Design and Implementation of an Ontology for the Computable Representation of Clinical Prediction Rules

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Abstract

Objective: A lack of acceptance has hindered the widespread adoption and implementation of clinical prediction rules (CPRs). The use of clinical decision support systems (CDSSs) has been advocated as one way of facilitating a broader dissemination and validation of CPRs. This requires computable models of clinical evidence based on open standards rather than closed proprietary content.

Methods: The on-going TRANSFoRm project has developed ontological models of CPRs suitable for providing CPR based decision support.

Results: This paper describes the design and implementation of a generic ontology model for the representation of computable CPRs. The conceptual validity and implementation of the ontology is discussed using an illustrative example of a CPR in the form of the Alvarado Score for acute appendicitis.

Conclusions: We demonstrate how the model is used to query the structure of this particular rule, providing a generic computable representation suitable for the representation of CPRs in general.

Keywords

Clinical prediction rules, ontology, clinical decision support

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1 Introduction

Although many diverse examples of clinical prediction rules (CPRs) in primary care can be identified in research literature, their use has yet to gain widespread acceptance among clinicians [1, 2]. There are a number of valid concerns that influence why clinicians are reluctant to use them as part of their day-to-day clinical practice.

Despite the existence of an accepted development lifecycle for producing CPRs, many of them have traditionally focussed solely on the derivation phase of the CPR lifecycle [3]. Many derived CPRs are subject to poor or non-existent CPR validation and impact analysis. This lack of validation severely limits their perceived applicability to the same restricted patient populations defined in the original derivation research populations. Complications may arise when there are multiple rules derived by different researchers for any chosen clinical condition. As an example, a clinical condition such as Pulmonary Embolism has numerous variations of CPRs that may pertain to it [4]. This can lead to confusion and a lack of clarity about which CPR variations are the "correct" or "best" ones to use.

With some exceptions the format for dissemination of CPRs is largely literature based, putting an onus on clinicians to search literature for suitable CPRs [5]. This is compounded by the fact that literature based rules are by their nature static in content and do not provide for recording of versioned rule changes. This may have implications for the applicability of any particular CPR as changes take place over time in the demographics of the original rule derivation study population.

One suggested way of addressing these limitations is through development of clinical decision support systems (CDSSs) based on computable models of clinical evidence [6, 7, 8]. The ultimate vision is to provide for computable representations of CPRs that allow derivation, validation, dissemination, versioning and on-going revision from empirical sources of electronic primary care patient data. This can be complemented using extraction of patient cues and demographics from electronic health records (EHRs) as a trigger for initiating appropriate rule execution.

The TRANSFoRm project has developed computable ontological models of CPRs to support their electronic derivation, implementation and validation [9]. We describe the models and conceptual validity through implementation of a well studied CPR, the Alvarado score [10, 11]. We demonstrate how clinical questions are expressed as ontological queries for use by a CPR based CDSS currently being developed by the TRANSFoRm project.

2 Definition and application of Clinical Prediction Rules

2.1 CPR Definition

It is necessary to clearly define at the outset what we mean when we talk about using a clinical prediction rule. A CPR "is a clinical tool that quantifies the individual contributions that various components of the history, physical examination, and basic laboratory results make toward the diagnosis, prognosis, or likely response to treatment in a patient" [12, 13]. The formal characteristics of a CPR can be clearly identified based on this definition. Typically a CPR is derived from a statistical model and will be constructed and structured based on the following distinct parts:

- A clinical outcome that relates to a defined diagnostic, prognostic or treatment outcome associated with a selected clinical condition.
- A set of diagnostic cues and associated criteria that is indicative of the clinical outcome being assessed by the rule.
- A statistically derived scoring scheme that quantifies the relative contribution of each cue where present to the clinical outcome.
- A threshold based scoring scheme that defines relative clinical interpretations of risk categories for all possible scores for the rule.
- An optional decision indicating a clinical action in response to each risk category to be recommended based on each of the defined threshold scores.

2.2 Application of CPRs as part of a defined Diagnostic Strategy

In order to understand how CPRs may be potentially applied as a diagnostic tool in clinical practice it is useful to place their use in a broader diagnostic context. A clinician needs to formulate and consider the evidence for all possible differential diagnoses when a patient first presents with a particular clinical complaint. This is done by considering each differential diagnosis and can involve "ruling out" differentials based on the underlying diagnostic cues as presented by the patient. CPRs can provide a useful tool to assist with these potential "rule outs" using the results of applying suitable CPRs obtained to any particular patient case [13]. Their appropriate use can be applied as a tool to reduce the possibility of diagnostic error at the outset through consideration of possible differentials [12, 13]. As an example a patient presenting with abdominal pain who scores less than 4 on the Alvarado score, could indicate a potential "rule out" for acute appendicitis for that patient.

3 Model Development Methodology

The development of the formal models of clinical prediction rules described here followed a number of distinct steps subsequently described in detail:

- Clinical use case development.
- Functional requirements definition of the CPR model.
- Model design based on functional requirements.
- Model construction and clinical evidence population.
- Clinical use case implementation and validation.

3.1 Clinical Use Case Development

The models presented here provide the backend knowledgebase to be used as part of a broader piece of work currently in progress to develop a functional diagnostic decision support system as part of the TRANSFoRm project. The CDSS will consume and ask clinical questions of the models described here that provide the underlying knowledgebase. This CDSS tool will be deployed and used by primary care practitioners to assist them in formulating and quantifying differential diagnoses to consider for patients presenting with three defined diagnostic conditions. The use of electronic CPRs will be deployed as part of the diagnostic strategy for ruling out of potential differential diagnoses. The three primary care patient safety use cases will be used to test and validate the fully functional CDSS being developed by TRANSFoRm.

The selected patient safety use cases focus on potential diagnoses relating to patients presenting with the general complaints of chest pain, abdominal pain or dyspnoea. These were chosen for the cognitive challenge they present in primary care with potential for diagnostic error [14, 15]. Reviews of evidence based sources identified CPRs supporting selected diagnoses for these patient safety use cases [10, 16]. In total 41 clinical prediction rules were identified relating to 20 diagnostic conditions relating to the three patient safety use cases. In this paper we describe the model representation of a single CPR called the Alvarado Score relating to a diagnosis of appendicitis for a patient presenting with abdominal pain.

3.2 Functional Requirements Definition of the CPR Model

In considering the model design requirements it is useful to first consider the functional requirements of any application that will use those developed models. The models described here will be ultimately queried by the TRANSFoRm CDSS. The CDSS will want to query particular diagnostic conditions, retrieve associated CPRs for any condition and query all of the constituent rule structures for any selected CPR. We have therefore defined our model requirements based on the different CPR related questions it needs to be able to answer. The functional requirements can be stated as clinical questions we wish to be able to ask of our CPR model. We identified the following questions as general functional requirements that we want to able to answer using the finished CDSS tool:

- What are the differential diagnoses to consider for a selected patient reason for encounter (RFE)?
- What are the related CPRs associated with a selected diagnosis?
- What are the cues, criteria and associated scores of a selected CPR?
- What are the scoring interpretation schemes of a selected CPR?

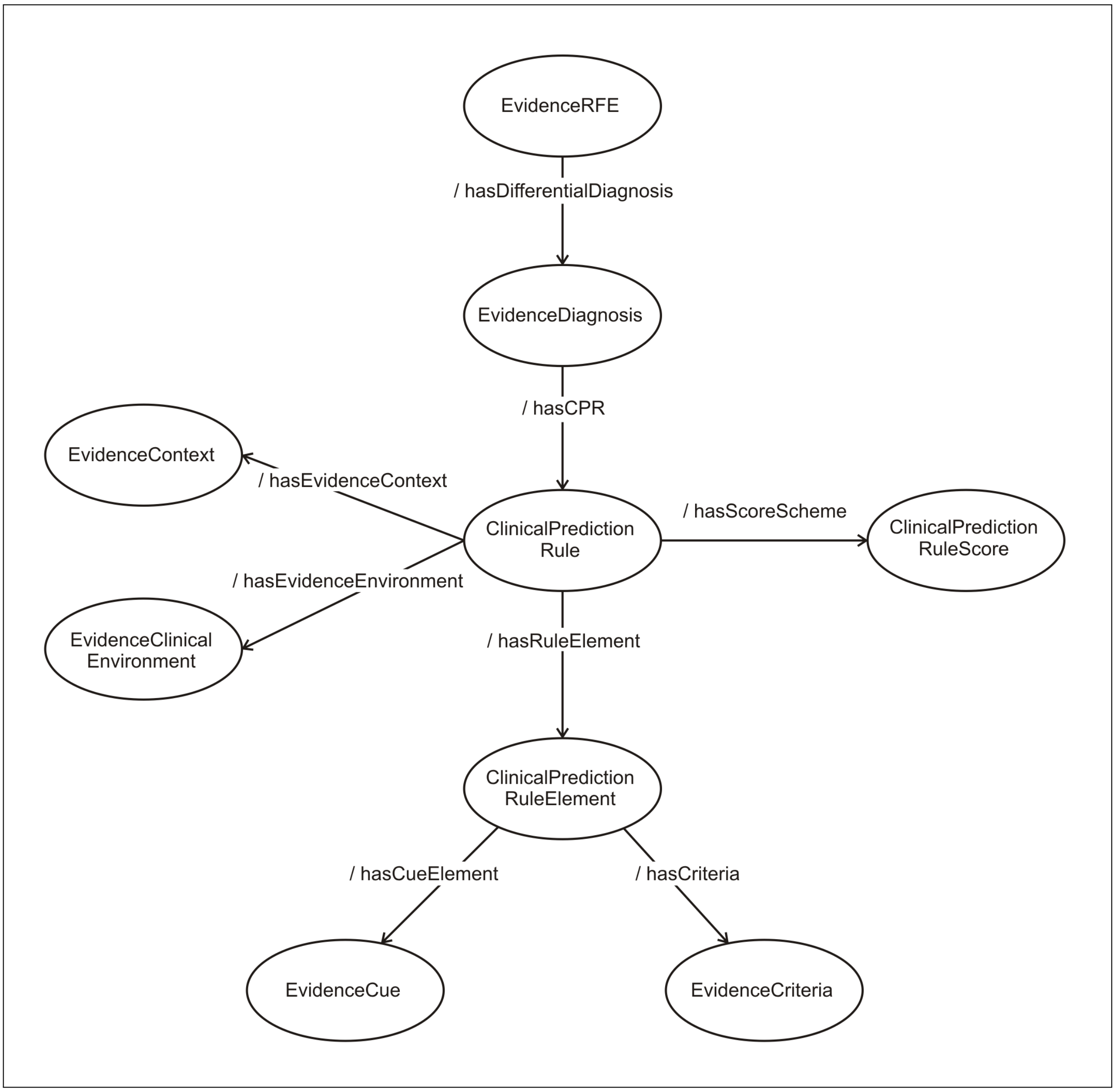

Figure 1: Relationship of CPR ontology concepts.

- What are the population characteristics associated for application of a selected CPR?
- What is the clinical setting associated for application of a selected CPR?
- What are the supporting literature sources for a selected CPR?
- What is the current version number of a selected CPR?

3.3 Model Design based on Functional Requirements Definition

An ontology representation was chosen as the basis for the CPR model to support dissemination of CPRs using open standards that support a simple underlying data structure. Many methodologies have been proposed for design and development of ontologies [17]. The approach we have selected uses an application focussed approach where ontology requirements are expressed as "competency questions" that can then be used as a set of functional requirements to validate ontology completeness [18]. In our example, the functional requirements we have already defined can be considered to also define suitable ontology competency questions. If our ontology is designed correctly we should be able to express all our competency questions as formal ontology queries that generate correct clinical results with respect to our selected clinical use cases when executed (in this case representation of the Alvarado Score for appendicitis). Competency questions were deconstructed to identify the required formal ontology concepts and defined relationships that exist between them. The ontology concepts and relationships identified are shown in Figure 1. Although named inverse relationships exist for all relationships within the constructed ontology, we have only shown relationships in one direction in the diagram for clarity. For example the relationship 'hasDifferentialDiagnosis' has a corresponding inverse relationship called 'isDifferentialDiagnosisOf' that is not explicitly shown.

These core CPR ontology concepts are described in Table 1 along with examples of clinical instances and associated attributes of those concepts.

A fundamental requirement of the TRANSFoRm project is the appropriate use of standard clinical vocabularies, terminologies and classifications to add semantic meaning to any ontology terms being used through binding of vocabulary terms.

Table 1: Core CPR Ontology Classes with Descriptions and Class Attribute Examples.

Class Name and Description	**Class Instance**	**Attribute Examples**
EvidenceRFE: The patient reported reason for encounter (RFE)	AbdominalPainRFE	hasUMLSCode C0000737 hasIPC2Code D06 hasICD10Code R10.0 hasReadCode XaA06 YaYkf
EvidenceDiagnosis: A differential diagnosis of a particular RFE	Appendicitis	hasUMLSCode C0003615 hasIPC2Code D88 hasICD10Code K35 hasReadCode J20..Y30Di
ClinicalPredictionRule: A versioned CPR associated with a particular diagnosis with links to supporting literature URLs	AlvaradoScore1_0	hasRuleVersion 1_0 hasSupportingLiteratureURL http://www.biomedcentral.com/content /pdf/1741-7015-9-139.pdf
ClinicalPredictionRuleElement: One individual element of the CPR that is associated with one cue and the criteria to apply to it for a particular CPR	AlvaradoScoreElement1	
EvidenceCue: An associated sign, symptom, risk or clinical test that may be associated and reused in more than one CPR	Nausea	hasUMLSCode C0375548 hasIPC2Code D09 hasICD10Code R11.0 hasReadCode X75qw.Y7Cjf
EvidenceCriteria: The criteria and weighted rule score associated with a ClinicalPredictionRuleElement. The presence or absence of the cue and score is indicated through the criteria attributes	AlvaradoElementCriteria1	isPresent = True hasScoreInterpretation 1
ClinicalPredictionRuleScore: A score range to be used for clinical interpretation of the rule along with the textual interpretation of that score level	AlvaradoScoreLevel3	hasStartScore 7 hasEndScore 10 hasScoreInterpretation "Surgery"
EvidenceContext: A group of classes that defines the evidence population demographics used to derive the rule	Adult, Male, Ireland	hasAgeGreaterThan 17 hasISOCode 1 hasISOCode "IE"
EvidenceClinicalEnvironment: The clinical setting or context in which the rule was derived and is suitable for application	PrimaryCare	

A TRANSFoRm vocabulary service has been developed to allow runtime access to a number of vocabularies through defined web service interface methods [19]. The Unified Medical Language System [UMLS] has been used as a pivot terminology from which mappings have been provided to others including the International Classification of Primary Care Version 2 (ICPC2), SNOMED Clinical Terms, the International Classification of Diseases Version 10 (ICD10) and Read Codes [20, 21, 22, 23].

The CPR ontology model provides attributes (as shown in Table 1) to allow association of selected terminological codes to instances of the EvidenceRFE, EvidenceDiagnosis and EvidenceCue concepts. Multiple code system terms can be associated to any instance. At present these terms are manually entered into the ontology.

In order to facilitate CPR execution based on coded RFEs or diagnostic cues extracted from individual patient EHRs, future development will focus on integrating the ontology models with the TRANSFoRm vocabulary service. This will allow querying at runtime using only UMLS associations to pivot to the appropriate terminology implemented by the EHR data. This can also provide for coded ontology content to be represented and populated dynamically into the ontology through application of data mining techniques to electronic sources of coded primary care data.

3.4 Model Construction and Clinical Evidence Population

This constructed ontology design has been expressed using the ontology language/resource description framework (OWL/RDF) representation and implemented using the Protégé 4.1 ontology designer [24, 25, 26]. It is hosted using a Sesame triple store for query formulation, testing and future dynamic programmatic update of ontology content [27, 28]. The clinical content for the ontology was manually populated as instances of the ontology concepts to reflect the structure of the Alvarado score as described in literature [10, 11].

3.5 Ontology Metrics

The CPR ontology model is part of a larger clinical evidence ontology model that also supports the general representation of diagnostic knowledge. The knowledge-base metrics for the full ontology are:

- Number of ontology classes = 43
- Number ontology relationships = 101
- Data of ontology attributes = 48
- Number of ontology class instances = 505

Table 2: Competency Questions 1-4 (from Table 1) Expressed as SPARQL Queries with Associated Results.

SPARQL (Protocol and RDF Query Language)	**Query Result (Instance Relation Value)**
SELECT ?DifferentialDiagnosis WHERE {?DifferentialDiagnosis isDifferentialDiagnosisOf AbdominalPainRFE .}	Appendicitis, BacterialEnteritis ChronsDisease, CorPulmonale EctopicPregnancy, Pyelonephritis UrinaryTractInfection
SELECT ?CPR WHERE {?CPR isCprOf Appendicitis.}	AlvaradoScore1_0
SELECT ?CueElement ?Property ?Value WHERE {?RuleElement isRuleElementOf AlvaradoScore1_0. ?CriteriaElement isCriteriaOf ?RuleElement. ?CueElement isCueElementOf ?RuleElement. ?CriteriaElement ?Property ?Value. ?Property rdf:type owl:DatatypeProperty. }	MigrationOfPain isPresent true MigrationOfPain hasScoreInterpretation 1 Anorexia isPresent true Anorexia hasScoreInterpretation 1 Nausea isPresent true Nausea hasScoreInterpretation 1 RightLowerQuadrantTenderness isPresent true RightLowerQuadrantTenderness hasScoreInterpretation 2 ReboundPain isPresent true ReboundPain hasScoreInterpretation 1 ElevatedTemperature isPresent true ElevatedTemperature hasScoreInterpretation 1 Leucocystosis isPresent true Leucocystosis hasScoreInterpretation 2 WhiteBloodCellShiftLeft isPresent true WhiteBloodCellShiftLeft hasScoreInterpretation 1
SELECT ?ScoreElement ?Property ?Value WHERE {?ScoreElement isScoreSchemeOf AlvaradoScore1_0 . ?ScoreElement ?Property ?Value. ?Property rdf:type owl:DatatypeProperty. } ORDER By ?ScoreElement	AlvaradoLevel1 hasScoreInterpretation "Discharge" AlvaradoLevel1 hasStartScore1 AlvaradoLevel1 hasEndScore 4 AlvaradoLevel2 hasScoreInterpretation "Observation/Admission" AlvaradoLevel2 hasStartScore 5 AlvaradoLevel2 hasEndScore 6 AlvaradoLevel3 hasScoreInterpretation "Surgery" AlvaradoLevel3 hasStartScore 7 AlvaradoLevel3 hasEndScore 10

4 Clinical Use Case Implementation and Validation

4.1 The Alvarado Score as a CPR example

A particular clinical example of a well studied CPR is the Alvarado Score which we will use as a clinical example to illustrate use of our models. This rule categorises the risk of patients having potential acute appendicitis based on the presence or absence of 8 diagnostic indicators. The risk of appendicitis is expressed as three score-based risk categories with associated recommended treatment options. This rule has been designed to be suitable for primary care and is based on the presence of diagnostic cues without the need for imaging [10]. Reviews have highlighted the importance of capturing the demographic context of the derivation study population. Clinical performance of the Alvarado score has been shown to vary in different populations depending on gender and age, performing best for adult males [11]. This demographic variability should be reflected in any model design.

Using the example of appendicitis and the Alvarado Score we identified the following questions as functional requirements that we want to able to answer using the finished CDSS tool:

- What are the differential diagnoses to consider for a reason for encounter (RFE) of abdominal pain?
- What are the CPRs associated with the differential diagnosis of appendicitis?
- What are the cues, criteria and associated scores of the Alvarado score?
- What are the scoring interpretation schemes of the Alvarado score?
- What are the population characteristics associated for application of the Alvarado score?
- What is the clinical setting associated for application of the Alvarado score?
- What are the supporting literature sources for the Alvarado score?
- What is the current version number of the Alvarado score?

4.2 Expression of CPR Model Queries

The competency questions previously defined as functional requirements were expressed as Protocol and RDF Query Language (SPARQL) ontology queries using the ontology concepts and relationships previously identified [28]. These queries were executed and results checked for consistency with respect to the clinical evidence sources used to populate the ontology. Queries and results are shown in Table 2 for four competency questions

4.3 Development of Clinical Evidence Service

The evidence defined in the ontology has been made available to the TRANSFoRm CDSS through a REST based web service [29]. This allows the CDSS to access ontology resources through defined URL constructs that are linked to programmatically implemented SPARQL queries. The Sesame infrastructure provides a programmable API that can be used to programmatically connect to and query the ontology using SPARQL queries. The rest interface was developed using Java implementing the Jersey REST implementation [30].

System interoperability is supported by allowing query results to be returned to any third party consumer tool in a number of supported data formats including XML, JSON and plain text responses. In addition, the Sesame infrastructure also provides its own REST based interface that can be used directly to execute SPARQL queries to return responses in native RDF data formats. The components of the evidence service are shown in Figure 2.

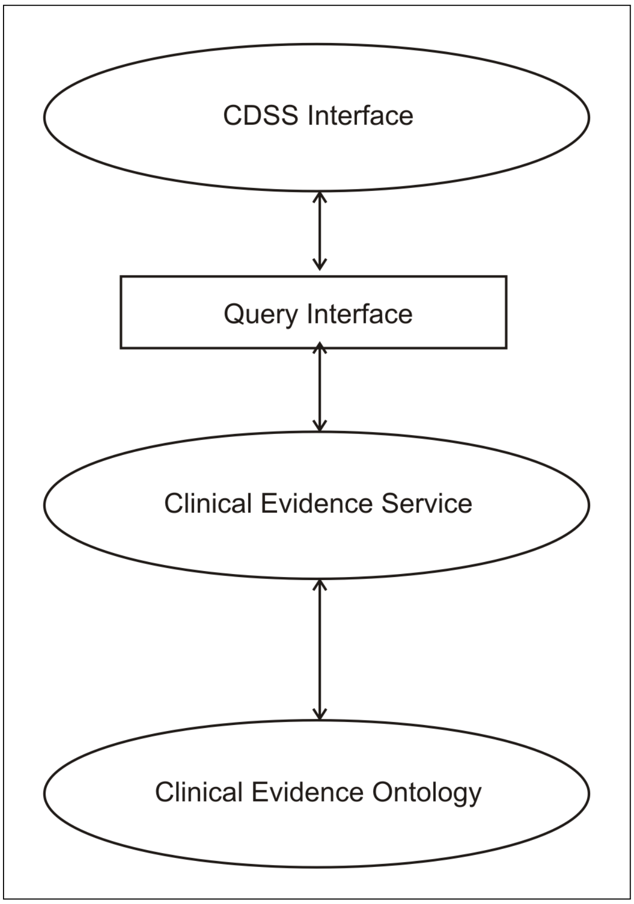

Figure 2: Evidence service components.

As an example, the structure of the Alvarado score can be accessed using the URI http://localhost:8080/ClinicalEvidenceRESTService /interfaces/query/cprs/AlvaradoScore1_0. A sample of the generated XML output is shown in Figure 3.

4.4 Implementation of a Diagnostic Strategy using Evidence Service Calls

We previously referred to the role of CPRs as part of a broader diagnostic strategy to "rule out" a potential diagnosis. The steps to be implemented would require:

- Obtaining the list of supported patient RFEs
- Obtaining a list of differential diagnoses to consider based on a presenting patient RFE
- Obtaining a list of the CPRs available for any differential diagnosis associated with the RFE
- Obtaining the cues, criteria and scores for any chosen CPR to apply
- Obtaining the scoring scheme and decisions for any chosen CPR
- Execution of the CPR based on a comparison to the patient cues provided to determine if a "rule out" may be appropriate

Using the example of a patient presenting with abdominal pain and an investigation of possible appendicitis, the clinical evidence service can be used to implement these steps using the following series of REST based calls to present results as XML, JSON, plain text or RDF data formats:
../ClinicalEvidenceRESTService/interfaces/query/rfes
../ClinicalEvidenceRESTService/interfaces/query /differentials/AbdominalPainLocalisedOtherRFE

```
http://localhost:8080/ClinicalEvidenceRESTService/interfaces/query/cprs/AlvaradoScore1_0

<?xml version="1.0" encoding="UTF-8" standalone="true"?>
- <cpRs>
    <cprName>AlvaradoScore1_0</cprName>
  - <cprelement>
      <cprElementCriteria>hasScoreInterpretation</cprElementCriteria>
      <cprElementCue>MigrationOfPain</cprElementCue>
      <cprElementScore>1</cprElementScore>
    </cprelement>
  - <cprelement>
      <cprElementCriteria>isPresent</cprElementCriteria>
      <cprElementCue>MigrationOfPain</cprElementCue>
      <cprElementScore>true</cprElementScore>
    </cprelement>
  - <cprelement>
      <cprElementCriteria>hasScoreInterpretation</cprElementCriteria>
      <cprElementCue>Anorexia</cprElementCue>
      <cprElementScore>1</cprElementScore>
    </cprelement>
  - <cprelement>
      <cprElementCriteria>isPresent</cprElementCriteria>
      <cprElementCue>Anorexia</cprElementCue>
      <cprElementScore>true</cprElementScore>
    </cprelement>
  - <cprelement>
      <cprElementCriteria>hasScoreInterpretation</cprElementCriteria>
      <cprElementCue>Nausea</cprElementCue>
      <cprElementScore>1</cprElementScore>
    </cprelement>
  - <cprelement>
      <cprElementCriteria>isPresent</cprElementCriteria>
      <cprElementCue>Nausea</cprElementCue>
      <cprElementScore>true</cprElementScore>
    </cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
  + <cprelement>
</cpRs>
```

Figure 3: XML generated from evidence service to provide criteria for the Alvarado Score rule.

../ClinicalEvidenceRESTService/interfaces/query
/cprs/Appendicitis
../ClinicalEvidenceRESTService/interfaces/query
/cprs/AlvaradoScore1_0
../ClinicalEvidenceRESTService/interfaces/query
/cprs/score/AlvaradoScore1_0

At present, the actual third party tool consumer would implement a web service client to provide the logic to compare appropriate EHR patient coded data RFEs and cues to the information returned by the service. Future work will parameterise the evidence service to allow submission of patient data as XML directly to the web service which will do the evidence comparison itself, returning a CPR result based on the patient data provided.

5 Discussion

A core requirement for the development of the CPR model was that it be a generalisable representation of the common structure of CPRs and not just suitable for the representation of specific examples of rules as found in literature. The efficacy of using CPRs as tools to be deployed in decision support systems has been shown to be effective but focussed on implementing specific instances of CPRs rather than supporting their more general usage through a service based knowledgebase [31]. We have used the model to represent 41 clinical prediction rules relating to 20 diagnoses including the Finnish Diabetes Risk Score [32], the Edwards Score [33] (tuberculosis) and the Little Symptom rule [34] (urinary tract infection).

In considering how this model relates to other initiatives to represent electronic clinical guidelines it is important to consider the original definition of a CPR previously provided. Each CPR is defined to be a discreet independent clinical tool to be used in its own right with respect to a particular patient. They do not attempt to define a complex clinical workflow or series of clinical steps to be implemented. From this point of view they are potentially useful tools to support decision-making in primary care where time pressures apply to consultations with each patient. As such, they could be considered to be either stand alone tools or are analogous to decision points found in more complex electronic guidelines that do define computable workflows, such as Guideline Interchange Format (GLIF) or the Guideline Elements Model (GEM) [35, 36].

The previous definition of a CPR also allows for an optional clinical decision or action to be taken based on the score outcome of the rule (sometimes then referred to as a Clinical Decision Rule). It was considered to be out of the scope of this work to represent these clinical decisions as computable entities in their own right and they have been treated as informational textual descriptions in the ontology e.g. "Surgery". It could be possible though to represent these decisions as separate concepts in their own right within the ontology e.g. CPRClinicalDecision. The workflow content of these clinical decisions could be modelled separately as GLIF or GEM based guidelines with an appropriate reference or link from our ontology concepts.

There are limitations to this work because the TRANSFoRm project as a whole is still a work in progress. The future development of the clinical decision support system that consumes our evidence service will be necessary to do a full clinical validation of the models that we propose here. What we have presented here is a conceptual validation of the ontology structure and the implementation in a way that supports system interoperability (through recognised data representation standards such as XML, JSON and RDF) along with semantic interoperability (through the use of the TRANSFoRm vocabulary service).

6 Conclusion

The research described in this paper can encourage the wider use and acceptance of clinical prediction rules by clinicians in three ways; by making CPRs more accessible and searchable than literature equivalents; through provision of a computable representation that allows for development of versioned rules from data mined sources of aggregated primary care data that are more sensitive to clinicians own patient populations; through provision of a web service allowing the deployment of CPRs as part of third party decision support tools linked to EHRs to facilitate easier use and execution.

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References

[1] Keogh C, Wallace E, O'Brien KK, Murphy PJ, Teljeur C, McGrath B, Smith SM, Doherty N, Dimitrov BD, Fahey T. Optimized retrieval of primary care clinical prediction rules from MEDLINE to establish a Web-based register. Journal of Clinical Epidemiology 2011;64(8):848-60.

[2] Reilly BM, Evans AT. Translating clinical research into clinical practice: impact of using prediction rules to make decisions. Annals of Internal Medicine 2006;144(3):201 .

[3] Wallace, E., Smith, S., Perera-Salazar, R., Vaucher, P., McCowan, C., Collins, G., Verbakel, J., Lakhanpaul, M. and Fahey, T. Framework for the impact analysis and implementation of Clinical Prediction Rules (CPRs). BMC Medical Informatics and Decision Making, 11, 1 2011), 62.

[4] Chunilal, S. D., Eikelboom, J. W., Attia, J. and et al. Does this patient have pulmonary embolism? JAMA, 290, 21 2003, 2849-2858.

[5] The Doctor's Toolbag [Internet]. British Medical Journal [cited 31 July 2013]. Available from http://group.bmj.com/products/mobile-apps/doctors-toolbag-iphone-app

[6] Lang ES, Wyer PC, Haynes RB. Knowledge Translation: Closing the Evidence-to-Practice Gap. Annals of Emergency Medicine 2007;49(3):355-363.

[7] Keogh C, Fahey T. Clinical prediction rules in primary care: what can be done to maximise their implementation? Clinical Evidence [Internet] 2010 [cited 31 July 2013]. Available from http://www.clinicalevidence.com/x/mce/file/05-10-10.pdf

[8] Roshanov P, Misra S, Gerstein H, Garg A, Sebaldt R, Mackay J, Weise-Kelly L, Navarro T, Wilczynski N, Haynes RB and others. Computerized clinical decision support systems for chronic disease management: A decision-maker-researcher partnership systematic review. Implementation Science 2011;6(1):92.

[9] TRANSFoRm Project Homepage [Internet]. TRANSFoRm project [cited 31 July 2013]. Available from http://www.transformproject.eu

[10] Alvarado A. A practical score for the early diagnosis of acute appendicitis. Annals of Emergency Medicine 1986;15(5):557-64.

[11] Ohle R, O'Reilly F, O'Brien KK, Fahey T, Dimitrov BD. The Alvarado score for predicting acute appendicitis: a systematic review. BMC Medicine 2011;9:139.

[12] McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature. JAMA: the journal of the American Medical Association 2000;284(1):79-84.

[13] Falk G, Fahey T. Clinical prediction rules. British Medical Journal 2009;339.

[14] Kostopoulou O. Diagnostic errors: Psychological theories and research Implications. In: Hurwitz B, Sheikh A, editors. Health Care Errors and Patient Safety: Wiley Online Library; 2009. p 95-111.

[15] Kostopoulou O, Delaney BC, Munro CW. Diagnostic difficulty and error in primary care–a systematic review. Family Practice 2008;25(6):400-13.

[16] Wagner JM, McKinney WP, Carpenter JL. Does This Adult Patient Have Appendicitis? McGraw-Hill Medical, City, 2009. p 53-63.

[17] Fernandez-Lopez M, Gomez A. Overview and analysis of methodologies for building ontologies. The Knowledge Engineering Review 2002;17(02):129-156.

[18] Gruninger M, Fox MS. Methodology for the Design and Evaluation of Ontologies. In Proceedings of the Workshop on Basic Ontological Issues in Knowledge Sharing, IJCAI (Vol. 95).

[19] TRANSFoRm Vocabulary Service [Internet]. University of Birmingham [cited 31 July 2013]. Available from http://www.eutransformvs.bham.ac.uk:8081/evs/

[20] Unified Medical Language System [Internet]. U.S. National Library of Medicine [cited 20 December 2013]. Available from http://www.nlm.nih.gov/research/umls

[21] International Classification of Primary Care Version 2 [Internet]. World Health Organisation [cited 20 December 2013]. Available from http://www.who.int/classifications/icd/adaptations/icpc2/en/

[22] SNOMED Clinical Terms [Internet]. U.S. International Health Terminology Standards Organisation [cited 20 December 2013]. Available from http://www.ihtsdo.org/snomed-ct/

[23] International Classification of Diseases Version 10 [Internet]. U.S. World Health Organisation [cited 20 December 2013]. Available from http://www.who.int/classifications/icd/en/

[24] Web Ontology Language [Internet]. World Wide Web Consortium [cited 31 July 2013]. http://www.w3.org/TR/owl2-overview/

[25] Resource Description Framework [Internet]. World Wide Web Consortium [cited 31 July 2013]. Available from http://www.w3.org/RDF/

[26] Protégé Homepage [Internet]. Stanford University [cited 31 July 2013]. Available from http://protege.stanford.edu/

[27] Sesame [Internet]. OpenRDF [cited 31 July 2013]. Available from http://www.openrdf.org/index.jsp

[28] SPARQL Standard [Internet]. World Wide Web Consortium [cited 31 July 2013]. Available from http://www.w3.org/TR/rdf-sparql-query/

[29] Fielding, R. T. and Taylor, R. N. Principled design of the modern Web architecture. ACM Transactions on Internet Technology (TOIT), 2, 2 2002), 115-150.

[30] Jersey Web Services in Java [Internet]. Oracle Corporation [cited 31 July 2013]. Available from https://jersey.java.net/

[31] McGinn, T.G., McCullagh, L., Kannry, J., Knaus, M., Sofianou, A., Wisnivesky, JP. Efficacy of an evidence-based clinical decision support in primary care practices: a randomized clinical trial. JAMA Internal Medicine 2013;173(17):1584-91

[32] Soriguer, F., Valdes, S., Tapia, M. J., Esteva, I., Ruiz de Adana, M. S., Almaraz, M. C., Morcillo, S., Garcia Fuentes, E., Rodriguez, F. and Rojo-Martinez, G. Validation of the FINDRISC (FINnish Diabetes RIsk SCore) for prediction of the risk of type 2 diabetes in a population of southern Spain. Pizarra Study]. Medina Clinica (Barc), 138, 9 (Apr 14 2012), 371-376.

[33] Narayan, S., Mahadevan, S. and Serane, V. T. Keith Edwards score for diagnosis of tuberculosis. Indian Journal of Pediatrics, 70, 6 (Jun 2003), 467-469.

[34] Bent, S., Nallamothu, B. K., Simel, D. L., Fihn, S. D. and Saint, S. Does this woman have an acute uncomplicated urinary tract infection? JAMA, 287, 20 (May 22-29 2002), 2701-2710.

[35] Wang, D., Peleg, M., Tu, S. W., Boxwala, A. A., Ogunyemi, O., Zeng, Q., ... Shortliffe, E. H. Design and implementation of the GLIF3 guideline execution engine. Journal of biomedical informatics 2004 37(5), 305-318.

[36] Guideline Elements Model [Internet]. Yale School of Medicine [cited 20 December 2013]. Available from http://gem.med.yale.edu/default.htm