypersensitivity*

2.26.5 List of References for *Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)*

- Cacoub P, Musette P, Descamps V. The DRESS syndrome: a literature review. Am J Med 2011;124:588-97.

- Tas S, Simonart T. Management of drug rash with eosinophilia and systemic symptoms (DRESS syndrome): an update. Dermatology 2003;206:353-6.

- Bocquet H, Bagot M, Roujeau JC. Drug-induced pseudolymphoma and drug hypersensitivity syndrome (Drug Rash with Eosinophilia and Systemic Symptoms: DRESS). Semin Cutan Med Surg 1996;15(4):250-7.

- Pirmohamed M, Friedman PS, Molokhia M, et al. Phenotype standardization for immune-mediated drug-induced skin injury. Clin Pharmacol Ther 2011;89(6):896-901.

- Chaiken BH, Goldberg BI, Segal JP. Dilantin sensitivity. Report of a case of hepatitis with jaundice, pyrexia, and exfoliative dermatitis. N Engl J Med 1950;242(23):897-8.

- Saltzstein SL, Ackerman LV. Lymphadenopathy induced by anticonvulsant drugs and mimicking clinically pathologically malignant lymphomas. Cancer 1959;12(1):164-82.

- Kardaun SH, Sidoroff A, Valeyrie-Allanore L, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic syndromes: does a DRESS syndrome really exist. Br J Dermatol 2007;156:609-11.

- Walsh SA, Creamer D. Drug reaction with eosinophilia and systemic symptoms (DRESS): a clinical update and review of current thinking. Clin Experimen Dermatol 2011;36(1):6-11

- Sullivan JR, Shear NH. The drug hypersensitivity syndrome: what is the pathogenesis? Arch dermatol 2001;137(3):357-64.

- Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): A reaction induced by a complex interplay among herpesviruses and antiviral and antidrug immune responses. Allergol Int 2006;55:1-8.

- Phillips EJ, Chung WH, Mockenhaupt M, et al. Drug hypersensitivity: pharmacogenetics and clinical syndromes. J All Clin Immunol 2011;127(Suppl 3):S60-6.

- RegiSCAR website. Heep://regiscar.uni-freiburg.de/. Accessed April 5, 2012.

- Incivek (telaprevir) Prescribing Information. Vertex Pharmaceuticals Inc. Cambridge;MA. June 2012.

- Shaughnessy KK, Bouchard SM, Mohr MR, et al. Minocycline-incudes drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: a systematic review. Drug Saf 2009;32(5):391-408.

- Ganeva M, et al. Carbamazepine-induced drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome: report of four cases and brief review. Int J Dermatol 2008;47(8):853-60.

- Elzagallaai AA, Knowles SR, Rieder MJ, et al. Patch testing for the diagnosis of anticonvulsant hypersensitivity syndrome: a systematic review. Drug Saf 2009;32(5):391-408.

- Chen YC, Chir HC, Chu CY. Drug reaction with eosinophilia and systemic symptoms: a retrospective study of 60 cases. Arch Dermatol 2010;146(12):1373-9.

- Pirmohamed M, Aithal GP, Behr E, et al. The phenotype standardization project: improving pharmacogenetic studies of serious adverse drug reactions. Clin Pharmacol Ther 2011;89(6):784-5.

2.27 Dyslipidaemia (SMQ)

(Production Release November 2005)

2.27.1 Definition

- Defined as altered, most often excessive, concentration of lipids (cholesterol and/or triglycerides) in blood
- Result of a genetic predisposition, secondary causes, or of a combination of both
- Five forms:
  - Hypercholesterolemia
  - Hypertriglyceridemia
  - Combined hyperlipidaemia
  - Secondary dyslipidaemia
  - Hypolipidaemia
- Cholesterol-carrying lipoproteins are differentiated on the basis of their buoyant properties as LDL, VLDL, and HDL and may vary on the amount of cholesterol present in each particle, in the number of circulating particles, or both
- With the exception of high HDL, elevated concentration of lipid in blood, particularly cholesterol, is one of the major risk factors for atherosclerosis
- Hypercholesterolemia and hypertriglyceridemia *per se* do not produce specific symptoms, unless associated with the disease of an organ involved in the metabolism of lipid (e.g., pancreatitis)
- Some clinical manifestations of atherosclerosis occur after decades of silent onset and progression of lesions
- Acute hypercholesterolemia is not known to occur as adverse response to drug
- Acute hypertriglyceridaemia may be the expression of excessive (binge-like) consumption of fat-rich foods or alcohol, or it may relate to diabetes – especially when not properly controlled – or pancreatitis

2.27.2 Inclusion/Exclusion Criteria

- Included:
  - Terms with roots of "lipid," "cholesterol," "triglyceride," and "lipoprotein"
  - Medical terms closely related to lipids, lipoproteins, cholesterol and triglycerides in blood
  - Terms were derived from three SOCs (SOC *Metabolism and nutrition disorders*, SOC *Investigations*, and SOC *Congenital, familial and genetic disorders*)

- Nine terms representing familial alterations of lipid metabolism (to retrieve cases describing inborn disorder of lipoprotein metabolism that may have been aggravated (or improved))
- ICD-9 classification of “Disorders of lipoid metabolism” was also used as a reference
- During the 18-24 month review, the CIOMS WG development team confirmed that, based on the testing results, lipid investigation result terms that are relevant to this SMQ are: blood cholesterol, blood triglycerides, and hyperlipidemia. Other lipid test result terms did not retrieve cases of interest.

- Excluded:
  - Terms for lipid storage diseases, e.g., PT *Gaucher’s disease*
  - The following terms not directly pertinent to the scope of this SMQ: PT *Cholesterosis*, PT *Fat embolism*, all “lipoid” containing terms (e.g., PT *Pneumonia lipoid)*, PT *Lipid proteinosis*, PT *Lipaemia retinalis*, PT *Lipiduria*, PT *Lipoprotein deficiency*, and PT *Low density lipoprotein apheresis*

2.27.3 Notes on Implementation and/or Expectation of Query Results

Dyslipidaemia (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.27.4 List of References for *Dyslipidaemia (SMQ)*

- Harrison’s Principles of Internal Medicine, 16th Edition.
- Ross R: Atherosclerosis - an inflammatory disease. N Engl J Med 340:115-126, 1999.
- Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III – Third Report of the National Cholesterol Education Program (NCEP) NIH - U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES - NIH Publication No.02-5215, September 2002.

2.28 Embolic and thrombotic events (SMQ)

(Production Release March 2007)

2.28.1 Definition

- Thrombosis arises from the interplay of many influences. Virchow observed that the main influences in the pathogenesis of thrombosis are disturbances of the vessel wall, of the blood components, and of the dynamics of flow
- Thrombotic disorders are diseases characterized by formation of a thrombus that obstructs vascular blood flow locally or detaches and embolizes to occlude blood flow downstream
- Embolism is the sudden blocking of a vessel by a clot or foreign material which has been brought to its site of lodgement by the blood current.
- (Thrombo-)phlebitis is an inflammation of a vein (phlebitis) associated with thrombus formation (thrombosis).

2.28.2 Inclusion/Exclusion Criteria

- Included:
  - Embolism and thrombosis from HLGT *Embolism and thrombosis*
  - PT *Budd-Chiari syndrome* and PT *Paget-Schroetter syndrome*
  - Infarction- and stroke-related events
  - Terms that are procedure-related (e.g. PT *Thrombectomy*, PT *Thromboembolectomy*)
  - Prophylaxis terms related to embolism and thrombosis
  - Investigation terms related to embolism and thrombosis
  - Thrombophlebitis terms related to embolism and thrombosis
  - Terms referring to occlusion of arteries and veins associated with embolism and/or thrombosis
  - Terms referring to mesenteric events related to embolism and thrombosis
  - Amaurosis terms, PT *Cerebrovascular accident* and PT *Haemorrhagic infarction*
  - Terms referring to transient (ischemic) events related to embolism and thrombosis
  - Terms referring to diplegia, hemiparesis, hemiplegia, hemiplegia transient, monoparesis, monoplegia, paresis, paraparesis, paraplegia, quadriparesis and quadriplegia are included (terms referring to palsy, paresis, plegia and paralysis with no probable relationship to embolism and thrombosis are excluded)

- PT *Shunt occlusion*, PT *Thrombosis in device,* PT *Implant site thrombosis* and PT *Shunt thrombosis*
- Terms referring to embolism and thrombosis in the cerebrum or cerebellum

- Excluded:
  - Risk factor terms (e.g. related to hyperviscosity, or to hereditary, infective/septic or autoimmune causes)
  - Laboratory test terms without indication of result (i.e., the unqualified test term)
  - Air, cement and fat emboli terms
  - Terms for non-specific vessel anomalies
  - Terms referring to palsy, paresis, plegia and paralysis with no probable relationship to embolism and thrombosis (terms referring to diplegia, hemiparesis, hemiplegia, hemiplegia transient, monoparesis, monoplegia, paresis, paraparesis, paraplegia, quadriparesis and quadriplegia are included).

2.28.3 Hierarchy Structure

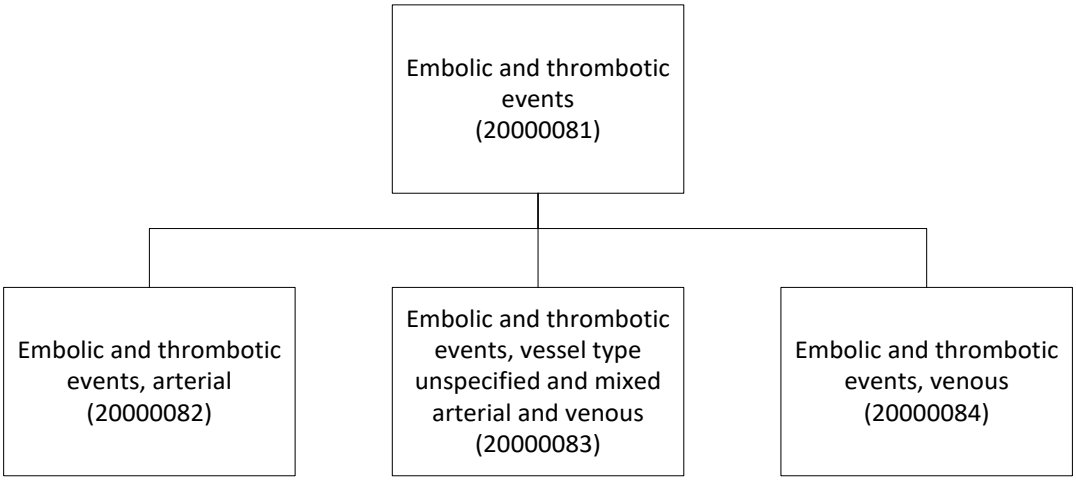

Figure 2-7. Hierarchy Structure of *Embolic and thrombotic events (SMQ)*

Embolic and thrombotic events (SMQ) (Level 1) is divided into three Level 2 sub-SMQs:

- Embolic and thrombotic events, arterial (SMQ) (PTs designated as narrow search terms)
- Embolic and thrombotic events, venous (SMQ) (PTs designated as narrow search terms)
- SMQ Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ) (PTs designated as broad search terms)

NOTE: The names of the sub-SMQs in the CIOMS WG documentation differ from this Introductory Guide summary as follows:

CIOMS WG Document	**This Document**
SMQ *Embolic and thrombotic events, arterial, venous, non-specific*	*Embolic and thrombotic events (SMQ)*
SMQ *Embolic and thrombotic events, arterial only*	*Embolic and thrombotic events, arterial (SMQ)*
SMQ *Embolic and thrombotic events, venous only*	*Embolic and thrombotic events, venous (SMQ)*
SMQ *Embolic and thrombotic events, non-specific*	*Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)*

Table 2-4. Link Table between CIOMS WG Document and SMQ Introductory Guide for *Embolic and thrombotic events (SMQ)*

- The term “sub-SMQ” corresponds to the “sub-group” as described in the CIOMS documentation.
- In order to get all relevant terms of embolism and thrombosis, it may be necessary to combine the sub-SMQs of this SMQ.

  Central nervous system vascular disorders (SMQ) [formerly, *Cerebrovascular disorders (SMQ)*], *Vasculitis (SMQ)*, and *Thrombophlebitis (SMQ)* should also be taken into consideration.

NOTE: In Version 14.0, *Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)* was modified in scope to include only narrow search terms. This SMQ formerly included only broad terms.

2.28.4 Notes on Implementation and/or Expectation of Query Results

The *Embolic and thrombotic events (SMQ)* is a hierarchical SMQ, and has only narrow terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.28.5 List of References for *Embolic and thrombotic events (SMQ)*

- Concise Oxford Textbook of Medicine. Ledingham, John G. G., Warrell, David A. 1st Edition © 2000 Oxford University Press.

2.29 Eosinophilic pneumonia (SMQ)

(Production Release March 2009)

2.29.1 Definition

- Eosinophilic pneumonias are characterized by accumulation of eosinophils in alveolar spaces, interstitium, or both. Peripheral eosinophilia is common.
- Causes include:
  - Infections (especially helminthic)
  - Drug-induced pneumonitis (e.g., antibiotics, phenytoin, l-tryptophan)
  - Inhaled toxins (e.g., cocaine)
  - Systemic disease (e.g., Churg Strauss syndrome)
  - Allergic bronchopulmonary aspergillosis
- Diagnosis based on:
  - Eosinophilia in peripheral blood (>450/µL), bronchoalveolar lavage fluid (>5% of differential), or lung biopsy
  - Opacities on chest X-ray (sometimes called PIE or pulmonary infiltrates with eosinophilia syndrome)
- Chronic eosinophilic pneumonia
  - Unknown etiology. Suspected to be allergic diathesis.
  - Fulminant illness with cough, fever, weight loss, accompanied by or preceded by asthma in 50% of cases
  - Bilateral peripheral pulmonary opacities described as “photographic negative” of pulmonary edema are virtually pathognomonic
- Acute eosinophilic pneumonia
  - Unknown etiology but may be acute hypersensitivity reaction to unidentified inhaled antigen
  - Acute febrile illness with cough, dyspnea, malaise, myalgias, night sweats, and pleuritic chest pain
- Loeffler’s syndrome
  - Characterized by absent or mild respiratory symptoms, fleeting migratory pulmonary opacities, and peripheral blood eosinophilia
  - Etiology may be parasitic infections, especially Ascaris lumbricoides, but identifiable agent often not found

2.29.2 Inclusion/Exclusion Criteria

- Included:
  - Specific terms related to eosinophilic pulmonary disease such as PT *Eosinophilic pneumonia,* PT *Pulmonary eosinophilia*, and PT *Loeffler's syndrome* are included in the narrow search
  - Terms for a variety of pulmonary conditions that are not specifically eosinophilic but possibly indicative of pneumonia are included in the broad search (e.g., PT *Alveolitis* and PT *Lung infiltration*)
  - Terms for clear clinical symptoms of pneumonia are included in the broad search (e.g., PT *Hypoxia* and PT *Hyperventilation*)
  - Based on testing with the algorithm, two very nonspecific terms, PT *Pneumonia* and PT *Myalgia*, are included in the broad search
  - Terms relating to peripheral blood eosinophils containing the word "abnormal" (e.g., PT *Eosinophil count abnormal*).
- Excluded:
  - All infections, fibrosis, sarcoidosis, and hemorrhage terms
  - Terms for nonspecific signs and symptoms of pneumonia (e.g., PT *Cough* and PT *Dyspnoea*)
  - Terms for eosinophilic conditions elsewhere than the lung (e.g., PT *Eosinophilic colitis,* PT *Eosinophilic myocarditis*)
  - Terms relating to peripheral blood eosinophils containing the word "normal" (e.g., PT *Eosinophil count normal*)
  - Terms relating to peripheral blood eosinophils without a qualifier (e.g., PT *Eosinophil count*)
  - Neonatal terms
  - Terms indicating an inherited disorder
  - Terms for tumors or malignancies of the lung

NOTE: Two nonspecific terms, PT *Pneumonia* and PT *Myalgia*, are included in the broad search. If the broad search is used without the algorithm, these terms may need to be excluded as being too noisy.

2.29.3 Algorithm

Eosinophilic pneumonia (SMQ) consists of:

- Narrow search (Category A or narrow scope) containing specific PTs that describe eosinophilic pneumonia
- Broad search contains additional terms (broad scope) which are added to those included in the narrow search. The broad scope terms are divided into two categories:
  - Category B: Eosinophilia terms
  - Category C: Terms possibly indicative of pneumonia and the two nonspecific terms PT *Pneumonia* and PT *Myalgia*.

Cases to be selected for further review would include any cases reporting at least one of the PTs listed for Category A (narrow scope terms) or any case reporting a combination of at least one PT from each of the two groups of PTs listed as Categories B and C of broad scope terms. A or (B and C).

2.29.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Eosinophilic pneumonia (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow and broad searches (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Eosinophilic pneumonia (SMQ)* is A or (B and C). Cases filtered by the algorithm can be listed for output.

2.29.5 List of References for *Eosinophilic pneumonia (SMQ)*

- The Merck Manual assessed online as http://www.merck.com/mmpe/sec05/ch055/ch055d.html .
- Harrisons Principles of Internal Medicine, McGraw Hill accessed online as http://www.accessmedicine.com/search/searchAMResult.aspx?searchStr=Eosinophilic+pneumonia+&rootTerm=eosinophilic+pneumonias&searchtype=1&rootID=12837&gobacklink=1&drug=1

2.30 Extrapyramidal syndrome (SMQ)

(Production Release March 2007)

2.30.1 Definition

- Drug-induced movement disorders may occur in association with levodopa or dopamine agonist therapy or drugs with central dopamine receptor antagonist properties, anticholinergic drugs, some anticonvulsant drugs, and amphetamines
- Definition: disturbance of motor function caused by lesions or dysfunctions of the extrapyramidal motor system
  - May present as hyperkinetic-hypotonic or as akinetic-rigid disorder
- Drug-induced Parkinsonism, dystonia, akathisia, and tardive dyskinesia, and their associated clinical findings are included concepts in this SMQ.
- Sub-SMQs for:
  - Akathisia: subjective feelings of restlessness, objective signs of restlessness, or both
  - Dyskinesia (including tardive dyskinesia): involuntary choreoathetoid movements commonly involving orofacial region, fingers, and toes. Athetoid movements of head, neck, and hips may also occur.
  - Dystonia: brief or prolonged contractions of muscles resulting in abnormal movements or postures, including oculogyric crises, tongue protrusion, trismus, torticollis, laryngeal-pharyngeal dystonias, and dystonic postures of the limbs and trunk
  - Parkinson's-like events: triad of resting tremor, rigidity and bradykinesia that can appear identical to Idiopathic Parkinson's disease. Other Parkinson's-like features include bradyphrenia (slowed thinking), excessive salivation, drooling, shuffling gait, micrographia, hypophonia, and diminished postural reflexes.

2.30.2 Inclusion/Exclusion Criteria

- Included:
  - Parkinson's disease and parkinsonism terms, including clinical signs and symptoms
  - Other forms of extrapyramidal disorders such as non-Parkinson-associated tremors, focal dystonias (e.g., torticollis), drug-associated movement disorders (e.g., tardive dyskinesia), and akathisia
  - Neonatal terms related to the above
  - Associated investigations

- PT *Tremor* created some “noise” in phase I testing; however, due to its power to pick up most of the reports in the positive controls during phase I testing, this PT remains in the list of terms selected for this SMQ.
- PT *Blepharospasm* is included in subgroup *Dystonia (SMQ)*: Although PT *Blepharospasm* has been included in subgroup *Dystonia (SMQ)*, there had been some post-testing discussion about the utility of this broad search term to the SMQ overall. Thus, the WG team would greatly appreciate users’ comments on the utility of this particular term.

- Excluded:
  - Progressive supranuclear palsy
  - Cortical-basal ganglionic degeneration
  - Striatonigral degeneration
  - Machado-Joseph disease (spinocerebellar ataxia type 3)
  - Neuroleptic malignant syndrome
  - Tourette’s disorder
  - Tremor of non-extrapyramidal origin (essential tremor, intention tremor, head titubation)
  - PT *Excessive eye blinking*
  - PT *Restless legs syndrome*
  - PT *Myotonia*
  - PT *Dyspnoea*
  - Terms for neonatal Parkinson-like events (e.g., PT *Foetal hypokinesia*)

2.30.3 Hierarchy Structure

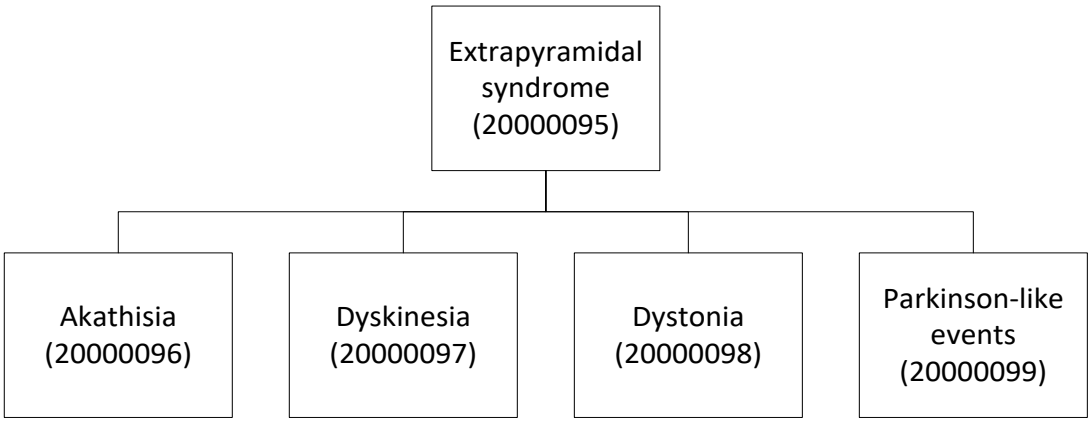

Figure 2-8. Hierarchy Structure of *Extrapyramidal syndrome (SMQ)*

2.30.4 Notes on Implementation and/or Expectation of Query Results

Extrapyramidal syndrome (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.30.5 List of References for *Extrapyramidal syndrome (SMQ)*

- Stedman's Medical Dictionary, 27th edition, 2000.
- Harrison's Principles of Internal Medicine, 14th edition, 1998, p 2356 – 63.
- CIOMS, Reporting Adverse Drug Reactions, 1999, p 29 – 30.
- Kaplan & Sadock's Synopsis of Psychiatry: Behavioral sciences and clinical psychiatry, 8th edition, 1998, pp 955-963.
- The case of the frozen addicts by J W Langston and Jon Palfreman – Publisher New York: Pantheon Books © 1995 ISBN: 0679424652 OCLC: 31608154.

2.31 Extravasation events (injections, infusions and implants) (SMQ)

(Production Release September 2007)

2.31.1 Definition

- Extravasation of drug product administered by venous access is a local complication can be associated with pain and swelling
  - Can be associated with pain and swelling
  - Some products (*e.g.*, certain chemotherapeutic agents) may be associated with more serious sequelae including tissues necrosis
- May be caused by:
  - Damage to posterior wall of vein or occlusion of vein proximal to injection site
  - Occlusion of vein proximal to injection site
- Extravasation broadly defined as discharge or escape of blood or other fluid normally found in a vessel or tube, into surrounding tissues
  - For purposes of this SMQ, “extravasation” relates to complication of drug delivery (injection, effusion, etc.) or to a device
  - Includes potential sequelae of extravasation
  - Pain, erythema, and swelling are typically observed

2.31.2 Inclusion/Exclusion Criteria

- Included:
  - Terms with “extravasation” that are related to drug delivery or devices
  - PT *Extravasation*
    - PT *Extravasation* is unassociated with any drug delivery mechanism (it is in SOC *General disorders and administration site conditions*)
    - Based on pharmaceutical company testing results, it retrieved cases of interest and was determined to be suitable for inclusion
  - Terms with “injection”, “infusion”, “implant”, “catheter,” “vascular access,” and “device” when combined with “induration”, “edema”, “effusion”, “swelling”, “irritation”, “necrosis”, and “ulcer”
    - Individual terms with such combinations were subsequently selected for inclusion based on their relevance to scope of SMQ
  - For future maintenance of this SMQ, PT terms with “instillation” could be considered for inclusion if they fit definition of SMQ
  - Terms for administration site pain and erythema (see NOTE below)
- Excluded:

- PT *Extravasation blood* and PT *Extravasation of urine*
- PT *Contrast media reaction*
- PT *Wrong technique in product usage process*
- PT *Systemic leakage*
- "Application site" terms (See NOTE below)
- PT *Injection site reaction* and other plain "site reaction" PTs (*e.g.*, PT *Infusion site reaction*) as these are non-specific

NOTE: Administration site pain and erythema are symptoms of extravasation (and are currently included in this SMQ) but can occur without it. These terms could retrieve more cases of interest than is practical in certain databases, depending on coding practices. This should be borne in mind when applying this SMQ.

NOTE: In general, "application site" terms are considered not appropriate for the scope of this SMQ, even though they did retrieve a few cases of interest during pre-production testing. MedDRA users should consider – based on their own data – if "application site" terms may have been used when coding cases related to extravasation and include relevant terms as needed.

NOTE: Users should consider including cases coded to LLT *Catheter related complication*. This term is not currently linked to an included PT in this SMQ, but may retrieve cases of interest.

2.31.3 Notes on Implementation and/or Expectation of Query Results

Extravasation events (injections, infusions and implants) (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.31.4 List of References for *Extravasation events (injections, infusions and implants) (SMQ)*

- Brown, S. Complications with the Use of Venous Access Devices. U.S. Pharmacist. http://www.uspharmacist.com/ http://www.uspharmacist.com/oldformat.asp?url=newlook/files/Feat/ACF2FF9.cfm&pub_id=8&article_id=131.
- Stedman's Medical Dictionary, 27th Edition, 2000.
- Wickham, R. Long-Term Central Venous Catheters: Issues for Care. *Semin Oncol Nurs* 1992;8,2(May):133-147.

2.32 Fertility disorders (SMQ)

(Production Release September 2011)

2.32.1 Definition

- During the development of *Pregnancy and neonatal topics (SMQ)*, the CIOMS SMQ Working Group agreed that “fertility disorders” should be developed into a Level 1 SMQ
- Infertility:
  - Failure to conceive (regardless of cause) after 1 year of unprotected intercourse
  - Up to 15% of couples of reproductive age are affected
  - Trend by many women to delay child-bearing is also a factor
- Both male and female factors are involved in infertility, each gender accounting for approximately 35% of cases
  - Combination of male and female factors accounts for 20% of infertility cases
  - In remaining 10%, etiology is not known.
- Some couples have normal results of standard infertility tests for infertility; postulated etiologies are:
  - Dysfunctional interaction between sperm and oocyte
  - Poor quality of embryo
  - Disruption at implantation site
- Identifying a mutation or absence of a specific gene as reason for infertility may be possible in the future
- Certain lifestyle factors have been linked to risk of infertility:
  - Environmental and occupational factors
  - Toxic effects related to tobacco, marijuana, or other drugs
  - Excessive exercise
  - Inadequate diet associated with extreme weight loss or gain
  - Advanced age
- Drugs associated with development of infertility are:
  - Antineoplastic therapies (cyclophosphamide, chlorambucil, etc.)
  - Combinations of antineoplastic agents and steroid drugs
  - Certain antibiotics
  - Thyroid supplements
  - Others

2.32.2 Inclusion/Exclusion criteria

- Included:
  - Terms for medical conditions reflecting fertility problems (e.g., PT *Premature follicular ripening*)

- Terms for procedures related to fertility (e.g., PT *In vitro fertilisation*)
- Terms for investigations (abnormal) related to fertility issues (e.g., LLT *Sperm count decreased*)

- Excluded:
  - Terms for sexual dysfunction that do not directly affect fertility (e.g., PT *Libido disorder*)
  - Terms for conditions that are the result of chromosomal abnormalities (e.g., PT *Klinefelter's syndrome*) or that are otherwise not likely to be drug associated (e.g., PT *Anorchism*)

NOTE: For users that wish to search data for sexual dysfunction events/cases, please note that almost all pertinent MedDRA terms can be found in two HLGTs, namely, HLGT *Sexual dysfunctions, disturbances and gender identity disorders* and HLGT *Sexual function and fertility disorders*.

2.32.3 List of References for *Fertility disorders (SMQ)*

- Puscheck, EE and Woodward, TL. Infertility. eMedicine, 21 December 2010, http://emedicine.medscape.com/article/274143-overview.
- Buchanan, JF and Davis, LJ. Drug-induced infertility. Drug Intell Clin Pharm, 1984, 18(2): 122 – 32.

2.33 Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)

(Production Release September 2007)

2.33.1 Definition

- The goal of this SMQ is gathering and ordering a number of gastrointestinal non-specific conditions
  - Constructed around symptoms frequently attributed to drugs, (*e.g.*, nausea, vomiting, dyspepsia, gastroesophageal reflux disease, diarrhea and constipation)
  - Applies to gastrointestinal tract from esophagus to rectum
- For this SMQ, “nonspecific” means conditions are possible manifestations of multiple diseases

2.33.2 Inclusion/Exclusion Criteria

- Included:
  - Any nonspecific functional condition affecting any part of the gastrointestinal tract
  - Nonspecific inflammatory manifestations affecting any part of the gastrointestinal tract
  - Nonspecific dysfunctional manifestations affecting any part of the gastrointestinal tract
  - Disorders relative to mucosal erosions
  - Terms from SOC *Investigations*
  - Terms from SOC *Surgical and medical procedures* have been included
- Excluded:
  - Any dysfunction or inflammation in oropharyngeal cavity
  - Inflammatory or dysfunctional conditions which are independent, well defined nosologic entities (e.g., PT *Crohn's disease* and PT *Colitis ulcerative* are not included) (See NOTE below)
  - Infective gastroenteritis

NOTE: To search for cases of more specific pathology, the following SMQs could be considered: SMQ *Acute pancreatitis*; SMQ *Gastrointestinal perforation, ulceration, haemorrhage or obstruction*; and SMQ *Pseudomembranous colitis*

NOTE: The term *Laxative abuse* was initially part of the narrow scope of *Gastrointestinal nonspecific dysfunction (SMQ)* as a PT. In Version 10.1, *Laxative*

abuse was demoted to an LLT under PT *Drug abuse*. In Version 20.0, PT *Drug abuse* was demoted under new PT *Drug use disorder*. PT *Drug use disorder* is considered too non-specific for *Gastrointestinal nonspecific dysfunction (SMQ)*. Therefore, the term *Laxative abuse* is no longer part of *Gastrointestinal nonspecific dysfunction (SMQ)*. If a user finds the term *Laxative abuse* to be helpful in case identification, LLT *Laxative abuse* could be added to the user's query

NOTE: In the original CIOMS WG documentation, the name of sub-SMQ *Gastrointestinal nonspecific symptoms and therapeutic procedures* was SMQ *Gastrointestinal non-specific symptomatology and therapeutic procedures*.

2.33.3 Hierarchy Structure

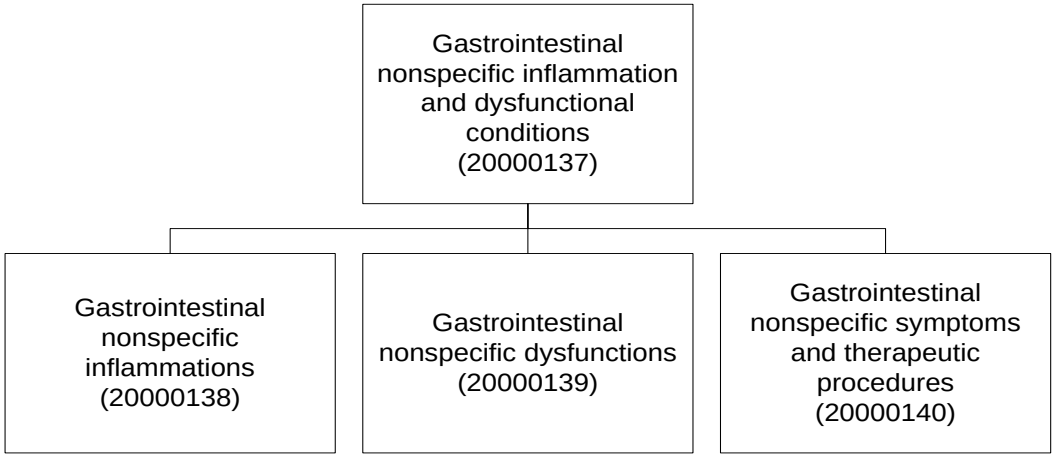

Figure 2-9. Hierarchy Structure of *Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)*

2.33.4 Notes on Implementation and/or Expectation of Query Results

Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.33.5 List of References for *Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)*

- Harrison's Principles of Internal Medicine, 16th Edition.
- Medline database.
- The Merck Manual.
- Dorland’s illustrated medical dictionary.

2.34 Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)

(Production Release September 2007)

2.34.1 Definition

- Gastrointestinal perforation:
  - Perforation: act of boring or piercing through a part or a hole made through a part or substance
  - Gastrointestinal perforation – perforation of all layers of gastrointestinal tract
    - Uncovered – in direct contact with the whole peritoneal cavity
    - Covered – localized by the omentum or other organs
  - Characterized by localized or diffused peritonitis
    - Manifested as generalized, rigidity of abdominal wall, severe pain and ileus

  Uncovered perforation is confirmed by demonstration of free gas in abdominal cavity (X-ray of diaphragmatic region with patient in upright position)
- Ulceration:
  - Local defect, or excavation, of surface of an organ or tissue
  - Produced by sloughing of inflammatory necrotic tissue
- Gastrointestinal hemorrhage:
  - Hemorrhage – escape of blood from any vessel or tissue
  - Gastrointestinal hemorrhage – escape of blood from any part of gastrointestinal tract
- Gastrointestinal obstruction:
  - Obstruction – act of blocking or clogging or state or condition of being clogged
  - Gastrointestinal obstruction – hindrance to passage of gastrointestinal contents

2.34.2 Inclusion/Exclusion Criteria

- Included:
  - Terms related to perforation of any part of gastrointestinal tract
  - Terms for ulcers of any part of gastrointestinal tract
  - Terms for obstruction and stenosis of any part of gastrointestinal tract: a possible consequence of scarring due to ulceration
  - Terms for hemorrhage of any part of gastrointestinal tract

- Terms for medical and surgical procedures and for diagnostic investigations related to perforation, ulceration, or hemorrhage
    - A group of non-specific diagnostic investigations and medical and surgical procedures have been included because the phase I test on a pharmaceutical company's database indicated that these terms were useful for identifying relevant cases.

- Excluded:
    - Terms related to gastrointestinal neoplasms, including malignant ulcers
    - Terms for taste disorders
    - Terms related to oropharyngeal lesions (user should consider *Oropharyngeal disorders (SMQ)*)
    - Terms for congenital disorders

NOTE: Prior to Version 16.1, the terms in *Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)* were broad scope only. In Version 16.1, the terms included in *Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)* have been reclassified to be either broad or narrow in scope.

NOTE: In Version 13.0, the following sub-search SMQs under *Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)* have been changed in scope from broad terms only to narrow terms only: *Gastrointestinal haemorrhage (SMQ)*, *Gastrointestinal obstruction (SMQ)*, *Gastrointestinal perforation (SMQ)*, and *Gastrointestinal ulceration (SMQ)*.

2.34.3 Hierarchy Structure

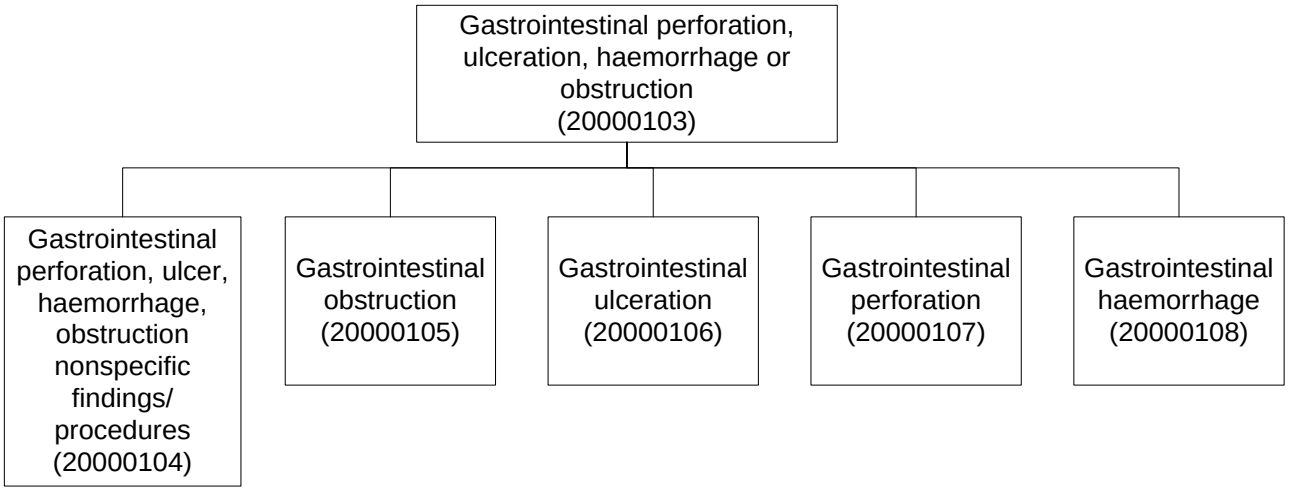

Figure 2-10. Hierarchy Structure of *Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)*

- Sub-SMQ *Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)* is referred to as SMQ *Non-specific investigations, medical and surgical procedures i*n the original CIOMS WG (pre-production) documentation.
- To retrieve all relevant cases related to gastrointestinal perforation, ulceration, haemorrhage, or obstruction, it may be necessary to combine the sub-SMQs, resulting in a broad search. Additionally, *Oropharyngeal disorders (SMQ)* should be taken into consideration.

2.34.4 Notes on Implementation and/or Expectation of Query Results

Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.34.5 List of References for *Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ)*

- Reporting Adverse Drug Reactions – Definitions of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS); 1999.
- Dorland's Illustrated Medical Dictionary – Saunders 2003, 30th Edition.

2.35 Generalised convulsive seizures following immunisation (SMQ)

(Production Release September 2012)

2.35.1 Definition

- *Generalised convulsive seizures following immunisation (SMQ)* was developed to address the occurrence of this form of seizure as an adverse event following immunization, in accordance with the Brighton Collaboration case definition for “Generalized convulsive seizure as an adverse event following immunization”

- “Seizure” is an abnormal paroxysmal discharge of cerebral neurons because of cortical hyperexcitability. Categories include:
  - Partial seizures (i.e., focal or localization related seizures)
  - Generalized seizures

- Generalized seizures are classified as:
  - Atonic
  - Tonic
  - Clonic
  - Tonic-clonic
  - Myoclonic
  - Absence

- Seizures are characterized by:
  - Sudden, involuntary muscular contractions
  - Sensory disturbances
  - Autonomic dysfunction
  - Behavioral abnormalities
  - Impairment or loss of consciousness

- Generalized convulsive seizure: patient becomes unconscious and has convulsions over whole body

- The Brighton Collaboration case definition of generalized convulsive seizure as AEFI describes the following levels of diagnostic certainty:
  - Level 1 of diagnostic certainty
    - Witnessed sudden loss of consciousness **AND**
    - Generalized, tonic, clonic, tonic-clonic, or atonic motor manifestations
  - Level 2 of diagnostic certainty
    - History of unconsciousness **AND**
    - Generalized, tonic, clonic, tonic-conic, or atonic motor manifestations
  - Level 3 of diagnostic certainty
    - History of unconsciousness **AND**
    - Other generalized motor manifestations

2.35.2 Inclusion/Exclusion criteria

- Included:
  - Terms that describe only forms of generalized convulsive seizures or that may have been used to code such as event (e.g., PT *Clonic convulsion*)
  - Terms for characteristic signs and symptoms of generalized convulsive seizures especially as related to level of consciousness and generalized motor manifestations (e.g., PT *Tonic clonic movements*)
  - Terms for events in line with the Brighton Collaboration (BC) definitions of and criteria for generalized convulsive seizures
- Excluded
  - Terms for forms of seizure where there may be loss of consciousness but without generalized motor manifestations (e.g., PT *Petit mal epilepsy*)
  - Terms for forms of epilepsy where etiology is established and/or unrelated to an Adverse Event Following Immunisation (AEFI) (e.g., PT *Myoclonic epilepsy and ragged-red fibres*)
  - Terms for investigations and procedures related to generalized convulsive seizures (e.g., PT *Electroencephalogram abnormal*). The rationale for this exclusion is that the BC definition states that generalized convulsive seizure after immunization is usually of short duration, and diagnosis is frequently based on clinical history alone. Also, investigations such as electroencephalograms (EEGs) are rarely available, and if available, interpretation is complex (inter-ictal sensitivity of EEGs is about 40%)

NOTE: Based on testing of *Generalised convulsive seizures following immunisation (SMQ),* **this SMQ is deemed not suitable for pharmaceutical products** as several previously “narrow” PTs that are relevant for those products are not present in this algorithmic SMQ.

2.35.3 Algorithm

To apply the algorithm for this SMQ, a report is considered a relevant case for further review if:

- It includes a term from Category A

OR

- It includes a term from Category B (terms related to level of consciousness and other neurological events) **and** a term from Category C (terms for motor manifestations and observed effects of generalized convulsions)

2.35.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Generalised convulsive seizures following immunisation (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Generalised convulsive seizures following immunisation (SMQ)* is A or (B and C). Cases filtered by the algorithm can be listed for output.

2.35.5 List of References for *Generalised convulsive seizures following immunisation (SMQ)*

- Ko, DY. Generalized tonic-clonic seizures. http://emedicine.medscape.com/article/1184608-overview

- Bonhoeffer, J et al. Generalized convulsive seizure as an adverse event following immunization: case definition and guidelines for data collection, analysis, and presentation. Vaccine 22 (2004) 557–562

2.36 Glaucoma (SMQ)

(Production Release March 2008)

2.36.1 Definition

- Group of eye diseases characterized by increase in intraocular pressure (IOP)
- Causes pathologic changes in optic disk and typical defects in field of vision
- Serious loss of vision and blindness can be prevented with early treatment
- Two main types:
  - Angle-closure glaucoma: drainage canals within eye are physically blocked
    - Acute form: sudden increase in IOP due to buildup of aqueous humor. Optic nerve damage and vision loss can occur within hours
    - Chronic form: may cause vision damage without symptoms
  - Open-angle glaucoma: drainage system remains open; may cause vision damage without symptoms
    - Most common form glaucoma
    - Symptoms include peripheral vision loss, mild, chronic headaches, blurred or foggy vision, difficulty adapting to darkness, and halos around lights
- Other types:
  - Normal (or low) tension glaucoma: optic nerve is damaged although IOP is consistently within normal range
  - Childhood glaucoma: rare; starts in infancy, childhood, or adolescence
    - Similar to open-angle glaucoma; few, if any, early symptoms
    - Blindness can result if left untreated
    - Thought to be inherited
  - Congenital glaucoma: usually appears soon after birth, although it may also occur in first year of life
    - Signs include tearing, light sensitivity, and cloudiness of cornea
    - More common in boys; can affect one or both eyes
  - Secondary glaucoma: increased IOP due to structural problem in eye
    - May be due to eye injury or other medical conditions
    - Treatment aimed at underlying cause and toward lowering IOP
- Causes of glaucoma

- Approximately 100,000 glaucoma cases in US have mutation of GLC1A gene (chromosome 1); speculated that gene product may be involved in eye pressure regulation
- Increased risk with elevated IOP, family history, ethnic background, and older age
    - African Americans have higher rates of glaucoma leading to blindness
    - Primary open-angle glaucoma is leading cause of blindness among African Americans and Alaska Natives, occurring 6-8 times more often than in whites, often in earlier stages of life
- Increased IOP is from either increased production or decreased drainage of aqueous humor; pressure may damage optic nerve
- Other factors may contribute as people with normal IOP can get vision loss from glaucoma. Also, some with high IOP never develop optic nerve damage

- Other symptoms include severe eye pain, facial pain, pupil non-reactive to light, eye redness, blurred vision, nausea, vomiting, abdominal pain, and bulging eye

2.36.2 Inclusion/Exclusion Criteria

- Included:
    - All PTs in HLGT *Glaucoma and ocular hypertension*
    - Terms for diagnostic and therapeutic procedures
    - Terms for related complications
    - Narrow search terms: Only diagnostic terms, signs and symptoms, laboratory findings and procedural terms that are specific or clearly related to glaucoma
    - Broad search terms: Signs, symptoms, diagnoses, and test results that are not exclusively specific to glaucoma but may have additional value by identifying potential cases
- Excluded:
    - Congenital terms, including terms for systemic congenital abnormalities (e.g. PT *Anterior chamber cleavage syndrome*, PT *Prader-Willi syndrome*)
    - SOC *Investigations* terms with qualifier “normal” and those with no qualifier
    - Terms for risk factors
    - Terms for causes of secondary glaucoma other than developmental, (e.g. iritis, uveitis, cataract, chemical or physical eye injuries)

- Terms for headache, nausea, and vomiting (too broad)

NOTE: This SMQ is one of several SMQs developed or under development for ophthalmological disorders. When the entire set of SMQs is developed, a search may require use of more than one SMQ, or the entire group of SMQs, depending upon the goal of the search.

2.36.3 Notes on Implementation and/or Expectation of Query Results

Glaucoma (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.36.4 List of References for *Glaucoma (SMQ)*

- Dorland's Medical Dictionary.
- Merck Manual, Sec.8, Ch.100, Glaucoma. http://www.merckmanuals.com/professional/index.html
- http://www.emedicinehealth.com/glaucoma_overview/article_em.htm
- http://www.ncbi.nlm.nih.gov/disease/Glaucoma.html
- Edward B. Feinberg, MD, MPH, Glaucoma, Encyclopedia update 7/24/2004.
- http://www.nlm.nih.gov/medlineplus/ency/article/001620.htm#Definition.
- e-Medicine – Glaucoma, Secondary Congenital – Article by Inci Irak, MD last updated December 1, 2005 www.emedicine.com/oph/topic141.htm.

2.37 Guillain-Barre syndrome (SMQ)

(Production Release September 2007)

2.37.1 Definition

- Guillain-Barre syndrome (GBS) is an immune-mediated, acute inflammatory demyelinating polyneuropathy (AIDP)
- Condition commonly follows a viral or mycoplasmal illness affecting the upper respiratory or alimentary tracts
- Other antecedent events include certain vaccinations
- Immune responses directed toward infecting organisms likely cross-react with neural tissues including Schwann cell surface membrane (resulting in AIDP) or axonal membrane (acute axonal forms)
- GBS is usually characterized by:
  - Weakness or paralysis affecting more than one limb, usually symmetrically
  - Loss of tendon reflexes
  - Increased cerebrospinal fluid (CSF) protein without pleocytosis
- Other features may include:
  - Motor and sensory involvement
  - Facial or cranial nerve involvement
  - Electrophysiologic evidence of demyelination
- Acute form of GBS has a typically rapid evolution from hours to days, usually reaching maximum level of weakness within four weeks
- Condition is classified as chronic inflammatory demyelinating polyneuropathy (CIDP) if patient's symptoms continue to progress beyond 4 weeks, or relapses occur. Peak disability in CIDP usually occurs in two months.

2.37.2 Inclusion/Exclusion Criteria

- Included:
  - PT *Guillain-Barre syndrome*, terms reflective of sub-types of GBS (*e.g.*, PT *Miller Fisher syndrome*) and terms synonymous with GBS (*e.g.*, PT *Chronic inflammatory demyelinating polyradiculoneuropathy*)
  - Paralysis and paresis terms (excluding congenital and non-symmetrical terms, *e.g.*, PT *Hemiparesis*)
  - Weakness/ muscular weakness and musculoskeletal terms (*e.g.*, PT *Hypotonia*, PT *Muscular weakness*, and PT *Asthenia*)

- Related neurological and neuromuscular disorders (*e.g.*, PT *Demyelination* and PT *Radiculopathy*)
- Neurological signs and symptoms (*e.g.*, PT *Areflexia* and PT *Loss of proprioception*)
- Sensory and motor deficits (*e.g.*, PT *Extensor plantar response* and PT *Sensorimotor disorder*)
- Investigation terms supportive of GBS diagnosis (*e.g.*, PT *CSF protein increased* and PT *Electromyogram abnormal*)

- Excluded:
  - Congenital terms
  - Trauma and injury terms (*e.g.*, PT *Peripheral nerve injury*)
  - Broad pain terms (*e.g.*, PT *Back pain*)
  - Hemiparalysis / hemiparesis terms
  - Histopathology procedures – nerve and muscle (except PT *Biopsy peripheral nerve abnormal*)
  - Therapies for GBS (*e.g.*, PT *Plasmapheresis*)

2.37.3 Algorithm

NOTE: Cases of interest can be retrieved without the algorithm. Several algorithms were tested by the CIOMS WG during development of this SMQ, and none of them were found to be superior. Because of this, an algorithm and categories are not included in the data files. However, application of an algorithm may be helpful when it is expected that a large number of cases will be retrieved by broad scope terms. Users who are interested in implementing an algorithmic approach for this SMQ are encouraged to refer to the CIOMS WG documentation (https://www.meddra.org/standardised-meddra-queries) for detailed information on an algorithm for this SMQ, including category term lists.

Despite the difficulty for the CIOMS WG in selecting an algorithm, they asked the MSSO to document the following recommended approach:

Cases to be selected for further review would include any cases meeting any one of the criteria listed below:

- At least one of the PTs listed for Category A (narrow scope) or
- Any case reporting at least two PTs from Category B or
- Any case reporting at least one PT from Category B and at least one PT from Category C or
- Any case reporting at least one PT each from Categories B, C, and D

- Certain drugs with high numbers of reports for terms such as paresthesias, hypoesthesias and muscular weakness, do capture more “noise” with the algorithm 2B and 1B+1C. It is recommended that for products such as these algorithm 1B + 1C + 1D is used is as it can eliminate much “noise” resulting in false hits.

Categories are defined as follows:

- Category A (Narrow scope)
  - PT *Chronic inflammatory demyelinating polyneuropathy*, PT *Demyelinating polyneuropathy*, PT *Guillain-Barre syndrome*, and PT *Miller Fisher syndrome*, which represent GBS and sub-types of GBS
- Category B (Broad)
  - Very commonly seen signs and symptoms from well-documented cases of Guillain-Barre syndrome and its variants (*i.e*., Category A) based on testing from pharmaceutical company and Regulatory Authority databases. Also, includes specific types of paresthesias and hypoesthesias. Most terms relate to paresthesias, hypoesthesias and neuropathies.
- Category C (Broad)
  - Commonly seen signs, symptoms and diagnostic laboratory work from well-documented cases of Guillain-Barre syndrome and its variants based on testing
- Category D (Broad)
  - Less frequently seen signs, symptoms and diagnostic laboratory work based on testing and signs, symptoms and diagnostic laboratory work that may be seen in Guillain-Barre syndrome and its variants, but were not observed in the databases tested

2.37.4 Notes on Implementation and/or Expectation of Query Results

Guillain-Barre syndrome (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.37.5 List of References for *Guillain-Barre syndrome (SMQ)*

- Textbook of Clinical Neurology, 2nd Edition, pp1085-1089, 2003.
- Cecil Textbook of Medicine, 22nd Edition, pp 2379-2381, 2004.
- Harrison’s Internal Medicine, 16th Edition, pp 2513-2518, 2005.
- Ferri F. Guillain-Barré syndrome. *Ferri’s Clinical Advisor: Instant Diagnosis and Treatment,* 2006 ed. Available at http://www.mdconsult.com/php/231760506-2/homepage

- Cha-Kim A. Guillain-Barré syndrome. *eMedicine*. Available at http://www.emedicine.com/pmr/topic48.htm. Accessed May 22, 2006.
- Aarli JA. Role of Cytokines in Neurologic Disorders. *Current Medicinal Chemistry.* 2003; 10:1931-1937.
- Stedman's Medical Dictionary. 26th edition. Williams & Wilkins. Baltimore, MD; 1995.

2.38 Haematopoietic cytopenias (SMQ)

(Production Release November 2005)

2.38.1 Definition

- Definitions and classifications of inherited and acquired bone marrow failure provided in standard medical textbooks could not be used as a basis for the definition of this SMQ
  - Those classifications do not differentiate between inherited diseases and acquired conditions
  - They include a number of premalignant or malignant conditions
- There are CIOMS definitions of terms and usage criteria for aplastic anemia, agranulocytosis, bone marrow depression, granulocytopenia, leukopenia, neutropenia, and pancytopenia; however, it was not possible to strictly follow those definitions
  - The definitions include signs and symptoms of cytopenic conditions
  - Some are nonspecific and are not considered worthwhile even for a broad SMQ search
  - Furthermore, the definitions include distinct ranges of laboratory values which are not reflected in MedDRA terms

2.38.2 Inclusion/Exclusion Criteria

- Included:
  - Terms referring to direct alterations of the hematopoiesis
  - Hematological signs and diagnoses of bone marrow depression
  - Hematological investigation results of bone marrow depression
  - Specific diagnostic procedures
  - “Neonatal” terms are included in the broad searches (the term “neonatal” does not allow a conclusion whether the condition is of acquired or inherited origin)
  - Certain “abnormal” terms are included in the broad searches
- Excluded:
  - Clinical signs and symptoms
  - Therapeutic procedure such as bone marrow transplant or stem cell transplant (because they are nonspecific)
  - Strictly inherited (and thus not drug-induced) bone marrow diseases

- Terms referring to hemolytic anemia, antibody associated anemia, iron deficiency anemia, and megaloblastic anemia
- Agranulocytosis is addressed in a separate SMQ.
- In general, inherited premalignant and malignant conditions are excluded.

NOTE: In Version 15.1, PT *Haemoglobin decreased* and PT *Haemoglobin abnormal* were each added as broad search terms to PT to *Haematopoietic erythropenia (SMQ)*, on the basis of comprehensive testing using a wide variety of drug data. Please be aware that although these terms were successful in identifying cases of interest, they also were frequently associated with reports unrelated to hematopoietic erythropenias.

NOTE: In Version 14.0, the word "haematopoietic" was added to the names of three sub-SMQs of *Haematopoietic cytopenias (SMQ)* to reflect the focus of these SMQs on disorders of **production,** and not destruction, of blood cells. The name of sub-SMQ *Cytopenia and haematopoietic disorders affecting more than one type of blood cell (SMQ)* was also slightly modified:

Original SMQ Name	New SMQ Name in MedDRA v14.0
Cytopenia and haematopoietic disorders affecting more than one type of blood cell	*Haematopoietic cytopenias affecting more than one type of blood cell*
Erythropenia	*Haematopoietic erythropenia*
Leukopenia	*Haematopoietic leukopenia*
Thrombocytopenia	*Haematopoietic thrombocytopenia*

Table 2-5. Modifications of sub-SMQ names under *Haematopoietic cytopenias (SMQ)* in V. 14.0

2.38.3 Hierarchy Structure

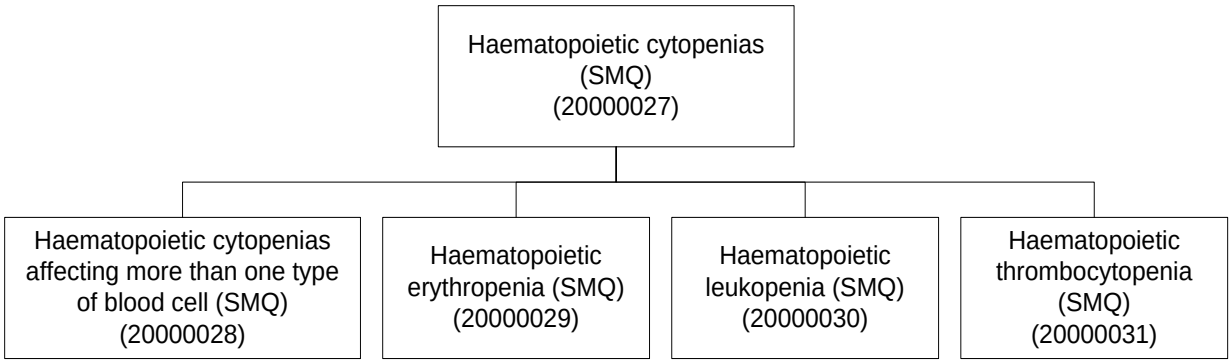

Figure 2-11. Hierarchy Structure of *Haematopoietic cytopenias (SMQ)*

2.38.4 Notes on Implementation and/or Expectation of Query Results

Haematopoietic cytopenias (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.38.5 List of References for *Haematopoietic cytopenias (SMQ)*

- CIOMS publication, “Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use”.

2.39 Haemodynamic oedema, effusions and fluid overload (SMQ)

(Production Release March 2008)

2.39.1 Definition

- Drug-induced edema has been described for a number of medications
- Mechanisms:
  - Enhanced sodium and water reabsorption by kidneys
  - Potent vasodilators and calcium channel blockers (cause capillary leakage)
  - Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit renal prostaglandin synthesis
  - Other drug products associated with peripheral edema:
    - Antidepressants
    - Estrogens
    - Corticosteroids
    - COX-2 inhibitors
- Edema definition:
  - Presence of abnormally large amounts of fluid in intercellular tissue spaces
  - Usually refers to demonstrable amounts of fluid in subcutaneous tissues
  - May be localized (due to venous or lymphatic obstruction or increased vascular permeability) or systemic (due to heart failure or renal disease)
  - Sometimes designated by other terms according to site (ascites, hydrothorax, or hydropericardium)
  - Massive generalized edema is called anasarca
  - Synonyms: dropsy and hydrops
- Effusion definition:
  - Escape of fluid from lymphatics or blood vessels into a cavity or tissues
  - Results from altered hydrostatic forces

2.39.2 Inclusion/Exclusion Criteria

- Included:
  - Terms consistent with definition, including terms for specific cavities and body sites (e.g., PT *Ascites*)

- Terms for therapy or management of edema (e.g., PT *Cerebral oedema management*)
- Terms for fluid or volume overload conditions (*e.g*., PT *Hypervolaemia*)
- Terms for device- and administration-associated edemas and effusions (*e.g*., PT *Catheter site oedema*)

- Excluded:
  - Terms related to procedure-associated edema, *e.g*., PT *Post procedural oedema*
    - Exception: administration- and device-associated edema (*e.g*., PT *Catheter site oedema* is **included**)
  - Terms for edema that have remote or improbable association therapy (*e.g*., PT *Pulmonary oedema post fume inhalation*)
  - Eye-related edema, swelling, and effusion terms
  - PT *Oedematous pancreatitis* and PT *Neoplasm swelling*
  - PT *Peripheral venous disease*
    - LLT *Venous oedema* and LLT *Venous edema* were added to MedDRA Version 9.1, and are currently linked to PT *Peripheral venous disease*. Because peripheral vascular disease and venous insufficiency are unlikely to be drug-associated, such terms are excluded
  - Angioneurotic oedema as it is due to a well described immune-mediated phenomenon
  - Many of the terms that are in existing SMQ *Angioedema,* particularly the ones that are relatively characteristic of that condition:
    - PT *Allergic oedema,* PT *Breast oedema,* PT *Circumoral oedema,* PT *Lip oedema,* PT *Epiglottic oedema,* PT *Face oedema,* PT *Gingival oedema,* PT *Laryngeal oedema,* PT *Laryngotracheal oedema,* PT *Nasal oedema,* PT *Nipple oedema,* PT *Oedema genital,* PT *Oedema mouth,* PT *Palatal oedema,* PT *Periorbital oedema,* PT *Pharyngeal oedema,* PT *Scrotal oedema,* PT *Tongue oedema,* PT *Tracheal oedema,* PT *Vaginal oedema,* PT *Vulval oedema,* PT *Gingival swelling,* PT *Oropharyngeal swelling,* PT *Auricular swelling,* PT *Breast swelling,* PT *Nipple swelling,* PT *Penile swelling,* PT *Scrotal swelling,* PT *Lip swelling,* PT *Swelling face*, and PT *Swollen tongue*.

2.39.3 Notes on Implementation and/or Expectation of Query Results

Haemodynamic oedema, effusions and fluid overload (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.39.4 List of References for *Haemodynamic oedema, effusions and fluid overload (SMQ)*

- Schroth, BE. Evaluation and management of peripheral edema. J Amer Acad Phys Assist, www.jaapa.com/.
- Harrison's Internal Medicine.
- Dorland's Medical Dictionary.
- Stedman's Medical Dictionary 27th Edition, 2000.

2.40 Haemolytic disorders (SMQ)

(Production Release April 2005)

2.40.1 Definition

- Hemolytic disorder is defined as anemia with signs of premature destruction of red blood cells and compensatory erythroid hyperplasia.
- Hemolytic anemia is characterized by
  - Increased reticulocyte values
  - Increased unconjugated serum bilirubin
  - Decreased (or absent) serum haptoglobin
- Causes can be grouped as follows:
  - Internal abnormalities of red blood cells (e.g., enzyme defects, hemoglobinopathies)
  - Abnormalities of the red cell membrane (e.g., hereditary spherocytosis, paroxysmal nocturnal hemoglobinuria, spur cell anemia)
  - Extrinsic factors (e.g., splenomegaly, drug-induced antibodies, microangiopathic hemolysis, infections, toxins)

2.40.2 Inclusion/Exclusion Criteria

- Narrow scope: terms indicating hemolysis, i.e., containing the words “haemolysis” or “haemolytic,” are generally included. Blood group incompatibilities as well as immunological signs or test results indicative for hemolysis are also included. The above conditions associated with “newborn” are included.
- Broad scope: a few additional terms of laboratory findings which are potentially, but not necessarily, due to hemolysis, are included.
- PT *Reticulocytosis* is defined as broad scope due to its minimum value based on Phase I testing.
- Non-specific symptoms of anemia, such as fatigue, have generally been excluded.
- Other signs, symptoms, and investigation findings that are not specific to hemolytic anemia, such as jaundice, icterus, flow murmur, increased LDH, anemia (not otherwise specified), and bilirubinemia (not otherwise specified) are excluded.
- The various types of hemoglobinopathies were generally excluded. Hemolysis under such circumstances is one of the clinical expressions due to the underlying hemoglobinopathy rather than being influenced by drug treatment.

- Predisposing factors, such as inherited red blood cell enzyme abnormalities and cell membrane defects, are excluded. However, PT *Glucose-6-phosphate dehydrogenase deficiency* is not excluded, because haemolytic anemia is a very frequent manifestation of glucose-6-phosphate dehydrogenase deficiency.

- Infection or intoxication terms that do not have “hemolysis” or “hemolytic” stated explicitly are excluded.

2.40.3 Notes on Implementation and/or Expectation of Query Results

Haemolytic disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.40.4 List of References for *Haemolytic disorders (SMQ)*

- Reporting Adverse Drug Reactions. Definitions and criteria for their use. CIOMS publication, Geneva, 1999.

2.41 Haemorrhages (SMQ)

(Production Release March 2006)

2.41.1 Definition

- Hemorrhage is the escape of blood from the vessels; bleeding.
- Small hemorrhages are classified according to size as petechiae (very small), purpura (up to 1cm), and ecchymoses (larger).
- A large accumulation of blood within a tissue is called a hematoma.

2.41.2 Inclusion/Exclusion Criteria

- Included:
  - Terms explicitly referring to hemorrhage, hematoma, bleeding, ecchymosis, purpura, petechiae, treatment for hematoma/bleeding/hemorrhage, and rupture of blood vessels, including the heart and its chambers.
  - PT *Blood urine* was included in *Haemorrhage terms (excl laboratory terms) (SMQ),* and in *Haemorrhage laboratory terms (SMQ)*, although it could be interpreted as a laboratory test only without stating explicitly that blood was present in urine.
    - This term is usually used in order to describe the finding of blood in urine.
    - Note: Coders should have chosen PT *Blood urine present* if the intent was to code blood being present in the urine (macroscopically even without test).

- Excluded:
  - Terms referring to gastrointestinal obstructions
  - Terms referring to ulcers and perforations without explicit mentioning of bleeding
  - Normal values of laboratory test terms, except PT *Blood urine* because it could be a sign of blood in urine instead of only an unqualified investigational term (see above)
  - Hemorrhagic fever terms (e.g., PT *Bolivian haemorrhagic fever*) as they are of infectious etiology and are not related to adverse drug reactions
  - PT *Cardiac tamponade*, because the PT *Pericardial haemorrhage* is already included in this SMQ and sufficiently describes this event

2.41.3 Hierarchy Structure

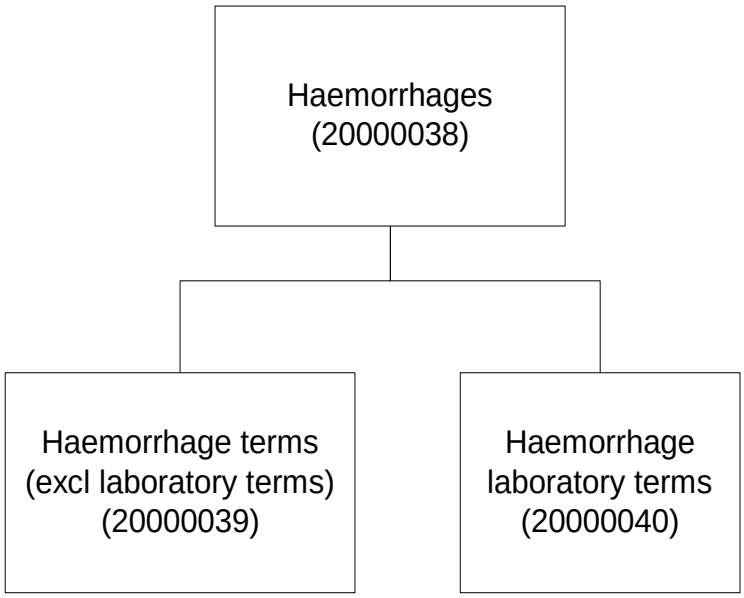

Figure 2-12. Hierarchy Structure of *Haemorrhages (SMQ)*

This SMQ is a two-level hierarchy consisting of a comprehensive search for hemorrhages (first level) and two sub-SMQs (second level), namely:

- *Haemorrhage terms (excl laboratory terms) (SMQ)*
- *Haemorrhage laboratory terms (SMQ)*

(NOTE: Sub-SMQ *Haemorrhage terms (excl laboratory terms) (SMQ)* corresponds to the “Haemorrhage, narrow” search described in the CIOMS documentation.)

2.41.4 Notes on Implementation and/or Expectation of Query Results

Haemorrhages (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.41.5 List of References for *Haemorrhages (SMQ)*

- Dorland’s illustrated medical dictionary, Saunders, Philadelphia, 2000.

2.42 Hearing and vestibular disorders (SMQ)

(Production Release March 2009)

2.42.1 Definition

- SMQ is intended to include ear disorders that may be drug related
- Two sub-SMQs created for two functions of ear:
  - Hearing
  - Balance
- Hearing may be impaired, disturbed, or accentuated
  - Hearing loss and abnormal hearing are not separated in this SMQ due to overlap of the these conditions in certain patients
- In this SMQ, included terms are for vestibular disorders generally that originate from inner ear
- Definition: hearing – ability to perceive sound; sensation of sound as opposed to vibration
  - Hearing impairment may result from:
    - A lesion in external auditory canal or middle ear (conductive hearing loss); **or**
    - A lesion in inner ear or VIIIth cranial nerve (sensorineural)
  - Sensorineural hearing loss can be further differentiated as:
    - Sensory (cochlea); **or**
    - Neural (VIIIth cranial nerve)
- Definition: vestibular – related to vestibule of ear
  - Vestibular (inner ear) disorders can cause:
    - Dizziness, vertigo, imbalance, hearing changes, nausea, fatigue, anxiety, difficulty concentrating, and other symptoms
  - Other effects on person's day-to-day functioning, ability to work, relationships with family and friends, and quality of life

2.42.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for hearing disturbances of any type (loss as well as accentuation/hyperacusis)
  - Terms for balance disorders originating in inner ear
  - Narrow search terms included diagnoses

- Terms for signs, symptoms, and procedures are generally included in broad search

- Excluded:
  - Terms for disorders that originate from higher centers in the central nervous system
  - Terms for congenital causes
  - Terms for infections/infectious causes
  - Neoplasm terms
  - Terms for CNS disorders that result in hearing problems (e.g., cerebrovascular accident) or balance problems (e.g., cerebellar disorders)
  - Terms for conditions resulting from physical trauma (e.g., PT *Deafness traumatic)*

NOTE: Although dizziness has many causes and clearly can contribute noise, it was suggested to leave PT *Dizziness* in the broad search (of sub-SMQ *Vestibular disorders (SMQ)*) as "vertigo" and "dizziness" may be used interchangeably.

2.42.3 Hierarchy Structure

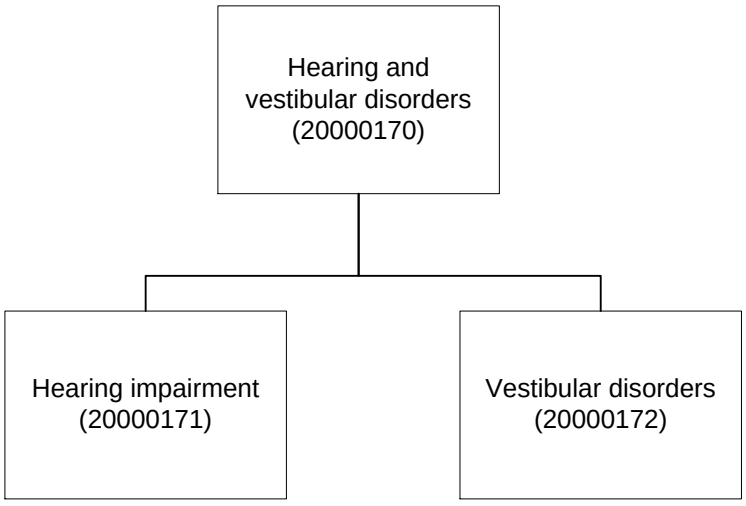

Figure 2-13. Hierarchy Structure of *Hearing and vestibular disorders (SMQ)*

2.42.4 Notes on Implementation and/or Expectation of Query Results

Hearing and vestibular disorders (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.42.5 List of References for *Hearing and vestibular disorders (SMQ)*

- Stedman's Medical Dictionary, 27th edition, 2000.
- Merck Manual of Diagnosis and Therapy, 17th edition, 1999.
- Vestibular Disorders Association, www.vestibular.org.
- Otorhino-Laryngology, James B. Snow, Jr., 1979.

2.43 Hepatic disorders (SMQ)

(Production Release April 2005)

2.43.1 Definition

Hepatic disorders (SMQ) is relatively complicated because it covers events that relate to an entire organ system. It comprises

- A comprehensive search of all terms possibly related to the liver, irrespective whether they are possible related to drug effects
- A number of sub-SMQs on some specific liver related topics
- Searches for terms for potentially drug related liver disorders

SMQ Code	SMQ Term
20000008	*Liver related investigations, signs and symptoms (SMQ)*
20000009	*Cholestasis and jaundice of hepatic origin (SMQ)*
20000010	*Hepatitis, non-infectious (SMQ)*
20000011	*Liver neoplasms, malignant and unspecified (SMQ)*
20000208	*Liver malignant tumours (SMQ)*
20000209	*Liver tumours of unspecified malignancy (SMQ)*
20000012	*Liver neoplasms, benign (incl cysts and polyps) (SMQ)*
20000013	*Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)*
20000014	*Congenital, familial, neonatal and genetic disorders of the liver (SMQ)*
20000015	*Liver-related coagulation and bleeding disturbances (SMQ)*
20000016	*Liver infections (SMQ)*
20000017	*Hepatic disorders specifically reported as alcohol-related (SMQ)*
20000018	*Pregnancy-related hepatic disorders (SMQ)*

Table 2-6. Topics of *Hepatic disorders (SMQ)*

Each of the above topics is a standalone SMQ. Some of them are further grouped hierarchically based on their relationship to drug adverse events (refer to the section “Hierarchy Structure” below).

2.43.2 Inclusion/Exclusion Criteria

- The top level SMQ *Hepatic disorders (SMQ)* is intended to include all liver-related terms.
- *Hepatic disorders (SMQ)* only lists terms linking to primary SOCs but many terms of other SOCs also have secondary links to the SOC *Hepatobiliary disorders*.
- The term “hepatitis” is frequently misused in adverse reaction reporting by referring to any liver damage, whether or not histological lesions have been confirmed. This problem cannot, of course, be solved by any SMQ and requires an analysis of narratives and laboratory data fields.
- *Liver related investigations, signs and symptoms (SMQ)*: Most of the terms of this sub-SMQ belong to HLGT *Hepatobiliary investigations* in SOC *Investigations*. Many terms of this HLGT, however, relate to investigations as such (without a qualifier term, such as “increased”) or to investigations with a normal outcome; these terms are not included in this search. In addition, this SMQ contains all terms of HLT *Hepatobiliary signs and symptoms* in SOC *Hepatobiliary disorders* and a few PTs from other SOCs.
- *Cholestasis and jaundice of hepatic origin (SMQ)*: This search includes all conditions associated with jaundice or cholestasis of possible hepatic origin and therefore excludes PTs indicating jaundice caused by extrahepatic conditions, such as PT *Jaundice extrahepatic obstructive*. Various other etiologies are excluded.
- *Liver neoplasms, malignant and unspecified (SMQ)*: All terms of this sub-SMQ belong to HLGT *Hepatobiliary neoplasms malignant and unspecified* in SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*. Metastatic tumors to liver are excluded.
- *Liver neoplasms, benign (incl cysts and polyps) (SMQ)*: All terms of this sub-SMQ belong to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*.
- *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)*: This sub-SMQ is not intended to be used alone generally, but in combination with *Hepatitis, non-infectious (SMQ)*. The SMQ does not include PT *Cardiac cirrhosis*.
- PT *Liver injury* is included in *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)*. This term was added to the SMQ in MedDRA Version 10.0. The expression "liver injury" is often interpreted as chemical such as might occur as a result of drug exposure; however, in some instances, it could also be used to denote trauma to the liver. Users should review the types of cases retrieved by the PT carefully to determine if non-traumatic or traumatic liver injury has occurred

- *Liver-related coagulation and bleeding disturbances (SMQ)*: This sub-SMQ includes decreases of coagulation factor levels that may be due to reduced liver function, and changes in blood coagulation parameters depending on these factors. Terms in this sub-SMQ are from SOC *Investigations*.
- *Hepatic disorders specifically reported as alcohol-related (SMQ)*: This SMQ contains terms specifically related to alcohol-associated disorders. These have not been included in any of the other sub-SMQs since alcohol-related terms are normally not searched for when looking for drug-induced liver injuries. Possible alcohol-related events that also can have other caused (e.g., cirrhosis) have not been included in this sub-SMQ.
- *Pregnancy-related hepatic disorders (SMQ)*: This search contains terms specifically related to pregnancy-associated disorders. These have not been included in any of the other sub-SMQs since they are normally not searched for when looking for drug-induced liver injuries
- Terms solely associated with disorders of the gallbladder and the bile duct are excluded.
- Investigation terms without indicating a result or with a normal outcome are excluded
- The inclusion of liver neoplasm search (20000011) was questioned by one subscriber in Phase II testing because of its rareness. The Working Group decided to keep it based on the fact that it is possible although rare.
- Terms for liver conditions due to trauma are excluded.

NOTE: In Version 14.1, sub-SMQ *Events specifically reported as alcohol-related (SMQ)* was renamed to *Hepatic disorders specifically reported as alcohol-related (SMQ)*, representing a more precise description for this SMQ.

NOTE: In Version 14.0, two new sub-SMQs have been added to existing sub-SMQ *Liver neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: In Version 12.1, the following sub-SMQs were renamed:

Former Sub-SMQ Name in Version 12.0	New Sub-SMQ Name in Version 12.1
Possible drug related hepatic disorders - comprehensive search (SMQ)	*Drug related hepatic disorders - comprehensive search (SMQ)*
Possible drug related hepatic disorders - severe events only (SMQ)	*Drug related hepatic disorders - severe events only (SMQ)*
Liver neoplasms, benign (SMQ)	*Liver neoplasms, benign (incl cysts and polyps) (SMQ)*
Possible liver-related coagulation and bleeding disturbances (SMQ)	*Liver-related coagulation and bleeding disturbances (SMQ)*

Table 2-7. Modifications of sub-SMQ names under *Hepatic disorders (SMQ) in V. 12.1*

NOTE: In Version 12.1, the following sub-SMQs were modified in scope to include both broad and narrow search terms (formerly included only broad terms):

- *Cholestasis and jaundice of hepatic origin (SMQ)*
- *Congenital, familial, neonatal and genetic disorders of the liver (SMQ)*
- *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)*
- *Hepatitis, non-infectious (SMQ)*
- *Liver infections (SMQ)*
- *Liver related investigations, signs and symptoms (SMQ)*

NOTE: In Version 12.1, the following sub-SMQs were modified in scope to include narrow search terms (formerly included only broad terms):

- *Hepatic disorders specifically reported as alcohol-related (SMQ)*
- *Liver neoplasms, benign (incl cysts and polyps) (SMQ)*
- *Liver neoplasms, malignant and unspecified (SMQ)*
- *Liver-related coagulation and bleeding disturbances (SMQ)*
- *Pregnancy-related hepatic disorders (SMQ)*

2.43.3 Hierarchy Structure

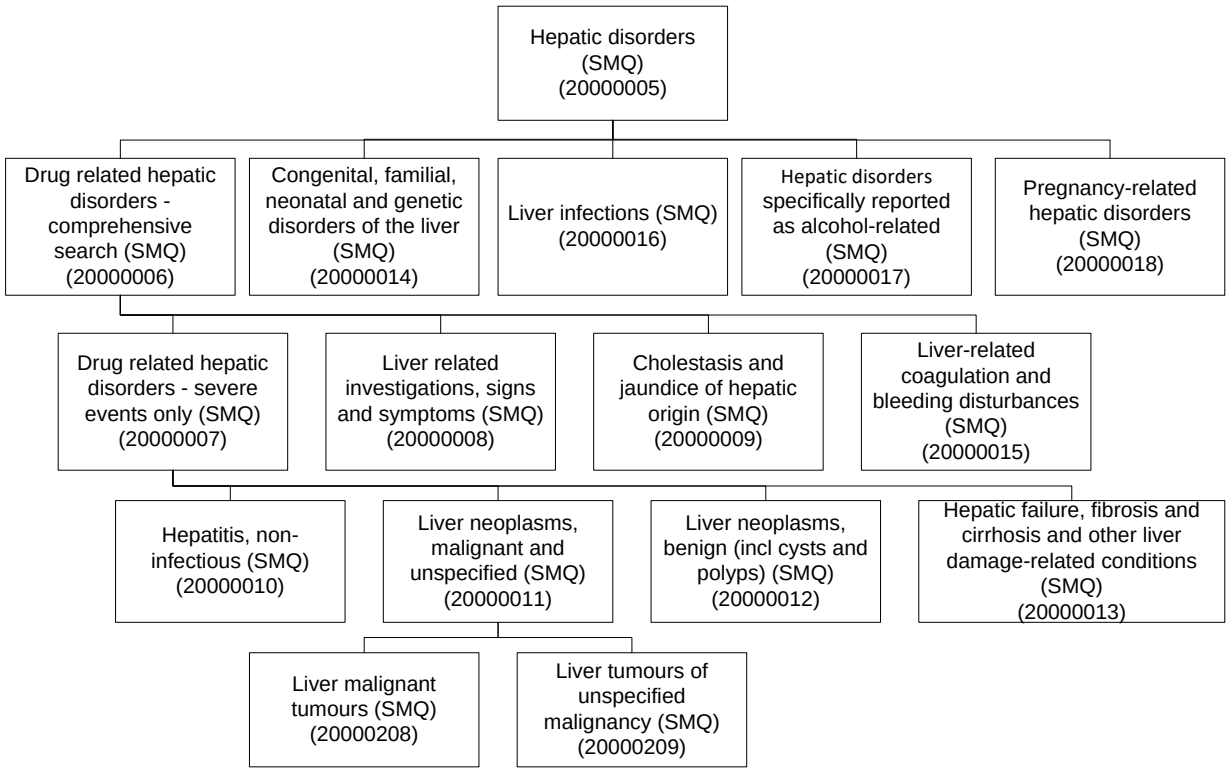

Figure 2-14. Hierarchy Structure of *Hepatic disorders (SMQ)*

Hepatic disorders (SMQ) consists of a series of SMQs in a hierarchical relationship to one another:

- The top SMQ *Hepatic disorders (SMQ)* is a comprehensive search of all terms possibly related to the liver, irrespective of whether they are possibly related to drug effects.
- *Drug related hepatic disorders - comprehensive search (SMQ)* excludes non-drug related events, such as congenital, infection, alcohol, and pregnancy related events, from the top SMQ *Hepatic disorders (SMQ)* search.
- Under *Drug related hepatic disorders - comprehensive search (SMQ)*, another sub-search for severe drug related liver toxicity is represented by *Drug related hepatic disorders - severe events only (SMQ)*.

2.43.4 Notes on Implementation and/or Expectation of Query Results

Hepatic disorders (SMQ) is a hierarchical SMQ with both broad and narrow search terms.

The following eight sub-SMQs have both broad and narrow search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

- *Cholestasis and jaundice of hepatic origin (SMQ)*
- *Congenital, familial, neonatal and genetic disorders of the liver (SMQ)*
- *Drug related hepatic disorders - comprehensive search (SMQ)*
- *Drug related hepatic disorders - severe events only (SMQ)*
- *Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)*
- *Hepatitis, non-infectious (SMQ)*
- *Liver infections (SMQ)*
- *Liver related investigations, signs and symptoms (SMQ)*

The following five sub-SMQs have only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

- *Hepatic disorders specifically reported as alcohol-related (SMQ)*
- *Liver neoplasms, benign (incl cysts and polyps) (SMQ)*
- *Liver neoplasms, malignant and unspecified (SMQ)*
- *Liver-related coagulation and bleeding disturbances (SMQ)*
- *Pregnancy-related hepatic disorders (SMQ)*

Because terms for supporting investigation, sign and symptom terms are grouped in sub-SMQ *Liver related investigations, signs and symptoms (SMQ)*, subordinate SMQs of *Hepatic disorders (SMQ)*, which contain only diagnosis and pathognomonic investigation result, are not independent queries. For example, to find relevant cases of "liver infections", those retrieved by sub-SMQ *Liver infections (SMQ)* may not be sufficient. Cases retrieved by terms for supporting investigation result terms, such as liver function tests (located in sub-SMQ *Liver related investigations, signs and symptoms (SMQ)*) may need to be included to get a complete set of relevant cases. Similar to *Biliary disorders (SMQ)* some level of manual intervention is required when applying subordinate SMQs. Medical judgment may need to be applied.

2.43.5 List of References for *Hepatic disorders (SMQ)*

- Harrison's Principles of Internal Medicine 16th ed, Mc Graw Hill, 2005, pp 1808-1880.

2.44 Hostility/aggression (SMQ)

(Production Release September 2007)

2.44.1 Definition

- Aggression: a form of behavior which leads to self-assertion; it may arise from innate drives and/or a response to frustration; it may be manifested by destructive and attacking behavior, by covert attitudes of hostility and obstructionism, or by a healthy self-expressive drive to mastery
- Hostility: a tendency to feel anger toward and to seek to inflict harm upon a person or group

2.44.2 Inclusion/Exclusion Criteria

- Included:
  - PT *Screaming* (as it may be a precursor of aggression or hostility, such as in a patient with dementia)
  - PT *Gun shot wound,* PT *Drowning,* PT *Asphyxia,* PT *Human bite,* PT *Bite,* PT *Imprisonment,* PT *Theft* (as it is unclear if the patient was the victim or perpetrator)
  - PTs denoting high risk for hostility or aggression: PT *Delusional disorder*, *persecutory type;* PT *Jealous delusion*; PT *Mania*; etc.
  - PTs containing LLTs with high risk for hostility or aggression: PT *Injury* (LLT *Criminal injury*); PT *Personality disorder* (LLT *Aggressive personality*); PT *Psychiatric symptom* (LLT *Violence-related symptom*)*; PT *Psychotic disorder* (LLT *Psychotic behaviour*)*

    * LLT *Violence-related symptom* and LLT *Psychotic behaviour* were promoted to PT level in V10.1. As a result, PT *Psychiatric symptom*, with no related LLTs remaining underneath once LLT *Violence-related symptom* was promoted, was removed from this SMQ.
  - Symptoms/syndromes highly associated with hostility/aggression that are commonly a part of the illness (*e.g.* reports including PT *Bipolar disorder,* PT *Bipolar I disorder,* and PT *Bipolar II disorder* as events might contain a patient who was manic or hypomanic)
  - PT *Paranoia* and PT *Paranoid personality disorder* (as they are high risk for aggression or hostility)
  - PT *Irritability* and PT *Agitation* (as fairly high risk for and highly associated with hostility/aggression)

- Excluded:
  - Suicide and self-injury related PTs, and dementia and delirium related PTs were excluded due to the availability of SMQs for these conditions
  - Psychosis related PTs that are not highly associated with hostility/aggression. (There is a separate SMQ *Psychosis and psychotic disorders (SMQ)*).
  - Alcohol and illicit drug PTs as they are not likely to be caused by medications
  - PT *Thinking abnormal* (too non-specific)
  - PT *Child maltreatment syndrome* (as it denotes child as a victim, based on radiologic findings)
  - Metabolic syndromes (hyperthyroidism, etc.) that could possibly lead to hostility/aggression were excluded as too non-specific
  - Terms denoting the patient as a victim of crime or aggressive behavior (where it was clear the patient was the victim)
  - "Abused" terms (e.g., LLT *Verbally abused*) rather than *abuse* terms were excluded as not likely to be self -inflicted. However, in some databases it may be necessary to include these terms because certain coding practices may include "abused" in place of "abuse".
  - PT *Asocial behaviour* (not typically aggressive)
  - Terms that are not specific for aggression: PT *Negativism,* and its associated LLT *Oppositional*; PT *Restlessness*; PT *Nervousness*; PT *Anxiety*; PT *Frustration tolerance decreased*; and PT *Grandiosity*
  - PT *Shoplifting* (not pertaining to aggression or hostility)
  - Mental retardation terms (most patients with mental retardation are not hostile/aggressive)
  - PT *Neuropsychological test abnormal* and PT *Psychiatric evaluation abnormal* (too broad)

2.44.3 Notes on Implementation and/or Expectation of Query Results

Hostility/aggression (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.44.4 List of References for *Hostility/aggression (SMQ)*

- Dorland's Illustrated Medical Dictionary, 29th Edition, 2000.
- The On-Line Medical Dictionary, CancerWEB project, Dec 1998.

2.45 Hyperglycaemia/new onset diabetes mellitus (SMQ)

(Production Release March 2006)

2.45.1 Definition

- Diagnosis of diabetes mellitus is usually based on elevated levels of fasting plasma glucose or a random plasma glucose accompanied by classic symptoms.
- Hyperglycemia in diabetes mellitus occurs as a result of reduced insulin secretion, decreased glucose usage, or increased glucose production.
- Type I diabetes mellitus:
  - About 10% of all cases
  - Insulin deficiency resulting from autoimmune beta cell destruction (type IA) or idiopathic (type IB)
- Type II diabetes mellitus:
  - About 90% of all cases
  - Heterogeneous disorder of glucose metabolism characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production
- Both types involve genetic susceptibility:
  - For type I, interaction with some environmental exposure
  - For type II, involves risk factors (e.g., obesity)
- Other less common etiologies:
  - Specific genetic defects of insulin secretion or action
  - Diseases of the exocrine pancreas (e.g., chronic pancreatitis)
  - Endocrinopathies producing insulin counter-regulatory hormones (e.g., Cushing's syndrome)
  - Viral infections (e.g., cytomegalovirus)
  - Certain drugs or chemicals
  - Associated with other genetic syndromes (e.g., Down's syndrome)
  - Complication in about 4% of pregnancies
- Drugs have been associated with hyperglycemia that can progress to new onset diabetes mellitus.
  - Can mimic type I or II
  - Mechanisms:

        - Diminished insulin production, inhibited insulin secretion, and reduced beta cell volume (e.g., cyclosporine)
        - Autoimmune destruction of beta cells and increased insulin antibody titers (e.g., interleukin-2)
        - Hormone stimulated gluconeogenesis and decreased insulin sensitivity (e.g., glucocorticosteroids)
        - Decreased insulin sensitivity (e.g. protease inhibitors)
    - Often reversible by discontinuation of drug, or can be controlled with oral antidiabetic agents and/or insulin
- Common symptoms: polydipsia, polyphagia, polyuria, and weight loss
- Other metabolic abnormalities: hypercholesterolemia and/or hypertriglyceridemia
- Insulin concentrations:
    - Low in type I
    - High early during type II; decrease as disease progresses
- Acute complications:
    - Diabetic ketoacidosis (DKA) particularly type I
    - Nonketotic hyperosmolar state (NKHS) particularly type II diabetes
        - Both DKA and NKHS can result in neurologic symptoms that can progress to coma.
- Long term complications are microvascular (e.g., retinopathy), macrovascular (e.g., coronary artery disease), and neuropathic (e.g., paresthesias).
    - Microvascular effects appear to be related to degree of hyperglycemia.
    - Macrovascular effects may be related to chronic hyperglycemia and possible other concurrent factors (e.g., hypertension).

2.45.2 Inclusion/Exclusion Criteria

- Included:
    - Terms representing acute manifestations of diabetes mellitus/hyperglycemia
    - Other terms representing:
        - Diabetes mellitus and major complications
    - Abnormalities of insulin or glucose metabolism expected in patients with diabetes mellitus or hyperglycemia
    - Terms with roots of “diabet-,” “glucose,” “insulin,” “ketone,” and “ketosis”

- Most terms led to HLGT *Glucose metabolism disorders (incl diabetes mellitus)*
    - PTs linked to this HLGT were reviewed for suitability
- Narrow search terms were those considered to be very specifically related to a new diagnosis of, or manifestations, signs, or symptoms of new onset diabetes mellitus.
- Broad search terms, also indicative of new onset of diabetes, but less specific for it
- PT *Ketosis*, although a broad description that may capture cases not related to hyperglycemia, was left in the SMQ because during Phase I testing, several reports were captured where no other term has been reported (i.e., it identified cases that would otherwise have been missed)
- PT *Weight increased* retrieved a large number of reports with "noise" during Phase I testing. It was included because that the Working Group agreed that it is relevant to the scope of this SMQ. It might be evaluated by other MedDRA users.
- Certain PTs (*Blood cholesterol increased*, *Blood triglycerides increased*, *Weight decreased*) need to be included for completeness sake, and if the narrow search identifies a sufficient number of cases for a review then cases reporting only these PTs may not need to be reviewed further. However, should the narrow search return an insufficient number of cases for review, then cases reporting these PTs should be reviewed to determine if the patients in those cases appear to be at high risk for subsequent development of diabetes mellitus or hyperglycemia. This approach may be database or product-dependent.

- Excluded:
    - Terms representing long term complications
    - Infection terms and pancreatitis terms (based on phase I testing; not specific enough for diabetes mellitus)

2.45.3 Notes on Implementation and/or Expectation of Query Results

Hyperglycaemia/new onset diabetes mellitus (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.45.4 List of References for *Hyperglycaemia/new onset diabetes mellitus (SMQ)*

- Oki JC and Isley WL. Diabetes mellitus. Pharmacotherapy: A Pathophysiologic Approach (5th Ed). DiPiro JT, Talbert RL, Yee GC et al (Eds). McGraw-Hill: New York, 2002. pg. 1335-1358.

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- Vanrenterghem YFC. Which calcerineurin inhibitor is preferred in renal transplantation: tacrolimus or cyclosporine? Curr Opin Nephrol Hypertension 1999; 8(6):669-674.
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- Henderson DC. Atypical antipsychotic-induced diabetes mellitus. CNS Drugs 2002; 16(2):77-89.
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- Melkersson K and Dahl M-L. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004; 64(7)701-723.

2.46 Hypersensitivity (SMQ)

(Production Release March 2013)

2.46.1 Definition

- Aim of this SMQ:
  - Support database searches for potentially drug/vaccine related hypersensitivity/allergic reactions in connection with Risk Management Plans, PSUR and other surveillance activities
  - Designed to retrieve all types of cases possibly related to hypersensitivity/ allergic reactions
  - Not intended to differentiate between different types of hypersensitivity reactions such as the Coombs classification
- A number of SMQs for specific allergic conditions already exist (e.g. SMQ *Anaphylactic reaction*, SMQ *Angioedema*)
- "Hypersensitivity" is often used in a very general way to describe a large number of conditions related to an exaggerated response of the body to a foreign agent
  - A more restricted use is for allergic reactions of all types
- Many terms included in SMQ *Hypersensitivity* do not permit differentiation between hypersensitivity/allergic reactions and other causes for the given event and therefore further analysis of cases retrieved by the SMQ is required

2.46.2 Inclusion/Exclusion criteria

- Included:
  - All terms indicative of potential drug/vaccine and other medical product related hypersensitivity/allergic conditions
    - Narrow = conditions for which allergy is one of the main causes
    - Broad = conditions for which other causes are more likely
  - Terms for results of investigations indicative of hypersensitivity/allergy

NOTE: In a number of instances, for events having a similar phenomenological appearance, some PTs were included as either narrow or broad scope terms and some not at all depending on the likelihood of a relationship to drug/vaccine administration. For example, of the many rhinitis terms available in MedDRA, only PT *Rhinitis allergic* (narrow scope) and various seasonal/perennial rhinitis terms (broad scope) were included. Similarly, of the various asthma-related terms, only PT Aspirin-exacerbated respiratory disease was included as narrow and PT *Asthma,* PT *Asthma late onset,* PT *Status asthmaticus,* PT *Asthmatic crisis,* PT *Childhood asthma,* PT *Occupational asthma* were included as broad scope terms.

- Excluded:

- Terms for autoimmune disorders
    - If, however, these conditions are required in a search, the user is referred to HLGT *Autoimmune disorders* which provides a comprehensive grouping of such terms
- Terms for transplant rejections, which if required are covered by HLT *Transplant rejections*
- Terms for idiosyncratic reactions
    - If these are required (reactions representing an abnormal reaction to a drug, not caused by allergy), the user is referred to PT *Idiosyncratic drug reaction*
- Allergy terms related to other causes e.g. PT *Allergy to animal,* PT *Allergy to metals*, PT *Food allergy*
- Prophylaxis terms, e.g. PT *Anaphylaxis prophylaxis,* PT *Asthma prophylaxis*
- Urticaria terms relating to non-drug/vaccine related causes, e.g. PT *Urticaria vibratory*

2.46.3 List of References for *Hypersensitivity (SMQ)*

- [None provided]

2.47 Hypertension (SMQ)

(Production Release September 2008)

2.47.1 Definition

- Hypertension is defined as high arterial blood pressure
- Causes:
  - Unknown (essential or idiopathic hypertension)
  - Associated with other primary diseases (secondary hypertension)
- Various criteria for its threshold range from 140 mm Hg systolic and 90 mm Hg diastolic to 200 mm Hg systolic and 110 mm Hg diastolic
- Per 2003 ESH/ESC Hypertension Guidelines and NHLBI, optimal blood pressure is less than 120/80 mm Hg. Prehypertension is defined as blood pressure120-139/80-89 mm Hg.
- Newer definitions characterize hypertension as a complex progressive cardiovascular syndrome
- Majority of patients are asymptomatic; hypertension only identified by measuring blood pressure
- Signs and symptoms:
  - Headache (only in severe hypertension)
  - Other possibly related complaints: Dizziness, flushed face, early fatigability, palpitation, and nervousness
  - Complaints referable to vascular effects: Epistaxis, hematuria and blurring of vision
  - Common presentations of hypertensive emergencies: Chest pain, dyspnoea, and neurologic deficit
  - Neurologic presentations: Occipital headache, cerebral infarction or hemorrhage, visual disturbance, or hypertensive encephalopathy
- No early pathological changes occur in primary hypertension. Ultimately, generalized arteriolar sclerosis develops, particularly in the kidneys.
- Hypertension is an important risk factor for cardiovascular events, such as myocardial infarction and stroke. Early diagnosis and treatment is essential.

2.47.2 Inclusion/Exclusion Criteria

- Included:
  - All terms referring to what is defined as primary/essential/idiopathic hypertension

- Secondary forms of hypertension *e.g.*, caused by renal vascular or parenchymal diseases, or hypertension due to endocrine causalities, if indicated as such (*e.g.*, PT *Endocrine hypertension*, PT *Renovascular hypertension*)
- PT *Metabolic syndrome*, because hypertension is part of the definition
- Pregnancy related hypertensive disorders, e.g., PT *Pre-eclampsia*, PT *HELLP syndrome*
- Abnormal values involved in activation of the Renin-Angiotensin-System
- Abnormal values of sympathomimetic hormones/neurotransmitters
- Diagnostic markers and therapeutic procedural terms for hypertension, e.g., PT *Catecholamines urine increased*
- Terms referring to end-organ damages as long as the terms have "hypertensive" as part of the concept, e.g. PT *Retinopathy hypertensive*. For a complete set of potential end organ damage terms more specific SMQs need to be applied e.g. *Ischaemic heart disease (SMQ)*, *Central nervous system haemorrhages and cerebrovascular accidents (SMQ)*

- Excluded:
  - Congenital conditions/disorders which may be associated with or lead to hypertension, *e.g.*, PT *Congenital hyperthyroidism*, PT *Liddle's syndrome*
  - Pulmonary hypertension, portal hypertension, intracranial hypertension, intraocular hypertension and their specific signs and symptoms
  - Medical conditions including late organ effects that may be consequent to hypertension, e.g., myocardial infarction, stroke, atherosclerosis, unless "hypertensive" is part of their concept.
  - Neurological manifestation of hypertensive encephalopathy in malignant hypertension, e.g. brain edema, convulsion, coma
  - Cardiovascular risk factors, e.g., central obesity, diabetes mellitus, smoking, hyperlipidemias and many more
  - Commonly observed signs and symptoms of hypertension, e.g., headache and dizziness
  - Terms referring to potential causes of secondary hypertension e.g., PT *Phaeochromocytoma*, PT *Cushing's syndrome*, PT *Cushingoid* and PT *Adrenal adenoma*

NOTE: Users of this SMQ should consider searching for etiology, signs and symptoms and consequence terms excluded from this SMQ (see Table 2 in original CIOMS WG documentation) if hypertension may be a de novo signal. Users may also consider using other SMQs, such as *Ischaemic heart disease (SMQ)* and *Central nervous system haemorrhages and cerebrovascular accidents (SMQ)* to identify consequences of hypertension.

NOTE: In Version 14.0, *Hypertension (SMQ)* was modified in that all laboratory terms that are not specific hypertension diagnostic concepts were changed from narrow to broad scope. This SMQ formerly included only narrow terms.

2.47.3 Notes on Implementation and/or Expectation of Query Results

Hypertension (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.47.4 List of References for *Hypertension* (SMQ)

- Journal of Hypertension 2003, Vol 21 No 10.
- Journal of Hypertension 1999, Vol 17 No 2.
- Harrison's Principles of Internal Medicine, 16th Ed (2005). Part 8, Sect. 4.
- Dorland's Medical Dictionary, 30th Edition, 2003.

2.48 Hypoglycaemia (SMQ)

(Production Release March 2016)

2.48.1 Definition

- Hypoglycemia is characterized by reduced plasma glucose to a level (usually less than 50 mg/dL) that may cause signs or symptoms (e.g., mental status changes). Hypoglycemia typically arises from abnormalities in the mechanisms involved in glucose homeostasis.

  - For the diagnosis of hypoglycemia, the “Whipple triad” is generally observed as low blood sugar, presence of symptoms, and reversal of these symptoms when the blood sugar level is restored to normal.

  - The true prevalence is 5-10% of patients who present with symptoms suggestive of hypoglycemia.

  - Hypoglycemic symptoms are related to sympathetic activation and brain dysfunction due to the decreased glucose levels. This results in sweating, palpitations, tremulousness, anxiety, and hunger. Reduction in cerebral glucose availability (neuroglycopenia) may cause confusion, difficulty with concentration, irritability, hallucinations, focal impairment, coma and eventually death.

- Various forms and causes of hypoglycemia include:

  - Drugs – ethanol, haloperidol, pentamidine, quinine, salicylates, sulfonamides ("sulfa drugs") and oral hypoglycemic agents have been associated with hypoglycemia as have numerous other drugs.

  - Surreptitious sulfonylurea use/abuse – self-induced hypoglycemia that may be observed in healthcare workers or in relatives who care for diabetic family members.

  - Exogenous insulin – for example, insulin-producing tumors of the pancreas (islet cell tumors), and non–beta-cell tumors.

  - Reactive hypoglycemia – idiopathic, due to alimentary problems (e.g., patients with previous upper gastrointestinal surgery), or congenital enzyme deficiencies (e.g., hereditary fructose intolerance).

  - Fasting hypoglycemia

    - Nesidioblastosis is a medical term for hyperinsulinemic hypoglycemia attributed to excessive function of pancreatic beta cells with an abnormal

microscopic appearance. Most recently, nesidioblastosis has been used to describe a form of acquired hyperinsulinism with beta cell hyperplasia found in adults, especially after gastrointestinal surgery.
    - Inherited enzyme deficiencies and defects in fatty acid oxidation may also be involved.

- Other causes of hypoglycemia include the following:
    - Autoimmune hypoglycemia
    - Critical illnesses
    - Exercise (diabetic patients)
    - Pregnancy
    - Renal glycosuria
    - Ketotic hypoglycemia of childhood
    - Adrenal insufficiency
    - Hypopituitarism
    - Starvation
    - Laboratory test artifact

- Therapy for hypoglycemia is glucose. Other medications may be used based on the underlying cause or accompanying symptoms.

2.48.2 Inclusion/Exclusion Criteria

- Included:
    - Terms for various forms of hypoglycemia, which generally include the word "hypoglycaemia" or a variant of "hypoglycaemia" in the term (e.g., PT *Hypoglycaemia unawareness*)

    - Terms for relevant laboratory findings supporting the diagnosis of hypoglycemia (e.g. PT *Blood glucose decreased*)

    - Terms for characteristic signs and symptoms of hypoglycemia (e.g., PT *Hunger*, PT *Incoherent*)

    - Terms for relevant therapeutic interventions that may signal a case of hypoglycemia.

- Excluded:
    - Terms for etiologies of hypoglycemia (e.g., PT *Insulinoma*, PT *Metabolic surgery*)

    - Terms for congenital forms of hypoglycemia (e.g., PT *Diencephalic syndrome of infancy*)

    - Terms that relate mainly to diabetes mellitus (e.g., PT *Glucose tolerance impaired*)

- Terms for non-specific symptoms that occur with hypoglycemia but are not highly characteristic and could potentially cause “noise” (e.g., PT *Abnormal behaviour*; PT *Malaise*; PT *Fatigue*)

2.48.3 Notes on Implementation and/or Expectation of Query Results

Hypoglycaemia (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

The broad scope search should be applied with caution because the generally nonspecific nature of the signs and symptoms of hypoglycemia are likely to result in background noise. During testing, broad scope terms demonstrated poor differentiation between the positive and negative controls.

2.48.4 List of References for *Hypoglycaemia (SMQ)*

- Hamdy, O. Hypoglycaemia. Medscape Reference. http://emedicine.medscape.com/article/122122-overview#showall

- Merck Manual, 17th ed.

2.49 Hypokalaemia (SMQ)

(Production Release March 2019)

2.49.1 Definition

- Hypokalemia is a plasma potassium (K) concentration of less than 3.5 mEq/L caused by a deficit in total body potassium stores or abnormal movement of potassium into cells(1)
- Causes:
  - Decreased intake of potassium
  - Excessive losses of potassium from the kidneys or from the gastrointestinal tract
  - Drugs known to cause hypokalemia include diuretics, laxatives, antimicrobials, mineralo -and glucocorticoids, and beta-2 receptor agonists.(1,2)
- Clinical signs are dependent on the degree of potassium depletion and may include
  - Muscle weakness, muscle cramping, fasciculations
  - Paralytic ileus
  - Hypoventilation, and hypotension (when hypokalemia is severe)
- ECG changes typically occur when serum potassium is < 3 mEq/L, and include
  - ST segment sagging, T wave depression, and U wave elevation
  - With marked hypokalemia, the T wave becomes progressively smaller and the U wave becomes increasingly larger
- Hypokalemia may cause arrhythmias including
  - Premature ventricular and atrial contractions, ventricular and atrial tachyarrhythmias, and 2nd- or 3rd-degree atrioventricular block
  - Ventricular fibrillation may eventually occur
- Treatment
  - Oral potassium replacement, giving 20 to 80 mEq/day unless patients have ECG changes or severe symptoms
  - For hypokalemic arrhythmias, intravenous potassium chloride is given through a central vein, at a maximum of 40 mEq/h and only with continuous cardiac monitoring; routine IV infusion should be no more than 10 mEq/h.

2.49.2 Inclusion/Exclusion Criteria

- **Included:**

- Terms directly referring to hypokalemia or potassium wasting
- Investigations directly referring to decreased or abnormal potassium levels both in blood and urine
- Investigations closely associated with states of hypokalemia, such as ECG investigations typical of low potassium levels (e.g., PT *Electrocardiogram U-wave prominent,* PT *Electrocardiogram T wave inversion*).
- Cardiac arrhythmias characteristic of hypokalemia
- Other signs and symptoms frequently associated with low potassium levels (e.g., PT *Hypotension*, PT *Hypoventilation*)

- **Excluded**:
  - Very specific and closely related causes of hypokalemia (e.g., PT *Hyperaldosteronism*, PT *Fanconi syndrome acquired*, PT *Potassium wasting nephropathy*, PT *Renal tubular acidosis*)
  - Non-specific muscle related signs and symptoms and tone abnormalities (e.g., PT *Muscle spasticity*, PT *Muscle weakness*)
  - Unqualified investigation terms (e.g., PT *Blood potassium*)
  - Signs and symptoms poorly related to low potassium levels
  - Congenital forms of hypokalemia

2.49.3 Notes on Implementation and/or Expectation of Query Results

Hypokalaemia (SMQ) has both narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.49.4 List of References for *Hypokalaemia (SMQ)*

1. Merck Manual, Professional version; March 2018
2. Kardalas E. et al. Hypokalemia : a clinical update ; Endocr Connect 2018 Apr; 7 (4): R135 – R 146. Published online 2018 Mar 14. doi: 10.1530/EC-18-0109

2.50 Hyponatraemia/SIADH (SMQ)

(Production Release September 2007)

2.50.1 Definition

- Hyponatremia has been reported in association with a variety of medical conditions such as:
  - Adrenal insufficiency, congestive heart failure, hepatic cirrhosis, nephritic syndrome, hypothyroidism, psychogenic polydipsia, hyperglycemia, acute or chronic renal failure, vomiting, diarrhea and SIADH
- Hyponatremia can be:
  - Hypovolemic: associated with sodium and water depletion (as a result of vomiting or diarrhea)
  - Hypervolemic: associated with fluid overload and edema (as a result of congestive heart failure or nephritic syndrome)
  - Isovolemic: associated with normal or modest extracellular volume expansion (most common cause is SIADH)
- SIADH is associated with a variety of medical conditions such as:
  - Neoplasms (particularly carcinomas), central nervous system (CNS) disorders (stroke, intracranial hemorrhage or hematoma, encephalitis or meningitis, or acute psychosis), or pulmonary disorders (pneumonia, tuberculosis, asthma, or chronic obstructive pulmonary disease)
- Both hyponatremia and SIADH are also associated with a variety of drugs such as:
  - CNS active drugs: tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), trazodone, anticonvulsants (particularly carbamazepine), and the neuroleptics
  - Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen,
  - Thiazide diuretics and furosemide
  - Sulfonylureas (particularly chlorpropamide)
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Many anti-neoplastic agents (particularly cyclophosphamide)
- Hyponatremia usually defined as serum sodium < 135 mEq/L
  - If mild or gradual, may be asymptomatic
  - If severe (serum sodium < 120 mEq/L) or rapid, presenting signs and symptoms are suggestive of water intoxication

- Cerebral edema symptoms: headache, mental confusion, disorientation, encephalopathy, tremors, gait disturbances, convulsions, and coma
- Other symptoms: nausea, vomiting, and muscle weakness or cramps
- Other laboratory abnormalities (in addition to decreased serum sodium): decreased plasma osmolality, increased or decreased urine osmolality, and increased or decreased urine sodium concentration

- Diagnosis of SIADH based on exclusion of other causes of hyponatremia

2.50.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for the following concepts:
    - Hyponatremia
    - SIADH
    - Laboratory indices for decreased serum sodium concentrations
    - Laboratory indices for decreased serum osmolality
    - Laboratory indices for changes in urine sodium concentration
    - Laboratory indices for changes in urine osmolality
    - PT *Water intoxication* (since signs and symptoms of SIADH can mimic this)
    - PT *Brain oedema* (based on SMQ testing results)
  - Narrow search includes PTs specifically related to hyponatremia, SIADH, and abnormal or decreased serum sodium or antidiuretic hormone concentrations
  - Broad search includes additional PTs for abnormalities of blood electrolytes or osmolality, or abnormalities of urine sodium or osmolality suggestive of hyponatremia and/or SIADH, PT *Water intoxication*, and PT *Brain oedema*
- Excluded:
  - See NOTE below regarding cases retrieved by this SMQ.

NOTE: Diagnosis of hyponatremia and/or SIADH depends on presence of relevant laboratory abnormalities. Since these laboratory tests are likely to have been performed as part of the differential diagnosis and subsequently reported if abnormal for the more severe CNS manifestations of these conditions (such as convulsions or coma), cases reporting such severe manifestations and not also reporting the relevant abnormal laboratory results are excluded from this SMQ. Similarly, cases reporting less severe manifestations (such as nausea, vomiting, confusion, or headache) and not also

reporting relevant abnormal laboratory results are also excluded from this SMQ since if the less severe symptoms are the only reported events they are likely to be uninformative and will contain insufficient information to asses a possible role of hyponatremia and/or SIADH in the etiology of the reported events.

2.50.3 Notes on Implementation and/or Expectation of Query Results

Hyponatraemia/SIADH (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.50.4 List of References for *Hyponatraemia/SIADH (SMQ)*

- Foote EF. Syndrome of inappropriate antidiuretic hormone secretion and diabetes insipidus. Drug-Induced Diseases: Prevention, Detection, and Management. Tisdale JE and Miller DA (Eds). American Society of Health-System Pharmacists: Bethesda, MD, 2005. pg. 611-624.
- Joy MS and Hladik GA. Disorders of sodium, water, calcium, and phosphorus homeostasis. Pharmacotherapy: A Pathophysiologic Approach (5th Ed). DiPiro JT, Talbert RL, and Yee GC et al (Eds). McGraw-Hill: New York, NY. 2002. pg. 953-979.
- Robertson GL. Disorders of the neurohypophysis. Harrison's Principles of Internal Medicine (16th Ed). Kasper DL, Braunwald E, and Fauci AS et al (Eds). McGraw-Hill: New York, NY. 2005. pg. 2097-2104.
- Singer GG and Brenner BM. Fluid and electrolyte disturbances. Harrison's Principles of Internal Medicine (16th Ed). Kasper DL, Braunwald E, and Fauci AS et al (Eds). McGraw-Hill: New York, NY. 2005. pg. 252-263.

2.51 Hypotonic-hyporesponsive episode (SMQ)

(Production Release September 2011)

2.51.1 Definition

- Hypotonic-hyporesponsive episode (HHE) is characterized by:
  - Sudden onset of reduced muscle tone
  - Hyporesponsiveness (to verbal or other stimuli)
  - Changed skin color (pallor, cyanosis)

  - Has occurred after immunization with the following vaccines:
    - Diphtheria
    - Tetanus
    - Haemophilus influenzae type b
    - Hepatitis B vaccines

  - Most reports followed administration of pertussis component vaccines

  - More often associated with:
    - Whole-cell vaccines than acellular types
    - During primary immunization, generally following the first dose

  - Unclear if observed phenomena are related to:
    - Characteristics of the vaccine
    - An immunologic phenomenon
    - Toxic component(s) in the vaccine
    - Combination of factors

  - In US vaccine surveillance system (VAERS), slightly more females (53%) than males experienced HHE, however, more reports of HHE in males have been noted in the Netherlands vaccine surveillance system

  - Time to onset of signs after immunization is generally three to four hours but can range from immediately to up to 48 hours post-immunization

  - Episode typically lasts six to thirty minutes

  - Up to one-third of cases also describe a fever

- The Brighton Collaboration (BC) HHE Working Group – in developing a case definition for HHE – described diagnostic algorithms with three levels of certainty based on clinical observations at the time of the episode:

Parameter	Level of Diagnostic Certainty				
	Level 1	Level 2		Level 3	
Responsiveness	Hyporesponsive or unresponsive	Hyporesponsive or unresponsive	Hyporesponsive or unresponsive	Hyporesponsive or unresponsive	Unknown
Muscle tone	Hypotonia	Hypotonia	Unknown	Normal	Hypotonia
Skin changes	Pallor or cyanosis	Unknown	Pallor or cyanosis	Pallor or cyanosis	Pallor or cyanosis

Table 2-8. Algorithmic levels of diagnostic certainty for Hypotonic-hyporesponsive episodes

2.51.2 Inclusion/Exclusion criteria

- Included:
  - Terms for the diagnostic entity itself (PT *Hypotonic-hyporesponsive episode*)
  - Terms for signs and symptoms either directly or indirectly derived from the BC definition of HHE (e.g., PT *Cyanosis*)
- Excluded:
  - Terms which are not related to the diagnosis of HHE

NOTE: The BC definition specifically states that there are no laboratory studies that are helpful in confirming the diagnosis of HHE. These should not be considered as definitively excluded from the SMQ as future advancements in the diagnosis and treatment of HHE may involve laboratory studies.

NOTE: Based on results of all tests, the BC Level 1 algorithm is the recommended algorithm on which to base the SMQ (see Section 2.43.3)

2.51.3 Algorithm

The algorithm categories for SMQ *Hypotonic-hyporesponsive episode* are defined as follows:

- Category A: Narrow terms
- Category B: Hypotonia
- Category C: Hyporesponsive
- Category D: Pallor/Cyanosis

To apply the algorithm for this SMQ, a report is considered a relevant case for further review if:

A case of interest is one with:

- It includes a term from Category A (narrow scope)

  OR

- It includes at least one term from Category B + Category C + Category D

Users may choose to use additional algorithms.

2.51.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Hypotonic-hyporesponsive episode (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Hypotonic-hyporesponsive episode (SMQ)* is A or (B and C and D). Cases filtered by the algorithm can be listed for output.

2.51.5 List of References for *Hypotonic-hyporesponsive episode (SMQ)*

- Buettcher, M et al. Hypotonic-hyporesponsive episode (HHE) as an adverse event following immunization in early childhood: case definition and guidelines for data collection, analysis, and presentation. Vaccine 2007; 25: 5875 – 5881.
- DuVernoy, TS, Braun, MM and the VAERS Working Group. Hypotonic-hyporesponsive episodes reported to the Vaccine Adverse Event Reporting System (VAERS), 1996-1998. Pediatrics 2000; 106(4): e52.
- Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics*. 1981;68(5):650-659.
- Daptacel® [package insert]. Toronto, Ontario, Canada: Sanofi Pasteur Limited; 2008.
- Recombivax® [package insert]. Whitehouse Station, NJ: Merck & Co, Inc.; 2007.

2.52 Infective pneumonia (SMQ)

(Production Release September 2017)

2.52.1 Definition

- Pneumonia is acute inflammation of the lungs caused by infection
  - Pneumonia is the most common fatal hospital-acquired infection and the most common overall cause of death in developing countries
  - An estimated two to three million people in the United States develop pneumonia each year, of whom about 60,000 die
  - In the US, pneumonia, along with influenza, is the eighth leading cause of death and is the leading infectious cause of death

- Causes, symptoms, treatment, preventive measures, and prognosis of Infective pneumonia differ, depending on:
  - Whether the infection is bacterial, viral, fungal, or parasitic
  - Whether it is acquired in the community, hospital, or other health-care-associated location
  - Whether it develops in a patient who is immunocompetent or immunocompromised

- Clinical manifestations:
  - Can vary from indolent to fulminant in presentation and from mild to fatal in severity
  - The patient is frequently febrile with tachycardia, or may have a history of chills and/or sweats
  - Cough may be either nonproductive or productive; pleuritic chest pain may occur
  - Other symptoms may include fatigue, headache, myalgias, arthralgias, and gastrointestinal symptoms
  - Common complications of severe pneumonia include respiratory failure, septic shock and multiorgan failure, coagulopathy, and exacerbation of comorbid illnesses
  - Presentation may not be obvious in the elderly, who may initially display new-onset or worsening confusion with few other manifestations.

- Initial diagnosis is usually based on chest x-ray and clinical findings

- Other diagnostic modalities:
  - Gram’s stain and culture of sputum
  - Blood culture
  - Urinary antigen tests for pneumococcal and legionella antigens
  - Polymerase chain reaction tests for respiratory viral infection
  - Serology - rise in pathogen-specific IgM antibody titers

- Biomarkers, e.g., C-reactive protein and procalcitonin

- Treatment most commonly employs appropriate antimicrobial agents and supportive measures

2.52.2 Inclusion/Exclusion criteria

- Included:
  - Terms representing infective pneumonias (with or without the word “pneumonia” or “pneumonitis”), including those typically associated with an immunocompromised patient
  - Site unspecified infection terms of pathogens which often cause pneumonia (e.g.; PT *Pneumococcal infection*), except those causing infections of the immune-compromised host
  - Pathogens predominantly causing pneumonia are included in the narrow search. Other pathogens that may be associated with pneumonia are included in the broad search.
  - Signs and symptoms specific of pneumonia (e.g. PT *Pleuritic pain*)
  - Positive results of tests under HLGT *Microbiology and serology investigations* related to pathogens which often cause pneumonia
  - Terms pertaining to diagnostic imaging, blood gas, auscultation, or other investigation terms closely related to infective pneumonia

- Excluded:
  - Immune mediated and eosinophilic pneumonias (which can be identified using SMQ *Eosinophilic pneumonia*)
  - Pneumonias resulting from injury, radiation, toxicity or medical procedures, except PT *Post procedural pneumonia*, since post-operative / post-procedural pneumonias are usually a type of hospital-acquired pneumonia caused by infection. PT *Pneumonia aspiration* is also excluded.
  - Site-unspecified infection terms of pathogens which cause pneumonia of the immune-compromised host (e.g., PT *Pneumocystis jirovecii pneumonia* is included, but PT *Pneumocystis jirovecii infection* is not)
  - Site unspecified infection terms of pathogens that rarely cause pneumonia
  - Bronchitis terms

- Unspecific signs and symptoms of pneumonia (malaise, chills, rigor, fever, dyspnea)
- Congenital terms
- Unqualified investigations or investigations not specific for pneumonia

2.52.3 Notes on Implementation and/or Expectation of Query Results

Infective pneumonia (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.52.4 List of References for *Infective pneumonia (SMQ)*

- *Harrison's Principles of Internal Medicine*, 19th edition
- *Merck Manual*, 19th edition

2.53 Interstitial lung disease (SMQ)

(Production Release March 2006)

2.53.1 Definition

- Interstitial lung diseases (ILDs) are a heterogeneous group of conditions that involve the alveolar walls and perialveolar tissue.
  - Are nonmalignant and are not caused by any defined infectious agents
- Initial response is inflammation in the air spaces and alveolar walls.
  - If chronic, inflammation spreads to adjacent portions of interstitium and vasculature and eventually produces interstitial fibrosis.
- Scarring and distortion of lung tissue leads to significant derangement of gas exchange and ventilatory function.
- Inflammation also can involve the conducting airways.
  - Bronchiolitis obliterans associated with organizing pneumonia is probably part of the spectrum of ILD.
- ILDs have been difficult to classify because approximately 180 known individual diseases are characterized by interstitial lung involvement (either primary disease or part of a multiorgan process, e.g., collagen vascular diseases).
- ILDs can be classified into two groups:
  - Known causes
  - Unknown causes
- Each of these groups can be divided into subgroups:
  - Presence of histologic evidence of granulomas in interstitial or vascular areas
  - Absence of granulomas

2.53.2 Inclusion/Exclusion Criteria

- Included:
  - Terms referring to lung diseases characterized by alveolitis, interstitial inflammation, and fibrosis
  - ILDs with known cause and unknown cause
  - ILDs with granulomas (e.g., sarcoidosis) and those without granulomas (e.g., Goodpasture’s syndrome).
  - Narrow search terms include those specifically indicating an interstitial pulmonary reaction or possibly worsening of ILD under treatment with a suspect drug.

    - Including ILDs with possible allergic component and interstitial lung reactions to radiation
    - Interstitial lung reactions to radiation would also be expected to be included as these might signify increased sensitivity to radiation toxicity combined with drug exposure and would thus still qualify as an adverse reaction
    - PT *Lung infiltration* is included in narrow search to increase sensitivity based on the Phase I testing
  - Broad search terms include those referring to interstitial pulmonary disease, even if not expected to be a drug-related event (e.g., adult respiratory distress syndrome and pulmonary hemorrhage syndrome terms, which are indicative of ILD)
- Excluded:
  - Signs and symptoms of interstitial lung disease
  - Terms relating to infections and occupational exposure
  - Terms not related to direct or allergic toxicity of suspect medical treatment
  - Abnormal chest X-ray terms
  - Non-cardiogenic pulmonary edema terms
  - The following conditions are excluded unless the narrative indicates the involvement of interstitial pulmonary reaction: amyloidosis, inherited insterstitial pulmonary diseases, gastrointestinal or liver disease, GVHD, inorganic dust induced interstitial lung diseases

2.53.3 Notes on Implementation and/or Expectation of Query Results

Interstitial lung disease (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.54 Ischaemic colitis (SMQ)

(Production Release March 2008)

2.54.1 Definition

- Ischaemic colitis is injury of large intestine that results from interruption of its blood supply
- Caused by transient reduction in blood flow to colon
- Most patients are elderly, but also occurs in younger age groups associated with oral contraceptive use, vasculitis, and hypercoagulable states
- Clinical picture depends upon degree and rate of development of ischemia
  - Acute fulminant ischaemic colitis:
    - Severe lower abdominal pain, rectal bleeding, and hypotension
    - Dilatation of colon (severe cases)
    - Signs of peritonitis (severe cases)
  - Subacute ischaemic colitis:
    - Most common clinical variant
    - Produces lesser degrees of pain and bleeding (occurring over several days or weeks)
- Ischemic colitis is second most common cause of lower gastrointestinal bleeding
- Diagnosis made by colonoscopy
- Usually develops in absence of major vessel occlusion
- Associated factors:
  - Decreased cardiac output
  - Arrhythmia
  - Trauma
  - Surgery (e.g., aorto-iliac surgery)
  - Vasculitis
  - Coagulation disorders
  - Chronic obstructive pulmonary disease
  - Irritable bowel syndrome
  - Specific drugs
- More than two thirds of patients respond to conservative measures (IV fluids, bowel rest, antibiotics). Surgery rarely required

2.54.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for ischemic colitis and other forms of colitis
  - Terms for associated conditions that typically develop as a consequence of ischemic colitis
  - Related investigation terms
- Excluded:
  - Terms that, in MedDRA, relate exclusively to infections
    - NOTE: terms that have a primary link to SOC *Infections and infestations* and a secondary link to another SOC are therefore included – *e.g*., PT *Colon gangrene*
  - Terms relating to gastrointestinal strictures and stenoses
  - Terms for nonspecific clinical symptoms of ischemic colitis (*e.g*., PT *Abdominal pain*)
  - PT *Melaena*
    - Refers to upper gastrointestinal bleeding
    - Created too much noise during database testing

(NOTE: In the broad search, terms describing hemorrhage tended to retrieve cases that were “noise” especially for one of the tested positive control products. The “noise” may be considerable if the compound is used in patients with gastrointestinal disease.)

2.54.3 Notes on Implementation and/or Expectation of Query Results

Ischaemic colitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.54.4 List of References for *Ischaemic colitis (SMQ)*

- Satyaprasad V Alapati SV, Mihas AA. When to suspect ischemic colitis. Postgrad Med 1999;105 (4).
- Michel Huguier et al.Ischemic colitis; Am J Surg 2006; 192: 679 – 684.
- Higgins PDR, Davis KJ, Laine L. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther 2004; 19; 729 – 738.
- Harrison’s Principles of Internal Medicine, 11th edition 1987; 1297.

2.55 Ischaemic heart disease (SMQ)

(Production Release March 2006)

2.55.1 Definition

- Myocardial ischemia refers to lack of oxygen due to inadequate perfusion of the myocardium; causes an imbalance between oxygen supply and demand.
- Most common cause of myocardial ischemia is obstructive atherosclerotic disease of epicardial coronary arteries.

2.55.2 Inclusion/Exclusion Criteria

- Included:
  - All types of conditions related to myocardial ischemia
- Excluded:
  - Terms representing known risk factors for myocardial ischemia
  - PT *Aspartate aminotransferase abnormal* and PT *Aspartate aminotransferase increased* are excluded because they retrieved a large number of irrelevant cases in Phase I testing

NOTE: Original version of the broad searches included PT *Aspartate aminotransferase abnormal* and PT *Aspartate aminotransferase increased*. These terms were removed based on test results (retrieved a large number of irrelevant cases). If examining older data (i.e., prior to year 2000), one might consider including these terms in the query.

2.55.3 Hierarchy Structure

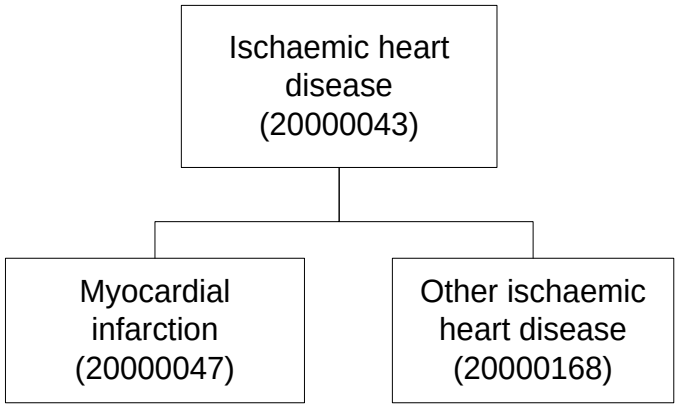

Figure 2-15. Hierarchy Structure of *Ischaemic heart disease (SMQ)*

In Version 12.0, per user's request, *Other ischaemic heart disease (SMQ)* was added at level 2 to group the PTs that had been linked to *Ischaemic heart disease (SMQ)* but did not belong to the level 2 sub-SMQ *Myocardial infarction (SMQ)*. Unlike *Myocardial infarction (SMQ)*, *Other ischaemic heart disease (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic - *Ischaemic heart disease (SMQ)*.

2.55.4 Notes on Implementation and/or Expectation of Query Results

Ischaemic heart disease (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.55.5 List of References for *Ischaemic heart disease (SMQ)*

- Harrison's textbook of Internal Medicine.

2.56 Lack of efficacy/effect (SMQ)

(Production Release November 2005)

2.56.1 Definition

- "Efficacy" is defined as:
  - Ability of an intervention to produce desired beneficial effect in expert hands and under ideal circumstances
  - In pharmacology, the ability of a drug, biologic, or device to produce desired therapeutic effect
    - Independent of potency (amount of the product needed for desired effect)
- "Effect" is defined as the result produced by an action
- Lack of efficacy/effect is therefore evidence of less than the expected effect of a product
- There might be subpopulations that have a higher risk for lack of efficacy/effect; in order to identify such cases, one needs to consider types of events that may be reported in such situations for the specific product and indication
- Some company databases may have created a "lack of efficacy" flag at a case level that may also be used to search for cases

2.56.2 Inclusion/Exclusion Criteria

- Included:
  - "Generic" terms that apply to a broad cross section of products or product classes
    - This SMQ may apply to drugs, blood component/blood derivative biologics (e.g., packed red blood cells, immune globulins), devices, cellular tissue, and gene therapeutics.
  - PT *Drug tolerance* was included in this SMQ in addition to PT *Drug tolerance increased*
  - "Additional product-specific terms" address vaccines, devices, and narrowly defined products or product classes
- Excluded:
  - Terms that applied to only narrowly defined products or product classes (e.g., antihypertensives, anti-hemophilic factors)
  - Nonspecific terms (e.g., PT *Inhibitory drug interaction*)

- Users that are interested in the retrieval of Lack of efficacy/effect cases for vaccines, narrowly defined products, or product classes are recommended to review the appropriate section in the original CIOMS WG document for *Lack of efficacy/effect (SMQ)*.

2.56.3 Notes on Implementation and/or Expectation of Query Results

Lack of efficacy/effect (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.56.4 List of References for *Lack of efficacy/effect (SMQ)*

- Dorland's Illustrated Medical Dictionary, 30th Edition; 2003. pp 590-2.

2.57 Lacrimal disorders (SMQ)

(Production Release September 2009)

2.57.1 Definition

- Disorders that affect lacrimal gland and drainage system:
  - Secretory dysfunction (lacrimal insufficiency)
  - Blockage of nasolacrimal duct
  - Occlusion/stenosis of punctum
  - Lacrimal gland neoplasms
  - Inflammations and infections
- Clinical manifestations:
  - Excessive tear production
  - Dry eyes
- Causes:
  - Systemic diseases, e.g., rheumatoid arthritis
  - Drugs (e.g., diuretics) which may also exacerbate symptoms of a dry eye

2.57.2 Inclusion/Exclusion criteria

- Included:
  - Terms for lacrimal apparatus procedures (e.g., PT *Dacryocystectomy*)
  - Terms for neoplasms of lacrimal gland and duct
  - Terms for diseases and disorders of lacrimal gland and duct
  - Terms for inflammations and infections of lacrimal apparatus
- Excluded:
  - Terms for non-specific symptoms of acute dacryocystitis such as fever and leukocytosis
  - Terms for congenital lacrimal conditions (e.g., PT *Dacryostenosis congenital*)
  - Terms for trauma to lacrimal system

NOTE: Following testing and discussions with the CIOMS SMQ Working Group, it was decided that signs and symptoms of general eye disorders will be included in a separate SMQ. Therefore, the final term list for *Lacrimal disorders (SMQ)* consists only of **narrow** terms.

NOTE: PT *Tearfulness* was initially included in this SMQ as a broad term because it relates to tears and because it was thought possible that some organizations may have cases coded to PT *Tearfulness* that represent increased lacrimation of a physiologic nature (due to miscoding). Please note that this term is linked to SOC *Psychiatric disorders* under HLT *Mood alterations with depressive symptoms*. Based on the results of testing in both industry and regulatory databases, the CIOMS Working Group decided to leave all broad terms – including PT *Tearfulness* – out of the final term list for this SMQ.

NOTE: LLT *X-ray of nasolacrimal duct abnormal* is linked to PT *Face and mouth X-ray abnormal*, however, this PT has not been included in the term list for this SMQ because it is too broad for inclusion. The SMQ user may wish to review cases coded to LLT *X-ray of nasolacrimal duct abnormal* in addition to those retrieved by the included SMQ terms.

2.57.3 Notes on Implementation and/or Expectation of Query Results

Lacrimal disorders (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.57.4 List of References for *Lacrimal disorders (SMQ)*

- Elkington, AR and Khaw, PT. Eyelid and lacrimal disorders. BMJ. 1988 August 13; 297(6646): 473–477.
- Westfall, CT. Lacrimal disease. Curr Opin Ophthalmol, 1995, 6;V: 100 – 104
- Thampy, H. Eyelid and lacrimal disorders. http://www.firstinmedicine.com/summarysheets_files/Ophthalmology/Eyelid%20and%20Lacrimal%20Disorders.pdf (specific url not currently accessible)
- Disorders of the lacrimal apparatus. Merck Manual, 17th edition, 1999.

2.58 Lactic acidosis (SMQ)

(Production Release November 2005)

2.58.1 Definition

- Lactic acidosis is a form of high anion gap metabolic acidosis (fall in blood pH and reduced HCO_3 accompanied by a compensatory increase in ventilation (especially Kussmaul respiration) resulting in decreased PCO_2
- Intrinsic cardiac contractility may be depressed, but inotropic function can be normal because of catecholamine release
- Peripheral arterial vasodilatation and central vasoconstriction can be present; the decrease in central and pulmonary vascular compliance predisposes to pulmonary oedema
- Central nervous system function is depressed, with headache, lethargy, stupor, and, in some cases, even coma
- Glucose intolerance may occur
- Characterized by an increase in plasma L-lactate, which may be secondary to poor tissue perfusion (type A) or to aerobic disorders (type B; includes drugs and toxins)
- Acidosis is seldom significant unless blood lactate exceeds 5 mmol/l
- Clinical presentation in type B lactic acidosis:
  - Symptoms listed in order of frequency: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain
  - Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness (mild confusion to coma; may be accompanied by profound lethargy)
  - Definitive diagnosis depends on the identification of lactate as the organic anion causing the acidosis

2.58.2 Inclusion/Exclusion Criteria

- Included:
  - Relevant terms from SOC *Investigations* containing the word “abnormal” (e.g., PT *Blood lactic acid* abnormal) in the broad search
  - PT *Metabolic acidosis* or PT *Acidosis* in the broad search

- Excluded:
  - Terms for SOC *Investigations* with the qualifier “normal” and those with no qualifier
  - PTs that indicate clearly that the type of acidosis is not a lactic acidosis, but is of another etiology, e.g., PT *Diabetic ketoacidosis*
  - Terms for foetal and neonatal events (e.g., PT *Foetal acidosis*)
  - PTs indicating an inherited disorder, such as PT *MELAS syndrome*
  - Terms representing other known causes of lactic acidosis (such as terms for shock, anemia, malignancies, etc.)
  - Other non-specific terms (e.g., PT *Headache*)

2.58.3 Notes on Implementation and/or Expectation of Query Results

Lactic acidosis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.58.4 List of References for *Lactic acidosis (SMQ)*

- Braunwald E, Fauci A, Kasper D. Harrison’s Principles of Internal Medicine. 15th Edition, 2001 pp 285-9.
- Weatherall D, Ledingham J and Warrell D. Oxford Textbook of Medicine. Third edition, 1996; volume 2 pp 1541-44.

2.59 Lens disorders (SMQ)

(Production Release September 2008)

2.59.1 Definition

- Most common cause of reduced vision (particularly cataracts)
- Responsible for about 35% of cases of visual impairment
- Cataracts
  - May result from a number of processes (mainly age-related)
  - Usually progress slowly, but frequently only detected when reach a certain level of severity, or during ophthalmological examination
  - Symptoms often subtle (e.g., yellow vision) and often an anatomically severe cataract will not be associated with an equally severe functional loss of vision
  - Symptoms may include glare, blurred vision, altered color perception, change of refraction, and monocular diplopia
- A “sudden appearance” reported as an adverse event could actually result from a pre-existing condition
- Care should be taken in evaluating apparent association between these lesions and drug therapy.
- Definitions (from multiple sources):
  - Aphakia: absence of lens; may occur congenitally or from trauma, but is most commonly caused by extraction of a cataract
  - Cataract:
    - Congenital or acquired lack of clarity of the lens
    - Clouding of the lens
    - Opacity of lens or capsule of eye causing impairment of vision or blindness

2.59.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for resulting complications such as PT *Aphakia*
  - Therapeutic procedural terms and related complications
  - **Selected** PTs linked to HLT *Lens structural change, deposit and degeneration (excl cataracts)* (except PT *Aphakia congenital* which is excluded), HLT *Lens therapeutic procedures,* and HLT *Cataract conditions* (excluding PT *Cataract congenital*) (see also exclusion criteria)
- Excluded:

- Terms for congenital disorders with cataract as part of the syndrome. Please note that all congenital terms were initially considered for inclusion and then excluded (after discussion at the CIOMS WG meeting in August 2007)
- Terms in SOC *Social circumstances* (no more specific terms than PT *Blindness* were identified)
- Terms for infectious complication terms following cataract surgery
- Very broad terms, e.g. PT *Congenital eye disorder*, or PT *Eye operation*
- Terms for refractive and accommodative disorders
- The following terms were excluded: PT *Exfoliation syndrome* (which includes LLT *Pseudoexfoliation of lens capsule*), PT *Intraocular lens implant*, PT *Intraocular lens repositioning*, PT *Removal of foreign body from lens*, and PT *Blindness* (too non-specific)
- Terms related to trauma

NOTE: As of Version 23.0, the exclusion criterion "Terms in SOC *Investigations*" was removed from the list of exclusion criteria, because PT *Lens density increased*, added in Version 23.0, is a term in SOC *Investigations* that has been included in *Lens disorders* (SMQ). Prior to the addition of this term, there were no terms in SOC *Investigations* that were judged sufficiently specific to have been included in *Lens disorders* (SMQ).

NOTE: As of Version 18.1, PT *Phacocystectomy* and PT *Lenticular Operation* are no longer designated as excluded from *Lens disorders (SMQ)*, and are thus added to the SMQ because of their potential relevance to case identification.

NOTE: As of Version 18.0, the following terms are no longer designated as excluded from *Lens disorders (SMQ),* and are thus added to the SMQ because of their potential relevance to case identification: PT *Lenticular opacities*; PT *Lenticular pigmentation*; and PT *Posterior capsule opacification*.

NOTE: This SMQ is one of several SMQs developed or under development for ophthalmological disorders. When the entire set of SMQs is developed, a search may require use of more than one SMQ, or the entire group of SMQs, depending upon the goal of the search.

2.59.3 Notes on Implementation and/or Expectation of Query Results

Lens disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.59.4 List of References for *Lens disorders (SMQ)*

- West S Epidemiology of cataract: accomplishments over 25 years and future directions. Ophthalmic Epidemiol 2007 Jul-Aug;14(4):173-8.

- Abraham AG; Condon NG; West Gower E The new epidemiology of cataract. Ophthalmol Clin North Am 2006 Dec;19(4):415-25.
- Robman L; Taylor H External factors in the development of cataract Eye 2005 Oct;19(10):1074-82..

2.60 Lipodystrophy (SMQ)

(Production Release September 2009)

2.60.1 Definition

- HIV associated lipodystrophy:
- Abnormal central fat accumulation (lipohypertrophy)and localized loss of fat tissue (lipoatrophy)
- Some patients have only lipohypertrophy or only lipoatrophy; others have a mixed clinical presentation (less common)
- Lipohypertrophy and lipoatrophy are distinct entities with different risk factors and underlying metabolic processes
- Lipohypertrophy:
- Enlarged dorsocervical fat pad
- Circumferential expansion of the neck
- Breast enlargement
- Abdominal visceral fat accumulation
- Lipoatrophy:
  - Peripheral fat wasting
  - Loss of subcutaneous tissue in face, arms, legs, buttocks
  - Involvement of face is most common (may confer a social stigma on patient)
- Additional features of HIV lipodystrophy syndrome:
- Hyperlipidemia
- Insulin resistance
- Hyperinsulinemia
- Hyperglycemia
- Increased risk for development of diabetes mellitus and atherosclerosis
- Mechanisms for development of this syndrome are not completely understood
- HIV-1 protease inhibitor drugs and nucleoside reverse transcriptase inhibitors are implicated as follows:
- Decreased production of retinoic acid and triglyceride uptake
- Inhibition of mitochondrial DNA (mtDNA) polymerase gamma
- Inhibition of lipid metabolism

- Prevention of development of adipocytes
- There is evidence suggesting decreased insulin sensitivity, beta-cell dysfunction, and down-regulated estrogen receptor expression in adipose tissue
- HIV-1 – in absence of highly active antiretroviral treatment (HAART) – may itself cause dyslipidemia and lipodystrophy by various mechanisms
- Resting energy expenditure and lipid oxidation are higher in HAART-treated HIV-positive patients with vs. without lipodystrophy
- Symptoms include:
- Increasing abdominal girth (increasing belt or waist size**)**
- Bloating/distension
- Fat accumulation in back of neck (buffalo hump)/increasing neck size
- Increasing breast size (including gynecomastia) with or without breast pain
- Other new fat accumulations:
  - Circumscribed (lipomas)
  - General (e.g., increase chest size)
- Lipoatrophy findings:
- Marked depletion of fat in nasolabial and buccal fat pad
- Thinness of extremities with prominent veins
- Loss of volume in subgluteal region
- Laboratory findings:
- Hypertriglyceridemia
- Hypercholesterolemia
- Low levels of high density lipoprotein
- Hyperglycemia

2.60.2 Inclusion/Exclusion criteria

- Included:
  - Terms for conditions of lipodystrophy, lipoatrophy, and lipohypertrophy (e.g., PT *Lipodystrophy acquired*)
  - Terms for signs and symptoms of lipodystrophy (e.g., PT *Fat tissue increased*, PT *Central obesity*)
  - Terms for related metabolic conditions characteristic of lipodystrophy in HIV patients (e.g., PT *Insulin resistance*); see Exclusion criteria for exceptions

- Terms for laboratory findings (and associated clinical conditions) characteristic of lipodystrophy in HIV patients (e.g., PT *Blood cholesterol increased*, PT *Hypertriglyceridaemia*); note that laboratory terms qualified by the word “abnormal” are also included (e.g., PT *Blood cholesterol abnormal*)
- Terms for procedures associated with lipodystrophy (e.g., PT *Lipoma excision*)

- Excluded:
  - Terms for congenital conditions (e.g., PT *Congenital generalised lipodystrophy*)
  - PT *HIV wasting syndrome* as this is a distinct syndrome unrelated to HIV associated lipodystrophy
  - Terms for long term metabolic consequences associated with lipodystrophy such as terms related to atherosclerosis
  - Diabetes mellitus and hyperglycemia terms (based on testing results)
  - PT *Obesity* and PT *Abdominal distension*; in testing, these terms were either very “noisy” or not efficient in returning cases of interest

NOTE: Users may wish to consider including PT *Abdominal distension* if they are interested in events related to pre-natal exposure to antiretroviral therapy as this event has been described in this setting

2.60.3 Notes on Implementation and/or Expectation of Query Results

Lipodystrophy (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

Although the clinical and investigational terms included in *Lipodystrophy (SMQ)* primarily represent specific concepts that are relevant to the identification of cases of lipodystrophy, the included broad scope term PT *Dyslipidaemia* had proven to be of value in retrieving reports of interest during the testing phase of the development of this SMQ. If it is desirable to conduct a customized query using *Lipodystrophy (SMQ)* that would include additional concepts that relate to disorders of lipid metabolism, users may consider the inclusion of selected terms from *Dyslipidaemia (SMQ)*, or *Dyslipidaemia (SMQ)* in its entirety, for such a search.

2.60.4 List of References for *Lipodystrophy (SMQ)*

- Robles, DT. *Lipodystrophy, HIV*. eMedicine, 24 June 2008. http://www.emedicine.com/derm/topic877.htm
- WHO/Forum for Collaborative HIV Research Joint Meeting: ARV Drugs Adverse Events, Case Definition, Grading, Laboratory Diagnosis and

Treatment Monitoring, Background Document (Draft), 28 – 29 February 2008.

2.61 Malignancies (SMQ)

(Production Release March 2007)

2.61.1 Definition

- For a definition of malignant tumours, reference was made to relevant textbooks (e.g. DeVita et al 2005, Peckham et al 1995)

- *Malignancies (SMQ)* includes terms for: all types of malignant or unspecified tumours; malignancy related conditions; malignancy related therapeutic and diagnostic procedures; and tumour markers. [Note: premalignant disorders are in a separate SMQ: *Premalignant disorders (SMQ)*.]

- This SMQ consists of ten sub-SMQs which can be used separately or in combination.

- *Malignancies (SMQ)* is subdivided into four sub-SMQs:
  - *Malignant or unspecified tumours (SMQ)*
  - *Malignancy related conditions (SMQ)*
  - *Malignancy related therapeutic and diagnostic procedures (SMQ)*
  - *Tumour markers (SMQ)*

- Sub-SMQ *Malignant or unspecified tumours (SMQ)* contains all MedDRA terms for malignant or unspecified tumors, which is further subdivided into two separate sub-SMQs:
  - *Malignant tumours (SMQ)*
  - *Tumours of unspecified malignancy (SMQ)*

- Sub-SMQ *Malignant tumours (SMQ)* is subordinated by:
  - *Haematological malignant tumours (SMQ)*
  - *Non-haematological malignant tumours (SMQ)*

- Sub-SMQ *Tumours of unspecified malignancy (SMQ)* is subordinated by:
  - *Haematological tumours of unspecified malignancy (SMQ)*
  - *Non-haematological tumours of unspecified malignancy (SMQ)*

2.61.2 Inclusion/Exclusion Criteria

- Included:
  - *Malignant or unspecified tumours (SMQ)*
    - All MedDRA terms for malignant or unspecified tumors

- *Malignancy related conditions (SMQ)*
  - Terms for malignancy related conditions

- *Malignancy related therapeutic and diagnostic procedures (SMQ)*
  - Terms for therapeutic and diagnostic procedures used to treat malignancies
  - Some of these procedures are also used for the treatment of non-malignant conditions

- *Tumour markers (SMQ)*
  - MedDRA terms related to tumor markers
  - For European Group on Tumour Markers, please reference the web site at http://ar.iiarjournals.org/content/27/4A/1901

- Excluded:
  - Cyst terms

  - Terms related to benign tumors

  - For *Malignant or unspecified tumours (SMQ)*
    - Terms for malignancy related conditions are excluded from this sub-SMQ.
    - Nevus terms are excluded.

NOTE: In version 20.0, four additional sub-SMQs were added to *Malignancies (SMQ)* to further enhance specificity options for case identification: *Haematological malignant tumours (SMQ)* and *Non-haematological malignant tumours (SMQ)* were added as sub-SMQs of *Malignant tumours (SMQ)*; *Haematological tumours of unspecified malignancy (SMQ)* and *Non-haematological tumours of unspecified malignancy (SMQ)* were added as sub-SMQs of *Tumours of unspecified malignancy (SMQ).* The entire hierarchy of sub-SMQs that comprise *Malignancies (SMQ)* is depicted in Figure 2-16.

NOTE: During development and testing phase, the WG identified PT *Prolactinoma* (which has subsequently been demoted as an LLT under PT *Prolactin-producing pituitary tumour* in Version 19.1) should be under benign classification and recommended to remove this PT from the search list of *Malignant or unspecified tumours (SMQ)*. A change request was submitted to the MSSO for the correction of MedDRA classification.

NOTE: Because liver ablation is an accepted procedure primarily used to treat patients with unresectable hepatic malignancies, PT *Liver ablation* has been added as a broad term to *Liver malignant tumours (SMQ)* in Version 17.0 to facilitate case identification.

NOTE: In Version 14.0, two new sub-SMQs have been added to sub-SMQ *Malignant or unspecified tumours (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: The sub-SMQ *Malignant or unspecified tumours (SMQ),* linked to *Malignancies (SMQ),* is intended to represent all anatomical locations. If a user is interested in tumors in a particular anatomical site, there are other SMQs and sub-SMQs for anatomical-specific malignant and unspecified neoplasms, such as *Prostate neoplasms, malignant and unspecified (SMQ)*, sub-SMQ *Liver neoplasms, malignant and unspecified (SMQ)*.

NOTE: *Malignancy related conditions (SMQ),* together with terms in *Malignant or unspecified tumours (SMQ)* and *Malignancy related therapeutic and diagnostic procedures (SMQ)*, will identify cases referring to malignancies and cases of malignancy related conditions or procedures reported for pre-existing malignancies

NOTE: The sub-SMQ *Malignancy related therapeutic and diagnostic procedures (SMQ)* includes a variety of PTs which describe chemotherapy or radiotherapy treatment. Please be aware, however, that there are some MedDRA LLTs which relate to chemotherapeutic or radiotherapeutic associated adverse events and are not included in this sub-SMQ. Such LLTs are not linked to chemotherapy or radiotherapy PTs. The following are several examples:

SOC	PT	LLT
Metabolism and nutrition disorders	*Decreased appetite*	*Anorexia post chemotherapy*
Blood and lymphatic system disorders	*Anaemia*	*Anaemia post chemotherapy*
Gastrointestinal disorders	*Diarrhoea*	*Diarrhoea post chemotherapy*
Injury, poisoning and procedural complications	*Procedural vomiting*	*Vomiting post radiotherapy*
Immune system disorders	*Secondary immunodeficiency*	*Immunodeficiency secondary to chemotherapy*

Table 2-9. Terms not included in sub-SMQ *Malignancy related therapeutic and diagnostic procedures (SMQ)*

2.61.3 Hierarchy Structure

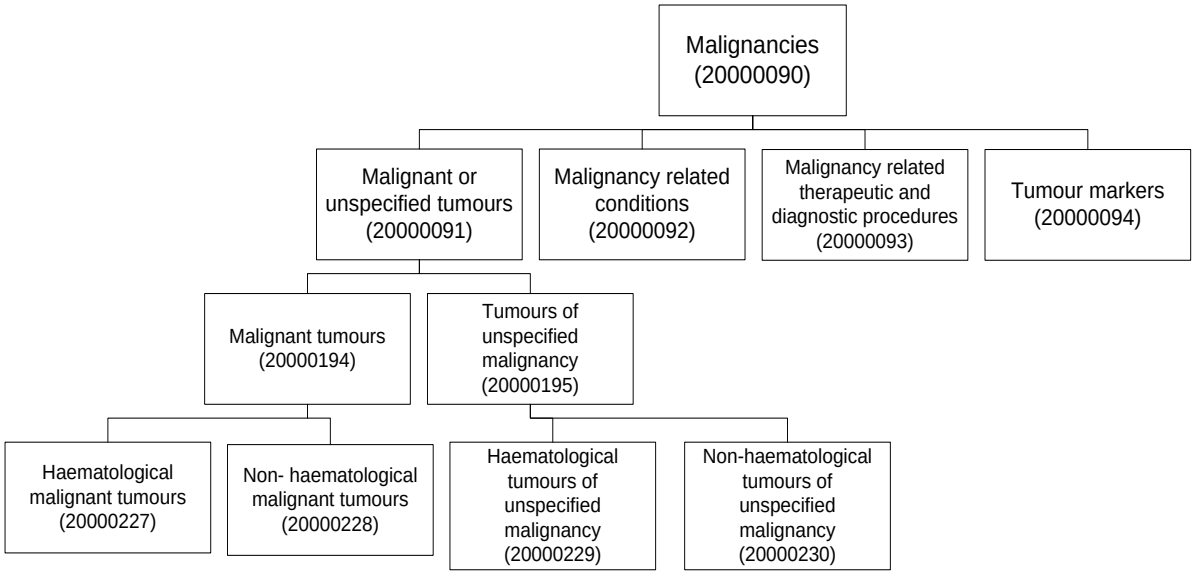

Figure 2-16. Hierarchy Structure of *Malignancies (SMQ)*

2.61.4 Notes on Implementation and/or Expectation of Query Results

Malignancies (SMQ) is a hierarchical SMQ with only narrow search terms. Therefore, narrow search and broad search return the same result for superordinate and all subordinate SMQs. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.61.5 List of References for *Malignancies (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H,.Veronesi, U. Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://egtm.eu/

2.62 Malignant lymphomas (SMQ)

(Production Release March 2013)

2.62.1 Definition

- Lymphoma = heterogeneous group of malignancies generally divided into non-Hodgkin lymphoma (NHL) and Hodgkin disease

- NHL
  - About 85% of lymphomas
  - Median age at diagnosis is sixth decade
  - Some forms of NHL – such as Burkitt lymphoma and lymphoblastic lymphoma – occur in younger patients
  - Classified by several different systems (e.g., Working Formulation, REAL classification) based on morphology and clinical behavior.
  - Variety of laboratory and imaging studies are used to evaluate and stage NHL
  - Treatment depends on stage, grade, type and various patient factors (symptoms, age, etc.)
  - May result from:
    - Chromosomal translocations
    - Infections (Epstein-Barr virus [EBV] and hepatitis C virus)
    - Environmental factors (radiation exposure and chemotherapy)
    - Immunodeficiency states
    - Chronic inflammation
  - Clinical presentation depends on location of disease and biologic characteristics (e.g., low grade vs. high grade)
  - Peripheral adenopathy and B symptoms (fever, night sweats, weight loss) are characteristic for some forms of NHL

- Hodgkin lymphoma
  - Has histologic findings, biologic behavior, and clinical characteristics distinct from NHL
  - Excisional lymph node biopsy generally recommended to establish diagnosis
  - Various imaging studies used to determine disease stage
  - Lymphadenopathy and constitutional B symptoms are characteristic
  - Treated with multiagent chemotherapy, plus or minus radiation therapy
  - Etiology of Hodgkin lymphoma has not been established
    - Certain infectious agents, e.g. EBV, may be involved
    - HIV infected patients have a higher incidence
    - Genetic predisposition may also play a role

2.62.2 Inclusion/Exclusion criteria

- Included:
  - Terms that describe various types of non-Hodgkin's lymphoma (e.g., PT *Mantle cell lymphoma stage III*)
  - Terms for various forms of Hodgkin's disease/Hodgkin lymphoma (e.g., PT *Hodgkin's disease nodular sclerosis refractory*)
  - Relevant investigation terms that have at least the potential to retrieve cases of interest with minimal noise; these terms are generally broad scope terms (e.g., PT *Lymphocyte morphology abnormal*)
- Excluded:
  - Terms for congenital conditions
  - Terms for lymphoproliferative disorders except select disorders such as PT *Post transplant lymphoproliferative disorder* because of the relationship to immunosuppressive therapy and potential for development into lymphoma
  - Terms for non-specific signs and symptoms of lymphoma. Almost all signs and symptoms of lymphoma are non-specific. The most characteristic sign of lymphoma – lymphadenopathy – can be seen with a variety of non-lymphoma and non-neoplastic conditions. Symptoms are typically constitutional, e.g. "B symptoms" such as weight loss, fever, night sweats, etc.)
  - Terms for histiocytoses

NOTE: Testing in a regulatory database determined that some cases of interest were found with PT *Pseudolymphoma* for data entered in 2006 or earlier; for more recent cases, PT *Pseudolymphoma* did not retrieve relevant cases. Inclusion of PT *Pseudolymphoma* in the broad scope for searches of data from 2006 and earlier might be considered.

2.62.3 List of References for *Malignant lymphomas (SMQ)*

- Vinjamaram, S. Non-Hodgkin lymphoma. http://emedicine.medscape.com/article/203399-overview
- Dessain, SK. Hodgkin lymphoma. http://emedicine.medscape.com/article/201886-overview

2.63 Medication errors (SMQ)

(Production Release March 2016)

2.63.1 Definition

- Medication errors are defined as any preventable events that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer.
  - Such events may be related to professional practice, health care products, procedures and systems, including prescribing, order communication, product labeling, packaging and nomenclature, compounding, dispensing, distribution, administration, education, monitoring and use.
  - A medication error can ultimately result in an adverse drug reaction (medication error with an ADR) or may have no clinical consequences (medication error without an ADR).
  - A medication error can also be intercepted prior to the patient's exposure to the error.
  - A potential medication error is a scenario which does not involve an actual patient, and represents circumstances or information capable of leading to the occurrence of a medication error

- Medication errors cause a large number of ADRs annually:
  - create a major public-health burden representing 18.7–56% of all adverse drug events among hospital patients.
  - may cause unintended harm
  - are considered preventable.

- Medication errors result from a variety of human (e.g., healthcare professional; care giver; patient) and product-related reasons, for example:
  - miscommunication of drug orders due to poor handwriting
  - confusion between drugs with similar names
  - poor packaging design
  - confusion of dosing units
  - unclear instructions

- Medication errors can have an impact on:
  - patients
  - healthcare professionals
  - pharmaceutical manufacturers

- regulatory agencies
- health insurance providers
- national patient safety organisations

2.63.2 Inclusion/Exclusion Criteria

- Included:
  - Terms referring to a medication error according to the above definition. These terms are included as narrow scope terms.
  - Terms which do not specifically represent a medication error, but have a significant potential to identify medication errors for their frequent association with them, such as product label issue terms, product exposure terms, and terms referring to administration of contraindicated drugs or other unapproved uses. These terms are generally included as broad scope terms.

- Excluded:
  - Intentional/deliberate use terms: by definition these are not medication errors
  - Product contamination terms
  - Transmission of infectious agent terms
  - Off label use terms
  - Drug interaction terms
  - Counterfeit product terms
  - Drug incompatibility terms
  - Exposure terms that do not refer to product or drug exposure such as PT *Exposure to body fluid*
  - Terms for non-specific and broad concepts that might produce substantial “noise” in data retrieval, e.g., PT *Device issue*, PT *Product quality issue*, PT *Poisoning*

2.63.3 Notes on Implementation and/or Expectation of Query Results

Medication errors (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.63.4 List of References for *Medication errors (SMQ)*

- Creation of a better medication safety culture in Europe: Building up safe medication practices Expert Group on Safe Medication Practices (2006).

- Guideline on good pharmacovigilance practices (GVP). Module VI – Management and reporting of adverse reactions to medicinal products.

- Center for Drug Evaluation and Research (CDER), the Division of Medication Error Prevention and Analysis (DMEPA): http://www.fda.gov/drugs/drugsafety/medicationerrors/

- Guidance for Industry. Safety Considerations for Product Design to Minimize Medication Errors. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research December 2012 Drug Safety.

- European Medicine Agency: Medication errors. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000570.jsp

- Health Canada's role in the Management and Prevention of Harmful Medication Incidents. http://www.hc-sc.gc.ca/dhp-mps/medeff/cmirps-scdpim-eng.php#a1

- National Coordinating Council for Medication Error Reporting and Prevention (US); 2001. About medication errors. https://www.nccmerp.org/about-medication-errors. Accessed December 1, 2017.

2.64 Myelodysplastic syndrome (SMQ)

(Production Release September 2013)

2.64.1 Definition

- Myelodysplastic syndrome (MDS) = heterogeneous group of related clonal disorders of hematopoiesis
- Characterized by:
  - Hyper- or hypocellular bone marrow
  - Abnormal cell morphology
  - Abnormal maturation
  - Peripheral blood cytopenias
  - Ineffective blood cell production
- All three myeloid cell lineages (erythrocytic, granulocytic, and megakaryocytic) may be involved.
- Considered a premalignant condition
  - Subgroup of patients often progresses to acute myelogenous leukemia (AML).
- May present with:
  - Anemia
  - Thrombocytopenia
  - Neutropenia
- Diagnostic approach includes:
  - Complete blood count with differential, peripheral blood smear
  - Bone marrow studies
- Treatment:
  - Supportive therapy, including transfusions
  - Possible bone marrow stimulation
  - Cytotoxic chemotherapy
  - Bone marrow transplantation has a limited role
- May be caused by exposure to:
  - Cytotoxic chemotherapy
  - Radiation
  - Viral infection
  - Genotoxic chemicals (e.g., benzene)
- May be **primary** (i.e., no known exposure) or **secondary** (i.e., related to exposures described above)
- Cytogenetics include patients with:
  - Normal karyotype

  - Balanced chromosomal abnormality and generation of fusion oncogenes
  - Complex karyotypes (usually more than three abnormalities)
- May occur at any age but primarily affects the elderly
- French-American-British classification:
  - Refractory anemia (RA)
  - RA with ringed sideroblasts (RARS)
  - RA with excess blasts (RAEB; 6-20% myeloblasts)
  - RAEB in transition to AML (RAEB-T; 21-30% myeloblasts)
  - Chronic myelomonocytic leukemia (CMML)
- 2008 WHO classification:
  - Refractory cytopenia with unilineage dysplasia
  - RARS
  - RAEB
  - Refractory cytopenia with multilineage dysplasia
  - MDS with isolated deletion of 5q
  - MDS, unclassifiable
  - Childhood MDS

2.64.2 Inclusion/Exclusion criteria

- Included:
  - Terms for diseases/disorders as presented under international classifications of MDS (e.g., PT *Refractory anaemia with ringed sideroblasts*)
  - Terms for relevant laboratory findings highly specific for MDS, including some bone marrow terms (e.g., PT *Bone marrow myelogram abnormal*)
  - Terms for other associated conditions related to the clinical expression of MDS, even if not associated with a single or specific investigation result (e.g., PT *Pancytopenia*)
  - Terms for therapeutic procedures highly specific for MDS (e.g., PT *Allogenic bone marrow transplantation therapy*)

- Excluded:
  - Terms for non-specific signs, symptoms and procedures related to the trilineage cytopenias of MDS (e.g., PT *Fatigue* for anemia; PT *Contusion* for thrombocytopenia, infection terms for neutropenia, etc.)
  - Transfusion terms

NOTE: SMQ *Myelodysplastic syndrome* focuses on cases likely to represent this condition; hence, broad concepts that could represent findings in MDS – e.g., PT *Leukopenia* – but could also represent a host of unrelated conditions are specifically excluded from this SMQ. The user may wish to apply *Myelodysplastic syndrome (SMQ)* initially to search for cases of interest; the user may optionally wish to also apply *Haematopoietic cytopenias (SMQ)* to extend the range of cases that represent cytopenias and that may also describe forms of MDS.

2.64.3 List of References for *Myelodysplastic syndrome (SMQ)*

- Besa, EC**,** Woermann, UJ, Krishnan, K. Myelodysplastic syndrome. eMedicine, 10 October 2011; http://emedicine.medscape.com/article/207347-overview
- Tefferi, A and Vardiman, JW. Myelodysplastic syndromes. N Engl J Med 2009, 361(19): 1872 - 1885

2.65 Neuroleptic malignant syndrome (SMQ)

(Production Release March 2006)

2.65.1 Definition

- Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal disorder characterized by hyperthermia, muscle rigidity, altered consciousness, and autonomic dysfunction as a complication of treatment with neuroleptic drugs.
- The mechanism by which NMS occurs appears to be related to the antidopaminergic activity of the neuroleptic drugs.
- Symptoms similar to NMS have been reported:
  - In non-schizophrenic patients treated with dopamine-depleting drugs (such as reserpine)
  - Following withdrawal of indirect dopamine receptor agonists in patients with Parkinson's disease
  - In association with intoxication from anticholinergic agents, amphetamines, lithium carbonate, cocaine, and phencyclidine
- Diagnosis is usually based on the development of severe muscle rigidity and elevated temperature in patients treated with neuroleptic drugs that is accompanied by some combination of autonomic dysfunction (diaphoresis, incontinence, tachycardia, elevated or labile blood pressure), dysphagia, tremor, myoclonus, changes in consciousness ranging from confusion to coma, mutism, leucocytosis, and laboratory evidence of muscle injury such as elevated creatine phosphokinase (CPK)
- There do not appear to be any major differences in the clinical presentation reported with the traditional neuroleptics and the newer atypical antipsychotic agents.

2.65.2 Inclusion/Exclusion Criteria

- Included:
  - PTs related to NMS and its major manifestations, such as fever, rigidity, myoclonus, tremor, muscle injury, altered consciousness, autonomic dysfunction, leukocytosis, and increased CPK.
- Excluded:
  - There were no specific exclusion criteria used.

2.65.3 Algorithm

Cases to be selected for further review would include any cases reporting at least one of the PTs listed for Category A (narrow scope) or any case reporting some combination of at least one PT from each of the three groups of PTs listed as Categories B, C and D (broad scope).

- Category A* (narrow scope)
  - PT *Neuroleptic malignant syndrome,* PT *Serotonin syndrome,* or PT *Hyperthermia malignant* representing specific reports of NMS or the similar conditions serotonin syndrome or malignant hyperthermia (which might be easily misdiagnosed as NMS).
- Category B, C, and D* (broad scope): the definitions of category B, C, and D are as follows:
  - Category B (fever-related PTs)
  - Category C (muscle rigidity or injury-related PTs)
  - Category D (other relevant NMS-related PTs, including investigation results)

*Note that Category A corresponds to Category 1 as described in the CIOMS documentation. Categories B, C, and D correspond to Category 2 fever-related search terms, Category 2 muscle rigidity/injury-related search terms, and Category 2 other relevant NMS-related search terms, respectively.

2.65.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Neuroleptic malignant syndrome (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Neuroleptic malignant syndrome (SMQ)* is A or (B and C and D). Cases filtered by the algorithm can be listed for output.

2.65.5 List of References for *Neuroleptic malignant syndrome (SMQ)*

- Levenson JL. Neuroleptic malignant syndrome. *Amer J Psychiatry* 1985; 142(10):1137-1145.

- Caroff SN and Mann SC. Neuroleptic malignant syndrome. *Medical Clinics of North America* 1993; 77(1):185-202.
- Neuroleptic malignant syndrome. *Diagnostic and Statistical Manual of Mental Disorders (4th Ed)*. American Psychiatric Association: Washington DC, 1994, pg. 739-742.
- Velamoor VR. Neuroleptic malignant syndrome: recognition, prevention and management. *Drug Safety* 1998; 19(1):73-82.
- Neuroleptic malignant syndrome. *Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for Their Use*. Bankowski Z, Bruppacher R, Crusius I *et al* (Eds). Council for International Organizations of Medical Sciences: Geneva, 1999, pg. 31-32.
- Simpson GM, Pi EH, and Sramek JJ. Neuroleptic and antipsychotic drugs. *Meyler's Side Effects of Drugs (14th Ed)*. Dukes MNG and Aronson JK (Eds). Elsevier: New York, 2000, pg. 139-163.
- Crismon ML and Dorson PG. Schizophrenia. *Pharmacotherapy: A Pathophysiologic Approach (5th Ed)*. DiPiro JT, Talbert RL, Yee GC *et al* (Eds). McGraw-Hill: New York, 2002, pg. 1219-1242.
- Hasan S and Buckley P. Novel antipsychotics and the neuroleptic malignant syndrome: a review and critique. *Amer J Psychiatry* 1998; 155(8):1113-1116.
- Caroff SN, Mann SC, and Campbell EC. Atypical antipsychotics and neuroleptic malignant syndrome. *Psychiatric Annals* 2000; 30(5):314-321.
- Ananth J, Parameswaran S, and Gunatilake S *et al.* Neurolepetic malignant syndrome and atypical antipsychotic drugs. *J Clin Psychiatry* 2004; 65(4):464-470.

2.66 Noninfectious diarrhoea (SMQ)

(Production Release September 2013)

2.66.1 Definition

- *Noninfectious diarrhoea (SMQ)* intended to retrieve cases that may be drug related
  - May include antibiotic associated diarrhea not caused by *Clostridium difficile* or other infectious pathogens
- Diarrhea defined as:
  - Increased frequency of bowel movements (>3 in 24 hours), and/or
  - Decreased stool consistency, and/or
  - Increased stool weight (>200g in 24 hours)
- Common side effect of many classes of medications
- Accounts for high percentage of all adverse drug effects
- Hundreds of drugs have been implicated in causing diarrhea. Most frequent are:
  - Antibiotics
  - Laxatives
  - Antihypertensives
  - Lactulose or sorbitol containing products
  - Antineoplastics
  - Antiretroviral drugs
  - Magnesium containing compounds
  - Antiarrhythmics
  - Non-steroidal anti-inflammatory drugs
  - Colchicine
  - Antacids and acid-reducing agents
  - Prostaglandin analogs
  - Many supplements
- Mechanisms of noninfectious diarrhea:
  - Non-inflammatory (e.g., osmotic or secretory diarrhea)
  - Inflammatory (e.g., cytotoxic effects of agents leading to intestinal mucositis)

2.66.2 Inclusion/Exclusion criteria

- Included:
  - Terms indicating diarrhea

- Terms for gastrointestinal inflammatory conditions mainly associated with diarrhea, such as enteritis, colitis, caecitis, jejunitis, gastroenteritis concepts
- Terms for gastrointestinal signs for diarrhea, e.g. PT *Anal incontinence*
- Terms for laboratory concepts indicating non-infectious etiology for diarrhea, e.g. PT *Culture stool negative*
- Terms for therapy concepts for diarrhea, e.g. PT *Antidiarrhoeal supportive care*

- Excluded:
  - Terms with infective etiologies, e.g. PT *Bacterial diarrhoea*, PT *Pseudomembranous colitis*
  - Terms for malabsorption and intolerance syndromes commonly associated with diarrhea, e.g. PT *Lactose intolerance*, PT *Coeliac disease,* PT *Intestinal resection,* PT *Short-bowel syndrome*
  - Terms for diagnostic/etiology concepts where diarrhea is a common sign, e.g. PT *Diverticulitis*, PTs indicating an inflammatory bowel disease (such as PT *Crohn's disease*, PT *Colitis ulcerative,* PT *Inflammatory bowel disease,* PT *Mastocytic enterocolitis)*, PT *Carcinoid syndrome*, PT *Hyperthyroidism*, PT *Gastrointestinal amyloidosis*, PT *Lupus enteritis*, PT *HIV enteropathy*, PT *Short-bowel syndrome*
  - PT *Necrotising colitis* as testing did not show evidence of non-infectious origin in the reviewed cases

2.66.3 List of References for *Noninfectious diarrhoea (SMQ)*

- Chassany O, Michaux A, Bergmann JF. Drug-induced diarrhoea. Drug Safety, 2000; 22(1):53-72

2.67 Noninfectious encephalitis (SMQ)

(Production Release September 2007)

2.67.1 Definition

- Encephalitis is defined as inflammation of the brain
- Commonly has an infectious etiology
- May also be drug-induced (focus of this SMQ)
- Mixed disorders such as encephalomyelitis, encephalomyeloradiculitis, or encephalo-myelopathy may present with overlapping symptoms
- Signs and symptoms include:
  - Acute febrile illness characteristic of meningitis
  - Confusion
  - Behavioral abnormalities, including frank psychosis
  - Altered level of consciousness
  - Focal or generalized seizures
  - Focal neurological disturbances including aphasia, ataxia, hemiparesis, involuntary movements, cranial nerve deficits
- Involvement of the hypothalamic-pituitary axis may result in temperature dysregulation, diabetes insipidus, or development of SIADH
- Characteristic cerebrospinal fluid (CSF) profile consists of lymphocytic pleocytosis, mildly elevated protein concentration and normal glucose concentration
- MRI, CT, and EEG abnormalities may occur

2.67.2 Inclusion/Exclusion Criteria

- Included:
  - Terms relating to irritability, confusion, stupor, coma, seizures, cranial neuropathies, altered consciousness, personality changes, and paresis (in the broad search as they may be expected to cause noise)
  - PT *Psychiatric symptom (*could be used to code various psychiatric symptoms that might be reported with encephalitis)
  - PTs containing “neonatal” (a possible drug-induced cause cannot be excluded e.g., PT *Coma neonatal*)
  - LLT *Meningoencephalitis* maps to PT *Encephalitis* and hence is covered by inclusion of this PT

- PT *Musculoskeletal stiffness* was included (in the broad search) because it contains the LLTs *Neck stiffness* and LLT *Back stiffness*, despite the potential risk of retrieving cases with other LLTs such as LLT *Stiff fingers*
- PTs for delirium (possible consequence of encephalitis, e.g., PT *Delirium* and PT *Delirium febrile*)
- Investigation terms with a qualifier (*e.g*. PT *Electroencephalogram abnormal*)
- Seizure terms except those with known etiology (such as PT *Hypoglycaemic seizure*, see exclusion criteria)
- Terms relating to focal central nervous system signs, such as ataxia, aphasia, and cortical blindness

- Excluded:
  - PTs indicating an infectious origin (*e.g*. PT *Encephalitis cytomegalovirus,* PT *Encephalitis protozoal,* PT *Creutzfeldt-Jakob disease,* and PT *Encephalitis lethargica* - etiology of latter not clear but believed to form part of spectrum of post-streptococcal autoimmune diseases).
  - PT *Delirium tremens* (generally associated with alcohol or anxiolytic withdrawal, not encephalitis)
  - PT *Drug withdrawal convulsions* (caused by a drug, not encephalitis)
  - There are no MedDRA terms for encephalomyeloradiculitis
  - PT *Lupus encephalitis* (unlikely drug related)
  - PTs indicating a congenital/inherited disorder (e.g., PT *Congenital syphilitic encephalitis)*
  - Nonspecific PTs relating to malaise, fever, headache, nausea, vomiting, dehydration, sleep abnormalities, mood/anxiety (with the exception of PT *Mood altered*), affect, vascular collapse and shock
  - PTs indicating involvement of the hypothalamic-pituitary axis in encephalitis (such as PTs relating to temperature dysregulation, diabetes insipidus, or the development of SIADH)
  - PT *Echoencephalogram abnormal* (not typically used to diagnose encephalitis)
  - PT *Encephalotomy* (does not pertain to encephalitis)
  - PT *Hypoglycaemic seizure* (having a stated etiology of hypoglycemia, whereas other types of seizures were included)
  - Investigation terms without a qualifier (*e.g*., PT *Electroencephalogram*)

- Terms containing the word “normal” (*e.g.*, PT *Electroencephalogram normal*)

2.67.3 Notes on Implementation and/or Expectation of Query Results

Noninfectious encephalitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.67.4 List of References for *Noninfectious encephalitis (SMQ)*

- Andreoli T, Behrman R, Bhattacharya B et al. Dorland’s Illustrated Medical Dictionary, 30th edition, dated 2003. Saunders, Philadelphia.
- Beehrs M and Berkow R. The Merck Manual of Diagnosis and Therapy. 17th edition; 1999: 1431-42.
- Kasper D, Braunwald E, Fauci A, et al. Harrison’s Principles of Internal Medicine. 16th edition, 2005, page 2480-83.

2.68 Noninfectious encephalopathy/delirium (SMQ)

(Production Release September 2007)

2.68.1 Definition

- Encephalopathy and delirium commonly have infectious or metabolic etiologies
- May also be drug-induced (focus of this SMQ). In the case of metabolic disorders, it is possible that drug plays a contributory or causative role for underlying metabolic abnormality.
- Encephalopathy and delirium may be reported synonymously; however delirium may be narrower in scope
- Encephalopathy
  - Defined as any degenerative or diffuse disease of the brain that alters brain structure or function
  - Many sub-forms including:
    - Biliary
    - Demyelinating
    - Wernicke's
    - Secondary to infections (e.g. HIV, cytomegalovirus)
    - Secondary to drug-induced metabolic disorders such as hepatic encephalopathy, hyperammonemia, hypoglycemia, hyponatremia, uremia.
    - Leukoencephalopathy (encephalopathy with white matter lesions) may be secondary to drug-induced hypertension
  - Hallmark is altered mental state
  - Other symptoms include lethargy, fluctuation of level of consciousness, nystagmus, tremor, dementia, seizures, myoclonus, muscle weakness
  - Cerebral edema is common
- Delirium (Acute confusional state)
  - Delirium is a clinical state characterized by fluctuating disturbances in cognition, mood, attention, arousal, and self-awareness
  - May be due to primary brain diseases or secondary to other diseases. Causes include:
    - Metabolic
    - Toxic (drugs)
    - Structural (vascular occlusion and cerebral infarction)

- Intracerebral hemorrhage
- Primary or metastatic brain tumors
- Infections

- Signs and symptoms include: clouding of consciousness with disorientation, changes in personality and mood, delusions, hallucinations (commonly visual), paranoia, withdrawal, agitation, disordered speech

2.68.2 Inclusion/Exclusion Criteria

- Included:
  - Terms relating to irritability, confusion, drowsiness, stupor, coma, seizures, altered consciousness and personality changes (in the broad search as they are expected to possibly cause noise)
  - PTs containing the terms “encephalopathy” or “delirium” (*e.g*. PT *Hepatic encephalopathy*, PT *Hypertensive encephalopathy*, PT *Hypoglycaemic encephalopathy*, PT *Delirium febrile*, and PT *Uraemic encephalopathy*)
  - PT *Psychiatric symptom* (testing showed that in some cultures it is used to code delirium)
  - PTs containing “neonatal” (a possible drug-induced cause cannot be excluded, *e.g*., PT *Encephalopathy neonatal*)
  - PT *Reye's syndrome* (involves brain damage and subsequent encephalopathy)
  - LLT *Bilirubin encephalopathy*, mapping to PT *Kernicterus* (has been reported in association with certain drugs taken in pregnancy *e.g*., trimethoprim/sulfamethoxazole)
  - PT *Subacute myelo-opticoneuropathy* is a clinical syndrome reported from Japan; hydroxyquinolones have been implicated as an etiologic factor
  - Investigation terms with a qualifier (*e.g*. PT *Electroencephalogram abnormal*)
  - Seizure terms except those with known etiology (such as PT *Hypoglycaemic seizure*, see exclusion criteria)
  - Coma and unconsciousness concepts except those with known etiology (such as PT *Coma acidotic*, see Exclusion criteria)

- Excluded:
  - PTs indicating an infectious origin (*e.g*., PT *Creutzfeldt-Jakob disease*, and PT *Progressive multifocal leukoencephalopathy*)
  - PT *Lupus encephalitis* which contains LLT *SLE encephalopathy* (unlikely drug related)
  - PTs indicating a congenital/inherited disorder such as PT *Opsoclonus myoclonus (*contains LLT *Myoclonic encephalopathy of infants)*, and PT *MELAS Syndrome (*which is mitochondrial encephalopathy, lactic acidosis, and stroke)
  - PT *Mitochondrial encephalomyopathy* and related diseases classified as mitochondrial myopathies/encephalopathies
  - PT *Wernicke's encephalopathy* (results from a deficiency in vitamin B-1, often due to alcoholism)
  - Nonspecific PTs relating to malaise, fever, headache, nausea, vomiting, dehydration, sleep abnormalities, mood/anxiety (with the exception of PT *Mood altered*), affect, vascular collapse and shock
  - PT *Echoencephalogram abnormal* (not typically used to diagnose encephalopathy or delirium)
  - LLT *Post-traumatic encephalopathy*, mapping to PT *Post concussion syndrome* (as it is an inter-current event)
  - PT *Encephalotomy* (does not pertain to encephalopathy or delirium)
  - PTs referring to possible causes of encephalopathy (such as hyperammonemia, hypoglycemia, hyponatremia, uremia, hypertension, etc) were excluded
  - PT *Hypoglycaemic seizure* (having a stated etiology of hypoglycemia, whereas other types of seizures were included)
  - Investigation terms without a qualifier (*e.g*., PT *Electroencephalogram*)
  - Terms containing the word “normal” (*e.g*., PT *Electroencephalogram normal*)
  - Coma and unconsciousness concepts having a stated etiology (such as PT *Coma acidotic,* PT *Hyperglycaemic unconsciousness)*

2.68.3 Notes on Implementation and/or Expectation of Query Results

Noninfectious encephalopathy/delirium (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.68.4 List of References for *Noninfectious encephalopathy/delirium (SMQ)*

- Jain K. Drug induced neurological disorders. 2001; 2nd edition: p. 23.
- National Institute of Neurological Disorders and Stroke, 2006.
- Encephalopathy. Gale Encyclopedia of Neurological Disorders 2005. From the Thomson Gale Group Inc.
- Beehrs M and Berkow R. The Merck Manual of Diagnosis and Therapy. 17th edition; 1999: 362-3.
- Beehrs M and Berkow R. The Merck Manual of Diagnosis and Therapy. 17th edition; 1999: Chapter 171.

2.69 Noninfectious meningitis (SMQ)

(Production Release September 2007)

2.69.1 Definition

- Meningitis is defined as an inflammation of the meninges
- Commonly has an infectious etiology
- May also be drug-induced (focus of this SMQ)
- Aseptic meningitis:
  - Characterized by CSF mononuclear pleocytosis and an absence of bacteria on examination and culture
  - May be caused by viruses
  - Rare but well-recognized complication of drug therapy
  - Drug-induced aseptic meningitis (DIAM) has distinct presentation with fever, neck stiffness, headache, confusion, nausea and vomiting
  - Major categories of causative agents are nonsteroidal anti-inflammatory drugs (NSAIDs), antimicrobials, intravenous immunoglobulins, monoclonal antibodies and vaccines
- Chronic meningitis:
  - Meningeal inflammation lasting more than one month
  - Causative agents include chemotherapy drugs that are injected directly into the CSF (e.g., methotrexate), drugs used in organ transplantation (e.g., cyclosporine and OKT3) and even NSAIDs
  - Symptoms similar to those of acute bacterial meningitis, but develop more slowly and gradually; fever often less severe. Include headache, confusion, backache, weakness, numbness, and facial paralysis
- Mixed disorders such as encephalomyelitis, encephalomyeloradiculitis, or encephalo-myelopathy may present with overlapping symptoms

2.69.2 Inclusion/Exclusion Criteria

- Included:
  - Terms related to irritability, confusion, stupor, coma, seizures, cranial neuropathies, altered consciousness and facial or cranial nerve paresis (in broad search as they are expected to possibly cause noise)
  - PTs containing “neonatal” as a possible drug-induced cause cannot be excluded (*e.g.*, PT *Somnolence neonatal*)

- PT *Agitation* and PT *Agitation neonatal* (may be reported in neonates or children as a presenting sign of meningitis)
- LLT *Meningoencephalitis* maps to the PT *Encephalitis* and hence is included in *Noninfectious encephalitis (SMQ)*
- The PT *Musculoskeletal stiffness* was included (in the broad search) because it contains the LLT *Neck stiffness* and LLT *Back stiffness*, despite the potential risk of retrieving cases with other LLTs such as LLT *Stiff fingers* or LLT *Limbs stiffness*
- Seizure terms are included except those with explicit etiologies not related to meningitis, such PT *Hypoglycaemic seizure* and PT *Drug withdrawal convulsions* (see exclusion criteria below)

- Excluded:
  - PTs indicating an infectious origin (*e.g.*, PT *Adenovirus encephalomyeloradiculitis,* PT *Meningitis bacterial*, etc.)
  - As of the initial version of this SMQ, there are no MedDRA terms for encephalomyeloradiculitis.
  - PT *Waterhouse-Friderichsen syndrome* (typical for a meningococcal meningitis)
  - PTs indicating a congenital/inherited disorder
  - PTs related to neoplasms
  - Nonspecific PTs relating to malaise, fever, headache, nausea, vomiting, and dehydration
  - PT *Echoencephalogram abnormal* (not typically used to diagnose meningitis)
  - PT *Encephalotomy* (does not pertain to meningitis)
  - PT *Hypoglycaemic seizure* and PT *Drug withdrawal convulsions* (having explicit etiologies not related to meningitis), whereas other types of seizures were included

2.69.3 Notes on Implementation and/or Expectation of Query Results

Noninfectious meningitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.69.4 List of References for *Noninfectious meningitis (SMQ)*

- Andreoli T, Behrman R, Bhattacharya B et al. Dorland's Illustrated Medical Dictionary, 30th edition, dated 2003. Saunders, Philadelphia.

- Beehrs M and Berkow R. The Merck Manual of Diagnosis and Therapy. 17th edition; 1999: 1431-42.
- Nettis E, Calogiuri E, Colanardi M, et al. Drug-induced aseptic meningitis. Curr Drug Targets Immune Endocr Metabol Disord. 2003 Jun;3(2):143-9.

2.70 Ocular infections (SMQ)

(Production Release September 2010)

2.70.1 Definition

- Three main forms
  - Affecting the cornea and conjunctiva
  - Endophthalmitis (infection inside the eye)
  - Infections of the ocular adnexa and orbit
- Treatment of eye infections
  - Based on severity of symptoms and magnitude of possible outcome
  - Severe conjunctivitis requires aggressive management with broad spectrum antibiotics
  - Vision loss can occur despite treatment
  - Patients who have had recent surgery are at risk for developing endophthalmitis
- Numerous bacterial, viral, and fungal organisms can cause ocular infections

2.70.2 Inclusion/Exclusion criteria

- Included:
  - All terms directly related to or describing an eye infection (e.g., PT *Candida endophthalmitis*) – these are generally the narrow terms. This includes infections of the orbital and periorbital structures: conjunctiva, eyelids and lashes, lacrimal system, cornea, episclera, iris, retina and optic nerve
  - Terms that may not be actual infections terms but could represent ocular infections (e.g., PT *Uveitis*) – these are generally broad terms
- Excluded:
  - Terms for ocular disorders due to non-infective causes (e.g., allergy, autoimmune conditions, injury)
  - Terms for congenital and neonatal eye conditions
  - Terms that are non-specific eye symptoms (e.g., PT *Eye pain*)

NOTE: Several of the broad search terms in this SMQ that sometimes, but not always, have an infectious origin – such as PT *Conjunctivitis*, PT *Iritis*, PT *Optic*

neuritis and *Uveitis* – were noisy in the test databases. However, these terms may not be noisy in other databases.

2.70.3 Notes on implementation and/or Expectation of query results

Ocular infections (SMQ) has narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.70.4 List of References for *Ocular infections (SMQ)*

- Donahue SP, Khoury JM, and Kowalski RP. Common ocular infections. A prescriber's guide. Drugs. 1996 Oct;52(4):526-40.
- Sherwal, BL and Verma, AK. Epidemiology of ocular infection due to bacteria and fungus – a prospective study. JK Science Vol. 10 No.3, July-September 2008.

2.71 Ocular motility disorders (SMQ)

(Production Release September 2010)

2.71.1 Definition

- Ocular motility disorders
  - Gaze palsy
  - Internuclear ophthalmoplegia
  - Oculomotor nerve lesions
  - Trochlear nerve lesions
  - Abducens nerve lesions
  - Diabetic ophthalmoplegias
  - Painful ophthalmoplegias
  - Myesthenia gravis
  - Ocular myopathies
- Extraocular muscles controlling eye movements:
  - Medial and lateral rectus
  - Inferior and superior rectus
  - Superior and inferior oblique
- Cranial nerve palsies
  - Oculomotor nerve palsy
    - May be caused by brain injury, aneurysm, hemorrhage, tumor, or diabetes
    - Affected eye turns outward when the unaffected eye looks straight ahead; this causes double vision
  - Trochlear nerve palsy
    - Often has no identified cause but may be due to head injury
    - Both eyes or only one may be affected
    - Affected eye is not able to turn inward or down. Double vision results
  - Abducens nerve palsy
    - May have a number of causes including head injury, tumors, multiple sclerosis, aneurysms, CNS infection, etc.
    - Affected eye cannot turn outward

2.71.2 Inclusion/Exclusion criteria

- Included:
  - Terms describing eye movement disorders (e.g., PT *Ophthalmoplegia*)
  - Terms describing disorders of the relevant cranial nerves (e.g., PT *IVth nerve paresis*)
  - Terms for signs and symptoms of ocular motility disorder (broad search terms) – (e.g., PT *Diplopia*)
- Excluded:
  - Non specific terms (e.g., PT *Visual impairment*)

NOTE: The CIOMS SMQ Working Group noted that users of *Ocular motility disorders (SMQ)* may want to cross refer to *Extrapyramidal syndrome (SMQ),* particularly for older databases where the coding may not be sufficiently specific to use “eye” terms.

2.71.3 Notes on implementation and/or Expectation of query results

Ocular motility disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.71.4 List of References for *Ocular motility disorders (SMQ)*

- Clinical Neurology, 7th edition. Simon, R, Greenberg, D and Aminoff, M. Ch. 4, Disturbances of vision.

- Merck Manual. Palsies of Cranial Nerves That Control Eye Movement. http://www.merck.com/mmhe/sec06/ch096/ch096d.html

2.72 Opportunistic infections (SMQ)

(Production Release March 2020)

2.72.1 Definition

- Opportunistic infection is an infection by an organism that does not ordinarily cause disease in an individual with an intact immune system but becomes pathogenic in an immunocompromised host
- While there is no clear definition of opportunistic infections widely accepted for all immunocompromised states, the common risk factor associated with opportunistic infection is a compromised immune function. Compromised immune function can be the result of a congenital or acquired immune deficiency, certain malignancies, cytotoxic chemotherapy, immunosuppressive therapy, biologic immune modulators, chronic medical conditions such as diabetes or cystic fibrosis, or mechanical damage to the skin or mucosa caused by inflammation (e.g., ulcerative colitis) or injury (e.g., severe burns).
- The etiologic agents leading to opportunistic infections may be different depending on the cause of the immunocompromise. The majority of serious infections occurring in this setting are similar to those seen in the general population, some infections are more likely to be associated with immunosuppression (or degree of immunosuppression), occur more severely in those who are immunosuppressed, or have important public health or clinical considerations (such as tuberculosis) that distinguish them those infections encountered in the general population.
- Opportunistic infections can be markers of specific types of immunosuppression and can serve as clinical indicators of specific underlying immune defects (e.g., Pneumocystis jirovecii and HIV)

2.72.2 Inclusion/Exclusion Criteria

- Included:
  - Infections caused by an unusual pathogen (unusual or non-existent in the immunocompetent host), which is highly characteristic of the immunocompromised state (e.g., Pneumocystis jirovecii pneumonia in the HIV infected patient)
  - Infections caused by usual pathogens of the immunocompetent host, but of an anatomical location, severity, treatment resistance or relapse rate rarely encountered in the normal host (e.g., disseminated herpes zoster in the lymphoma patient)
  - Pathogens listed in internationally recognized opportunistic infection prevention guidelines of clinically relevant immunocompromised states, such as HIV infection; bone marrow or solid organ transplant; or treatment-induced immunosuppression (as is used in cancer or biologic therapies of immune-mediated inflammatory diseases)

- Relevant investigation terms associated with these organisms. These investigation terms are generally in the broad scope, though some laboratory tests used to identify highly characteristic opportunistic pathogens are part of the narrow scope.
- Neonatal infections with the characteristics defined above
- In general, superficial infections of skin, outer ear, cornea, mouth mucosa, oropharynx, bladder, and genital organs, tend to be part of the “broad” scope, whereas deep or disseminated infections are mostly included in the “narrow” scope

- Excluded:
  - Secondary immunodeficiency states which are the cause or contribute to the appearance of opportunistic infections, such as leukemias, lymphomas, bone marrow depression states, diabetes, extensive burns, malnutrition, etc.
  - Congenital conditions (e.g., primary immunodeficiency syndrome)
  - Unqualified investigation terms

2.72.3 Notes on Implementation and/or Expectation of Query Results

Opportunistic infections (SMQ) has features of narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.72.4 List of References for *Opportunistic infections (SMQ)*

- Schreier R. eMedicine [Internet]. Infections in the immunocompromised host. https://emedicine.medscape.com/article/973120-overview. (Accessed 1 August 2019).
- Winthrop KL, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance Annals of the Rheumatic Diseases 2015;74:2107-2116.
- Centers for Disease Control and Prevention. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients, Recommendations of CDC, the Infectious Disease Society of America, and the American Society of Blood and Marrow Transplantation MMWR. 2000 Oct 20; 49 (RR10): 1-128.
- Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007 Dec 20; 357: 2601-2614. doi: 10.1056/NEJMra064928
- Tomblyn M et al. Guidelines for preventing infectious complications among hematopoietic cell transplantation recipients: a global perspective. Bio Bone Marrow Transplant. 2009 Oct; 15, (10): 1143-238. doi: 10.1016/j.bbmt.2009.06.019
- U.S. Department of Health and Human Services [Internet]. Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and

Adolescents. https://aidsinfo.nih.gov/guidelines/html/4/adult-and-adolescent-opportunistic-infection/0. (Accessed 1 August 2019).

2.73 Optic nerve disorders (SMQ)

(Production Release September 2008)

2.73.1 Definition

- Optic nerve transmits impulses generated by retinal photoreceptors to the brain
- Damage anywhere along the optic nerve or to visual areas of brain can result in loss of vision
- No overall definition for optic nerve disorders; SMQ focuses on optic neuropathy, optic neuritis (inflammation), and papilledema (swelling of optic nerve)
- Causes of optic neuropathy:
  - Toxins, including lead, methanol, ethylene glycol, tobacco or arsenic
  - Compromised blood supply
  - Nutritional deficiencies, especially vitamin B12
  - Drugs, including chloramphenicol, isoniazid, ethambutol or digoxin
- Characteristics of loss of vision:
  - May be rapid (minutes or hours) or gradual over 2-7 days
  - One or both eyes affected, depending on cause
  - Vision can range from almost normal to complete blindness
  - Both eyes usually affected in optic neuropathy due to toxins or nutritional deficiency
  - Small area of vision loss at center of visual field slowly enlarges and can progress to complete blindness

2.73.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow search
    - All terms that contain “optic”
    - Terms relating to the optic disc
    - Terms for diseases that frequently affect the optic nerve, such as multiple sclerosis
  - Broad search
    - Terms for signs and symptoms of visual disturbance
    - Terms relating to inflammation of cerebral vessels

    - Nonspecific terms relating to cranial nerves or non-specified surgical procedures relating to the eye and orbita

- Excluded:
  - Nonspecific brain abnormalities found by imaging techniques
  - Congenital terms

NOTE: Nonspecific terms relating to the cranial nerves should be included in general or left out as a whole.

NOTE: This SMQ is one of several SMQs developed or under development for ophthalmological disorders. When the entire set of SMQs is developed, a search may require use of more than one SMQ, or the entire group of SMQs, depending upon the goal of the search.

2.73.3 Notes on Implementation and/or Expectation of Query Results

Optic nerve disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.73.4 List of References for *Optic nerve disorders (SMQ)*

- Merck Manual Online, published by Merck Research Laboratories. http://www.merckmanuals.com/professional/index.html

2.74 Oropharyngeal disorders (SMQ)

(Production Release September 2007)

2.74.1 Definition

- Oropharynx includes oral cavity bounded by:
  - Buccal aspect of lips
  - Palate
  - Floor of mouth
  - Posterior pharyngeal wall

2.74.2 Inclusion/Exclusion Criteria

- Included:
  - Terms related to lesions and disorders falling wholly or partly within any part of oral cavity or pharynx
  - Oropharyngeal neoplasms, cysts, and pre-neoplastic lesions
  - Oropharyngeal infections
  - Gingival disorders
  - For sub-SMQ *Gingival disorders (SMQ)*
    - All terms with “gingival” including those that are not clearly infection or neoplasms such as PT *Gingival discolouration,* PT *Gingival hypertrophy*
    - Terms related to the gums such as PT *Periodontal destruction* and PT *Periodontitis*
  - For sub-SMQ *Oropharyngeal allergic conditions (SMQ)*
    - Terms for allergic conditions which can be observed within oral cavity such as oedemas
  - For sub-SMQ *Oropharyngeal neoplasms (SMQ)*
    - Terms for neoplasms that occur within oral cavity
  - For sub-SMQ *Oropharyngeal infections (SMQ)*
    - Terms for infections that can be observed within oral cavity, such as those caused by viruses and bacteria
  - For sub-SMQ *Oropharyngeal conditions (excl neoplasms, infections and allergies)(SMQ)*: includes lesions not clearly related to specific infections, neoplasms or allergic reactions but due to the following etiology
    - Injuries
    - Ulcers

    - Hypoesthesias
    - Hemorrhages
    - Unspecified disorders
- Excluded:
  - Terms related to lesions or disorders of larynx and structures below larynx
  - Terms related to lesions or disorders of nasal cavity
  - Terms related to congenital, familial and genetic disorders
  - Surgical, therapeutic and medical procedures of the oropharynx*
  - Investigations related to the oropharynx (e.g. biopsy)*
  - For sub-SMQ *Oropharyngeal neoplasms (SMQ)*
    - Terms for dental neoplasms

* Some terms of these types were initially included and tested, but subsequently excluded following discussions among the CIOMS WG team for this SMQ topic.

NOTE: In Version 16.0, *Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic (SMQ)* was renamed to *Oropharyngeal conditions (excl neoplasms, infections and allergies) (SMQ)*.

NOTE: In Version 14.0, at the recommendation of the CIOMS SMQ Working Group, approximately 50 salivary gland terms have been added to the sub-SMQs of *Oropharyngeal disorders (SMQ)*, because it was determined that salivary gland disorders fall into the definition and scope of this SMQ.

NOTE: In Version 13.0, the following sub-search SMQs under *Oropharyngeal disorders (SMQ)* have been changed in scope from broad terms only to narrow terms only: *Gingival disorders (SMQ), Oropharyngeal allergic conditions (SMQ), Oropharyngeal infections (SMQ), Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic (SMQ)* [please note that in Version 16.0, this SMQ name was changed to *Oropharyngeal conditions (excl neoplasms, infections and allergies)(SMQ)],* and *Oropharyngeal neoplasms (SMQ)*.

2.74.3 Hierarchy Structure

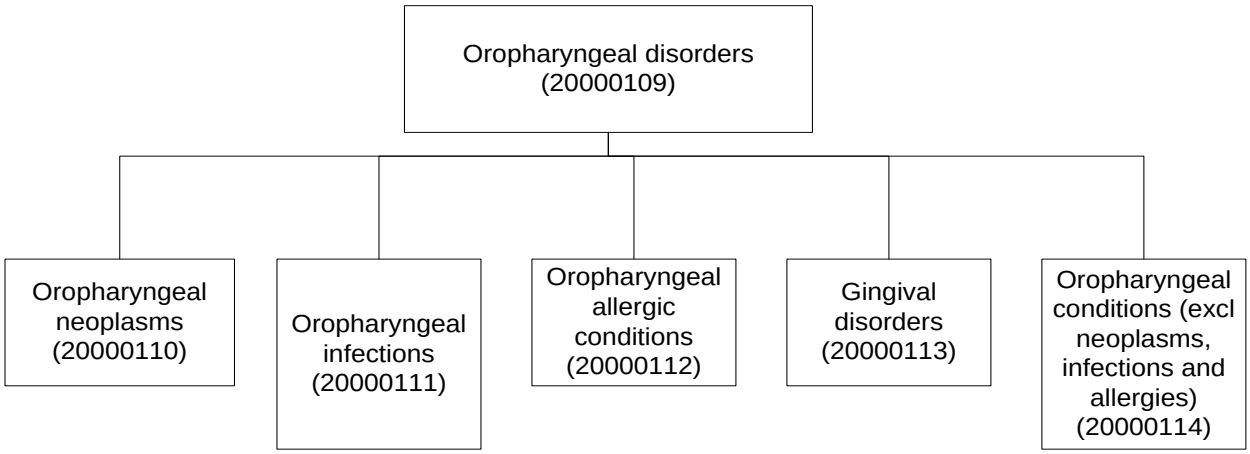

Figure 2-17. Hierarchy Structure of *Oropharyngeal disorders (SMQ)*

- Sub-SMQ *Oropharyngeal conditions (excl neoplasms, infections and allergies) (SMQ)* is referred as SMQ *Oropharyngeal lesions* in the CIOMS Working Group original documentation)

2.74.4 Notes on Implementation and/or Expectation of Query Results

Oropharyngeal disorders (SMQ) is a hierarchical SMQ with only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.74.5 List of References for *Oropharyngeal disorders (SMQ)*

- Reporting Adverse Drug Reactions – Definitions of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS); 1999.
- Dorland's Illustrated Medical Dictionary – Saunders 2003, 30th Edition.

2.75 Osteonecrosis (SMQ)

(Production Release March 2010)

2.75.1 Definition

- Osteonecrosis occurs as a result of compromise to the blood supply to bone
- Hip (femoral head) is a common location, but other bones can also be affected
- Two main forms:
  - Traumatic
    - More common
    - Due to direct injury and damage of blood supply
  - Non-traumatic
    - Associated with several risk factors/conditions including corticosteroid use, alcohol abuse, sickle cell anemia, Gaucher disease, systemic lupus erythematosus, coagulopathies, hyperlipidemia, organ transplantation, caisson disease, thyroid disorders and genetic factors
    - Some cases are idiopathic
- Symptoms of osteonecrosis of the femoral head:
  - Groin pain (occasionally buttock pain); deep, throbbing and worsens upon walking
  - May also be a “catching” or popping sensation with motion
- Physical examination:
  - Pain with range of motion and walking
  - Limitation of internal rotation
  - Trendelenburg gait often present
  - Plain radiographs of hip are often normal
- Osteonecrosis of jaw (ONJ):
  - Associated with use of biphosphonates
  - Typically occurs in the setting of recent dental surgery
  - Signs and symptoms include pain, tooth mobility, mucosal swelling, erythema and ulceration

2.75.2 Inclusion/Exclusion criteria

- Included:
  - PT *Osteonecrosis* and PT *Osteoradionecrosis*
  - Terms for procedures for osteonecrosis (e.g., PT *Hip arthroplasty*)
  - Terms for investigations for diagnosis of osteonecrosis (e.g., PT *Face and mouth X-ray abnormal*)
  - Terms for signs and symptoms relatively specific for osteonecrosis (e.g., PT *Pain in jaw*). Since osteonecrosis has a predilection for certain bones (e.g., femoral head, jaw), terms selected tend to reflect those sites
  - Terms for various infectious and non-infectious forms of osteomyelitis; this is to account for the association of mandibular osteomyelitis and osteonecrosis in the setting of use of biphosphonate products
  - Terms related to procedures and complications of osteomyelitis (e.g., PT *Bone sequestrum*)
- Excluded:
  - PT *Necrosis*, PT *Necrosis ischaemic*, PT *Bone disorder*, PT*Jaw disorder* and other broad concepts (e.g., PT *Ulcer*) as they are too non-specific

NOTE: For the broad search, PT *Bone pain* may create noise, depending on the product, and users may consider removing this PT for their own purposes.

NOTE: In light of pharmacovigilance interest in osteonecrosis of the jaw, narrow PT *Osteonecrosis of jaw*, broad PT *Exposed bone in jaw*, and other broad search terms in *Osteonecrosis (SMQ)* will facilitate identification of cases of osteonecrosis of the jaw.

2.75.3 Notes on Implementation and/or Expectation of Query Results

Osteonecrosis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.75.4 List of References for *Osteonecrosis (SMQ)*

- Osteonecrosis. Merck Manual Home Edition. http://www.merck.com/mmhe/sec05/ch064/ch064a.html
- Levine, M., Rajadhyaksha, A., and Mont, M. Osteonecrosis, hip. eMedicine, http://www.emedicine.com/orthoped/TOPIC430.HTM
- Tofferi, J. and Gilliland, W. Avascular necrosis. http://www.emedicine.com/Med/topic2924.htm
- Purcell, PM and Boyd, IW. Biphosphonates and osteonecrosis of the jaw. Med J Australia 2005; 182(8): 417 – 418.

- Grbic, JT et al. Incidence of Osteonecrosis of the Jaw in Women With Postmenopausal Osteoporosis in the Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly Pivotal Fracture Trial. *J Am Dent Assoc* 2008;139;32-40.
- Ruggiero, SL and Mehrotra, B. Biphosponate-related osteonecrosis of the jaw: diagnosis, prevention, and management. Annu. Rev. Med 2009; 60: 85-96.
- Cimatti L, Borderi M, Gibellini D, Re MC. Bone alterations during HIV infection. New Microbiol. 2008 Apr; 31(2):155-64.

2.76 Osteoporosis/osteopenia (SMQ)

(Production Release September 2009)

2.76.1 Definition

- Osteoporosis = systemic skeletal disorder characterized by:
  - Decreased bone mass (decreased mass per unit volume of normally mineralized bone)
  - Deterioration of bone microarchitecture
  - Osteopenia = milder form of bone loss
- Increased fracture risk even with minimal trauma; most common sites for such bone loss and resultant fractures are thoracic and lumbar vertebrae, ribs, upper femur, lower radius
- Usually causes no signs or symptoms except height loss and kyphosis until fractures occur
- Pathogenesis
  - Genetic factors (e.g., hereditary such as osteogenesis imperfecta)
  - Medications (especially glucocorticoids)
  - Diet
  - Race
  - Gender
  - Lifestyle
  - Physical activity
- Type 1 (postmenopausal)
  - Most common type
  - Results from sex hormone deficiency
  - Increased recruitment/responsiveness of osteoclast precursors and increased bone resorption outpace bone formation
  - Decreased trabecular bone leads to an increased risk of Colles (distal radius) and vertebral fractures
  - Estrogen deficiency may cause bone to become more sensitive to parathyroid hormone, leading to increased calcium release from bone, decreased renal calcium excretion, and increased production of 1,25-dihydroxyvitamin D
  - Increased production of 1,25(OH)2 D3 causes
    - Increased gastrointestinal calcium absorption
    - Increased calcium resorption from bone

    - Increased renal tubular calcium resorption
  - Gonadal deficiency may also increase production of cytokines that have an influence on osteoclasts
- Type 2 (senile)
  - Occurs in both genders
  - Decreased formation of bone and decreased renal production of 1,25(OH)2 D3 occurring late in life
  - Loss of cortical and trabecular bone leads to increased fracture risk in hip, long bones, vertebrae
- Type 3
  - Secondary to effects of medications (e.g., glucocorticoids)
  - Or due to other conditions that cause increased bone loss by various mechanisms
- Bone mineral density is frequently used as an approximate measure of bone strength
  - WHO defines osteoporosis as bone density that is 2.5 standard deviations below mean for young adult white females
- Markers of bone turnover (bone specific alkaline phosphatase, osteocalcin, type I procollagen peptides, and urinary deoxypyridinoline) sometimes used to monitor response to therapy

2.76.2 Inclusion/Exclusion criteria

- Included:
  - Terms for conditions of osteoporosis and osteopenia, including variants (e.g., PT *Osteopenia*, PT *Osteoporosis postmenopausal*)
  - Terms for signs and symptoms (e.g., PT *Body height below normal*, PT *Kyphosis*) including fracture types that are characteristic of osteoporosis (e.g., PT *Hip fracture*, PT *Spinal compression fracture*)
  - Terms for investigations used in assessment of patients (e.g., PT *N-telopeptide urine increased*, PT *Bone density decreased*); note that laboratory terms qualified by “abnormal” are also included (e.g., PT *Body height abnormal*)
  - Terms for procedures associated with osteoporosis (e.g., PT *Hip arthroplasty*)
  - PT *Post-traumatic osteoporosis* – although cause of this condition is related to trauma, possibility that a drug may exacerbate it might need to be considered
- Excluded:

- Congenital terms *(e.g.,* PT *Osteoporosis-pseudoglioma syndrome*)
- PT *Osteoporosis circumscripta cranii* (a form of Paget's disease)
- Terms for all fractures except those highly characteristic of osteoporosis, (i.e., hip, radius, proximal femur, and ribs [for drug-induced osteoporosis])
- PT *Kyphoscoliotic heart disease* – although kypho(scolio)sis is a complication of osteoporosis, it is decided to limit terms for complications to primary/proximal ones and not to secondary complications
- PT *Blood alkaline phosphatase increased* – this was noted to be "noisy" on early testing of this SMQ, retrieving cases related to liver disease. Users should note that they may wish to consider searching cases coded to LLTs related to bone form of alkaline phosphatase (e.g., LLT *Blood alkaline phosphatase bone increased*)
- Terms from SOC *Social circumstances* such as PT *Walking disability*, PT *Wheelchair user*, etc.

2.76.3 Notes on Implementation and/or Expectation of Query Results

Osteoporosis/osteopenia (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.76.4 List of References for *Osteoporosis/osteopenia (SMQ)*

- Hobar, C. Osteoporosis. eMedicine, 16 December 2005. (http://www.emedicine.com/MED/topic1693.htm)
- WHO/Forum for Collaborative HIV Research Joint Meeting: ARV Drugs Adverse Events, Case Definition, Grading, Laboratory Diagnosis and Treatment Monitoring, Background Document (Draft), 28 – 29 February 2008.
- Dorland's Medical Dictionary.

2.77 Ovarian neoplasms, malignant and unspecified (SMQ)

(Production Release September 2008)

2.77.1 Definition

- Developed to detect all malignant and unspecified tumors related to ovary
- Covers all malignant and unspecified neoplasms related to ovary and in addition:
  - Malignancy related conditions
  - Malignancy related therapeutic and diagnostic procedures
  - Tumor markers

2.77.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for malignant or unspecified neoplasms with a clear reference to ovary
  - Terms for conditions related to malignant or unspecified neoplasms of the ovary, including:
    - Procedures
    - Investigations
    - Tumor markers
    - Signs and symptoms pointing to such disorders
- Excluded:
  - Terms for malignant or unspecified neoplasms without a clear reference to ovary
  - Terms for unspecified site malignancy related therapeutic and diagnostic procedures and tumor markers
  - Terms for metastases to the ovary
  - Terms related to vulva and vagina
  - PT *Ovarian operation* as it is not a malignancy specific therapeutic procedure. (This term may, however, be added if a very broad search is required).

NOTE: In Version 14.0, two new sub-SMQs have been added to *Ovarian neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: For searches of non-specific malignancy related conditions and malignancy related therapeutic and diagnostic procedures, it is recommended to use the respective lower level sub-SMQ of *Malignancies (SMQ)*.

2.77.3 Hierarchy Structure

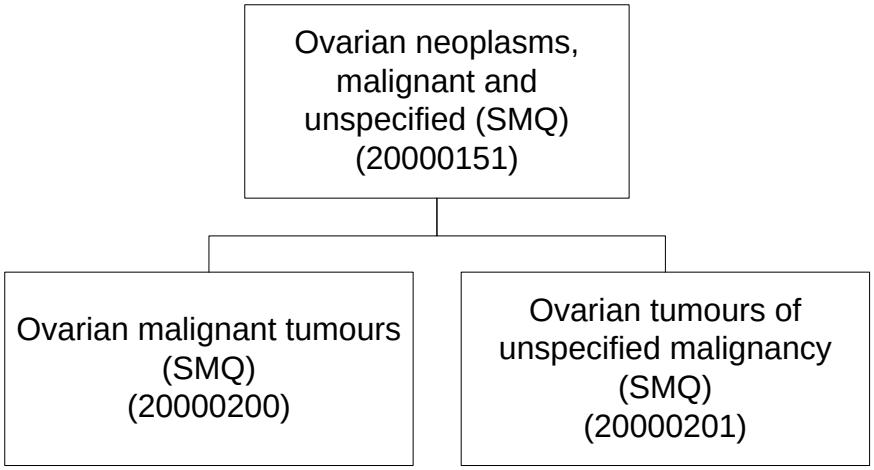

Figure 2-18. Hierarchy Structure of *Ovarian neoplasms, malignant and unspecified (SMQ)*

2.77.4 Notes on Implementation and/or Expectation of Query Results

Ovarian neoplasms, malignant and unspecified (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.77.5 List of References for *Ovarian neoplasms, malignant and unspecified (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H,.Veronesi, U. Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://www.egtm.eu/

2.78 Periorbital and eyelid disorders (SMQ)

(Production Release September 2009)

2.78.1 Definition

- Eyelids
  - Maintain health of underlying eye by protecting cornea
  - Assist in distribution and elimination of tears
- Eyelid structure
  - Anterior layer of skin and orbicularis oculi muscle
  - Posterior layer of tarsus and conjunctiva
  - Orbicularis oculi muscles (innervated by CN VII) closes eyelid
  - Upper eyelid is raised by levator muscle (innervated by CN III) and Müller's muscle
  - Orbital septum – originating from orbital rim – inserts into upper lid and lower lid
    - Septum limits spread of eyelid bleeding or infection to posterior orbital structures
  - Glands along eyelid margin contribute to lipid component of tears
    - May become inflamed
    - Meibomian glands lie within tarsus
    - Pilosebaceous glands of Zeiss and apocrine glands of Moll are anterior to meibomian glands within distal eyelid margin
- Problems that can afflict eyelids
  - Neoplasms
  - Inflammation and infection
  - Structural problems (e.g., ectropion)
- Most eyelid disorders do not threaten vision but may produce irritative symptoms (burning, foreign body sensation or pain)
- Blepharitis (eyelid inflammation) is characterized by erythematous eyelids with debris accumulation along eyelid margin

2.78.2 Inclusion/Exclusion criteria

- Included:
  - Terms for eyelid procedures (e.g., PT *Blepharectomy*)

  - Eyelash terms
  - Periorbital terms
- Excluded:
  - Signs and symptoms of eyelid and periorbital disorders that could be shared with other eye disorders
  - Common skin conditions that can affect the eyelid and periorbital region (e.g., seborrheic keratosis) unless qualified with a word indicating eyelid is involved (e.g., PT *Eyelids pruritus* is included)
  - Known causes of, or syndromes associated with, eyelid and periorbital disorders (e.g., PT *Myasthenia gravis,* PT *Horner's syndrome*)
  - Congenital terms (e.g., PT *Congenital eyelid malformation*)
  - Infection terms
  - Terms related to CN III and CN VII - although involved with motor control of eyelid, they are not considered relevant for this SMQ
  - Terms related to eyelid and periorbital injury

NOTE: Some “eyelid” terms at the LLT level have not been included in the term list for this SMQ because their parent PTs may be too broad for inclusion. The SMQ user may wish to review these LLTs and determine if they wish to capture cases coded with these terms in addition to those retrieved by the included SMQ terms. These LLTs are: LLT *Erythema circumocular-blepharal*, LLT *Feeling of warmth blepharal*, LLT *Hypertrichosis of eyelid*, LLT *Hypotrichosis of eyelid*, *LLT Papular rash circumocular-blepharal*, and LLT *Xeroderma of eyelid*.

2.78.3 Notes on Implementation and/or Expectation of Query Results

Periorbital and eyelid disorders (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.78.4 List of References for *Periorbital and eyelid disorders (SMQ)*

- Carter, S.R. Eyelid disorders: diagnosis and management. Amer. Fam. Phys. 57:(11), June 1998. http://www.aafp.org/online/en/home/publications/journals/afp.html

2.79 Peripheral neuropathy (SMQ)

(Production Release November 2005)

2.79.1 Definition

- Impairment of the peripheral motor, sensory and autonomic nervous system
- Diagnosis is on clinical grounds, supplemented by electrophysiological investigation
- At least one of the following must be present:
  - Muscular weakness with diminished tone, or flaccid paralysis (diminished tendon reflexes and wasting)
  - Sensory disturbances, including pain
  - Impairment of autonomic function.

2.79.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for “peripheral neuropathy” and related concepts
  - Terms for signs, symptoms and laboratory findings as described in the CIOMS definition
  - Autonomic terms (e.g., PT *Autonomic neuropathy*) and associated muscle findings (e.g., PT *Muscle atrophy*) were also included.
- Excluded:
  - Terms related to peripheral nerve injury
  - In general, demyelinating neuropathy terms (*e.g*. PT *Chronic inflammatory demyelinating polyneuropathy*) are excluded.
  - Terms for neuropathies associated with other medical conditions, such as PT *Diabetic neuropathy*.

NOTE: PT Paralysis flaccid, a feature of neuropathy, was excluded from *Peripheral neuropathy (SMQ)* through MedDRA Version 18.0, because it is an extreme and uncommon finding. In MedDRA Version 18.1, PT *Paralysis flaccid* was demoted to an LLT under PT *Paralysis*. PT *Paralysis* is not included in *Peripheral neuropathy (SMQ)*.

2.79.3 Notes on Implementation and/or Expectation of Query Results

Peripheral neuropathy (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.79.4 List of References of *Peripheral neuropathy (SMQ)*

- Bankowski Z, Bruppacher R, Crusius I et al. Reporting adverse drug reactions, definition of terms and criteria for their use. Council for International Organizations of Medical Sciences (CIOMS), 1999 p 32.

2.80 Pregnancy and neonatal topics (SMQ*)*

(Production Release March 2011)

2.80.1 Definition

- *Pregnancy and neonatal topics (SMQ)* was developed:
  - To replace original *Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders) (SMQ)*
    - Original SMQ had discrepancies in term inclusion resulting in maintenance issues
  - To make it more compatible with regulatory goals related to pregnancy and neonatal topics
- Fertility-related topics and developmental disorders are not part of this SMQ but will be considered for separate, standalone SMQs
- CIOMS SMQ Working Group team referenced EMA's *Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data* as a guide for term inclusion
- In the guideline, pregnancy outcomes are defined as:
  - Live birth, normal
  - Live birth, abnormal
    - Pre-term, term, post-term birth
    - Small for gestational age infants/ Intrauterine growth retardation
    - Drug withdrawal syndrome in the neonate
    - Malformations
    - Morbidity
  - Fetal death
    - Ectopic
    - Miscarriage
    - Stillbirth
  - Termination of pregnancy
- Lactation associated disorders (functional and related to neonatal exposures through breast milk) are also in this SMQ.

2.80.2 Inclusion/Exclusion criteria

- Included:
  - Overall inclusion criteria for *Pregnancy and neonatal topics (SMQ)*:
    - Terms for pregnancy complications and outcomes
    - Terms for neonatal disorders and conditions
    - Terms for normal pregnancy and outcomes
    - Terms for abortion (induced and spontaneous) and stillbirth
    - Terms for conditions related to labor
    - Terms for lactation topics, both functional and related to exposures to the baby via breast milk
    - Terms for fetal disorders
    - Terms for procedures related to congenital and fetal disorders
  - For SMQ *Congenital, familial and genetic disorders*
    - All PTs in SOC *Congenital, familial and genetic disorders*
  - For *Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)*
    - Terms for abnormal labor, pregnancy, delivery
    - Terms for relevant investigations
    - Terms for relevant procedures
    - Terms related to ectopic pregnancy
    - Terms for placenta issues
    - Uterine terms related to pregnancy, labour and delivery
    - Terms for conditions that increase the risk of pregnancy complication
    - Terms for malpresentation
  - For *Lactation related topics (incl neonatal exposure through breast milk) (SMQ)* (includes additional sub-SMQs *Functional lactation disorders (SMQ)* and *Neonatal exposures via breast milk (SMQ)*
    - Terms related to lactation disorders and conditions occurring in the context of pregnancy
    - Terms related to breast and nipple complications associated with lactation (e.g., PT *Mastitis postpartum*)
    - Terms for drug exposures and intoxications via breast milk
    - Terms for feeding disorders

- For *Foetal disorders (SMQ)*
  - All terms related to the condition of the fetus
- For *Neonatal disorders (SMQ)*
  - All terms related to the neonate/newborn
  - All PTs related to procedures to correct/address congenital disorders in the neonatal period (e.g., PT *Systemic-pulmonary artery shunt*)
- For *Termination of pregnancy and risk of abortion (SMQ)*
  - Terms for spontaneous and induced abortions and stillbirth
  - Terms for complications of abortion and termination of pregnancy
  - Terms for relevant procedures and investigations
  - Terms for risk factors for abortions
  - Consists of all PTs linked to HLGT *Abortions and stillbirth*
- For *Normal pregnancy conditions and outcomes (SMQ)*
  - Terms related to normal pregnancy conditions and outcomes, including terms from SOC *Social circumstances*
  - Terms for unintended pregnancy
  - Terms for investigation results indicative of pregnancy

- Excluded:
  - Overall exclusion criteria for *Pregnancy and neonatal topics (SMQ)*
    - Unqualified investigation terms
    - Terms for fertility and sexual dysfunction (these are proposed to exist in a separate, standalone [Level 1] SMQ)
    - Terms for developmental disorders (these are proposed to exist in a separate, standalone [Level 1] SMQ)
    - PT *Toxoplasmosis prophylaxis* - unlikely to be drug-related
  - For *Congenital, familial and genetic disorders (SMQ)*
    - All terms that are **not** in SOC *Congenital, familial and genetic disorders*
  - For *Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)*
    - Terms for abortions and stillbirths

- For *Lactation related topics (incl neonatal exposure through breast milk) (SMQ)* includes additional sub-SMQs *Functional lactation disorders (SMQ)* and *Neonatal exposures via breast milk (SMQ)*
  - Terms for non-pregnancy associated lactation conditions (e.g., PT *Galactorrhoea*)
- For *Foetal disorders (SMQ)*
  - Terms related to fetal presentation (e.g., PT *Foetal arm prolapse*) and fetal position (e.g., PT *Unstable foetal lie*)
  - Terms for risk factors for fetal disorders
- For *Neonatal disorders (SMQ)*
  - Terms for developmental disorders (proposed for a separate, standalone SMQ)
  - Congenital terms
  - PT *Distal intestinal obstruction syndrome* (LLT *Meconium ileus equivalent syndrome* links to PT *Distal intestinal obstruction syndrome*. However, the PT is a more general condition in patients of any age with cystic fibrosis)
- For *Termination of pregnancy and risk of abortion (SMQ)*
  - Terms indicative of a non-viable ectopic pregnancy
- For *Normal pregnancy conditions and outcomes (SMQ)*
  - Terms for conditions related to risk to the fetus/pregnancy

NOTE: In version 14.0, *Pregnancy and neonatal topics (SMQ)* is a new SMQ that was added to replace *Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders) (SMQ)*. Consequently, *Adverse pregnancy outcome/reproductive toxicity (incl neonatal disorders) (SMQ)* has been changed to inactive status.

NOTE: In version 14.0, all of the PTs under *Congenital, familial and genetic disorders (SMQ)* have been changed from broad to narrow scope.

NOTE: Because *Neonatal disorders (SMQ)* excludes congenital terms, users of *Neonatal disorders (SMQ)* should consider whether the addition of *Congenital, familial and genetic disorders (SMQ)* to the search is appropriate for the question in hand.

2.80.3 Hierarchy Structure

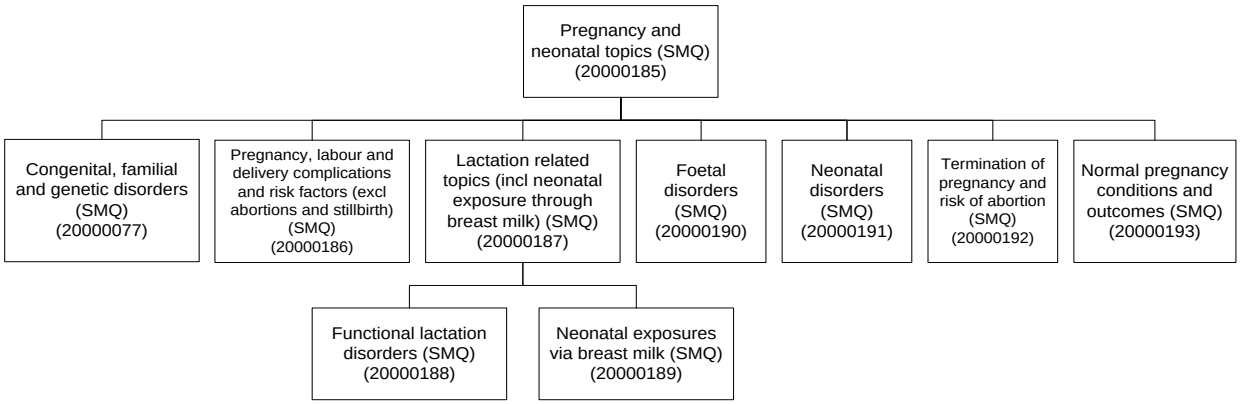

Figure 2-19. Hierarchy Structure of *Pregnancy and neonatal topics (SMQ)*

2.80.4 List of References for *Pregnancy and neonatal topics (SMQ)*

- *Guideline on the Exposure to Medicinal Products during Pregnancy: Need for Post-Authorisation Data*. London, 14 November 2005, EMEA/CHMP/313666/2005.

2.81 Premalignant disorders (SMQ)

(Production Release March 2007)

2.81.1 Definition

- Premalignant lesions: morphologically identifiable lesions that sometimes precede the development of invasive cancer
  - Also called precancers, preneoplastic lesions, incipient cancers, intraepithelial neoplasias, and preinvasive cancers
  - May lack constitutive properties of cancer
  - May have certain attributes that are absent in cancers
  - Need not progress to cancer
  - Often have a high rate of regression
  - When premalignant lesion progresses, cancer is the obligate outcome

2.81.2 Inclusion/Exclusion Criteria

- Included:
  - Atypias, e.g., intraepithelial neoplasias found at LLT level, usually placed under “dysplasia” PTs
  - All terms in HLT *Myelodysplastic syndromes*
  - All terms under HLT *Myeloproliferative disorders (excl leukaemias)*
  - All terms under HLT *Skin preneoplastic conditions NEC*
  - Selected terms in HLT *Gastrointestinal mucosal dystrophies and secretion disorders*
  - Terms from SOC *Investigations* and SOC *Surgical and medical procedures* related to identifying and treating precancerous processes (see Excluded)
- Excluded:
  - Terms already defined as malignant processes e.g., all carcinomata “in situ”
  - Risk factors either leading to precancerous lesions or associated with a higher incidence of a malignant process
  - Cell markers and hormones or proteins that can be used as predictors of malignancy
  - Terms referring to abnormal biopsy results (e.g., PT *Biopsy colon abnormal*) because they are non-specific and did not yield significant data on testing

NOTE: Terms for abnormal biopsy results are excluded from SMQ *Premalignant disorders (SMQ)*. After retrieving data with SMQ *Premalignant disorders (SMQ)* or any of its sub-SMQs, the user may refer to *Malignancies (SMQ)* to identify "biopsy abnormal" terms if additional data retrieval is deemed necessary.

NOTE: Because *Premalignant disorders, general conditions and other site specific disorders (SMQ)* contains non site-specific terms such as PT *Dysplasia*, in order to retrieve all relevant cases for the site-specific sub-searches for *Blood premalignant disorders (SMQ)*,*Gastrointestinal premalignant disorders (SMQ)*, *Reproductive premalignant disorders (SMQ)*, and *Skin premalignant disorders (SMQ)*, it may be necessary to combine the subordinate SMQ with *Premalignant disorders, general conditions and other site specific disorders (SMQ)*. Medical judgment may need to be applied.

NOTE: *Premalignant disorders (SMQ)* focuses on the premalignant conditions themselves for safety analysis purposes. This SMQ specifically excludes terms for malignancy risk factors, such as:

- Genetic predispositions for malignancy (e.g., PT *Li-Fraumeni syndrome*)
- Lifestyle issues (e.g., PT *Tobacco user*)
- Certain inflammatory/infectious conditions that increase risk for malignancy (e.g., PT *Hepatitis chronic active*, PT *Colitis ulcerative*)

Some organizations may require a search for malignancy risk factors based on MedDRA terms coded, for example, in a medical history field. An approach for this may be to focus initially on whatever body system or cancer type is of concern. For example, if skin malignancies are of interest, the user should consider searching the medical history fields for terms related to sun exposure (e.g., PT *Actinic elastosis*, PT *Sunburn*, etc.). For a more comprehensive search of all malignancy risk factors, a careful and broad search of related MedDRA terms would be needed, including terms for genetic predispositions, lifestyle-associated terms, and certain inflammatory/infectious terms as noted above.

2.81.3 Hierarchy Structure

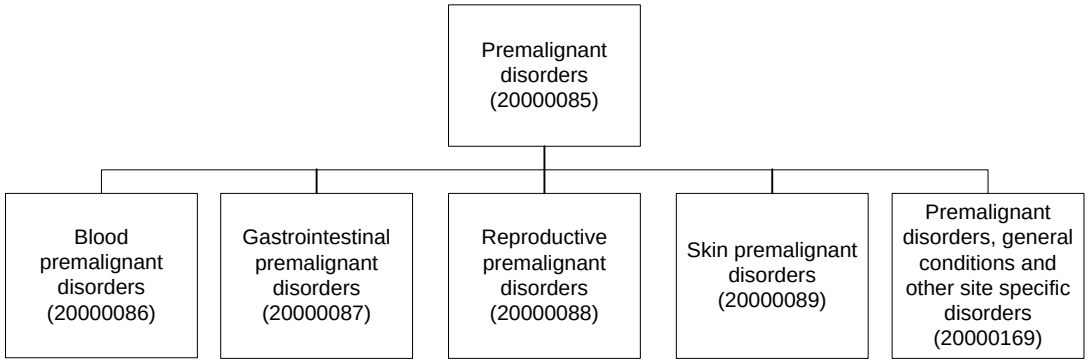

Figure 2-20. Hierarchy Structure of *Premalignant disorders (SMQ)*

NOTE: In Version 14.0, *Premalignant disorders (SMQ)* was modified in scope to include narrow search terms only. This SMQ formerly included both narrow and broad search terms.

NOTE: Also in Version 14.0, approximately 130 PTs in the five sub-SMQs of *Premalignant disorders (SMQ)* have been made inactive per recommendation of the CIOMS SMQ Working Group for the following reasons:

- "Biopsy abnormal" concepts (e.g., PT *Biopsy lip abnormal*) and other nonspecific procedure terms (e.g., PT *Nasal polypectomy*) are unlikely to retrieve events/cases of interest.

- Upon review, some terms were nonspecific, or were either already malignant (e.g., PT *Chronic myelomonocytic leukaemia*) or not truly premalignant (e.g., PT *Seborrhoeic keratosis*)

- Terms for risk factors (e.g., PT *Coeliac disease*) were made inactive because most SMQs generally exclude terms for risk factors; instead, wording on approaches to retrieving data related to malignancy risk factors have been added to the SMQ Introductory Guide.

NOTE: In Version 12.0, per user's request, *Premalignant disorders, general conditions and other site specific disorders (SMQ)* was added at level 2 to group the PTs that had been linked to *Premalignant disorders (SMQ)* but did not belong to any of the level 2

sub-SMQs. Unlike other level 2 sub-SMQ (e.g. *Blood premalignant disorders (SMQ)*), *Premalignant disorders, general conditions and other site specific disorders (SMQ)* is not a standalone SMQ topic. It should only be used as part of its superordinate SMQ topic - *Premalignant disorders (SMQ)*.

- Four sub-groups allow for more specific searches:
  - *Blood premalignant disorders (SMQ)*
  - *Gastrointestinal premalignant disorders (SMQ)*
  - *Reproductive premalignant disorders (SMQ)*
  - *Skin premalignant disorders (SMQ)*

Terms not pertaining to above four groups are gathered directly underneath the *Premalignant disorders, general conditions and other site specific disorders (SMQ)*.

- Users can refine searches by differentiating:
  - "Obligate" lesions (definite or probable progression to malignancy)
  - "Facultative" lesions (possible progression)

2.81.4 Notes on Implementation and/or Expectation of Query Results

Premalignant disorders (SMQ) is a hierarchical SMQ, and has only narrow terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.81.5 List of References for *Premalignant disorders (SMQ)*

- Classifying the precancers: A metadata approach (Jules J Berman and Donald E Henson).
- Heenan PJ, Elder DJ, Sobin LH (1996) WHO International Histological Classification of Tumors. Berlin, Heidelberg, New York, Tokyo: Springer.
- Berman JJ, Henson DE. A Comprehensive Classification and Data Implementation for the Precancers.
- http://www.pathinfo.com/jjb/preclass.htm , 2002 (This web site may not currently be active).
- Harrison's Principles of Internal Medicine, 16th Edition.
- Dorland's Medical Dictionary.

[NOTE: See CIOMS WG original documentation for additional web site references used]

2.82 Prostate neoplasms, malignant and unspecified (SMQ)

(Production Release September 2008)

2.82.1 Definition

- Developed to detect all malignant and unspecified tumors related to prostate
- Covers all malignant and unspecified neoplasms related to prostate and in addition:
  - Malignancy related conditions
  - Malignancy related therapeutic and diagnostic procedures
  - Tumor markers

2.82.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for malignant or unspecified neoplasms with a clear reference to prostate
  - Terms for conditions related to malignant or unspecified neoplasms of the prostate, including:
    - Procedures
    - Investigations
    - Tumor markers
    - Signs and symptoms pointing to such disorders
- Excluded:
  - Terms for malignant or unspecified neoplasms without a clear reference to prostate
  - Terms for unspecified site malignancy related therapeutic and diagnostic procedures and tumor markers
  - Terms for metastases to the prostate
  - PT *Prostatic operation* as it is not a malignancy specific therapeutic procedure. (This term may, however, be added if a very broad search is required).

NOTE: In Version 14.0, two new sub-SMQs have been added to *Prostate neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: For searches of non-specific malignancy related conditions, malignancy related therapeutic and diagnostic procedures, it is recommended to use the respective lower level sub-SMQ of *Malignancies (SMQ)*.

NOTE: PT *Transurethral prostatectomy* is omitted from this SMQ based on testing results and because this is not a procedure that would normally be used for a malignant neoplasm of the prostate.

2.82.3 Hierarchy Structure

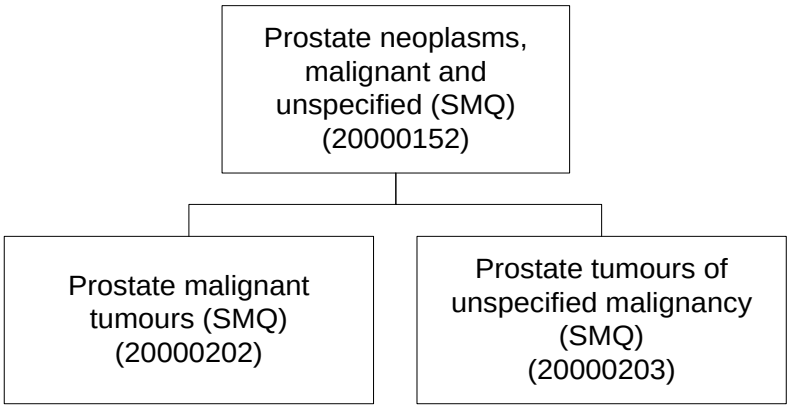

Figure 2-21. Hierarchy Structure of *Prostate neoplasms, malignant and unspecified (SMQ)*

2.82.4 Notes on Implementation and/or Expectation of Query Results

Prostate neoplasms, malignant and unspecified (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.82.5 List of References for *Prostate neoplasms, malignant and unspecified (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H,.Veronesi, U. Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://www.egtm.eu/

2.83 Proteinuria (SMQ)

(Production Release September 2014)

2.83.1 Definition

- Proteinuria is the presence of an excess of serum proteins in the urine (>300 mg/24h)
  - Isolated proteinuria is urinary protein without other symptoms or urinary abnormalities
  - In many renal disorders, proteinuria occurs with other urinary abnormalities (e.g., hematuria)
  - The presence of protein in the urine is toxic to the kidneys and causes renal damage
  - Proteinuria caused by renal disorders usually is persistent (i.e., present on serial testing)
  - The upper limit of normal urinary protein excretion is considered to be 150 mg/day, which can be measured in a 24-h urine collection or estimated by random urine protein/creatinine ratio (values > 45 mg/mmol are abnormal); for albumin it is about 30 mg/day
  - Albumin excretion between 30 and 300 mg/day (20 to 200 µg/min) is considered microalbuminuria, and higher levels are considered macroalbuminuria
  - When in the nephrotic range, proteinuria can cause significant protein wasting
  - May be associated with foamy urine

- **Classification of proteinuria:**
  - *Glomerular proteinuria*
    - Results from glomerular disorders
    - Increased glomerular permeability allows increased amounts of plasma proteins (sometimes very large amounts) to pass into the filtrate
  - *Tubular proteinuria*
    - Results from impaired reabsorption of protein by the proximal tubule
    - Proteinuria mostly from smaller proteins such as immunoglobulin light chains rather than albumin
    - Often accompanied by other defects of tubular function (e.g., HCO3 wasting, glucosuria, aminoaciduria) and sometimes by glomerular pathology (which also contributes to the proteinuria)

- *Overflow proteinuria*
  - Excessive amounts of small plasma proteins (e.g., immunoglobulin light chains produced in multiple myeloma) exceed the reabsorptive capacity of the proximal tubules

- *Functional proteinuria*
  - Increased renal blood flow (e.g., due to exercise, fever, high-output heart failure) delivers increased amounts of protein to the nephron, resulting in increased protein in the urine (usually < 1 g/day)
  - Resolves when renal blood flow returns to normal

- *Orthostatic proteinuria*
  - A benign condition (most common among children and adolescents)
  - Proteinuria occurs mainly when the patient is upright
  - Urine typically contains more protein during waking hours (when people are more often upright) than during sleep
  - Very good prognosis
  - Requires no special intervention

2.83.2 Inclusion/Exclusion Criteria

- Included:
  - Terms containing the word “proteinuria”
  - Terms (investigational or not) referring to the levels of albumin in urine or blood, including quantification of 24 h urine albumin excretion either by direct methods or derived ones (albumin-to-creatinine ratio). Reduced losses of albumin (microalbuminuria) are also included.
  - Terms (investigational or not) referring to the levels of other proteins (other than albumin) which escape usual dipstick detection in urine or blood, such as Beta 2 microglobulin, immunoglobulin light chains (Bence-Jones protein), myoglobin, etc.
  - Acquired nephrotic syndrome (PT *Nephrotic syndrome*) is included for its close relationship with large urine protein loss, as well as the PT *Protein deficiency* and PT *Oedema due to renal disease*, which despite not being specific for nephrotic syndrome, are both relevant downstream consequences of it.
- Excluded:
  - Potential causes of proteinuria, which include renal glomerular and tubular diseases, with the exception of PT *Nephrotic syndrome*
  - Other complications of nephrotic syndrome (except PT *Protein deficiency* and PT *Oedema due to renal disease*) such as hypercoagulability,

thromboembolism, or hyperlipidemia, because of the likelihood of introducing noise in the search.

- Urinalysis and renal function testing usually performed after or in the context of proteinuria, such as measurement of serum electrolytes, BUN, creatinine, and glucose, determination of GFR, etc.
- Congenital terms are excluded
- Non-qualified investigation terms are excluded, except for PT *Protein urine* which returned significant counts in testing and was considered to represent a way of reporting proteinuria using a non-qualified term

2.83.3 Notes on Implementation and/or Expectation of Query Results

Proteinuria (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.83.4 List of References for *Proteinuria* (SMQ)

- Harrison's Principles of Internal Medicine: Chapter 44. Azotemia and Urinary Abnormalities
- Merck Manual for Health Care Professionals: Proteinuria
- Merck Manual for Health Care Professionals: Overview of Nephrotic Syndrome
- Current Diagnosis & Treatment: Nephrology & Hypertension: Chapter 1. Approach to the Patient with Renal Disease

2.84 Pseudomembranous colitis (SMQ)

(Production Release March 2007)

2.84.1 Definition

- Pseudomembranous colitis is a severe, necrotizing process that involves the large intestine and occurs as a complication of antibiotic therapy
- It occasionally occurs in the absence of antibiotic exposure; a predisposing condition is often present, e.g., recent bowel surgery, uraemia, intestinal ischaemia, chemotherapy, bone marrow transplantation
- The responsible pathogen is “Clostridium difficile”, a member of the normal flora that overgrows in the presence of certain antibiotics or in the absence of normal bacterial flora due to other factors
- Culture and toxin tests are available to identify C. difficile but a positive microbiology test(s) in the absence of clinical findings does not support a definitive diagnosis of pseudomembranous colitis
- Many reports of diarrhoea associated with antibiotic therapy may not have definitive diagnoses or specific tests for pseudomembranous colitis
- Uncomplicated antibiotic-induced diarrhoea usually subsides spontaneously within two weeks of antibiotic discontinuation
- For persisting symptoms or frank colitis, aggressive therapy may be required to restore balance of the bacterial flora within the lumen of the intestinal tract

2.84.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for “Clostridium colitis” and related concepts
  - Terms for signs, symptoms, and laboratory findings, as described in the definition
  - Species-level microbial terms that specify “C. difficile”
  - Nonspecific "clostridia" terms (e.g., PT *Clostridial infection*) so that possible C. difficile is not overlooked, but terms such as "C. perfringens" would not be included
  - Inclusion of PT *Diarrhoea* and PT *Diarrhoea haemorrhagic* in the narrow searches for the antibiotic products were justified, as several cases were retrieved that would not otherwise have been detected. However, careful review of the case narratives is indicated to categorize such cases as being relevant to the medical condition of interest. For the negative control compounds, PT *Diarrhoea* within the broad search created a lot of noise. Thus, use of PT *Diarrhoea* and PT *Diarrhoea haemorrhagic* is recommended for use only in narrow searches with antibiotics.

- Excluded:
  - Microbial terms that specify non-C. difficile species
  - Terms for mucosal disorders that do not specify involvement of the large intestine.

2.84.3 Notes on Implementation and/or Expectation of Query Results

Pseudomembranous colitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.84.4 List of References for *Pseudomembranous colitis (SMQ)*

- Merck Manual of Diagnosis and Therapy, 1999. 17th Edition.
- Principles and Practices in Infectious Diseases, Mandell, Douglas, and Bennett, 2nd edition.

2.85 Psychosis and psychotic disorders (SMQ)

(Production Release September 2007)

2.85.1 Definition

- Psychosis refers to a mental disorder characterized by gross impairment in reality testing evidenced by:
  - Delusions
  - Hallucinations
  - Markedly incoherent speech
  - Disorganized and agitated behavior, usually without apparent awareness on the patient's part
- Psychosis is also used in a more general sense to refer to mental disorders in which mental functioning is sufficiently impaired as to interfere grossly with patient's capacity to meet the ordinary demands of life
- Psychosis can be caused by many psychiatric disorders such as:
  - Schizophrenia
  - Schizoaffective disorder
  - Delusional disorder
  - Brief psychotic reaction
  - Mania with psychosis
  - Depression with psychosis
  - Dementia
  - Delirium
- Psychosis is also associated with:
  - Certain illicit drugs (cocaine, amphetamine, etc.)
  - Medications (dopamine agonists, l-dopa, psychostimulants, etc.)
  - In Schizophrenia, Schizophreniform disorder, Schizoaffective disorder, and Brief Psychotic disorder, the term psychotic refers to delusions, any prominent hallucinations, disorganized speech or disorganized or catatonic behavior.

2.85.2 Inclusion/Exclusion Criteria

- Included:
  - Specific types of psychosis and those etiologies in which the PT mentions psychosis (*e.g*., PT *Psychotic disorder due to a general medical condition*). Considered narrow in scope.
  - Symptoms commonly seen with psychosis or psychotic disorders or indicate the presence of psychosis (*e.g*., PT *Neologism*, PT *Paranoia*). Considered narrow in scope.
  - Certain "broad" PTs (*e.g.,* PT *Major depression*) in order to capture underlying LLTs that mentioned psychosis (*e.g*., LLT *Depression psychotic*). Considered broad in scope.
  - Psychotic disorders that are not typically medication-induced (*e.g*., Schizophrenia) in order to capture the possibility that a medication may exacerbate the underlying illness (*e.g*., dopamine agonists exacerbating schizophrenic psychosis) and that a reporter may prematurely diagnose a psychotic patient with schizophrenia before recognizing a medication-induced psychosis
- Excluded:
  - Antipsychotic drug level terms, such as PT *Antipsychotic drug level above therapeutic*, PT *Antipsychotic drug level below therapeutic*, PT *Antipsychotic drug level increased*, PT *Antipsychotic drug level therapeutic* because these medications may be used for many symptoms other than psychosis
  - PT *Psychotic family member*, PT *Schizophrenic relative* as they relate to another person having psychosis
  - PT *Toxicity to various agents* contains LLT *Poisoning by psychodysleptics (hallucinogens)* but also many other non-related LLTs that would create a large amount of "noise"
  - PT *Drug abuser* contains LLTs of Hallucinogen abuse but many others that would not consistently produce psychosis
  - PT *Drug use disorder* contains LLTs of hallucinogen dependence but many others that would not consistently produce psychosis
  - PT *Maternal drugs affecting foetus* contains LLT *Hallucinogenic agents affecting fetus or newborn via placenta or breast milk* but it is impossible to tell if a fetus or newborn is psychotic
  - PTs that are potential etiologies of psychosis but do not mention psychosis (*e.g.,* PT *Porphyria*, PT *Delirium*). PT *Schizoid personality disorder* as it is not usually associated with psychosis and because a psychotic disorder must be ruled out in order to make the diagnosis

- Symptoms that may occur with psychosis or psychotic disorders but are very common in the absence of psychosis *(e.g*., types of anxiety, confusion, disorientation, etc.)
- Depression (with the exception of PT *Major depression*) and suicide related terms as they are common in the absence of psychosis
- Non-specific investigation terms including PT *Mental status changes,* PT *Psychiatric evaluation abnormal,* PT *Neurological examination abnormal*

2.85.3 Notes on Implementation and/or Expectation of Query Results

Psychosis and psychotic disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.85.4 List of References for *Psychosis and psychotic disorders (SMQ)*

- Dorland's Illustrated Medical Dictionary, 29th Edition, WB Saunders 2004.
- American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC, 1994.

2.86 Pulmonary hypertension (SMQ)

(Revised March 2016; Original Production Release September 2007)

2.86.1 Definition

- The Fifth World Symposium on Pulmonary Hypertension, 2013, established a new classification of pulmonary hypertension, and a new definition of pulmonary hypertension was released in 2015, which impacted the case identification parameters for *Pulmonary hypertension (SMQ)*.

- A detailed review of the original terms included in this SMQ revealed the presence of several conditions which are rarely associated with pulmonary hypertension (e.g. PT *Hepatic cirrhosis*); excessively "noisy" signs and symptoms; several sign and symptom term concepts typically associated with pulmonary hypertension were noted not to be included; and other terms were found to be not fully consistent with selection criteria.

- In light of the above, a decision was made to revise *Pulmonary hypertension (SMQ)*. A new definition and new SMQ inclusion/exclusion criteria were established based upon the conclusions of the Fifth World Symposium on Pulmonary Hypertension, and of The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). The term list for this SMQ was updated accordingly, and the terms were subjected to testing.

- PH has been defined in the past as a resting mean pulmonary arterial pressure (mPAP) >25 mm Hg, or an mPAP with exercise >30 mm Hg. The subgroup of PH known as pulmonary arterial hypertension (PAH) adds the criterion that the pulmonary arterial wedge pressure must be ≤ 15 mm Hg. Some definitions have also included pulmonary vascular resistance (PVR), requiring that it be ≥2 or 3 Wood units.
  Potential weaknesses of the previous definition relate to the fact that the level, type, and posture of exercise had not been specified. Furthermore, the normal exercise pulmonary arterial pressure (PAP) varies with age.

- Clarification of the definition based on available evidence was an important objective of the 2015 ESC/ERS guideline:

  The new definition of PH is a resting mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. Further studies are needed to better determine the natural history of patients with mPAP 21 to 24 mm Hg.
  - The exercise and pulmonary vascular resistance (PVR) criteria should be eliminated.
  - A resting mPAP of 8 to 20 mm Hg should be considered normal, based on available evidence.

2.86.2 Inclusion/Exclusion Criteria

- Included:
  - Terms directly related to pulmonary hypertension (PT *Portopulmonary hypertension*; PT *Pulmonary arterial hypertension*)
  - Acute forms of pulmonary hypertension (PT *Pulmonary hypertensive crisis*; PT *Acute right ventricular failure*; PT *Cor pulmonale acute*), were first considered for exclusion, but were finally included in view that some drugs may cause acute pulmonary hypertension.
  - Specific consequences of pulmonary hypertension (PT *Cor pulmonale chronic*; PT *Right ventricular hypertrophy*; PT *Tricuspid valve incompetence*)
  - Highly specific etiologic conditions which often result in pulmonary hypertension (PT *Pulmonary vascular resistance abnormality*; PT *Pulmonary vein stenosis* ; PT *Pulmonary veno-occlusive disease*)
  - Investigations and therapeutic procedures specifically used in pulmonary hypertension (PT *Pulmonary endarterectomy*; PT *Pulmonary arterial pressure increased*; PT *Vascular resistance pulmonary increased*)
  - Signs and symptoms highly related to pulmonary hypertension (PT *Right ventricular heave*; PT *Hepatojugular reflux*)
- Excluded:
  - Etiologic conditions which are only occasionally associated with pulmonary hypertension (PT *Cirrhosis alcoholic*; PT *Cryptogenic cirrhosis*; PT *Chronic obstructive pulmonary disease*)
  - Nonspecific investigations or therapeutic procedures which are only weakly related to pulmonary hypertension (PT *Catheterisation cardiac abnormal*; PT *Carbon dioxide decreased*; PT *Chest X-ray abnormal*)
  - Signs and symptoms not specific to pulmonary hypertension, which often appear in other conditions or syndromes and can cause noise in a search (PT *Dizziness*)
  - Nonqualified investigation terms
  - Congenital terms

2.86.3 Notes on Implementation and/or Expectation of Query Results

Pulmonary hypertension (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.86.4 List of References for *Pulmonary hypertension (SMQ)*

- Diagnosis and Assessment of Pulmonary Arterial Hypertension. Journal of the American College of Cardiology Vol. 54, No. 1, Suppl S.

- Updated Clinical Classification of Pulmonary Hypertension. Journal of the American College of Cardiology Vol. 54, No. 1, Suppl S.

- Guidelines for the diagnosis and treatment of pulmonary hypertension. European Heart Journal (2009) 30, 2493–2537.

- Assessment of right ventricular volumes and ejection fraction by echocardiography: from geometric approximations to realistic shapes. Ellen Ostenfeld and Frank A Flachskampf

- Department of Clinical Physiology, Ska°nes Universitetssjukhus, Lund University, 22185 Lund, Sweden.

2.87 Renovascular disorders (SMQ)

(Production Release March 2010)

2.87.1 Definition

- Renovascular disorders include:
  - Atherosclerotic renal artery stenosis (most common primary disease of the renal arteries)
  - Fibromuscular dysplasia of the renal arteries
  - Embolic renal artery occlusion
  - Renovascular microvascular disorders
- All can result in renal dysfunction, usually evidenced by high plasma renin levels
- Usually present in one of three forms:
  - Asymptomatic renal artery stenosis
  - Renovascular hypertension
  - Ischemic nephropathy
- Primarily due to constriction of afferent renal artery resulting in decreased perfusion pressure of larger circulation and/or microcirculation
  - Disorder of larger circulation commonly due to unilateral or bilateral renal artery stenosis
  - Microcirculation disorders commonly due to small vessel thrombosis:
    - From proximal upstream thrombi (e.g., in the stenosed renal artery)
    - From distal sites (e.g., intracardiac thrombi)
- Mechanisms of chemotherapy-induced renal dysfunction include:
  - Damage to kidney vasculature or structures
  - Hemolytic uremic syndrome
  - Prerenal perfusion deficits
- Renovascular disorders may result in progressive severe hypertension with the usual sequelae of this condition

2.87.2 Inclusion/Exclusion criteria

- Included:
  - Narrow search: All terms in HLT *Renal vascular and ischaemic conditions* except PT *Thrombotic microangiopathy* and terms containing “necrosis” (broad search)
  - Narrow search: Terms relating to renal hypertension

- Broad search: PT *Haemolytic uraemic syndrome* and related terms, e.g., PT *Thrombotic microangiopathy* and PT *Thrombotic thrombocytopenic purpura*
- Broad search: Terms in HLT *Renal vascular and ischaemic conditions* containing the word “necrosis”
- Broad search: Relevant investigation terms, e.g., PT *Arteriogram renal abnormal*

- Excluded:
  - Congenital terms

2.87.3 Notes on Implementation and/or Expectation of Query Results

Renovascular disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.87.4 List of References for *Renovascular disorders (SMQ)*

- Bloch MJ, Basile J. Clinical insights into the diagnosis and management of renovascular disease. An evidence-based review. Minerva Med 2004 Oct;95(5):357-73.
- Kendrick J and Chonchol M. Renal artery stenosis and chronic ischemic nephropathy: epidemiology and diagnosis. Adv Chronic Kidney Dis 2008 Oct;15(4):355-62.
- Kintzel PE. Anticancer drug-induced kidney disorders. Drug Saf 2001 Jan;24(1):19-38.
- Nally JV. Acute renal failure in hospitalized patients. Cleveland Clinic J Med 2002; 69: 569-574.
- Thatte L, and Vaamonde CA. Drug-induced nephrotoxicity-The crucial role of risk factors. Postgraduate Medicine1996;100: 1-15.

2.88 Respiratory failure (SMQ)

(Production Release March 2015)

2.88.1 Definition

- Respiratory failure is a life-threatening impairment of oxygenation or carbon dioxide elimination that affects breathing function or the lungs themselves, and can result in failure of the lungs to function properly.

- Two main pathophysiological etiologies (may occur singly, or in combination):
  - Inadequate oxygenation (impaired gas exchange)
  - Inadequate carbon dioxide elimination (decreased ventilation resulting in a rise in $PaCO_2$)

- Common precipitating conditions:
  - Acute exacerbations of asthma and chronic obstructive pulmonary disease
  - Overdoses of drugs that suppress ventilatory drive
  - Conditions that cause respiratory muscle weakness (e.g., Guillain-Barré syndrome, myasthenia gravis, botulism)

- Typical signs and symptoms:
  - Dyspnea
  - Tachypnea
  - Use of accessory muscles of respiration
  - Tachycardia
  - Diaphoresis
  - Cyanosis
  - Altered consciousness
  - Without treatment, eventually obtundation, respiratory arrest, and death

- Diagnostic measures:
  - Patient observation and clinical evaluation
  - Arterial blood gases
  - Chest x-ray

- Treatment includes:
  - Correction of underlying cause
  - Supplemental oxygen
  - Control of secretions
  - Ventilatory assistance

2.88.2 Inclusion/Exclusion Criteria

- Included:

- Terms indicating respiratory failure/depression/arrest, including terms for neonatal respiratory events
- Terms for signs and symptoms associated with respiratory failure, e.g. PT *Use of accessory respiratory muscles*, PT *Xyphoid retraction*
- Breathing abnormalities indicating respiratory failure, e.g. PT *Orthopnoea*, PT *Tachypnoea*
- Relevant treatment terms for respiratory failure, e.g. PT *Continuous positive airway pressure*
- Laboratory terms indicating respiratory failure, e.g. PT *Venous oxygen saturation abnormal*
- Relevant imaging investigations, e.g. PT *Ventilation/perfusion scan abnormal*

- Excluded:
  - Terms for conditions predisposing to respiratory failure, e.g. PT *Pickwickian syndrome*, PT *Sleep apnoea syndrome*
  - Toxic causes, e.g. PT *Carbon monoxide poisoning*
  - Non-respiratory causes for low PO_2 pressure, such as anaemia

2.88.3 Notes on Implementation and/or Expectation of Query Results

Respiratory failure (SMQ) has narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

Initial testing of this SMQ was based on the term list of the existing *Acute central respiratory depression (SMQ)* and a term list from a company “home grown” search. During the test period additional PTs for inclusion were identified and were tested as well. However, the initial aim to broaden the scope of the existing *Acute central respiratory depression (SMQ)* to include terms for chronic and peripheral causes for respiratory failure was abandoned as it would have weakened the specificity and produced excessive “noise” for the retrieval of cases specific to centrally acting drugs associated with acute central respiratory depression. Consequently, the *Respiratory failure (SMQ)* was developed as a stand alone SMQ.

2.88.4 List of References for *Respiratory failure (SMQ)*

- The Merck Manual. Professional edition. Critical care medicine. Respiratory failure and Mechanical Ventilation

- Harrison's Principles of Internal Medicine, 18e. Part 11. Disorders of the Respiratory System. Chapter 251. Approach to the Patient with Disease of the Respiratory System

- Harrison's Principles of Internal Medicine, 18e. Chapter 35. Hypoxia and Cyanosis

- Medscape. Family Medicine. Respiratory Failure

2.89 Retinal disorders (SMQ)

(Production Release March 2009)

2.89.1 Definition

- Retinal disorders are manifested by a variety of signs and symptoms; no overall definition possible
- SMQ focuses on retinal disorders with damage of retina due to:
  - Blockage of its blood supply
  - Nutritional deficiencies
  - Toxins
  - Diseases affecting retina

2.89.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow search:
    - All terms that contain “retin,” except those which represent retinal infections (see Exclusion criteria)
    - Terms relating to the macula
    - Terms for visual disturbances related to the retina, such as tunnel vision
    - Investigational terms specific for retinal disorders
  - Broad search:
    - Terms for signs and symptoms of visual disturbance
    - Investigational terms that are not necessarily specific for retinal disorders
- Excluded:
  - Terms for other diseases which might impact the retina as a clinical consequence but that do not necessarily affect it and where no specific terms exist in MedDRA, respectively
  - Congenital terms
  - Terms pertaining to retinal infections

2.89.3 Notes on Implementation and/or Expectation of Query Results

Retinal disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.89.4 List of References for *Retinal disorders (SMQ)*

- The Merck Manual – Online Medical Library.

2.90 Retroperitoneal fibrosis (SMQ)

(Production Release September 2006)

2.90.1 Definition

- Retroperitoneal fibrosis (RPF; also known as Ormond's disease) is a rare disorder that is idiopathic in most cases (68%).
- Evidence suggests autoimmunity.
  - Response to ceroid leaking from arteries thinned by atheromatous plaque
- Many diverse causes for the 34% non-idiopathic cases
  - Drugs:
    - Methysergide, ergotamine, some beta-adrenergic blocking agents, hydralazine, and methyldopa
  - Other associations (immune-mediated):
    - E.g., primary biliary cirrhosis, systemic lupus erythematosus
  - Malignant form (poor prognosis):
    - Occurs in response to metastatic tumor cells in the retroperitoneum
  - Other implicated causes:
    - Abdominal aortic aneurysm, ureteric injury, infection, retroperitoneal malignancy, radiation therapy, and chemotherapy
- Characterized by extensive deposition of fibrous tissue in retroperitoneal space compressing ureters bile ducts, blood vessels, and other structures
- Symptoms generally vague; clinical picture nonspecific
  - Radiologic and other imaging modalities needed to confirm diagnosis
- Insidious symptomatology:
  - Flank pain, back pain, lower abdomen pain, malaise, anorexia, weight loss, pyrexia, nausea, vomiting, lower extremity edema and/or thrombophlebitis, and symptoms of arterial compromise of abdomen or lower extremities (e.g., intermittent claudication)

2.90.2 Inclusion/Exclusion Criteria

- Included:
  - PT *Retroperitoneal fibrosis* and terms representing associated conditions that develop as a consequence such as "hydroureter," "hydronephrosis," etc.
  - Relatively few signs/symptom terms chosen for query because they are vague; diagnosis is often based on supporting imaging studies

  - PT *Flank pain* chosen as this is one of the few consistent symptoms
  - PT *Abdominal adhesions* was included
  - Related investigations (e.g., PT *Urine output decreased*)
  - Based on the testing results, it was decided in the CIOMS working group to include both PT *Abdominal pain* and PT *Abdominal pain lower*.
- Excluded:
  - Terms that do not fit within definition of RPF or which are so non-specific as to be deemed not useful
  - Terms for associated immune-mediated disorders (e.g., rheumatoid arthritis)
  - Terms related to malignant form of RPF (e.g., metastases to retroperitoneum)

2.90.3 Notes on Implementation and/or Expectation of Query Results

Retroperitoneal fibrosis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.90.4 List of References for *Retroperitoneal fibrosis (SMQ)*

- CIOMS, Reporting Adverse Drug Reactions, 1999, p 20 – 21.
- Khan, AN. *Retroperitoneal fibrosis*. 13 September 2002. http://www.emedicine.com/radio/topic605.htm
- Diamond, JR. Clinical manifestations and diagnosis of retroperitoneal fibrosis. UpToDate®, 27 February 2005 http://www.utdol.com/

2.91 Rhabdomyolysis/myopathy (SMQ)

(Production Release December 2004)

2.91.1 Definition

- Myopathy is a disorder of striated muscle, with or without changes in muscle mass, and may be accompanied by muscle pain or tenderness.
- Rhabdomyolysis is a syndrome resulting from extensive necrosis of skeletal muscle with release of muscle contents, particularly creatine kinase (CK) and other muscle enzymes (such as aminotransferases and lactic dehydrogenase), creatinine, potassium, uric acid, myoglobin, calcium, and phosphorus into the systemic circulation. Some cases are related to hereditary metabolic or structural abnormalities effecting skeletal muscle cells, such as disorders of glycogen and lipid metabolism. However, the majority of cases occur in healthy individuals due to a variety of non-hereditary causes such as trauma (due to crushing injuries or excessive exercise), bacterial and/or viral infections (such as Staphylococcus or influenza), medications (such as HMG-CoA reductase inhibitors and antipsychotics), recreational drugs (such as cocaine, amphetamines, and alcohol), toxins (such as tetanus and some snake venoms), and ischemia. Rhabdomyolysis varies from mild and self-limiting to severe and possibly life-threatening.
- Muscle signs and symptoms usually include muscle pain, weakness, tenderness, and contractures, usually involving large muscles such as those of the calves, thighs, and lower back, but can also involve the chest, abdomen, palate and throat, and masticatory muscles.
- Other non-specific symptoms can include weight gain, fatigue, malaise, fever, nausea, tachycardia, and dark red or cola-colored urine. Potentially serious systemic sequelae include acute renal failure, compartment syndrome, disseminated intravascular coagulation, cardiomyopathy, and respiratory failure.
- Laboratory abnormalities usually indicative of rhabdomyolysis include elevated creatine kinase (CK, particularly CK-MM, often markedly elevated), myoglobinuria, and increased serum myoglobin. Other laboratory findings may include elevated serum creatinine, lactic dehydrogenase, and aminotransferases. Hypocalcemia and potentially life-threatening hyperkalemia (in patients with acute renal failure) may also occur. Diagnosis can be confirmed by muscle biopsy.

2.91.2 Inclusion/Exclusion Criteria

- Narrow scope: diagnoses and laboratory test results that are unique or directly lead to rhabdomyolysis/myopathy. For example, PT *Muscle necrosis* (diagnosis) and PT *Myoglobin urine present* (test result).
- Broad scope: terms not specifically reported as rhabdomyolysis or myopathy but reporting other musculoskeletal, renal, metabolic, or laboratory PTs that might

involve rhabdomyolysis or myopathy. These terms have the potential of identifying positive cases. For example, PT *Muscle fatigue* (symptom) and PT *Blood creatinine increased* (test result).

- Because of the variety of clinical manifestations associated with rhabdomyolysis or myopathy, it is possible that cases may not have been initially classified and coded as such. In an attempt to provide sufficient sensitivity to the SMQ, it encompassed events such as compartment syndrome and other, non-myopathy-related muscle events (myalgia, muscle fatigue or weakness, musculoskeletal pain or discomfort, or abnormal muscle biopsy) or other non-musculoskeletal events suggestive of possible rhabdomyolysis or myopathy (renal failure and related events, increased CK or other muscle enzymes, hypocalcaemia, or chromaturia).
- In an effort to make the query relatively specific, not all possibly rhabdomyolysis- or myopathy-related events were included (for example, not all PTs listed under the HLT *Myopathies* are included).
- No specific exclusions are defined for this SMQ.

NOTE: Due to MedDRA rules and conventions, LLT *Rhabdomyolysis-induced renal failure* is placed under PT *Acute kidney injury*. Therefore, LLT *Rhabdomyolysis-induced renal failure* is included as a broad search term even though it would logically be a narrow term because its PT *Acute kidney injury* is a broad term.

2.91.3 Notes on Implementation and/or Expectation of Query Results

Rhabdomyolysis/myopathy (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.91.4 List of References for *Rhabdomyolysis/myopathy (SMQ)*

- Basic requirements for the use of terms for reporting adverse drug reactions (IV). *Pharmacoepidemiology and Drug Safety* 1993; 2:149-153.
- Reporting Adverse Drug Reactions. Definitions and criteria for their use. *CIOMS publication*, Geneva, 1999.
- Poels PJE and Gabreëls FJM. Rhabdomyolysis: a review of the literature. *Clin Neurol Neurosurg* 1993; 95:175-192.
- Omar MA, Wilson JP, and Cox, TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Annals Pharmacother* 2001; 35:1096-1107.
- Prendergast BD and George CF. Drug-induced rhabdomyolysis – mechanisms and management. *Postgrad Med J* 1993; 69:333-336.

2.92 Scleral disorders (SMQ)

(Production Release March 2010)

2.92.1 Definition

- Sclera
  - Dense, white fibrous outer protective layer of eye
  - Consists largely of collagen
  - Histologic structure similar to cornea
  - Varies in thickness from 0.3 mm to about 0.6 mm
  - Continuous with cornea (anterior) and dural sheath of optic nerve (posterior)
  - Lamina fusca – layer of brown pigment on scleral inner surface
  - Optic nerve axons pass through lamina cribrosa (collagen and elastic tissue bands at posterior scleral foramen)
  - Posterior ciliary arteries and nerves reach ciliary body through shallow groove on inner surface of sclera
- Episclera
  - Thin layer of elastic tissue on outer surface of anterior sclera
  - Contains blood vessels that feed sclera
- Signs and symptoms of sclera disorders
  - Lacrimation
  - Hyperemic patches
  - Globe perforation
  - Discoloration
  - Plaque deposits
  - Redness
  - Eye pain
  - Photophobia
  - Loss of vision
- Conditions affecting sclera
  - Blue sclera
    - Occurs in certain connective tissue disorders (e.g., osteogenesis imperfecta, Ehlers-Danlos syndrome, etc.)

- Also may be in normal newborns and patients with keratoconus or keratoglobus

- Scleral ectasia
  - Occurs with prolonged elevation of intraocular pressure early in infancy (e.g., congenital glaucoma)
  - May also be congenital or following injury, inflammation of sclera
- Staphyloma
  - Result of bulging of uvea into ectatic sclera
  - Generally have poor vision and high myopia (posterior staphyloma)
  - Posterior staphyloma may be associated with subretinal neovascularization, choroidal atrophy
- Episcleritis
  - Localized inflammation of vascularized connective tissue overlying sclera
  - Affects patients mainly in third or fourth decade of life, females three times more frequently than males
  - About one-third of patients have an associated disorder (e.g., ocular rosacea, atopy, gout, infection, or collagen-vascular disease)
  - Signs and symptoms include redness, mild irritation/discomfort, episcleral injection
  - Course is generally self-limited (1–2 weeks)
- Scleritis
  - Cellular infiltration, destruction of collagen, and vascular remodeling
  - May be immunologically mediated, result of infection or initiated by local trauma
  - Occurs in women more commonly than men, typically in fifth or sixth decades of life
  - Bilateral in one-third of cases
  - Pain, tender globe, slightly reduced visual acuity, mildly elevated intraocular pressure
  - One-third of patients may have concurrent keratitis or uveitis
  - Occlusive vasculitis indicates a poor prognosis
  - Scleral thinning and perforation may occur
- Scleromalacia perforans
  - Scleral necrosis (without inflammation)
  - Seen almost exclusively in patients with rheumatoid arthritis

- Hyaline degeneration
  - Seen in people over age 60
  - Small, round, translucent gray areas, about 2–3 mm, located anterior to insertion of rectus muscles
  - Asymptomatic and is not associated with complications

2.92.2 Inclusion/Exclusion criteria

- Included:
  - Terms for specific scleral disorders (e.g., PT *Scleromalacia*)
  - Terms for signs and symptoms characteristic of scleral disorders (e.g., PT *Scleral discolouration*)
  - Terms for episcleral conditions (e.g., PT *Episcleral hyperaemia*)
  - Terms for results of investigations related to sclera disorders (e.g., PT *Biopsy sclera abnormal*)
  - Terms for procedures related to sclera (PT *Scleral buckling surgery*)
- Excluded:
  - Congenital terms
  - Terms for nonspecific signs and symptoms of scleral disorders that could be shared with other eye disorders (they will be in a separate SMQ) e.g., PT *Visual impairment*
  - Terms for conditions that represent complications of scleral disorders (e.g., glaucoma, uveitis, etc.)
  - Infectious terms (e.g., LLT *Syphilitic episcleritis* is linked to PT *Eye infection syphilitic*)
  - Unqualified investigation terms (e.g., PT *Biopsy sclera*)

2.92.3 Notes on Implementation and/or Expectation of Query Results

Scleral disorders (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.92.4 List of References for *Scleral disorders (SMQ)*

- Riordan-Eva, P. *Vaughan & Asbury's General Ophthalmology*, Chapter 1: Anatomy & Embryology of the Eye.
- Cunningham, ET and Shetlar, DJ. *Vaughan & Asbury's General Ophthalmology*, Chapter 7: Uveal Tract & Sclera.

- Gaeta, TJ. Scleritis. eMedicine, 14 April 2008, http://www.emedicine.com/EMERG/topic521.htm
- Hampton, R. Episcleritis. eMedicine, 18 March 2008. http://www.emedicine.com/oph/topic641.htm
- *Merck Manual*, 17th edition, p 717.

2.93 Sepsis (SMQ)

(Production Release September 2019)

2.93.1 Definition

- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis is caused by an infection of any organisms including bacterial, fungal and viral agents.

- Etiology:

    - In patients with an intact immune system, gram-positive and gram-negative bacteria are the most common cause

    - In patients with a compromised immune system, uncommon bacterial and fungal species are more commonly the cause

    - Many factors increase the risk of developing sepsis including indwelling vascular catheters or other invasive devices, recent surgical procedures, diabetes mellitus, cirrhosis, and compromised immune systems

    - Staphylococcal and streptococcal toxins can cause toxic shock syndrome, which is a unique, but rare, form of septic shock

    - Common sites of infection include the urinary, biliary, and gastrointestinal tracts as well as the lungs

- Clinical signs are dependent on the predisposing conditions and are often non-specific. These may include:

    - Signs of infection including fever, tachycardia, diaphoresis, and tachypnea

    - As the condition deteriorates, signs and symptoms consistent with end-organ damage can present. These include hypotension, altered mental status, confusion, renal insufficiency, and hypoxia.

- Diagnosis of sepsis requires a combination of clinical signs and symptoms along with positive cultures of blood, urine, or other sites of infection

- Mortality in patients with septic shock has improved since the adoption of global sepsis screening criteria, however it averages 30 to 40%

- Treatment:

    - Control of the infectious source should be undertaken promptly. All invasive devices should be removed or changed if possible. Necrotic tissue should be excised. Abscesses should be drained.

    - Treatment of sepsis centers on treatment with broad-spectrum antibiotics and circulatory support

        - Vasopressors and IV fluids are often used to support overall perfusion

        - Oxygen is administered in the event of respiratory insufficiency

        - Support for other conditions which may arise, including adrenal insufficiency or renal insufficiency, is also required

    - Patients with septic shock generally require intensive care

    - Blood sugar control is critical for patients with diabetes as hyperglycemia will impede the ability to respond adequately to the infection

2.93.2 Inclusion/Exclusion Criteria

- **Included:**

    - Terms referring to sepsis, septic conditions, septicemia, bacteremia, fungemia, and viremia

    - Terms for positive blood cultures

    - Terms for relevant biomarkers of sepsis (e.g., PT *Procalcitonin increased*, PT *Procalcitonin abnormal*)

    - Terms for toxic and septic shock

- **Excluded**:

- Terms for non-specific symptoms likely to return a considerable amount of "noise" (e.g., PT *Pyrexia,* PT *White blood cell count increased*, PT *Chills)*

- Laboratory, microbiology, and serology investigation terms that are not specific for sepsis (e.g., PT *Shigella test positive,* PT *C-reactive protein increased)*

- Unqualified investigation terms (e.g., PT *Septic screen*)

- Congenital conditions associated with sepsis

NOTE: In MedDRA Version 22.1, based on a review by experts from regulatory authorities and industry, *Sepsis (SMQ)* was created as an additional stand-alone SMQ and the relevant sepsis terms in *Agranulocytosis (SMQ)* were made inactive. It may be necessary to combine *Sepsis (SMQ)*, *Agranulocytosis (SMQ)*, and *Toxic-septic shock conditions (SMQ)* to perform a comprehensive search.

2.93.3 Notes on Implementation and/or Expectation of Query Results

Sepsis (SMQ) has both narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.93.4 List of References for *Sepsis (SMQ)*

- Merck Manual, Professional version; February 2018.
- Rhodes, A., et al. (2017). Surviving Sepsis Campaign: International guidelines for management of sepsis and septic shock: 2016. *Critical Care Medicine*, 45 (3), 486-552.
- World Health Organization (2017). Improving the prevention, diagnosis, and clinical management of sepsis. *Seventieth World Health Assembly* A70/13.
- Singer, M., et al. (2016). The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA*, 315(8): 801-10.

2.94 Severe cutaneous adverse reactions (SMQ)

(Production Release April 2005)

2.94.1 Definition

This SMQ was developed to identify cases of severe, sometimes life-threatening skin reactions that are often drug-induced.

Severe cutaneous adverse reactions (SCARs) include

- Erythema multiforme
  - EM is an acute disease characterized by symmetrically distributed papular lesions affecting mainly the extremities, often with mucosal erosions.
  - The typical lesion is target-shaped; it is concentrically organized with three different colored zones, often with a blister in the center, and it is clearly demarcated from the surrounding skin.
  - There may be general symptoms such as fever and malaise.
- Stevens-Johnson syndrome
  - SJS is characterized by widespread skin lesions which may either be target-shaped or consist of erythematous macules with epidermal detachment, together with severe mucosal erosions.
  - SJS includes erosions of the skin up to 10% of body surface area. The general symptoms are more marked than in erythema multiforme.
- Toxic epidermal necrolysis
  - TEN is characterized by widespread erythematous areas with epithelial necrosis and epidermal detachment exceeding 10% body surface area, leaving bare dermis.
  - There are often also small erythematous or purpuric lesions with or without blisters.
  - Extensive mucosal erosions are frequent. General symptoms, usually severe, include high fever, malaise, and painful skin.
- Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) (Please note that DRESS syndrome has also been referenced in the literature as “Drug rash with eosinophilia and systemic symptoms”)
  - DRESS syndrome is characterized by an extensive rash, fever, lymphadenopathy, hematologic abnormalities, hepatitis, and involvement of the kidneys, lungs, heart, or pancreas
  - Characteristic hematologic abnormalities seen with this condition are eosinophilia, thrombocytopenia, and atypical lymphocytosis.

- The onset of symptoms is often delayed, occurring 2–6 weeks after drug initiation

- Acute generalized exanthematous pustulosis (AGEP)
  - AGEP is a rare, acute pustular eruption characterized by the development of numerous nonfollicular sterile pustules on a background of edematous erythema
  - The eruption develops within hours or days of drug exposure and resolves spontaneously in one to two weeks after drug discontinuation.
  - Fever and peripheral blood leukocytosis are usually present
  - It predominantly affects the main body folds and upper trunk, but facial involvement is possible.

These conditions are characterised by cutaneous eruptions that may be exanthematous, urticarial, vesicular, or pustular, with variable extension.

2.94.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow scope: diagnosis terms that represent the above five conditions (EM, SJS, TEN, DRESS and AGEP) are included.
  - Broad scope: MedDRA PTs that represent the signs/symptoms included in the criteria for the diagnoses of each of the above five conditions (EM, SJS, TEN, DRESS and AGEP) are included.
- Excluded:
  - MedDRA PTs that are signs or symptoms of a skin condition but not included in the criteria for the diagnosis of EM, SJS, TEN, DRESS and AGEP are excluded, *e.g*., PT *Dermatitis herpetiformis* and PT *Keratolysis exfoliativa acquired*.
  - General, non-specific, and often mild skin reactions (e.g., rash) are excluded, *e.g*., PT *Ulcer* and PT *Vascular skin disorder*.

2.94.3 Notes on Implementation and/or Expectation of Query Results

Severe cutaneous adverse reactions (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.94.4 List of References for *Severe cutaneous adverse reactions (SMQ)*

- Roujeau JC and Stern RS. Severe adverse cutaneous reactions to drugs. *New England Journal of Medicine* 1994; 331: 1272-1285.

- Reporting Adverse Drug Reactions. Definitions of terms and criteria for their use. *CIOMS publication*, Geneva 1999.

- RegiSCAR group (http://regiscar.uni-freiburg.de).

- Severe Cutaneous Adverse Reactions to Drugs (SCAR): Definitions, Diagnostic Criteria, Genetic Predisposition, Jean-Claude Roujeau, Laurence Allanore, Yvonne Liss, Maja Mockenhaupt (http://www.dermatol-sinica.com/web/data/20091130043801.pdf)

2.95 Shock (SMQ)

(Production Release September 2006)

2.95.1 Definition

- A condition of profound and generally acute hemodynamic and metabolic disturbance characterized by failure of the circulatory system to maintain adequate perfusion of vital organs
- Clinical indicators:
  - Reduced mean arterial pressure, tachycardia, tachypnea, cool skin and extremities, acutely altered mental status, oliguria, hypotension (usually, but not always, present), narrow differential pressure (difference between systolic and diastolic blood pressure), low cardiac output leading to a delayed capillary refill
  - End result is tissue hypoxia, often manifested by lactic acidosis
- Clinical manifestations of hypovolemic or cardiogenic shock:
  - Hypotension, hyperventilation, cold, clammy, cyanotic skin, a weak and rapid pulse, oliguria, mental confusion, and combativeness or anxiety
- Clinical manifestations of septic shock:
  - Chills and fever, warm flushed skin, a lower degree of hypotension, and an increase in cardiac output
  - If unresponsive to therapy, septic shock progresses to the clinical pattern described for hypovolemic and cardiogenic shock
- Forms of shock:
  - Hypovolemic
    - Most common form
    - Results either from loss of blood (hemorrhagic shock) or from loss of plasma alone
    - Drug-related hypovolemic shock cannot represent a credible drug-related event unless a drug has a marked effect on blood volume
  - Traumatic
    - Almost always produces the clinical pattern of hemorrhagic hypovolemia
  - Cardiogenic
    - Caused by failure, often sudden, of heart as an effective pump (e.g., acute myocardial infarction, severe cardiomyopathy, etc.)
    - Acute aggravation of chronic conditions of cardiac impairment can represent a challenge in evaluation of pharmacological causality

- Septic
  - Caused by the systemic reaction to severe infection with participation of biologically active soluble mediators
- Neurogenic
  - Produces extreme vasodilatation with acute drop of arterial pressure
  - Inducers of neurogenic shock: cerebral trauma, profuse hemorrhage, spinal cord injuries, deep general or spinal anesthesia, or toxic central nervous depression
- Anaphylactic
  - Manifestation of immune-mediated acute hypersensitivity
  - Exposure of a sensitized individual to a specific antigen, including drugs (e.g., penicillin) results in angioedema, followed by vascular collapse often accompanied by life-threatening respiratory distress
  - Anaphylactoid shock defines a pseudoanaphylactic reaction mimicking the same clinical picture described above
- Hypoglycemic
  - Often caused by inappropriate treatment of unbalanced or unstable diabetes with excess insulin (often in combination with oral antidiabetic medications)
  - Also observed in severe adrenocortical insufficiency

2.95.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow: All PTs containing “shock“ with the potential of representing an adverse drug reaction
  - Broad:
    - Organ failure terms
    - Terms containing the word “anuria”
    - Terms containing the word “hypoperfusion”
- Excluded:
  - Conditions occurring prior to manifestation of shock (e.g., myocardial infarction, thromboembolic events)
  - Terms not consistent with conditions as described above
  - Electrical shock and traumatic shock terms

- Terms representing minor organ dysfunction, not necessarily due to circulatory failure, were considered too broad and were generally excluded
- Terms lacking specificity (e.g., tachycardia, tachypnea, oliguria)
  - Some were excluded after review of phase I testing results
- Terms representing chronic conditions were generally excluded

The CIOMS WG for SMQs reviewed phase II feedback on this SMQ at their May 2006 meeting. Some terms were recommended to be added, and the WG agreed that some would be of value. One such recommended term was “acute cardiac failure”. It was recommended by the CIOMS WG that users use *Cardiac failure (SMQ)* if there is a need for such terms in one’s query. Terms for hemorrhage and left ventricular failure were also considered too broad for inclusion. Again, users should consider using the existing *Haemorrhages (SMQ)* if necessary to assist in performing a specific query.

NOTE: There are two SMQs related to anaphylaxis: *Anaphylactic reaction (SMQ)* and *Anaphylactic/anaphylactoid shock conditions (SMQ)*. The two SMQs have different focuses. *Anaphylactic/anaphylactoid shock conditions (SMQ)* is specific for more severe anaphylactic manifestations, i.e. those that result in shock, and not less severe ones such as rash. *Anaphylactic reaction (SMQ)* widens the search beyond shock conditions by including such terms as PT *Type I hypersensitivity*.

2.95.3 Hierarchy Structure

This is a hierarchical SMQ with one overall (Level 1) SMQ (SMQ *Shock*) and six (Level 2) sub-SMQs.

- Each sub-SMQ has narrow and broad search terms.
- Broad terms are the same for all six sub-SMQs; narrow term set for each sub-SMQ is distinct.

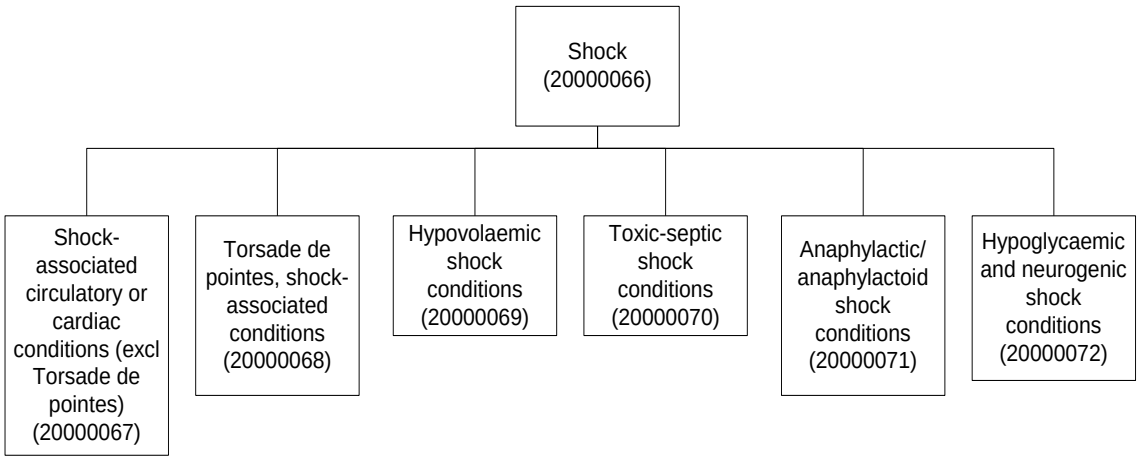

Figure 2-22. Hierarchy Structure of *Shock (SMQ)*

NOTE: The names of the sub-SMQs in the CIOMS WG documentation differs from this bulleted summary as follows:

CIOMS WG Document	This Document
SMQ *Cardiac/circulatory conditions*	*Shock-associated circulatory or cardiac conditions (excl Torsade de pointes) (SMQ)*
SMQ *Torsade de pointes*	*Torsade de pointes, shock-associated conditions (SMQ)*
SMQ *Hypovolaemic conditions*	*Hypovolaemic shock conditions (SMQ)*
SMQ *Toxic/septic conditions*	*Toxic-septic shock conditions (SMQ)*
SMQ *Anaphylactic/anaphylactoid conditions*	*Anaphylactic/anaphylactoid shock conditions (SMQ)*
SMQ *Other shock conditions*	Renamed to *Hypoglycaemic and neurogenic shock conditions (SMQ)*

Table 2-10. Link Table between CIOMS WG Document and SMQ Introductory Guide for *Shock (SMQ)*

2.95.4 Notes on Implementation and/or Expectation of Query Results

Shock (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.95.5 List of References for *Shock (SMQ)*

- Harrison's Principles of Internal Medicine 16th ed, Mc Graw Hill, 2005, pp 1581, 1600-1605.
- Dorland's Illustrated Medical Dictionary, 28th ed, Philadelphia WB Saunders Co.
- Reporting Adverse Drug Reactions, Definitions and Criteria for Their Use, CIOMS, Geneva, 1999.
- Harrison's Principles of Internal Medicine 16th ed, Mc Graw Hill, 2005, pp 1367-71.

2.96 Skin neoplasms, malignant and unspecified (SMQ)

(Production Release March 2009)

2.96.1 Definition

- SMQ developed to detect all types of malignant and unspecified tumors related to the skin
- SMQ covers all types of malignant and unspecified neoplasms related to skin; also:
  - Malignancy related conditions (specific for skin)
  - Malignancy related therapeutic procedures (specific for skin)
  - Malignancy related diagnostic procedures (specific for skin)

2.96.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for:
    - Malignancy related conditions (specific for skin)
    - Malignancy related therapeutic procedures (specific for skin)
    - Malignancy related diagnostic procedures (specific for skin)
  - Terms for malignant and unspecified neoplasms with a clear reference to the skin
  - Terms related to malignant and unspecified neoplasms of the skin, including:
    - Terms for conditions
    - Terms for procedures
    - Terms for investigations
    - Terms for tumor markers
    - Terms for signs and symptoms of such disorders
    - Terms for potential skin related terms of penis or vulva
- Excluded:
  - Terms for malignant and unspecified neoplasms unrelated to skin
  - Terms for non-site specific malignancy related therapeutic procedures
  - Terms for non-site specific malignancy related diagnostic procedures
  - Terms for non-site specific tumor markers
  - Terms related to the cervix
  - Terms for metastases to skin

- PT *Skin operation* because it is not a malignancy specific therapeutic procedure (see NOTE below)

NOTE: In Version 14.0, two new sub-SMQs have been added to *Skin neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: PT *Skin operation* may be added if a very broad search is required.

NOTE: For searches of non-specific malignancy related conditions, malignancy related therapeutic procedures, and malignancy related diagnostic procedures, it is recommended to use sub-SMQs of *Malignancies (SMQ)*.

2.96.3 Hierarchy Structure

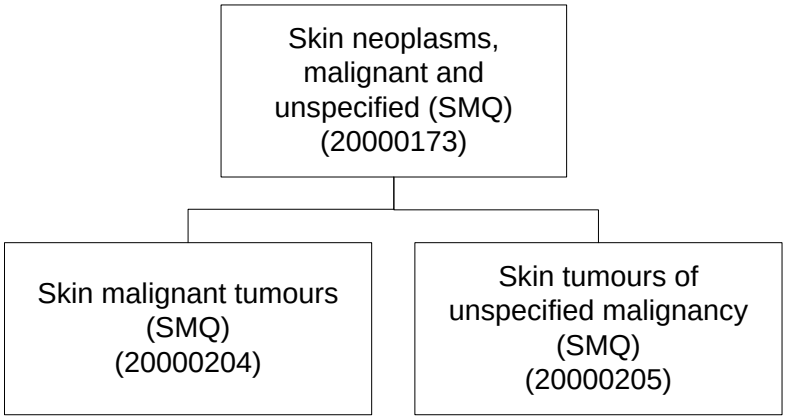

Figure 2-23. Hierarchy Structure of *Skin neoplasms, malignant and unspecified (SMQ)*

2.96.4 Notes on Implementation and/or Expectation of Query Results

Skin neoplasms, malignant and unspecified (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.96.5 List of References for *Skin neoplasms, malignant and unspecified (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H,Veronesi, U. Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://www.egtm.eu

2.97 Systemic lupus erythematosus (SMQ)

(Production Release March 2006)

2.97.1 Definition

- Chronic inflammatory autoimmune disorder affecting many body systems with variable severity
- Thought to be caused by interactions between susceptible genes and environmental factors such as estrogen containing hormones, ultraviolet light, and Epstein-Barr Virus (EBV) resulting in production of autoantibodies against nuclear antigens (particularly DNA), cytoplasmic antigens, and blood cell antigens
  - Antibodies to double-stranded DNA and Sm polypeptides occur in 30-60% of patients.
  - Antiphospholipid antibodies may also occur, including lupus anticoagulant, anticardiolipin antibodies, and those that cause false-positive tests for syphilis.
  - Complement activation leads to immune complex deposition in blood vessels.
- Drugs may trigger systemic lupus erythematosus (SLE) symptoms *de novo* or exacerbate existing symptoms.
  - Drug-induced SLE only rarely affects the kidney.
  - Antinuclear antibodies in drug-induced SLE are directed mostly against histones and rarely against double stranded DNA.
- Clinical presentations vary in severity and onset.
  - Systemic symptoms: anorexia, weight loss, malaise, myalgia, arthralgias, and fever
  - Cutaneous manifestations
    - Common is a macular “butterfly” erythema (across the face).
    - Discoid lesions and maculopapular lesions on the face, neck, chest, and elbows
    - Erythema on sides of the palms; red or purple macular lesions on volar finger surfaces
    - Other cutaneous symptoms: alopecia, periungual erythema, mucus membrane lesions, purpura, and photosensitivity
  - Polyarthritis (90% of patients) of wrists, hands, and knees
    - Joint deformities in 10% of patients
  - Nephritis is a serious manifestation.
    - May be asymptomatic

- May have proteinuria, diffuse membranoproliferative glomerulonephritis, abnormal urinalysis (hematuria, pyruia, urinary casts), or increased serum creatinine
- May develop hypertension and nephrotic syndrome (increased risk for end stage renal disease)

– Central nervous system manifestations
- Headaches, epilepsy, psychoses, organic brain syndrome, and personality changes
- Stroke or transient ischemic attacks due to vascular occlusion

– Other manifestations/complications
- Cardiovascular: pericarditis, myocarditis, fibrinous (Libman-Sachs) endocarditis, and valve insufficiencies
- Pulmonary: pleurisy with or without effusion
- Hematologic: anemia, leucopenia, and thrombocytopenia due to hemolysis
- Gastrointestinal: abdominal pain, nausea, vomiting, and diarrhea
- Ocular: sicca syndrome, nonspecific conjunctivitis, retinal vasculitis, and optic neuritis

2.97.2 Inclusion/Exclusion Criteria

- Included:
  – Terms that fit within the definition of SLE (including symptoms, signs, and laboratory findings)
  – Words/roots searched: “lup-,” “erythemato-,” “SLE –“ and “LE-“
  – HLT *Lupus erythematosus and associated conditions*
    - All PTs in both primary and secondary locations in this HLT are included except PT *Lupoid hepatic cirrhosis*, which is excluded.
  – Additional terms representing the diagnostic criteria of the American College of Rheumatology (ACR), e.g., Malar rash, Arthritis, Renal disorder, etc.
  – PT *Antinuclear antibody positive* is placed in narrow search based on the Pre-Phase II Working Group discussion.
- Excluded:
  – PT *Lupoid hepatic cirrhosis* (not a true lupus condition), PT *Pancytopenia*, PT *Cardiac tamponade*, PT *Nasal septum ulceration*, PT *Nasal ulcer*, PT *Lip ulceration*, PT *Anaemia*, PT *Arthralgia*, PT *Rheumatoid arthritis*, PT *Alopecia*, PT *Pyrexia*, and Coombs test terms

2.97.3 Algorithm

Nine categories are defined as follows:

Category	Definition	Term Weight
A	Narrow terms	Not applicable
B	Photosensitivity	1
C	Oral ulcers	2
D	Arthritis	3
E	Serositis	3
F	Renal disorder	1
G	Neurologic disorder	2
H	Haematologic disorder	3
I	Immunologic disorder	3

Table 2-11. Categories of *Systemic lupus erythematosus (SMQ)*

The “weight” system for broad terms was developed empirically and relates to the frequency of the terms and the probability that these relate to the well-known occurrence of SLE in patients receiving these drugs.

The algorithm was applied as follows:

- The PTs mentioned in the case report are grouped according to the pre-determined categories. Occurrence of multiple PTs within a category is counted only once.
- The category that the term is attributed to is then multiplied by its empirically pre-determined “weight” (for example – three for categories Hematologic disorder, Serositis, and Immunologic disorder) and summed for all the categories.
- If this sum is greater than six, it is proposed that the case report qualifies as a suspected SLE case report. For example, a case report which has PTs in the categories of Hematologic disorder (3), Immunologic disorder (3), and Renal disorder (1) will classify as a SLE broad search case report (3 + 3 + 1 = 7).

2.97.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Systemic lupus erythematosus (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Systemic lupus erythematosus (SMQ)* is A or the sum of category weights > 6. Cases filtered by the algorithm can be listed for output.

2.97.5 List of References for *Systemic lupus erythematosus (SMQ)*

- Guidelines for referral and management of systemic lupus erythematosus in adults. American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Guidelines. Arthritis Rheum 1999;42:1785-96.
- Hellman DB, Stone JH. Arthritis and musculoskeletal disorders. In: Tierney, Jr. LM, McPhee SJ, Papadakis MA, editors. Current medical diagnosis and treatment. 43rd ed. New York: McGraw-Hill Companies, Inc.; 2004. Available via intranet at STAT!Ref Online Medical Database. Teton Data Systems, Jackson, Wyo. (Version 3.3.6, 2004).
- Hahn BH. Disorders of the immune system, connective tissues, and joints. In: Kasper DL, Fauci AS, Longo DL, Braunwald E, Hauser SL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill Companies; 2005. Available via intranet at STAT!Ref Online Medical Database. Teton Data Systems, Jackson, Wyo. (Version 3.3.6, 2004).
- Diffuse connective tissue disease. In: Beers MH, Berkow R, editors. The merck manual of diagnosis and therapy. 11th ed. Whitehouse Station: Merck Research Laboratories; 1999. Available via intranet at STAT!Ref Online Medical Database. Teton Data Systems, Jackson, Wyo. (Version 3.3.6, 2004).
- Trethewey P. Systemic Lupus Erythematosus. Dimens Crit Care Nurs 2004;23:111-5.
- CIOMS Publication, "Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use," pp 19 – 20, 1999.
- The Merck Manual, Seventeenth Edition, pp 426 – 430, 1999.
- "Harrison's Principles of Internal Medicine," 14th edition, pp 1874 – 1880, 1998.

2.98 Taste and smell disorders (SMQ)

(Production Release March 2006)

2.98.1 Definition

- Causes of disorders of smell and taste include psychiatric disorders, nasal and sinus disease, poor dental hygiene, and intracranial disorders.
  - Often occur concurrently in a patient
  - Medicinal products associated with disturbances of taste and smell
  - Chemotherapy products
  - Antihypertensive products
  - Hyperlipidemic products
- Key terms and definitions:
  - Ageusia = absence of the sense of taste
  - Dysgeusia = perversion of the sense of taste; a bad taste in the mouth
  - Hypogeusia = a parageusia involving diminished sensitivity of taste
  - Anosmia = absence of the sense of smell
  - Hyposmia = a parosmia involving diminished sensitivity of smell
  - Parosmia = any disease or perversion of olfaction

2.98.2 Inclusion/Exclusion Criteria

- Included:
  - Terms related to disturbances of taste or smell, regardless of the direction (e.g., PT *Hypogeusia*), degree (e.g., PT *Anosmia*), or nature of impairment (PT *Parosmia*)
  - Terms related to hallucinatory perceptions
  - Terms related to the clinical evaluation of these types of sensory disorders (e.g., PT *Olfactory test abnormal*)
  - All included PTs in both primary and secondary placements in HLT *Taste disorders* and HLT *Olfactory nerve disorders* are included in SMQ
  - Two PTs in HLT *Perception disturbances NEC* (PT *Hallucination, gustatory* and PT *Hallucination, olfactory*) are included
  - Terms containing the roots “taste,” “tasti-,” “geus-,” “smell,” “gustat-,” “-osmia,” and “olfact-“
- Excluded:
  - Due to the limited scope of this SMQ, no specific exclusions were applied

NOTE: In the company database phase I testing, the cases of unpleasant taste and smell of the medical substance were also coded using the same terms. Medical review is required to distinguish between reports of the medical disorder and the physical properties of the treatment compound.

NOTE: In Version 12.1, *Taste and smell disorders (SMQ)* was modified in scope to include only narrow search terms, from formerly only broad terms.

2.98.3 Notes on Implementation and/or Expectation of Query Results

Taste and smell disorders (SMQ) has only narrow search terms. Therefore, the narrow search and broad search return the same result. The detailed notes are documented in section 1.5.2.1.

2.98.4 List of References for *Taste and smell disorders (SMQ)*

- *The Merck Manual*, 17th ed., 1999, p 687.
- Harrison's Principles of Internal Medicine, 14th ed., 1998, pp 173 – 175.
- Doty, RL et al. Influences of antihypertensive and antihyperlipidemic drugs on the senses of taste and smell: a review. J Hypertens 21: 1805 –1813.
- Dorland's Medical Dictionary, 28th ed., 2001.

2.99 Tendinopathies and ligament disorders (SMQ)

(Production Release March 2015)

2.99.1 Definition

- Chronic tendinopathies and ligament disorders are pathological conditions of tendons and ligaments, resulting mainly from repeated minor strain.

- Formerly called “tendonitis” or “ligamentitis

- Etiologic factors:
  - Degenerative processes are thought to be the principal underlying pathology
  - Repeated minor strain is considered to be the main precipitating factor
  - Drug-associated forms of the disorder have also been described
  - An understanding of the pathophysiology continues to evolve

- The most commonly injured tendons and ligaments include:
  - The supraspinatus tendon and long head of the biceps muscle
  - Medial and lateral extensors of the elbow
  - Patellar tendon
  - Achilles tendon
  - Posterior tibialis tendon

- Risk factors for tendinopathies and ligament disorders include both intrinsic and extrinsic factors, such as:
  - Overuse (sports activities, training errors, fatigue)
  - Cold environment during outdoor training
  - Faulty footwear/equipment
  - Drugs
    - Fluoroquinolone antibiotics in particular
    - Associations with oral contraceptives, injected corticosteroids and statins have also been suggested

- Commonly described presenting symptoms:
  - Pain at the site of the affected tendon or ligament
  - Morning stiffness, local tenderness, swelling and reduced articular range of motion may also be observed

- Therapeutic approaches:
  - Exercise
  - Shock wave therapy
  - Growth factors
  - Nitric oxide

- Sclerosant therapy
- Gene therapy
- Tissue engineering

2.99.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for disorders of tendons and ligaments (e.g., PT *Ligament disorder,* PT *Ligament rupture,* PT *Tendon rupture*, PT *Tendonitis*)
  - Terms for therapeutic procedures for tendon/ligament disorders (e.g., PT *Ligament operation*, PT *Tendon graft*, PT *Tenolysis*)
  - Terms related to abnormal results of investigations for tendon/ligament disorders (e.g., PT *Biopsy ligament abnormal*, PT *Biopsy tendon abnormal*)
  - Terms for signs and symptoms specific to tendon/ligament disorders (e.g., PT *Ligament pain*, PT *Tendon pain*)
  - Non-infective, non-traumatic fascia disorders and fasciitis are included as broad scope terms, since fascia are either adjacent to or contiguous with tendons and tendon sheaths.
- Excluded:
  - Terms for congenital tendinopathies or ligament disorders
  - Terms for hernial conditions
  - Terms for infectious tendinopathies or ligament disorders (e.g., PT *Infective tenosynovitis*)
  - Terms for non-specific signs and symptoms (e.g., PT *Pain*, PT *Swelling*) that would likely create excessive “noise”

NOTE: In v20.0, the following inclusion criterion was added to *Tendinopathies and ligament disorders (SMQ)*: Non-infective, non-traumatic fascia disorders and fasciitis are included as broad scope terms since fascia are either adjacent to or contiguous with tendons and tendon sheaths.

2.99.3 Notes on Implementation and/or Expectation of Query Results

Tendinopathies and ligament disorders (SMQ) has narrow and broad search terms. The detailed notes are documented in Section 1.5.2.1.

2.99.4 List of References for *Tendinopathies and ligament disorders (SMQ)*

- Riley, G. Tendinopathy – from basic science to treatment. http://www.medscape.org/viewarticle/569113

- Abate M, Silbernagel KG, Siljeholm C, Di Iorio A, De Amicis D, Salini V, Werner S, Paganelli R. Pathogenesis of tendinopathies: inflammation or degeneration? Arthritis Res Ther 2009; 11(3): 235

- Kaleagasioglu, F and Olcay, E. Fluoroquinolone-induced tendinopathy: etiology and preventive measures. Tohoku J Exp Med 2012: 226: 251 – 258

- Marie I, Delafenêtre H, Massy N, Thuillez C, Noblet C, Network of the French Pharmacovigilance Centers. Tendinous disorders attributed to statins: a study on ninety-six spontaneous reports in the period 1990-2005 and review of the literature. Arthritis Rheum. 2008 Mar 15;59(3):367 – 37

2.100 Thrombophlebitis (SMQ)

(Production Release September 2007)

2.100.1 Definition

- Thrombophlebitis is an inflammation of a vein (phlebitis), associated with thrombus formation (thrombosis) (definition based on Dorland's Illustrated Medical Dictionary).

2.100.2 Inclusion/Exclusion Criteria

- Included:
  - Terms related to phlebitis / venous inflammation
    - With thrombus formation included narrow scope
    - Without thrombus formation included broad scope
  - Prophylaxis terms
    - With thrombus formation included narrow scope
    - Without thrombus formation included broad scope
  - Laboratory test terms with indication of test result
    - With thrombus formation included narrow scope
    - Without thrombus formation included broad scope
- Excluded:
  - Risk factor terms (*e.g.*, hereditary, infective or autoimmune causes)
  - Laboratory test terms without indication of test result (*i.e.*, the unqualified test term or "normal" test results)
  - PT *Haemorrhoids* due to too much “noise”

User comments on the utility of including site-specific thrombosis terms would be appreciated.

NOTE: In order to get all relevant terms of thrombophlebitis, it may be necessary to combine this SMQ with the *Embolic and thrombotic events (SMQ)*.

2.100.3 Notes on Implementation and/or Expectation of Query Results

Thrombophlebitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.100.4 List of References for *Thrombophlebitis* (SMQ)

- Dorland's Illustrated Medical Dictionary. William Alexander Newman Dorland. 30th Edition, June 2003, Saunders, an Elsevier imprint.

2.101 Thyroid dysfunction (SMQ)

(Production Release March 2009)

2.101.1 Definition

- Thyroid dysfunction can present as hypo- or hyperactive thyroidal function
- Hypothyroidism is thyroid hormone deficiency
  - Primary hypothyroidism is due to thyroid disease; TSH is increased
    - Most common cause is autoimmune
    - Other common causes are post-therapeutic, occurring after radioactive iodine therapy, surgery, radiation or lithium therapy
  - Secondary hypothyroidism occurs when:
    - Hypothalamus produces insufficient TRH or pituitary produces insufficient TSH
  - Signs and symptoms of hypothyroidism include:
    - Cold intolerance, constipation, personality changes, dementia or frank psychosis
    - Hoarse voice, facial puffiness, coarse hair and skin, fluid retention, decreased metabolism, paresthesias, decreased libido, menstrual irregularities, bradycardia, pericardial effusions
- Hyperthyroidism is excessive production of iodinated thyroid hormones, T3 and T4
  - Graves' disease (toxic diffuse goiter) is most common cause
    - Characterized by hyperthyroidism, goiter, exophthalmos, pretibial myxedema
  - Inflammatory thyroid disease (thyroiditis) includes subacute granulomatous thyroiditis, Hashimoto's thyroiditis, and silent lymphocytic thyroiditis
  - Drug-induced hyperthyroidism can result from lithium or interferon-alpha
  - Signs and symptoms of hyperthyroidism include:
    - Hyperactivity, increased sweating, increased appetite, weight loss, insomnia, weakness, frequent bowel movements, hypomenorrhea, tremor; tachycardia, and atrial fibrillation
    - Eye signs include stare and eyelid retraction. Infiltrative ophthalmopathy is specific to Graves' disease.
    - Thyroid storm is life-threatening emergency; patients may present with fever, psychosis, coma, cardiovascular collapse

2.101.2 Inclusion/Exclusion Criteria

- Included:
  - Terms relevant for hypothyroidism and hyperthyroidism
  - Terms for specific signs and symptoms such as PT *Exophthalmos*
  - Thyroid investigation terms including PTs containing the word “abnormal” (e.g., PT *Thyroxine abnormal*).
  - Thyroid-related terms in SOC *Investigations* are included in the broad searches for both sub-SMQs as these terms are not indicative of hyperthyroidism or hypothyroidism specifically
- Excluded:
  - Terms for non specific signs and symptoms such as PT *Nervousness*, PT *Palpitations*, and PT *Constipation*
  - Terms containing the word “normal” (e.g., PT *Iodine uptake normal*)
  - Neonatal terms
  - PTs indicating an inherited disorder
  - Terms for tumors or malignancies of thyroid

2.101.3 Hierarchy Structure

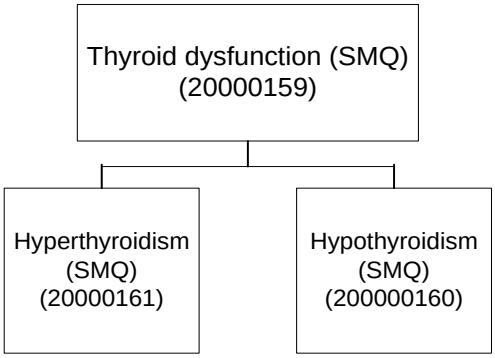

Figure 2-24. Hierarchy Structure of *Thyroid dysfunction (SMQ)*

2.101.4 Notes on Implementation and/or Expectation of Query Results

Thyroid dysfunction (SMQ) is a hierarchical SMQ with narrow and broad search terms. Other than the hierarchy structure, the implementation for this SMQ is similar to the non-hierarchical SMQs with narrow and broad search terms (see section 1.5.2.1). The superordinate SMQ can be applied by combining the terms in the subordinate SMQs.

2.101.5 List of References for *Thyroid dysfunction (SMQ)*

- Dorland's Medical dictionary accessed online on as http://www.dorlands.com/def.jsp?id=100051907
- The Merck Manual accessed online as http://www.merck.com/mmpe/sec19/ch282/ch282c.html
- Harrisons Principles of Internal Medicine, Mc Graw Hill accessed online as http://accessmedicine.com/public/about_am.aspx
- http://www.dorlands.com/def.jsp?id=100051347
- http://www.merck.com/mmpe/sec12/ch152/ch152e.html#sec12-ch152-ch152e-239

2.102 Torsade de pointes/QT prolongation (SMQ)

(Production Release December 2004)

Torsade de pointes/QT prolongation (SMQ) was released as a stand alone SMQ in December 2004. In MedDRA release 9.1, it was moved under *Cardiac arrhythmias (SMQ)* as a level 2 sub-SMQ. In MedDRA Version 10.1, it has again become a standalone level 1 SMQ.

2.102.1 Definition

- Torsade de pointes (TdP) is a form of rapid ventricular tachycardia whose underlying cause appears to be related to delayed ventricular repolarization, primarily resulting from blockade of potassium conductance.
- Electrocardiogram (ECG) findings: TdP is associated with or may be preceded by polymorphic QRS complexes that change in amplitude and cycle length, prolonged QT or QTc interval, prominent U waves, T wave alternans or bizarre T wave aberrations, or “long-short sequences.”
- Signs and symptoms: The arrhythmia can resolve spontaneously, but acquired forms often recur until the underlying cause is corrected, and can progress to ventricular fibrillation. Clinical manifestations during prolonged episodes can include episodes of palpitations, dizziness, syncope, and, rarely, sudden death; however, patients are often unaware of palpitations.

2.102.2 Inclusion/Exclusion Criteria

- Included:
  - Narrow scope: diagnoses and laboratory test results that are unique or directly lead to torsade de pointes/QT prolongation. For example, PT *Long QT syndrome* (diagnosis) and PT *Electrocardiogram QT prolonged* (test result).
  - Broad scope: signs, symptoms, diagnoses, and test results that are closely related to Torsade de pointes/QT prolongation. These terms have the potential in identifying positive cases. For example, PT *Cardiac death* (outcome) and PT *Electrocardiogram U-wave abnormality* (test result).
  - To make this search reasonably sensitive, the types of PTs identified included concepts of TdP, QT/QTc prolongation, ventricular arrhythmia/fibrillation/flutter/tachycardia, U- or T-wave abnormalities, syncope, and sudden death.
  - PT *Syncope* (symptom) produced some “noise” (i.e., many non-relevant cases retrieved) during phase I testing. However, a decision was made to retain it in the SMQ as it is a significant symptom of this condition.

- PT *Ventricular tachycardia* is included in narrow search to obtain LLT *TdP ventricular tachycardia* and LLT *Polymorphic ventricular tachycardia*. LLT *TdP ventricular tachycardia* has been moved to PT *Torsade de pointes* since this SMQ was developed.

- Excluded:
  - Non-serious events as well as general signs, symptoms, and ECG results are excluded, such as palpitations, dizziness. During Phase I testing, it was decided that these terms are uninformative and not likely to contain sufficient information to contribute meaningful information.

2.102.3 Notes on Implementation and/or Expectation of Query Results

Torsade de pointes/QT prolongation (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.102.4 List of References for *Torsade de pointes/QT prolongation (SMQ)*

- Zipes DP. Specific arrhythmias: diagnosis and treatment. *Heart Disease: A Textbook of Cardiovascular Medicine (5th Ed)*. Braunwald E (Ed). WB Saunders: Philadelphia, 1997, pg. 640-704.
- Marriott HJL and Conover MB. Polymorphic ventricular tachycardia. *Advanced Concepts in Arrhythmias (3rd Ed).* Mosby: New York, 1998, pg. 293-310.
- Definitions and basic requirements for the use of terms for reporting adverse drug reactions (XI): cardiovascular system disorders. *Pharmacoepidemiology and Drug Safety* 1998; 7:351-357.
- Reporting Adverse Drug Reactions. Definitions and criteria for their use. *CIOMS publication*, Geneva, 1999.
- Josephson ME and Zimetbaum P. The tachyarrhythmias. *Harrison's Principles of Internal Medicine (15th Ed).* Braunwald E, Fauci AS, Kasper DL *et al* (Eds). McGraw-Hill: New York, 2001, pg. 1292-1309.
- Bauman JL and Schoen MD. Arrhythmias. *Pharmacotherapy: A Pathophysiologic Approach (5th Ed).* DiPiro JT, Talbert RL, Yee GC *et al* (Eds). McGraw-Hill: New York, 2002, pg. 273-303.

2.103 Tubulointerstitial diseases (SMQ)

(Production Release September 2014)

2.103.1 Definition

Renal tubulointerstitial diseases is a group of kidney diseases, specifically involving the interstitium and tubules, that develop as a result of primary injury or inflammation and which progress to decreased renal function. The glomeruli may be affected only late in the disease course or not at all.

- Two classes of tubulointerstitial disease:

  - Acute tubulointerstitial disease:
    - Develops over days to months
    - Characterized by inflammatory infiltrate and edema that affect the renal interstitium
    - Leads to acute renal insufficiency or failure
    - In severe cases can lead chronic renal failure and/or permanent renal injury
    - Principal etiologies: infections; drugs

  - Chronic tubulointerstitial disease:
    - Can gradually develop over years
    - Involves interstitial infiltrate, fibrosis, tubular atrophy and dysfunction, and eventually renal dysfunction
    - Interstitial inflammation and scarring of the renal parenchyma is associated with gross changes, including papillary blunting and marked calyceal deformities; can be detected by imaging
    - Systemic insults, such as genetic disorders, hypertension, toxins, etc., feature symmetric and bilateral disease
    - Other causes of chronic disease may result in unequal renal scarring, and may involve one or both kidneys
    - Principal etiologies include: toxins; drugs; autoimmune, genetic, and neoplastic disorders; obstructive uropathy

2.103.2 Inclusion/Exclusion Criteria

- Included:

  - Terms related to the definition or representing renal tubular disorders strongly associated with tubulointerstitial diseases (e.g., PT *Tubulointerstitial nephritis*; PT *Renal tubular disorder*)

- Nephropathies and renal disorders resulting from the impairment of tubular function or derangement of the tubulointerstitial region of the kidney (e.g., PT *Fanconi syndrome acquired*; PT *Kidney fibrosis*)

- Urinalysis and urinary abnormalities closely associated to renal tubular dysfunction (e.g., PT *Eosinophils urine present*; PT *Isosthenuria*)

- Acid-base disorders and electrolyte and fluid balance conditions and investigations which are consequences of renal tubular dysfunction (e.g., PT *Urine phosphorus increased*; PT *Acidosis hyperchloraemic*).

- Etiologic terms frequently resulting in tubulointerstitial diseases (e.g., PT *Nephritis allergic*; PT *Nephropathy toxic*)

- Excluded:

  - Congenital terms, with the exception of PT *Aminoaciduria* (which may be used to code acquired forms of aminoaciduria, especially before the PT *Acquired aminoaciduria* was added in MedDRA Version 16.0)

  - Nonspecific renal disorders, urinary tract signs and symptoms or urinary investigations which may be downstream effects of tubulointerstitial disease, but are not specific to it, and may appear in many other forms of renal and non-renal dysfunctions, because they are likely to return considerable “noise” (e.g., PT *Flank pain*; PT *Oliguria*; PT *Costovertebral angle tenderness*)

  - Some initially considered image and histopathology investigations occasionally associated with tubulointerstitial diseases, were finally excluded due to lack of specificity (e.g., PT *Biopsy kidney abnormal*; PT *Kidney enlargement*; PT *Renal scan abnormal*); however, this does not preclude that new, more specific concepts of these types of investigations may be added in the future

  - Other non-renal disorders, signs, symptoms or investigations which may be downstream effects of tubulointerstitial disease, but are not specific to it, and are likely to return considerable “noise” (e.g., PT *Eosinophilia*; PT *Eosinophil count increased*; PT *Blood immunoglobulin E increased*)

  - Etiologies for the development of tubulointerstitial disease that are not generally drug related (e.g., PT *Myeloma cast nephropathy*).

  - All forms of urolithiases

- Nonqualified investigation terms (exception: relevant "abnormal" investigation terms are included)

NOTE: Severe forms of acute tubulointerstitial nephritis may lead to acute renal failure. For this reason, searches combining both *Tubulointerstitial diseases (SMQ)* and *Acute renal failure (SMQ)* may be of interest in some cases.

2.103.3 Notes on Implementation and/or Expectation of Query Results

Tubulointerstitial diseases (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.103.4 List of References for *Tubulointerstitial diseases (SMQ)*

- Harrison's Principles of Internal Medicine: Chapter 285. Tubulointerstitial Diseases of the Kidney

- Merck Manual for Health Care Professionals: Tubulointerstitial Diseases

- Current Diagnosis & Treatment: Nephrology & Hypertension: Chapter 36. Acute Tubulointerstitial Nephritis

- Current Diagnosis & Treatment: Nephrology & Hypertension: Chapter 37. Chronic Tubulointerstitial Nephritis

- Coltran RS, Rennke H, and Kumar V. : Robbins Basic Pathology. 7th ed. Philadelphia: Saunders, 2003. Chapter 14:526-527.

2.104 Tumour lysis syndrome (SMQ)

(Production Release September 2013)

2.104.1 Definition

- Tumor lysis syndrome (TLS): caused by release of tumor cell contents either from spontaneous cell lysis or in response to therapy
- Characteristic findings:
  - Hyperuricemia
  - Hyperkalemia
  - Hyperphosphatemia
  - Hypocalcemia
- Can lead to downstream effects:
  - Renal insufficiency
  - Cardiac arrhythmia
  - Seizures
  - Death (due to multiorgan failure)
- Dying cells also release cytokines which may cause a systemic inflammatory response syndrome and multiorgan failure
- Occurs most frequently in patients with high grade non-Hodgkin lymphoma and acute leukemia
  - Other tumors can also be implicated
- Patients at highest risk having pre-existing:
  - Chronic renal insufficiency
  - Oliguria
  - Dehydration
  - Hypotension
  - Acidic urine
- Management of TLS is directed toward, the metabolic and renal complications through supportive care
- Distinction between “laboratory” TLS and “clinical” TLS
  - “Laboratory” TLS requires two or more of the following abnormalities within 3 days before and 7 days after starting therapy:
    - Hyperuricemia
    - Hyperkalemia
    - Hyperphosphatemia
    - Hypocalcemia
  - “Clinical” TLS occurs when “laboratory” TLS has been established and is also accompanied by:
    - Increased creatinine level

- Seizures
- Cardiac dysrhythmia, **or**
- Death

- Renal injury in TLS is an important aspect of the disorder
  - Occurs when calcium phosphate, xanthine and uric acid precipitate in renal tubules leading to obstruction and inflammation

2.104.2 Inclusion/Exclusion criteria

- Included:
  - The “diagnostic” term for TLS – i.e., PT *Tumour lysis syndrome*
  - Terms for the metabolic conditions that are manifestations of TLS (e.g., PT *Hyperuricaemia*, PT *Hypocalcaemia*)
  - Terms for investigation results that represent the metabolic manifestations of TLS (e.g., PT *Blood uric acid increased*, PT *Blood calcium decreased*)
  - Terms for the renal manifestations of TLS, since these are so significantly connected to the other metabolic manifestations and are highly characteristic of the syndrome (e.g., PT *Acute kidney injury*)
  - Terms for the investigation results corresponding to the renal manifestations of TLS (e.g., PT *Blood creatinine increased*)

- Excluded:
  - Terms for the underlying etiologies and precipitating factors for TLS (e.g., PT *Burkitt's lymphoma*, PT *Chemotherapy*)
  - Terms for “downstream” clinical effects of the metabolic manifestations of TLS (e.g., PT *Seizure*; PT *Arrhythmia*)

NOTE: During discussions between the development team for SMQ *Tumour lysis syndrome* and the CIOMS SMQ Working Group, it was pointed out that PT *Urate nephropathy* is fairly characteristic of TLS, and a proposal was made to move this term from the broad scope terms in Category C to a narrow scope, Category A. However, it was decided to keep the term in the broad scope Category C with other clinical manifestations, but to alert the user of the SMQ that PT *Urate nephropathy* is somewhat “borderline” between a narrow and broad scope term in this SMQ.

2.104.3 Algorithm

Tumour lysis syndrome (SMQ) consists of:

- **Narrow search** (Category A or narrow scope) containing PTs that represent the clinical diagnosis of tumour lysis syndrome.

- **Broad search** contains additional terms (broad scope) which are added to those included in the narrow search. The broad scope terms are divided into two categories:
  - Category B: Laboratory findings
  - Category C: Findings related to impaired renal function or renal disease

  Cases to be selected for further review would include any cases reporting at least one of the PTs listed for Category A (narrow scope terms) or any case reporting a combination of at least one PT from each of the two groups of PTs listed as Categories B and C of broad scope terms. A or (B and C).

2.104.4 Notes on Implementation and/or Expectation of Query Results

In addition to narrow and broad searches, *Tumour lysis syndrome (SMQ)* is an algorithmic SMQ. The algorithm is a combination of broad search terms among various categories to further refine the identification of cases of interest. The algorithm can be implemented in a post-retrieval process as noted below:

- First, retrieve relevant cases by applying the SMQ query as a narrow/broad SMQ (see section 1.5.2.1).
- Post-retrieval process, software applies the algorithmic combination to screen the cases retrieved above. For small data sets of retrieved cases, the algorithm may be applied on manual review of cases. The algorithm for *Tumour lysis syndrome (SMQ)* is A or (B and C). Cases filtered by the algorithm can be listed for output.

2.104.5 List of References for *Tumour lysis syndrome (SMQ)*

- Howard, HC, Jones, DP and Pui, C-H. The tumor lysis syndrome. New Engl J Med 2011; 364:19, 1844 – 54
- Krishnan, K, Jaishankar, D and Ikeda, A. Tumor lysis syndrome. eMedicine (October 2012) http://emedicine.medscape.com/article/282171-overview

2.105 Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ)

(Production Release September 2008)

2.105.1 Definition

- Developed to detect all malignant and unspecified tumors related to uterus and fallopian tube
- Covers all malignant and unspecified neoplasms related to uterus and fallopian tube and in addition:
  - Malignancy related conditions
  - Malignancy related therapeutic and diagnostic procedures
  - Premalignant conditions

2.105.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for malignant or unspecified neoplasms with a clear reference to uterus and fallopian tube
  - Terms for conditions related to malignant or unspecified neoplasms of the uterus and fallopian tube, including:
    - Procedures
    - Investigations
    - Tumor markers
    - Signs and symptoms pointing to such disorders
- Excluded:
  - Terms for malignant or unspecified neoplasms without a clear reference to uterus and fallopian tube
  - Terms for unspecified site malignancy related therapeutic and diagnostic procedures and tumor markers
  - Terms related to placenta
  - Terms for metastases to uterus and fallopian tube, including PT *Metastases to reproductive organ*
  - PT *Uterine operation* and PT *Fallopian tube operation* as they are not malignancy specific therapeutic procedures. (These terms may, however, be added if a very broad search is required).

NOTE: In Version 14.0, two new sub-SMQs were added to *Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ)* to allow users to retrieve malignant-only events/cases; events/cases of neoplasms of unspecified malignancy; or a combination of malignant and unspecified neoplasm events/cases.

NOTE: For searches of non-specific malignancy related conditions and malignancy related therapeutic and diagnostic procedures, it is recommended to use the respective lower level sub-SMQ of *Malignancies (SMQ)*.

2.105.3 Hierarchy Structure

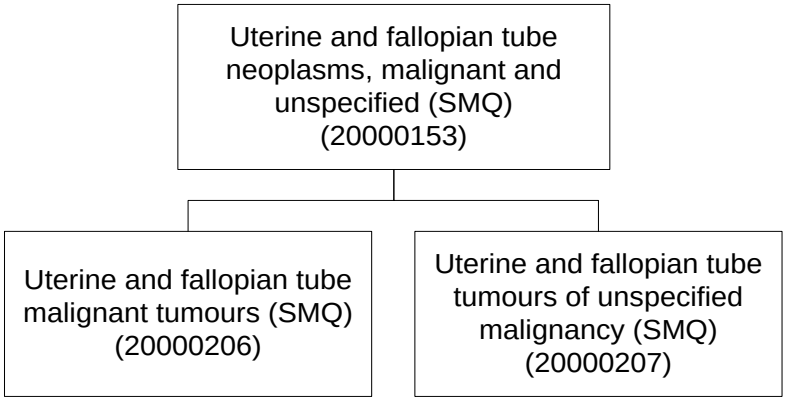

Figure 2-25. Hierarchy Structure of *Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ)*

2.105.4 Notes on Implementation and/or Expectation of Query Results

Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.105.5 List of References for *Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ)*

- DeVita VT, Hellman S, Rosenberg SA. Cancer: Principles and Practice of Oncology. 7th Edition, 2005.
- Peckham, M; Pinedo, H,.Veronesi, U. Oxford Textbook of Oncology. 1995.
- European Group on Tumour Markers (EGTM). http://www.egtm.eu/

2.106 Vasculitis (SMQ)

(Production Release March 2009)

2.106.1 Definition

- Vasculitis: inflammation of blood vessel walls
- Clinical and pathological features vary depending on site and type of blood vessels affected
- Primary vasculitis: vasculitis is the primary process. Examples are:
  - Temporal arteritis
  - Polyarteritis nodosa
  - Wegener's granulomatosis
- Vasculitis can be a secondary feature as with:
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
- Characterized by inflammation of and damage to blood vessels
  - Vessel lumen is usually compromised
  - Associated with ischemia of tissues supplied by the involved vessel
- Broad and heterogeneous group of syndromes may result from this process
- Any type, size, and location of blood vessel may be involved
- May be confined to a single organ, such as skin, or may simultaneously involve several organ systems

2.106.2 Inclusion/Exclusion Criteria

- Included:
  - Terms for primary vasculitides (e.g., PT *Henoch-Schonlein purpura,* PT *Behcet's syndrome,* or PT *Granulomatosis with polyangiitis* [which includes LLT *Wegener's granulomatosis*])
  - Terms containing "vasculitis" (e.g. PT *Cutaneous vasculitis,* PT *Lupus vasculitis,* or PT *Rheumatoid vasculitis*)
  - Terms containing "arteritis" (e.g., PT *Arteritis coronary* or PT *Polyarteritis nodosa*)
  - Terms containing "angiitis" (e.g., PT *Microscopic polyangiitis* or PT *Thromboangiitis obliterans*)
  - Terms for forms of purpura indicative of a vascular condition such as PT *Henoch-Schonlein purpura* and PT *Chronic pigmented purpura* (narrow, which includes LLT *Majocchi's purpura*) and PT *Palpable purpura* (broad)

- Terms for laboratory test results that may indicate vasculitis (e.g., PT *Antineutrophil cytoplasmic antibody increased*)

- Excluded:
  - Terms for symptoms of vasculitis as they are dependent on particular blood vessels involved by inflammatory process
  - Terms for secondary vasculitis associated with an infective or allergic process and malignancy (e.g., PT *Arthritis allergic* and PT *Phlebitis infective*)
  - Congenital terms (e.g., PT *Infantile septic granulomatosis*)
  - Terms for conditions relating exclusively to inflammation of veins (e.g., PT *Thrombophlebitis* and PT *Phlebitis* (user may wish to refer to SMQ *Thrombophlebitis*)
  - All general and specific purpura terms that are not specifically indicative of a vasculitic condition (e.g., PT *Purpura,* PT *Purpura senile,* PT *Thrombotic thrombocytopenic purpura,* and PT *Purpura non-thrombocytopenic*, etc)
  - Terms for conditions for which patients are at risk for vasculitis, such as rheumatoid arthritis and other autoimmune diseases
  - Terms for systemic lupus erythematosus (user may wish to refer to SMQ *Systemic lupus erythematosus*)
  - Terms for eosinophilic conditions (user may wish to refer to SMQ *Eosinophilic pneumonia*)
  - Terms for laboratory tests that may be increased in vasculitis, but are highly non-specific (e.g., PT *Antinuclear antibody positive*, PT *C-reactive protein increased*, and PT *Red blood cell sedimentation rate increased*)

NOTE: In initial testing by the CIOMS Working Group, broad terms retrieved too few cases to adequately evaluate differentiation between positive and negative control compounds tested. The terms chosen for the broad search, however, are felt to be medically appropriate and may prove useful in some databases.

2.106.3 Notes on Implementation and/or Expectation of Query Results

Vasculitis (SMQ) has narrow and broad search terms. The detailed notes are documented in section 1.5.2.1.

2.106.4 List of References for *Vasculitis (SMQ)*

- Savage COS et al. ABC of Arterial and Vascular Disease, Vasculitis. BMJ 2000 May; 320 1325-1328.
- The Vasculitis Syndromes. In: Harrison's Internal Medicine16th Edition [book online]. The McGraw-Hill Companies, 2007. http://www.accessmedicine.com. Accessed may 8, 2007.

APPENDIX I – LIST OF ABBREVIATIONS USED IN THIS DOCUMENT

Abbreviation	Definition
CIOMS	Council for International Organizations of Medical Sciences
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
JMO	Japanese Maintenance Organization
LLT	Lowest level term
MAG	MedDRA Analytical Grouping
MedDRA	Medical Dictionary for Regulatory Activities
MSSO	(MedDRA) Maintenance and Support Services Organization
NEC	Not elsewhere classified
PT	Preferred term
SMQ	Standardised MedDRA Query
SOC	System organ class
SSC	Special search category
SSQ	Standardised Search Queries

APPENDIX II – COMPREHENSIVE LISTING OF ACTIVE SMQs AND SUB-SMQs

Following is a comprehensive alphabetical listing of all active SMQs with respective sub-SMQs. Algorithmic SMQs are identified with an asterisk*. The original production release dates are also indicated:

Accidents and injuries (SMQ) [September 2007]
Acute central respiratory depression (SMQ) [September 2007]
Acute pancreatitis (SMQ)* [November 2005]
Acute renal failure (SMQ) [April 2005]
Agranulocytosis (SMQ) [November 2005; Revised September 2019]]
Anaphylactic reaction (SMQ)* [November 2005]
Angioedema (SMQ) [November 2005]
Anticholinergic syndrome (SMQ)* [September 2006]
Arthritis (SMQ) [September 2013]
Asthma/bronchospasm (SMQ) [November 2005]
Biliary disorders (SMQ) [September 2007]

- Biliary neoplasms (SMQ)
  - Biliary neoplasms benign (incl cysts and polyps) (SMQ)
  - Biliary neoplasms malignant and unspecified (SMQ)
    - Biliary malignant tumours (SMQ) [March 2011]
    - Biliary tumours of unspecified malignancy (SMQ) [March 2011]
- Congenital biliary disorders (SMQ)
- Functional, inflammatory and gallstone related biliary disorders (SMQ)
  - Biliary tract disorders (SMQ)
  - Biliary system related investigations, signs and symptoms (SMQ)
  - Gallbladder related disorders (SMQ)
  - Gallstone related disorders (SMQ)
- Infectious biliary disorders (SMQ)

Breast neoplasms, malignant and unspecified (SMQ) [September 2008]

- Breast malignant tumours (SMQ) [March 2011]
- Breast tumours of unspecified malignancy (SMQ) [March 2011]

Cardiac arrhythmias (SMQ) [September 2006]

- Arrhythmia related investigations, signs and symptoms (SMQ)
- Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias) (SMQ)
  - Bradyarrhythmias (incl conduction defects and disorders of sinus node function) (SMQ)
    - Bradyarrhythmia terms, nonspecific (SMQ)
    - Conduction defects (SMQ)
    - Disorders of sinus node function (SMQ)
  - Cardiac arrhythmia terms, nonspecific (SMQ)
  - Tachyarrhythmias (incl supraventricular and ventricular tachyarrhythmias) (SMQ)
    - Supraventricular tachyarrhythmias (SMQ)

        - Tachyarrhythmia terms, nonspecific (SMQ)
        - Ventricular tachyarrhythmias (SMQ)
    - Congenital and neonatal arrhythmias (SMQ)

Cardiac failure (SMQ) [March 2007]

Cardiomyopathy (SMQ) [September 2008]

Central nervous system vascular disorders (SMQ) [September 2006]

- Central nervous system haemorrhages and cerebrovascular conditions (SMQ)
    - Conditions associated with central nervous system haemorrhages and cerebrovascular accidents (SMQ)
    - Haemorrhagic central nervous system vascular conditions (SMQ)
    - Ischaemic central nervous system vascular conditions (SMQ)
- Central nervous system vascular disorders, not specified as haemorrhagic or ischaemic (SMQ)

Chronic kidney disease (SMQ) [March 2013]

Conjunctival disorders (SMQ) [September 2009]

Convulsions (SMQ) [March 2007]

Corneal disorders (SMQ) [March 2009]

Dehydration (SMQ) [March 2018]

Dementia (SMQ) [March 2007]

Demyelination (SMQ) [September 2008]

Depression and suicide/self-injury (SMQ) [March 2006]

- Depression (excl suicide and self injury) (SMQ)
- Suicide/self-injury (SMQ)

Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)* [March 2016]

Drug abuse, dependence and withdrawal (SMQ) [September 2007]

- Drug abuse and dependence (SMQ)
- Drug withdrawal (SMQ)

Dyslipidaemia (SMQ) [November 2005]

Embolic and thrombotic events (SMQ) [March 2007]

- Embolic and thrombotic events, arterial (SMQ)
- Embolic and thrombotic events, venous (SMQ)
- Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous (SMQ)

Eosinophilic pneumonia (SMQ)* [March 2009]

Extrapyramidal syndrome (SMQ) [March 2007]

- Akathisia (SMQ)
- Dyskinesia (SMQ)
- Dystonia (SMQ)
- Parkinson-like events (SMQ)

Extravasation events (injections, infusions and implants) (SMQ) [September 2007]

Fertility disorders (SMQ) [September 2011]

Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ) [September 2007]

- Gastrointestinal nonspecific dysfunction (SMQ)
- Gastrointestinal nonspecific inflammation (SMQ)

- Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)

Gastrointestinal perforation, ulceration, haemorrhage or obstruction (SMQ) [September 2007]
- Gastrointestinal haemorrhage (SMQ)
- Gastrointestinal obstruction (SMQ)
- Gastrointestinal perforation (SMQ)
- Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures (SMQ)
- Gastrointestinal ulceration (SMQ)

Generalised convulsive seizures following immunisation (SMQ)* [September 2012]

Glaucoma (SMQ) [March 2008]

Guillain-Barre syndrome (SMQ) [September 2007]

Haematopoietic cytopenias (SMQ) [November 2005]
- Haematopoietic cytopenias affecting more than one type of blood cell (SMQ)
- Haematopoietic erythropenia (SMQ)
- Haematopoietic leukopenia (SMQ)
- Haematopoietic thrombocytopenia (SMQ)

Haemodynamic oedema, effusions and fluid overload (SMQ) [March 2008]

Haemolytic disorders (SMQ) [April 2005]

Haemorrhages (SMQ) [March 2006]
- Haemorrhage laboratory terms (SMQ)
- Haemorrhage terms (excl laboratory terms) (SMQ)

Hearing and vestibular disorders (SMQ) [March 2009]
- Hearing impairment (SMQ)
- Vestibular disorders (SMQ)

Hepatic disorders (SMQ) [April 2005]
- Congenital, familial, neonatal and genetic disorders of the liver (SMQ)
- Drug related hepatic disorders - comprehensive search (SMQ)
    - Cholestasis and jaundice of hepatic origin (SMQ)
    - Drug related hepatic disorders - severe events only (SMQ)
        - Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
        - Hepatitis, non-infectious (SMQ)
        - Liver neoplasms, benign (incl cysts and polyps) (SMQ)
        - Liver neoplasms, malignant and unspecified (SMQ)
            - Liver malignant tumours (SMQ) [March 2011]
            - Liver tumours of unspecified malignancy (SMQ) [March2011]
    - Liver related investigations, signs and symptoms (SMQ)
    - Liver-related coagulation and bleeding disturbances (SMQ)
- Hepatic disorders specifically reported as alcohol-related (SMQ)
- Liver infections (SMQ)
- Pregnancy-related hepatic disorders (SMQ)

Hostility/aggression (SMQ) [September 2007]

Hyperglycaemia/new onset diabetes mellitus (SMQ) [March 2006]

Hypersensitivity (SMQ) [March 2013]

Hypertension (SMQ) [September 2008]

Hypoglycaemia (SMQ) [March 2016]
Hypokalaemia (SMQ) [March 2019]
Hyponatraemia/SIADH (SMQ) [September 2007]
Hypotonic-hyporesponsive episode (SMQ)* [September 2011]
Infective pneumonia (SMQ) [September 2017]
Interstitial lung disease (SMQ) [March 2006]
Ischaemic colitis (SMQ) [March 2008]
Ischaemic heart disease (SMQ) [March 2006]
- Myocardial infarction (SMQ)
- Other ischaemic heart disease (SMQ)

Lack of efficacy/effect (SMQ) [November 2005]
Lacrimal disorders (SMQ) [September 2009]
Lactic acidosis (SMQ) [November 2005]
Lens disorders (SMQ) [September 2008]
Lipodystrophy (SMQ) [September 2009]
Malignancies (SMQ) [March 2007]
- Malignancy related conditions (SMQ)
- Malignancy related therapeutic and diagnostic procedures (SMQ)
- Malignant or unspecified tumours (SMQ)
    - Malignant tumours (SMQ) [March 2011]
        - Haematological malignant tumours (SMQ) [March 2017]
        - Non-haematological malignant tumours (SMQ) [March 2017]
    - Tumours of unspecified malignancy (SMQ) [March 2011]
        - Haematological tumours of unspecified malignancy (SMQ) [March 2017]
        - Non-haematological tumours of unspecified malignancy *(SMQ)* [March 2017]
- Tumour markers (SMQ)

Malignant lymphomas (SMQ) [March 2013]
Medication errors (SMQ) [March 2016]
Myelodysplastic syndrome (SMQ) [September 2013]
Neuroleptic malignant syndrome (SMQ)* [March 2006]
Noninfectious diarrhoea (SMQ) [September 2013]
Noninfectious encephalitis (SMQ) [September 2007]
Noninfectious encephalopathy/delirium (SMQ) [September 2007]
Noninfectious meningitis (SMQ) [September 2007]
Ocular infections (SMQ) [September 2010]
Ocular motility disorders (SMQ) [September 2010]
Opportunistic infections (SMQ) [March 2020]
Optic nerve disorders (SMQ) [September 2008]
Oropharyngeal disorders (SMQ) [September 2007]
- Gingival disorders (SMQ)
- Oropharyngeal allergic conditions (SMQ)
- Oropharyngeal infections (SMQ)
- Oropharyngeal conditions (excl neoplasms, infections and allergies) (SMQ)
- Oropharyngeal neoplasms (SMQ)

Osteonecrosis (SMQ) [March 2010]
Osteoporosis/osteopenia (SMQ) [September 2009]
Ovarian neoplasms, malignant and unspecified (SMQ) [September 2008]
- Ovarian malignant tumours (SMQ) [March 2011]
- Ovarian tumours of unspecified malignancy (SMQ) [March 2011]

Periorbital and eyelid disorders (SMQ) [September 2009]
Peripheral neuropathy (SMQ) [November 2005]
Pregnancy and neonatal topics (SMQ) [March 2011]
- Pregnancy, labour and delivery complications and risk factors (excl abortions and stillbirth) (SMQ)
- Congenital, familial and genetic disorders (SMQ)
- Lactation related topics (incl neonatal exposure through breast milk) (SMQ)
    - Functional lactation disorders (SMQ)
    - Neonatal exposures via breast milk (SMQ)
- Foetal disorders (SMQ)
- Neonatal disorders (SMQ)
- Termination of pregnancy and risk of abortion (SMQ)
- Normal pregnancy conditions and outcomes (SMQ)

Premalignant disorders (SMQ) [March 2007]
- Blood premalignant disorders (SMQ)
- Gastrointestinal premalignant disorders (SMQ)
- Premalignant disorders, general conditions and other site specific disorders (SMQ)
- Reproductive premalignant disorders (SMQ)
- Skin premalignant disorders (SMQ)

Prostate neoplasms, malignant and unspecified (SMQ) [September 2008]
- Prostate malignant tumours (SMQ) [March 2011]
- Prostate tumours of unspecified malignancy (SMQ) [March 2011]

Proteinuria (SMQ) [September 2014]
Pseudomembranous colitis (SMQ) [March 2007]
Psychosis and psychotic disorders (SMQ) [September 2007]
Pulmonary hypertension (SMQ) [September 2007; Revised March 2016]
Renovascular disorders (SMQ) [March 2010]
Respiratory failure (SMQ) [March 2015]
Retinal disorders (SMQ) [March 2009]
Retroperitoneal fibrosis (SMQ) [September 2006]
Rhabdomyolysis/myopathy (SMQ) [December 2004]
Scleral disorders (SMQ) [March 2010]
Sepsis (SMQ) [September 2019]
Severe cutaneous adverse reactions (SMQ) [April 2005]
Shock (SMQ) [September 2006]
- Anaphylactic/anaphylactoid shock conditions (SMQ)
- Hypoglycaemic and neurogenic shock conditions (SMQ)
- Hypovolaemic shock conditions (SMQ)
- Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)

- Torsade de pointes, shock-associated conditions (SMQ)
- Toxic-septic shock conditions (SMQ)

Skin neoplasms, malignant and unspecified (SMQ) [March 2009]
- Skin malignant tumours (SMQ) [March 2011]
- Skin tumours of unspecified malignancy (SMQ) [March 2011]

Systemic lupus erythematosus (SMQ)* [March 2006]

Taste and smell disorders (SMQ) [March 2006]

Tendinopathies and ligament disorders (SMQ) [March 2015]

Thrombophlebitis (SMQ) [September 2007]

Thyroid dysfunction (SMQ) [March 2009]
- Hyperthyroidism (SMQ)
- Hypothyroidism (SMQ)

Torsade de pointes/QT prolongation (SMQ) [December 2004]

Tubulointerstitial diseases (SMQ) [September 2014]

Tumour lysis syndrome (SMQ)* [September 2013]

Uterine and fallopian tube neoplasms, malignant and unspecified (SMQ) [September 2008]
- Uterine and fallopian tube malignant tumours (SMQ) [March 2011]
- Uterine and fallopian tube tumours of unspecified malignancy (SMQ) [March2011]

Vasculitis (SMQ) [March 2009]