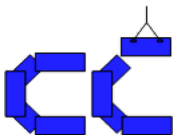


The Untapped Potential of the Protocol Representation Model

Jeffrey Abolafia, Rho, Inc.

Frank DiIorio, CodeCrafters, Inc.



Introduction: CDISC

The CDISC mission

- provide “end-to-end” standards that improve clinical trial operations

Familiar standards with a *high* implementation rate

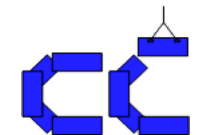
- SDTM
- ADaM
- define-xml

Familiar standards with a *lower* implementation rate

- CDASH

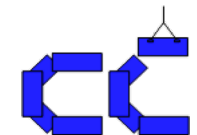
And then there is the
**Protocol Representation
Model (PRM)**

- Adoption rate of < 5%



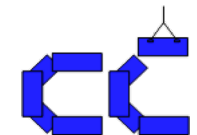
Introduction: CDISC

- Another CDISC goal: improve clinical trial operations
- Greatest value of standards gained by implementing at study *startup*
- But most organizations use a downstream (work flow, timeline) approach
- This standards implementation strategy often results in increased
 - Time
 - \$\$\$\$\$
 - Resistance to adoption

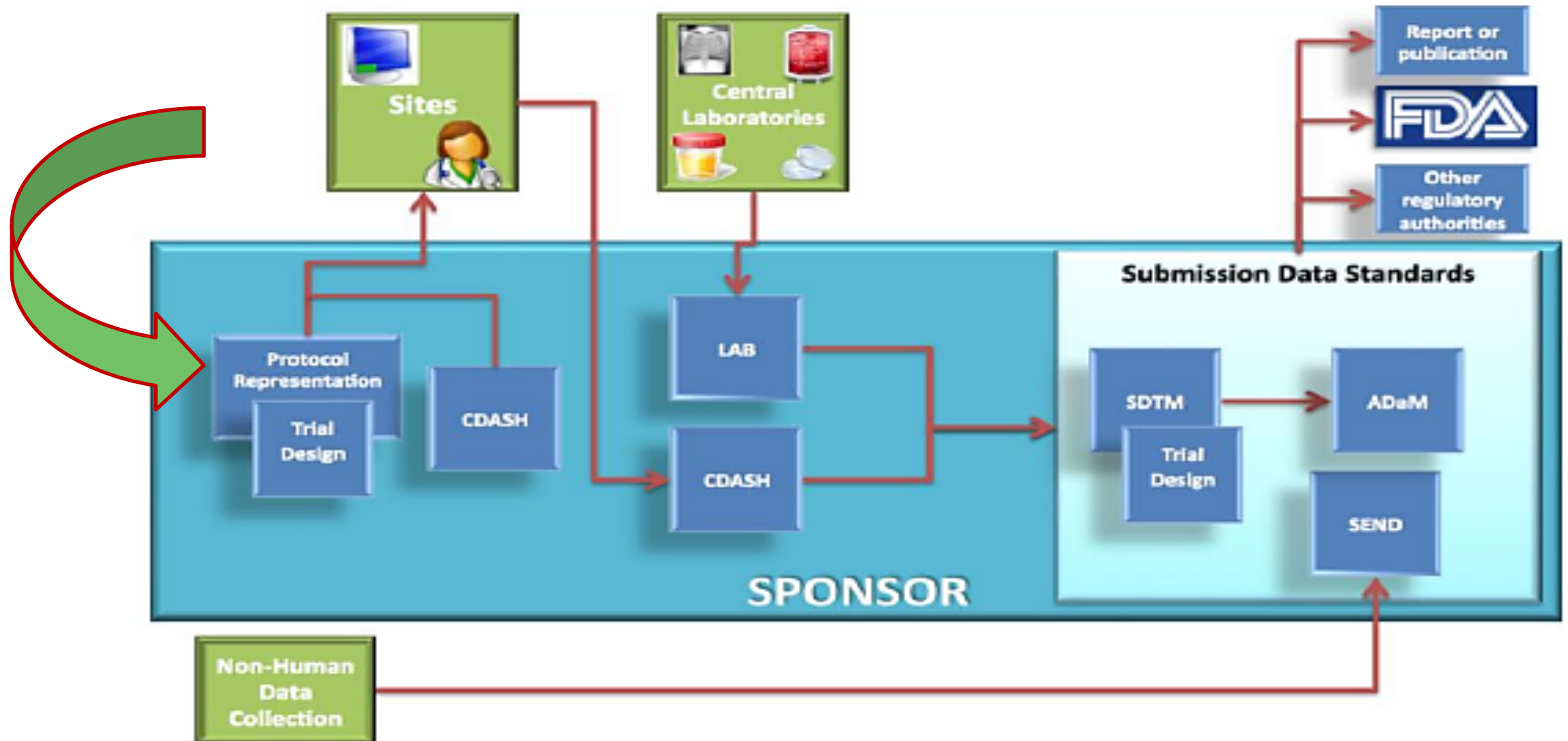


Background: Protocols and the PRM

- Protocol is the study “blueprint,” rich in information and is the basis for study implementation, objectives
- Relevant for *all* service areas and regulatory agencies
- Typically stored as Word or PDF document
 - This information not machine readable or easy to re-use
- PRM recognizes protocol’s importance and use throughout the life cycle of a study
 - Next slide shows how PRM fits in with other CDISC standards.



Study Work Flow Using CDISC Standards



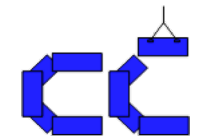
What We'll Talk About Today

What is the PRM?

Considerations for implementation

The business case for PRM implementation

Examples of use at Rho



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

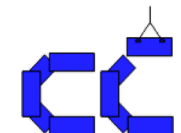
2. SYNOPSIS

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		

PROTOCOLS AND RE-USE: CONSIDER ...

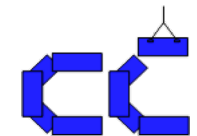
- How many times is protocol info re-used?
- Is the source always the same?
- Are you sure about semantic consistency?
- Are you sure about consistent *spelling*?
- What do you have to do to make sure?
- Wouldn't it be better if you had a single source?

Keep these in mind as we discuss the PRM.



What Is The PRM?

- A recognition of the importance of the study protocol
- A machine-readable XML schema - a *model* – for organizing common elements of a protocol
- No *deliverable per se!*
- A “living document” – the schema is extensible
- A means for making protocol elements easily accessible for downstream applications
 - This requires database, interface, tool set (discussed later)
 - These requirements are common to *any* standard’s successful adoption.



History of the PRM

2002

- CDISC, HL7, FDA began standardization

2010

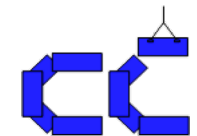
- Version 1.0 released

And then ...

- Not much traction
- Not many presentations at conferences

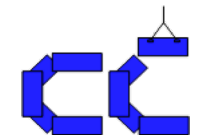
2016 -> present

- PRM Concept Team
- Harmonize concepts from TS, CTR, CFAST TA, others
- Released to NCI web site March 2017



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



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:

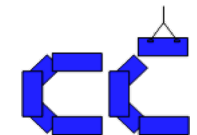
Eligibility criteria such as minimum age, maximum age, and subject ethnicity.

Study Design Part 1:

Experimental design; items such as Arms and Epochs.

Study Design Part 2:

Schedule of Events and Activities.



The Business Case: PRM, Standards

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



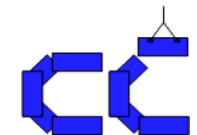
shorten the recruitment cycle



reduce # of handoffs

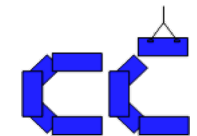


shorten the time for protocol review



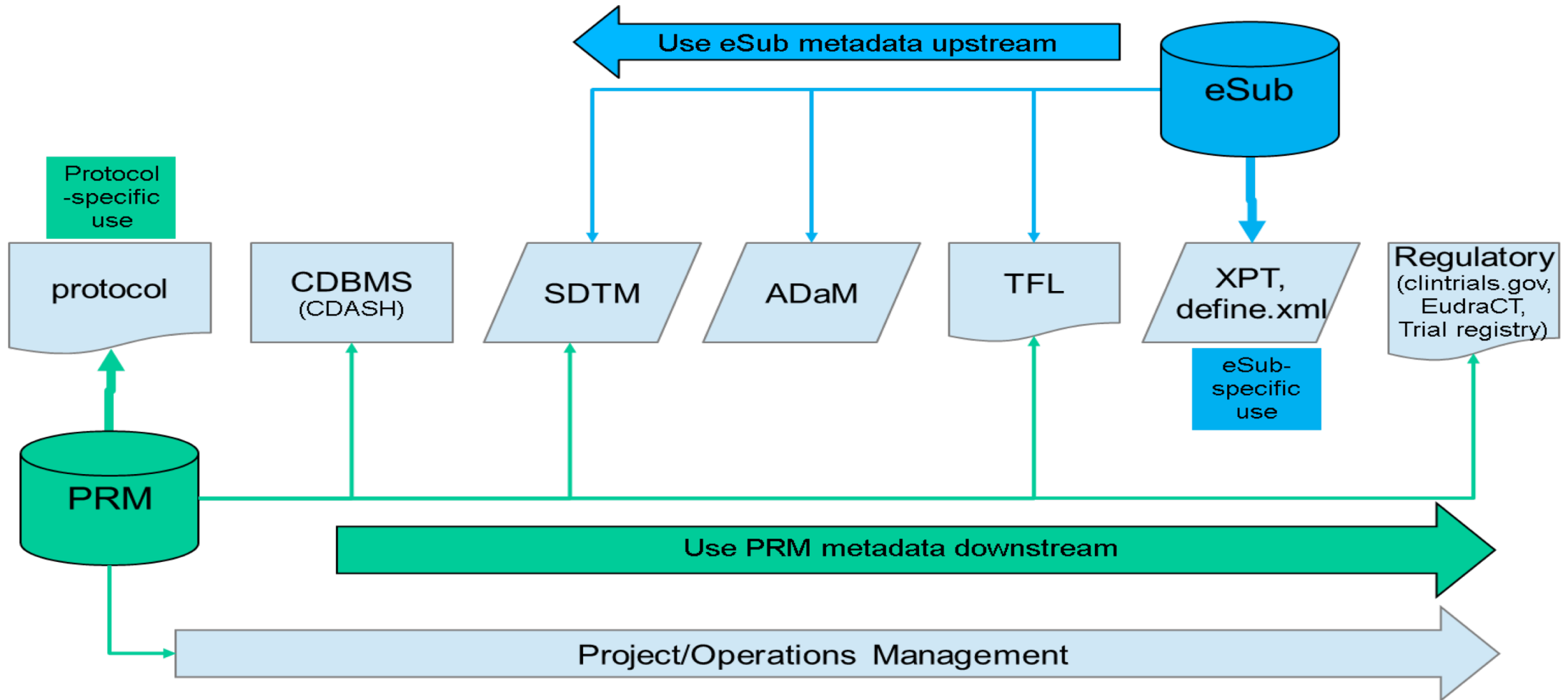
The Business Case: PRM

- Streamline protocol development
 - Structured authoring approach
 - Information can be stored in a database/library and re-used
 - Ensures 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
 - This is similar to use of eSub metadata (*next slide*)



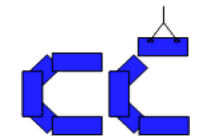
Metadata Usage Upstream/Downstream

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



Implementation

- **Database:** Storage is database “agnostic” (anything but Excel! 😊)
- Originally described using UML to harmonize with BRIDG
- **Interface** [1] should follow the flow of protocol development [2] easily support repository
- **Tools** for access: simple (e.g., SAS macro) access to database tables and views
- Data transfer: ODM/XML, CDISC Study Design Model schema can be used if protocol metadata needs to be sent to client/FDA



Interface 1 of 2: Selection Criteria

	Design	Agents	Objectives	Endpoints	Intervention	Observation	Population	Subject Selection
Protocol ▼								
General								
Trial Design								
Statistics								
Schedule of Events ▼								
Epochs								
Procedures								
Arms								
Events								
Schedule								
Plan Activities <								
Track Activities <								
Overall Status								
Sites								
Data Systems								

Inclusion Selection Criteria ?	Sequence ?	
Age 12 months to less than 48 months, either gender.	1	
Clinical history of peanut allergy or avoidance of peanut without ever having eaten peanut.	2	
Serum IgE to peanut of > 5 kUA/L determined by UniCAPTM.	3	
Wheal = 3mm on skin prick test to peanut extract compared to a negative control.	4	
A clinical reaction as defined in Protocol Section 6.4.1.3 at or below ingestion of 1 g peanut flour (500 mg peanut protein) during screening blinded OFC.	5	
Written informed consent from parent/guardian.	6	
Exclusion Selection Criteria ?	Sequence ?	
History of severe anaphylaxis with hypotension to peanut.	7	
Documented clinical history of allergy to oat.	8	
Suspected allergy to oat and a wheal greater than or equal to 7mm on skin prick test to oat extract compared to a negative control.	9	
Chronic disease other than asthma, atopic dermatitis, rhinitis requiring therapy; e.g., heart disease or diabetes.	10	
Active eosinophilic gastrointestinal disease in the past 2 years.	11	
Participation in any interventional study for the treatment of food allergy in the 6 months prior to visit 1.	12	

Interface 2 of 2: Intervention Criteria

Home

Protocol ▾

- General
- Trial Design
- Statistics

Schedule of Events ▾

- Epochs
- Procedures
- Arms
- Events
- Schedule

Plan Activities <

Track Activities <

Overall Status

DesignAgentsObjectivesEndpointsInterventionObservationPopulationSubject Selection

Blinding ?

Open Label ▾

Control ?

None ▾

☐ Healthy or Patient Population ?

☐ Randomized ?

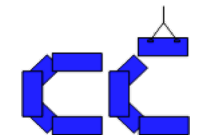
Save

PRM Implementation at Rho

- Rho has a long history of using metadata to create standard-compliant documentation and data
- 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 Usage of PRM Metadata: Current

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



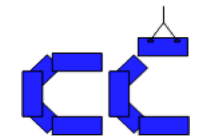
[1] Rho Usage of PRM Metadata: Protocol Development

Step 1

- Adopt standard 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



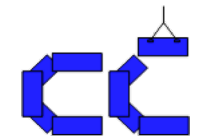
[1] Rho Usage of PRM Metadata: Protocol Development : Take 2

Step 1

- Adopt standard protocol template
- Map PRM to template

Step 2

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



[1] Rho Usage of PRM Metadata: Protocol Development

Bracketed
text are
database
fields

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]

[1] Protocol Development Tool (“very beta”)

Nav bar follows protocol order

Protocol elements in database

Edit/insert Into document

ITN055AI CALIBRATE Protocol v 2.0 (9 October 2015) clean.docx - Microsoft Word

Page Layout References Mailings Review View Rho Writing Tools

Navigation

Search Document

1. Background and Rationale

1.1 Background

1.2 Scientific Rationale

1.2.1 The Role of B Cells in Aut...

1.2.2 Rationale for Combining ...

1.2.3 Rationale for Conducting ...

1.3 Preclinical and Clinical Experie...

1.3.1 Preclinical Studies

1.3.2 Clinical Studies

1.4 Summary of Known and Potent...

1.4.1 Risks Associated with Ritu...

1.4.2 Risks Associated with Beli...

1.4.3 Risks Associated with Cycl...

1.4.4 Risks Associated with Cor...

1.4.5 Risks of Sequential Thera...

1.4.6 Risks Associated with Mo...

1.4.7 Induction of Tolerance an...

2. Objectives

2.1 Primary Objective

2.2 Secondary Objectives

2.3 Exploratory Objectives

3. Study Design

3.1 Description

Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis

Protocol ITN055AI

Version 2.0 (October 9, 2015)

[IND 117212]

This clinical study is supported and conducted by the Immune Tolerance Network, which is sponsored by the National Institute of Allergy and Infectious Diseases.

Protocol Co-Chair
Betty Diamond, MD
Professor of Medicine
Feinstein Institute
North Shore Hospital
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Email: bdiamond@nshs.edu

Protocol Co-Chair
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Microbiology/Immunology
Division of Rheumatology
University of California, San Francisco
533 Parnassus Avenue, Box 0633
San Francisco, CA 94143
Tel: 415-750-2104 Fax: 415-750-6920

Fields

Double-click a field to add it to the document

Study > Protocol > General

Enter search text

Title (Rituximab Plus Cyclophosphamide Followed by Belimumab for the Treatment of Lupus Nephritis)

Short Title (XXXX)

Identification Number (XXXX)

Study Brand Name (Long) (XXXX)

Study Brand Name (Short) (XXXX)

Principal Investigator (XXXX)

Lead (XXXX)

Multicenter (XXXX)

Planned Number of Sites (XXXX)

Therapeutic Area (XXXX)

Regulatory Investigational Product Number (XXXX)

Version (XXXX)

Protocol Approval Date (XXXX)

Amendment Number (XXXX)

Amendment Date (XXXX)

Planned Countries (XXXX)

Consortium/Organization (XXXX)

Sponsor (XXXX)

Clinical Trial Phase (XXXX)

Lead Indication (XXXX)

Indication (XXXX)

DAI (XXXX)

Arch (XXXX)

Insert

Insert as Text

Capture Field Value

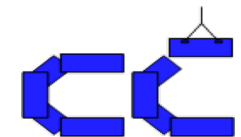
[2] Rho Usage of PRM Metadata: CDMS Setup

Step 1

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

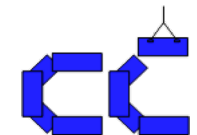
Step 2

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



[3] Rho Usage of PRM Metadata: SDTM Trial Design Data

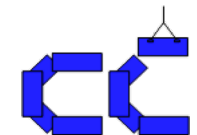
- Over 25 concepts in our PRM map directly to the SDTM Trial Summary (TS) dataset
- Harmonized the controlled terminology in our PRM with the SDTM Trial Design Datasets
- Currently adding all SDTM Trial Design concepts to our PRM
- Almost all SDTM Trial Design datasets can be produced from our PRM
-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



[3] Rho Usage of PRM Metadata: SDTM Trial Design Data

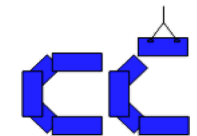
```
%setup (program=T:\Submissions\Rho\CDASHToSDTM,  
        study=CDASHToSDTM01) ;  
  
%let domain = TI ;  
  
data &domain;  
    set ora.v_study_incl(in=ini)  
        ora.v_study_excl(in=ine) ;  
    where study_uid = &studyid ;  
    domain = "&domain" ;  
    if          (ini) then iecat = 'Inclusion' ;  
    else if (ine) then iecat = 'Exclusion' ;  
  
run ;
```

Easily
“macrofized”



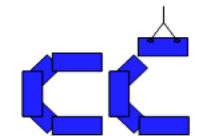
[4] Rho Usage of PRM Metadata: Management/Tracking

- 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



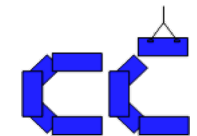
[4] Rho Usage of PRM Metadata: Management/Tracking

Table														
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'Era
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 (CTLA4lg) 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 Dermatitis to Assess the Immunogenicity of Fluzone Intradermal	Proof of efficacy	Leung



Rho Usage of PRM Metadata: Proposed

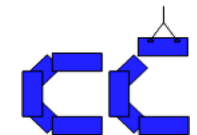
- Registries (e.g., ClinicalTrials.gov)
- Other regulatory documents
- Link to other data systems for a project



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!!



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

