Methods of Information in Medicine, 50 (1): 62-73, 2011

An Evolutionary Approach to Realism-Based Adverse Event Representations

Werner Ceusters
Center of Excellence in Bioinformatics & Life Sciences, Buffalo NY, USA
Department of Psychiatry, University at Buffalo, NY, USA

Maria Capolupo
Independent consultant, Buffalo NY, USA

Georges de Moor
Research in Advanced Medical Informatics and Telematics (RAMIT) vzw, University of Gent, Gent, Belgium

Jos Devlies
Research in Advanced Medical Informatics and Telematics (RAMIT) vzw, University of Gent, Gent, Belgium

Barry Smith
Center of Excellence in Bioinformatics & Life Sciences, Buffalo NY, USA
Department of Philosophy, University at Buffalo, New York, USA

Summary
BACKGROUND: Part of the ReMINE project involved the creation of an ontology enabling computer-assisted decision support for optimal adverse event management. OBJECTIVES: The ontology had to satisfy the following requirements: (1) to be able to account for the distinct and context-dependent ways in which authoritative sources define the term 'adverse event', (2) to allow the identification of relevant RAPS information on the basis of the disease history of a patient as documented in electronic health records, and (3) to be compatible with present and future ontologies developed under the OBO Foundry framework. METHODS: We used as feeder ontologies the Basic Formal Ontology, the Foundational Model of Anatomy, the Ontology of General Medical Science, the Information Artifact Ontology and the Ontology of Mental Health. We further used relations defined according to the pattern set forth in the OBO Relation Ontology. In light of the use of the ontology for the representation of adverse events that actually occurred and therefore are registered in a database, we also applied the principles of Referent Tracking. RESULTS: We merged the upper portions of the feeder ontologies and introduced 22 additional representational units of which 13 are generally applicable in biomedicine and 9 in the adverse event context. We provided for each representational unit a textual definition that can be translated into equivalent formal definitions. CONCLUSION: The resulting ontology satisfies all requirements set forth. Merging the existing ontologies, although all designed under the OBO Foundry principles, brought new insight into what the representational units of such ontologies actually denote.

Keywords: Ontology, Referent Tracking, Adverse events, Patient safety

1 Introduction

The goal of the European Union funded ReMINE project is to develop a prediction, detection and monitoring platform for managing risks against patient safety (RAPS). This involved the development of an ontology by carrying out three types of activities. First was the description of the domain of adverse events as cognized by human beings. This formed the basis for a taxonomy organized in ways familiar to clinicians [1]. The taxonomy then served as input for the two other types of activities: the development of (1) a purpose-independent domain ontology for adverse events, and (2) a series of application ontologies derived from the former to support applications for guideline checking and protocol monitoring in the three specific areas covered by the ReMINE pilot sites: stroke management, emergency medicine and obstetrics.

In this paper, we report on our efforts to design the upper level parts of the domain ontology in such a way that it remains faithful to both the cognitive perspective adhered to by clinicians, terminologists, and software engineers on the hand and the principles for high quality ontology development as advanced under a realist agenda on the other hand.

2 Objectives

2.1 Detect confusions and clarify distinctions in adverse event terminology

The goal of the domain ontology is to support the management of a repository populated through input from the ReMINE pilot sites that keeps track of incidents involving patients that can be qualified as 'adverse events'. The cognitive engineering position defended in the ReMINE project [1] describes an adverse event as '*an incident (a perdurant) that occurred to a patient during the past, that is documented in a database of adverse events and that is an expectation of some future happening that can be prevented*' [2]. This definition adds yet another aspect to the variety of ways the term '*adverse event*' is already defined in the literature, 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 which rest on a confusion between an entity and an observation or record thereof [3]. This multitude of definitions is brought about by the many organizations and initiatives that have set themselves the noble goal of reducing the occurrence of adverse events, especially since the year 2000, when the Institute of Medicine published its report *To Err is Human: Building a Safer Health System* [4]. Table 1 contains a small selection of adverse event definitions by authoritative sources, drawn from a larger collection that we composed for our work in [5]. A first objective for the ontology was thus to bring clarity to the terminological wilderness that grew out of all these efforts. Problems arise not only because of differences amongst initiatives in terms of scope, health care settings involved, jurisdictions, and objectives – the consequence being that definitions resulting from such efforts are not applicable outside the original boundaries – but also because of a widespread failure to adopt sound ontological and terminological principles in analysing and conveying what is relevant. Our objective here is to show that by using the right ontological approach, a data repository built on a suitably modified version of the ReMINE definition can not only be used to detect and monitor adverse events, but also to advance the state of the art towards the development of better mitigation and prevention strategies.

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	[37]
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	[38]
D3	***adverse drug reaction***	an undesirable response associated with use of a drug that either compromises therapeutic efficacy, enhances toxicity, or both.	JTC	[37]
D4	***adverse event***	an ***observation*** (i.e. an act of recognizing and noting a fact or an occurrence of an event of interest) 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	[33]
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	[39]
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	[40]
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	[41]
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	[37]
D9	***adverse event***	an injury that was caused by medical management and that results in measurable disability.	QUIC	[42]
D10	***adverse event***	an incident (a perdurant) that occurred to a patient during the past, that is documented in a database of adverse events and that is an expectation of some future happening that can be prevented'	ReMINE	[2]

2.2 Identify RAPS information in electronic health record systems

Adverse events, whatever the definition applied, occur primarily in relation to diagnostic or therapeutic procedures. Information about the context of these events can thus be found in the disease history of a patient as documented in electronic health records (EHRs), insofar they are available and adequately used. EHR systems, however, do not come standardly with background knowledge and corresponding algorithms that are able to infer whether reported signs and symptoms are to be considered adverse events, let alone could have been prevented or require mitigation procedures. The ReMINE solution here is to exploit a data annotation application which allows a RAPS manager to annotate clinical data as being indicative for an adverse event. Over time, the annotations will constitute a knowledge base – a 'RAPS repository' – that can be used to suggest appropriate annotations automatically. This requires an adequate formal representation of the adverse event domain which is compatible with clinical terminologies and ontologies used in EHRs. Achieving this was the second objective of our endeavor.

2.3 Ensure compatibility with the OBO Foundry framework

Many of the ontologies being employed in specific life science disciplines and in associated clinical specialisms are still built by groups working independently or with no resort to common ontological standards. Increasingly, one or other version of description logic such as OWL DL is being used in their development. However, the use of a logical representation language is clearly not enough to ensure high quality of an information resource [6], and even ontologies employing the same formal language are often not combinable into a single resource because of multiple incompatibilities between the ways this language is used by different groups to express biological or clinical information. [7]

The goal of the OBO (Open Biomedical Ontologies) Foundry is to counter such tendencies by promoting the creation of a single, expanding family of ontologies designed to be interoperable and logically well-formed and to incorporate accurate representations of biological reality by adhering to a set of common principles [8], of which the most important for our purposes are:

(1) that terms and definitions should be built up compositionally out of component representations taken either from the same ontology or from other, more basic, feeder ontologies;

(2) that ontologies should use upper-level categories drawn from Basic Formal Ontology [9] together with relations unambiguously defined according to the pattern set forth in the OBO Relation Ontology [10];

(3) that for each domain there should be convergence upon exactly one Foundry ontology [11].

Following these principles was the third objective of our effort.

3 Material and methods

We based our work on three collections of terms that we obtained from the ReMINE pilot. We further used the results of our analysis conducted on a number of distinct and mutually incompatible adverse event definitions found in the literature [12].

We used as feeder ontologies the *Basic Formal Ontology* (BFO) [13], the *Foundational Model of Anatomy* [14], and preliminary versions of three ontologies under development: the Disease and Diagnosis components of the *Ontology of Biomedical Investigations* which now is distributed as the *Ontology for General Medical Science* [15], the *Information Artifact Ontology* [16] and the *Ontology for Mental Health* [17]. As further required by the Foundry, we used relations that are unambiguously defined according to the pattern set forth in the OBO *Relation Ontology* (RO) [10].

In light of the use of the domain ontology for the representation of adverse events that actually occurred and therefore are registered in a database, we also applied the principles of Referent Tracking (RT) [18]. Whereas BFO – and ontologies in general – focus on what is generic (*types*), RT focuses on what is specific (*instances*).

3.1 Basic Formal Ontology

Basic Formal Ontology (BFO) is a framework encapsulating best practices in ontology development that underlies all OBO Foundry Ontologies [8, 19].

BFO has a *realist* orientation based on the view that terminologies and ontologies are to be aligned not on '*concepts'* but rather on entities in reality [20]. Central to this view are three assumptions.

The first is that biological reality exists objectively in and of itself, i.e. independently of the perceptions or beliefs or theories of cognitive beings. Thus not only do a wide variety of entities exist in reality (human beings, hearts, bacteria, disorders, ...), but also how these entities relate to each other – that certain hearts are parts of human beings, that certain bacteria cause disorders in human beings – is not a matter of agreements made by scientists but rather of objective fact.

The second assumption is that reality is accessible to us and that its structure can be discovered: it is scientific research that allows human beings to find out what entities exist and what relationships obtain between them.

The third assumption is that an ontology should mirror its corresponding domain of reality. Thus an important aspect of the quality of an ontology is determined by the degree to which not merely its individual representational units – i.e. any symbolic representation (a code, a character string, an icon, …) which *denotes* a portion of reality and which is not constructed out of smaller parts which play a similar denoting role [21] – correspond to entities in reality but also the structure according to which these units are organized mimics the corresponding structure of reality. Realism-based ontology development was introduced into biomedical informatics some fifteen years ago as a means of detecting and avoiding the systematic mistakes characteristic of concept-based terminologies [22-26], mistakes which are not eliminated through the use of description logics or similar computational devices [27].

BFO acknowledges only those entities which exist in reality, and rejects all types of putative entities postulated merely as artifacts of specific logical or computational frameworks. The corresponding logical and computational artifacts themselves, however, are indeed accepted as part of reality. BFO captures a small number of basic categories into which the entities in reality are divided, thereby distinguishing, at the highest level of its organisation:

(1) *particulars* such as ***Werner Ceusters*** from *universals* such as HUMAN BEING,

(2) *continuants* such as ***Werner Ceusters' heart*** from *occurrents* of which *processes* such as ***the beating of Werner Ceusters' heart*** are the most salient,

(3) *independent entities* such as ***Werner Ceusters' heart*** from *dependent entities* such as ***the function of Werner Ceusters' heart***.

Dependent entities are such that they cannot exist – in the ontological rather than biological sense – without some instance of the category independent entity.
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, Werner Ceusters*'s writing of this paper** being a **part of *Werner Ceusters*' life**);

(2) <*p, u*>*-relations*: from particular to universal (for example: ***Werner Ceusters*** being an instance of HUMAN BEING);

(3) <*u, u*>*-relations*: from universal to universal (for example: HUMAN BEING being a subkind of ORGANISM) [10].

Relations involving a continuant particular are time-indexed: ***Werner Ceusters' brain*** is **part of *Werner Ceusters*** since the formation of his brain, whereas in his early developmental stages, he could do unproblematically without one.

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 [28]. 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 a record. As ontologies serve integration of information at the level of universals and defined classes which particulars instantiate or are members of, so referent tracking serves integration of information at the level of these particulars themselves, which, if they are catered for at all in current electronic health record systems, are represented in heterogeneous and unstable ways.

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 [29]. This calculus is based on a distinction between three levels [21]:

(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.

4 Results

The results described here build further upon and improve the results presented in two earlier publications [12, 30]. Work reported on in [12] was carried out before the Ontology of General Medical Science was initiated which required a post-hoc alignment of the representational units then proposed. The results presented in [30] were obtained on the basis of term lists from only two of the three pilot sites in the ReMINE project.

Table 2. Upper level of the representations in the ReMINE Domain Ontology

Term	Category	Description
REPRESENTATION	L2/3-DC	[RT] CONTINUANT which is the **bearer of** an INFORMATION CONTENT ENTITY
REFERRING REPRESENTATION	L2/3-DC	[RT] REPRESENTATION which is intended and believed **to denote** some portion of reality and which succeeds in doing so.
NON-REFERRING REPRESENTATION	L2/3-DC	[RT] REPRESENTATION which, for whatever reason, fails to denote something.
UNRECOGNIZED NON-REFERRING REPRESENTATION	L2/3-DC	[RT] NON-REFERRING REPRESENTATION which, although non-referring, is intended and believed to have a referent.
RECOGNIZED NON-REFERRING REPRESENTATION	L2/3-DC	[RT] NON-REFERRING REPRESENTATION which was once intended and believed to have a referent, but which, as a result of advances in knowledge, is no longer believed to do so.
OBSERVATION	L2/3-DC	[RT] REPRESENTATION of a portion of reality **resulting from** an act of perception (i.e. from an act of observ*ing*)
DIAGNOSIS	L2/3-DC	REPRESENTATION asserting a particular to be the **instance of** some universal or **member of** some class **resulting from** an INTERPRETIVE PROCESS that has as input one or more **OBSERVATIONS** about that particular
HARM DIAGNOSIS	L2/3-DC	[AEO] REPRESENTATION **resulting from** a **HARM ASSESSMENT** and involving a conclusion to the effect that a certain PROCESS is or is not a **HARM**
POSITIVE HARM DIAGNOSIS	L2/3-DC	**[AEO] HARM DIAGNOSIS** involving a conclusion that a certain PROCESS is a **HARM**
DISEASE DIAGNOSIS	L2/3-DC	[OGMS:DIAGNOSIS] REPRESENTATION that (1) asserts the presence of an instance of DISEASE in a given ORGANISM and (2) **results from** an INTERPRETIVE PROCESS that has as input a *CLINICAL PICTURE* of that ORGANISM

Table 3. Upper level of the independent continuants in the ReMINE Domain Ontology

INDEPENDENT CONTINUANT	L1-U	[BFO] CONTINUANT in which other entities **inhere** and which itself cannot **inhere** in anything.
SITE	L1-U	[BFO] INDEPENDENT CONTINUANT consisting of a characteristic spatial shape in relation to some arrangement of other continuant entities and of the medium which is enclosed in whole or in part by this characteristic spatial shape.
HEALTHCARE FACILITY	L1-DC	MATERIAL ENTITY in which under normal circumstances **ACTS OF CARE** are performed
MATERIAL ENTITY	L1-U	[BFO] INDEPENDENT CONTINUANT that is spatially extended and whose identity is independent of that of other entities and can be maintained through time.
ANATOMICAL STRUCTURE	L1-DC	[FMA] MATERIAL ENTITY that is part of an **ORGANISM** that has been generated by the coordinated expression of the **ORGANISM's** own structural genes
MENTAL HEALTH-RELATED ANATOMICAL STRUCTURE	L1-U	[OMH] ANATOMICAL STRUCTURE in which there **inheres** the DISPOSITION to be the **agent of** a MENTAL
RAPS REPOSITORY	L3-DC	[AEO] MATERIAL ENTITY **formed-by DENOTATORS** that **denote PROCESSES IN THE CONTEXT OF CARE** and are the **subject of** a **POSITIVE HARM DIAGNOSIS**
OBJECT	L1-U	[BFO] MATERIAL ENTITY that is spatially extended, has an external boundary that is maximally self-connected and possesses an internal unity
ORGANISM	L1-U	ANATOMICAL STRUCTURE which is an individual member of a species
HUMAN BEING	L1-U	[FMA] ORGANISM which is an individual member of the human species
CAREGIVER	L1-DC	**HUMAN BEING** in which there inheres a **CAREGIVER ROLE**
SUBJECT OF CARE	L1-DC	**HUMAN BEING undergoing** ACTS OF CARE
BODILY COMPONENT	L1-DC	[OGMS] MATERIAL ENTITY **within** or **on** the surface of an **ORGANISM**, including ANATOMICAL STRUCTURES, body flora, pathogens, toxins, and their combinations
DISORDER	L1-DC	[OGMS] A combination of BODILY COMPONENTS *of* or *in* an **ORGANISM** (1) that is not part of the life plan for an **ORGANISM** of the relevant type (thus aging or pregnancy are not clinically abnormal), (2) that is causally linked to an elevated risk of pain or other feelings of illness or of death or dysfunction on the part of the organism, and (3) that it is such that this elevated risk exceeds a certain threshold level.
MATERIAL REPRESENTATION	L3-DC	[RT] MATERIAL ENTITY which is a REPRESENTATION
DENOTATOR	L3-DC	[RT] MATERIAL REPRESENTATION **denoting** a portion of reality
ADVERSE EVENT DENOTATOR	L3-DC	[AEO] **DENOTATOR denoting** a **RAPS EVENT**

Table 4. Upper level of the dependent continuants in the ReMINE Domain Ontology

DEPENDENT CONTINUANT	L1-U	[BFO] CONTINUANT that is **dependent on** an INDEPENDENT CONTINUANT
GENERICALLY DEPENDENT CONTINUANT	L1-U	[BFO] DEPENDENT CONTINUANT that is **dependent on** one or other INDEPENDENT CONTINUANT
INFORMATION CONTENT ENTITY	L2/3-U	[IAO] GENERICALLY DEPENDENT CONTINUANT **which is about** a portion of reality
SPECIFICALLY DEPENDENT CONTINUANT	L1-U	[BFO] DEPENDENT CONTINUANT that during its entire existence is **dependent on** at least one specific INDEPENDENT CONTINUANT
ANATOMICAL STRUCTURE INTEGRITY	L1-U	SPECIFICALLY DEPENDENT CONTINUANT of an ANATOMICAL STRUCTURE deviation from which would bring it about that the ANATOMICAL STRUCTURE in which it **inheres** would either (1) itself become dysfunctional or (2) cause dysfunction in another ANATOMICAL STRUCTURE
COGNITIVE REPRESENTATION	L2-U	[OMH] SPECIFICALLY DEPENDENT CONTINUANT of an ANATOMICAL STRUCTURE which yields this structure to be a REPRESENTATION
INTENTION	L2-U	[OMH] COGNITIVE REPRESENTATION **in** an **ORGANISM about** parts of the LIFE of that ORGANISM that motivates that **ORGANISM** to **participate** in some PROCESS
CARE INTENTION	L2-DC	INTENTION **in** a **CAREGIVER** that motivates him or her towards an **ACT OF CARE**
REALIZABLE ENTITY	L1-U	[BFO] SPECIFICALLY DEPENDENT CONTINUANT that **inheres in** a CONTINUANT and is not exhibited in full at every time in which it inheres in it. The realization of a REALIZABLE ENTITY is a PROCESS that occurs under certain circumstances.
ROLE	L1-U	[BFO] REALIZABLE ENTITY whose realization brings about some result or end that is not essential to a CONTINUANT in virtue of the kind of thing that it is.
CAREGIVER ROLE	L1-DC	ROLE **inhering** in a **HUMAN BEING** mandated to be the **agent of ACTS OF CARE**
DISPOSITION	L1-U	[BFO] REALIZABLE ENTITY **inhering in** an INDEPENDENT CONTINUANT that under specific circumstances and in conjunction with the laws of nature becomes realized in a PROCESS in which the INDEPENDENT CONTINUANT **participates**
DISEASE	L1-U	[OGMS] DISPOSITION (1) to undergo PATHOLOGICAL PROCESSES that (2) exists in an **ORGANISM** because of one or more DISORDERS in that **ORGANISM**
UNDERLYING DISEASE	L1-DC	the DISEASE **inhering in** the **SUBJECT OF CARE** which is part of what serves to motivate performance of the **ACT OF CARE**

Table 5. Upper level of the process in the ReMINE Domain Ontology

HISTORY	L1-U	[RT] PROCESS **formed by** PROCESSES in which a CONTINUANT **participates** or **has participated**
LIFE	L1-U	[RT] HISTORY OF an ORGANISM
BODILY PROCESS	L1-U	[OGMS] PROCESS in which at least one BODILY COMPONENT of an ORGANISM or the ORGANISM as a whole **participates**
COGNITIVE PROCESS	L1-U	[OMH] BODILY BROCESS which brings into being, sustains or destroys a COGNITIVE REPRESENTATION
INTERPRETIVE PROCESS	L1-U	[OMH] COGNITIVE PROCESS which brings into being, sustains or destroys COGNITIVE REPRESENTATIONS on the basis of an OBSERVATION
PATHOLOGICAL PROCESS	L1-U	[OGMS] BODILY PROCESS that is a **manifestation of** a DISORDER
ANATOMICAL STRUCTURE CHANGE	L1-DC	BODILY PROCESS involving a change in an ANATOMICAL STRUCTURE
PROCESS IN THE CONTEXT OF CARE	L1-DC	PROCESS which is part of the HISTORY of a **HEALTHCARE FACILITY**, or of the LIFE of a **CAREGIVER** insofar this PROCESS is executed under the mandate associated with his **CAREGIVER ROLE**
ACT OF CARE	L1-DC	**PROCESS IN THE CONTEXT OF CARE** (1) which **has as agent** a CAREGIVER and (2) as (passive) **participant** a **SUBJECT OF CARE**, and (3) is **motivated by** an **UNDERLYING DISEASE** and a **CARE INTENTION**
RAPS EVENT	L1-DC	[AEO] PROCESS **denoted-by** a **DENOTATOR** in a **RAPS REPOSITORY**
HARM	L1-DC	[AEO] PROCESS **resulting in** an expansion in the range of circumstances of the sort occurring in the HISTORY of an INDEPENDENT CONTINUANT under which that CONTINUANT would **participate** in PROCESSES involving some sort of loss or detriment, whether physically, functionally, socially, economically, etc.
BODILY HARM	L1-DC	[AEO] **HARM** consisting of a change in the **STRUCTURE INTEGRITY** of an ANATOMICAL STRUCTURE bringing about a change in the range of circumstances under which the ANATOMICAL STRUCTURE would become dysfunctional or cause dysfunction in another structure
PREVENTION	L1-DC	PROCESS **resulting in** a decrease in the range of circumstances of the sort occurring in the HISTORY of a CONTINUANT under which that CONTINUANT would **participate** in PROCESSES involving some sort of loss or detriment, whether physically, functionally, socially, economically, etc.
MITIGATION	L1-DC	[AEO] **PREVENTION** carried out in response to a **HARM**
HARM ASSESSMENT	L1-DC	[AEO] INTERPRETIVE PROCESS to determine whether another PROCESS is an instance of **HARM**

4.1 Core representational units

Tables 2 to 5 contain those representational units (RU) of the upper level part of the ReMINE ontology which are sufficient to represent the various configurations that may obtain between the occurrence of an incident, whether that incident involves some harm, whether it has been recognized as such by some cognitive agent, and whether it has been reported upon in the ReMINE adverse event database. For each RU we provide a term, a category, and a textual description.

The RUs are organized in a subsumption hierarchy: within each table we start with the most generic term for respectively representations (Table 2), independent continuants (Table 3), dependent continuants (Table 4) and processes (Table 5). Less generic terms are indented towards the right.

The categories shown in the second column of each of these tables are formed on the basis of two criteria. The first concerns whether the specific entities – 'particulars' in BFO's terminology [21] – are a matter of (L1) first-order reality such as a disorder in a specific patient, (L2) beliefs or cognitive representations about portions of first-order reality on the side of a cognitive being, for instance a diagnosis formed by a clinician, or (L3) some durable representation of a first- or second-order entity (e.g. a statement in some record that the patient suffers from an allergy). The second criterion is whether the particulars are **instances of** a universal (indicated by 'U') or **members of** a defined class ('DC'), the latter being defined as a collection of particulars that share at least one characteristic (e.g. being located in Buffalo) that is relevant in some context [21].

For terms and phrases used in the descriptions shown in the third column of each of these tables, we used the following typographical conventions: (1) terms that express relationships are printed in **bold**, (2) terms borrowed from the feeder ontologies or referent tracking are in SMALL CAPS, (3) terms introduced in the ReMINE ontology are printed in bold **SMALL CAPS**. Terms printed in italic *SMALL CAPS* are further defined in the originating feeder ontology but for reasons of space and relevance not in this paper.

The descriptions for terms printed in SMALL CAPS are preceded by a label between square brackets that indicates the provenance of the term: Basic Formal Ontology (BFO), Ontology of General Medical Science (OGMS), Information Artifact Ontology (IAO), Foundational Model of Anatomy (FMA), Ontology of Mental Health (OMH), and Referent Tracking (RT). Newly introduced terms (22 terms) whose descriptions are preceded by '[AEO]' are intended to become part of an Adverse Event Ontology (9 terms) which is independent of the ReMINE Ontology and should become part of the OBO Foundry. Terms which are not preceded by a label (13 terms), as well as the terms preceded by '[RT]', should find their way to other ontologies in the OBO Foundry family.

4.2 Examples of use

4.2.1 The place of 'adverse events'

The representational units for the core classes identified above can be used to represent all possible portions of reality which feature entities that can be referred to by means of the term '*adverse event*' under any of the definitions listed in Table 1. As an example, Table 6 lists the particulars and relationships involved in a case in which a patient born at time t_0 undergoing anti-inflammatory treatment and physiotherapy since t_2 for an arthrosis present since t_1 develops a stomach ulcer at t_3.

This table thereby provides an example of an adverse event case analysis of the sort that is made possible by the framework here presented. The relationships employed in this table are

drawn from [10, 31]. We preserve the formatting conventions proposed in [10], except that we pick out particulars using bold italic. We introduce the primitive **is_about** relation holding between a representational unit and the entity in reality about which this unit contains information at a certain time. We further take certain shortcuts in our representation of the temporal relationships involved in such an analysis, by simply stating for example that t0 **earlier** t1 **earlier** t2 **earlier** t3.

Table 6. Example of an adverse event case analysis

IUI	Particular description	Relationships
#1	the patient who is treated	***#1*** **member_of** SUBJECT OF CARE **since** t_2
#2	***#1***'s treatment	***#2*** **member_of** ACT OF CARE ***#2*** **has_participant** ***#1*** **since** t_2 ***#2*** **has_agent** ***#3*** **since** t_2
#3	the physician responsible for #2	***#3*** **member_of** CARE GIVER **since** t_2
#4	***#1***'s arthrosis	***#4*** **member_of** UNDERLYING DISEASE **since** t_1
#5	***#1***'s anti-inflammatory treatment	***#5*** **part_of** ***#2*** ***#5*** **member_of** ACT OF CARE
#6	***#1***'s physiotherapy	***#6*** **part_of** ***#2*** ***#6*** **member_of** ACT OF CARE
#7	***#1***'s stomach	***#7*** **part_of** #1 **since** t_2 ***#7*** **instance_of** ANATOMICAL STRUCTURE **since** t_2
#8	***#7***'s structure integrity	***#8*** **instance_of** ANATOMICAL STRUCTURE INTEGRITY **since** t_0 ***#8*** **inheres_in** ***#7*** **since** t_0
#9	***#1***'s stomach ulcer	***#9*** **part_of** ***#7*** **since** t_3 ***#9*** **instance_of** DISORDER **since** t_3
#10	coming into existence of ***#9***	***#10*** **has_participant** ***#9*** **at** t_3 ***#10*** **instance_of** BODILY PROCESS
#11	change brought about by ***#9***	***#11*** **has_agent** ***#9*** **since** t_3 ***#11*** **has_participant** ***#8*** **since** t_3 ***#11*** **instance_of** HARM
#12	noticing the presence of ***#9***	***#12*** **has_participant** ***#9*** **at** t_{3+x} ***#12*** **has_agent** ***#3*** **at** t_{3+x} ***#12*** **instance_of** COGNITIVE PROCESS
#13	cognitive representation in ***#3*** about ***#9***	***#13*** **is_about** ***#9*** **since** t_{3+x} ***#13*** **instance_of** COGNITIVE REPRESENTATION **since** t_{3+x}

We also allow for temporal annotations additional to those described in [10], at the same time remaining faithful to EN 12388:2005: Health Informatics – Time Standards for Healthcare Specific Problems [32].

Under the proposed scenario, ***#10***, i.e. the appearance of ***#9***, would (modulo the wide variation in interpretations that can be given to the majority of the definitions found) qualify as an adverse event as defined by the Institute of Medicine (definition D5).
However, for definition D9, it would rather be ***#9*** itself that would so qualify, while for D4, the definition of 'adverse event' proposed by the BRIDG consortium [33], it would be either

#12 or ***#13***. The counterintuitive nature of the latter case has its roots in certain conflations in the HL7 RIM [34], by which BRIDG is heavily inspired.

4.2.2 Building a RAPS repository

ReMINE's pragmatic definition for the term 'adverse event' (D10 in Table 1) provides useful information that can easily be understood by human beings, but that can not be formally defined in a way that allows unambiguous interpretation by software agents. This is for several reasons. First, there is nothing in reality that exhibits all the listed features simultaneously. Clearly, nothing that happened in the past (an occurrent in BFO's terminology, which is a synonym for 'perdurant') can be an expectation (a cognitive continuant).

Second, the pragmatic definition does not explicitly specify what sorts of incidents are to be considered as adverse events. Under one reading, one could assume that an incident becomes an adverse event by the mere fact of being reported '*in a database of adverse events*'. But that – if applied incautiously – would violate the principle that the past cannot be changed: something which is not an adverse event at the time it happens, can not become one afterwards. Further questions raised by this definition are, accordingly: who has the authority to add reports, what criteria are used by that authority, how to deal with false positives and negatives?

For the envisioned RAPS repository to be able to represent reality faithfully and to enable use of its data to advance the state of the art in adverse event management, the system should be set up in such a way that it can accommodate annotations for incidents separately from beliefs about whether these incidents are adverse events, and in such a way that adequate quality control measures are put into place. How to do so, is demonstrated in Table 7 which is set up in a similar way as Table 6. It represents a situation in which an incident (#1) that happened at time t_2 to a patient (#2) after some intervention (#3 at t_1) is judged at t_3 to be an adverse event, thereby giving rise to a belief (#4) about #1 on the part of some person (#5, a caregiver as of time t_6). Then applying ReMINE's definition for adverse event requires the introduction (at t_4) of an entry (#6) to that effect in the database (#7, installed at t_0). Using the core representational units discussed above and a syntax as in [10] expanded with the temporal representations standardized in CEN EN12388 [32], one can then make the assertions listed in Table 7.

Table 7. Fragment of a RAPS repository

1. #3 **instance_of** *ACT OF CARE*	9. #4 **inheres_in** #5 **since** t_3
2. #3 **has_participant** #2 **at** t_1	10. #5 **member_of** *CAREGIVER* **since** t_6
3. #2 **member_of** *SUBJECT OF CARE* **at** t_1	11. t_6 **earlier** t_1
4. #1 **instance_of** PROCESS	12. #7 **instance_of** *RAPS REPOSITORY* **since** t_0
5. #1 **has_participant** #2 **at** t_2	13. #6 **instance_of** *ADVERSE EVENT DENOTATOR* **since** t_4
6. t_1 **earlier** t_2	14. #6 **part_of** #7 **since** t_4
7. #4 **member_of** *POSITIVE HARM DIAGNOSIS* **since** t_3	15. #6 **is_about** #1
8. #4 **is_about** #1	16. #6 **has_author** #5

5 Discussion

5.1 A common ground for adverse event definitions

Already a very superficial analysis of the definitions in Table 1 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' be referring to when he uses that phrase?*". Indeed, the authors of the listed definitions must have had very distinct entities in mind: we cannot imagine even one single example of an entity which would be such that, were it placed before these authors, they would each in turn be able to point to it while the first would say – faithfully and honestly – "*that is an observation*" (definition D4), the second: "*that is an injury*" (definition D9), the third: "*that is a laboratory finding*" (definition D6), and so on. Clearly, nothing which **is** an injury can **be** a laboratory finding, although, of course, laboratory findings can aid in diagnosing an injury 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 (by either a human being or a device) if we are to arrive at a laboratory finding.

However, because all the authors of the mentioned systems use the term '*adverse event*' in some context for a variety of 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 (some portion of reality) which is such that the entities within it can be used as referents for the various meanings of '*adverse event*'.

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

The definitions for the term '*adverse event*' and for other closely related terms differ amongst themselves in that they require a representation which resorts to one, two or all three levels of reality as described above. Definition D9 is an example in which all terms refer to level 1 entities: '*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*** the first order reality which forms his environment. 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, for example in a manual or textbook.

5.3 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 to be conducted unproblematically in realist terms. Often multiple interpretations can be given to one or more terms used within such a definition, whereby each interpretation suggests a denotation at a

distinct level of reality. An example is definition D3, in which the response that is described as being *undesirable* can be understood in three different ways:

(1) as denoting something on level 1, namely a *realizable entity* (a *disposition* or *tendency* [35]), which exists objectively as an increased health risk; in this sense any event '*that either compromises therapeutic efficacy, enhances toxicity, or both*' is undesirable;

(2) as denoting something on level 2, so that, amongst all of 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) as denoting something relating to level 3, so a particular event occurring on level 1 is *undesirable* only when it is an instance of a type of event that is listed in some guideline, good practice management handbook, i.e. in some published statement of 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 within one single definition when the latter is analyzed in realist terms is provided by the attempt at a literal interpretation of D5, and more precisely of the use, there, of the term '*act of omission*', especially if that term is taken in such a way that it does not denote anything which exists either now or in the past. In Referent Tracking terms, there would thus be nothing to which a IUI could be assigned. Indeed, while we believe that the phrase 'action not taken' is a linguistic description (level 3 entity) that can be used adequately and meaningfully in reporting some feature of a complex portion of reality (level 1 entity), such a use does not yet signify that the term denotes directly some entity in that portion of reality. While terms of the form 'doing something' do have referents in first order reality, there are no such referents denoted by terms like 'doing nothing'.

5.4 Building an unambiguous RAPS repository

This approach, which in contrast to related work reported in [3] provides an evolutionary view on reality, allows us to track in detail and with various kinds of subtleties how the relevant portions of reality and the stakeholders' beliefs therein evolve over time. Some subtleties are built into the ontology. As an example, criterion (3) for ACT OF CARE excludes those processes whose agents are caregivers but which are not performed under the caregiver role (e.g. a doctor hurting a patient in a car accident on the parking lot of a care facility). Other subtleties come with the referent tracking approach exemplified in Tables 6 and 7. So is clinician #5 in the described scenario in Table 7 careful (perhaps erroneously so) *not* to assert that '#1 **member_of** HARM' (#17), although he could have done so. If his diagnosis, as expressed in assertion 7 in Table 7, is correct, then #17 would correspond with reality too. If, on the other hand, his diagnosis is incorrect, then the presence of #17 in the repository would be an error. However, such errors can be corrected at later stages without losing information about the original beliefs [36].

If RAPS repository #7 were faithful to reality, each member of RAPS EVENT would be a member of HARM. Furthermore, if #7 were locally complete, each member of HARM that occurred in the realm in which #7 is installed would be a member of RAPS EVENT. Many other assertions can be added expressing other beliefs about #1, or even beliefs about somebody else's beliefs. Distinct clinicians, depending on what definition they apply, may indeed hold different beliefs about whether a specific incident such as #1 (1) really happened, (2) is of a specific sort, or (3) counts as an adverse event. They may further differ in their beliefs about

what caused the incident, and about how to prevent future happenings of incidents of the same sort in the future. Moreover, they may change their beliefs over time.

6 Conclusion

We have used the principles of Basic Formal Ontology (BFO), including 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 to serve a number of important purposes, and that, when used appropriately, it avoids the inconsistencies and incompatibilities inherent in other approaches. We further used these principles to develop an ontology and associated data annotation scheme for adverse event management in the ReMINE project. The three-layered structure of reality – what is the case, what is believed, and what is represented – as argued for in BFO, turns out to be essential in this domain.

Merging the existing ontologies, although all designed under the OBO Foundry principles, was not an easy task and the proposal advanced here will most likely undergo further changes. More work is required on the formulation of descriptions and definitions of respectively universals and defined classes such that both necessary and sufficient conditions for instantiation and membership can be specified. This is not only true for the ReMINE ontology as the basis for a universal Adverse Event Ontology, but also for all feeder ontologies from which representational units have been borrowed.

Additional work will also include linking these ontologies to existing terminological resources that enjoy a broad domain coverage but suffer from formal rigor.

7 Acknowledgements

The work described was in part funded by the European Union through Grant Agreement 216134 is and also supported by grant R21LM009824 from the National Library of Medicine and by the NIH Roadmap grant 1 U 54 HG004028. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of the National Library of Medicine or the National Institutes of Health.

References

1. Arici, S. and P. Bertele, *ReMINE Deliverable D4.1: RAPS Taxonomy: Approach and Definition*. 2008.
2. Ceusters, W., M. Capolupo, and J. Devlies, *ReMINE Deliverable D4.2: RAPS Domain Ontology*. 2009, RAMIT VZW: Gent.
3. Smith, B., W. Ceusters, and R. Temmerman, *Wüsteria*, in *Connecting Medical Informatics and Bio-Informatics. Medical Informatics Europe 2005*, R. Engelbrecht, et al., Editors. 2005, IOS Press: Amsterdam. p. 647-652.
4. Institute of Medicine, *To Err is Human: Building a Safer Health System*, ed. Linda T. Kohn, Janet M. Corrigan, and M.S. Donaldson. 2000, Washington DC: National Academy Press.
5. Ceusters, W., et al. *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.
6. Schorlemmer, M. and Y. Kalfoglou, *Institutionalising Ontology-Based Semantic Integration.* Journal of Applied Ontology, 2008. **3**(3): p. 131-150.
7. Brinkley, J.F., et al., *A framework for using reference ontologies as a foundation for the semantic web*, in *Proceedings of the AMIA Fall Symposium*. 2006. p. 95-100.
8. Smith, B., et al., *The OBO Foundry: coordinated evolution of ontologies to support biomedical data integration.* Nature Biotechnology, 2007. **25**: p. 1251-1255.

9. IFOMIS. *Basic Formal Ontology*. 2009 August 2009 [cited 2009 September 7]; Available from: http://www.ifomis.uni-saarland.de/bfo/.
10. Smith, B., et al., *Relations in biomedical ontologies.* Genome Biology, 2005. **6**(5): p. R46.
11. Smith, B., *Ontology (Science)*, in *Formal Ontology in Information Systems - Proceedings of the Fifth International Conference (FOIS 2008)*, C. Eschenbach and M. Grüninger, Editors. 2008, IOS Press: Amsterdam. p. 21-35.
12. Ceusters, W., et al., *Introducing Realist Ontology for the Representation of Adverse Events*, in *Formal Ontology in Information Systems*, C. Eschenbach and M. Gruninger, Editors. 2008, IOS Press: Saarbrücken. p. 237-250.
13. Grenon, P., B. Smith, and L. Goldberg, *Biodynamic Ontology: Applying BFO in the Biomedical Domain*, in *Ontologies in Medicine*, D.M. Pisanelli, Editor. 2004, IOS Press: Amsterdam. p. 20-38.
14. Rosse, C. and J.L.V. Mejino, *A reference ontology for bioinformatics: The Foundational Model of Anatomy.* Journal of Biomedical Informatics, 2003. **36**: p. 478-500.
15. Scheuermann, R.H., W. Ceusters, and B. Smith, *Toward an Ontological Treatment of Disease and Diagnosis*, in *Proceedings of the 2009 AMIA Summit on Translational Bioinformatics, San Francisco, California, March 15-17, 2009*. 2009, American Medical Informatics Association. p. 116-120.
16. Ruttenberg, A., B. Smith, and W. Ceusters. *Information-Artifact-Ontology*. 2008 [cited 2008 December 10]; Available from: http://code.google.com/p/information-artifact-ontology/.
17. Ceusters, W. and B. Smith, *The Ontology of Mental Disease.* Journal of Biomedical Informatics - Special issue on Translational Ontologies, 2010 (under review).
18. Rudnicki, R., et al., *What Particulars are Referred to in EHR Data? A Case Study in Integrating Referent Tracking into an Electronic Health Record Application*, in *American Medical Informatics Association 2007 Annual Symposium Proceedings, Biomedical and Health Informatics: From Foundations to Applications to Policy*, Teich JM, Suermondt J, and H. C, Editors. 2007: Chicago, IL. p. 630-634.
19. Spear, A.D., *Ontology for the Twenty First Century: An Introduction with Recommendations*. 2006, Institute for Formal Ontology and Medical Information Science: Saarbrucken, Germany.
20. Smith, B., *From Concepts to Clinical Reality: An Essay on the Benchmarking of Biomedical Terminologies.* Journal of Biomedical Informatics, 2006. **39**(3): p. 288-298.
21. Smith, B., et al., *Towards a Reference Terminology for Ontology Research and Development in the Biomedical Domain*, in *KR-MED 2006, Biomedical Ontology in Action.* 2006: Baltimore MD, USA
22. Johansson, I., *Bioinformatics and Biological Reality.* Journal of Biomedical Informatics, 2006. **39**(3): p. 274-287.
23. Ceusters, W., B. Smith, and L. Goldberg, *A terminological and ontological analysis of the NCI Thesaurus.* Methods of Information in Medicine, 2005. **44**: p. 498-507.
24. Ceusters, W., et al., *Ontology-based error detection in SNOMED-CT®.* in *MEDINFO 2004*, M. Fieschi, E. Coiera, and Y.-C.J. Li, Editors. 2004, IOS Press: Amsterdam, The Netherlands. p. 482-486.
25. Ceusters, W., et al., *Mistakes in medical ontologies: Where do they come from and how can they be detected?*, in *Ontologies in Medicine. Studies in Health Technology and Informatics*, D.M. Pisanelli, Editor. 2004, IOS Press: Amsterdam, The Netherlands. p. 145-164.
26. Smith, B. *Ontology and the Logistic Analysis of Reality*. in *Proceedings of the International Workshop on Formal Ontology in Conceptual Analysis and Knowledge Representation*. 1993. Padova: Institute for Systems Theory and Biomedical Engineering of the Italian National Research Council.
27. Ceusters, W. and B. Smith, *Ontology and Medical Terminology: why Descriptions Logics are not enough.*, in *Towards an Electronic Patient Record (TEPR 2003)*. 2003: San Antonio.
28. Ceusters, W. and B. Smith, *Strategies for Referent Tracking in Electronic Health Records.* Journal of Biomedical Informatics, 2006. **39**(3): p. 362-378.
29. Ceusters, W. and B. Smith, *A Realism-Based Approach to the Evolution of Biomedical Ontologies*, in *Biomedical and Health Informatics: Proceedings of the 2006 AMIA Annual Symposium*. 2006, American Medical Informatics Association: Washington DC. p. 121-125.
30. Ceusters, W., et al., *An Evolutionary Approach to the Representation of Adverse Events.* Stud Health Technol Inform., 2009. **150**: p. 537-41.
31. Smith, B. and P. Grenon, *The Cornucopia of Formal-Ontological Relations.* Dialectica, 2004. **58**(3): p. 279-296.
32. European Committee for Standardization, *EN 12388:2005. Health informatics - Time standards for healthcare specific problems.* 2005.
33. Weng, C., M. Becich, and D. Fridsma, *Collective Domain Modeling across Clinical Trials Standards: Needs, Challenges, and Design Implications*, in *Information Technology and Communications in Health (ITCH)*. 2007: Victoria, BC, Canada.

34. Smith, B. and W. Ceusters, *HL7 RIM: An Incoherent Standard*, in *Studies in Health Technology and Informatics. Ubiquity: Technologies for Better Health in Aging Societies - Proceedings of MIE2006*, A. Hasman, et al., Editors. 2006, IOS Press: Amsterdam. p. 133-138.
35. Jansen, L., *Tendencies and other Realizables in Medical Information Sciences.* The Monist, 2007. **90**(4): p. 534-555.
36. Ceusters, W., *Dealing with Mistakes in a Referent Tracking System*, in *Proceedings of Ontology for the Intelligence Community 2007 (OIC-2007)*, H. KS, Editor. 2007: Columbia MA. p. 5-8.
37. The Joint Commission. *Sentinel Event Glossary of Terms*. 2008 [cited 2008 April 14]; Available from: http://www.jointcommission.org/SentinelEvents/se_glossary.htm.
38. U.S. Food and Drug Administration, *IND Safety Reports*, Code of Federal Regulations Title 21 Volume 5 § 312.32, Editor. 2007.
39. Committee for Data Standards for Patient Safety - Institute of Medicine, *Patient Safety: Achieving a New Standard of Care*, ed. A. P, et al. 2004, Washington DC: The National Academies Press.
40. National Cancer Institute, *Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0*. 2006.
41. CDISC Submission Data Standards Team, *CDISC SDTM Implementation Guide (Version 3.1.2) - Study Data Tabulation Model Implementation Guide: Human Clinical Trials*. 2007.
42. Quality Interagency Coordination Task Force. *Glossary of Terms*. 2008 [cited 2008 April 14]; Available from: http://www.quic.gov/report/mederr8.htm.