Cost-Effective Standards Implementation: A New Paradigm for the Drug Development Life Cycle

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Warning 

This presentation contains a mixture of:

- Reality
- Aspirations
- Authors' vision for how we can greatly increase workflow efficiency, especially for analysis reporting

Agenda

- Background
- Traditional Approach
- New Approach
- Starting with the End – “Tables First”
- Standards Implementation Strategy
- Standards from End to End
- Implementation Example
- The Future

Introduction

Wrong Question:

- How do CDISC standards facilitate generic programming?

Better Question:

- How can we implement standards to meet FDA submission requirements?

Right Question:

- How can we use CDISC standards as part of a cost-effective drug development strategy?

Current Regulatory Environment

- CDISC standards *de facto* standard for submission deliverables
- Recent FDA draft guidance
- PDUFA
- Sponsor communications with FDA
- FDA investment in CDISC
- Increased number of CDISC submissions

But First: Some Ugly Facts about Drug Development

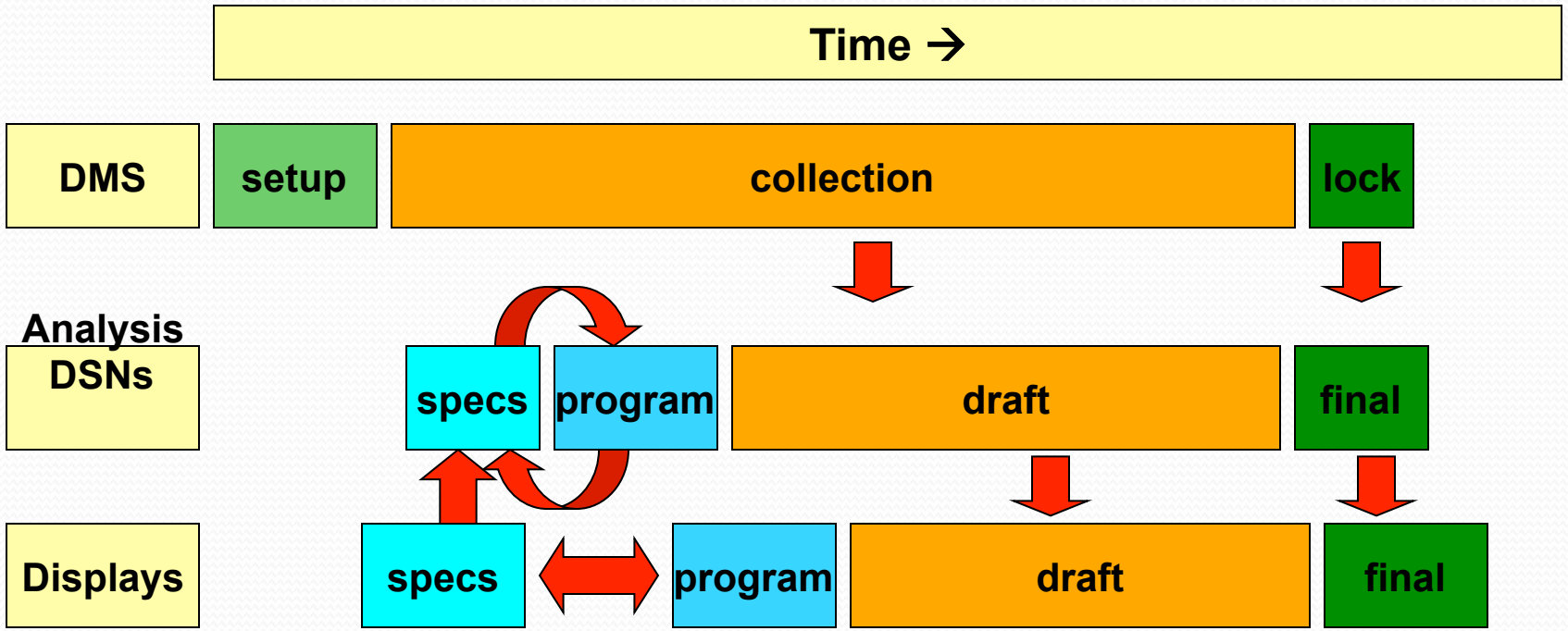
Patent life of a new compound or treatment: **20** years

Typically:

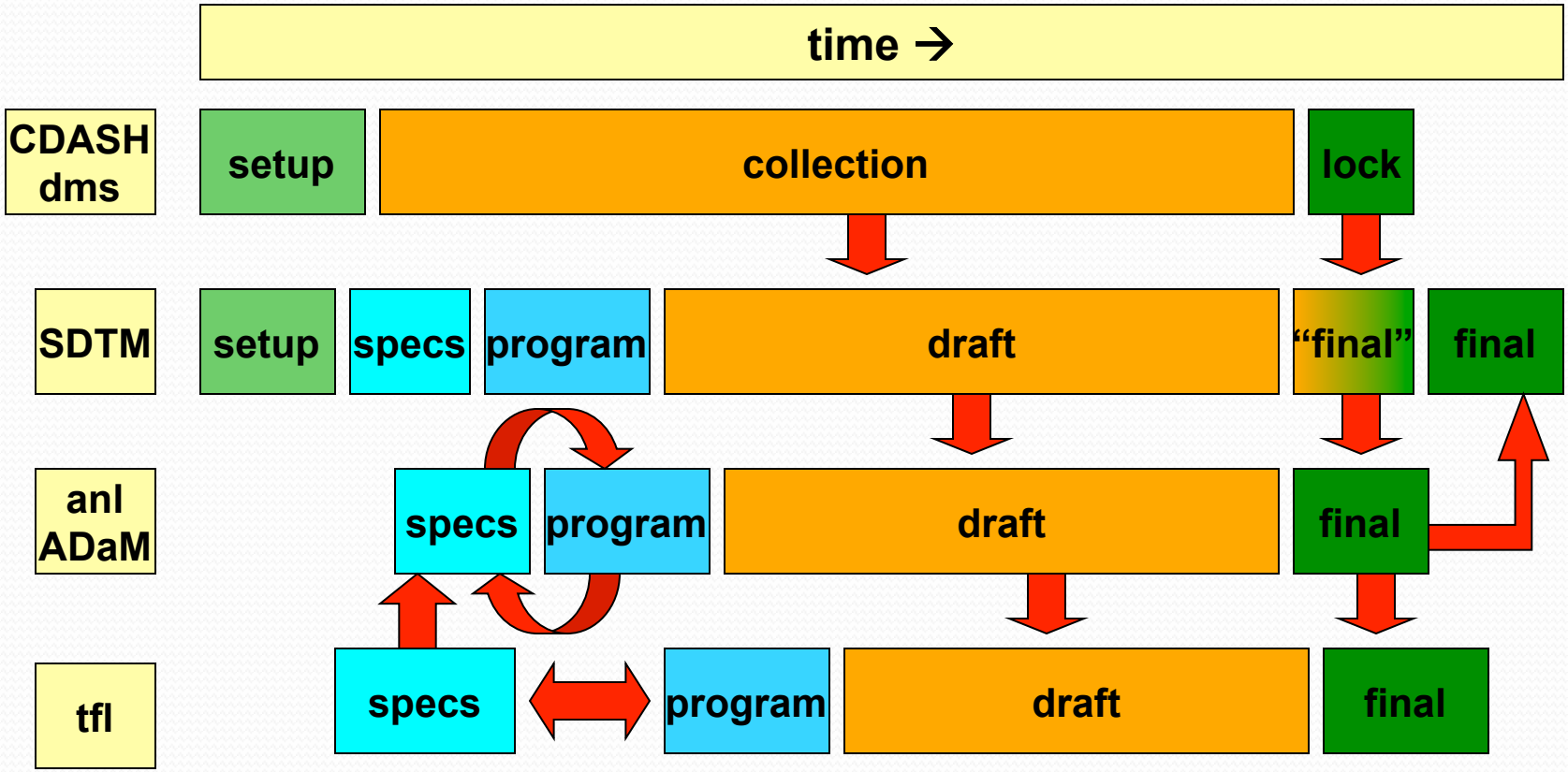
- Time from patent to approval: **> 12** years and **growing**.
- Time available to recoup investment, make profit: **< 8** years and **decreasing**.
- Cost of developing a new drug through initiation of marketing: estimates range from **$0.6 billion - $1.2 billion**. **$1.0 billion** is a typical number cited.

Background

Pre-CDISC Clinical Trial Workflow



Workflow for CDISC Project



CDISC = More of Everything

Non-CDISC Project Deliverables:	CDISC Project Deliverables:
▪ Data Management data ▪ CRT data ▪Analysis datasets ▪ Dataset specifications ▪ Annotated CRF ▪Define,pdf for clinical and analysis databases ▪TLFs	▪ Data Management data ▪ SDTM datasets - Domain datasets - SUPPQUAL datasets - Trial Design datasets - Controlled Terms for variables ▪ ADaM datasets ▪ Results-level metadata ▪ 2 Annotated CRFs (DM, SDTM) ▪ Define.xml and Define.pdf for SDTM ▪ Define.pdf for ADaM ▪ Additional validation/documentation ▪TLFs

CDISC Sponsor Impact: Short Term

Short Term

- More work
- Need to assimilate standards into processes
- More project parts to consider in the timeline
- Additional workflow process to coordinate
- Need to build new tools
- Lots of training
- New set of deliverables = more profit/business opportunities
- More coordination needed for more deliverables
- Legacy conversions

CDISC Sponsor Impact: Long Term

Long Term

- Corporate standard
- Standardized datasets across studies and therapeutic areas
- Facilitates data exchange with multiple partners
- More efficient work flow
- Ability to use standard tools/processes
- Facilitates data integration
- Faster and higher quality review

CDISC Sponsor Impact: Poor Implementation

If Implemented Poorly

- A lot more work
- Delays in study timelines
- Delays in assembling NDA
- Lower quality submission
- Delays in approval
- Increased costs
- **Less remaining time on patent**

CDISC Sponsor Impact: Successful Implementation

If Implemented Successfully

- Studies can be setup faster and more efficiently
- No delays in current timeline metrics
- Lower costs
- Easier to assemble submission
- Easier to Review
- Faster Approval?
- Warehousing and retrieval of information in future
- **More remaining time on patent**

How Do We Get There? Implementation Strategies

- **Tables first philosophy** -> "start with the end"
- **Data standards implementation plan**
  - Develop at IND time
  - When to start? Phase I ? Phase III?
  - **NO LEGACY CONVERSIONS!!**
  - "End to End" standards implementation
  - Outsource?
- **Extend standards to the beginning and to the end**
  - "from protocol to display"
- **Take advantage of standards- "Make routine things routine"**
  - Metadata libraries
  - General macros/programs

Keys to Implementation

1. START WITH THE END

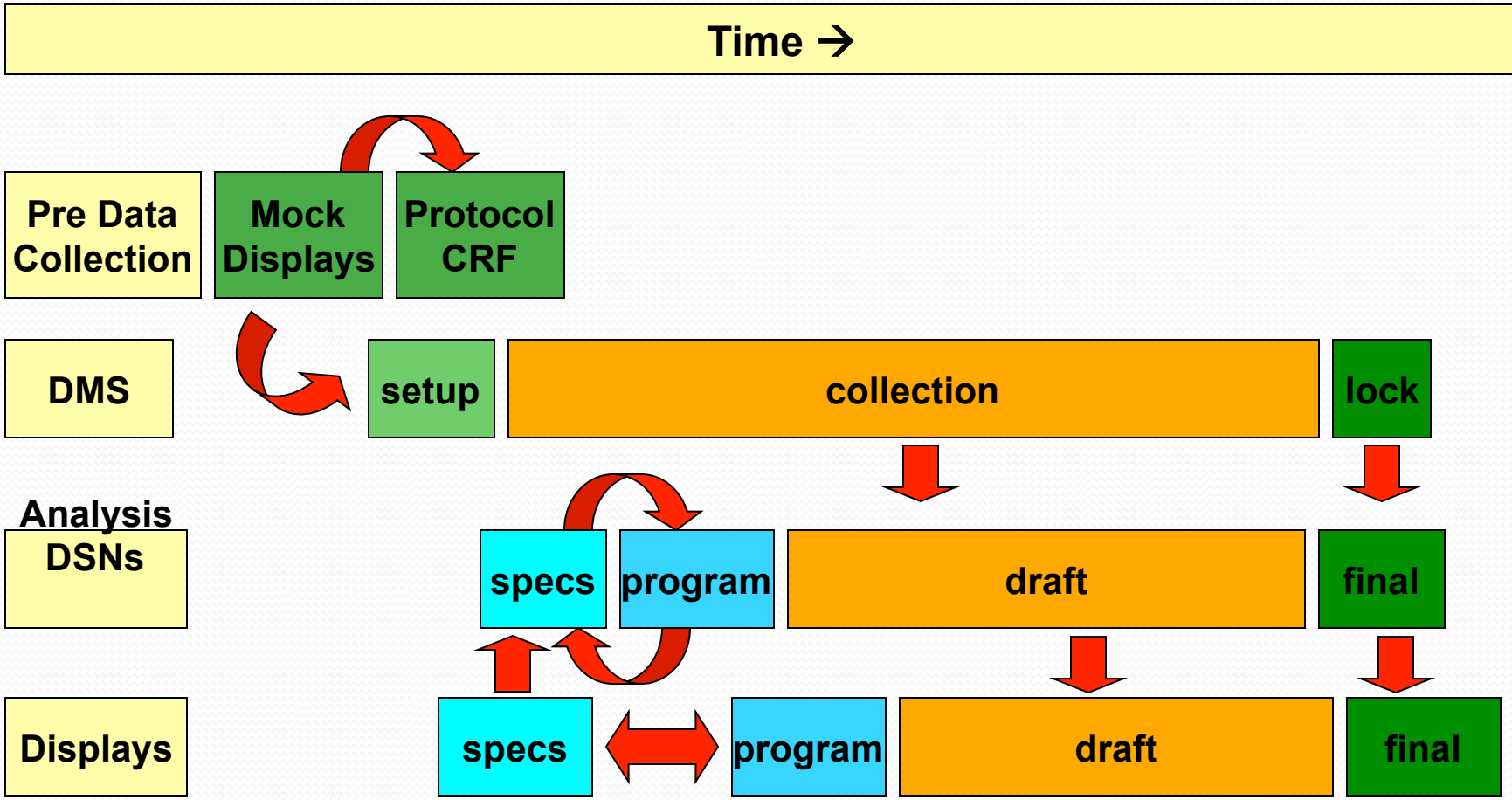
New Approach: Start With the End

- Key Concepts
  - Based on non-stop continuous product development
  - Effectively use of data standards throughout the life cycle of a project
  - Use of adaptive study designs
- ISE/ISS mock displays first (based on target product profile or draft label)
- Determines what displays/analyses needed to demonstrate safety and efficacy
- Determines what studies are needed
- Each study contributes to evidence needed for approval
- Approach is dynamic

New Approach: Start With the End

- For a given study
  - Start with what displays are needed to meet goals of the study
  - Generate mock displays , which …
  - Identify required data
- Mock displays are driving force
  - They dictate date to collect
  - They identify what data streams are needed
- After mock displays:
  - Protocol
  - CRFs
  - DMS
  - Analysis / displays

Tables-First Data Flow



Benefits of New Approach

- Less time between studies and phases
- More focused data collection
- Early start on analysis part of the study
- From mock displays we know
  - What data to collect
  - Study design (visits, tests…)
  - What CRF pages/fields we need
  - What analysis datasets & variables we need
- Work flow is more focused and efficient!

Keys to Implementation

2. Data Standards Implementation Plan

Data Standards Implementation Plan

- Likely to be required at IND time
- Strategy
  - SDTM and ADaM for *all* Studies, implemented while studies are conducted
  - Non-CDISC submission (still not required)
  - SDTM and ADaM only for Phase III
  - Legacy conversions for all studies during or after Phase III
  - Outsource

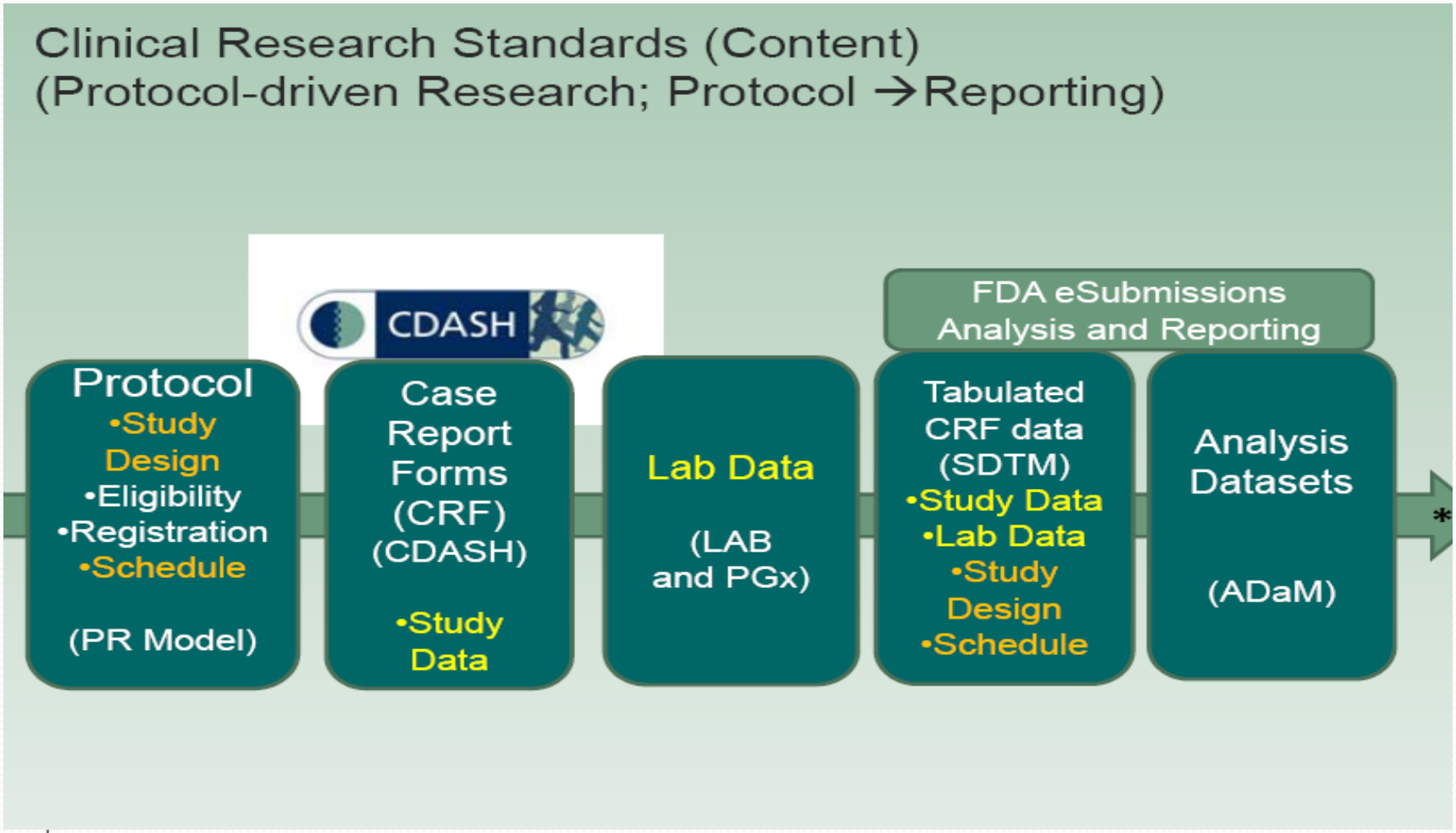
Data Standards Implementation Plan

- **Size Matters!**
- **Business Model**
  - Taking current product to approval?
  - Taking current product to proof of concept?
  - Partnering as soon as possible?
  - Selling as soon as possible?

Keys to Implementation

3. Extend the Use of Standards

Extend Standards End-to-End (Part 1)



Underutilizing anything?

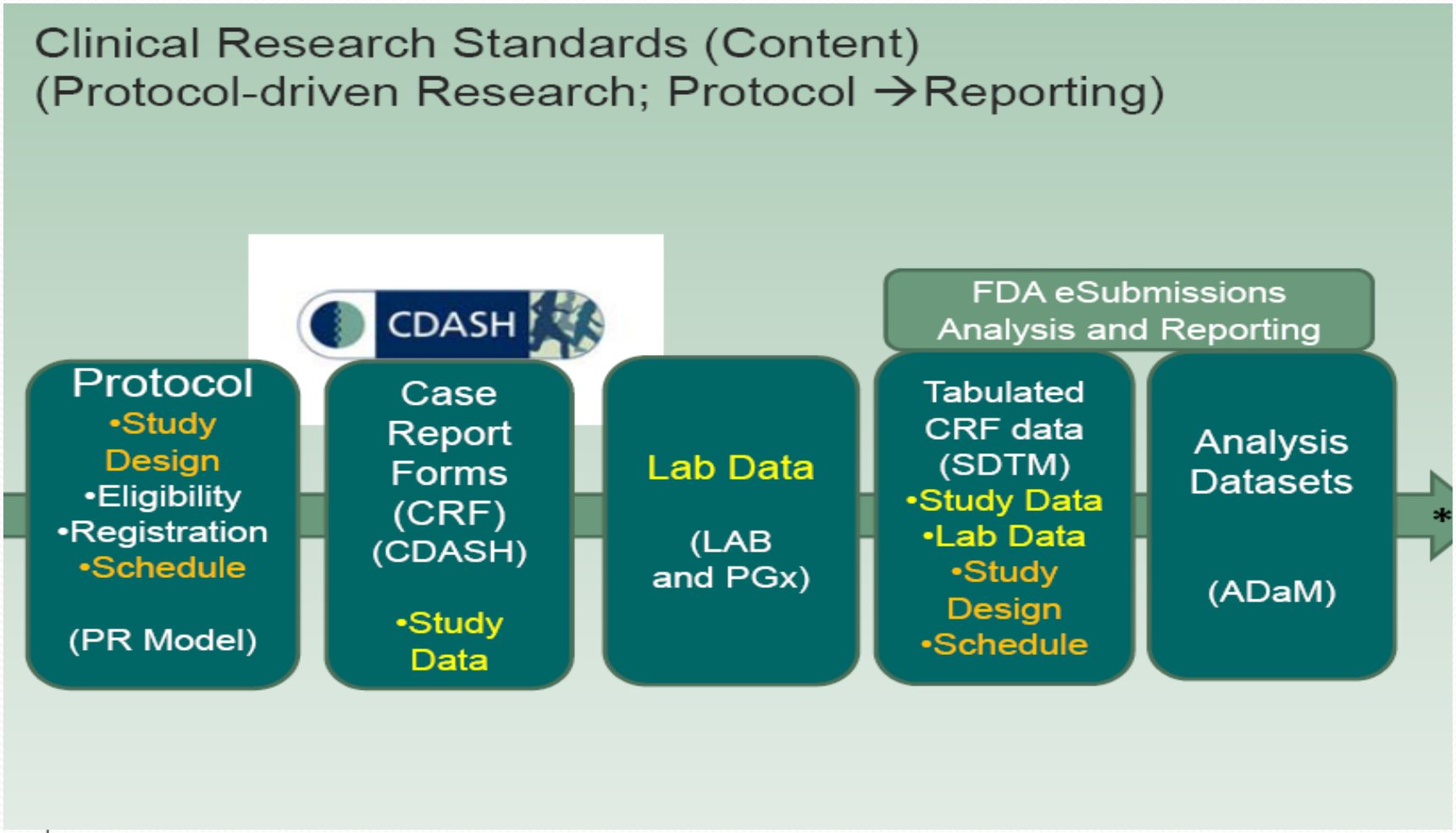
Extend Standards: Protocol Representation Model (PRM)

- Relatively new; not often used
- Facilitates expedited drug development
- Enables more efficient protocol development
- Facilitates setting up data collection system
- 21 of 35 required study outline concepts map to SDTM trial summary dataset
- 25 of the required study outline concepts for ClinicalTrials.gov, EudraCT, and ICTRP

PRM: Benefits, Efficiencies

- Regulatory Submission Preparation
  - Pre-IND (PIND) meeting package
  - Investigational New Drug Applications (INDs) and Clinical Trial Authorizations (CTAs)
  - Annual Reports/Development Safety Update Reports (DSURs)
  - End-of-Phase 2 (EOP2)meeting package
  - Pre-New Drug Application/Biologic License Application meeting package
  - NDA/BLA/Marketing Authorization Application
  - 120-Day Safety Updates
  - Annual Reports/Periodic Safety Update Reports (PSURs)

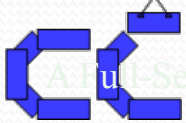
Extend Standards End-to-End (Part 2)



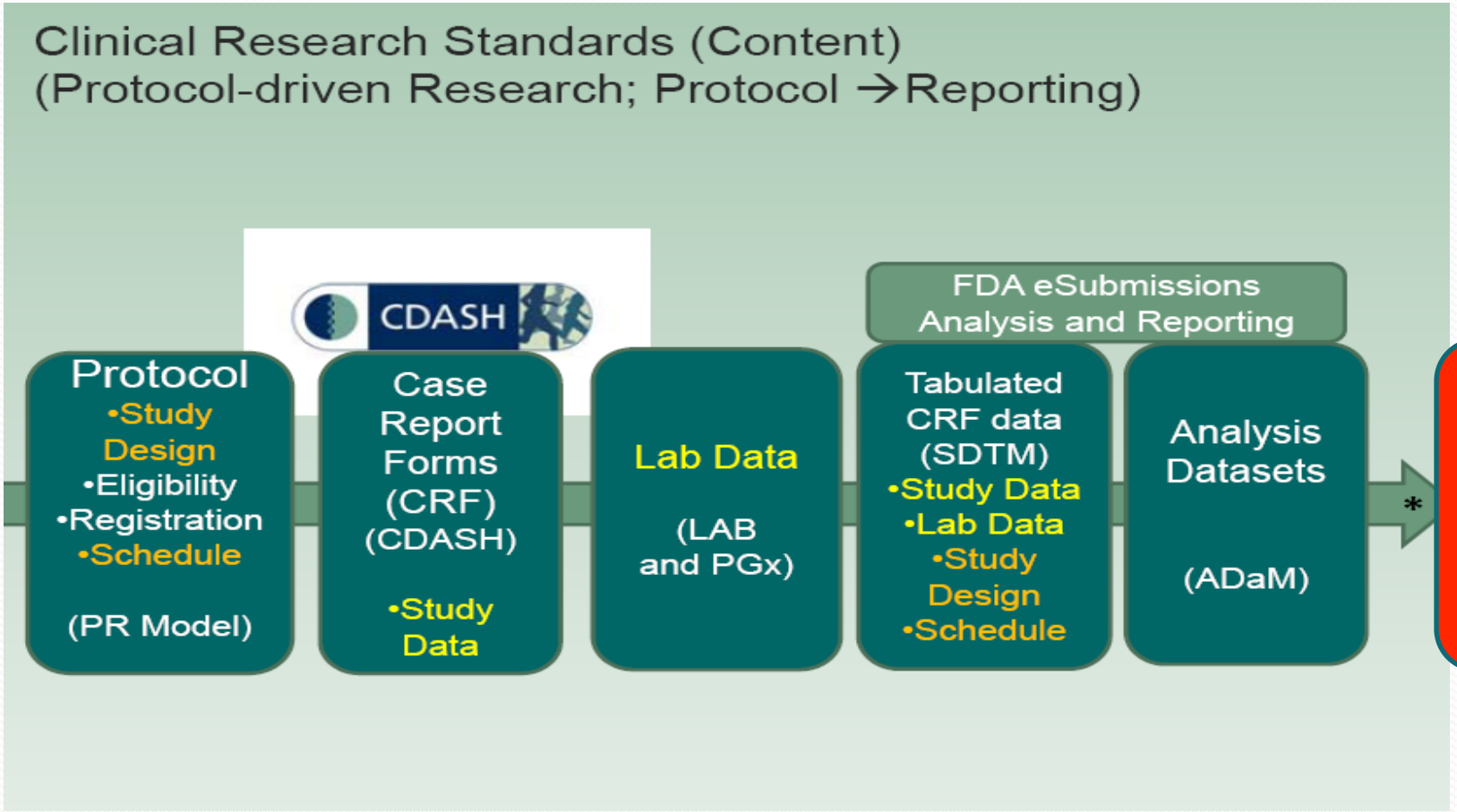
***Missing* anything?**

Extend Standards: Displays/Reporting

- Standards not extended to reporting
- Fewer papers/presentations using metadata effectively for reporting
- Relatively little discussion of results level metadata
- Surprising since data is collected with the ultimate goal of reporting
- Focus of FDA Working Group 5



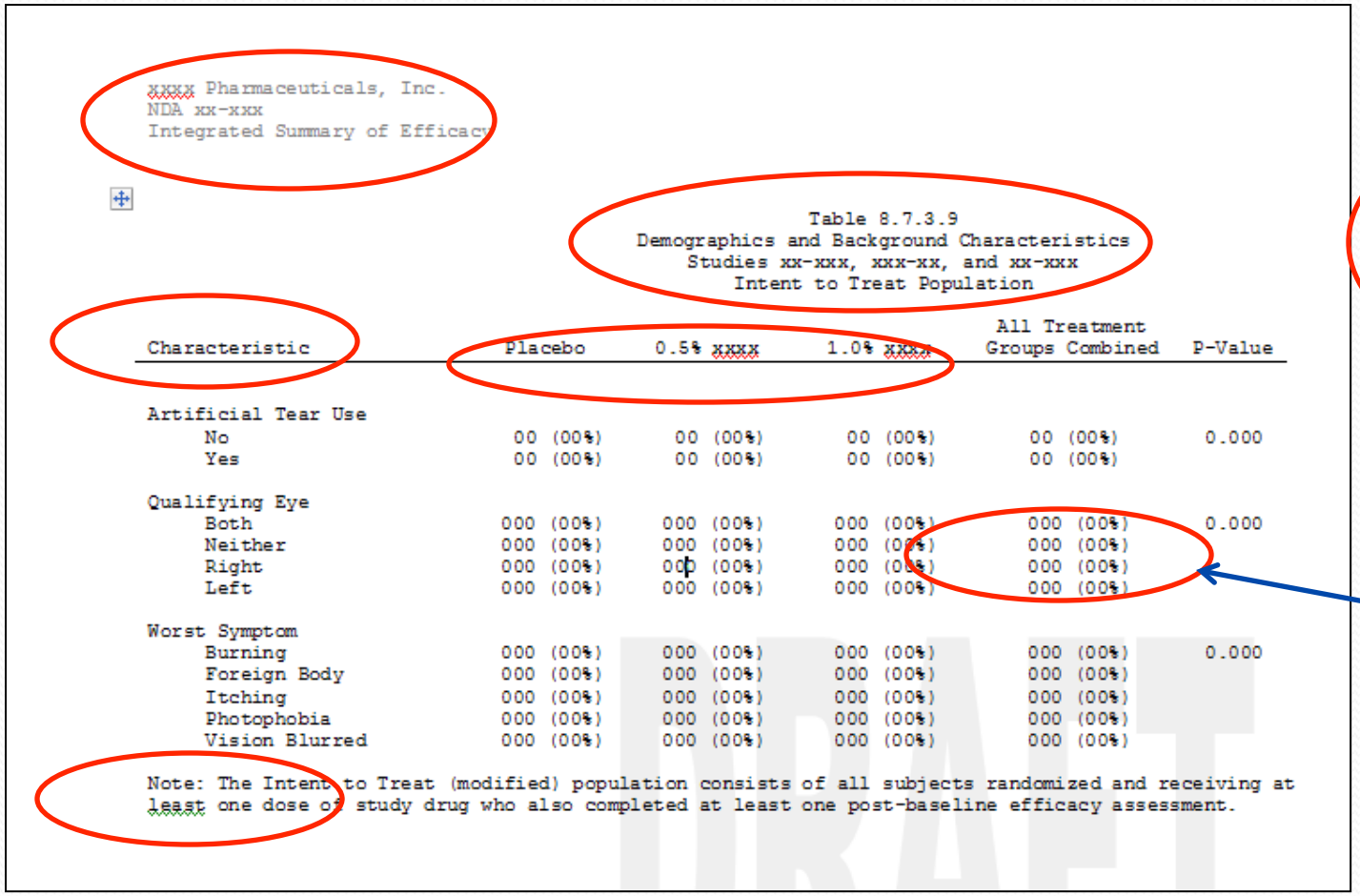
Standards Now Truly End-to-End



Standard Displays: Background

- Rho (a CRO) evaluated displays from over 15 sponsors across a wide spectrum of therapeutic areas
- Result
  - There are many displays that are common across sponsor and therapeutic area
  - Most common displays were safety related
  - With well designed metadata, the same display shell can be re-used many times throughout a project and across domains and projects
  - Same domains as CDASH (i.e. AE PE VS MH ECG)
  - **Most of what changes from project to project can be extracted from display and project level metadata**

Standard Displays: Sample Shell



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NDA xx-xxx
Integrated Summary of Efficac

Table 8.7.3.9
Demographics and Background Characteristics
Studies xx-xxx, xxx-xx, and xx-xxx
Intent to Treat Population

Characteristic	Placebo	0.5% xxxx	1.0% xxxx	All Treatment Groups Combined	P-Value
Artificial Tear Use					
No	00 (00%)	00 (00%)	00 (00%)	00 (00%)	0.000
Yes	00 (00%)	00 (00%)	00 (00%)	00 (00%)	
Qualifying Eye					
Both	000 (00%)	000 (00%)	000 (00%)	000 (00%)	0.000
Neither	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Right	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Left	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Worst Symptom					
Burning	000 (00%)	000 (00%)	000 (00%)	000 (00%)	0.000
Foreign Body	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Itching	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Photophobia	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
Vision Blurred	000 (00%)	000 (00%)	000 (00%)	000 (00%)	

Note: The Intent to Treat (modified) population consists of all subjects randomized and receiving at least one dose of study drug who also completed at least one post-baseline efficacy assessment.

DRAFT

Metadata

Formatting

Standard Displays: Sample Shell

ADaM Annotation

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NDA xx-xxx
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Vision Blurred	000 (00%)	000 (00%)	000 (00%)	000 (00%)	

Note: The Intent to Treat (modified) population consists of all subjects randomized and receiving at least one dose of study drug who also completed at least one post-baseline efficacy assessment.

Display Level Metadata

Number	TableLetter	Title	StudyNumb	StudyLabel	Population	Population Label	SubPopulation	TableShell
8.7.10.1	TEM	Worst Symptom Score (Study Eye) -- Weel	03-105'	Study 03-105	mittpop=1	Intent to Treat Populatic		BG
8.7.10.10	TEX	Worst Symptom Score (Study Eye) -- Weel	03-103'	Study 03-103	pppop=1	Per Protocol Population		AO
8.7.10.10	TEV	Worst Symptom Score (All Dry Eyes) -- We	03-103'	Study 03-103	mittpop=1	Intent to Treat Populatic	qualeyes in ('OS','OD','Both	(Will not need.
8.7.10.11	TEY	Worst Symptom Score (Study Eye) -- Weel	03-103', '03-105	Studies 03-103	mittpop=1	Intent to Treat Populatic		BG
8.7.10.12	TEZ	Worst Symptom Score (Study Eye) -- Weel	03-103', '03-105	Studies 03-103	mittpop=1	Intent to Treat Populatic		BH
8.7.10.13	TFA	Worst Symptom Score (All Dry Eyes) -- We	03-103', '03-105	Studies 03-103	mittpop=1	Intent to Treat Populatic		BW
8.7.10.14	TFC	Worst Symptom Score (Study Eye) -- Weel	03-103', '03-105	Studies 03-103	pppop=1	Per Protocol Population		BG

Footnotes	Dataset	Outcome	TreatmentVar	TreatmentValues	TimeVar
ITT5,FT45,FT22,FT24,FT3, SRC5	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
PPP3, FT22,FT43, FT4, FT5,FPT2,SRC3	SYMP	MWRSTE	TRTCD	1,2,3,4,5	WEEK
ITT3, SRC3	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
ITT345, FT22,FT43,FT3, FT33, SRC35	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
ITT345, FT43,FT22,FT4, FT5,FT33, SRC35	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
ITT345, FT43, FT22, FT6, FT7, FT33, SRC35	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
PPP35, FT22,FT43,FT3, FT33, SRC35	SYMP	MWRSTE	TRTCD	1,3,4	WEEK

TimePoints	BaselineVar	VariablesRequired	TablePrograa
-1,0,1,2,3,4,5,6,7,8,9,10,11,12,16,2(			ISE_TEM.SAS
-1,0,1,2,3,4,5,6,7, 99.4,99.6			ISE_TEX.SAS
-1,0,1,2,3,4,5,6,7, 99.4,99.6	BMWRSTF		ISE_TEV.SAS
-1,0,1,2,3,4,5,6,99.4, 99.6			ISE_TEY.SAS
-1,0,1,2,3,4,5,6,99.4, 99.6			ISE_TEZ.SAS
-1,0,1,2,3,4,5,6,99.4, 99.6	BMWRSTF		ISE_TFA.SAS
-1,0,1,2,3,4,5,6,99.4, 99.6			ISE_TFC.SAS

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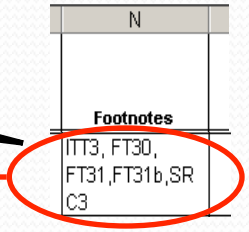
Footnote Level Metadata

Values in the “Tables” sheet column “Footnotes” correspond to row values of “Footnote Code” in the “Footnotes” sheet



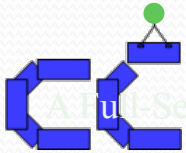
Footnote codes are entered in the order in which the formatted footnote will appear in the table.

	A	B	C	D
1	Footnote Code	Population Label	Study ID Label	Footnote Text
2	ITT3	Intent to Treat Population	Study 03-103	Note: The Intent to Treat (modified) population consists of all subjects randomized and receiving at least one dose of study drug who also completed the baseline and at least one post-baseline assessment of corneal staining, conjunctival staining, and ocular symptoms.
13	SRC3		Study 03-103	Source: Study Report 03-103, Appendix 16.4
14	FT30			Note: Worst symptom is defined as the symptom with the highest (most severe) rating in the study eye at Visit 2, averaging across diary entries for days during the placebo run-in period.
15	FT31			Note: P-values correspond to the test of an overall treatment effect adjusting for site. Categorical variables were assessed via the Cochran-Mantel-Haenszel chi-square test and continuous variables were assessed via analysis of variance.
16	FT31b			Note: For treatment comparisons for race, categories are collapsed to Caucasian and Non-Caucasian.

A change to the footnote text will be reflected in all tables using the footnote. There are no changes to individual programs.

Complementary Metadata: Project-Level

- Name and description of study
- Location on network of study
- Location of study database, format, and macro libraries
- Other directory locations
- SAS Options
- Treatment group information
- Visit information
- Client specific presences for displays
  - Styles
  - formats



Generalized Programs

Complete Calling Program (ISE_TAI.SAS)

```
%inc 'S:\RHO\sponsor\project\prog\setup.sas' / nosource2 ;
%setup(cad=yes);


%GetTable(tbl=TAI);
```

Read Project level metadata to get project level information

Read display metadata for rows related to table TAI. Write SAS macro variables, then run the shell associated with the table.

Shell Program Excerpts Illustrating Macro Variable Usage

```
data randsel;  *Randomized selected for study and subpopulation*;
      set demo;
      &WhereStatements.
run;

ods pdf file="&PDFdest." style=&style. notoc;
ods escapechar='`';
ods listing close;

&TitleLines.
&FootnoteLines.
```

Created by GetTable, using data from Display metadata.

Created by Setup macro. It identifies a style sheet that controls the appearance of the PDF output.

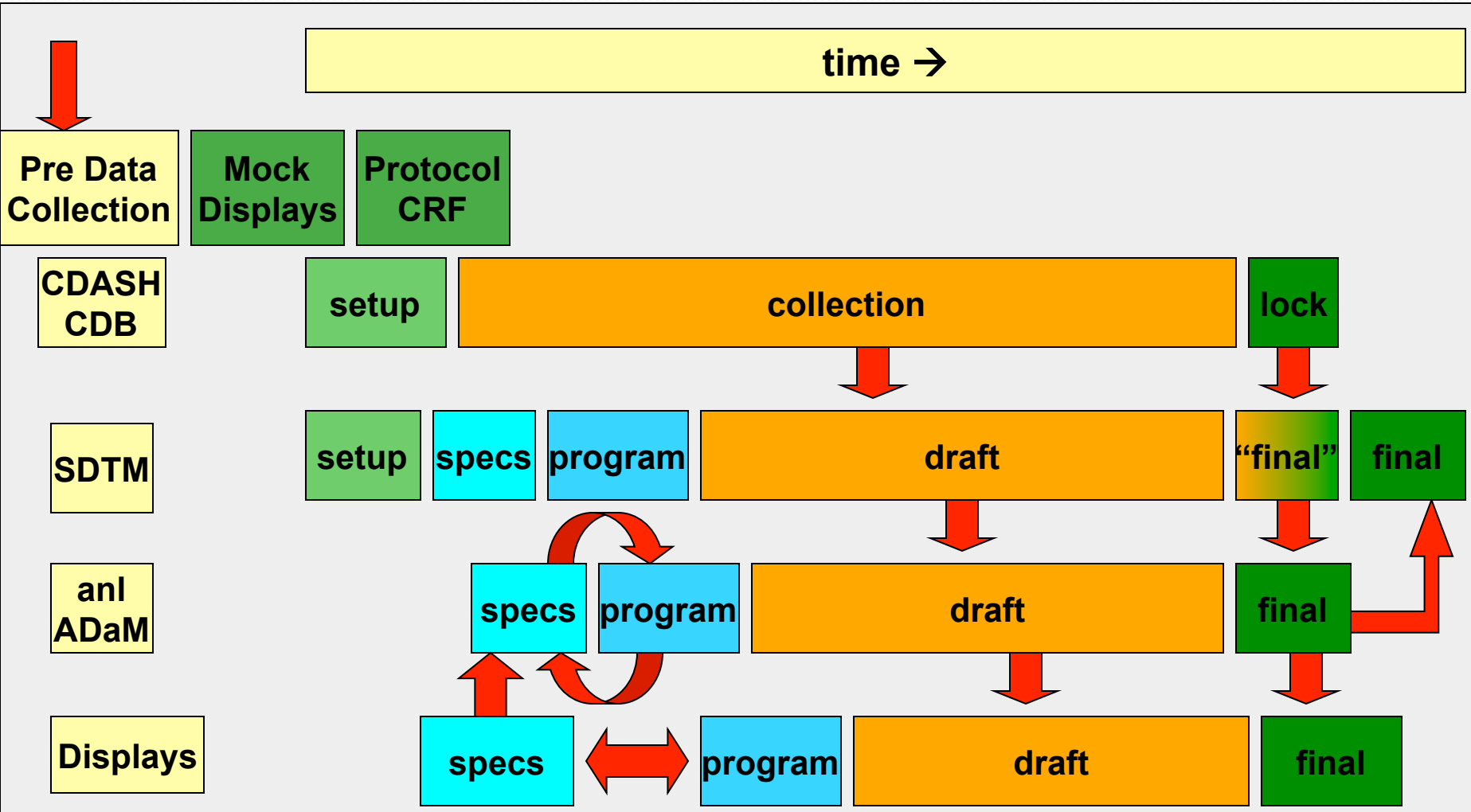
Created by GetTable, using data from Titles/ Footnotes metadata. The values have the appropriate indentation, page numbers, etc.

Assembling the Pieces: An Implementation Example

Recommended Study Approach

- For a given study
  - Start with what displays are needed to meet goals of the study
  - Generate mock displays
  - What data are needed to generate mock displays
- Mock displays are driving force
  - Dictate data to collect
  - What data streams are needed
- After mock displays
  - Construct clinical data base
  - Prepare Case Report Forms
  - Prepare Protocol Summary

Workflow


time →
Pre Data Collection
Mock Displays
Protocol CRF
CDASH CDB
setup
collection
lock
SDTM
setup
specs
program
draft
“final”
final
anl ADaM
specs
program
draft
final
Displays
specs
program
draft
final

Pre Data Collection: Mock Displays

- Step 1: Develop Mock Displays
- Mock displays for a study are generated from TFL library
- TFL library
  - Standard displays across therapeutic areas
  - Annotated to a standard like ADaM
  - Validated programs to produce displays
  - TFL level metadata

Mock Display: Sample Shell

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Right	000 (00%)	000 (00%)	000 (00%)	000 (00%)	
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Note: The Intent to Treat (modified) population consists of all subjects randomized and receiving at least one dose of study drug who also completed at least one post-baseline efficacy assessment.

ADaM Annotation

Dataset: ADEFF1

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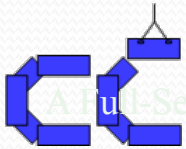
Pre-Data Collection: Protocol, CRF, and CDB

- Using mock displays, and PRM generate the Protocol
  - Use libraries and data elements from previous protocols
- CRF and clinical database (CDB) designed from:
  - Output from PRM (ODM XML)
  - CDISC CDASH standards library
  - Therapeutic specific libraries
  - CRF library
- Benefits
  - Faster, standardized study set up
  - Uniformity across studies
  - less metadata mapping from source data to SDTM

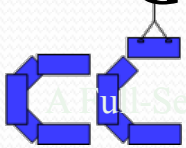
Clinical Data Base → SDTM

- Specifications (metadata) used to map data from clinical data base to SDTM
- SAS programs are developed to create SDTM data sets
- If clinical data base uses a standard like CDASH
  - Specifications/programs can be re-used from study to study
  - Specifications can be obtained from a metadata repository
    - Machine readable specifications a possibility?
  - Programs can be obtained from a library
- Datasets are validated to SDTM standard



SDTM Implementation Goals

- Streamline process of converting DM data to SDTM
- Faster and cheaper SDTM
- Package DM->SDTM
- Make DM-> SDTM more attractive for Phase I/II studies
- Higher quality
- Lower validation requirements
- Facilitate creation of analysis datasets
- **Give the FDA what they want!!**



SDTM Implementation at Rho

- SDTM metadata(specifications) libraries
  - Specifications mapping data from CDASH(DM) to SDTM
  - Pre-populate as much metadata as possible
  - Programs creating SDTM datasets from CDASH(DM)
  - Controlled Terminology libraries
- Client-specific SDTM libraries

SDTM → ADaM

- Specifications (metadata) used to map data from SDTM database to ADaM
- SAS programs are developed to create ADaM datasets
- If source is standard like SDTM
  - Specifications/programs can be re-used from study to study
  - Specifications can be obtained from a metadata repository
  - Programs can be obtained from a library
- Datasets are validated to ADaM standard

ADaM Implementation at Rho

- Create ADaM metadata library
- Populate metadata in library (using SDTM as source)
- Create analysis dataset program templates
- Create TFL library where ADaM is the source
  - Annotated mock displays
  - Display level metadata
  - Display programs

End of Study

- Validate SDTM and ADaM datasets to respective standard
  - Validate during dataset creation process
    don't wait until submission time!!
  - OPENCDISC or proprietary macro
- Documentation
  - Create Define file (define.xml and, optionally, define.pdf)
    - Source should be metadata
    - proprietary macro / program /external software
  - Data guide
    - Document data sets and issues

End of Study: What's Next

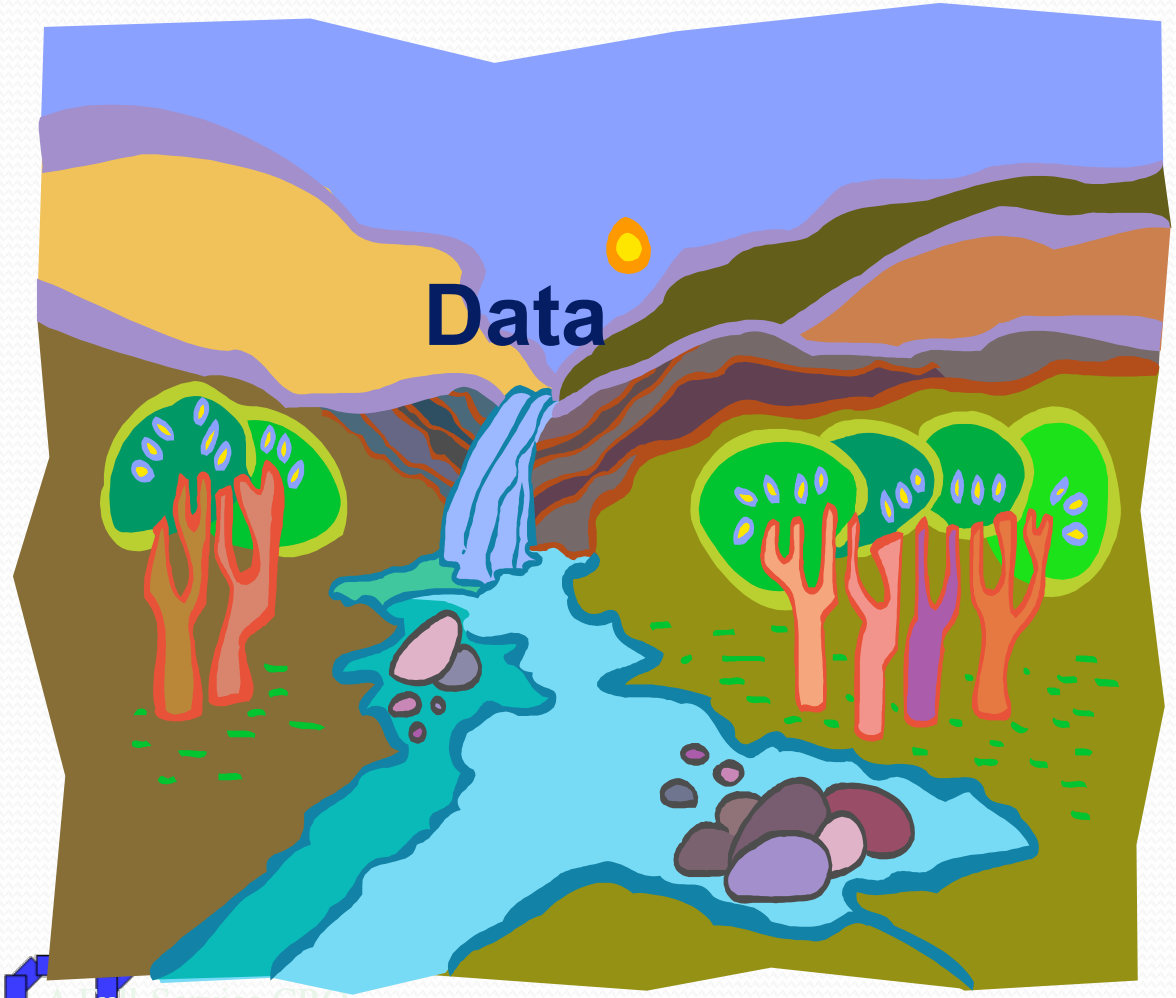
- If Phase III studies are successful → submission!!
- Study level data should already be submission ready
- Study level data is integrated to use as input for ISS/ISE
  - Source is study level ADaM databases
  - ADaM facilitates data integration

The Future

- "Embrace change, grasshopper!": Change of mindset
- Use of PRM for trial design datasets and SAP
- Extension of CDASH Standards
- Better use of SDTM trial design datasets
- Evolution of therapeutic specific standards
- Extend TFL library and metadata
  - Develop therapeutic specific displays
  - CDISC (or other) Standard set of displays
- Extend tables-first concept

The End

Tables First + Data Standards



Turn off your mind relax and let your data float downstream

Thank you for attending our Presentation!

Send questions or comments to:

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