

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

Immune Tolerance Network

OVERVIEW AND MISSION
STATEMENT OF VALUES
ORGANIZATIONAL STRUCTURE
SPONSORS & PARTNERS
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NEWS AND PRESS

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Sponsoring Organizations

The Immune Tolerance Network is the product several years of planning by the National Institutes of Health and the extramural research community. We are grateful for the enormous effort and insight of our sponsors, who have brought this project to life and continue to support the mission of the Network.

National Institute Of Allergy And Infectious Disease

The NIAID provides the major support for scientists conducting research aimed at developing better ways to diagnose, treat and prevent the many infectious, immunologic and allergic diseases that afflict people worldwide. NIAID is composed of four extramural divisions: the Division of AIDS; the Division of Allergy, Immunology and Transplantation; the Division of Microbiology and Infectious Diseases; and the Division of Extramural Activities. In addition, NIAID scientists conduct intramural research in laboratories located in Bethesda, Rockville and Frederick, Maryland, and in Hamilton, Montana.

National Institute Of Diabetes And Digestive And Kidney Diseases

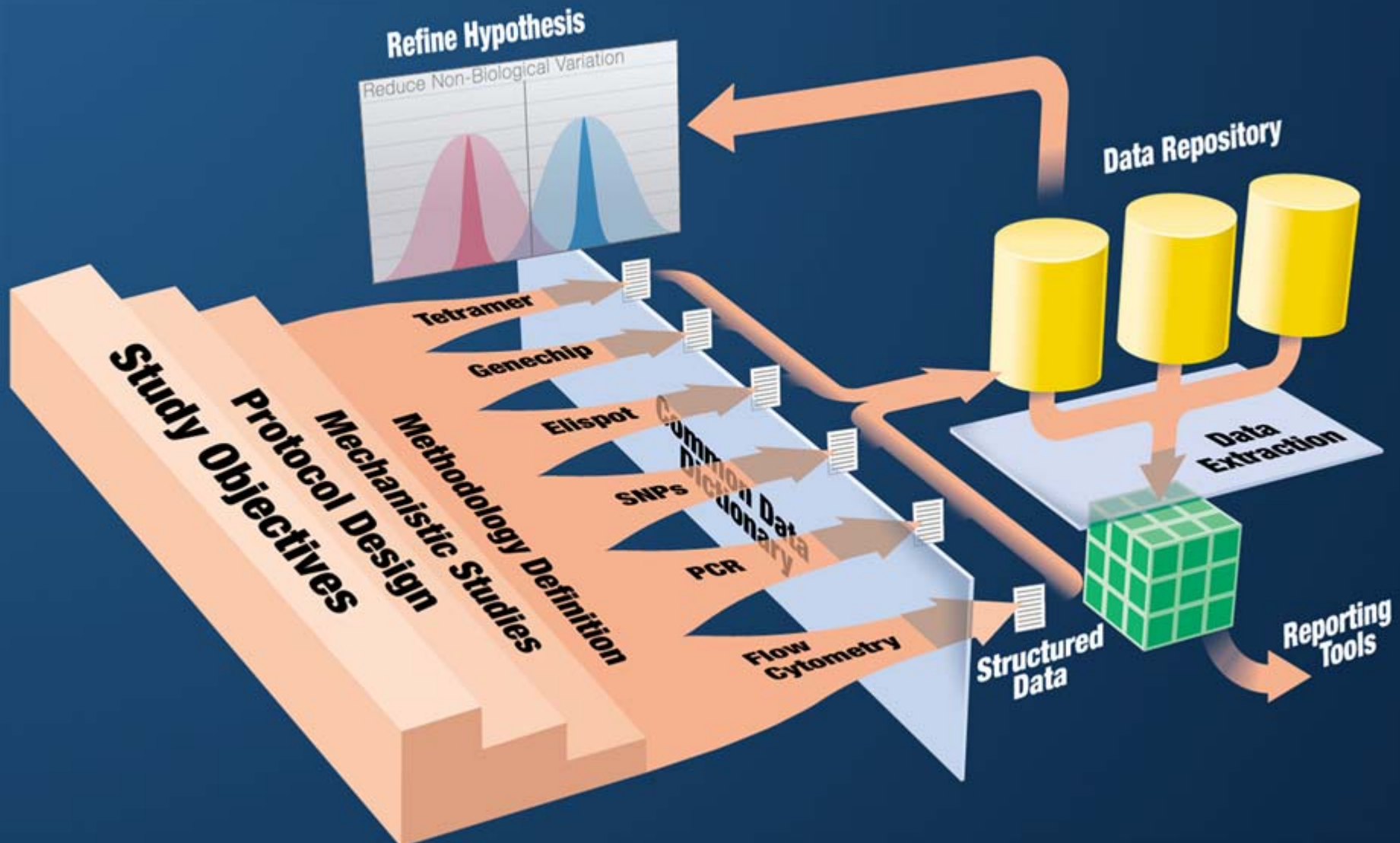
The NIDDK conducts and supports research on many of the most serious diseases affecting public health. The Institute supports much of the clinical research on the diseases of internal medicine and related subspecialty fields as well as many basic science disciplines. NIDDK extramural research is organized into divisions of program areas: the Division of Diabetes, Endocrinology, and Metabolic Diseases, the Division of Digestive Diseases and Nutrition, and the Division of Kidney, Urologic, and Hematologic Diseases.

Juvenile Diabetes Research Foundation

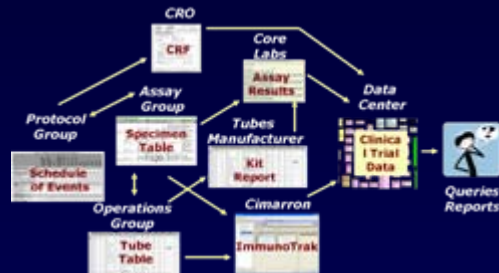
The Juvenile Diabetes Research Foundation (JDRF) is a not-for-profit, voluntary health agency with chapters and affiliates throughout the world. JDRF's main objective is to support and fund research to find a cure for diabetes and its complications. JDRF gives more money directly to diabetes research than any other private health agency in the world. The organization awards research grants for laboratory and clinical investigations and sponsors a variety of career development and research training programs for new and established investigators. JDRF also sponsors international workshops and conferences for biomedical researchers. Individual chapters offer support groups and other activities for families affected by diabetes.

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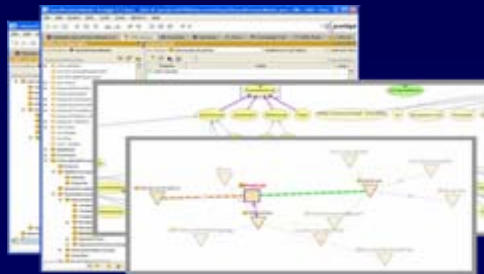
Major stages in an ITN clinical trial are study specification, implementation, and assessment



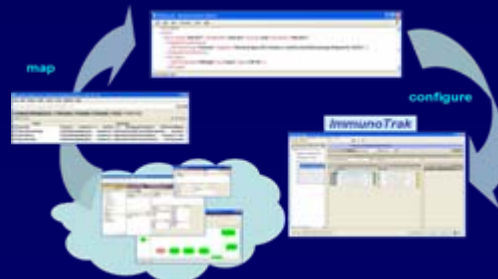
This presentation discusses the use of ontologies to support clinical trials in ITN



The need for semantic integration

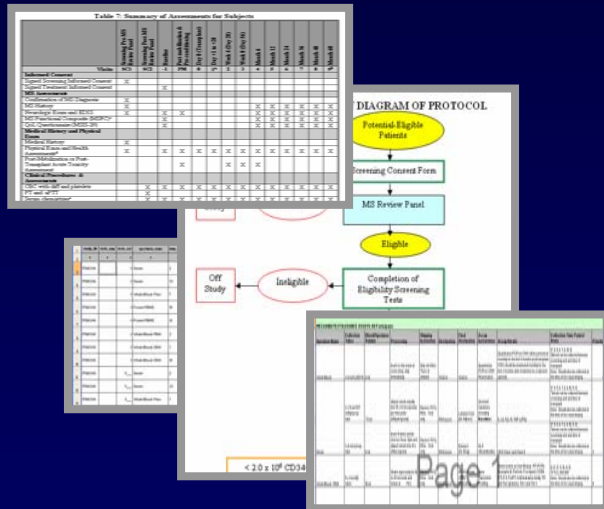


A suite of ontologies

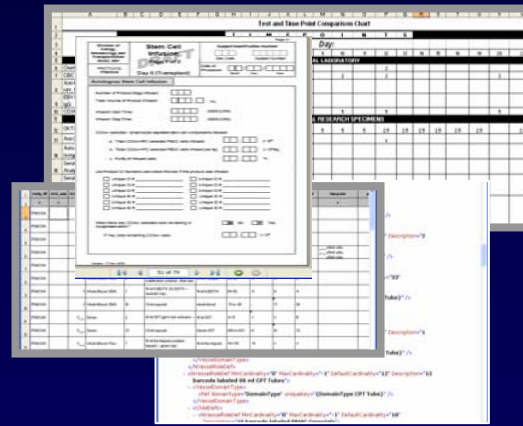


A knowledge-based architecture

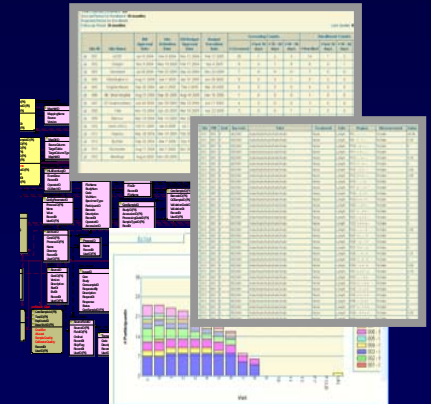
A variety of questions are posed by different personnel during each stage of a clinical trial



Specification

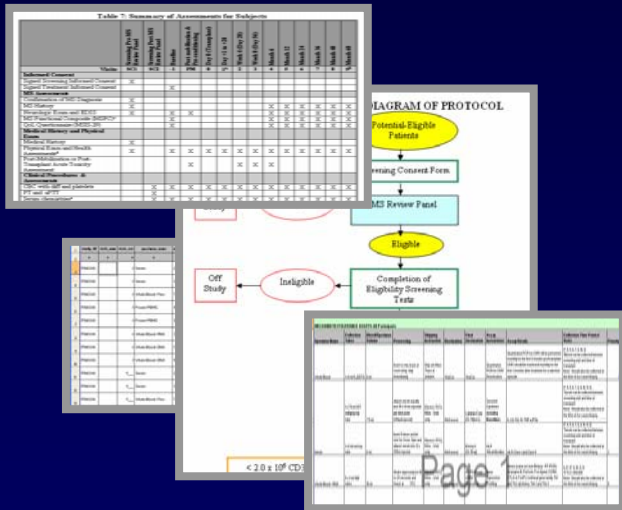


Implementation



Management

Example questions related to trial specification



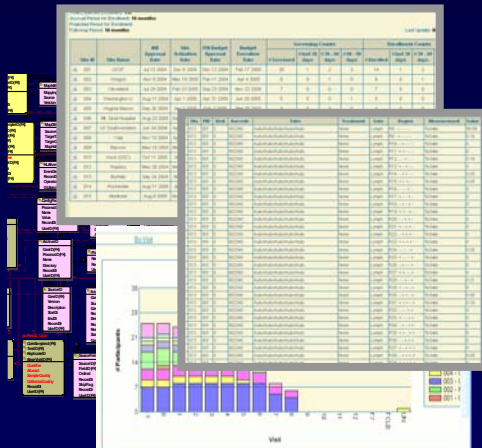
- **Is there another protocol similar to this one?**
- **What clinical activities or mechanistic assays should be planned?**
- **What specimens need to be collected to perform an assay?**
- **At which visits should these activities occur?**

Example questions related to trial implementation

The image shows a complex clinical trial data entry form titled "Study and Test Point Comparison Chart". The form is divided into several sections, including "Study and Test Point Comparison Chart", "Study and Test Point Comparison Chart", and "Study and Test Point Comparison Chart". It contains numerous checkboxes, text boxes, and dropdown menus for data entry. The form is overlaid on a grid of data points, which appears to be a calendar or timeline. The form is titled "Study and Test Point Comparison Chart" and contains various fields for data entry, including checkboxes, text boxes, and dropdown menus. The form is overlaid on a grid of data points, which appears to be a calendar or timeline. The form is titled "Study and Test Point Comparison Chart" and contains various fields for data entry, including checkboxes, text boxes, and dropdown menus. The form is overlaid on a grid of data points, which appears to be a calendar or timeline.

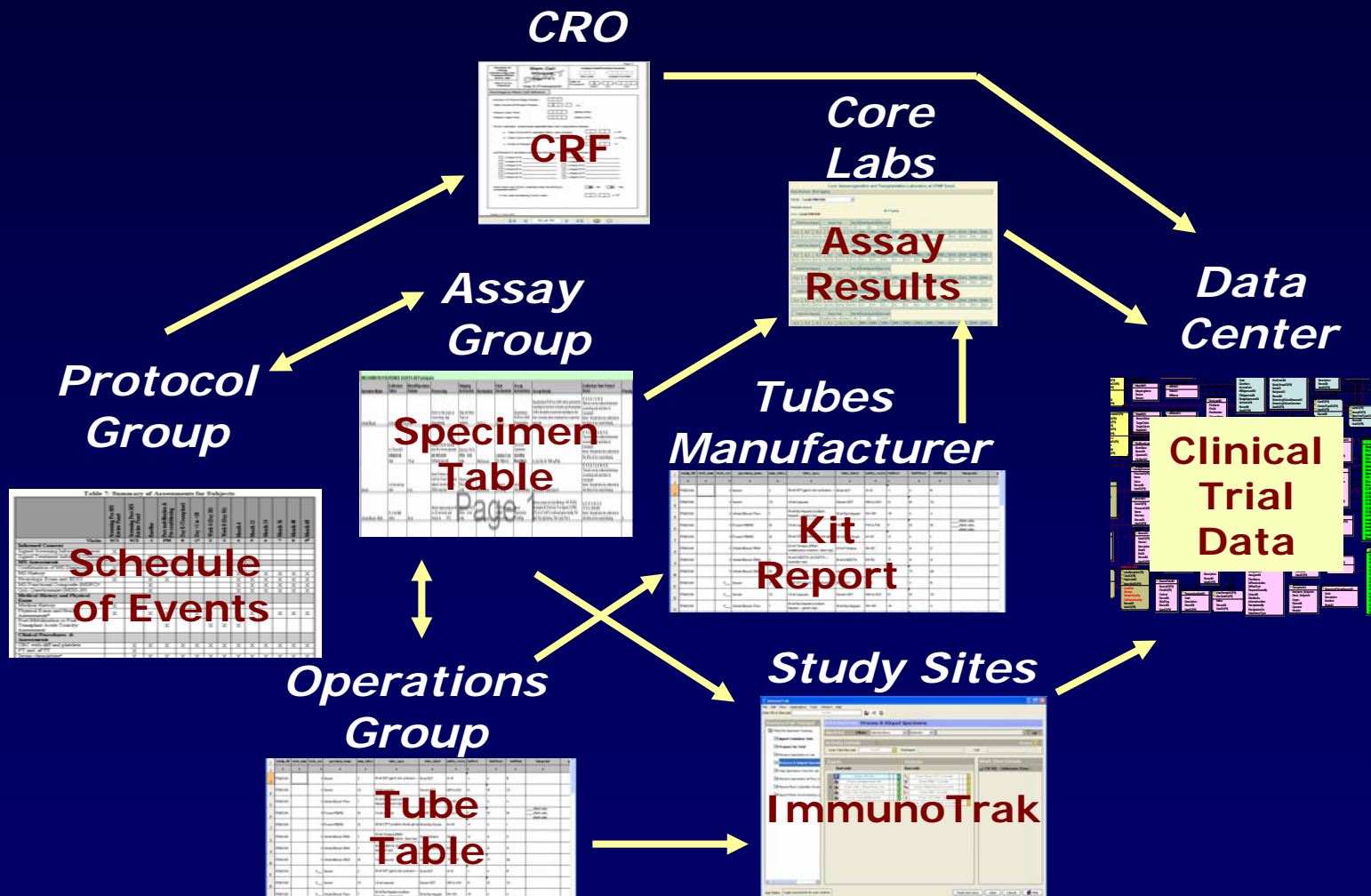
- When is the next visit for this participant?
- What mechanistic assays should be performed for this visit?
- Where should this specimen container be shipped?

Example questions related to trial management

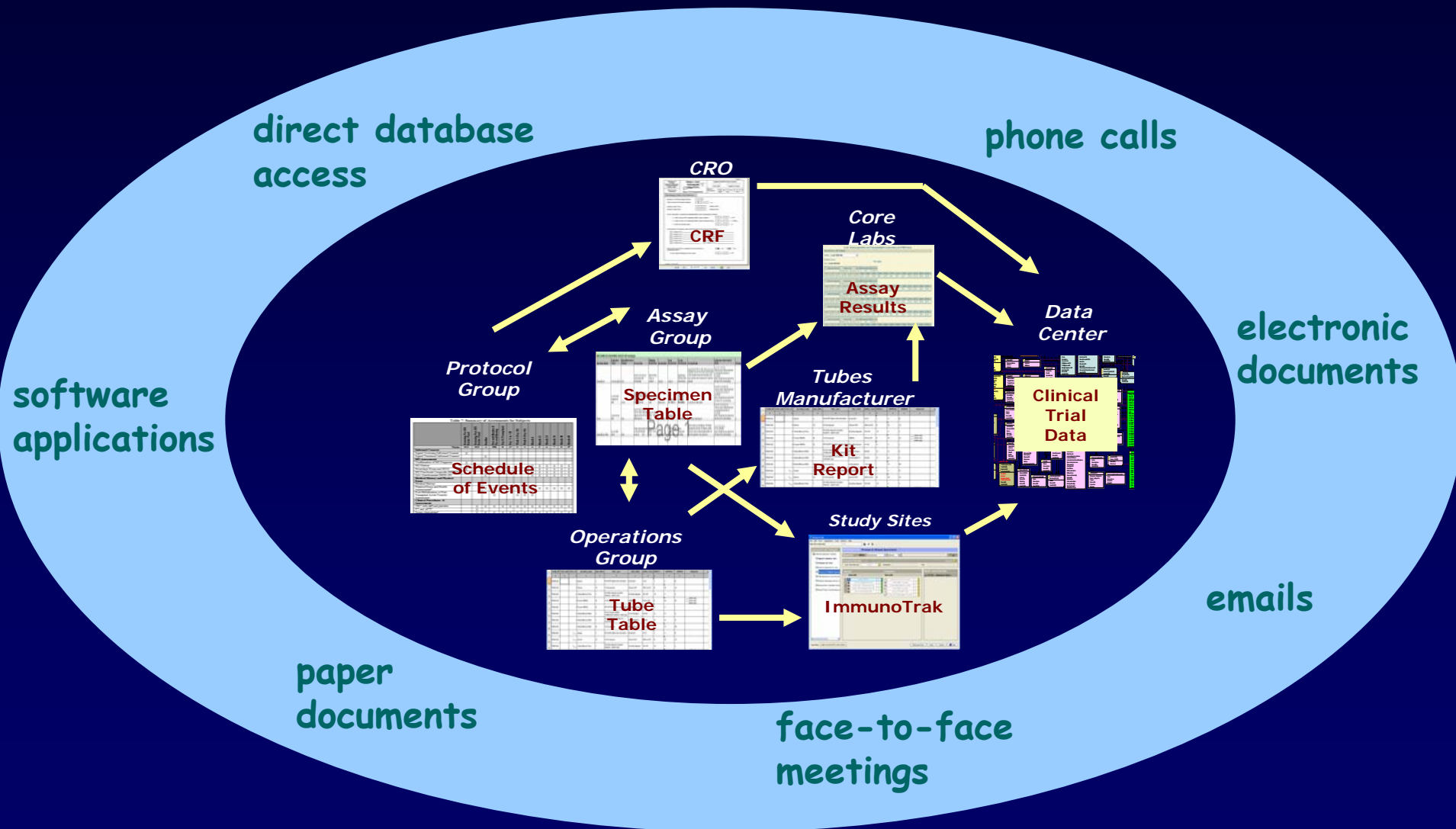


- **How many participants are in the follow-up period?**
- **What are the results of an assay for a particular participant before transplant?**
- **What is the enrollment data by sites for these four trials?**
- **What are the total number of specimens accessioned?**

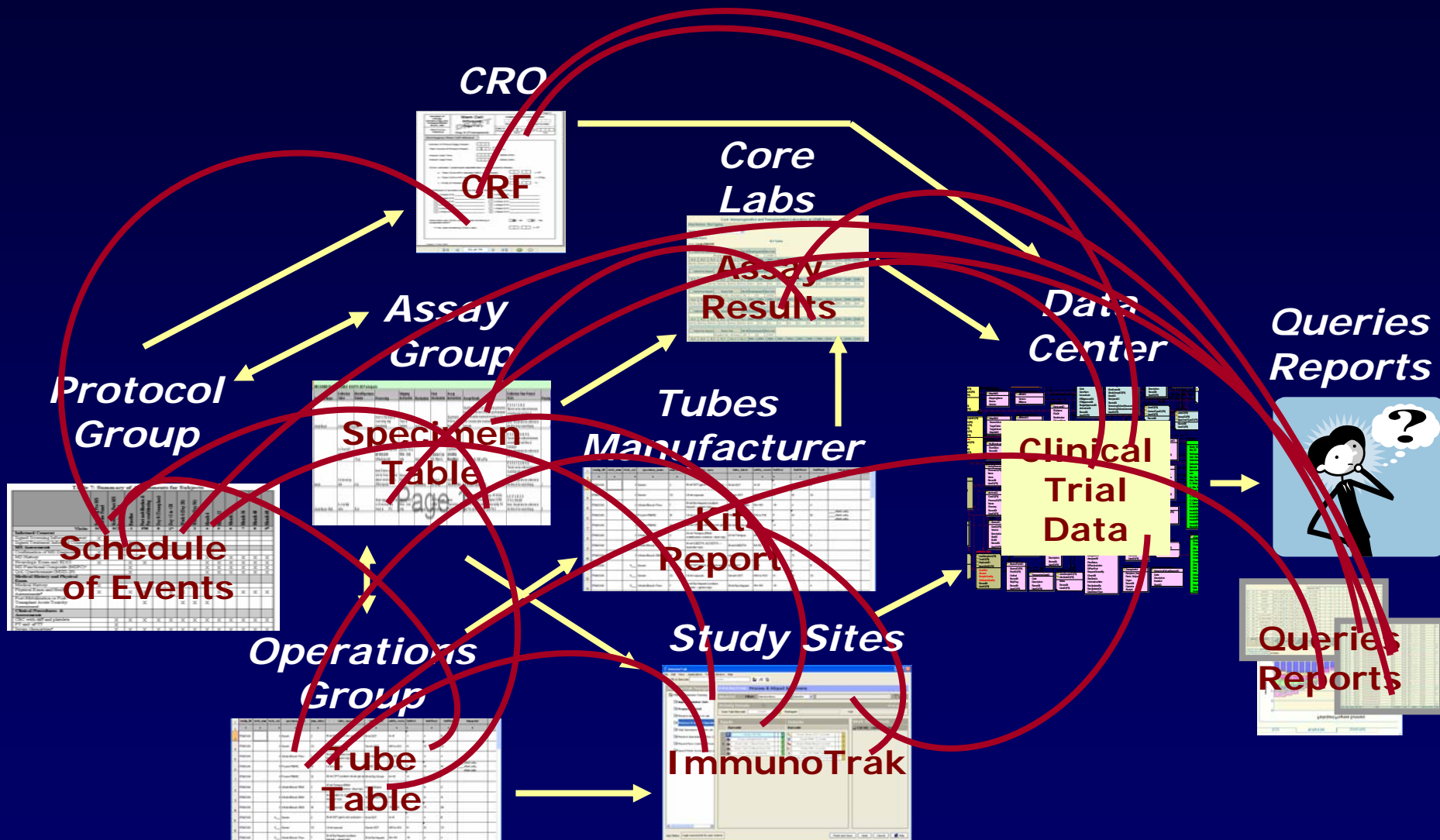
Personnel collaborate to specify, implement, and manage a clinical trial



Multiple communication modalities are used in this collaboration

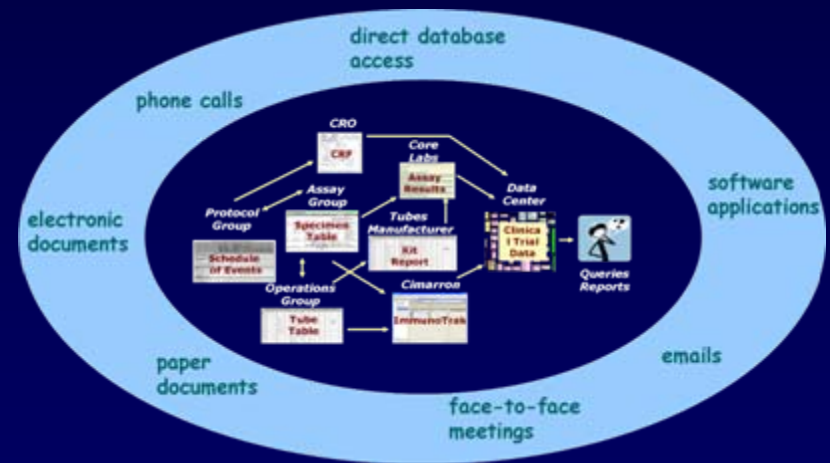


Trial information encoded by different groups is needed in queries and reports

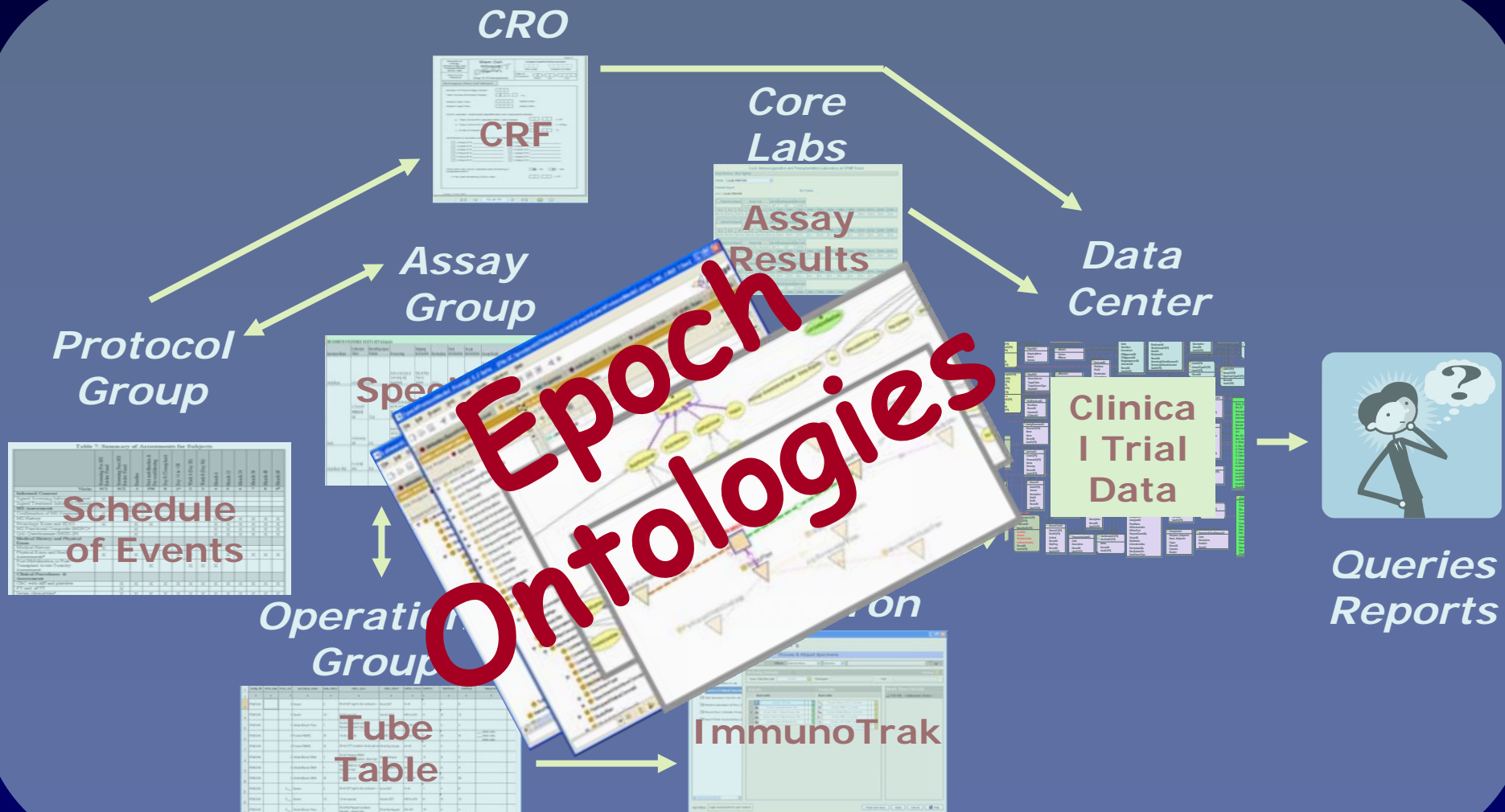


When enterprise-wide knowledge about trials is not formally encoded, problems can arise

- 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

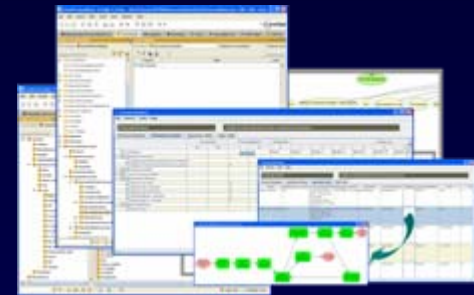


We have created an ontological framework to enable standardization and integration

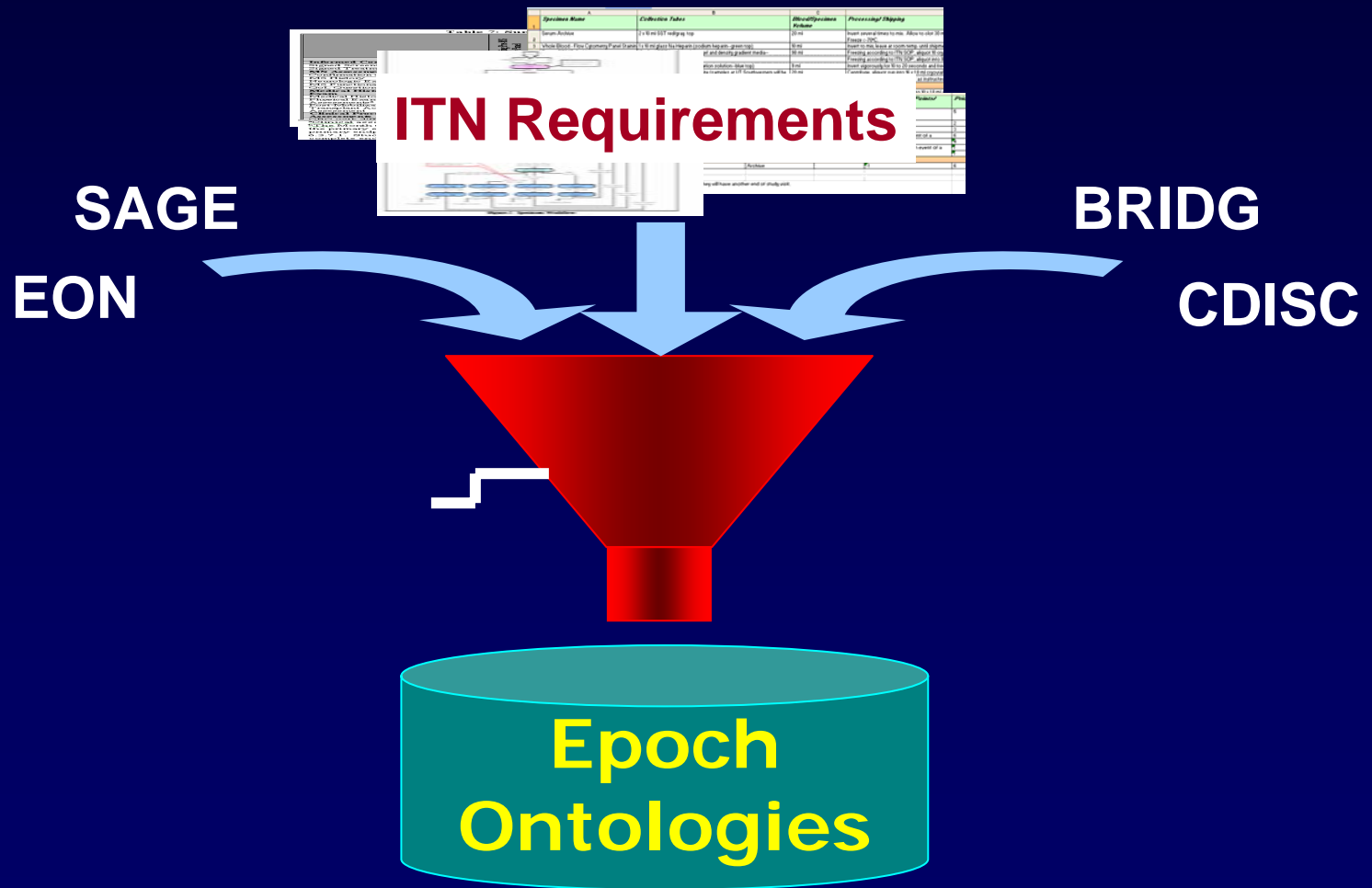


Our ontology work focuses on developing knowledge-based methods

- 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																
		3x / 7 days														
		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	49	56	63	70	77	84	91
	Visit															
	-1	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Medication Administration																
				3x	days											
Encounter																
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
Comprehensive chemistry	X				X	X		X			X					
Basic chemistry							X		X	X						X
Amylase ⁴	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.

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 ₂ EDTA lavender 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: DR4GAD, DR4IA-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

Specimen Workflow Table contains information on the processing of biological specimens

Standard Test	Collection	Blood/ Specimen Volume	Processing/ Shipping	Shipping	Assay	Final Destination	Assay Instructions	Collect
Specimen		Processing Instruction		ASSAYS				
Whole Blood- Quantitative PCR for CMV and EBV Reactivation	1 x 2 ml K ₂ EDTA 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 and p collection reagent	-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	Autoantibod y 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			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.	ITN Isolation Core	ITN Core	Tetramer: DR4GAD, DR4IA-2, DR3- proinsulin, ELISPOT	0,5,8,10,12
Whole Blood-Gene Expression Profiling	2 x 3 ml tempus tubes	6 ml	or 10 cryovials 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

**Core
Laboratory**

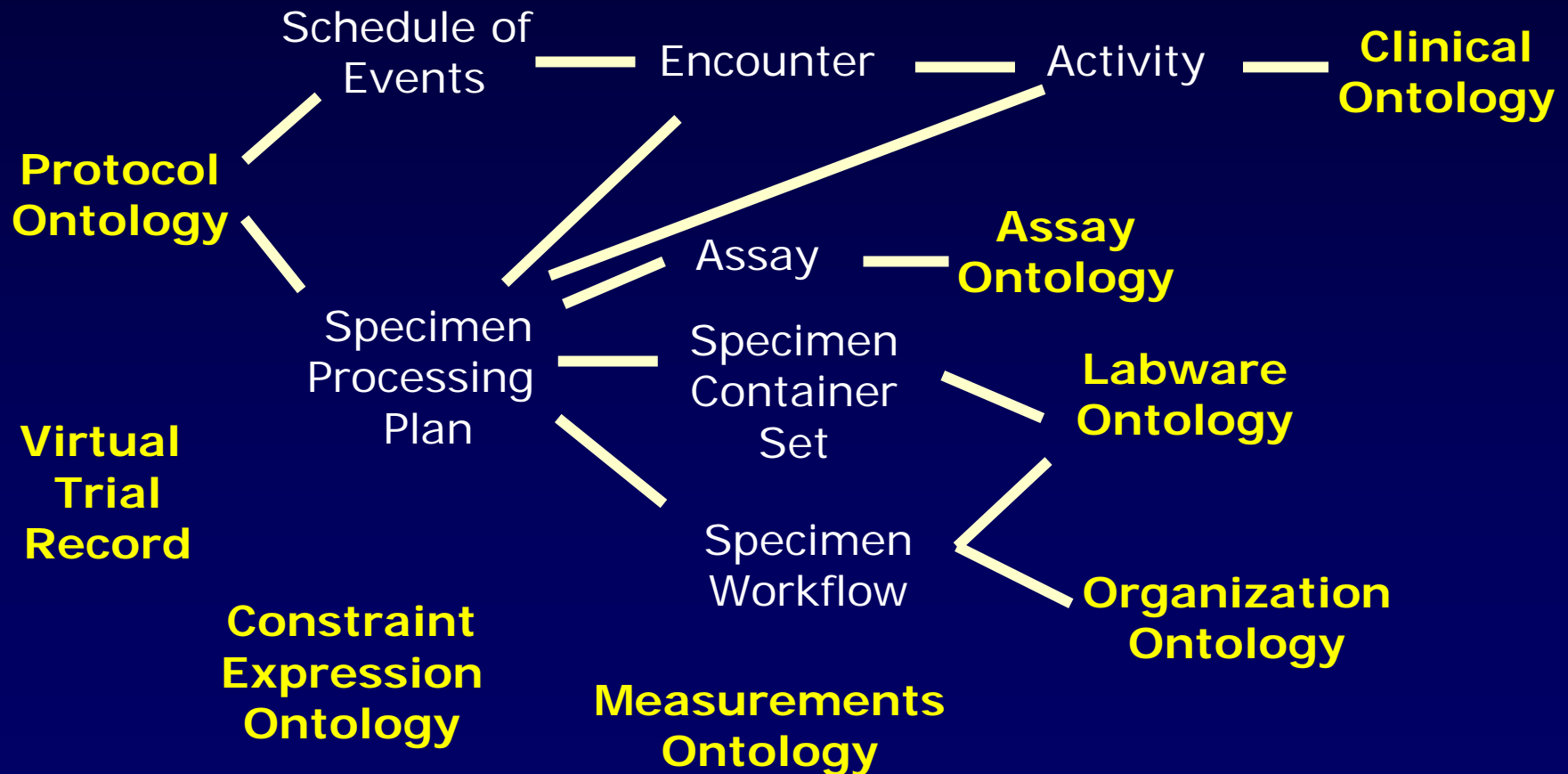
**Specimen
Container**

**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 screenshot displays the Protégé 3.3 beta interface for editing the ProtocolOntology. The window title is "ProtocolOntology Protégé 3.3 beta (file: C:\projects\ITN\Epoch0.96\ontologies\Epoch\ProtocolOntology.pprj, OWL / RDF Files)". The menu bar includes File, Edit, Project, OWL, Code, Tools, Window, and Help. The toolbar contains various icons for file operations and editing. The main interface is divided into several panes:

- Metadata (ProtocolOntology.owl)**: The active tab, showing the class hierarchy.
- SUBCLASS EXPLORER**: Displays the asserted hierarchy for the ProtocolOntology project. The hierarchy includes:
 - org:Facility
 - assay:Assay
 - lab:LabWare
 - lab:PreprocessingCondiitor
 - lab:SpecimenMetaclass_16
 - lab:StorageConditions
 - ce:ConstraintExpression
 - mo:Measurement
 - mo:Unit
 - PROTOCOL EVENT TYPE
 - ProtocolEntity
 - FacilitiesPlanEntity
 - Protocol
 - ProtocolEventEntity
 - StudyDesignEntity
 - StudyScheduleEntity
- CLASS EDITOR**: The active pane for editing the Protocol class. It shows the class name "Protocol" and its instance of owl:Class. The "Inferred View" checkbox is unchecked. The "Annotations" tab is selected, showing a table with the following data:

Property	Value	Lang
rdfs:comment	Protocol is the main class in the Protocol Ontology. It primarily captures the protocol schema, the events that are planned and their schedule. 	
- Properties and Restrictions**: A list of properties and their restrictions for the Protocol class:
 - hasFacilitiesPlan (single FacilitiesPlan)
 - hasLongTitle (single string)
 - hasPrimaryScheduleOfEvents (single ScheduleOfEvents)
 - hasProtocolId (single string)
 - hasSchedulesOfEvents (multiple ScheduleOfEvents)
 - hasSpecimenWorkflow (single SpecimenWorkflow)
- Superclasses**: A list of superclasses for the Protocol class, including ProtocolEntity.
- Disjoints**: A list of disjoints for the Protocol class.

The bottom status bar shows the "Logic View" and "Properties View" tabs, with "Properties View" currently selected.

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

ProtocolOntology Protégé 3.3 beta (file:VC:\projects\ITN\Epoch0.96\ontologies\Epoch\ProtocolOntology.pprj, OWL / RDF Files)

File Edit Project OWL Code Tools Window Help

Metadata (ProtocolOntology.owl) OWLClasses Properties Individuals Forms

SUBCLASS EXPLORER CLASS EDITOR

For Project: ProtocolOntology For Class: Protocol (instance of owl:Class) ☐ Inferred View

Asserted Hierarchy

- org:Facility
- assay:Assay
- lab:LabWare
- lab:PreprocessingCondition
- lab:SpecimenMetaclass_16
- lab:StorageConditions
- ce:ConstraintExpression
- mo:Measurement
- mo:Unit
- PROTOCOL EVENT
- ProtocolEntity
 - FacilitiesPlanEntity
 - Protocol
 - ProtocolEventEntity
 - StudyDesignEntity
 - StudyScheduleEntity

Protocol

captures the protocol schema, the events that are planned and their schedule.

Annotations

Lang
t primarily

Properties and Restrictions

- hasFacilitiesPlan (single FacilitiesPlan)
- hasLongTitle (single string)
- hasPrimaryScheduleOfEvents (single ScheduleOfEvents)
- hasProtocolId (single string)
- hasSchedulesOfEvents (multiple ScheduleOfEvents)
- hasSpecimenWorkflow (single SpecimenWorkflow)

Logic view Properties view

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

The image shows the Protégé 3.3 beta interface for editing the ProtocolOntology. The main window displays the 'SUBCLASS EXPLORER' and 'CLASS EDITOR' for the 'Protocol' class. An orange arrow points from the 'Protocol' class in the hierarchy to the 'Edit rdfs:comment at Protocol' dialog box.

The 'Edit rdfs:comment at Protocol' dialog box shows the following text:

Protocol is the main class in the Protocol Ontology. It primarily captures the protocol schema, the events that are planned and their schedule.

The dialog also displays a table of attributes and their comments:

Attribute	Comment
hasProtocolId	a unique identifier for a protocol
hasTitle	short title of a protocol
hasLongTitle	long title of a protocol
hasStudyDesign	the study design mainly specifies the arms of the protocol and the duration of the protocol
hasSchedulesOfEvents	a set of schedules of events (SOEs) lists planned events and their timings. A protocol can have multiple SOEs for different arms or different phases (such as the Withdrawal phase) of the protocol.
hasPrimaryScheduleOfEvents	if there are more than one SOE in a protocol, a primary SOE is typically associated with the normal plan
hasSpecimenWorkflow	a sequence of activity events to collect and process biological specimens
hasFacilitiesPlan	enumerates the study sites, bio-repositories and laboratories involved in the protocol implementation

The dialog box also includes a 'Language' dropdown menu and 'OK' and 'Cancel' buttons.

At the bottom of the Protégé window, the 'Properties View' tab is selected.

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

Protocol Browser

File Search Tools Help

Protocol# ITNxxxxx Study of a New Therapy for the Treatment of a Disease

Protocol Synopsis Schedule of Events Specimen Table Tube Table

	Screening		Pre-Treatment		Treatment	Follow-up					
	S1	S2	-1	E	0	1	2	3	4	5	6
Visit Time			Baseline		Day 0	Week 1	Week 3	Month 5	Month 8	Month 10	Month 2
Informed Consent											
Signed Screening Informed Consent	X										
Signed Treatment Informed Consent			X								
MS Assessments											
Clinical Assessments											
Mechanistic Studies											
Serum-Archive			X								
Specimen1-Assay1			X								
Specimen2-Assay2			X								
Whole Blood - Assay3			X								
Specimen4 - Assay4			X								
Study Treatment											
New Drug											

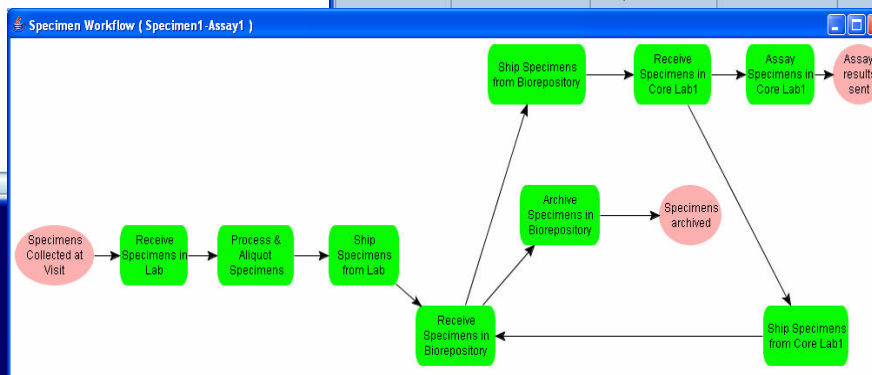
Protocol Browser

File Search Tools Help

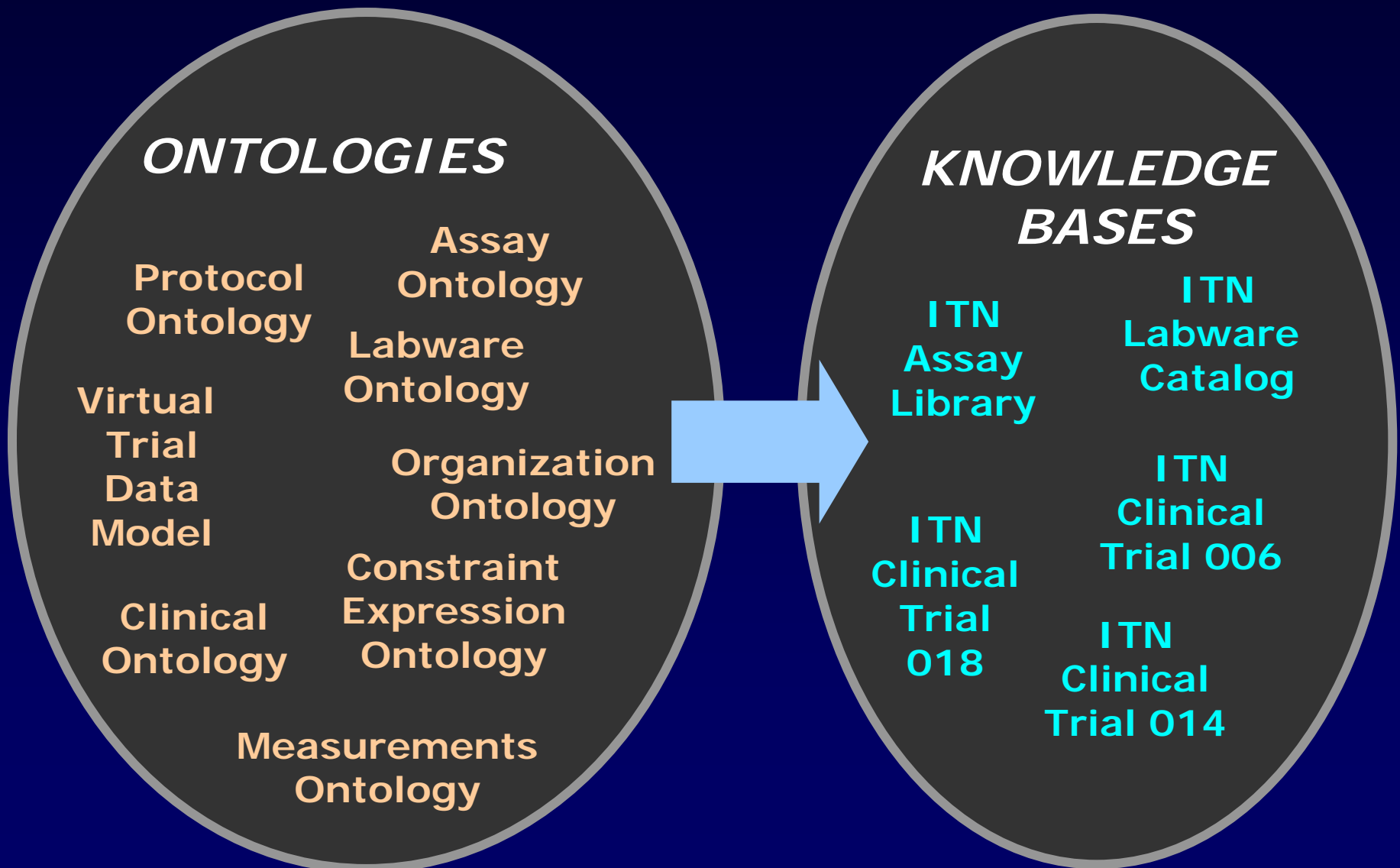
Protocol# ITNxxxxx Study of a New Therapy for the Treatment of a Disease

Protocol Synopsis Schedule of Events Specimen Table Tube Table

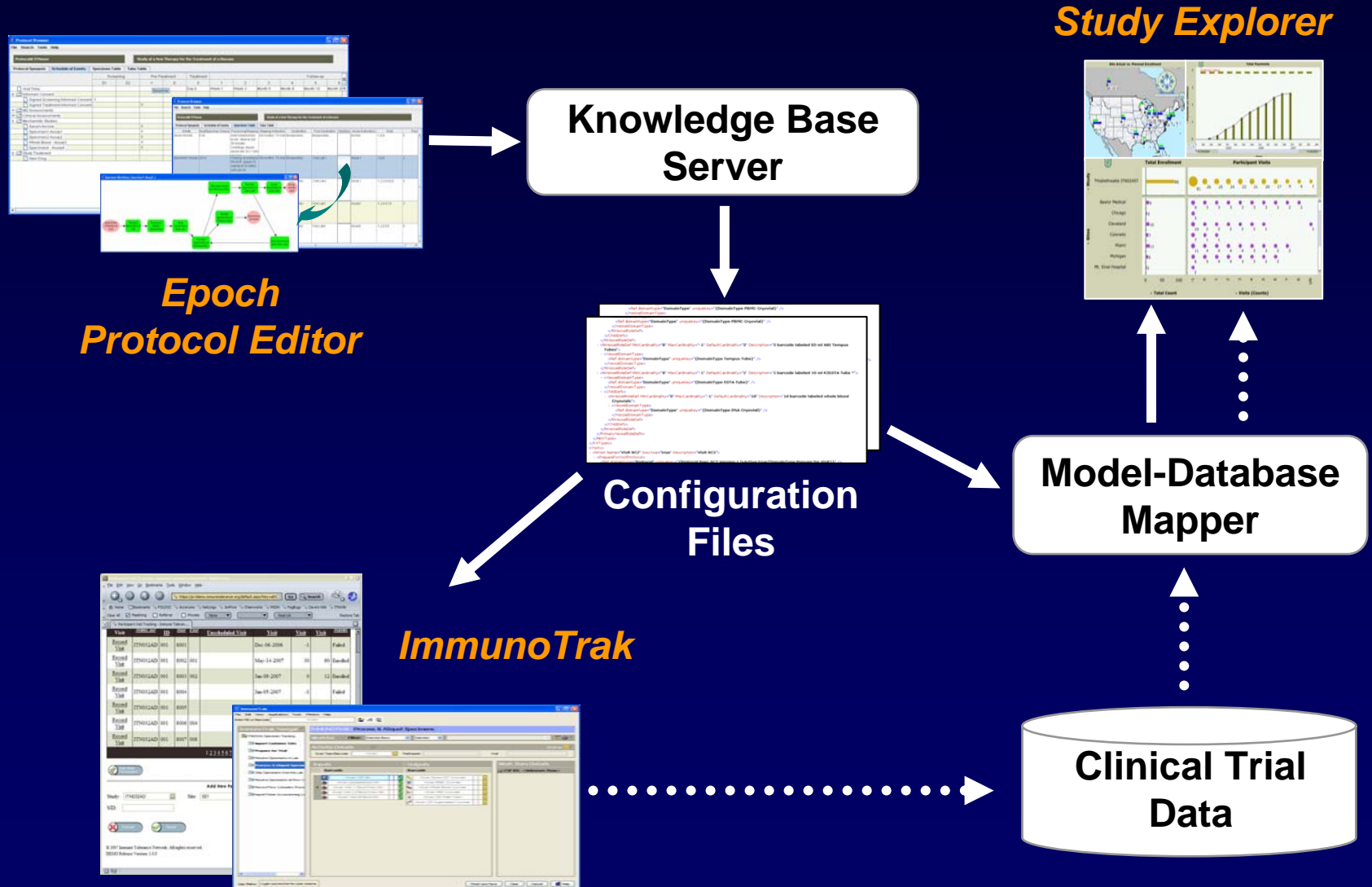
Activity	Blood/Specimen Volume	Processing/Shipping	Shipping Instruction	Destination	Final Destination	Workflow	Assay Instructions	Visits	Priori
Serum-Archive	0 ml	Invert several times to mix. Allow to clot 30 minutes. Centrifuge, aliquot serum into 33 x 1.8ml cryovials.	Dry Ice Mon - Fri only	Biorepository	Biorepository		Archive	-1,6,8	5
Specimen1-Assay1	20 ml	Freezing according to ITN SOP, aliquot 10 cryovial at 10 million cells per ml.	Dry Ice Mon - Fri only	Biorepository	Core Lab1		Assay 1	-1,6,8	2
					Core Lab2		Assay 1	-1,2,3,5,6,8,9	4
					Core Lab3		Assay3	-1,2,4,5,7,9	3
					Core Lab4		Assay4	-1,2,4,5,9	6



Instantiation of the Epoch ontologies generates clinical trial knowledge bases



The Epoch architecture supports knowledge-driven specification of software tools



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 ?