

Standardised MedDRA® Queries (SMQs)

CIOMS Working Group on Standardised MedDRA Queries (SMQs)

(Abbreviation: CIOMS SMQ WG)

MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

CIOMS IMA WG:

Role and Composition

Role

To develop a standardized approach to the identification of reports that may represent defined medical conditions with potential impact on benefit-risk evaluations.

Composition

Senior scientists from

- Industry (n=14))covering all three
- Regulatory Agencies (n=9))ICH Regions
- MedDRA Maintenance and Support Services Organization (MSSO), Japanese Maintenance Organization (JMO)
- Other institutions eg. WHO, CIOMS

Background of SMDs

MedDRA is a clinically validated medical terminology for

- Coding,
- Classification and
- Retrieval

of clinical regulatory information including drug safety data.

Special Search Categories (SSCs), initially released with MedDRA, did not meet retrieval requirements

Background of SMDQs (cont'd)

- Since January 2003, the joint effort of the CIOMS SMDQ WG and MSFO has been directed at producing Standardised MedDRA Queries (SMDQs).
- The ICH process is being utilised. Key players include:
 - CIOMS Working Group on Standardised MedDRA Queries (SMDQs), (CIOMS SMDQ WG).
 - ICH MedDRA Advisory Panel on SMDQs
 - MedDRA Management Board
 - MedDRA MSFO and JMO
- SMDQs are an integral part of the MedDRA and are provided without an additional subscription cost

Definition of SMOs

- Groupings of terms from one or more System Organ Classes that relate to a defined medical condition or area of interest.
- Intended to aid in identification and retrieval of potentially relevant reports/cases from a MedDRA coded database (pre- and postmarketing).
- Include terms related to signs, symptoms, diagnoses, syndromes, physical findings, laboratory and other physiologic test data, etc., that are associated with the medical condition of interest.
- The focus is on the Preferred Term.

Process for development of SMDs

- CIOMS SMD WG identifies SMDs for development.
- CIOMS SMD WG tests SMD (Phase I) and refines as necessary.
- MSO provides SMDs to MedDRA users for phase II (pre-release) testing.
- CIOMS SMD WG and MSO review results of Phase II testing and make appropriate changes.

Process for development of SMDs (cont'd)

- ICH MedDRA Advisory panel on SMDs advises MedDRA MB.
- MedDRA MB endorses (production) release of SMD by MSSO.
- MSSO routinely maintains SMDs (eg. updates as needed with each version release).
- Significant issues in production SMQs will be brought back by MSSO to CIOMS SMD WG for its consideration.

Methodology for selecting content of SMD

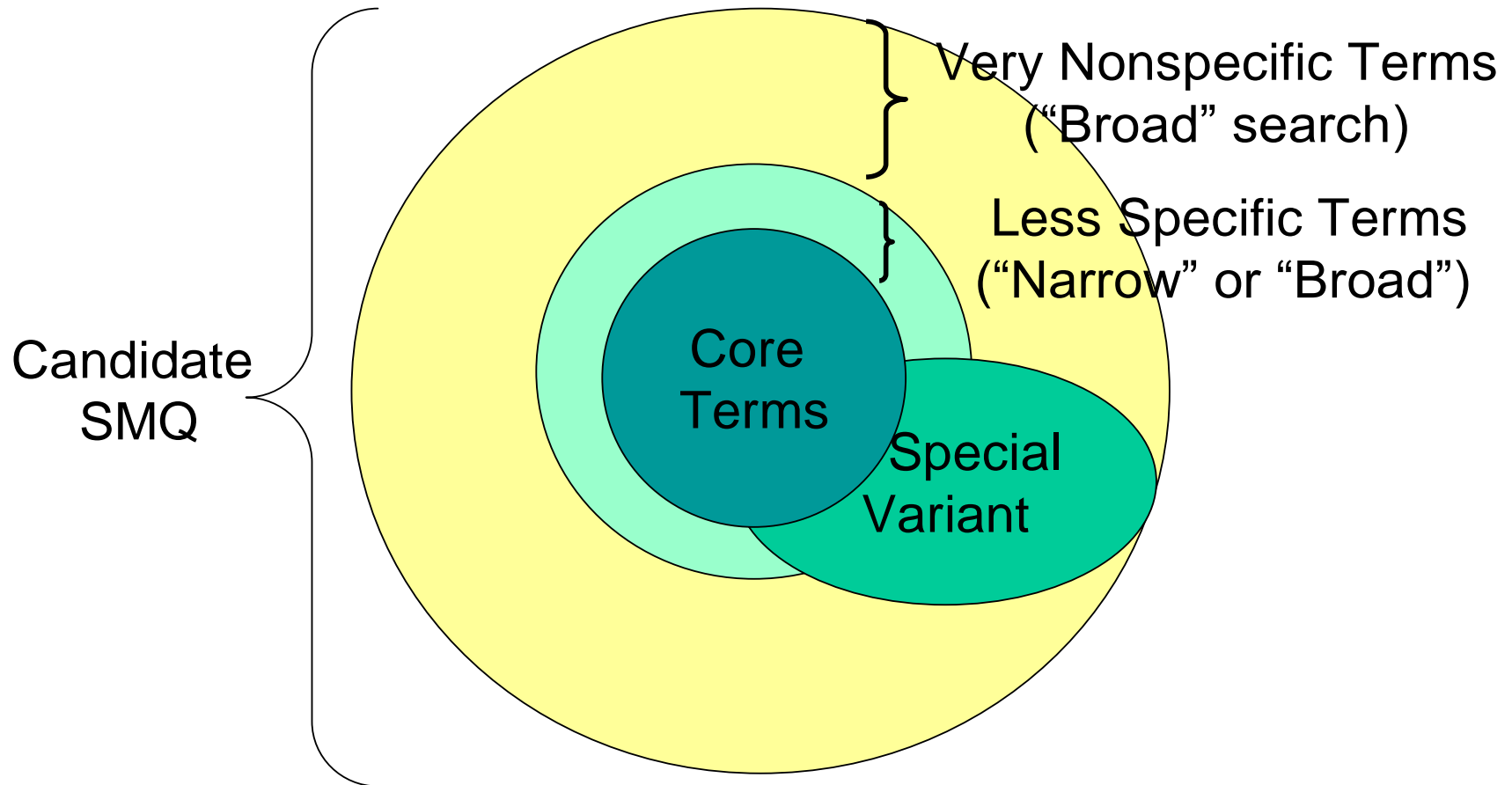
- Define the medical condition of interest based upon relevant literature.
- Conduct "bottom up" searches with the MedDRA hierarchy.
- Identify all PTs associated with the selected LLTs. Identify appropriate terms higher up the MedDRA hierarchy.
- Check for other suitable terms with "top down" review of the MedDRA hierarchy.

Content of IIRP: Narrow vs Broad

IIRPs may include very specific as well as less specific terms. These constitute two types of searches:

- “Narrow”: to identify cases that are highly likely to represent the condition of interest (a “narrow” scope)
- “Broad”: to identify all possible cases, including some that may prove to be of little or no interest on closer inspection (a “broad” scope).

Figure 1. Schematic View of MedDRA Terms Included in “Narrow” and “Broad” Searches.



Core terms are included in both “Narrow” and “Broad” searches; Special variant terms may be included to modify a given search

Content of ICD (cont'd)

Algorithms

- Better case identification may result if cases are selected by a defined *combination* of selected terms eg. the requirement of at least one term in each group of several subgroups of terms.
- May work best for "syndrome" types of events (e.g., anaphylactic reaction).

Content of ICD (cont'd)

Algorithms

Column A - Upper airway / Respiratory	Column B - Urticaria, angioedema, etc.	Column C - Cardiovascular / Hypotension
Acute respiratory failure	Allergic oedema	Blood pressure decreased
Asthma	Angioneurotic oedema	Blood pressure diastolic decreased
Bronchial oedema	Erythema	Blood pressure systolic decreased

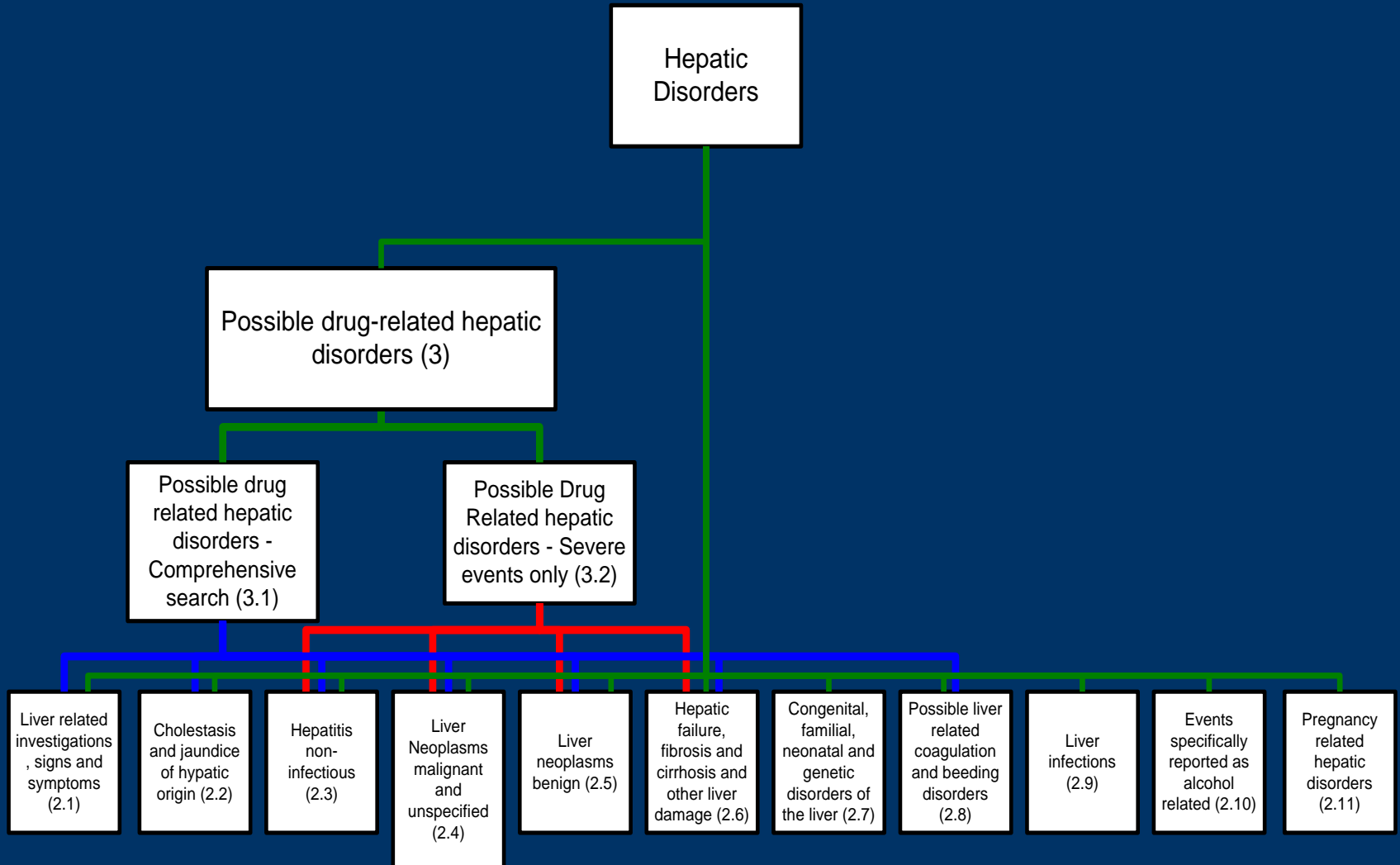
- Case = Term from Column A and term from Column B
- Case = Term from either Column A or Column B plus Term from Column C

Content of SMD (cont'd)

Hierarchy

- Some SMDs may have a hierarchical relationship similar to the hierarchical structure of MedDRA.
- Consist of one or more subordinate SMDs that could be combined to create a superordinate (more inclusive) SMD.

Example of hierarchy in SMDs



Phase I testing of SMDs by CIOMS SMD WG

- Identification of eligible databases and testers.
- Ideally testing using one industry and one regulatory database.
- Using drugs that are labelled for the condition represented by the SMD. A negative control is desirable.
- Analysis of test results. Based on clinical judgement, amendments and further testing may be required.
- Documentation.

Phase I testing by CIOMS 3rd WG (cont'd)

Documentation includes:

- Introduction and background
- Definitions (CIOMS or other reference)
- Inclusion/exclusion criteria
- Methodology, including broad/narrow, algorithm, etc.
- Testing; short description of testing results (including MedDRA version used)
- Discussion
- Annexes - tables/listing, references

Phase II (pre-release) testing of SMDs

- After completion of Phase I testing, the MISO will make candidate SMD specifications and draft documentation available to MedDRA subscribers for Phase II testing (pre-production release) and comment.
- Feedback received will be considered by the CIOMS SMD WG and MISO and any necessary changes made prior to production release of each SMD.

Maintenance of SMDs

- Maintenance will be performed by the MSO
(eg. potential changes with addition of new MedDRA terms and revision with each new MedDRA version.)
- Users may request changes in production SMDs using the SMD change request process.
- As maintenance will result in matching versions of MedDRA and fully released SMDs, the version of MedDRA in the safety database and the version of the utilised SMD should be the same.

When should SMCs be used? (1)

- Safety summaries for licence applications
- Safety studies:
The relevant SMC(s) should be stated and fully referenced in the protocol.
- Answering queries from regulators, health professionals or manufacturer
- Formal reviews of identified safety issues
eg. Expert reports, periodic safety update reports

When should SMDs be used? (2)

- Comparing frequency of the specified medical condition between products (pharmacovigilance signal detection):
Use SMD instead of individual PTs in Bayesian techniques, Proportional reporting ratios etc.
- Risk management programmes
- Profiling the safety of individual medicines

Strengths and Weaknesses of SMDs

Strengths

- Standardisation of search terms
- Reproducible results
- Aids comparison of products in same class

Weaknesses

- May not be comprehensive
 - Balance in choice of terms: Too inclusive leads to "noise" (retrieval of non relevant cases); Less inclusive results in missing cases*
- MedDRA version of database must match that of SMD.
- Cannot resolve differences in coding working practices
- Cannot resolve language translation factors

How to document the use of an SMD (1)

- Executive summary
- Background information:
 - *Type of query/ background of request*
 - *Background of drug: Mechanism of action, patient exposure etc*
 - *Background of adverse event*
- Methodology
 - *data source, in-licensed or not*
 - *Search and selection strategy: MedDRA version, any modifications to SMD and Rationale for changes, Full list of case identifiers in appendix.*
 - *Medical analysis*

How to document the use of an SMD (2)

- Results
 - Overview of information from database:
eg. summary of data, cut off date for search, demographics, serious cases, deaths. graphical displays.
 - Cases: narratives or tables
 - Summary of data:
eg. highlight relevant information, company assessment
 - Additional information:
eg. literature, late breaking information
- Discussion and Conclusion

Production/near production SMDs (Jan2005)

Production version released

- Rhabdomyolysis/myopathy
- Torsade de pointes/QT prolongation

Near production release

- Acute renal failure
- Haemolytic disorders
- Hepatic disorders
- Severe cutaneous adverse reactions

Candidate SMQs in development

(Phase II testing, Jan 2005)

- Acute pancreatitis
- Agranulocytosis
- Anaphylactic reaction
- Angioedema
- Asthma/bronchospasm
- Haematopoietic cytopenia
- Hyperlipidaemia
- Lack of efficacy/effect
- Lactic acidosis
- Peripheral neuropathy
- Suicide/depression

Candidate SMDs in later development (Jan 2005)

- Adverse pregnancy outcome
- Anticholinergic syndrome
- Arrhythmia
- Cardiac Failure
- Circulatory Failure (incl. shock)
- Drug abuse/dependence
- Eye disorders (could be 3 separate SMDs)
- Haemorrhages
- Hyperglycaemia/diabetes mellitus
- Interstitial lung disorder incl. pulmonary fibrosis
- Ischaemic heart disease
- Neuroleptic malignant syndrome
- Systemic lupus erythematosus
- Thrombosis/embolism
- Vasculitis

Candidate SMOs in earlier stages of development (Jan 2005)

- Cerebrovascular disorder
- Perforation, ulcer bleeding (GI)
- Pseudomembranous colitis
- Retroperitoneal fibrosis
- Serotonin syndrome
- Smell and taste disorders

Feedback requested from users

- Feedback from Phase 2 testing
 - Guidance for feedback provided on MJSO website www.meddrugsso.com
- Suggestions for new SMDs
- Comments relating to application of SMDs

Information on ՏՄՔՏ

- CIOMS web site:
www.cioms.ch /What's New
(see CIOMS publication on ՏՄՔՏ)
- ՄԿՏՕ web site:
www.meddramsso.com
- ՅՊՕ web site
www.sjp.jp/~jmo2/

Members (January 2005)

- *Regulatory Authorities:* AFSSAPS (France); BfArM (Germany); EMA (European Union); Health Canada; FDA (USA)¹; MHLW² (Japan); MHRA (United Kingdom); MPRA (Sweden); and TGA (Australia)
- *Pharmaceutical Industry:* Amgen; AstraZeneca; Aventis-Sanofi; Boehringer-Ingelheim; Bristol-Myers Squibb; Eisai; Eli-Lilly; GlaxoSmithKline; Johnson and Johnson; Novartis¹; Organon; Pfizer; Pharmacia; Roche; Schering AG, Schering-Plough and Wyeth.
- *Others:* CIOMS; Degge Group, Ltd.; Elliot Brown Consulting, Ltd.^{1,3}; IFPMA (ICH Secretariat); JPMRA; MedDRA MSSO and JMO, and WHO (Uppsala Monitoring Centre)

Notes: ¹Original Participant in the Working Group; ²Observer; ³Resigned December 2003;