

MedDRA Literature Commentary

Subject of commentary:

Bousquet, C, Henegar, C, Lillo-Le Louet, A, Degoulet, P and Jaulent, MC.
Implementation of automated signal generation in pharmacovigilance using a knowledge-based approach. *International Journal of Medical Informatics* (2005) 74, 563-571.

Commentary:

This article presents a data-mining tool (PharmaMiner) that is designed to improve automated signal detection algorithms for pharmacovigilance purposes.

The article begins by describing the application of automated algorithms to detect safety signals in large pharmacovigilance databases. The authors note that a limitation of quantitative methods based on Bayesian analysis is that they do not take into account the semantic information existing in the vocabularies used to code adverse events. A new data-mining tool (PharmaMiner) was therefore built to group semantically linked adverse events and to apply Bayesian and statistical analysis methods on these groups to detect potential signals.

The authors provide a brief overview of MedDRA and refer to a previous study in which MedDRA is described as a first generation system¹. They note some limitations of MedDRA; they do not consider it to be truly multi-axial, the grouping of terms by high level categories is not accurate, and it lacks formal definitions of terms. It is noted that the finer granularity of MedDRA compared to other terminologies such as WHO-ART and COSTART lowers the performance of automated detection algorithms and that studies have argued that automatic grouping of similar medical conditions would increase the power of detection algorithms. Special Search Categories (SSCs) are briefly described and it is noted that these are created manually rather than having them generated automatically based on semantic definitions of MedDRA terms. The authors do not include any mention of Standardised MedDRA Queries (SMQs) as a tool for case identification.

The main part of the article provides a sophisticated and technical description of the methodology of the development of the PharmaMiner tool that is beyond the scope of this commentary. However, it is possible to summarize the testing process for this data mining tool. A subset of the French Pharmacovigilance database containing over 42,000 case reports was used as the test database. A total of 846 WHO-ART PTs had been used to code adverse events in this subset and these terms were first mapped to 694 equivalent MedDRA PTs using a UMLS network. (The authors do not comment on this mapping ratio but it would not generally be expected that a particular number of WHO-ART terms would map to a smaller number of MedDRA terms. An internal study by the MSSO has found that mapping verbatim terms to either WHO-ART or to MedDRA results in approximately two times as many resulting PTs MedDRA compared to WHO-ART). The authors also used an ontology editor to create a formal ontology providing semantic definitions of MedDRA terms. Only 530 MedDRA terms were defined, representing a very small proportion of the MedDRA terminology, but it was felt to be

sufficient for the test database. (Of note, MedDRA Version 5.1 was referenced in this article; the current MedDRA version as of the publication date is Version 8.0).

The PharmaMiner tool uses five measures of signal detection – the WHO Bayesian method and four statistical methods. In addition, the tool uses three methods of terminological reasoning (TR), grouping concepts in a hierarchy by subsumption. Terminological reasoning was used within the MedDRA hierarchy (MedDRA TR), within the ontology created for MedDRA (Ontology TR) and within the ontology in combination with another terminological technique called approximate matching (Ontology TR + AM).

The results of the testing found that grouping of cases using terminological reasoning and approximate matching within the ontology (Ontology TR + AM) identified more occurrences of drug-adverse reaction associations than using the original MedDRA hierarchy without any terminological reasoning. The differences were statistically significant with each of the five signal detection methods.

In the discussion, the authors note that this is the first experience with using terminological reasoning to improve performances of current signal detection algorithms. It is seen to be a promising technique but large computer resources were needed to run the tool. Other limitations are discussed including difficulties with NOS and NEC terms in MedDRA and the fact that the ontology of only 530 MedDRA terms would not be large enough for use in databases coded with MedDRA. It is also noted that although the tool generates more drug-adverse reaction associations, it is not known if the system highlights more relevant signals or is generating more noise. The authors also note that the present implementation of the tool does not take into account drug-drug interactions, complex adverse reaction syndromes or comparison of adverse reaction profiles in drug groups.

Summary:

This is a sophisticated and technical article written from a medical informatics perspective. It describes how the PharmaMiner tool combines terminological reasoning with signal detection algorithms to improve automated signal generation. It is unclear why the authors describe MedDRA as not truly multi-axial; it is multi-axial within the context of its own organization (it SOC hierarchies). Furthermore, the statement that the MedDRA 'high level' groupings are not accurate is arguable; although they continue to be refined by input of MedDRA users, the grouping terms in MedDRA logically organize related concepts below them in medically meaningful ways for the purpose of classification and analysis. The authors do not provide an example of an 'inaccurate' grouping in MedDRA.

Finally, the article does not discuss the approach to case identification used by SMQs which are now in widespread testing and implementation phases with the MedDRA subscriber community.

1. Bousquet, C, Lagier, G, Lillo-Le Louet, A, Le Beller, C, Venot, A and Jaulent, MC. Appraisal of the MedDRA Conceptual Structure for Describing and Grouping Adverse Drug Reactions. Drug Safety 2005; 28(1), 19 – 34.