An Ontological Representation of Adverse Drug Events

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Abstract. A standardized, controlled vocabulary allows adverse drug events (ADE) information to be described in an unambiguous way in knowledge bases, which is critical for clinical decision support systems for patient medication safety. In this paper, we describe our preliminary effort on development of an ontological representation pattern for the ADE domain. We discuss clinical implications of the effort and potential challenges on its integration with existing data standards.

Keywords: Adverse Drug Event (ADE), Ontology, Knowledge Base, Semantic Web Technology.

1 Introduction

Adverse drug events (ADE) are a well-recognized cause of patient morbidity and increased health care costs in the United States. Multiple studies have demonstrated that a clinical decision support (CDS) system based on a standardized ADE knowledge base can be useful to help physicians reduce the risk of their patients' medications [1,2]. In a previous study, for instance, we proposed a comprehensive framework for building a standardized ADE knowledge base known as *ADEpedia* (http://adepedia.org) through combining ontology-based approaches with Semantic Web technology [3]. However, there is no standardized, controlled vocabulary available that allows the ADE information to be described in an unambiguous way in such a knowledge base.

An ontological representation of the ADE domain would provide computable semantics for an ADE knowledge base, and facilitate semantic integration of ADE related data standards. In the present work, we describe our preliminary effort on development of an ontological representation pattern for the ADE domain. We discuss clinical implications of the effort and potential challenges with respect to its integration with existing data standards.

2 Related work

Stetson et al (2001) developed an ontology representing the intersection of medical errors, information needs and the communication space [4]. The main use of that ontology was to help guide the rational deployment of informatics interventions. Herman et al (2005) created a vaccine adverse event ontology for public health [5]. Mokkarala et al (2008) described their efforts in developing a comprehensive medical error ontology to serve as a standard representation for medical error concepts from various existing published taxonomies [6]. Ceusters et al (2011) described an evolutionary approach to realism-based adverse event representations [7]. The ontology is designed under the OBO foundry principles and merged with the Basic Formal Ontology (BFO) in upper level. Although these ontology development efforts are relevant to the ADE domain and would be useful starting points, the semantics of the ADE domain remain poorly specified. For example, in the Adverse Event Ontology (AEO) [8], there are only two ADE related concepts defined: the concept "drug adverse event" under its parent "adverse event" and the concept "drug administration" under its parent "medical intervention". For another example, Bousquet, et al (2008) [9] proposed an ontological model for adverse drug reactions, in which the main categories "Investigation", "Accident" and "Disorder" are related to "Drug" with the "Is_related_to" link.

3 An ontological representation pattern of the ADE

We proposed an ontological representation pattern for the ADE domain. We also performed a case study for representing real ADE data using the domain pattern.

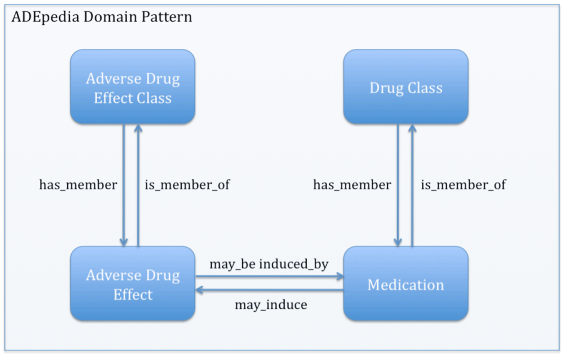

Figure 1. Proposed pattern for the ADE domain

Fig. 1 shows the proposed pattern for the ADE domain. In the pattern, we defined four major types: Adverse Drug Effect Class, Drug Class, Adverse Drug Effect and Medication. We also defined the relationships between the four types. The relationships are "may_induce", "may_be_induced_by", "has_member" and "is_member_of". Table 1 shows the relationship definition using the vocabulary of RDF Schema (RDFS) [10].

With the pattern specified, we will be able to represent real ADE data. Table 2 shows the example instances for each of the four types defined in the pattern. An ICD-10-CM [11] code "*Adverse effect of anticoagulants*" is used as an instance of the

type ADE Category; a NDF-RT (National Drug File-Reference Terminology) [12] code "*Anticoagulants*" as an instance of the type Drug Class; a SNOMED CT [13] code "*Blood in urine*" as an instance of the type ADE; and a RxNORM [12] code "*Warfarin sodium*" as an instance of the type Medication.

Table 1. Relationship definition using RDF Schema

```
<adepedia:may_induce> a <rdf:Property>;
        <rdfs:domain> <adepedia:Medication>;
        <rdfs:range> <adepedia:AdverseDrugEffect> .
<adepedia:may_by_induced_by> a <rdf:Property>;
        <rdfs:domain>  <adepedia:AdverseDrugEffect>;
        <rdfs:range> <adepedia:Medication> .
<adepedia:has_member> a <rdf:Property>;
        <rdfs:domain>  <adepedia:AdverseDrugEffectClass>;
        <rdfs:range> <adepedia:AdverseDrugEffect> .
<adepedia:is_member_of> a <rdf:Property>;
        <rdfs:domain>  <adepedia:AdverseDrugEffect>;
        <rdfs:range> <adepedia:AdverseDrugEffectClass> .
<adepedia:has_member> a <rdf:Property>;
        <rdfs:domain>  <adepedia:DrugClass>;
        <rdfs:range> <adepedia:Medication> .
<adepedia:is_member_of> a <rdf:Property>;
        <rdfs:domain>  <adepedia:Medication>;
        <rdfs:range> <adepedia:DrugClass> .
```

4 Discussion

This study was motivated by our ongoing ADEpedia project aiming to develop a standardized ADE knowledge base. We have extracted both medication and ADE data using FDA Structured Product Labels (SPL) [14]. In the knowledge base, the medication data are represented by RxNORM codes and the ADE data are represented by SNOMED CT and MedDRA [15] codes. We use "may_induce" and "may_be_induced_by" to represent the drug-ADE relationship. We chose the predicates because they cover uncertainty between a drug and an ADE. For example, "Severe nausea occurs in 20% of patients for a given medication". We are also exploring the approach to represent this kind of frequency and severity knowledge of the ADEs.

From clinical perspective, clinical decision support (CDS) rules related to drugs and ADEs are generally expressed using a therapeutic or pharmacologic class (e.g. *ACE Inhibitors*) or a class of ADEs (e.g. adverse effects on cardiovascular system), rather than an individual drug or an ADE. Therefore, we plan to aggregate the medications to drug classes and the ADEs to ADE classes for our ADEpedia knowledge base.

In the proposed pattern, we use "has_member" or "is_member_of" to explicitly represent the drug-class membership relation. Note that the relation between individual drugs and drug classes or between individual

Table 2. The example instances of the four major types of the ADE representational pattern in RDF Turtle format

```
_:b0 a <adepedia:AdverseDrugEffectClass>;
    <adepedia:code> "T45.515";
    <adepedia:displayName> "Adverse effect of
anticoagulants";
    <adepedia:codeSystemName> "ICD-10-CM" .
_:b1 a <adepedia;DrugClass>;
    <adepedia:code> "C8812";
    <adepedia:displayName> "Anticoagulants";
    <adepedia:codeSystemName> "NDF-RT" .
_:b2 a <adepedia:Medication>;
    <adepedia:code> "114194";
    <adepedia:displayName> "Warfarin Sodium";
    <adepedia:codeSystemName> "RxNORM" .
_:b3 a <adepedia:AdverseDrugEffect>;
    <adepedia:code> "34436003";
    <adepedia:displayName> "Blood in urine";
    <adepedia:codeSystemName> "SNOMED CT" .
```

ADEs and ADE classes is generally represented through a taxonomic relation (isa) in biomedical terminologies [16]. Usually, the isa relation is translated to the "rdfs:subClassOf" in the vocabulary of RDF Schema.

In addition, we consider existing ADE relevant data standards can provide standardized codes as the instances (or subtypes) of the four types defined in the pattern. For instances, Bodenreider, et al (2010) investigated drug classes in biomedical terminologies from the perspective of clinical decision support. For 134 target drug classes, SNOMED CT was identified as the single best source with 75% coverage [16]. Pathak, et al (2010) analyzed categorical information in two publicly available drug terminologies: RxNorm and NDF-RT [12]. For the ADEs and ADE classes, we consider that SNOMED CT, MedDRA [15] and ICD [11] will be good candidate sources for further investigation.

In summary, we identified and defined a domain pattern for the ADE knowledge representation and we consider this pattern can be a starting pointing for an ontological representation of ADE domain. We believe that a community-based effort would be required to achieve a comprehensive standardized ontology for the domain, which would facilitate the semantic interoperability of the ADE knowledge bases in heterogeneous CDS systems and ultimately improve patient safety.

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