

Reporting Adverse Events: Basis for a Common Representation

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Abstract. The process of adverse event reporting aims to monitor the status of patients in clinical trials or to provide ongoing monitoring of the safety of interventions once they are in the market. Such reports help identify issues with treatment safety and efficacy, and allow for better education of health practitioners and the general public, ultimately allowing us to learn from our mistakes. However if such reports are to be maximally useful, the information they contain must be unambiguously shared, via standardization and accurate documentation. Towards this end, we briefly review existing reporting standards and then define *adverse event*, as well as other relevant terms, in a manner consistent with the use of the term in existing reporting guidelines. Novel aspects of this work include attention to the distinction between the classification of adverse events based on reporting versus the pathological process types they attempt to monitor, and integration with relevant OBO ontologies to minimize redundant definitional work as well as enable integration of adverse event reporting into the broader landscape of representation for translational medicine. Implementation of a prototype that incorporates this approach is discussed - the Adverse Events Reporting Ontology (AERO).

1 Introduction

In the clinical community, adverse events denote any untoward medical occurrence following a medical intervention. Adverse event reporting is a major part of clinical research, and an important tool to improve patient safety. By collecting and analyzing adverse events we can better understand and prevent them, as well as communicate issues and evidence among researchers, policy-makers and public, letting us learn from, and take action based on, our mistakes. However, the manner by which adverse events are classified and reported differs from agency to agency and from treatment type to treatment type. Therefore, in order to achieve large scale integration of reports of adverse events, a careful approach to their representation must be agreed upon.

We first document the widespread agreement on what adverse events are, using examples from the Brighton Collaboration guidelines for reporting adverse events following immunization, and addresses current limitations in reporting systems that limit

their effective wider scale use. An early implementation of this approach is our Adverse Events Reporting Ontology (AERO).

2 Background

What is an adverse event?

The Guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting [1], defines an adverse event as “Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.” The guide then adds “An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.” The Report of Adverse Event Following Immunization (AEFI) user guide [2] from the Public Health Agency of Canada (PHAC) adheres to this

definition and adapts it for AEFI reporting: “An AEFI is any untoward medical occurrence in a vaccine which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine”.

Not detailed in this statement is the additional fact that reporting guidelines often provide protocols for determining and reporting the likelihood that specific pathological processes have occurred, and that such protocols and reporting conventions differ from jurisdiction to jurisdiction, from investigation to investigation, and by symptom and severity.

Therefore adverse events as recorded in reports, contrary to what might otherwise be presupposed, are not necessarily processes, are not necessarily of the type reports say they are, are not necessarily causally related to the intervention which led to them being reported, and the terms used to describe them are not necessarily univocal.

This matches the usage made for example within the Vaccine Adverse Event Reporting System (VAERS) [3], which asserts that “VAERS collects data on any adverse event following vaccination, be it coincidental or truly caused by a vaccine”.

In particular we distinguish adverse event from adverse side effect, where the latter is of a type determined to be causally related to the intervention.

It is a goal of our work to nonetheless provide a coherent account and workable system for managing these reports in such a way as to maximize their utility.

When are adverse events reported?

Current guidelines [2] specify that events should be reported on the basis of their temporal association with the medical intervention. For example, in the case of AEFIs depending on (i) the type of immunizing agent (30 days after live vaccine or 7 days after killed or subunit vaccine) or (ii) biological mechanism (up to 8 weeks for immune-mediated events). Even though in some cases, and based on their personal experience, clinicians may think that some adverse events are most probably caused by the intervention, and even take action based to guard the patient’s health based on this assessment, they nonetheless must report any event occurring in the respective

corresponding time frame. In that way, records accumulated from many clinicians may be reviewed by safety committees, where evidence towards causality establishment will be reviewed and policy recommendations, based on unbiased evidence, can be made.

Issues with current adverse event reporting systems

While all practitioners agree on the importance of reporting adverse events in increasing public health safety, current methods used for spontaneous adverse events reporting are not sufficient, mitigating their usefulness. For example, there is no standardization of the terminology used in the current Electronic Data Capture (EDC) used by PHAC [4]. At best, a Medical Dictionary of Regulatory Activities (MedDRA) [5, 6] code is assigned after parsing the clinician’s input, but this code is not linked to any definition. This in turn may lead to heterogeneity in the diagnoses recorded – physicians may have slightly different interpretations of what constitutes a seizure for example. Several studies highlight the potential issues in using MedDRA for adverse event reporting, ranging from inaccurate reporting as several terms are non-exact synonyms, to lack of semantic grouping features impairing processing in pharmacovigilance [7–10]. Additionally, in many systems, only the adverse event code as determined by the system (e.g. resulting from parsing the textual input) is saved, and information about signs and symptoms used in the determination of that code are lost. This limits the ability of analysts to review the set of symptoms observed in order to establish a consistent diagnosis. The resultant lack of consistency limits the ability to query and assess important safety issues the resulting datasets might otherwise support.

A general review of systems used in other countries provides similar results. The Adverse Event Reporting System (AERS) [11] and VAERS systems used in the US rely on MedDRA to encode adverse events. They follow the international safety reporting guidance [12] which specifies: “Only the MedDRA Lowest Level Term (LLT) most closely corresponding to the reaction/event as reported by the primary source should be provided”. In Europe, the Vaccine European New Integrated

Collaboration Effort (VENICE) [13] group reports [14] that only 71% (17/24) of the countries states have adopted a classification of AEFIs, and that those chosen classifications are heterogeneous: 38% WHO¹ and 62% other or not specified.

Brighton collaboration artifacts

The Brighton Collaboration [15] is a global network of experts that aims to provide high quality vaccine safety information. It has done extensive work towards standardizing the assessment and reporting of adverse events following vaccination. The Brighton Collaboration published four artifacts of interest to our current work. The case definitions they provide relate symptoms and signs to assessments of whether a particular type of pathological process has occurred, assigning qualitative levels of certainty. They provide guidelines for three activities – data collection, analysis, and presentation of results, aiming to make collected data comparable, informed by the case definitions. By determining and publishing these guidelines, the collaboration creates methodological standards that enable accurate risk assessment. The case definitions neither require, nor assess a causal relation between a given adverse event and the immunization process. Rather, the case definitions are designed to define levels of diagnosis certainty based on known information about AEFIs.

The Brighton Collaboration has published a number of papers presenting these guidelines and case definitions, each aimed at reporting potential pathological processes, such as Seizure [16] and Guillain-Barré Syndrome [17]. In our prototype we have worked with the seizure case definition.

¹ The reports can be difficult to even interpret – the WHO Adverse Reaction Terminology (WHO-ART) is a non-open terminology and only a 1997 version appears to be publicly visible, hosted at <http://biportal.bioontology.org/ontologies/40404>. It lacks many terms that are essential for AE reporting, such as those related to seizure. More importantly, WHO-ART follows a 4-level structure similar to MedDRA, and therefore suffers some of the same defects.

3 Implementation

Our prototype aims to address a number of issues. While complete, the textual article-like format of the Brighton case definitions makes it difficult for clinicians to confirm that they see the relevant symptoms when making the adverse event diagnosis: case definitions are buried within the scientific paper. In the textual form, the case definition is not amenable to automated diagnosis – clinicians cannot choose which symptoms are observed and then infer the proper event diagnosis. A formal and logical description of vaccine adverse events would allow software tools to process the information and present only relevant items in a checklist to the physician, making it easier to validate upon data entry. Therefore, an ontology-based system at the time of data entry will increase data accuracy and completeness. For example, when the clinicians select seizure as adverse event, they will be offered a list of symptoms that may have manifested. By selecting the ones they did observe, the system will be able to confirm their diagnosis, potentially specifying it, such as assigning a level of certainty based on the Brighton case definition. The system will also be able to call the diagnosis into question, by warning that the set of events selected does not allow for unambiguous diagnosis. In the latter case, the system will also provide a list of such events that would allow determination. Taken together, those will enable, at the time of data entry, to unambiguously refer to a specific set of symptoms, each carefully defined, and establish a diagnosis, which remains linked to its associated symptoms. The adverse event will also be formally expressed, making it amenable to further querying for example for statistical analysis “what percentage of patients presented with motor manifestations?”) at different levels of granularity (e.g., facilitating queries such as “what percentage of patients presented with tonic-clonic motor manifestations?”) Finally, by agreeing on a common defined vocabulary we can increase data interoperability, and enable cross databases queries across different centres or against public datasets, such as literature references or other AEFI datasets.

In the following sections we present a proof of concept prototype, the AERO, based on the seizure case definition from the Brighton group.

Incorporating existing relevant resources

In implementing a distinct resource for adverse event reporting, 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, to dedicate more work time for terms that need to be created *de novo*. When only few terms of interest were identified in external ontologies, those have been imported relying on the Minimum Information to Reference an External Ontology Term (MIREOT) guideline [18]. For example the Vaccine Ontology (VO) [19] defines the *vaccination* process as an “administering substance in vivo that involves in adding vaccine into a host (e.g., human, mouse) in vivo with the intend [sic] to invoke a protective immune response”, and we use it to define vaccine adverse events. Similarly, we use classes from the Ontology for General Medical Science (OGMS) [20]. OGMS represents pathological entities, diseases and diagnosis, and some of its classes such as *disorder* and *sign* are at the root of very important AERO hierarchies; more details on their usage is shown below. In other cases, we decided to import external ontologies as a whole: (i) the Relations Ontology (RO) [21] contains a set of common relations, (ii) the Information Artifact Ontology (IAO) [22] deals with information entities and metadata, and (iii) the Basic Formal Ontology (BFO) is used as our upper-level ontology. Those resources are commonly used by the Open Biomedical Ontologies (OBO) Foundry [23] ontologies, of which AERO aims to be a part; relying on them for our prototype will improve integrability of our resource within the Foundry framework.

Adverse event class

Consider the following cases in which the clinician wishes to report adverse events:

- sensorineural deafness reported after measles, mumps, and rubella immunization. This disturbance of the cochlea or auditory nerve results in hearing impairment, often loss of ability to hear high frequencies [24],
- infection such as in the case of leflunomide in treatment of arthritis [25],

- any of the dermatological adverse events observed in patients treated with etanercept [26],
- headaches reported following use of proton pump inhibitors such as lansoprazole [27],
- rashes, extremely common for example at the injection site.

These cases indicate that the type of an adverse event can be either of BFO’s upper level classes – *occurrent* or *continuant*. OGMS currently defines *sign* as “A quality of a patient, a material entity that is part of a patient, or a processual entity that a patient participates in, any one of which is observed in a physical examination and is deemed by the clinician to be of clinical significance.” and *symptom* as “A quality of a patient that is observed by the patient or a processual entity experienced by the patient, either of which is hypothesized by the patient to be a realization of a disease.”. Those classes are siblings of the *bfo:continuant* and *bfo:occurrent* classes, directly asserted under *bfo:entity*². Adverse events clearly match those definitions: they can be quality of the patient (for example, pallor or cyanosis), a material entity part of the patient (e.g., rash), or a processual entity that parts of a patient participates in (e.g., seizure).

Prototype development

Following this, we logically define *aero:adverse event* as the union of *aero:adverse event process* and *aero:disorder resulting from an adverse event process* (i.e., the adverse event *continuant* described above). An *aero:adverse event process* is “a processual entity occurring in a pre determined time frame following administration of a compound or usage of a device”; this can be logically translated (using the Manchester OWL syntax [28]) as:

² Throughout this paper we will adopt the notation *prefix:label* for entities, where *prefix* is the commonly used resource abbreviation.

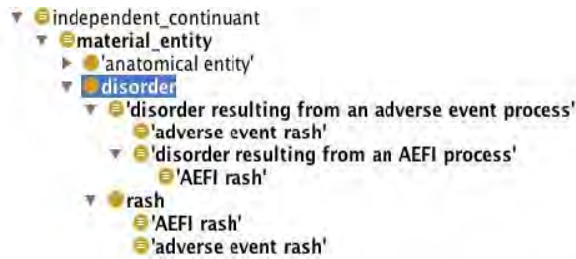


Figure 1. The disorder hierarchy as built in AERO, under the *ogms:disorder* class. The class *adverse event rash* is logically defined as the intersection of *disorder resulting from an adverse event process* and *rash*.

```
Class: 'adverse event process'
EquivalentTo:
  processual_entity
  and (preceded_by some
    ('adding a material entity
     into a target'
     or 'administering
      substance in vivo'))
```

where the classes *adding a material entity into a target* and *administering substance in vivo* are imported from the Ontology of Biomedical Investigations (OBI) [29]. The AERO definition of *adverse event process* is meant to be inclusive, and cover cases such as those described by the Manufacturer and User Facility Device Experience (MAUDE); for example the case of a patient fitted with bioprosthetic heart valves who dies within the following 4 months³. It is also worth noting that this definition of adverse event does not imply causation between the sign observed and the compound administration/device utilization, but is rather based on temporal association.

The adverse event continuant hierarchy was built under the *ogms:disorder* class (Figure 1), which is defined as “A material entity which is clinically abnormal and part of an extended organism. Disorders are the physical basis of disease.” To avoid any language ambiguity by associating the terms event and continuant in the label of the class *adverse event continuant*, it was renamed *disorder resulting from an adverse event process*. As a general way of overcoming the potential issue between terms in use by clinicians and ontological usage in the context of the OBO Foundry, in which it may be

confusing to associate the word “event” to a hierarchical position under continuant, we chose to rely on the *OBO Foundry unique label* IAO annotation property (http://purl.obolibrary.org/obo/IAO_0000589). Classes such as *adverse event rash* (EquivalentTo: *disorder resulting from an adverse event process* and *rash*) will therefore have an OBO Foundry unique label annotation with value “rash resulting from an adverse event process”.

Finally, as presented in the background section, adverse event definitions are based on the Brighton case definitions. We built under the IAO class *directive information entity* and defined a diagnosis guideline as a “A directive information entity that establishes a diagnosis based on a set of signs or symptoms” and its subclass *Brighton case definition* with definition “A clinical guideline in which a set of signs is described to establish a diagnosis of adverse events with a related degree of certainty, as defined by the Brighton Collaboration, <http://www.brightoncollaboration.org/>”.

The resulting inferred hierarchy, presented in figure 2, shows how defined classes are positioned under their respective parents.

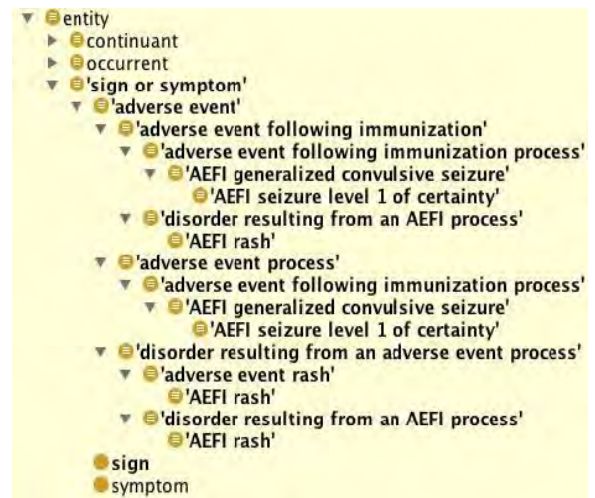


Figure 2. The resulting inferred hierarchy. Leaf terms such as *AEFI rash* are inferred under several parents based on their logical restrictions. The adverse event process class is also a subclass of *bfo:occurent*.

³ http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/detail.cfm?mdrfoi_id=1942591

4 Discussion

Related efforts

As pointed out by Ceusters and al. [30], the term adverse event has been described in multiple ways. They consider adverse events as being those for which causality has been demonstrated, arguing that “the past cannot be changed: something which is not an adverse event at the time it happens cannot become one at some point thereafter.” This view is adopted by the Adverse Events Ontology (AEO)⁴, which defines adverse event as “a pathological bodily process that is induced by a medical intervention”. This definition however presents several issues that make it unusable for reporting vaccine adverse events. First, at the time of data entry, there is no certainty that the adverse event has been induced by the intervention. Instead, in clinical settings, all reactions are reported and forwarded to a committee that will later on try and establish causality. As demonstrated above, such causality will never be formerly established, rather a network of proofs is collected via epidemiologic studies and/or case reports, and supported by demonstration of biological plausibility. Second, reported adverse events may not always be processes – continuants such as rash are reported by clinicians and need to be accommodated as well. Describing the process leading to the rash is a first step as is done in the AEO, but i) this process is not always known ii) clinicians do not report nor are particularly interested in the process - they rather care about the dermatological disorder observed. Finally, that an adverse event rash and a rash non temporally associated with a medical intervention are of the same type, which should be described in a distinct, external symptom ontology - view shared by Dr. Ceusters⁵. It then becomes obvious that this rash is the universal being observed, and its nature whether we can prove or not that it is caused by the intervention – does not change. We can declare the observed rash as an adverse event on the basis of its temporal association, via a defined class as is done in AERO, describe how it follows some reporting

guidelines such as Brighton, and later on assign a category of evidence for causality, which would be an information entity attached to the original adverse event rash after review by the safety committee.

Current issues

While implementing the prototype, several ontological issues arose. Adverse event is defined as a process or continuant *preceded_by* some medical intervention or drug administration. The *preceded_by* relation is imported from the RO, and defined as “P preceded_by P’ if and only if: given any process p that instantiates P at a time t, there is some process p’ such that p’ instantiates P’ at time t’, and t’ is earlier than t”. This relation does not specify a timeframe for the events to be considered related, and an immunization process happening right after one’s birth would *de facto* precede most of the subsequent events in their life. A comment on this relation in the RO file⁶ indicates that this is an area RO developers are considering improving, and they suggest stronger relations such as *immediately_preceded_by* or an indication that the instances P and P’ share participants. Another issue related to use of relations appears when logically defining *disorder resulting from an adverse event process*. We use the relation *is specified output* to represent that each disorder results from the adverse event process. However, the range of this relation is *planned_process* – processes executed following a plan and with the intent to achieve a specific objective – which obviously adverse event processes are not. We expect BFO2⁷ to provide a suitable relation for this case. Finally, there is currently no relation linking a disease and its set of signs and symptoms. This issue has been raised in OGMS⁸ but poses the question of the universality of the association between a disease and its symptoms. We currently are unable to associate all instances of the disease with the whole set of symptoms (e.g., not every instance of influenza disease is associated with an instance of fever, and certainly not vice versa). We propose here to use the case definitions (or any other source of

⁴ <http://sourceforge.net/projects/aeo/>

⁵ http://sourceforge.net/mail/archive/message.php?msg_id=27040555

⁶ <http://www.obofoundry.org/ro/ro.owl>

⁷ <http://code.google.com/p/bfo/>

⁸ <http://code.google.com/p/ogms/issues/detail?id=45>

canonical knowledge) to relate a set of signs and symptoms to a specific class, defined based on the guideline considered. For example, while not all seizures cases present with witnessed loss of consciousness (and vice versa, not all loss of consciousness are associated with a seizure episode), we can say that, *according to the Brighton case definition*, if there is a sudden witnessed loss of consciousness (in conjunction with another set of symptoms) then we can diagnose a seizure with level 1 of certainty.

Future work

Some elements of the current prototype deserve a bit more attention. For example, the levels of diagnosis certainty as defined by Brighton should probably be some type of information entity that would then be attached to the *AEFI seizure* class. Similarly, the degree of severity of adverse event, as well as their expectedness, is important information that should be modelled in the ontology. Serious adverse events⁹ are life-threatening or causing death, as well as requiring hospitalization or permanent disability. Unexpected adverse events¹⁰ are those not mentioned in drug manufacturers notices for examples. Of course, unexpected, serious, adverse event are of special concern to the safety committee. We also expect to be able to outsource our definitions of “normal” symptoms and signs. For example, the *rash* class in figure 1 should be imported from a common symptom ontology. This would however require consensus definition for those elements, which may prove difficult. We have had extensive discussion with the developers of the AEO that aided the preparation of this paper, and both groups hope we will be able to reconcile the two resources in the future.

Finally, we would like to proceed with testing of the prototype in a real use context. In the PHAC/CIHR Influenza Research Network (PCIRN) network, clinicians rely on reporting forms developed by Dacima [4]. We are in

contact with those developers to implement an extension of these forms, allowing us to maintain the interface users are already familiar with. At data entry time, they will be presented with a succession of choices augmented by their precise description and checks ensuring signs described match the adverse event reported and vice-versa. This will lead in an increased accuracy and quality of reported adverse events, and will ultimately improve patient safety.

Availability

The AERO project, including ontology and documentation which is available at:

<http://purl.obolibrary.org/obo/aero>.

AERO is also listed on the OBO library at: <http://obofoundry.org/cgi-bin/detail.cgi?id=AERO>

and under BioPortal at:

<http://bioportal.bioontology.org/visualize/45521>.

Participation in the AERO is welcome and contributions in any form are encouraged.

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⁹ <http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/ich/efficac/e2a-eng.php#a2B>

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