



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

Adverse Events Category	AE/Supra-ordinate Term	Select AE	MedDRA Preferred Term	MedDRA Code
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		Hypersensitivity NOS	10020755
ALLERGY/IMMUNOLOGY	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)		Rhinitis allergic NOS	10039087
ALLERGY/IMMUNOLOGY	Allergy/Immunology - Other (Specify, __)		Not available	90004000
ALLERGY/IMMUNOLOGY	Autoimmune reaction		Autoimmune disorder NOS	10003815
ALLERGY/IMMUNOLOGY	Serum sickness		Serum sickness	10040400
ALLERGY/IMMUNOLOGY	Vasculitis		Vasculitis NOS	10047128
AUDITORY/EAR	Auditory/Ear - Other (Specify, __)		Not available	90004002
AUDITORY/EAR	Hearing: patients with/without baseline audiogram and enrolled in a monitoring program		Hearing disability	10053491



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

Category	AE supra-ordinate term	Select AE	MedDRA LLT (v90)	CTEP Codes
ALLERGY/IMMUNOLOGY	Allergic reaction/hypersensitivity (including drug fever)		Hypersensitivity	10020751
ALLERGY/IMMUNOLOGY	Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)		Allergic rhinitis	10001723
ALLERGY/IMMUNOLOGY	Allergy/Immunology - Other (Specify, ___)		Immune system disorder	10021425
ALLERGY/IMMUNOLOGY	Autoimmune reaction		Autoimmune disorder	10061664
ALLERGY/IMMUNOLOGY	Serum sickness		Serum sickness	10040400
ALLERGY/IMMUNOLOGY	Vasculitis		Vasculitis	10047115
AUDITORY/EAR	Auditory/Ear - Other (Specify, ___)		Ear disorder	10014004
AUDITORY/EAR	Hearing: patients with/without baseline audiogram and enrolled in a monitoring program		Hearing test abnormal	10057540

INFECTION	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	Appendix	Appendicitis	90030158
INFECTION	Infection with normal ANC or Grade 1 or 2 neutrophils	Appendix	Appendicitis	90030306
INFECTION	Infection with unknown ANC	Appendix	Appendicitis	10003011



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?

Category	AE supra-ordinate term	Select AE	CTEP Provisional code (MedDRA60)	MedDRA LLT (v90)
METABOLIC/LABORATORY	Bilirubin (hyperbilirubinemia)		10005364	Hyperbilirubinemia
METABOLIC/LABORATORY	Calcium, serum-high (hypercalcemia)		10020583	Hypercalcemia
METABOLIC/LABORATORY	Calcium, serum-low (hypocalcemia)		10020947	Hypocalcemia
METABOLIC/LABORATORY	Cholesterol, serum-high (hypercholesteremia)		10020603	Hypercholesterolemia

Category	AE supra-ordinate term	Select AE	CTEP Provisional code (MedDRA60)	MedDRA LLT (v90)
BLOOD/BONE MARROW	CD4 count		10007839	CD4 lymphocytes decreased
BLOOD/BONE MARROW	Hemoglobin		10018876	Hemoglobin decreased
BLOOD/BONE MARROW	Neutrophils/granulocytes (ANC/AGC)		10029363	Neutrophil count decreased



CTCAE Grades

CTCAE Severity Grades

- Example: AE "Hemolysis"

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Laboratory evidence of hemolysis only (e.g., direct antiglobulin test [DAT, Coombs'] schistocytes)	Evidence of red cell destruction and ≥ 2 gm decrease in hemoglobin, no transfusion	Transfusion or medical intervention (e.g., steroids) indicated	Catastrophic consequences of hemolysis (e.g., renal failure, hypotension, bronchospasm, emergency splenectomy)	Death

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*

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Transient flushing or rash; drug fever 38°C (100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death

Base Term vs. Grade term (cont)

- Example 2: AE "Cardiac ischemia/infarction" mapped to LLT *Myocardial ischemia*

Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death



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

Base term	Grade 1	Grade2	Grade 3	Grade 4	Grade 5
Allergic reaction/hypersensitivity (including drug fever)	Transient flushing or rash; drug fever <math><38^{\circ}\text{C}</math> (<math><100.4^{\circ}\text{F}</math>)	Rash; flushing; urticaria; dyspnea; drug fever >math>\geq 38^{\circ}\text{C}</math> (>math>\geq 100.4^{\circ}\text{F}</math>)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
LLT	LLT	LLT	LLT	LLT	LLT
Hypersensitivity	Hypersensitivity	Hypersensitivity	Hypersensitivity	Anaphylaxis	Death

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

Base term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Allergic reaction/hypersensitivity (including drug fever)	Transient flushing or rash; drug fever <math>< 38^{\circ}\text{C}</math> (<math>< 100.4^{\circ}\text{F}</math>)	Rash; flushing; urticaria; dyspnea; drug fever $\geq 38^{\circ}\text{C}$ ($\geq 100.4^{\circ}\text{F}$)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
LLT	LLT	LLT	LLT	LLT	LLT
Hypersensitivity	Hot flushes transient of face; Rash; Drug fever	Rash; Flushing; Urticaria; Dyspnea; Drug fever	Bronchospasm; Urticaria; Allergic edema; Allergic angioedema; Hypotension	Anaphylaxis	Death



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