Blue Ribbon Panel Discussion Points

Proposed HLGT and HLT Hierarchical Changes to Improve MedDRA's Ability to Support Data Analysis

(Examples are based on MedDRA Version 9.1)

1. INTRODUCTION

In 2004, the MSSO received feedback from the MedDRA user community regarding the terminology hierarchy groupings, such as the ambiguity of "NEC" naming, the confusion of multi-axial HLTs in the cumulative data output, the possible alternative secondary groupings for congenital PTs to aid data analysis, and the difficulties in analyzing signs and symptoms (*e.g.*, diarrhea, rash)[1].

In early 2005, in response to subscribers' requests, the MSSO conducted a feasibility study on MedDRA hierarchy structure modifications to improve its utility in supporting statistical analysis and reporting[2]. The existing MedDRA rules and conventions, such as primary SOC allocation, were reviewed in this context. The following are the areas involved and proposals made by the MSSO:

- Proposal 1: Review "NEC" HLTs and HLGTs (Note: "NEC" stands for "not elsewhere classified;" only HLTs and HLGTs in MedDRA may contain "NEC" as part of the term text.)
  - Explore alternative namings for clearer indication of their content
  - Review large sized HLT groupings for possible reduction of the number of subordinate PTs by building subgroupings
- Proposal 2: Group PTs representing congenital disorders and their acquired counterparts to the same HLT where applicable
- Proposal 3: Allow multi-axiality of SOC *Investigations*
- Proposal 4: Allow multi-axiality of SOC *Social circumstances*
- Proposal 5: Eliminate multi-axial HLTs (meaning an HLT shows in more than one SOC) in cumulative data outputs when only the primary paths are displayed
- Proposal 6: Change primary SOC for post procedural terms. Should it be SOC *Injury, poisoning and procedural complications* or should it be the site of manifestation SOC?
- Proposal 7: Consider whether hyper- and hypo- metabolic disorders should be under the same HLT in SOC *Metabolism and nutrition disorders*

Based on feedback from the user community, the MedDRA Management Board directed the MSSO to implement proposal 2 and 7 in Version 9.0. Proposal 6 was rejected by the Board based on subscriber comments. The remaining proposals were deferred to this Blue Ribbon Panel for discussion.

Therefore, the focus of this BRP is as follows:

- Review “NEC” HLTs and HLGTs
  - Explore alternative namings for clearer indication of their content
  - Review large sized HLT groupings for possible reduction of the number of subordinate PTs by building subgroupings
- Allow multi-axiality of SOC *Investigations*
- Allow multi-axiality of SOC *Social circumstances*
- Eliminate multi-axial HLTs (meaning an HLT shows in one than SOC) in cumulative data outputs when only the primary path is displayed

2. POTENTIAL MEDDRA HIERARCHY MODIFICATIONS

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” such as SOC *Investigations*, SOC *Social circumstances*, and SOC *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*, SOC *Gastrointestinal disorders*, SOC *Hepatobiliary disorders*, etc. The term is used to differentiate these from disorder SOCs that are based on etiology, such as SOC *Congenital, familial and genetic disorders*, SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*, and SOC *Infections and infestations*.

2.1 REVIEW “NEC” HLTS AND HLGTS

2.1.1 Issues with “NEC” HLTs and HLGTs

There are two issues regarding “NEC” HLT and HLGT groupings:

- The acronym “NEC” is not intuitive. It does not reflect the grouped subordinate concepts explicitly.
- Oversized “NEC” HLTs:

  The MSSO has received feedback from subscribers that analyzing HLTs with a large number of subordinate PTs proves challenging at times. An MSSO survey[1], which was conducted during the time of the feasibility study, indicated that subscribers generally understood that certain groupings at the HLT and HLGT levels are large because of the nature of the MedDRA terminology.

  Based on our analysis using 50 subordinate PTs as the dividing line (arbitrary), there are 46 HLTs containing more than 50 PTs:

  - 31 out of 46 HLTs are in SOC *Investigations*. A large number of PTs within an HLT in SOC *Investigations* is common because each term for an investigation in this SOC is accompanied by several terms for the qualitative results of that test. For example, PT *Blood glucose* is accompanied by another six PTs for test results of normal (PT *Blood glucose normal*), abnormal (PT *Blood glucose abnormal*), etc.
  - 15 other HLTs involve the following non-SOC *Investigations*
    - SOC *General disorders and administration site conditions*
    - SOC *Infections and infestations*

- SOC *Injury, poisoning and procedural complications*
- SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
- SOC *Nervous system disorders*
- SOC *Surgical and medical procedures*

2.1.2 Implementation Options

- "NEC" naming: Replace "NEC" with a more meaningful name if subordinate PTs are relatively "pure" in concept, for example:
  - Rename HLT *Heart failures NEC* to HLT *Heart failures, laterality unspecified*

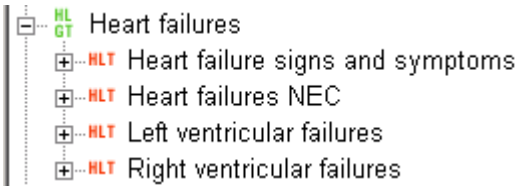


Figure 2-1. Current HLTs linked to HLGT *Heart failures*

  - Rename HLT *Headaches NEC* to HLT *Non-migraine headaches*

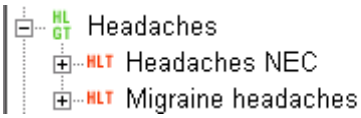


Figure 2-2. Current HLTs linked to HLGT *Headaches*

It is also proposed that "NEC" will not be eliminated from MedDRA because a miscellaneous grouping is needed at the HLT and HLGT level per the original pragmatic design of MedDRA. Therefore, this proposal is intended to be applied wherever it is appropriate.

- Large HLT groupings: Eight of 15 non-SOC *Investigations* HLTs are "NEC" HLTs (Table 2-1). It is possible to review and identify new and specific sub-groupings from these "NEC" HLTs to reduce their current size per the proposal outlined above.

Count of PTs	HLT	HLGT	SOC
172	Therapeutic procedures NEC	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
123	Bacterial infections NEC	Bacterial infectious disorders	Infections and infestations

Count of PTs	HLT	HLGT	SOC
102	Injection and infusion site reactions	Administration site reactions	General disorders and administration site conditions
75	Infections NEC	Infections - pathogen class unspecified	Infections and infestations
74	Viral infections NEC	Viral infectious disorders	Infections and infestations
73	Non-site specific procedural complications	Procedural and device related injuries and complications NEC	Injury, poisoning and procedural complications
70	General signs and symptoms NEC	General system disorders NEC	General disorders and administration site conditions
69	Fungal infections NEC	Fungal infectious disorders	Infections and infestations
61	Prophylactic procedures NEC	Therapeutic procedures and supportive care NEC	Surgical and medical procedures
61	Metastases to specified sites	Metastases	Neoplasms benign, malignant and unspecified (incl cysts and polyps)
59	Implant and catheter site reactions	Administration site reactions	General disorders and administration site conditions
55	Central nervous system haemorrhages and cerebrovascular accidents	Central nervous system vascular disorders	Nervous system disorders
55	Therapeutic and nontherapeutic responses	Therapeutic and nontherapeutic effects (excl toxicity)	General disorders and administration site conditions
53	Application and instillation site reactions	Administration site reactions	General disorders and administration site conditions
50	Non-site specific injuries NEC	Injuries NEC	Injury, poisoning and procedural complications

Table 2-1. Non-SOC *Investigations* HLTs (All SOCs represent the primary SOC allocation)

Question #1 to Panel:

Should the MSSO implement these changes?

If so, which SOC(s) should take the priority in implementing this action? Note that the MSSO has referenced FDA data on the frequency of reported adverse events by SOC; these are presented in Table Appendix A-1. Should the MSSO use these data to determine the priority order of SOCs to be addressed?

Is a maximum of 50 PTs linked to a single HLT appropriate?

2.2 ALLOW MUTI-AXIALITY OF SOC *Investigations*

2.2.1 Issue With the Multi-axiality of SOC *Investigations*

Based on current MedDRA rules, SOC *Investigations* is currently non-multi-axial. In other words, the terms within SOC *Investigations* (e.g., laboratory findings, physiologic testing findings, radiologic findings, etc.) do not have multi-axial links to the potentially corresponding diagnoses terms in the disorder SOCs. For example, PT *Platelet count decreased* (SOC *Investigations*) has no axial link to PT *Thrombocytopenia* in SOC *Blood and lymphatic system disorders*.

2.2.2 Implementation Options

- SOC *Investigations* could remain **non**-multi-axial for the following reasons:
  - Many investigation results are contributing factors in assisting clinical diagnosis and do not directly lead to the diagnosis.
  - The ICH M1 Expert Working Group (EWG), which constructed MedDRA on behalf of ICH had discussions regarding possible SOC *Investigations* secondary linkages. The outcome was to leave it non-multi-axial because there is not always a direct relationship between a particular investigation result and a diagnosis. For example, elevated serum potassium could be due to exogenous sources of potassium, associated with acidosis, or due to kidney disease.
  - Investigation results are frequently non-specific. For example, an elevated transaminase (AST/ALT) could be interpreted as either a level of enzyme that has risen but is still within normal range; or it may indicate possible hepatocellular injury caused by diverse etiologies represented by terms in SOC *Hepatobiliary disorders* (e.g., alcohol, chronic viral hepatitis, autoimmune hepatitis, hepatic steatosis); or it may be elevated in conditions represented by terms in other SOCs such as myocardial infarction (SOC *Cardiac disorders*). As a result, attempting to add secondary links for investigation results to the related diagnostic HLTs in other SOCs could potentially lead to a large number of secondary links to a test result. This could cause conflict with the MedDRA placement rule that obligates a PT to have only one HLT link per SOC. Also, unlimited numbers of secondary links for certain laboratory terms might complicate data presentation and analysis, especially when using a secondary SOC analysis.
- Add secondary links to **certain** investigation results
  - All investigation PTs are primarily linked to SOC *Investigations*
  - Allow secondary links to apply to certain PTs in SOC *Investigations*
  - Be conservative by applying specifically defined criteria:

- Investigation results that could **only** represent the specific disease or diagnosis would be linked to the corresponding disorder SOCs. For example, PT *HIV antigen positive* (investigation result) would be linked together with PT *HIV infection* (diagnosis).

- Rationale:
  - Since many investigation results assist in clinical diagnosis, only those investigation results that represent the disease or diagnosis will be secondarily linked from SOC *Investigations* to the same HLT where the diagnostic term is linked. This criterion is proposed to avoid uncontrollable secondary links to an investigation result.
  - Example 1: PT *HIV antibody positive* would be secondarily linked to HLT *Retroviral infections* and HLT *Acquired immunodeficiency syndromes* where PT *HIV infection* is grouped, but PT *HIV antibody negative* and PT *HIV antibody* would not be linked. Similarly, PT *Hepatitis B antigen positive* will be secondarily linked to HLT *Hepatic viral infections* and HLT *Hepatitis viral infections*, but PT *Hepatitis B antibody* would not be.
  - Example 2: PT *Protein urine present* would be secondarily linked to HLT *Urinary abnormalities* where PT *Proteinuria* is grouped.
- Pros:
  - Allows easy retrieval of diagnosis and test results representing the diagnosis from the same HLT in the disorder SOCs
- Cons:
  - Indirect (non-specific) or contributing investigation results would still need to be retrieved separately from SOC *Investigations*.
  - A large number of PTs could be linked to an HLT. For example, in Figure 2-3, the number of PTs linked to HLT *Hepatic viral infections* is increased from 19 to 42 to include hepatitis related antibody and antigen investigation results.
  - That multi-axiality would not be applied to all investigation results leads to some degree of inconsistency. Based on this conservative approach, liver function test terms such as PT *Alanine aminotransferase increased* and PT *Aspartate aminotransferase increased* would not be linked despite being relevant diagnostic test results.
  - Although this approach groups the investigation results and the diagnosis under the same HLT, it does not provide direct associations between the associated PT concepts. As shown in Figure 2-3, PT *Hepatitis B antigen* positive is linked under HLT *Hepatic viral infections* in SOC *Hepatobiliary disorders*. But one still needs to associate this investigation result to an associated

diagnosis such as PT *Congenital hepatitis B infection* or PT *Hepatitis B*.

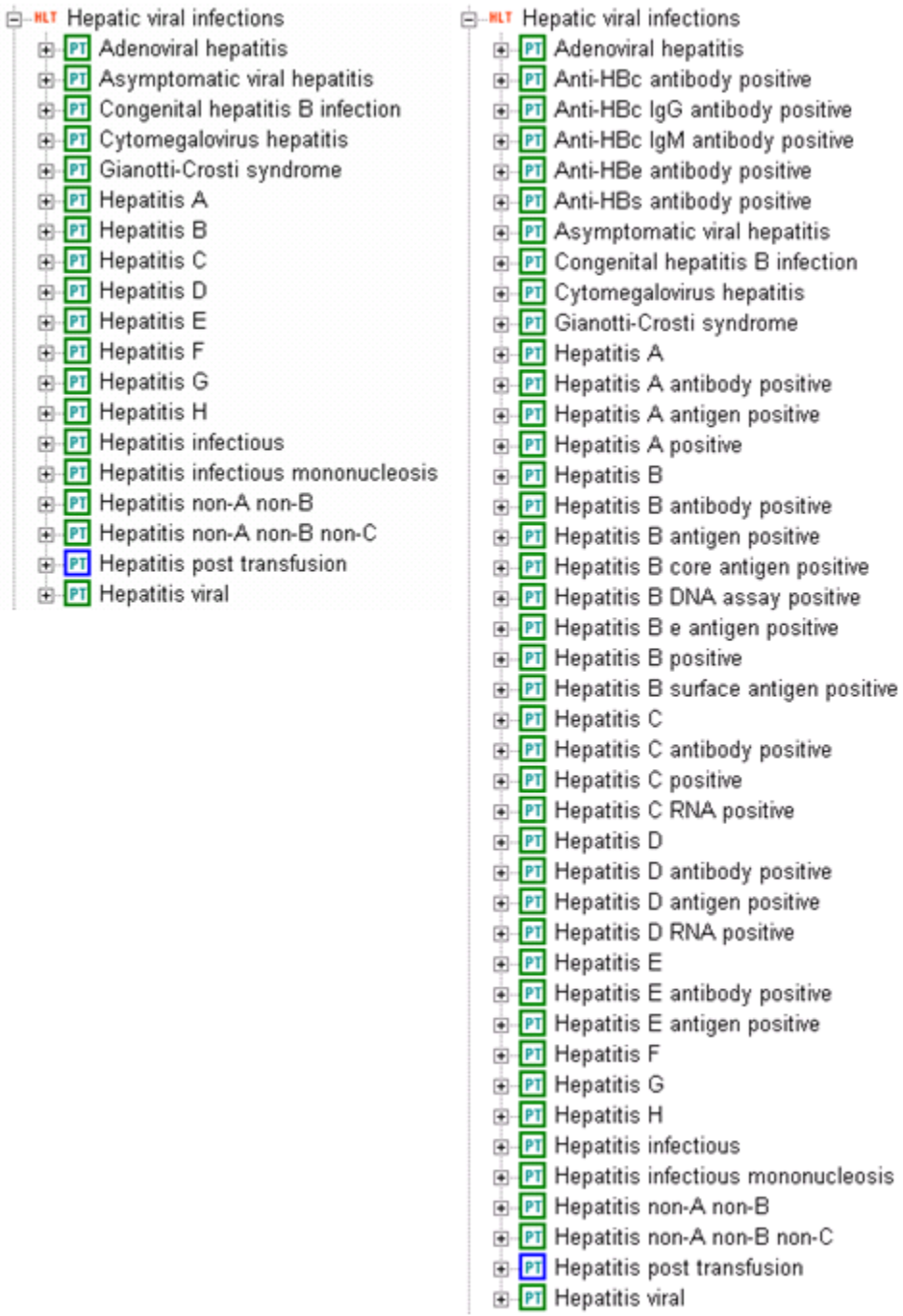


Figure 2-3. PTs subordinate to HLT *Hepatic viral infections* before and after the investigation results are linked

Question #2 to the Panel:

Should SOC *Investigations* be left as is or made multi-axial?

If yes to the multi-axial option, does the Panel support the MSSO's proposed criteria for creating secondary links for investigation results?

If neither approach is ideal, should the MSSO consider a non-conventional proposal to solve this issue (see section 2.2.3)?

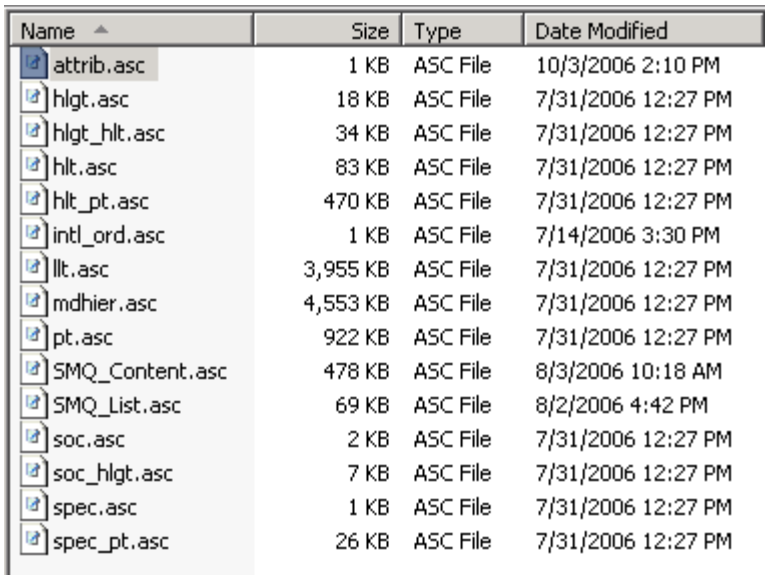
2.2.3 The Concept Property – "Is a diagnostic test for"

Would it be helpful to MedDRA users if a property attribute relationship is created outside of the MedDRA hierarchy to connect the associated concepts? A "property attribute relationship" refers a relation or linkage in addition to hierarchy that helps to define the concept of interest.

For investigation results, this property attribute would be called "Is a diagnostic test for" as suggested by Corneliu Henegar, *et al*.[3] For example, both PT *Alanine aminotransferase increased* and PT *Aspartate aminotransferase increased* would have the "Is a diagnostic test for" relationship with the diagnosis term PT *Hepatitis A*.

2.2.3.1 "attrib.asc" File

The "Is a diagnostic test for" relationship could be implemented in an additional ascii file called "attrib.asc". Having this property in a file separate and external to the 14 "traditional" MedDRA ascii files assures that the current MedDRA hierarchy groupings and distributed ascii files (Figure 2-4) are not impacted; in other words, a user can opt not to use the "attrib.asc" files. The resulting list of distributed MedDRA ascii files is shown in Figure 2-4, and the "attrib.asc" file format is shown in Figure 2-5.



Name	Size	Type	Date Modified
attrib.asc	1 KB	ASC File	10/3/2006 2:10 PM
hlgt.asc	18 KB	ASC File	7/31/2006 12:27 PM
hlgt_hlt.asc	34 KB	ASC File	7/31/2006 12:27 PM
hlt.asc	83 KB	ASC File	7/31/2006 12:27 PM
hlt_pt.asc	470 KB	ASC File	7/31/2006 12:27 PM
intl_ord.asc	1 KB	ASC File	7/14/2006 3:30 PM
llt.asc	3,955 KB	ASC File	7/31/2006 12:27 PM
mdhier.asc	4,553 KB	ASC File	7/31/2006 12:27 PM
pt.asc	922 KB	ASC File	7/31/2006 12:27 PM
SMQ_Content.asc	478 KB	ASC File	8/3/2006 10:18 AM
SMQ_List.asc	69 KB	ASC File	8/2/2006 4:42 PM
soc.asc	2 KB	ASC File	7/31/2006 12:27 PM
soc_hlgt.asc	7 KB	ASC File	7/31/2006 12:27 PM
spec.asc	1 KB	ASC File	7/31/2006 12:27 PM
spec_pt.asc	26 KB	ASC File	7/31/2006 12:27 PM

Figure 2-4. MedDRA ascii files (including attrib.asc)

```
10001551$Is a diagnostic test for$10019719$
10003481$Is a diagnostic test for$10019719$
10005287$Is a diagnostic test for$10019719$
10059570$Is a diagnostic test for$10019719$
10005364$Is a diagnostic test for$10019719$
10019725$Is a diagnostic test for$10019719$
10058751$Is a diagnostic test for$10019719$
10057398$Is a diagnostic test for$10019719$
10001551$Is a diagnostic test for$10009208$
10001565$Is a diagnostic test for$10009208$
10003481$Is a diagnostic test for$10009208$
10005287$Is a diagnostic test for$10009208$
10003481$Is a diagnostic test for$10028596$
10005474$Is a diagnostic test for$10028596$
10005630$Is a diagnostic test for$10028596$
10014391$Is a diagnostic test for$10028596$
10014392$Is a diagnostic test for$10028596$
10014395$Is a diagnostic test for$10028596$
10028625$Is a diagnostic test for$10028596$
10058268$Is a diagnostic test for$10028596$
10058267$Is a diagnostic test for$10028596$
10058269$Is a diagnostic test for$10028596$
```

Figure 2-5. attrib.asc file format

2.2.3.2 Utilities of the Attribute File

The “attrib.asc” file provides the connection between diagnosis and diagnostic test results within MedDRA. This attribute feature not only provides the list of diagnostic tests associated with a particular diagnosis (Figure 2-6, top), but also

provides the list of diagnoses related to a certain investigation result (Figure 2-6, bottom).

Test result	Relationship	Diagnosis
Alanine aminotransferase increased	Is a diagnostic test for	Hepatitis A
Aspartate aminotransferase increased	Is a diagnostic test for	Hepatitis A
Blood albumin decreased	Is a diagnostic test for	Hepatitis A
Blood alkaline phosphatase increased	Is a diagnostic test for	Hepatitis A
Blood bilirubin increased	Is a diagnostic test for	Hepatitis A
Hepatitis A antibody positive	Is a diagnostic test for	Hepatitis A
Hepatitis A antigen positive	Is a diagnostic test for	Hepatitis A
Hepatitis A positive	Is a diagnostic test for	Hepatitis A
Alanine aminotransferase increased	Is a diagnostic test for	Cirrhosis alcoholic
Albumin globulin ratio decreased	Is a diagnostic test for	Cirrhosis alcoholic
Aspartate aminotransferase increased	Is a diagnostic test for	Cirrhosis alcoholic
Blood albumin decreased	Is a diagnostic test for	Cirrhosis alcoholic
Aspartate aminotransferase increased	Is a diagnostic test for	Myocardial infarction
Blood creatine phosphokinase MB increased	Is a diagnostic test for	Myocardial infarction
Blood lactate dehydrogenase increased	Is a diagnostic test for	Myocardial infarction
Electrocardiogram ST segment depression	Is a diagnostic test for	Myocardial infarction
Electrocardiogram ST segment elevation	Is a diagnostic test for	Myocardial infarction
Electrocardiogram T wave inversion	Is a diagnostic test for	Myocardial infarction
Myoglobin blood increased	Is a diagnostic test for	Myocardial infarction
Troponin I increased	Is a diagnostic test for	Myocardial infarction
Troponin increased	Is a diagnostic test for	Myocardial infarction
Troponin T increased	Is a diagnostic test for	Myocardial infarction

Test result	Relationship	Diagnosis
Alanine aminotransferase increased	Is a diagnostic test for	Cirrhosis alcoholic
Alanine aminotransferase increased	Is a diagnostic test for	Hepatitis A
Aspartate aminotransferase increased	Is a diagnostic test for	Cirrhosis alcoholic
Aspartate aminotransferase increased	Is a diagnostic test for	Hepatitis A
Aspartate aminotransferase increased	Is a diagnostic test for	Myocardial infarction
Blood albumin decreased	Is a diagnostic test for	Cirrhosis alcoholic
Blood albumin decreased	Is a diagnostic test for	Hepatitis A

Figure 2-6. Utilities of "Is a diagnostic test for" relationship

2.3 ALLOW MULTI-AXIALITY OF SOC *Social circumstances*

2.3.1 Issue With Multi-axiality of SOC *Social circumstances*

The purpose of SOC *Social circumstances* is for encoding patient social history or background. It provides a grouping for social factors that may give insight into personal issues that could have an effect on the event being reported. The MedDRA Introductory Guide states that "SOC *Social circumstances* contains information about the person, not the adverse event. As an example, terms such as PT *Drug addict* and PT *Death of spouse* are found in this SOC, whereas their respective disorder terms such as LLT *Drug addiction* and PT *Death* are found in SOC *Psychiatric disorders* and SOC *General disorders and administration site conditions*, respectively." However, "some terms currently contained within this SOC are the only option for capturing certain ADR/AEs." – "MedDRA Term Selection: Points to Consider" Release 3.6, section 3.17

Some terms linked to HLT *Drug and chemical abuse* in SOC *Social circumstances* are closely related to a corresponding relevant psychologic condition. For example:

- Drug "abuser" and "abuse" related terms are in SOC *Social circumstances* (Figure 2-4)
- Drug "dependence" related terms are in SOC *Psychiatric disorders* (Figure 2-4)

Depending on the wording in the ADR/AE report, the coded MedDRA term could be in SOC *Social circumstances* if the wording is "drug abuse" or in SOC *Psychiatric disorders* if the wording is "drug dependence." This makes analysis difficult. On this issue, the guidelines from "MedDRA Term Selection: Points to Consider" Release 3.6 states in section 3.17 that "This SOC contains terms that are similar to terms in the disorder SOCs. Users should be aware of the impact that use of these terms will have on data retrieval, data analysis, and reporting."

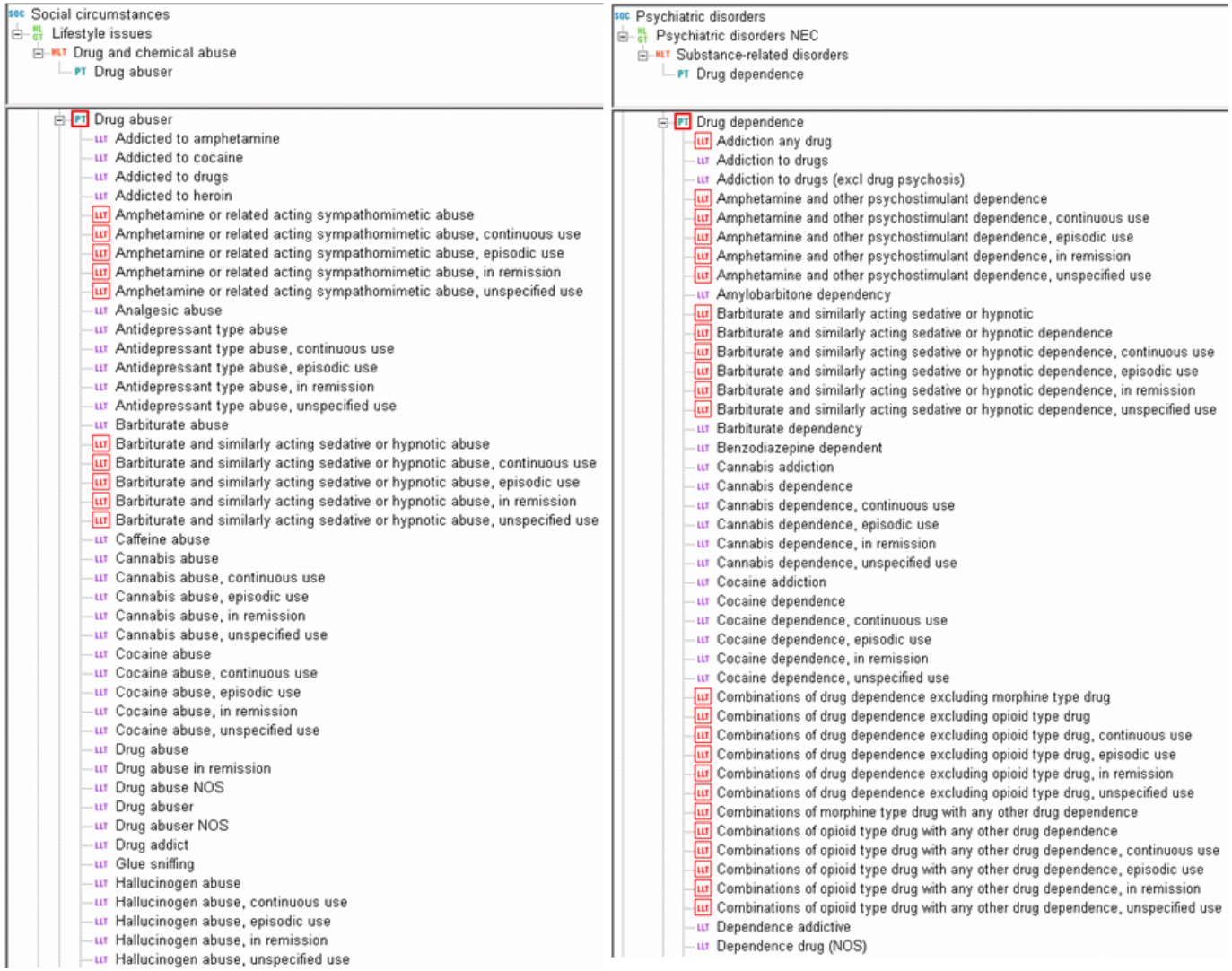


Figure 2-7. "Abuse" and "Dependence" terms

2.3.2 Implementation Options

- Since the involved terms are isolated within a single HLT and movement of these terms would not drastically alter SOC *Social circumstances,* it is proposed to move the "abuse" terms from SOC *Social circumstances* to SOC *Psychiatric disorders*. This would resolve the current disconnection between the "abuse" terms in SOC *Social circumstances* and "dependence" terms in SOC *Psychiatric disorders*.
- If the move proposal is not agreeable, creating secondary links for SOC *Social circumstances* to connect "abuse" and "abuser" PTs to HLT *Substance-related disorders* in SOC *Psychiatric disorders* allows the concepts of "abuse" and "dependence" to be logically grouped and represented in SOC *Psychiatric disorders*.

Question #3 to the Panel:

Should "abuse" terms be moved to SOC *Psychiatric disorders*?

OR should SOC *Social circumstances* be made multi-axial?

2.4 ELIMINATE MULTI-AXIAL HLTS IN CUMULATIVE DATA OUTPUT

2.4.1 Issue With the Multi-axial HLTs in Cumulative Data Output

In the cumulative data output when only primary paths are displayed, a few HLTs appear in two different SOCs with different subordinate PTs.

As shown in Figure 2-5, the HLT groupings for “Skin neoplasms benign” in both SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* and SOC *Skin and subcutaneous tissue disorders* have the same number of PTs when both primary and secondary PTs are listed.

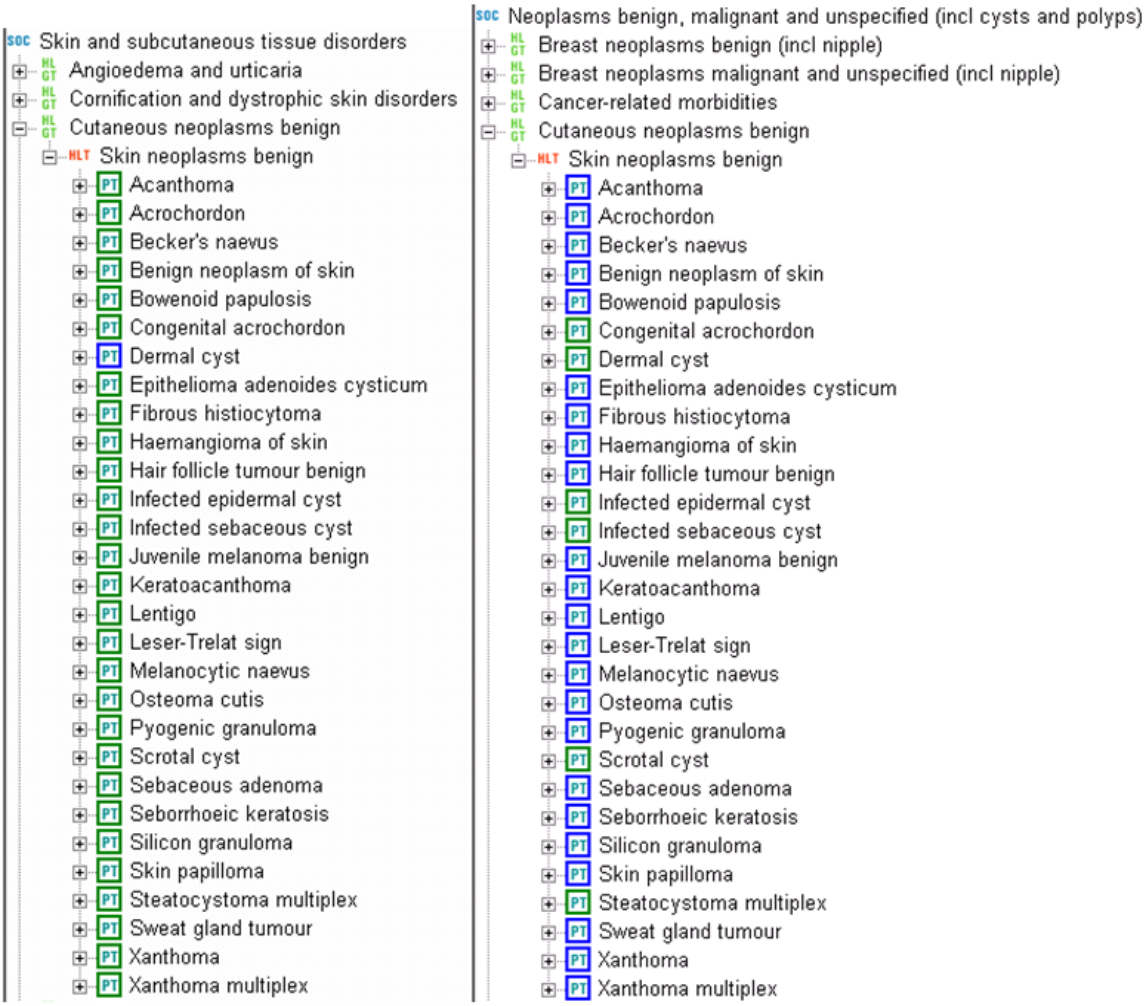


Figure 2-8. PTs under HLT *Skin neoplasms benign*

However, in the primary SOC view, only the “blue” PTs are listed under HLT *Skin neoplasms benign*. In this case, users are confused by why the same HLT name represents one PT in SOC *Skin and subcutaneous tissue disorders* and another set of PTs in SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*.

2.4.2 Implementation Option

Eliminate multi-axiality of the involved HLTs by renaming the groupings. For example, regarding HLT *Skin neoplasms benign*:

- The HLGT and HLT names in SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)* would remain unchanged
- The HLGT name in SOC *Skin and subcutaneous tissue disorders* would be changed to HLGT *Benign cutaneous neoplasms*
- The HLT name in SOC *Skin and subcutaneous tissue disorders* would be changed to HLT *Benign skin neoplasms*

When two HLTs contain the same PTs (primary and secondary), a "lexical variant" approach (e.g., "Skin neoplasms benign" vs. "Benign skin neoplasms" in the above example) would be used in their naming to indicate that these two grouping have the same scope. The "lexical variants" then allow for proper placement in MedDRA.

Question #4 to Panel:

Should this proposal (elimination of multi-axial HLTs by a renaming approach) be implemented?

If so, should multi-axiality be eliminated from all HLTs and HLGTs because the same problem could occur again as long as there are still multi-axial HLTs?

3. Reference

(1) J Kübler, R Vonk, S Beimel, et al. Adverse event analysis and MedDRA: business as usual or challenge? **Drug Information J.** 2005:39:63–72.

(2) A Zhao-Wong, E. Rump, T. Moraleda, P. Mozzicato, P. Revelle, “Proposed Terminology Changes to Facilitate the Analysis of MedDRA-coded Data” **Drug Information J.** 2006:40:291-303

(3)C Henegar, C Bousquet, A Louët, P Degoulet M Jaulent, “Building an ontology of adverse drug reactions ofr automated signal generation in pharmacovigilance” Computers in Biology and Medicine, April 2005 (http://www.intl.elsevierhealth.com/journals/cobm/)

Appendix A FDA FOI Data Analysis

Data from the first three quarters of 2005 FDA AERS data published through FOI (Freedom of Information) were used to generate the following frequency table.

SOC Name	Count	Percentage
General disorders and administration site conditions	186320	13.8%
Nervous system disorders	146170	10.8%
Investigations	130714	9.7%
Gastrointestinal disorders	112092	8.3%
Psychiatric disorders	89432	6.6%
Cardiac disorders	88039	6.5%
Injury, poisoning and procedural complications	69687	5.2%
Respiratory, thoracic and mediastinal disorders	68952	5.1%
Musculoskeletal and connective tissue disorders	63932	4.7%
Infections and infestations	61670	4.6%
Skin and subcutaneous tissue disorders	54287	4.0%
Vascular disorders	39553	2.9%
Metabolism and nutrition disorders	35108	2.6%
Renal and urinary disorders	29548	2.2%
Blood and lymphatic system disorders	28658	2.1%
Eye disorders	27053	2.0%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25728	1.9%
Hepatobiliary disorders	20265	1.5%
Surgical and medical procedures	17640	1.3%
Reproductive system and breast disorders	11620	0.9%
Immune system disorders	10411	0.8%
Social circumstances	8477	0.6%
Pregnancy, puerperium and perinatal conditions	8085	0.6%
Ear and labyrinth disorders	6233	0.5%
Congenital, familial and genetic disorders	4913	0.4%
Endocrine disorders	3207	0.2%

Table Appendix A-1. The Frequency of SOCs Representing Reported Adverse Events