Blue Ribbon Panel on CTCAE-MedDRA Mapping

6 April 2006
MedDRA MSSO

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Agenda

0800 - Welcome and Introduction
0830 - Summary of the CTCAE-MedDRA Mapping Update
0945 - Break
1000 - Need for a Standardized Mapping of CTCAE Grades to MedDRA
1115 - Break
1130 - Panel discussion continued
1215 - Lunch
1315 - Options for Implementation
1400 - Break
1415 - Panel discussion continued
1500 - Review of Recommendations of BRP; Q&A
1600 - Meeting adjourned
Introduction

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

• Moderators:
  – Judy Harrison
  – Anna Zhao-Wong

• Panelists:
  – Ruthann Giusti
  – Carmen Kreft-Jais
  – Michelle Mahoney
  – JoAnn Medbery
  – Bob Pratt
  – Yasuo Sakurai
  – Ann Setser
  – Philippe Thouvay
Summary of the CTCAE-MedDRA Mapping Update
Uses of Mapping

- Internal use in NCI databases as unique identifiers for CTCAE terms

<table>
<thead>
<tr>
<th>Adverse Events Category</th>
<th>AE/Supra-ordinate Term</th>
<th>Select AE</th>
<th>MedDRA Preferred Term</th>
<th>MedDRA Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td></td>
<td>Hypersensitivity NOS</td>
<td>10020755</td>
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<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</td>
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<td>Rhinitis allergic NOS</td>
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<tr>
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<td>Allergy/Immunology - Other (Specify, __)</td>
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<td>ALLERGY/IMMUNOLOGY</td>
<td>Autoimmune reaction</td>
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<td>Autoimmune disorder NOS</td>
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<td>ALLERGY/IMMUNOLOGY</td>
<td>Serum sickness</td>
<td></td>
<td>Serum sickness</td>
<td>10040400</td>
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<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Vasculitis</td>
<td></td>
<td>Vasculitis NOS</td>
<td>10047128</td>
</tr>
<tr>
<td>AUDITORY/EAR</td>
<td>Auditory/Ear - Other (Specify, __)</td>
<td>Not available</td>
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<td>90004002</td>
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<tr>
<td>AUDITORY/EAR</td>
<td>Hearing: patients with/without baseline audiogram and enrolled in a monitoring program</td>
<td></td>
<td>Hearing disability</td>
<td>10053491</td>
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</tbody>
</table>
Uses of Mapping (cont)

• Many MedDRA subscribers use CTCAE for NCI sponsored clinical trials; potential uses of mapping include:
  – Converting CTCAE terms to MedDRA terms in clinical trial databases for purposes of analysis and reporting
  – Serious adverse event reporting
Mapping Issues

• Mapping has been a challenge to apply for MedDRA users
  – Mapping is limited to MedDRA PTs
  – Mapping is based on an older version of MedDRA (Version 6.0)
  – “Other (Specify,___)” terms are “open-ended”
  – Approx. 50% of AE terms are not mapped (NCI code)
  – Grades of AE terms are not mapped
Mapping Update

• The update review includes:
  – Update the mapped MedDRA v6.0 PT to V9.0 LLT
    • Accuracy, PTC compliance
  – Provide mapping of v9.0 LLTs to the previously unmapped CTCAE terms
    • MedDRA term addition, complete mapping
  – Document the rules and conventions used in the mapping
    • Provide better understanding of the mapping
    • Promote proper usage of the mapping
Current Mapping Conventions

• Use single concept in mapping
  – Infection with grade 3 or 4 neutrophils: Only the infection concept is mapped to MedDRA
    – Suggest that MedDRA users code “neutrophil count decreased” concept separately
    – Supported by recommendation of “MedDRA Term Selection: Points to Consider” (Section 3.4 Combination terms)
Current Mapping Conventions (cont)

• Infection and “-itis” terms
  – CTCAE “Otitis middle ear (non-infectious)”
    • Previously mapped to *Otitis media serous NOS* (infection)
    • Currently mapped to *Middle ear inflammation* (inflammation)

• “Other (Specify, ___)” terms
  – CTCAE “Cardiac Arrhythmia (Other, specify ___)” is mapped to LLT *Arrhythmia*
## Current Mapping Format

28% “900..” codes in CTEP Codes Column

<table>
<thead>
<tr>
<th>Category</th>
<th>AE supra-ordinate term</th>
<th>Select AE</th>
<th>MedDRA LLT (v90)</th>
<th>CTEP Codes</th>
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</thead>
<tbody>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic reaction/hypersensitivity (including drug fever)</td>
<td>Hyposensitivity</td>
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<td>10020751</td>
</tr>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)</td>
<td>Allergic rhinitis</td>
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<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Allergy/Immunology - Other (Specify, __)</td>
<td>Immune system disorder</td>
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<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Autoimmune reaction</td>
<td>Autoimmune disorder</td>
<td></td>
<td>10061664</td>
</tr>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Serum sickness</td>
<td>Serum sickness</td>
<td></td>
<td>10040400</td>
</tr>
<tr>
<td>ALLERGY/IMMUNOLOGY</td>
<td>Vasculitis</td>
<td>Vasculitis</td>
<td></td>
<td>10047115</td>
</tr>
<tr>
<td>AUDITORY/EAR</td>
<td>Auditory/Ear - Other (Specify, __)</td>
<td>Ear disorder</td>
<td></td>
<td>10014004</td>
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<tr>
<td>AUDITORY/EAR</td>
<td>Hearing: patients with/without baseline audiogram and enrolled in a monitoring program</td>
<td>Hearing test abnormal</td>
<td></td>
<td>10057540</td>
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<tr>
<td>INFECTION</td>
<td>Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC &lt;1.0 x 10e9/L)</td>
<td>Appendix</td>
<td>Appendicitis</td>
<td>90030158</td>
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<tr>
<td>INFECTION</td>
<td>Infection with normal ANC or Grade 1 or 2 neutrophils</td>
<td>Appendix</td>
<td>Appendicitis</td>
<td>90030306</td>
</tr>
<tr>
<td>INFECTION</td>
<td>Infection with unknown ANC</td>
<td>Appendix</td>
<td>Appendicitis</td>
<td>10003011</td>
</tr>
</tbody>
</table>
Maintenance Schedule

- Update the mapping at each MedDRA release (bi-annual)
- CTCAE new version release will be synchronized with MedDRA release
Panel Discussion

• Does the updated mapping of CTCAE base terms meet subscribers’ needs?
• Is the maintenance schedule sufficient?
### User Feedback

- Should it be mapped to condition or lab?

<table>
<thead>
<tr>
<th>Category</th>
<th>AE supra-ordinate term</th>
<th>Select AE</th>
<th>CTEP Provisional code (MedDRA60)</th>
<th>MedDRA LLT (v90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>METABOLIC/LABORATORY</td>
<td>Bilirubin (hyperbilirubinemia)</td>
<td></td>
<td>10005364</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>METABOLIC/LABORATORY</td>
<td>Calcium, serum-high (hypercalcemia)</td>
<td></td>
<td>10020583</td>
<td>Hypercalcemia</td>
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<tr>
<td>METABOLIC/LABORATORY</td>
<td>Calcium, serum-low (hypocalcemia)</td>
<td></td>
<td>10020947</td>
<td>Hypocalcemia</td>
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<tr>
<td>METABOLIC/LABORATORY</td>
<td>Cholesterol, serum-high (hypercholesterolemia)</td>
<td></td>
<td>10020603</td>
<td>Hypercholesterolemia</td>
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<tr>
<td>BLOOD/BONE MARROW</td>
<td>CD4 count</td>
<td></td>
<td>10007839</td>
<td>CD4 lymphocytes decreased</td>
</tr>
<tr>
<td>BLOOD/BONE MARROW</td>
<td>Hemoglobin</td>
<td></td>
<td>10018876</td>
<td>Hemoglobin decreased</td>
</tr>
<tr>
<td>BLOOD/BONE MARROW</td>
<td>Neutrophils/granulocytes (ANC/AGC)</td>
<td></td>
<td>10029363</td>
<td>Neutrophil count decreased</td>
</tr>
</tbody>
</table>
CTCAE Grades
CTCAE Severity Grades

- Example: AE “Hemolysis”

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs’] schistocytes)</td>
<td>Evidence of red cell destruction and ≥2 gm decrease in hemoglobin, no transfusion</td>
<td>Transfusion or medical intervention (e.g., steroids) indicated</td>
<td>Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)</td>
<td>Death</td>
</tr>
</tbody>
</table>
Base Term vs. Grade Term

- Some grade terms represent a different medical concept from base term

- Example 1: AE “Allergic reaction/hypersensitivity (including drug fever)” mapped to LLT Hypersensitivity

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient flushing or rash; drug fever&lt;38°C (&lt;100.4°F)</td>
<td>Rash; flushing; urticaria; dyspnea; drug fever≥38°C (≥100.4°F)</td>
<td>Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension</td>
<td>Anaphylaxis</td>
<td>Death</td>
</tr>
</tbody>
</table>
Base Term vs. Grade term (cont)

- Example 2: AE “Cardiac ischemia/infarction” mapped to LLT

Myocardial ischemia

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic arterial narrowing without ischemia</td>
<td>Asymptomatic and testing suggesting ischemia; stable angina</td>
<td>Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated</td>
<td>Acute myocardial infarction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
Base Term vs. Grade term (cont)

- Mapping without consideration for different grade concepts
  - Loss of information
  - Affect ability to retrieve cases of interest using queries and search tools, including Standardised MedDRA Queries (SMQs)
    - Case mapped to LLT *Myocardial ischemia* would not be retrieved by SMQ *Myocardial infarction*; case mapped to LLT/PT *Acute myocardial infarction* would be retrieved
Approaches to Grade Mapping

• Data received
  – CTCAE grade with narrative, e.g., SAEs
  – CTCAE grade without narrative

• Clinical trial databases
  – CTCAE, MedDRA, combination, grades

• Safety databases
  – Typically in MedDRA

• Mapping approaches
  – Code according to base term only
  – Code according to grades, using narrative if available
    • Coder’s judgment or company conventions
Panel Discussion

- With the different approaches taken by MedDRA users, is there a need for a standardized mapping of CTCAE grades to MedDRA?
If “Yes”

• What are the options for implementation?
  – One to one grade mapping
  – One to many grade mapping
One to One Grade Mapping

• Criteria
  – Each grade is treated as one concept
  – The grade is mapped to the same LLT as its base term, except:
    • The grade that is represented by a distinctly different single LLT in MedDRA

<table>
<thead>
<tr>
<th>Base term</th>
<th>Grade 1</th>
<th>Grade 2</th>
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<th>LLT</th>
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</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
<td>Anaphylaxis</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
One to Many Grade Mapping

• Criteria
  – One CTCAE grade is mapped to the all possible MedDRA LLTs that match the listed conditions of that particular grade

<table>
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<th>Base term</th>
<th>Grade 1</th>
<th>Grade 2</th>
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<th>LLT</th>
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<th>LLT</th>
<th>LLT</th>
<th>LLT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Hot flushes transient of face; Rash; Drug fever</td>
<td>Rash; Flushing; Urticaria; Dyspnea; Drug fever</td>
<td>Bronchospasm; Urticaria; Allergic edema; Allergic angioedema; Hypotension</td>
<td>Anaphylaxis</td>
<td>Death</td>
<td></td>
</tr>
</tbody>
</table>
If “No”

• What guidance should be provided to users?
Panel Discussion

• Future directions
Thank You
BRP Recommendations

• A standardized mapping of grades is important for consistency
  – A guidance document for consistent use is also needed
BRP Recommendations (cont)

• The stakeholders involved (industry, regulators, cooperative groups, CTEP, MSSO and others) should begin a dialogue to address the optimal use of both terminologies
  – A collaborative working group should be formed
  – Optimal data collection practices and conventions could also be addressed
  – If needed, both terminologies could be modified to achieve harmonization and create an optimal mapping
  – Provide guidance for dealing with legacy data
BRP Recommendations (cont)

• Current mapping:
  – Address the laboratory terms in CTCAE so that they consistently map to MedDRA investigation terms