Technical advance articles Composite CDE: modeling composite relationships between common data elements for representing complex clinical data

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Abstract

Background: Semantic interoperability is essential for improving data quality and sharing. The ISO/IEC 11179 Metadata Registry (MDR) standard has been highlighted as a solution for standardizing and registering clinical data elements (DEs). However, the standard model has both structural and semantic limitations, and the number of DEs continues to increase due to poor term reusability. Semantic types and constraints are lacking for comprehensively describing and evaluating DEs on real-world clinical documents. Methods: We addressed these limitations by defining three new types of semantic relationship (dependency , composite , and variable) in our previous studies. The present study created new and further extended existing semantic types (hybrid atomic and repeated and dictionary composite common data elements [CDEs]) with four constraints: ordered , operated , required , and dependent . For evaluation, we extracted all atomic and composite CDEs from five major clinical documents from five teaching hospitals in Korea, 14 Fast Healthcare Interoperability Resources (FHIR) resources from FHIR bulk sample data, and MIMIC-III (Medical Information Mart for Intensive Care) demo dataset. Metadata reusability and semantic interoperability in real clinical settings were comprehensively evaluated by applying the CDEs with our extended semantic types and constraints. Results: All of the CDEs (n =1142) extracted from the 25 clinical documents were successfully integrated with a very high CDE reuse ratio (46.9%) into 586 CDEs (259 atomic and 20 unique composite CDEs), and all of CDEs (n=238) extracted from the 14 FHIR resources of FHIR bulk sample data were successfully integrated with high CDE reuse ration (59.7%) into 96 CDEs (21 atomic and 28 unique composite CDEs), which improved the semantic integrity and interoperability without any semantic loss. Moreover, the most complex data structures from two CDE projects were successfully encoded with rich semantics and semantic integrity. Conclusion: MDR-based extended semantic types and constraints can facilitate comprehensive representation of clinical documents with rich semantics, and improved semantic interoperability without semantic loss.

Background

Data harmonization and interoperability are essential for advancing biomedical research. These features can be achieved by representing clinical data in a standard format, and they are crucial for facilitating understanding and sharing data across diverse translational studies [1, 2]. A common data element (CDE) is defined as the fundamental unit of data which contains information with a clear conceptualized meaning, together with its representation, and is considered the correct approach for standardizing data and improving data quality and efficiency.

The ISO/IEC 11179 Metadata Registry (MDR) standard describes a method of standardizing and registering data elements (DEs) to make them understandable and shareable between studies and institutions. An MDR-based CDE collects data uniformly, allowing data interoperability between clinical studies, since they are specified, based on a metadata model that consists of a sets of attributes, which are delineating the definition, identification, representation, classification, and permissible values [3–5].

CDEs are increasingly being used by clinical researchers in trials, for harmonizing data collected across diverse studies. The use of standardized CDEs provides various benefits to investigators, including (1) rapid and efficient study start-up by enabling access to defined CDEs and case report forms (CRFs), and (2) enriched data sharing and data aggregation using standard definitions and forms [6].

The use of CDEs has recently been extended to clinical practice by using standardized CDEs for representing the clinical information in electronic health records (EHRs). For example, Newton *et al.* included phenotype data in EHRs using CDEs in order to facilitate EHR-driven genomic studies [7]. The National Institutes of Health have developed ISO/IEC 11179 MDR-based CDEs that provide a controlled terminology for data descriptors, and they encouraged clinical researchers to use CDEs in order to facilitate data harmonization [5]. CDEs have been adopted in numerous clinical domains including cancer, stroke, epilepsy, rare diseases, emergency medicine, and radiology for patient care, and research. Utilizing CDEs will facilitate secondary data use (i.e., ‘collect once and use many times’), which is an approach to standardization that spans silos in primary and secondary data use [8].

However, ISO/IEC 11179 MDR-based CDEs do not provide the ability to describe constraints for a CDE and relationships among different CDEs, instead merely focusing on the representations of single independent CDEs, which makes it difficult to either correctly compose or interpret CDEs of clinical documents [9–12]. Although the ISO/IEC 11179 standard describes a derived data element (DDE) [13] detailing the relationship between a DE, the rule controlling its derivation, and another DE from which it is derived. This approach is inherently limited by the DDE as it requires one or more input DEs, and the DDE becoming an output DE. For example, systolic blood pressure (SBP) and diastolic blood pressure (DBP) can be easily defined as two separate DEs annotated with standardized metadata conforming to the ISO/IEC 11179 MDR standard. However, these two DEs are only input DEs, and a separate output DE is needed as the DDE. Also, a constraint between the two DEs such as 'the SBP must be greater than the DBP' is usually described outside of the DEs, for there is no necessary reason for the DEs to carry constraint information.

To address these challenges in our previous study, [9] we proposed three types of semantic relationships (*variable*, *dependency*, and *composite* relationships) representing semantic constraints or rules among multiple CDEs. These relationships can be described as follows: First, CDEs are in a *variable* relationship when they can be systematically derived from a base CDE by applying a standardized concept from a controlled vocabulary. For example, the meanings of two CDEs for 'normal value range of laboratory test, Albumin' and 'normal value range of laboratory test, Homocysteine' are closely related, differing only in the laboratory test names of 'Albumin' and 'Homocysteine.' The *variable* relationship can systematically represent all these variations as a single CDE, 'DE: Normal value range of lab test *x*,' by applying a controlled vocabulary such as LOINC. The *variable* relationship can therefore systematically reduce the number of CDEs required. Second, a CDE is in a *dependency* relationship when the value of the CDE is determined by the value(s) of the CDE(s). For example, the value of a certain CDE may be defined as the sum of the values of a set of CDEs in a questionnaire. Third, the *composite* relationship can be conveniently applied to integrate several interrelated CDEs into a *composite* CDE. For example, the medical history of a patient is likely to be more informative when body parts are correctly assigned, which can be achieved by grouping 'DE: Body System for Medical History' and 'DE: Medical History Specify' into the *composite* CDE of 'DE: Medical History.' However, we realized that our previous work, supports relatively simple semantic relationships among CDEs and is not robust enough to cover many other specific challenges associated with CDEs used in clinical forms.

The present study further proposed extending semantic types (*hybrid* atomic and *repeated* and *dictionary* composite CDEs) and four semantic constraints (*ordered*, *operated*, *required*, and *dependent*) for correctly representing even more complex but essential semantic relationships between CDEs that are found in real-world clinical documents. We found useful patterns characterizing challenging cases, that required further semantic definitions and descriptions as the following 4 cases;

1.1 Data entries with multiple data types

A data type determines the type of data that can be entered and stored in a DE, and each DE contains only one data type [14]. However, we found that free-text-based data entry in many clinical documents stored in EHRs often allows multiple data types to be entered and stored in the same attribute. For example, a laboratory result for syphilis normally has a numeric data type that allows numeric values (e.g., '0.8') as input. However, this also often requires the entry of string or logical data such as 'negative' or 'false' as input. Sometimes creating two strictly separate CDEs for a laboratory result for syphilis (i.e., numeric and string) may cause greater confusion than if the data are harmonized and made interoperable, and sometimes it is better to allow either numeric or string data types in the same value domain. We created a value property (*hybrid*) to make it possible to ensure that conventionally multiple data types are available in the same CDE (i.e., numeric or string) in order to reduce confusion by explicitly defining the *hybrid* data type for CDEs.

1.2 Dictionary data entries

Data may refer to a controlled biomedical vocabulary for several reasons, such as adherence to standards, semantic enrichment for better understanding, and input validation for improving semantic integrity. A CDE referring to a controlled biomedical vocabulary was defined as being in a *variable* relationship in our previous study [9]. We extended the concept of the *variable* relationship to *dictionary data entries* in order to tightly link a set of CDEs via a 'foreign key' between a real-world dictionary database and a controlled biomedical vocabulary. This also ensured that a set of CDEs and tuples with rich attributes provided by the dictionary were linked with their proper data type definitions and value domains.

1.3 Tabular data entries with repeated data entry

Clinical data is frequently in tabular format. A tabular data entry is an enclosed structure in which a composed set of DEs is repetitively listed for repeated observations. For example, body weight and height may be measured for each patient when he/her visits for treatment. The set of data items such as body weight, height, and date of measurement should be collected both together and repeatedly. We created a value property (*repeat*) to ensure that the values that belong to the same set of CDEs are identified as such.

1.4 Required and derived data

Particular CDEs on a clinical document that are highly interrelated need to be defined by semantic constraints. For example, the value of a certain CDE that has a value other than null should be described by the *required* constraint. *Derived* values such as BMI (body mass index) can be automatically calculated from the values of body weight and height CDEs.

Methods

2.1 Data resource: 2 CDE projects

The National Institute of Neurological Disorders and Stroke (NINDS) CDE Project, [15] is an ongoing effort to develop data standards for use in clinical research in neuroscience. It was initiated in 2006 to standardize data collection across neurological-disorder-related clinical studies funded by the NINDS. As of October 2016, the NINDS CDE project included 20 studies with 11,296 distinct CDEs. The NINDS CDEs are not fully compliant with ISO/IEC 11179, instead only providing simple DE descriptions and definitions. However, a part of NIND CDEs that are registered in National Cancer Institute (NCI) cancer Data Standards Registry (caDSR) and reviewed by the NCI cancer Biomedical Informatics Grid project manager, conforms fully with the ISO/IEC 11179 MDR standard. In the present study we used part of the NINDS CDEs, which are 308 (3.1%) stroke and general CDEs of the NINDS that are registered in the caDSR. Selected CDEs within the context of their CRFs were explored for challenging cases requiring new semantic relationships.

The DialysisNet and Avatar Beans Project is a tablet- and phone-based mobile application developed by the Health Avatar Initiative [16]. The project started in 2013, and it has established clinical data standards for managing and harmonizing hemodialysis data across multiple medical institutions in Korea [17, 18]. This project aims to improve the management of chronic kidney disease and end-stage renal disease by using an integrated mobile application for data collection and documentation. The DialysisNet application was initially built upon 122 distinct hemodialysis related CDEs based on CRFs from major four hemodialysis centers. We used 11,428 DEs from the above 2 projects for defining new DE relationships and constraints.

2.2 Designate key concepts

The CRFs and clinical documents from the two CDE projects incorporate all the data collection items with CDEs. We first examined the CDEs to formalize the above mentioned 4 challenging cases. Figure 1 displays the formal relationship between atomic CDE (aCDE) and composite CDE (cCDE) with type-specific constraints. Since the core structure of a CDE is a name–value pair augmented by DE concept-domain and value-domain details, the aCDE is a single unambiguously described data item [18]. Our previous and simple-minded definition of cCDE as a set of interrelated aCDEs [9] was extended to include two new semantic relationships: *dictionary* and *repeated* cCDEs. We extracted aCDEs and cCDEs from the above mentioned 2 DE projects (NINDS, DialysisNet CDE Projects) and applied the extended semantic types and constraints. We then mapped and integrated the CDEs in order to comprehensively evaluate the metadata reusability and semantic interoperability in the clinical-practice setting.

2.3 Evaluation scheme

For the purpose of evaluating the utility of the newly proposed semantic types and constraints, we used three different data sources: (1) deriving DEs from clinical documents, (2) Fast Healthcare Interoperability Resources (FHIR) based structured data, and (3) practical clinical dataset from MIMIC-III (Medical Information Mart for Intensive Care).

For utilizing deriving DEs from clinical docments, we collected 25 clinical documents used in clinical practice, comprising 5 documents covering admission notes, initial medical examination notes, discharge notes, emergency notes, and operation notes from each of 5 major teaching hospitals in Korea: Seoul National University Hospital, Ajou University Medical Center, Pusan National University Hospital, Gachon University Gil Hospital, and Chonnam National University Hospital. It contains Patient, PastHistory, AdmissionInformation, Operation, FamilyHistory, SocialHistory, LabResult, Medication, VitalSign, Treatments, and PhysicalExam [17]. We chose these 25 clinical documents since these documents are used in common by all 5 hospitals and are essential in the process of patient admission to discharge, for representing the specificity of the data. However, the limits of these 25 clinical documents are their insufficiency in providing a richness of depth and detail concerning the levels of clinical data. Thus, we added two different structured data from the FHIR bulk sample data and the MIMIC-III demo dataset.

FHIR is propagated as an open standard describing data formats and elements, known as "resources" and an application programming interface (API) for exchanging EHR. FHIR's clinical resource definitions are concrete, intuitive concepts such as MedicationPrescription, AdverseReaction, Procedure, and Condition. The standard was created by the Health Level Seven International (HL7) healthcare standards organization.

For utilizing FHIR based structure data, we downloaded FHIR bulk sample data, which is exported from a FHIR server to a pre-authorized client by using FHIR bulk Downloader sample app (Figure 2) [19-21]. Among 145 resources of FHIR version 4 [22], the FHIR bulk sample data contains 14 resources which are: AllergyIntolerance, CarePlan, Claim, Condition, Goal, Encounter, Observation, DiagnosticReport, Immunization, MedicationRequest, ImagingStudy, Organization, Patient, and Procedure. Although we could analyze metadata of all FHIR resources through the structural information provided by HL7, it was necessary to review the actual sample data with metadata to confirm the relationships and constraints among the data. Thus, we used only 14 out of the entire FHIR resources.

The MIMIC-III clinical database contains comprehensive clinical data relating to tens of thousands of Intensive Care Unit patients. MIMIC-III is a large, freely-available database comprising of deidentified health-related data associated with over 40,000 patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012. The Dataset has 26 tables which includes vital signs, medications, laboratory measurements, observations and notes charted by care providers, fluid balance, procedure codes, diagnostic codes, imaging reports, hospital length of stay, survival data, and more. For utilizing MIMIC-III dataset, we downloaded the MIMIC-III demo dataset that is limited to 100 patients. Although there are many differences in the amount of data, the metadata and data-schema are same [23, 24].

Since the above two data sources have a structure between the data, the evaluation process consisted of the following three steps: CDE extraction, CDE integration, and construction of semantic relationships among the CDEs. We counted the numbers of CDEs generated in each step as a measure of the structural efficiency. However, for the rest data resource, the MIMIC-III demo dataset is a relational database, containing tables of data relating to patients. A table is a data storage structure which is similar to a spreadsheet: each column contains consistent information (e.g., patient identifiers), and each row contains an instantiation of that information (e.g. a row could contain the integer 340 in the patient identifier column which would imply that the row’s patient identifier is 340) [24]. We manually reviewed the relationships among the columns of each table, whether there were cases that were covered by our proposed CDE relationships and constraints.

Results

3.1 Overview of all types of semantic relationships

To address the challenges described above, we defined aCDEs and cCDEs using three new semantic types (*hybrid*, *dictionary*, and *repeated*) and three new types of constraints (*ordered*, *operated*, and *required*) in addition to the existing two semantic relationships (*dependent* and *variable* relationships) defined in our previous study [9]. The newly defined *composite* semantic type replaced the old *composite* relationship that we defined previously [9].

Figure 1 displays aCDEs and cCDEs with their specific constraints. An aCDE can be constrained using *variable* and *hybrid* relationships by classifying them as *variable* aCDE and *hybrid* aCDE, respectively. The definition of cCDE as a set of interrelated aCDEs in our previous study [9] was extended to include a clear definition, a separate identifier for reuse, and constraints among aCDEs inside a cCDE. cCDEs can be classified into *dictionary* and *repeated* cCDEs. One of the existing semantic relationships, the *dependent* relationship in our previous study, was extended to four constraints: *ordered*, *operated*, *required*, and *dependent*. As shown in the lower-left box in Figure 1, the *ordered* constraint does not apply to an aCDE.

3.2 Data entries with multiple data types: *Hybrid aCDE*

A *hybrid* aCDE is a particular type of aCDE that allows a value domain with multiple (or hybrid) data types. Technically it includes several aCDEs having the same DE concept but different value domains. Figure 2A shows part of a hemodialysis report form, from the DialysisNet and Avatar Beans Project. A time-tagged *hybrid* aCDE was applied to the *Time* attribute in a tabular data-entry format. The *hybrid* aCDE for *Time* (‘DE:*47616* Hemodialysis_Time_Hybrid_DE’) was derived from two aCDEs: ‘DE:*43239* Hemodialysis_Time_DE’ allowing a time data type, and ‘DE:*47614* Hemodialysis_Time_String_DE’ allowing an enumerated string data type, supporting *Finish* and *Start* (Figure 2B). The *hybrid* aCDE can capture either a time or an enumerated string value, such as ‘DE:*47616*.’

3.3 TabULar data entries: *Repeated cCDE*

A *repeated* cCDE is a cCDE that captures data input multiple times in a tabular format. The definition of the *repeated* cCDE prevents the unnecessary creation of redundant CDEs. A *repeated* cCDE efficiently captures and displays changes in input values over a certain time span, as shown in Figure 2A. We first grouped eight aCDEs (i.e., DE:*47616*, DE:*43340*, DE:*43197*, DE:*43195*, DE:*43155*, DE:*43092*, DE:*43372*, and DE:*43166*) to create a cCDE, and then assigned them as a *repeated* relationship to create a *repeated* cCDE (‘DE:*47575* Hemodialysis_Repeated_Componsite _DE’) (Figure 3). As shown in Figure 2, DE*:47616* is a *hybrid* aCDE contained in the *repeated* cCDE (DE:*47575*).

3.4 dictionary data entries: *Dictionary* cCDE

Our previous study [9] defined a *variable* CDE as a CDE that contains a controlled biomedical vocabulary variable. Similarly, a cCDE containing a *variable* aCDE as the primary key of a dictionary table can be defined as a *dictionary* cCDE. This approach provides a way to encode an entire dictionary table as well as a controlled vocabulary into a single *dictionary* cCDE, and thereby capture comprehensive biomedical knowledge from a database. A *dictionary* cCDE provides a useful means to apply relevant attributes of a dictionary database to constrain and validate input values to the *dictionary* cCDE.

Figure 4A displays a typical data-entry document for laboratory test results in a tabular format. The ‘Electrolyte Laboratory Tests’ form from ‘Recommended Labs for Stroke’ of the NINDS CDE project [25] consists of six attributes, including the laboratory test name, laboratory test result, unit of the laboratory test result, an indicator for whether the laboratory test result was abnormal, and another indicator for whether the laboratory test result was clinically significant when the laboratory test result was abnormal. Figure 4B shows a part of the structured NINDS ‘Electrolyte Laboratory Tests Dictionary’ reference table. The *Unit of Result* attribute supports multiple units that are delimited by ‘^’. The *Normal Range* attribute is also separated according to the *Unit of Result* and is represented in JSON (Javascript object notation)-type encoding.

A dictionary cCDE can systematically capture the entire ‘Electrolyte Laboratory Tests’ data-entry document ‘DE:*47571* Laboratory_Test_NINDS_Composite_DE,’ which is composed of six aCDEs (Figure 4C) that include a *variable* aCDE for *Test*, ‘DE:*43938* Laboratory_Finding_Test_Name_DE,’ which functions as the foreign key to refer to the primary key, and ‘Lab Test Name’ of the ‘Electrolyte Laboratory Tests Dictionary’ table (Figure 4B).

Now that the *dictionary* cCDE (DE:*47571*) is related to the NINDS ‘Electrolyte Laboratory Tests’ dictionary table via the *variable* aCDE (DE:*43938*), it provides a means to evaluate the validity of an input value to *Result* and *Units for Result* for a *Test* [‘Sodium (Na+)’] value of 138 mEq/L, with respect to the *Normal Range* (i.e., 135~145 mEq/L) provided by the dictionary table. The input value of *Was test result abnormal?* can also be input automatically using the biomedical knowledge provided by the dictionary table. Moreover, when the value of *Was test result abnormal?* (DE:*47566*) is ‘Abnormal,’ the value of *If abnormal, Clinically Significant?* (DE:*44135*) can automatically be constrained to contain a value other than null. This constraint can be encoded by a *Dependent Rule*, as shown in Figure 4C.

Figure 4C shows how a *dictionary* cCDE accompanied by its constraint rules are defined. For the two evaluation cases listed in Figure 4B, both a *Dictionary Rule* and a *Dependent Rule* are defined by symbolic logic (or pseudocode) with the accompanying *Descriptions*. A *Dictionary Rule* defines how to use biomedical knowledge contained in a dictionary table, and a *Dependent Rule* defines the interrelatedness of aCDEs in a cCDE by using *dependent* constraint relationships.

3.5 derived data: *Constraints*

We defined four constraints that support the creation of a robust clinical document by specifying the interrelationship among many aCDEs. We defined four classes of operators: assignment, arithmetic, logical, and relational. *Order* can only be applied to aCDEs contained in a cCDE. However, the other three constraints (*operated*, *required*, and *dependent*) can be applied to independent aCDEs on a document and those contained in a cCDE (Figure 1). We created symbolic logic with prefix notation [26] (Table 1) to describe the order of operations and to formulate constraints. More practical examples are shown in Figure 5 to demonstrate how constraints are applied to a *repeated* cCDE as well. The four constraints are described as follows:

1. **Operated**. Table 1A presents the standard BMI formula [BMI (in kg/m^2) = weight / (height ´ height)] in a prefix notation as (/ CDE30 CDE31 CDE31 100 100), where CDE30 and CDE31 represent *Body Weight Value* in kg and *Body Height Value* in cm, respectively. Both the ‘cm’ and ‘m’ units of measurements can be supported by applying an IF conditional statement to manage different units: (IF (= CDE31.unit_of_measure 'm') (/ CDE30 CDE31 CDE31) (/ CDE30 CDE31 CDE31 100 100)).
2. **Required**. A *Required* constraint applied to an aCDE means that the aCDE must have a value other than null. Table 1B lists the demographic information of a clinical document, constraining ‘*Patient Age (*CDE40*)’ and ‘*Gender (*CDE41*)’ as *required* by the statement (Required CDE40 CDE41).
3. **Dependent**. It might be necessary to dynamically enable or disable a certain aCDE according to the value(s) of other aCDE(s). For example, a gender-specific CDE might only be applied to subjects of the applicable gender. Table 1C presents an example for checking whether a patient is a current (*CDE20*) or past (*CDE21*) smoker in order to obtain the age when tobacco use was started (*CDE22*). A nonsmoker can conveniently skip *CDE22* if (= CDE20 CDE21 'No') by setting the value of CDE22 as null. In other words, a rule such as (IF (or (!= CDE20 'Yes') (!= CDE21 'Yes')) CDE22 NULL) can be imposed. Another constraint can be imposed to check illogical input values such as (= CDE20 CDE21 'Yes') if necessary.
4. **Order**. The ordering of aCDEs (especially in a cCDE) is important for certain conditions and contexts. CDEs in Table 1C can be ordered by a constraint statement such as (Ordered CDE20 CDE21 CDE22).

Table 1. Encoding *operated, required,* and *dependent* constraints for CDEs with prefix notation. Examples of (A) an *operated* constraint for calculating BMI, (B) a *required* constraint for demography information, (C) a *dependent* constraint for smoking history, and (D) an *ordered* constraint.

Constraints	Example of Clinical Documents	Set of CDE ID and CDE Name
	Prefix Notation for Formulating Constraints	
A) Operated	Weight (kg): Height (cm): BMI (kg/m^2):	*CDE30* Body Weight Value in kg *CDE31* Body Height Value in cm *CDE32* Body Mass Index Value
	(IF (= CDE31.unit_of_measure 'm') (/ CDE30 CDE31 CDE31) (/ CDE30 CDE31 CDE31 100 100)); (/ CDE30 CDE31 CDE31 100 100)	
B) Required	1) *Patient Age: 2) *Gender ☐ Female ☐ Male ☐ Unknown ☐ Unspecified ☐ Not reported 3) Ethnicity: ☐ Hispanic or Latino ☐ Unknown ☐ Not Hispanic or Latino ☐ Not reported	*CDE40* Patient Age *CDE41* Patient Gender *CDE42* Patient Ethnicity
	(Required CDE40 CDE41)	
C) Dependent	Smoking History 1. *Current tobacco use? ☐ Yes ☐ No ☐ Unknown 1. *Past tobacco use? ☐ Yes ☐ No ☐ Unknown 1. Age when tobacco use started (years)? (Skip if Q1 and Q2 are both No)	*CDE20* Current Smoking Indicator *CDE21* Past Smoking Indicator *CDE22* Age When Tobacco Use Started
	(IF (or (!= CDE20 'Yes') (!= CDE21 'Yes')) CDE22 NULL)	
D) Ordered	(Ordered CDE20 CDE21 CDE22)	

3.6 Evaluation STUDY

To evaluate the usefulness of our newly extended composite semantic relationships, we applied them to CDEs that were systematically extracted from five major clinical documents used at five teaching hospitals in Korea, and from FHIR bulk sample data. At first, we focused on deriving CDEs from clinical documents, which has many explicit cases, that clearly show the relationship between CDEs. However, we wanted to prove that our proposed relationships and constraints were valid in structured clinical data as well. This is the reason that we chose two difference types of source data: unstructured and structured data. The evaluation process consisted of the following steps: CDE extraction, CDE integration by using the new aCDEs and cCDEs, and semantic enrichment. We examined how the number of CDEs had been reduced from CDE extraction to CDE integration, measuring the structural and semantic efficiency of DEs on clinical documents.

Although HL7 FHIR supports mainly structured data, it also provides a document related resource, Questionnaire. To see whether our proposed DE types can cover FHIR Questionnaire, we matched elements of the FHIR Questionnaire resource to our developed relationships and constraints for another evaluation.

For evaluation with derived CDEs from clinical documents, we first extracted 84, 48, 70, 83, and 37 CDEs from the following 5 clinical documents used at Hospital A: admission note, initial medical examination note, discharge note, emergency note, and operation note, respectively. We found that 95 (29.5%) of the 322 CDEs were reused in at least 2 of the 5 clinical documents, resulting in 227 unique aCDEs. We then created clinically relevant cCDEs and applied semantic relationships to them. Of the 84 aCDEs extracted from admission notes at Hospital A, 55 were successfully captured by 10 created cCDEs. Finally, 16 cCDEs successfully captured 110 (48.5%) of the 227 unique CDEs, such that 133 (=16 + 117) CDEs (41.3%) were sufficient to represent the initial 322 CDEs extracted from the 5 clinical documents used at Hospital A (Table 2).

In the CDE extraction step, we found that applying CDE is an effective way to reduce redundant CDEs (22.2~37.9%) at each hospital. This means that there were many CDEs shared across the five different documents used at each hospital. We found that an even higher CDE reduction rate of 48.7% could be achieved by integrating the information for all five hospitals, which indicates that various CDEs were commonly used across the different hospitals. The CDE integration step involved integrating aCDEs into clinically relevant cCDEs to further structure the clinical documents, and then integrating the cCDEs across different clinical documents. For example, when a vital sign related cCDE contained three aCDEs ('body weight,' 'body temperature,' and 'blood pressure') and another vital sign related cCDE contained an additional aCDE ('description the reason of unstable vital sign'), we integrated this into a vital-sign cCDE comprising four aCDEs. The application of these three steps constantly decreased the number of CDEs. Supplementary Tables S1–S3 list the cCDEs and how they were distributed in each document at each hospital. These tables also provide a detailed view of how the 20 unique cCDEs comprised 327 sub-aCDEs. The integrated CDEs not only reduced the number of CDEs, with a reuse ratio of up to 46.9% [=(1142 – 20 – 586)/1142] (Table 2), but also greatly improved the semantic accuracy and interoperability.

Table 2. Numbers of aCDEs and cCDEs extracted from five clinical documents used at five teaching hospitals in Korea.

Hospital		Admission Notes	Initial Medical Examination Notes	Discharge Notes	Emergency Notes	Operation Notes	Total No. of CDEs	[f] No. of Unique CDEs	[g] CDE Reuse Rate
A	[a] CDE	84	48	70	83	37	322	227	29.5%
	[b]cCDE [c](aCDE)	10 (55)	9 (40)	6 (34)	6 (45)	2 (10)	33 (184)	16 (110)	
	[d] aCDE	29	8	36	38	27	138	117	
	[e] cCDE + aCDE	39	17	42	44	29	171	133	24.5%
C	CDE	30	35	20	27	26	138	87	37.0%
	cCDE (aCDE)	2 (14)	3 (20)	2 (11)	3 (15)	1 (5)	11 (65)	5 (35)	
	aCDE	16	15	9	12	21	73	52	
	cCDE + aCDE	18	18	11	15	22	84	57	33.3%
G	CDE	70	28	44	54	11	207	161	22.2%
	cCDE (aCDE)	4 (23)	3 (17)	2 (11)	2 (17)	1 (5)	12 (73)	7 (50)	
	aCDE	47	11	33	37	6	134	111	
	cCDE + aCDE	51	14	35	39	7	146	118	18.8%
P	CDE	204	123	46	43	12	428	266	37.9%
	cCDE (aCDE)	7 (177)	4 (99)	3 (34)	3(39)	0 (0)	15 (349)	7 (177)	
	aCDE	27	24	12	4	12	79	89	
	cCDE + aCDE	34	28	15	7	12	94	96	36.2%
S	CDE	12	6	9	10	10	47	31	34.0%
	cCDE (aCDE)	1 (3)	0	0	1 (4)	0	2 (7)	1 (4)	
	aCDE	9	6	9	6	10	40	27	
	cCDE + aCDE	10	6	9	7	10	42	28	31.9%
Total	CDE	400	240	189	217	96	1142	606	53.1%
	Unique CDE	297	162	142	178	57	836	586	29.9%
	cCDE (aCDE)	15 (224)	14 (152)	9 (71)	9 (90)	2 (10)	49 (547)	20 (327)	
	aCDE	73	10	71	88	47	289	259	
	cCDE + aCDE	88	24	80	97	49	338	279	46.9%

[a] Number of CDEs extracted from each clinical document from each hospital

[b] Number of cCDEs created for each clinical document

[c] Number of aCDEs contained in [b]cCDEs

[d] Number of remaining aCDEs that are not contained in any of the cCDEs in each clinical document

[e] Total number of CDEs consisting of [b]cCDEs and [d]aCDEs that are not contained in any of the cCDEs in each clinical document

[f] Number of unique CDEs across the five clinical documents

[g] Reuse ratio of CDEs across the five documents

We found that the compositions of the clinical documents differed quite markedly across the included hospitals. The clinical documents at Hospitals P and S contained the largest (n=266) and smallest (n=31) numbers of independent DEs, respectively. We also found that even the same clinical documents showed huge variations in DE numbers, such as with the number of admission notes varying from 12 at Hospital S to 204 at Hospital P. Hospital P also had the largest number of aCDEs for initial medical examination notes (n=123), while Hospital A had the largest number of aCDEs for emergency notes (n=83) and operation notes (n=37).

We also applied constraint rules for the five clinical documents used at the five hospitals (Table 3). We could not determine if a DE was a *hybrid* aCDE, partly due to the lack of actual input values and partly due to poor descriptions of the response values for the clinical documents. We designated the cCDEs as *general* cCDEs to distinguish them from *repeated* and *dictionary* cCDEs. A cCDE was on average reused twice among the five documents by the hospitals. We also found that the clinical documents at Hospital A were the best structured and contained the greatest detail, with more cCDEs and constraint rules compared to the documents at the other hospitals.

Table 3. Numbers of aCDEs, cCDEs, and constraints at five teaching hospitals in Korea.

CDE Semantic Type	Hospital:	A	C	G	P	S
aCDE	Hybrid	0	0	0	0	0
	Variable	5	2	2	3	0
cCDE	General	9 (20)	2 (6)	3 (8)	2 (2)	0
	Repeated	2 (5)	1 (2)	2 (2)	2 (6)	1 (2)
	Dictionary	5 (10)	2 (3)	2 (2)	3 (8)	0
Constraints	Operated	4 (9)	1 (5)	2 (5)	1 (1)	0
	Required	10 (25)	3 (8)	5 (11)	3 (11)	0
	Dependent	15 (26)	0	3 (8)	3 (10)	1 (2)
	Ordered	11 (29)	4 (10)	5 (11)	3 (12)	1 (2)

The numbers before the parentheses represent unique counts.

We evaluated our developed DE relationships and constraints with the same method but from different data sources, that were 14 FHIR resources from FHIR bulk sample data. We first extracted 238 CDEs and found 142 (=238-96) CDEs (59.7%) were reused in at least 2 of 14 FHIR resources, resulting in 96 unique aCDEs. We then created clinically relevant cCDEs and applied semantic relationships to them. 48 cCDEs successfully captured 194 (81.5%) of 238 CDEs. Finally, 28 cCDEs successfully captured 75 of the 96 unique CDEs, such that 49 (=28+21) CDEs were enough to represent the initial 238 CDEs extracted from 14 FHIR resources (Table 4). Supplementary Tables S4–S5 list the cCDEs and how they were distributed in each FHIR resources. The fact that more than half of the CDEs has been reused, shows that the FHIR based data is standardized and is well structured. Half of the FHIR resources, for instance: AllergyIntolerance, Condition, Encounter, Goal, MedicationRequest, Organization, and Procedure, were represented by *repeated* cCDE, which means all extracted CDEs of each FHIR resource became a component aCDEs of the *repeated* cCDE. These structured data have been reused frequently among different FHIR resources.

While we were mapping our proposed DE types to FHIR resources, we found that *hybrid* aCDE, *operated,* and *dependent* constraints were not applicable in FHIR resources. For the case of *hybrid* aCDE, though only one datatype is allowed for each data in the FHIR specification, there was no restriction on the datatype in the FHIR bulk sample data, since the data was represented by JSON, and XML. While the *required* and *ordered* constraints were explicitly indicated, the other constraints were not valid in FHIR resources because the rule by which two or more data values were related could not be expressed (Table 5).

Table 4. Numbers of aCDEs and cCDEs extracted from 14 FHIR resources of FHIR bulk sample data.

#	FHIR Resource	[a]CDE	[b]cCDE [c](aCDE)	[d] aCDE	[e] cCDE + aCDE
1	AllergyIntolerance	13	2(13)	0	2
2	CarePlan	18	4(15)	3	7
3	Claim	21	5(13)	6	11
4	Condition	13	2(13)	0	2
5	DiagnosticReport	13	3(9)	4	7
6	Encounter	15	4(15)	0	4
7	Goal	4	1(4)	0	1
8	ImagingStudy	23	3(14)	11	14
9	Immunization	12	1(4)	8	9
10	MedicationRequest	14	3(14)	0	3
11	Observation	22	5(18)	4	9
12	Organization	15	4(15)	0	4
13	Patient	42	8(29)	8	16
14	Procedure	13	3(13)	0	3
	[f] Total No. of CDEs	238	48(194)	44	92
	[g] No. of unique CDEs	96	28(75)	21	49

[a] Number of CDEs extracted from each FHIR resource sample data

[b] Number of cCDEs created for each FHIR resource sample data

[c] Number of aCDEs contained in [b]cCDEs

[d] Number of remaining aCDEs that are not contained in any of the cCDEs in each FHIR resource sample data

[e] Total number of CDEs consisting of [b]cCDEs and [d]aCDEs that are not contained in any of the cCDEs in each FHIR resource sample data

[f] Total number of CDEs across 14 FHIR resources

[g] Total number of unique CDEs across 14 FHIR resources

Another evaluation is mapping between our DE types to document related FHIR resource, Questionnaire. Figure 6 represents the mapping of the FHIR structure in extracts on the left side, linked via arrows to the corresponding developed CDE relationships and constraints. The relevant elements in the FHIR Questionnaire resource were *group* and *question*, which represents the cCDE, and aCDE (the data model of a single question). Among our developed three CDE relationships and four constraints, the *repeated* cCDE relationship and the *required* and *operated* constraints were straightforwardly mapped. The FHIR Questionnaire resource is to define both collection forms, surveys and other structures that can be filled out with their context. It has a certain structure to represent relationships among DEs, but value related constraints cannot be modelized. For instance, it cannot be represented whether the value allows for multiple data types (*Hybrid* aCDE), or whether one value can be changed depending upon another element's value (Constraint: *Dependent*).

For evaluations with a real dataset, we analyzed 26 tables of the MIMIC-III demo database. These tables were divided into three categories which were classified by different data characteristics: (1) 14 tables for hospital data, (2) 3 tables for online definitions, and (3) 19 tables for care-value and meta-version ICU related data (Supplementary Tables S6). We first manually reviewed the relationships among the columns of each table. The evaluation process was conducted only for cases in which a relationship was found through the following steps: CDE extraction, CDE integration by using aCDEs and cCDEs, and then the construction of semantic relationships among the CDEs.

We found four *hybrid* aCDEs that allows numeric data and text data. For example, *VALUE* in LABEVENTS allows for string data and numeric data. If this value is numeric, then VALUENUM represents the same data in a numeric format with an appropriate unit from VALUEUOM for its usability in calculations. The four general cCDEs in Table 5 list cCDEs that includes the *hybrid* aCDE. We also found three *variable* aCDEs associated with its particular *dictionary* cCDE. For example, ICD9_CODE in DIAGNOSES_ICD is matched to the same value as ICD9_CODE in D_ICD_DIAGNOSES. And each table became a *repeated* cCDE because it is composed of a set of related items. All tables have a *required* constraint, and two tables have an *operated* constraint. As MIMIC data is a relational database, it is not *dependent* and *ordered* on constraints that are applicable to the MIMIC data as the value of one column does not affect the data of the other column, and because there is no order between the data (Table 5). Supplementary Tables S6-7 lists specific results which the MIMIC-III metadata matched to our proposed relationships and constraints.

Table 5. Numbers of aCDEs, cCDEs, and constraints in FHIR bulk data and MIMIC-III demo data.

CDE Semantic Type	Data Source:	FHIR	MIMIC-III
aCDE	Hybrid	N/A	4
	Variable	3	4
cCDE	General	18(64)	4(12)
	Repeated	7(87)	26(180)
	Dictionary	3(17)	4(17)
Constraints	Operated	N/A	2
	Required	34	52
	Dependent	N/A	N/A
	Ordered	2	N/A

Discussion

4.1 comparison with related studies

Standardizing data using CDEs based on ISO/IEC 11179 is clearly one of most effective ways to harmonize data collected from various clinical studies. This approach provides the following advantages: (1) providing a consistent data collection tool, and (2) improving the study quality and reducing the cost of data entry, cleansing by having uniform data. However, the inherent limitation of ISO/IEC 11179 not providing a data structure for representing interrelationships among CDEs has resulted in a gap between the development of CDEs and their utilization on clinical forms for comprehensive representations.

To overcome this obstacle, ISO/IEC 11179 provides DDEs to enhance interrelated DEs. A DDE is a DE whose values are derived through a transformation of the values of one or more source DEs. For example, the DDE of the 'length of stay in a hospital' is derived from two independent DEs that calculate the number of days from two input DEs: 'admission date' and 'discharge date.' However, this strategy is far from enough to cover all use cases of interrelated DEs that we describe in Background.

Table 6 compares the DDE and our CDE semantic relationships. The value of a DDE is derived from input DE(s). Our CDE semantic relationship provides rich semantics for creating aCDEs and cCDEs that feature *repeat* and *dictionary* properties, supporting references to outside biomedical resources as described in Table 6. The relatively simple-minded concept of the DDE may be inadequate to cover various CDE semantic relationships, since a DDE covers only two constraints: *Operated* and *Ordered*.

Table 6. Differences between DDE and our CDE semantic relationships.

CDE Semantic Type		Characteristic	Difference from a DDE
aCDE	Hybrid	Allowing the entry of multiple data types in a hybrid aCDE requires aCDEs that support different data types for the same data item	A DDE does not support the entry of multiple types of data
	Variable	Connecting to an outside dictionary database	No dictionary-associated constraint in a DDE
cCDE	General	Containing a set of aCDEs	Do not have output DE(s), but a DDE can be a cCDE
	Repeated	Allowing sequential data entry into a *repeated* cCDE	No *repeated* property in a DDE
	Dictionary	Bringing biomedical knowledge from an outside dictionary database to a *dictionary* cCDE containing a *variable* aCDE as a foreign key to the dictionary table with the *repeated* property	No dictionary connection allowed for a DDE
Constraint	Operated	Allowing mathematical/algebraic expressions between related aCDEs	A DDE has this constraint with the [a] CALCULATION type
	Required	Forcing aCDE to have a value other than null	No *required* constraint in a DDE
	Dependent	Dynamic enabling and disabling of an aCDE via a predicate	No *dependent* constraint in a DDE
	Ordered	Ordering a set of aCDEs	A DDE has this constraint by default

[a] CALCULATION type in DDE only covers arithmetic operators (i.e., +, -, *, /) but, the operated constraints include not only arithmetic operators but also logical operators (i.e., <, >).

There have also been efforts to address the issues of interrelated DE(s) by applying external data models. The CDISC (clinical data interchange standards consortium) ODM (operational data model), which is an XML-based standardized data model that supports the acquisition and exchange of metadata specifically related to clinical studies, can also be used to overcome the limitations of ISO/IEC 11179; however, it is not sufficiently comprehensive to generate CRFs by importing elements directly [27, 28]. Lin *et al.* also suggest using the openEHR approach for modeling CDEs [29]. Though this approach provides a comprehensive structure with two-level modeling, several limitations when implementing openEHRs have been identified in various studies, such as immaturity of archetype modification operations, insufficient support for hierarchical archetypes due to their granularity [30, 31], and the cost burden of development and adoption due to the complexity of defining openEHRs. Therefore, instead of utilizing external data models, we propose improving and extending the existing composite relationship by specifying two subtypes of aCDE, three subtypes of cCDEs, and four constraints to take advantage of utilizing CDEs and related technologies.

The newly released version of HL7 FHIR provides the ElementDefinition type, which is the core of the FHIR metadata layer, and is closely (conceptually) aligned to ISO/IEC 11179. It has the result of mapping to the other standards as well to help implementers and clinical researchers understand the content and use it correctly. However, they found that the principles from both standards were totally different. FHIR does not differentiate between a DE and a DE value, and the FHIR specification is heavily type dependent. For instance, HL7 FHIR provides the pair of Questionnaire and QuestionnaireResponse resources and a pair of Appointment and AppointmentResponse resources at the same time. Also, the FHIR specification includes constraints and other concerns that are outside the scope of ISO 11179. Thus, the HL7 admitted that there still was a shortage of connection between HL7 FHIR and ISO/IEC 11179. It is said that the FHIR Infrastructure work group is considering rolling the DataElement resource into the StructureDefinition resource. If this is done, DataElement resource will be treated as a type of logical model (whether there will be a distinct 'type' for it is unclear) [32].

Since the FHIR specification includes concepts for the group and constraints, they were matched with our proposed concepts of *composite* and the part of constraints (ordered, operated). However, some of the DE types that we have proposed are not provided by FHIR. We detailed whether our proposed DE types were covered by FHIR. Since the FHIR Questionnaire is the only resource, which is related to clinical forms or documents, we distinguished from the other FHIR resources (Table 7).

Table 7. Comparison of our proposed DE types with the FHIR Questionnaire resource and the other FHIR resources.

CDE Semantic Type		FHIR Questionnaire	FHIR other resources
aCDE	Hybrid	No, it doesn't support the entry of multiple types of data.	Not applicable, there is no restriction on the datatype as it is represented JSON, XML.
	Variable	Yes, it is supported by "coding".	Yes, it is supported by "coding".
cCDE	General	Yes, it is supported because the FHIR is following a structured model.	Yes, it is supported because the FHIR is following a structured model.
	Repeated	Yes, it is supported by "repeats".	Yes, it is supported because the FHIR is allowing repeated representation of the group of items.
	Dictionary	Not applicable, it doesn't support any value related rule.	Not applicable, it doesn't support any value related rule.
Constraint	Operated	Allowing only logical operations.	Only resources that have the "operator" are supported (e.g., Observation Resouce).
	Required	Yes, it is supported by "required".	Yes, it is supported by "required".
	Dependent	Not applicable, it doesn't support any value related rule.	Not applicable, it doesn't support any value related rule
	Ordered	Although not explicit, it is included in the structure.	Only resources that have "sequences" are supported (e.g., Claim Resouce)

4.2 overcoming the challenges of understanding semantic relationships of form-lEVeL data

This paper has presented an in-depth evaluation of the ISO/IEC 11179 MDR standard based CDE semantic interrelationships in the context of formalizing clinical document structures. For converting form-level data into DE-level data, two cCDEs (*repeated* and *dictionary* cCDEs) and their related constraints were developed, which provide the following benefits:

1. **Repeated cCDEs support clinical data management in a tabular format in a clinical document.** Since multiple value sets are supported to be represented in a unified tabular format, a *repeated* cCDE is useful for managing sequential data entry in a tabular format and for analyzing how the values change over time. A *repeated* cCDE enables standard MDR-based CDE-level descriptions and evaluations of clinical data entry in a tabular format.
2. **Dictionary cCDEs enable biomedical knowledge to be brought from a dictionary database via a variable aCDE.** Data items referencing a certain standard terminology appear frequently on clinical forms. A *dictionary* cCDE can help to include rich semantics from externally managed biomedical terminologies and/or dictionaries, with rich attributes being applied for input data validation.
3. **Four different types of constraints enable rich evaluations of input values.** A prefix notation with functional logic programming can be applied for evaluating user-defined constraints in order to ensure contextual correctness and interrelationships among data items on clinical document.

4.3 advantages of using CDEs and CDE relationships for building clinical documents

The data element is the atomic unit of data and is associated with a data element concept (DEC, an abstract unit of knowledge for representing semantics) and a value domain (representation of data including the data type and permissible values) according to the ISO/IEC 11179 MDR standard. The DEC is the combination of an object class (a set of entities) and a property (a peculiarity common to all member of an object class). As these two components of DEC are matched to the standard medical terminologies, it strengthens the semantic part. It is an advantage to use CDE. Our proposed new DE types comply with this part in the ISO/IEC 11179 standard.

As verified in the evaluation part of this study, building clinical documents with CDEs can provide three major advantages. First, it prevents the generation of redundant data by facilitating predefined and registered CDEs to the MDR. Second, it ensures semantic data integrity since an MDR-based CDE has comprehensive and standardized metadata attributes for data description and the proposed cCDE provides a means to encode rich constraints for inter-CDE relationships. The health data of a patient that are fragmented, dispersed, and duplicated in a variety of clinical documents across different medical centers should be integrated, and mapping data items to CDEs facilitates data integration and semantic interoperability across different clinical documents. Third, clinical data exchange and sharing can be greatly facilitated by this approach.

4.4 limitation and future work

The real-life clinical documents provide reasonable examples of reality, but particular instances of reality do not necessarily always provide good representative examples. For instance, we found that the quality of data in the clinical documents is dependent on whether the clinicians who wrote these documents were well trained in terminology representation to be inclusive in writing correctly and sufficiently valid clinical documents. If the document provides poor examples, then the outcome of the evaluation will also poor. It is not only the problem of clinical documents, but also it can be applied to when a clinical researcher creates data in the FHIR model, or a physician inputs clinical data in the EHR. Thus, we should measure the data quality (DQ), which is one of the aspects of the interoperability that reveals the process of standardizing EHRs to ensure the selected clinical documents are a good representation of the evaluation.

We also found that issue was, whether our proposed DE types ensure semantical consistency with the use of standard biomedical terminologies. For the instance of data transfer and the purpose of interoperability, it is important to examine how well our proposed DE types correspond to the standard biomedical terminologies, and how we can address the issue of terminology variations. Although the DEC part of the ISO/IEC 11179 is matched to the standard medical terminologies, when multiple standard biomedical vocabularies are used in the complicated DEs, the above issue can occur.

A similar issue can occur when we utilize the dictionary cCDE, since it includes a biomedical vocabulary. For instance, the dictionary cCDE can take into account different ‘versions’ of a particular lab test with different time stamps, which could end with a differing variance of normal ranges. In other words, even if we reference the same standard vocabulary for the dictionary cCDE, the result could be different. We will measure another DQ for semantical consistency from the two issues mentioned above as a future work.

Conclusion

The sharing and understanding of data from multiple different domains can be facilitated by standardization. An MDR-based CDE is considered a type of standardized data with specified concept and value domains. However, ISO/IEC 11179 MDR-based CDEs do not provide the ability to describe constraints on a CDE or relationships among different CDEs, instead merely focusing on single independent CDEs, which makes it difficult to either correctly compose or interpret CDEs on clinical documents. We developed MDR-based extended semantic types and constraints, and it can facilitate comprehensive representation of clinical documents with rich semantics and improved semantic interoperability.

Abbreviations

aCDE Atomic CDE

BMI Body mass index

cCDE Composite CDE

CDE Common data element

CDISC Clinical data interchange standards consortium

CRF Case report form

DDE Derived data element

DE Data element

DQ Data Quality

EHR Electronic health record

FHIR Fast Healthcare Interoperability Resources

JSON Javascript object notation

MDR Metadata registry

MIMIC-III Medical Information Mart for Intensive Care

NINDS National institute of neurological disorders and stroke

ODM Operational data model

Declarations

7.1 Ethics approval and consent to participate

Not Applicable. To give you more description, we have not used any of patients' data. The data described in the Methods section are metadata, which is data about data including data 'specifications' and 'definitions'. We have had no chance of using patients' private and/or personal information at all in writing the manuscript.

7.2 Consent to publish

Not Applicable

7.3 Availability of data and material

Not Applicable

7.4 Competing interests

None of the authors has conflicts of interest with other persons or organizations that could inappropriately influence their work.

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7.6 Authors’ contributions

H.H.K and J.H.K designed the study and wrote the paper. Y.R.P contributed to provide source data for development and evaluation. J.H.K supervised the project. All authors discussed the results and commented on the manuscript at all stages.

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Not Applicable

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Additional File Details

Supplementary Table S1. List of general, dictionary, and repeated cCDEs with the numbers of operated, required, dependent, and ordered constraints extracted from five clinical documents used at five teaching hospitals in Korea.

Supplementary Table S2. Distribution of aCDEs and cCDEs extracted from five clinical forms used at five teaching hospitals in Korea.

Supplementary Table S3. List of 327 aCDEs comprising 20 cCDEs. The order of the cCDEs is identical to that in Supplementary Table S1.

Supplementary Table S4. Distribution of aCDEs and cCDEs extracted from 14 FHIR resources of FHIR bulk sample data. List of unique 75 aCDEs comprising by 28 cCDEs from 238 aCDEs. The absence of *repeated* cCDE for some FHIR resources means that the configuration of aCDEs has been changed for each data.

Supplementary Table S5. List of 75 aCDEs comprising by 28 cCDEs. The order of the cCDEs is identical to that in Supplementary Table S4.

Supplementary Table S6. List of categorized MIMIC-III database in which matched by aCDE, cCDE and constraints. Six tables are related *hybrid* and *variable* aCDE (23%), four tables are related *dictionary* cCDE (15%), and all tables are related to *required* constraints.

Supplementary Table S7. List the detail elements of MIMIC-III database, which were matched to our proposed DE types. *Hybrid* aCDEs in four tables, *variable* aCDE in four tables, *operated* constraint in two tables.

Figures

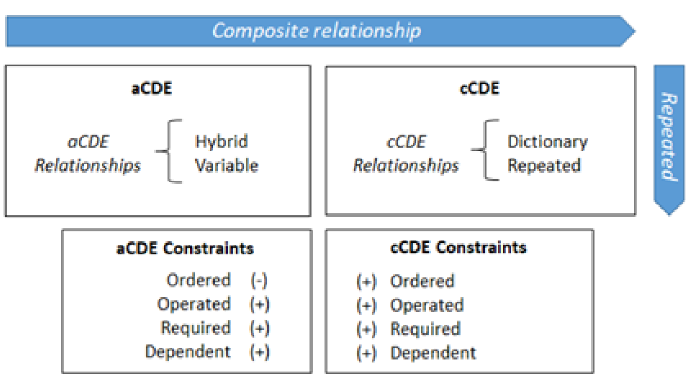
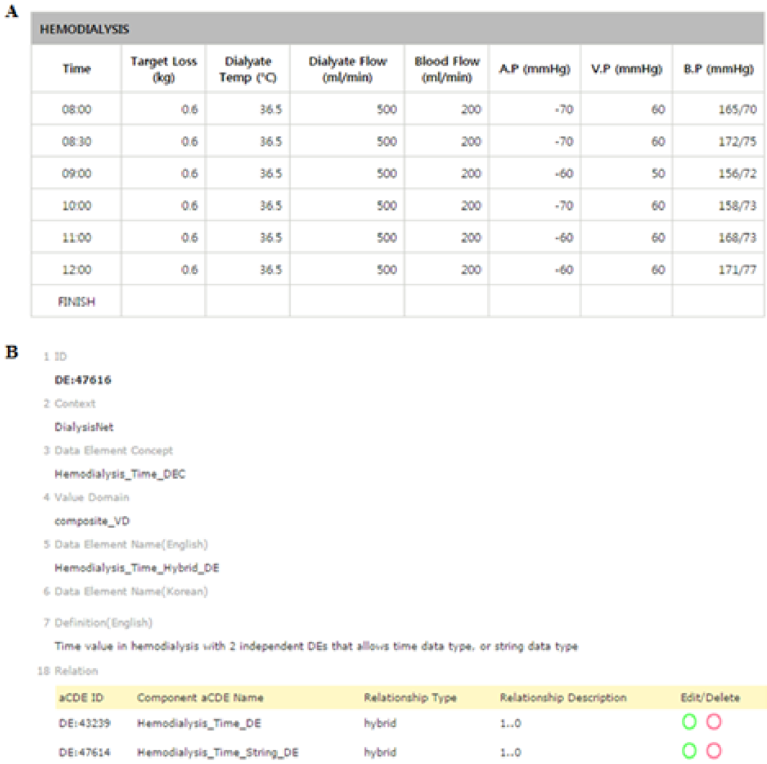


Figure 1

Overview of the formal relationship between aCDE and cCDEs with extended semantic types and CDE-type specific constraints.



A

HEMODIALYSIS							
Time	Target Loss (kg)	Dialyate Temp (°C)	Dialyate Flow (ml/min)	Blood Flow (ml/min)	A.P (mmHg)	V.P (mmHg)	B.P (mmHg)
08:00	0.6	36.5	500	200	-70	60	165/70
08:30	0.6	36.5	500	200	-70	60	172/75
09:00	0.6	36.5	500	200	-60	50	156/72
10:00	0.6	36.5	500	200	-70	60	158/73
11:00	0.6	36.5	500	200	-60	60	168/73
12:00	0.6	36.5	500	200	-60	60	171/77
FINISH							

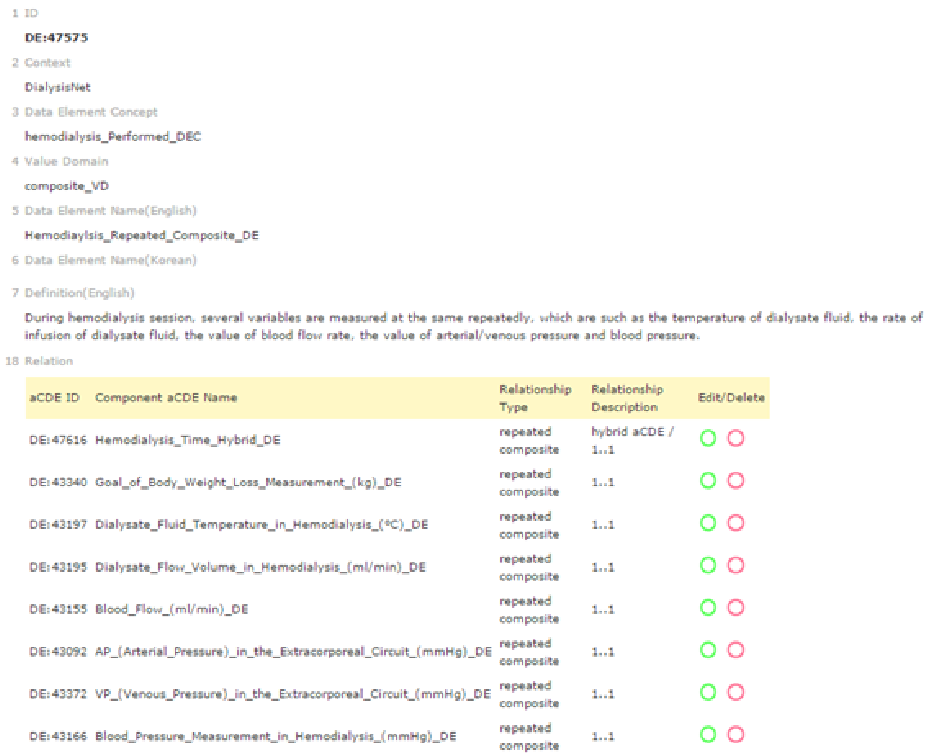
B

1 ID
DE:47616
2 Context
DialysisNet
3 Data Element Concept
Hemodialysis_Time_DEC
4 Value Domain
composite_VD
5 Data Element Name(English)
Hemodialysis_Time_Hybrid_DE
6 Data Element Name(Korean)
7 Definition(English)
Time value in hemodialysis with 2 independent DEs that allows time data type, or string data type
18 Relation

aCDE ID	Component aCDE Name	Relationship Type	Relationship Description	Edit/Delete
DE:43239	Hemodialysis_Time_DE	hybrid	1..0	
DE:47614	Hemodialysis_Time_String_DE	hybrid	1..0	

Figure 2

An example hybrid aCDE from a hemodialysis report. (A) The hemodialysis table of the DialysisNet Project has a tabular data-entry format, where Time (DE:47616) allows two different data types: time and an enumerated string. (B) The hybrid aCDE (DE:47616) contains two aCDEs (DE:43239 and DE:47614) in a hybrid relationship (http://chmr2.snubi.org:8083/chmr/data_element_view.jsp?id=28476).



1 ID

DE:47575

2 Context

DialysisNet

3 Data Element Concept

hemodialysis_Performed_DEC

4 Value Domain

composite_VD

5 Data Element Name(English)

Hemodiaylsis_Repeated_Composite_DE

6 Data Element Name(Korean)

7 Definition(English)

During hemodialysis session, several variables are measured at the same repeatedly, which are such as the temperature of dialysate fluid, the rate of infusion of dialysate fluid, the value of blood flow rate, the value of arterial/venous pressure and blood pressure.

18 Relation

aCDE ID	Component aCDE Name	Relationship Type	Relationship Description	Edit/Delete
DE:47616	Hemodialysis_Time_Hybrid_DE	repeated composite	hybrid aCDE / 1..1	
DE:43340	Goal_of_Body_Weight_Loss_Measurement_(kg)_DE	repeated composite	1..1	
DE:43197	Dialysate_Fluid_Temperature_in_Hemodialysis_(°C)_DE	repeated composite	1..1	
DE:43195	Dialysate_Flow_Volume_in_Hemodialysis_(ml/min)_DE	repeated composite	1..1	
DE:43155	Blood_Flow_(ml/min)_DE	repeated composite	1..1	
DE:43092	AP_(Arterial_Pressure)_in_the_Extracorporeal_Circuit_(mmHg)_DE	repeated composite	1..1	
DE:43372	VP_(Venous_Pressure)_in_the_Extracorporeal_Circuit_(mmHg)_DE	repeated composite	1..1	
DE:43166	Blood_Pressure_Measurement_in_Hemodialysis_(mmHg)_DE	repeated composite	1..1	

Figure 3

Example of the composition of a repeated cCDE from a hemodialysis report form. A repeated cCDE, 'DE:47575 Hemodialysis_Repeated_Componsite _DE,' composed of eight aCDEs from a tabular data-entry format (Figure 2A) for the DialysisNet hemodialysis project (http://chmr2.snubi.org:8083/chmr/data_element_view.jsp?id=28449).

A

ELECTROLYTE LABORATORY TESTS

Date Collected (MM/DD/YYYY):	Test	Result	Units for Result	Was test result abnormal?	If abnormal, Clinically Significant?
01/08/2016	Sodium (Na+)	138	mEq/L	☒ Normal ☐ Abnormal ☐ Unknown	☐ Clinically significant ☐ Not clinically significant
01/08/2016	Potassium (K+)	5.3	mEq/L	☒ Normal ☐ Abnormal ☐ Unknown	☐ Clinically significant ☐ Not clinically significant

B

ID	Lab Class	Lab Test Name	Lab Test Definition	Data Type	Unit of Result	Normal Range
1	Electrolyte Laboratory Test	Sodium (Na+)	A measurement of the sodium (Na+) in a biological specimen. SI or American Units are preferred.	Numeric	mg/dL^mEq/L	[{ "unit": "mg/dL", "range": "31-34" }, { "unit": "mEq/L", "range": "135-145" }]
2	Electrolyte Laboratory Test	Potassium (K+)	A measurement of the potassium (K+) in a biological specimen. SI or American Units are preferred.	Numeric	mg/dL^mEq/L	[{ "unit": "mg/dL", "range": "14-20" }, { "unit": "mEq/L", "range": "3.5-5.2" }]

C

1 ID

DE:47571

2 Context

NINDS

3 Data Element Concept

Laboratory_Test_DEC

4 Value Domain

composite_VD

5 Data Element Name(English)

Laboratory_Test_NINDS_Composite_DE

18 Relation

aCDE ID	Component aCDE Name	Relationship Type	Relationship Description	Edit/Delete
DE:30470	Laboratory_Test_Date_DE	dictionary composite	1..1	
DE:43938	Laboratory_Finding_Test_Name_DE	dictionary composite	variable aCDE / dic_ID:1	
DE:47570	Laboratory_Test_Result_Numeric_Value_DE	dictionary composite	1..1	
DE:44246	Laboratory_Test_Result_Unit_of_Measure_Unified_Code_for_Units_of_Measure_Code_DE	dictionary composite	1..1	
DE:47566	Laboratory_Test_Result_Status_DE	dictionary composite	1..1	
DE:44135	Laboratory_Finding_Clinical_Significance_Abnormal_Yes_No_Indicator_DE	dictionary composite	1..1	

19 Relation Rule

Rule Type	Rule	Description

Dictionary	function_GET_DB(DE:43938.dic_DB_ID);
	function_CHECK_normal_range(DE:43938, DE:47570, DE:44246);
	IF(!= DE:47570.VD.data_type dic.Data_Type) 'false';
	IF(!= DE:44246 dic.Unit) 'false'
		Bring DB (NIND_Lab_DB) as referencing dic_DB_ID in variable aCDE (DE:43938).
		Variable aCDE (DE:43938) are concatenated to bring the relevant row of dictionary DB.
		According to the rule from 'Normal Range' attribute of DB, value of aCDE (DE:47566) is filled out automatically.
		First, values of unit related local aCDE (DE:44246), lab result related local aCDE (DE:47570) are collected as input values of DB related normal range checking process.
		Second, it chceks whether the lab result is in the corresponding normal range.
		Other information from DB such as the data type of the lab result value related aCDE (DE:47570) and unit related aCDE (DE:44246) are checked by 'Data Type' and 'Unit' attributes of DB, respectively.

Dependent	IF (!= DE:47566 'Abnormal') DE:44135 NULL	If the lab test result is abnormal (DE:47566.value == 'Abnormal'), the value of indicator whether the lab result is clinically significant (DE:44135) should be NULL

Figure 4

Creation of a dictionary cCDE for a CRF. (A) The 'Electrolyte Laboratory Tests' table on a clinical document is provided as an example tabular data-entry document to capture laboratory test results for sodium (Na+) and potassium (K+) along with two clinical evaluation attributes. (B) We constructed the 'Electrolyte Laboratory Tests Dictionary' table by extracting the relevant attributes from the CDEs defined in the 'Recommended Labs for Stroke' from the NINDS CDE project. (C) The dictionary cCDE (DE:47571) consists of six aCDEs that include a variable aCDE (DE:43938) that relates the dictionary cCDE to the dictionary table in Figure 4B. Two rules for clinical evaluation are presented (http://chmr2.snubi.org:8083/chmr/data_element_view.jsp?id=28445).


A

MEDICAL HISTORY

*Use BODY SYSTEM categories for medical history

• Constitutional symptoms (e.g., fever, weight loss) • Eyes • Ears, Nose, Mouth, Throat • Cardiovascular Respiratory • Gastrointestinal • Genitourinary • Musculoskeletal • Integumentary (skin and/or breast) Neurological • Psychiatric • Endocrine • Hematologic/Lymphatic • Allergic/Immunologic

Date (Req.)	Body System (Req.)	Medical Hisotry ((Req., one item per line)	Start Date (Req.)	Ongoing? (Req.)	End Date
				Yes No	
				Yes No	
				Yes No	

B

1 ID

DE:47617

2 Context

NINDS

3 Data Element Concept

Past Medical Illnesses_DEC

4 Value Domain

composite_VD

5 Data Element Name(English)

NINDS_Medical_History_Repeated_Composite_DE

6 Data Element Name(Korean)

7 Definition(English)

For collecting all significant medical history items, including surgeries from the the participant/subject in the focused study. It includes medical history date, related body system, medical history, start and end date.

18 Relation

aCDE ID	Component aCDE Name	Relationship Type	Relationship Description	Edit/Delete
DE:37059	Examination_Date_DE	repeated composite	1..1	
DE:47621	body_system_NINDS_medical_history_DE	repeated composite	1..1	
DE:31106	Medical_History_DE	repeated composite	1..1	
DE:47618	medical_history_start_date_DE	repeated composite	1..1	
DE:44078	Personal_Medical_History_Ongoing_Indicator_DE	repeated composite	1..1	
DE:47619	medical_history_end_date_DE	repeated composite	1..0	

19 Relation Rule

Rule Type	Rule	Description
Ordered	Ordered DE:37059 DE:47621 DE:31106 DE:47618 DE:44078 DE:47619	It follows the order as measure date(DE:37059), related body system (DE:47621), particular medical histody (DE:31106), start date (DE:47618), ongoing indicator (DE:44078), and end date (DE:47619)
Required	Required DE:37059 DE:47621 DE:31106 DE:47618 DE:44078	All component aCDEs are required to have values, except the end date (DE:47619)
Operated	< DE:47618 DE:47619	The start date (DE:47618) should be earlier than the end date (DE:47619)
Dependent	IF (!= DE:44078 "Yes") DE:47619 NULL	If the medical history is ongoing (DE:44078.value == "Yes"), the value of the end date (DE:47619) should be NULL

Figure 5

Encoding Operated, Ordered, Required, and Dependent constraints for a repeated cCDE. (A) A ‘Medical History’ clinical document presented in a tabular format containing six attributes. (B) A repeated cCDE is created with the corresponding six aCDEs along with four constraint rules: (1) the start date (DE:47618) should be earlier than the end date (DE:47619): (< DE:47618 DE:47619); (2) all attributes are required to have values other than null, except for the end date (DE:47619): (Required DE:37059 DE:47621 DE:31106 DE:47618 DE:44078); (3) when a certain medical history is not ongoing (DE:44078), the end date (DE:47619) cannot be obtained, and vice versa: (IF (!= DE:44078 'Yes') DE:47619 NULL); and (4) aCDEs can be ordered according to a constraint statement such as (Ordered DE:37059 DE:47621 DE:31106 DE:47618 DE:44078 DE:47619) (http://chmr2.snubi.org:8083/chmr/data_element_view.jsp?id=28477).

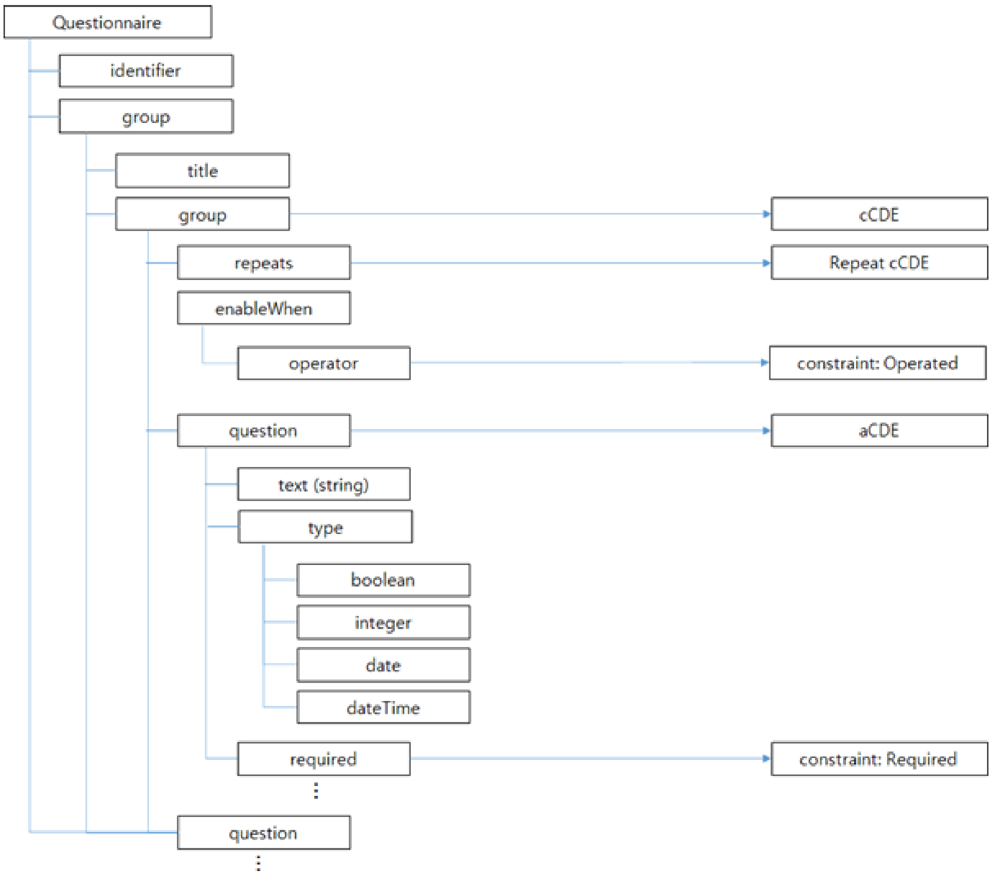


Figure 6

Mapping result of the FHIR Questionnaire resource mapped to the proposed CDE relationships and constraints.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTables.pdf