Feasibility Study of MedDRA® Hierarchy Modifications
(Analysis was based on MedDRA Version 8.0)

Introduction

In response to subscribers' requests, the MSSO conducted a feasibility study on MedDRA hierarchy structure modifications. Within ICH regions, MedDRA is the standardized medical terminology for pharmaceutical industry and regulators at all phases of drug development for coding, data presentation, retrieval, and analysis. Many MedDRA users have moved from the initial implementation and focus on coding to data retrieval and analysis. The MSSO is actively involved in several activities to ensure the proper maintenance and development of MedDRA to meet the needs of the users.

Based on subscribers' inputs, the MSSO explored the possibility of modifications to MedDRA's grouping terms (i.e. HLTs and HLGTs) to improve their utility in supporting statistical analysis and reporting. The existing MedDRA rules and conventions, such as primary SOC allocation, were reviewed in this context. The following are the areas involved:

- Review "NEC" HLTs (including "NEC" HLGTs)
- Group congenital PTs and their acquired counterparts under the same HLT where applicable
- Multi-axiality of SOC *Investigations*
- Multi-axiality of SOC *Social circumstances*
- Multi-axial HLTs in Cumulative Data Output
- Primary SOC for Post Procedural Terms
- Consider whether hyper- and hypo- metabolic disorders should be under the same HLT in SOC *Metabolism and nutrition disorders*

The posted spreadsheets contain proposed MedDRA changes based on the topics listed above. The correlation between the topics and the spreadsheets are as follows:

Topic	xls	Notes on Interpretation
Review "NEC" HLTs (including "NEC" HLGTs)	#1	Further changes are planned to be performed on subscriber requests
Group congenital PTs and their acquired counterparts under the same HLT where applicable	#2	Further changes are planned to be performed on subscriber requests
Multi-axiality of SOC *Investigations*	#3	Further second allocations are planned to be performed on subscriber requests
Multi-axiality of SOC *Social*	#4	Further changes are planned to be

Topic	xls	Notes on Interpretation
circumstances		performed on subscriber requests
Multi-axial HLTs in Cumulative Data Output	#5	Further changes are planned to be performed on subscriber requests
Primary SOC for Post Procedural Terms	#6	Further changes are planned to be performed on subscriber requests

Note to Readers

- The term "disorder SOCs" used in this document refers to MedDRA SOCs that classify diseases, such as SOC *Metabolism and nutrition disorders*. The term is used to differentiate from MedDRA supporting SOCs: SOC *Investigations*, *Social circumstances* and *Surgical and medical procedures*.

- The term "anatomical SOCs" used in this document refers to a subgroup of MedDRA disorder SOCs. Each anatomical SOC classifies diseases of a specific anatomical body system, such as SOC *Cardiac disorders*, *Gastrointestinal disorders*, *Hepatobiliary disorders*, etc. The term is used to differentiate from those disorder SOCs that are based on etiology, such as SOC *Congenital, familial and genetic disorders*, *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*, and *Infections and infestations*.

1. Review "NEC" HLTs (including "NEC" HLGTs): "NEC" stands for "Not Elsewhere Classified".

- Issue1: Oversized HLT groupings
    a. 168 HLTs have 30 or more PTs
        i. 64 HLTs have 50 or more PTs

- Proposed solution1:
    a. Identify and subdivide new HLT groupings where applicable
    b. Prioritize on HLTs that
        i. Are requested by subscribers
        ii. Have 30 or more subordinate PTs in the top 5 disorder SOCs in Appendix A

    MSSO review: There are 9 NEC HLTs in the top 5 disorder SOCs (See Appendix A) that have more than 30 PTs. They are:

SOC	HLT	PT Count
General disorders and administration site conditions	General signs and symptoms NEC	94
Nervous system disorders	Neurological signs and symptoms NEC	62
Respiratory, thoracic and mediastinal disorders	Upper respiratory tract infections NEC	48
Respiratory, thoracic and mediastinal disorders	Parenchymal lung disorders NEC	36
Gastrointestinal disorders	Gastrointestinal disorders NEC	36
Nervous system disorders	Congenital and hereditary central nervous system disorders NEC	33
Respiratory, thoracic and mediastinal disorders	Laryngeal and adjacent sites disorders NEC (excl infections and neoplasms)	32
Nervous system disorders	Nervous system disorders NEC	31
Nervous system disorders	Central nervous system vascular disorders NEC	30

- Issue2: The word “NEC” does not reflect the grouped subordinate concepts explicitly

- Proposed solution2:
    a. Replace “NEC” with a more meaningful name if subordinate PTs are relatively Pure in concept
        i. Such as rename HLT Heart failures NEC to HLT Heart failures, laterality unspecified

Affected MedDRA terms under this proposal are listed in spreadsheet #1

For example, ID #A.1 (Column A):

- The proposal is to rename HLT *Abdominal wall conditions NEC* to *Abdominal condtions NEC* (Column B).
- This proposed change will affect the following existing hierarchy terms (Column D): HLT *Abdominal wall conditions NEC* and HLT *Gastrointestinal disorders NEC*.
- The proposed change occurs in SOC *Gastrointestinal disorders* (Column E).
- The rationale behind this proposal is (Column F): The change of name allows HLT *Abdominal condtions NEC* to group some abdominal PTs under HLT *Gastrointestinal disorders NEC*. This complex change is part of the effort to reduce the number of PTs under HLT *Gastrointestinal disorders NEC*, which has 36 subordinate PTs.

2. Group congenital PTs and their acquired counterpart under the same HLT where applicable

- Issue:
    a. Congenital PT and its acquired counterpart are under different HLTs in some disorder SOCs
    b. For example: in SOC *Cardiac disorders*
        HLT *Aortic valvular disorders*
            PT *Aortic valve stenosis*
        HLT *Congenital cardiac valve disorders*
            PT *Congenital aortic valve stenosis*

- Proposed solution:
    a. Group congenital and acquired terms under the same HLT in disorder SOCs
    b. For example: again in SOC *Cardiac disorders*
        HLT *Aortic valvular disorders*
            PT *Aortic valve stenosis*
            PT *Congenital aortic valve stenosis*

    c. Rationale:
        i. SOC *Congenital, familial and genetic disorders* is the primary SOC for all congenital PTs. In this SOC, congenital disorders are classified according to their anatomical appearance at the HLGT level. This SOC will remain unchanged.

        ii. Anatomical SOCs are the secondary links for congenital terms. Anatomical SOCs shall provide useful alternative groupings for congenital PTs instead of a repeating of what already provided in SOC *Congenital, familial and genetic disorders*.

        iii. The separation of congenital and non-congenital terms in anatomical SOCs makes it difficult for data presentation and data population. For instance, to study aortic valve disorders, one must search HLT *Aortic valvular disorders* and HLT *Congenital cardiac valve disorders* because congenital conditions may be included in the analysis of drug influence. It is known that some drugs worsen the symptoms of a congenital disorder or trigger the onset of a certain congenital condition.

MSSO review: identify the paired congenital and acquired concepts at the PT level in MedDRA and propose the movements.

Affected MedDRA terms are listed in spreadsheet #2

Column A: the congenital PT to be moved
Column B: the acquired PT to be moved

As an example, the first proposal is to move PT *Amblyopia congenital* (Column A) from HLT *Congenital eye disorders NEC* (Column C) to HLT *Amblyopia NEC* (Column D). Therefore, PT *Amblyopia congenital* will be grouped under the same HLT (*Amblyopia NEC*) with PT *Amblyopia* in SOC *Eye disorders*.

3. Muti-axiality of SOC *Investigations*

- Issue: No connection between laboratory test result and clinical diagnosis in MedDRA.

- Proposed solution:

  a. Allow secondary links to apply to certain PTs in SOC *Investigations*
  b. All investigation PTs are primarily linked to SOC *Investigations*
  c. Be conservative with specifically defined criteria:
     i. Only the test results that represent the diseases or diagnoses will be linked to corresponding SOCs that classify disorders
     ii. Such as PT *HIV antigen positive* (test result)
     PT *HIV infection* (diagnosis)

  d. Rationale:

     Due to the fact that many tests are contributing factors in assisting clinical diagnosis, we recommend that only those test results that represent the disease diagnosis will be secondarily linked from SOC *Investigations* to the same HLT where the diagnostic term is linked.

     For example:
     i. PT *HIV antibody positive* will be secondarily linked to HLT *Retroviral infections* and HLT *Acquired immunodeficiency syndromes* where PT *HIV infection* is grouped, but not PT *HIV antibody negative* or *HIV antibody*. Similarly, PT *Hepatitis B antigen positive* will be secondarily linked to HLT

Hepatic viral infections and HLT *Hepatitis viral infections*, but not PT *Hepatitis B antibody*.

ii. PT *Blood pressure decreased* will be secondarily linked to HLT *Vascular hypotensive disorders* where PT *Hypotension* is grouped. PT *Blood pressure decreased* will not be linked to many other disorders because they also have hypotension.

iii. PT *Protein urine present* will be secondarily linked to HLT *Urinary abnormalities* where PT *Proteinuria* is grouped.

MSSO review: The following search criteria have been applied for second linkages of Investigational terms:

- In SOC *Investigations*: query terms of serology positive, test positive, identified, antibody positive, antigen positive, increased, decreased
- In disorder SOCs: query term with suffixes: -uria, -aemia, -inosis, ytosis; prefixes: hypo-, hyper-; and some concepts such as deficiency, imbalance, abnormalities.

Based on the above search criteria, terms identified by the MSSO are listed in spreadsheet #3. Further second allocations are planned to be performed on subscriber requests.

For example, the first proposal is to link PT *Albumin urine present* (Column B) secondarily to HLT *Urinary abnormalities* (Column D) so that the laboratory test result (*Albumin urine present*) and diagnosis (*Albuminuria* in Column C) are grouped together in disorder SOC (*Renal and urinary disorders*). Column E and F are additional secondary links if applicable.

4. Multi-axiality of SOC *Social circumstances*

- Issue:
  a. Drug abuser and abuse related terms are in SOC *Social circumstances*
  b. Drug dependence related terms are in SOC *Psychiatric disorders*

- Proposed solution:
  a. Create secondary links to connect abuse and abuser PTs to HLT *Substance-related disorders* in SOC *Psychiatric disorders*

b. Rationale: Allow the concepts of abuse and dependence to be logically grouped and represented in SOC *Psychiatric disorders*.

MSSO review: The following key criteria have been applied for second links to disorder SOCs for PT terms from SOC *Social circumstances*: Use/abuse/user/dependency/dependencies/addict/addiction/disability.

The affected terms are listed in spreadsheet #4.

For example, the first proposal is to link PT *Alcoholic* (Column A) secondarily to HLT *Substance-related disorders* (Column C) so that both PT *Alcoholic* and PT *Alcoholism* (Column B) are both grouped under HLT *Substance-related disorders* in disorder SOC (*Psychiatric disorders*).

5. Multi-axial HLTs in Cumulative Data Output

- Issue:
  a. The same HLT appears in two different SOCs with different subordinate PTs
  b. Example: in an accumulative data output
     SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
     HLT *Skin neoplasms benign*
     PT *Haemangioma of skin*
     SOC *Skin and subcutaneous tissue disorders*
     HLT *Skin neoplasms benign*
     PT *Dermal cyst*

- Proposed solution:
  a. Break the multi-axiality of HLTs involved

MSSO review: Identify the multi-axial HLTs in cumulative data output when only primary path is displayed. Provide proposals to break the multi-axiality of involved HLTs.

Affected HLTs are listed in spreadsheet #5. The first column is the HLTs identified. The second column shows the current multi-axial situation. The third column shows the proposed single-axial situation.

For example, the first HLT on the list is *Haematologic neoplasms NEC* (column A). Column B – G shows the current multi-axial HLGT *Haematopoietic neoplasms (excl leukaemias and lymphomas)* and its

subordinate HLTs including HLT *Haematologic neoplasms NEC* in both Blood SOC and Neoplasm SOC. Column H – M shows the proposed changes which are adding new HLTs and HLGT so that HLT *Haematologic neoplasms NEC* will become single-axial to Blood SOC.

6. Primary SOC for Post Procedural Terms

- Issue:
    a. Post procedural events are primary to SOC Injury, poisoning and procedural complications
    b. Non procedural related events are primary to site of manifestation
    c. For example:
        i. PT *Diarrhoea* – listed under SOC *Gastrointestinal disorders* (primary linkage).
        ii. PT *Post procedural diarrhoea* – listed under SOC *Injury, poisoning and procedural complications* (primary linkage).

- Proposed solution:
    a. Change the primary SOC of post procedural PTs to site of manifestation

    MSSO review: query all post procedural PTs.

    Terms affected are listed in spreadsheet #6.

    For example, the first proposal is change the primary SOC of PT *Hypoinsulinaemia postoperative* (Column B) from SOC *Injury, poisoning and procedural complications* (Column A) to SOC *Endocrine disorders* (Column C).

7. Consider whether hyper- and hypo- element metabolic disorders shall be under the same HLT in SOC *Metabolism and nutrition disorders*

- Issue: Inconsistent scopes between related HLTs result in inconsistency in frequency analysis and incidence tables.

    For example, calcium HLTs vs HLTs of magnesium, sodium, potassium…
    a. Calcium disorders are represented by three HLTs:
        i. HLT *Calcium decreased disorders*
        ii. HLT *Calcium increased disorders*
        iii. HLT *Calcium metabolism disorders NEC*
    b. Magnesium disorders are represented by one HLT:

i. HLT *Magnesium metabolism disorders*

c. Sodium disorders are represented by one HLT:
    i. HLT *Sodium imbalance*
d. Potassium disorders are represented by one HLT:
    i. HLT *Potassium imbalance*

- Proposed action:
    a. Merge three Calcium HLTs into one HLT *Calcium metabolism disorders*.

        MSSO review: Merge three calcium HLTs.

    b. Rationale:
        i. The “increased” and “decreased” disorders are clearly distinguished at the PT level by hyper- and hypo- PTs.

        ii. In the majority of cases, to differentiate “increased” and “decreased” at the HLT level makes the HLT’s scope the same as a PT. As a result, not only the number of HLTs will increase exponentially, but also the function of HLT as a higher level grouping term is lost.

        iii. Maintain consistency at HLT level is important in analyzing MedDRA coded data. The proposed merge of three calcium HLTs will make the calcium disorder HLT consistent with other element HLTs.

Appendix A: The frequency of reported SOCs
(Based on published FDA AERS data, first three quarters of 2004)

SOC	Count	Percentage
General disorders and administration site conditions	110379	13.6%
Investigations	88274	10.9%
Nervous system disorders	84362	10.4%
Gastrointestinal disorders	69189	8.5%
Psychiatric disorders	54811	6.8%
Respiratory, thoracic and mediastinal disorders	42966	5.3%
Injury, poisoning and procedural complications	40558	5.0%
Infections and infestations	37934	4.7%
Cardiac disorders	37594	4.6%
Musculoskeletal and connective tissue disorders	36033	4.4%
Skin and subcutaneous tissue disorders	35552	4.4%
Vascular disorders	21552	2.7%
Metabolism and nutrition disorders	21254	2.6%
Blood and lymphatic system disorders	18593	2.3%
Renal and urinary disorders	18226	2.2%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16146	2.0%
Eye disorders	15096	1.9%
Hepatobiliary disorders	13600	1.7%
Reproductive system and breast disorders	12553	1.5%
Surgical and medical procedures	8368	1.0%
Pregnancy, puerperium and perinatal conditions	6736	0.8%
Immune system disorders	6430	0.8%
Social circumstances	5480	0.7%
Ear and labyrinth disorders	4026	0.5%
Congenital, familial and genetic disorders	2772	0.3%
Endocrine disorders	1953	0.2%