Diagnostic criteria and clinical guidelines standardization to automate case classification

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ABSTRACT

When increased rates of adverse events following immunization are reported, regulatory action can be taken by public health agencies charged with protecting the safety of the public. However, to even be interpreted, reports of adverse events must be encoded in a consistent way. Regulatory agencies rely on *guidelines* to help determine such encoding. Their application, if done manually, is expensive and time consuming. In the interest of making this process more efficient it is desirable to represent these guidelines in a format amenable to automated processing. This paper describes the Adverse Event Reporting Ontology (AERO), which provides a representation of guidelines classifying adverse events. The representation is novel in that it supports a balance between the ability to express different organizations guidelines and the need to use common terminology wherever possible. Having developed the framework with immunization related adverse events in mind, we show that it is nonetheless flexible enough to be applied to a different domain - malaria diagnosis. We also demonstrate how OWL reasoning can be leveraged to help compute such assessments and discuss prospects and hopes for adoption of the approach.

1 INTRODUCTION

An adverse event is an unexpected medical condition that is temporally proximate to administration of some medical intervention. Reports of adverse events are gathered by regulatory agencies in order to monitor the risks of medical interventions and take action in the interest of public safety. However, to even be interpreted, reports of adverse events must be encoded in a consistent way. Regulatory agencies rely on *guidelines* to help determine such encoding. Their application, if done manually, is expensive and time consuming. In the interest of making this process more efficient it is desirable to represent these guidelines in a format amenable to automated processing. A case in point is administration of vaccines. A computable representation of adverse events following vaccination would allow software tools to automatically process information from reporting systems (Chen *et al.*, 1994) that are used to monitor the general population. The Brighton Collaboration (The Brighton Collaboration, 2011), has done extensive work towards development of guidelines for classifying AEFIs (Bonhoeffer *et al.*, 2002). Our work aims to leverage these guidelines by embedding them in the semantic web framework. Within that computable framework we can automate the classification of reports of adverse events, and so improve the efficiency of discovering potential risks. When developing the Adverse Events Reporting Ontology (AERO), care was taken to reuse, when possible, work done in the context of other efforts. Reusing terms from other resources allowed us to rely on knowledge of domain experts who curated them and to dedicate more work time for terms that need to be created de novo. AERO reuses terms from the Open Biomedical Ontologies (OBO) Foundry (Smith B. et al., 2007) suite of ontologies, which improves the ability to interoperate with other resources that also use ontologies developed within the Foundry framework. Further details pertaining to the development of the AERO can be found in (Courtot *et al.*, 2011).

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2 GUIDELINE REPRESENTATION AND EVALUATION IN AERO

2.1 What guidelines are applied to

Figure 1 depicts the representation of a patient examination, a typical way in which a set of findings is collected in our post-licensing signal detection work. The process representation is from Ontology of Biomedical Investigations (OBI). A patient examination is a planned process with (at least) three participants - the patient being examined, the clinician doing the examination, and the collection of findings created as a result. The class clinical finding is of information entities that are about medically relevant entities - material entities, qualities, processes, dispositions that are typically localized in an anatomical system or region.

2.2 Guidelines

A guideline is represented as an information entity, an *iao:directive information entity* (IAO, 2012a). We relate the recipe and the Brighton case definition to the process of assessment by a composition of relations defined in Information Artifact Ontology (IAO) and Basic Formal Ontology (BFO). Figure 2 illustrates details of one such case, the case definition for anaphylaxis occurring after immunization. Our current implementation accomplishes this classification by defining classes that correspond to the criteria by which each of the possibilities is determined. For example Brighton gives a set of conditions which, if obtained, provide the strongest evidence that a case of anaphylaxis has occurred *aero:level 1 of certainty of anaphylaxis according to Brighton* (AERO, 2012). *aero:level 1 of certainty of anaphylaxis according to Brighton* is given a complete logical definition which is the expression encoding the criteria depicted in the lower middle of the figure. If the report has a set of finding components which together satisfy this

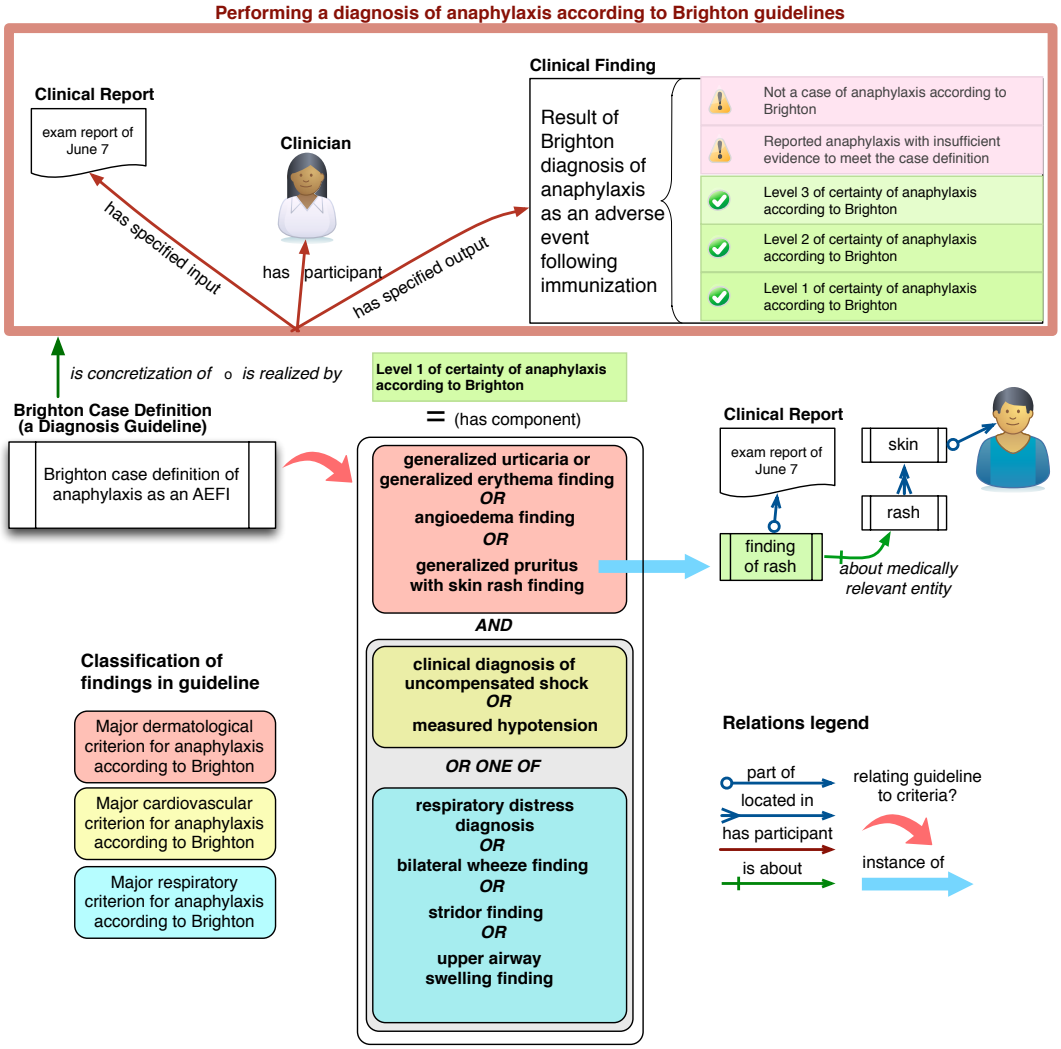

Fig. 2. The elements of an assessment of anaphylaxis according to Brighton as implemented in AERO. Performing a diagnosis involves assessing a number of criteria each (e.g. lower middle box) implemented as a class expression that classifies a set of findings. The diagnosis of Level 1 of certainty of anaphylaxis is made by the clinician if the written criteria apply, and by our OWL implementation if the class expression subsumes the set of findings shown in illustration as a *Clinical Report*. One contributor to the subsumption is the instance of finding of rash which is inferred to be of type generalized pruritus with skin rash finding. Note that finding subsumption is generally defined in terms of what the findings are about, illustrated by the pointers from finding of rash leading towards the patient.

class, then the report is classified as *aero:level 1 of certainty of anaphylaxis according to Brighton*.

2.3 Assessment pipeline

Figure 2 shows how the various elements are linked together to form the diagnosis pipeline for the assessment of anaphylaxis level 1 according to the Brighton guideline. The patient examination by the physician shown in Figure 1 results in a set of clinical findings which are then used to perform a diagnosis of anaphylaxis according to the Brighton guidelines. The output of this process is the determination of the level 1 of certainty of anaphylaxis according to Brighton, a type of Brighton diagnosis of anaphylaxis as an Adverse Event Following Immunization (AEFI), itself a Brighton diagnosis and clinical finding. The Brighton case definition of anaphylaxis as an AEFI is a type of Brighton case definition, which is itself a type of diagnosis guideline. In the AERO, the Brighton case definition for the anaphylaxis level 1 of certainty is modelled as an equivalent class. It *has component* the different findings, grouped in sets according to their importance in the establishment of the diagnosis. For example, the major cardiovascular criteria set for anaphylaxis according to Brighton is the disjoint union of a clinical diagnosis of uncompensated shock and a measured hypotension finding. A clinical diagnosis of uncompensated shock is a clinical finding, but also a diagnosis established based on the presence of 3 or more uncompensated shock signs, but at most one of each type.

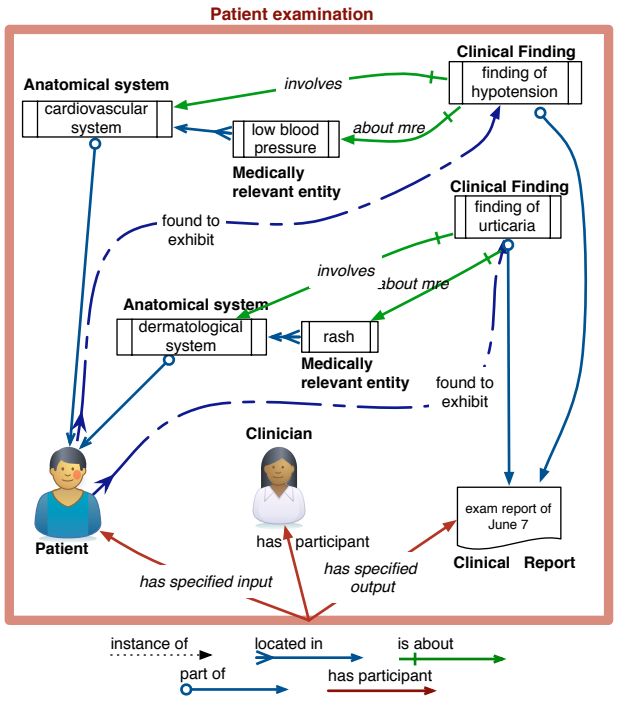

Fig. 1. Entities represented in patient examination and recording of findings: During an *obi:planned process*(red surrounding box) a clinician examines a patient - the specified input- and produces a report which is a set of *ogms:clinical findings* - the specified output. Each finding *iao:is about* a medically relevant entity (here a rash or low blood pressure) as well as the anatomical system or part proximate (here the skin or cardiovascular system). The report is a set of findings, each related to the report by the *aero:has component* relation.

3 THE World Health Organization (WHO) SEVERE MALARIA GUIDELINE FITS THE SAME FRAMEWORK

The WHO divides malaria into two categories, severe malaria and mild (or uncomplicated) malaria. Severe malaria is a life-threatening form of the disease requiring immediate hospital care and therefore correct classification of malaria is critical for appropriate patient treatment. The WHO specifies a list of criteria for severe malaria diagnosis (World Health Organization, 2000) including severe anemia, hyperparasitemia, hyperlactatemia, hypoglycemia, and over ten other different signs or symptoms. The WHO severe malaria guideline is not as complicated as the Brighton guideline as it does not need to relate symptoms and signs to specific anatomical systems. It does define symptoms and signs assessment based on laboratory measurement data in keeping with the approach described in the Guideline representation in AERO section but without a detailed implementation component. Applying the AERO developed pattern, severe malaria is modelled as the union of different criteria specified by the WHO. The *iao:scalar measurement datum* class (IAO, 2012b) is used to logically represent measurement data to facilitate the diagnosis process. Formal and logical representation of severe malaria diagnosis and some related criteria using Manchester syntax is shown in Figure 3.

```
severe malaria according to WHO criteria
= 'WHO diagnosis of malaria' and
    (('has component' some 'hyperlactatemia finding
                    according to WHO severe malaria criteria')
  or ('has component' some 'severe anemia finding
                    according to WHO severe malaria criteria')
  or ('has component' some 'hyperparasitemia finding
                    according to WHO severe malaria criteria')
  or ('has component' some ...) ... )

WHO diagnosis of malaria
= 'has component' some 'presence of malaria parasites positive finding'

hyperlactataemia finding according to WHO severe malaria criteria
= 'plasma lactate concentration measurement datum'
        and ('has measurement unit label' value millimolar) and
            ('has measurement value' only decimal[> 5])

severe anemia finding according to WHO severe malaria criteria
= ('has component' some ('hematocrit measurement datum'
        and ('has measurement unit label' value 'volume percentage') and
            ('has measurement value' only decimal[< 15])))) or
  ('has component' some ('hemoglobin concentration measurement datum'
        and ('has measurement unit label' value 'gram per liter') and
            ('has measurement value' only decimal[< 5])))
```

Fig. 3. Implementation of the WHO severe malaria guideline by applying the AERO guideline design pattern.

The diagnosis pipeline for severe malaria is the same as assessment of anaphylaxis level 1 according to the Brighton guideline shown in Figure 2. The Web Ontology Language (OWL) representation was tested by laboratory results and clinicians diagnosis published by Krupka, *et al.* (Krupka *et al.*, 2012) and is available online [1].

4 RESULTS

The pattern we developed in AERO allows for automated classification of the patients based on a set of signs and symptoms they present, and the associated clinical findings assessed by their physician in compliance with a selected guideline, as shown in Figure 1. Signs and symptoms are assessed by the physician during a patient examination, and the corresponding findings are of type generalized urticaria finding and measured hypotension finding respectively. These two clinical findings can then be inferred to be of type major cardiovascular criterion for anaphylaxis according to Brighton and major dermatological criterion for anaphylaxis according to Brighton. A diagnosis of level 1 of anaphylaxis is reached as they match the Brighton case definition for the components required. In the malaria implementation, automatic diagnostic classification results obtained match the WHO diagnosis shown in the paper by Krupka, *et al.* (Krupka *et al.*, 2012).

5 DISCUSSION

It is critical in health care in general, and in analysis of adverse event in particular to be able to store medical data as well as the guideline that was used to assess it. In (Gagnon *et al.*, 2010), Gagnon *et al.* demonstrate that depending on the guideline considered, the number of anaphylaxis cases after injection of the adjuvanted H1N1 pandemic vaccine varies. The National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) considers that reduced blood pressure is enough to

[1] `http://adverse-event-reporting-ontology.googlecode.com/svn/trunk/src/examples/malaria/ontology/aero-malaria_diagnosis.owl`

diagnose anaphylaxis after exposure to allergens (National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network , 2012), while two or more organ systems need to be involved as per Brighton. During immunization, decrease of blood pressure is frequently caused by fear of the syringe or the vaccine, and may lead to false positives when diagnosed with the NIAID/FAAN guideline.

Knowing which guideline was used for diagnosis establishment is therefore important to be able to weigh cases as more or less important depending on their evidence and supporting or not detection of a safety signal and further actions by health authorities. An additional possible contribution is to allow for various versions of the same guidelines to be encoded. Different changes, such as scientific research progress, may warrant guidelines update (Shekelle *et al.*, 2001), and we need to be able to at a minimum accommodate their co-existence. Ideally, we would be able to partly reconcile them, and facilitate migration from data encoded in the previous version to the newer one.

6 CONCLUSION

Our results demonstrate that the pattern defined in AERO is applicable to the automated classification of AEFI according to the Brighton guidelines. It can be implemented in other applications, such as automatic malaria classification based on the WHO severe malaria guideline. The latter illustrates the potential to generalize the AERO diagnosis guideline pattern to formal and logical description of various diagnosis guidelines and facilitate automated disease diagnosis and validation.

7 NEXT STEPS

The pattern described above has been designed with the overall goal of analyzing reports of AEFI from national systems such as the Vaccine Adverse Event Reporting System (VAERS) (Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), agencies of the U.S. Department of Health and Human Services, 2012) used in the United States and the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS) in Canada in an automated way. Both systems currently rely on Medical Dictionary of Regulatory Activities (MedDRA) to encode adverse events data. A mapping will be made to convert MedDRA codes to AERO annotations. We will then be able to use this mapping to process the existing MedDRA annotations on the data to infer if a Brighton criteria has been met or not.

AVAILABILITY

The AERO project, including documentation and links to the ontology is available at `http://purl.obolibrary.org/obo/aero`. The ontology is listed in the OBO library at `http://obofoundry.org/cgi-bin/detail.cgi?id=AERO` and in the BioPortal at `http://bioportal.bioontology.org/ontologies/1580`.

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