Automatic Generation of MedDRA terms Groupings using an Ontology

Gunnar DECLERCK^{a,1}, Cédric BOUSQUET^{a,b} and Marie-Christine JAULENT^a ^a INSERM, UMRS 872 EQ20, Université Paris Descartes, France. ^b Department of Public Health, CHU University of Saint Etienne, France.

Abstract. In the context of PROTECT European project, we have developed an ontology of adverse drug reactions (OntoADR) based on the original MedDRA hierarchy and a query-based method to achieve automatic MedDRA terms groupings for improving pharmacovigilance signal detection. Those groupings were evaluated against standard handmade MedDRA groupings corresponding to first priority pharmacovigilance safety topics. Our results demonstrate that this automatic method allows catching most of the terms present in the reference groupings, and suggest that it could offer an important saving of time for the achievement of pharmacovigilance groupings. This paper describes the theoretical context of this work, the evaluation methodology, and presents the principal results.

Keywords. Pharmacovigilance, knowledge engineering, ontology, MedDRA terminology, SMQ, semantic reasoning.

Introduction

Pharmacovigilance is the branch of pharmacological sciences dedicated to postmarketing drug surveillance and prevention of adverse drug reactions (ADRs). An important activity related to pharmacovigilance is the reporting and coding of case reports by monitoring centres. ADRs are usually coded with the MedDRA terminology (Medical Dictionary for Drug Regulatory Activities) or WHO-ART (World Health Organization-Adverse Reaction Terminology). Case reports are stored in databases that constitute putative knowledge on suspected ADRs. Beyond the collect and the coding activities, the discipline seeks to identify statistical relationships between groups of ADRs and drugs, what is called a signal. Commonly used methods search databases for significant occurrence disproportionalities (see [1] for details). Once discovered, such a relationship may lead to clinical, pharmacological and epidemiological studies in order to assess the causal relationship between the drug and ADR.

However it appears today that statistical approaches, when confined to pure quantitative computation of data, are not sufficient [1,2]. Their performances are especially limited by the fact that they do not take into account the semantic level of information present in case reports. For example a signal of bullous eruption could be detected by grouping similar medical conditions such as "Epidermolysis bullosa", "Stevens-Johnson syndrome" or "Bullous impetigo" while no signal would be detected for each single term with the same drug. For that reason, we assume that grouping

¹ Corresponding Author: Centre de recherche des Cordeliers, 15 rue de l'école de médecine, Paris, 75006, France; E-mail: gunnar.declerck@crc.jussieu.fr

terms is a prerequisite to statistical approaches [1-5]. We propose knowledge-based approaches for grouping together similar case reports on the basis of the semantic information present in the controlled ADR vocabularies [1-3].

In a previous study [3], accounting for those knowledge-based approaches, we have developed an ontology of ADRs (named OntoADR), based on the original MedDRA hierarchy, to support the realization of automatic groupings of terms using semantic reasoning. The objective of the present study is to evaluate MedDRA terms groupings obtained with this ontology by comparing them to existing handmade reference groupings. We first present OntoADR and the method used to perform and evaluate the groupings, and then the results obtained for 13 safety topics.

1. Material and method

1.1. OntoADR ontology

OntoADR includes 34994 concepts using a total of 157572 definitional axioms. 20856 concepts come from MedDRA 13.0, the others from Snomed-CT [6]. Concepts are defined with semantic properties corresponding to relations used in the medical domain. 26 relations were selected from Snomed-CT, among which: HASFINDINGSITE, which specifies the body site affected by a condition; HASASSOCIATEDMORPHOLOGY, which describes the morphologic changes that are characteristic features of a disease; or HASOCCURRENCE, which refers to the specific period of life during which a condition first occurs. Formal definitions of MedDRA terms were realized using mappings with Snomed-CT concepts as defined in the UMLS (Unified Medical Language System) metathesaurus or were designed manually by medical experts and knowledge engineers. Several methods of semi-automatic completion of the formal definitions, exploiting the linguistic information of MedDRA terms, were also used. MedDRA terms are thus defined in OntoADR by sets of properties corresponding to a decomposition of their medical meaning. For instance, the MedDRA concept "Eyelid bleeding" (which has been mapped with the Snomed-CT concept "Hemorrhage of eyelid") is defined with the following properties: HASASSOCIATEDMORPHOLOGY SOME 'HEMORRHAGE' AND HASFINDINGSITE SOME 'EYELID STRUCTURE'. 'Hemorrhage' and 'Eyelid structure' are Snomed-CT concepts that have been imported into OntoADR to fill the semantic relations used to express the meaning of MedDRA concepts.

1.2. Design of OntoADR query-based groupings

To design our automatic query-based groupings, we focused on a list of 13 safety topics (consisting in broad categories such as *acute renal failure* or *peripheral neuropathy*) initially identified by Trifirò et al. [7] as first importance ADRs and further refined by the PROTECT consortium (see acknowledgments) (see Figure 1). For each safety topic, OWL (Web Ontology Language) queries have been designed to express in formal terms the medical meaning targeted by the topic. Those queries have then been used with OntoADR to achieve automatic groupings of MedDRA PTs (Preferred Terms). Semantic criteria that have to be fulfilled by the terms to be selected are expressed using the semantic relations describing OntoADR concepts and OWL logical connectors. For instance, *Upper gastrointestinal bleeding* safety topic can be described using the following query: HASASSOCIATEDMORPHOLOGY SOME

"HEMORRHAGE' AND HASFINDINGSITE SOME 'UPPER DIGESTIVE TRACT STRUCTURE'. The query can then be used to select MedDRA terms that are defined with those two properties in OntoADR (which is for example the case of: "Duodenal ulcer haemorrhage", "Gastric haemorrhage" or "Mallory-Weiss syndrome").

1.3. Evaluation of OntoADR query-based groupings

To evaluate this grouping method, the groupings achieved with the querying process have been compared with standard MedDRA groupings targeting the same or analogous safety topics. These gold standards are of two types: a) original MedDRA hierarchy groupings of PTs (High Level Terms: HLTs or High Level General Terms: HLGTs); b) MedDRA Standard Medical Queries (SMQs). SMQs are collections of PTs developed manually by the MSS0 (*Maintenance and Support Services Organization*) [4] that refer to a common clinical condition but are not necessarily hierarchically related.

Due to the limited topics covered by standard MedDRA groupings, original MedDRA hierarchy groupings and SMQs could not be identified for all safety topics investigated by our study. In few cases we manually selected the PTs from a given HLT, SMQ or HLGT (see Figure 1). In addition, MedDRA groupings taken as gold standard do not always exactly fit the condition targeted by the safety topic. A heuristic information about the semantic proximity between each gold standard and the corresponding safety topic was then *a priori* set by a medical expert (see Figure 1: (+) for imperfect semantic match; (++) for perfect or quasi-perfect semantic match). For instance the MedDRA HLT "Bullous conditions" was taken as gold standard for the safety topic "Bullous eruptions" and therefore assessed as having a perfect semantic match. "Acute renal failure" safety topic was assessed as having a perfect semantic match with the SMQ bearing the same name, but only an imperfect semantic match with the HLT "Renal failure and impairment" also taken as gold standard. Indeed, "Renal failure and impairment" is more general than "Acute renal failure", because it is not limited to acute conditions. MedDRA groupings having a perfect semantic match were primarily considered to evaluate the OntoADR groupings.

The recall, precision and F-measure rates were calculated to compare the set of terms obtained with query-based OntoADR method and the set of terms present in the gold standards. For instance, the OntoADR grouping *Upper gastrointestinal bleeding* comprises 29 PTs, of which 25 are present in the gold standard *Gastrointestinal haemorrhage* SMQ. Two PTs of this SMQ (*Duodenal operation* and *Ulcer haemorrhage*) are not returned by the OntoADR query. In this example we obtain a recall rate of 92.6%, a precision rate of 86.2% and a F-measure rate of 89.3%. We present in the next section the results obtained for the 13 safety topics.

2. Results

General results are shown in Figure 1. Upper part of mean values: results for all MedDRA reference groupings. Bottom part: results when considering only MedDRA reference groupings having a perfect (++) semantic match with the safety topic. Recall and precision rates show that our automatic grouping method allows catching most of the terms present in the reference groupings. The results are still better when considering only MedDRA groupings with a perfect semantic match (++). We can also

observe that recall and precision rates are better for original MedDRA hierarchy groupings (HLT/HLGT) than for SMQ groupings.

Safety topic	MedDRA gold standards		sem.	RESULTS		
			match	Recall	Precision	F-measure
1. Bullous eruptions	HLT	Bullous conditions	++	81,3%	33,3%	47,3%
2. Acute renal failure	SMQ	Acute renal failure	++	57,9%	51,2%	54,3%
	HLT	Renal failure and impairment	+	47,8%	55%	51,2%
3. Anaphylactic shock	SMQ	Anaphylactic/anaphylactoid shock	+	34,5%	38,5%	36,4%
	HLT	Anaphylactic responses	+	100%	100%	100%
4. Rhabdomyolysis	SMQ	Rhabdomyolysis/myopathy	+	46,7%	47,7%	47,2%
5. Aplastic anaemia / pancytopenia	SMQ	Cytopenia and haematopoietic	+	55%	55%	55%
	HLT	Marrow depression and hypoplastic	++	93,3%	70%	80%
6. Neutropenia	SMQ	Leukopenia SELECT	++	100%	63,6%	77,8%
	HLT	Neutropenias	++	100%	59,1%	74,3%
7. Cardiac valve fibrosis	HLGT	Cardiac valve disorders SELECT	++	100%	100%	100%
8. Extrapyramidal disorders	SMQ	Extrapyramidal syndrome	+	64,9%	48,5%	55,6%
	HLT	Dyskinesias and movement disorders	+	100%	71,4%	83,3%
9. Confusional state	SMQ	Noninfectious encephalopathy	+	16,0%	48,1%	24,1%
	HLT	Confusion and disorientation	++	100%	42,9%	60%
10. Thrombocytopenia	SMQ	Thrombocytopenia	++	100%	43,3%	60,5%
	HLT	Thrombocytopenias	++	100%	36,7%	53,7%
11. Upper gastrointestinal bleeding	SMQ	Gastrointestinal haemorrhage SELECT	++	92,6%	86,2%	89,3%
12. Peripheral neuropathy	SMQ	Peripheral neuropathy	++	66,7%	29%	40,4%
	HLGT	Peripheral neuropathies	++	98,9%	74,8%	85,2%
13. Maculo-papular erythematous	HLT	Rashes, eruptions and exanthems NEC	+	100%	20,4%	33,9%
eruptions						
MEANV	ALUES	(+) and (++) groupings	SMQ	63,4%	51,1%	54,0%
		HLT/HLGT		92,8%	60,3%	69,9%
			тот	78,8%	55,9%	62,3%
		only (++) groupings	SMQ	83,4%	54,7%	64,5%
		HLT	/HLGT	96,2%	59,5%	71,5%
			тот	90,9%	57,5%	68,6%

Figure 1. Recall, precision and F-measure rates of automatic OntoADR groupings. When a selection of PTs has been made in the MedDRA grouping taken as gold standard, *SELECT* is indicated in the third column.

3. Discussion

This paper presents the evaluation of an automatic query-based ADR terms grouping method in the context of pharmacovigilance. Our results demonstrate that this method can efficiently support the realization of automatic ADR groupings using OWL queries. This is a promising result, because MedDRA terms groupings for pharmacovigilance (mainly SMQs) are so far achieved manually, and an automation of the process, even partial, could allow an important saving of time.

The greater heterogeneity of terms in SMQs compared to HLTs and HLGTs makes it more difficult to catch all the terms with a single query. For instance, most of the terms of the *Acute renal failure* SMQ do not fit the strict definition of the condition. Instead, they correspond to more general, associated or close medical conditions (*Renal impairment, Nephritis, Renal failure, Nephropathy toxic*) or to results of analyses, clinical signs or therapeutic procedures (*Blood creatinine abnormal, Urine output decreased, Dialysis*). The main difficulty to catch those terms with a query is that they are related to the medical condition via an empirical knowledge relation. By principle, such relations are not represented in ontologies, describing only the formal semantics of concepts, and not the empirical relations between the realities that are named by the concepts. One solution to catch that kind of terms is to complete the query with complementary assertions. These assertions specify explicitly the types of medical entities related to the topic one wants to retrieve, for instance the biological results. In the case of *Acute renal failure*, specific assertions will allow to select terms relating to analyses measuring the creatinine or urea ratio in blood. One could also decide to put empirical knowledge into OntoADR, for instance a relation specifying what are the clinical signs of medical conditions (HASFORCLINICALSIGN). But this solution might have important drawbacks: a) it is time-consuming and requires representing expert knowledge; b) medical knowledge is rapidly evolving, thus requiring constant updating of the ontology; c) it can bring forth some problems in the conceptual reasoning phase: especially, the OWL reasoning algorithms can only work if assertions used to define the concepts are necessary conditions (it is a prerequisite for the application of the inheritance transfer of definitional properties); d) the possibility of using those empirical relations in queries is not obvious because some signs are only signs of a given pathology if accompanied by other signs and some signs may be absent: some complementary rules are thus necessary.

Some of the terms present in MedDRA groupings taken as gold standard are not retrieved by our automatic queries, but terms absent from those reference groupings are also caught, and the question arises whether this difference in content has an impact (and if so is it positive?) on the signals detected by traditional statistical methods. A further study will address the question of the reliability of those query-based groupings for signal detection, by comparing their performances with those of standard MedDRA groupings, first of all of SMQs.

Acknowledgments This work was supported by funding from the European project PROTECT (<u>http://www.imi-protect.eu/</u>). Grant agreement N°115004. We acknowledge Eric Sadou, Adrien Fanet, Anne Jamet and Julien Souvignet who contributed to the development of ontoADR.

References

- Bousquet C, Henegar C, Lillo-Le Louët A, Degoulet P, Jaulent MC. Implementation of automated signal generation in pharmacovigilance using a knowledge based approach. Int J Med Inform. 2005; 74(7-8): 563-571.
- [2] Bousquet C, Lagier G, Lillo-Le Louët A, Le Beller C, Venot A, Jaulent MC. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. Drug Saf. 2005; 28(1): 19-34.
- [3] Jaulent MC, Alecu I. Evaluation of an ontological resource for pharmacovigilance. Stud Health Technol Inform. 2009; 150: 522-526.
- [4] Mozzicato P. Standardised MedDRA Queries: Their role in signal detection. Drug Saf. 2007; 30(7): 617-619.
- [5] Nadkarni PM, Darer JA. Determining correspondences between high frequency MedDRA concepts and SNOMED: a case study. BMC Med Inform Decis Mak. 2010; 10(1):66
- [6] SNOMED Clinical Terms® User Guide, 2010 July International Release.
- [7] Trifirò G, Pariente A, Coloma PM, Kors JA, Polimeni G, Miremont-Salamé G, Catania MA, Salvo F, David A, Moore N, Caputi AP, Sturkenboom M, Molokhia M, Hippisley-Cox J, Acedo CD, van der Lei J, Fourrier-Reglat A. Data mining on electronic health record databases for signal detection in pharmacovigilance: which events to monitor? Pharmacoepidemiol Drug Saf. 2009; 18(12):1176-84.