MedDRA Blue Ribbon Panel: Proposed Revisions to the Neoplasms SOC

12 April 2011
EMA, London, UK
Acknowledgments

The MSSO is grateful to

for hosting this Blue Ribbon Panel meeting
Agenda

0900 – 0915  Introduction
   BRP members and MSSO staff
0915 – 0945  Background of topic
0945 – 1030  “Cyst” terms – delink from Neoplasms SOC?
   Panel discussions/recommendations;
   Observer comments
[1030 – 1045  Break]
Agenda (cont)

1045 – 1145 Specific histologic sub-types of neoplasms
Panel discussions/recommendations; Observer comments

1145 – 1245 Update MedDRA with current neoplasm classifications
Panel discussions/recommendations; Observer comments

[1245 – 1315 Break]
Agenda (cont)

1315 – 1330  Summary of Panel
   Recommendations – Final comments by Observers

1330  Meeting concludes
Panel Members

Stewart Geary (Eisai)
Jean-Marie Heim (Bristol-Myers Squibb)
Sebastian Monzon (Roche)
Gisele Sarosy (National Cancer Institute, USA [ret])
Atsuo Takashima (National Cancer Center, Japan)
Kevin Blake (EMA)
Multiple FDA experts (FDA)
Why a Blue Ribbon Panel (BRP)?

- Provides a forum for MedDRA experts to discuss and make recommendations
- When there is a need for a broad discussion on a challenging MedDRA issue
- Engage subject matter experts
- Observers (audience), submitted comments
- Goal is to develop recommendations for MedDRA Management Board to consider
Background of Topic – Proposed Revisions to Neoplasm SOC
How MedDRA Is Used

• An international multi-lingual terminology
• Standardized communications
• Applied in all phases of development cycle
• Classification for a wide range of clinical information
• Support for multiple medical product areas
Scope of MedDRA

IN
- Diseases
- Diagnoses
- Signs
- Symptoms
- Therapeutic indications
- Investigation names & qualitative results
- Medical & surgical procedures
- Medical, social, family history
- Medication errors
- Product quality, device issues
- Terms from other terminologies

OUT
- Frequency qualifiers
- Numerical values for results
- Severity descriptors
- Not an equipment, device, diagnostic product dictionary
- Not a drug dictionary
- Patient demographic terms
- Clinical trial study design terms
Organization of MedDRA

SOC = Cardiac disorders

HLGT = Cardiac arrhythmias

HLT = Rate and rhythm disorders NEC

PT = Arrhythmia

LLT Arrhythmia NOS

LLT Arrhythmia

LLT Dysrhythmias

LLT Arrhythmia cardiac (NOS)
SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps)

- Characteristics:
  - Contains terms for **benign** and **malignant** neoplasms
  - Contains terms for **cysts** and **polyps**
  - Terms for benign and malignant neoplasm – this is the **primary** SOC
    - Secondary SOC is site of manifestation
  - Terms for cysts and polyps – this is the **secondary** SOC
    - Primary SOC is site of manifestation
### SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps) (cont)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Primary SOC</th>
<th>Secondary SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign lung neoplasm</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
</tr>
<tr>
<td>Chest wall cyst</td>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
</tr>
</tbody>
</table>
Neoplasm SOC

• One of the largest MedDRA SOCs
  • Approx. 10% of all MedDRA PTs have primary or secondary link

• Growth rate parallels MedDRA’s overall growth since 1999 (v2.1)
History of Neoplasm SOC

• Initially developed from publication of US National Cancer Institute
  – Except non-Hodgkin’s lymphomas (used International Lymphoma Study Group Classification)

• Basic SOC organization has not changed since 1999
History of Neoplasm SOC (cont)

• Over the years, some users have pointed out deficiencies

• A few years ago, MSSO informally polled users:
  - Not much interest in addressing deficiencies
  - Used mainly for indications, not AE coding; not considered a priority
MedDRA at US NCI

• Terminology serves an important role in NCI's research, clinical, and information efforts

• NCI works with many partners
  – Create and publish controlled terminology
  – Help develop and communicate information useful to scientists, clinicians, patients, and the public
MedDRA at US NCI (cont)

- NCI Enterprise Vocabulary Services (EVS) provides services and resources
  - NCI Thesaurus
  - NCI Metathesaurus

- Facilitate standardization of terminology across the Institute and larger biomedical community
MedDRA at US NCI (cont)

• Pathologist at NCI
  – Responsible for EVS concept modeling, defining semantic links/definitions for diseases, anatomy, cytogenetics, morphology, molecular biology, labs, etc.
  – Sources include:
    - MedDRA
    - SNOMED CT
    - ICD10; ICD9CM; ICD O
    - Gene Ontology
    - HL7
    - CDISC
    - Others

• Proposals to MSSO derived from challenges in mapping
MedDRA at US NCI (cont)

- Cancer Therapy Evaluation Program (CTEP) uses MedDRA
  - CTCAE (Common Terminology Criteria for Adverse Events)
  - Diseases
  - Prior Therapies
  - “Other Causes” (Indications)
What Has Changed?

• “Traditional” cancer therapeutics:
  - Local control with surgery and/or radiation, with combination chemotherapy for systemic control
  - Anti-hormonal therapies for certain malignancies (breast, prostate)

• More recently, focus on genetics of malignancy in development of therapies
**Targeted Cancer Therapy**

- “The key to successful therapies is identification of critical, dysfunctional nodes in oncogenic networks whose effective inhibition will result in abrogation and/or reversal of the malignant state by apoptosis and/or differentiation. The specific targeted therapy or combination of therapies should be less toxic to normal tissue, coupled to a large therapeutic window that targets the ‘context of vulnerability’ of the tumor.”
  
## Examples of Targeted Cancer Therapies

<table>
<thead>
<tr>
<th>Neoplasm</th>
<th>Genetics</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic myelogenous leukemia</td>
<td>BCR-ABL</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Gastrointestinal stromal tumors</td>
<td>C-KIT/PDGFR</td>
<td>Imatinib</td>
</tr>
<tr>
<td>Breast and other carcinomas</td>
<td>HER-2</td>
<td>Trastuzumab</td>
</tr>
</tbody>
</table>
Specificity of Diagnosis

• “First, simply diagnosing ‘non-small-cell carcinoma’ is no longer adequate when a specific cell type can be determined. Oncologists increasingly need a specific cell type diagnosis whenever possible.”
  
  – William Check, PhD, *CAP Today*, June 2010
Proposal 1: Remove “Cyst” Terms from Neoplasm SOC
Remove “Cyst” Terms from Neoplasm SOC

• Rationale:
  - “Cyst” is an anatomic designation which only very rarely confers the quality of “neoplasia” (abnormal growth of cells)
Remove “Cyst” Terms from Neoplasm SOC (cont)

• Mechanics:
  - Removal of secondary link of most “cyst” terms
  - Keep remaining primary links
  - Example:

<table>
<thead>
<tr>
<th>PT</th>
<th>Primary SOC</th>
<th>Secondary SOC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Currently</td>
<td>Bone cyst Musculoskeletal and connective tissue disorders</td>
<td>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</td>
</tr>
<tr>
<td>If as proposed</td>
<td>Bone cyst Musculoskeletal and connective tissue disorders</td>
<td>[None]</td>
</tr>
</tbody>
</table>
Remove “Cyst” Terms from Neoplasm SOC (cont)

• Please consider the following:
  – Would analysis of data coded with terms in Neoplasm SOC be enhanced, made more difficult, or remain the same?
  – Approximately 100 “cyst” PTs in Neoplasm SOC – and approx. 140 LLTs
  – Risks vs. benefits to balance medical correctness against impact on legacy and future coded data
Remove “Cyst” Terms from Neoplasm SOC (cont)

• QUESTION 1A:
  - Does the Panel recommend making this change to the “cyst” terms in MedDRA?
Remove “Cyst” Terms from Neoplasm SOC (cont)

• QUESTION 1B:
  – If the Panel does not recommend making this change, does it have another recommendation?
  – Or should “cyst” terms remain in their current location in Neoplasm SOC?
Remove “Cyst” Terms from Neoplasm SOC (cont)

User Comments

Microsoft Office
Word Document
Discussion
Proposal 2: More Specific Tumor Types at PT Level
More Specific
Tumor Types at PT Level

- Histology often correlates with prognosis
  - E.g., adenocarcinoma of lung worse prognosis than squamous cell
  - Large cell neuroendocrine lung carcinomas worse prognosis than other large cell carcinomas
- NH lymphomas – divided into B,T, NK-cell type; stage, phenotype and histology guide treatment
More Specific Tumor Types at PT Level (cont)

- Some specificity currently at LLT, but in some cases, certain subtypes are missing
  - E.g., no term for cribriform carcinoma of breast; no term for alveolar adenoma of lung
Genetic Terms in MedDRA

- MSSO is currently working to add relevant pharmacogenetic terms proactively to MedDRA
- Some well-recognized oncogenes, other cancer-related genetic markers
  - E.g., K-RAS, c-MYC, etc.
- Potential to augment histologic specificity of terms
More Specific Tumor Types at PT Level (cont)

• Rationale:
  – Oncologic therapies are being targeted at specific histologic types of tumors
  – Often combined with genetics
  – Increased specificity in MedDRA would allow for aggregation and analysis of specific tumor types
  – Some specificity currently at LLT, but in some cases, certain subtypes are missing
More Specific
Tumor Types at PT Level (cont)

• Impact:
  - Could be thousands of terms, including promotion of existing LLTs
    • 1909 PTs and 8383 LLTs in the Neoplasm SOC
    • Not all LLTs and PTs may be affected
  - Adding terms for subtypes that are not in MedDRA currently
  - Related to Proposal No. 3
More Specific Tumor Types at PT Level (cont)

• Other considerations:
  - May still need non-specific terms (e.g., PT Breast cancer) for reports when specific tumor type unknown
  - Currently PTs for many malignant neoplasms include stage of tumor
  - Panel is asked to consider fate of the existing “stage” PTs
“Stage” PTs in MedDRA

- HLT
- Ovarian neoplasms malignant (excl germ cell)
  - PT
  - Malignant ovarian cyst
  - PT
  - Ovarian cancer
  - PT
  - Ovarian cancer metastatic
  - PT
  - Ovarian cancer recurrent
  - PT
  - Ovarian epithelial cancer
  - PT
  - Ovarian epithelial cancer metastatic
  - PT
  - Ovarian epithelial cancer recurrent
  - PT
  - Ovarian epithelial cancer stage I
  - PT
  - Ovarian epithelial cancer stage II
  - PT
  - Ovarian epithelial cancer stage III
  - PT
  - Ovarian epithelial cancer stage IV
  - PT
  - Ovarian low malignant potential tumour
  - PT
  - Ovarian stromal cancer
More Specific
Tumor Types at PT Level (cont)

• Question 2A:
  – Should the MSSO add specific histologic subtypes of neoplasms to the PT level?
More Specific
Tumor Types at PT Level (cont)

• Question 2B:
  - If yes for 2A, what is the optimal approach?
    • MSSO to add terms proactively
    • Populate through Change Request process
    • Add terms in one MedDRA release or over multiple releases
    • Another approach?
More Specific
Tumor Types at PT Level (cont)

• Question 2C:
  – If yes for 2A, what should be the fate of existing “stage” terms in MedDRA (currently at the PT level)?
  • Note: “stage” terms also include “metastatic” and “recurrent” qualifiers
More Specific
Tumor Types at PT Level (cont)

• Question 2D:
  - How would increased specificity affect coding and retrieval?
    • E.g., how would one code a term describing a specific lung tumor and its EGFR status?
More Specific
Tumor Types at PT Level (cont)

User Comments
Discussion
Proposal 3: Update the Neoplasm SOC Tumor Classifications
Update Tumor Classifications

• Many tumor classification systems
  – French-American-British [FAB] classification for acute leukemia
  – World Health Organization (WHO)
    • For many – but not all – organ systems
  – ICD-O

• Evolve and change over time
  – Maintenance implications for MedDRA
Update Tumor Classifications (cont)

• Some neoplasms currently in MedDRA are not up-to-date
  – e.g., PT/LLT *Cystosarcoma phyllodes* should be “phyllodes tumor”

• There are gaps in MedDRA
  – Many neoplasms listed in standard classifications systems are missing
Update Tumor Classifications (cont)

- Rationale and impact
  - Similar to those for proposal No. 2
- If “gaps” of missing histologic subtypes were filled, increase in PTs could be in the 100s
- Existing out-of-date terms would need to be addressed
  - Probably be made non-current LLTs
Update Tumor Classifications (cont)

• Considering both Proposal Nos. 2 & 3
  - If “yes” to Question 2A, then standard tumor classification systems used as basis for new terms
  - A more limited approach (if “no” on Proposal No. 2)
    • MSSO to update existing neoplasm terms to be consistent with modern neoplasm classifications
Update Tumor Classifications (cont)

- Example: Renal cell carcinoma

- Example: Pancreatic exocrine carcinoma
Update Tumor Classifications (cont)

• Question 3:
  – Should standard neoplasm classification systems (e.g., WHO classifications) be used as the basis for neoplasm terms in MedDRA?
Update Tumor Classifications (cont)

User Comments

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Word Document
Discussion
Thank You