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Single Day Event

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Eli Lilly and Company

Standard Analyses and Displays for Common Data in Clinical Trials

PHUSE SDE
21 May 2021

phuse.global

Outline

- Background
- Summary of PHUSE final deliverables related to Standard Analyses
- Summary of ongoing projects related to Standard Analyses

Disclaimer

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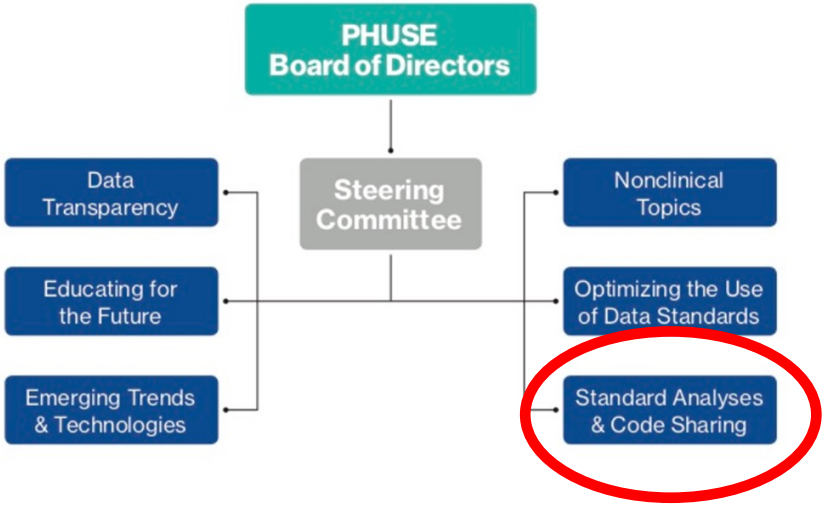
Background

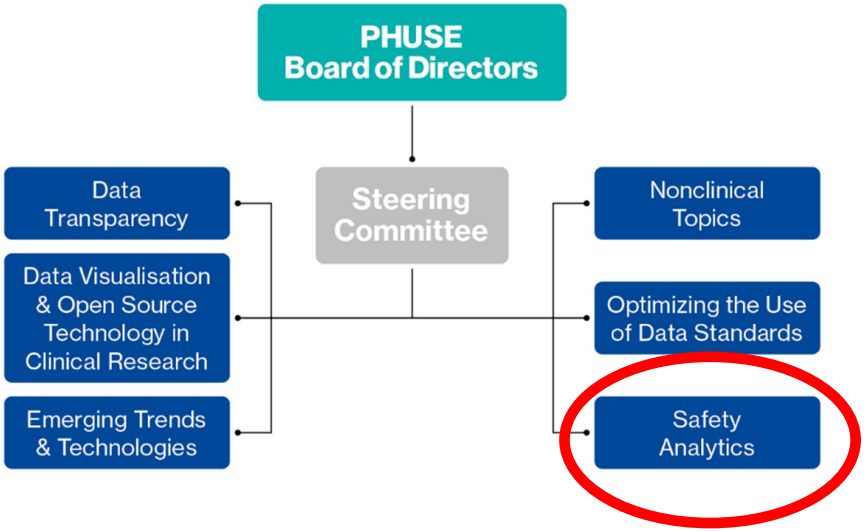
- PHUSE-authored Standard Analyses
  - Started at the beginning of the PHUSE/FDA collaboration (2012)
  - Focus is on data common across therapeutic areas (laboratory measurements, vital signs, electrocardiograms, adverse events, demographics, medications, disposition)

Background

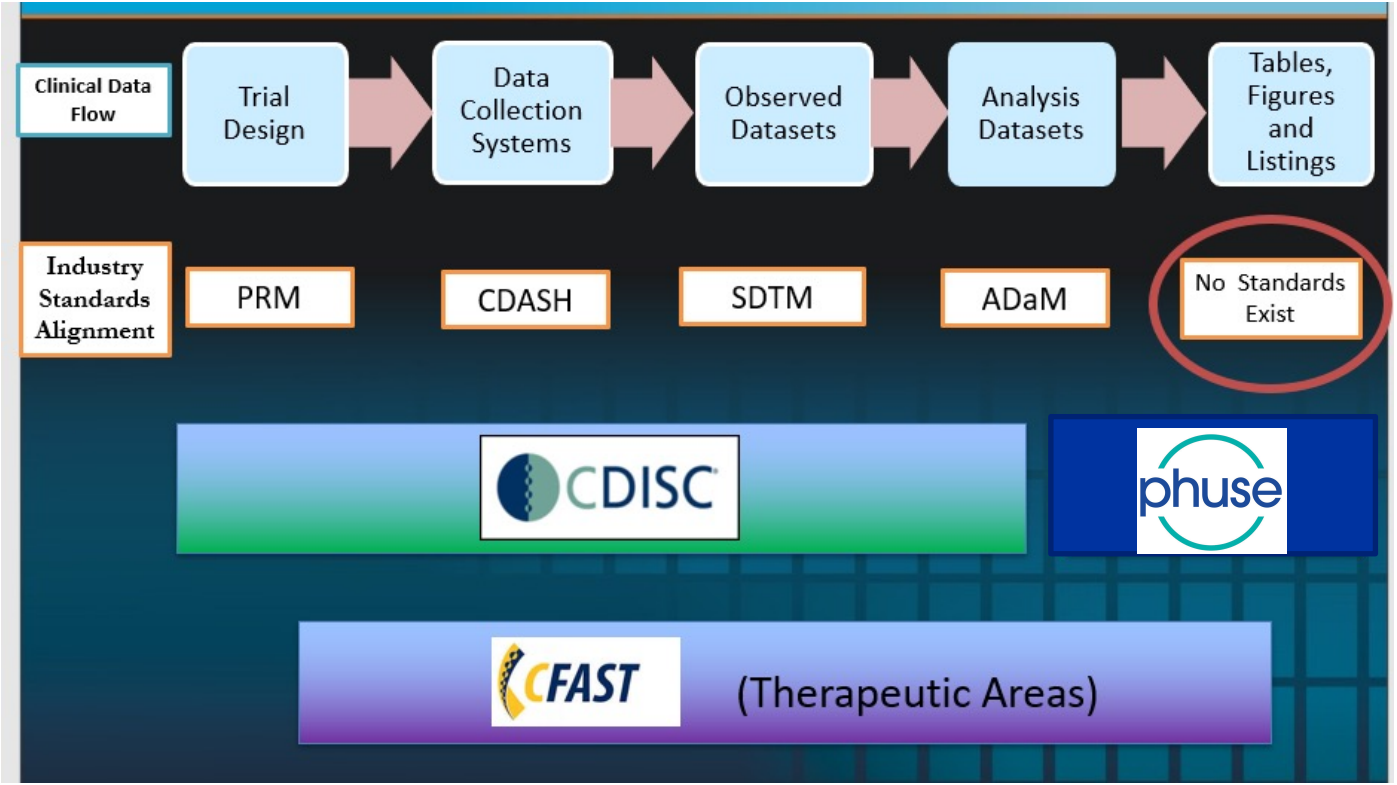
Old Working Groups Before June 2020



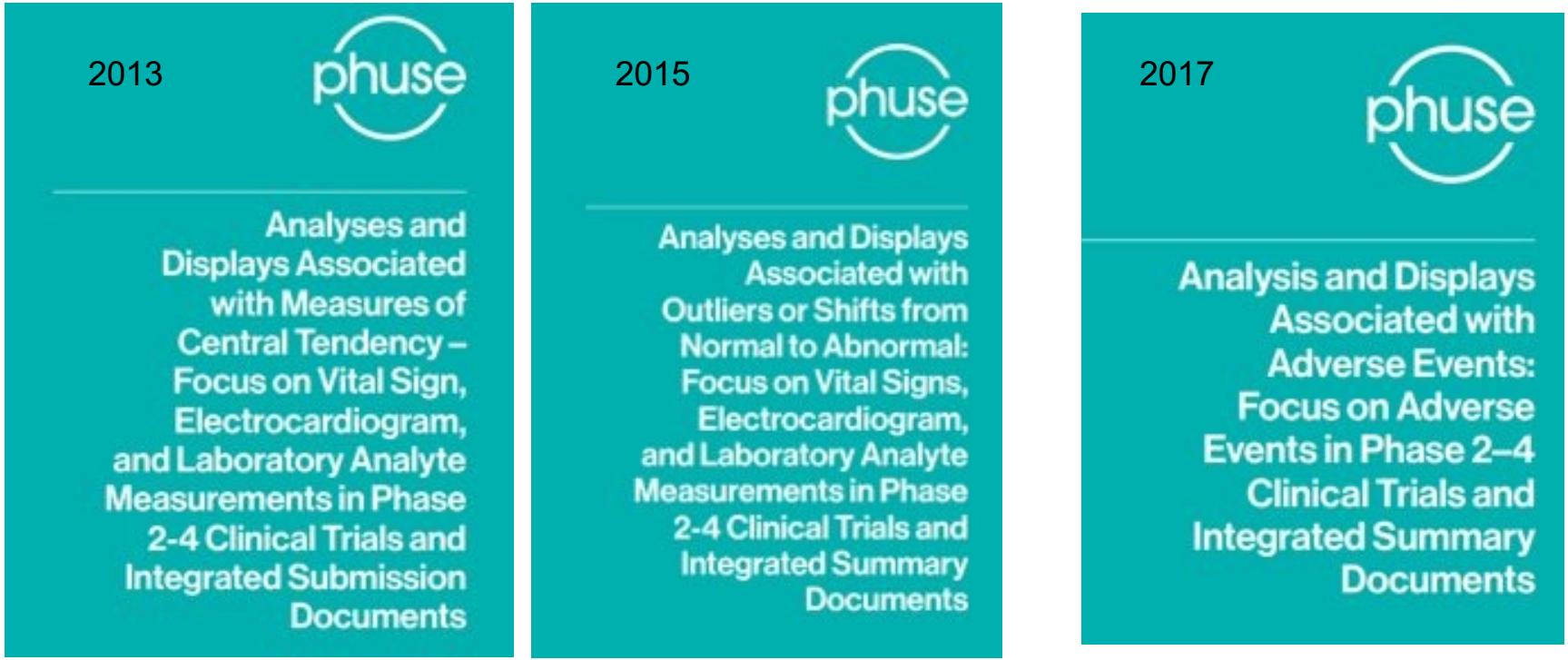
New Working Groups After June 2020



Analysis & Display white papers



Final Deliverables



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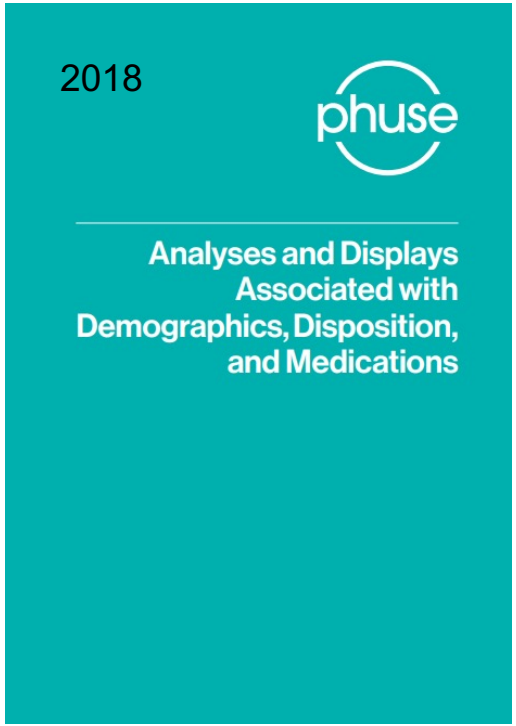
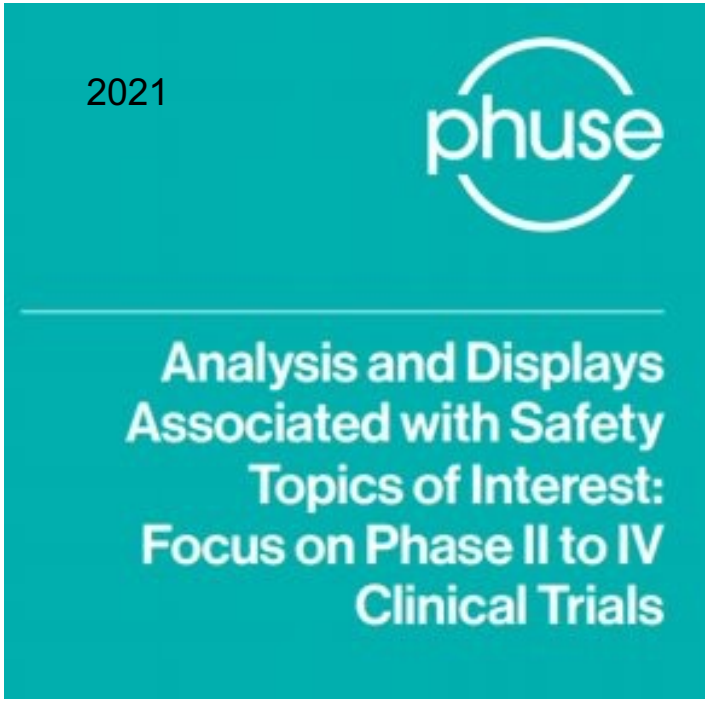




Final Deliverables

2018 Educational video
Topics for pooling data from multiple studies
(Study-size adjusted percentages)

2019 Safety Analytics Workshop
(Planning and Interpreting Safety Analyses for Individual Studies)

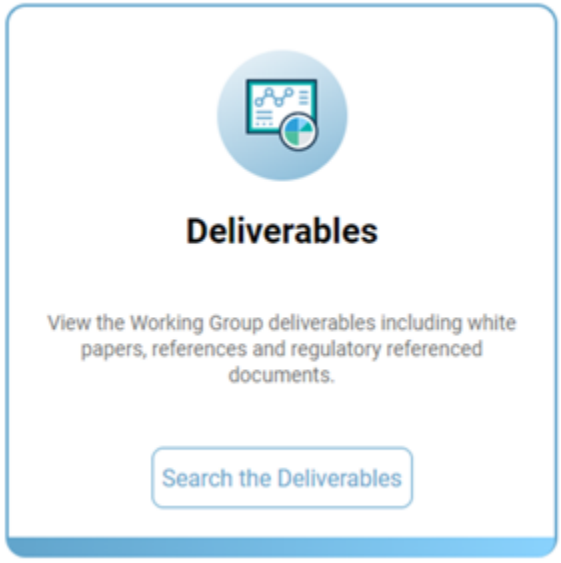
2020 Educational Workshop
Planning and Interpreting Safety Analyses for Integrated Summaries

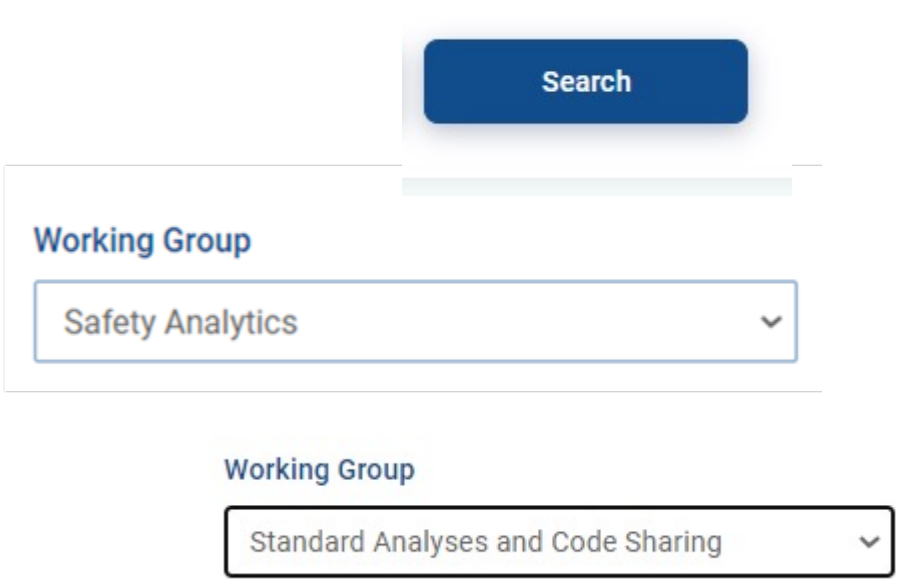
Other Final Deliverables

- 2014 Non-compartmental PK WP (archived)
- 2014 Reference code for some Lab/AE/Vital analyses contributed to Code Repository
- 2015 Code Repository governance and infrastructure
- 2016 QT/QTc studies WP (archived)
- 2016-7 FDA contributed SAS code to Code Repository, associated WP showing the displays
- 2017 Lilly contributed 2 interactive safety review packages to Code Repository
- 2017 Validation steps
- 2018 Updated SDTM and ADaM pilot data in Code Repository
- 2019 Interactive volcano plot proof-of-concept and pilot completed
- 2019 Script Metadata
- 2019 TS domain
- 2020 AE collection, treatment-emergent definition survey results
- 2020 General output tips and consideration
- 2020 Best practices for quality control
- 2020 Clinical Data Scientists Guide to Studies Impacted by COVID-19

How to Find Deliverables

Go to www.phuse.global, Click on Deliverables

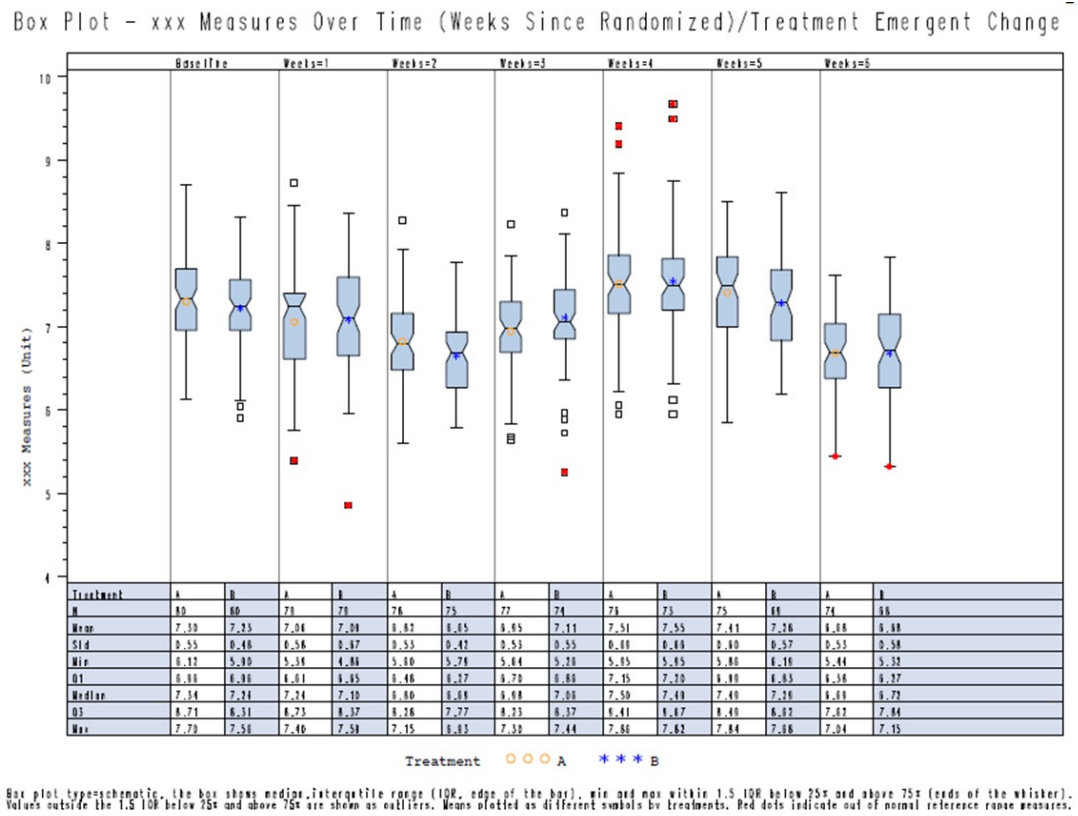




Labs, Vitals, ECGs White Papers

- 2013 central tendency, 2015 outliers/shifts
- Educational information, recommended analyses/displays, shells, Statistical Analysis Plan (SAP) language
- Main messages
  - Need both a central tendency and outlier/shift approach
  - Mean changes over time – recommend boxplot, but there are pros/cons across choices
  - Change from baseline to endpoint – really doesn't have a purpose, but it appears it's still predominant in practice

Labs, Vitals, ECGs White Papers



Treatment	A	B	A	B	A	B	A	B	A	B	A	B	A	B
N	80	80	78	78	76	75	77	74	78	73	75	68	74	66
Mean	7.30	7.23	7.06	7.09	6.82	6.85	6.95	7.11	7.51	7.55	7.41	7.26	6.88	6.88
Std	0.55	0.46	0.56	0.67	0.53	0.42	0.53	0.55	0.80	0.68	0.80	0.57	0.53	0.58
Min	6.12	5.80	5.34	4.86	5.10	5.24	5.04	5.28	5.15	5.85	5.86	6.16	5.44	5.32
Q1	6.80	6.80	6.61	6.65	6.46	6.27	6.70	6.88	7.15	7.10	6.90	6.83	6.36	6.37
Median	7.34	7.24	7.24	7.10	6.80	6.84	6.98	7.06	7.50	7.49	7.40	7.26	6.83	6.72
Q3	8.71	8.31	8.73	8.37	8.26	7.27	8.23	8.37	8.41	8.87	8.40	8.02	7.03	7.84
Max	7.79	7.56	7.40	7.58	7.15	8.03	7.30	7.44	7.86	7.82	7.84	7.86	7.04	7.15

Box plot type=schematic, the box shows median,interquatile range (IQR, edge of the box), min and max within 1.5 IQR below 25% and above 75% (ends of the whisker). Values outside the 1.5 IQR below 25% and above 75% are shown as outliers. Means plotted as different symbols by treatments. Red dots indicate out of normal reference range measures.

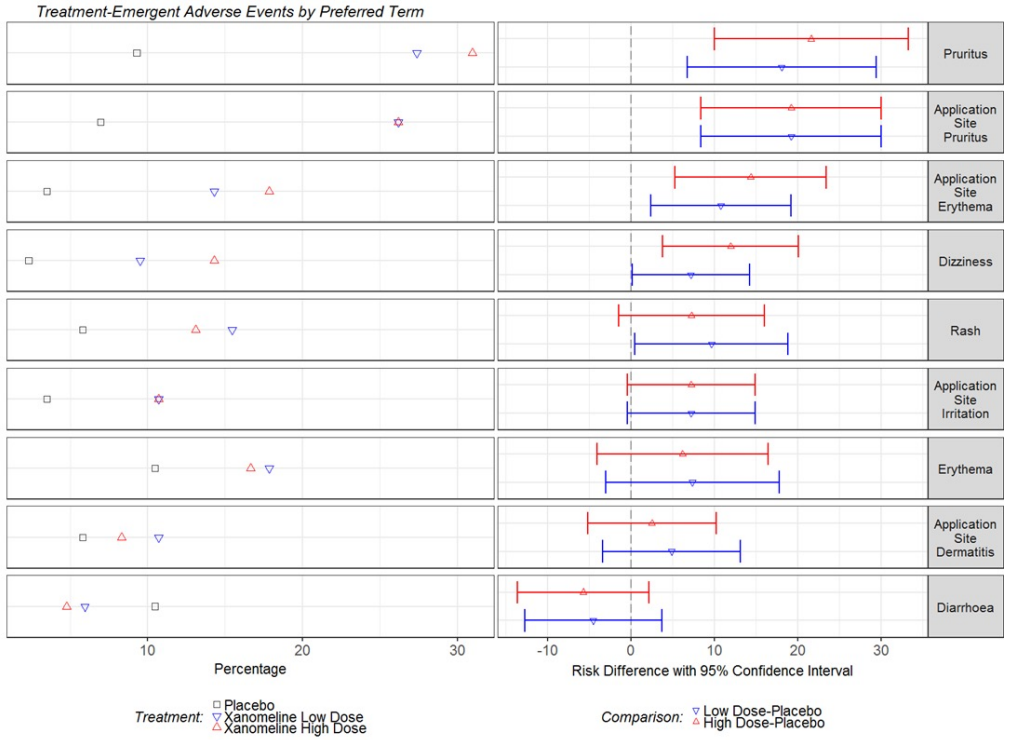
Demographics, Disposition, Medications White Paper

- 2014, updated in 2018
- Educational information, recommended analyses/displays, shells, SAP language
- Main messages
  - Generally, need both study and study treatment disposition
  - Generally, summarize medications by preferred name, not ATC category

Adverse Events White Paper

- 2017
- Educational information, recommended analyses/displays, shells, SAP language
- Main messages
  - Definitions for AE-related terms
  - Guiding principles for handling events after stopping study medication
  - Figure instead of table for TEAEs
  - Don’t need a summary for events considered related by the investigator
  - Integrated analyses – Use proper meta-analytical methods, recommend study-size adjusted percentage

Adverse Events White Paper

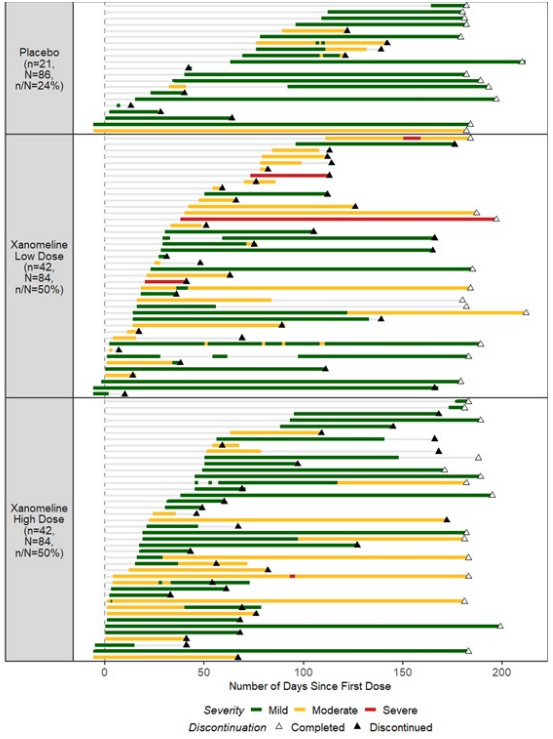


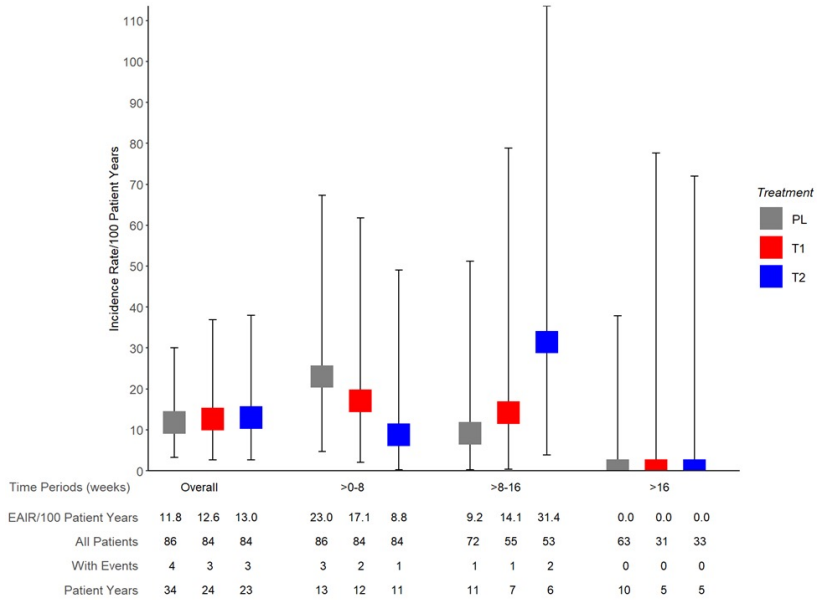
Adverse Events are based on 10% in either treatment group.

Safety Topics of Interest White Paper

- 2021
- Educational information, recommended analyses/displays, shells
- Main messages
  - Graphical patient profiles for case reviews
  - Onset/duration plot is often useful
  - Counting patients, counting events, versus time to first event
  - Summarizing by time block

Safety Topics of Interest





Safety Analytics Workshop: Part 1 (Individual Studies)

- 2019 PHUSE Computational Science Symposium
- Slides and recording are posted
- Start of crowd-sourcing education
- Primary source – Labs and Adverse Event White Papers
- Main messages
  - There's a training gap across all functions
  - There are some poor practices in predominant practice that need to be replaced with better methods
  - 29 common pitfalls, 18 FAQs addressed

Safety Analytics Workshop: Part 2 (Integrated Summaries)

- 2020 PHUSE Computational Science Symposium
- Slides and recording are posted
- Continues crowd-sourcing education
- Primary source – Labs and AE WPs
- Main messages
  - Avoid confounding, stratify by study
  - Recommend study-size adjusted percentages

Themes

- Education
  - Train all those involved in safety analyses
  - Stop poor practices, evolve to better practices
  - Tools need to follow good analytical principles, help avoid poor practices
- Standardization
- Visualization
- Crowd-sourcing

Ongoing Projects

Safety Analytics Working Group

Listings for CSRs	Hepatotoxicity Analyses and Displays	Lab Analyses and Displays	Adverse Event Collection	Treatment Emergent Definition
• Mercy Navarro • Nancy Brucken	• Terry Walsh • Melvin Munsaka	• Wei Wang • Charles Beasley	• Aimee Basile • Mary Nilsson	• Bill Palo • Mary Nilsson

Potential Future Projects

- Adverse Event White Paper – version 2
- Vitals signs, ECGs White Papers – version 2's
- Estimands for safety
- Disposition collection
- Hepatotoxicity collection
- EU Layperson summaries
- Defining gender-specific MedDRA PTs

Even More Potential Projects

- Preparing for the FDA Type C meeting on integrated safety plans recommendations
- Notable criteria, narratives, and TOSNP
- Combining studies for integrated analyses
- Analysis of genomic and biomarkers
- Writing statistical results for safety
- Safety population definition recommendation
- Analysis and Display of adjudicated data
- Safety in rare diseases
- Analyses for clinpharm studies
- Safety updates recommendations

Get Involved!

If you would like to join one of our active projects, contact: Workinggroups@phuse.global

If you would like to take the lead in one of the potential future projects, then complete and submit this New Project Request template

The Global Healthcare Data Science Community

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