Epoch Ontological Framework to support Clinical Trial Management

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Overview

- Clinical trials are used to determine whether new drugs or treatments are both safe and effective.
- Complex clinical trials involve collaboration among many groups using different software applications.
- Lack of standardization and reduced efficiency leads to poor productivity.
- We are building an ontological framework called **Epoch** to improve semantic interoperability among clinical trial management applications.

The Immune Tolerance Network

- ITN is an international collaboration designed to accelerate the development of immune tolerance therapies
- Funds, plans, implements, monitors, and assesses investigator-initiated clinical trials of novel tolerance-promoting therapies in
  - Autoimmune diseases
  - Transplantation
  - Allergy and Asthma
- Provides services to undertake comprehensive mechanistic studies that complement each trial

Schedule of Events

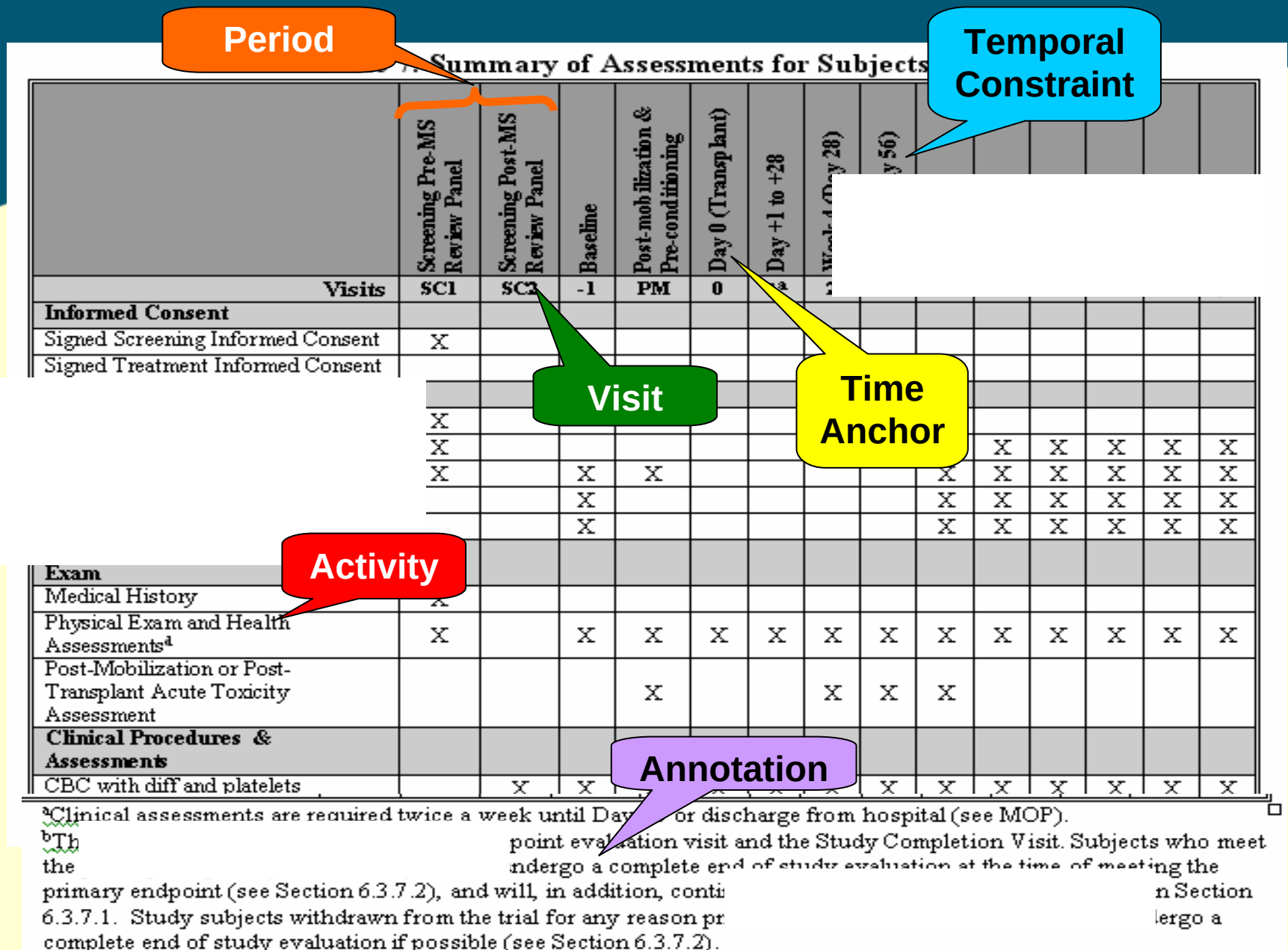
Table 7: Summary of Assessments for Subjects

Visits	Screening Pre-MS Review Panel SC1	Screening Post-MS Review Panel SC2	Baseline -1	Post-mobilization & Pre-conditioning PM	Day 0 (Transplant) 0	Day +1 to +28 1[a]	2	3	4	5	6	7	8	9[b]
Informed Consent														
Signed Screening Informed Consent	X													
			X											
	X													
	X								X	X	X	X	X	X
	X		X	X					X	X	X	X	X	X
			X						X	X	X	X	X	X
			X						X	X	X	X	X	X
Medical History and Physical Exam														
Medical History	X													
Physical Exam and Health Assessments[d]	X		X	X	X	X	X	X	X	X	X	X	X	X
Post-Mobilization or Post-Transplant Acute Toxicity Assessment				X			X	X	X					
Clinical Procedures & Assessments														
CBC with diff and platelets		X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Cli… ek until Day 28 or discharge from hospital (see MOP).

[b] The … visit is the study primary endpoint evaluation visit … who meet the primary endpoint (Section 3.2.1) should undergo a complete er… ng the primary endpoint (see Section 6.3.7.2), and will, in addition, continue to be followed on the schedule listed in Section 6.3.7.1. Study subjects withdrawn from the trial for any reason prior to the 60-month evaluation should undergo a complete end of study evaluation if possible (see Section 6.3.7.2).

Schedule of Events



Summary of Assessments for Subjects

Visits	Screening Pre-MS Review Panel SC1	Screening Post-MS Review Panel SC2	Baseline -1	Post-mobilization & Pre-conditioning PM	Day 0 (Transplant) 0	Day +1 to +28 [a]	[illegible] (Day 28)	[illegible] y 56)					
Informed Consent													
Signed Screening Informed Consent	X												
Signed Treatment Informed Consent													
	X												
	X								X	X	X	X	X
	X		X	X					X	X	X	X	X
			X						X	X	X	X	X
			X						X	X	X	X	X
Exam													
Medical History	X												
Physical Exam and Health Assessments[d]	X		X	X	X	X	X	X	X	X	X	X	X
Post-Mobilization or Post-Transplant Acute Toxicity Assessment				X			X	X	X				
Clinical Procedures & Assessments													
CBC with diff and platelets		X	X					X	X	X	X	X	X

[a]Clinical assessments are required twice a week until Day [illegible] or discharge from hospital (see MOP).

[b]Th [illegible] point eva[illegible]ation visit and the Study Completion Visit. Subjects who meet the [illegible] ndergo a complete end of study evaluation at the time of meeting the primary endpoint (see Section 6.3.7.2), and will, in addition, conti[illegible] n Section 6.3.7.1. Study subjects withdrawn from the trial for any reason pr[illegible] lergo a complete end of study evaluation if possible (see Section 6.3.7.2).

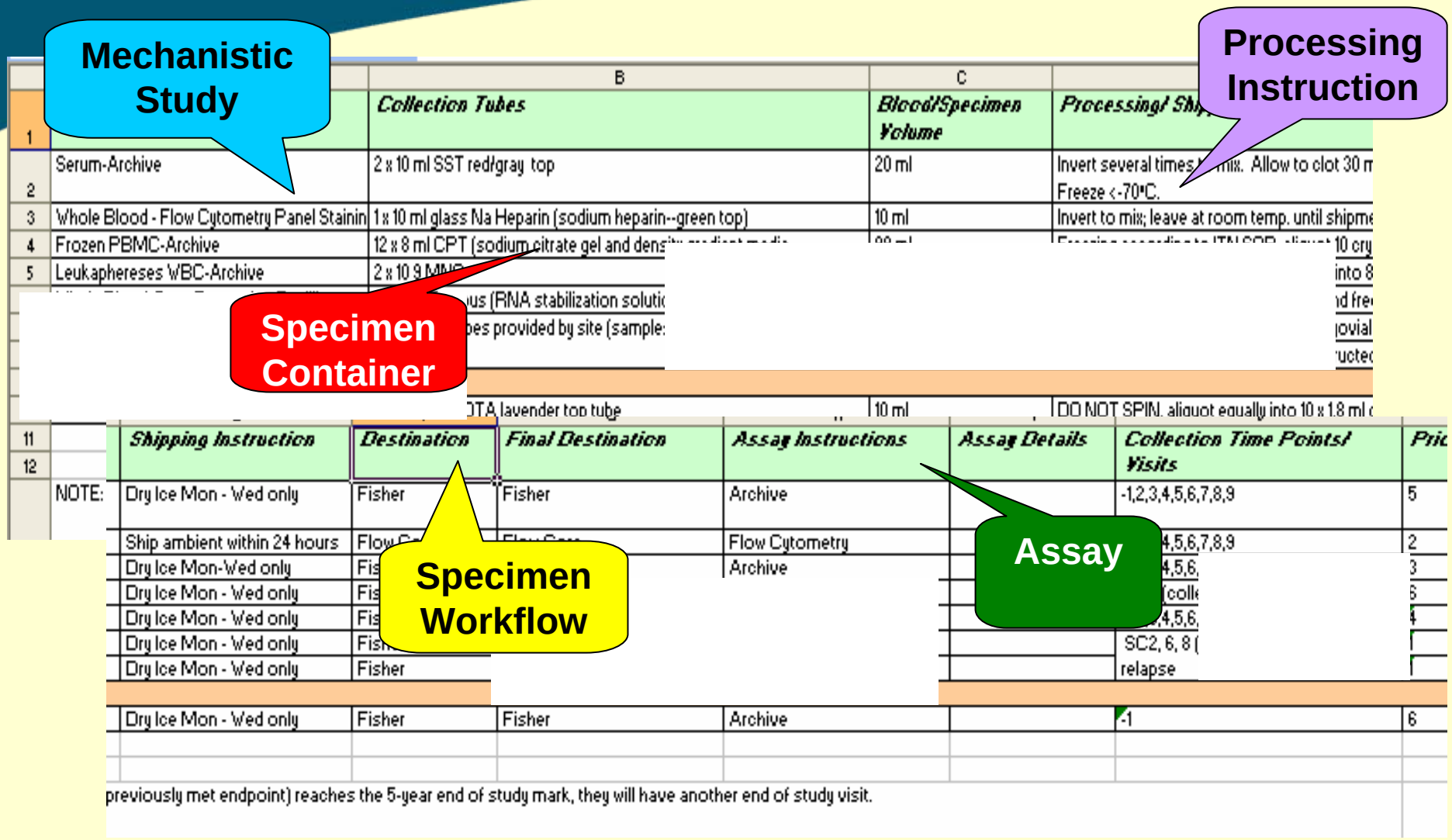
Specimen Table

	A	B	C	
1	***Specimen Name***	***Collection Tubes***	***Blood/Specimen Volume***	***Processing/ Shipping***
2	Serum-Archive	2 x 10 ml SST red/gray top	20 ml	Invert several times to mix. Allow to clot 30 m Freeze <-70°C.
3	Whole Blood - Flow Cytometry Panel Stainin	1 x 10 ml glass Na Heparin (sodium heparin--green top)	10 ml	Invert to mix; leave at room temp. until shipme
4	Frozen PBMC-Archive	12 x 8 ml CPT (sodium citrate gel and dens		10 cry
5	Leukaphereses WBC-Archive	2 x 10 9 MNC		into 8
		us (RNA stabilization soluti		d fre
		bes provided by site (sample		jovial
				ucte
		DTA lavender top tube	10 ml	DO NOT SPIN. aliquot equally into 10 x 1.8 ml c

		Shipping Instruction	***Destination***	***Final Destination***	***Assay Instructions***	***Assay Details***	***Collection Time Points/ Visits***	***Pric***
11								
12								
	NOTE:	Dry Ice Mon - Wed only	Fisher	Fisher	Archive		-1,2,3,4,5,6,7,8,9	5
		Ship ambient within 24 hours	Flow Core	Flow Core	Flow Cytometry		-1,2,3,4,5,6,7,8,9	2
		Dry Ice Mon-Wed only	Fisher	Fisher	Archive		-1,2,3,4,5,6,	3
		Dry Ice Mon - Wed only	Fisher				-1,6,8 (colle	3
		Dry Ice Mon - Wed only	Fisher				-1,2,3,4,5,6,	4
		Dry Ice Mon - Wed only	Fisher				SC2, 6, 8 (	
		Dry Ice Mon - Wed only	Fisher				relapse	
		Dry Ice Mon - Wed only	Fisher	Fisher	Archive		-1	6

previously met endpoint) reaches the 5-year end of study mark, they will have another end of study visit.

Specimen Table



	B	C	
1	Collection Tubes	Blood/Specimen Volume	Processing/ Shi
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		Ship ambient within 24 hours	Flow		Flow Cytometry		4,5,6,7,8,9	2
		Dry Ice Mon-Wed only	Fis		Archive		4,5,6,	3
		Dry Ice Mon - Wed only	Fis				(colle	3
		Dry Ice Mon - Wed only	Fis				4,5,6,	4
		Dry Ice Mon - Wed only	Fish				SC2, 6, 8 (	
		Dry Ice Mon - Wed only	Fisher				relapse	
		Dry Ice Mon - Wed only	Fisher	Fisher	Archive		-1	6

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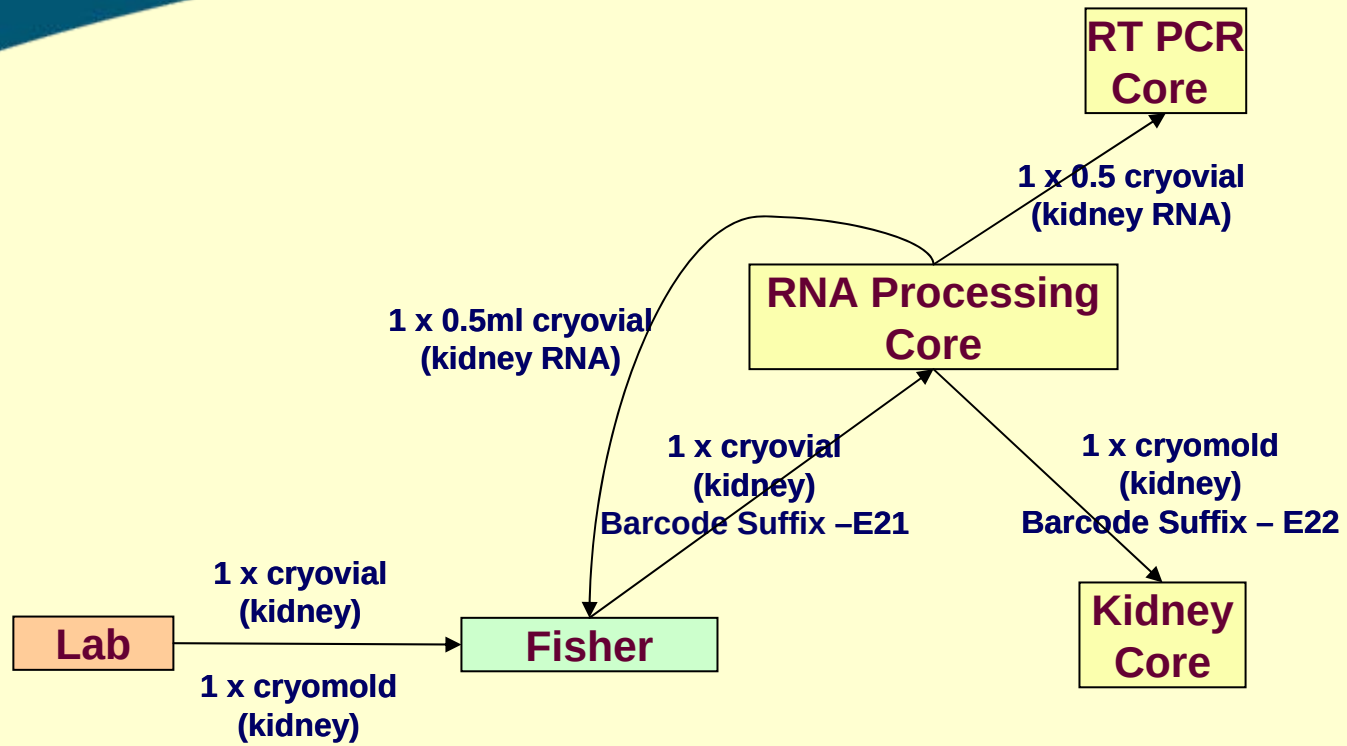
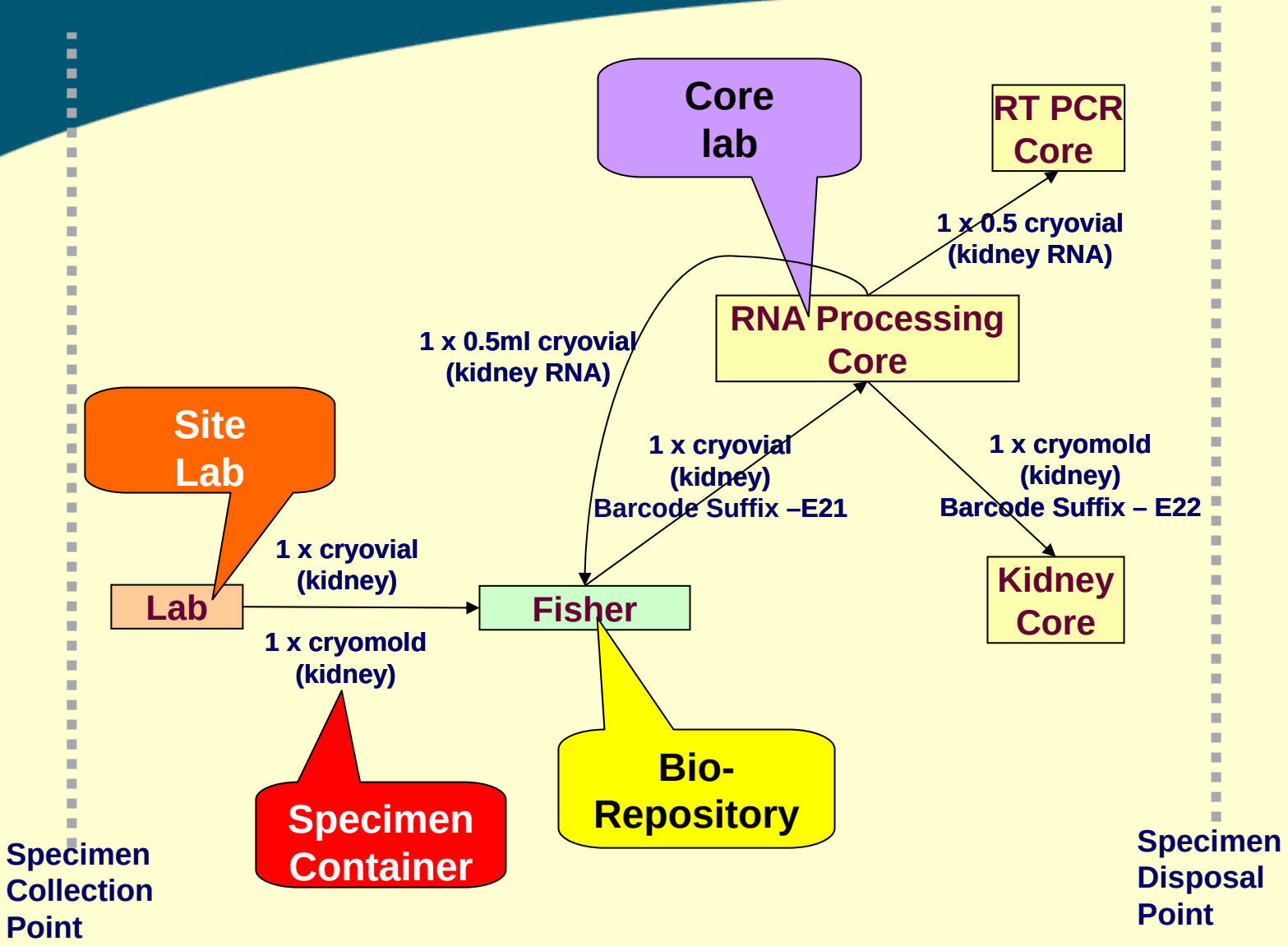
Specimen Workflow



Specimen Collection Point

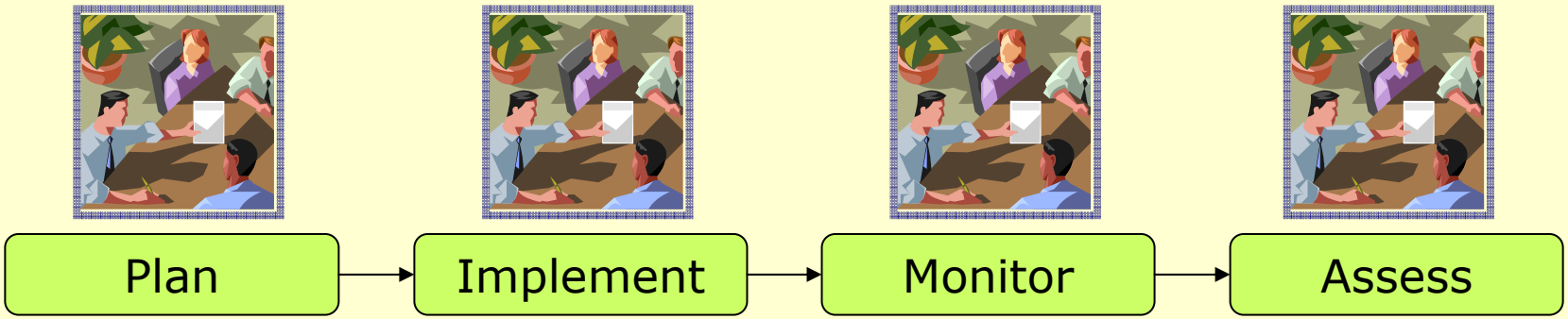
Specimen Disposal Point

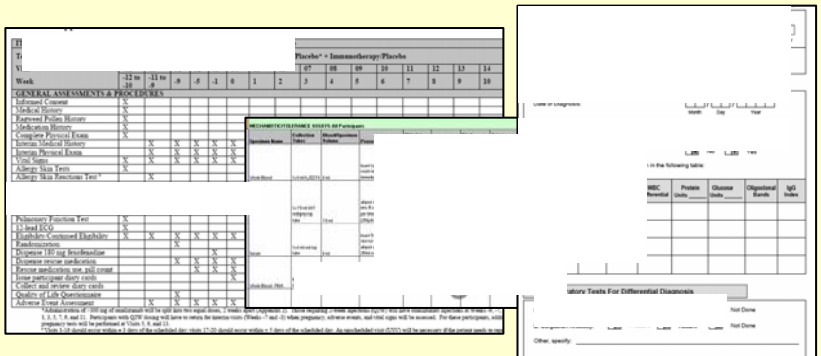
Specimen Workflow

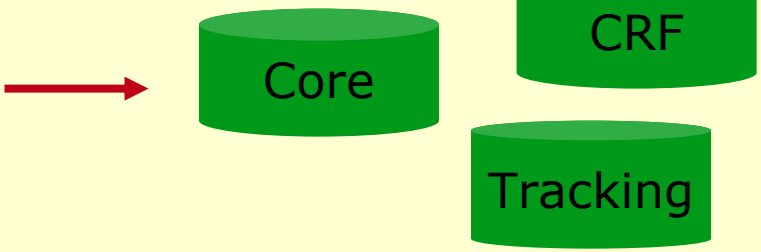


Challenges in Trials Management

- Knowledge about protocols, assays, and specimen flow is captured in documents and spreadsheets







What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant

Table 7: Summary of Assessments for Subjects

Visits	Screening Pre-MS Review Panel SC1	Screening Post-MS Review Panel SC2	Baseline -1	Post-mobilization & Pre-conditioning PM	Day 0 (Transplant) 0	Day +1 to +28 1[a]	Week 4 (Day 28) 2	3	4	5	6	7	8	9[b]
Informed Consent														
Signed Screening Informed Consent	X													
			X											
	X													
	X								X	X	X	X	X	X
	X		X	X					X	X	X	X	X	X
			X						X	X	X	X	X	X
			X						X	X	X	X	X	X
Exam														
Medical History	X													
Physical Exam and Health Assessments[d]	X		X	X	X	X	X	X	X	X	X	X	X	X
Post-Mobilization or Post-Transplant Acute Toxicity Assessment				X			X	X	X					
Clinical Procedures & Assessments														
CBC with diff and platelets		X	X	X	X	X	X	X	X	X	X	X	X	X

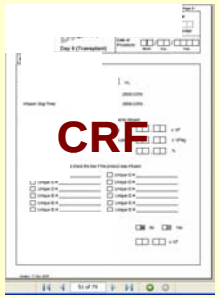
[a] Clinical assessments are required twice a week until Day 28 or discharge from hospital (see MOP).

[b] Th… point evaluation visit and the Study Completion Visit. Subjects who meet the … ndergo a complete end of study evaluation at the time of meeting the primary endpoint (see Section 6.3.7.2), and will, in addition, conti… n Section 6.3.7.1. Study subjects withdrawn from the trial for any reason pr… lergo a complete end of study evaluation if possible (see Section 6.3.7.2).

What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant

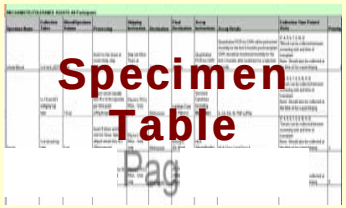
What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant

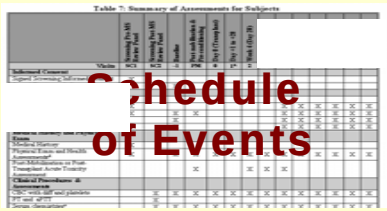
CRO **Day 0, Transplant**



Assay Group **0**

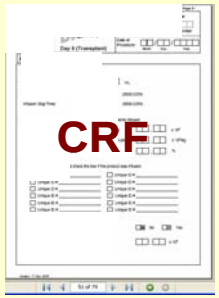
Protocol Group **0**





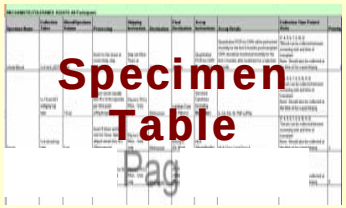
What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant

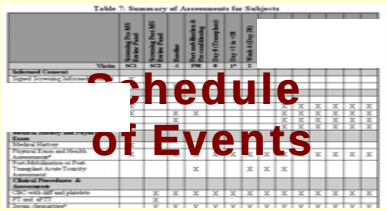
CRO **Day 0, Transplant**



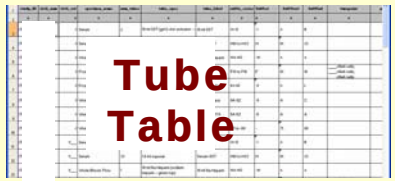
Assay Group **0**

Protocol Group **0**



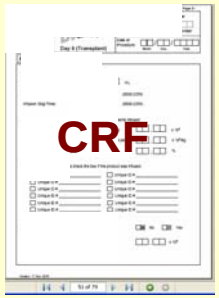


Operations Group **v 0**



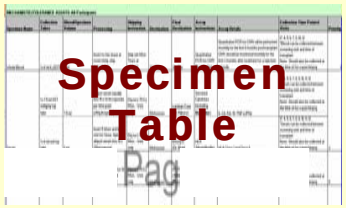
What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant

CRO **Day 0, Transplant**

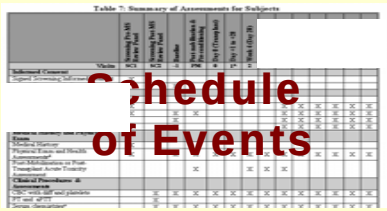


Assay Group **0**

Protocol Group **0**

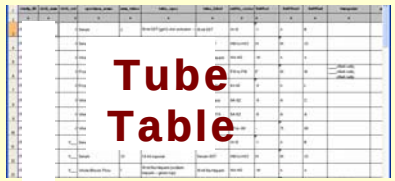


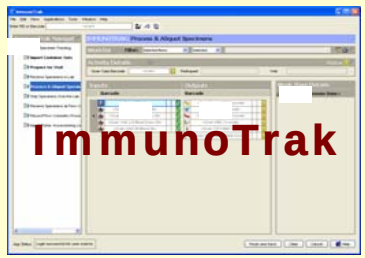
Fisher **v 0**



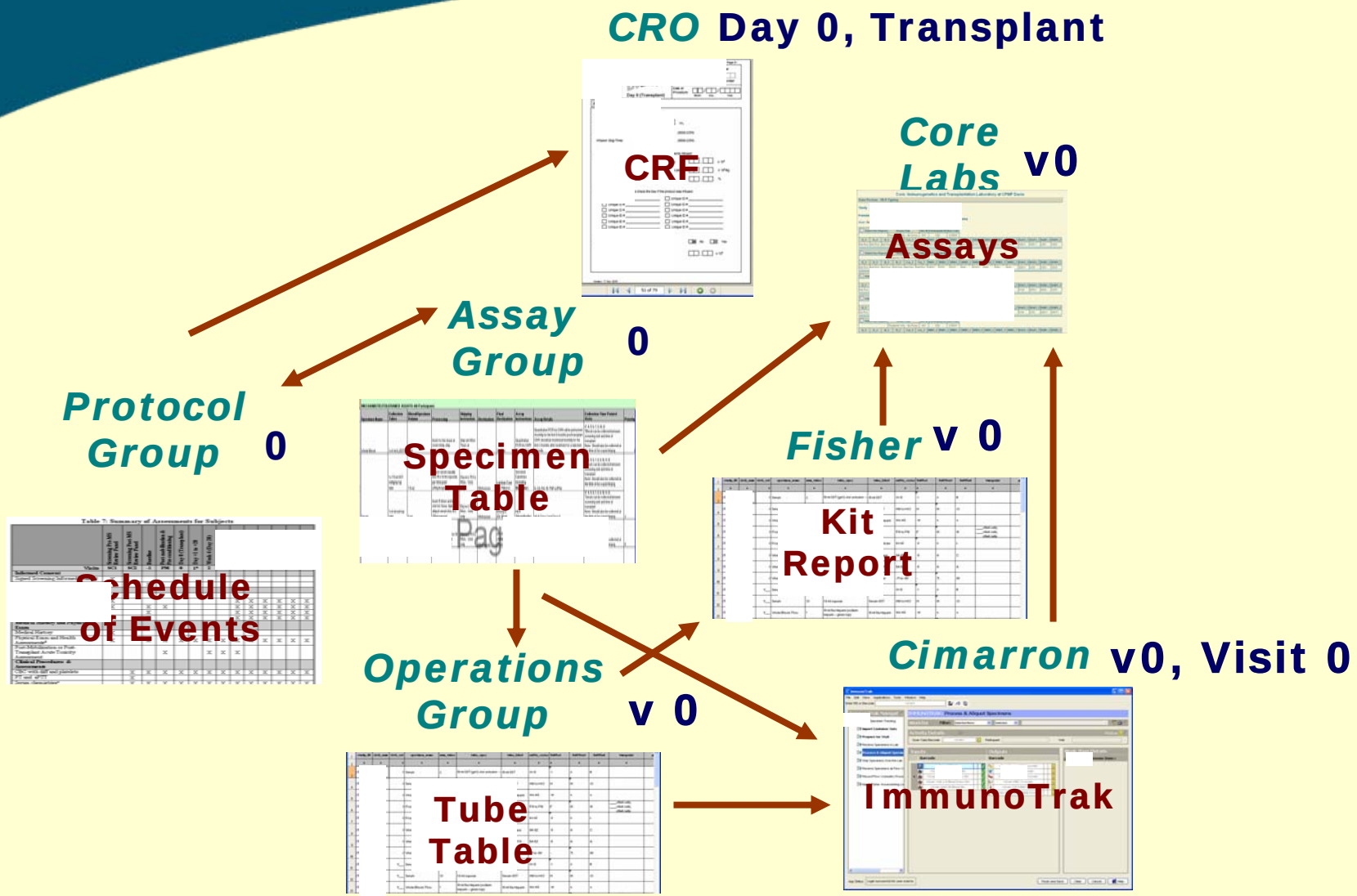
Operations Group **v 0**

Cimarron **v0, Visit 0**





What is in a visit name?
Visit 0, v0, v 0, 0, Day 0, Transplant



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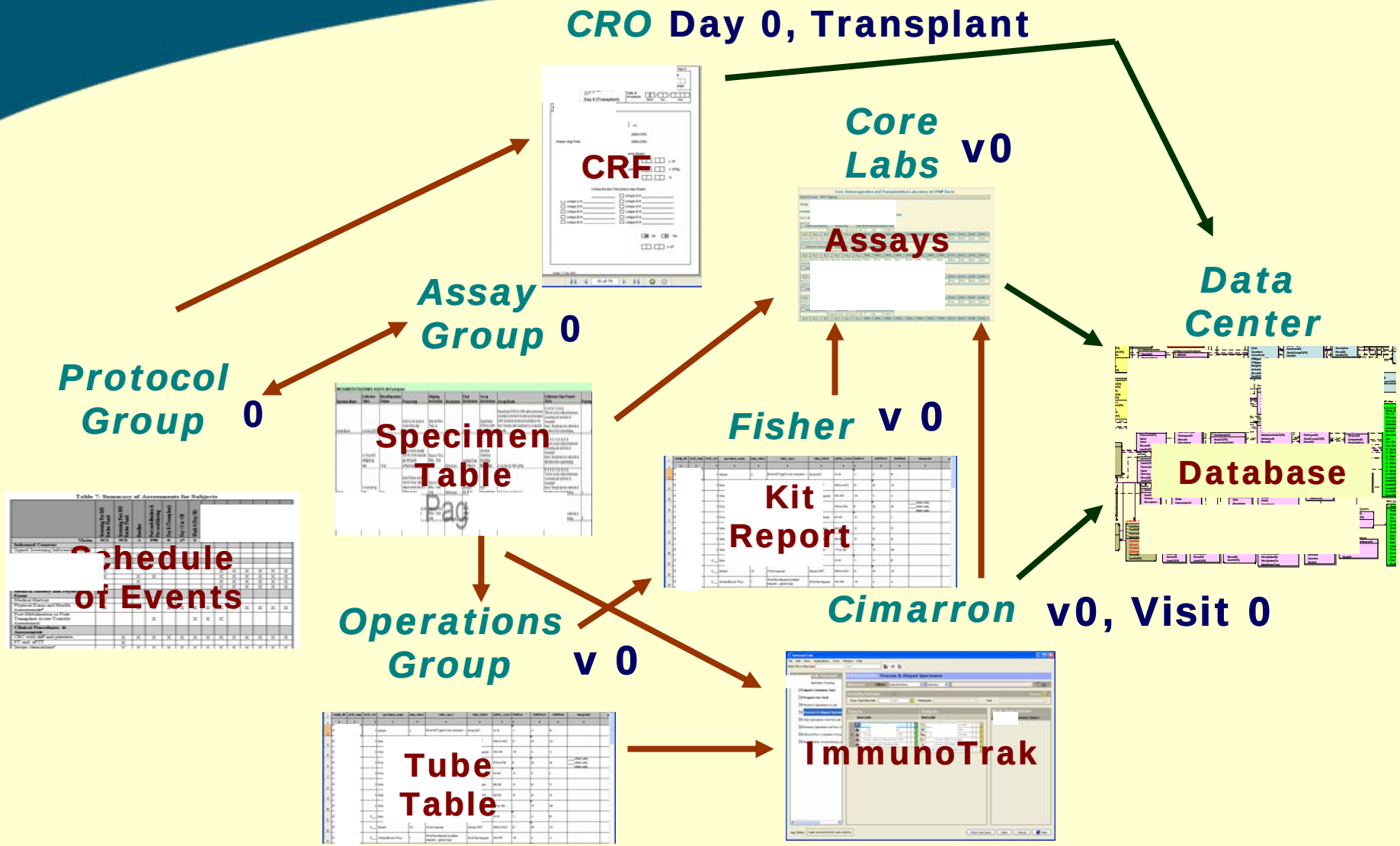

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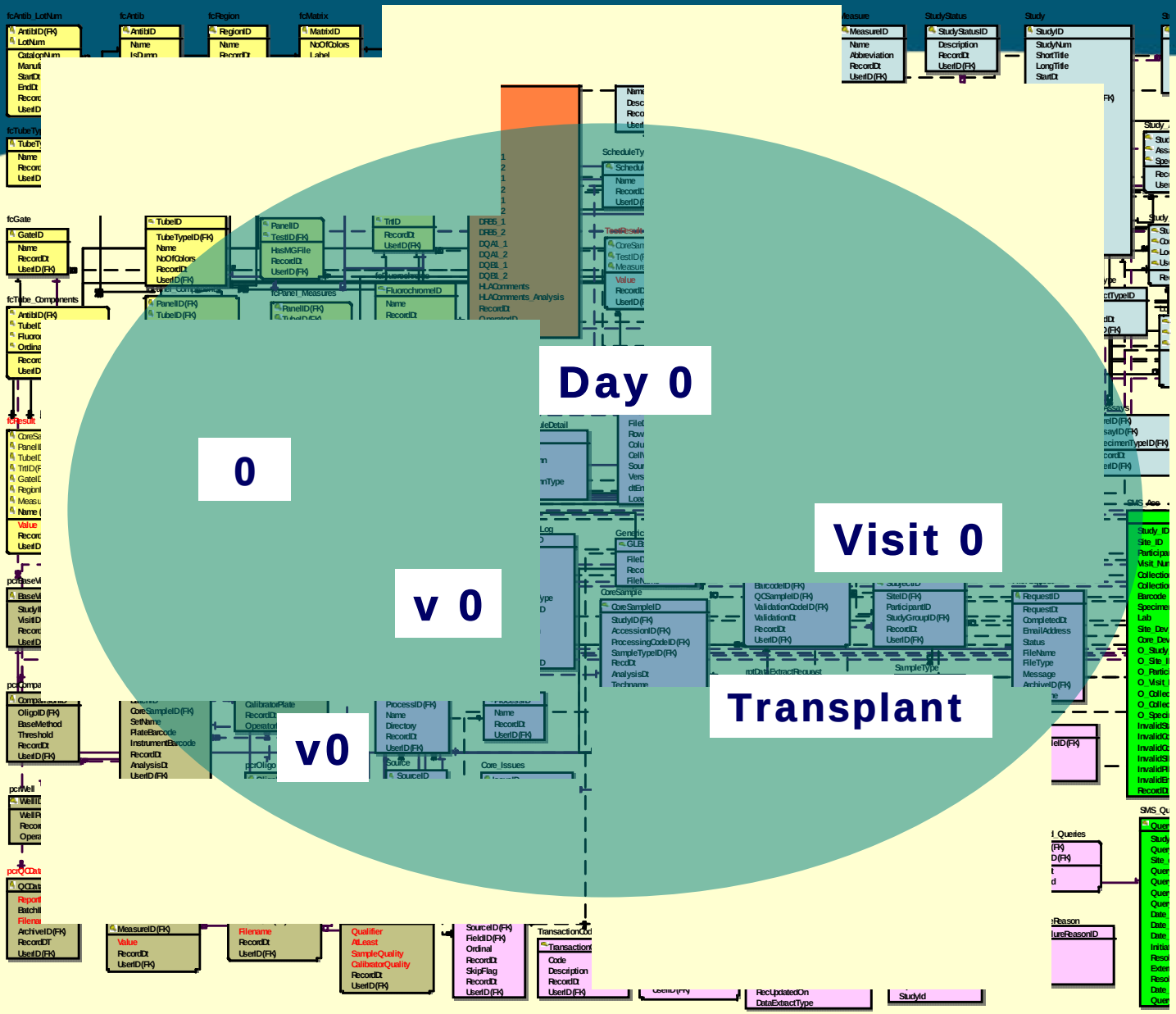

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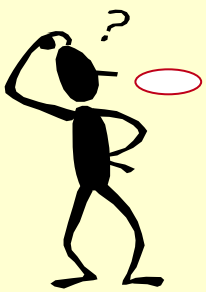
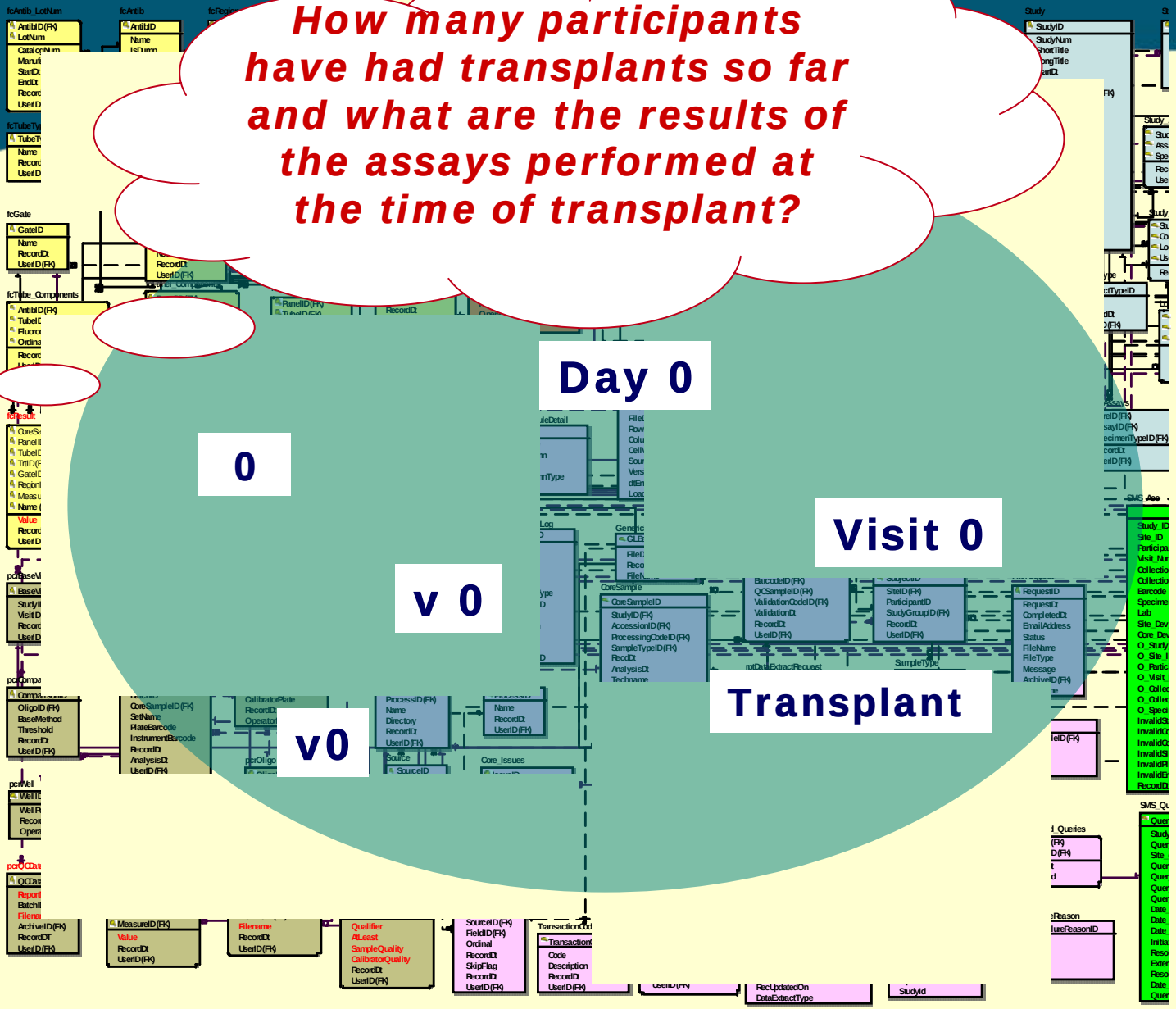


How many participants have had transplants so far and what are the results of the assays performed at the time of transplant?



Challenges in Trials Management

- Enterprise-wide knowledge about trials management is not formally encoded, leading to challenges in
  - Standardization
  - Data integrity
  - Data analysis
  - Data integration
- Significant efforts may be needed to resolve inconsistencies after a trial has started

Epoch

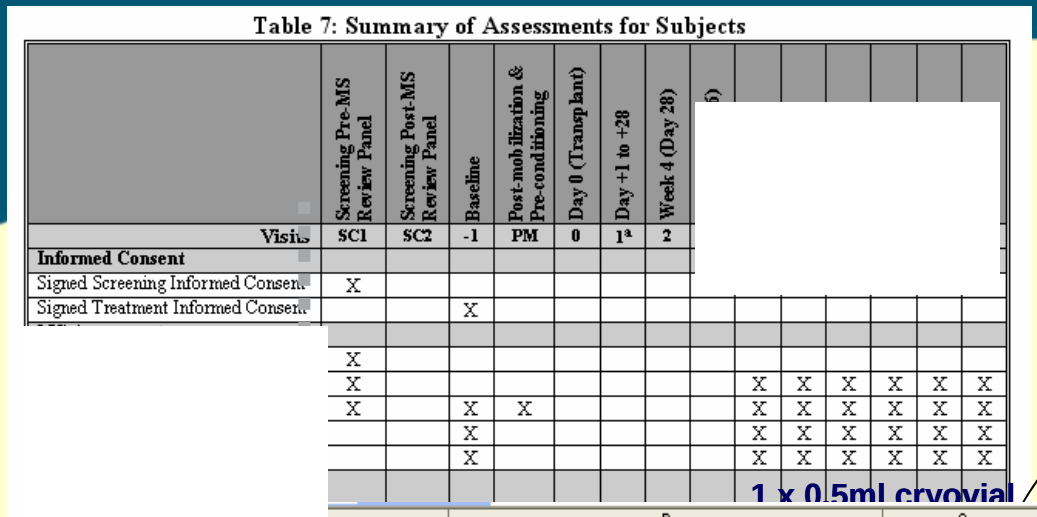
An Ontological Framework for Clinical Trials Management

ITN Informatics Core at Stanford

The goals of our collaboration are to

- Design tools to help acquire and maintain knowledge about protocol and assay designs
- Use this knowledge to drive data collection during a trial
- Implement querying methods to support trial management, and ad hoc data analysis

Building Ontologies for ITN — Epoch



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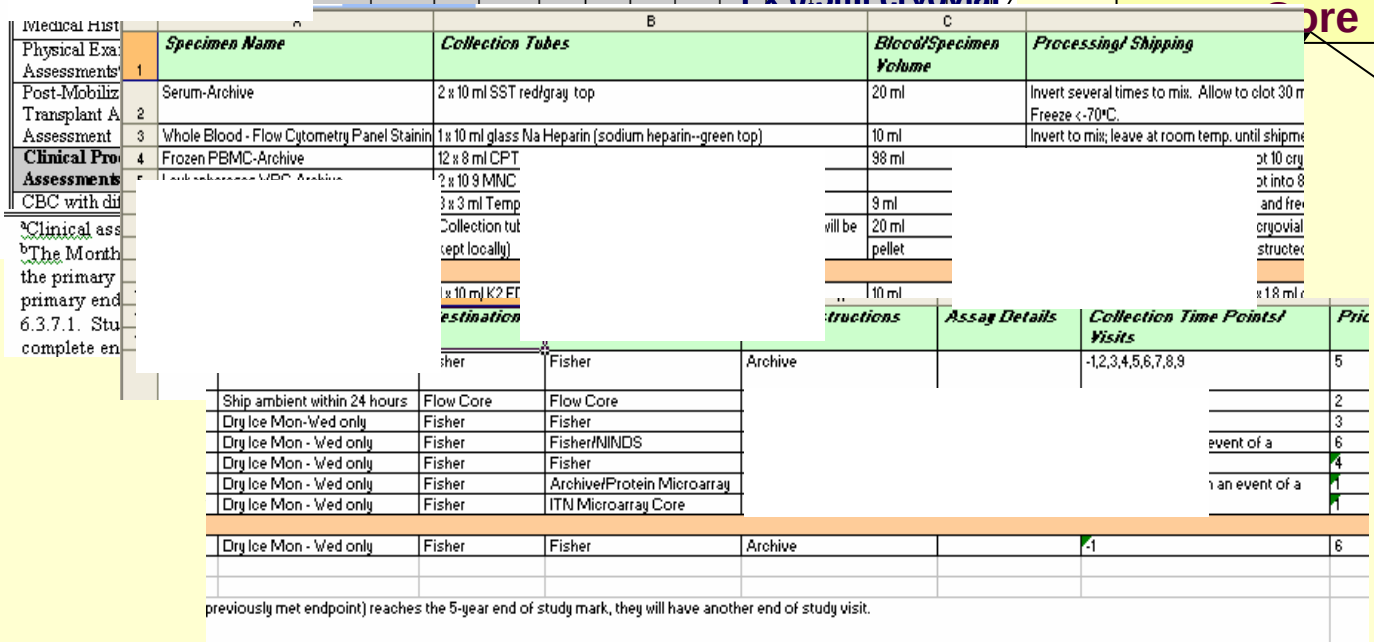
Informed Consent								
Signed Screening Informed Consent	X							
Signed Treatment Informed Consent			X					
	X							
	X							X X X X X X
	X		X	X				X X X X X X
			X					X X X X X X
			X					X X X X X X

1 x 0.5ml cryovial



	A	B	C
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5	Leukapheresis PBC Archive	2 x 10 9 MNC		ot into 8
		3 x 3 ml Temp	9 ml	and free
		Collection tut	20 ml	cryovial
		cept locally)	pellet	structed
		x 10 ml K2 ED	10 ml	x 18 ml c

Destination	*Instructions*	*Assay Details*	*Collection Time Points/ Visits*	*Pric*
Fisher	Fisher	Archive	-1,2,3,4,5,6,7,8,9	5
Ship ambient within 24 hours	Flow Core	Flow Core		2
Dry Ice Mon-Wed only	Fisher	Fisher		3
Dry Ice Mon - Wed only	Fisher	Fisher/NINDS	event of a	6
Dry Ice Mon - Wed only	Fisher	Fisher		4
Dry Ice Mon - Wed only	Fisher	Archive/Protein Microarray	an event of a	1
Dry Ice Mon - Wed only	Fisher	ITN Microarray Core		1
Dry Ice Mon - Wed only	Fisher	Fisher	Archive	-1	6

previously met endpoint) reaches the 5-year end of study mark, they will have another end of study visit.

RT PCR Core

1 x 0.5 cryovial (kidney RNA)

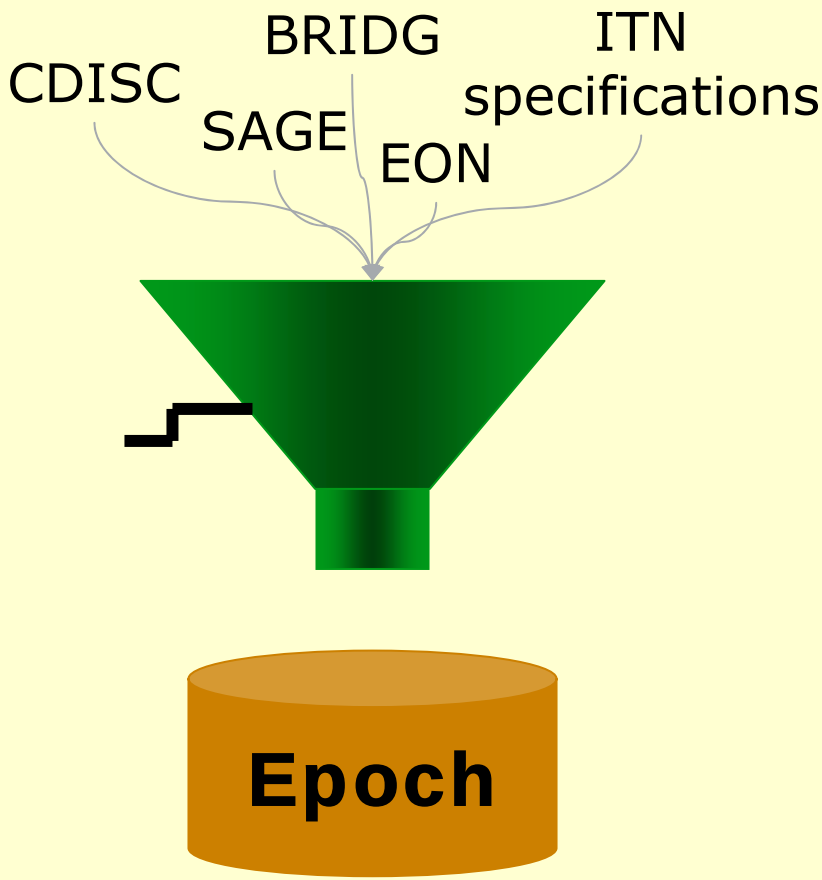
RNA Processing Core

1 x cryomold (kidney) Barcode Suffix – E22

Kidney Core

Specimen Disposal Point

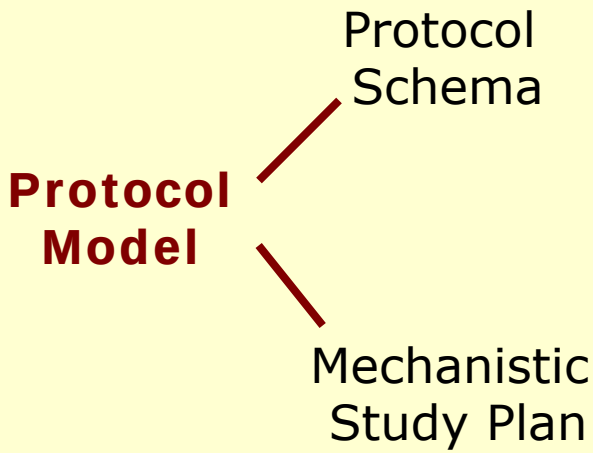
Building Ontologies for ITN — Epoch



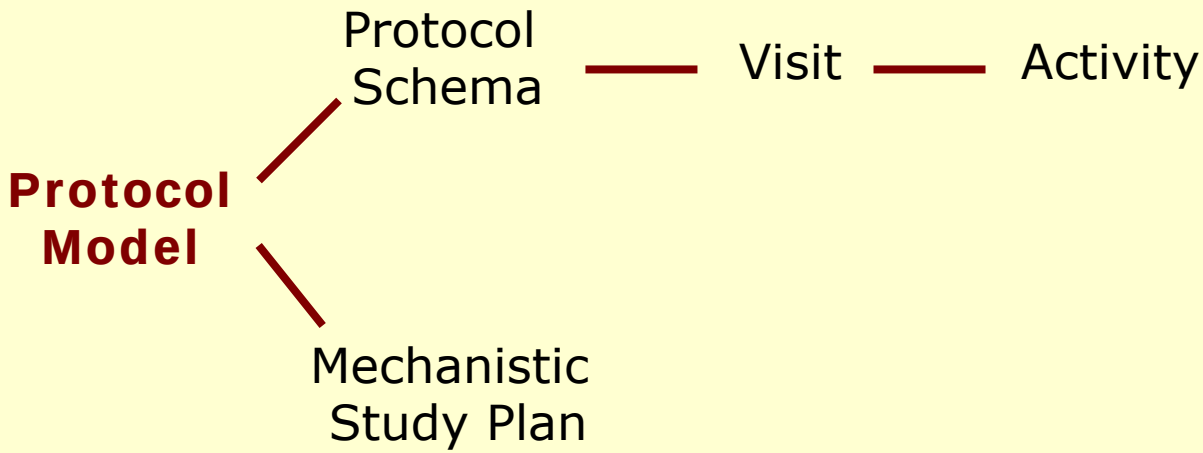
Epoch Ontologies

Protocol Model

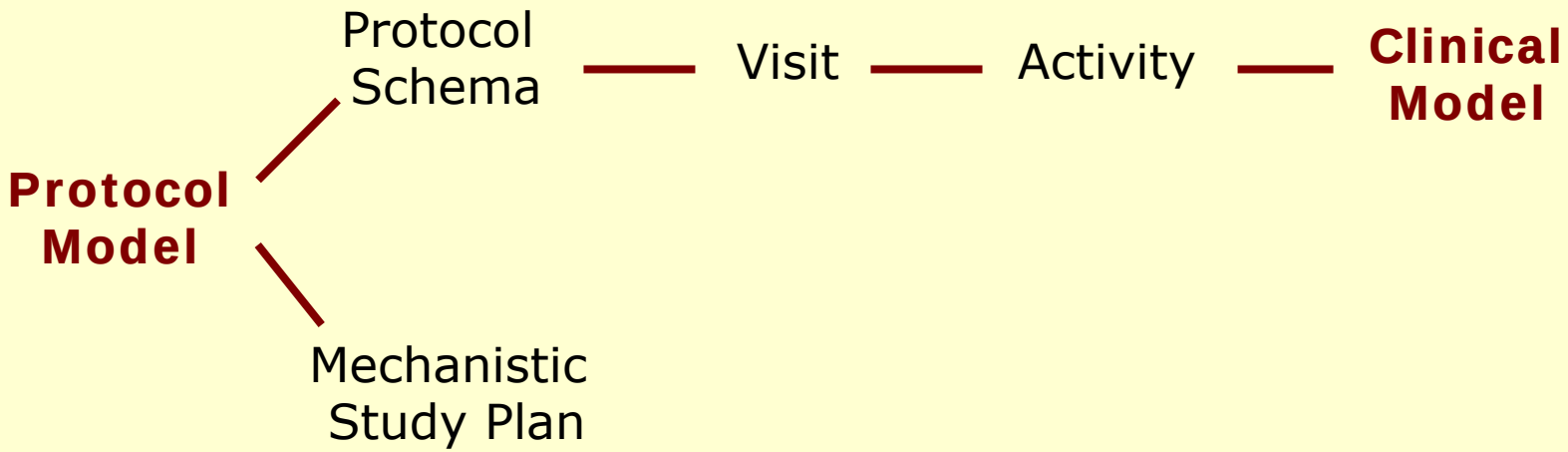
Epoch Ontologies



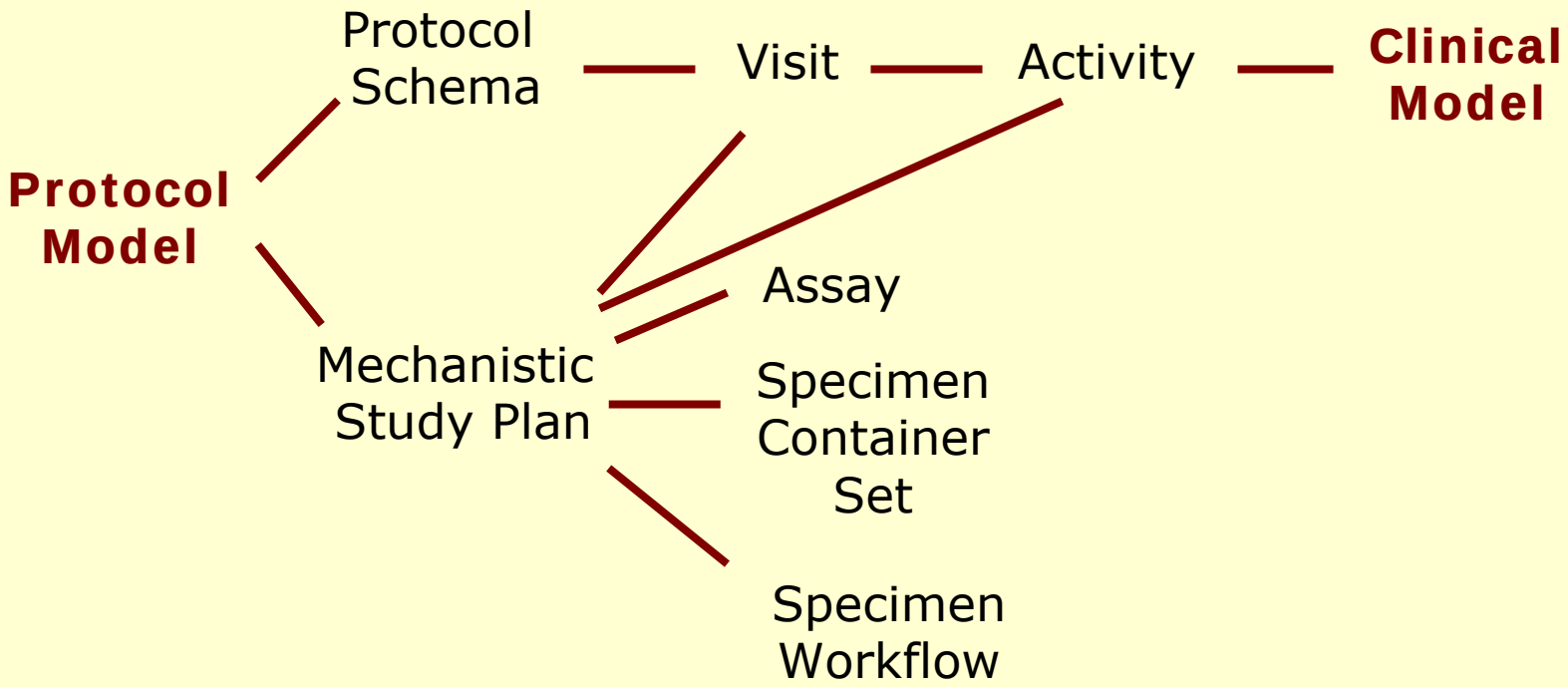
Epoch Ontologies



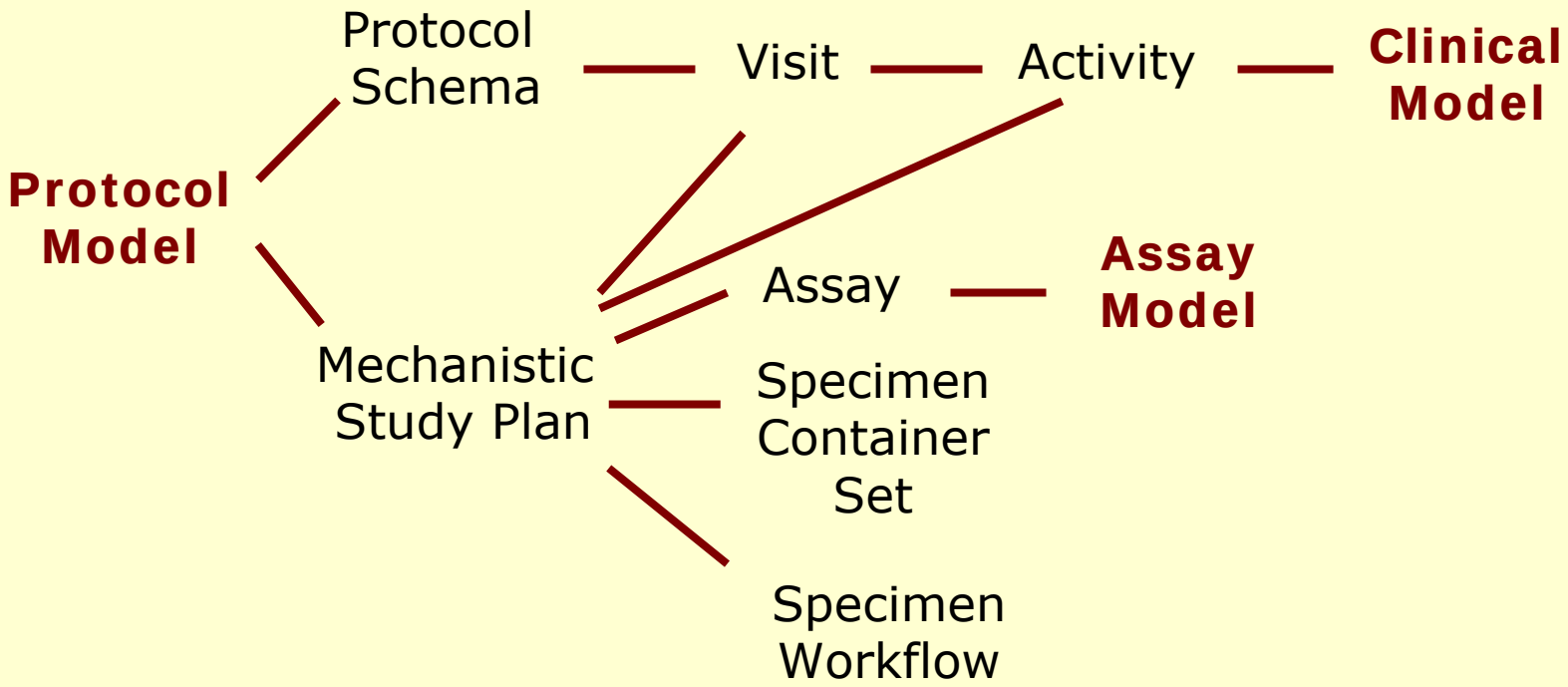
Epoch Ontologies



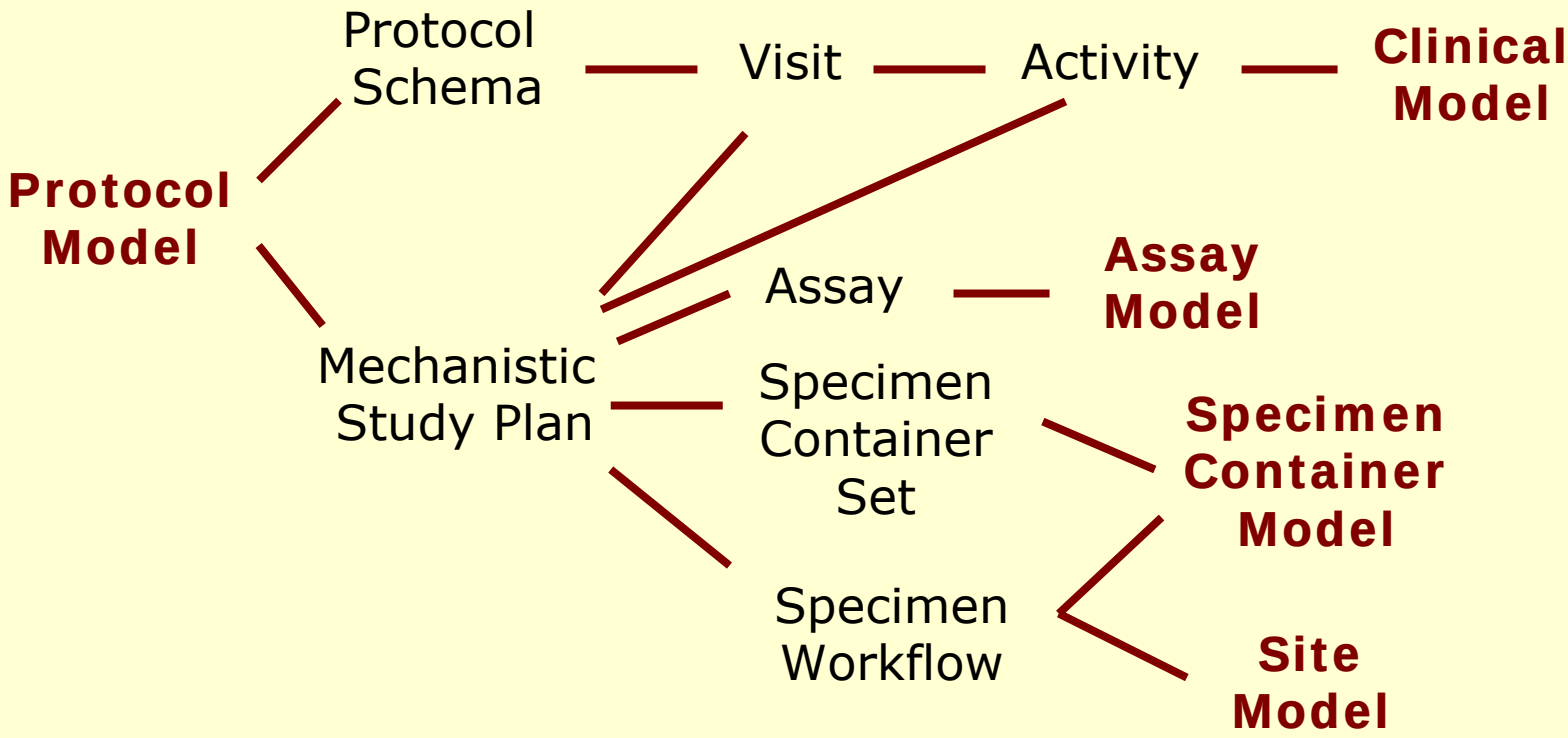
Epoch Ontologies



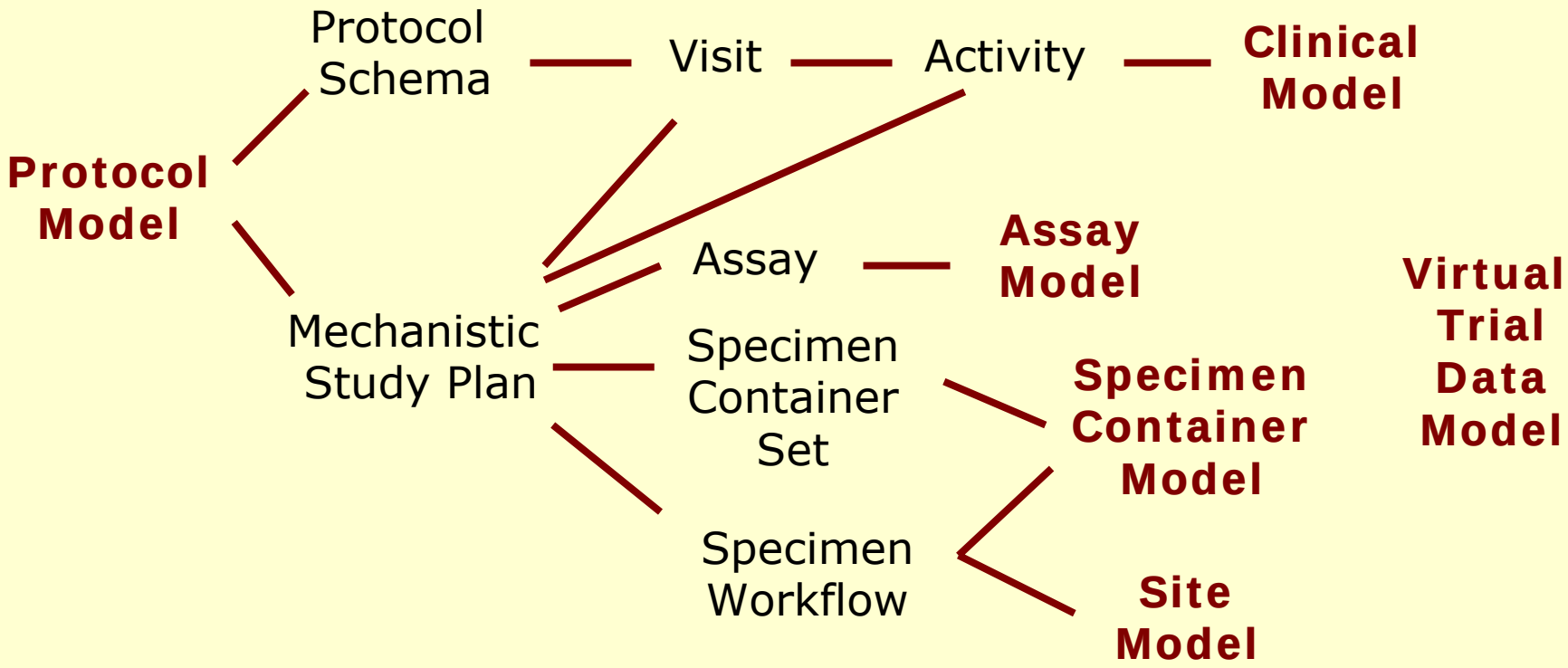
Epoch Ontologies



Epoch Ontologies



Epoch Ontologies



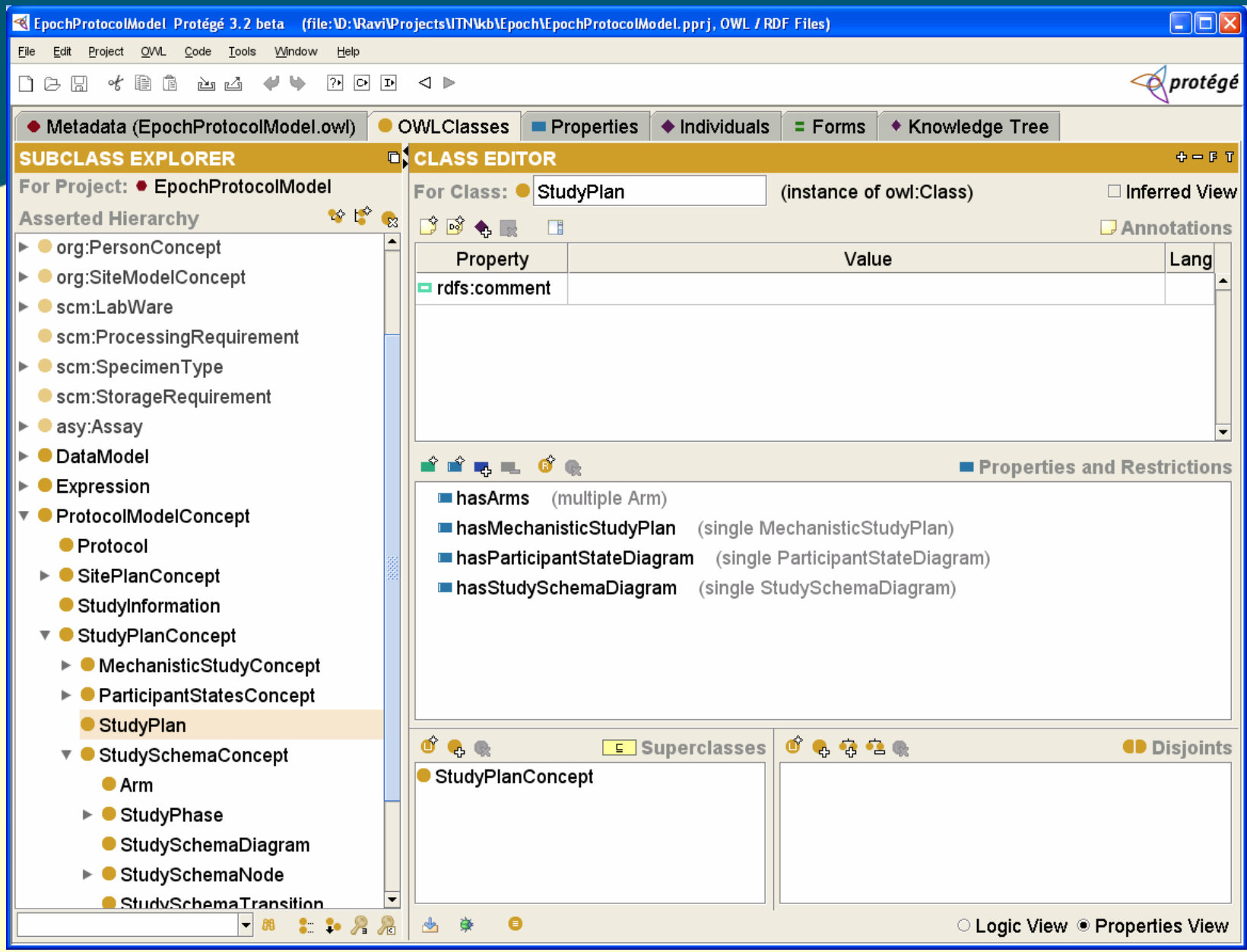
Knowledge-Acquisition Environment

OWL (the Web Ontology Language proposed by W3C)

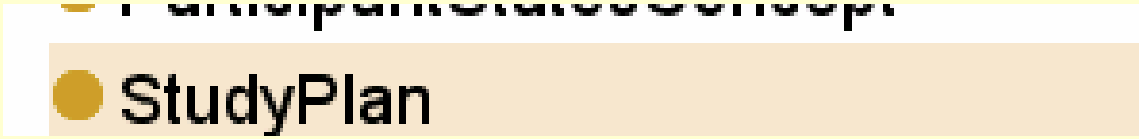
SWRL (the Semantic Web Rule Language) to specify constraints and queries

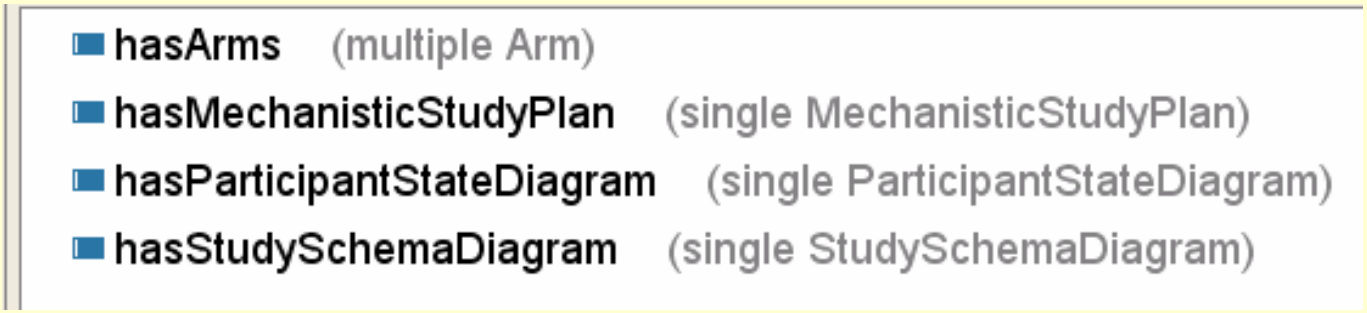
Protégé-OWL editor to enter ontologies in OWL and SWRL

Epoch Protocol Model

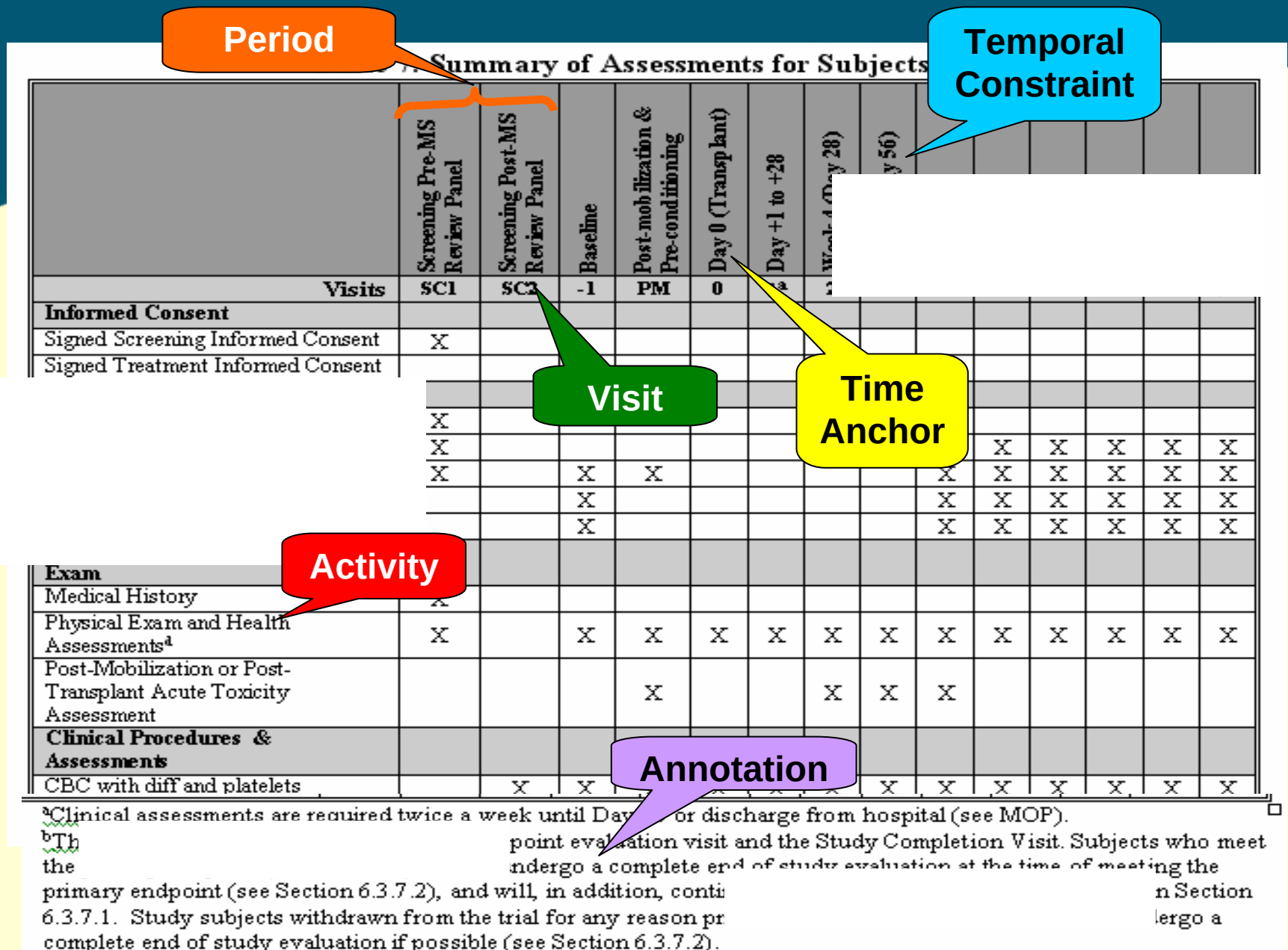


Epoch Protocol Model





Schedule of Events



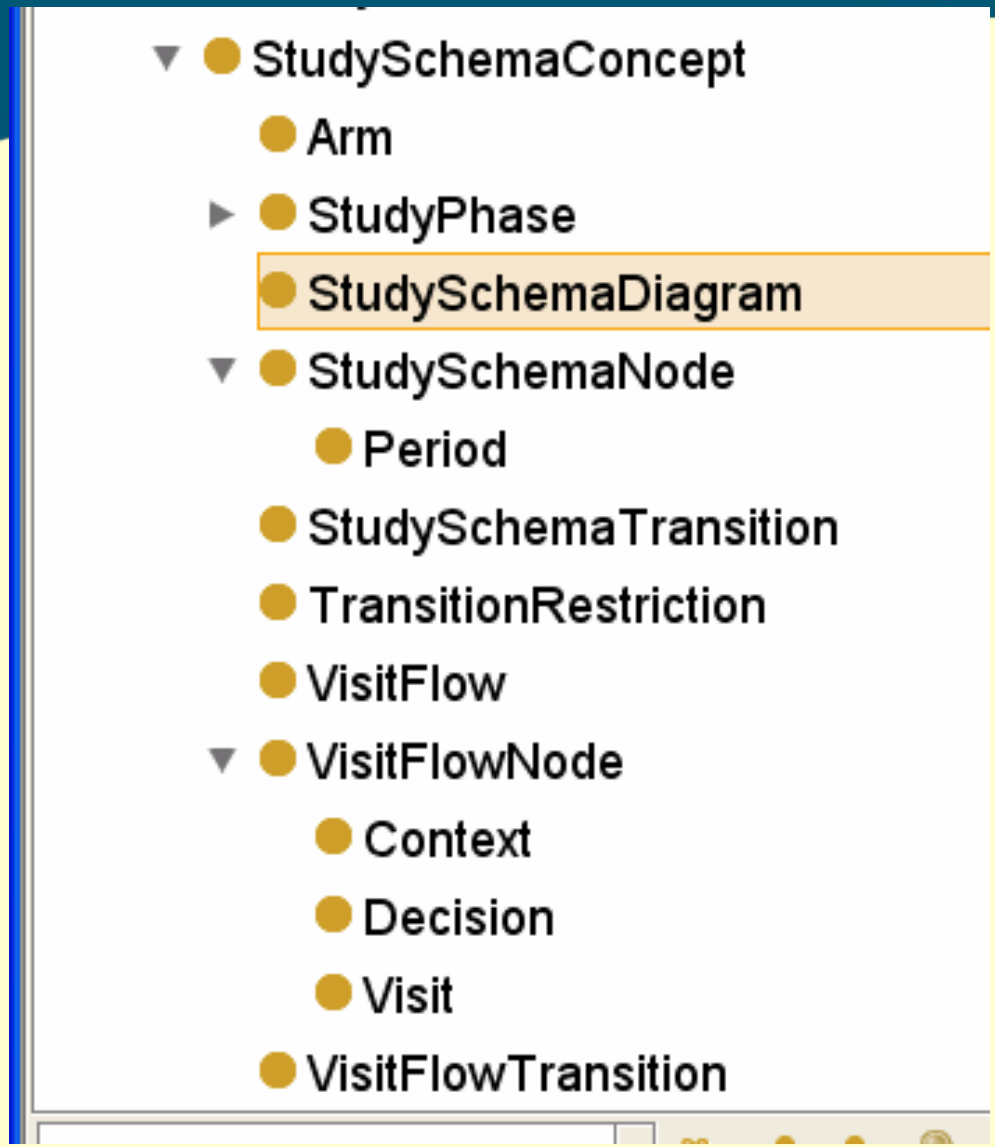
Summary of Assessments for Subjects

Visits	Screening Pre-MS Review Panel SC1	Screening Post-MS Review Panel SC2	Baseline -1	Post-mobilization & Pre-conditioning PM	Day 0 (Transplant) 0	Day +1 to +28 [a]	[illegible] (Day 28)	[illegible] y 56)					
Informed Consent													
Signed Screening Informed Consent	X												
Signed Treatment Informed Consent													
	X												
	X								X	X	X	X	X
	X		X	X					X	X	X	X	X
			X						X	X	X	X	X
			X						X	X	X	X	X
Exam													
Medical History	X												
Physical Exam and Health Assessments[d]	X		X	X	X	X	X	X	X	X	X	X	X
Post-Mobilization or Post-Transplant Acute Toxicity Assessment				X			X	X	X				
Clinical Procedures & Assessments													
CBC with diff and platelets		X	X					X	X	X	X	X	X

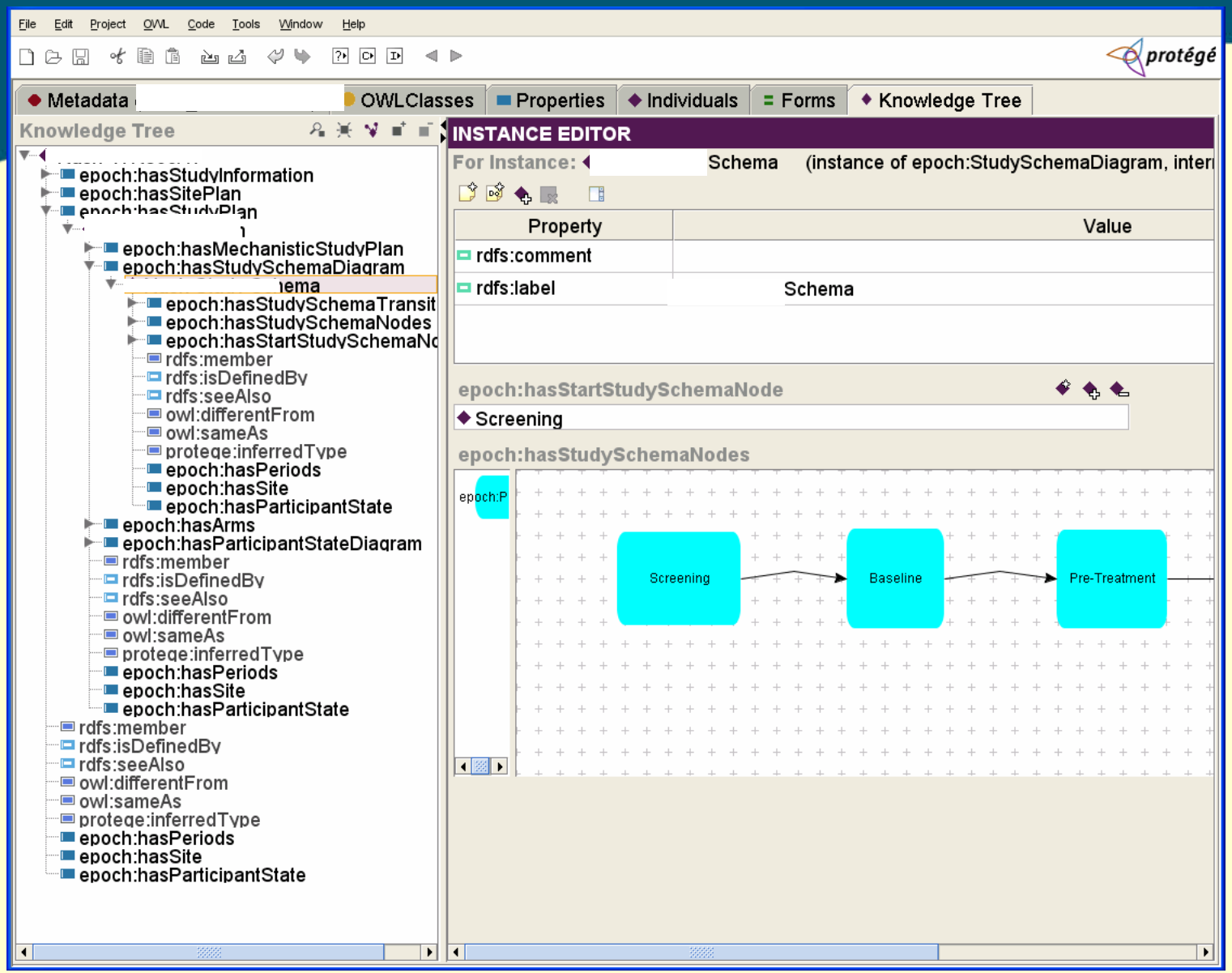
[a]Clinical assessments are required twice a week until Day [illegible] or discharge from hospital (see MOP).

[b]Th [illegible] point eva[illegible]ation visit and the Study Completion Visit. Subjects who meet the [illegible] ndergo a complete end of study evaluation at the time of meeting the primary endpoint (see Section 6.3.7.2), and will, in addition, conti[illegible] n Section 6.3.7.1. Study subjects withdrawn from the trial for any reason pr[illegible] lergo a complete end of study evaluation if possible (see Section 6.3.7.2).

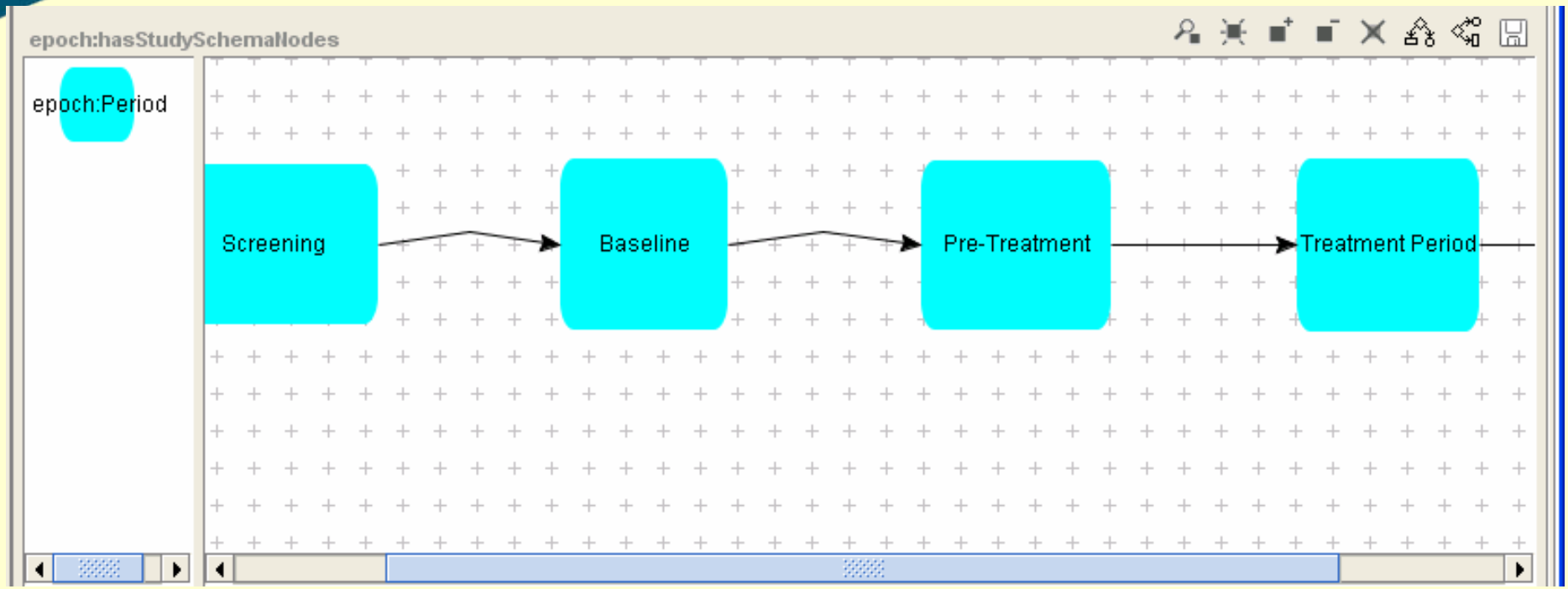
Protocol Model – Study Schema



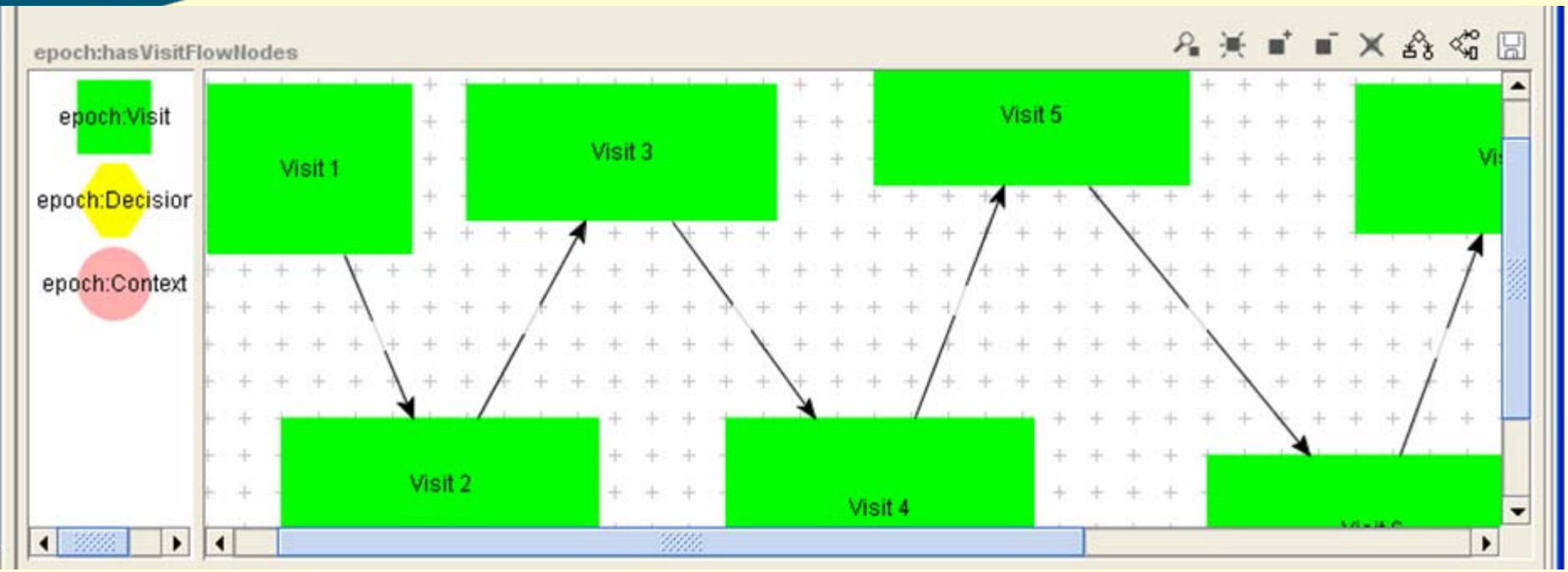
Study Schema



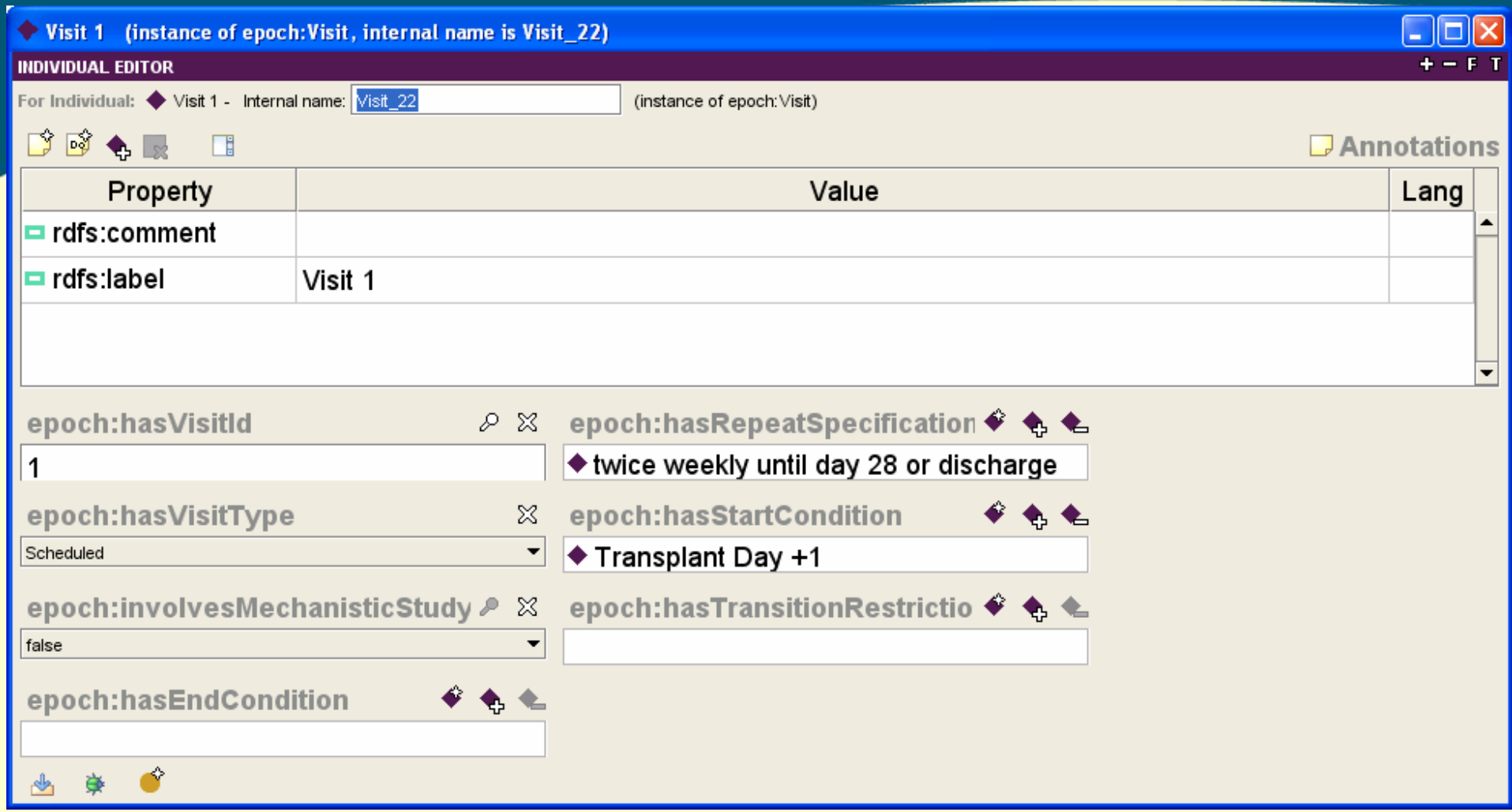
Study Schema – a Temporal Sequence of Periods



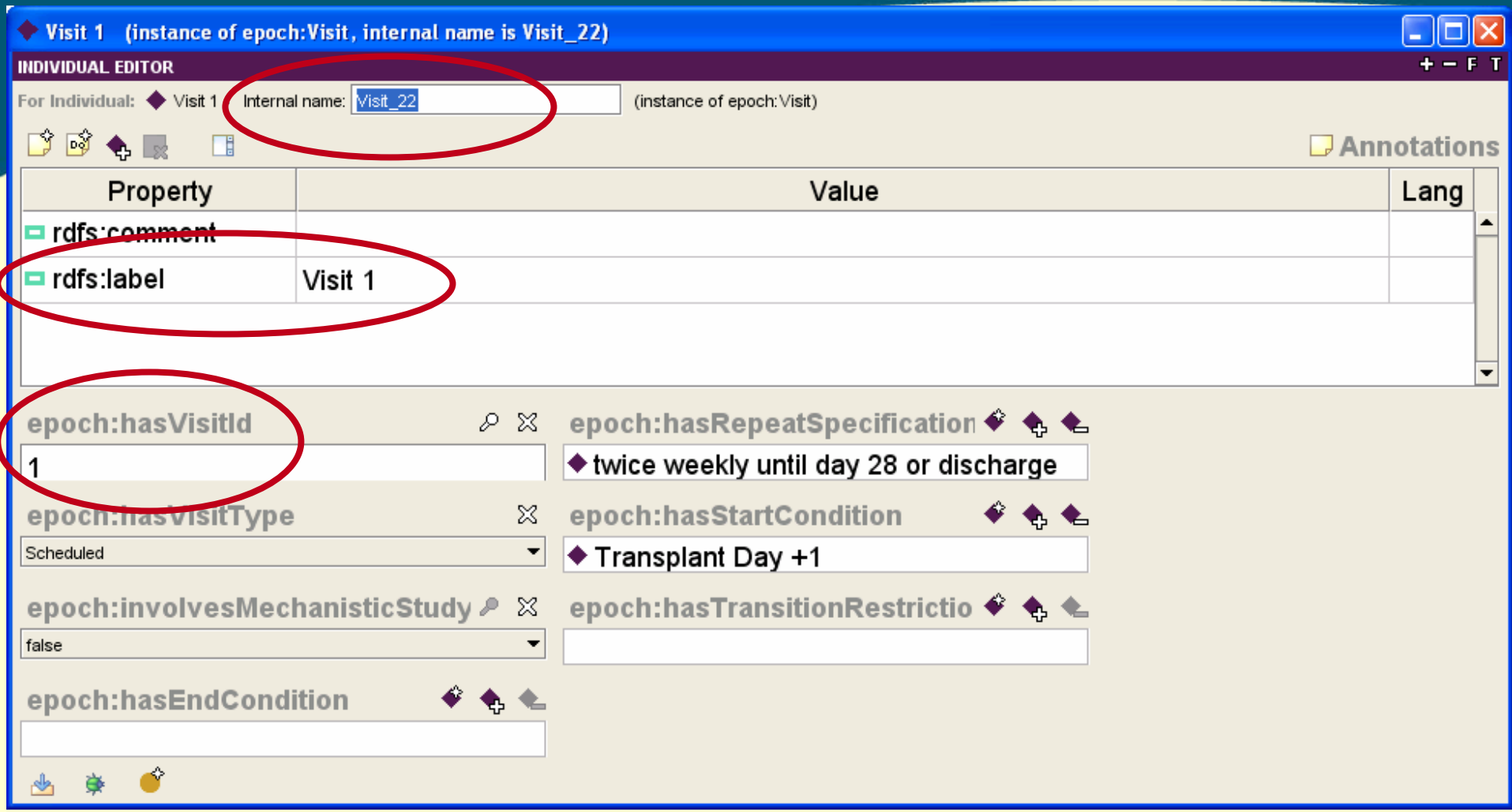
Visit Flow – a Temporal Sequence of Visits



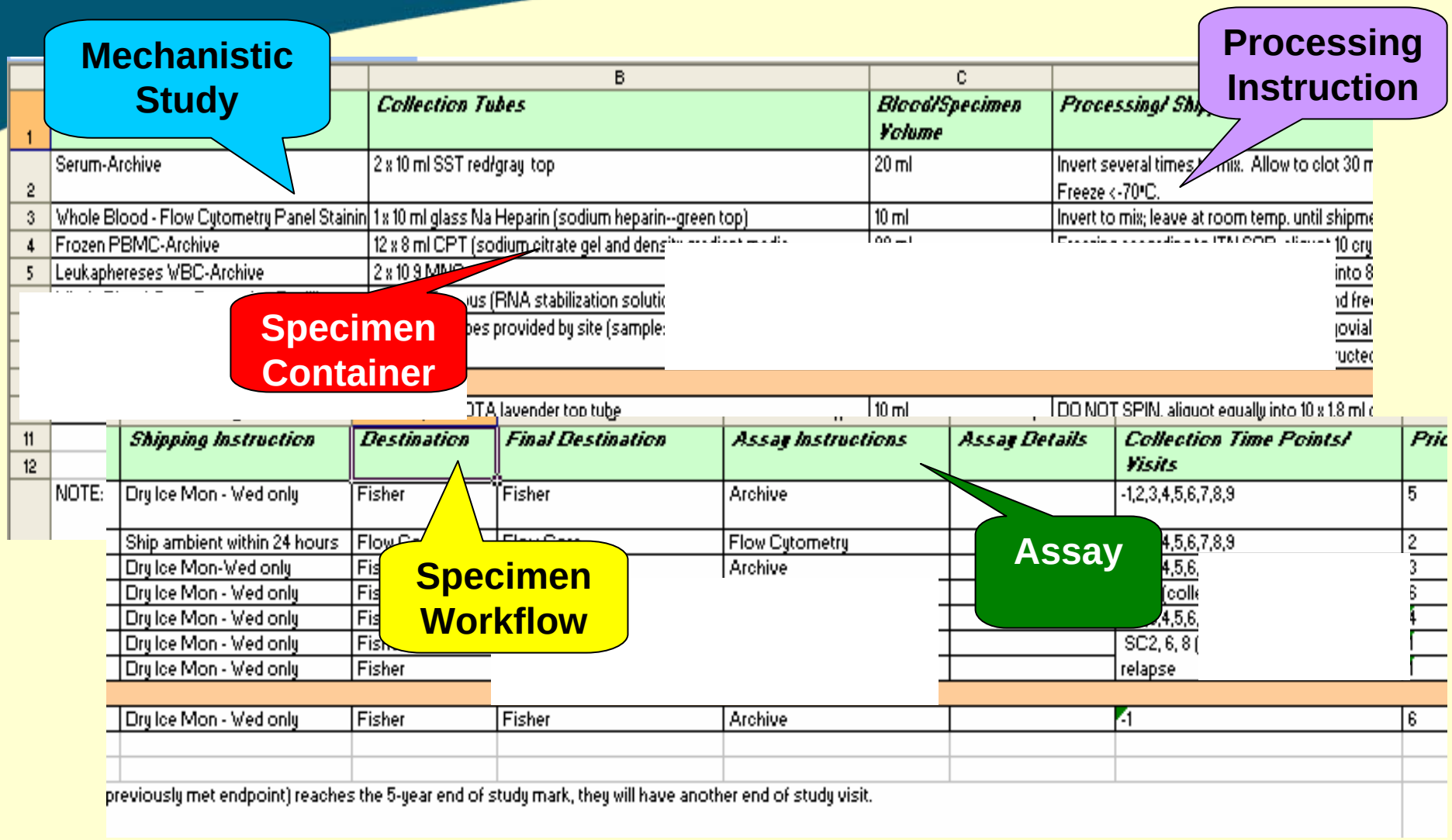
Visit


Visit 1 (instance of epoch:Visit, internal name is Visit_22)
INDIVIDUAL EDITOR
For Individual: Visit 1 - Internal name: Visit_22 (instance of epoch:Visit)
Annotations
Property
Value
Lang
rdfs:comment
rdfs:label
Visit 1
epoch:hasVisitId
1
epoch:hasRepeatSpecification
twice weekly until day 28 or discharge
epoch:hasVisitType
Scheduled
epoch:hasStartCondition
Transplant Day +1
epoch:involvesMechanisticStudy
false
epoch:hasTransitionRestrictio
epoch:hasEndCondition

Visit – different Visit names



Specimen Table

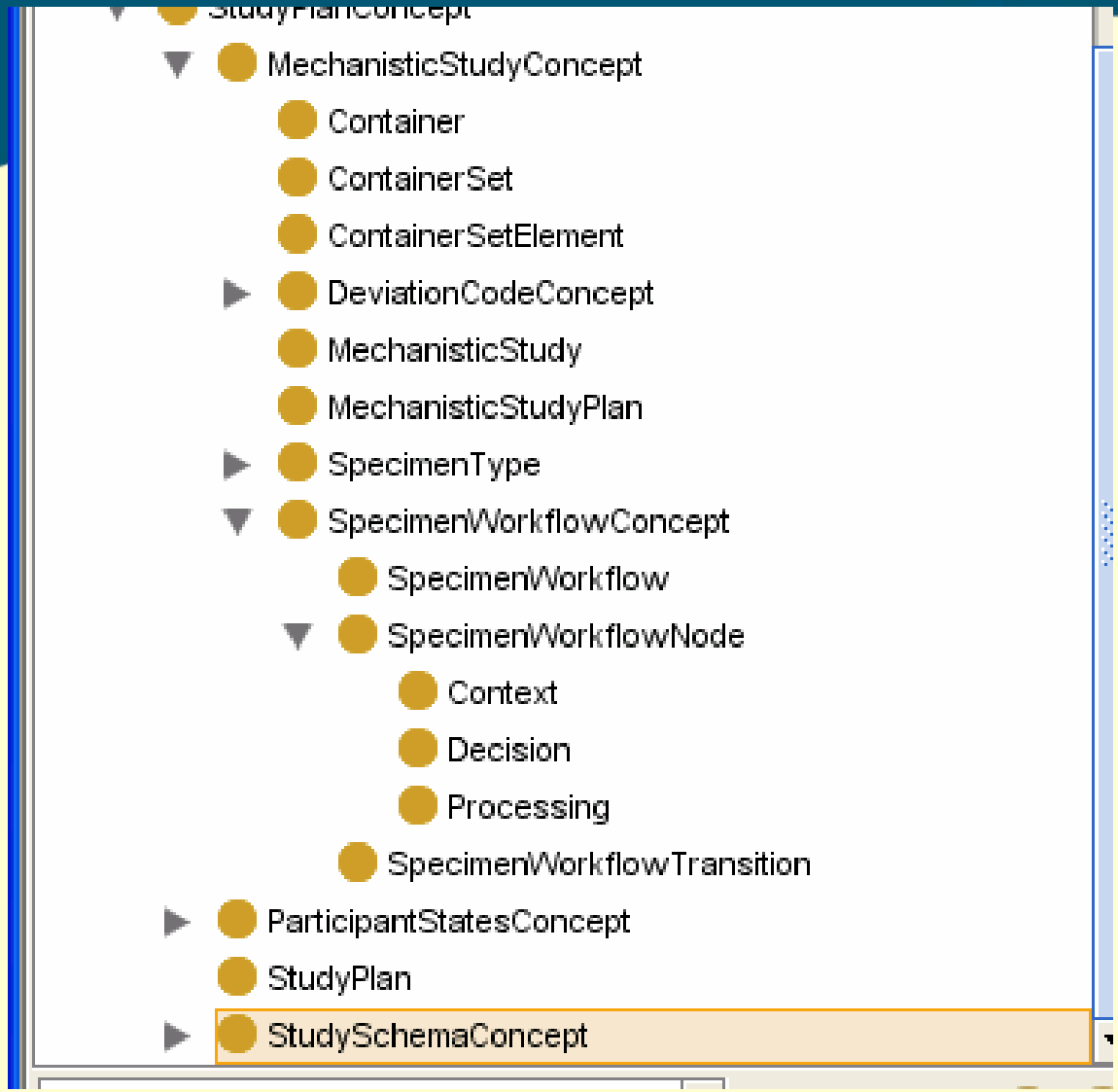


	B	C	
1	Collection Tubes	Blood/Specimen Volume	Processing/ Shi
2	Serum-Archive	2 x 10 ml SST red/gray top	20 ml	Invert several times mix. Allow to clot 30 m Freeze <-70°C.
3	Whole Blood - Flow Cytometry Panel Stainin	1 x 10 ml glass Na Heparin (sodium heparin--green top)	10 ml	Invert to mix; leave at room temp. until shipme
4	Frozen PBMC-Archive	12 x 8 ml CPT (sodium citrate gel and dens		10 cry
5	Leukaphereses WBC-Archive	2 x 10 9 MNC		into 8
		us (RNA stabilization soluti		d fre
		es provided by site (sample		ovial
				ucte
		TA lavender top tube	10 ml	DO NOT SPIN. aliquot equally into 10 x 1.8 ml

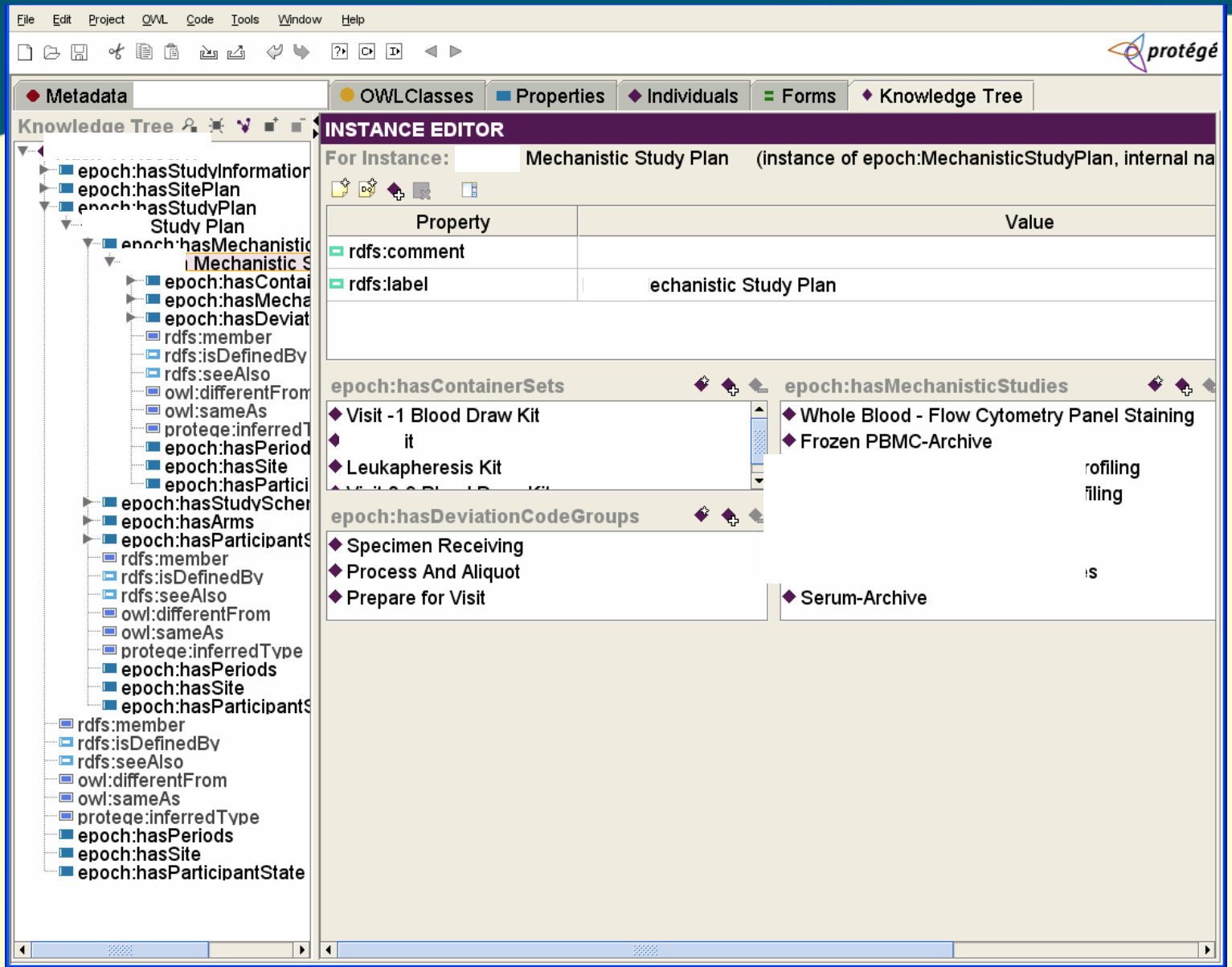
		Shipping Instruction	Destination	Final Destination	Assay Instructions	Assay Details	Collection Time Points/ Visits	Pric
11								
12								
	NOTE:	Dry Ice Mon - Wed only	Fisher	Fisher	Archive		-1,2,3,4,5,6,7,8,9	5
		Ship ambient within 24 hours	Flow		Flow Cytometry		4,5,6,7,8,9	2
		Dry Ice Mon-Wed only	Fis		Archive		4,5,6,	3
		Dry Ice Mon - Wed only	Fis				(colle	3
		Dry Ice Mon - Wed only	Fis				4,5,6,	4
		Dry Ice Mon - Wed only	Fish				SC2, 6, 8 (	
		Dry Ice Mon - Wed only	Fisher				relapse	
		Dry Ice Mon - Wed only	Fisher	Fisher	Archive		-1	6

previously met endpoint) reaches the 5-year end of study mark, they will have another end of study visit.

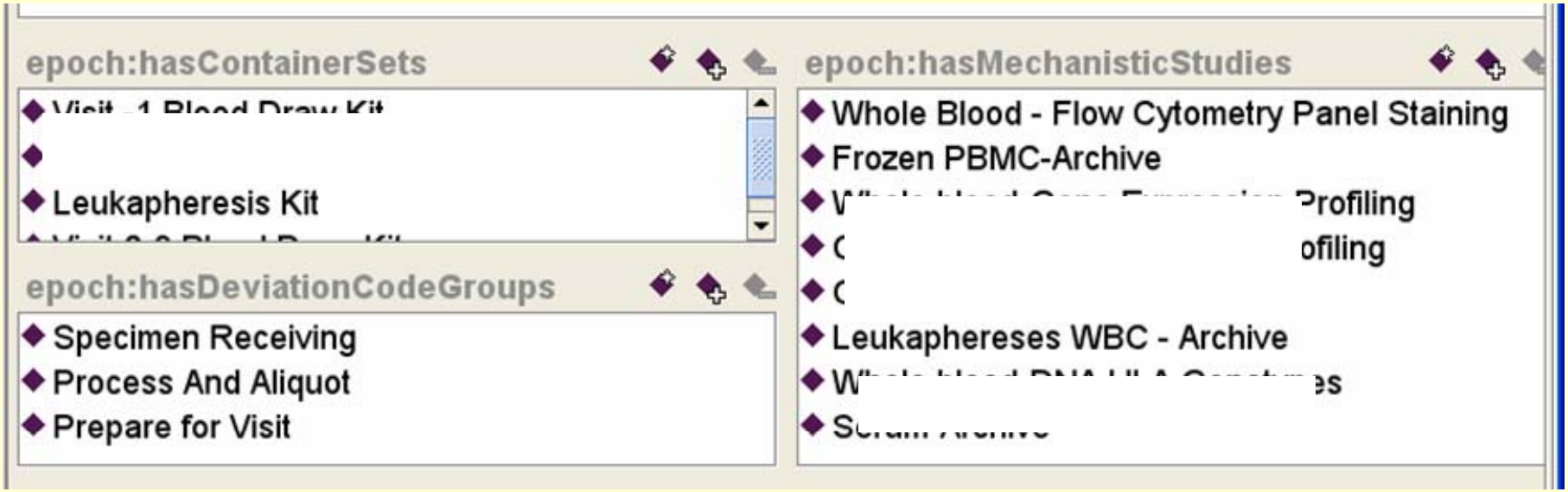
Protocol Model - Mechanistic Study Plan



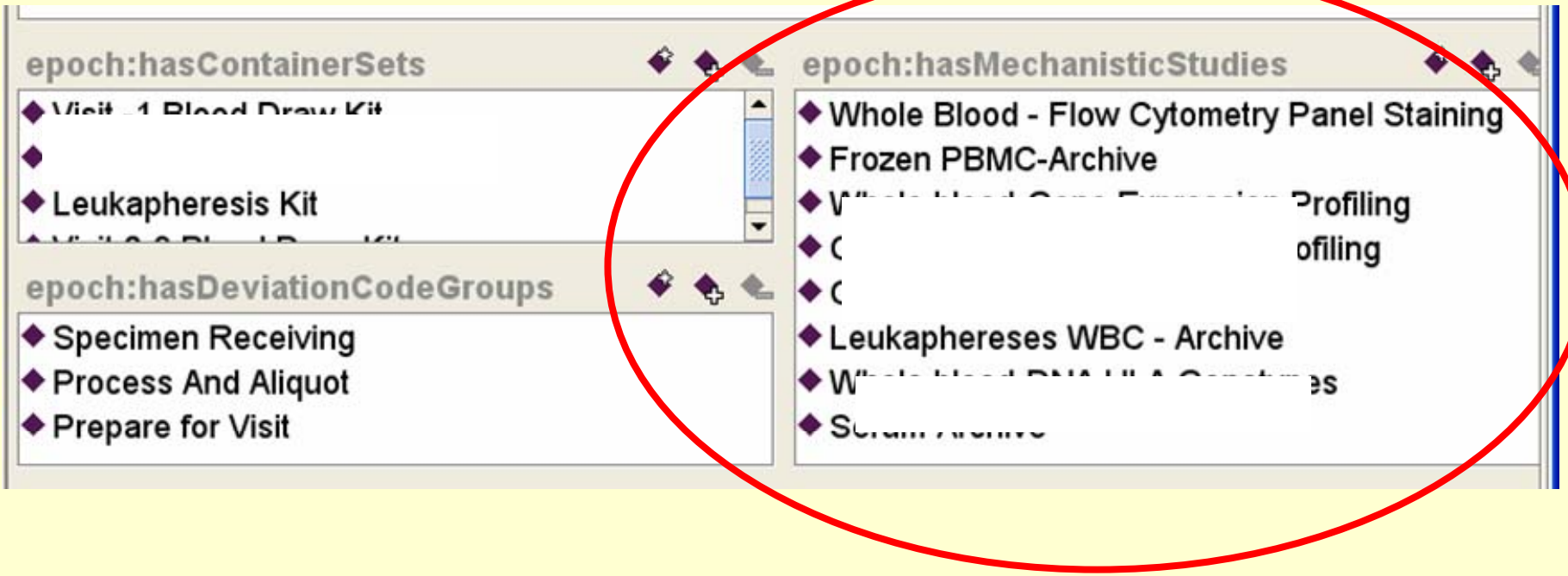
Mechanistic Study Plan



Mechanistic Study Plan

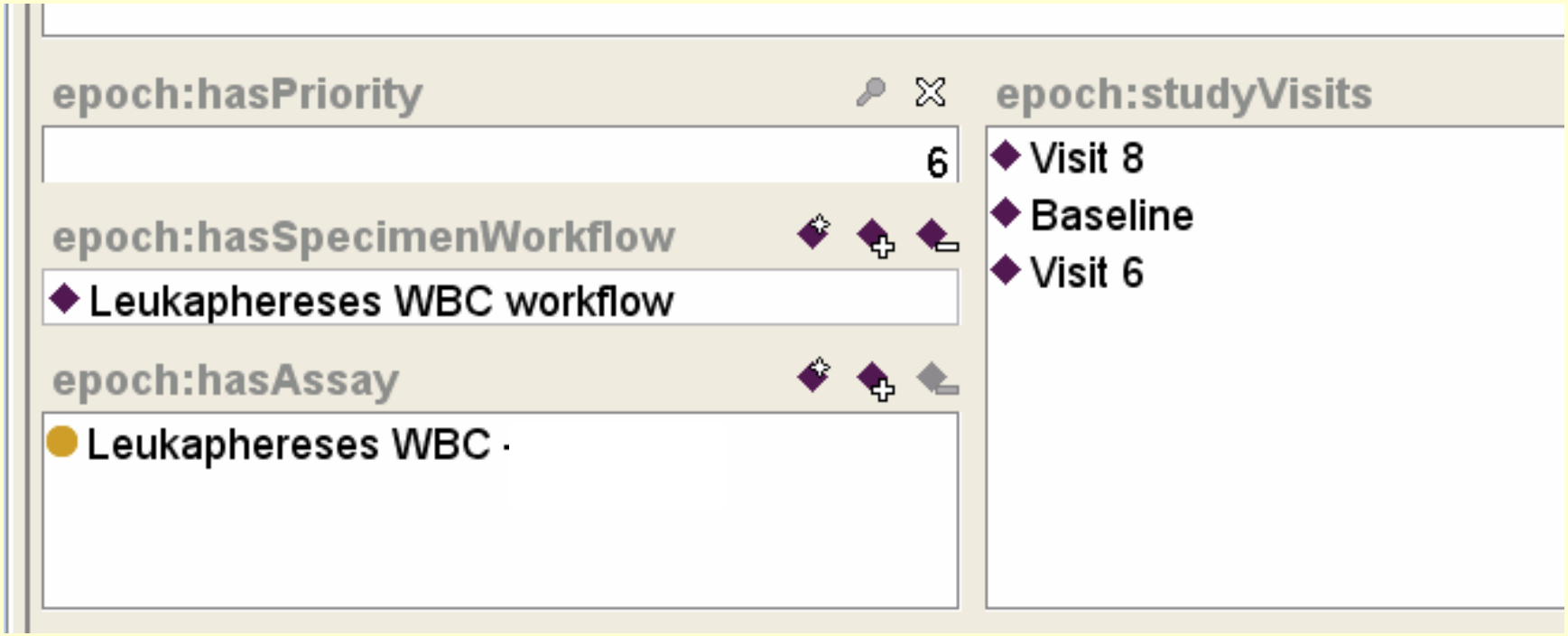


Mechanistic Study Plan



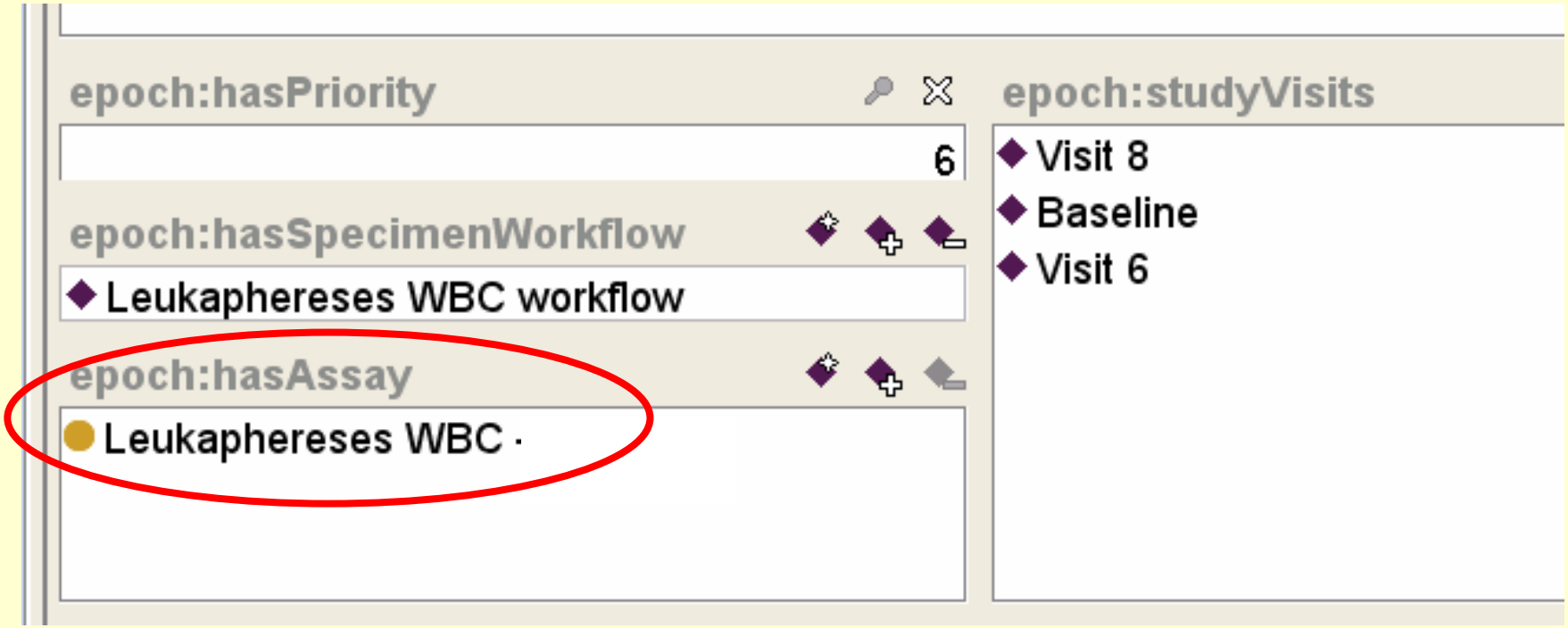
A Mechanistic Study

◆ Leukaphereses WBC - Archive

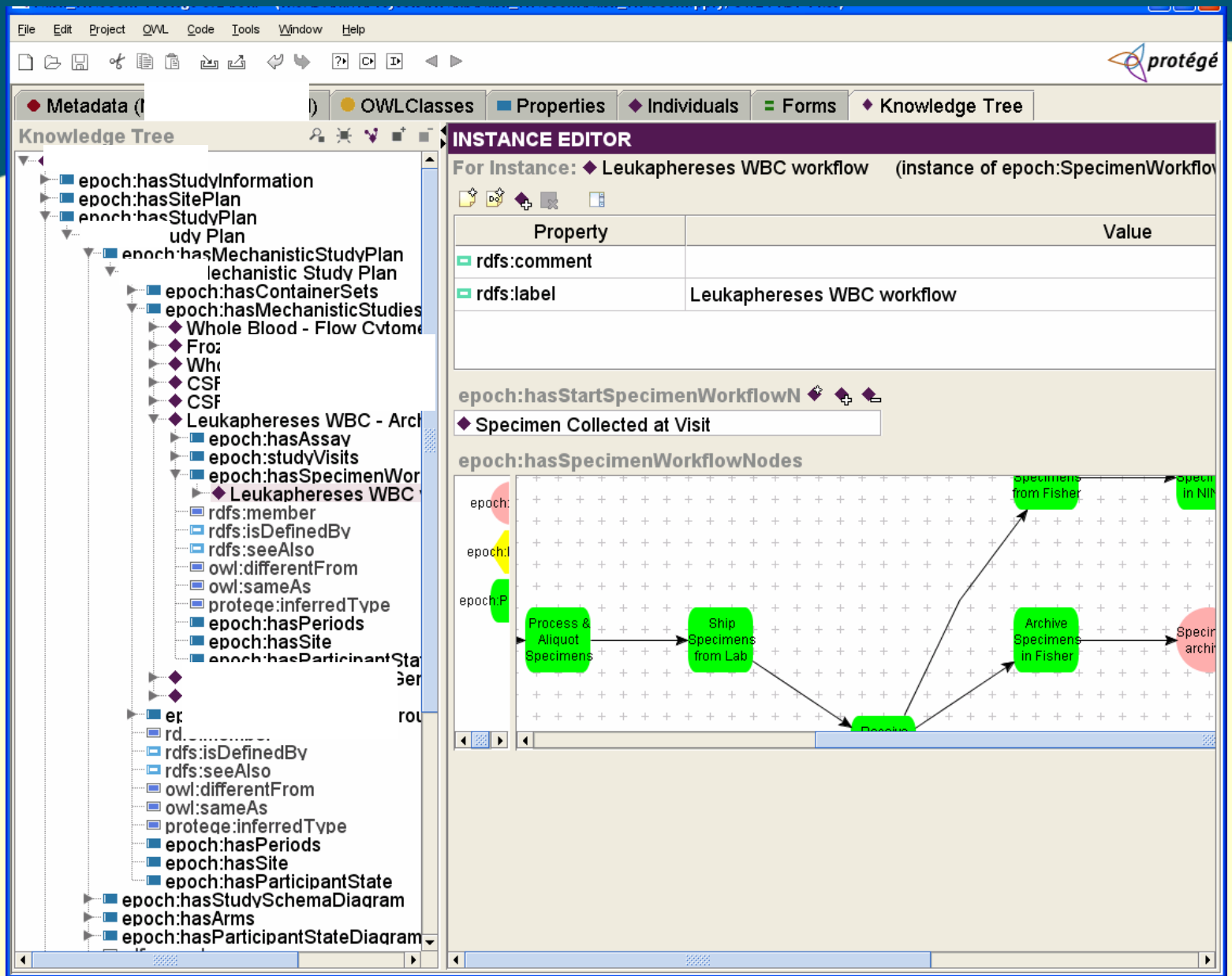


A Mechanistic Study

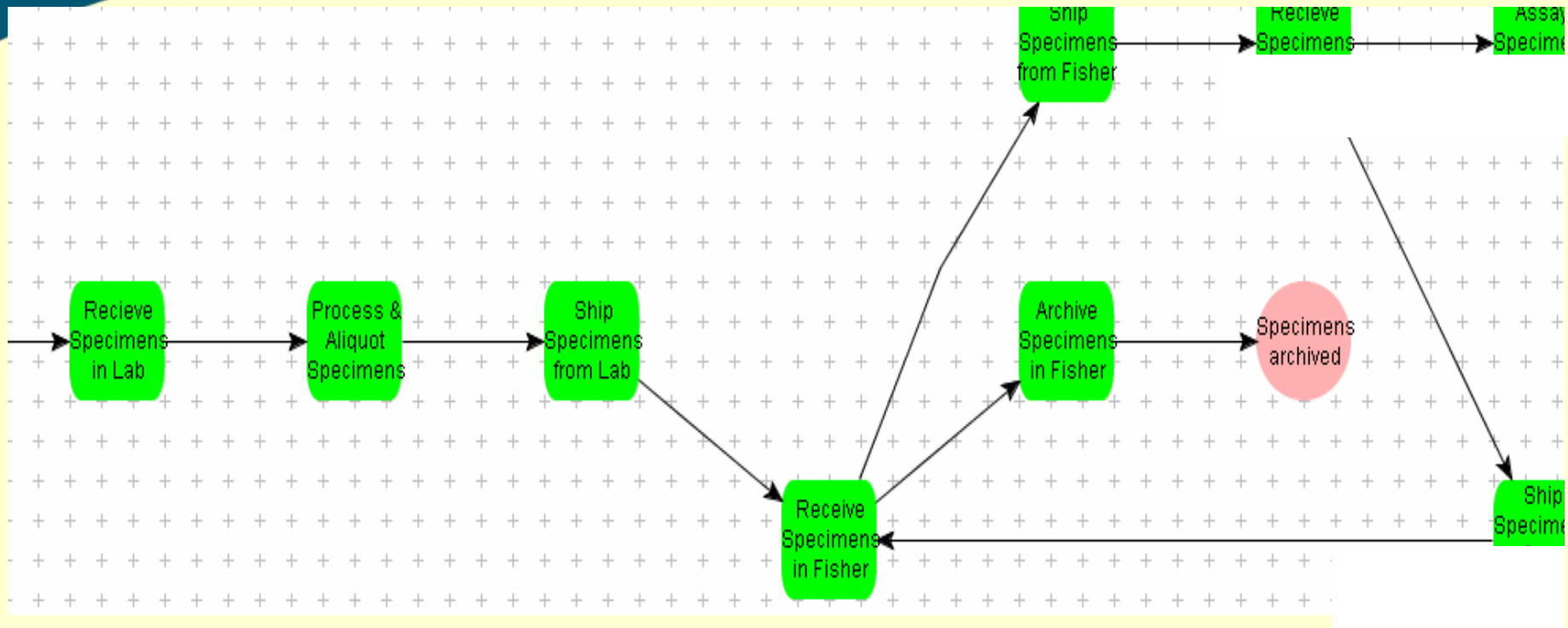
◆ Leukaphereses WBC - Archive



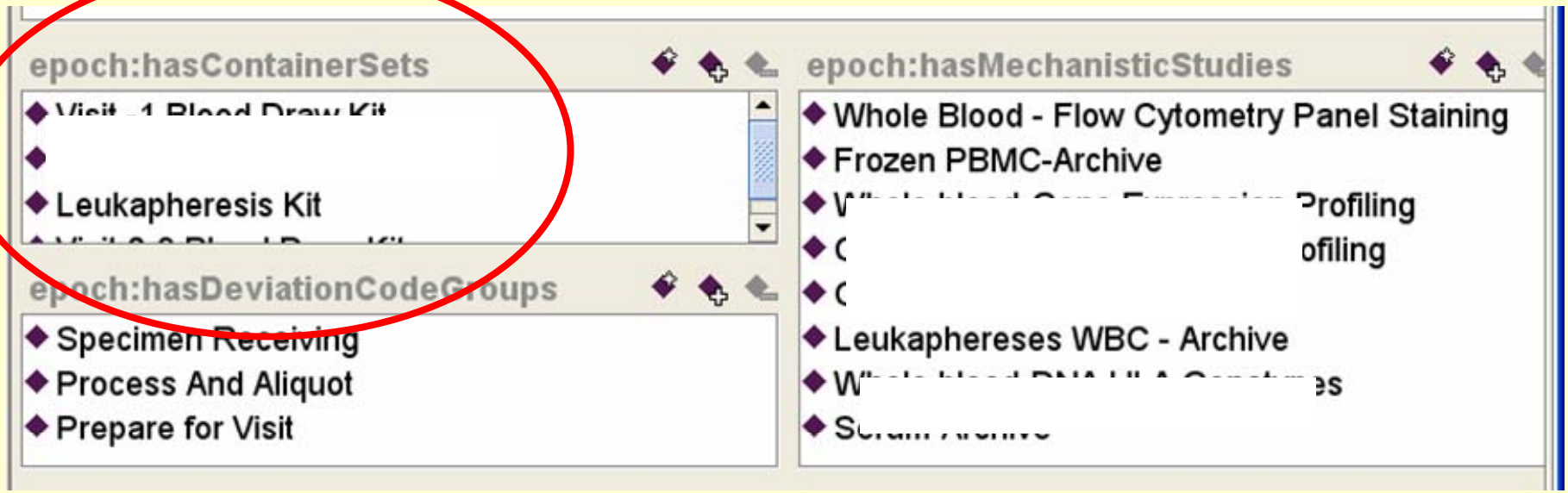
Specimen Workflow



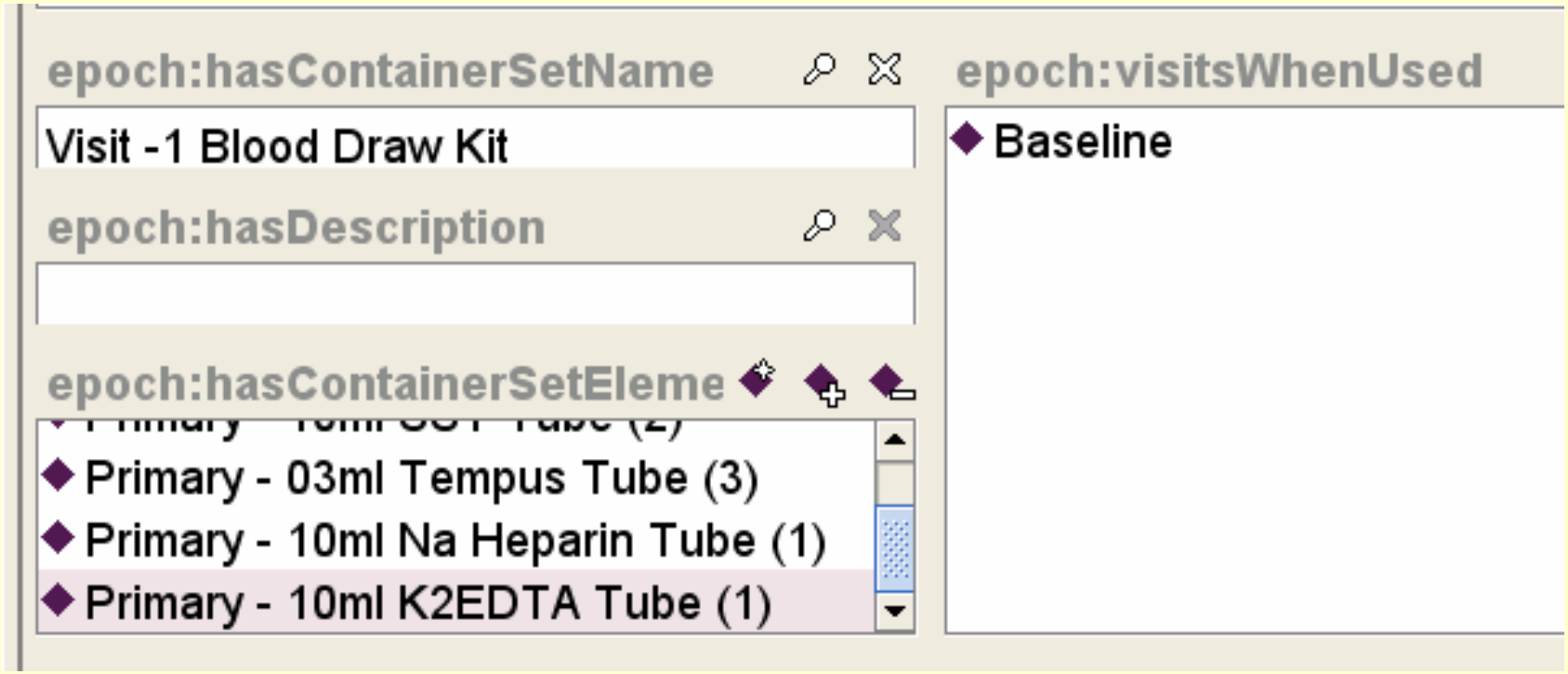
Specimen Workflow



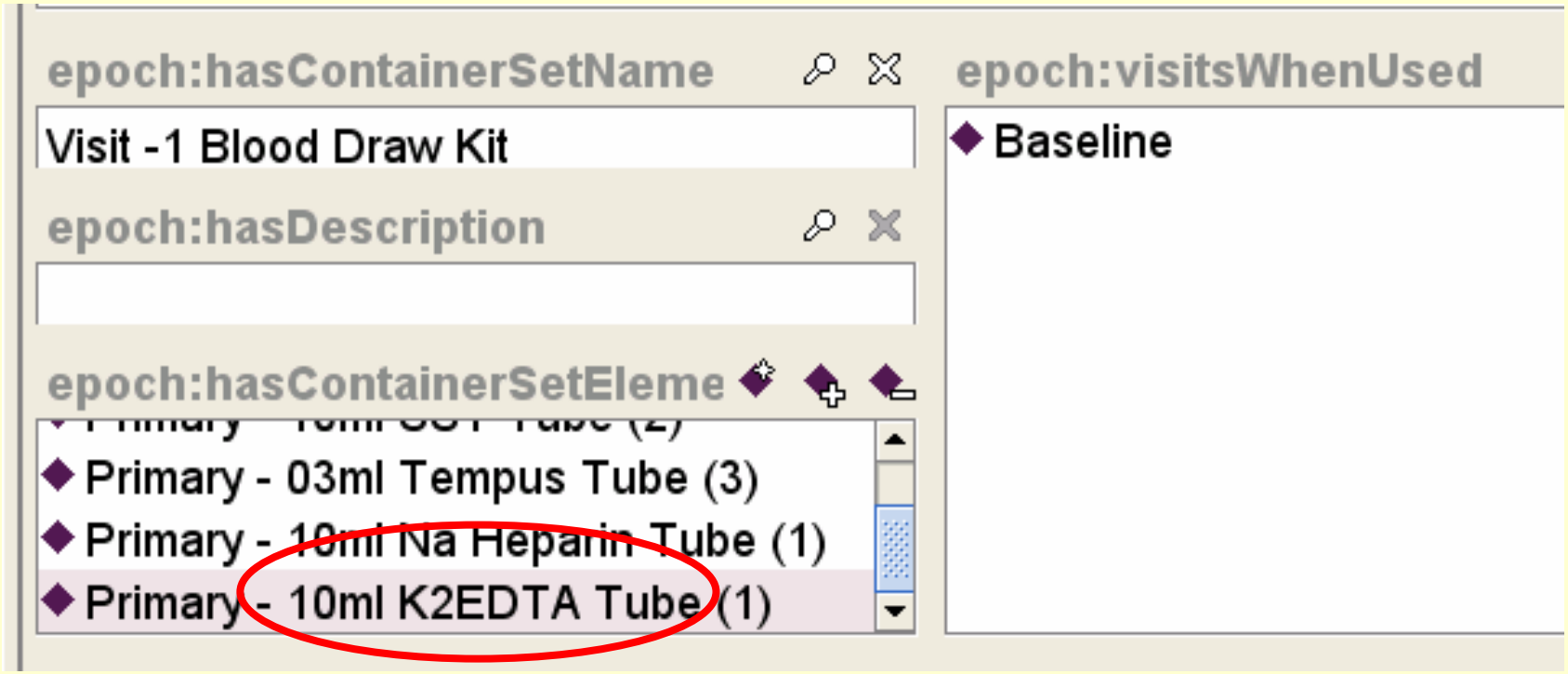
Mechanistic Study Plan



Specimen Container Set



Specimen Container Set



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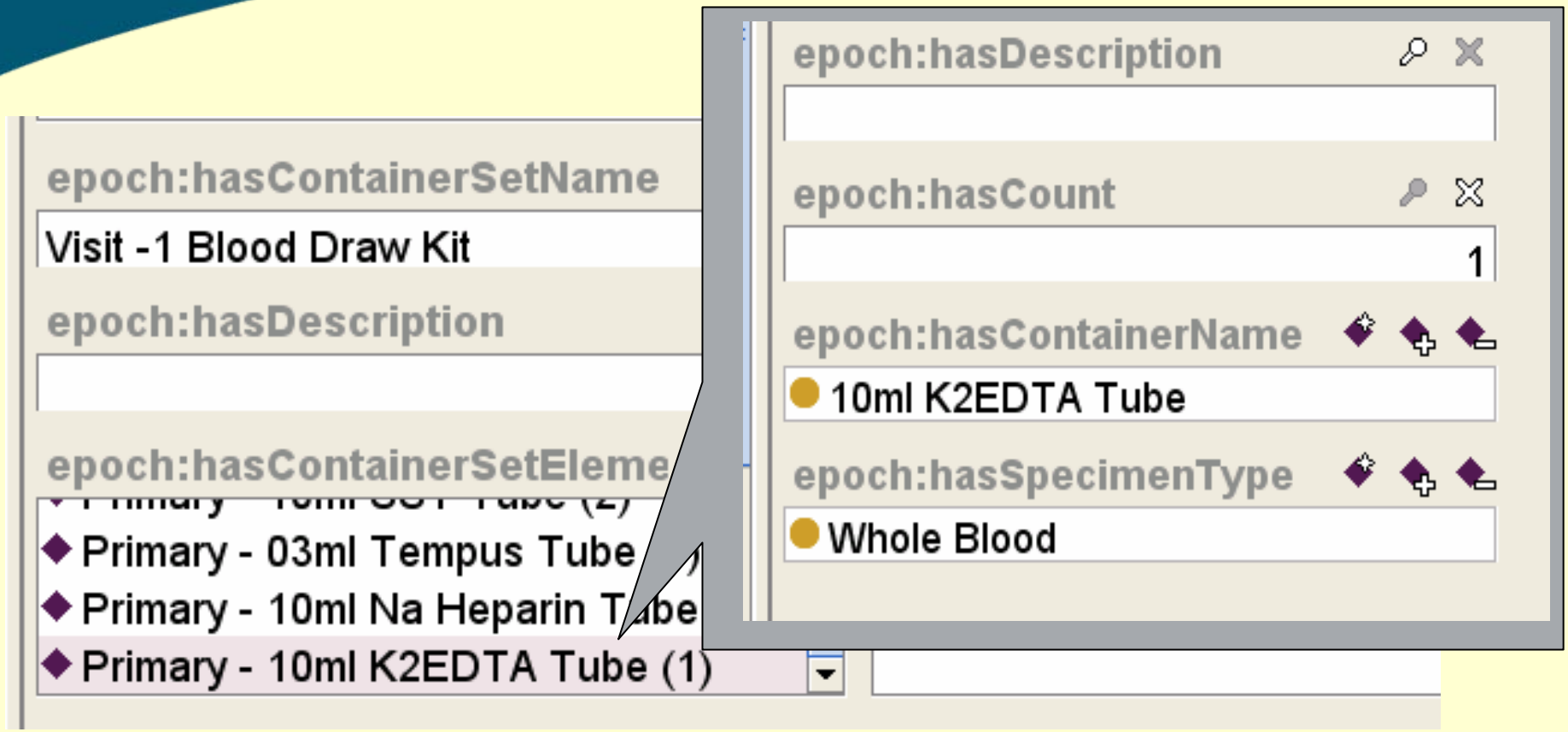
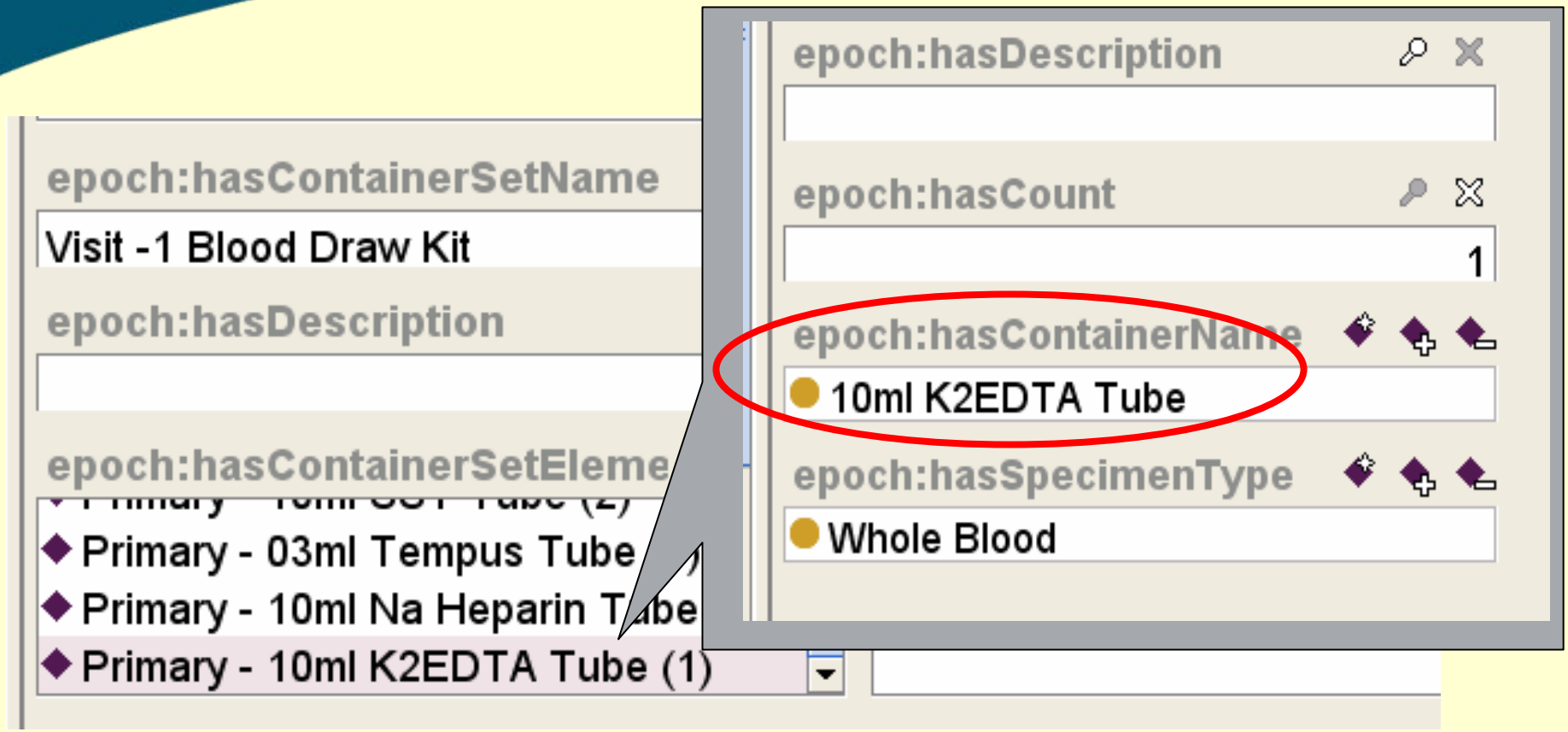
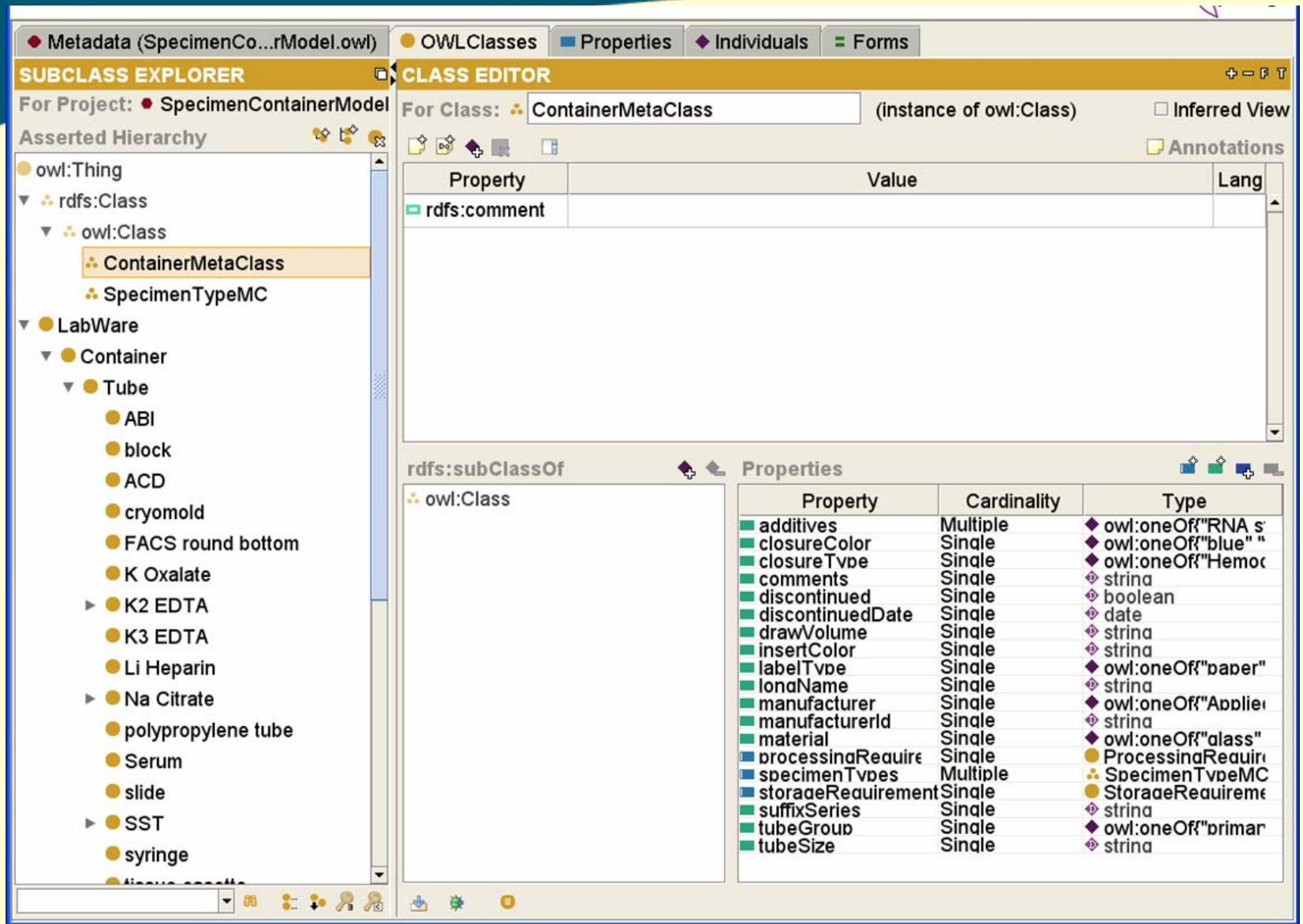


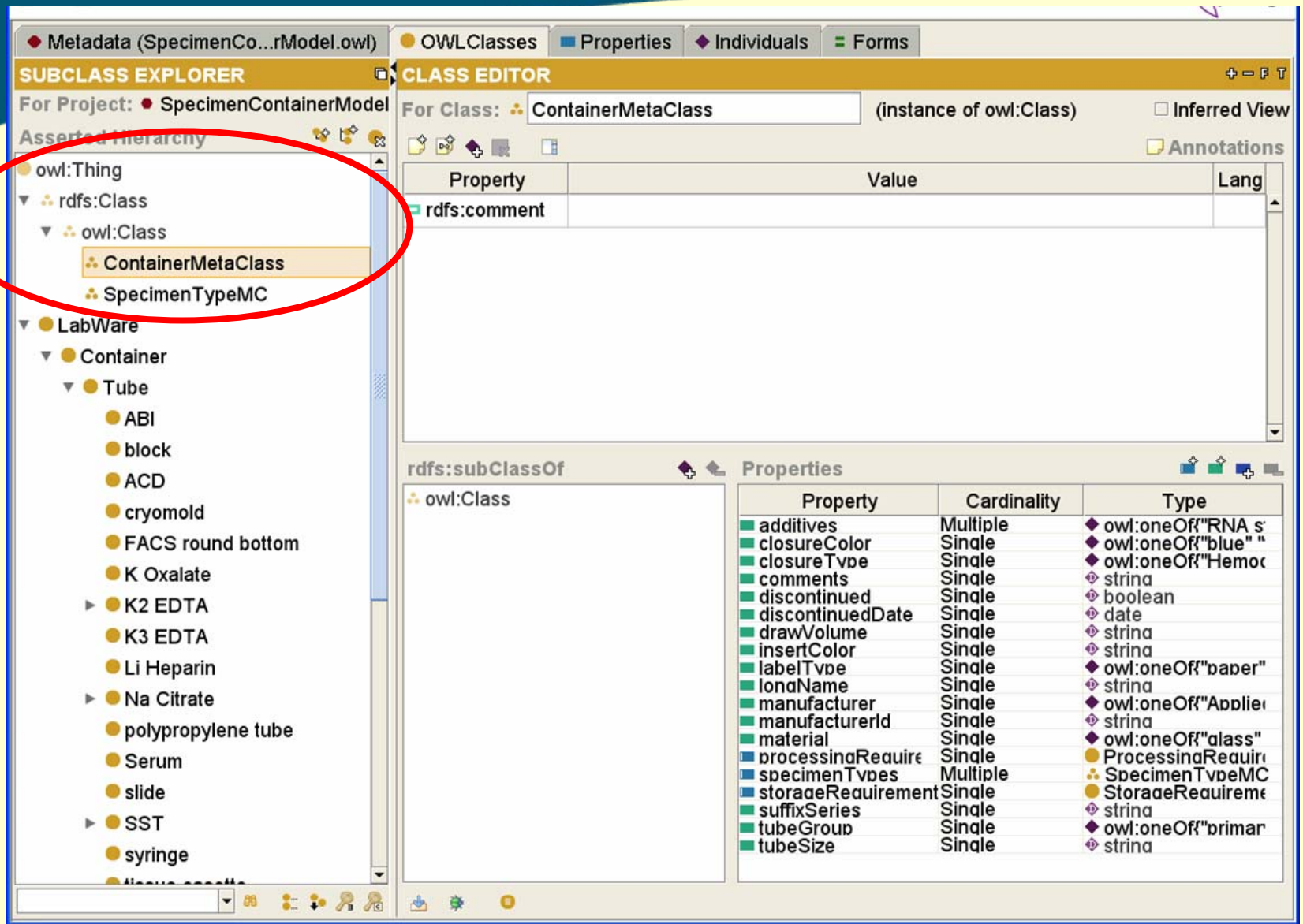
Specimen Container Set



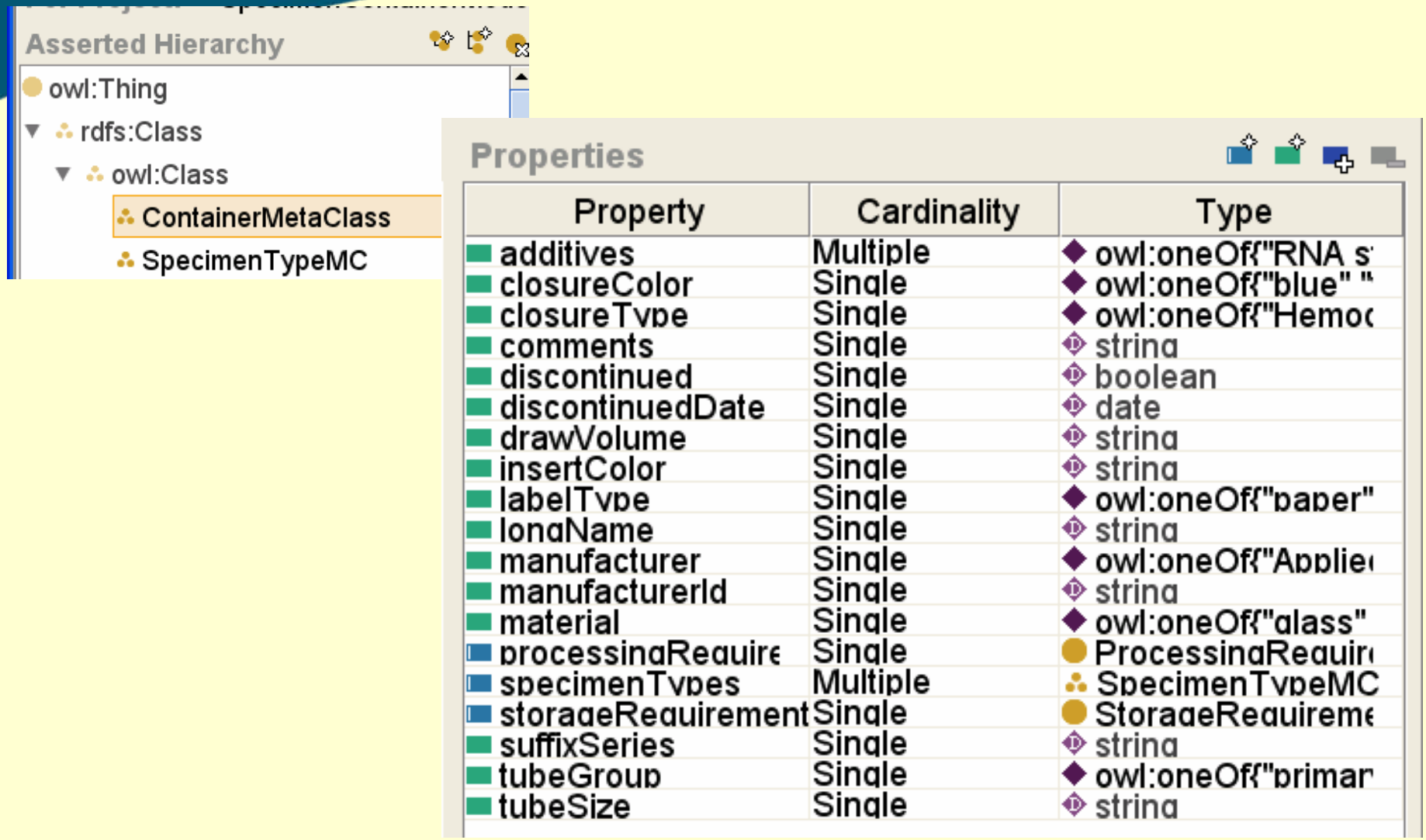
Specimen Container Ontology – using OWL Full meta model



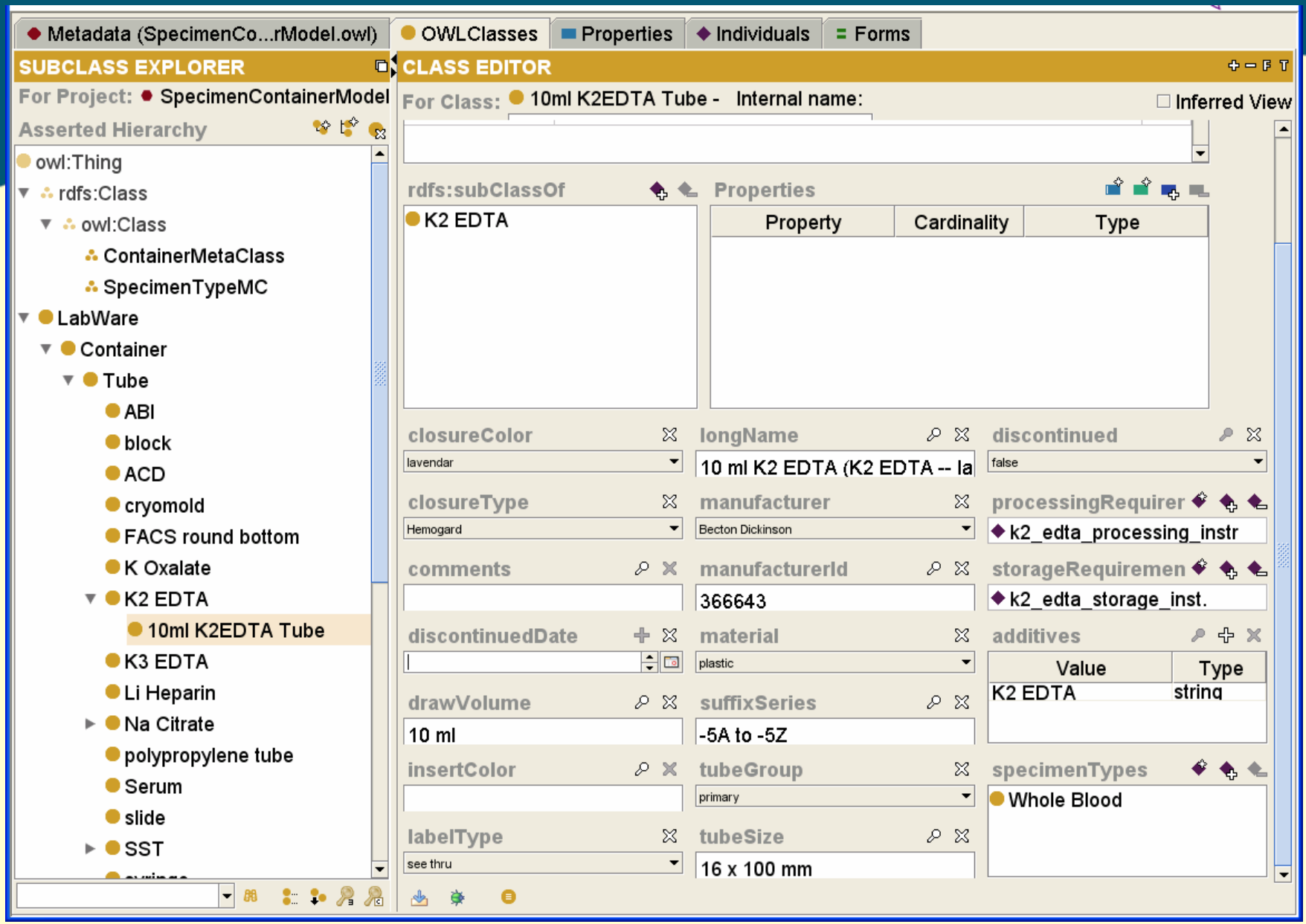
Specimen Container Ontology – using OWL Full meta model



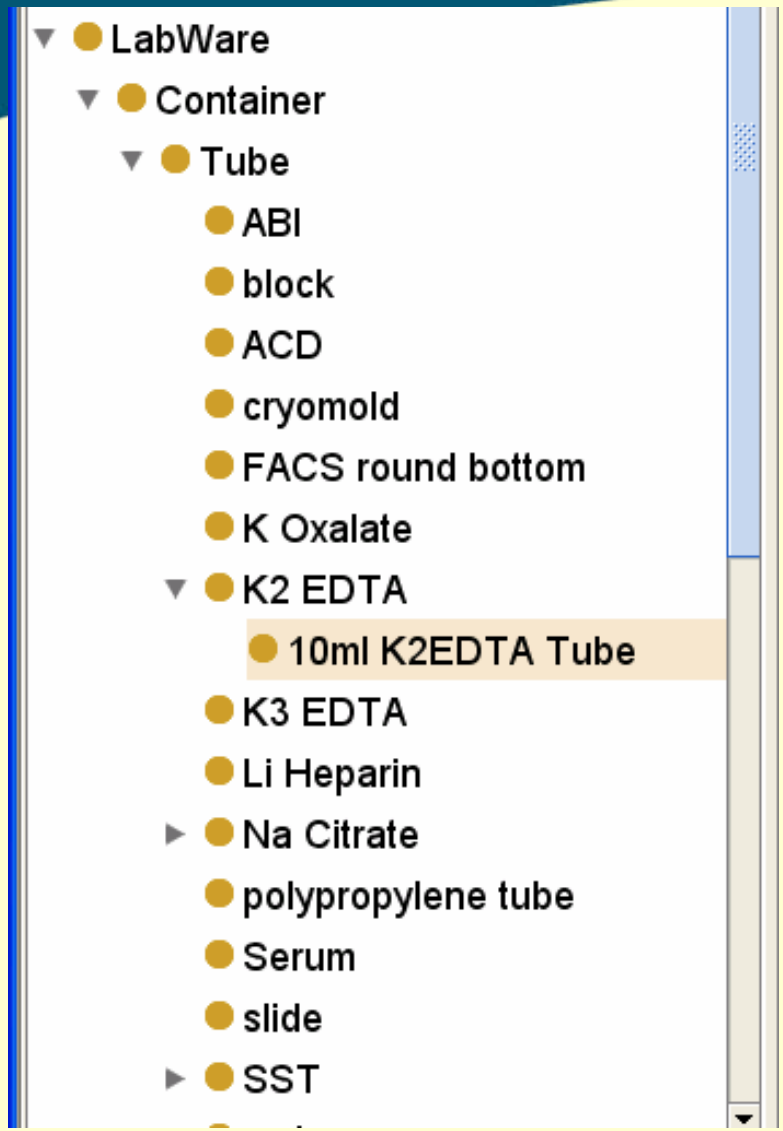
Specimen Container Ontology – using OWL Full meta model



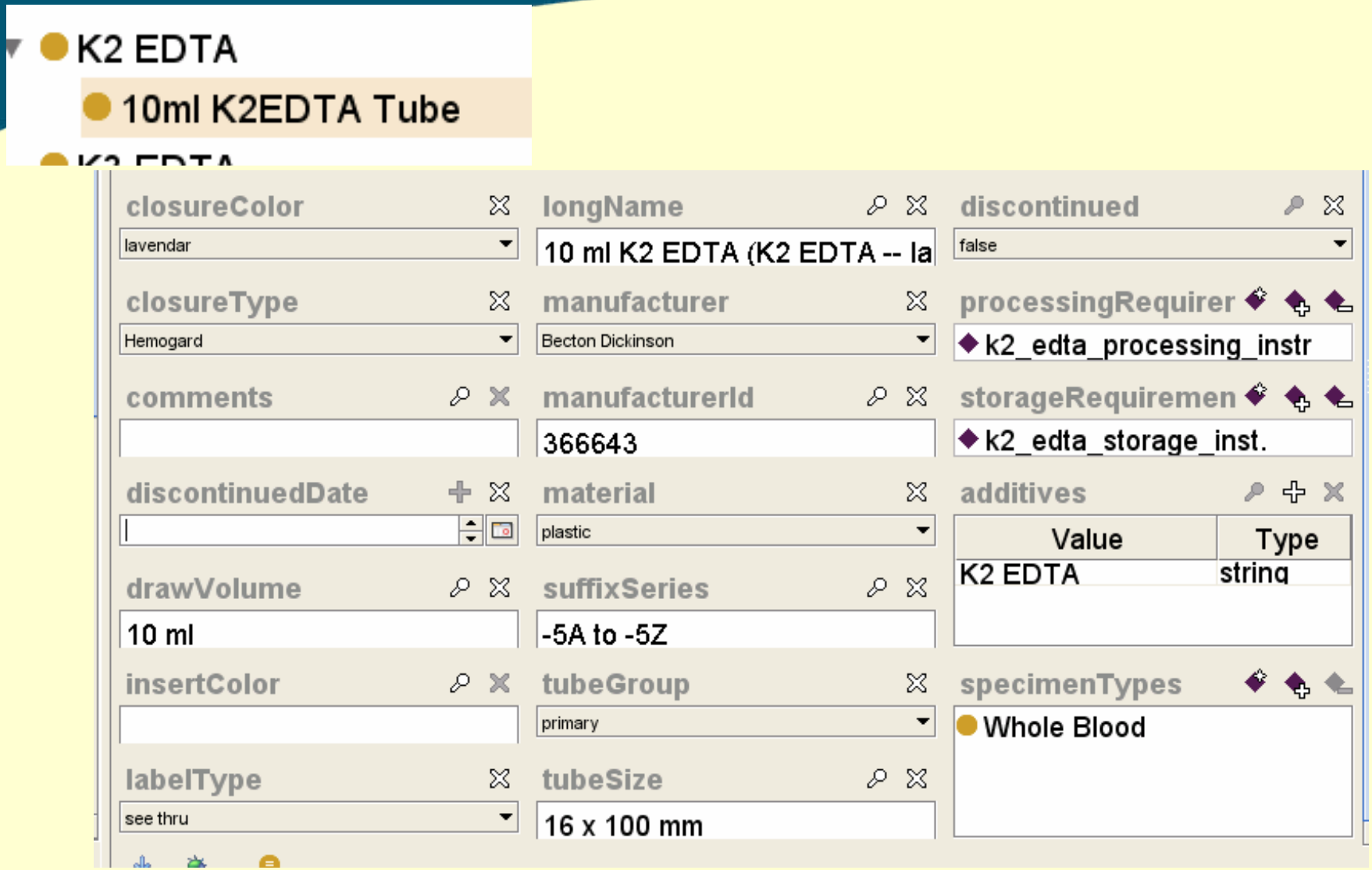
Specimen Container Ontology



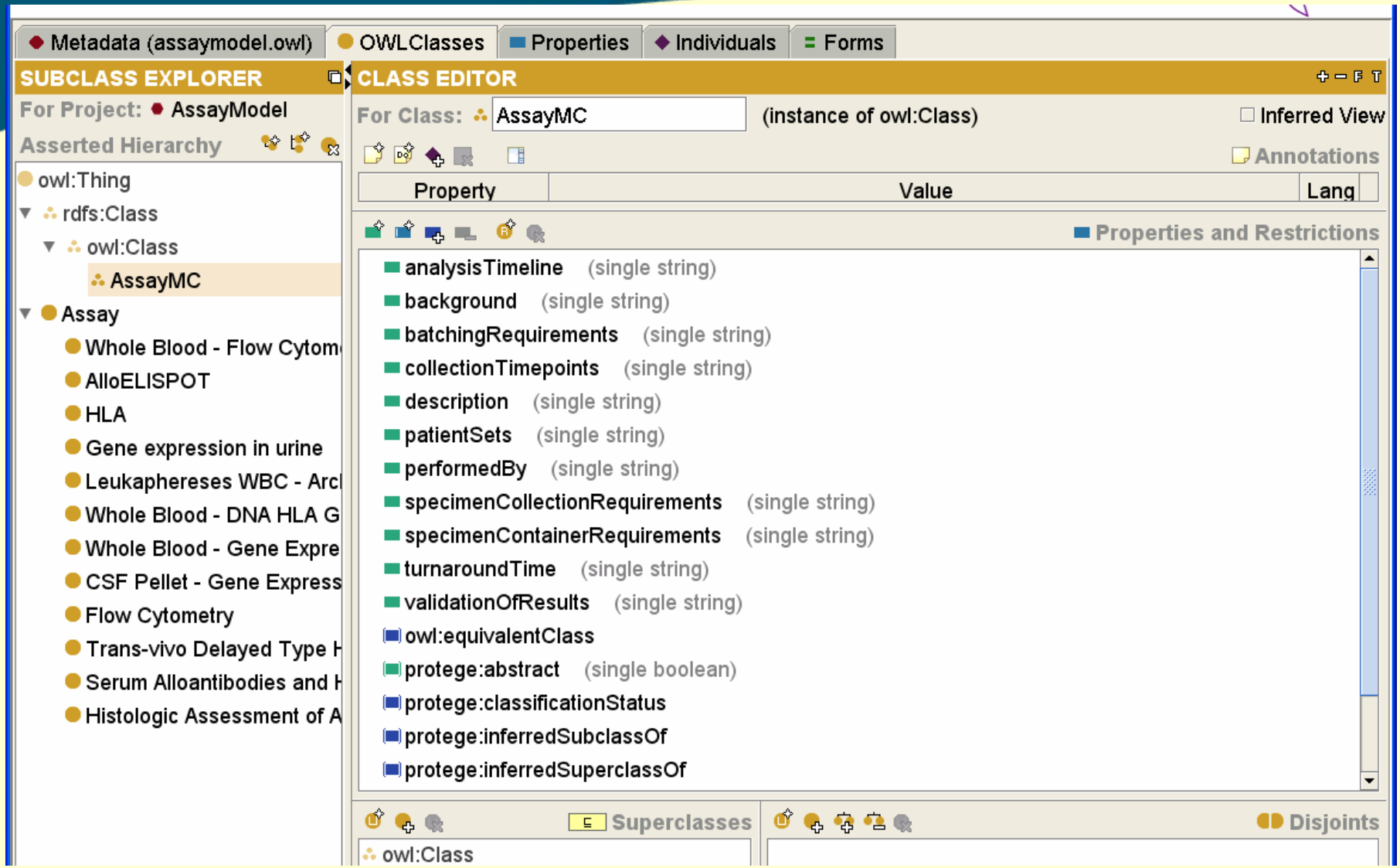
A Hierarchy of Specimen Containers



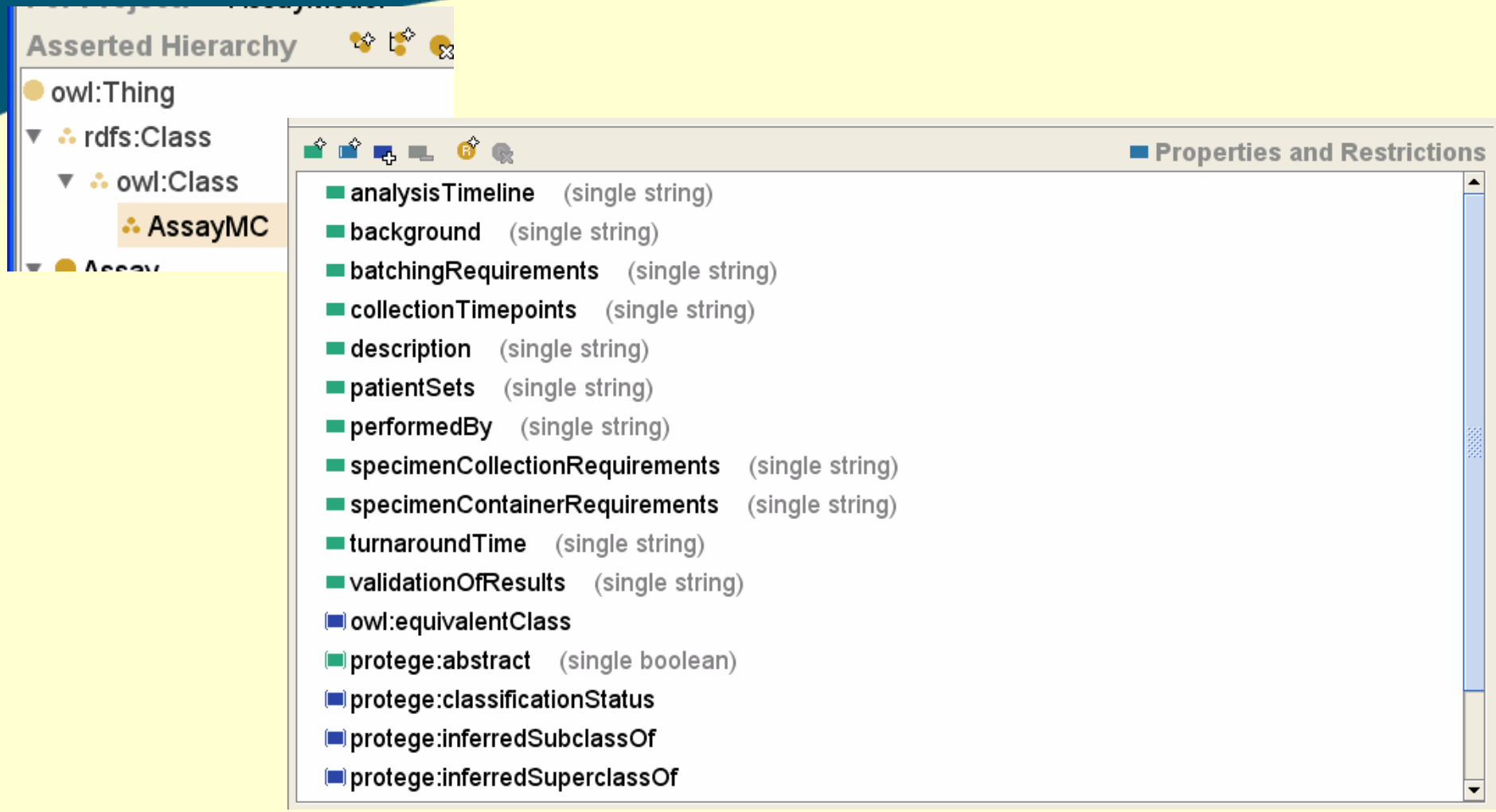
A Specimen Container



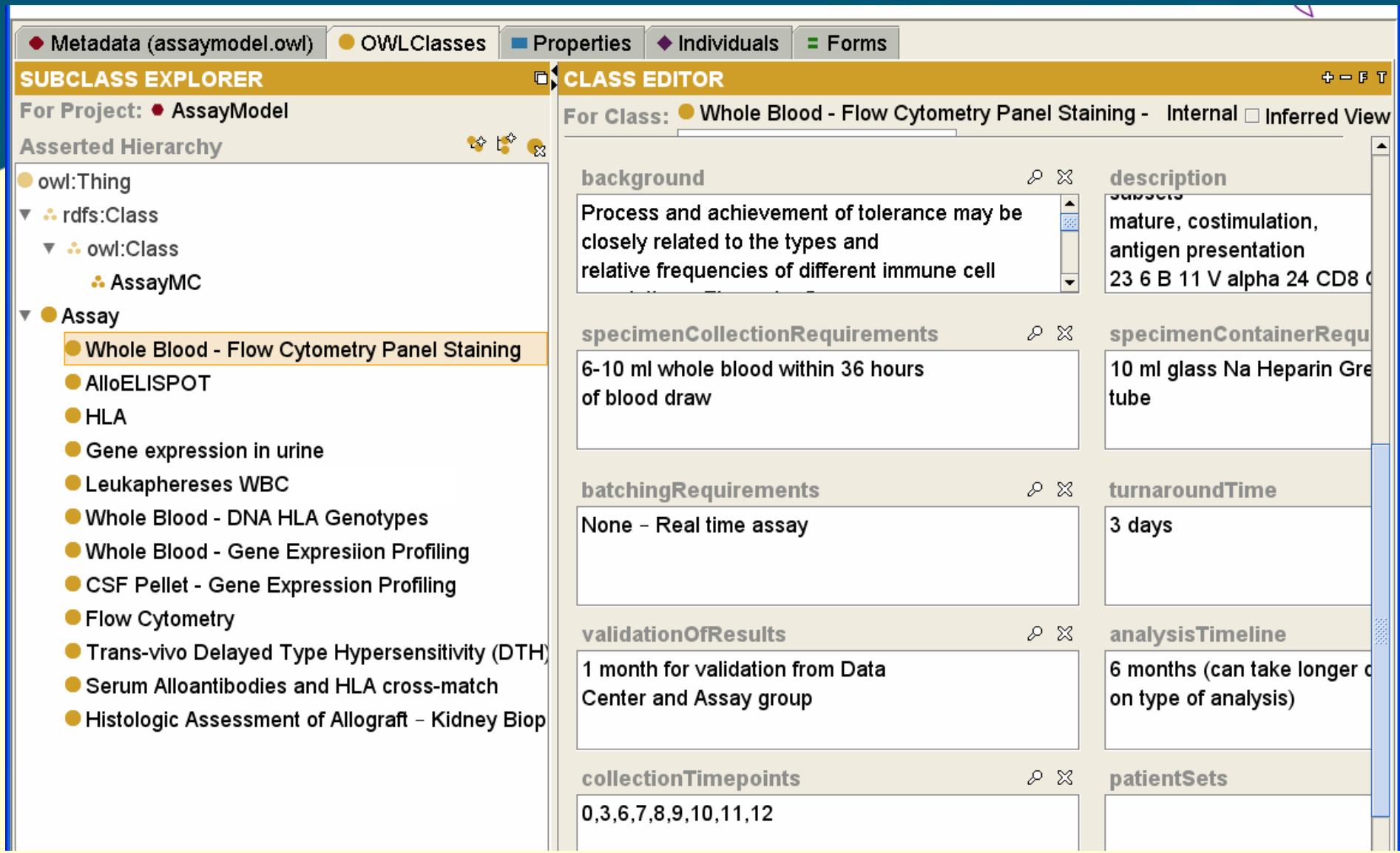
Assay Ontology – using OWL Full meta model



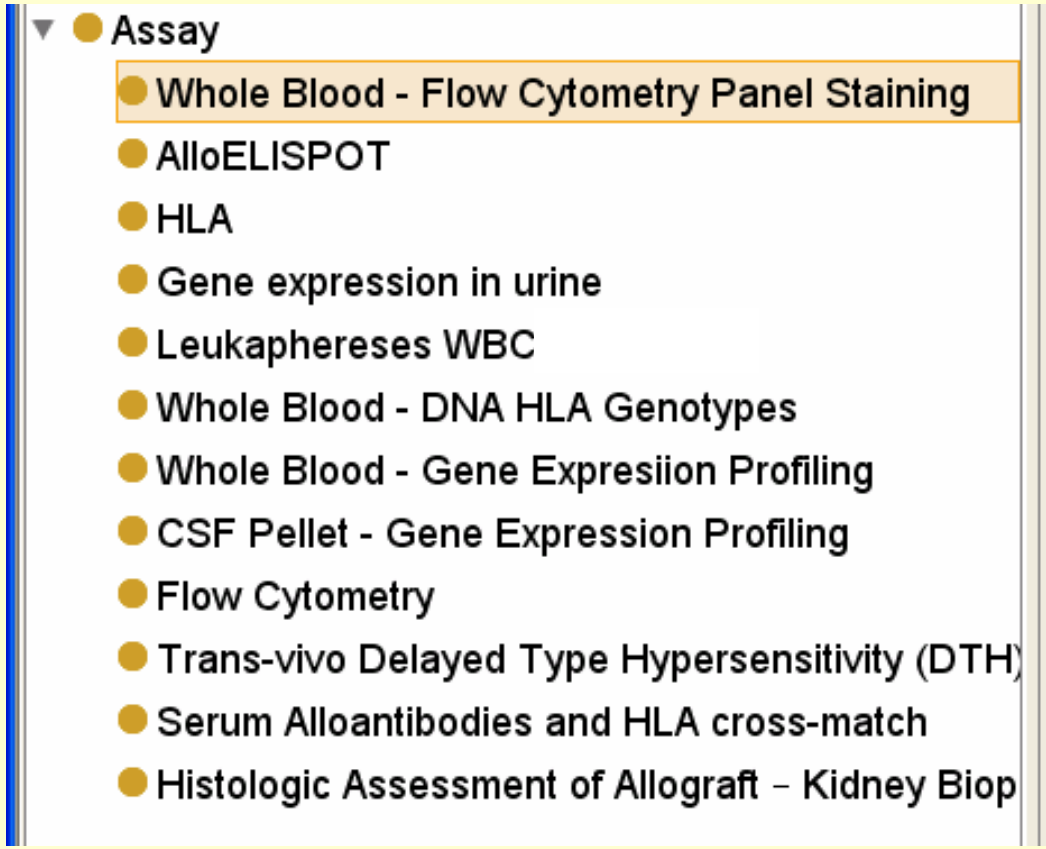
Assay Ontology – using OWL Full meta model



Assay Ontology



Assay Ontology



An Assay

Whole Blood - Flow Cytometry Panel Staining

background

Process and achievement of tolerance may be closely related to the types and relative frequencies of different immune cell

description

Examination of PBMC surface molecule expression will be performed using 5 color antibody combinations. The monoclonal

specimenCollectionRequirements

6-10 ml whole blood within 36 hours of blood draw

specimenContainerRequirements

10 ml glass Na Heparin Green Top tube

batchingRequirements

None – Real time assay

turnaroundTime

3 days

validationOfResults

1 month for validation from Data Center and Assay group

analysisTimeline

6 months (can take longer depending on type of analysis)

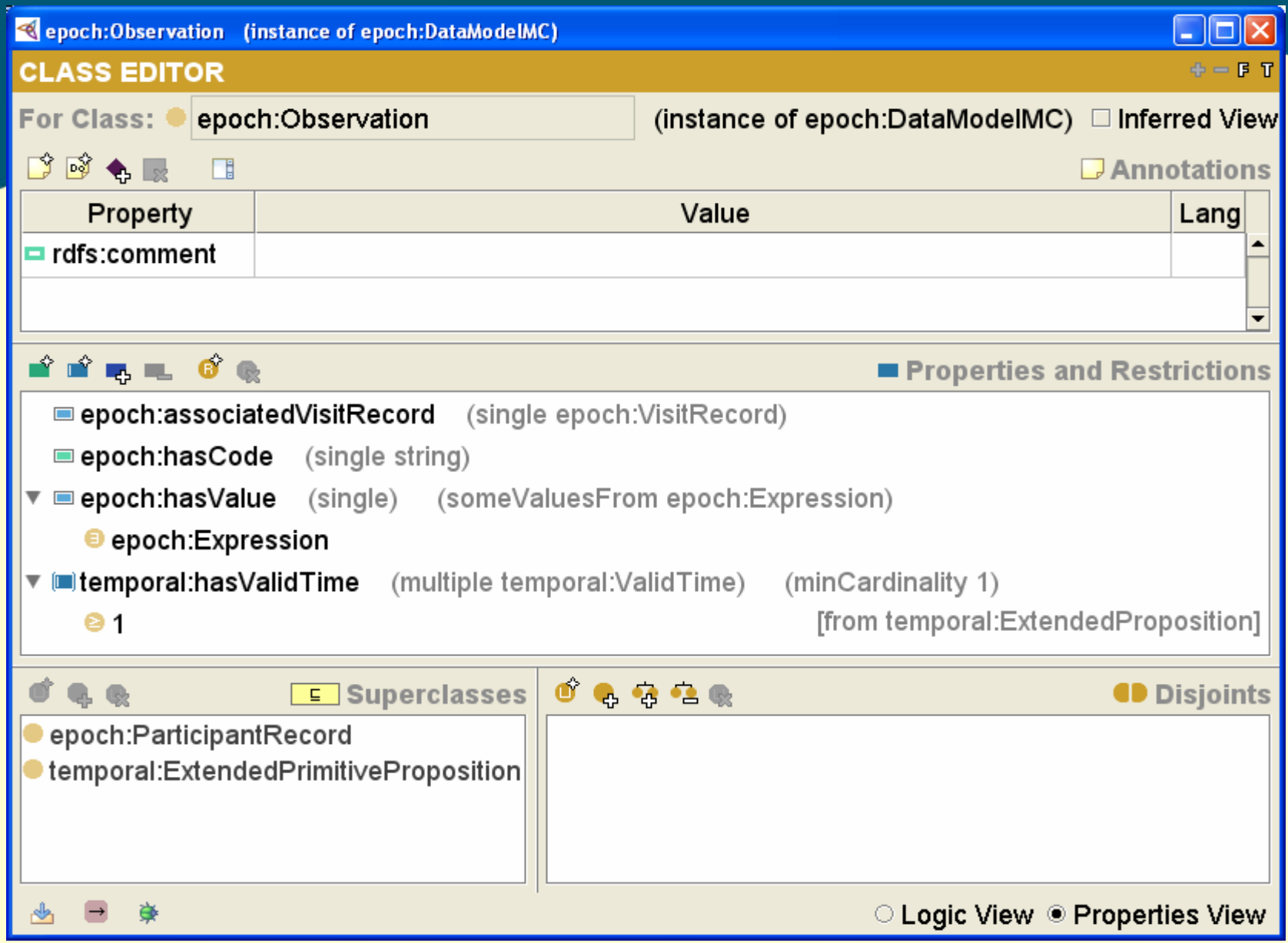
collectionTimepoints

0,3,6,7,8,9,10,11,12

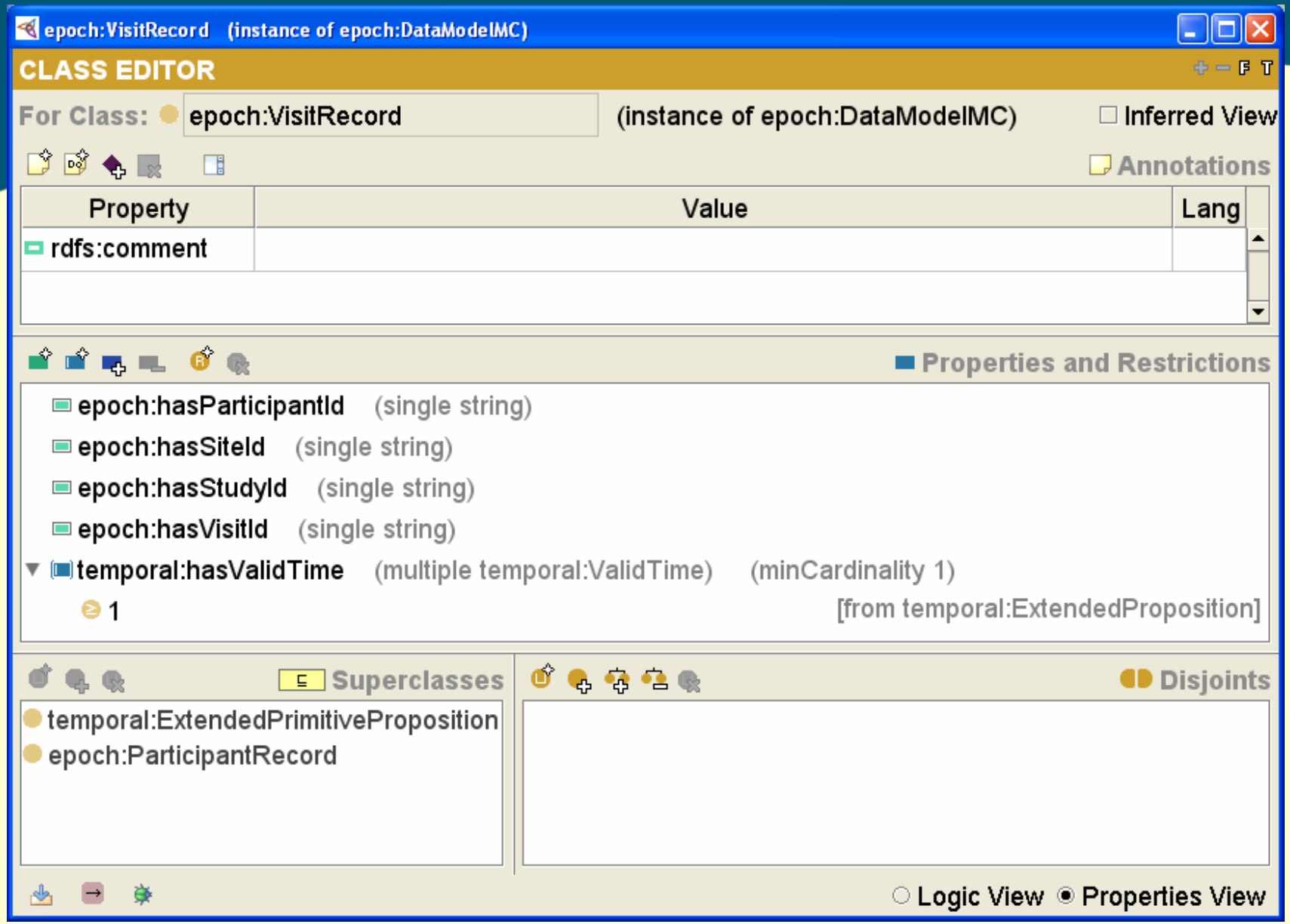
patientSets

performedBy

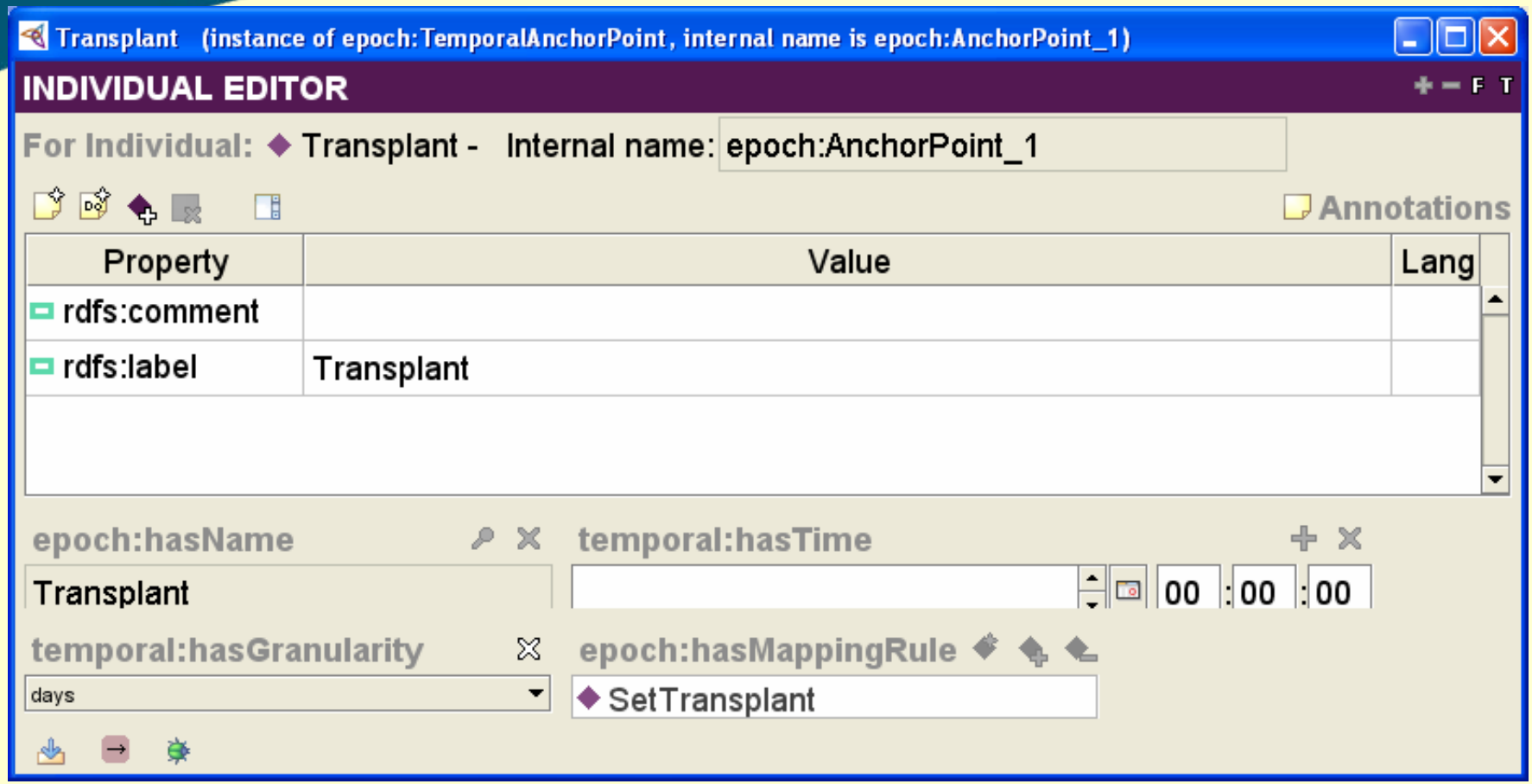
Virtual Trial Data Model - Observation



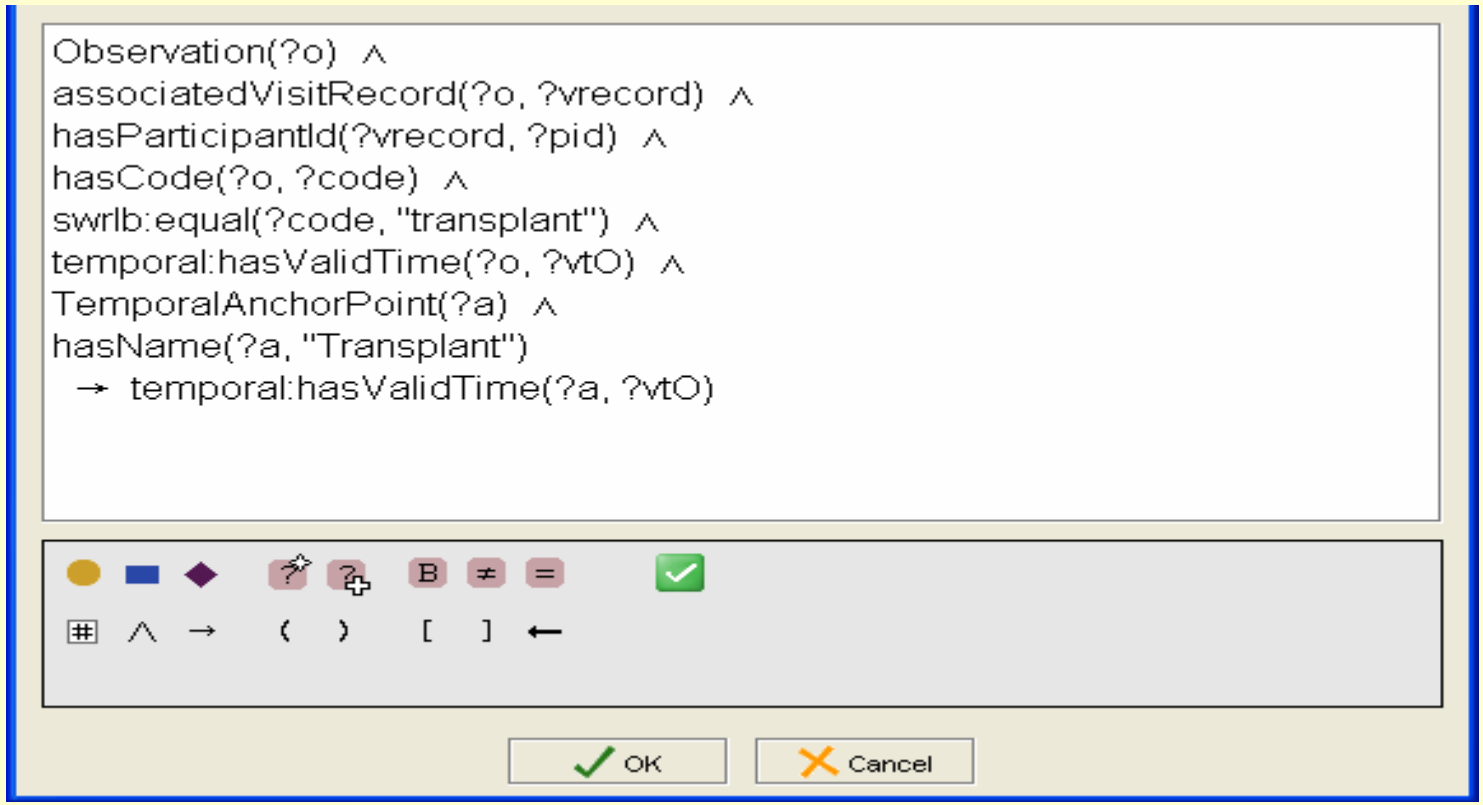
Virtual Trial Data Model - VisitRecord



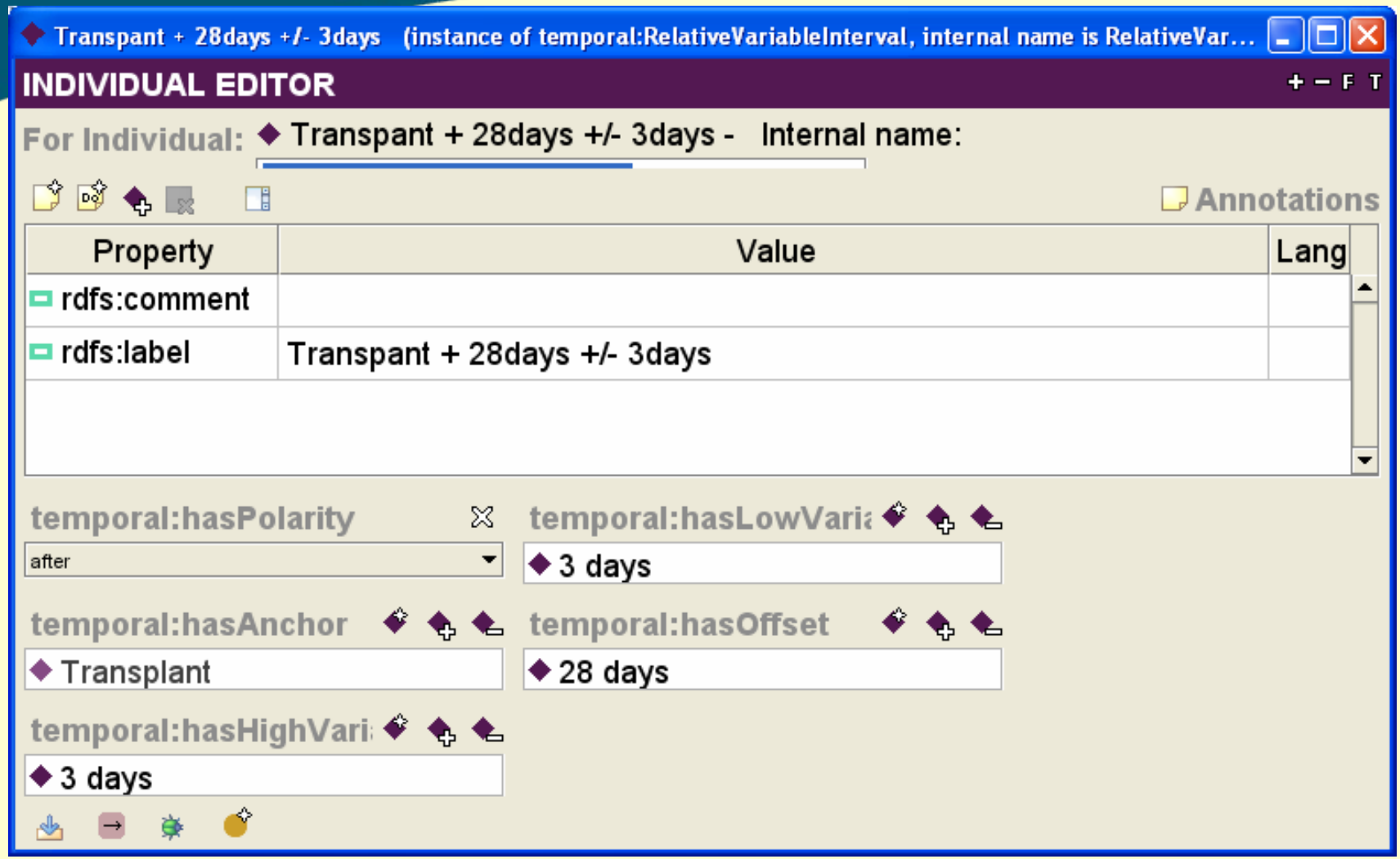
Anchor Point - Transplant



SWRL Rule to set Transplant Time

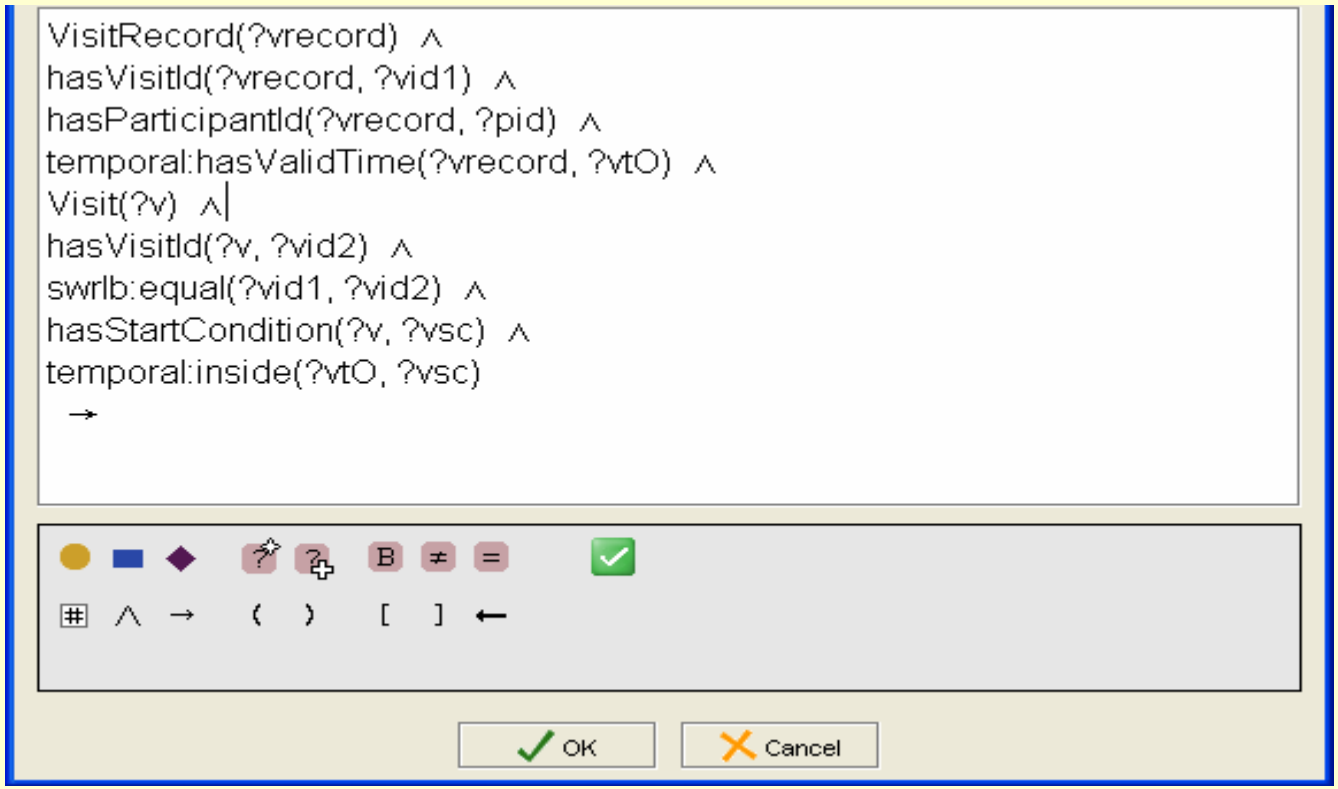


Visit Time Window



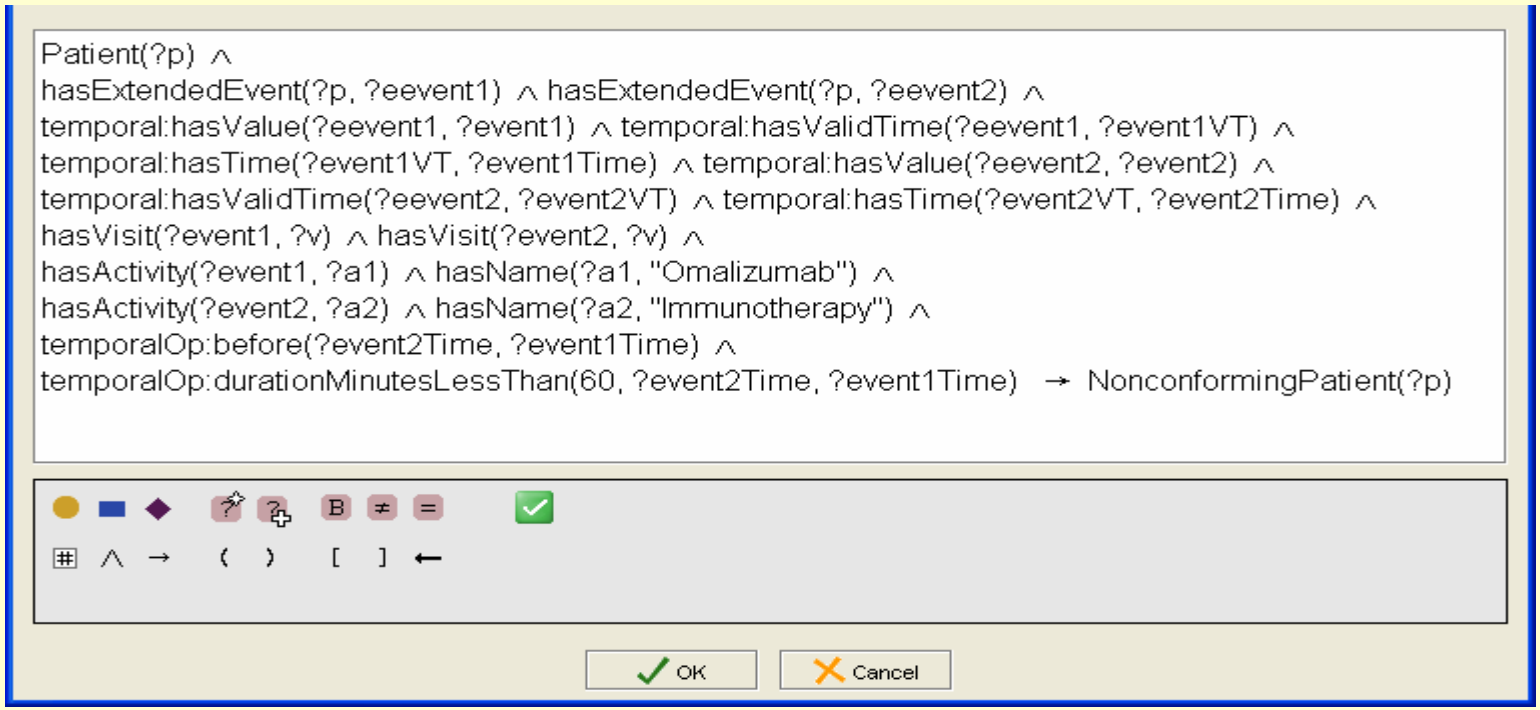
Visit Time constraint as a SWRL rule

Check if the participant's visits occurred within the visit time window specifications



Constraints expressed as SWRL rules

On days that both immunotherapy and omalizumab are administered, omalizumab will be injected 60 minutes after the immunotherapy.

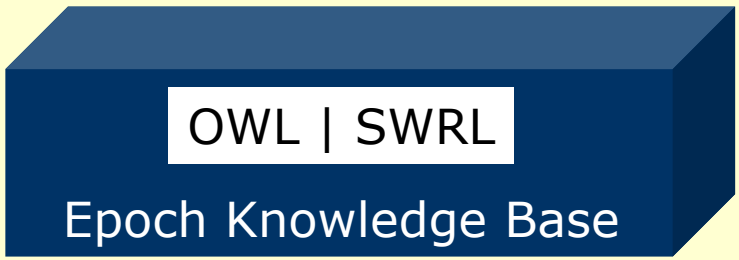


ITN Informatics Core at Stanford

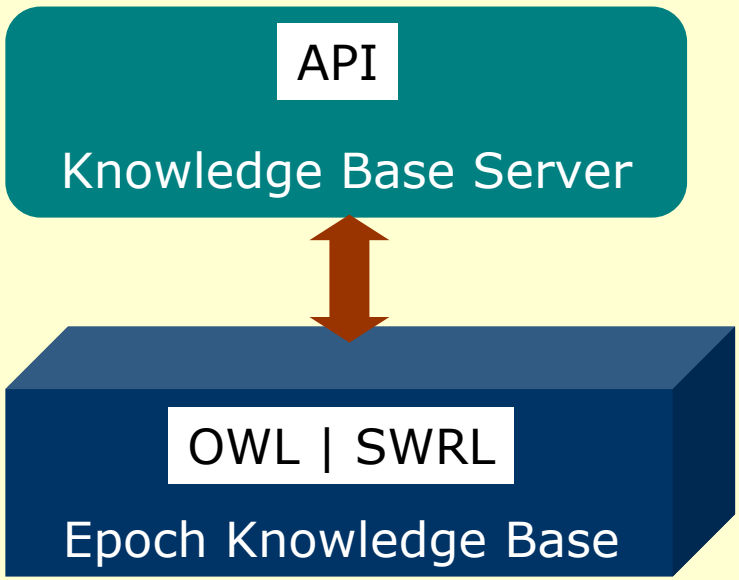
The goals of our collaboration are to

- Design tools to help acquire and maintain knowledge about protocol and assay designs
- Use this knowledge to drive data collection during a trial
- Implement querying methods to support trial monitoring, protocol tracking, and ad hoc data analysis

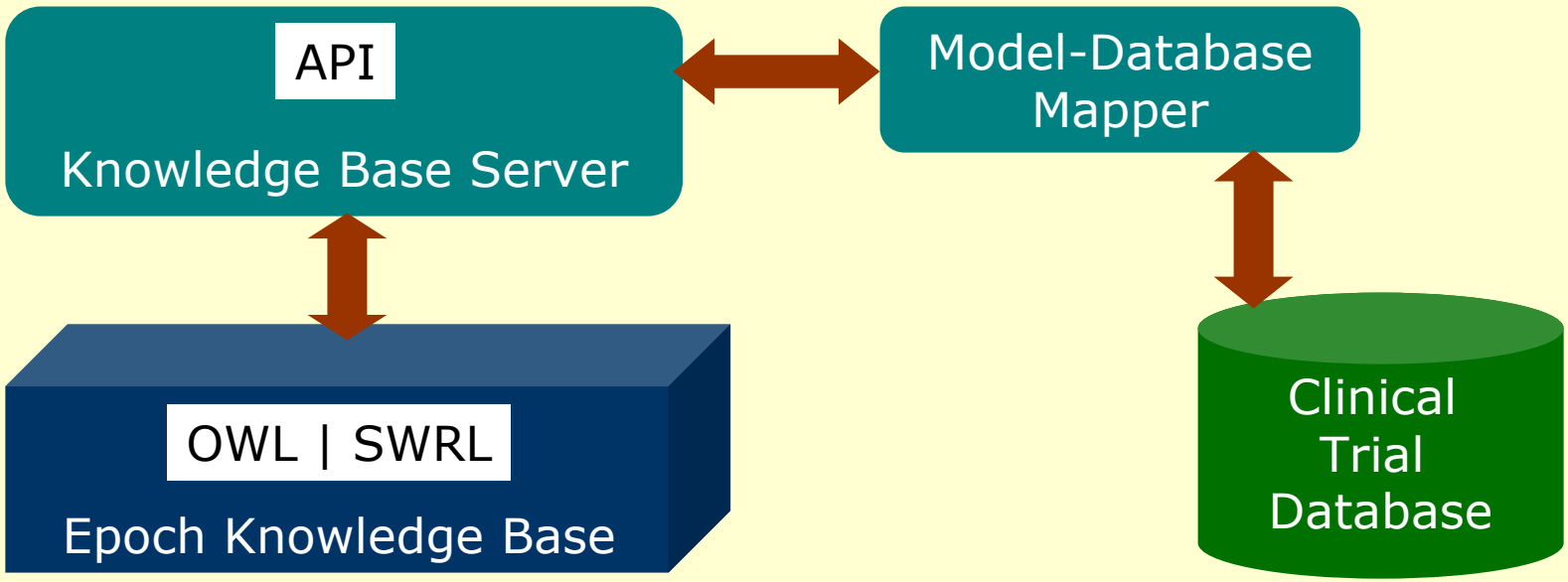
Epoch Architectural Plan



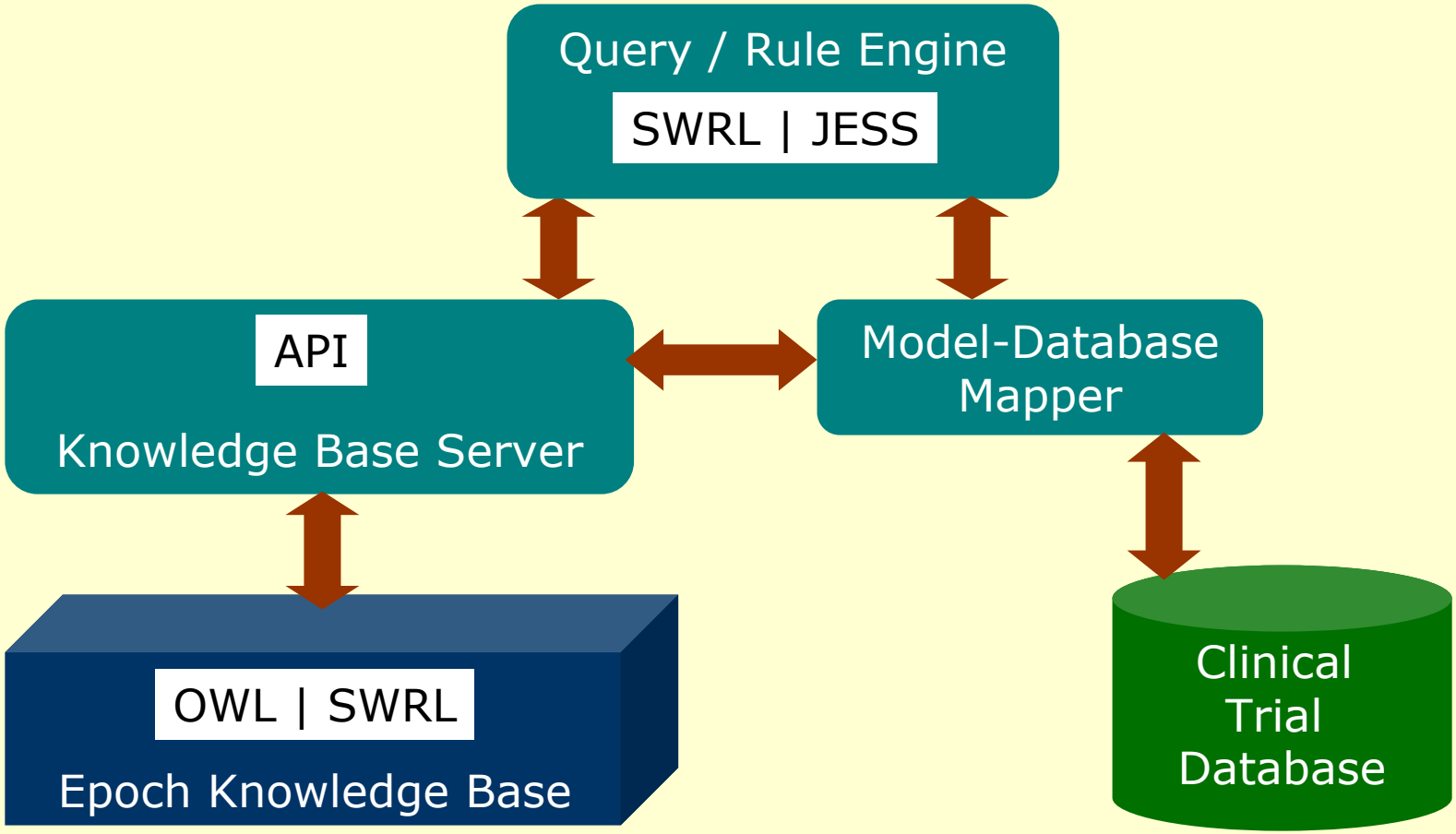
Epoch Architectural Plan



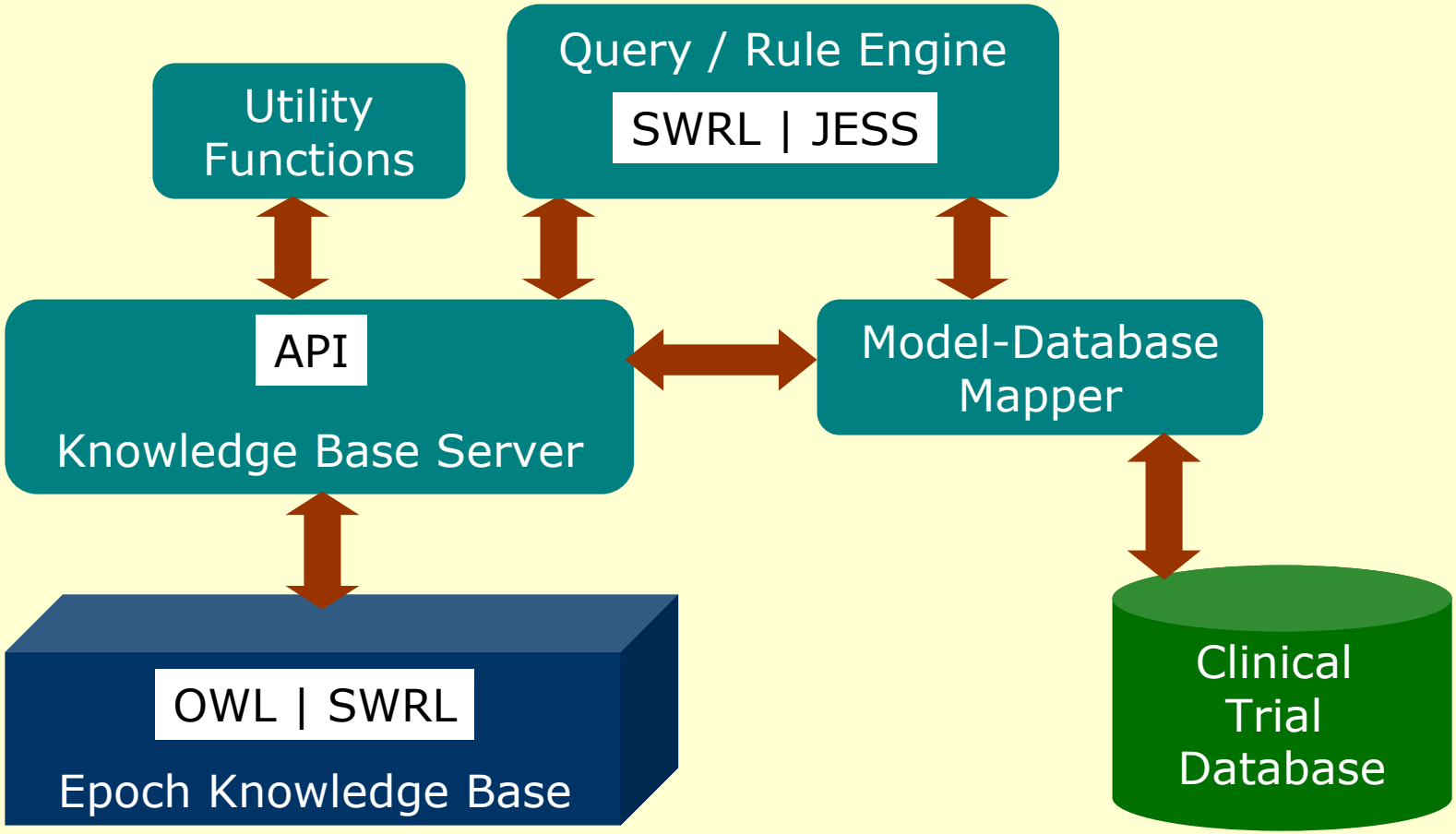
Epoch Architectural Plan



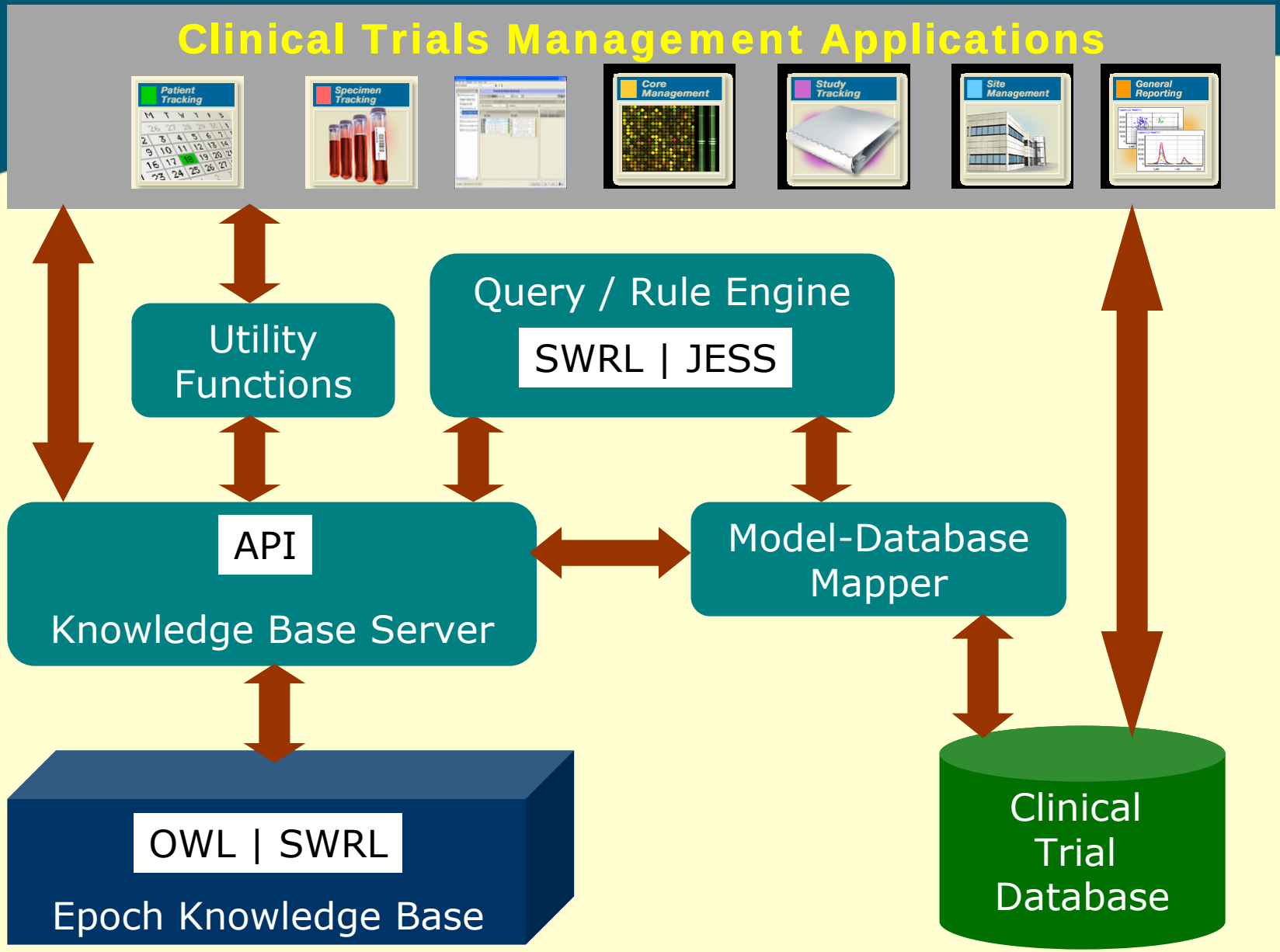
Epoch Architectural Plan



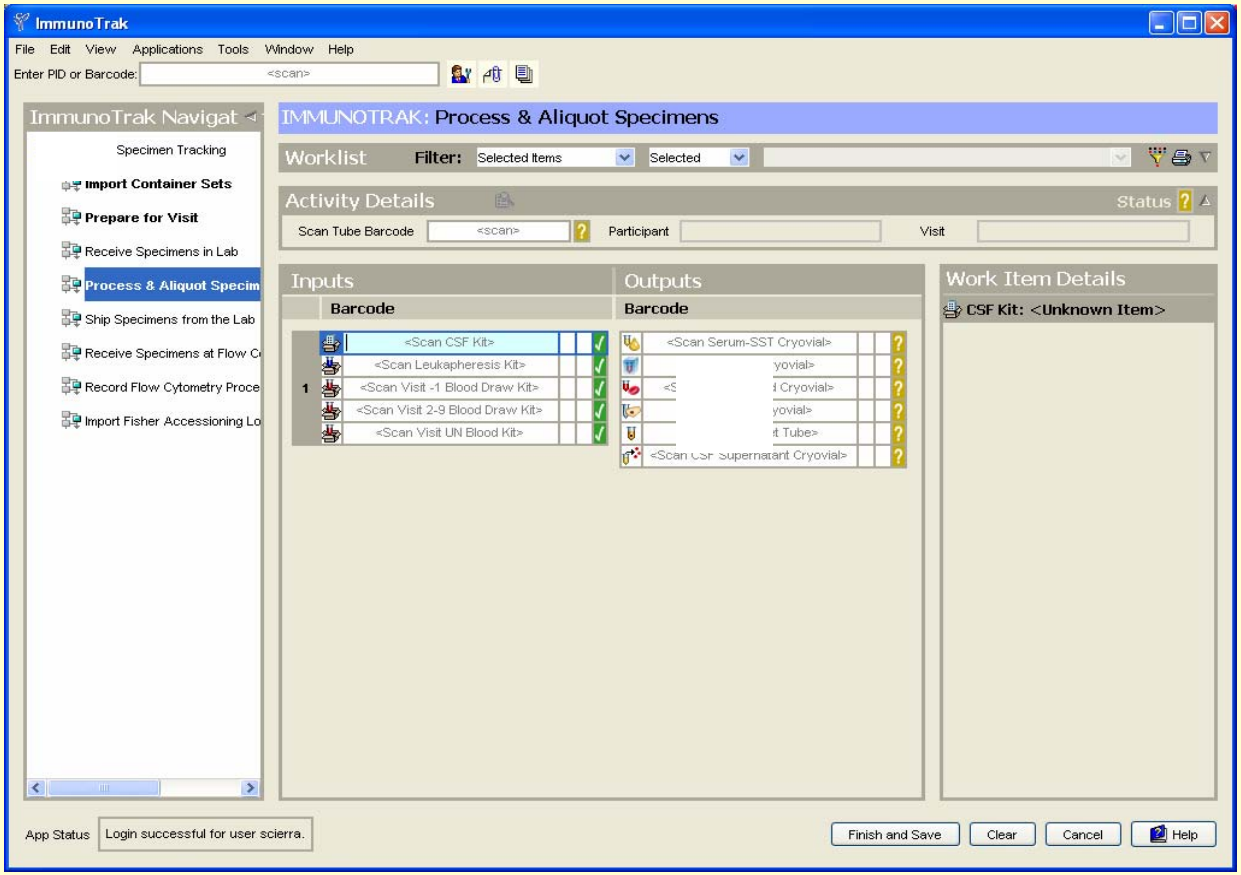
Epoch Architectural Plan



Epoch Architectural Plan



Configuration of ImmunoTrak – the Specimen Workflow Application



ImmunoTrak Configuration File

```
    </PrimaryVesselRoleDefs>
  </NKitType>
- <NKitType Name="Visits 2-9 Blood Kit" Description="Visits 2-9 Blood Kit">
  - <KitDomainType>
      <Ref domaintype="DomainType" uniquekey="{DomainType V2 Blood Kit}" />
    </KitDomainType>
  - <PrimaryVesselRoleDefs>
    - <NVesselRoleDef MinCardinality="0" MaxCardinality="-1" DefaultCardinality="2" Description="2
        barcode labeled 10 ml SST Tubes">
      - <VesselDomainType>
          <Ref domaintype="DomainType" uniquekey="{DomainType SST Tube}" />
        </VesselDomainType>
      - <ChildDefs>
        - <NVesselRoleDef MinCardinality="0" MaxCardinality="-1" DefaultCardinality="33"
            Description="33 barcode labeled Serum-SST Cryovials">
          - <VesselDomainType>
              <Ref domaintype="DomainType" uniquekey="{DomainType Serum Tube}" />
            </VesselDomainType>
          </NVesselRoleDef>
        </ChildDefs>
      </NVesselRoleDef>
    - <NVesselRoleDef MinCardinality="0" MaxCardinality="-1" DefaultCardinality="1" Description="1
        barcode labeled 10 ml Na Heparin Tube">
      - <VesselDomainType>
          <Ref domaintype="DomainType" uniquekey="{DomainType NaHeparin Tube}" />
        </VesselDomainType>
      </NVesselRoleDef>
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        barcode labeled 08 ml CPT Tubes">
      - <VesselDomainType>
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        </VesselDomainType>
      - <ChildDefs>
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```
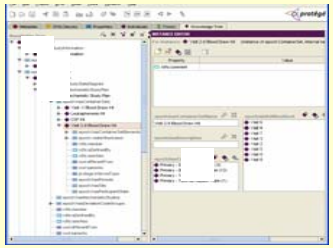

Configuration of ImmunoTrak – the Specimen Workflow Application

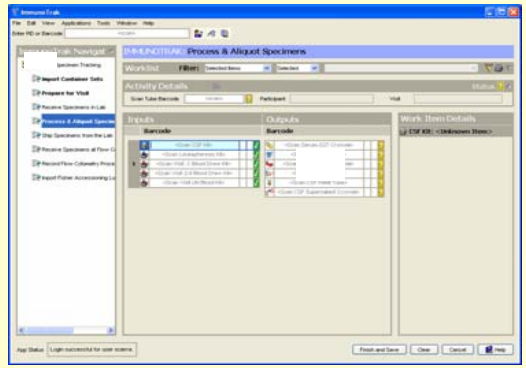


Epoch Knowledge Base

1

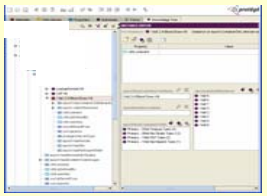
ImmunoTrak Configuration

2



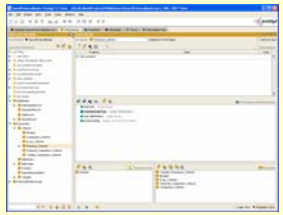
ImmunoTrak – Specimen Workflow

Ontology Mapping to generate XML Document



Epoch Ontology

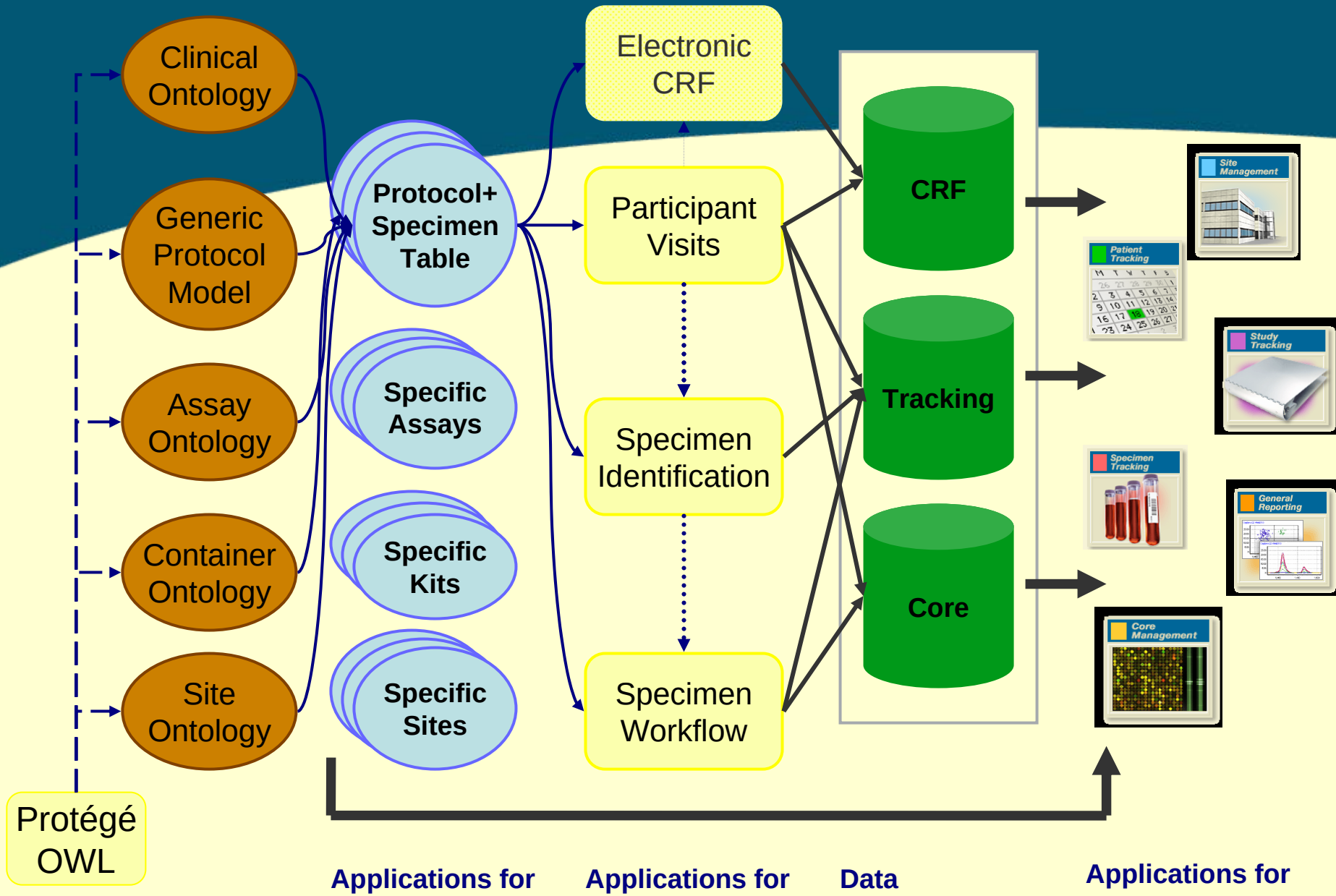
SWRL



XML Document Ontology

ImmunoTrak Configuration XML

```
Protocol(?p) ^ hasSitePlan(?p, ?sp) ^ hasStudySites(?sp, ?site) ^
hasSiteID(?site, ?siteID) ^ hasParticipant(?site, ?participants) ^
hasParticipantIDs(?participant, ?participantID) ^
hasStudyInformation(?sp, ?studyInfo) ^ hasStudyID(?studyInfo,
?hasStudyID)
-> XMLDocument(?p) ^ hasNodeName(?p, "Study") ^
XMLComponent(?participant) ^ hasNodeName(?participant,
"Participant") ^ hasComponents(?p, ?participant) ^
hasAttribute(?participant, ?participantID) ^
hasAttributeName(?participantID, "id">
```


Clinical Ontology
Generic Protocol Model
Assay Ontology
Container Ontology
Site Ontology
Protégé OWL
Protocol+ Specimen Table
Specific Assays
Specific Kits
Specific Sites
Electronic CRF
Participant Visits
Specimen Identification
Specimen Workflow
CRF
Tracking
Core
Site Management
Patient Tracking
Study Tracking
Specimen Tracking
General Reporting
Core Management
Epoch Ontologies
Applications for Knowledge Specification
Applications for Data Collection
Data Repository
Applications for Clinical Trials Management

What our approach buys us

- A centralized, modifiable repository of the knowledge to drive site-oriented applications
- The ability to use reference ontologies to structure ITN knowledge
- A scaleable architecture that can lead to computer-supported trial design
- The ability to use logic for inferring relationships among the data