

## Pilot Study Concept Paper

### 1 Executive Summary

The November 2006 Blue Ribbon Panel (BRP) recommended that the MSSO conduct a pilot study on the MedDRA concept attribute relationship, which allows the connection between two MedDRA concepts at the Preferred Term (PT) level. This feature is intended to improve MedDRA's utility in data retrieval and analysis.

This concept paper describes:

- Feasibility of introducing this feature into MedDRA based on information in other existing medical terminologies
- Plans for user testing of the sample concept attributes incorporated in a testing version of the MedDRA terminology
- Estimated cost of the pilot and risk/benefit analysis of concept attribute implementation

### 2 Introduction

#### 2.1 Background:

MedDRA is comprised of 26 System Organ Classes (SOCs), which represent parallel axes that are not mutually exclusive. This characteristic is called "multi-axiality" and not only allows terms to be represented in more than one SOC, but also to be grouped by different classifications. This allows for retrieval and presentation via different data sets. In order to ensure comprehensive and consistent data retrieval, multi-axial links of terms to their SOCs are pre-assigned. This characteristic is irrespective of which SOC is selected at data retrieval.

#### 2.2 Issue

Due to current MedDRA rules, SOC *Investigations* is currently uni-axial. This means that terms within SOC *Investigations* do not have multi-axial linkages that would connect them to the potentially corresponding diagnoses in SOCs that classify medical disorders (e.g., SOC *Gastrointestinal disorders*). However, there are reasons to leave SOC *Investigations* uni-axial. First, many investigation results are contributing factors that assist in clinical diagnosis and do not directly lead to the diagnosis. Also, investigation results are frequently non-specific. Attempting to add secondary links for investigation results terms to the related diagnostic terms in other SOCs could potentially lead to a large number of secondary links for a given test result. This could cause conflict with the MedDRA placement rule that obligates a PT to have only one High Level Term (HLT) link per SOC.

### 2.3 Proposed Solution from the BRP

This issue was one of the topics discussed at the November 2006 BRP meeting held in Ingelheim, Germany (<http://meddramssso.com/MSSOWeb/activities/blueribbonpanels.htm>). The Panel supported the idea of “concept attributes” and recommended a pilot study to address the following:

- Level of effort from the MSSO to implement such a feature
- Pros and cons of concept attributes (by volunteer user testing)

A “concept attribute” is a relationship that can be created in MedDRA to connect the relevant investigation results to a diagnosis (see Figure 1-1). As shown in the figure below, through a concept attribute, PT *Alanine aminotransferase increased* is linked to PT *Hepatitis A*. The relationship is named “Is a diagnostic test for” and it is an independent linkage outside of existing MedDRA hierarchy. A separate ascii file would be generated to handle this relationship. This approach to implementation allows MedDRA users the option of using the concept attributes or to ignore them with no change required to their software systems.

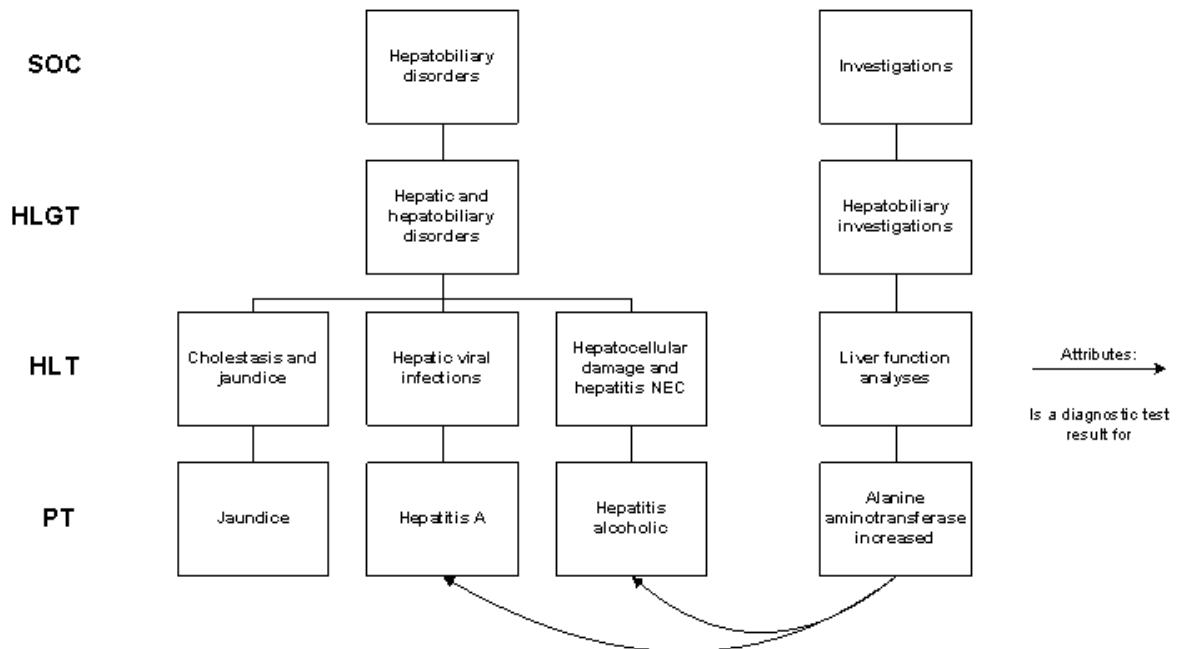


Figure 2-1. MedDRA Concept Attribute Example

The MSSO proposes three phases for the pilot study. At the end of each phase, the MSSO will present the findings of that phase to the Board. The MSSO will also present a detailed plan for the next phase to include MSSO cost estimates (both with existing staff and any additional expertise) for short term efforts as well as long term support. The Board will then approve each phase of the concept attribute effort before proceeding to the next phase.

### 3 Phase I – Introducing Concept Attributes into MedDRA

#### 3.1 Building the Concept Attributes *de novo*

To develop the concept attributes *de novo* is not a trivial task. According to Henegar and Bousquet (see document link below), using the ontology tool that they have, it took 300 hours for an expert of the domain to define 530 MedDRA PreferredTerms (from 10 MedDRA SOCs) by establishing attributes related to a particular concept, e.g., relevant signs, symptoms, and laboratory results. In their discussion, they estimated that 4 years is needed for a single physician to model the remaining 15,000 PTs (Note: the number of PTs is now 17,867 in Version 10.1).

Note that in defining MedDRA concept ontologically, Bousquet's group has provided more links ("is a" and "non is a") than the scope of the proposed MedDRA concept attributes, such as linking a PT to more than one HLT in a SOC (is a relationship), which MedDRA rules clearly prohibit. Nevertheless, the level of effort in creating such relationships and verifying them is not negligible and will draw significant amount of the MSSO's limited medical resources for a significant duration of time (perhaps a year or so). This would necessitate an increase of medical staff and acquisition of necessary ontology tools. Therefore, we do not believe that the *de novo* method is optimal.



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#### 3.2 Building the Concept Attributes upon Available Relationships in Other Terminologies

An alternative to the *de novo* method is to explore the content of other medical terminologies, such as UMLS (belonging to the US National Library of Medicine), SNOMED, and the NCI thesaurus (belonging to the US National Cancer Institute) to take advantage of existing attribute relationships therein. If this approach is feasible, it may allow the MSSO to implement the concept attributes in MedDRA without increasing the burden (costs) on subscribers.

Based on our preliminary research, the "relationship to other concept", which is the "non-is a" relationship, exists in UMLS and the NCI thesaurus, and perhaps others as well. In the NCI thesaurus it is called "disease\_has\_finding" or "disease\_has\_abnormal\_cell", etc.

For each terminology that the MSSO is researching, the following questions need to be addressed:

- Can the MSSO get access to the terminology and be able to extract the needed information easily? Some terminologies might be built in such way that particular software needs to be developed in order to access and extract the needed data.
- Does the terminology have the linkage/relationship that connects a medical diagnosis and a laboratory test result? This is the type of relationships that we are interested in.
- If so, what type of test results are they? In other words, are these test results compatible with MedDRA investigation terms (e.g., are they qualitative, not quantitative results)? In some cases, if the test results are too general, we will not be able to apply them as MedDRA concept attributes.

Assuming the MSSO is successful in identifying a candidate terminology to use for this purpose, a next step would be to estimate the cost and effort to extract and implement concept attributes into MedDRA, including necessary quality control processes. Future maintenance would need to be estimated at the end of Phase II period. For example, is there a way to estimate the number of change requests related to concept attributes?

### 3.2.1 NCI Thesaurus

Although NCI thesaurus has a number of relationships used to relate disease concepts and various abnormalities and abnormal findings, they are not compatible to MedDRA terminology. For example, one of the relationships is called “Disease\_Has\_Finding”. But the finding or the investigation term is much more detailed than those in MedDRA. As shown in Figure 3-1, the NCI term is “Carcinomatous Component Present”, but a MedDRA investigation term would be “Biopsy abnormal” or “Histology abnormal”. Therefore, NCI Thesaurus is not a candidate for the concept attribute pilot study.













Relationships to other concepts:		
Disease_Has_Normal_Tissue_Origin	 	Oral Cavity Epithelium
Disease_Has_Abnormal_Cell	 	Malignant Squamous Cell
Disease_Excludes_Abnormal_Cell	 	Neoplastic Smooth Muscle Cell
Disease_Has_Finding	 	Carcinomatous Component Present
Disease_Has_Primary_Anatomic_Site	 	Oral Cavity
Disease_Has_Associated_Anatomic_Site	 	Palate

Figure 3-1 Sample Relationships from NCI Thesaurus

### 3.2.2 SNOMED-CT

The MSSO contacted the College of American Pathologists and was told that SNOMED CT does not have the types of linkages to support development of MedDRA concept attributes.

Also based on our knowledge, SNOMED CT has LOINC as its Finding component and LOINC terms are not configured in the same way as terms in MedDRA SOC *Investigations*.

### 3.2.3 UMLS System

The MSSO has conducted some preliminary investigations of the UMLS system. The following types of relationships in UMLS may contain the data that are of interest (identified with an asterisk):

- Assorted, symbolic relationships
  - Hierarchical
  - Non-hierarchical
    - analyzed by
    - associated finding of
    - disease\_may\_have\_finding\*
    - has\_finding\_method
    - is\_finding\_of\_disease\*
    - is\_interpreted\_by
    - may\_be\_finding\_of\_disease\*
- Statistical relationships: Topic based
  - Anatomy
  - Chemistry
  - Complications
  - Congenital
  - Diagnosis\*
  - Diagnostic use\*
  - Etiology
  - Methods\*
- Categorization relationships – semantic relationship

The MSSO will identify and contract with a subject expert in UMLS system. This expert will identify and extract the relationships of interest from the UMLS system.

The MSSO IT experts will incorporate the extracted concept attributes into a small set of MedDRA terms. The incorporated attribute links will go through a quality check by MSSO physicians.

The expected time for this task is 3 - 6 months. The cost analysis is listed in Table 3-1 below.

Task	Cost	Duration
Contractor: Identify and extract links from UMLS	\$6000 (\$150 per hour)	40 hr
Phase I MSSO staff: two physicians, two engineers: incorporate the extracted links into a small set of MedDRA, medical and technical QC	Within existing MSSO budget	3-6 month (part time)

**Table 3-1 Phase I Tasks, Cost, and Duration**

The MSSO believes the concept attribute development and maintenance effort can be done with existing MSSO resources if the task does not have fixed delivery points. The MSSO proposes that the development and future ongoing maintenance of concept attributes should not have response time requirements so the work can be completed when the ongoing MedDRA maintenance is not consuming the time of all MSSO medical staff.

## 4 Phase II – User Testing

The benefit of the concept attribute relationships in the analysis of MedDRA-coded data will be tested by volunteers from the user community. At the end of phase I, the MSSO will contact the regulators, industry associations, MedDRA Expert Panel members, and MedDRA Points to Consider Working Group members for testing volunteers.

The testing will be done on a small set of MedDRA terms that have been assigned concept attribute relationships. The testing involves the input from safety physicians as well as statisticians in both clinical trial and pharmacovigilance scenarios. The following types of feedback are needed to make a recommendation:

- Are the concept attribute relationships helpful in creating *ad hoc* safety surveillance queries?
- Are the concept attribute relationships helpful in populating relevant MedDRA-coded adverse event/adverse reaction, laboratory report in a medical meaningful way by statisticians?
- What are the limitations of concept attribute relationships? Can improvements be made?
- Do you support the implementation of concept attributes?

A successful test indicates that the concept attributes are a useful tool in addition to the hierarchy to help safety physicians and statisticians to analyze MedDRA-coded data.

## MedDRA MSSO

The MSSO staff is responsible for the coordination of the soliciting volunteers, coordinating tests, collecting and analyzing test results. Again, these tasks will be done on a part-time basis.

Phase II is estimated to be completed in 2 - 4 months.

Task	Cost	Duration
One physician, one engineer: coordination, analyzing results	Within existing MSSO budget	2-4 month (part time)

Table 4-1 Phase II Tasks, Cost, and Duration

## 5 Phase III – Decision Making

At the end of the phase II, the MSSO will provide the results of subscriber testing and future maintenance estimation requirements (i.e., costs) to the Management Board for consideration of whether or not the concept attribute relationships should be implemented in MedDRA.

Task	Cost	Duration
One physician: draft the documentation	Within existing MSSO budget	1 month (part time)
One physician: peer reviewer		

Table 5-1 Phase III Tasks, Cost, and Duration

## 6 Risk Assessment

### 6.1 Pilot Study

There is no risk to MedDRA terminology by conducting the pilot study because the pilot is done in a small set of MedDRA in a testing environment. The pilot study has no impact on the MedDRA official releases. Although the human resource is shared within the MSSO between the pilot study and MedDRA maintenance, MedDRA release takes priority.

### 6.2 Full Implementation of Concept Attributes

The risk is minimal because the impact on the terminology maintenance by concept attributes will be evaluated before the final decision is made. Appropriate adjustments will be made accordingly.