

Socializing the Deliverables from the Standard Analyses and Displays Project Team – The Adverse Event White Paper is Ready for Use!

PhUSE SDE

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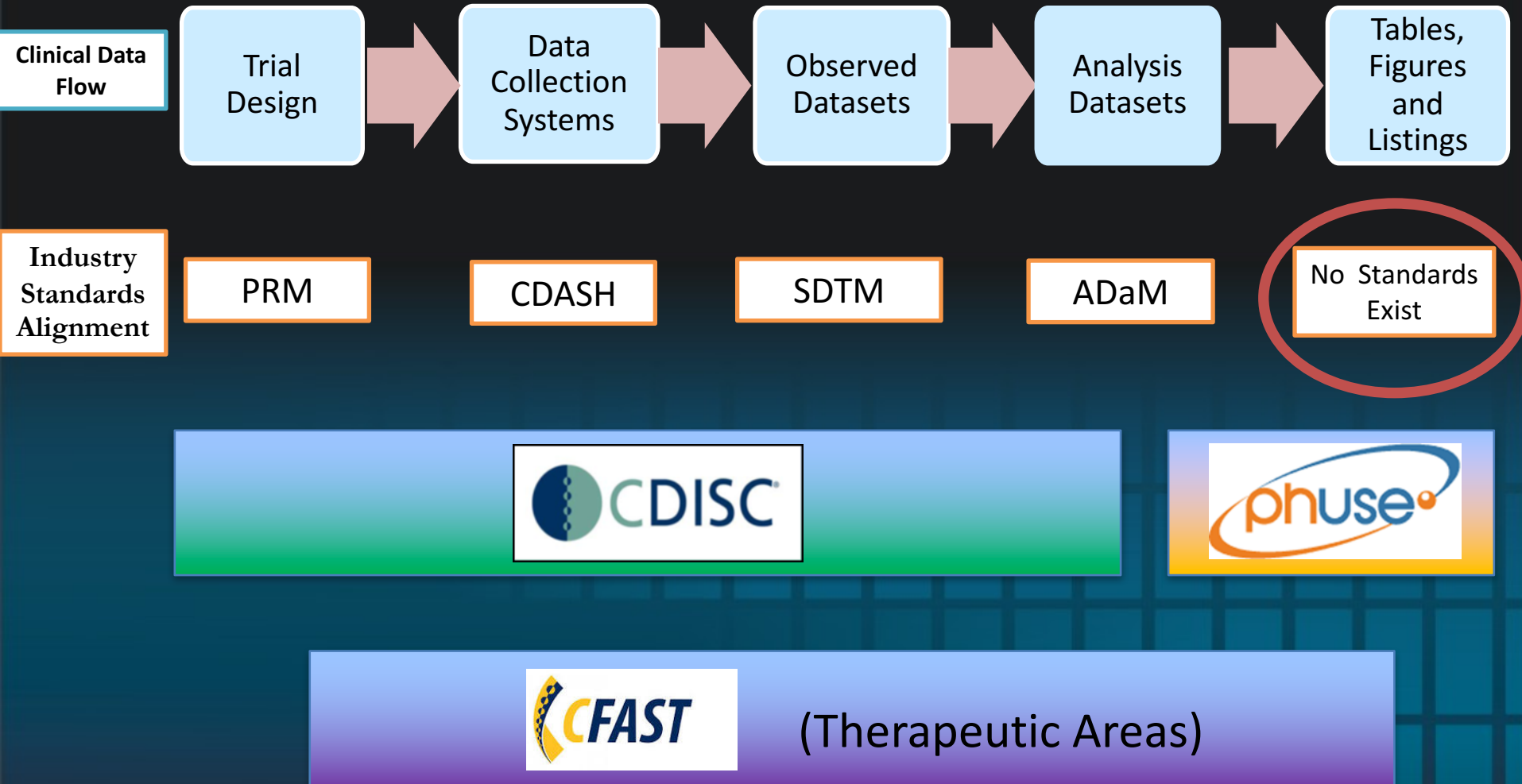


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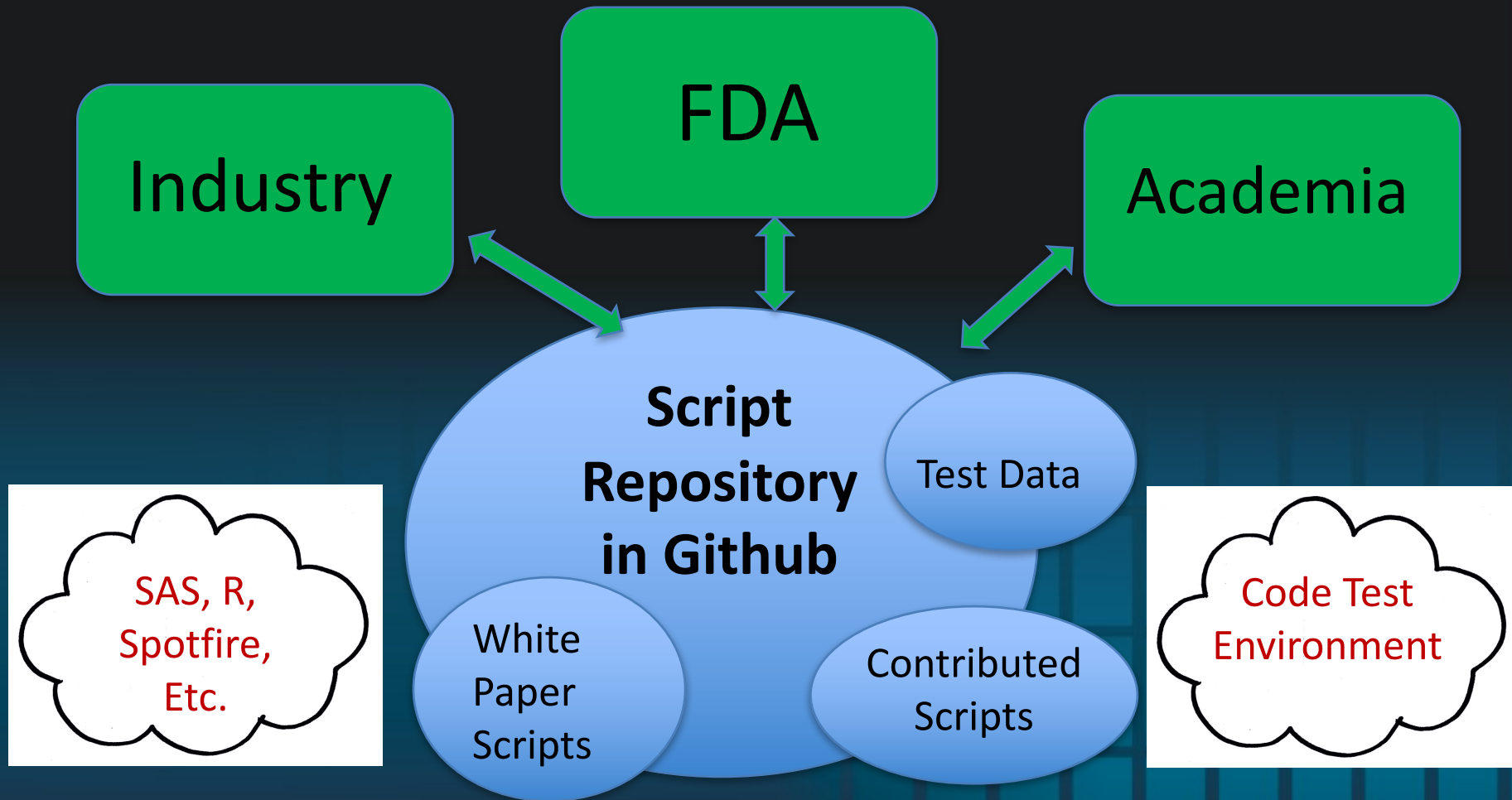


Vision: Fill the Gap on Analysis and Display Standards





Vision: Script Repository (Shared Reusable Code Library)





Focus Areas

- **Three Focus Areas, 6 active projects**

Script Repository
(4 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, Alfredo Rojas)

[Repository Content and Delivery](#) (RCD,
Gustav Bernard, Andrew Miskell)

[Repository Governance and
Infrastructure](#) (RGI, Mike Carniello,
Hanming Tu)

[Test Data Factory](#) (TDF, Peter Schaefer)

Accomplishments: White Papers

- 7 White Papers Finalized
 - Vital Signs, ECGs, Labs - Central Tendency (2013)
 - Non-Compartmental Pharmacokinetics (2014)
 - Demographics, Disposition, Medications (2014)
 - Vital Signs, ECGs, Labs – Outliers and Shifts (2015)
 - Thorough QT/QTc Studies (2016)
 - Adverse Events (2017)
 - Screen Shots of the Displays Created using Scripts Contributed by the FDA (2017)

How to find final white papers: Go to www.phuse.eu, Click on Working Groups, Click on CS Deliverables Catalog



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Adverse Event White Paper

- Recommended analyses/displays for individual studies and integrated summaries
- Example Statistical Analysis Plan language
- Indicates which displays are most suited for interactive tools
- Proposes common nomenclature
- Discusses analytical and statistical topics/methods
 - P-values and CIs in safety
 - Events occurring after study drug stops
 - Alternative methods when percentages are biased
 - Consolidating MedDRA PTs that are almost identical medically



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Adverse Event White Paper

- Goal
 - Improve efficiency
 - Improve expertise in analytics
 - Avoid poor pooling practices
 - Improve shared learning
 - Improve safety review experience



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Adverse Event White Paper – Example Method

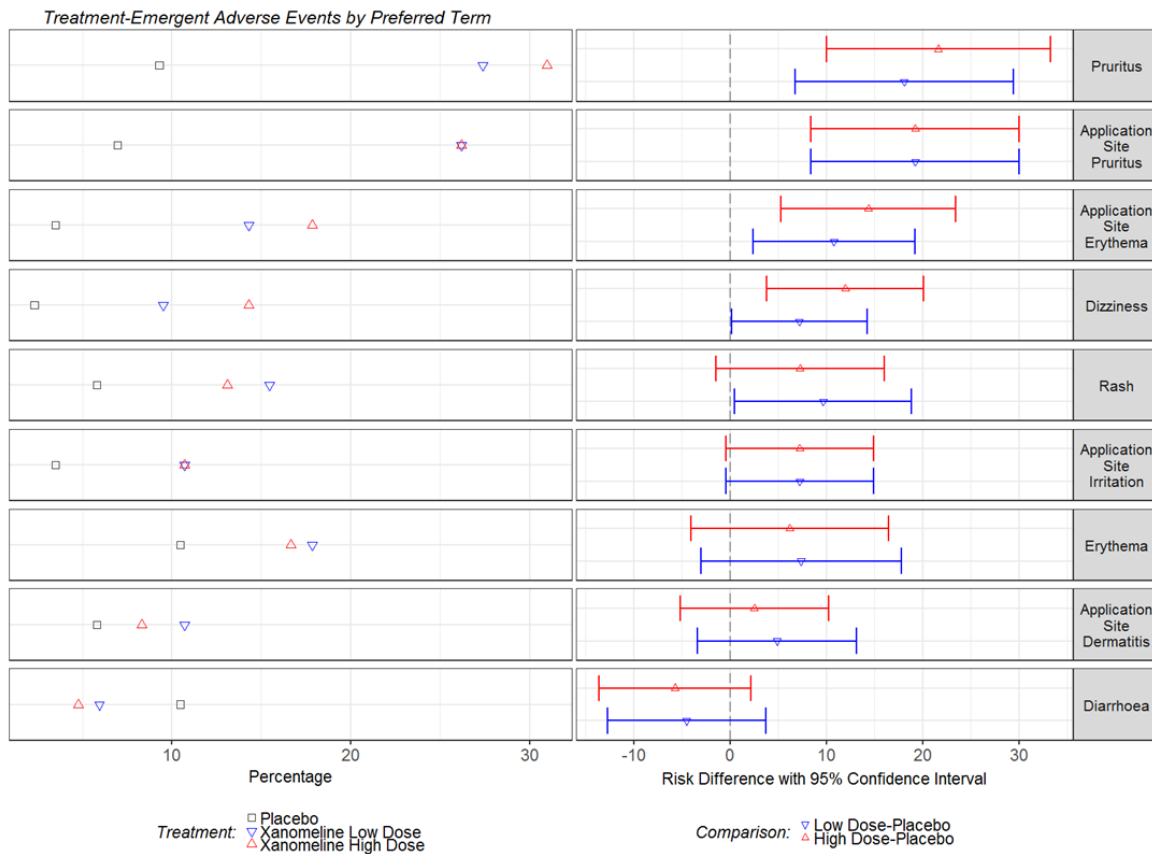
	New drug n/N (%)	Placebo n/N (%)	Proportion of total patients by study
Study 1	30/300 (10%)	10/100 (10%)	$w_1 = 400/2450$
Study 2	133/700 (19%)	67/350 (19%)	$w_2 = 1050/2450$
Study 3	200/500 (40%)	200/500 (40%)	$w_3 = 1000/2450$
Incidence from crude pooling	363/1500 (24%)	277/950 (29%)	
Study-size adjusted incidence	$w_1 \times (30/300) +$ $w_2 \times (133/700) +$ $w_3 \times (200/500) = 26\%$	$w_1 \times (10/100) +$ $w_2 \times (67/350) +$ $w_3 \times (200/500) = 26\%$	



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Adverse Event White Paper – Example Display



Adverse Events are based on 10% in either treatment group.



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Adverse Event White Paper

We concur with sources that include “person-time” or “exposure-adjusted” in the name when time is used in the denominator for clarity.

overly broad inclusion of events (or patients with an event) can lead to an underestimation of the true relative risk

percentages for sex-specific AEs should be determined using the appropriate number of sex - specific patients as the denominator

We do not believe summary tables for AEs considered related by the investigator are necessary for individual studies, nor necessary in submission documents to regulatory agencies other than the PMDA.

Our recommendations for how to handle TEAEs occurring post study drug depend on the design of the study and the expected characteristics of the study drug(s).

We think avoiding multiplicity methods is acceptable



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White Papers – Next Steps

	Version 1		Version 2	
	Public Review	Published	Public Review	Published
Vital Signs, Labs, ECG – Central Tendency		Oct 2013 	Q4 2017	
Non-Compartmental PK		March 2014 		
Demographics, Disposition, Medications		Oct 2014 	Q4 2017	
Vital Signs, Labs, ECG – Outliers / Shifts		Sept 2015 	Q4 2017	
QT/QTc Studies		March 2016 		
Adverse Events		Feb 2017 		
Treatment-Emergent Definitions	Q3 2017			
Hepatotoxicity	Q3 2017			
Questionnaires	Q4 2017			
Events of Special Interest	Q4 2017			

Working Group Needs

- More project team members
- Increased participation in white paper reviews – Help recruit!
- Use/reference recommendations in existing final white papers!
 - Forward to any existing standards groups
 - Link to white papers from Statistical Analysis Plans
- Participate in re-usable code development
 - Write, Test, Qualify, Review, Improve
- Keep eyes open for existing scripts that need a public home
- Advertise! Advertise! Advertise!



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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)



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Important Links

- Working Group:
 - Main Page: http://www.phusewiki.org/wiki/index.php?title=Standard_Scripts
 - Projects:
 - [P01 - SDA](#): Script discovery and acquisition (Rebeka M Revis; Alfredo Rojas)
 - [P02 - RCD](#): Repository content and delivery (Gustav Bernard; Andrew Miskell; FDA Liaison: Mat Soukup)
 - [P03 - RGI](#): Repository governance and infrastructure: (Mike Carniello and Hanming Tu)
 - [P07 - CPE](#): Communication, Promotion and Education (Jared Slain and Wendy Dobson)
 - [P08 - ADW](#): Analysis and Display White papers (Mary Nilsson)
 - [P09 - TDF](#): Test Data Factory (Peter Schaefer)
- Repository:
 - Github: <https://github.com/phuse-org/phuse-scripts>
- Publications: <http://www.phuse.eu/css-deliverables>
- Index Pages:
 - Simple Index: <https://github.com/phuse-org/phuse-scripts/wiki/Simple-Index>.
 - Standard Index: <https://github.com/phuse-org/phuse-scripts/wiki/Standard-Script-Index>
 - Mirrored Index: http://www.phusewiki.org/wiki/index.php?title=Standard_Script_Index



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Thank you! 😊



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Back-up slides and links



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Accomplishments: Repository

- Scripts developed by volunteers
 - 6 Scriptathons (plus additional work by project members) resulting in several scripts at various stages
 - Focused on creating scripts associated with the displays in the white papers, starting with ADaM data
 - The specifications for the scripts include assumptions and required ADaM variables
 - Starting with CDISC pilot data
 - Scripts developed based on white paper
 - Central Tendency package Qualification Completed: 6 Recommended displays in CT White Paper



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Working Group Next Steps

- Continue work on Test Data Factory Project
 - Provide updated CDISC pilot test data
- Continue work on the Script Repository
 - Increase usability, quality, and acceptability of the code
 - Develop scripts based the recommendations from white papers
- Continue work on white papers
 - See next slide
- Continue work on communication, promotion, and education
 - Develop training material



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Accomplishments: Repository

- Script Repository
 - MIT license chosen
 - <https://github.com/phuse-org/phuse-scripts/blob/master/LICENSE.md>
 - Qualification guidelines developed
 - http://www.phusewiki.org/wiki/index.php?title=WG5_Project_02#Qualification_Process
 - User-friendly front end developed
 - <https://github.com/phuse-org/phuse-scripts/wiki/Simple-Index>
 - Repository has been updated to have a place to store scripts developed by other groups



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Accomplishments: Repository

- Scripts contributed by other groups
 - FDA: <https://github.com/phuse-org/phuse-scripts/wiki/JumpStart-Scripts>
 - Non-clinical: <https://github.com/phuse-org/phuse-scripts/tree/master/contributed/Nonclinical>
 - Data Handle: <https://github.com/phuse-org/phuse-scripts/tree/master/lang/SAS/datahandle>
 - Spotfire Templates: <https://github.com/phuse-org/phuse-scripts/tree/master/contributed/Spotfire>



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