Learning Objectives

- Understanding when to contact the FDA for discussion around integrated safety analysis plans
- Understanding common mistakes in integrated safety analysis
- Using best practices for integrated safety analysis

Common Mistakes When Pooling Clinical Trial Safety Data

Small Business and Industry Assistance (SBIA) Webinar
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Presenting on behalf of the PHUSE Safety Analytics Working Group, a public-private partnership with the FDA

Disclaimers

- The opinions expressed in this document are those of the author and should not be construed to represent the opinions of PHUSE, members' respective companies or organizations, or FDA's views or policies.
- The common mistakes are from the collective experience by members of the PHUSE Safety Analytics Working Group
  - Some examples are from what has been seen during planning, so are often addressed prior to submission

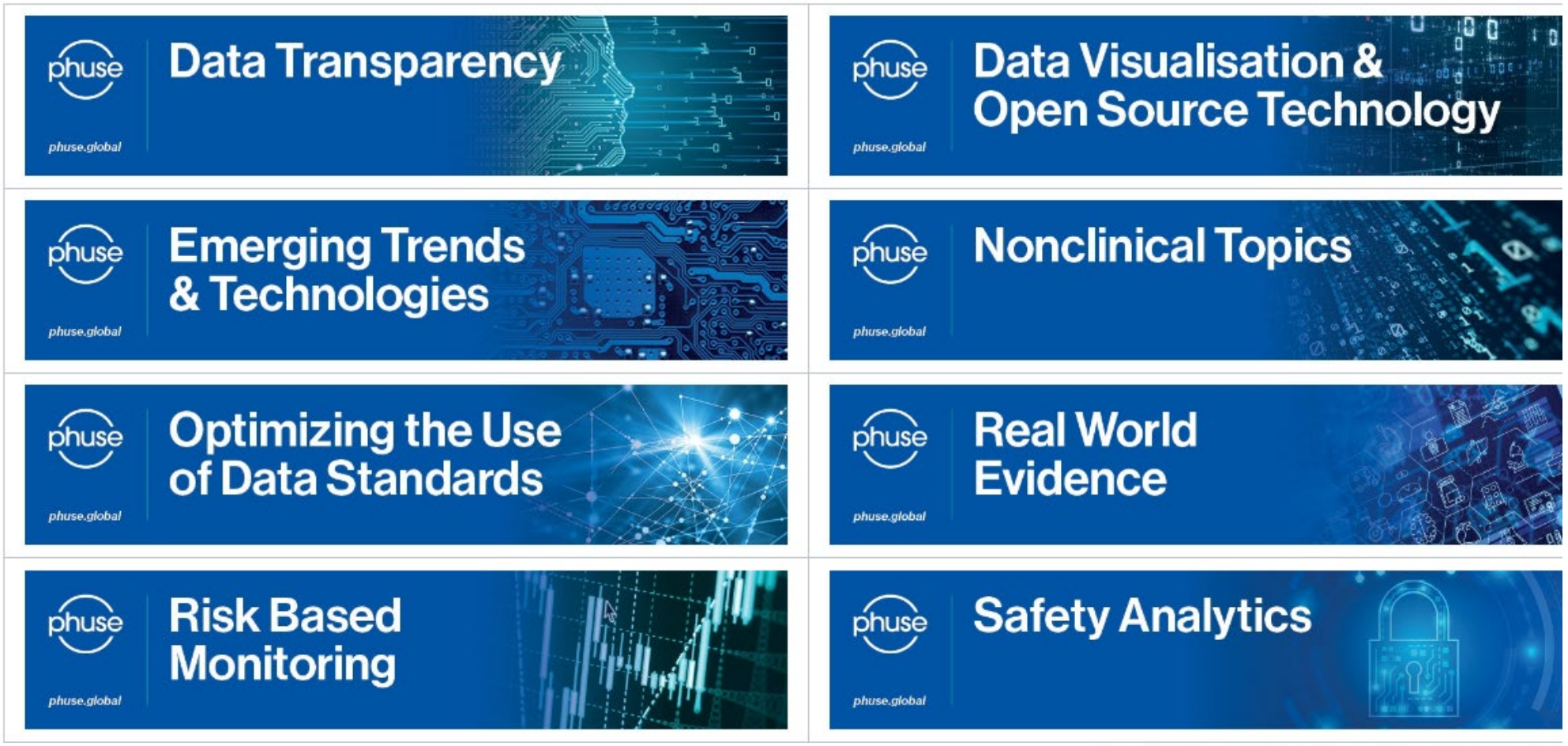
Background

- PHUSE is an Independent, not-for-profit organization run by volunteers, started in 2004
- FDA/PHUSE working group collaboration started in 2012
  - Public-private partnership

www.phuse.global
Working Groups

Rosario LA, Kropp TJ, Wilson SE, Cooper CK. Join FDA/PHUSE working groups to help harness the power of computational science. Drug Information Journal, 2012, 46(5): 523-524

Background – PHUSE Working Groups Today



Safety Analytics Working Group

- A collaboration working to improve the content and implementation of clinical trial safety analyses for medical research, leading to better data interpretations and increased efficiency in the clinical drug development and review processes
- Co-leads: Mary Nilsson (Lilly), Greg Ball (ASAPprocess), Scott Proestel (FDA)

Safety Analytics Education Project Team
Co-leads: William Palo (AbbVie), Chris Smith (FDA)

Why are we having this webinar?

- The knowledge needed to conduct proper integrated clinical trial safety analyses isn't typically covered in schools
  - The gap in safety analytics knowledge spans multiple disciplines (including statistics)
  - It's a myth that safety analysis planning and interpretation is easy
- There are some aspects of predominant practice that can be improved
- There's a general lack of awareness of useful references

Common Mistake #1: Not having an integrated planning document (or not early enough)

Individual Studies

- Planning document procedures are relatively clear and consistent
  - Statistical analysis plans

Integrated plans

- Planning document practices are inconsistent
  - ASAP, PSAP, iSAP, LOA only

ASAP = Aggregate Safety Assessment Plan

PSAP = Program Safety Analysis Plan

iSAP = integrated Safety Analysis Plan

LOA = List of Analyses

Safety planning document definitions

Statistical Analysis Plan (SAP)	Integrated Safety Analysis Plan (iSAP)	Program Safety Analysis Plan (PSAP)	Aggregate Safety Assessment Plan (ASAP)
• Study-level • Usually focused on CSRs, might include key manuscripts	• Submission-level • SCS/ISS	• Molecule-level • Usually focused on CSR and SCS/ISS analyses, may include some collection documentation	• Molecule-level • Ongoing safety reviews, IND safety reporting rule, CSRs, SCS/ISSs, etc.

CSR=Clinical Study Report; SCS=Summary of Clinical Safety; ISS=Integrated Summary of Safety

Poll (Applicable to industry representatives)

- Does your company/organization have a procedure outlining requirements for integrated safety analysis plans (for the Summary of Clinical Safety and/or Integrated Summary of Safety in a drug application)?
  - Yes
  - No
  - Not sure

Safety planning recommendation

- Sponsors might benefit from having a procedure outlining company expectations with respect to integrated safety plans
  - Include timing, ownership, document type (could be flexible)

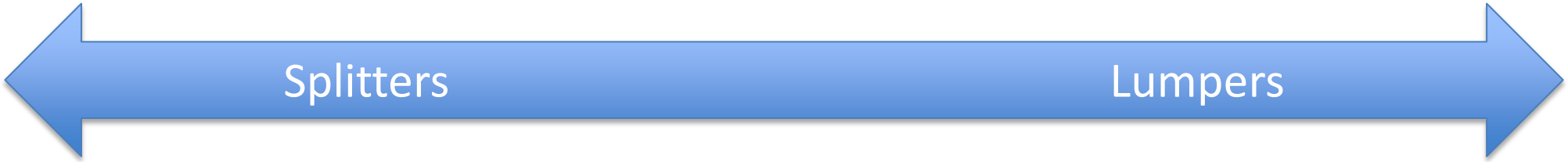
Timing	Ownership	Document Type
• Data collection plan for safety topics of interest prior to protocol approvals • Analysis plan in time for regulatory feedback, and in time for programming, table/figure review iterations	• Analysis planning usually owned by the statistics function • Regardless of ownership, integrated planning should be considered a cross-disciplinary effort	• iSAP, PSAP, and/or ASAP • Just having a list of analyses (LOA) is often insufficient

Common Mistake #2: Not asking for FDA input early enough

- Leverage the FDA's offer to conduct a Type C meeting specifically on integrated safety planning
  - Send the integrated planning document as a pre-read
- If a dedicated Type C meeting isn't feasible, send the integrated safety planning document to the FDA as part of another interaction (for example, bundled with other questions)

Common Mistake #3: Not understanding how to create integrated analysis sets

- There are likely multiple “right” ways to create integrated analysis sets for any given clinical program
  - There are some “wrong” ways
- Expect a lot of varying opinions both within your team and across regulatory reviewers



Example of confounding

Study	New Drug	Placebo	Active
1	4/400 (1%)	4/400 (1%)	
2	50/1000 (5%)		50/1000 (5%)
Pooled	**54/1400 (3.9%)**	**4/400 (1%)**	**50/1000 (5%)**

Study and treatment are confounded. Any differences (or lack of a difference) in pooled percentages could be due to treatment, or they could be due to study – In this example, the differences are due to study

Example of confounding

	Placebo	Low Dose	Middle Dose	High Dose
Study 1	10/100 (10%)	10/100 (10%)	10/100 (10%)	
Study 2	20/100 (20%)		20/100 (20%)	20/100 (20%)
Pooled	30/200 (15%)	10/100 **(10%)**	30/200 **(15%)**	20/100 **(20%)**

Study and treatment dose are confounded. As with the last example, the differences are due to study

Red flag: If the display includes crudely pooled percentages, and the treatment arms that are being compared come from different studies

Integrated analysis sets recommendations

- Ignore phase designation
  - Base pooling decisions on the actual study population, doses, design
- Don’t combine healthy volunteers with patients
- Typically, an “all study drug” integrated analysis set is helpful
  - Provides counts of patients for events across those taking study drug (regardless of study, dose, design)
  - Provides some value in finding rare events that might require further scrutiny, but has little value in treatment arm comparisons

Integrated analysis sets recommendations

- Typically, controlled integrated analysis sets are formed
  - Usually provides the most helpful data in identifying events requiring further scrutiny
  - Create controlled integrated analysis sets in a manner that allows for the proper use of meta-analytical methods
  - It’s OK to combine studies of different lengths and different populations (within reason), assuming proper use of meta-analytical methods

Integrated analysis sets recommendations

- What a team decides to pool for signal detection purposes
  - does not need to match what will be presented in regional labels
  - does not need to match what is done for specific safety topics of interest

Note: All results included in proposed labelling should be included in the application somewhere (could be an appendix as opposed to the body of the SCS/ISS) for annotation purposes

Example – Integrated Analysis Sets

Study	Description	Treatment arms
1	Phase 1 study, healthy volunteers	
2	Phase 2 study, 12 weeks treatment period, 4 week follow-up period	Placebo, Low dose (LD), Middle dose (MD), High dose (HD)
3	Phase 3 study, 24 weeks treatment period, 12 week open-label extension, 4 week follow-up period	Placebo, MD, HD
4	Phase 3 study, 24 weeks treatment period, 4 week follow-up period	Placebo, MD, HD
5	Extension study, 52 weeks, Study 2 and 4 patients feed into it (responders stay on same dose, nonresponders take HD), 4 week follow-up	MD, HD
6	Phase 3 study, 28 weeks treatment period, 4 week follow-up period	MD, HD

Example – Integrated Analysis Sets

Study	Description	Treatment arms
1	healthy volunteers	
2	12 weeks treatment period, 4 week follow-up period	Placebo, LD, MD, HD
3	24 weeks treatment period, 12 week open-label extension, 4 week follow-up period	Placebo, MD, HD
4	24 weeks treatment period, 4 week follow-up period	Placebo, MD, HD
5	Extension study, 52 weeks, Study 2 and 4 patients feed into it (responders stay on same dose, nonresponders take HD), 4 week follow-up	MD, HD
6	28 weeks treatment period, 4 week follow-up period	MD, HD

Placebo-controlled: Studies 2,3,4 Study Drug (doses pooled) vs placebo

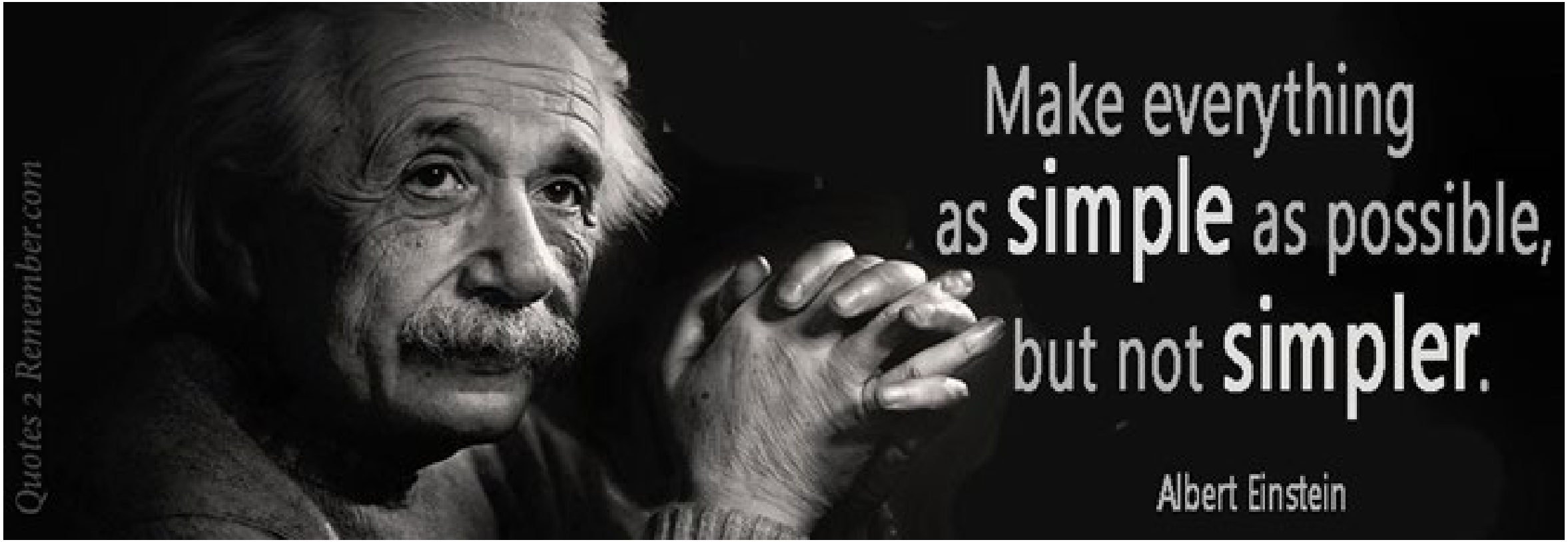
Multi-dose, placebo-controlled: Studies 2,3,4 MD vs HD vs placebo

Dose Effects: Studies 2,3,4,6 MD vs HD

All Study Drug: Studies 2,3,4,5,6 Doses pooled

If the LD arm is sufficiently large, a Bayesian indirect/mixed model can be considered to assess adverse event dose relationships

Common Mistake #4: Over-simplifying safety summaries



Poll

- Do you know what Simpson's paradox is?
  - No
  - I have heard of it, but not sure I fully understand it
  - Yes, I have heard of it and I fully understand it

Simpson's paradox example

Study	Placebo n/N (%)	Treated n/N (%)	Odds ratio
1	44/6127 (0.72)	88/10,324 (0.85)	1.2
2	18/2643 (0.68)	30/2650 (1.13)	1.7
3	82/2936 (2.79)	54/1483 (3.64)	1.3
Combined	144/11,706 (1.23)	172/14,457 (1.19)	0.97
Meta-analysis Method	Adjusted % = 1.05	Adjusted % = 1.36	Mantel-Haenszel odds ratio = 1.31

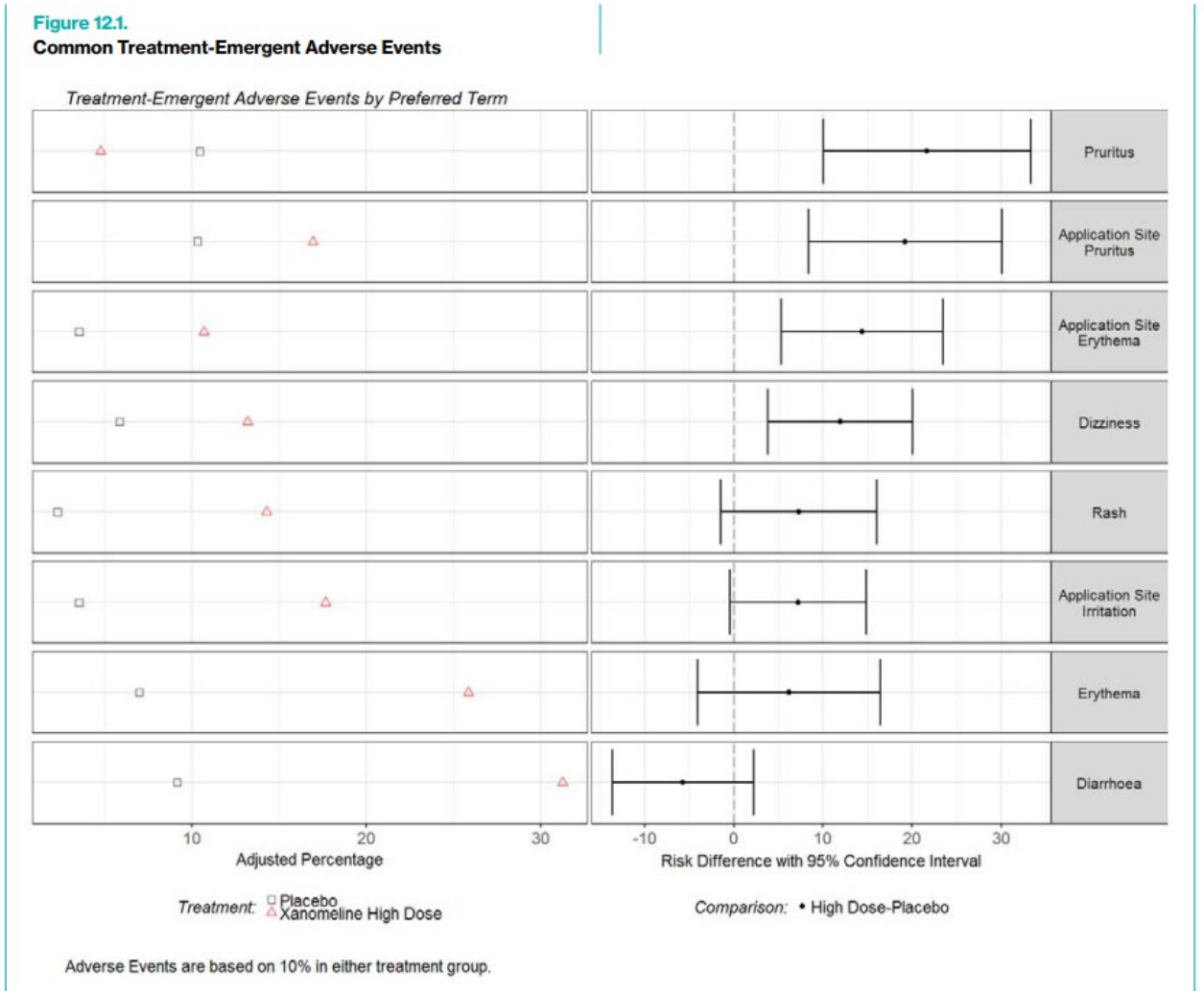
Even if you're aware enough to only pool studies that include the same treatment arms, crude pooling can still lead to misleading results

Safety analysis recommendations

- For controlled integrated analysis sets, use proper meta-analytical methods
  - Generally, include risk difference, risk ratio, and/or odds ratio **stratified by study** and 95% confidence intervals (avoids Simpson's paradox)
  - Generally, include study-size adjusted percentages
    - From a practical perspective, there are some situations in which it may not be worth the effort and/or page space to include
      - Crowe B. Topics in Pooling Data from Multiple Studies. Study-size Adjusted Percentages: Why, When and What? PHUSE Standard Analyses & Code Sharing Working Group, 2017. Link

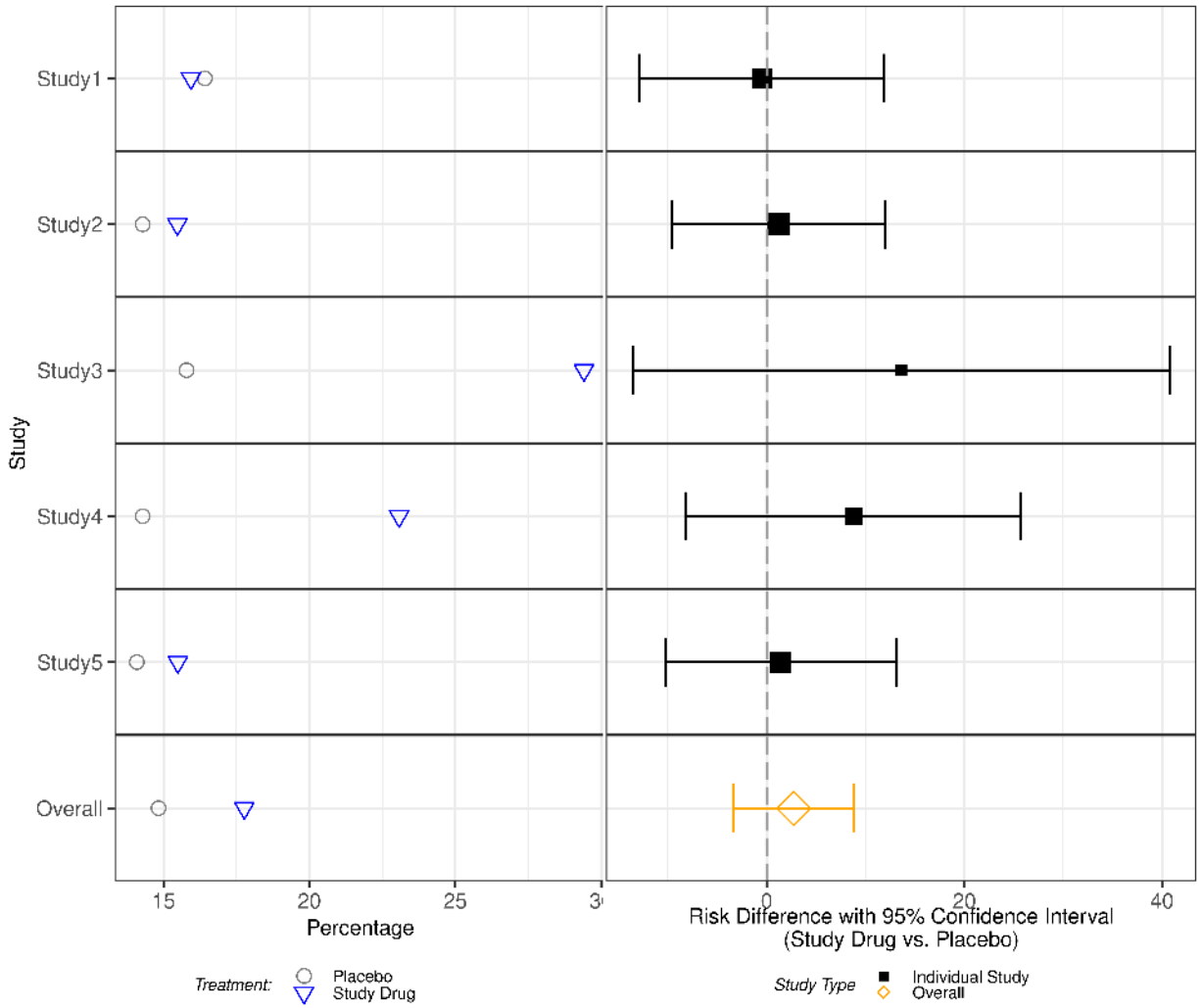
Example display for common treatment emergent adverse events

From the 2017 PHUSE adverse event white paper



Notes: Adjusted percentage is the study-size adjusted percentage
Risk difference is the Mantel-Haenszel risk difference stratified by study

Example display for a safety topic of interest



Notes: For the Overall row, the percentage is the study-sized adjusted percentage and the risk difference is the Mantel-Haenszel risk difference stratified by study

Example display for a rare safety topic of interest

From the 2021 PHUSE safety topics of interest white paper

Table 8.2. Collage of Incidence of Treatment-Emergent [Event Cluster]

Study Event Term, n (%)	Placebo *a	Active Comparator *b	TrtDose1	TrtDose2	TrtDose3	TrtDose4	TrtDose5
Study 1 (XXXX)	N=xx				N=xx		N=xx
No Events							
Study 2 (XXXX)	N=xx		N=xx		N=xx	N=xx	N=xx
No Events							
Study 3 (XXXX)		drug name N=xx		N=xx	N=xx		
No Events							
Study 4 (XXXX)	N=xxx			N=xxx		N=xxx	
No Events							
Study 5 (XXXX)		drug name N=xxx		N=xxx		N=xxx	
PT name 1		0 (0.0)		2 (0.7)		0 (0.0)	
Study 6 (XXXX)	N=177	drug name N=439*b N1=315, N2=124	N=49	N=302	N=10	N=304	N=45
PT name 2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (2.2)
PT name 3	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)

Abbreviations: N = patients assigned to this treatment group who received at least one dose of study medication; N1 = patients who received this treatment starting at randomisation; N2 = patients who received this treatment after 6 months of placebo; n = number of patients in specified category.
*a - The planned Placebo period in studies X, Y, Z is 26 weeks, which is shorter than the overall study durations of 104 weeks, 52 weeks and 26 weeks, respectively. Rates in the Placebo group are not directly comparable to rates in other groups.
*b - Active comparator and treatment include any patients from Studies X and Y, respectively, who began the study receiving placebo and reached the timepoint where they began to receive active treatment (indicated by N2). If an event is treatment-emergent relative to original baseline after that timepoint, it is included in this table (independent of the Placebo period).

Safety analysis recommendations

- Use the proper metric
  - No metric is perfect, need to understand limitations in interpretation
  - Relying on percentages is often OK, but not always
    - See Section 10.9 of the 2017 PHUSE adverse event white paper

- Observed percentage
- Percentage from Kaplan-Meier model
- Exposure-adjusted incidence rate
- Hazard rate

Common Mistake #5: Unnecessary Volume

- Too many integrated analysis sets
  - If an integrated analysis set is very close to another integrated analysis set, ask yourself if it adds sufficient value
- Too many analyses
  - Some analyses are only applicable for when there is a control arm
    - Not every analysis needs to be done for every analysis set
  - Some commonly produced analyses add little value (for example, summaries of events considered related by the investigator)

Common Mistake #6: Overuse of past methods

- Barrier to improving safety analytics
  - Assuming doing what has been done in the past, or doing what everyone else does is the best way to go forward

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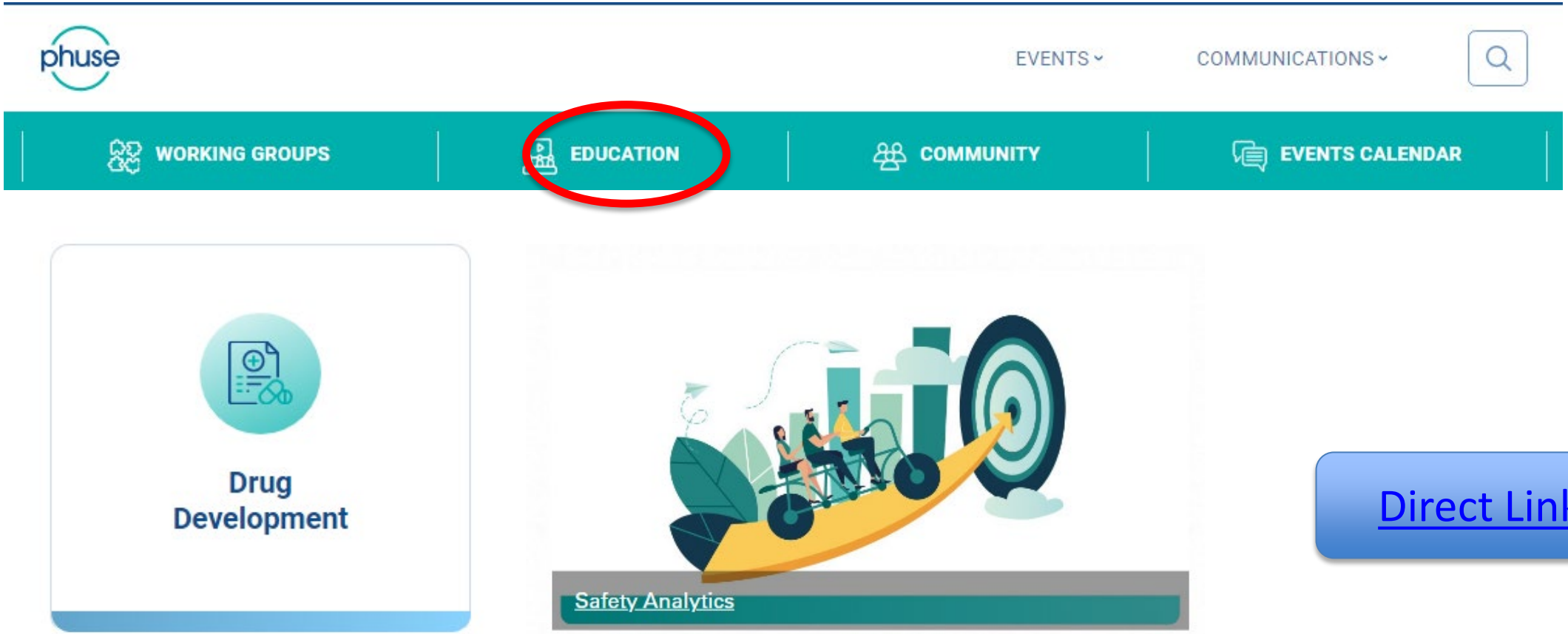

Direct Link

Challenge Question

- When combining data from multiple randomized controlled trials within a clinical program, it's considered a meta-analysis and meta-analytical methods should typically be used
  - True
  - False
- Correct answer = True

References

- PSAP
  - Crowe B, Xia HA, Berlin J, Watson DJ, Shi H, Lin SL, Kuebler J, Schriver RC, Santanello N, Rochester G, Porter JB, Oster M, Mehrotra D, Li Z, King EC, Harpur ES, Hall DB. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clinical Trials, 2009; 6(5): 430-440.
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  - Crowe, B., Brueckner, A., Beasley, C., & Kulkarni, P. (2013). Current practices, challenges, and statistical issues with product safety labeling [Statistics in biopharmaceutical research]. Stat Biopharm Res, 5(3), 180-193.
- ASAP
  - Hendrickson BA, Wang WW, Ball G, McShea C, et al. Aggregate Safety Assessment Planning for the Drug Development Life Cycle. Therapeutic Innovation & Regulatory Science. 2021;55:717-732.
  - Ball G, Kurek R, Hendrickson BA, Buchanan J, Wang WW, Duke SP, Bhattacharyya A, Li M, O'Brien D, Weigel J, Wang W, Jiang Q, Ahmad F, Seltzer JH, Herrero-Martinez, E Tremmel L (2020). Global Regulatory Landscape for Aggregate Safety Assessments: Recent Developments and Future Directions. Therapeutic Innovation & Regulatory Science, 54(2):447-461.
  - Reimagining a Safety Submission – Aggregate Safety Assessment Planning. 2023. link
- FDA Type C meeting for integrated safety
  - Sutter, S. US FDA Looks To Standardize Premarketing Safety Assessments. Pink Sheet 08 Sep 2019

References

- Study-sized adjusted percentage
  - Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents. 2017. link
  - Crowe B. Topics in Pooling Data from Multiple Studies. Study-size Adjusted Percentages: Why, When and What? PHUSE Standard Analyses & Code Sharing Working Group, 2017. link
  - Xia, H. A., Crowe, B., Schriver, R. C., Oster, M., & Hall, D. B. (2011). Planning and core analyses for periodic aggregate safety data reviews. Clinical Trials, 8(2), 175-182.
- Bayesian indirect/mixed model
  - Fu H, Price KL, Nilsson ME, Ruberg SJ. Identifying potential adverse events dose-response relationships via Bayesian indirect and mixed treatment comparison models. J Biopharm Stat. 2013;23(1):26-42.
- Pooling/Simpson's paradox
  - Food and Drug Administration. 2018. "Draft Guidance: Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products." link
  - CIOMS Working Group X. 2016. *Evidence Synthesis and Meta-Analysis for Drug Safety: Report of CIOMS Working Group X*. Geneva, Switzerland: Council for International Organizations of Medical Sciences (CIOMS).
  - Crowe B, Wang WV, Nilsson ME. Advances in techniques for combining data from multiple clinical trials, in *Advances in collating and using trial data*, M. Resche- Rigon and S. Chevret, Editors. 2014, Future Science. 20-37.
  - Berlin, J.A., Crowe, B. J., Whalen, E, Xia, H. A., Koro, C. E., and Kuebler, J. 2013. "Meta-analysis of clinical trial safety data in a drug development program: answers to frequently asked questions". *Clin Trials*, **10**, 20-31.

References

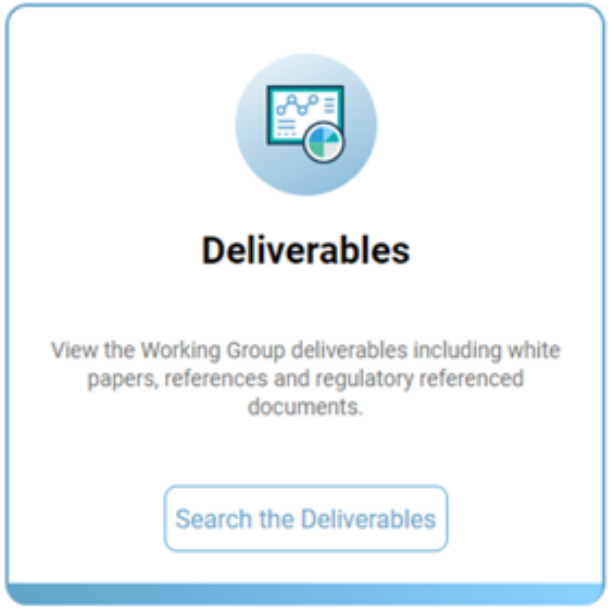
- Unnecessary volume

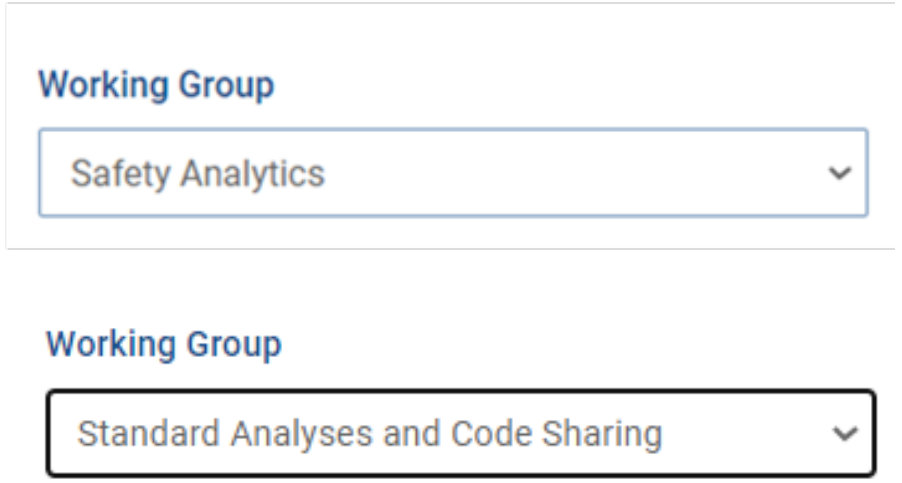
- Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents. 2017. link
- Nilsson M. Planning and Interpreting Safety Analyses for Integrated Summaries Workshop, PHUSE Computational Science Symposium, September 2020. link_to_presentation link_to_slides
- Nilsson M. Safety Analytics Workshop, PHUSE Computational Science Symposium, June 2019. link_to_presentation link_to_slides
- Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Documents. [serial online] 2017. link
- Nilsson M. Clinical trial safety analyses – Common pitfalls and FAQs Workshop, PHUSE EU Connect, November 2021. link

Backup Slides

Finding PHUSE Deliverables

www.phuse.global





Adverse Drug Reaction

- Adverse Drug Reaction (ADR) – An adverse event reasonably likely to be caused by a study drug and it may occur as part of the pharmacological action of the study drug or may be unpredictable in its occurrence

Common Pitfall: Believing ADR determination is based on numeric criteria

Factors used to determine ADRs:
•Strength of evidence for an imbalance between the study drug and placebo
•Magnitude of the observed effect
•Observed dose relationship
•Biological plausibility
•Clinical relevance of any individual case
•Dechallenge/Rechallenge
•Severity and/or seriousness of the event
•Consistency of findings across studies, indications or studied populations, similar events, and similar compounds
•Epidemiological data
•Relevant non-clinical data
•Background incidence of the event
•Identifiable subgroups at risk
•Other relevant assessments of association; including, previous assessments on signals/safety observations

Purpose-related definitions

- Signal detection – Analyses and displays used to determine which events or changes in labs/vitals/ECGs require further evaluation for dCSI/ADR consideration
- Signal clarification – Additional analyses and displays used to facilitate the assessment of whether an event or change in labs/vitals/ECGs should be in the dCSI or considered an ADR
- Signal characterization - Additional summaries used to characterize events or changes in labs/vitals/ECGs once they are included in the dCSI or identified as an ADR
- Signal communication - Additional summaries used for documents that communicate ADRs (for example, regional labelling)

dCSI = Development core safety information
ADR = Adverse drug reaction

Common Pitfalls:
- Not understanding the purpose of an analysis
- Thinking a table/figure needs to meet all purposes

FAQ

- What's the difference between an integrated analysis set and a pooled analysis?
  - Most tend to use these words interchangeably
  - One FDA guidance document suggests a distinction
    - Pooled = merge the data
    - Integration = side-by-side presentation
  - However, there is no alignment on any distinction

Study-sized adjusted percentage

	New Treatment, n/N (%)	Placebo, n/N (%)	Total patients in the study
Phase 2 Study	30/300 (10.0%)	10/100 (10.0%)	400
Phase 3 Study	133/700 (19.0%)	67/350 (19.1%)	1050
Phase 3 Study in Refractory Patients	200/500 (40.0%)	200/500 (40.0%)	1000
Percentages from Crude Pooling	363/1500 (24.0%)	277/950 (29.0%)	2450
Study-Size Adjusted Percentages	$\frac{400}{2450} \times \frac{30}{300} + \frac{1050}{2450} \times \frac{133}{700} + \frac{1000}{2450} \times \frac{200}{500}$ = 26.1%	$\frac{400}{2450} \times \frac{10}{100} + \frac{1050}{2450} \times \frac{67}{350} + \frac{1000}{2450} \times \frac{200}{500}$ = 26.2%	

Treatment-Emergent Adverse Events by Preferred Term in Descending Risk Difference within System Organ Class
Integrated placebo-controlled analysis set (Study drug doses pooled versus placebo)

System Organ Class Preferred Term	Study Drug (N=XX) n (%)	adj%	Placebo (N=XX) n (%)	adj%	RD (95% CI)[a]
Number of patients >=1 TEAE	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
[System Organ Class #1]	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
[Preferred Term #1]	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
[Preferred Term #2][b]	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
[System Organ Class #2]	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
[Preferred Term #1][c]	xx (xx.x)	xx.x	xx (xx.x)	xx.x	xx.x (xx.x, xx.x)
….					

Abbreviations: Adj%=study-size adjusted percentage; N=number of patients; n=number of patients with at least one row event; RD=risk difference; TEAE=treatment-emergent adverse event.
Percentages are calculated relative to the treatment group N. Patients may be counted in more than one row.
System organ class is sorted by descending RD of TRT-PL.
[a]Mantel-Haenszel risk difference stratified by study and confidence interval from [insert method].
[b]Denominator adjusted because sex-specific event for males: N=XX (Treatment), N=XX (Placebo) *[For applicable PTs]*.
[c]Denominator adjusted because sex-specific event for females: N=XX (Treatment), N=XX (Placebo) *[For applicable PTs]*.

Treatment-Emergent Adverse Events by Preferred Term in Descending Risk Difference within System Organ Class
Integrated placebo-controlled analysis set (High dose versus low dose versus placebo)

System Organ Class Preferred Term	PL (N=XX) n (%) [adj%]	LD (N=XX) n (%) [adj%]	HD (N=XX) n (%) [adj%]	LD&HD (N=XX) n (%) [adj%]	LD-PL RD (95% CI)[a]	LD-PL RD (95% CI)[a]	LD&HD-PL RD (95% CI)[a]
Number of patients >= 1 TEAE	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
[System Organ Class #1]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
[Preferred Term #1]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
[Preferred Term #2][b]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
[System Organ Class #2]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
[Preferred Term #1][c]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx (xx.x) [xx.x]	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
….							

Abbreviations: Adj%=study-size adjusted percentage; N=number of patients; n=number of patients with at least one row event; RD=risk difference; TEAE=treatment-emergent adverse event; PL=Placebo; LD=Low dose; HD=High Dose.
Percentages are calculated relative to the treatment group N. Patients may be counted in more than one row.
System organ class is sorted by descending RD of LD&HD-PL.
[a]Mantel-Haenszel risk difference stratified by study and confidence interval from [insert method].
[b]Denominator adjusted because sex-specific event for males: N=XX (Placebo); N=XX (Low Dose); N=XX (High Dose) *[For applicable PTs]*.
[c]Denominator adjusted because sex-specific event for females: N=XX (Placebo); N=XX (Low Dose); N=XX (High Dose) *[For applicable PTs]*.

Treatment-Emergent Adverse Events by Preferred Term in Descending Frequency within System Organ Class
Integrated all study drug analysis set (Doses pooled)

System Organ Class Preferred Term	During SD (N=XX) n (%)	During SD and After (N=XX) n (%)
Number of patients >= 1 TEAE	xx (xx.x)	xx (xx.x)
[System Organ Class #1]	xx (xx.x)	xx (xx.x)
[Preferred Term #1]	xx (xx.x)	xx (xx.x)
[Preferred Term #2]a	xx (xx.x)	xx (xx.x)
[System Organ Class #2]	xx (xx.x)	xx (xx.x)
[Preferred Term #1]b	xx (xx.x)	xx (xx.x)

Abbreviations: N=number of patients; n=number of patients with at least one row event; TEAE=treatment-emergent adverse event; SD=Study drug.
Percentages are calculated relative to the treatment group N. Patients may be counted in more than one row.
[a]Denominator adjusted because sex-specific event for males: N=XX *[For applicable PTs]*.
[b]Denominator adjusted because sex-specific event for females: N=XX *[For applicable PTs]*.

Metrics

- Percentage (observed): the number of patients with a TEAE, n, divided by N, the number of patients who had the potential to develop the event at the start of the study
- Percentage (Kaplan Meier): the percentage of patients estimated to have had a (first) event by the specified time point, after accounting for dropouts at or prior to time point.
  - Always >= the observed percentage at the timepoint because the formula takes into account the number of patients who have the event among the number of patients who are still at risk of having the event *at each time point*, that is by excluding patients who were not still being followed at each event time. (KM estimates percentages of patients who haven't had the event. We use 1 minus that to get event percentage.)
- Exposure-adjusted incidence rate (EAIR): Number of patients with a (first) TEAE during a given time period divided by total person-time at risk
- Hazard rate: an instantaneous version of EAIR