Blue Ribbon Panel on Proposed HLGT/HLT Changes to Improve MedDRA Data Analysis

16 November 2006
Ingelheim, Germany

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Agenda

0900 – Welcome and Introduction
0915 – Review “NEC” HLTs and HLGTs
1045 – Break
1100 – Multi-Axiality of SOC Investigations
1230 – Lunch
1330 – Multi-Axiality of SOC Social circumstances
1500 – Break
1515 – Eliminate Multi-Axial HLTs in Cumulative Data Output
1600 – Break
1615 – Review of Recommendations of BRP; Q&A
1700 – Meeting adjourned
Introduction

• Logistics
• Purpose/background of BRPs
• Roles and Responsibilities
  – Panelists
  – Observers
  – MSSO
• Introduction of Panel members
Participants

• Panelists:
  – Gottfried Kreutz (CIOMS)
  – Jürgen Kübler (EU Industry/Subject Expert)
  – Reiji Tezuka (Japan)
  – George Rochester (US regulator)
  – Greg Gribko (US Industry)

• Moderators:
  – Anna Zhao-Wong
  – Eva Rump
Review “NEC” HLTs and HLGTs
“NEC” Is Not Intuitive

- The acronym “NEC” is not intuitive, i.e., it does not reflect grouped subordinate concepts explicitly.
Proposed Changes

• Explore alternative naming convention to convey content more clearly
  – Replace “NEC” with a more meaningful name if subordinate PTs are relatively “pure”
    • E.g., Rename HLT Heart failures NEC to HLT Heart failures, laterality unspecified
  – Only “where applicable”
    • HLT/HLGT groupings for “miscellaneous” PTs may always be needed
Oversized “NEC” HLTs

- Analyzing MedDRA coded data by HLTs with large numbers of subordinate PTs proves to be challenging at times.
- Based on our analysis using 50 PTs as dividing line (arbitrary), there are 46 HLTs (3%) containing $\geq 50$ PTs.
Oversized “NEC” HLTs (cont)

• Among the 46 HLTs with \( \geq 50 \) PTs:
  – 31 HLTs are in SOC *Investigation*
  – Among the 15 non-investigation HLTs:
    • Many of them (8) are “NEC” ones
## Oversized “NEC” HLTs (cont)

<table>
<thead>
<tr>
<th>Count of PTs</th>
<th>HLT</th>
<th>HLGT</th>
<th>SOC</th>
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</thead>
<tbody>
<tr>
<td>172</td>
<td>Therapeutic procedures NEC</td>
<td>Therapeutic procedures and supportive care NEC</td>
<td>Surgical and medical procedures</td>
</tr>
<tr>
<td>123</td>
<td>Bacterial infections NEC</td>
<td>Bacterial infectious disorders</td>
<td>Infections and infestations</td>
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<tr>
<td>75</td>
<td>Infections NEC</td>
<td>Infections - pathogen class unspecified</td>
<td>Infections and infestations</td>
</tr>
<tr>
<td>74</td>
<td>Viral infections NEC</td>
<td>Viral infectious disorders</td>
<td>Infections and infestations</td>
</tr>
<tr>
<td>70</td>
<td>General signs and symptoms NEC</td>
<td>General system disorders NEC</td>
<td>General disorders and administration site conditions</td>
</tr>
<tr>
<td>69</td>
<td>Fungal infections NEC</td>
<td>Fungal infectious disorders</td>
<td>Infections and infestations</td>
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<tr>
<td>61</td>
<td>Prophylactic procedures NEC</td>
<td>Therapeutic procedures and supportive care NEC</td>
<td>Surgical and medical procedures</td>
</tr>
<tr>
<td>50</td>
<td>Non-site specific injuries NEC</td>
<td>Injuries NEC</td>
<td>Injury, poisoning and procedural complications</td>
</tr>
</tbody>
</table>

**Count of PTs**: Count of Post-Termination (PT) Events. **HLT**: High Level Term. **HLGT**: High Level Group Term. **SOC**: System Organ Class.
Proposed Changes

• Review oversized HLTs and possibly reduce the number of subordinate PTs by building new HLTs, for example
  – HLT *Therapeutic procedures NEC*
    • New HLT *Physiotherapeutic procedures*
    • New HLT *Drug therapies*
    • New HLT *Naturopathic procedures*
User Feedback

• Support the proposed concept or idea
• Large number of subordinate PTs is OK if the HLT group is specific and medically meaningful
• Rename NEC HLTs where possible but keep NEC if not possible
• Opinions are different on which HLTs should change and how to change them
• It is necessary to make implementation schedule
Panel Discussion

• Should MSSO review and implement these changes if and where applicable?
  – if yes; which SOCs should take priority?

• Is a maximum of 50 PTs to a single HLT appropriate?
  – if no, can the panel recommend an appropriate number of PTs?
Multi-Axiality for SOC Investigations
Single Axial SOC

- **SOC Investigations** is a single axial SOC

**SOC**
- Hepatobiliary disorders

**HLGT**
- Hepatic and hepatobiliary disorders
  - Hepatobiliary investigations

**HLT**
- Cholestasis and jaundice
  - Liver function analyses
- Hepatic viral infections
- Hepatocellular damage and hepatitis NEC

**PT**
- Jaundice
- Hepatitis A
- Hepatitis alcoholic
- Alanine aminotransferase increased
Proposed Change: Multi-Axiality of SOC Investigations

- MedDRA rules required:
  - Primary SOC allocation
  - One PT can only be linked to one SOC through one path

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(Yes) (No) (No)
Proposed Change: Multi-Axiality of SOC Investigations (cont)

• Proposed conventions:
  – All investigation PTs would be primarily linked to SOC Investigations
  – Apply secondary links to investigation results that meet the following criterion:
    • Investigation results that could only represent the specific disease or diagnosis (pathognomonic)
  – Example:
    • PT *Hepatitis A antigen positive* – Yes. Multiaxial to SOC Hepatobiliary disorders
    • PT *Alanine aminotransferase increased* – No.
Potential Consequence of Proposed Changes
User Feedback

- Although the secondary links help, incompleteness would jeopardize the good intention of this proposal.
- Not happy with some proposed secondary links, such as
  - Link PT *Blood pressure decreased* to HLT *Vascular hypotensive disorders*
Panel Discussion

• Should SOC *Investigations* be left as is or made multi-axial?
• If yes to the multi-axial question, does the Panel support the proposed criteria for creating secondary links for investigation results?
A Different Option

SOC

HLGT

HLT

PT

Hepatobiliary disorders

Hepatic and hepatobiliary disorders

Investigations

Hepatobiliary investigations

Cholestasis and jaundice

Hepatic viral infections

Hepatocellular damage and hepatitis NEC

Liver function analyses

Jaundice

Hepatitis A

Hepatitis alcoholic

Alanine aminotransferase increased

Attributes:

Is a diagnostic test result for
A Different Option (cont)

- The same result can be achieved by adding attributes to investigation terms
- Attributes provide medical information about a term
  - For example, investigation terms could include the attribute “Is a diagnostic test for”
Concept Attribute

- Concept attributes are handled by an additional file – "attrib.asc"
• Concept attributes are handled by an additional file – “attrib.asc” (cont)
User Feedback

- Only received two comments
- Helpful to smaller users where there isn't instant access to a physician
- Not agree
  - Difficult to understand
  - Require significant amount of time and effort
Panel Discussion on Concept Attribute
Multi-Axiality for SOC Social circumstances
Issue with Terms in SOC Social circumstances

- The “lifestyle” terms, LLT Drug addict, LLT Drug abuse are in SOC Social circumstances

- The corresponding psychiatric conditions, e.g., LLT Drug addiction, are in SOC Psychiatric disorders
User Feedback

• Some support moving “abuse” terms to SOC *Psychiatric disorders* instead of secondary links

• Some have great concern of potential massive implication of such change (secondary links to SOC *Social circumstances*)

• Additional guide on how to use terms in SOC *Social circumstances* would be necessary (e.g., PTC document)
Panel Discussion

- Should “abuse” terms, e.g., LLT *Drug abuse* be moved to SOC *Psychiatric disorders*?

- Should SOC *Social circumstances* be made multi-axial to allow other concepts to be grouped by second SOC linkages
Eliminate Multi-Axial HLTs in Cumulative Data Output
Multi-Axiality in MedDRA

- The representation of a medical concept in multiple SOCs
- Allows terms to be grouped by different classifications
- Allows retrieval and presentation via different data sets
- Each PT has only one primary SOC
Multi-Axial View
Primary SOC Rule and Multi-Axial HLTs

• When PTs under the multi-axial HLT have different primary SOC allocations, the following display will occur in the primary SOC view
Primary SOC View

Skin and subcutaneous tissue disorders
- Angioedema and urticaria
- Cornification and dystrophic skin disorders
- Cutaneous neoplasms benign
  - Dermal cyst

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
- Breast neoplasms benign (incl nipple)
- Breast neoplasms malignant and unspecified (incl nipple)
- Cancer-related morbidities
- Cutaneous neoplasms benign
  - Skin neoplasms benign
    - Acanthoma
    - Acrochordon
    - Becker's naevus
    - Benign neoplasm of skin
    - Bowenoid papulosis
    - Epithelioma adenoides cysticum
    - Fibrous histiocytoma
    - Haemangioma of skin
    - Hair follicle tumour benign
    - Juvenile melanoma benign
    - Keratoacanthoma
    - Lentigo
    - Leser-Trelat sign
    - Melanocytic naevus
    - Osteoma cutis
    - Pyogenic granuloma
    - Sebaceous adenoma
    - Seborrheic keratosis
    - Silicon granuloma
    - Skin papilloma
    - Sweat gland tumour
    - Xanthoma
    - Xanthoma multiplex
Proposed Changes

- Eliminate multi-axiality of involved HLTs by renaming:

| Proposed New Hierarchy of Single-axial (Yellow highlight indicates new term) |
|--------------------------------|--------------------------------|--------------------------------|
| Skin SOC                      | HLGT Benign cutaneous neoplasms | HLT Benign skin neoplasms     |
| Neoplasm SOC                  | HLGT Cutaneous neoplasms benign  | HLT Skin neoplasms benign     |
Proposed Changes (cont)

• OR correct the root cause:
  – Different primary SOC allocations among PTs under the multi-axial HLT

    • Option 1: Change the primary SOC for cyst and polyps terms from site of manifestation to SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*

    • Option 2: Remove the link of cyst and polyp terms from SOC *Neoplasms benign, malignant and unspecified (incl cysts and polyps)*
User Feedback

- Comments are supportive in principle
- Some suggest eliminating multi-axial HLTs completely
- Objection received for changing the primary SOC of cyst and polyp terms
- The lexical variant approach is potentially confusing and does not translate into other languages
  - JMO suggested to add SOC abbreviation at the end of multi-axial HLTs? E.g.,
    - HLT *Skin neoplasms benign*(Skin)
    - HLT *Skin neoplasms benign*(Neopl)
Panel Discussion

• 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?
Panel Recommendations
Panel Recommendations

• “NEC” HLTs
  – “NEC” naming should not be revised unless there is a more medically meaningful name within the hierarchy
  – Large-sized “NEC” groupings should be analyzed for possible new groupings with the following priority:
    • Oversized HLTs (≥50 PTs)
    • Medium or large HLTs with higher frequencies in a regulator’s database
    • Utilize regulatory risk assessment areas for prioritization
Panel Recommendations (cont)

• “NEC” HLTs (cont)
  – HLT re-grouping should be based on medicine, such as pathology or physiology:
    • Avoid force fitting of PTs for the purpose of reducing HLT size
    • Avoid over-granularity at the HLT level
    • Consider the use of age and gender criteria
  – Consider a schedule that completes the implementation in a short timeframe:
    • Consider the potential of consecutive complex releases
Panel Recommendations (cont)

• **SOC Investigations**:  
  – Recommend a pilot study on concept attribute approach:
    • MSSO to develop a sample set of investigation terms with concept attributes
    • To be tested by regulators and industry volunteers
Panel Recommendations (cont)

- SOC *Social circumstances*
  - Request PTC Working Group to provide additional guidance on SOC *Social circumstances*, specifically, addict/dependence/abuse terms
Panel Recommendations (cont)

- SOC *Social circumstances* (cont)
  - No change to current SOC structure
  - Review “abuse” related LLTs:
    - Clarify the PT/LLT wordings to differentiate terms in SOC *Social circumstances* from those in SOC *Psychiatric disorders*
      - Move “abuse” terms to SOC *Psychiatric disorders* and keep them as independent PTs from “dependence” counterparts
      - Keep terms that refer to people, such as PT *Drug abuser*, in SOC *Social circumstances*
Panel Recommendations (cont)

• Multi-Axial HLTs in Cumulative Data Output:
  – Create separate HLTs for cyst and polyps terms
    • Consult expert pathologists and oncologists
  – Review all multi-axial HLTs to ensure primary SOCs are appropriate
Next Step

- BRP recommendations will be presented to MedDRA Management Board for approval