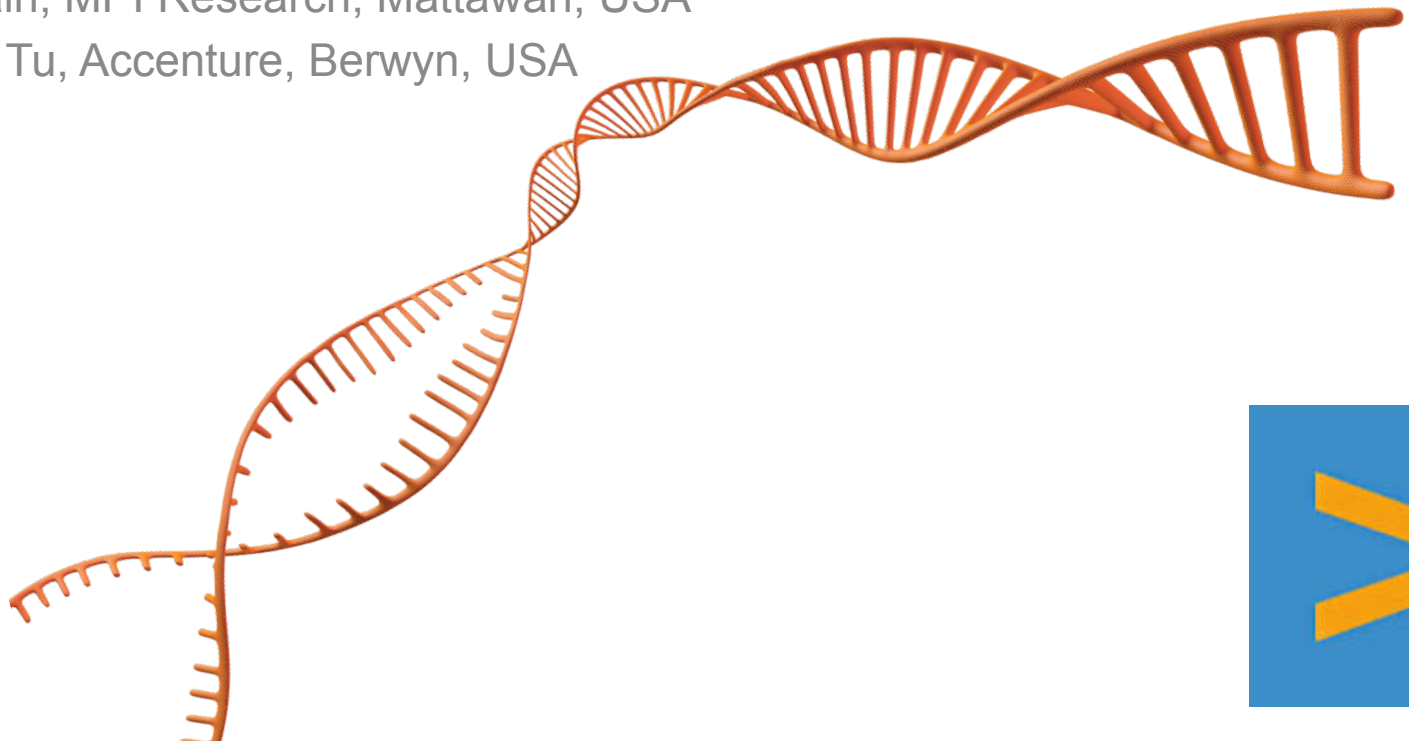


CS07: Get a Jump Start on Clinical Data Analysis and Visualization with Standard Scripts

Jared Slain, MPI Research, Mattawan, USA
Hanming Tu, Accenture, Berwyn, USA



FDA JumpStart Service



Purpose

- 1 Assess and report on whether data is fit for purpose
 - Quality
 - Tool loading ability
 - Analysis ability
- 2 Load data into tools for reviewer use and run automated analyses that are universal or common (e.g., demographics, simple AE)
- 3 Provide analyses to highlight areas that may need a focus for review

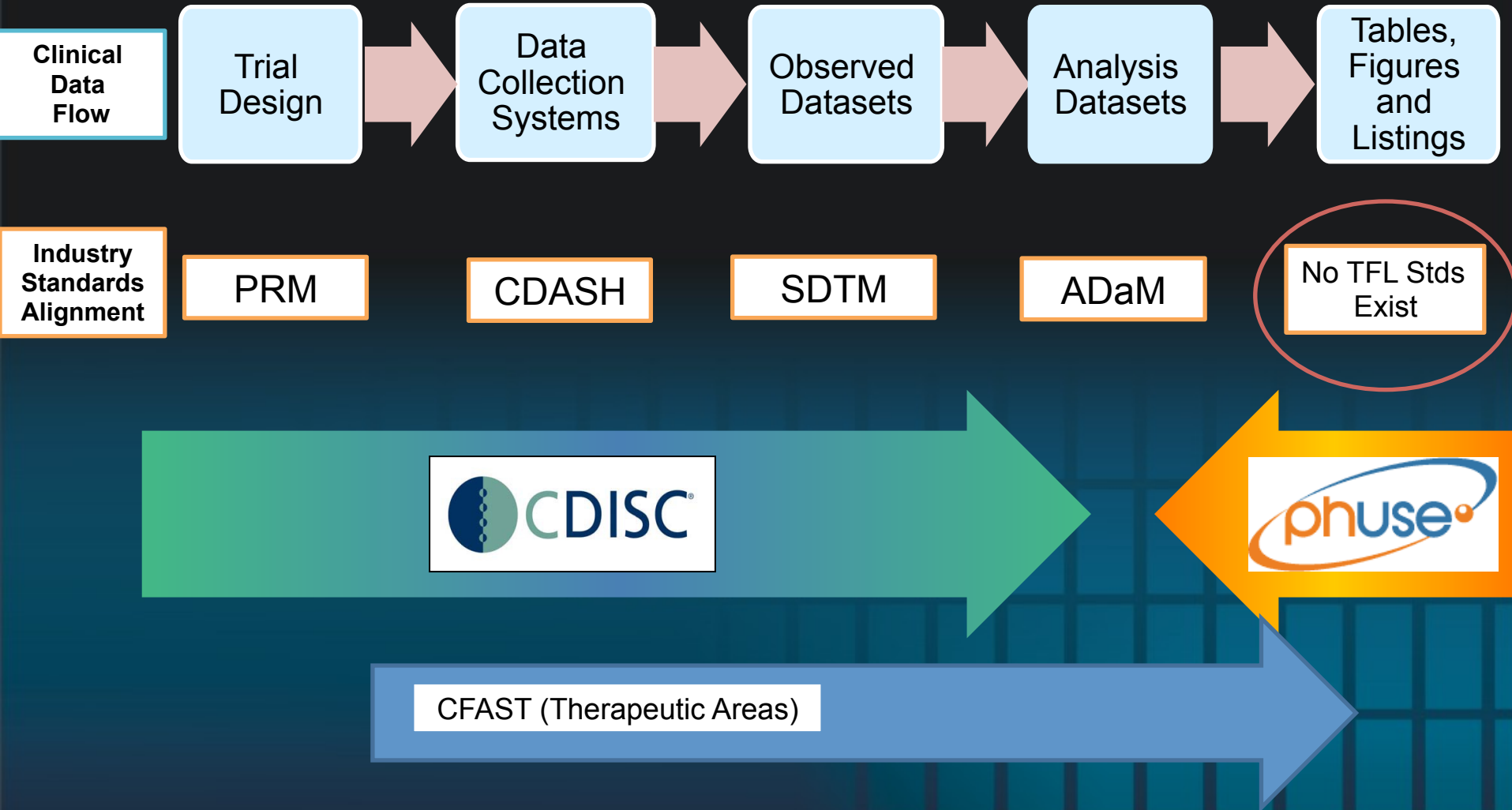
Benefits

- 1 Understand data, analyses that can be performed, and identify potential information requests for the sponsor
- 2 Improves the efficiency of review by setting up tools and performing common analyses, which provides time to focus on more complex analyses
- 3 Points to a possible direction for deeper analysis





Vision: Fill the Gap on Analysis Standards





Focus Areas

Three Focus Areas, Five Active Projects

Script Repository
(3 projects)



Analyses and Display
White Papers
(ADW, Mary Nilsson)

Communication,
Promotion, Education
(CPE, Jared Slain and
Wendy Dobson)

Script Discovery and Acquisition (SDA,
Rebeka Revis, Michael Man)
Repository Content and Delivery (RCD,
Gustav Bernard, Andrew Miskell)
Repository Governance and
Infrastructure (RGI, Mike Carniello,
Hanming Tu)

Scripts Used in JumpStart

- Background
 - Received the first few prior to CSS 2015
 - More scripts prior to CSS 2016
- Location
 - [Standard Scripts and Analyses GitHub Repository](#)
 - [Tested/SAS folder](#)
 - http://www.phusewiki.org/wiki/index.php?title=User_Guide_for_Standard_Script_Repository
- Technical Specifications
 - SAS 9.2
 - SDTM
 - Documentation stored with code



Seven Scripts Received So Far

- Adverse Event (AE) Severity
- AE Toxicity
- Demographics
- Disposition
- Exposure
- Liver Labs
- MedDRA at a Glance

Script Header

```

/*
/* EXTERNAL FILES USED: ae_setup.sas -- Merges AE, DM, and EX */
/* ae_oncology_aggregate.sas -- Does the analysis */
/* ae_oncology_output.sas -- Creates the output */
/* xml_output.sas -- XML formatting macros */
/* data_checks.sas -- Generic variable checks */
/* sl_gs_output.sas -- Script Launcher settings output */
/* err_output.sas -- Error output when missing vars */
/* mdhier_x_y.sas7bdat -- MedDRA hierarchy ver. X.Y */
/*
/* PARAMETERS REQUIRED: meddrapath -- location of MedDRA hierarchy datasets */
/* saspath -- location of the external SAS programs */
/* utilpath -- location of the external SAS programs */
/*
/* study_lag -- window in days after last exposure */
/* where AEs should be kept in analysis */
/*
/* toxgr_min -- minimum valid toxicity grade */
/* toxgr_max -- maximum valid toxicity grade */
/* toxgr_grp5_sw -- group toxgrade 5 with 3&4 */
/*
/* ver -- MedDRA version */
/* exp -- comparison treatment arm number */
/* ctl -- comparison control arm number */
/* cmptrm -- MedDRA levels to compare */
/* cmpgr -- toxicity grades to compare */
/* cmpsort -- variable to sort formatted output by */
/* cc -- continuity correction value */
/*
/* LOCAL ONLY: studypath -- location of the drug study datasets */
/* outpath -- location of the output */
/*
/* VARIABLES REQUIRED: AE -- AEBODSYS */
/* AEDECOD */
/* USUBJID */
/* DM -- ACTARM or ARM */
/* USUBJID */
/* EX -- USUBJID */
/*
/* VARIABLES USED: AE -- AESTDTC */
/* WHEN AVAILABLE AETOXGR */
/* DM -- RFSTDTC */
/*

```

Repository Structure | Tested/SAS Folder

- Folder for each endpoint category
 - AE, DM, DS, EX, LB, MedRA
- Folder for specification documents received from FDA with scripts
- Templates
 - Excel files to contain output
- Utilities (ZZ_Uutilities)
 - Used by multiple scripts
- Macros
 - Specific to a script



AE Severity

Adverse Events (AE)

- A series of AE severity panels are created

Program

- AE_v1.sas

Output

- Three files are produced

PhUSE

- An updated version is available
- Ae_v1upd.sas
- Review is ongoing

AE Severity | Data Tables

B38

Chest Pain

Adverse Events by Organ Class and Term

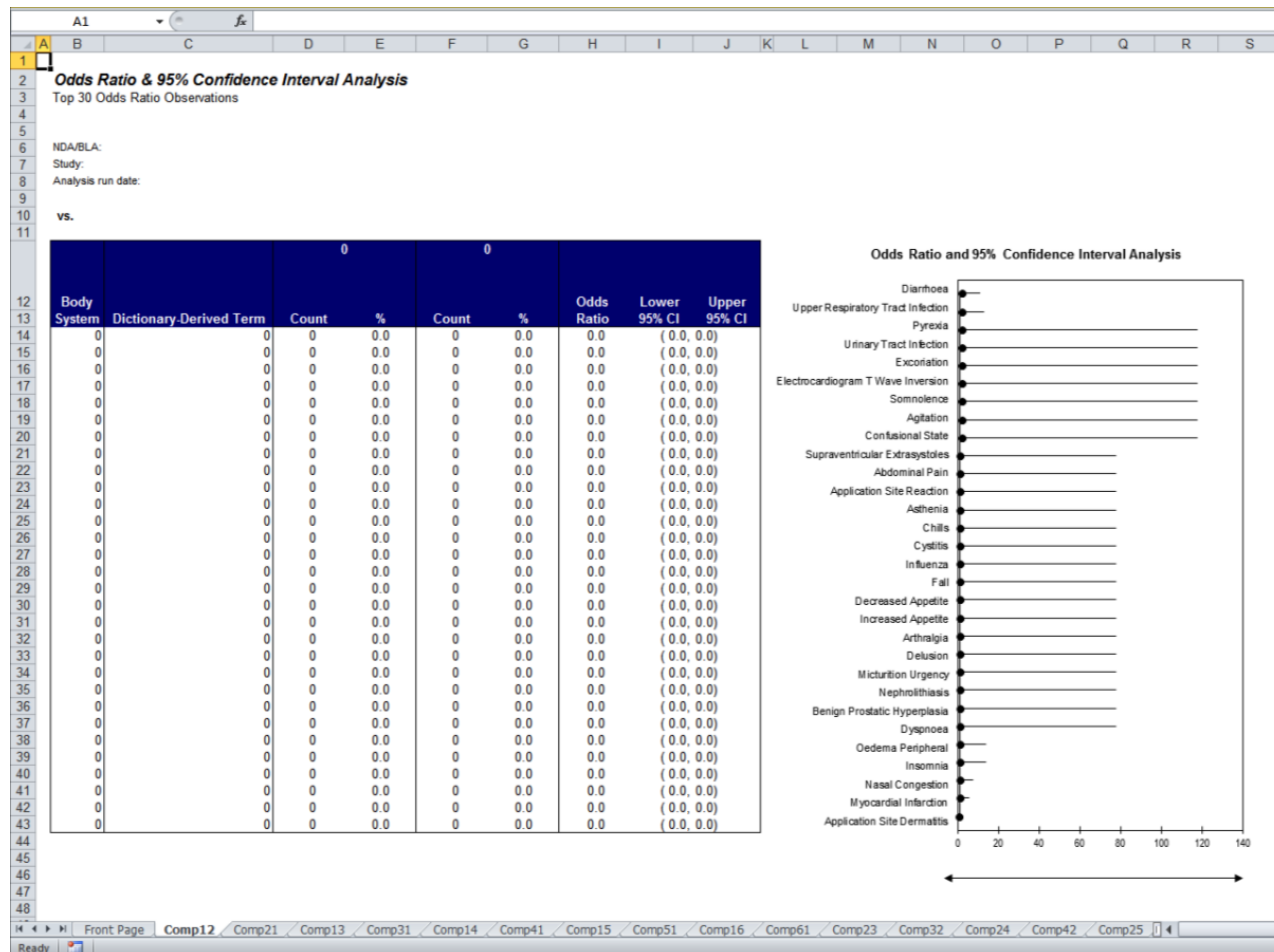
NDA/BLA:
Study: CDISC
Analysis run date: 2016-03-07 11:15:12 AM

Where subject count is the number of subjects in the treatment arm experiencing at least one adverse event per organ class and term and greater than 2% of subjects in any arm experienced at least one adverse event

Body System or Organ Class	Dictionary-Derived Term	Placebo		Xanomeline High Dose		Xanomeline Low Dose		Total	
		N=86		N=84		N=84		N=254	
		Subject Count	%	Subject Count	%	Subject Count	%	Subject Count	%
Cardiac Disorders	Sinus Bradycardia	2	2.3	8	9.5	7	8.3	17	6.7
Cardiac Disorders	Myocardial Infarction	4	4.7	4	4.8	2	2.4	10	3.9
Cardiac Disorders	Atrial Fibrillation	1	1.2	3	3.6	1	1.2	5	2.0
Cardiac Disorders	Ventricular Extrasystoles	0	0.0	1	1.2	2	2.4	3	1.2
Cardiac Disorders	Palpitations	0	0.0	0	0.0	2	2.4	2	0.8
Congenital, Familial And Genetic Disorders	Ventricular Septal Defect	0	0.0	2	2.4	1	1.2	3	1.2
Gastrointestinal Disorders	Diarrhoea	9	10.5	4	4.8	4	4.8	17	6.7
Gastrointestinal Disorders	Vomiting	3	3.5	7	8.3	3	3.6	13	5.1
Gastrointestinal Disorders	Nausea	3	3.5	6	7.1	3	3.6	12	4.7
Gastrointestinal Disorders	Abdominal Pain	1	1.2	1	1.2	3	3.6	5	2.0
Gastrointestinal Disorders	Salivary Hypersecretion	0	0.0	4	4.8	0	0.0	4	1.6
General Disorders And Administration Site Cond	Application Site Pruritus	6	7.0	22	26.2	22	26.2	50	19.7
General Disorders And Administration Site Cond	Application Site Erythema	3	3.5	15	17.9	12	14.3	30	11.8
General Disorders And Administration Site Cond	Application Site Dermatitis	5	5.8	7	8.3	9	10.7	21	8.3
General Disorders And Administration Site Cond	Application Site Irritation	3	3.5	9	10.7	9	10.7	21	8.3
General Disorders And Administration Site Cond	Application Site Vesicles	1	1.2	6	7.1	4	4.8	11	4.3
General Disorders And Administration Site Cond	Fatigue	1	1.2	5	6.0	5	6.0	11	4.3
General Disorders And Administration Site Cond	Oedema Peripheral	2	2.3	2	2.4	1	1.2	5	2.0
General Disorders And Administration Site Cond	Application Site Swelling	0	0.0	2	2.4	1	1.2	3	1.2
General Disorders And Administration Site Cond	Application Site Urticaria	0	0.0	1	1.2	2	2.4	3	1.2
General Disorders And Administration Site Cond	Malaise	0	0.0	2	2.4	1	1.2	3	1.2
General Disorders And Administration Site Cond	Pyrexia	2	2.3	1	1.2	0	0.0	3	1.2
General Disorders And Administration Site Cond	Application Site Pain	0	0.0	2	2.4	0	0.0	2	0.8
General Disorders And Administration Site Cond	Application Site Perspiration	0	0.0	2	2.4	0	0.0	2	0.8
General Disorders And Administration Site Cond	Chest Discomfort	0	0.0	2	2.4	0	0.0	2	0.8
General Disorders And Administration Site Cond	Chest Pain	0	0.0	2	2.4	0	0.0	2	0.8
General Disorders And Administration Site Cond	Oedema	0	0.0	0	0.0	2	2.4	2	0.8
Infections And Infestations	Nasopharyngitis	2	2.3	6	7.1	4	4.8	12	4.7
Infections And Infestations	Upper Respiratory Tract Infection	6	7.0	3	3.6	1	1.2	10	3.9
Infections And Infestations	Urinary Tract Infection	2	2.3	1	1.2	0	0.0	3	1.2
Infections And Infestations	Ear Infection	2	2.3	0	0.0	0	0.0	2	0.8
Injury, Poisoning And Procedural Complications	Contusion	1	1.2	2	2.4	1	1.2	4	1.6
Injury, Poisoning And Procedural Complications	Excoriation	2	2.3	1	1.2	1	1.2	4	1.6
Injury, Poisoning And Procedural Complications	Fall	1	1.2	1	1.2	2	2.4	4	1.6

Front Page1 AEs by Arm2 Serious AEs by Arm3 AEs by Severity4 Serious AEs by SeverityData Check SummaryGrouping and Subsetting

AE Severity | AE Odds Ratio Analysis



Relative Risk and 95% Confidence Interval Analysis

Symptom	Relative Risk (approx.)	95% CI (approx.)
Anxiety*	0.5	0.2 - 1.0
Constipation*	0.1	0.05 - 0.2
Nausea*	0.1	0.05 - 0.2
Fatigue*	0.1	0.05 - 0.2
Arthralgia*	0.1	0.05 - 0.2
Palpitations*	0.1	0.05 - 0.2
Decreased appetite*	0.1	0.05 - 0.2
Muscle spasms*	0.1	0.05 - 0.2
Dizziness*	0.1	0.05 - 0.2
Agitation*	0.1	0.05 - 0.2
Diarrhoea*	0.1	0.05 - 0.2
Haemorrhoids*	0.1	0.05 - 0.2
Vomiting*	0.1	0.05 - 0.2
Headache*	0.1	0.05 - 0.2

AE Toxicity

Adverse Events (AE)

- A series is created of AE toxicity panels

Program

- AE_oncology_v1.sas

Output

- One file is produced

PhUSE

- An updated version is available
- ae_oncology_v1upd.sas
- Review is ongoing

AE Toxicity | Toxicity Analysis

[illegible]

Demographics

Demographics

- Summarize study data based on the demographics of study participants

Program

- demographics_v1.sas

Output

- One file is produced

PhUSE

- Review continues

Ready 

Disposition

Disposition

- Charts the time to disposition event for all subjects and for exposed subjects

Program

- disposition_v2.sas

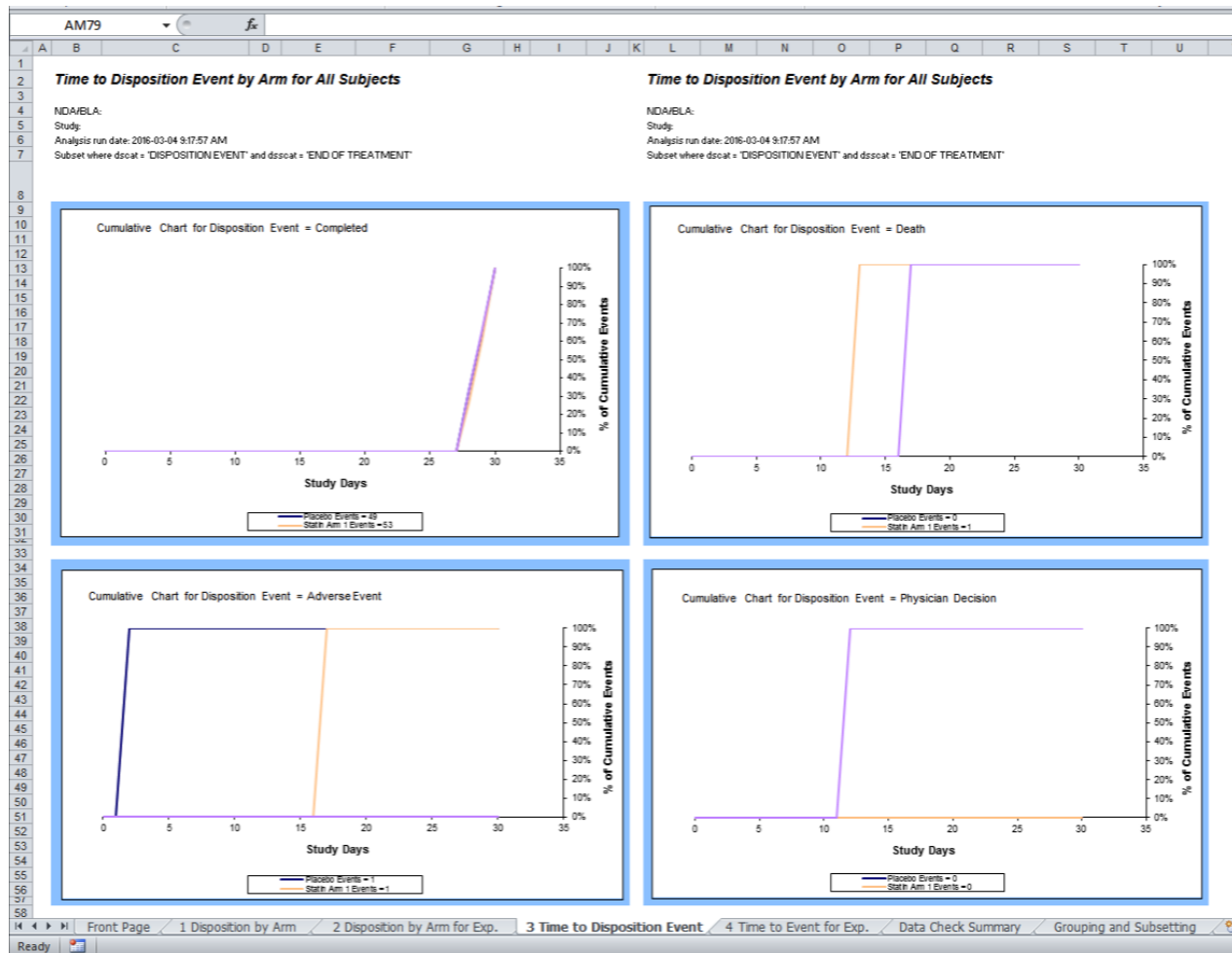
Output

- One file is produced

PhUSE

- Review continues

Disposition | Disposition Analysis



Exposure

Exposure

- Performs an analysis of the exposure events for subjects in the study

Program

- exposure_v1.sas

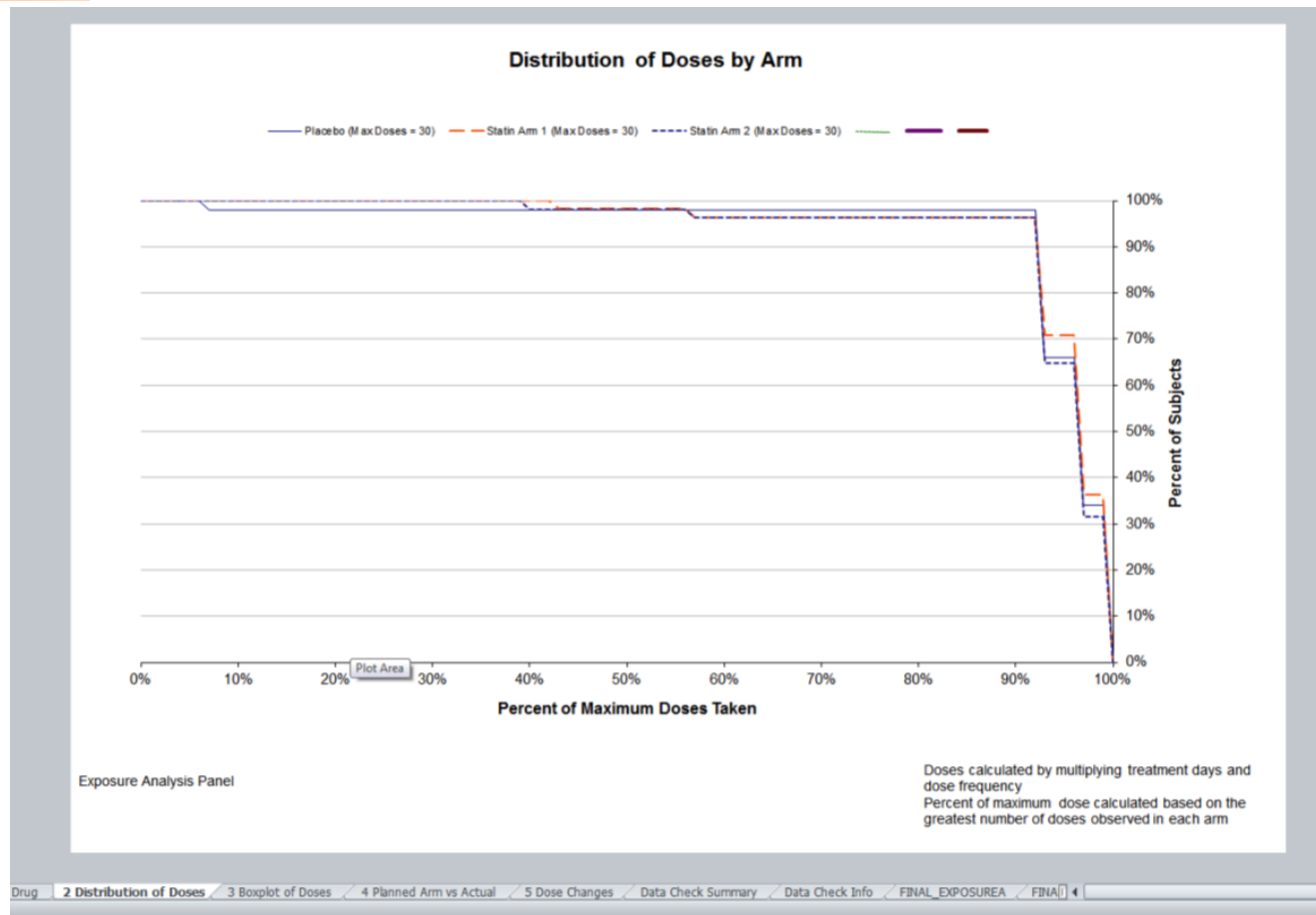
Output

- One file is produced

PhUSE

- Review continues

Exposure | Dosing Distribution

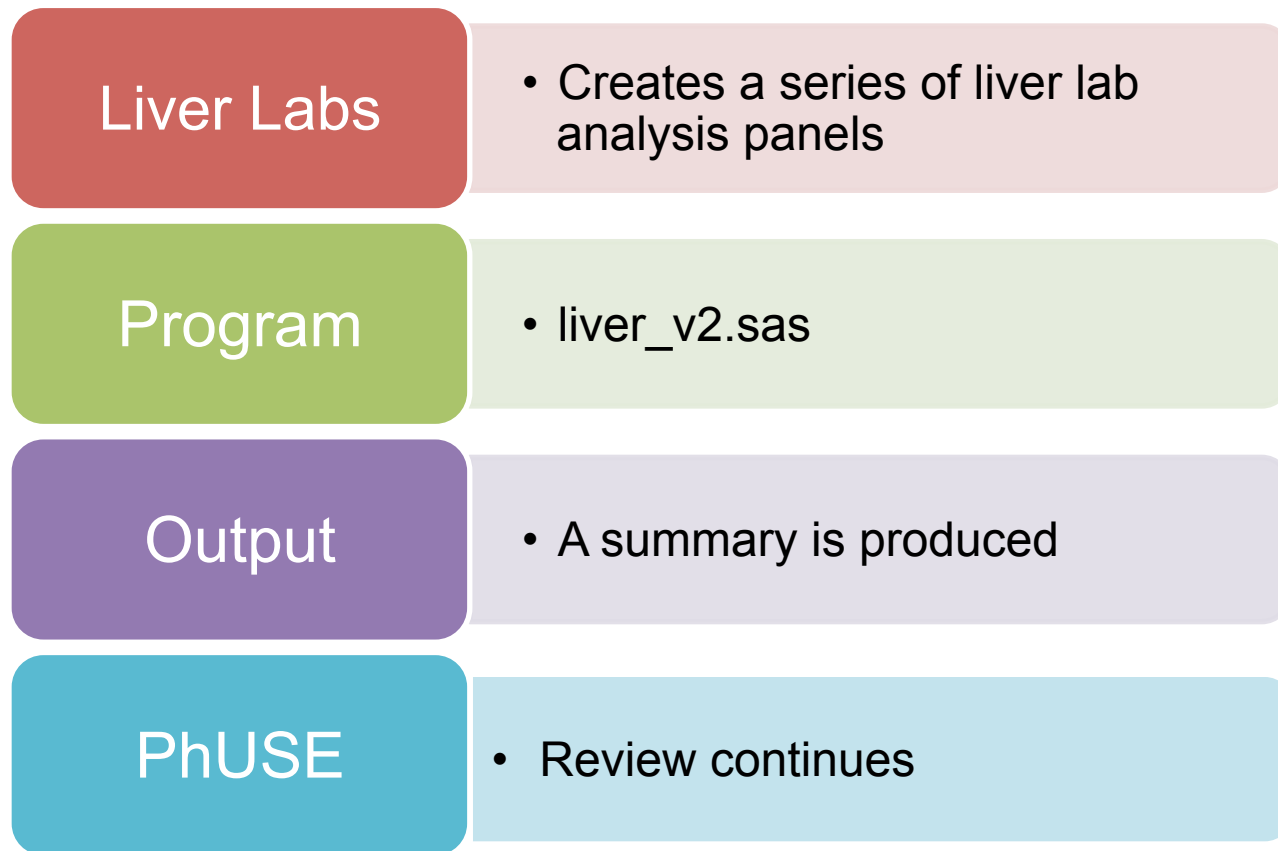


Exposure | Planned to Actual Dosing

A1		fx							
	A	B	C	D	E	F	G	H	I
1									
2	Planned Arm to Actual Treatment Comparison								
3									
4									
5	NDA/BLA:								
6	Study:								
7	Analysis run date:								
8									
10									
11									
12									
14	Placebo	52	Placebo	0 mg	50				
15			Statin	10 mg	2				
16	Statin Arm 1	53	Statin	10 mg	53				
17	Statin Arm 2	54	Statin	20 mg	54				
18									
19									
20									
21									
22									

* Subjects with more than one treatment will be counted more than once

Liver Labs



Liver Labs | Possible Hy's Law Cases

Possible Hy's Law Cases

NDA/BLA:

Study:

Analysis run date:

Combinations for Possible Hy's Law Cases: At the Same Visit

Liver Lab Test At Same Visit	0 N =		
	Event Count	Subject Count	% of Subjects
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP normal	0	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP normal	0	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP normal	0	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP > normal	0	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP > normal	0	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP > normal	0	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP missing	0	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP missing	0	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP missing	0	0	0.00

Notes: All scores are post-baseline. Cases that have the lab combinations occurring at the same visit.

Combinations for Possible Hy's Law Cases: At Any Time During the Study

Liver Lab Test Any Time During Study	0 N =	
	Subject Count	% of Subjects
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP normal	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP normal	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP normal	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP > normal	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP > normal	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP > normal	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 1.5 ULN & ALP missing	0	0.00
ALT or AST $\geq$ 3 ULN, TB $\geq$ 2 ULN & ALP missing	0	0.00
ALT or AST $\geq$ 5 ULN, TB $\geq$ 3 ULN & ALP missing	0	0.00

Notes: All scores are post-baseline. Subjects that have the lab combinations occurring at any point during the study.

MedDRA at a Glance

At a Glance

- Creates a series of AE panels by MedDRA level

Program

- Ae_meddra_w_flag_generation_v1.sas

Output

- One file is produced

MedDrA

Does not perform as expected

- “MedDRA at a Glance Error Summary.xls” was created but not accurate
- “MedDRA at a Glance Analysis Panel.xls” not created
- Expects input files not detailed in requirements
- Work continues to create a functioning version

MedDRA at a Glance | Max vs BL

A1

How to Participate

- Sign up for the PhUSE working group mailings
 - From phusewiki.org, click “Join a Working Group Now”
 - Standard Scripts Groups
 - CSS-WG-Standard-Scripts (Entire Working Group)
 - CSS-WG-Standard-Scripts-WhitePapers (White Paper Project Team)
 - CSS-WG-Standard-Scripts-Platform (Script Repository)
 - CSS-WG-SS-WhitePaperReviewers (Notified when a white paper is ready for review)
- See wiki pages for each of the projects (www.phusewiki.org)

