Protocol Representation: The Forgotten CDISC Model

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## 2. SYNOPSIS

<table>
<thead>
<tr>
<th>Name of Sponsor:</th>
<th>Name of Finished Product:</th>
<th>Name of Active Ingredient:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDISC Pilot Project</td>
<td>Transdermal Xanomeline</td>
<td>Xanomeline</td>
</tr>
</tbody>
</table>

### 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 cm² and 75 cm², 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

<table>
<thead>
<tr>
<th>The CDISC mission:</th>
<th>• provide “end-to-end” standards that improve clinical trial operations</th>
</tr>
</thead>
</table>
| 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

• 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
  – $$$$$$
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.

**SDTM**

**CDASH**

**ADaM**
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.
Information Flow Using CDISC Standards
History of the PRM

2002
• CDISC, HL7, FDA began standardization

2010
• Version 1.0 released

And then ...
• Not much traction
• No updates
• Not many presentations at conferences

Curious, since it has so many uses.
What We’ll Talk About Today

- What is the PRM?
- Considerations for implementation
- The business case for PRM implementation
- Examples of use at Rho
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.
## 4 Major Components of PRM v1.0

<table>
<thead>
<tr>
<th>Clinical Trial/Study Registry:</th>
<th>Background information based on the requirements from WHO and Clintrials.gov. Examples: Study Type, Registration ID, Sponsors, and Date of First Enrollment.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility:</td>
<td>Eligibility criteria such as minimum age, maximum age, and subject ethnicity.</td>
</tr>
<tr>
<td>Study Design Part 1:</td>
<td>Experimental design; items such as Arms and Epochs.</td>
</tr>
<tr>
<td>Study Design Part 2:</td>
<td>Schedule of Events and Activities.</td>
</tr>
</tbody>
</table>
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
## Interface (Selection Criteria)

### Inclusion Selection Criteria

1. Age 12 months to less than 48 months, either gender.
2. Clinical history of peanut allergy or avoidance of peanut without ever having eaten peanut.
3. Serum IgE to peanut of > 5 kUA/L determined by UniCAP™.
4. Wheal = 3mm on skin prick test to peanut extract compared to a negative control.
5. 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.
6. Written informed consent from parent/guardian.

### Exclusion Selection Criteria

7. History of severe anaphylaxis with hypotension to peanut.
8. Documented clinical history of allergy to oat.
9. 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.
10. Chronic disease other than asthma, atopic dermatitis, rhinitis requiring therapy, e.g., heart disease or diabetes.
11. Active eosinophilic gastrointestinal disease in the past 2 years.
12. Participation in any interventional study for the treatment of food allergy in the 6 months prior to visit.
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

PRho
Giving flight to research.
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
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

2001:
- metadata-driven specs for operational and analysis data
- metadata-driven construction of define.pdf

2003:
- use metadata to build transport files
- metadata-driven construction of define.pdf

2004+:
- metadata-based define.xml

2007:
- metadata-based define.xml

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
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
Rho Usage of PRM Metadata:
Protocol Development

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]
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
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 ;
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
# Rho Usage of PRM Metadata: management/tracking

<table>
<thead>
<tr>
<th>StudyID</th>
<th>Short Title</th>
<th>Phase</th>
<th>Study Type</th>
<th>Randomized</th>
<th>Planned Number Subjects</th>
<th>Multi-center</th>
<th>Identification Number</th>
<th>StudyBrandNameLong</th>
<th>StudyBrandNameShort</th>
<th>PlannedNumberSites</th>
<th>Duration</th>
<th>Title</th>
<th>Total/Purpose Classification</th>
<th>Principal Investigator</th>
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<tbody>
<tr>
<td>14</td>
<td>ARA08</td>
<td>II</td>
<td>IND Exempt Interventions</td>
<td>Parallel Group Design</td>
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<td>ARA08</td>
<td>StepRA</td>
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<td>Prevent CMV</td>
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<td>Prospective Multicenter</td>
<td>CyrusRemedroza (CMV)</td>
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<td>Interferon</td>
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<tr>
<td>5</td>
<td>CALIBRATE</td>
<td>II</td>
<td>IND (Phase 1)</td>
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<td>34 MONTHS</td>
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<td>ADRN Influenza Vaccine Study</td>
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<td>ADRN-05</td>
<td>Influenza Vaccine</td>
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<td>2 MONTHS</td>
<td>A Randomized, Open-Label, Phase 1 Study of Influenza Vaccine</td>
<td>Safety and Efficacy</td>
<td>Leung</td>
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<td></td>
</tr>
</tbody>
</table>

[CC Logo] [Rho Logo]
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
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