Introducing Realist Ontology for the Representation of Adverse Events

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Abstract. The goal of the REMINE project is to build a high performance prediction, detection and monitoring platform for managing Risks against Patient Safety (RAPS). Part of the work involves developing an ontology enabling computer-assisted RAPS decision support in the context of the disease history of a patient as documented in a hospital information system. A requirement of the ontology is to contain a representation for what is commonly referred to by the term '*adverse event*', one challenge being that distinct authoritative sources define this term in slightly different ways and utterly context-dependent. The presence of some common ground in all definitions is, however, obvious. Using the analytical principles underlying Basic Formal Ontology and Referent Tracking, both developed in the tradition of philosophical realism, we propose a formal representation of this common ground which involves the combination of a reference ontology consisting exclusively of universals and an application ontology which consists of defined classes. We argue that what in most cases is referred to by means of the term '*adverse event*' – when used generically – is a *defined class* rather than a *universal*. In favour for adverse event as a defined class are the arguments that (1) there is no definition for '*adverse event*' that carves out a collection of particulars which constitutes the extension of a universal, and (2) the majority of definitions require adverse events to be (variably) the result of some observation, assessment or (absence of) expectation thereby giving these entities a nominal or epistemological flavour.

Keywords. Basic Formal Ontology, Referent Tracking, adverse events, patient safety.

1. Introduction

'*High performance prediction, detection and monitoring platform for patient safety risk management (REMINE)*' is the name of a European Large Scale Integrating Project (IP) funded by the European Commission since Jan 1, 2008 [1]. The main objective is to develop a technological platform and best practice business processes allowing automated management and prevention of Risks against Patient Safety (RAPS).

Part of the work to be carried out consists of the development of an ontology that will support several functionalities offered by the envisioned technological platform. In this paper, we focus on one particular RAPS issue: *adverse events*.

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Table 1. Adverse event related definitions from authoritative sources

ID	Term	Definition	Source	Ref.
D1	***adverse drug event*** (adverse drug error)	Any incident in which the use of a medication (drug or biologic) at any dose, a medical device, or a special nutritional product (for example, dietary supplement, infant formula, medical food) may have resulted in an adverse outcome in a patient.	JTC	[2]
D2	***adverse drug experience***	any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: • an adverse event occurring in the course of the use of a drug product in professional practice; • an adverse event occurring from drug overdose whether accidental or intentional; • an adverse event occurring from drug abuse; • an adverse event occurring from drug withdrawal; and • any failure of expected pharmacological action.	FDA	[3]
D3	***adverse drug reaction***	an undesirable response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.	JTC	[2]
D4	***adverse event***	an ***observation*** of a change in the state of a subject ***assessed*** as being untoward by one or more ***interested parties*** within the ***context*** of a protocol-driven research or public health.	BRIDG	[4]
D5	***adverse event***	an event that results in unintended harm to the patient by an act of commission or omission rather than by the underlying disease or condition of the patient	IOM	[5]
D6	***adverse event***	any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure	NCI	[6]
D7	***adverse event***	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	CDISC	[7]
D8	***adverse event***	an untoward, undesirable, and usually unanticipated event, such as death of a patient, an employee, or a visitor in a health care organization. Incidents such as patient falls or improper administration of medications are also considered adverse events even if there is no permanent effect on the patient.	JTC	[2]
D9	***adverse event***	an injury that was caused by medical management and that results in measurable disability.	QUIC	[8]
D10	***error of omission***	An error which occurs as a result of an action not taken. Errors of omission may or may not lead to adverse outcomes.	JTC	[2]
D11	***observation***	an act of recognizing and noting a fact or an occurrence of an event of interest. An observation may involve examination, interviews, or measurement with devices. Observations are not intended to alter the state of the subject.	BRIDG	[4]
D12	***serious adverse drug experience***	Any adverse drug experience occurring at any dose that results in any of the following outcomes: • death, • a life-threatening adverse drug experience, • inpatient hospitalization • prolongation of existing hospitalization, • a persistent or significant disability/incapacity, • a congenital anomaly/birth defect.	FDA	[3] [9]

The term '*adverse event*' is in the literature defined in a variety of ways, superordinate terms frequently used being '*reaction*', '*effect*', '*event*', '*problem*', '*experience*', '*injury*', '*symptom*', '*illness*', '*occurrence*', '*change*', and even '*something*', '*act*', '*observation*' and '*term*', the latter four being the result of applying flawed terminological theories [10]. This multitude of definitions is brought about by the many organisations and initiatives that set the noble goal to reduce the occurrence of adverse events since the Institute of Medicine published its report '*To Err is Human: Building a Safer Health System*' [11]. **Table 1** contains a small selection of adverse event definitions by authoritative sources, drawn from a larger collection that we composed for our work [12].

Research aimed to bring some order in this domain falls in three categories. One is classification, as witnessed by the work of Chang *et al*. who developed – based on a set of criteria [13] – a classification schema consisting of five root nodes which were found to be the '*homogeneous elements*' encountered in relevant sources: ***Impact***, ***Type, Domain, Cause*** and ***Prevention and Mitigation*** [14]. Others, such as the BRIDG consortium, have tried to get rid of the multitude of definitions by reaching consensus on just one [4], with the result of being extremely reductionist. A third group of researchers focuses on building ontologies, most often, unfortunately, by using the very weak principles underlying '*concept*'-orientation [15], such that, for example, '*age*' and '*gender*' become a subclass of '*patient*' [16].

With researchers of the third group, we believe that '*ontology*' is indeed the right approach, but, in contrast to them, only when rigorous principles that go far beyond computational soundness are applied.

2. Objective and design

Our goal is to bring clarity in the terminological wilderness that grew out of all these efforts not only because of differences amongst initiatives in terms of scope, involved health care settings, jurisdictions, and objectives – the consequence being that definitions resulting from such efforts are not applicable outside the original boundaries – but also, for a large number of them, because of the failure to adopt sound ontological and terminological principles in analysing and conveying what is relevant. A definition such as " *'Adverse outcome' should be understood to mean not only a non-trivial adverse outcome* […] *but also an incident* […] *which results in a recognized potential risk of a non-trivial adverse outcome* […]" [17] (irrelevant detail omitted), is of the form '*an X is an X or a Y which leads to an X*' and is thus clearly uninformative.

To obtain our goal, we analysed the literature and collected all relevant definitions and descriptions that we found. We modified some of these definitions slightly in order to have them convey better what we judged to be the intended message.

We also studied a variety of classification systems, taxonomies, terminologies and concept-based ontologies – we use the term '*concept-based ontologies*' to differentiate such representational artifacts clearly from the realism-based ontology that is being developed under REMINE – in order to obtain a comprehensive list of entity types whose nature and interrelationships are to be studied and formally represented to satisfy the REMINE requirements.

3. Methodology

We performed our analysis following the principles advocated in Basic Formal Ontology and Referent Tracking.

3.1. Basic Formal Ontology

Basic Formal Ontology (BFO) is a framework encapsulating best practices in ontology development that is designed to serve as basis for the creation of high-quality shared ontologies in the biomedical domain [18, 19]. BFO acknowledges only those entities which exist in biological reality, and rejects all types of putative entities which are postulated merely as artifacts of specific logical or computational frameworks. BFO captures a small number of basic categories into which reality is divided thereby distinguishing at the highest level of its organisation (1) *particulars* such as ***Werner Ceusters*** from *universals* such as HUMAN BEING,[2] (2) *continuants* such as ***Werner Ceusters' heart*** from *occurrents* such as ***the beating of Werner Ceusters' heart***, and (3) *independent entities* such as ***Werner Ceusters' heart*** from *dependent entities* such as ***the function of Werner Ceusters' heart***, the latter being such that they cannot exist – in the ontological rather than biological sense – without some instance of the former. BFO also distinguishes three major families of relations between entities in the categories just distinguished: (1) *<p, p>-relations*: from particular to particular (for example: ***Werner Ceusters' s brain*** being part of ***Werner Ceusters***); (2) *<p, u>-relations*: from particular to universal (for example: ***Werner Ceusters*** being an instance of HUMAN BEING); and (3) *<u, u>-relations*: from universal to universal (for example: HUMAN BEING being a subkind of ORGANISM) [20].

3.2. Referent Tracking

Referent tracking has been introduced as a new paradigm for entry and retrieval of data in the Electronic Health Record (EHR) to avoid the multiple ambiguities that arise when statements in an EHR refer to disorders, lesions and other entities on the side of the patient exclusively by means of generic terms from a terminology or ontology [21]. Referent tracking avoids such ambiguities by introducing *IUIs* –Instance Unique Identifiers – for each numerically distinct entity that exists in reality and that is referred to in statements in the record.

Drawing on this framework, we have proposed a calculus for use in quality assurance of the complex representations created for clinical or research purposes, for example in coding of clinical trial data [22]. The calculus is based on a distinction between three levels [23]: (1) the level of reality (for example, in the medical domain, the reality on the side of the patient); (2) the cognitive representations of this reality for example as embodied in observations and interpretations on the part of clinicians and others; (3) the publicly accessible concretizations of these cognitive representations in artifacts of various sorts, of which ontologies and terminologies and Electronic Health Records are examples.

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[2] For clarity, we will from here on represent particulars in ***bold italic*** and universals in SMALL CAPS. Terms (or other representational units) denoting either universals or particulars will be written in italics between single quotes. For additional clarity, we will sometimes use the words '*particular*', '*universal*' and '*term*' explicitly to denote entities of the corresponding type.

4. Results

4.1. Terminological conventions

In line with the terminology proposed in [23], we will further use the term '*class'* to denote a collection of all and only those particulars to which a given general term applies. A class can either be (1) the extension of a universal, thus comprehending all and only those particulars which instantiate the corresponding universal (at that time) or (2) a subset of the extension of a universal defined as being such that the *members* of this class exhibit an additional property which is (a) not shared by all instances of the universal, and (b) also (can be) exhibited by particulars which are not instances of that universal. For such a class, we reserve the term '*defined class*'. By '*property*', we mean either a monadic quality or a relationship that a particular enjoys with another particular or a universal. By '*portion of reality*' we mean any combination of particulars (including classes and defined classes), universals and properties. We will use the term '*representational unit*' (RU) for any symbolic representation (a code, a character string, an icon, …) which *denotes* a portion of reality. Table 2 gives an overview of the type of representational artifacts that are useful for representing portions of reality and what sort of entities should be represented in each type of artifact. The latter is inspired by the view that *reference ontologies* should be the equivalent of scientific theories and therefore should represent what is generic in the world – whether or not in a specific domain – in a way that maximizes faithfulness and comprehensiveness with respect to reality. *Application ontologies*, in contrast, represent matters in a format that is more suitable for computation [24]. Examples of *inventories* are databases which store information about particulars, examples being Electronic Health Records or Adverse Event Registries.

4.2. Core representational units

Table 3 shows the minimal collection of classes related to entities in reality that must be taken into consideration for being able to represent the portion of reality around a particular patient on whose side an adverse event might have occurred in line with any of the definitions for adverse event and related notions analyzed thus far. The descriptions provided are ***not*** to be interpreted as definitions for the terms that we choose to use as denotations for the corresponding entities, but rather illustrate the roles played by various entities in a scenario in which an adverse event might have occurred.

Table 2: representational artifacts and their suggested representational units

Representational artifact	Contains representational units for …
Reference Ontology	• universals • relationships between universals along the principles of the Relation Ontology [20]
Application Ontology	• universals • defined classes • relationships between universals and defined classes along the principles of the Relation Ontology [20] • particulars required for defining defined classes
Inventory	• particulars • properties

Table 3: Universals and Defined Classes for the adverse events domain.

	Denotation	Class Type	Particular Type	Description (role in adverse event scenario)
Level 1				
C1	subject of care	DC	independent continuant	person to whom ***harm*** might have been done through an ***act under scrutiny***
C2	act under scrutiny	DC	act of care	***act of care*** that might have caused ***harm*** to the ***subject of care***
C3	act of care	U	process	activity carried out by a ***care giver*** to a ***subject of care***, motivated by an ***underlying disease*** and a ***care intention***,
C4	care giver	DC	independent continuant	person that performed an ***act of care*** to the ***subject of care***
C5	underlying disease	DC	dependent continuant	the disease in the ***subject of care*** which is part of the motivation for why the ***act of care*** is performed
C6	involved structure	DC	independent continuant	anatomical structure (of the ***subject of care***) involved in an ***act of care***
C7	structure change	U	process	change in an anatomical structure of a person
C8	structure integrity	U	dependent continuant	quality of an anatomical structure which determines the types of circumstances under which the anatomical structure would become dysfunctional if such circumstances were present
C9	integrity change	U	structure change	change in the ***structure integrity*** of an anatomical structure such that there are after the change a different number of types of circumstances under which the anatomical structure would become dysfunctional, than before the change
C10	harm	U	integrity change	change in the ***structure integrity*** of an anatomical structure such that there are after the change more types of circumstances than before under which the anatomical structure will become dysfunctional
C11	care effect	DC	integrity change	***integrity change*** brought about by an ***act of care***
C12	subject investigation	DC	process	looking for a ***structure change***
C13	harm assessment	U	process	pondering whether an ***observation*** is faithful to reality, and if so, whether the ***structure change*** denoted by the ***observation*** is a ***harm***
C14	care intention	DC	dependent continuant	intention of a ***care giver*** that motivates him towards an ***act of care***
Level 2				
C15	observation	DC	dependent continuant	cognitive representation about a ***structure change*** resulting from a ***subject investigation***
C16	harm diagnosis	DC	dependent continuant	cognitive representation, resulting from a ***harm assessment***, denoting whether a ***structure change*** is a ***harm***
C17	care effect belief	DC	dependent continuant	belief on the side of the ***care giver*** concerning the ***care effects*** that he ascribes to the ***act of care***
Level 3				
C18	care reference	DC	information entity	concretized (through text, diagram, …) piece of knowledge drawn from state of the art principles that can be used to support the appropriateness of (or correctness with which) processes are performed involving a ***subject of care***

Legend. ***Denotation***: generic term applicable to a member of the class. ***Class type***: indicates whether the class is the extension of a universal (U) or a defined class (DC). ***Particular type***: indicates what sort of particulars, in terms of Basic Formal Ontology, members of the corresponding class are.

Neither should any of the terms listed under the denotation-column by analysed outside the context of this paper. As an example, we ***do not*** claim that anything which by third parties would be referred to by means of the term '*observation*' falls under the description that we provided. The conditionals that are used in most of these descriptions reflect the fact that a particular portion of reality might be such that a phenomenon which is considered to be an adverse event under one definition, is not an adverse event in terms of another definition. The conditionals, excluding a few obvious exceptions, should not be interpreted as having to do with probabilities or uncertainty.

4.3. The place of 'adverse events'

The representational units for the core classes identified above can be used to represent all possible portions of reality in which figures an entity that can be referred to by means of the term '*adverse event*' under any of the definitions that we encountered. As an example, Table 4 lists the particulars and associated properties involved in a case in which a patient, born at time t_0, under anti-inflammatory treatment and physiotherapy since t_2 for arthrosis which is present since t_1, develops a stomach ulcer at t_3. The relationships for the properties are drawn from [20, 25], thereby keeping the format conventions proposed in [20], except for particulars which we pick out in bold italic. We introduce the primitive **is_about** relation holding between a representational unit and the entity in reality that this unit denotes at a certain time. We further make shortcuts in the representation of the temporal relationships by simply stating here that t_0 **earlier** t_1 **earlier** t_2 **earlier** t_3. We also allow for more temporal annotations than in [20], yet remaining faithful to EN 12388:2005: Health informatics - Time standards for healthcare specific problems [26].

Under this scenario, ***#10***, i.e. the appearance of ***#9***, would (at least probably – see discussion for some problematic issues with the wide variation in interpretations that can be given to the majority of the definitions) qualify as an adverse event as defined by the Institute of Medicine (definition D5).

Table 4: Example of an adverse event case analysis

IUI	Particular description	Properties
#1	the patient who is treated	***#1*** **member** C1 **since** t_2
#2	***#1***'s treatment	***#2*** **instance_of** C3 ***#2*** **has_participant** ***#1*** **since** t_2 ***#2*** **has_agent** ***#3*** **since** t_2
#3	the physician responsible for #2	***#3*** **member** C4 **since** t_2
#4	***#1***'s arthrosis	***#4*** **member** C5 **since** t_1
#5	***#1***'s anti-inflammatory treatment	***#5*** **part_of** ***#2*** ***#5*** **member** C2 **since** t_3
#6	***#1***'s physiotherapy	***#6*** **part_of** ***#2***
#7	***#1***'s stomach	***#7*** **member** C6 **since** t_2
#8	***#7***'s structure integrity	***#8*** **instance_of** C8 **since** t_0 ***#8*** **inheres_in** ***#7*** **since** t_0
#9	***#1***'s stomach ulcer	***#9*** **part_of** ***#7*** **since** t_3
#10	coming into existence of ***#9***	***#10*** **has_participant** ***#9*** **at** t_3
#11	change brought about by ***#9***	***#11*** **has_agent** ***#9*** **since** t_3 ***#11*** **has_participant** ***#8*** **since** t_3 ***#11*** **instance_of** C10 **at** t_3
#12	noticing the presence of ***#9***	***#12*** **has_participant** ***#9*** **at** t_{3+x} ***#12*** **has_agent** ***#3*** **at** t_{3+x}
#13	cognitive representation in ***#3*** about ***#9***	***#13*** **is_about** ***#9*** **since** t_{3+x}

However, for definition D9, it would rather be ***#9*** itself, while for D4, proposed by the BRIDG consortium [4], it would be either ***#12*** or ***#13***. The unclarity in the latter case is brought about by the confusions and conflations in the HL7 RIM [27] upon which BRIDG is heavily inspired.

Because of the various sorts of entities that qualify as adverse events depending on which definition is used, at least two adverse event classes need to be defined: one for adverse events under views that see adverse events as processes, and one for adverse events as continuants. A further distinction has to be made between adverse events as entities in first order reality, and phenomena in first order reality that, as posited by some definitions, can only be qualified as adverse events by resorting to cognitive representations or by subjecting first order phenomena to an analysis dictated by scientific theories.

5. Discussion

Already a very superficial analysis of the definitions in **Table 1**, thereby applying the analytical principles just sketched, demonstrates that the question "*What are adverse events?*" cannot be answered directly, but needs to be reformulated as "*What might the author of a particular sentence containing the phrase 'adverse event' refer to by that phrase?*". Indeed, the authors of these definitions must have had very distinct entities in mind: we cannot imagine any single entity to be such that if it were in front of the eyes of these authors, they would each in turn be able to point to it while the first author would say – faithfully and honestly – "*that is an observation*", the second one: "*that is a disease*", the third one: "*that is a laboratory finding*", and so forth. Clearly, nothing which **is** a disease can **be** a laboratory finding, although, of course, laboratory findings can aid in diagnosing a disease or in monitoring its evolution. Similarly, nothing which **is** a laboratory finding, can **be** an observation, although, of course, some observation must have been made (either by a human being or a device) to come to a laboratory finding. However, because all authors use the term '*adverse event*' in some context for each of these distinct entities, and because these contexts look quite similar – in each of them, more or less the same sort of entities seem to be involved – there is some common ground (a portion of reality) which is such that parts of it can be used as referents for the various meanings of '*adverse event*'.

5.1. Classifying adverse event related entities in terms of the three levels of reality

The definitions for the term '*adverse event*' and other closely related terms differ in the ways that they require a representation which resorts to one, two or all three levels of reality as described above. The first part of D12 (from the Food and Drug Administration) is an example in which all terms refer to level 1 entities: *drugs*, *drug doses*, *deaths*, *hospitalizations*, *disabilities*, and so forth, are all entities that exist in first order reality. Another example is D9: the terms '*injury*', '*medical management*', '*measurement*' and '*disability*', when used in the context of a specific patient that may or may not have experienced an adverse event, all ***denote*** existing entities on the side of that particular patient and his environment, and are not ***about*** something else: these terms thus denote level 1 entities. D2, in contrast, requires bringing level 2 and perhaps even level 3 entities into the picture, and this because of the clause '*any failure of expected pharmacological action*'. Expectations can only be raised by a cognitive

being and are part of the cognitive representation this cognitive being has constructed ***about*** first order reality. Thus, in this interpretation of D2, i.e. if the expectation concerning the pharmacological action is 'in the mind' of the particular clinician assessing whether the patient has an adverse drug experience, D2 involves a level 2 entity. However, if this expectation is something which is part of '*general knowledge*' or belongs to the '*state of the art*', then we are dealing with an additional level 3 entity: in order for the clinician assessing the case to have access to that '*general knowledge*', it must have been concretized in some enduring fashion.

5.2. Lack of clarity in definitions

D2 exhibits a characteristic which, unfortunately, is shared by the majority of the definitions encountered: they lack sufficient clarity of phrasing to allow an analysis in realist terms to be conducted unproblematically. Often various interpretations can be given to one or more terms used within a definition whereby each interpretation suggests a denotation at a distinct level of reality. An example is definition D3 in which the term '*undesirable'* can be interpreted in two different ways: (1) denoting something in level 1, a *realizable* such as a *disposition* or *tendency* [28], such that the event results objectively in an increased health risk – thus any event '*that either compromises therapeutic efficacy, enhances toxicity, or both*' is undesirable; (2) denoting something in level 2 such that amongst those events which influence therapeutic efficacy or toxicity only some are considered undesirable (for whatever reason) by either the patient, the caregiver or both, or (3) denoting something relative to level 3 to the effect that the particular event which occurs at level 1 is only undesirable when it is an instance of a type of event which is listed in some guideline, good practice management handbook, i.e. in something which is published about the state of the art in relevant matters.

In other cases, this sort of analysis results in detecting hidden assumptions, conflations or even serious inconsistencies either within one definition or in the combination of several definitions offered by the same source.

An example of an inconsistency in realist terms within one definition would result from the literal interpretation of D5, more precisely concerning the term '*act of omission*', especially if that term, as suggested by D10, does not denote something existing, or having existed in the past. In Referent Tracking terms, there would thus be nothing that can be assigned a IUI to. Indeed, 'doing nothing', so we believe, is a linguistic description (level 3 entity) that can be used adequately and meaningfully in reporting about a complex portion of reality (level 1 entity). But such use by itself doesn't mean that the term denotes directly and totally a level 1 entity: whereas for the term 'doing something' there is a referent in first order reality, there is no such referent pointed to by the term 'doing nothing'.

Consider the example given in [5] in which '*not testing a diabetic patient for* HbA_{1c}' is stated to be an '*act of omission*'. This is because since the work of the Diabetes Quality Improvement Project [29, 30] it is considered bad practice not to do such a test at regular intervals [31]. But clearly, if only a patient's disease (here the diabetes) and some adverse event exist as first order entities, then it is not possible that an '*act of omission*', i.e. not doing something what one is supposed to do according to the state of the art, would be the cause of the adverse event, and it must thus be the underlying disease. Events, so we believe, can only be caused by what exists. In the diabetes case, it is, clearly, the diabetes that causes the adverse event, although it is true

that if the test were taken, as well as further appropriate actions in line with the results of the test, it could be expected that no adverse event would have occurred. Therefore, a better definition for what D5 tries to denote would be: '*an event that results in unintended harm to the patient (1) by an act of commission rather than by the underlying disease or condition of the patient, or (2) by the underlying disease or condition of the patient in absence of appropriate actions being taken in line with the state of the art in dealing with the disease*'. This rephrased definition accounts better for something else the Institute of Medicine had probably in mind when producing D5, namely that many acts of commission are part of a procedure which for them being conducted 'lege artis' include taking actions that if they would not be taken, would lead to harm to the patient because of the act of commission. An example is incising an artery during some surgical procedure what inevitable leads to bleeding. It would be inappropriate, in such case, not to take actions to stop or reduce the bleeding. Here it is not the underlying disease which leads to harm to the patient, neither is it the 'not stopping the bleeding' which leads to the harm. Rather it is the bleeding caused by the incision.

6. Conclusion

We have used the principles of Basic Formal Ontology (BFO), the Relation Ontology (RO) and Referent Tracking (RT) as an analytical framework to study the ontological nature of what is denoted by the term '*adverse event*'. Our research indicates that this framework is adequate, and, when used appropriately, avoids the inconsistencies and incompatibilities inherent in other approaches. Nevertheless, some further developments, especially in RO are required to be able to deal more formally with some extensions that we proposed here: (1) an *aboutness* or *denotation* relation to relate level 2 and level 3 entities to level 1 entities, (2) a *membership* relation to link particulars to defined classes, and (3) the capacity to refer to (open-ended) time periods in addition to time instants.

7. References

[1] REMINE Consortium. REMINE: Supporting Hospitals in Risk Management. 2008 [cited 2008 April 9]; Available from: http://www.remine-project.eu/

[2] The Joint Commission. Sentinel Event Glossary of Terms. 2008 2008 [cited 2008 April 14]; Available from: http://www.jointcommission.org/SentinelEvents/se_glossary.htm

[3] U.S. Food and Drug Administration. IND Safety Reports. In: Code of Federal Regulations Title 21 Volume 5 § 312.32, ed. 2007.

[4] Weng C, Becich M, Fridsma D. Collective Domain Modeling across Clinical Trials Standards: Needs, Challenges, and Design Implications. *Information Technology and Communications in Health (ITCH)*. Victoria, BC, Canada 2007.

[5] Committee for Data Standards for Patient Safety - Institute of Medicine. Patient Safety: Achieving a New Standard of Care. Washington DC: The National Academies Press 2004.

[6] National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. 2006.

[7] CDISC Submission Data Standards Team. CDISC SDTM Implementation Guide (Version 3.1.2) - Study Data Tabulation Model Implementation Guide: Human Clinical Trials; 2007 July 25.

[8] Quality Interagency Coordination Task Force. Glossary of Terms. 2008 [cited 2008 April 14]; Available from: http://www.quic.gov/report/mederr8.htm

[9] U.S. Food and Drug Administration. Code of Federal Regulations; Title 21--Food And Drugs; Chapter I--Food And Drug Administration; Department Of Health And Human Services ; Subchapter D--Drugs For Human Use; Part 310 -- New Drugs; Subpart D--Records and Reports. 2007.

[10] Smith B, Ceusters W, Temmerman R. Wüsteria. In: Engelbrecht R, Geissbuhler A, Lovis C, Mihalas G, eds. *Connecting Medical Informatics and Bio-Informatics Medical Informatics Europe 2005*. Amsterdam: IOS Press 2005:647-52.

[11] Institute of Medicine. To Err is Human: Building a Safer Health System. Washington DC: National Academy Press 2000.

[12] Ceusters W, Capolupo M, Moor GD, Devlies J. Various Views on Adverse Events: a collection of definitions. 2008 April 20, 2008 [cited 2008 April 29]; Available from: http://www.org.buffalo.edu/RTU/papers/AdverseEventDefs.pdf

[13] The WHO World Health Organization Alliance for Patient Safety. Project to Develop the International Patient Safety Event Taxonomy: Updated Review of the Literature 2003-2005; Final Report. Geneva: World Health Organization; 2005 September.

[14] Chang A, Schyve PM, Croteau RJ, O'leary DS, Loeb JM. The JCAHO patient safety event taxonomy: a standardized terminology and classification schema for near misses and adverse events. International Journal for Quality in Health Care Advance Access. 2005;17(2):95-105.

[15] Smith B. From Concepts to Clinical Reality: An Essay on the Benchmarking of Biomedical Terminologies. Journal of Biomedical Informatics. 2006;39(3):288-98.

[16] Jeong S, Kim H-G. Design of Semantically Interoperable Adverse Event Reporting Framework. *The Semantic Web – ASWC 2006*. Berlin / Heidelberg: Springer 2006:588-94.

[17] College of physicians and surgeons of Newfoundland and Labrador. Disclosure of an Adverse Outcome. 2008 [cited 2008 April 16]; Available from: http://www.cpsnl.ca/PolicyDocument.asp?ID=21

[18] Spear AD. Ontology for the Twenty First Century: An Introduction with Recommendations. Saarbrucken, Germany: Institute for Formal Ontology and Medical Information Science 2006.

[19] Smith B, Ashburner M, Ceusters W, Goldberg L, Mungall C, Shah N, et al. The OBO Foundry: Remolding Biomedical Ontologies to Support Data Integration. Nature Biotechnology. 2007;25:1251-5.

[20] Smith B, Ceusters W, Klagges B, Köhler J, Kumar A, Lomax J, et al. Relations in biomedical ontologies. Genome Biology. 2005;6(5):R46.

[21] Ceusters W, Smith B. Strategies for Referent Tracking in Electronic Health Records. Journal of Biomedical Informatics. 2006 June;39(3):362-78.

[22] Ceusters W, Smith B. A Realism-Based Approach to the Evolution of Biomedical Ontologies. *Proceedings of AMIA 2006* 2006:121-5.

[23] Smith B, Kusnierczyk W, Schober D, Ceusters W. Towards a Reference Terminology for Ontology Research and Development in the Biomedical Domain. *KR-MED 2006, Biomedical Ontology in Action*. Baltimore MD, USA 2006.

[24] Menzel C. Reference Ontologies — Application Ontologies: Either/Or or Both/And? 2007 [cited 2008 April 28]; Available from: http://bioontology.org/wiki/images/d/d9/MenzelOntology.pdf

[25] Smith B, Grenon P. The Cornucopia of Formal-Ontological Relations. Dialectica. 2004;58(3):279-96.

[26] European Committee for Standardization. EN 12388:2005. Health informatics - Time standards for healthcare specific problems. 2005.

[27] Smith B, Ceusters W. HL7 RIM: An Incoherent Standard. In: Hasman A, Haux R, Lei Jvd, Clercq ED, Roger-France F, eds. *Studies in Health Technology and Informatics Ubiquity: Technologies for Better Health in Aging Societies - Proceedings of MIE2006*. Amsterdam: IOS Press 2006:133-8.

[28] Jansen L. Tendencies and other Realizables in Medical Information Sciences. The Monist. 2007 October 2007:(in press).

[29] McLaughlin S. The Diabetes Quality Improvement Project. Diabetes Spectrum. 2000;13(1):5-10.

[30] American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2005;28:S4-S36.

[31] National Committee for Quality Assurance. HEDIS 2008 Technical Specifications for Physician Measurement National Committee for Quality Assurance 2007.