Effective Use of Metadata in Analysis Reporting

Jeffrey M. Abolafia
Rho, Inc.,
Chapel Hill NC

Disclaimer

The views and opinions expressed in the following are those of the individual presenter and should not be attributed to Rho, Inc., its directors, officers, employees, Special Interest Area Communities or affiliates, or any organization with which the presenter is affiliated.

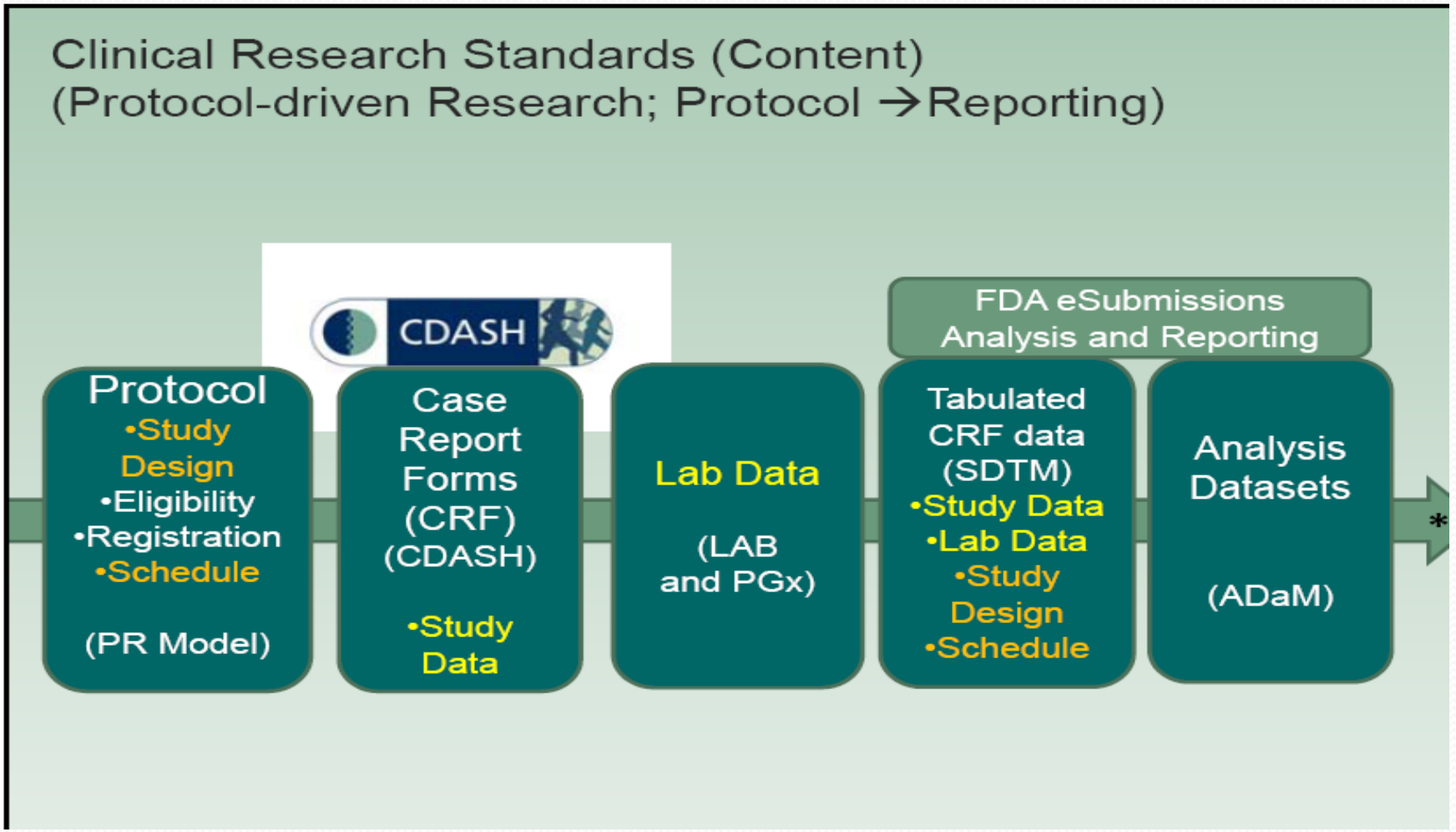
Warning

- This presentation contains a mixture of
  - Reality
  - Aspirations
  - Author's vision for how we can greatly increase efficiency for analysis reporting

Agenda

- Background
- Components for Efficient Display Production
- TFL Library
- The Metadata
- Tools and Programs
- Benefits
- What's Next

CDISC: End-to-End



Missing Anything ?

Background

- Metadata and CDISC standards used effectively for
  - Data collection
  - Standardized operational (clinical) data
  - Standardized Analysis data
  - Going from data collection to standardized operational data to standardized analysis data
- Lots of papers and presentations

Background

- 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
- Most data fields are collected because they are needed for reports

Components for Efficient Display Production

- **Standardized inputs (ADaM)**
- TFL library
  - Standard displays
  - Annotated to a standard like ADaM
  - Validated programs to produce displays
- TFL level metadata
- Other display level metadata
- Project level metadata
  - Trial design
  - Study configuration
- Validated library of tools
- **Tables first philosophy**

Current State: Standardized Input

- CDASH – standard collection fields
- SDTM - stable standard for clinical data
- ADaM – matured into a stable standard for analysis data
- SDTM/ADaM stable metadata models (that includes results level)
- Results level metadata often not used
- What About
  - Standard displays ?
  - Standard variables ?
  - Standard display metadata ? Results ? Trial Design?

Current State: Metadata Usage

- Current
  - Lessons learned from metadata usage for producing databases can be applied to displays
  - SDTM/ADaM
    - Extensive metadata
    - Sharp increase in use of machine readable metadata
    - Metadata driven applications
    - Project level metadata
- Prospective
  - ADaM has matured as a standard to facilitate semi-automation of producing displays
  - Extend results level metadata

Standard Displays: A Possibility?

- Where do standard CDASH/SDTM/ADaM variables come from?
- Variables needed or used for displays across diverse therapeutic areas
- Standard variables introduce the possibility of a standard set of displays

Standard Displays

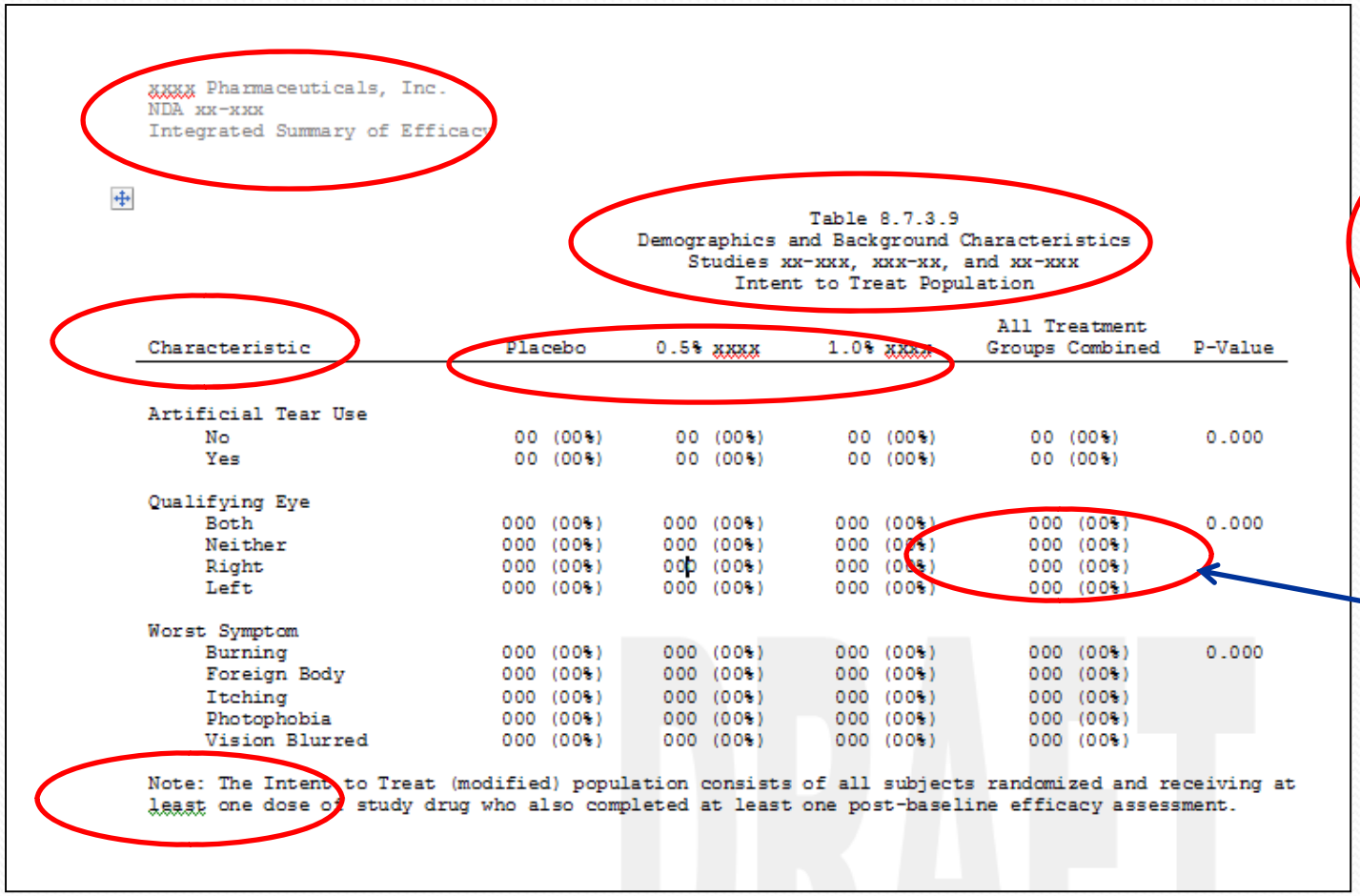
- Rho (a CRO) evaluated displays from over 15 sponsors across a wide spectrum of therapeutic areas
- Result
  - There are many displays that are common across sponsor and therapeutic area
  - Most common displays were safety related
  - With well designed metadata, the same display shell can be re-used 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: TFL Library

- Rho developed a TFL library consisting mainly of safety displays
- TFL shells
- Annotated for ADaM
- **TFL Metadata**
- Display Programs and tools
- Documentation
- Training

Note: TFL → **T**ables, **F**igures, and **L**istings

Standard Displays: Sample Shell



xxxx Pharmaceuticals, Inc.
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

xxxx Pharmaceuticals, Inc.
NDA xx-xxx
Integrated Summary of Efficacy

PARAM / AVALC

TRTP

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.

The Metadata

- **Display Level Metadata**
  - Contents – specific information about a single display
  - Structure – one record per display
- **Title / Footnote Metadata**
  - Contents – actual titles/footnotes used in displays
  - Structure – one record unique title/footnote
- **Study Level Metadata**
  - Contents
    - Project information
    - Library locations
    - Study design parameters including treatment groups
    - SAS Options/Client preferences
  - Structure – one record per study

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

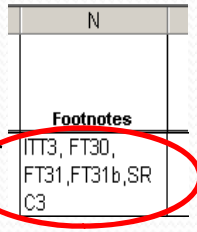
Footnotes	Dataset	Outcome	TreatmentVar	TreatmentValues	TimeVar
ITT5,FT45,FT22,FT24,FT3, SRC5	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
PPP3, FT22,FT43, FT4, FT5,FPT2,SRC3	SYMP	MWRSTE	TRTCD	1,2,3,4,5	WEEK
ITT3, SRC3	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
ITT345, FT22,FT43,FT3, FT33, SRC35	SYMP	MWRSTE	TRTCD	1,3,4	WEEK
ITT345,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

Rho
Giving flight to research

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.

Project Level Metadata

- 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

Metadata tools

- Tools are necessary to effectively access and use metadata
- Setup macro
- Gettables macro
- RhoTables®
- Auto-validation macro
- Stacking/bookmarking macro

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.

Tables First Philosophy

- Start early
- Each study has a purpose in a drug development program
- Almost all displays to be generated should be known before data collection
- While designing a study
  - Decide what displays are needed
  - Do they already exist in the TFL library
  - What new displays are needed
- Standard input data/metadata facilitate getting an early start

Benefits

- Traditional approach
  - Lots of repetition
  - Tedious
  - Manual processes that were error prone
- Table creation program is *greatly* simplified
- Handling of data and creation of the display is in one place (the metadata) rather than "n" places (separate programs)

Benefits

- Exploits similarities across displays/projects
- Reduces manual labor
- Increased use of cheaper labor
- Increase in automated validation
  - Improved communication – changes are made in one place: the metadata
- Faster, cheaper, and higher quality

"It's all about the metadata"

The Future

- Better use of SDTM trial design datasets
- ADaM Evolution
- Extend TFL library and metadata
- Develop therapeutic specific displays
- CDISC (or other) Standard set of displays
- Re-define validation requirements
- Tables first design

The End

Thank you for attending our presentation.

Send questions or comments to:

Jeff Abolafia (jeff_abolafia@rhoworld.com)

For a more technical discussion see:

"*The Design and Use of Metadata – Part Fine Art, Part Black Art*",F.C. DiIorio, and J.M. Abolafia. *Thirty-First Annual SAS Users Group International Conference, San Francisco, CA, March 2006.*