Protocol Representation: The Forgotten CDISC Model

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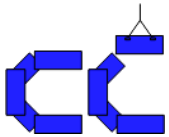


PROTOCOLS AND RE-USE: HOW MANY TIMES IS INFO RE-USED?

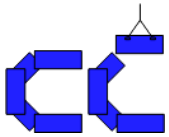
2. SYNOPSIS

Name of Sponsor: CDISC Pilot Project	**Name of Finished Product:** Transdermal Xanomeline	**Name of Active Ingredient:** Xanomeline
Case Study Title: Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease		
Investigators and Study Centers: This study was conducted at 17 centers. Due to the nature of this CDISC Pilot Project, a list of investigators is not provided.		
Publications: Not applicable		
Study Period: 06 July 2012 to 05 March 2015	**Development Phase:** Phase 2	
Objectives: The objectives of the study were to evaluate the efficacy and safety of transdermal xanomeline, 50 cm^2 and 75 cm^2, and placebo in subjects with mild to moderate Alzheimer's disease.		
Methodology: This was a prospective, randomized, multi-center, double-blind, placebo-controlled, parallel-group study. Subjects were randomized equally to placebo, xanomeline low dose, or xanomeline high dose. Subjects applied 2 patches daily and were followed for		

Consider these Questions About Protocol Re-use

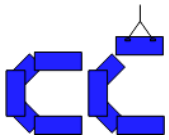
- How many times is protocol info re-used?
- Is the source always the same?
- Are you sure about semantic consistency?
- Are you sure about consistent *spelling*?
- What do you have to do to make sure?
- Would it be better if you had a single source?

Keep these in mind as we discuss the PRM.



Introduction

The CDISC mission:	• provide "end-to-end" standards that improve clinical trial operations
Familiar standards with a high implementation rate:	• SDTM • ADaM • define-xml
Familiar standards with a lower implementation rate:	• CDASH
And then there is the **P**rotocol **R**epresentation **M**odel (PRM)	• Adoption rate of < 5%



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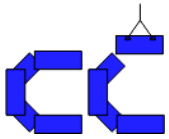
Introduction

- Another CDISC goal: improve clinical trial operations
- Greatest value of standards gained by implementing at study startup
- Most organizations use a downstream approach
- This standards implementation strategy often results in increased
  - TIME
  - $$$$$



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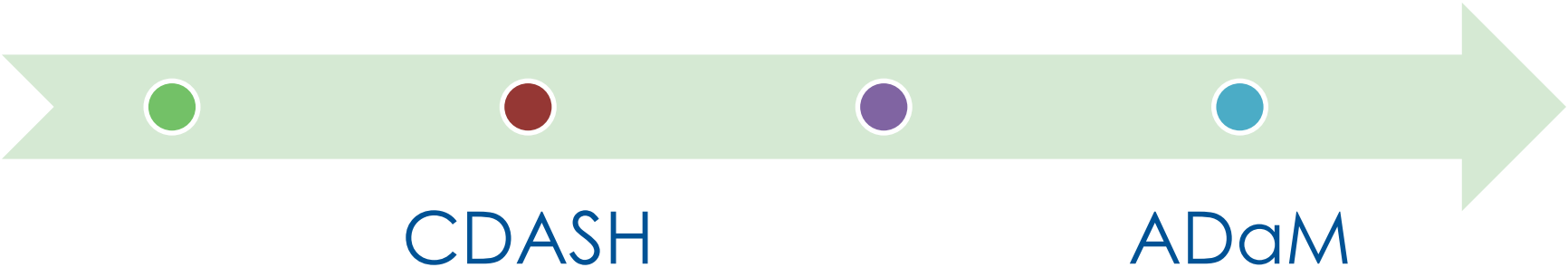
PRM Background

Along the "end-to-end" continuum:



PRM

- Recognizes the importance of the study protocol
- Identifies common features of protocols
- Makes the protocol machine-readable.

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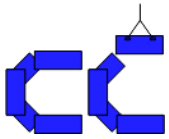
PRM Background

- Protocol is rich in information and provides a guide for a study
- Relevant for all service areas and regulatory agencies
- Typically stored as Word or PDF document
- Information not machine readable or easy to re-use
- Next slide shows how PRM fits in with other CDISC standards.



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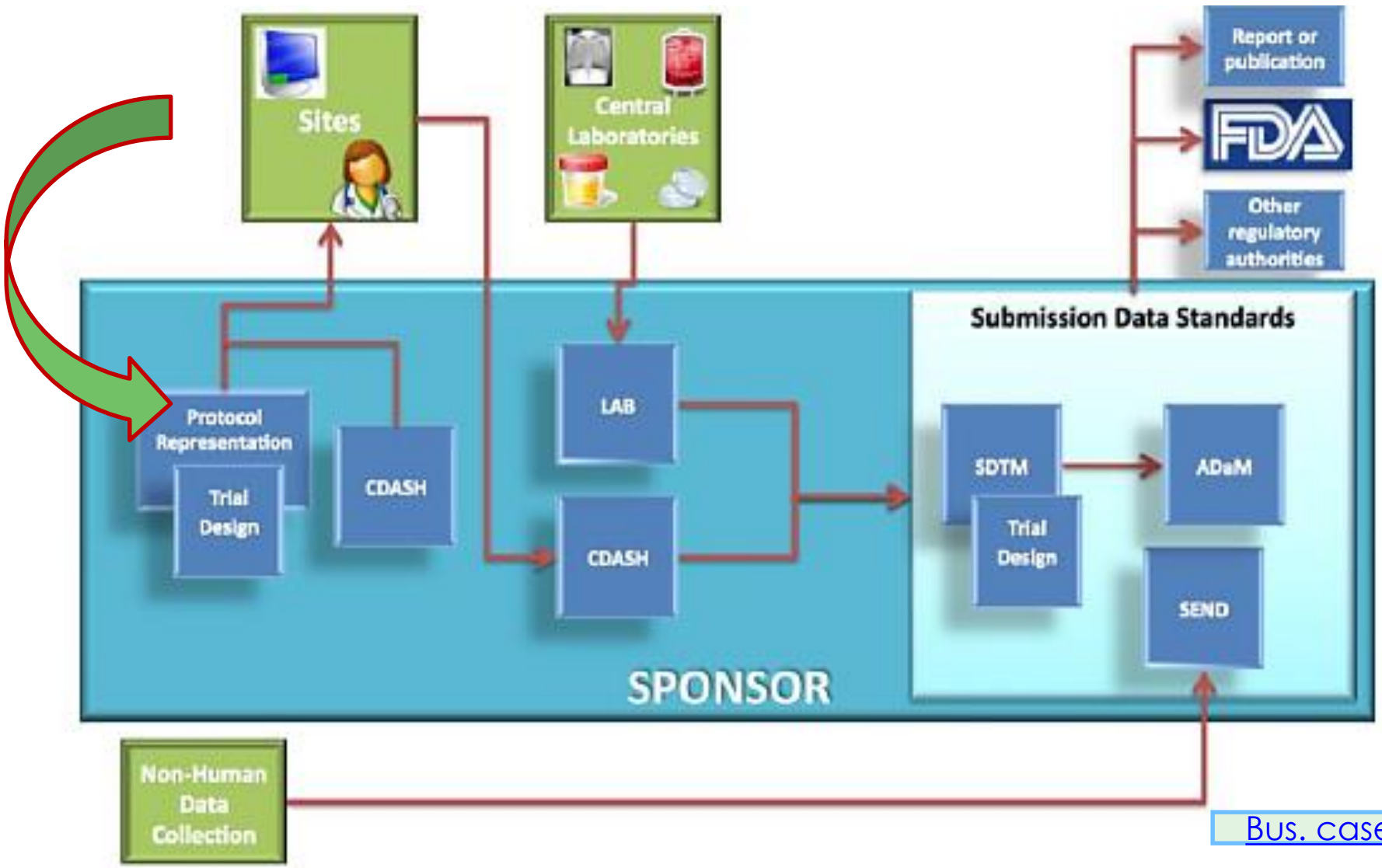
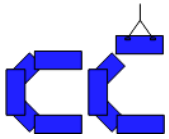
Information Flow Using CDISC Standards



Bus. case

History of the PRM

Curious, since it has so many uses.



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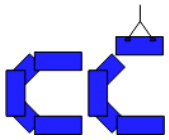
Background: Rationale for PRM

- "Protocol v1.0 was developed to support:
  - protocol document generation
  - research study (clinical trial) registration and tracking
  - regulatory oversight and review
  - single-sourced, downstream electronic consumption of protocol content, allowing users to create and quality control content once, and reuse for trial registries, protocol and case study report templates, SDTM study design and more"



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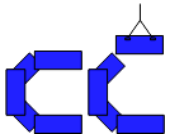
What We'll Talk About Today

- What is the PRM?
- Considerations for implementation
- The business case for PRM implementation
- Examples of use at Rho



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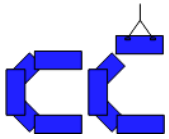
What Is The PRM?

- A *model* for organizing a protocol
- Not a deliverable *per se*
- A "living document" – the schema is extensible
- A means for making protocol elements easily accessible for downstream applications
  - This requires building a tool set (discussed later)
  - The tool set requirement common to *any* standard's successful adoption.



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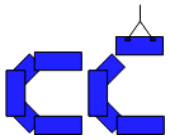
4 Major Components of PRM v1.0

Clinical Trial/Study Registry:	Background information based on the requirements from WHO and Clintrials.gov. Examples: Study Type, Registration ID, Sponsors, and Date of First Enrollment.
Eligibility:	Eligibility criteria such as minimum age, maximum age, and subject ethnicity.
Study Design Part 1:	Experimental design; items such as Arms and Epochs.
Study Design Part 2:	Schedule of Events and Activities.



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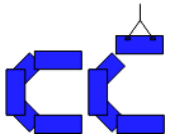
Implementation

- Database: Storage is database “agnostic” (anything but Excel! ☺)
- Originally described using UML to harmonize with BRIDG
- Interface: Should follow the flow of protocol development; easily support repository
- Tools for access: simple (e.g., SAS macro) access to database tables and views
- Data exchange: CDISC Study Design Model schema is an options if protocol metadata needs to be sent to client/FDA/other



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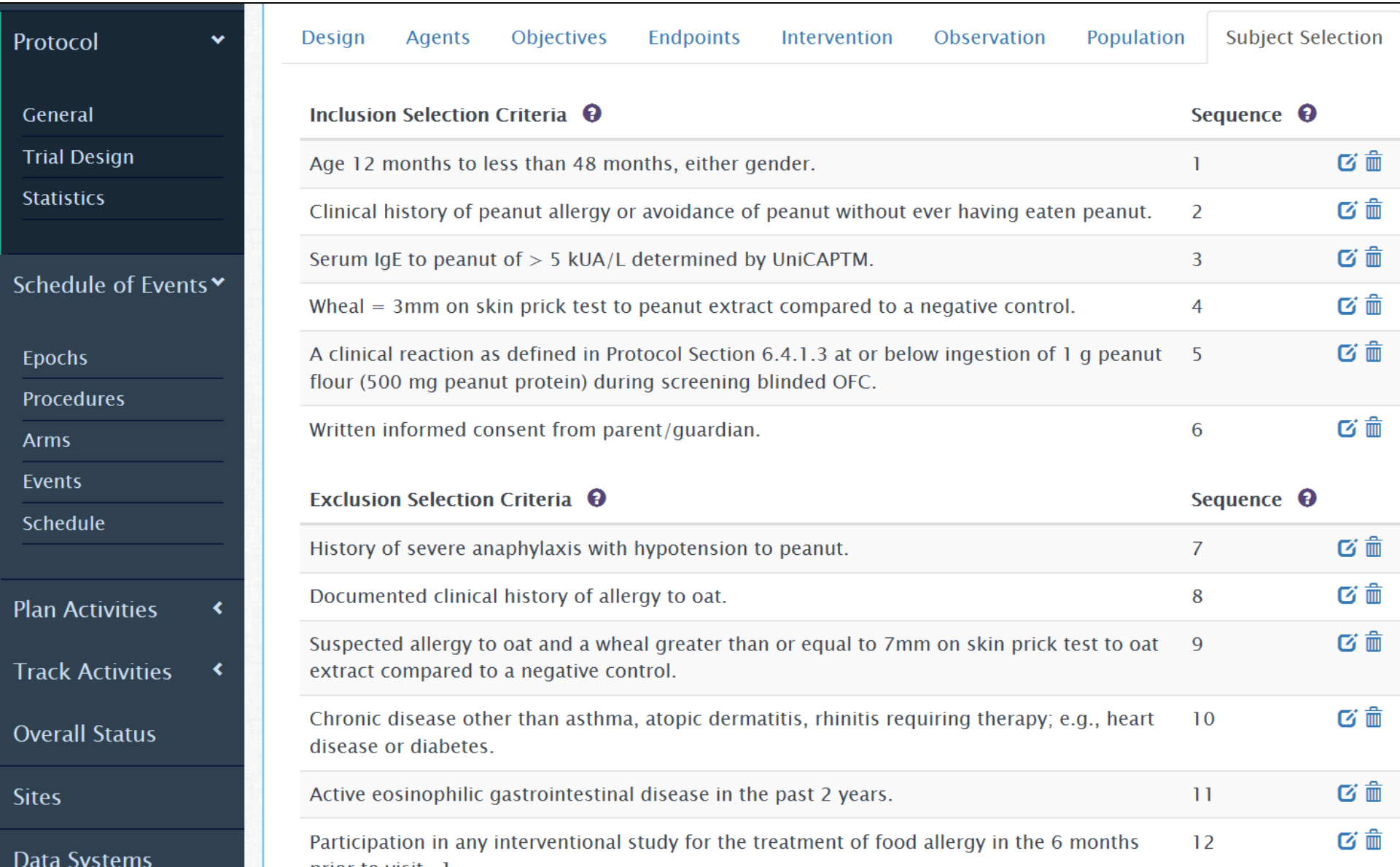
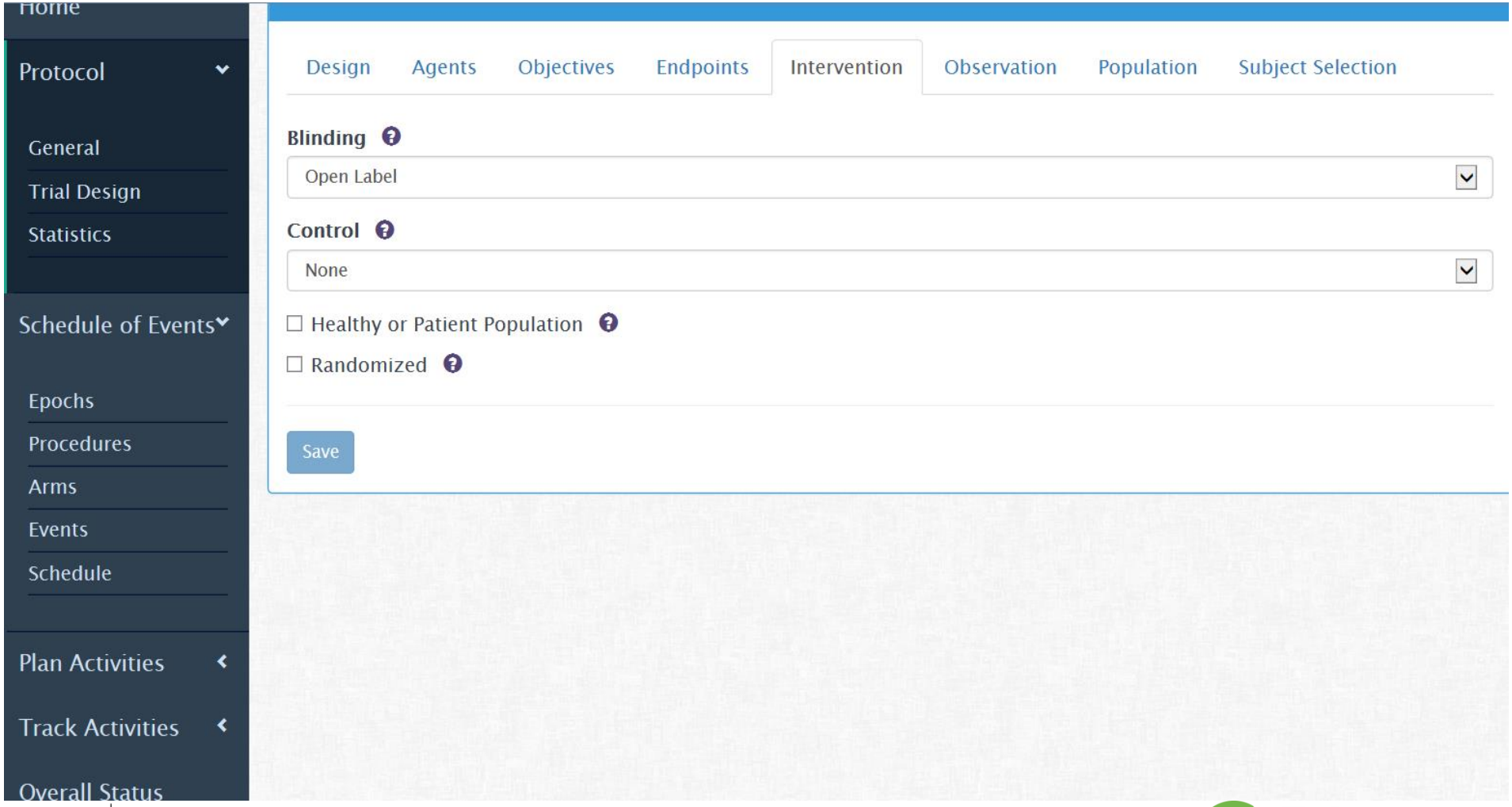
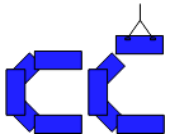
Interface (Selection Criteria)



Interface (Intervention Criteria)





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The Business Case for PRM

Implementing standards from the beginning can:

save up to 60% of non-subject participation time and cost

reduce study start up time 3-5 months

minimize # of protocol amendments

shorten the recruitment cycle

reduce # of handoffs

shorten the time for protocol review

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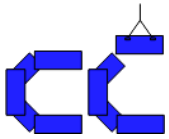
The Business Case for PRM

- Streamline protocol development
  - Structured authoring approach
  - Information can be stored in a library and re-used
  - Semantic consistency
- Protocols easier to understand
- Information easier to find
- PRM data can also be used downstream
  - CDASH / SDTM / ADaM datasets / reporting
  - Preparation of regulatory documents

Info flow



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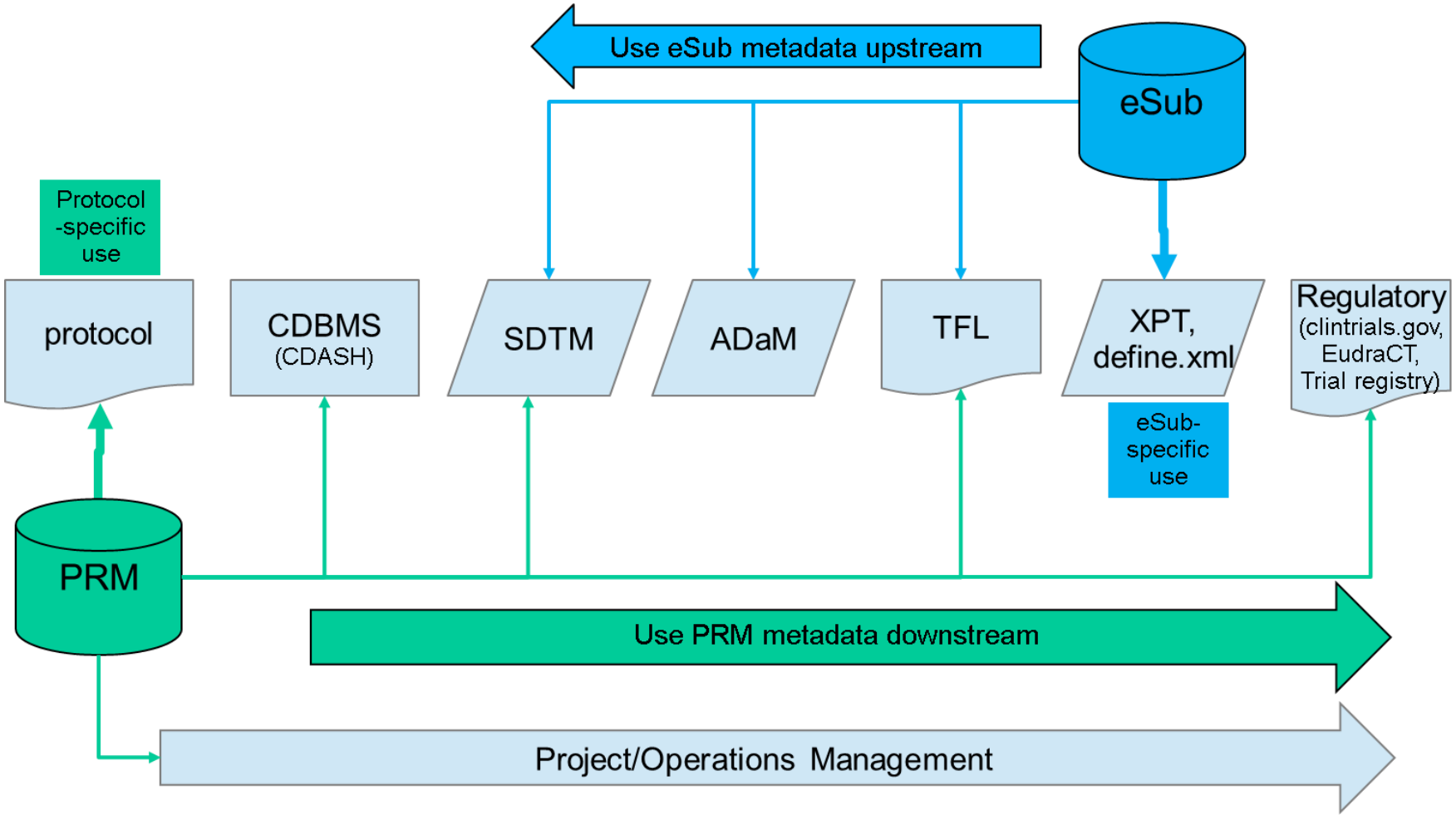
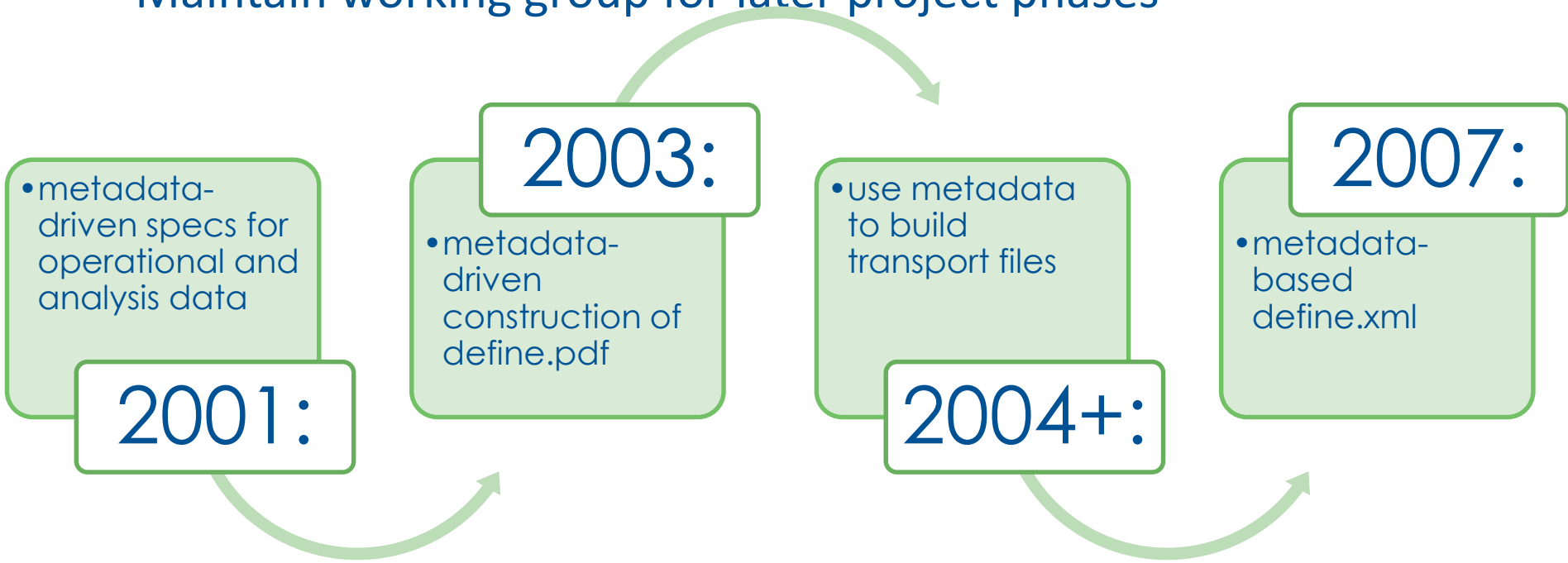
Metadata Usage Upstream/Downstream

Previous slides show that PRM, like eSub metadata, is most effective when used *throughout* the study life cycle



PRM Implementation at Rho

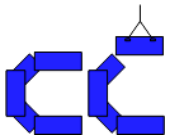
- Senior management directive: *complete* implementation of the end-to-end of standards
- Interdisciplinary: working group from multiple departments
- Initial "Priority" elements identified for interface, toolkit
- Maintain working group for later project phases



Rho history of implementing standards/metadata-based systems

Rho Usage of PRM Metadata: Current

- Protocol Development
- CDM System Setup
- SDTM Trial Design Datasets
- Operational and Statistical Reporting
- Management Tracking



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Rho Usage of PRM Metadata: Protocol Development

Step 1

- Adopt TransCelerate protocol template
- Map PRM to template
- After protocol developed, enter info in PRM

Step 2

- Enter protocol info in PRM first
- Generate protocol from PRM

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Rho Usage of PRM Metadata: Protocol Development

CONFIDENTIAL Protocol [Protocol Number]

Title Page

Protocol Title: [title]

Protocol Number: [protocol number]

Compound Number: [compound number]

Sponsor Name and Legal Registered Address: [sponsor name]

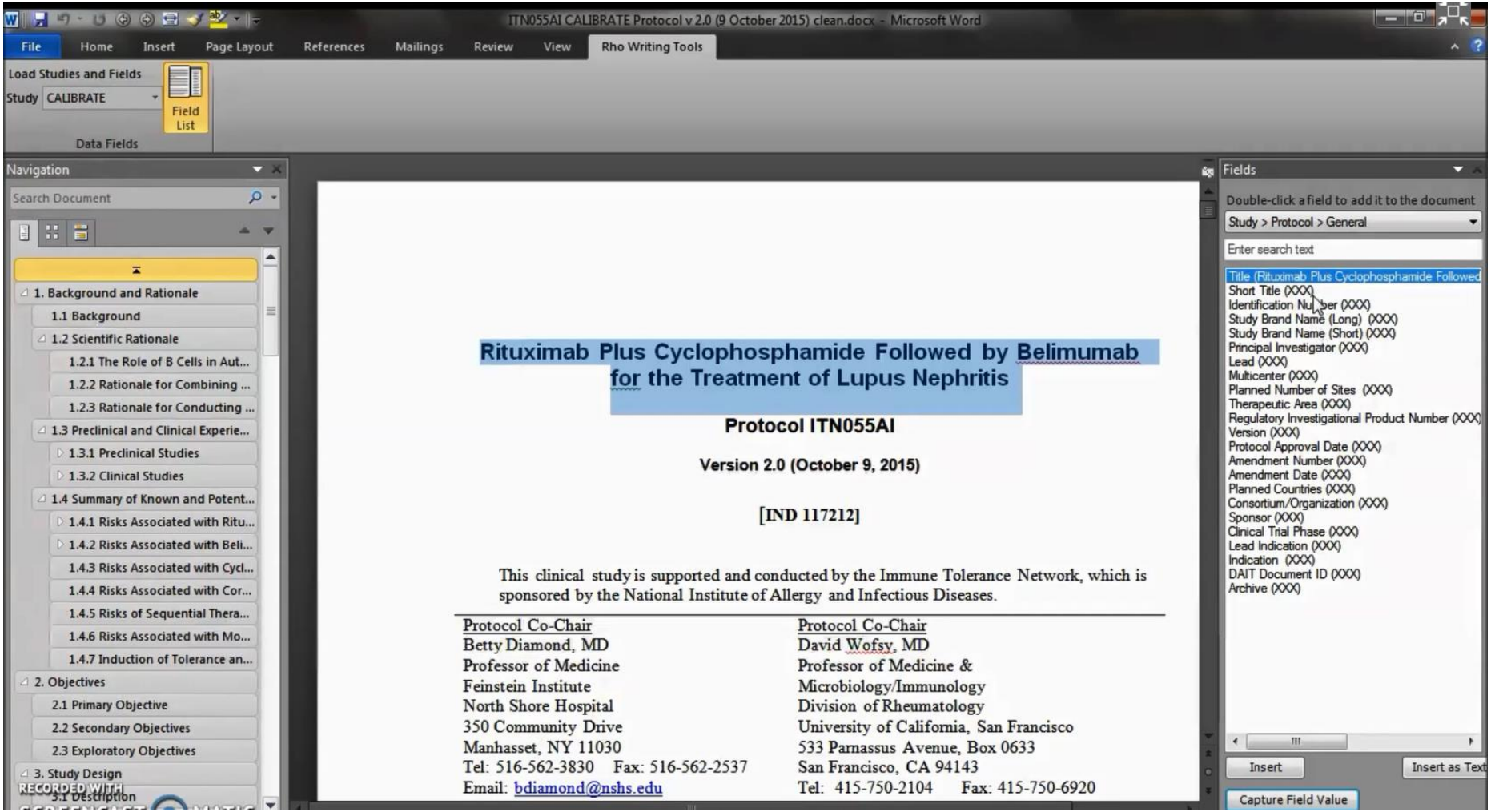
[address]

Regulatory Agency Identifying Number(s): [regulatory agency identifying number(s) as appropriate]

IND number: [IND number]

Approval Date: [Approval date]

Protocol Development Tool



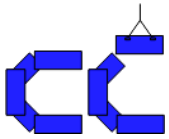
Rho Usage of PRM Metadata: CDMS Setup

Step 1

- PRM includes schedule of events module (CRFs and visits collected)
- Export as ODM XML

Step 2

- Import ODM XML into Medidata Rave or other EDC system
- Protocol and CDMS are aligned



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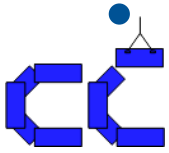
Rho Usage of PRM Metadata: SDTM Trial Design Data

- Over 25 concepts in our PRM map directly to the SDTM Trial Summary (TS) dataset
- Harmonized the controlled terminology in our PRM with the SDTM Trial Design Datasets
- Currently adding all SDTM Trial Design concepts to our PRM
- Almost all SDTM Trial Design datasets can be produced from our PRM
- Info entered by RAs, not programmers



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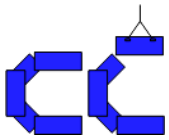
Rho Usage of PRM Metadata: SDTM Trial Design Data

```
%setup(program=T:\Submissions\Rho\CDASHToSDTM,
       study=CDASHtoSDTM01);
%let domain = TI ;

data &domain;
  set ora.v_study_incl(in=ini)
      ora.v_study_excl(in=ine) ;
  where study_uid = &studyid ;
  domain = "&domain" ;
  if          (ini) then iecat = 'Inclusion' ;
      else if (ine) then iecat = 'Exclusion' ;
run ;
```



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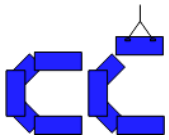
Rho Usage of PRM Metadata: management/tracking

- Metadata based system is multi-use
- Designed to improve trial operations
- Can be used to manage/track all projects
- PRM contains detailed info about every protocol
- For example
  - List all pain studies using a parallel group design
  - Can get # of active studies
  - List of all oncology studies



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Rho Usage of PRM Metadata: management/tracking

Formula | Layout | Sort | Filter | Group | Aggregate | Chart | Crosstab | Paging

Table

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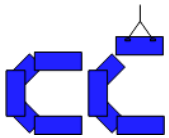
StudyUID	ShortTitle	Phase	StudyType	Configuration	PlannedNumberSubjects	Multicenter	IdentificationNumber	StudyBrandNameLong	StudyBrandNameShort	PlannedNumberSites	Duration	Title	TrialPurposeClassification	PrincipalInvestigator
14	ARA08	II	IND Exempt Intervention	Parallel Group Design	200	Y	ARA08	StopRA		21	3 YEARS	Strategy to Prevent the Onset of Clinically Apparent Rheumatoid Arthritis	Safety and Efficacy	Deane/Holers/Striebich
8601	Prevent CMV	NA	Observational		80	Y	CTOT-22			5	18 MONTHS	Prospective Multicenter Cytomegalovirus (CMV) Specific Immune Monitoring to Stratify Patient Risk and Guide Antiviral Prophylaxis after Lung Transplantation (PREVENT- CMV)	Proof of efficacy	Palmer
37	Interferon		Mechanistic		120	N	ADRN-01		Interferon	1	5 YEARS	Investigation of Reduced (Study Drug) Responses in Peripheral Blood Mononuclear Cells of Participants with Atopic Dermatitis and a History of Eczema Herpeticum		Leung
9	CALIBRATE	II	IND (Phases I-IV)	Parallel Group Design	40	Y	ITN055AI	Combination of Antibodies in Lupus Nephritis: Belimumab and Rituximab Assessment of Tolerance and Efficacy	CALIBRATE	12	120 MONTHS	Rituximab Plus Cyclophosphamide followed by Belimumab for the Treatment of Lupus Nephritis	Safety study	Diamond/Wofsy/Aranow/Dall'Er
24	PAUSE	II	Observational	Parallel Group Design	120	Y	ITN059AI	Psoriasis Treatment with Abatacept and Ustekinumab: A Study of Efficacy	PAUSE	15	47 MONTHS	Phase II Trial to Evaluate the Efficacy of Ustekinumab (anti-IL-12/23) followed by Abatacept (CTLA4Ig) for the Treatment of Psoriasis Vulgaris	Safety and Efficacy	Krueger
33	Peanut Protein Quantification Study for LEAP-ON	NA	Observational		640		ITN053AD		LEAP-ON PPQ	1	34 MONTHS	Evaluation of peanut protein quantification in dust in the LEAP-ON study	Proof of efficacy	Lack
63	ADRN Influenza Vaccine Study	NA	Mechanistic		368	Y	ADRN-05		Influenza Vaccine	5	9 MONTHS	A Randomized Open Label Mechanistic Study in Atopic Dermatits to Assess the Immunogenicity of Fluzone Intradermal	Proof of efficacy	Leung



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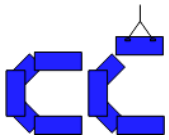
Rho Usage of PRM Metadata: Proposed

- Registries (e.g., ClinicalTrials.gov)
- Other regulatory documents
- Link to other data systems for a project



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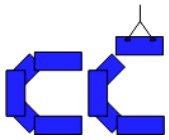
Closing Comments

PRM

- Can provide greatest value from standards implementation
- Provides a single, machine-readable source for trial concepts
- Content can be re-used throughout a study
- Improves quality and efficiency of deliverables
- Database is a valuable corporate asset
- Can facilitate regulatory review
- More time remaining on patent!!



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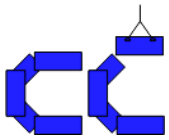
Thank you!

- Your comments and questions are appreciated and valued
- Contact the authors
  - Jeff Abolafia: Jeff_Abolafia@rhoworld.com
  - Frank DiIorio: Frank_DiIorio@rhoworld.com



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