MedDRA Data Analysis and Presentation (Principles and Applications)

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Topics

- Review of important MedDRA concepts
- MedDRA Data Retrieval and Presentation: Points to Consider document
- Developing queries using MedDRA

Topics (cont)

- Standardised MedDRA Queries (SMQs):
  - SMQ definition and background
  - SMQ data characteristics
  - SMQ testing, production maintenance, and versioning
  - Analysis of a data set using SMQs
  - SMQ applications
  - Customized searches

Review of Important MedDRA Concepts

MedDRA Definition

MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

Scope of MedDRA

OUT

Not a drug dictionary

Frequency qualifiers

IN

Medical conditions
Indications
Investigations (tests, results)
Medical and surgical procedures
Medical, social, family history
Medication errors
Product quality issues
Device-related issues
Product use issues
Pharmacogenetic terms
Toxicologic issues
Standardized queries

Patient demographic terms

Numerical values for results

Clinical trial study design terms

Severity descriptors

Not an equipment, device, diagnostic product dictionary

MedDRA Structure

System Organ Class (SOC) (27)

High Level Group Term (HLGT) (337)

High Level Term (HLT) (1,737)

Preferred Term (PT) (23,708)

Lowest Level Term (LLT) (80,262)

System Organ Classes

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

A Multi-Axial Terminology

- Multi-axial = the representation of a medical concept in multiple SOCs
  - Allows grouping by different classifications
  - Allows retrieval and presentation via different data sets
- All PTs assigned a primary SOC
  - Determines which SOC will represent a PT during cumulative data outputs
  - Prevents "double counting"
  - Supports standardized data presentation
  - Pre-defined allocations should not be changed by users

A Multi-Axial Terminology (cont)

SOC = Respiratory, thoracic and mediastinal disorders (Secondary SOC)

↕

HLGT = Respiratory tract infections

↕

HLT = Viral upper respiratory tract infections

SOC = Infections and infestations (Primary SOC)

↕

HLGT = Viral infectious disorders

↕

HLT = Influenza viral infections

PT = Influenza

Rules for Primary SOC Allocation

- PTs represented in only one SOC are automatically assigned that SOC as primary
- PTs for diseases, signs and symptoms are assigned to prime manifestation site SOC
- Congenital and hereditary anomalies terms have SOC *Congenital, familial and genetic disorders* as Primary SOC
- Neoplasms terms have SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* as Primary SOC
  - **Exception:** Cysts and polyps have prime manifestation site SOC as Primary SOC
- Infections and infestations terms have SOC *Infections and infestations* as Primary SOC

Primary SOC Priority

If a PT links to more than one of the exceptions, the following priority will be used to determine primary SOC:

- *1st:* *Congenital, familial and genetic disorders*
- *2nd:* *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
- *3rd:* *Infections and infestations*

A Multi-Axial Terminology (cont)

PTs in the following SOCs only appear in that particular SOC and not in others, i.e., they are not multi-axial

- *Investigations*
- *Surgical and medical procedures*
- *Social circumstances*

MSSO's MedDRA Browsers

- MedDRA Desktop Browser (MDB)
  - Download MDB and release files from MedDRA website
- MedDRA Web-Based Browser (WBB)
  - https://tools.meddra.org/wbb/
- Features
  - Both require MedDRA ID and password
  - View/search MedDRA and SMQs
  - Support for all MedDRA languages
  - Language specific interface
  - Ability to export search results and Research Bin to local file system

MedDRA Desktop Browser (MDB) and Web-Based Browser (WBB) Update

- New functionality for users
  - Preview upcoming (supplemental) changes in next release*
  - View primary **and** secondary link information
  - Upload terms to run against SMQs
  - Advanced search options (e.g., NOT, OR)

*Supplemental view not available on MDB

MedDRA Data Retrieval and Presentation: Points to Consider

ICH M1 Points to Consider Working Group (PtC WG)

November 2017, Geneva, Switzerland

- Regulators and industry from EU, US, and Japan
- Health Canada, Canada
- MFDS, Republic of Korea
- ANVISA, Brazil
- NMPA, China
- MSSO
- JMO
- WHO (Observer)

MedDRA Data Retrieval and Presentation: Points to Consider (DRP:PTC)

MedDRA® DATA RETRIEVAL AND PRESENTATION: POINTS TO CONSIDER

ICH-Endorsed Guide for MedDRA Users on Data Output

Release 3.17
Based on MedDRA Version 22.0

1 March 2019

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- Provides data retrieval and presentation options for industry or regulatory purposes
- Most effective when used in conjunction with MedDRA Term Selection: PTC document
- Recommended to be used as basis for individual organization's own data retrieval conventions

Data Retrieval PTC Points Addressed

- General Principles
  - Quality of Source Data
  - Documentation of Data Retrieval and Presentation Practices
  - Do Not Alter MedDRA
  - Organisation-Specific Data Characteristics
  - Characteristics of MedDRA that Impact Data Retrieval and Analysis
  - MedDRA Versioning
- General Queries and Retrieval
- Standardised MedDRA Queries
- Customised Searches

Quality of Source Data

- High quality data output is dependent on maintaining quality of original information reported by using consistent and appropriate term selection (Refer to *MedDRA Term Selection: Points to Consider* document)
- Method of conversion of data into MedDRA might impact retrieval and presentation - legacy data conversion using verbatims or coded terms

Documentation of Data Retrieval and Presentation Practices

- Organisation-specific guidelines
  - Consistent with Points to Consider documents
  - Coding conventions
  - Data retrieval and output strategies (including SMQs)
  - Quality assurance procedures
  - MedDRA version used for search
  - Search strategy methods
  - Version update processes
  - Processes for customised MedDRA queries

Organisation-Specific Data Characteristics

- Database structure (storage and use of hierarchy)
- Data storage (level of term, synonym/reported term)
- Data conversion (if applicable)
- Coding practices over time
- Limitations/restrictions (inability to view secondary SOCs)
- Term selection principles
  - More than one term selected increases counts
  - Diagnosis term only selected reduces counts

Do Not Alter MedDRA

- MedDRA is a standardized terminology with a pre-defined term hierarchy
- Users must not make *ad hoc* structural alterations, including changing the primary SOC allocation
- If terms are incorrectly placed, submit a change request to the MSSO

Impact of MedDRA's Characteristics – Grouping Terms

- HLGTs and HLTs provide clinically relevant groupings
  - HLGT *Cardiac arrhythmias*
    - HLT *Cardiac conduction disorders*
    - HLT *Rate and rhythm disorders NEC*
    - HLT *Supraventricular arrhythmias*
    - HLT *Ventricular arrhythmias and cardiac arrest*

Impact of MedDRA's Characteristics – Grouping Terms (cont)

- Caution - ensure all terms are relevant to output
  - HLT *Vascular tests NEC (incl blood pressure)*
    - PT *Blood pressure decreased*
    - PT *Blood pressure increased*
- Caution - related PTs in different locations in SOC
  - HLT *Bullous conditions*
    - PT *Stevens-Johnson syndrome*
  - HLT *Exfoliative conditions*
    - PT *Dermatitis exfoliative*

Which Level? – SOC *Investigations*

Adverse Event (MedDRA v18.0)	25 mg MyDrug (N=44)	Placebo (N=15)
SOC Investigations	13 (29.5%)	2 (13.3%)
PT Aspartate aminotransferase increased	6	0
PT Alanine aminotransferase increased	5	0
PT Gamma-glutamyltransferase increased	4	0
PT Blood creatine phosphokinase increased	2	1
PT Blood alkaline phosphatase increased	2	0
PT Blood glucose increased	1	1
PT Blood lactate dehydrogenase increased	2	0
PT Lipase increased	2	0
PT White blood cell count decreased	2	0
PT Amylase increased	1	0
PT Faecal fat increased	0	1

Patients may have more than one event reported

Which Level? – SOC *Investigations* (cont)

Adverse Event (MedDRA v18.0)	25 mg MyDrug (N=44)	Placebo (N=15)
SOC Investigations	13 (29.5%)	2 (13.3%)
PT Blood pressure increased	1	0
PT Blood urea increased	1	0
PT Occult blood positive	1	0
PT Liver function test abnormal	1	0
PT Monocyte count decreased	1	0
PT Protein urine present	1	0

Patients may have more than one event reported

Which Level? – SOC *Investigations* (cont)

Adverse Event (MedDRA v18.0)	25 mg MyDrug (N=44)	Placebo (N=15)
SOC Investigations	13 (29.5%)	2 (13.3%)
HLT Liver function analyses	16	0
HLT Tissue enzyme analyses NEC	4	0
HLT Digestive enzymes	3	0
HLT White blood cell analyses	3	0
HLT Skeletal and cardiac muscle analyses	2	1
HLT Carbohydrate tolerance analyses (incl diabetes)	1	1
HLT Faecal analyses NEC	1	1
HLT Vascular tests NEC (incl blood pressure)	1	0
HLT Renal function analyses	1	0
HLT Urinalysis NEC	1	0

Patients may have more than one event reported

Multi-Axiality

- Primary SOC allocation rules affect the way data are distributed across the terminology
- Impact on frequencies of medical condition of interest should be considered
- Example: for hepatic abnormality search in SOC *Hepatobiliary disorders*, SOC *Investigations* (laboratory test terms), SOC *Surgical and medical procedures* (e.g., PT *Liver transplant*)

Multi-Axiality (cont)

- Main presentation is by Primary SOC
- Secondary SOCs used for alternate views and presentation of data

MedDRA Versioning

- MedDRA is updated twice a year
  - 1 March X.0 release (all levels)
  - 1 September X.1 release (LLT and PT levels only)
- Version used in data retrieval and presentation should be documented
- Resources:
  - "What's New" document
  - Version report
  - MedDRA Version Analysis Tool (MVAT)
- Terms used for queries should be in same version as data being queried

MedDRA Versioning (cont): Effect of PT Demotion

MedDRA Version 18.1	Number of Events at PT Level
Metastatic pain (PT)	15
Cancer pain	5
MedDRA Version 19.0	**Number of Events at PT Level**
Metastatic pain (no longer a PT)	0
Cancer pain	20

MedDRA Versioning (cont): Effect of Primary SOC Change

MedDRA Version 18.0	Number of Events
SOC *Vascular disorders* PT *Intra-abdominal haematoma*	20
MedDRA Version 18.1	**Number of Events**
SOC *Vascular disorders*	0
SOC *Gastrointestinal disorders* PT *Intra-abdominal haematoma*	20

MedDRA Version Analysis Tool (MVAT)

- Web-based (https://tools.meddra.org/mvat)
- Free to all users
- Features
  - Version Report Generator (produces exportable report comparing any two versions)
  - Data Impact Report (identifies changes to a specific set of MedDRA terms or codes uploaded to MVAT)
  - Search Term Change (identifies changes to a single MedDRA term or code)
- User interface and report output available in all MedDRA languages

Exercise

How Many Cases of Autoimmune Diseases?

Adverse Event (MedDRA v22.0)	No. of cases
SOC Blood and lymphatic system disorders	
PT Anaemia	5
PT Autoimmune neutropenia	5
PT Evans syndrome	1
PT Platelet anisocytosis	1
PT Platelet toxicity	2
SOC Cardiac disorders	
PT Autoimmune myocarditis	4
PT Myocardial infarction	1
PT Myocarditis	2

How Many Cases of Autoimmune Diseases? (cont)

Adverse Event (MedDRA v22.0)	No. of cases
SOC Endocrine disorders	
PT Polyglandular autoimmune syndrome type I	2
PT Thyroid disorder	1
SOC Eye disorders	
PT Birdshot chorioretinopathy	2
PT Autoimmune uveitis	3
SOC Hepatobiliary disorders	
PT Primary biliary cholangitis	3
PT Hepatitis toxic	1
PT Hepatocellular injury	1

How Many Cases of Autoimmune Diseases? (cont)

Adverse Event (MedDRA v22.0)	No. of cases
SOC Immune system disorders	
PT Autoimmune disorder	4
SOC Musculoskeletal and connective tissue disorders	
PT Arthritis	1
PT Muscular weakness	2
PT Polymyalgia rheumatica	1
PT Rheumatoid arthritis	3
SOC Skin and subcutaneous tissue disorders	
PT Alopecia	1
PT Skin haemorrhage	1
PT Vitiligo	2

Secondary SOC Analysis Example

- In my dataset, which terms are autoimmune disorders?

Row ID	Term
1	Anaemia
2	Autoimmune neutropenia
3	Evans syndrome
4	Platelet anisocytosis
5	Platelet toxicity
6	Autoimmune myocarditis
7	Myocardial infarction
8	Myocarditis
9	Polyglandular autoimmune syndrome type I
10	Thyroid disorder
11	Birdshot chorioretinopathy
12	Autoimmune uveitis
13	Primary biliary cholangitis
14	Hepatitis toxic
15	Hepatocellular injury
16	Autoimmune disorder
17	Arthritis
18	Muscular weakness
19	Polymyalgia rheumatica
20	Rheumatoid arthritis
21	Alopecia
22	Skin haemorrhage
23	Vitiligo

Input

Primary SOC
Blood and lymphatic system disorders
Cardiac disorders
Endocrine disorders
Eye disorders
Hepatobiliary disorders
Immune system disorders
Musculoskeletal and connective tissue disorders
Skin and subcutaneous tissue disorders

Your Current Dilemma

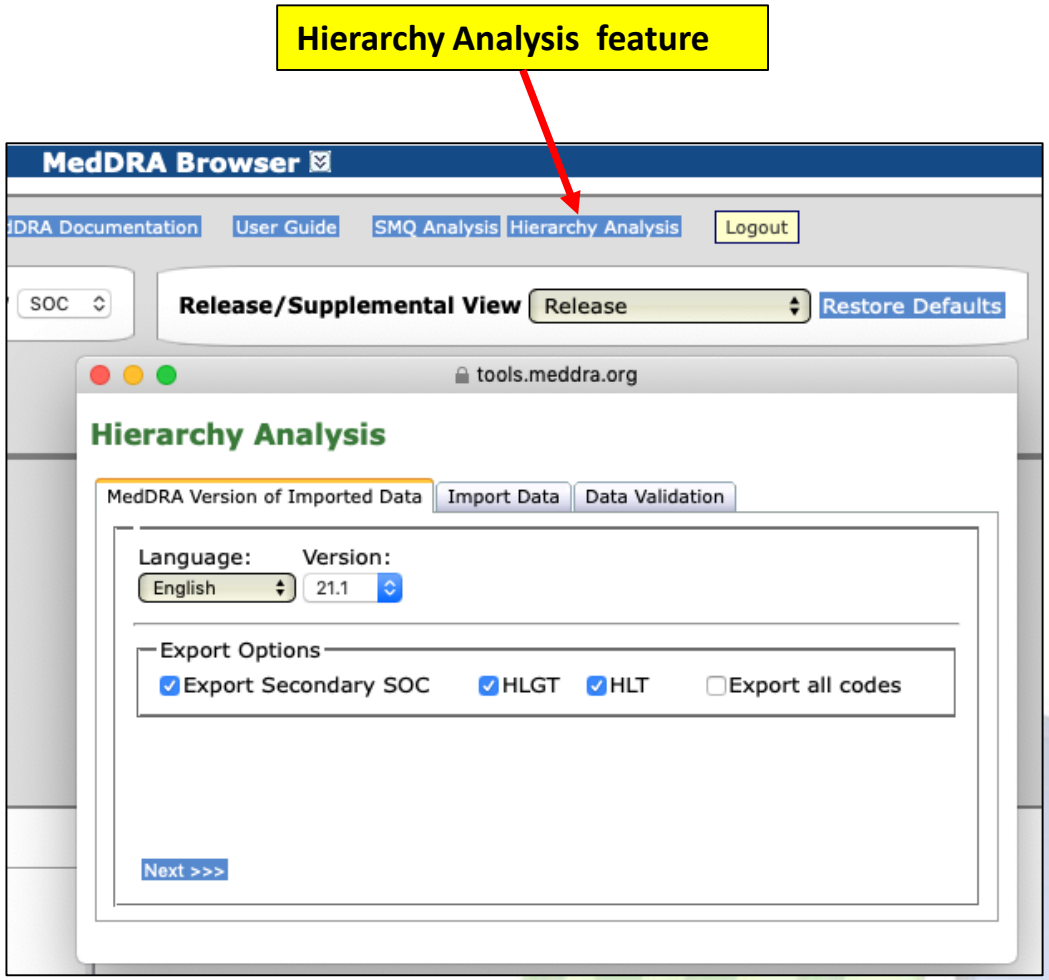
- My system only shows the primary SOC hierarchy. How do I view secondary SOC links for a set of terms?

Your Solution

- Utilize the new Hierarchy Analysis tool in the MedDRA browser

Secondary SOC Information

- Hierarchy Analysis feature
  - Upload terms in spreadsheet
  - Export with primary and secondary SOC hierarchies
  - No need for programming



Secondary SOC Information (cont)

- Create a properly formatted spreadsheet of your data to upload into the Hierarchy Analysis tool

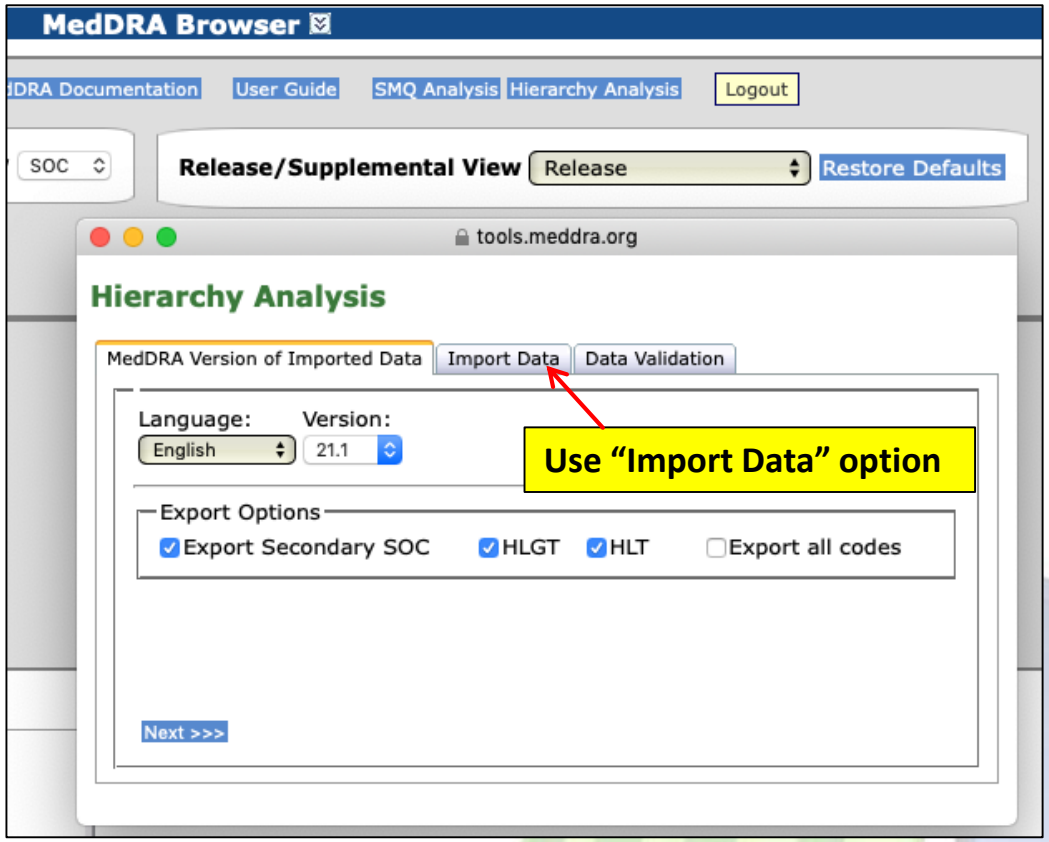
File Home Insert Page Layout Formulas Data

B6 f_x Platelet toxicity

	A	B	C
1	Row ID	Term	Code
2	1	Anaemia	10002034
3	2	Autoimmune neutropenia	10055128
4	3	Evans syndrome	10053873
5	4	Platelet anisocytosis	10066294
6	5	Platelet toxicity	10059440
7	6	Autoimmune myocarditis	10064539
8	7	Myocardial infarction	10028596
9	8	Myocarditis	10028606
10	9	Polyglandular autoimmune syndrome ty	10036072
11	10	Thyroid disorder	10043709
12	11	Birdshot chorioretinopathy	10072959
13	12	Autoimmune uveitis	10075690
14	13	Primary biliary cholangitis	10080429
15	14	Hepatitis toxic	10019795
16	15	Hepatocellular injury	10019837
17	16	Autoimmune disorder	10061664
18	17	Arthritis	10003246
19	18	Muscular weakness	10028372
20	19	Polymyalgia rheumatica	10036099
21	20	Rheumatoid arthritis	10039073
22	21	Alopecia	10001760
23	22	Skin haemorrhage	10064265
24	23	Vitiligo	10047642

Secondary SOC Information (cont)

- Hierarchy Analysis feature
  - Upload terms in spreadsheet
  - Export with primary and secondary SOC hierarchies
  - No need for programming



Secondary SOC Analysis Example (cont)

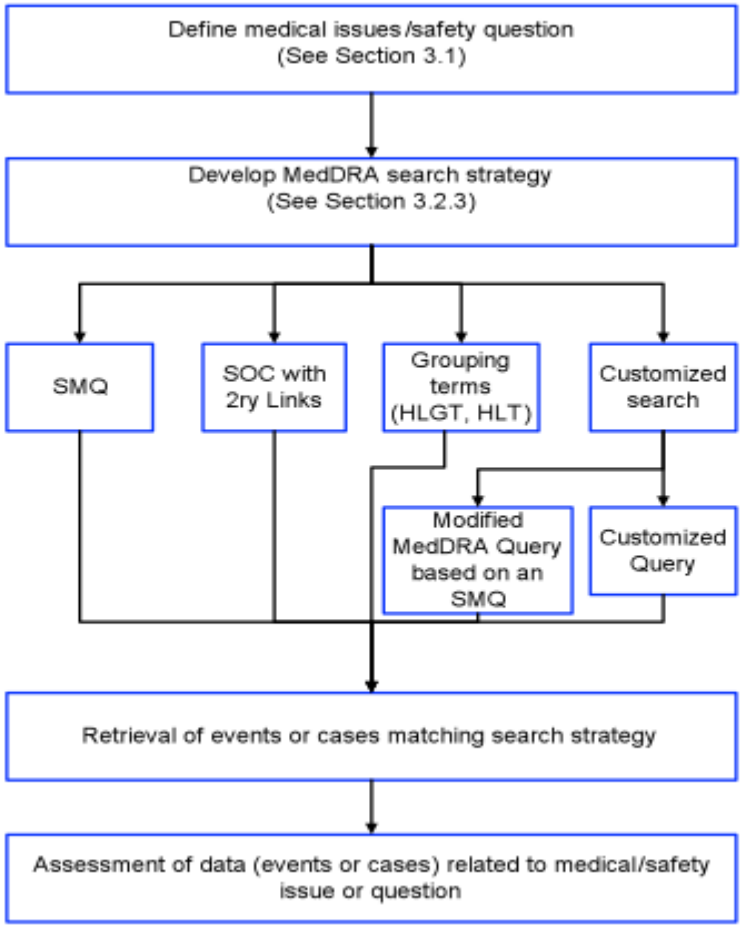
- Output sorted by secondary SOCs – there are 10 autoimmune disorders

Row ID	Term	Code	Level	PT	HLT	HLGT	SOC	Primary SOC
6	Autoimmune myocarditis	10064539	PT	Autoimmune myocarditis	Autoimmune disorders NEC	Autoimmune disorders	Immune system disorders	N
12	Autoimmune uveitis	10075690	PT	Autoimmune uveitis	Autoimmune disorders NEC	Autoimmune disorders	Immune system disorders	N
11	Birdshot chorioretinopathy	10072959	PT	Birdshot chorioretinopathy	Autoimmune disorders NEC	Autoimmune disorders	Immune system disorders	N
2	Autoimmune neutropenia	10055128	PT	Autoimmune neutropenia	Blood autoimmune disorders	Autoimmune disorders	Immune system disorders	N
3	Evans syndrome	10053873	PT	Evans syndrome	Blood autoimmune disorders	Autoimmune disorders	Immune system disorders	N
9	Polyglandular autoimmune syndrome type I	10036072	PT	Polyglandular autoimmune syndrome type I	Endocrine autoimmune disorders	Autoimmune disorders	Immune system disorders	N
13	Primary biliary cholangitis	10080429	PT	Primary biliary cholangitis	Hepatic autoimmune disorders	Autoimmune disorders	Immune system disorders	N
19	Polymyalgia rheumatica	10036099	PT	Polymyalgia rheumatica	Muscular autoimmune disorders	Autoimmune disorders	Immune system disorders	N
20	Rheumatoid arthritis	10039073	PT	Rheumatoid arthritis	Rheumatoid arthritis and associated conditions	Autoimmune disorders	Immune system disorders	N
23	Vitiligo	10047642	PT	Vitiligo	Skin autoimmune disorders NEC	Autoimmune disorders	Immune system disorders	N
14	Hepatitis toxic	10019795	PT	Hepatitis toxic	Poisoning and toxicity	Exposures, chemical injuries and poisoning	Injury, poisoning and procedural complications	N
5	Platelet toxicity	10059440	PT	Platelet toxicity	Poisoning and toxicity	Exposures, chemical injuries and poisoning	Injury, poisoning and procedural complications	N
18	Muscular weakness	10028372	PT	Muscular weakness	Neuromuscular disorders NEC	Neuromuscular disorders	Nervous system disorders	N
22	Skin haemorrhage	10064265	PT	Skin haemorrhage	Bruising, ecchymosis and purpura	Vascular haemorrhagic disorders	Vascular disorders	N
7	Myocardial infarction	10028596	PT	Myocardial infarction	Coronary necrosis and vascular insufficiency	Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Vascular disorders	N
3	Evans syndrome	10053873	PT	Evans syndrome	Anaemias haemolytic immune	Haemolyses and related conditions	Blood and lymphatic system disorders	Y
1	Anaemia	10002034	PT	Anaemia	Anaemias NEC	Anaemias nonhaemolytic and marrow depression	Blood and lymphatic system disorders	Y

Secondary SOC Analysis and Use of a Grouping Term

Adverse Event (MedDRA v22.0)	No. of cases
SOC Immune system disorders	
HLGT Autoimmune disorders	30
PT Autoimmune disorder	4
PT Autoimmune myocarditis	4
PT Autoimmune neutropenia	5
PT Primary biliary cholangitis	3
PT Birdshot chorioretinopathy	2
PT Evans syndrome	1
PT Polyglandular autoimmune syndrome type I	2
PT Polymyalgia rheumatica	1
PT Rheumatoid arthritis	3
PT Autoimmune uveitis	3
PT Vitiligo	2

General Queries and Retrieval

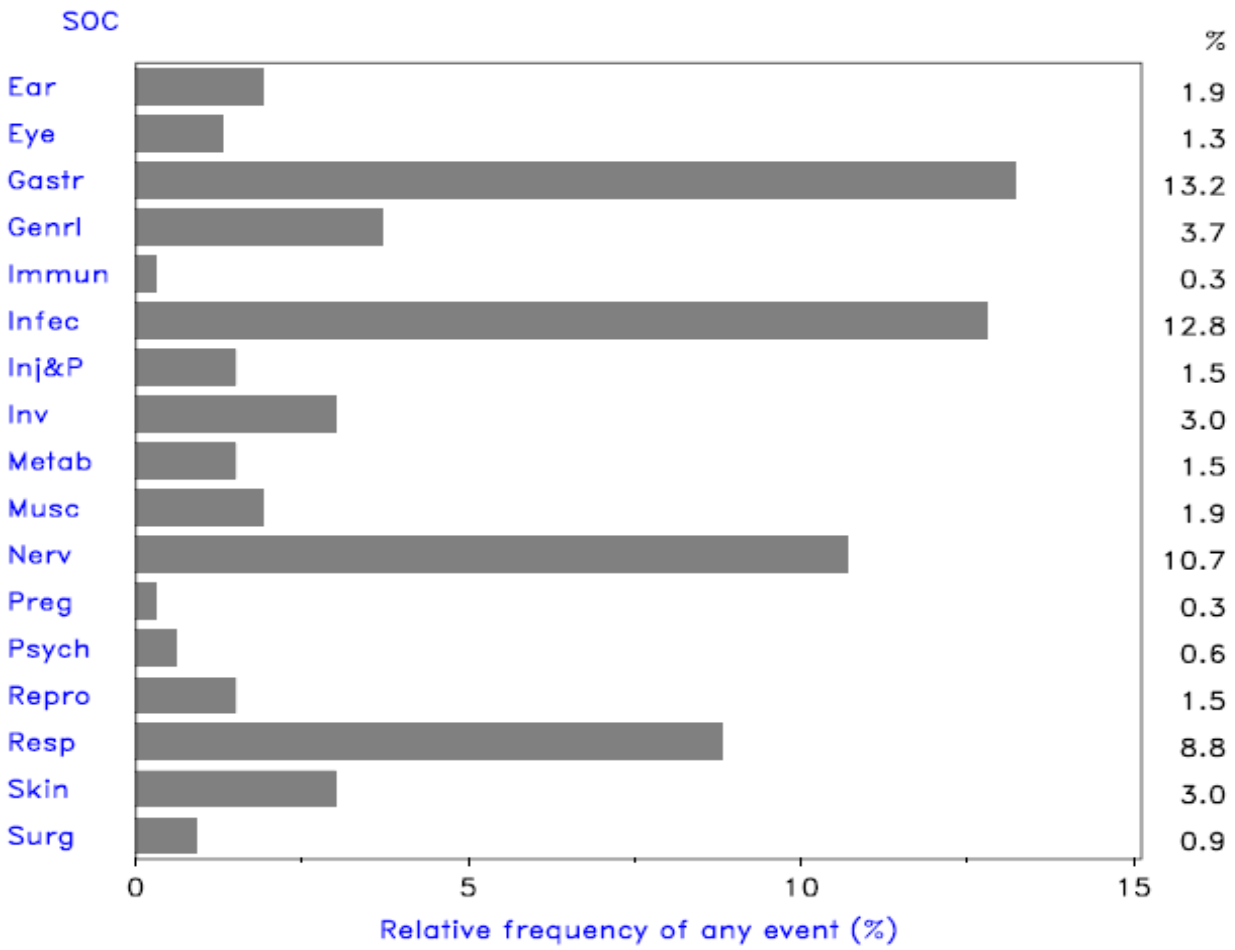


- Document search strategy
- Highlight overall distribution of ADRs/AEs
- Identify areas for in-depth analysis (focused searches)

Overview by Primary SOC

- Use Internationally Agreed Order of SOCs when applicable, e.g., the EU SPC guideline
  - See MedDRA Introductory Guide, ASCII files
- Consider use of HLTs and HLGTs
- Line listings, tables, graphs
- Benefits - Broad overview, PTs displayed only once
- Limitations - Incomplete groupings due to SOC allocation rules, lengthy output

Primary SOC Graphical Display Example



Primary SOC Output Listing Example

SOC Nervous system disorders	8
HLGT Mental impairment disorders	
HLT Mental impairment (excl dementia and memory loss)	
PT Disturbance in attention	1
HLGT Movement disorders (incl Parkinsonism)	
HLT Dyskinesias and movement disorders NEC	
PT Psychomotor hyperactivity	2
HLT Tremor (excl congenital)	
PT Tremor	3
HLGT Neurological disorders NEC	
HLT Disturbances in consciousness NEC	
PT Somnolence	1
HLT Neurological signs and symptoms NEC	
PT Dizziness	1

Focused Searches

Useful when further investigating concepts of interest

- Secondary SOC assignments
  - Programming required if database does not allow automated output by secondary SOC
  - Benefits - more comprehensive view of medically related events
  - Limitations - display by primary and secondary SOC could lead to double counting
- Grouping terms (HLGT/HLT)
- SMQ
- Customized search
  - Modified SMQ
  - *Ad hoc* query

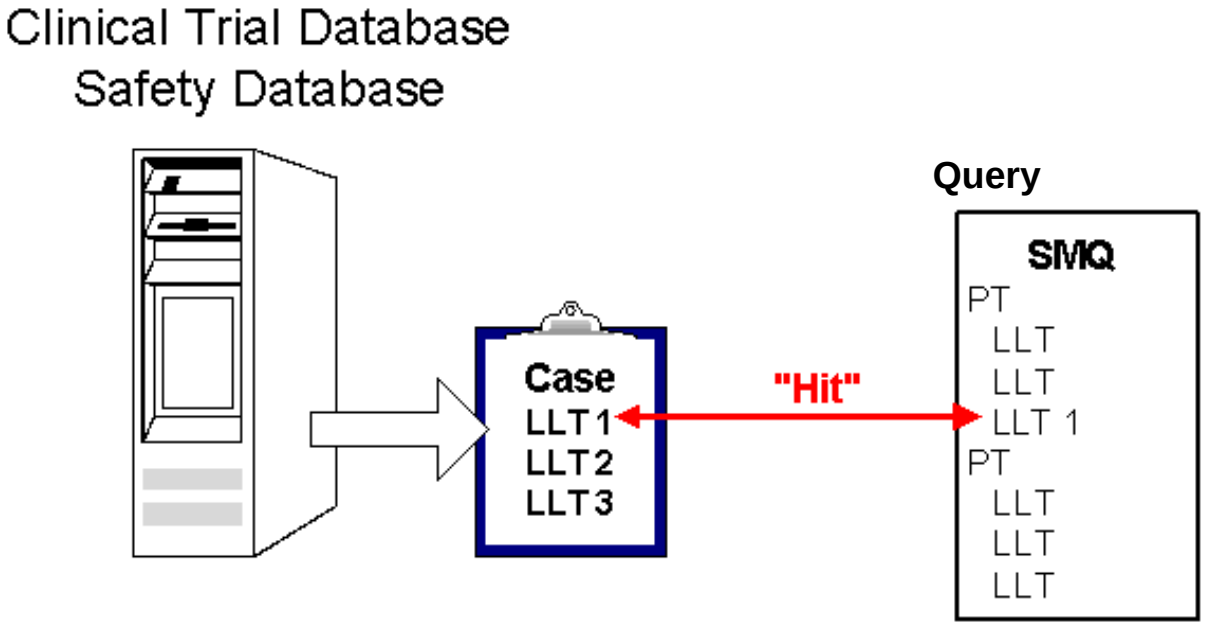
Secondary SOC Output Listing Example

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

Example as of MedDRA Version 19.0

Developing Queries Using MedDRA

What is a Query?



Query Strategy Tips

- Define the condition
- Develop inclusion/exclusion criteria
- Good browser is key component
- Search “non multi-axial” and “other/support” SOCs
- Search a term’s “neighbors”, including secondary locations
- Use grouping terms where applicable
- Avoid using LLTs (Exception: species information at LLT level in SOC *Infections and infestations*)
- Store for future use
- Review for impact of new MedDRA versions

Example and Hands-on Exercises

Example
Cardiac Arrhythmias

Example – Cardiac Arrhythmias

- Obvious starting point – HLGT *Cardiac arrhythmias* ("Top-down" search)
- Also use "Arrhythmia" terms as starting point of "Bottom-up" search
- What about non-multi-axial SOCs?

Example – Cardiac Arrhythmias (cont)

- SOC *Investigations*
  - PTs subordinate to HLT *ECG investigations* and HLT *Heart rate and pulse investigations* should be reviewed
    - Example: PT *Heart rate irregular*

Example – Cardiac Arrhythmias (cont)

- SOC *Surgical and medical procedures*

  Important to review:

  – PTs subordinate to HLT *Cardiac device therapeutic procedures**
    - Example: PT *Implantable defibrillator insertion*

  – PTs subordinate to HLT *Cardiac therapeutic procedures NEC**
    - Example: PT *Cardioversion*

*Note: Pacemaker and other cardiac therapeutic procedure terms were not included in SMQ *Cardiac arrhythmias*

Example – Cardiac Arrhythmias (cont)

- Because arrhythmias may produce various signs and symptoms, you may wish to review PTs subordinate to the following HLTs:
  - HLT *Disturbances in consciousness NEC*
  - HLT *Neurological signs and symptoms NEC*
  - HLT *Cardiac disorders NEC*
  - HLT *Cardiac signs and symptoms NEC*
  - HLT *Dyspnoeas*

Example – Cardiac Arrhythmias (cont)

- Lastly…
  - PTs subordinate to HLT *Death and sudden death* (under SOC *General disorders and administration site conditions*) should be reviewed
    - Example: PT *Cardiac death*

Cardiac Arrhythmias – Identifying Cases

Patient ID	Patient Events (PTs) MedDRA v19.0	Primary SOC	Case of interest?
01	Nausea Vomiting		Unlikely
02	Sudden death	General disorders and administration site conditions	Potential case. Needs review.
03	Electrocardiogram abnormal Dyspnoea Cardio-respiratory arrest	Investigations Respiratory, thoracic and mediastinal disorders Cardiac disorders	Potential case. Needs review.
04	Breast cancer Postmenopause		Unlikely
05	Syncope Palpitations	Nervous system disorders Cardiac disorders	Potential case. Needs review.
06	Pacemaker generated arrhythmia	General disorders and administration site conditions	Potential case. Needs review.
07	Atrial fibrillation Cardioversion	Cardiac disorders Surgical and medical procedures	Potential case. Needs review.
08	Long QT syndrome congenital	Congenital, familial and genetic disorders	Potential case. Needs review.
09	Cerebrovascular accident Prostate cancer		Unlikely
10	Cardiac assistance device user	Social circumstances	Potential case. Needs review

Developing Queries – Lessons Learned

- MedDRA is a potentially powerful tool for data retrieval, BUT it requires:
  - Solid medical knowledge
  - Solid MedDRA knowledge
- Size and complexity of MedDRA overcome lack of specificity of other terminologies, but may require a more "creative" approach to data retrieval
- WELL WORTH THE EFFORT to develop, share, and store in-house queries

Standardised MedDRA Queries (SMQs)

Standardised MedDRA Queries (SMQs)

- Collaboration between CIOMS (Council for International Organizations of Medical Sciences) and ICH (MSSO)
- Groupings of terms from one or more MedDRA SOCs related to medical condition or area of interest
- Terms relate to signs/symptoms, diagnoses, syndromes, physical findings, laboratory and other test data, etc.
- Intended to aid in case identification

SMQ Benefits and Limitations

- Benefits
  - Application across multiple therapeutic areas
  - Validated reusable search logic
  - Standardized communication of safety information
  - Consistent data retrieval
  - Maintenance by MSSO/JMO
- Limitations
  - Do not cover all medical topics or safety issues
  - Will evolve and undergo further refinement even though they have been tested during development

SMQ in Production - Examples

- As of Version 22.0, a total of 104 level 1 SMQs in production
  - Agranulocytosis
  - Anaphylactic reaction
  - Cerebrovascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Hypersensitivity
  - Ischaemic heart disease
  - Lack of efficacy/effect
  - Medication errors
  - Osteonecrosis
  - Peripheral neuropathy
  - Pregnancy and neonatal topics
  - Pseudomembranous colitis
  - Rhabdomyolysis/myopathy
  - Severe cutaneous adverse reactions
  - Systemic lupus erythematosus

SMQ Data Characteristics

SMQ Data Characteristics

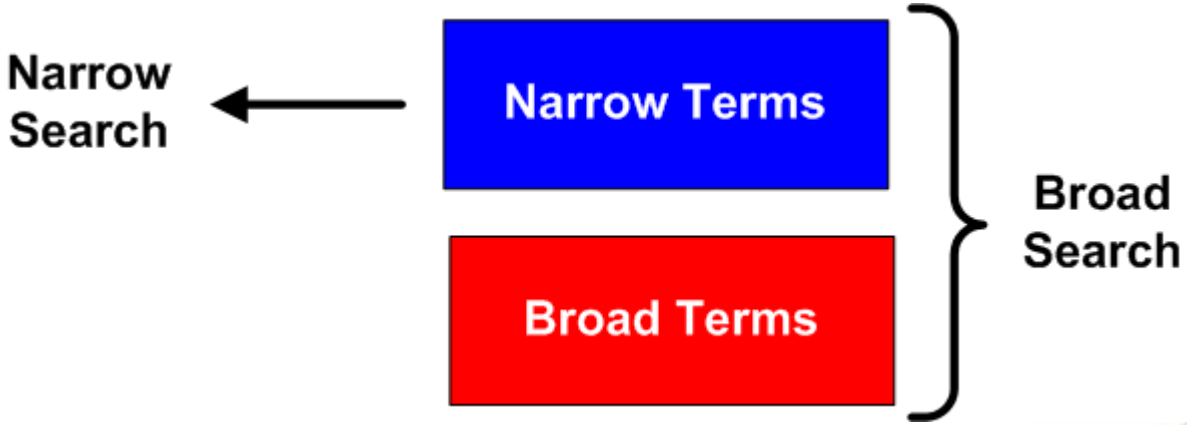
- MedDRA term inclusion
- Broad/narrow
- Algorithms
- Hierarchy
- SMQ status/term status within an SMQ
- SMQ files and documents

MedDRA Term Inclusion

- SMQs are constructed at MedDRA PT level
- LLTs that are subordinate to an included PT are also included

Narrow and Broad Searches

- "Narrow" scope – specificity (cases highly likely to be condition of interest)
- "Broad" scope – sensitivity (all possible cases)
- "Broad search" = All broad **+** all narrow terms



Narrow *vs.* Broad Example

SMQ *Lactic acidosis*

Definition

Lactic acidosis is a form of high anion gap metabolic acidosis - 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 - 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 - Acidosis is seldom significant unless blood lactate exceeds 5 mmol/l - Clinical presentation in type B lactic acidosis: o Symptoms: hyperventilation or dyspnea, stupor or coma, vomiting, drowsiness, and abdominal pain o Onset of symptoms and signs is usually rapid accompanied by deterioration in the level of consciousness.

Source

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

Note

Testing in two regulatory databases confirmed that the term list is adequate; in one regulatory database, the term "acidosis" identified cases, but this may be a phenomenon of the database characteristics (coding of verbatims to terms of an older terminology or other coding conventions).

Narrow Terms
Blood lactic acid increased
Hyperlactacidaemia
Lactic acidosis

Broad Terms
Acid base balance abnormal
Acidosis
Anion gap abnormal
Anion gap increased
Blood alkalinisation therapy
Blood bicarbonate abnormal
Blood bicarbonate decreased
Blood gases abnormal
Blood lactic acid abnormal
Blood pH abnormal
Blood pH decreased
Coma acidotic
Kussmaul respiration
Metabolic acidosis
PCO2 abnormal
PCO2 decreased
Urine lactic acid increased

Algorithmic SMQs

- Some SMQs are designed to utilize algorithms
- Better case identification among broad search terms may result if cases are selected by a defined combination of selected terms

Algorithmic SMQ Example

- *Anaphylactic reaction (SMQ):*
  - A case with any of the following PTs:
    - *Anaphylactic reaction*
    - *Anaphylactic shock*
    - *Anaphylactic transfusion reaction*
    - *Anaphylactoid reaction*
    - *Anaphylactoid shock*
    - *Circulatory collapse*
    - *Dialysis membrane reaction*
    - *Kounis syndrome*
    - *Procedural shock*
    - *Shock*
    - *Shock symptom*
    - *Type I hypersensitivity*

(Narrow search terms = Category A)

Algorithmic SMQ Example (cont)

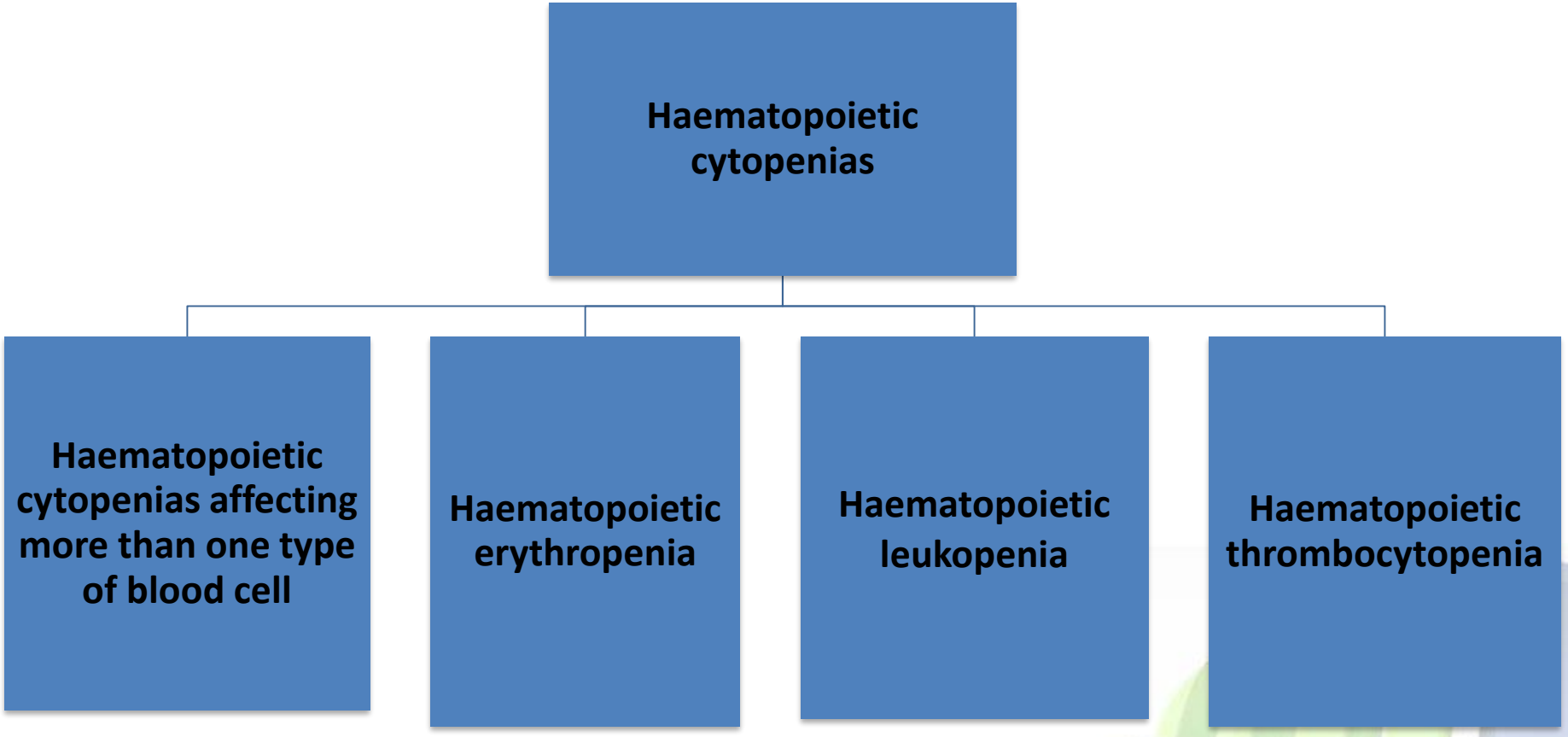
Category B – Upper airway/Respiratory	Category C – Angioedema/ Urticaria, etc.	Category D – Cardiovascular/ Hypotension
Acute respiratory failure	Allergic oedema	Blood pressure decreased
Asthma	Angioedema	Blood pressure diastolic decreased
Bronchial oedema	Erythema	Blood pressure systolic decreased

- Case = A (Narrow terms)
- Or Term from Category B **and** term from Category C
- Or Term from **either** Category B or Category C **plus** Term from Category D

Hierarchical SMQs

- Some SMQs may develop as set of queries related to one another in a hierarchical relationship
- Not related to MedDRA standard hierarchy
- One or more subordinate SMQs combined to create a superordinate, more inclusive SMQ

Hierarchical SMQ Example



SMQ Status/Term Status

- Each SMQ has a status (Active/Inactive)
- Similar in concept to MedDRA currency
- Terms assigned to an SMQ also have a status flag
  - Once a term is added to an SMQ, it will always be included in the SMQ but the status may be inactive

SMQ Files and Documents

- MedDRA distributed files unchanged by inclusion of SMQ files
- SMQ Introductory Guide
  - Recommended reading for optimal use of SMQs
  - Details of individual SMQs
  - Notes for implementation and/or expectation of results
- Production SMQ Spreadsheet
  - SMQs and included terms, SMQ summary
- SMQ changes: "What's New" document, Version Report, MVAT
- Original CIOMS Working Group documentation

SMQ Testing, Production Maintenance, and Versioning

SMQ Development Summary

- Pre-release testing by CIOMS SMQ Implementation Working Group members
  - Typically, at least one company and one regulator database
  - Cases retrieved reviewed for relevance
  - Fine-tuning of SMQ may require several iterations
- Production Phase: continue to be fine-tuned through the MSSO maintenance process

SMQ Versioning

- It is recommended that organizations use the SMQs with data coded with the same version of MedDRA
  - Match the MedDRA version of the SMQ with the MedDRA version of the coded data
  - Mismatches of SMQ and MedDRA coded data could produce unexpected results

SMQ Versioning (cont)

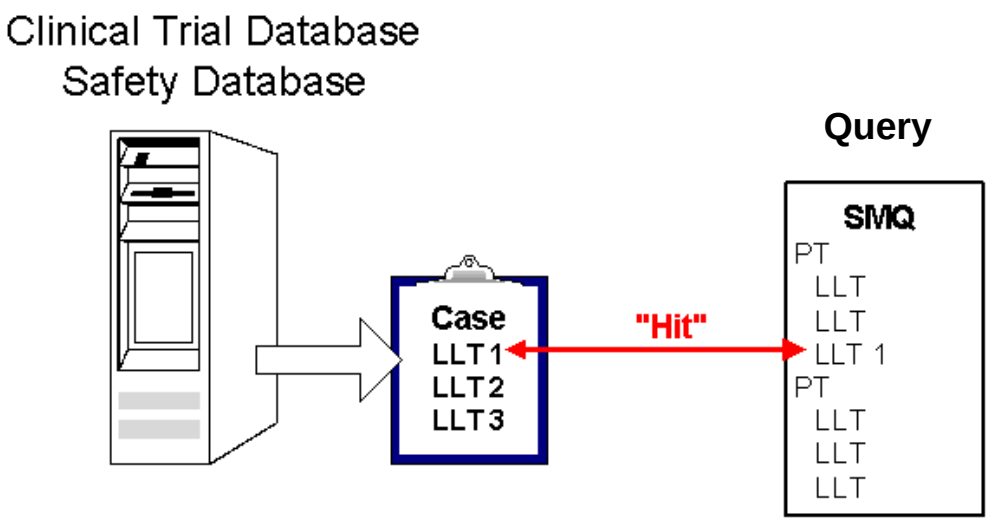
- Example of PT added to SMQs in MedDRA Version 19.0:
  - PT *End stage renal disease* in SMQ *Chronic kidney disease*
- Using version 18.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 19.0

Browser Demonstration SMQ View

How to “Run” SMQs

- IT perspective of SMQs = stored queries
- Code at LLT level; most organizations store coded data as LLTs
- SMQ ASCII files include PTs and LLTs
- Load SMQs into a query tool; run query against coded MedDRA terms in safety or clinical trial database for “Hits”
- Use SMQ options, if applicable
  - Narrow/broad search
  - Algorithms
  - Hierarchy

How to “Run” SMQs (cont)



Standardised MedDRA Query (SMQ) Analysis

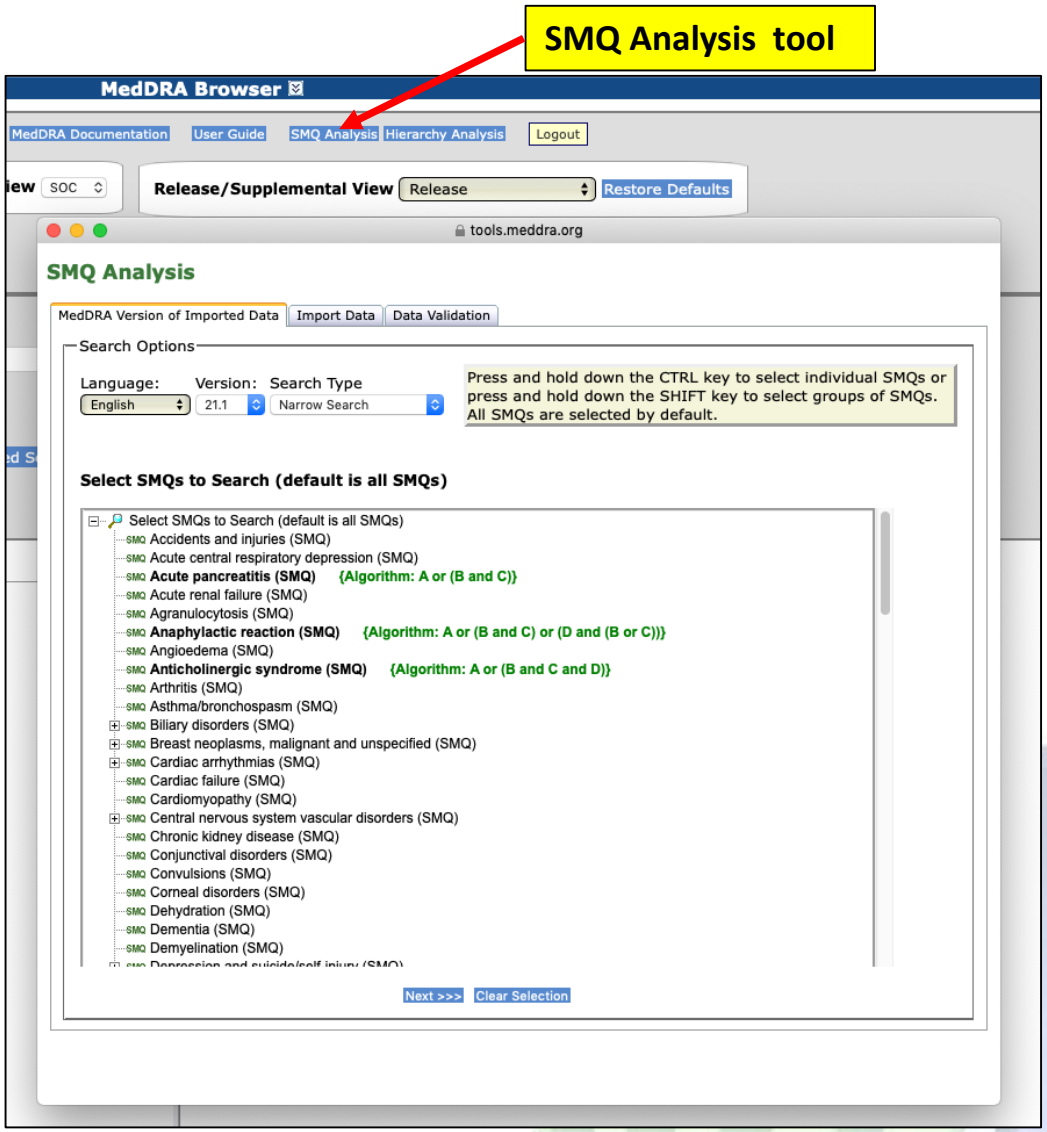
- In my dataset, which cases are "hits" for SMQs (potential cases of interest)?

A	B	C	D
Row ID	Term	Term Code	Case ID
1	Amylase abnormal	10072327	1
2	Abdominal distension	10000060	1
3	Acute kidney injury	10069339	2
4	Blood creatinine increased	10005483	2
5	Status asthmaticus	10041961	3
6	Gout	10018627	4
7	Joint effusion	10023215	4
8	Major depression	10057840	5
9	Suicidal ideation	10042458	5
10	Cataract operation	10063797	6
11	Abdominal pain	10000081	7
12	Diarrhoea	10012735	7
13	Palpitations	10033557	8
14	Atrial flutter	10003662	8
15	Pancreatitis acute	10033647	9
16	Dementia Alzheimer's type	10012271	10
17	Hypertension	10020772	10
18	Anaphylactic shock	10002199	11
19	Bronchospasm	10006482	12
20	Swelling face	10042682	12
21	Rash generalised	10037858	12
22	Hypotension	10021097	12
23	SLE arthritis	10040968	13
24	Haemolysis	10018910	14
25	Autoimmune nephritis	10077087	14
26	Double stranded DNA antibody positive	10069907	14
27	Photodermatosis	10051246	15
28	Pleural effusion	10035598	15
29	Epilepsy	10015037	15
30	Disease progression	10061818	16
31	Exercise tolerance decreased	10051301	16

Input

SMQ Analysis (cont)

- SMQ Analysis feature
- Apply SMQs to user's MedDRA-coded data
  - Narrow/broad
  - Hierarchical
  - Algorithmic (separate search option to apply algorithm)



SMQ Analysis (cont)

- Run broad search on all SMQs

A	B	C	D
Row ID	Term	Term Code	Case ID
1	Amylase abnormal	10072327	1
2	Abdominal distension	10000060	1
3	Acute kidney injury	10069339	2
4	Blood creatinine increased	10005483	2
5	Status asthmaticus	10041961	3
6	Gout	10018627	4
7	Joint effusion	10023215	4
8	Major depression	10057840	5
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10	Cataract operation	10063797	6
11	Abdominal pain	10000081	7
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27	Photodermatosis	10051246	15
28	Pleural effusion	10035598	15
29	Epilepsy	10015037	15
30	Disease progression	10061818	16
31	Exercise tolerance decreased	10051301	16

Input

SMQ Analysis (cont)

- Results of broad search on all SMQs
  - Includes narrow search
  - Includes hierarchical SMQs
  - Algorithmic SMQ analysis not shown

	A	B	C	D	E	F	G	H	I	J	K
1	SMQ Analysis	(SMQ analysis exercise v22.0.xlsx)			2/19/2019 6:33:38 PM						
2											
3	MedDRA English 21.1 (Search Type: Broad Search		SMQs Selected: All)								
4											
5	Row ID	LLT/PT Term	LLT/PT Code	PT	SMQ Matched	Scope	Category	Weight	Status	Case ID	SMQ Hierarchy
6	2	Abdominal distension	10000060	Abdominal distension	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	Narrow	A	0	Active	1	Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)
7	2	Abdominal distension	10000060	Abdominal distension	Acute pancreatitis (SMQ)	Broad	C	0	Active	1	
8	11	Abdominal pain	10000081	Abdominal pain	Retroperitoneal fibrosis (SMQ)	Broad	A	0	Active	7	
9	11	Abdominal pain	10000081	Abdominal pain	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	Narrow	A	0	Active	7	Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)
10	11	Abdominal pain	10000081	Abdominal pain	Acute pancreatitis (SMQ)	Broad	C	0	Active	7	
11	3	Acute kidney injury	10069339	Acute kidney injury	Tumour lysis syndrome (SMQ)	Broad	C	0	Active	2	
12	3	Acute kidney injury	10069339	Acute kidney injury	Toxic-septic shock conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
13	3	Acute kidney injury	10069339	Acute kidney injury	Torsade de pointes, shock-associated conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
14	3	Acute kidney injury	10069339	Acute kidney injury	Shock-associated circulatory or cardiac conditions (excl torsade de pointes) (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
15	3	Acute kidney injury	10069339	Acute kidney injury	Rhabdomyolysis/myopathy (SMQ)	Broad	A	0	Active	2	
16	3	Acute kidney injury	10069339	Acute kidney injury	Hypovolaemic shock conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
17	3	Acute kidney injury	10069339	Acute kidney injury	Hypoglycaemic and neurogenic shock conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
18	3	Acute kidney injury	10069339	Acute kidney injury	Drug reaction with eosinophilia and systemic symptoms syndrome (SMQ)	Broad	B	0	Active	2	Drug reaction with eosinophilia and systemic symptoms
19	3	Acute kidney injury	10069339	Acute kidney injury	Dehydration (SMQ)	Broad	A	0	Active	2	Dehydration (SMQ)
20	3	Acute kidney injury	10069339	Acute kidney injury	Anaphylactic/anaphylactoid shock	Broad	A	0	Active	2	Shock (SMQ)
21	3	Acute kidney injury	10069339	Acute kidney injury	Acute renal failure (SMQ)	Narrow	A	0	Active	2	Acute renal failure (SMQ)
22	1	Amylase abnormal	10072327	Amylase abnormal	Acute pancreatitis (SMQ)	Broad	B	0	Active	1	Acute pancreatitis (SMQ)
23	18	Anaphylactic shock	10002199	Anaphylactic shock	Hypersensitivity (SMQ)	Narrow	A	0	Active	11	Hypersensitivity (SMQ)
24	18	Anaphylactic shock	10002199	Anaphylactic shock	Anaphylactic/anaphylactoid shock	Narrow	A	0	Active	11	Shock (SMQ)
25	18	Anaphylactic shock	10002199	Anaphylactic shock	Anaphylactic reaction (SMQ)	Narrow	A	0	Active	11	Anaphylactic reaction (SMQ)

SMQ Analysis (cont)

- Results of algorithmic SMQ analysis

	A	B	C	D	E	F	G	H	I	J	K
1	SMQ Analysis	(SMQ analysis exercise v22.0.xlsx)			2/19/2019 6:28:51 PM						
2											
3	MedDRA English 21.1 (Search Type: Algorithmic Search		SMQs Selected: All)								
4											
5	Row ID	LLT/PT Term	LLT/PT Code	PT	SMQ Matched	Scope	Category	Weight	Status	Case ID	SMQ Level 1
6	1	Amylase abnormal	10072327	Amylase abnormal	Acute pancreatitis (SMQ)	Broad	B	0	Active	1	Acute pancreatitis (SMQ)
7	2	Abdominal distension	10000060	Abdominal distension	Acute pancreatitis (SMQ)	Broad	C	0	Active	1	Acute pancreatitis (SMQ)
8	18	Anaphylactic shock	10002199	Anaphylactic shock	Anaphylactic reaction (SMQ)	Narrow	A	0	Active	11	Anaphylactic reaction (SMQ)
9	19	Bronchospasm	10006482	Bronchospasm	Anaphylactic reaction (SMQ)	Broad	B	0	Active	12	Anaphylactic reaction (SMQ)
10	20	Swelling face	10042682	Swelling face	Anaphylactic reaction (SMQ)	Broad	C	0	Active	12	Anaphylactic reaction (SMQ)
11	21	Rash generalised	10037858	Rash generalised	Anaphylactic reaction (SMQ)	Broad	C	0	Active	12	Anaphylactic reaction (SMQ)
12	22	Hypotension	10021097	Hypotension	Anaphylactic reaction (SMQ)	Broad	D	0	Active	12	Anaphylactic reaction (SMQ)
13	23	SLE arthritis	10040968	SLE arthritis	Systemic lupus erythematosus	Narrow	A	0	Active	13	Systemic lupus erythematosus (SMQ)
14	25	Autoimmune nephritis	10077087	Autoimmune nephritis	Systemic lupus erythematosus	Broad	F	1	Active	14	Systemic lupus erythematosus (SMQ)
15	24	Haemolysis	10018910	Haemolysis	Systemic lupus erythematosus	Broad	H	3	Active	14	Systemic lupus erythematosus (SMQ)
16	26	Double stranded DNA antibody positive	10069907	Double stranded DNA antibody positive	Systemic lupus erythematosus (SMQ)	Broad	I	3	Active	14	Systemic lupus erythematosus (SMQ)
17	29	Epilepsy	10015037	Epilepsy	Generalised convulsive seizures following immunisation (SMQ)	Narrow	A	0	Active	15	Generalised convulsive seizures following immunisation (SMQ)
18	15	Pancreatitis acute	10033647	Pancreatitis acute	Acute pancreatitis (SMQ)	Narrow	A	0	Active	9	Acute pancreatitis (SMQ)

SMQ Applications

SMQ Applications

- Clinical trials
  - Where safety profile is not fully established, use multiple SMQs on routine basis as screening tool
  - Selected SMQs to evaluate previously identified issue (pre-clinical data or class effect)
- Post-marketing
  - Selected SMQs to retrieve cases for suspected or known safety issue
  - Signal detection (multiple SMQs employed)
  - Single case alerts
  - Periodic reporting (aggregate cases for safety and other issues, e.g., lack of efficacy)

Customized Searches

Customized Searches – Modified SMQs

- Do not modify SMQ unless there is a compelling reason – makes it non-standard
- "**Modified MedDRA query based on an SMQ**"
  - To be used to refer to an SMQ that has been modified
  - All modifications must be documented
  - Version updates and maintenance are responsibility of organization that created it
  - SMQ *Lack of efficacy/effect* often modified based on particular product

Modified MedDRA Queries Based on SMQs - Examples

- Additional PTs needed
  - For possible safety signal of dementia, user added PT *Disturbance in attention* to existing SMQ *Dementia*
- Excluding PTs
  - Antipsychotic (with known association with hypotension and fainting) being evaluated for QT prolongation
  - User excluded PT *Syncope* from SMQ *Torsade de pointes/QT prolongation*) to prevent "noise" in retrieval

Modified MedDRA Queries Based on SMQs – Examples (cont)

- Changing scope of SMQ term
  - Product being investigated for hyperglycaemia and diabetes mellitus; specific (narrow) search result is required
  - Include PT *Increased insulin requirement* (normally a broad search term) with the narrow search terms in *Hyperglycaemia/new onset diabetes mellitus* (SMQ)

Customized Searches – *Ad Hoc* Queries

- Need medical knowledge
- Need knowledge of structure and characteristics of MedDRA and of your data
- Refer to the *MedDRA Data Retrieval and Presentation: Points to Consider* document for query construction tips
- Save query for future use; maintenance needed for MedDRA version changes
- Consider submitting *ad hoc* query to MSSO via change request for possible development as an SMQ

Exercise

- SMQ *Lack of efficacy/effect* often needs to be modified based on the particular characteristics of a product
- Consider how you would create a Modified MedDRA Query based on SMQ *Lack of efficacy/effect* for:
  - An inhaled bronchodilator indicated for use in asthma
  - A contraceptive
- Remember to document changes!

MSSO Contacts

- Website
  - www.meddra.org
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - www.meddra.org/faq

MedDRA

Medical Dictionary
for Regulatory Activities

Questions?

ICH
harmonisation for better health