Epoch:
An Ontological Framework to Support Clinical Trials Management

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Acknowledgments

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… and many others …

Challenges of clinical trials management

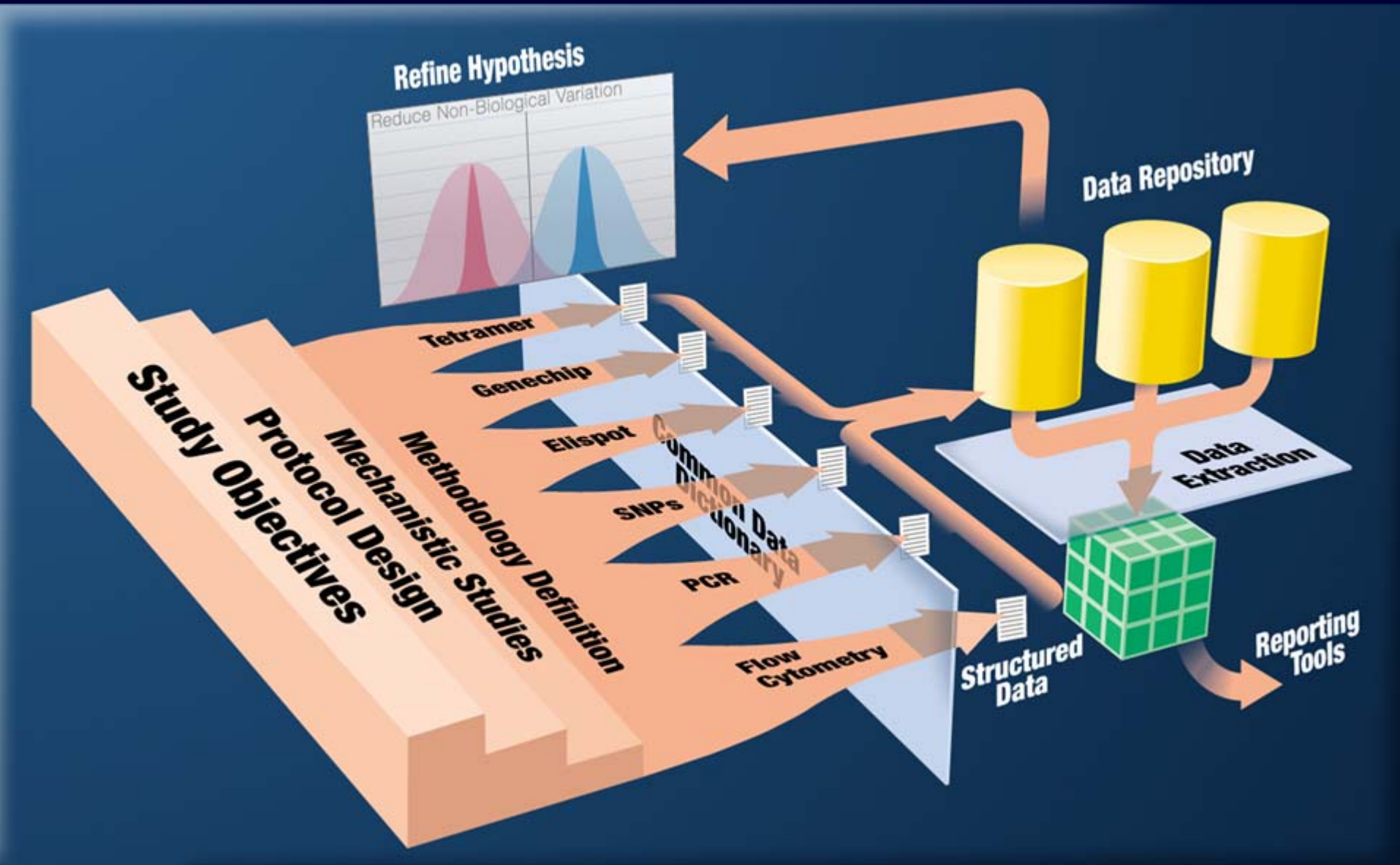
- The design and execution of complex clinical trials involve collaborations among many groups
- The use of disparate software tools for trial design and execution can lead to
  - Lack of formalization in trial specification
  - Ambiguities in trial implementation
  - Increased efforts in trial management
- The use of ontologies can enable a shared semantic understanding of clinical trials among personnel and software

The Immune Tolerance Network (ITN) accelerates the development of immune tolerance therapies

- Investigator-initiated clinical trials of novel tolerance-promoting therapies in
  - Autoimmune diseases
  - Transplantation
  - Allergy and Asthma

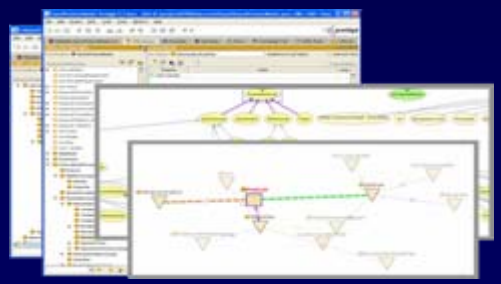
- Provides services to undertake comprehensive mechanistic studies that complement each trial

Major stages in an ITN clinical trial are study specification, implementation, and assessment



This presentation discusses the use of ontologies to support clinical trials in ITN

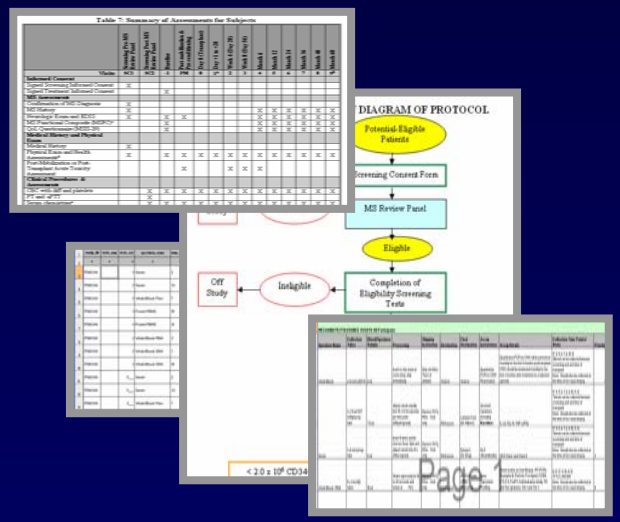
The need for semantic integration

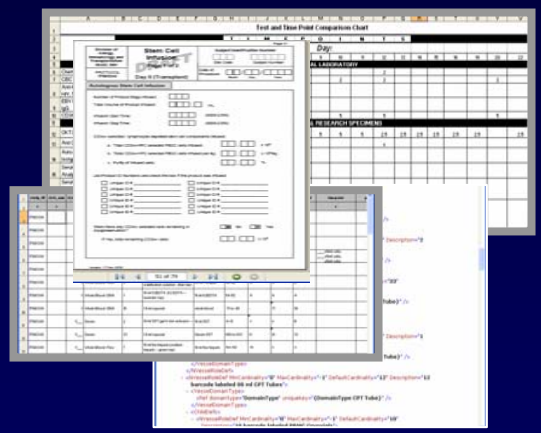


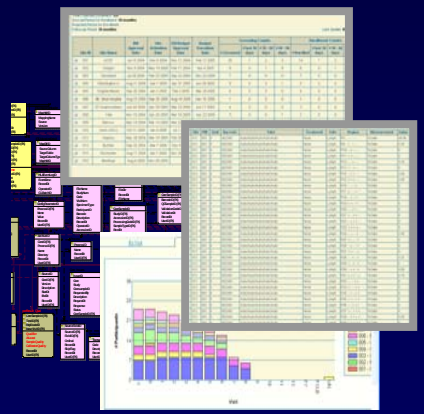
A suite of ontologies

A knowledge-based architecture

A variety of questions are posed by different personnel during each stage of a clinical trial

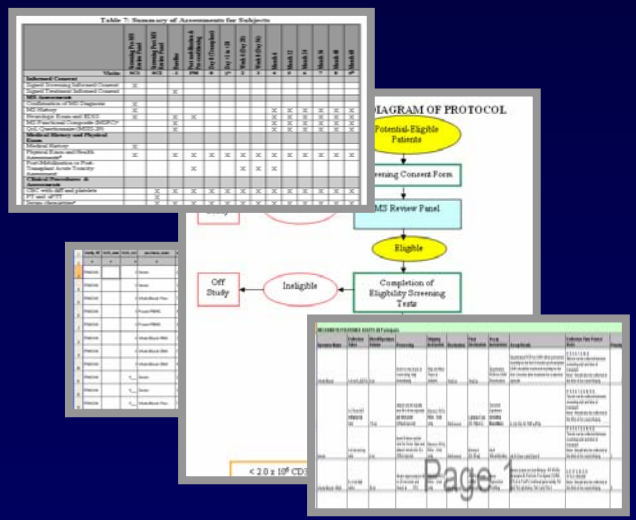






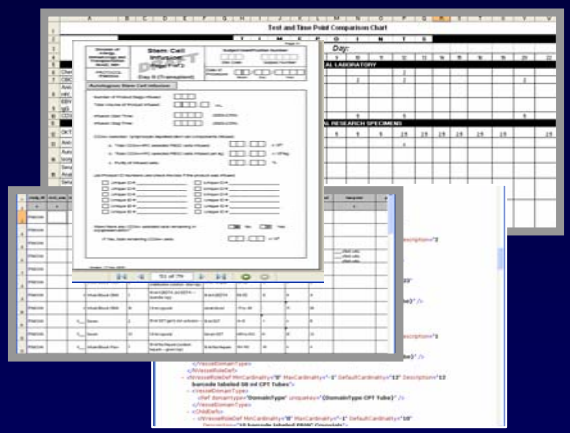
Specification **Implementation** **Management**

Example questions related to trial specification



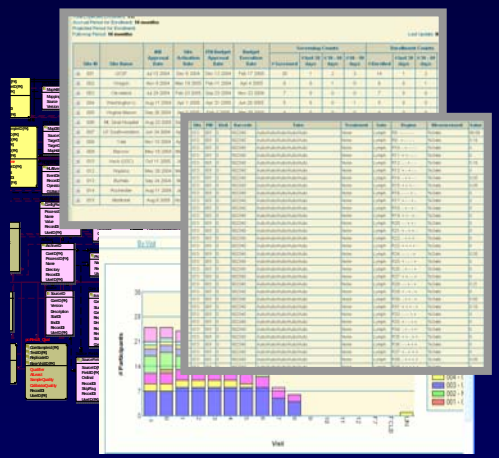
- Is there another protocol similar to this one?
- What clinical activities or mechanistic assays should be planned?
- What specimens need to be collected to perform an assay?
- At which visits should these activities occur?

Example questions related to trial implementation



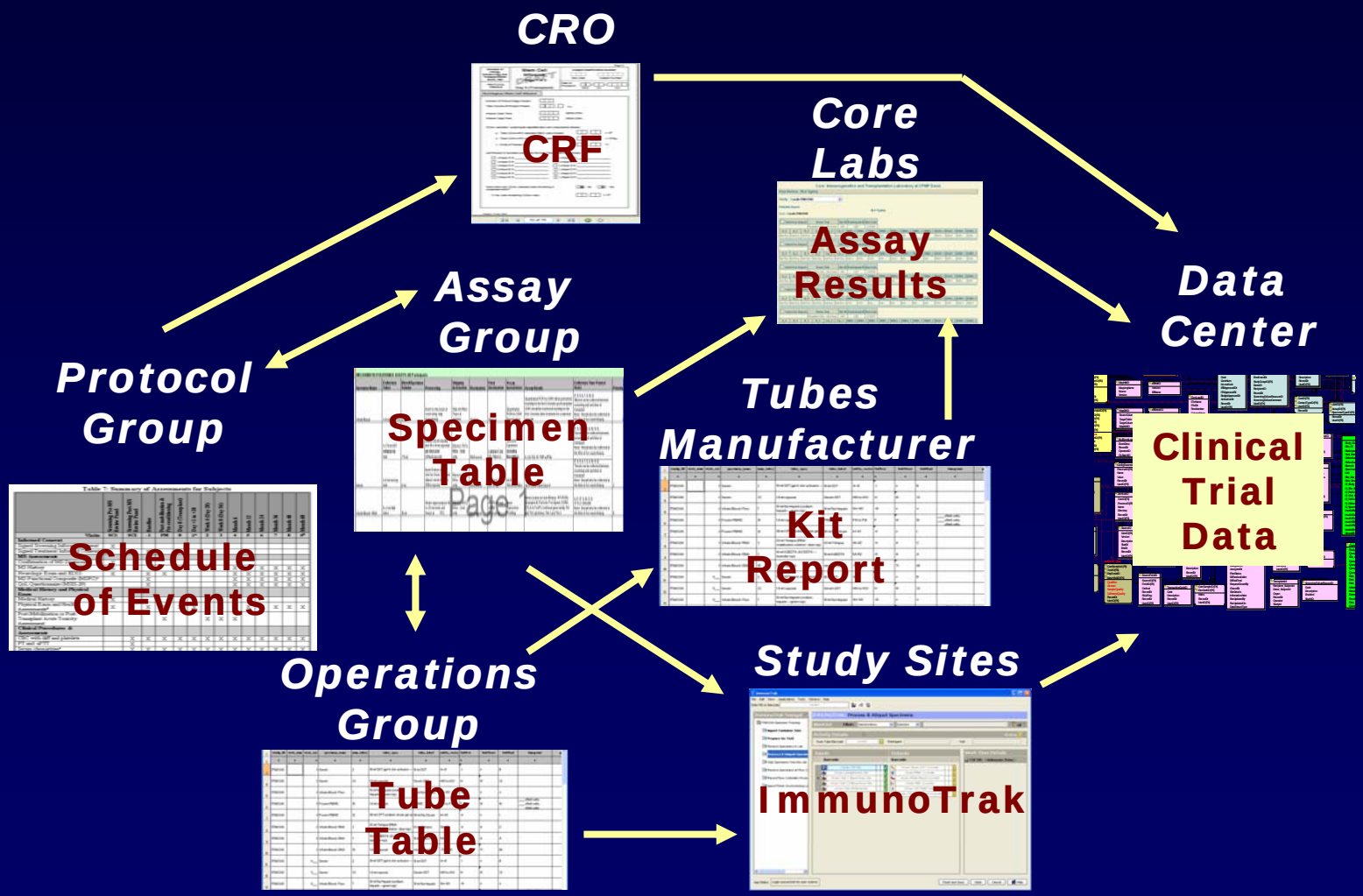
- When is the next visit for this participant?
- What mechanistic assays should performed for this visit?
- Where should this specimen container be shipped?

Example questions related to trial management

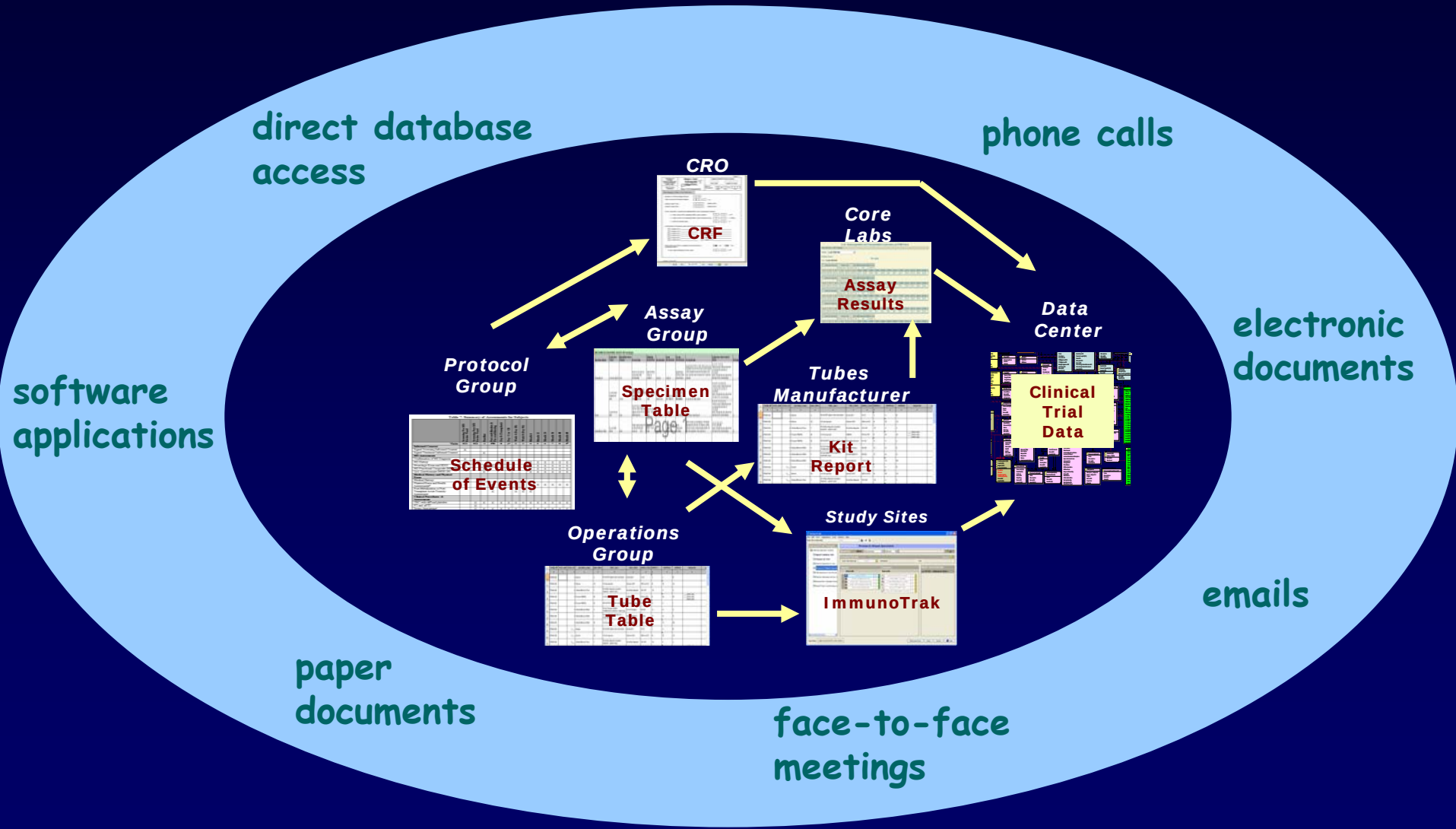


- How many participants are in the follow-up period?
- What are the results of an assay for a particular participant before transplant?
- What is the enrollment data by sites for these four trials?
- What are the total number of specimens accessioned?

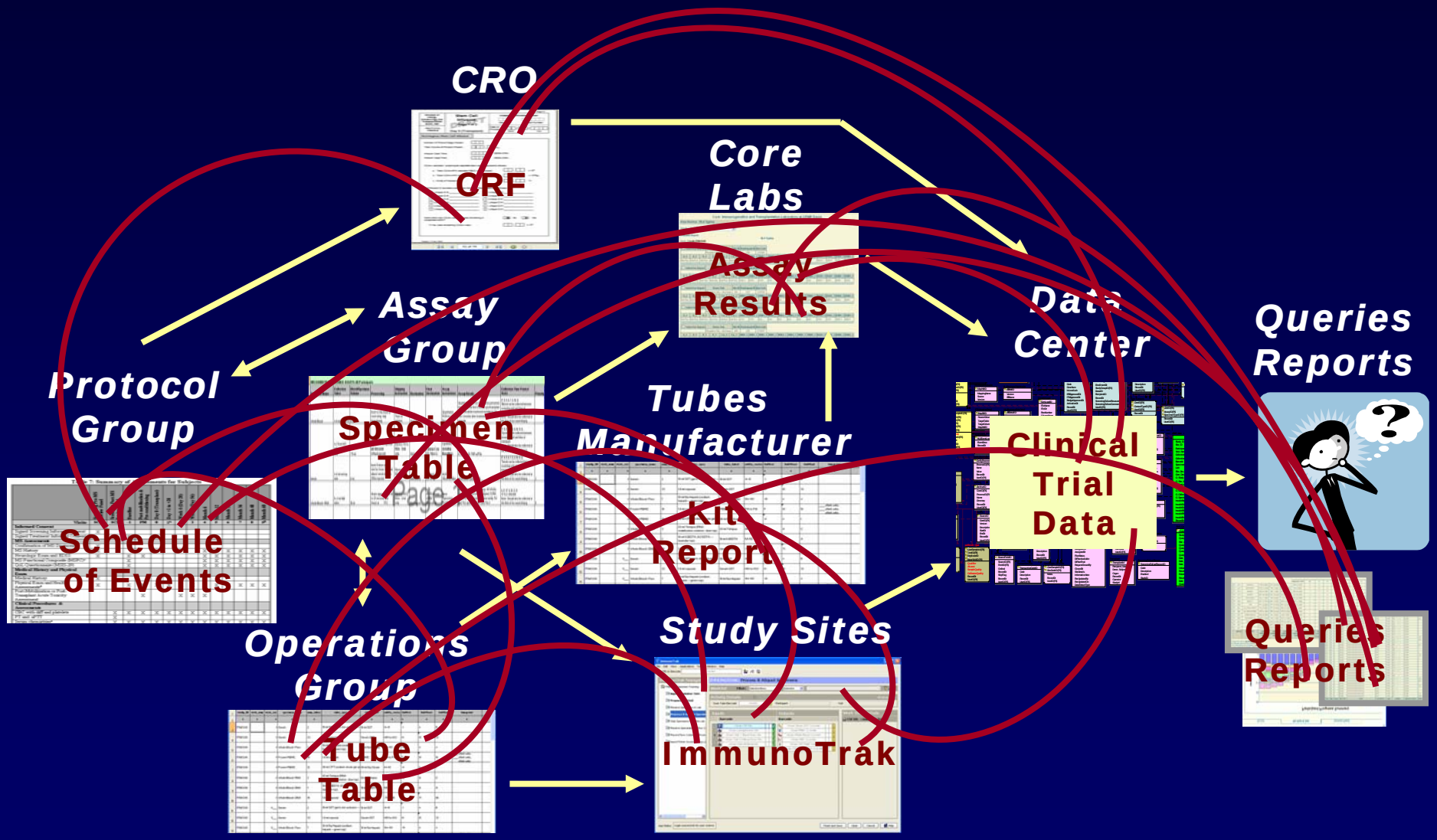
Personnel collaborate to specify, implement, and manage a clinical trial



Multiple communication modalities are used in this collaboration

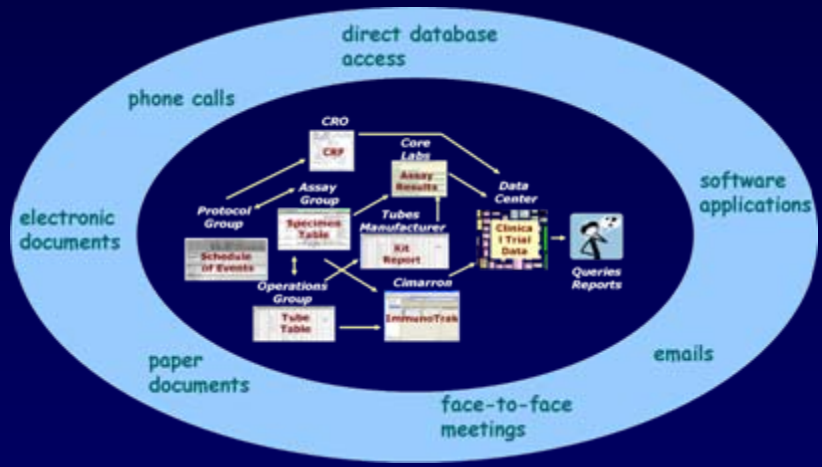


Trial information encoded by different groups is needed in queries and reports

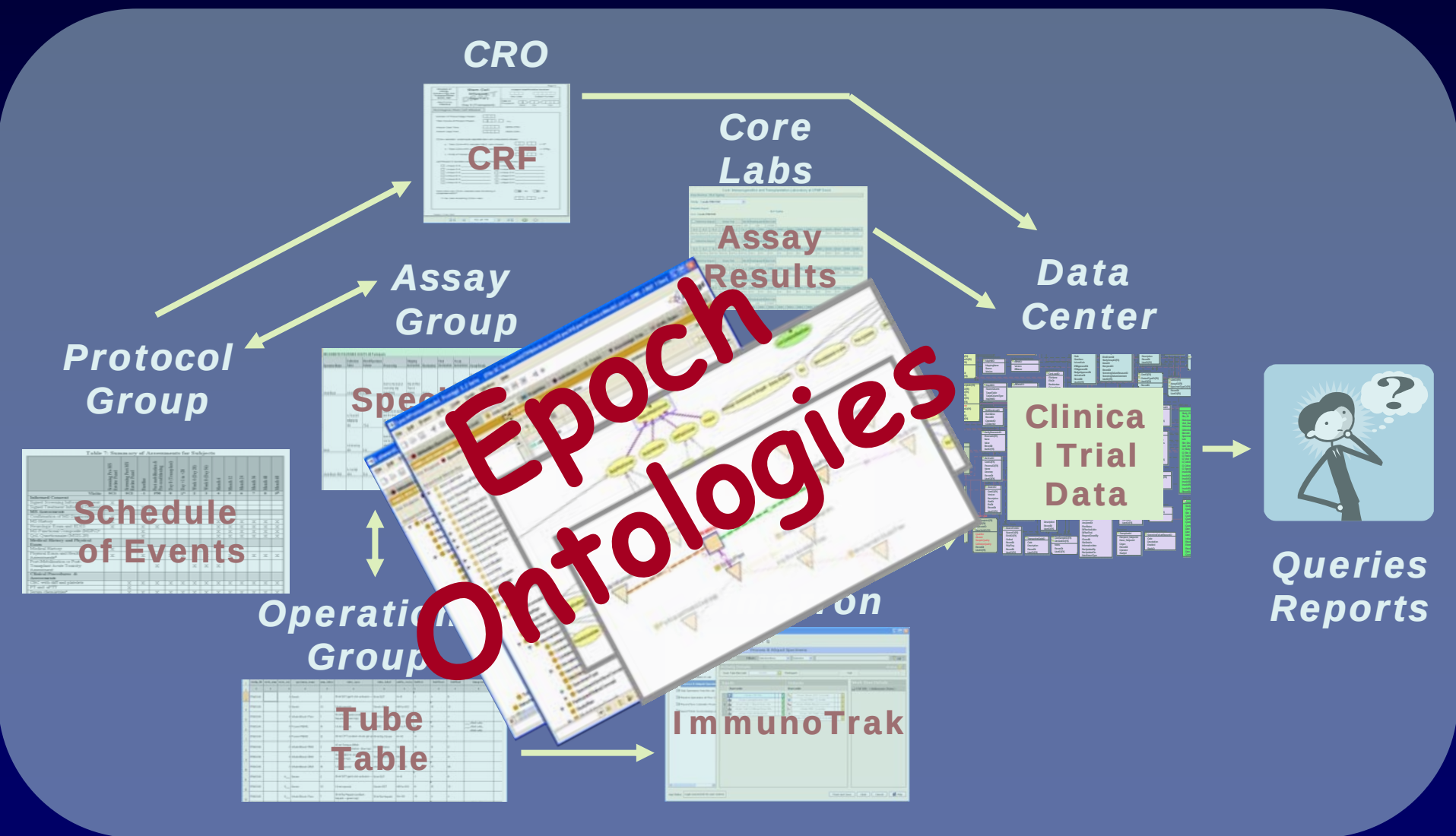


When enterprise-wide knowledge about trials is not formally encoded, problems can arise

- Verifying data integrity in real time is difficult
- Resolving inconsistencies after a trial has started may be required
- Integrating data generated from different software tools is hard
- Performing complex analyses across multiple trials may be very limited

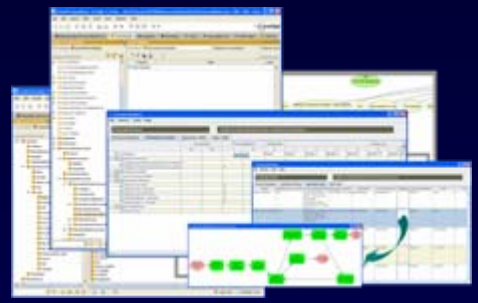


We have created an ontological framework to enable standardization and integration



Our ontology work focuses on developing knowledge-based methods

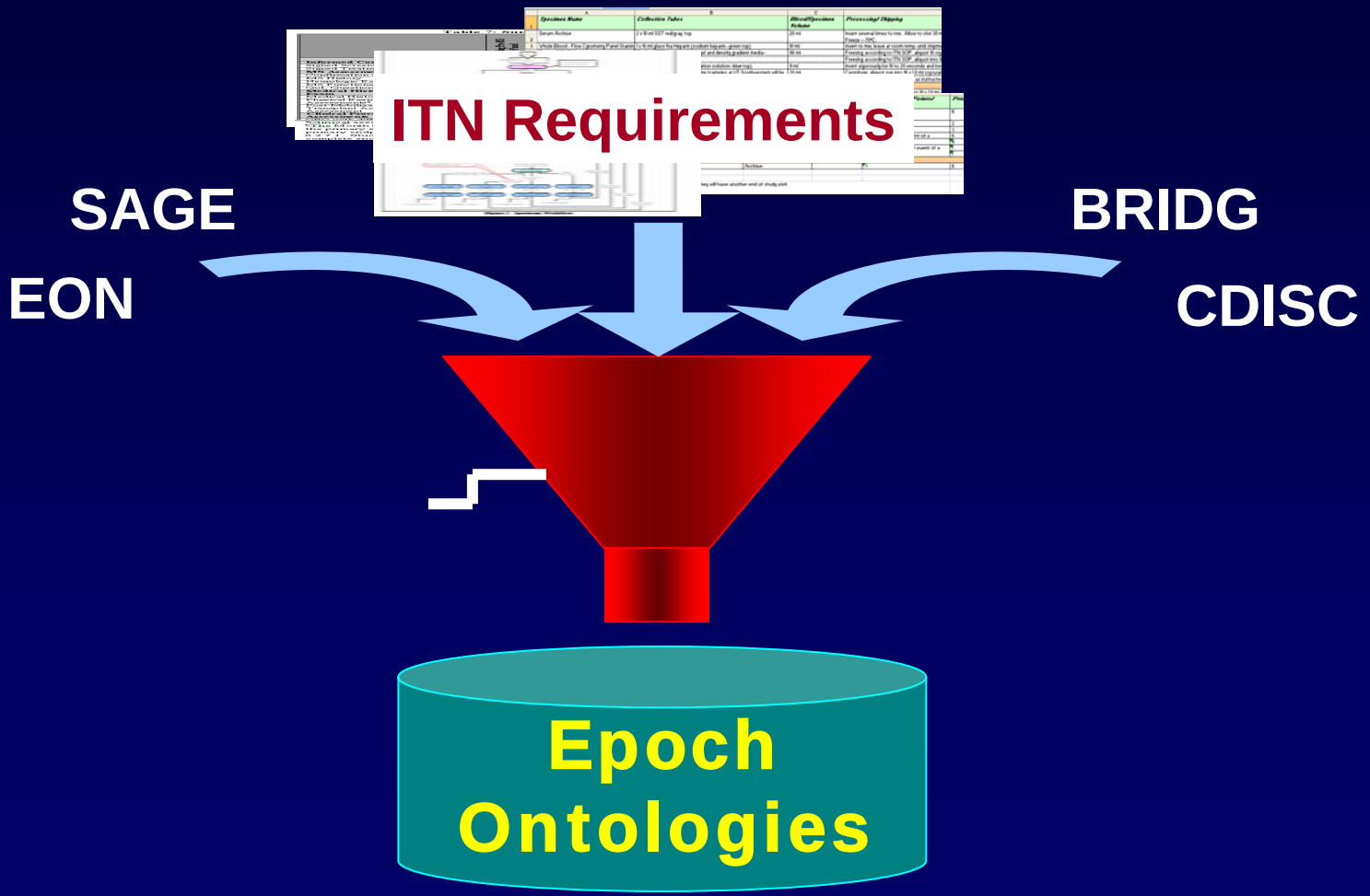
1. To help acquire and maintain knowledge for trial specification



2. To configure software tools for trial implementation

3. To support ad hoc data analysis for trial management

Our suite of ontologies is based on past and existing modeling work and on ITN requirements



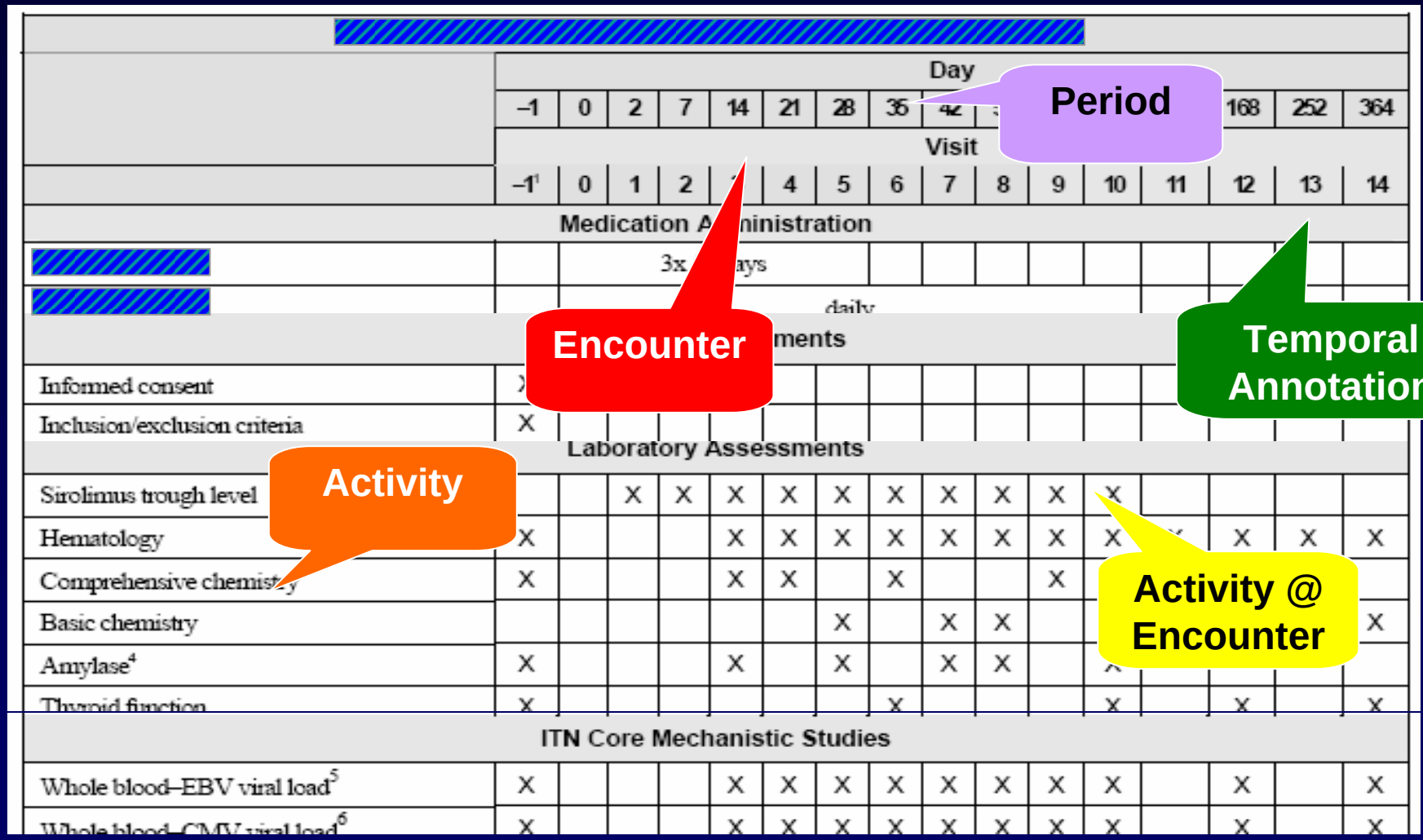
Schedule of Events lists the clinical activities and when they should be performed

(Title removed)																
	Day															
	–1	0	2	7	14	21	28	35	42	56	70	84	112	168	252	364
	Visit															
	–1[1]	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Medication Administration																
[redacted]		3x / 7 days														
[redacted]		daily														
General Assessments																
Informed consent	X															
Inclusion/exclusion criteria	X															
Laboratory Assessments																
Sirolimus trough level			X	X	X	X	X	X	X	X	X	X				
Hematology	X				X	X	X	X	X	X	X	X	X	X	X	X
Comprehensive chemistry	X				X	X		X			X		X		X	
Basic chemistry							X		X	X		X		X		X
Amylase[4]	X				X		X		X	X		X				
Thyroid function	X							X				X		X		X
ITN Core Mechanistic Studies																
Whole blood–EBV viral load[5]	X				X	X	X	X	X	X	X	X		X		X
Whole blood–CMV viral load[6]	X				X	X	X	X	X	X	X	X		X		X

[3] PPD test must be read 48-72 hours after placement.

[4] If amylase level is increased, follow-up lipase level will be performed.

Schedule of Events lists the clinical activities and when they should be performed



	Day														
	–1	0	2	7	14	21	28	35	42			168	252	364	
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Sirolimus trough level			X	X	X	X	X	X	X	X	X	X				
Hematology	X				X	X	X	X	X	X	X	X		X	X	X
Comprehensive chemistry	X				X	X		X			X					
Basic chemistry							X		X	X						X
Amylase[4]	X				X		X		X	X		X				
Thyroid function	X							X				X		X		X
ITN Core Mechanistic Studies																
Whole blood–EBV viral load[5]	X				X	X	X	X	X	X	X	X		X		X
Whole blood–CMV viral load[6]	X				X	X	X	X	X	X	X	X		X		X

Period

Encounter

Temporal Annotation

Activity

Activity @ Encounter

[3] PPD test must be read 48-72 hours after placement.

[4] If amylase level is increased, follow-up lipase level will be performed.

Specimen Workflow Table contains information on the processing of biological specimens

Standard Term	*Collection Tubes*	*Blood/ Specimen Volume*	*Processing/ Shipping*	*Shipping Instruction*	*Destination*	*Final Destination*	*Assay Instructions*	*Collect*
MECHANISTIC ASSAYS								
Whole Blood-Quantitative PCR for CMV and EBV Reactivation	1 x 2 ml K_2EDTA lavendar top	2 ml	Invert to mix, leave at ambient temperature, and ship immediately	Ship o/n ambient temperature Mon-Wed	Viracor	Viracor	Results sent directly to the site. Note: If EBV levels rise above 2000 copies/ml and pos for IgG or IgM, samples to be collected weekly until levels have been reduced below 2000 copies per ml	-1,3,4,5,6,7
Serum-Autoantibody Analysis	1 x 6.0 ml red top tube	6.0 ml	Aliquot serum into 13 cryovials and freeze <-70°C.	Dry ice Mon - Wed only.	ITN Repository	Autoantibody Core	Antigens: GAD65, ICA512/IA-2, insulin, ICA Note: two vials will be sent at screening, one to each autoantibody core for testing	-1,10,12,14
PBMC-Flow Cytometry Intracellular Staining	6 x 10 ml Kendall glass Na heparin tubes	60 ml	Assay will be performed using frozen cells.	Overnight at ambient temperature, Mon-Fri only.	ITN PBMC Isolation Core	ITN Core	See the MAR	0,5,8,10,12
PBMC-T Cell Assay			cryovials *Processed using ITN PBMC freezing protocol with plasma collection				Tetramer: DR4-GAD, DR4-IA-2, DR3-proinsulin, ELISPOT	
Whole Blood-Gene Expression Profiling	2 x 3 ml tempus tubes	6 ml	Invert to mix thoroughly for 10 to 20 seconds and freeze at -70°C	Dry ice Mon - Wed only	ITN Repository	RT PCR Core Microarray Core	Human U133 Chip 2.0 Plus	0,10,12,14

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Standard Te…	Collection	Blood/ Specimen …lume	Processing/ Shippin…	Shipping	…tion	Final Destination	Assay Instructions	Collect…
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PBMC-Flow Cytometry Intracellular Staining			Assay will be performed using frozen cells.				See the MAR	
PBMC-T Cell Assay	6 x 10 ml Kendall glass Na heparin tubes	60 ml	cryovials *Processed using ITN PBMC …	Overnight at ambient temperature, Mon-Fri only.	IT… Isolation Core	ITN Core	Tetramer: DR4-GAD, DR4-IA-2, DR3-proinsulin, ELISPOT	0,5,8,10,12
Whole Blood-Gene Expression Profiling	2 x 3 ml tempus tubes	6 ml	…or 10 … at -70°C	Dry ice Mon - Wed only	ITN Repository	RT PCR Core Microarray Core	Human U133 Chip 2.0 Plus	0,10,12,14

Specimen

Processing Instruction

Core Laboratory

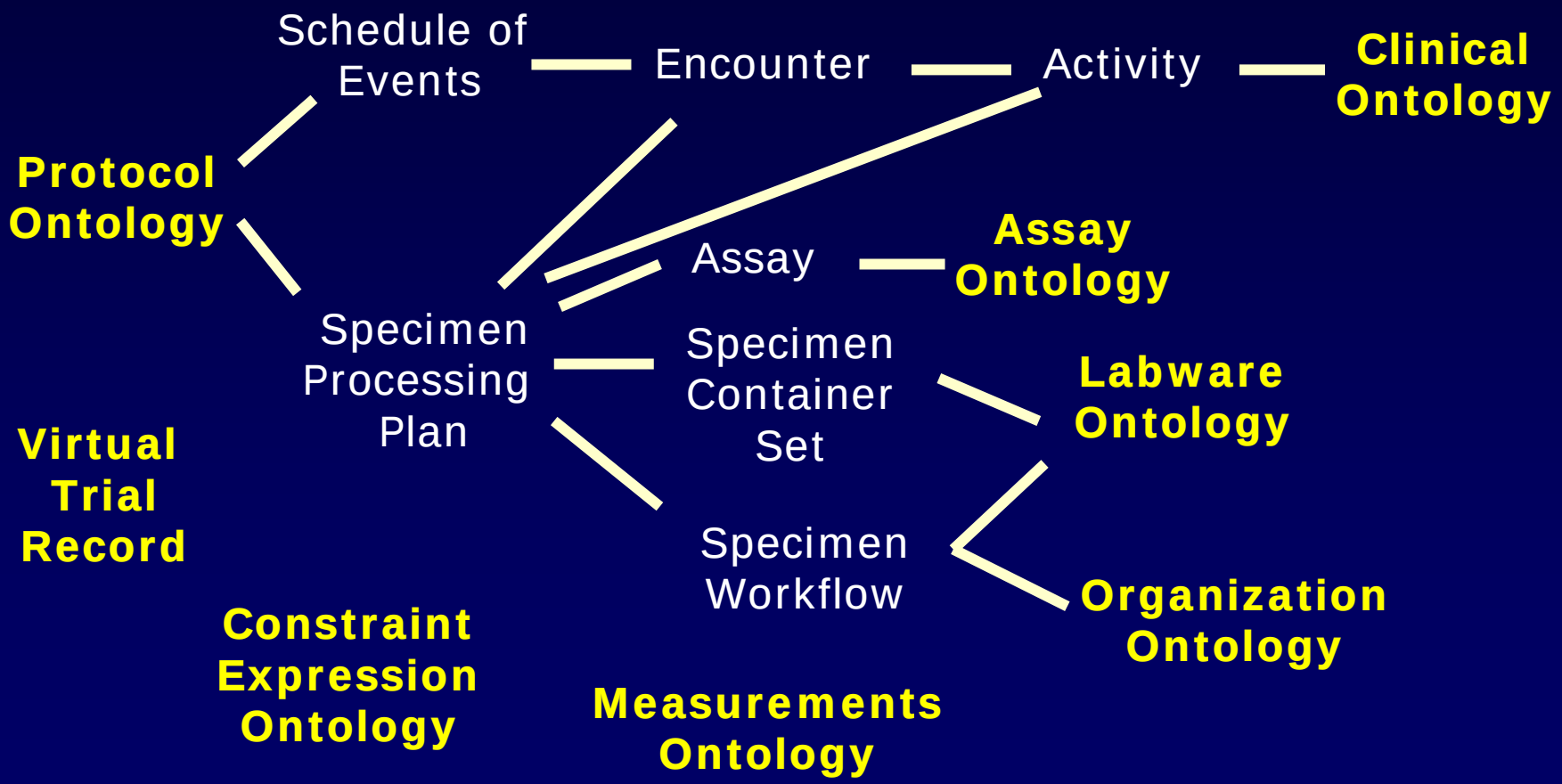
Specimen Container

Bio Repository

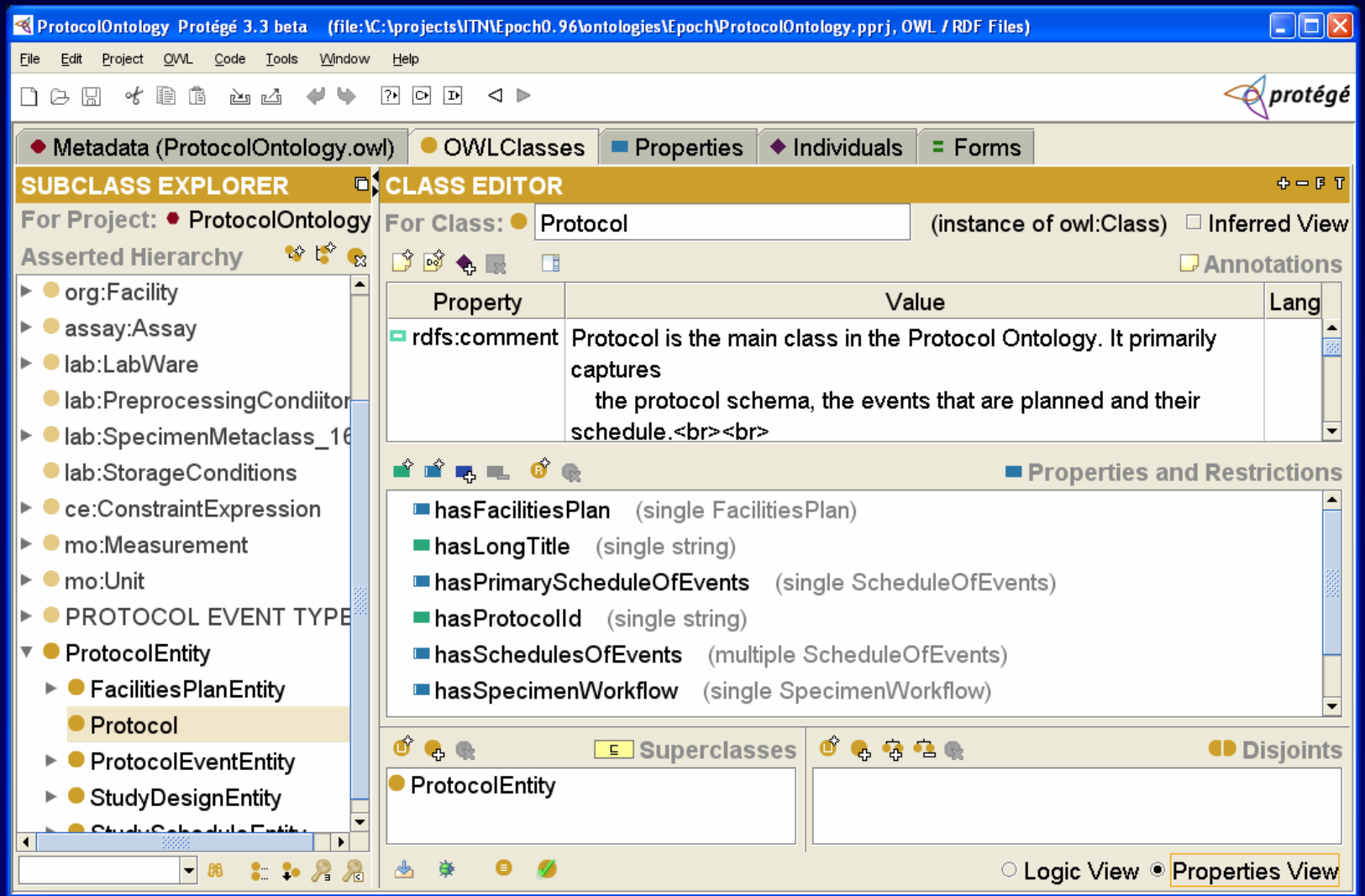
Assay

Shipping Instruction

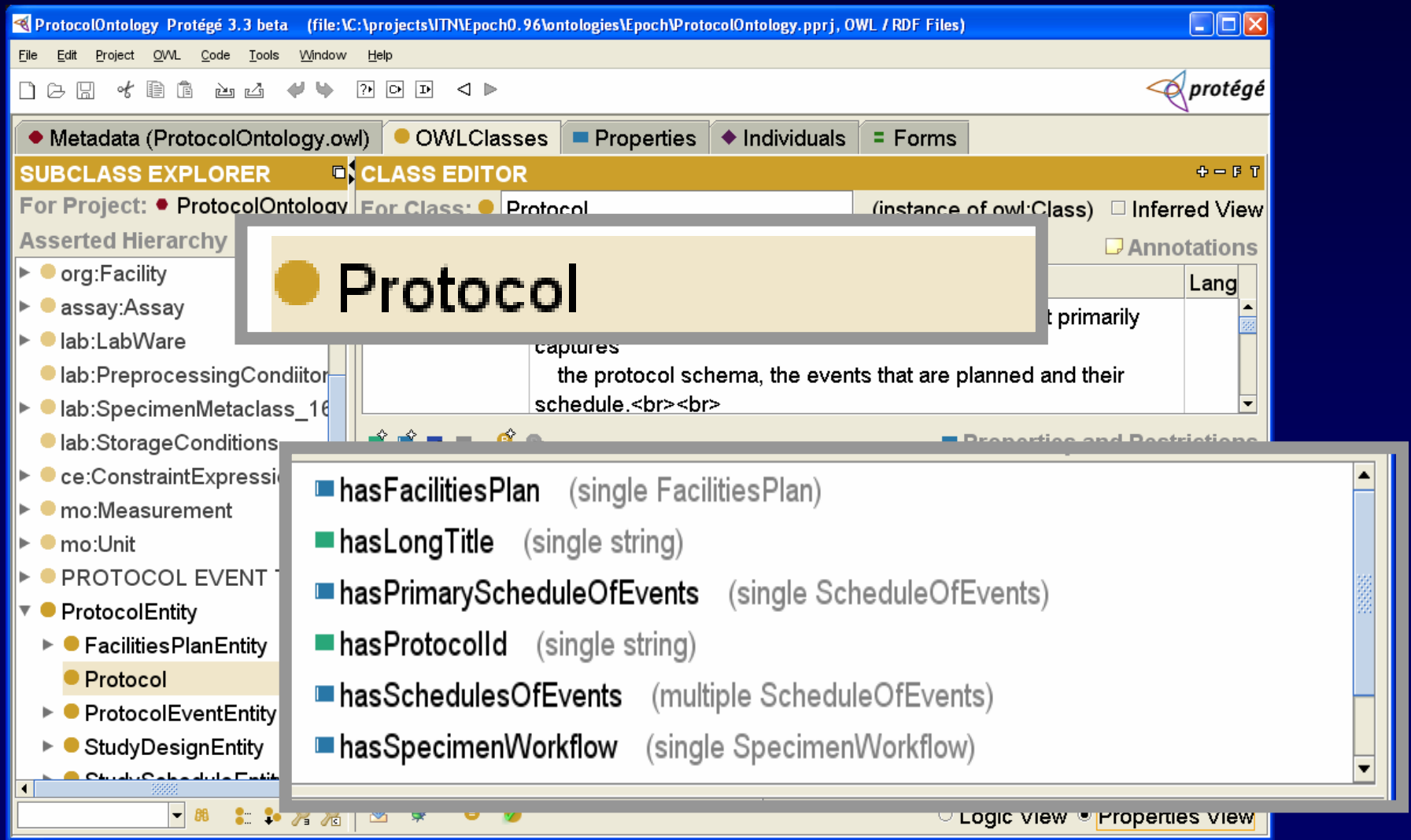
A suite of Epoch ontologies encapsulate clinical trial knowledge



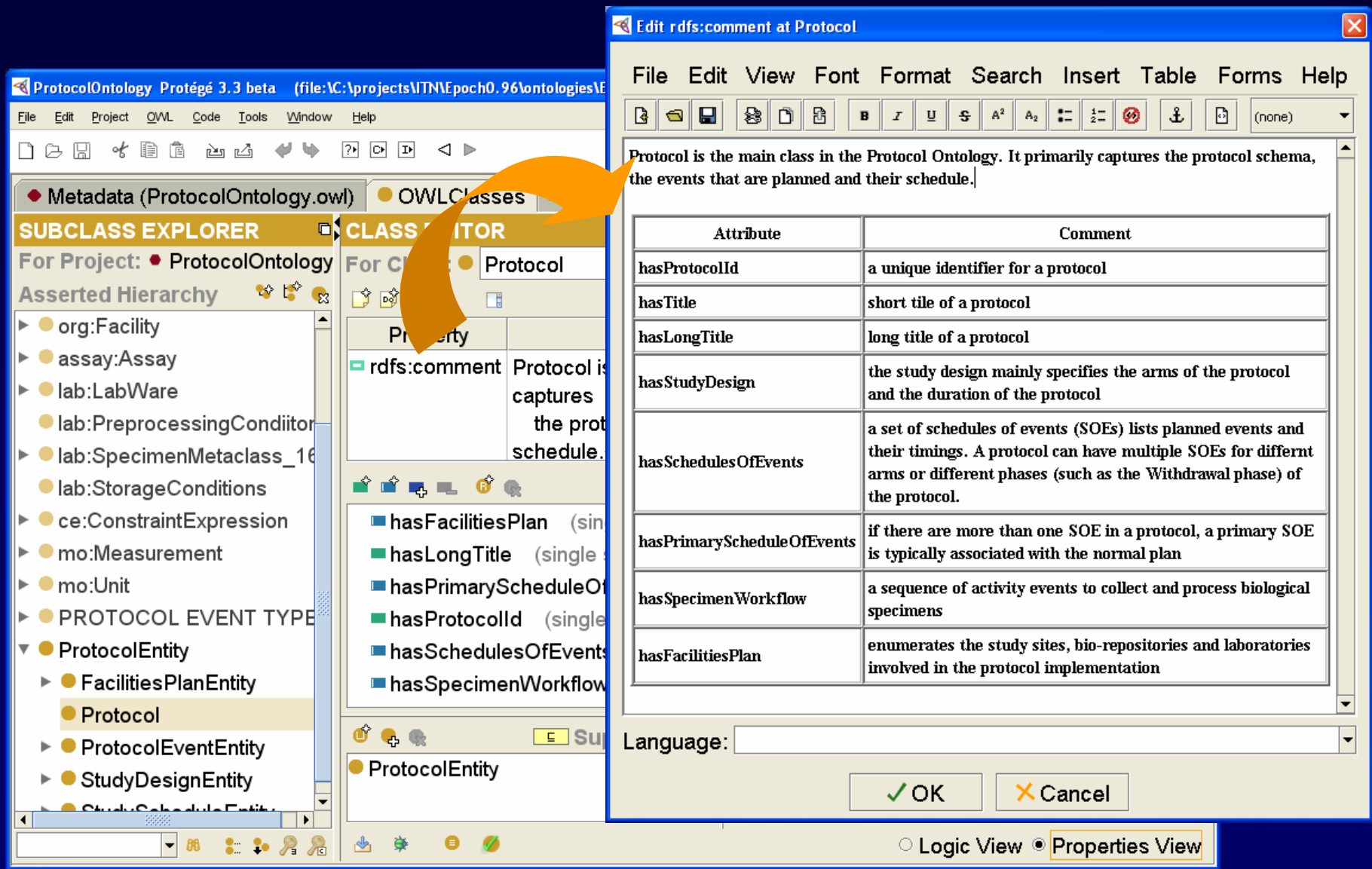
The ontologies are specified in OWL using the Protégé-OWL editor



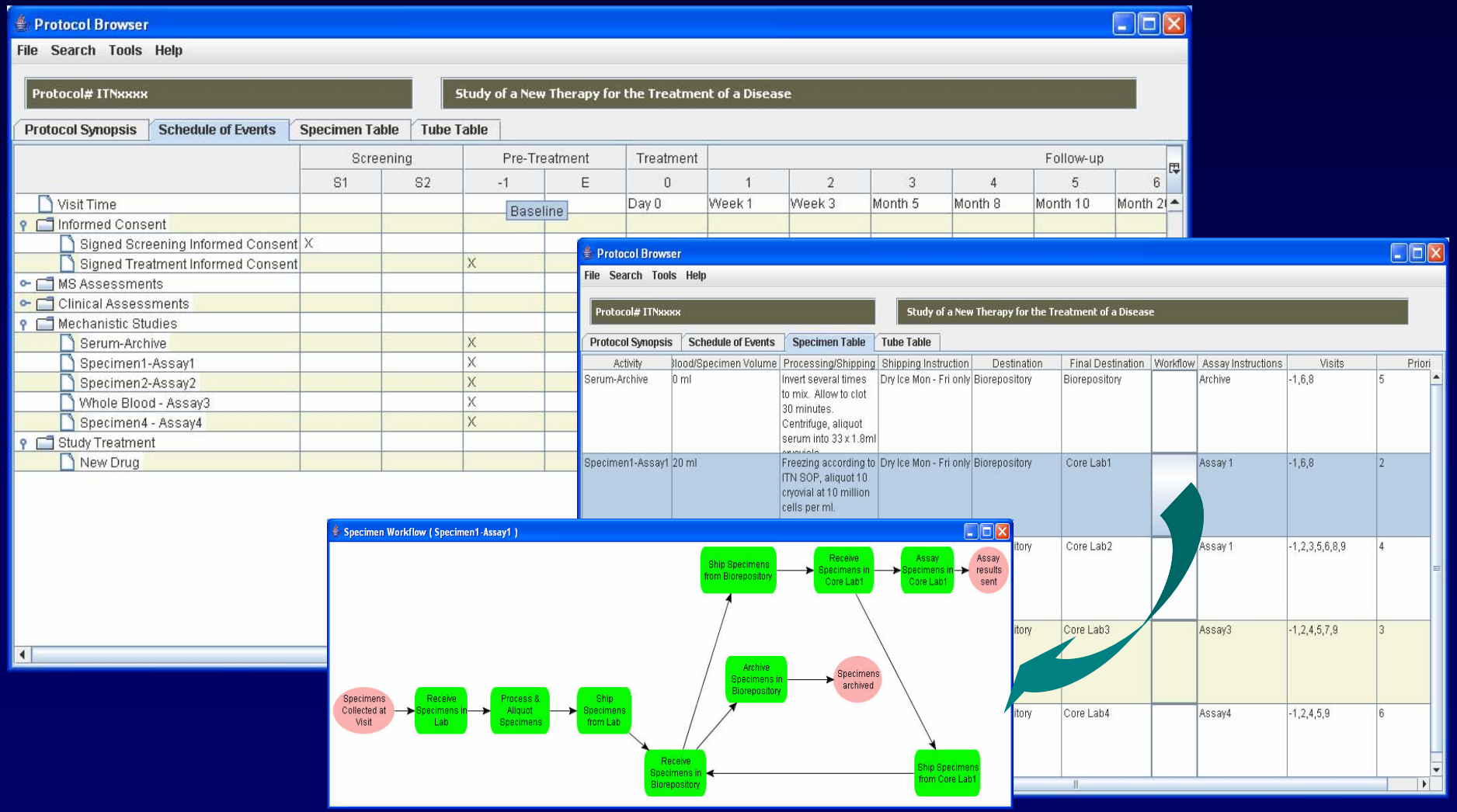
The Protocol Ontology consists of concepts and their attributes in the clinical trial domain



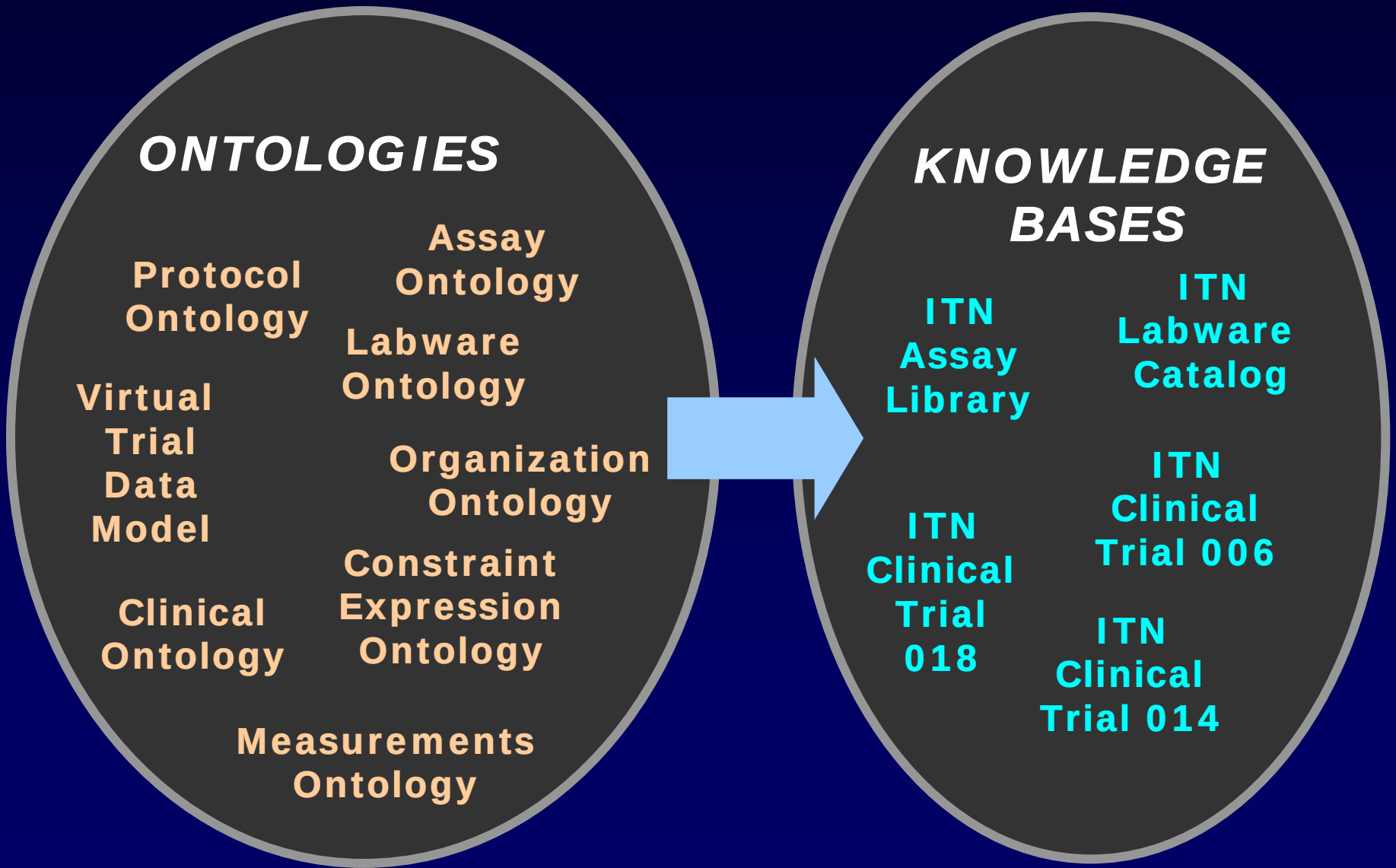
Documentation on each class and its attributes are maintained in the OWL ontology itself



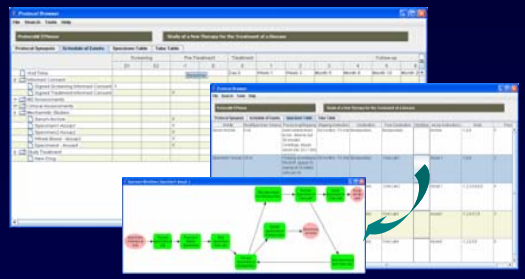
We are building custom user interfaces to enter and browse specific clinical trials



Instantiation of the Epoch ontologies generates clinical trial knowledge bases



The Epoch architecture supports knowledge-driven specification of software tools



Epoch Protocol Editor

Knowledge Base Server

Study Explorer

Configuration Files

Model-Database Mapper

ImmunoTrak

Clinical Trial Data

In conclusion, our work on Epoch allows

- A central, modifiable repository of knowledge to encode shared semantics among users and software tools
- A knowledge-based architecture for trial design, implementation and management
- The use of ontologies for inferring relationships among trial data for queries and reports
- The ability to use reference ontologies to annotate the knowledge used in clinical trial management

Questions ?