Implementation of Clinical Decision Support Services to Detect Potential Drug-Drug Interaction using Clinical Quality Language

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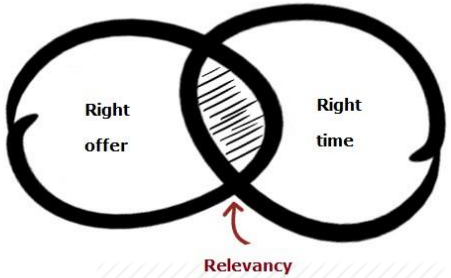
Drug - Drug Interactions

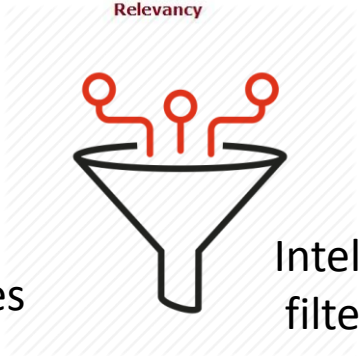
… can be mitigated

… by CDS via alerts

with the relevant reference information



presented at appropriate times



Intelligently filtered

Drug - Drug Interactions

- no complete source of PDDI
- no broadly accepted standards

- > most EHR vendors either develop their own internal rule engines based on their custom standards

Drug - Drug Interactions

can not be EXCHANGE

can not be REVIEW

can not be REUSE

A Minimum Representation of Potential Drug-Drug Interaction Knowledge and Evidence - Technical and User-centered Foundation

Final Community Group Report 18 May 2019

Latest editor's draft:

https://w3id.org/hclscg/pddi

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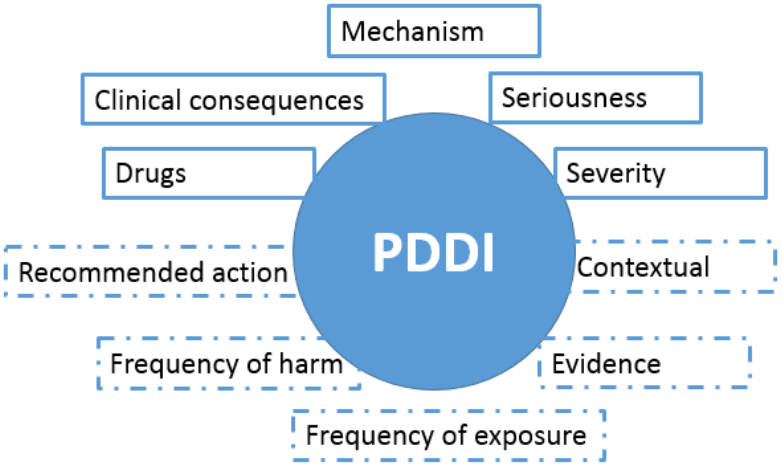
- W3C Standards Track
- a minimum information model for information about potential drug-drug interaction
- Final aim is to improve the usefulness of the artifacts within clinical workflows

https://www.w3.org/2019/05/pddi/index.html

PDDI Minimum Information Model



Drugs Involved

Clinical Consequences

Seriousness

Mechanism of Interaction and Evidence

Potential Drug-Drug Interaction between Digoxin 0.25 MG Oral Tablet and Cyclosporine 50 MG Oral Capsule

Increased risk of digitalis toxicity that may lead to cardiac arrhythmias

Digitalis toxicity is a serious potential clinical consequence because it can result in death, life-threatening hospitalization, and disability.

The mechanism of this interaction appears to be mediated through P-glycoprotein inhibition by cyclosporine. P-glycoprotein is a major transporter for digoxin efflux. Reference

Contextual Information, Recommended Actions, and Evidence

Patient received Digoxin #90 35 days ago.
The most recent Digoxin level was abnormal (2.3 ng/mL – 23 days ago)

Cancel Cyclosporine order

Accept Decline

Cancel Digoxin and start Cyclosporine

Accept Decline

Patient has moderate hypokalemia picked up a prescription for furosemide 20mg #90 81 days ago

Discontinue furosemide 20mg

Accept Reference

Add potassium 20meq daily

Accept Reference

HL7 FHIR Potential Drug-Drug Interaction (PDDI) CDS IG : STU Ballot 1

HL7 International

Home | Getting Started | Documentation | Artifacts | Downloads | Examples | Profiles | Terminology | Test Data

Potential Drug-Drug Interaction (PDDI) Clinical Decision Support (CDS) (v0.1.0: STU 1 Ballot 1) based on FHIR v3.5.0. See the Directory of published versions

6.0.0 Documentation

6.1.0 Preliminaries

This section contains documentation on how to implement PDDI CDS artifacts from a clinical and technical perspective. Implementation details are described using two specific knowledge artifacts as examples.

6.2.0 CPOE Workflow Hooks

Figure 1 depicts hook triggers for Level 1 and 2 Implementations. The primary difference in the Level 2 Implementation is the additional hook and defining the initial trigger at the top of the CPOE workflow. The Level 1 Implementation follows the CDS Hooks `medication-prescribe` specification, which does not necessarily define the triggering event.

Figure 1: Level 1 versus Level 2 Implementation Hooks

Contents

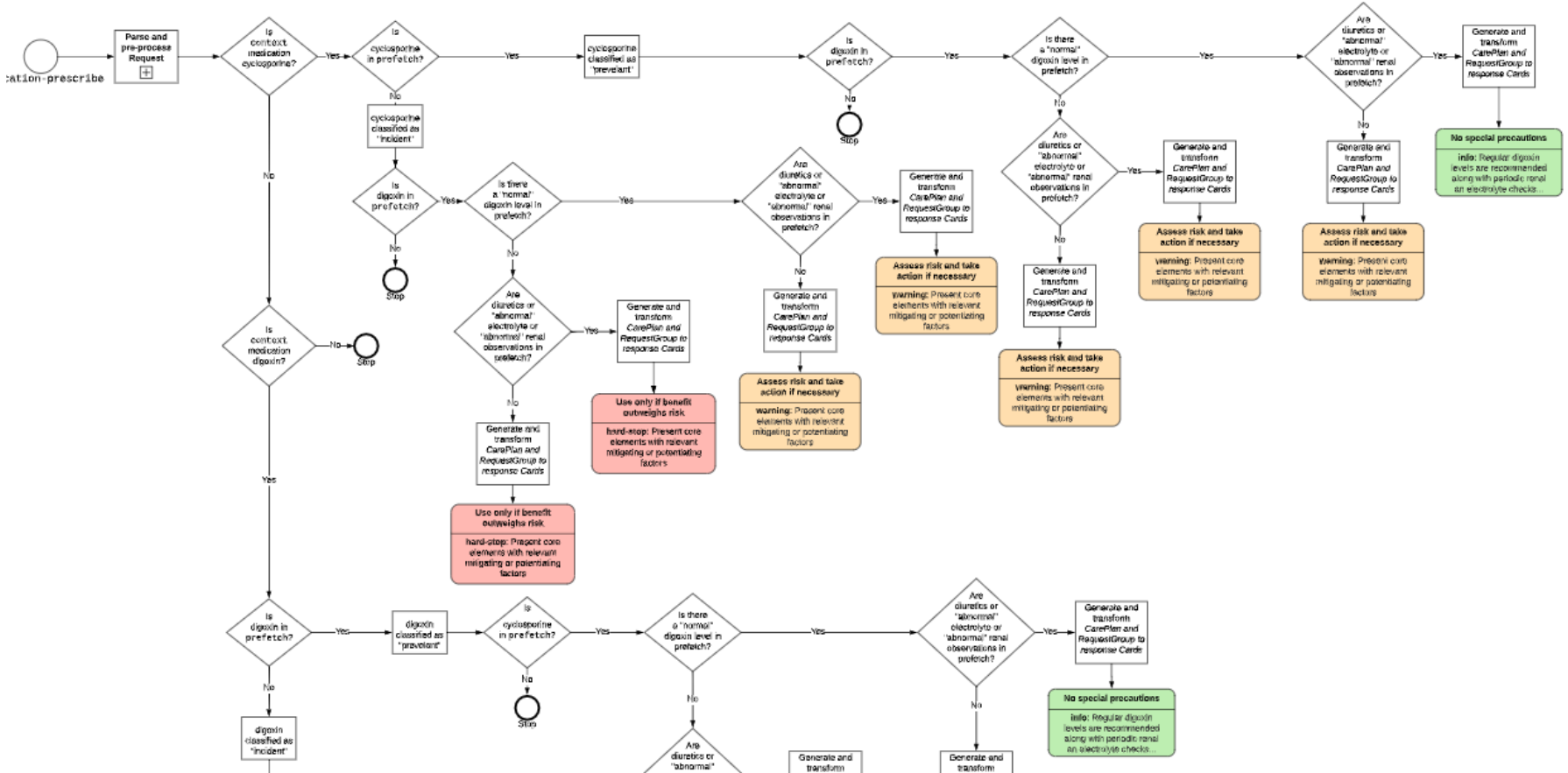
http://hl7.org/fhir/uv/pddi/2018Sep/documentation.html

Focus of the Study

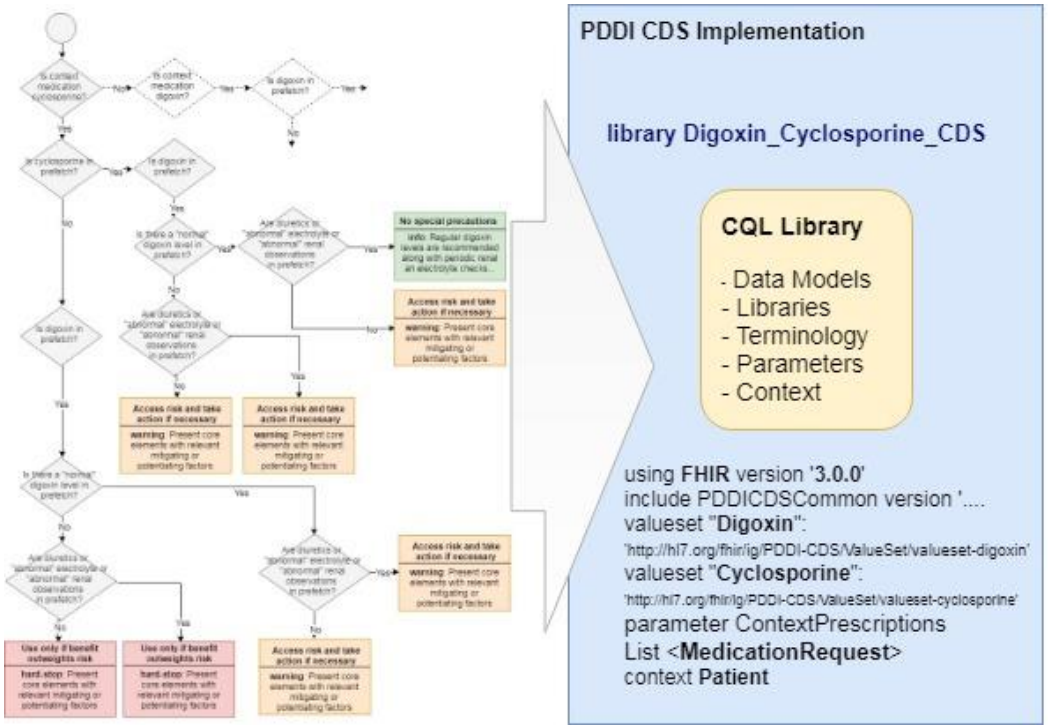
- ✓ demonstrate the use of the PDDI minimum information model
- ✓ present an example implementation of representing PDDI logic in CQL
- ✓ execution of rules by using the FHIR Clinical Reasoning module
- ✓ develop a prototype detects a PDDI and provides alerts using CDS Hooks to EHR systems that subscribe to the CDS services.

- We selected Digoxin-Cyclosporine and Warfarin-NSAIDs as use cases because they are non-trivial PDDIs for which alerts can be contextualized to specific patient cases.
- We use open source libraries including HAPI FHIR, CQL Evaluation Engine and CQF Ruler FHIR Clinical Reasoning module

Decision Flow

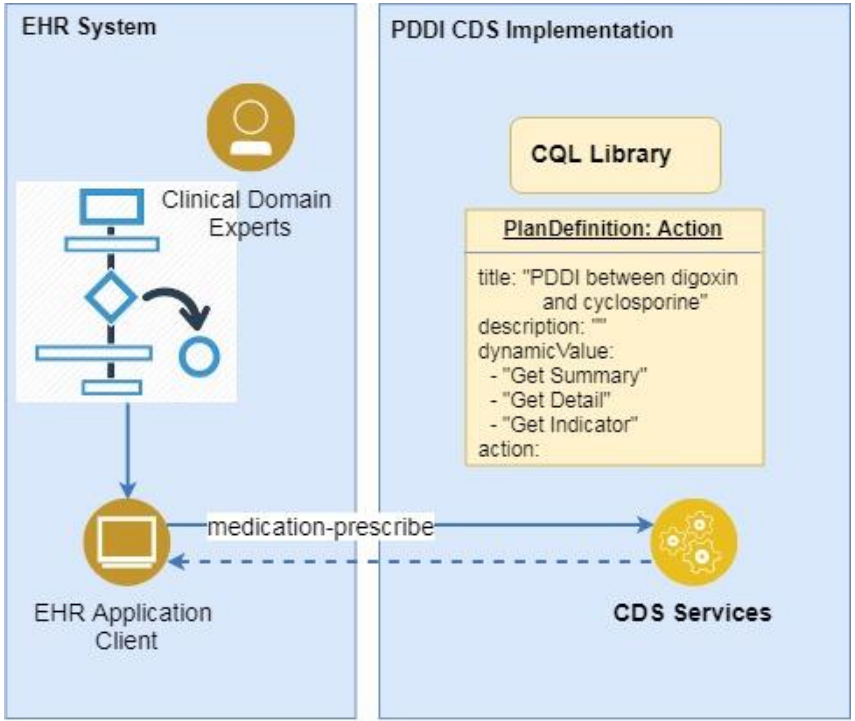


Clinical Quality Language (CQL)



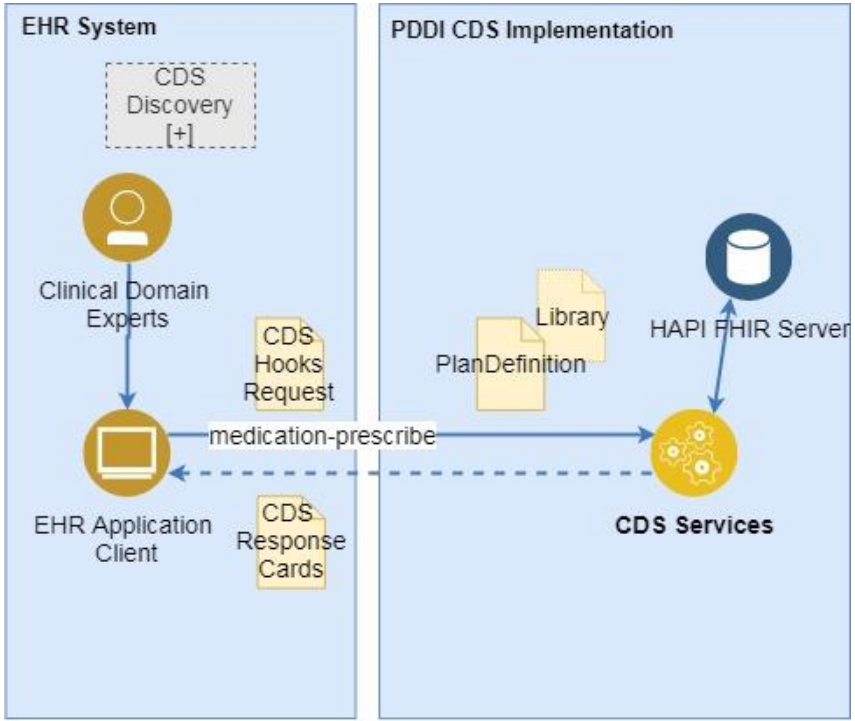
- a high-level, domain-specific query language
- can represent the PDDI information
- combining rules to describe the available data
- supports different data models – FHIR

Services Based Architecture



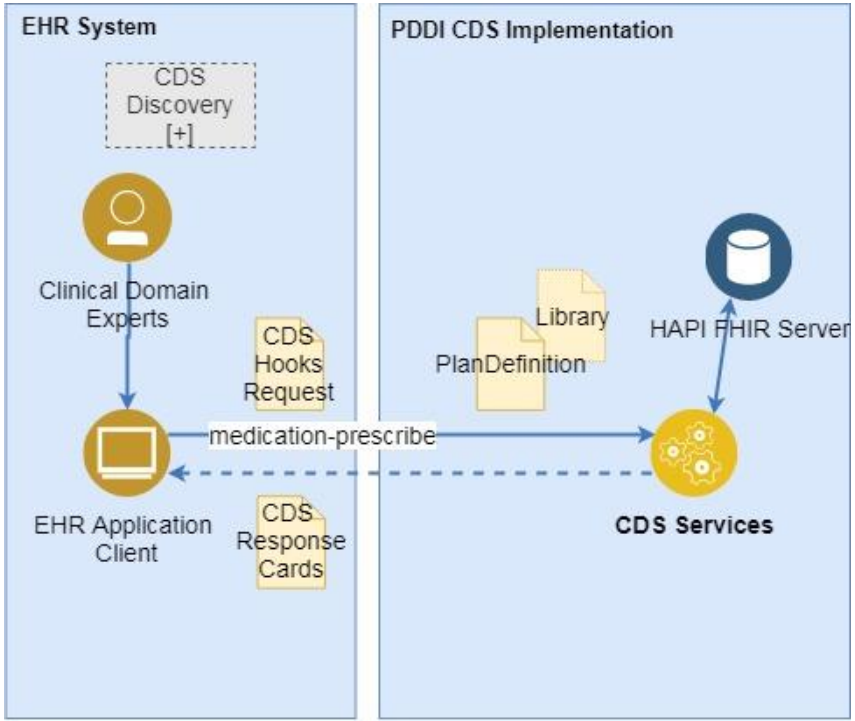
- CDS Service: near real-time support as remote services
- Context based CDS
  - medication-select: at the time of selecting a medication
  - medication-prescribe: at order authorization
- PlanDefinition: definition of a service (stored in FHIR server)
- Basic actions
  - registering for CDS services,
  - calling those services,
  - receiving the response : cards

CDS Service Discovery



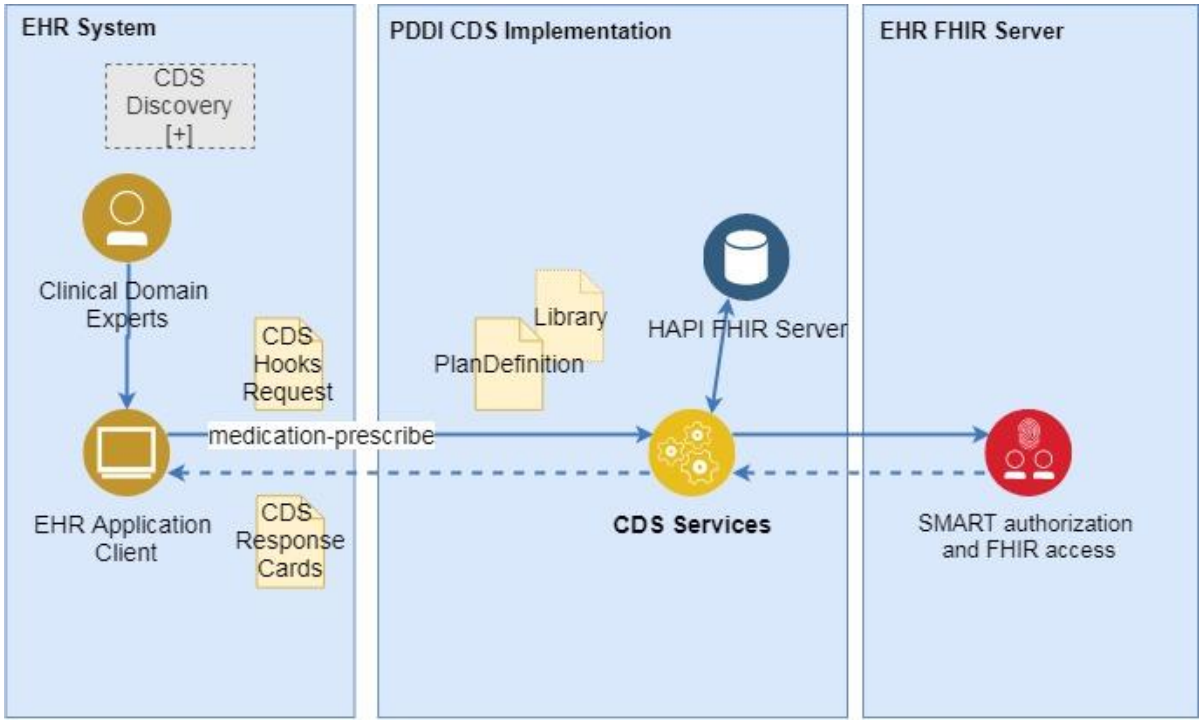
- Discovery Endpoint (CDS Services) :
- Hosted at a stable endpoint, i.e.
  - {baseUrl}/cds-services
- allows EHR to discover all available CDS services
  - {baseUrl}/cds-services/warfarin-nsaids-cds
  - {baseUrl}/cds-services/digoxin-cyclosporine-cds
- Each service contains:
  - Description of the service
  - When it should be invoked
  - Any data that is requested to be prefetched
- CDS hooks: service registry

CDS Hooks



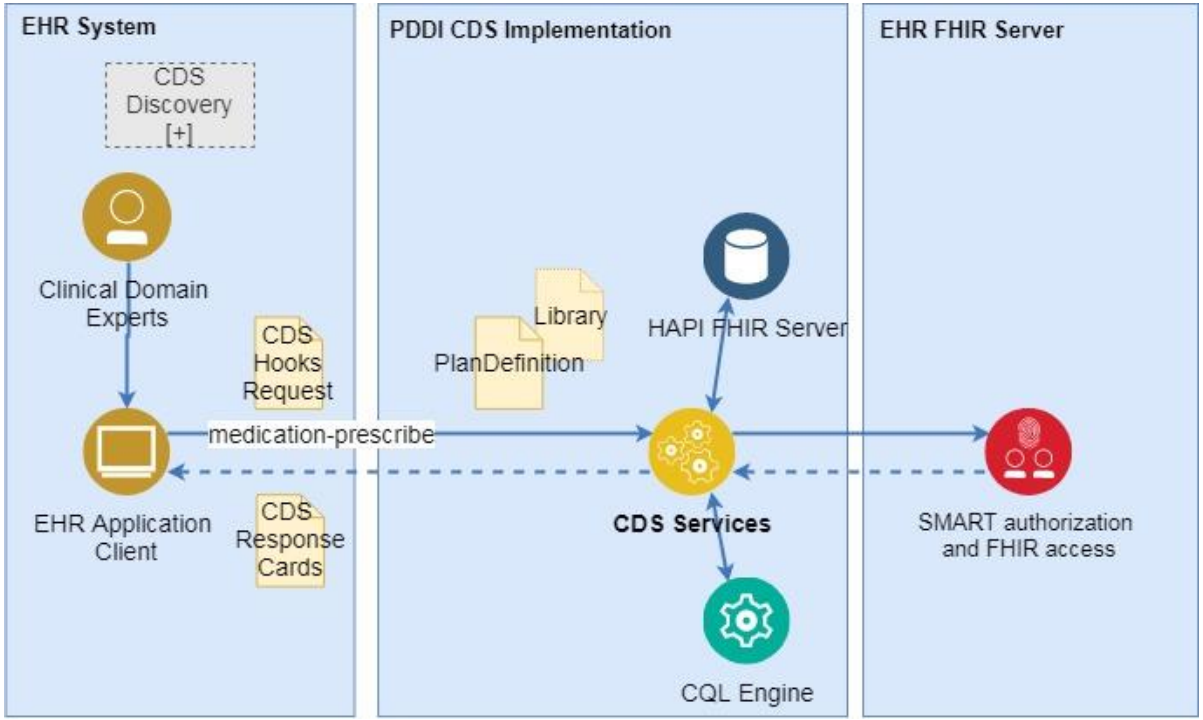
1) User activity inside the EHR triggers CDS hooks in real-time.
2) When a triggering activity occurs, the EHR notifies each CDS service registered for the activity. Each service gets:
   - context parameter: basic details about the EHR
   - prefect template parameter: service-specific data are required
3) Each CDS service can return any number of cards in response to the hook.

Getting Data: FHIR



- when a service is invoked, the request contains pre-queried data, called prefetched
- If the CDS service does not receive prefetch data in the request, it will query the EHR FHIR Server via network call with the authentication given by the EHR Application Client.

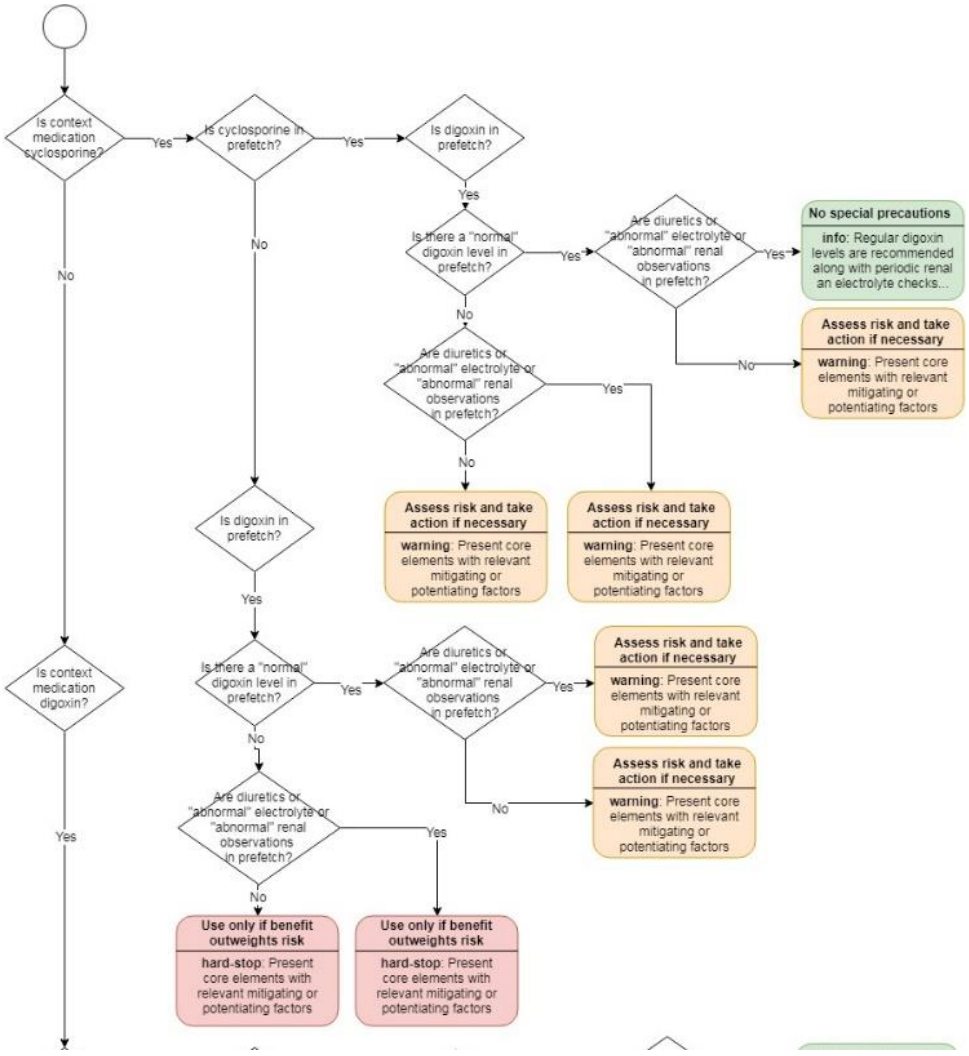
CQL Engine



- PlanDefinition and Library resources are loaded from FHIR server
- the CQL logic in the Library resource is decoded
- evaluated by CQL engine
- CDS Response Cards are generated and returned to the client.

Use Case

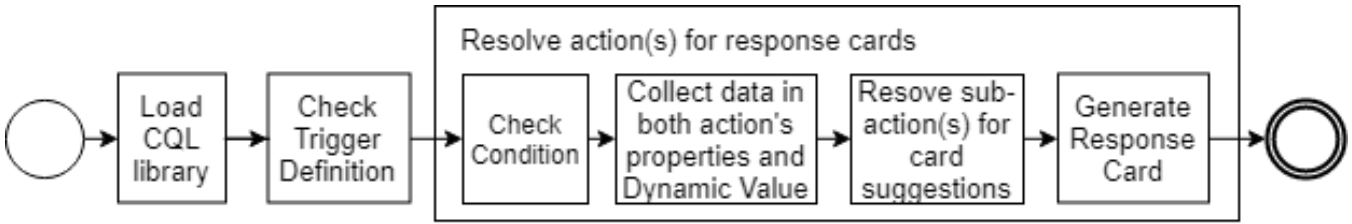
- Digoxin – Cyclosporine
- Warfarin – NSAIDs



Implementation

Plan Definition:

- Definition of the service served as a guide for the incoming request.
- Contains a set of definition including
  - Library, e.g., Library/digoxin-cyclosporine-cds
  - Trigger Definition, e.g., medication-prescribe
  - Condition, e.g., “Inclusion Criteria”
  - Actions
  - Dynamic Value, e.g., “Get Base Summary” “Get Base Detail” “Get Base Indicator”

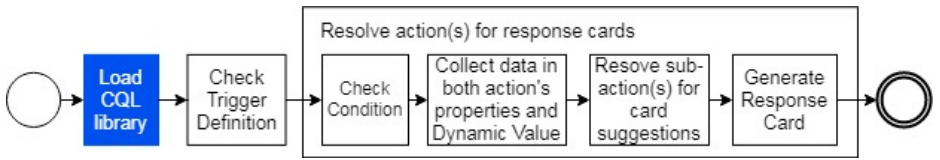


Implementation: CQL

A set of declarations, including data model, included libraries, valuesets, parameters, and context, provide information about the library.

```
library Digoxin_Cyclosporine_CDS version '1.0'

using FHIR version '3.0.0'

include PDDI_CDS_Common version '1.0' called Common

valueset "Digoxin": 'http://hl7.org/fhir/ig/PDDI-CDS/ValueSet/valueset
-digoxin'
valueset "Cyclosporine": 'http://hl7.org/fhir/ig/PDDI-CDS/ValueSet/val
ueset-cyclosporine'
...

parameter ContextPrescriptions List<MedicationRequest>

context Patient
```

- Library declaration
- Data models
- Included libraries
- Terminology declaration
- Parameter
- Context



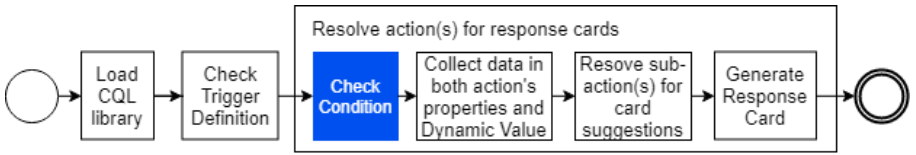
Implementation: CQL

Condition: “Inclusion Criteria”

```
define "Inclusion Criteria":
  (
    "Is Context medication cyclosporine"
      and "Is digoxin in prefetch"
  )
  or (
    "Is Context medication digoxin"
      and "Is cyclosporine in prefetch"
  )
```

```
define "Is Context medication cyclosporine":
  exists ("Cyclosporine Prescription")

define "Cyclosporine Prescription":
  ContextPrescriptions P
    where Common.ToCode(P.medication.coding[0]) in
"Cyclosporine"
```

```
define "Is digoxin in prefetch":
  exists ("Digoxin Rx")

define "Digoxin Rx":
  [MedicationRequest: "Digoxin"] MR
    where MR.authoredOn.value in Interval[Today() -
100 days, null]
```

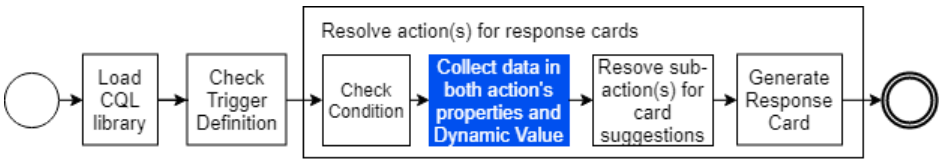


Implementation

Warning card

Dynamic Value,

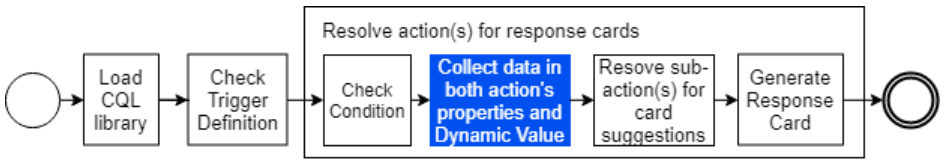
- "Get Base Summary"
- "Get Base Detail"
- "Get Base Indicator"
  - e.g., "warning", "hard-stop", "info"



Implementation: CQL

Dynamic Value: “Get Base Summary”

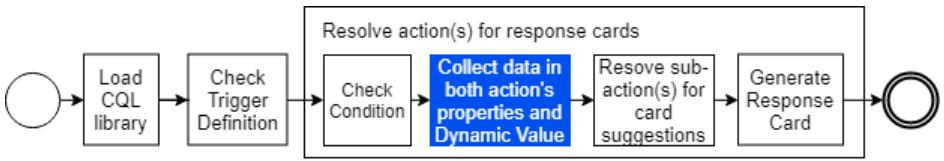
```
define "Get Base Summary":
  'Potential Drug-Drug Interaction between digoxin ('
    + (
      if "Is Context medication digoxin"
        then Common.GetDrugNames("Digoxin Prescription")
      else Common.GetDrugNames("Digoxin Rx")
    )
    + ') and cyclosporine ('
    + (
      if "Is Context medication cyclosporine"
        then Common.GetDrugNames("Cyclosporine Prescription")
      else Common.GetDrugNames("Cyclosporine Rx")
    )
    + ')'
```



Implementation: CQL

Dynamic Value: “Get Base Detail”

```
define "Get Base Detail":
  'Increased risk of digoxin toxicity. Assess risk and take action if necessary. \nDigoxin toxicity
is potentially serious. The clinical consequences may include anorexia, nausea, vomiting, visual
changes, and cardiac arrhythmias. \nThe mechanism of this interaction appears to be mediated through
P-glycoprotein inhibition by cyclosporine. P-glycoprotein is a major transporter for digoxin efflux.
'
```



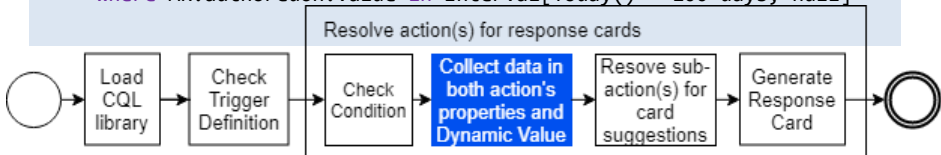
Implementation: CQL

Dynamic Value: “Get Base Indicator”

```
define "Get Base Indicator":
  if "Is Context medication cyclosporine" then
    if "Is cyclosporine in prefetch" then
      if "Is there a normal digoxin level in prefetch" then
        if "Are diuretics or abnormal electrolyte or abnormal
renal observations in prefetch"
          then 'info'
        else 'warning'
      else 'warning'
    else
      if "Is there a normal digoxin level in prefetch" then
        then 'warning'
      else 'hard-stop'
  else
    if "Is digoxin in prefetch" then
      if "Is there a normal digoxin level in prefetch" then
        if "Are diuretics or abnormal electrolyte or abnormal
renal observations in prefetch"
          then 'info'
        else 'warning'
      else 'warning'
    else 'warning'
```

```
define "Is there a normal digoxin level in prefetch":
  exists ("Normal Digoxin Observation")

define "Normal Digoxin Observation":
  Last (
    [Observation: "Digoxin LOINC"] O
      where O.effective.value in Interval[Today() - 30 days, null]
        and Common.ToQuantity(O.value) < 0.9 'ng/mL'
      sort by effective.value
  )
```

```
define "Are diuretics in prefetch":
  exists ("Aldosterone Antagonists Rx")
    or exists("Loop Diuretics Rx")

define "Aldosterone Antagonists Rx":
  [MedicationRequest: "Aldosterone Antagonists"] MR
    where MR.authoredOn.value in Interval[Today() - 100 days, null]

define "Loop Diuretics Rx":
  [MedicationRequest: "Loop Diuretics" MR
    where MR.authoredOn.value in Interval[Today() - 100 days, null]
```



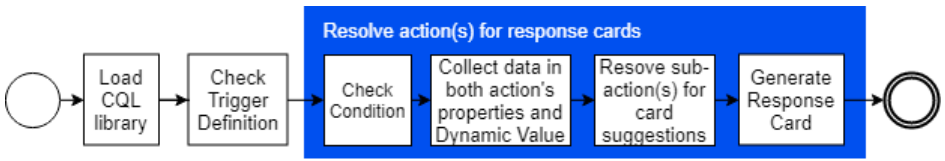
Implementation: Response Cards

Plan Definition - Action

```
"action": [
  {
    "title": "Potential Drug-Drug Interaction between
digoxin (product) and cyclosporine (product)",
    "description": "Increased risk of digoxin toxicity...",
    "dynamicValue": [... //Get Summary, Detail, Indicator]
    "action": [
      {
        "label": "Assess risk and take action if
necessary."
      }
    ]
  },
  ...

]
```

Response Card

```
{ "cards": [
    {
      "summary": "Potential Drug-Drug Interaction between
warfarin (Warfarin Sodium 0.5 MG Oral Tablet) and NSAID
(Ketorolac Tromethamine 10 MG Oral Tablet).",
      "indicator": "warning",
      "detail": "Increased risk of bleeding...",
      "suggestions": [
        {
          "label": "Assess risk and take action if
necessary."
        }
      ]
    },
    ...
] }
```

Implementation: Response Card

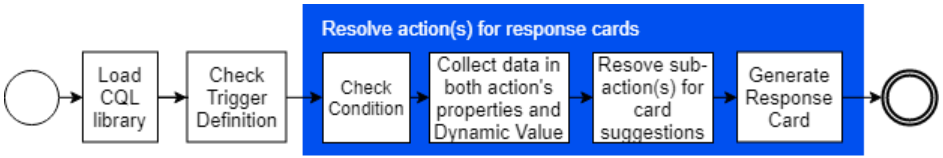
```
{ "cards": [
    {
      "summary": "Potential Drug-Drug Interaction between
warfarin (Warfarin Sodium 0.5 MG Oral Tablet) and NSAID
(Ketorolac Tromethamine 10 MG Oral Tablet).",
      "indicator": "warning",
      "detail": "Increased risk of bleeding...",
      "suggestions": [
        {
          "label": "Assess risk and take action if
necessary."
        },
        ...
      ]
    },
    ...
] }
```

Potential Drug-Drug Interaction between warfarin (Warfarin Sodium 0.5 MG Oral Tablet) and NSAID (Ketorolac Tromethamine 10 MG Oral Tablet).

Source: Potential Drug-Drug Interaction Clinical Decision Support

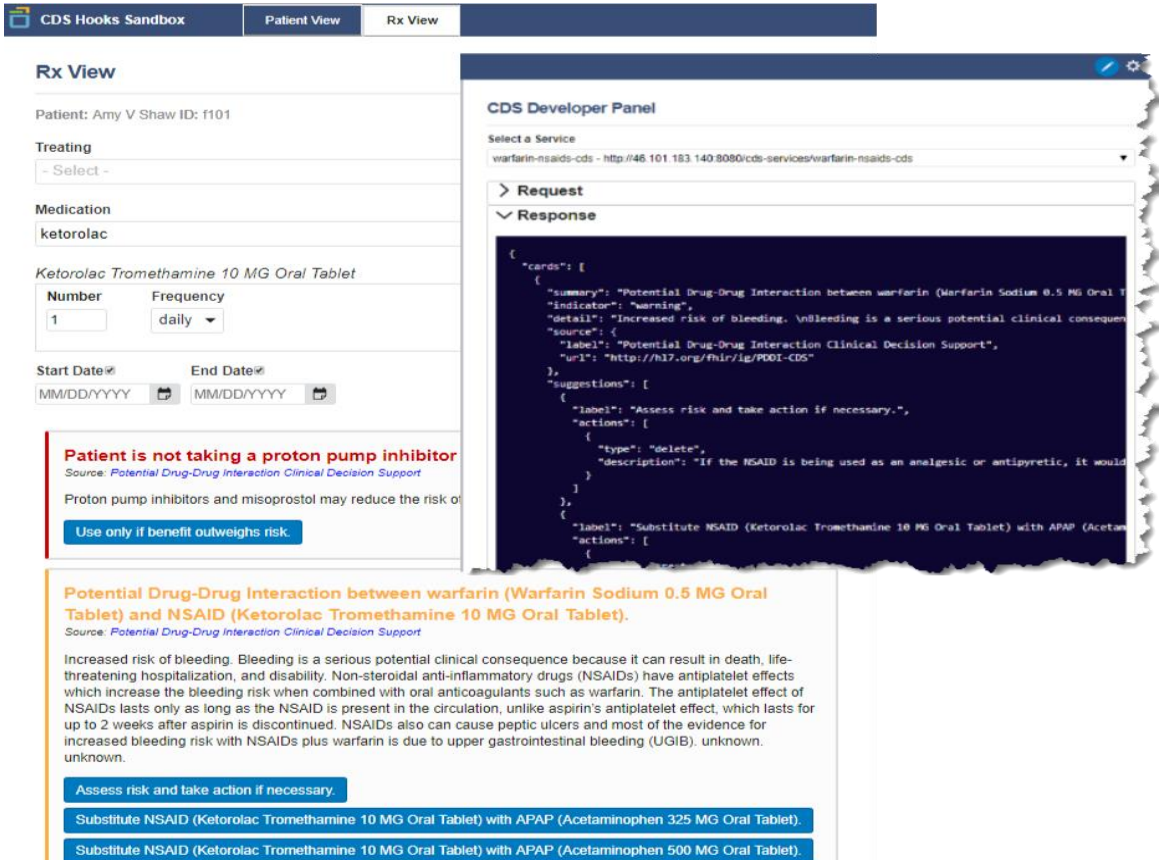
Increased risk of bleeding. Bleeding is a serious potential clinical consequence because it can result in death, life-threatening hospitalization, and disability. Non-steroidal anti-inflammatory drugs (NSAIDs) have antiplatelet effects which increase the bleeding risk when combined with oral anticoagulants such as warfarin. The antiplatelet effect of NSAIDs lasts only as long as the NSAID is present in the circulation, unlike aspirin's antiplatelet effect, which lasts for up to 2 weeks after aspirin is discontinued. NSAIDs also can cause peptic ulcers and most of the evidence for increased bleeding risk with NSAIDs plus warfarin is due to upper gastrointestinal bleeding (UGIB). unknown. unknown.

- Assess risk and take action if necessary.
- Substitute NSAID (Ketorolac Tromethamine 10 MG Oral Tablet) with APAP (Acetaminophen 325 MG Oral Tablet).
- Substitute NSAID (Ketorolac Tromethamine 10 MG Oral Tablet) with APAP (Acetaminophen 500 MG Oral Tablet).



Evaluation

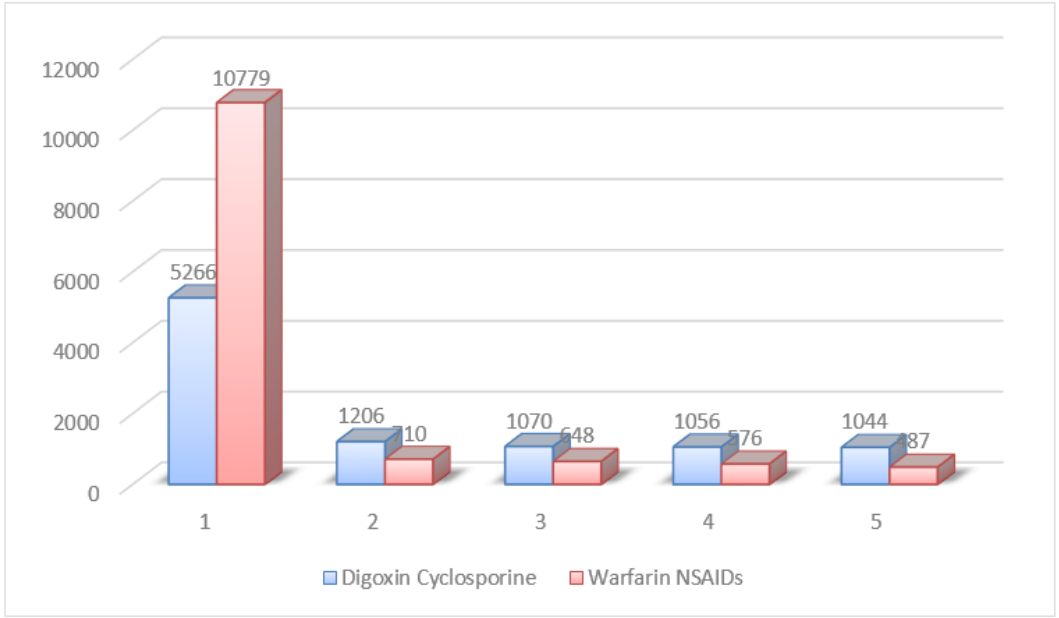
- The evaluation was done using CDS Hooks Sandbox tool developed by CDS Hooks team demonstrate how CDS Hooks would work with an EHR system.
- We performed the evaluation at the Connectathon held at the 32nd Annual Plenary & Working Group Meeting of HL7 held in September 2018-



Evaluation

Response time measurement in milliseconds for use cases in five consecutive times.

- a high amount of time is needed to process for the first request (due to no available cache data)
- The first request for Warfarin NSAIDs use case took up more time compared to the request for Digoxin Cyclosporine (due to the complexity)
- the response time for two use cases' request reduced steadily over time.



Conclusion

- Achievements:
  - We used CQL, FHIR, and CDS Hooks to implement PDDI CDS as a service.
  - Demonstrated the feasibility and that CQL was sufficiently expressive to cover to realistic use cases.
- Future Works:
  - Experiment with more data sets
  - Continue Level 2 implementation
  - Evaluate more on performances of CDS services

it matters since…

we are one step closer to

- REUSEABLE
- EXCHANEABLE
- AUDITABLE

PDDI rules

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