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Presented by Joy Zhu
Medical Officer, MedDRA MSSO

19-20 September 2019

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MedDRA: Safety Data Analysis and SMQs

Presented by Joy Zhu
Medical Officer, MedDRA MSSO

19 September 2019

MedDRA in SDTM

2.2.2 The Events Observation Class

Table 2.2.2 Events — Topic and Qualifier Variables — One Record per Event

Variable Name	Variable Label	Type	Role	Description
Topic Variable				
--TERM	Reported Term	Char	Topic	Topic variable for an event observation, which is the verbatim or pre-specified name of the event.
Qualifier Variables				
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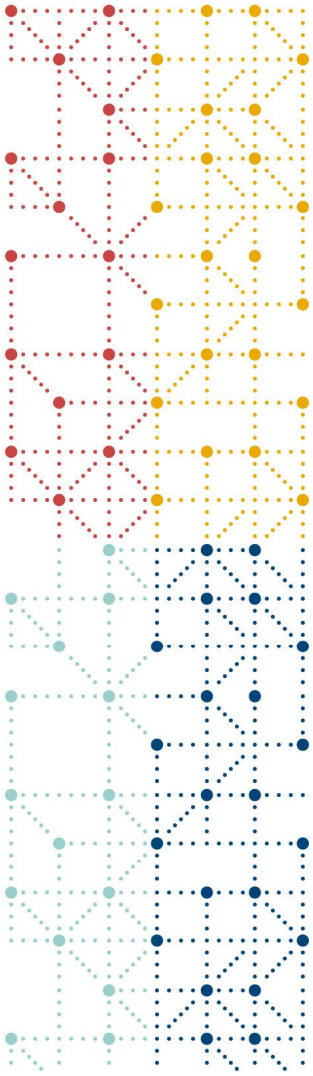
--LLT	Lowest Level Term	Char	Variable Qualifier of --TERM	MedDRA Lowest Level Term.
--LLTCD	Lowest Level Term Code	Num	Variable Qualifier of --LLT	MedDRA Lowest Level Term code.
--DECOD	Dictionary-Derived Term	Char	Synonym Qualifier of --TERM	Dictionary or sponsor-defined derived text description of the topic variable, --TERM, or the modified topic variable (--MODIFY), if applicable. Equivalent to the Preferred Term (PT in MedDRA).
--PTCD	Preferred Term Code	Num	Variable Qualifier of --DECOD	MedDRA Preferred Term code.
--HLT	High Level Term	Char	Variable Qualifier of --TERM	MedDRA High Level Term from the primary path.
--HLTCD	High Level Term Code	Num	Variable Qualifier of	MedDRA High Level Term code from the primary path.



Agenda

1. MedDRA overview
2. MedDRA Data Retrieval and Presentation: Points to Consider document
3. SMQ background and definition
4. SMQ data characteristics
5. SMQ applications

MedDRA was developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). The activities of the MedDRA Maintenance and Support Services Organization (MSSO) are overseen by an ICH MedDRA Management Committee, which is composed of the ICH parties, the Medicines and Healthcare products Regulatory Agency (MHRA) of the UK, Health Canada, and the WHO (as Observer).

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MedDRA Overview

What is MedDRA?

Med = Medical

D = Dictionary for

R = Regulatory

A = Activities

《监管活动医学词典》

MedDRA Definition

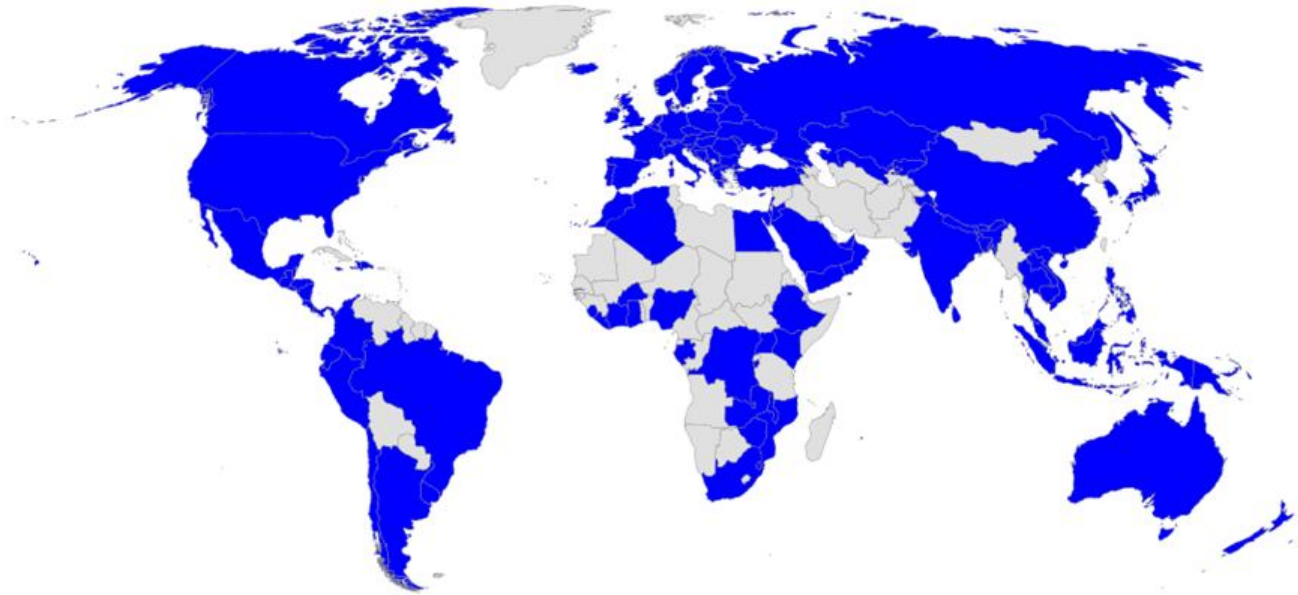
MedDRA is a clinically-validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry. The terminology is used through the entire regulatory process, from pre-marketing to post-marketing, and for data entry, retrieval, evaluation, and presentation.

WHO

WHEN

WHERE

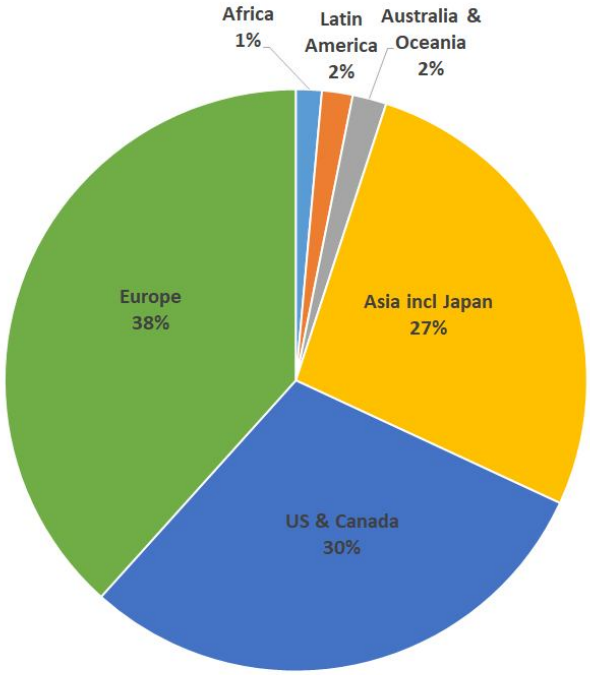
MedDRA Users Profile



MedDRA is in 125 countries

MedDRA Users Profile (cont)

- 5,800 Subscribing organizations by March 2019



Country	Count
United States	1594
Japan	793
United Kingdom	336
Germany	326
China	320
France	249
Italy	202
Spain	152
Canada	129
Republic of Korea	115
Australia	98
Netherland	98
Sweden	97
India	93
Switzerland	87

ICH Working Office, NMPA

- http://www.cde.org.cn/ichWeb

Regulatory Status in China

- http://www.nmpa.gov.cn/WS04/CL2093/229313.html

国家药品监督管理局
National Medical Products Administration

中国药品监管 中国药闻 中国药监APP 邮箱 政务信息报送

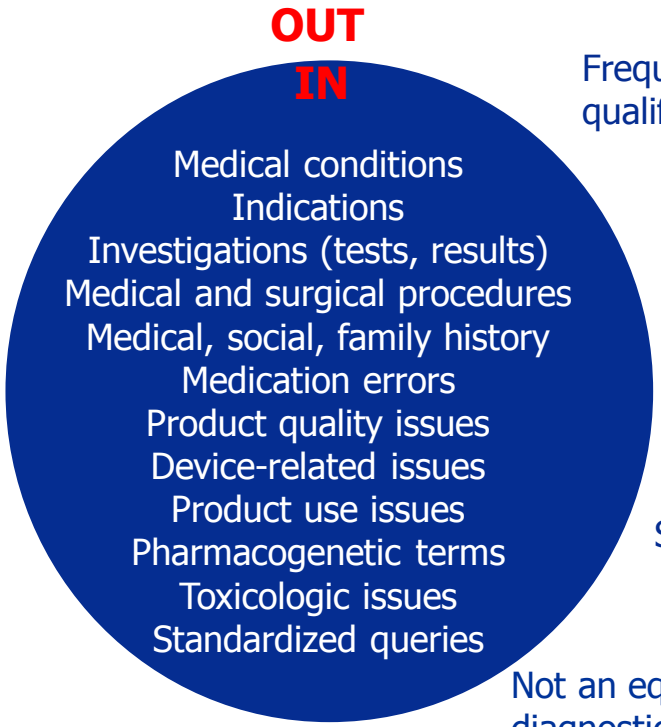
正在建设中...

总局关于适用国际人用药品注册技术协调会二级指导原则的公告（2018年第10号）

2018年01月25日 发布

为落实中共中央办公厅、国务院办公厅《关于深化审评审批制度改革鼓励药品医疗器械创新的意见》（厅字〔2017〕42号）精神，鼓励药品创新，推动药品注册技术标准国际接轨，加快药品审评审批，加强药品全生命周期管理，食品药品监管总局决定适用《M4：人用药物注册申请通用技术文档（CTD）》《E2A：临床安全数据的管理：快速报告的定义和标准》《E2D：上市后安全数据的管理：快速报告的定义和标准》《M1：监管活动医学词典（MedDRA）》和《E2B（R3）：临床安全数据的管理：个例安全报告传输的数据元素》五个国际人用药品注册技术协调会（ICH）二级指导原则。现就有关事项公告如下。

Scope of MedDRA



Not a drug dictionary

Frequency qualifiers

Patient demographic terms

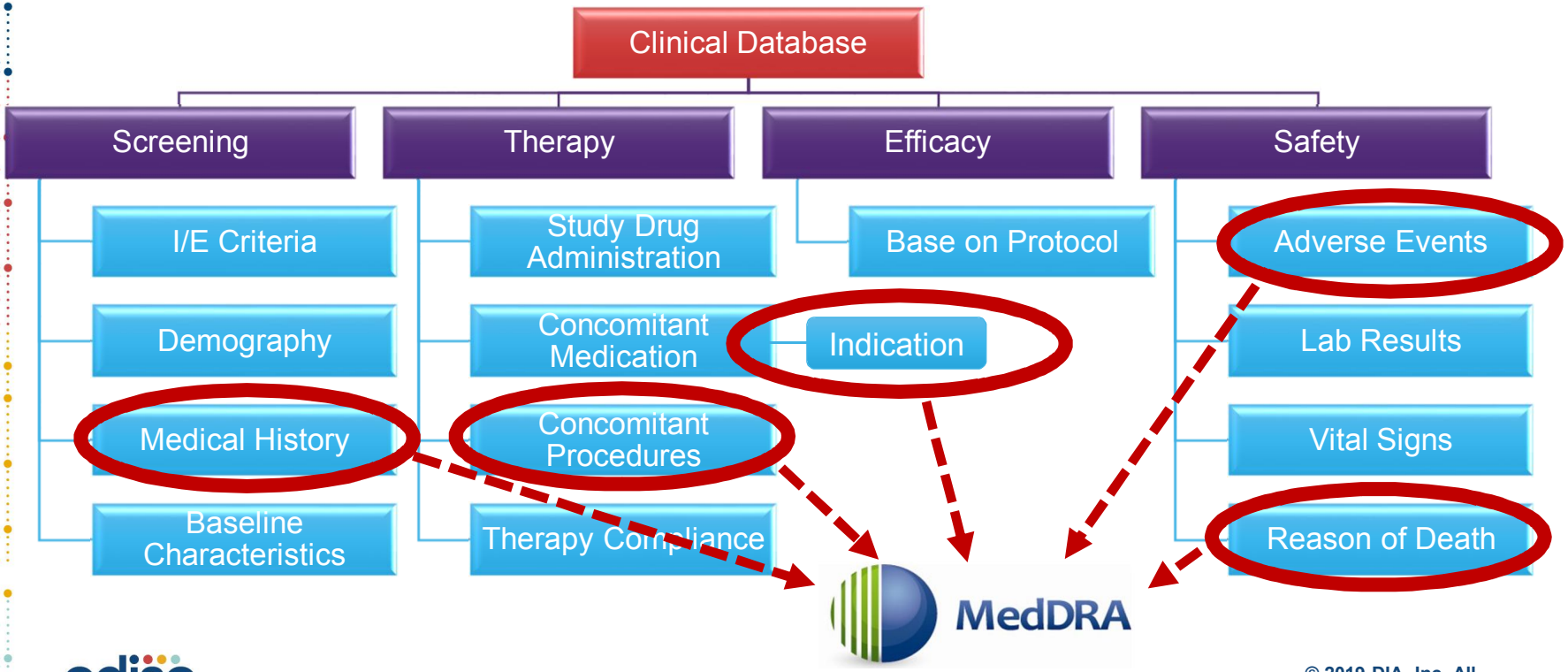
Numerical values for results

Clinical trial study design terms

Severity descriptors

Not an equipment, device, diagnostic product dictionary

Data to be Coded by MedDRA



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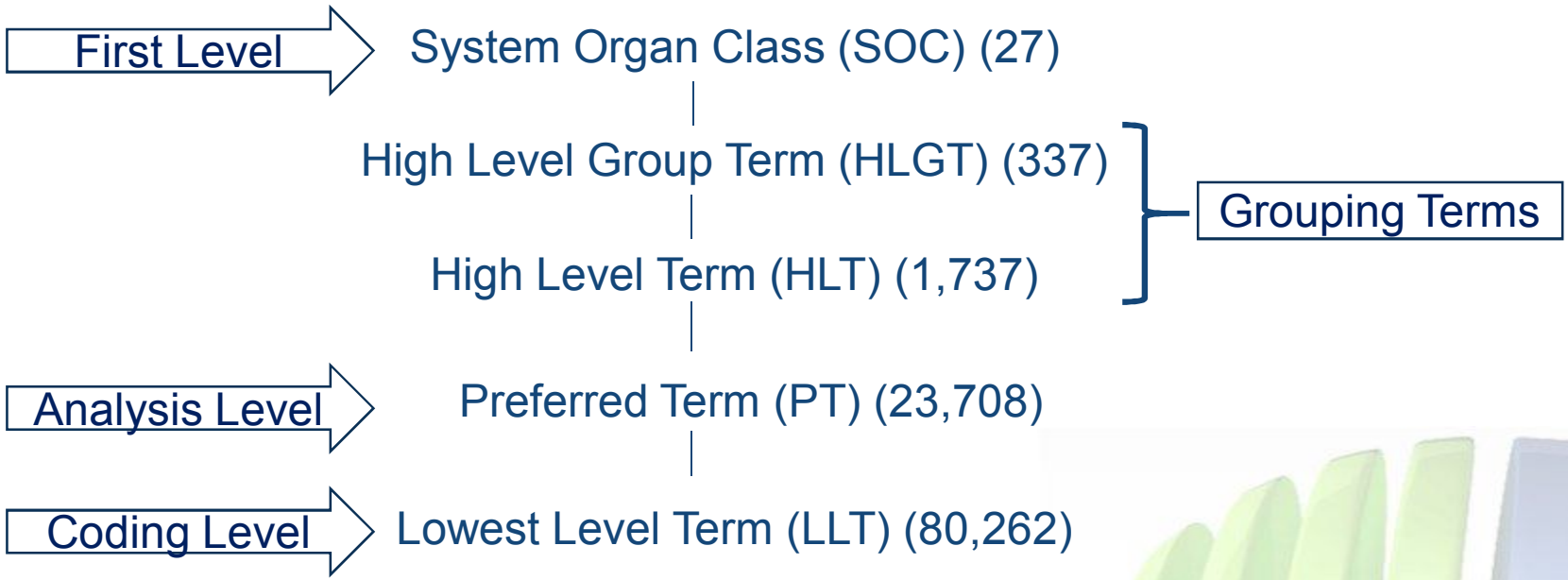
MedDRA Structure



MedDRA in SDTM

2.2.2 The Events Observation Class

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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

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

SOC = Infections and infestations (Primary SOC)

HLGT = Respiratory tract infections

HLGT = Viral infectious disorders

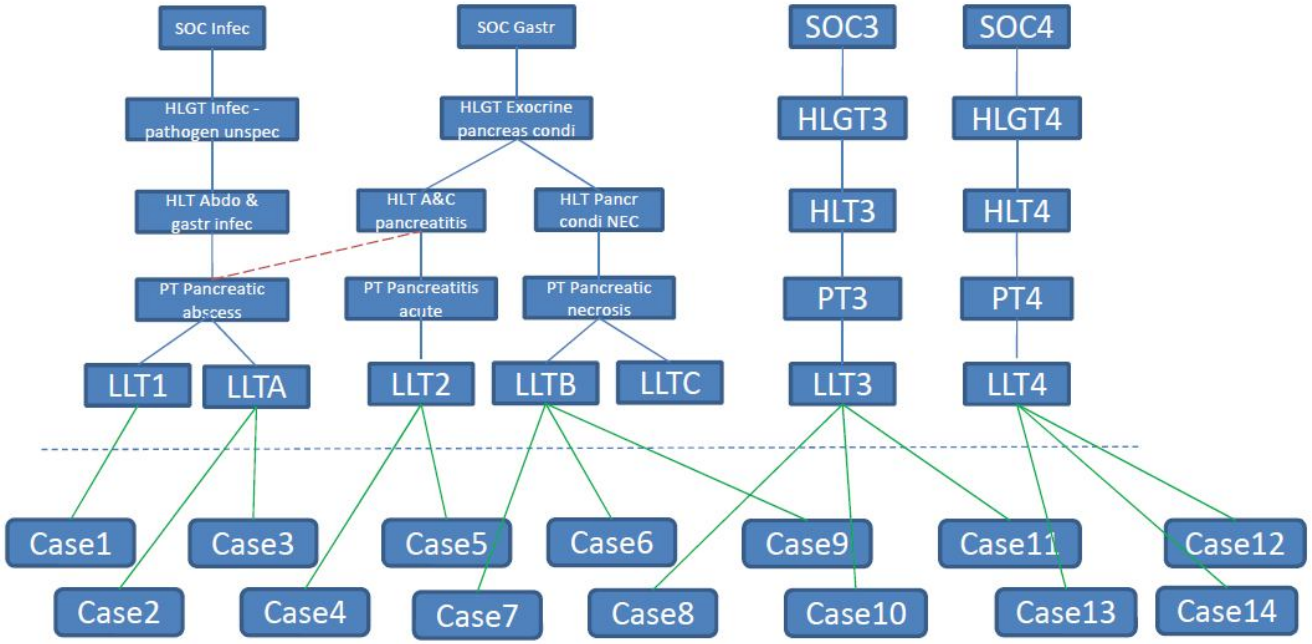
HLT = Viral upper respiratory tract infections

HLT = Influenza viral infections

PT = Influenza

Codes and Languages

MedDRA and Coded Cases



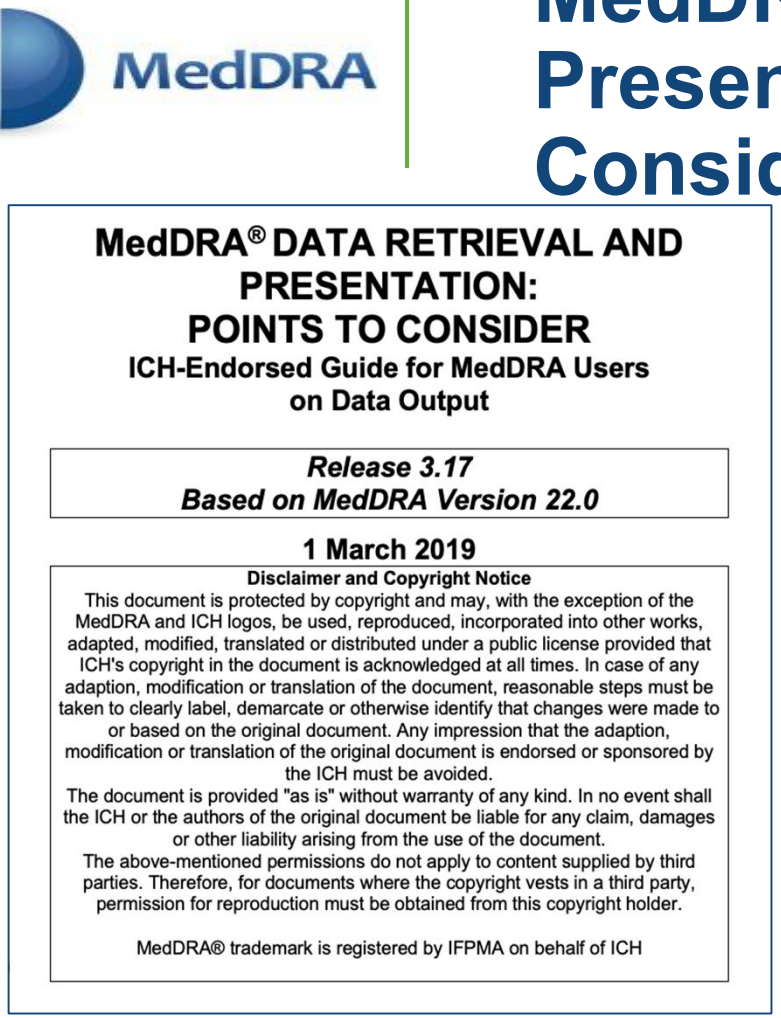
- Retrieve cases with MedDRA hierarchy

MedDRA Data Retrieval and Presentation: Points to Consider

PtC Documents

PtC Category	PtC Document	Purpose	Languages	Release Cycle
Term Selection	MedDRA Term Selection: Points to Consider	Promote accurate and consistent coding with MedDRA	English and Japanese	Updated with each MedDRA release
	MedDRA Term Selection: Points to Consider Condensed Version	Shorter version focusing on general coding principles to promote accurate and consistent use of MedDRA worldwide	All MedDRA languages (except English and Japanese)	Update as needed
Data Retrieval and Presentation	MedDRA Data Retrieval and Presentation: Points to Consider	Demonstrate how data retrieval options impact the accuracy and consistency of data output	English and Japanese	Updated with each MedDRA release
	MedDRA Data Retrieval and Presentation: Points to Consider Condensed Version	Shorter version focusing on general retrieval and analysis principles to promote accurate and consistent use of MedDRA worldwide	All MedDRA languages (except English and Japanese)	Update as needed
General	MedDRA Points to Consider Companion Document	More detailed information, examples, and guidance on specific topics of regulatory importance. Intended as a "living" document with frequent updates based on users' needs. First edition covers data quality and medication errors.	English and Japanese	Updated as needed

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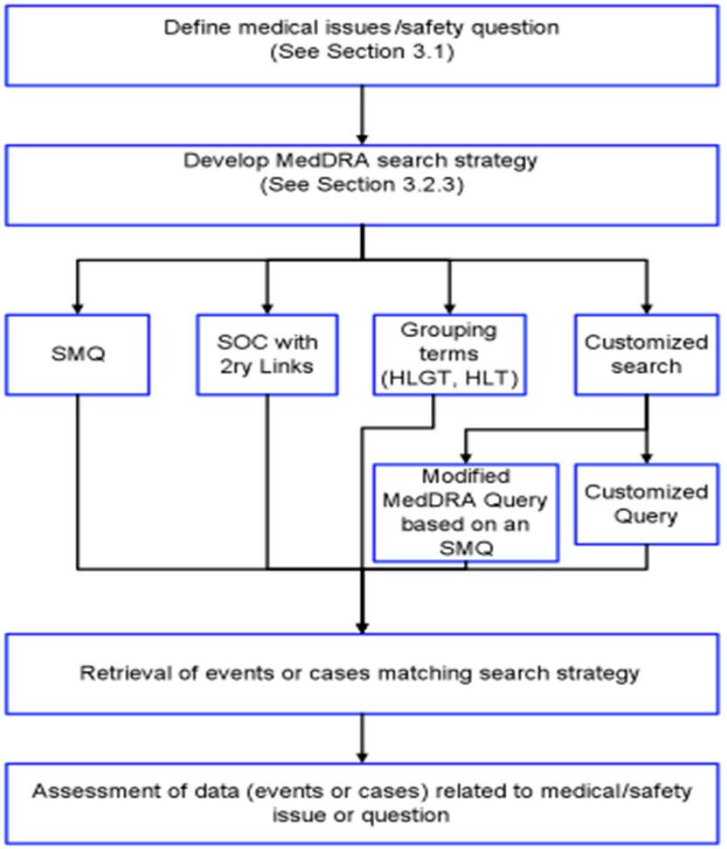
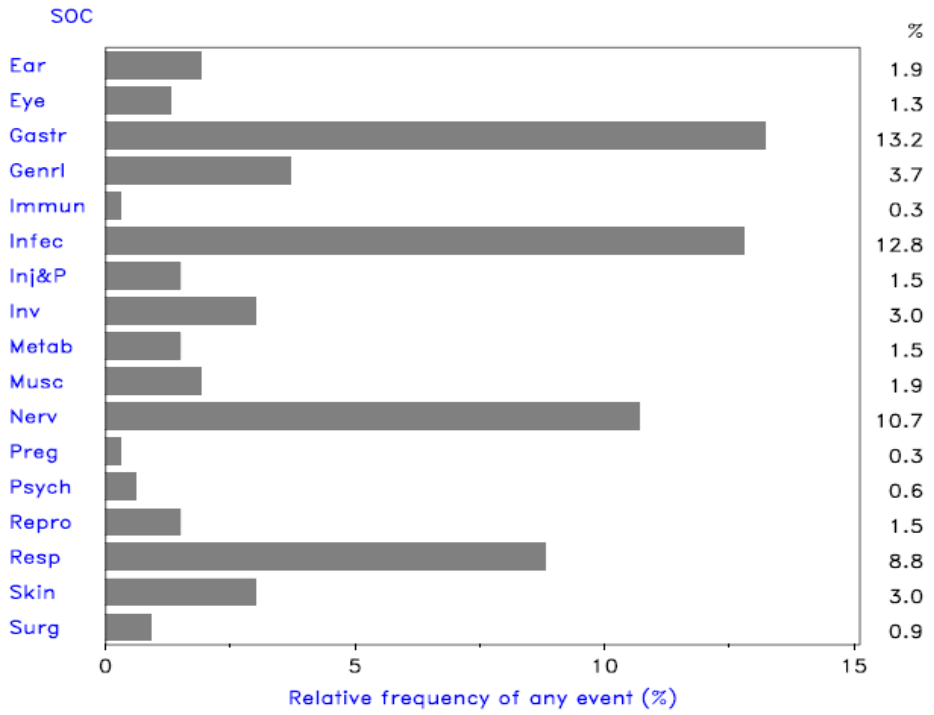
- Provides data retrieval and presentation options for industry or regulatory purposes
- Most effective when used in conjunction with MedDRA Term Selection: PTC document
- Recommended to be used as basis for individual organization's own data retrieval conventions

General Queries and Retrieval

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



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

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 in Production - Examples

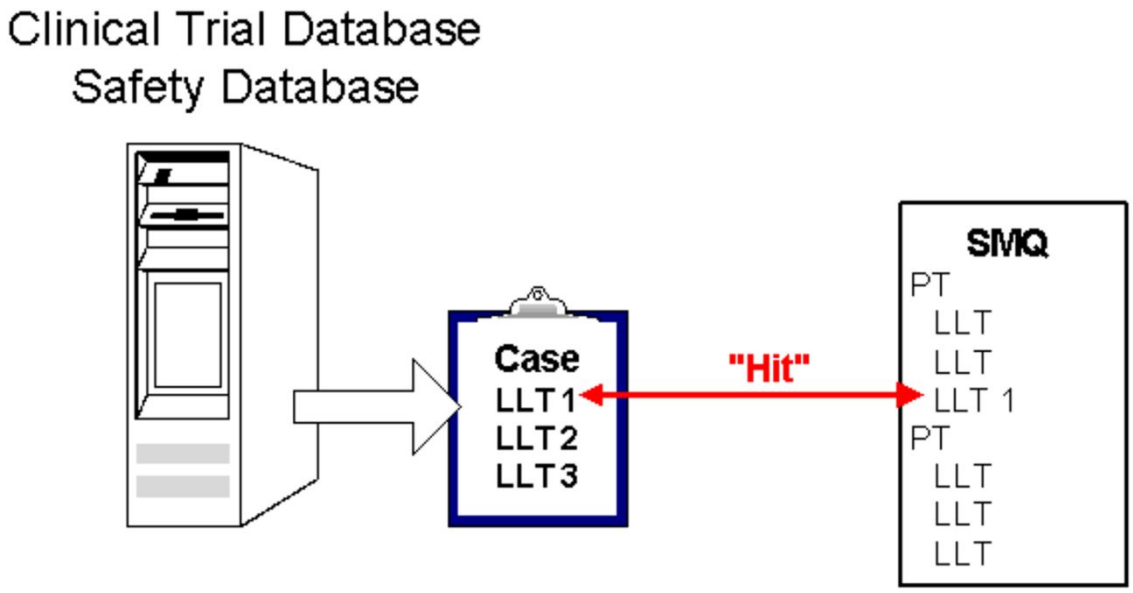
- As of Version 22.0, a total of 104 level 1 SMQs in production
  - Agranulocytosis
  - Anaphylactic reaction
  - Central nervous system vascular disorders
  - Convulsions
  - Depression and suicide/self-injury
  - Hepatic disorders
  - Hypersensitivity
  - Ischaemic heart disease
  - Lack of efficacy/effect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

SMQ 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

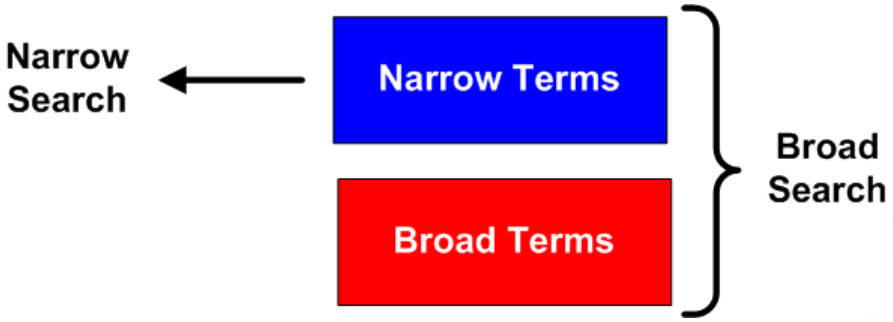
SMQ Data Characteristics

What is an SMQ?



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)

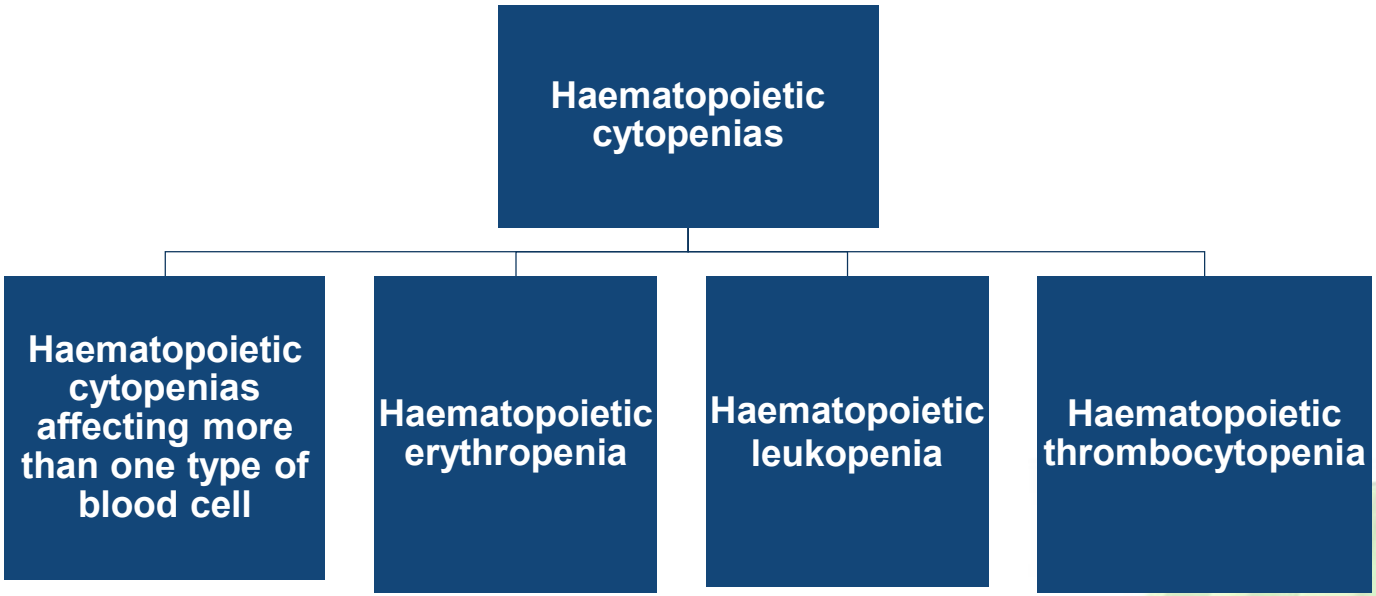
Category B – Upper airway/Respiratory	Category C – Angioedema/ Urticaria, etc.	Category D – Cardiovascular/ Hypotension
Acute respiratory failure	Allergic oedema	Blood pressure decreased
Asthma	Angioedema	Blood pressure diastolic decreased
Bronchial oedema	Erythema	Blood pressure systolic decreased

- 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

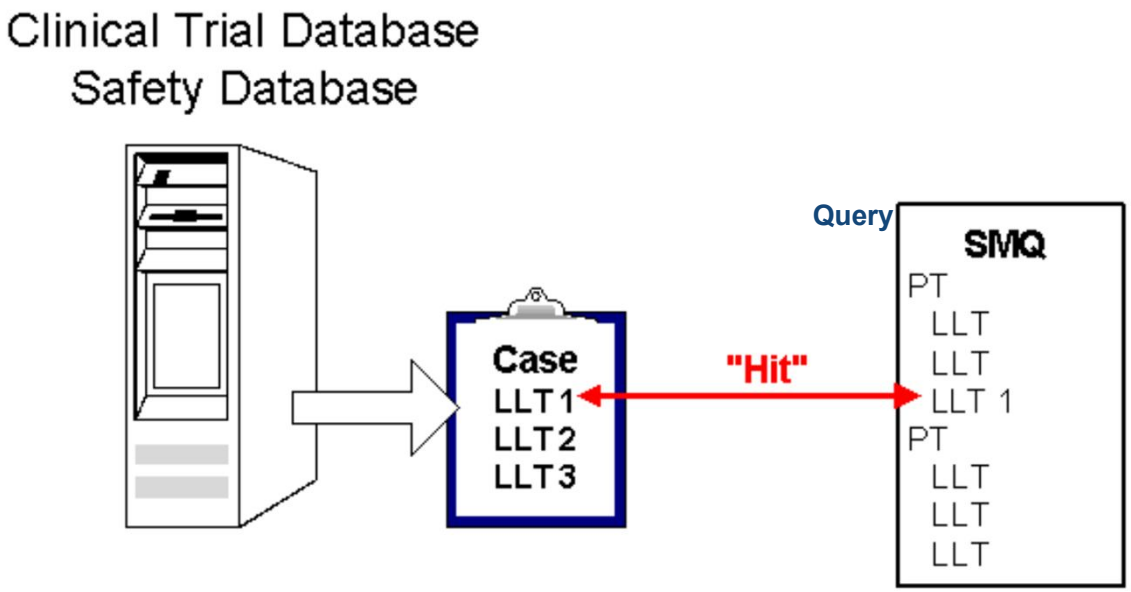
Hierarchical SMQ Example



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

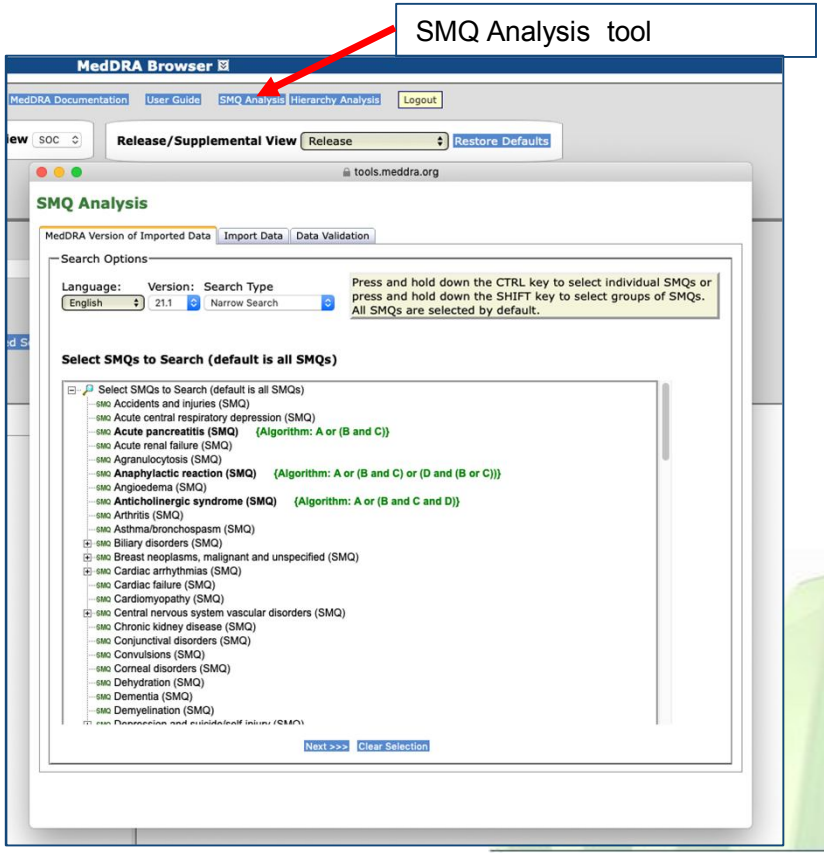
- In my dataset, which cases are “hits” for SMQs (potential cases of interest)?

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

000282 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

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000282 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	10073227	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)

EMA: Signal Detection Analysis

- ICSR coding at LLT level, analysis at PT level (medical concept):
  - ✓It may be important to conduct analysis at **higher level** of hierarchy: SOC, HLGT, HLT
    - When doing so, impact of axial and non multi-axial SOCs needs to be taken into account: relevant PTs in more than 1 SOC
  - ✓It may be important to conduct analysis at **SMQ** level to maximise likelihood that all terms related to a specific medical condition of interest are identified
- Challenge: strike the correct **balance**
  - ✓Too narrowly focused search (specificity): exclude events of potential relevance
  - ✓Too broad search (sensitivity): difficult to identify a trend or signal that may require further analysis (incl. case review)

Acknowledgement: Dr. Aniello Santoro, EMA

Use of SMQs at FDA – Reviewing Prescribing Information

- Proposed Prescribing Information:
- Warnings & Precautions:
  - Dizziness/Somnolence
  - Withdrawal of Antiepileptic Drugs
  - Suicidal Behavior and Ideation (class labeling)

SMQ (Narrow Search)	*RR*
(1) Hostility/aggression	4.4
(2) Vestibular disorders	4.258
(1) Hearing and vestibular disorders	4.088
(1) Hyponatraemia/SIADH	3.832
(2) Hearing impairment	3.832
(1) Dyslipidaemia *	2.555
(1) Biliary disorders	2.135
(2) Functional, inflammatory and gallstone related biliary disorders	2.135

- Final Prescribing Information
- Boxed Warning:
  - Serious Psychiatric and Behavioral Reactions
- Warnings & Precautions:
  - Falls
  - Dizziness & somnolence
  - Withdrawal of Antiepileptic Drugs
  - Suicidal Behavior and Ideation (class labeling)

Acknowledgement: Dr. Christopher Breder, Office of New Drugs, CDER, FDA

MSSO Contacts

- Website
  - www.meddra.org
- Free training (Face-to-Face training; Webinars)
  - https://www.meddra.org/training/schedule
- Email
  - mssohelp@meddra.org

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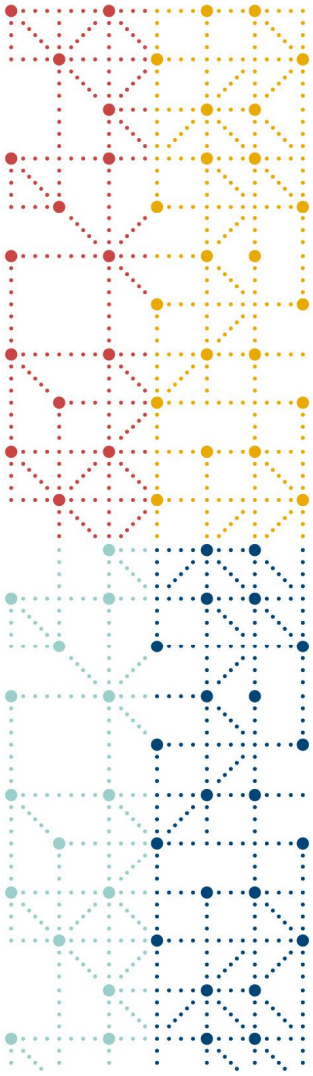

Thank You!

cdisc