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Review

Review

Using clinical reasoning ontologies to make smarter clinical decision support systems: a systematic review and data synthesis

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ABSTRACT

Objective: The study sought to describe the literature describing clinical reasoning ontology (CRO)–based clinical decision support systems (CDSSs) and identify and classify the medical knowledge and reasoning concepts and their properties within these ontologies to guide future research.

Methods: MEDLINE, Scopus, and Google Scholar were searched through January 30, 2019, for studies describing CRO-based CDSSs. Articles that explored the development or application of CROs or terminology were selected. Eligible articles were assessed for quality features of both CDSSs and CROs to determine the current practices. We then compiled concepts and properties used within the articles.

Results: We included 38 CRO-based CDSSs for the analysis. Diversity of the purpose and scope of their ontologies was seen, with a variety of knowledge sources were used for ontology development. We found 126 unique medical knowledge concepts, 38 unique reasoning concepts, and 240 unique properties (137 relationships and 103 attributes). Although there is a great diversity among the terms used across CROs, there is a significant overlap based on their descriptions. Only 5 studies described high quality assessment.

Conclusion: We identified current practices used in CRO development and provided lists of medical knowledge concepts, reasoning concepts, and properties (relationships and attributes) used by CRO-based CDSSs. CRO developers reason that the inclusion of concepts used by clinicians' during medical decision making has the potential to improve CDSS performance. However, at present, few CROs have been used for CDSSs, and high-quality studies describing CROs are sparse. Further research is required in developing high-quality CDSSs based on CROs.

Key words: clinical reasoning ontology, clinical decision support, clinical ontology, clinical concepts, ontology properties

INTRODUCTION

Clinical decision support systems (CDSSs), when integrated with electronic health record (EHR) systems, are an integral part of health information technology.[1,2] CDSSs assist clinicians during the health-related decision-making process by presenting situation-specific clinical knowledge and patient information, in an appropriate format, at the appropriate time of the care process.[2] Barriers to CDS development include lack of incentives, lack of standardized clinical terminology, outdated legacy EHR, lack of transferability of clinical decision support (CDS) logic from one system to another, lack of experts needed to translate medical knowledge into a CDS knowledge base (KB), and the low computer literacy of the end user.[3]

Clinicians encounter a significant number of alerts every day, and the usefulness of these alerts is questionable. Van der Sijs et al[4] conducted a systematic review to assess physician response to drug safety alerts and found that 49%-96% of alerts were overridden. Studies have noted that clinicians often override alerts that are considered clinically irrelevant, reveal information that is already known by the clinician, or do not take into account other relevant information pertinent to the case.[5,6] An unfortunate unintended consequence of CDSSs is "alert fatigue," due to their high false positive rate.[7] Traditionally, alerts have been designed to follow a rigid decision tree accessing only specific and limited patient information.[8] Hence, alert logic often misses important relevant patient information, leading to inappropriate alerting. Other factors contributing to high false positive rates include low alerting threshold, lack of personalization, lack of clinical importance, and inaccuracy per updated guidelines.[4,9,10]

Alert-based CDSSs usually are comprised of 3 components: a KB (encompassing scientific and medical information, patient information from the EHR and CDS logic), a user interface that allows the user to communicate with the system, and an inference engine that provides the platform for the functionality of the CDSS.[8] Currently, much of the patient data within EHRs, especially reasons for clinicians' decisions, are in unstructured text format. Most logic-based CDSSs that rely on structured data are unable to utilize data related to clinical reasoning because the clinical data present within the EHR and the data structure of the KB are insufficient for the effective function of traditional alert-based CDSSs.

One approach that developers have employed to improve CDSSs is to model clinical reasoning through ontologies to simulate the decision-making processes carried out by clinicians.[11–14] Clinical reasoning is the process used by clinicians to obtain and analyze data to reach a decision regarding a patient.[15] It requires general understanding of evidence-based medical knowledge and the ability to isolate relevant medical information related to the specific case, based on a specific patient's information.[16] In treating patients, clinicians are faced with questions such as "What is the patient's diagnosis?" and" When did symptoms start?" They are also faced with more complex questions related to reasoning such as "Why was a particular medication given over another?" or "What were the other diagnoses considered?" The data structures currently used within EHRs do not lend themselves readily to identifying answers to questions regarding clinical reasoning. This limitation also cripples the KBs used by current CDSSs. An ontology that details clinical reasoning will allow us to categorize and organize these reasons, thereby making them available for CDSS, and forms the basis for a more sophisticated system that utilizes previous patient-specific clinician reasoning when alerting.

An ontology is a formal representation of knowledge within a domain; typically, a hierarchically arranged set of unique terms known as concepts, their attributes, and the semantic relationships between those concepts.[17] Ontologies organize domain knowledge into structures that computers can read, and humans can understand. Clinical reasoning ontologies (CROs) represent the concepts used by clinicians reasoning about diagnostic and therapeutic interventions and making diagnoses.[18,19] Patient-specific clinical data are mapped into these CROs to make them usable in clinical reasoning axioms and to allow for the description of clinical decisions. CROs capture clinicians' reasoning process by defining clinical concepts, mapping patient data to these concepts, and the defining the semantic relationships between them. This data structure will enable the creation of a more personalized KB for CDSSs. For example, clinicians can indicate, when prescribing, that a certain medication should be prescribed to the patient even though the patient is on a medication that could potentially interact with the prescribed drug, because the patient has previously tolerated the medication combination. A CDSS could be designed to access this information and learn that although generally there is a drug-drug interaction, it is irrelevant for this patient, and therefore, do not alert. Thus, in utilizing CRO-based CDSSs, one could decrease the pernicious phenomena of overalerting, and mitigate alert fatigue by creating more personalized and smarter CDSSs.

The ability to reuse existing ontologies would reduce some of the barriers to the development of CDSSs and could possibly speed the development process. The Open Biological and Biomedical Ontology (OBO) Foundry, a collective that provides access to biological, biomedical, and clinical related ontologies, could be a potential source for a CRO.[20] However, the ontologies in OBO tend to focus on a specific aspect of clinical entities rather than cognitive processes. For example, the Human Disease Ontology classifies human-related diseases according to their etiology and provides a standardized ontology of disease and phenotypic terms that allow for semantic mapping of diseases across existing vocabularies.[21] Other ontologies, such as the Cardiovascular Disease Ontology, focus on specific disease processes.[22] Although OBO lists several such ontologies, an ontology encapsulating the "reasoning concepts" behind the clinical decision across overall patient-clinician encounter without restricting to a specific disease entity does not exist.[23]

In the absence of an existing standard, researchers are developing their own CROs to represent specific disease processes or different aspects of clinical workflows. The purpose of these ontologies includes improving interoperability,[24] improving information gathering,[25] aiding medical education,[26] administrative support,[27] and improving CDSSs.[11] At least some of the ontologies that are used in CDSSs appear to map some reasoning axioms creating partial CROs.[11–14]

Given the clinical importance of CRO-based CDSSs and lack of a comprehensive literature review of current research on CROs in CDSSs, we believe that a systematic review is needed that provides an overview of the existing CRO-based CDSSs, with a compilation and classification of the concepts and properties present within these ontologies. This paper represents such a review to identify and summarize published works that describe CDSSs based on clinical ontologies with a focus on ontologies that contain clinical reasoning concepts and semantic relationships. We included a catalogue of the concepts and properties used within these ontologies and identify the current practices for developing and applying CROs to CDSSs. The results of our summary provide a resource for researchers and developers working on CRO-based CDSSs to select characteristics applicable to their efforts and can be used as a reference to guide future research and potential synergies of current practices in CRO-based CDSSs.

The objective of this systematic review is to describe the literature outlining clinical reasoning ontologies used to empower CDSSs and identify and classify the concepts (medical knowledge concepts and reasoning concepts) and their properties (semantic relationships and attributes) within these ontologies to guide future research.

MATERIALS AND METHODS

We reviewed the literature with the objective of answering the following study questions:

1. What are the existing CROs used to empower CDSSs?
2. How are the CROs and the CDSSs evaluated by their developers?

3. What are the characteristics of the existing CROs that are used by researchers and developers working on CRO-based CDSSs (ie, medical knowledge concepts, reasoning concepts, semantic relationships, and attributes)?

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines as far as appropriate for this review, to minimize the selection bias of included studies.[28] A study protocol was written before the investigation (the study protocol was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis and published systematic reviews before investigation and was submitted to PROSPERO to be registered; the study was deemed as outside PROSPERO's scope).

Data sources and search strategy

We searched databases including PubMed, PubMed Central, and Scopus from their inception to January 30, 2019. Multiple search terms and combinations of search terms were tested to determine the search strategy that identified the broadest results possible. Consensus among the authors was reached before deciding on the search strings. MeSH (Medical Subject Headings) terms were not used in the search strings as they were found to identify many irrelevant studies. We found that including both singular and plural forms within the second query broadened the search and identified studies that would have otherwise been missed. We used the following search strings:

- PubMed and PubMed Central search terms:
  "Clinical cognition" OR "Clinical Reasoning" OR ("Ontology" AND "Evidence Based Medicine")
- Scopus and Google Scholar (GS) search terms:
  ("Decision support system" OR "Decision support systems") AND (ontology OR terminology)

We included GS as an additional source to capture any relevant "grey" literature. Grey literature comprises nonformal scholarly publications produced by organizations outside of traditional academic publishers and can include dissertations, technical reports, conference proceedings articles from nongovernmental organizations and policy institutions.[29] Many innovations in technology are initially published in these forms. There are some limitations to GS (eg, the search algorithm can personalize the search to the user, thus hindering replicability).[30] Additionally, studies on GS have suggested the search should be limited to the first few pages due to diminishing returns.[31] Indeed, we found that the relevancy of the articles greatly diminished after 10 pages; hence, we confined our search results to first 10 pages. The final search was conducted on February 2, 2019.

Study selection

The identified studies were evaluated according to the inclusion criteria: (1) studies exploring terminologies related to clinical reasoning and CDS, (2) studies exploring application or development of CDSSs that use CROs or clinical ontologies with reasoning axioms, and (3) studies exploring computerized methodology to draw relationships between clinical concepts.

The study selection was performed in stages. In stage 1, eligibility criteria were refined by 2 authors (P.I.D., J.J.C.) who independently reviewed subsets of 100 titles. The percent agreement was calculated following the independent review. Disagreements were discussed with the aim of revising and fine-tuning the eligibility criteria. This process was repeated with the revised criteria and another subset of 100 titles until a 94% agreement was reached. In stage 2, the titles were assessed for inclusion by a single reviewer (P.I.D.). The abstracts of all selected articles during stage 2 were then evaluated in stage 3 independently by the 2 reviewers (P.I.D., J.J.C.). Articles accepted, based on abstracts, by either reviewer advanced to the fourth stage of screening, in which 2 authors (P.I.D., J.J.C.) screened the full text of each article. The final article list is a compilation of articles accepted by both reviewers during stage 4.

Data extraction and synthesis

Data related to CDSS purpose, medical domain, computational methods, ontology scope and purpose, knowledge source, and characteristics such as concepts (medical knowledge and reasoning) and properties (relationship and attributes) were extracted from the study articles. The information provided within the articles was abstracted using an iteratively structured form by one of the authors (P.I.D.). The ontologies were categorized as new, existing, or revised based on whether the study article described using an ontology newly created by the CDS development team, used an existing ontology without modification, or used an existing ontology but modified to better fit CDSS scope, respectively. The other authors were consulted, as needed, for data extraction, and any conflicts were resolved via discussion and consensus.

We compiled concepts and properties used within the CRO. We reached group consensus about the classification of properties as either "relationships" or "attributes" and concepts as either "reasoning concepts" or "medical knowledge concepts." We combined the concepts and removed duplicates based on the descriptions provided within the text, tables, and concept maps provided in the publications. When necessary, a more descriptive term was used to identify the final concept based on its description. The same methodology was performed for properties. When a definition of a concept or property was unavailable within the article, we inferred the definition using the informed assessment of the 2 medical expert authors.

Last, we extracted data regarding the CDSSs, and any ontology evaluations performed by the development team (internal validity and usability testing). See Supplementary List 1 for definitions of characteristic terms.

Quality assessment

The ontology evaluation comprises intrinsic (ie. technical) and extrinsic (ie. usability) testing. We defined intrinsic evaluation as an assessment of the ontology based on a set of criteria: accuracy, clarity, internal consistency, completeness, conciseness, expandability, and efficiency.[32,33] Extrinsic evaluation relates to function and is defined as measurement of effectiveness of the CRO-based CDSS and its ease of use.[34] We based our definitions of evaluation criteria established by Gomez-Perez.[32]

We conducted the quality assessment by evaluating the quality related data described in the publications. Any mention of performance of accuracy, clarity, internal consistency, completeness, conciseness, expandability, or efficiency were grouped under intrinsic evaluation as per our definition, and any mention of user testing were categorized as extrinsic. We conducted our evaluation based on predefined criteria as indicated in Figure 1. The CDSSs were then categorized as high, moderate, or low level of quality. Owing to the descriptive nature of the included studies, the Cochrane risk of bias is not applicable.

RESULTS

The database searches yielded a total of 7770 results. After excluding duplicates and articles in which the full-text version was not

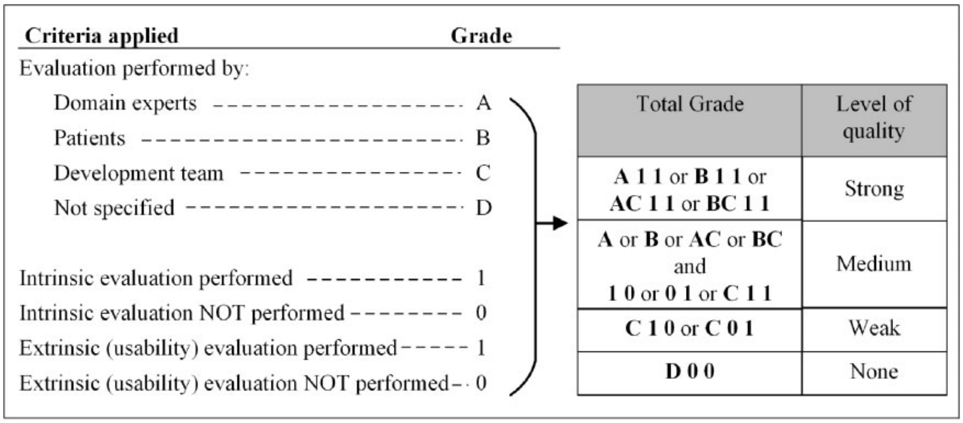

Figure 1. Criteria used for study quality assessment.

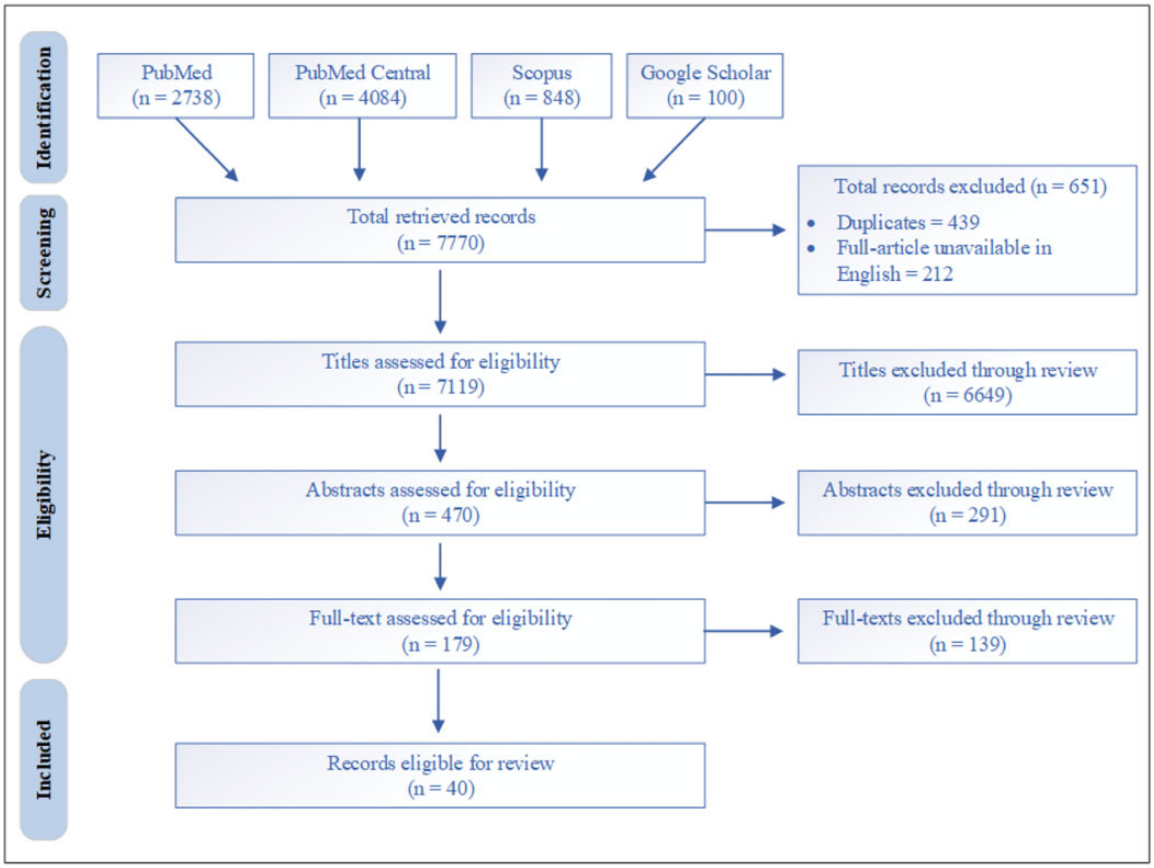

Figure 2. Search results.

available in English, we reviewed 7119 titles. Of these, 470 articles met eligibility criteria for abstract review, which led to 179 articles for full-text review. Forty studies met the inclusion criteria and were reviewed in detail. The selection of articles is outlined in Figure 2.

Characteristics of CDSSs

The characteristics of the CRO-based CDSSs are summarized in Table 1. The articles by Farrish and Grando[56] and by Grando et al[57] were identified as describing the same CRO-based CDSS; therefore, they were merged. Similarly, articles by Abidi[63] and Abidi et al[64] described the same CRO-based CDSS; hence, they were combined, resulting in 38 CRO-based CDSSs. All of the final 40 articles were found in either MEDLINE or Scopus. None of the final articles were exclusive to GS.

Rule-based computational methods use IF/THEN logic rules for inferencing. Ontology-based methods make inferences by following the relationships within the ontology. In addition, "algorithm" was used to describe when an inference was based on a specific calculation. Thirty CDSSs (79%) used rule-based computation for inferencing, 22 (58%) used an ontology-based method, 6 (16%) used algorithms, 3 (8%) used natural language processing, 3 (8%) used

Table 1. Summary of studies included (n = 38)

Author	Computational methods	Medical domain	CDSS purpose	Associated ontologies
Mohammed and Benlamri[11]	RB, proximity-based, machine learning	DM2 and HTN	Provides differential diagnosis recommendation based on patient's data and CPGs	Patient ontology, disease symptoms ontology
Sene et al[12]	RB, pattern-matching algorithm, NLP	Geriatric oncology	Assist during telemedicine based on CBR process and the conventional medical reasoning	Medical ontology
Denekamp and Peleg[13]	Multiphase, anchor-based, Bayesian	Diagnosis	Assist physicians in the process of MCM-oriented diagnosis	TiMeDDx - Knowledge model
Uciteli et al[35]	RB	Perioperative risk	Identify and analyze risks in perioperative treatment process to aid in avoiding errors	Risk identification ontology (RIO)
Bau et al[36]	RB	Diabetic management during surgery	Assist with the management of diabetic patients during surgery	Domain ontology
Merlo et al[37]	OB	Functional behavioral problems	Provide an evidence-based approach to behavioral experts in diagnosing behavioral problems	FBA ontology
Jimenez-Molina et al[38]	OB, fuzzy logic, algorithm	Chronic disease	Manage all stages of chronic patient diagnosis and treatment based on business process management approach	MCCS ontology, process ontology, actors ontology
Shen et al[39]	OB, machine learning	Infectious diseases	Diagnose infectious diseases based on patient entered data and provide antibiotic treatment recommendations	Domain ontology
El-Sappagh et al[40]	OB, RB	DM2	Assists with the treatment of DM2	DM2 Treatment Ontology (DMTO)
Abidi[41]	OB, RB, algorithm	Comorbidity conditions	A CPG integration framework to provide primary care physicians, institutional specific CPG medicated CDSs for comorbidities	Comorbidity CPG ontology
Beierle et al[42]	OB	BC	Support treatment decisions in cancer therapy by revising co-medications and drug interactions	Ontology for Cancer Therapy Application
Shang et al[43]	RB	Chronic disease (HTN and DM2)	Service oriented sharable CDSS that integrate multiple CPGs, for chronic diseases	Infrastructure ontology, special ontology
Berges[44]	OB	GHJ rehabilitation	Assist physiotherapists during the treatment processes related to GHJ	Telerehabilitation Ontology (TrhOnt)
Qi et al[45]	RB	SpA	Provides patients with a personalized home-based self-management system for SpA	SpA ontology
Alsomali et al[46]	RB	Penicillin-related adverse events	Alert clinicians of possible adverse drug events related to penicillin during drug prescription	Ontology of penicillin allergy
Zhang et al[47]	RB	CPG	A sharable CDSS for management of clinical pathways that integrates into hospital CDS applications and fits into existing workflows	Decision support knowledge base generic ontology
Wilk et al[27]	OB, RB	IHTs	Assist with formation of the IHTs to manage patients based on presentation-specific clinical workflows and team dynamics	IHT ontology

(continued)

Table 1. continued

Author	Computational methods	Medical domain	CDSS purpose	Associated ontologies
Zhang et al[48]	RB, OB	DM2	Provides patient specific recommendations on the management of inpatients with DM2	Semantic healthcare knowledge ontology
Rosier et al[49]	RB, OB	Cardiology	Improve AF-related CIED alert triage	Cardio-vascular disease ontology
Jafarpour et al[50]	RB, OB, algorithm	CPG	Provide computerized CDS based on CPGs using an OWL-based execution engine	CPG ontology
Alharbi et al[51]	RB	Diabetes	Decision support for diagnosis and treatment of diabetes based on CPG	Diabetes Ontology, Patient ontology
Shen et al[14]	OB, machine learning, NLP, fuzzy logic	Disease diagnosis and treatment	Provides clinicians and patients with an optimal personalized diagnostic and treatment plan	Knowledge Model Agent Type (KMAT) ontology
El-Sappagh et al[52]	RB	Diabetes	Assist with the diagnosis and management of diabetes	Case base ontology
Budovec et al[26]	RB	Radiology	Provides radiology differential diagnosis in an interactive website and an educational tool	Radiology Gamuts Ontology (RGO)
Wang et al[53]	RB, probability	General medical CPGs	Personalized CPGs for disease specific treatment to be used by individual hospitals.	Local ontology
Eccher et al[54]	RB, OB	Cancer therapy	Facilitate the interoperability between a CPG-based DSS for cancer treatment and an oncological EPR	Therapies ontology
Martínez-Romero et al[55]	RB, OB	CICU	Provides supervision and treatment assistance for critical patients in CICU with acute cardiac disorders	Critical Cardiac Care Ontology (C3O)
Farrish and Grando[56]; Grando et al[57]	RB	Medication	Assists with management of polypharmacy prescriptions for patients with MCC to reduce the overall treatment complexity	Drug ontology
Omaish et al[58]	RB, OB	ACS	Assists ED physicians with treatment of ACS patients based on computerized ACS CPGs	CPG ontology
Riaño et al[59]	OB, ranking of weighted options	Home care of chronic diseases	Assists with the management of chronically ill patients including development of personalized treatment plans	Case profile ontology
Adnan et al (2010)[60]	OB, NLP, RB	High risk discharge medications	provides advice recommendations for high risk discharge medications, to be used in the Electronic Discharge Summary	Medication information ontology
Prcela et al[61]	RB	Heart failure	provides CDS for heart failure	Heart failure ontology
Hussain and Abidi[62]	RB	CPGs in Imaging studies	Provides a framework to computerize CPGs and to execute modeled CPGs based on patient data to deliver recommendations	CPG ontology, domain ontology, patient ontology
Abidi[63]; Abidi et al[64]	RB	BC	An interactive BC follow-up CDSS for family physicians to assist with BC	CPG ontology, patient ontology, BC ontology

(continued)

Table 1. continued

Author	Computational methods	Medical domain	CDSS purpose	Associated ontologies
			management and to provide educational material to patients	
Fox et al[65]	OB	BC	Supports complex care pathways in BC	PROforma Task ontology, Goal ontology
Achour et al[66]	OB, RB	Blood transfusion	Assists clinicians with the prescription of blood products for transfusion	Domain ontology
Wheeler et al[67]	OB	HTN	A mobile self-management App to assists patients with the management of HTN	HTN management ontology
Sadki et al[25]	OB, RB, algorithm	BC	Allows structured patient data acquisition for the management of BC patients	BC Knowledge Model

ACS: acute coronary syndrome; App: application; BC: breast cancer; CBR: case-based reasoning; CDSS: clinical decision support system; CICU: cardiac intensive care unit; CPG: clinical pathway guideline; DM2: diabetes mellitus type 2; ED: emergency department; EPR: electronic patient record; FBA: functional behavioral assessment; GHJ: glenohumeral joint; HTN: hypertension; IHT: interdisciplinary healthcare team; MCC: multiple chronic conditions; MCCS: medical context and contextual services; MCM: main clinical manifestation; NLP: natural language processing; OB: ontology based; RB: rule based; SpA: spondylarthritis; TiMeDDx: name of the ontology.

machine learning, and 2 (5%) used fuzzy logic. Other computational methods included probability, proximity-based, anchor-based, and ranking of weighted option. Twenty (5 ontology-based and 15 rule-based) CDSSs used only 1 computational method.

A wide range of medical domains were addressed by the CDSSs: 12 dealt with management of chronic diseases (5 diabetes, 1 hypertension, 1 heart failure, and 5 multiple chronic diseases), 6 with cancer management (4 breast cancer and 2 general cancer treatment), 3 with cardiac-related conditions, 3 with medication management and adverse events, 3 with general clinical guidelines, 2 with radiology, 2 with diagnosis, and 7 with others (1 each of preoperative risk, infectious disease, glenohumeral joint rehabilitation, spondylarthritis treatment, healthcare teams, diagnosis and treatment, blood transfusion).

Characteristics of CROs

All the CROs were used as the KB for their respective CDSS. A total of 34 CDSSs (90%) used only 1 ontology, 4 CDSSs used 2 ontologies, and 2 CDSSs used 3 ontologies (Table 2). The ontology scope correlated with the medical domain. The types of knowledge sources employed during the ontology development (with the corresponding number of ontologies) included domain experts (n = 23), clinical pathway guidelines (CPGs) (n = 22), literature (n = 20), existing ontologies or terminologies (n = 14), EHR (n = 11), clinical workflows (n = 2), and software including websites (n = 1). Most CDSSs (81%) employed multiple sources with only 7 studies using 1 type of knowledge sources (4 using CPG only, 2 using existing ontology, 1 using literature). The size of the ontologies appears to vary significantly, although most publications did not mention the actual number of concepts and properties.

Quality assessment data

Our quality assessment revealed that 30 (79%) studies described the evaluation of the CRO-based CDSS. In 29 (76%) cases, intrinsic evaluations were performed and 20 (53%) studies employed test cases or comparison studies. A test case was defined as a set of variables under which the system's function is tested. For example, the accuracy of TiMeDDx was tested by analyzing the diagnosis inferred for patient vignettes describing multiple symptoms.[13] Comparison studies compared the outcome of the CDSS with a gold standard, domain expert, or another CDSS. For example, in the article by Shen et al,[39] the system's diagnostic capability was tested by comparing the diagnosis of the CDS to that of the clinician.

Nine of the publications mentioned performing intrinsic evaluation but did not elaborate the purpose. Usability testing was only performed in 6 CDSSs. Only 5 studies achieved a high quality level, while 10 had a medium quality level, and 23 had a weak quality level. Our assessment revealed that 8 studies did not report a formal evaluation of their CDS or CRO. The CRO-based CDSSs in our study set did not discuss testing related to clinical salience in practice or effects on clinical outcomes. Figure 3 summarizes the quality assessment of included studies.

Concepts and properties extracted from CROs

A total of 1315 concepts and 603 properties were identified from the study articles. We then removed duplicates and combined concepts with similar descriptions, producing a final list of 567 concepts. These were then categorized into 339 medical knowledge and 228 reasoning concepts. We considered concepts that describe medical information related to patient, disease processes, clinical workflows, and clinic function such as history, symptoms, assessment, treatment plan, lab tests, administration process, and risk factors, as medical knowledge concepts. The medical knowledge concepts from all the studies were grouped, duplicates were removed, and concepts with the same definition were combined, resulting in 126 unique medical knowledge concepts and 31 subconcepts. For example, we combined concepts *patient history*[46] and *history*[14,40] under the concept *history*; concepts *route of administration,*[40,59] *delivery option,*[12] and *application route*[42] under the concept *route of administration*; and concepts *rule,*[47] *logic,*[62] and *SWRL: Rule*[52] under the concept *Logic*. We determined that the concepts comprised 15 medical domains. See Supplementary Table S1 for full list of the medical knowledge concepts.

Table 2. Description of the ontologies identified within the CDSSs

Author	Ontology scope	Sources of knowledge	Ontology—source(s)[a]	Ontology size[b]	
				Concepts	Properties
Mohammed and Benlamri[11]	Patient parameter; diseases and symptoms	Existing ontologies	Multiple existing plus new	>241[b]	13 **
Sene et al[12]	Medical concepts in geriatric oncology	Lit, domain experts	New	61[b]	ND
Denekamp and Peleg[13]	Clinical data items related to diagnosis	Lit, CPG, domain experts	New	5[b]	6 **
Uciteli et al[35]	Perioperative risk	CPG, domain experts, existing ontology	Multiple existing	19[b]	13[b]
Bau et al[36]	Medical knowledge related to DM2 management	Domain expert, EHR, hospital clinical workflow	New	31[b]	13[b]
Merlo et al[37]	Structure and the semantics of functional behavioral assessment methods	Domain experts, lit	New	15[b]	15[b]
Jimenez-Molina et al[38]	Medical context; clinical pathways; healthcare professionals	CPG, domain experts, EHR	New	24[b]	24[b]
Shen et al[39]	Infectious disease	Existing ontologies, lit, CPG, websites	New	1 267 004	12[b]
El-Sappagh et al[40]	DM2	Lit, CPG, domain experts, EHR, existing ontologies	Multiple existing	>10 700	279
Abidi[41]	CPG	CPG, domain experts	New	102	58
Beierle et al[42]	Cancer drugs: active ingredients, interactions, drug regimens	Lit, EHR, existing software	Revised existing	40[b]	18[b]
Shang et al[43]	HTN and DM2 CPGs; disease concepts related to HTN and DM2	CPG	New	47	121
Berges[44]	Physiotherapy process related to glenohumeral joint	Existing ontologies and databases, EHR treatment protocol, domain experts	Multiple existing	2351	100
Qi et al[45]	Spondylarthritis and definitions for alert type	Lit, CPG, domain experts	New	22[b]	22[b]
Alsomali et al[46]	Penicillin allergy related adverse events	Lit, existing ontologies	New	52	15
Zhang et al[47]	Patient data, CDS related domain knowledge, CDS rules	CPG	New	62	94[b]
Wilk et al[27]	Clinical workflow, interdisciplinary healthcare team member and patient specific concepts	Lit, domain experts	Revised existing	21[b]	19[b]
Zhang et al[48]	DM2	Lit, CPG, EHR, domain experts, existing terminologies	New	127	196
Rosier et al[49]	AF and CIED alerts	Lit	New	252	25
Jafarpour et al[50]	Nursing, CHF, and AF CPGs	Existing ontology	Revised existing	12[b]	13[b]
Alharbi et al[51]	Diabetes	CPG, domain experts	New	7[b]	19
Shen et al[14]	Diagnosis, prognosis, and treatment (example: gastric cancer)	Lit, EHR	New	92[b]	58[b]
El-Sappagh et al[52]	Case base reasoning context in diabetes; patient attributes	Domain experts, lit, CPG, existing ontology, EHR	Multiple existing	132	48[b]
Budovec et al[26]	Radiology information needed for diagnosis	Lit, domain experts	New	4[b]	3[b]
Wang et al[53]	CPG	EHR, CPG, domain experts	New	88[b]	11[b]
Eccher et al[54]	Cancer treatment	Domain experts, oncological workflows, existing ontologies	New	82[b]	9[b]

(continued)

Table 2. continued

Author	Ontology scope	Sources of knowledge	Ontology—source(s)[a]	Ontology size[b]	
				Concepts	Properties
Martínez-Romero et al[55]	Medical care related to acute cardiac disorder in cardiac-ICU	Lit, domain experts	New	40[b]	7[b]
Farrish and Grando[56]; Grando et al[57]	Generic drugs and related information	Lit, existing ontologies, CPG, domain experts	Multiple existing	16[b]	35[b]
Omaish et al[58]	CPG related to ACS management	CPG, domain experts	New	29[b]	1[b]
Riaño et al[59]	Chronic disease management, home care	CPG, lit, EHR, domain experts, ICD10	New	143[b]	8[b]
Adnan et al[60]	Medication knowledge specific to post discharge patient information	EHR, lit, existing websites and terminologies	New	40[b]	7[b]
Prcela et al[61]	Heart failure	CPG (congestive and acute HF)	New	200	> 100
Hussain and Abidi[62]	Imaging CPG; patient health parameters	CPG (EU Radiation Protection 118 Referral Guideline for Imaging)	New	30[b]	7[b]
Abidi[63]; Abidi et al[64]	Structure of BC follow-up CPG; patient parameter; medical knowledge related to BC found within the CPG	CPG, domain experts	New	12[b]	45[b]
Fox et al[65]	BC (diagnosis, treatment, management)	Lit, CPG, existing ontologies	Multiple existing plus new	79[b]	ND
Achour et al[66]	blood transfusion	Domain experts, existing terminologies	New	17[b]	2[b]
Wheeler et al[67]	CPGs, behavior change theories, and associated behavior change strategies related to HTN	CPG, Lit, domain experts	New	50	71
Sadki et al[25]	Patient data in BC stage and management	CPG	New	4[b]	6[b]

AF: atrial fibrillation; BC: breast cancer; CDSS: clinical decision support system; CHF: congestive heart failure; CIED: cardiac implant electronic devices; CPG: clinical pathway guideline; DM2: diabetes mellitus type 2; EHR: electronic health record; HF: heart failure; HTN: hypertension; ICU: intensive care unit; Lit: literature; ND: not discernable.

[a]Identify if the clinical reasoning ontology discussed is new, existing, or revised; new—if it is a new ontology created by the development team specifically for the CDSS; existing—if the development team used an ontology that is already in existence without altering it; revised—if the development team used an already existing ontology but with some alterations to suit the CDSS purpose.

[b]Ontology size is not explicitly stated. The size is determined by adding the number of concepts and properties described within the article (in body or in images).

Reasoning concepts were also categorized by removing duplicates and combining the concepts with the same definition. For example, we grouped concepts *ActDocumentation*[48] and *Make record of data*[65] under the concept *Data documentation*; concepts *task*[67] and *enact tasks*[65] under the concept *enact tasks*; and concepts *Application_purpose,*[12] *Therapeutic purpose,*[14] and *Treatment_intent*[54] under the concept *Treatment_purpose*. Thirty-eight unique reasoning concepts with 86 subconcepts were identified. The reasoning concepts expanded over 5 medical domains. See Table 3 for full list of reasoning concepts and Supplementary Table S2 for their definitions.

Properties were also analyzed in similar fashion leading to 240 unique properties: 103 attributes and 137 relationships. The properties comprised relationships and attributes across 17 domains. Table 4 displays a sample list of properties, their facets, and their designation as attribute or property (see Supplementary Table S3 for the full list).

DISCUSSION

In this systematic review, we investigated the literature exploring CROs used to empower CDSSs. We assessed the characteristics of the existing CDSSs that use CROs and determined the current practices used by the developers in creating the CROs. Tables 1 and 2 list the key findings. In summary, although there are many clinical ontologies in existence, we only identified 38 studies that used them in CDSSs. Moreover, these CROs restricted themselves to a specific clinical workflow. Ontologies such as the Breast Cancer Ontology[42] and DMTO[53] only contain concepts related to a specific disease, whereas ontologies like RIO[36] and C3O[56] are restricted to specific workflows within a specific subspecialty. These limitations are understandable considering the enormity of the medical field. The restricted scope of the ontologies limits their applicability across the full medical domain.

Medical decisions involve complex inferential processes, some, if not all, at least in part use “reasoning.” The difficulty in developing

Table 3. List of reasoning concepts (see Supplementary Table S2 for reasoning concepts definitions)

Medical domain	Reasoning concept	Reasoning subconcepts
Action	Inform patient or colleague about	Process information, appointment, results, management, risk
	Data documentation	
	Enquiry to acquire information	Family history, personal history, current problem and background, past problem and associated information, availability of services, appointments
	Enquiry to recall for service	Arrange service
	Enquiry to request with response	Appointment, results, second opinion, specialist services, investigations
	Enquiry to confirm action has been done	
	Decision	Eligibility for participation in trails, eligibility for service, need for referral, diagnosis, detection, etiology, pathology, need for follow-up, investigation, prophylaxis, risk assessment, choice of therapy
	Assessment	COMB, automatic motivation, physical capability, psychological capability, reflective motivation, social opportunity, behavioral change technique
	Comparison of....	Comparison of behavior, comparison of outcomes
	Plan	Referral for service, follow-up, manage treatment pathway, arrange/rearrange services
	Acquire information/knowledge about specific setting	Acquire information about setting, acquire comparison data in setting
	Detect	
	Classify	Staging
	Eligibility	Investigations, referral, therapy, research trail
	Assess level of some parameter	Urgency, risk, need, quality
	Predict	
	Diagnosis	
	Prognosis	
	Action_description	Decisional_action_description, Drug_prescription_description, Clinical_action_description, Drug_administration_description, Surgical_action_description, Laboratory_exam_action_description
	Enact tasks	Communicate, Educate, Inform, Act_Observation, Act_Patient_Encounter, Act_Procedure, Act_Substance_Administration, Act_Registration, Act_Working_List, Act_Care_Plan, Feedback and monitoring
Goals	Achieve some state of world	Limit changes to current state, bring about required future state, empower staff, prevent unwanted future state, ensure compliance with plan
	Goal type	Cessation goal, acquisition goal, shapeable goal, intervention goal
Treatment	Treatment decision	Decide between alternative interventions, decide whether to carry out intervention or not, decide type of investigation, Decide scheduling of intervention
	Treatment_purpose	
	Dose modification	Add serum, decrease dose, increase dose, continue, finish
	Influential factors	Motivation, opportunity, obstacle, reward and threat
	Intervention function	
CPG	Similarity measure	Exact, difference, complex
	Confidence	
	Antecedents	
	Guideline_Step	Decision_Option, Diagnostic_Step, Discharge_Step, Admission_Step, Transfer_Step, Control_of_disease
	Associations	
	Repetition and substitution	
	Regulation	
	Covert learning	
	Scheduled consequences	
	Tip	
	TDFDomain (Theoretical Domains Framework)	

COMB: capability, opportunity, motivation, and behavior model; CPG: clinical pathway guideline.

a sophisticated CDSSs that only alerts the clinician when appropriate, reducing the need for overrides, or assists with complex decision-making processes such as providing a differential diagnosis that is personalized to each patient, lies with the difficulties associated with decoding what constitutes clinical reasoning. Many researchers have proposed different approaches for utilizing ontologies to decrypt clinical reasoning especially for the betterment of CDSSs.[11–14,35–67] We noted that even when CDSSs use CROs, most of them do so in combination with other inferencing methods such as rule-based inferencing to adequately represent the knowledge needed for the CDSS. This finding is expected given the complexity associated with clinical reasoning and KBs.

	Evaluated by	Intrinsic evaluation	Usability testing	Total grade	Quality level
Mohammed & Benlamri (2014)	A	1	0	A 1 0	Medium
Sene et al (2015)	C	1	0	C 1 0	Weak
Denekamp & Peleg (2010)	C	1	0	C 1 0	Weak
Uciteli et al (2017)	AC	1	1	AC 1 1	Strong
Bau et al (2014)	A	1	1	A 1 1	Strong
Merlo et al (2018)	AC	1	0	AC 1 0	Medium
Jimenez-Molina et al (2018)	AC	1	1	AC 11	Strong
Shen et al (2018)	C	1	0	C 1 0	Weak
El-Sappagh et al (2018)	C	1	0	C 1 0	Weak
Abidi (2017)	AC	1	1	AC 1 1	Strong
Beierle et al. (2017)	D	0	0	D 0 0	None
Shang et al. (2017)	C	1	0	C 1 0	Weak
Berges (2016)	C	1	0	C 1 0	Weak
Qi et al. (2016)	C	1	0	C 1 0	Weak
Alsomali et al (2016)	C	1	0	C 1 0	Weak
Zhang, Gou, et al (2016)	AC	1	0	AC 1 0	Medium
Wilk et al (2016)	C	1	0	C 1 0	Weak
Zhang, Tian, et al (2016)	AC	1	0	AC 1 0	Medium
Rosier et al (2016)	C	1	0	C 1 0	Weak
Jafarpour et al (2016)	AC	1	0	AC 1 0	Medium
Alharbi et al (2015)	C	1	0	C 1 0	Weak
Shen et al (2015)	AC	1	0	AC 1 0	Medium
El-Sappagh et al (2014)	AC	1	0	AC 1 0	Medium
Budovec et al (2014)	D	0	0	D 0 0	None
Wang et al (2014)	D	0	0	D 0 0	None
Eccher et al (2013)	C	1	0	C 1 0	Weak
Martínez-Romero et al (2013)	C	1	0	C 1 0	Weak
Farrish & Grando (2013), Grando et al (2012)	C	1	0	C 1 0	Weak
Omaish et al (2012)	A	1	0	A 1 0	Medium
Riaño et al (2012)	AC	1	1	AC 1 1	Strong
Adnan et al, 2010	D	0	0	D 0 0	None
Prcela et al, 2008	D	0	0	D 0 0	None
Hussain & Abidi, 2008	A	1	0	A 1 0	Medium
Abidi, 2007; Abidi et al, 2007	D	0	0	D 0 0	None
Fox, 2004	D	0	0	D 0 0	None
Achour et al, 2001	C	1	0	C 1 0	Weak
Wheeler et al, 2018	B	0	1	B 0 1	Medium
Sadki et al, 2018	D	0	0	D 0 0	None

Figure 3. Quality assessment of the clinical decision support systems and their ontologies.

Our analysis also revealed that most developers referred to multiple data sources during ontology development, including existing ontologies, domain experts, literature, clinical guidelines, and the EHR. Currently, however, there is neither a standard format to identify appropriate sources for an ontology nor a standard document to which developers can refer to as a starting point. CROs and CRO-based CDSSs are generally being developed and studied in isolation. We believe that the broader informatics community will benefit from knowing the best practices used by existing systems. More importantly, our study provides a list of concepts and properties for an initial starting point, as is found in other research fields such as drug development or genetic research. We note, for example, that there are multiple ontologies developed by different groups for clinical workflows related to breast cancer[25,42,63–65] and diabetes.[11,36,40,48,52] As such, we believe that our lists of medical knowledge concepts, clinical reasoning concepts, and properties will provide a foundation for starting the development process of future ontologies. Furthermore, our findings could be used as the basis for a standard to improve access to data by CDSS developers, implementers, or evaluators to improve the function and interoperability of EHR and CDSS.

Implications for EHR improvement and future research

Clinical ontologies are increasingly used as a means for improving various aspects of health care.[68–70] CDS is one such area in medicine in which clinical ontologies are being used to develop more efficient and accurate systems. Most CROs focused on a specific disease process, workflow, or subspecialty; hence, they tend to only map clinical reasoning concepts and relationships related those aspects. Thus, most CROs create only a partial representation of clinical knowledge used by clinicians. A more comprehensive CRO will facilitate better structuring of the KB and allow CDSSs to access a wider range of information that can both complement and improve extant

Table 4. List of properties (see Supplementary Table S3 for full list)

Domain	Property	Facet	Range	R vs. A
Record	has_Patient		Medical record	A
	hasHighLevelContext		High-level context	R
Patient	has_patient_profile		Patient properties	R
	has_patient_ID		Patient ID	A
	has_lab_test	has_Part, has_Unit, has_Status	Lab test details	R
	has_Lab_test_value		Test value	A
	has_diagnosis	hasSide	Diagnosis, location	R
	has_diagnosis_severity		Disease severity	A
	has_history	EndingDate	Patient's history	R
	has_Family_History	isRelativeOf	Family history	R
	has_treatment_plan		Treatment plan	R
	has_symptom_or_sign		Symptoms and sign	R
	has_presentation		Chief presentation	R
	has_measurement	has_UpperLimitValue, has_ExactValue	Value	A
	Disease_since_date		Date	A
	has_complication		Complication	R
	has_previous_treatment_plan		Treatment plan	R
	has_HealthcareProvider	hasSpecialty, plays_role_of, actorName	Healthcare provider	R
	has Alarm		Alarm types	R
	has_demographic	hasName, Sex, has Age, Ethnicity	Demographic data	R
Diagnostic process	observationMethod		Observation method	R
	observed_data		Data value	A
	Assessment_Reason		Reason	R
	has_pain		Pain level	A
	has_device	hasMedicalDevice, hasTool	Medical device	R
	has_Assessment		Assessment	R
	has_patient_reported_findings	has_VAS_value, has_ASDAS, etc	Questionnaire value	A
	has_Recommendation		Recommendation	R
Signs and symptoms	Is_assessed_by		Assessment name	R
	has_RecoveryRate		Recovery rate	A
	has_MortalityRate		Mortality rate	A
	is_not_caused_by		Factors	R
	cause_by		Causing factor	R
	is_symptom_of		Disease	R
Diagnosis and disease	hasSyndrome		Syndrome name	R
	has_severity		Severity level	A
	has_treatment	antibiotic2bacteria	Treatment	R
	has_causing_factors	bacteria2infection	Causing factor	R
	hasRisk		Risk factor	R
	affected_Body_Site		Body part	R
	hasLabTest		Lab test name	R
	hasStatus		Status	A
	hasSyndromeDuration		Time	A
	has_new_stage		Cancer stage	A
	is_transmitted_by		Vector	R
	has_complication		Complication list	R
	occurs_with		Disease, symptom	R
	hasExperimentalData		Experimental data	R
Treatment	hasHealthRecord	hasEHR_ID	Health record ID	A
	has_education_program	has_provider, has_section	Education program	R
	has_next_evaluation_date		Date	A
	part_of	part_of	Treatment plan	R
	has_intervention_goal	isAppropriateForInterventionGoal	Intervention goal	R
	has_pharmacological_plan		Medication list	R
	is_recommended_for_illness		Recommendation	R
Medication	Can_be_combined_with		Medication	R
	Contradict_with	Contradict_with_drug, _with_drug	Drug ingredient	R
	has_treatment_target	has_A1C_lowering_level, etc	Treatment target	A
	has_active_ingredient		Active ingredient	A
	has_administrationProcess		Administration process	R
	has_cost		Medication cost	A
	has_order_start_date		Date	A

(continued)

Table 4. continued

Domain	Property	Facet	Range	R vs. A
	has_order_stop_date		date	A
	has_dose	hasPatientDrugUnRec, etc	Dose	R
	dosage_Measurement_Unit		measurement unit	A
	has_cumulative_dose		accumulative dose	A
	has_maximum_dose	maximumDrugUnits, maximumDosage	medication dosage	R
	has_frequency (freq)	maximum_Freq, minimum_Freq	Drug frequency	A
	has_application_route		Drug application route	A
	has_explanation		Explanation	R
	has_toxicity		Toxicity	A
	has_Therapy_description	withSpecificFluids	Drug therapy direction	A
Nutrition	has_amount	has_calcium, has_carbohydrate_grams,	Quantity	A
	has_calories	has_total_calories,	Amount of calories	A
Time	has_time	number_of_times, hasExerciseTime	Time	A
	has_temporal_entity		Temporal data	A
	has_temporal_relation	equals, before, after, hasBeginning	Temporal relation	R
	Trend_in_TimePeriod		Time period	A
Alert	has_Alert	hasLow-, hasHigh- hasMedium-Alert	Alert level	A
	AssociatedToDynamicContext		Dynamic context	R
Anatomy	nerve_supply		nerve	R
	has_location		Anatomic location	R
CDS/CPG	has_input		CDS input	A
	has_Outcome		Outcome specification	A
	hasDecisionRule		CDS function, logic	R
	has_Trigger	hasTriggerSource, triggersException	CDS trigger	R
	has_logic_component	has Arc, hasEndNode, hasStartNode	Arc, Node	R
	hasInformationReturn		Treatment information	R
Risk	risk_for_adverse_situation		Risk situation	R
	Risk_related_recommendation		Diagnostic test	R
Clinical Team	executes		Clinical workflow	R
	hasPractitionerStatus		Practitioner status	R
	has_Action	has_directive, hasPatientAction, etc	Action	R
Task	Evokes		Diagnosis	R
	Synergistically_evokes		Diagnosis	R
	hasCondition		Medical condition	R
	has_status	hasTaskState, hasWorkFlowStatus	Task status	R
	is_followed_by		Task	R
	has_decision_option		Decision option	R
	has_act_relations	hasActPtn, hasPtnAct, hasActRelTarget	Relationship type	R
	is_assigned	is_responsible_for, managesPatient,	Medical team member	R
Universal	Priority		Priority level	A
	Reason	isWarrantedBy	Reason	R
	hasFunction		Function	R
	isInputOf		Indicator	R
	isOutputOf		Output	R
Functional terms	description		Rule description, model	R
	attribute		Attribute of model	A
	hasDataCategory	subclass, hasScenario	Subclass, scenario	R
	terminologyName		Name string	A
	code	procedureCode, DisplayName	Code	A
	hasStructuredData		Data type	A
	translation		Translating code	A

A: attribute; ASDAS: Ankylosing Spondylitis Disease Activity Score; CDS: clinical decision support; CPG: clinical pathway guideline; R: semantic relationship; VAS: visual analog scale.

CDSSs without being restrictive to only one aspect of patient care.[71] This inclusiveness would allow for the development of more complex CDSSs that can incorporate and act upon data related to the whole patient. In turn, CDSSs could be better personalized to provide alerts only when they are clinically relevant to the patient. This would lead to significantly fewer alerts and alleviate alert fatigue.

Developers of clinical ontologies and CDSSs should consider expanding the number and the types of reasoning concepts mapped in CROs. In our study, we identified 38 unique reasoning concepts that belonged to 5 medical domains. An expanded CRO can be used to identify and store reasoning behind many medical decisions that currently are only present in the free-text clinical notes (ie, history and physical examination, progress notes, consult notes, pathology reports, and radiology reports). There is a significant gap in existing CROs in mapping the data related to decisions one of the most important aspects of medical care. Clinicians are faced with many questions when reviewing a patient's records regarding the actions taken by others in the past. Unfortunately, the clinical reasoning for decisions regarding patient care in many cases is often buried in free-text notes.[72] A comprehensive CRO that captures the "why" of a decision will greatly assist clinicians in quickly accessing data and improving efficiency, and lead to better patient care.[73]

A CRO can also be used to improve the reuse of data for learning health systems. The Agency for Healthcare Research and Quality defines learning health systems as a healthcare system in which "internal data and experience are systematically integrated with external evidence and that knowledge is put into practice."[74] A CRO can assist in mapping the reasoning behind clinical decisions to be used for quality improvements, consensus of cases, case discussions in morning rounds, and use during multidepartmental conferences held to discuss complex patient cases. Moreover, easy access to reasoning can be a useful tool for the education of medical and nursing students and young clinicians, and as a component of continue education for clinicians.

Although we believe that our methods have been successful in identifying most or all ontology-based CDSSs, our efforts to summarize the ontologies used by these systems is limited, primarily because the foci of the articles we found generally dwelled more on the details of the logic and systems and less on cataloging the concepts and relations used. To the extent possible, we have compiled names and definitions provided in the articles, but given the limited details available, our ability to identify commonalities across systems was modest. However, now that the systems have been identified, along with their developers and general domains of interest, our study can provide a "starter set" of subsequent efforts to engage interested stakeholders to build a more comprehensive, well-defined ontology.

CONCLUSION

This review summarizes existing literature on CRO-based CDSSs. It identifies the current practices used within the development of the CROs and formulates lists of medical knowledge concepts, reasoning concepts, and properties (relationships and attributes) used by these CDSSs. The use of CROs, which map concepts used by clinicians' during medical decision making, can significantly improve CDSS functionality. Although many CDSSs have been developed using clinical ontologies, few use CROs. As a result, high-quality studies describing CROs are sparse. Further research is required in developing high quality CROs-based CDSSs.

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AUTHOR CONTRIBUTIONS

PID and JJC conceptualized, designed, and conducted the study including study selection, data extraction, and data analysis. PID drafted the manuscript with significant intellectual input form JJC, and JJC and TKC assisted with creating and editing the article. All authors approved the final version of the article.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *Journal of the American Medical Informatics Association* online.

CONFLICT OF INTEREST STATEMENT

None declared.

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