Summary of MedDRA MSSO's Blue Ribbon Panel Meeting
on CTCAE-MedDRA Mapping
6 April 2006
Northrop Grumman Corporation
Fair Lakes, VA, USA

Introduction

Pat Revelle, Director of MSSO, went over the logistics and introduced the members of the Blue Ribbon Panel.

The Panel members were:

Ruthann Giusti (FDA)
Carmen Kreft-Jais (AFSSAPS)
Michelle Mahoney (Mayo Clinic Comprehensive Cancer Center)
JoAnn Medbery (Johnson & Johnson)
Bob Pratt (FDA)
Yasuo Sakurai (JMO)
Ann Setser (CTEP)
Philippe Thouvay (Roche)

MSSO moderators were Anna Zhao-Wong and Judy Harrison.

There were approximately 30 observers in attendance.

Uses of the CTCAE-MedDRA Mapping

Dr. Zhao-Wong gave a brief overview of the CTCAE-MedDRA mapping. It has been posted since 2003 on the CTEP web site. She oriented the observers to the various columns and categories of the posted mapping. For terms that had no mapping, a CTEP code starting with "900-" had been assigned. She stressed that the numbers in the column for "CTEP Code" are internal CTEP mapping codes, used to provide unique identifiers for CTCAE terms in CTEP's databases only. Dr. Zhao-Wong noted that MedDRA is the current ICH standard for regulatory reporting and that MedDRA subscribers need a mapping to convert CTCAE terms to MedDRA for this purpose.

The issues that had been identified for the previous mapping (prior to the recent revision):

1. Mapping was to MedDRA at the PT level (MedDRA users need to code to the LLT level)

2. The previous mapping was to MedDRA Version 6.0 (the current version in April 2006 is Version 9.0)
3. The "Other (Specify ___)" terms had been misused by some users of CTCAE by not filling in the blank space with a specific term
4. Originally, 50% of terms were "900-" terms (i.e., no MedDRA term available)
5. Only the base terms were mapped; grades were not.

Current CTCAE-MedDRA Mapping

With the assistance of CTEP and some select MedDRA subscribers, the mapping has been recently updated by the MSSO. Three significant improvements were:

1. The mapping now is to MedDRA Version 9.0 LLTs
2. Mapping of the previous unavailable terms
3. Documented rules and conventions for the mapping were applied

The following is a sample of some of the mapping conventions that were applied:

1. Single concepts were mapped, even if some CTCAE terms had more than one concept (e.g., "Infection with grade 3 or 4 neutrophils")
2. Infection and "itis" terms were reviewed to be mapped appropriately (in MedDRA, some "itis" terms are infections and others are not)
3. A default mapping of the "Other (Specify___)" terms was made for the associated base term.

Dr. Zhao-Wong displayed a sample of the updated mapping. The "CTEP Codes" are those to be used internally at CTEP; MedDRA users should use the LLT text provided. The mapping and the conventions document are posted on the MSSO Web site.

The proposed maintenance schedule is that the mapping will be updated with each MedDRA release (twice yearly); and the MSSO will work with CTEP to synchronize CTCAE updates with MedDRA version releases.

Dr. Zhao-Wong posed the first questions for the Panel to consider:

Does the updated mapping of CTCAE base terms meet subscribers' needs?

Is the maintenance schedule sufficient?

Dr. Zhao-Wong first related some feedback received from subscribers (received by MSSO earlier). As for the updated mapping, one subscriber answered "yes",

but only to a certain extent; the mapping is not a complete lexical match, and not all grade terms follow the base terms.

The Panelists all agreed that mapping the base terms is not enough, and that grade terms should also be mapped. Some rules may need to be developed for consistency in capturing the severity grade. They also discussed the different ways that CTEP, regulators, industry and cooperative groups use both terminologies. The representative from Japan indicated support for a standardized mapping table between the two terminologies.

The Panel also supported the proposed maintenance schedule for the mapping.

Observers joined the discussion by pointing out some inconsistencies in the updated mapping in the way laboratory terms are handled, i.e., some to MedDRA investigation terms and some to condition/diagnosis terms. It was agreed that this should be addressed to improve the current mapping.

Grade Term Mapping

Dr. Harrison of the MSSO briefly described the CTCAE severity grading system. CTCAE terms have unique clinical descriptions of severity based on grades 1 through 5; however, not all grades are appropriate for all AEs. Also, a patient may not have to have all findings associated with a particular grade to have that grade assigned. Using the CTCAE terms “Allergic reaction/hypersensitivity” and “Cardiac ischemia/infarction” as examples, Dr. Harrison noted that some grades represent medical concepts that are distinctly different from the base term.

Dr. Harrison described the consequences of a CTCAE-MedDRA mapping without accounting for the grades:

1) Loss of information
2) Affects the ability to retrieve cases e.g., using SMQs (e.g., cases mapped to LLT *Myocardial ischaemia* would not be retrieved by *Myocardial infarction (SMQ)* while cases mapped to LLT *Myocardial infarction* would)

The MSSO had polled several MedDRA users on how CTCAE data were received and handled. CTCAE terms are received with or without an associated case narrative or verbatim description of the event. In clinical trial databases, AEs are stored as CTCAE terms, as MedDRA terms after conversion, or as a combination of both. Safety databases typically only contain MedDRA-coded data. Those polled were also asked “How do you convert CTCAE terms to MedDRA if you are not using the current CTCAE-MedDRA mapping?” Some replied that they code the CTCAE base term only. Others code based on the grade, and that information provided in the narrative or verbatim, together with

internal company conventions and medical judgment, were used to determine the MedDRA term.

Dr. Harrison posed the next question for the Panel to consider:

Is there a need for a standardized mapping between CTCAE and MedDRA that accommodates the CTCAE grades?

Dr. Harrison first related some feedback received from subscribers (received by MSSO earlier). Yes, a standardized mapping is good to enhance communications, however, there is a potential problem if an organization has already coded using internal mappings or conventions, and that needs to be taken into account.

The Panel generally agreed that mapping of grade terms is a good idea, and this was also the general opinion of observers. It was pointed out that different types of organizations (industry, regulators, CTEP, and cooperative groups) collect data differently, e.g., in some cases, a verbatim term is reported along with a CTCAE code. There are no standard approaches for data collection; proper training of investigators and CRAs is needed. However, to require an investigator to report a verbatim term with a CTCAE term could be a logistic problem for some organizations.

Finally summary of this issue:

1. Yes, we need a standardized mapping of grade terms to assure consistency
2. Data collection methods are also important

Dr. Harrison posed the next question for the Panel to consider:

How should a standardized mapping be implemented? What are the options?

Dr. Harrison described the differences between a one-to-one *vs.* a one-to-many mapping between CTCAE grades and MedDRA terms. In a one-to-one mapping, each CTCAE grade is mapped like a single medical concept even if there are multiple concepts within the grade. Generally, this would be mapped to the same MedDRA LLT as the base term except where the grade represents a different medical concept than the base term. For example, "Allergic reaction/hypersensitivity" grades 1 – 3 would be mapped to LLT *Hypersensitivity,* but grade 4 would be mapped to LLT *Anaphylaxis.*

In the one-to-many approach, one would capture as many concepts as possible within the description of the grade, keeping in mind that MedDRA does not provide for coding specific laboratory values or all descriptions of interventions.

Also, a patient does not have to have experienced all of the events listed in a grade, so a one-to-many mapping may assign" more MedDRA terms to an event than actually occurred for the patient (i.e., you "gain" information).

Dr. Harrison asked the Panel – are there other options?

The Panel felt that, although there is a need to map the grade, neither the one-to-one nor the one-to-many approach is optimal.

It was also recommended that the grade 5 terms currently mapped to "death" be revisited by the MSSO as coding only to LLT *Death* results in loss of information about the underlying problem (i.e., loss of the base term information).

Dr. Harrison asked the Panel – what's wrong with the *status quo*? The issue seems to be when CTCAE and MedDRA intersect in company databases. Can we not just keep going along as we do now?

The Panel felt that some sort of mapping is still necessary to reconcile data coded in the two terminologies.

A suggestion was made to simply add the CTCAE grade terms to MedDRA as LLTs, however, this was not endorsed by the Panel. If they were to be incorporated, they would need to be identified with a qualifier (e.g., "CTCAE grade 1"). The approach to analysis would also need to be considered.

One of the Panelists acknowledged that it is difficult to harmonize two different terminologies as they exist today. She proposed instead to build an improved version of CTCAE that breaks out the multiple concepts in the grade terms into distinct entities, as MedDRA does. This might facilitate a better mapping. The experts in the room were encouraged to form a collaborative group to achieve this goal.

The Panel and observers enthusiastically embraced the idea of a collaboration to improve both terminologies to make them more easily mapped to each other. The timing is right because both terminologies have had years of real life usage. Funding of such an effort needs to be considered, however. A time span of five years was proposed, but the CTEP Panelist felt that – with the support of informatics – it might even be feasible in two years.

The MSSO will accept feedback on the current mapping and work to improve current issues and inconsistencies identified during the BRP and collected from subscribers. However, the mapping will remain to base terms only pending the development of a collaborative group of interested parties who will work to develop a strategy to improve and harmonize both terminologies and extend the

mapping to the grade terms. The Panel stressed that such a collaboration should begin as soon as possible.

Dr. Zhao-Wong presented a summary of the Panel's recommendations. The recommendations will be presented soon to the MedDRA Management Board who will consider these recommendations and decide if they will endorse them.

Summary of BRP 4 Recommendations

- A standardized mapping of grades is important for consistency
  - A guidance document for consistent use is also needed
- 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
- Current mapping:
  - Address the laboratory terms in CTCAE so that they consistently map to MedDRA investigation terms

List of Abbreviations

AERS – Adverse Event Reporting System (FDA)
AFSSAPS - Agence Francaise de Securite Sanitaire des Produits de Sante (French regulatory agency)
caBIG – cancer Biomedical Informatics Grid
CRA – Clinical research associate
CRF – Case report form
CTCAE – Common Terminology Criteria for Adverse Events
CTEP - Cancer Therapy Evaluation Program (USA)
EU – European Union
FDA – Food and Drug Administration (USA)
ICH – International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND – Investigational New Drug
JMO – Japanese Maintenance Organization (MedDRA)
LLT – Lowest Level Term (MedDRA)
MedDRA – Medical Dictionary for Regulatory Activities
MSSO MedDRA Maintenance and Support Services Organization
NCI – National Cancer Institute (USA)
NYHA – New York Heart Association
PT – Preferred term (MedDRA)
SAE – Serious adverse event
SMQ – Standardised MedDRA Query
SOC – System Organ Class (MedDRA)