MedDRA
Medical Dictionary
for Regulatory Activities

Standardised MedDRA Queries (SMQs)

ICH harmonisation for better health 1

MedDRA

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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Course Overview

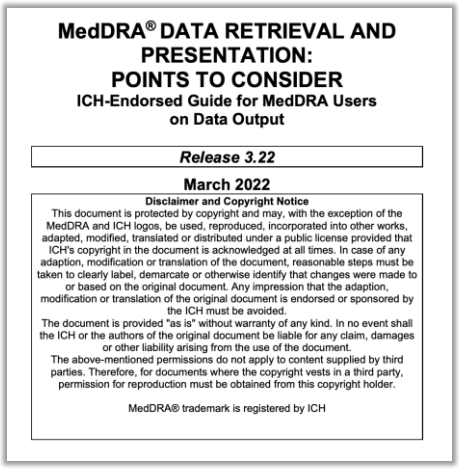
- Review content of the MedDRA Data Retrieval and Presentation: Points to Consider document
- Discuss the features of Standardised MedDRA Queries (SMQs) including:
  - Background and data characteristics
  - Impact of MedDRA versioning on SMQs
  - Benefits/limitations of SMQs

Course Overview (cont)

- Demonstration of SMQ Analysis Tool embedded in MedDRA browsers
- SMQ applications
- Two clinical scenarios for the use of SMQs
- Discuss the creation of customized searches
- Conclude with question and answer session

MedDRA Data Retrieval and Presentation: Points to Consider

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 3.22

March 2022

- 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

MedDRA Data Retrieval and Presentation: PTC (cont)

- Developed by a working group of the ICH Management Committee
- Updated annually - March
- Complete versions available in
  - English, Japanese, Chinese, Korean, Spanish, and Russian
- Condensed versions available for other MedDRA languages
- Available on MedDRA and JMO websites

Data Retrieval and Presentation : 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

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 the same version as data being queried

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)

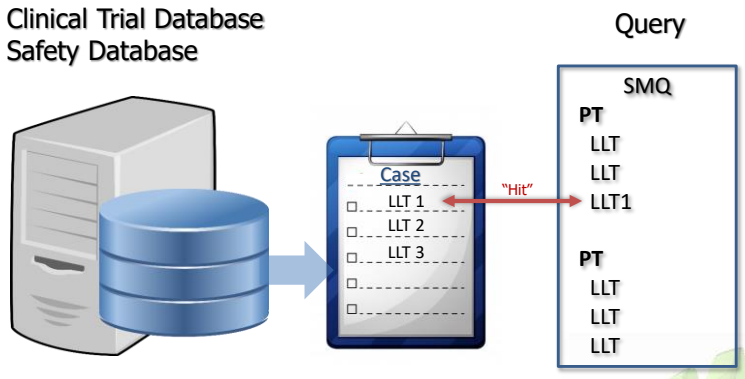
MedDRA Version Analysis Tool (MVAT) (cont)

- User interface and report output available in all MedDRA languages
- Ability to run reports on supplemental changes
- Option to run reports on secondary SOC changes
- Watch the two-part webinar on the use of MVAT under "Tools" tab on the "Training Materials" page of MedDRA website

  https://www.meddra.org/training-materials

Standardised MedDRA Queries (SMQs)

What is a Query?



Standardised MedDRA Queries (SMQs)

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

SMQs in Production - Examples

As of Version 25.0, a total of 110 level 1 SMQs in production

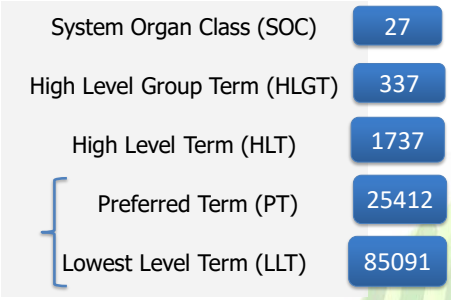
- Agranulocytosis
- Anaphylactic reaction
- Central nervous system vascular disorders
- Convulsions
- COVID-19
- Depression and suicide/self-injury
- Hepatic disorders
- Hypersensitivity
- Ischaemic heart disease
- Lack of efficacy/effect
- Medication errors
- Osteonecrosis
- Peripheral neuropathy
- Pregnancy and neonatal topics
- Pseudomembranous colitis
- Rhabdomyolysis/myopathy
- Severe cutaneous adverse reactions
- Shock
- Systemic lupus erythematosus

SMQ Data Characteristics

- MedDRA term inclusion
- Broad/narrow
- Algorithms
- Hierarchy
- SMQ status/term status within an SMQ
- Term versioning in an SMQ

MedDRA Term Inclusion

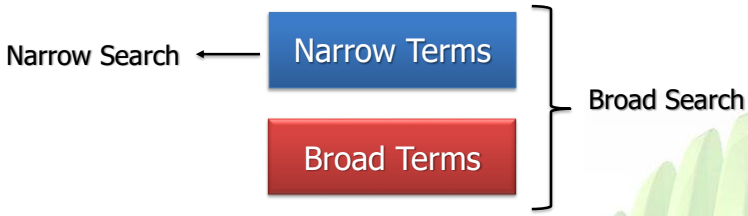
- SMQs are constructed at MedDRA PT level
- LLTs that are subordinate to an included PT are also included



MedDRA Version 25.0

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



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Narrow *vs*. Broad Example

Lactic acidosis (SMQ)

Narrow search terms

- Blood lactic acid increased
- Hyperlactacidaemia
- Lactic acidosis

Broad Search 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
- Carbon dioxide combining power abnormal
- Carbon dioxide combining power decreased
- Coma acidotic
- Kussmaul respiration
- Metabolic acidosis
- PCO2 abnormal
- PCO2 decreased
- Urine lactic acid increased|

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).

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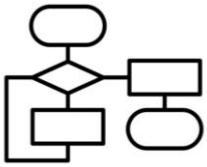
Algorithmic SMQs

- 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 (cont)

Anaphylactic reaction (SMQ)

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

A case =

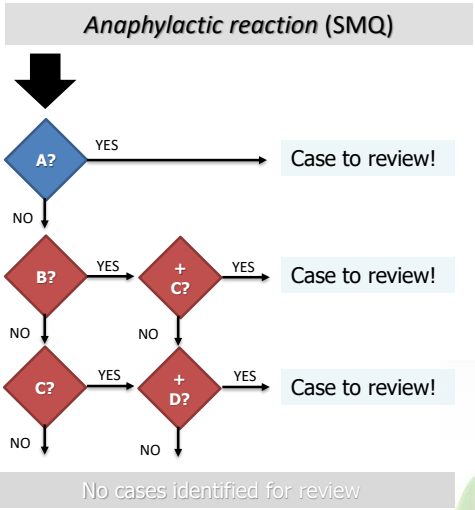
- Term Category A (Narrow terms)

or

- Term from Category B **and** term from Category C
- Term from **either** [Category B or Category C] **plus** Term from Category D

Not all Category B, C, and D terms are shown

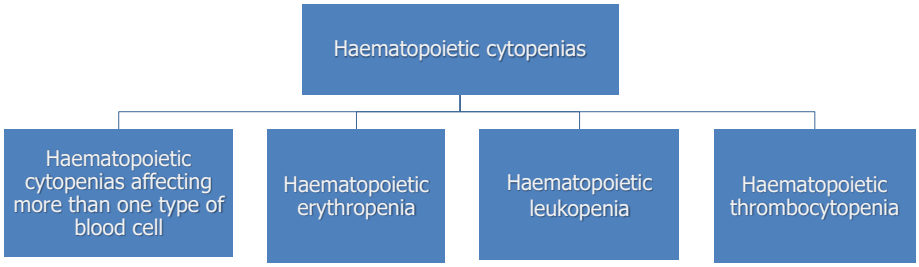
Algorithmic SMQ Example (cont)



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 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 23.0:
  - PT *Hormone receptor positive breast cancer* in SMQ *Breast malignant tumours*
- Using version 22.1 SMQs which do not contain these PTs would fail to identify cases coded to these terms in a database using MedDRA Version 23.0

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

Browser Demonstration SMQ View

Using the SMQ Analysis Tool in the MedDRA Browsers

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/

Mobile MedDRA Browser
https://mmb.meddra.org

MSSO's MedDRA Browsers (cont)

- Features
  - Each 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 (MDB and WBB only)

MDB and WBB Special Features

- Preview upcoming (supplemental) changes in next release*
  **Supplemental view not available on MDB*

- View primary **and** secondary link information
- Upload terms to run against SMQs
- Advanced search options (e.g., NOT, OR)

How to "Run" SMQs

- IT perspective of SMQs = stored queries
- Most organizations code and store data as LLTs
- SMQ ASCII files include PTs and LLTs
- Load SMQs into a query tool; run query against coded MedDRA terms in database for "Hits"
- Use SMQ options, if applicable
  - ✓ Narrow/broad search
  - ✓ Algorithms
  - ✓ Hierarchy

A Practical Question

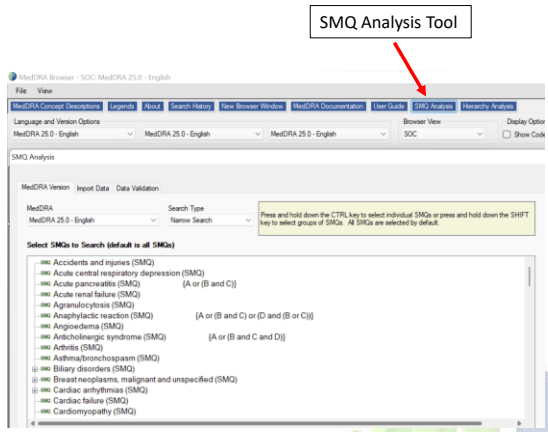
- In my dataset, which cases are "hits" for SMQs (potential cases of interest)?

Row ID	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	10037844	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
32	COVID-19 pneumonia	10084380	17
33	Acute respiratory distress syndrome	10001052	17

Input

Standardised MedDRA Query (SMQ) Analysis Tool

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



SMQ Analysis Tool (cont)

- Run broad search of all SMQs

Row ID	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
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31	Exercise tolerance decreased	10051301	16
32	COVID-19 pneumonia	10084380	17
33	Acute respiratory distress syndrome	10001052	17

Input

SMQ Analysis Tool (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 v25.0.xls	2/19/2022 10:24:36 PM								
2											
3	MedDRA English 25.0 (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 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	2	Abdominal distension	10000060	Abdominal distension	Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	Narrow	A	0	Active	1	Gastrointestinal nonspecific inflammati and dysfunctional
9	3	Acute kidney injury	10069339	Acute kidney injury	Rhabdomyolysis/myopathy (SMQ)	Broad	A	0	Active	2	Rhabdomyolysis/myop
10	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)
11	3	Acute kidney injury	10069339	Acute kidney injury	Torsade de pointes, shock-associated conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
12	3	Acute kidney injury	10069339	Acute kidney injury	Hypovolaemic shock conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)
13	3	Acute kidney injury	10069339	Acute kidney injury	Toxic-septic shock conditions (SMQ)	Broad	A	0	Active	2	Shock (SMQ)

SMQ Analysis Tool (cont)

- Results of algorithmic SMQ analysis

	A	B	C	D	E	F	G	H	I	J	K
1	SMQ Analysis	(SMQ analysis exercise v25.0.xlsx)			2/19/2022 10:32:25						
2											
3	MedDRA English 25.0 (Search Type: Algorithmic Search; SMQs Selected: All)										
4											
5	Row I	LLT/PT Term	LLT/PT Cod	PT	SMQ Matched	Scope	Category	Weight	Status	Case	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	10037844	Rash	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 (SMQ)	Narrow	A	0	Active	13	Systemic lupus erythematosu (SMQ)
14	24	Haemolysis	10018910	Haemolysis	Systemic lupus erythematosus (SMQ)	Broad	H	3	Active	14	Systemic lupus erythematosu (SMQ)
15	25	Autoimmune nephritis	10077087	Autoimmune nephritis	Systemic lupus erythematosus (SMQ)	Broad	F	1	Active	14	Systemic lupus erythematosu (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 erythematosu (SMQ)

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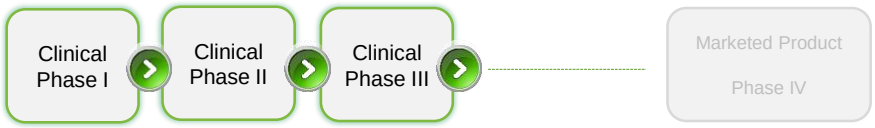
SMQ Applications

MedDRA

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)

SMQ Applications (cont)

- 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)

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Two SMQ Data Analysis Scenarios

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Scenario #1

- Your company started development of a new drug for onychomycosis projected to take eight years and cost $1.2 billion dollars

Onychomycosis

Scenario #1 (cont)

- As part of safety surveillance, you decide to periodically run SMQs for serious AEs against your data
- You identify five possible cases of hemolytic anemia in your 1,000 patient exposures
- Based on this unfavorable risk/benefit ratio (remember, your drug is for nail fungus), you suggest stopping the development project

Scenario #1 (cont)

- Your management reviews and follows your recommendation saving time, money and potential patient risk

Job well done !!!!!!

Scenario #2

- You are developing the fourth drug in a therapeutic class
- Other products in class are associated with development of high blood pressure and angioedema but, given the seriousness of the target disease, this is an acceptable risk

Scenario #2 (cont)

- During development and early post-marketing on your product, you routinely run *Hypertension (SMQ)* and *Angioedema (SMQ)* against your expanding safety data
- Over time, it becomes clear that your drug is <u>not</u> associated with either of these risks for the other drugs in your therapeutic class
- Your diligence has given patients a safer alternative for the treatment of their disease

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

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

Summary

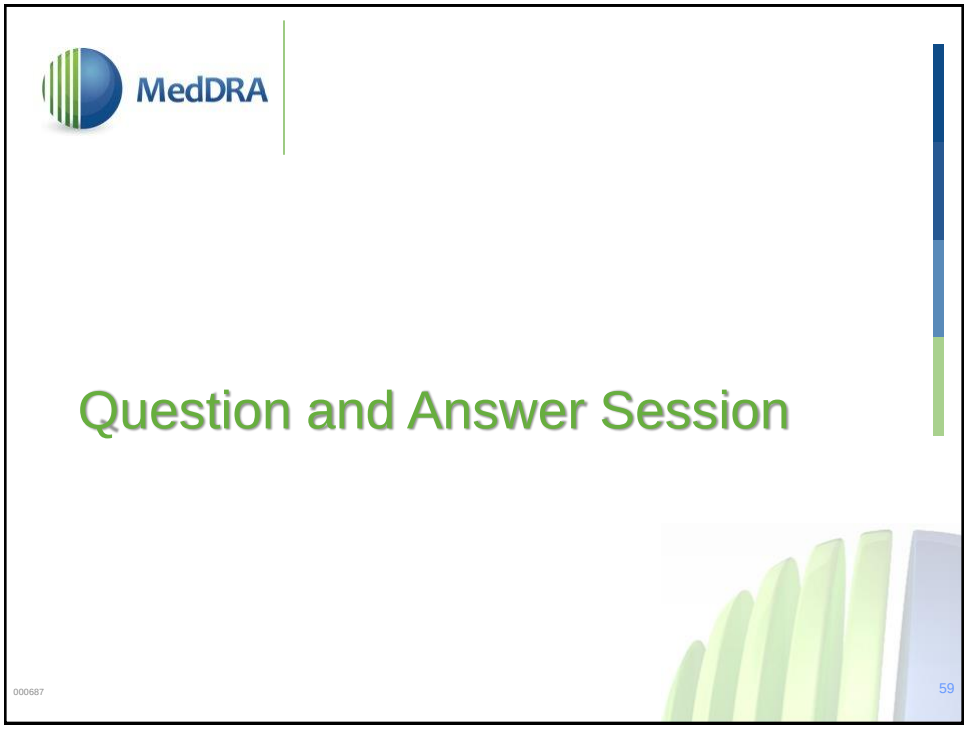
- ✓ Reviewed the MedDRA Data Retrieval and Presentation: Points to Consider document
- ✓ Discussed the characteristics, uses, applications and benefits of Standardised MedDRA Queries (SMQs) including their customization

MSSO Contacts

- Website
  - www.meddra.org
- Email
  - mssohelp@meddra.org
- Frequently Asked Questions
  - www.meddra.org/faq
- MedDRA Browsers
  - https://www.meddra.org/meddra-desktop-browsers (Desktop Browser)
  - https://tools.meddra.org/wbb/ (Web-Based Browser)
  - https://mmb.meddra.org (Mobile Browser)

MSSO Contacts (cont)

- Training Schedule
  - https://www.meddra.org/training/schedule
- MedDRA Support Documentation
  - https://www.meddra.org/how-to-use/support-documentation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Question and Answer Session
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