

CSS PhUSE White Paper Update on Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal

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Introduction:

Industry standards have evolved over time for data collection (CDASH), observed data (SDTM), and analysis datasets (ADaM). There is now recognition that the next step would be to develop standard tables and figures for common measurements across clinical trials and across therapeutic areas. The Development of Standard Scripts for Analysis and Programming Working Group is leading an effort to create several white papers providing recommended analyses and displays for common measurements, and has developed a Script Repository as a place to store shared code.

Last year we presented a poster on the first draft of the white paper titled "Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents". Since then, we have made a lot of improvements to this paper based on all the great comments we received during the review process. This poster will provide an update on the improvements.

Since March, 2014, we have ...

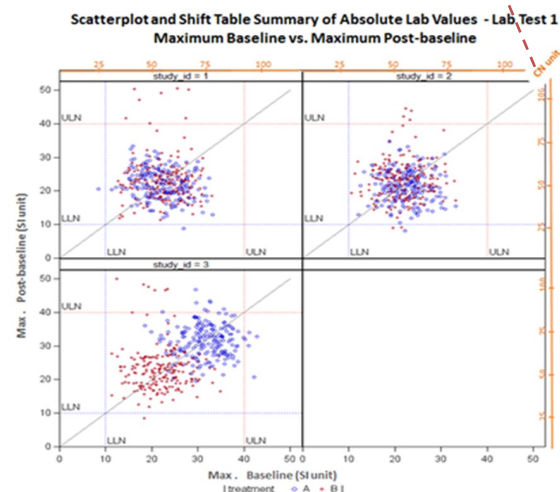
- Received reviews across industry colleagues in various organizations



- Added more details and clarity on various discussion topics
- Improved the TFL display
- Separated the 3-panel display to 2 pages with graph in one page and summary table in second page
 - Less crowded report
- Add Weighted (study size adjusted) percentage for integrated result

Second set of axes for CN unit

Example of the new display—Page 1



LLN=Lower limit of normal; ULN=Upper limit of normal; trst=treatment ; if the limits (LLN and ULN) vary across the population, the limits that apply to the majority of subjects are displayed in the scatter plot. There are two sets of axes - one for SUnit, one for CN unit. The black diagonal line represents no change from max. baseline to max. post baseline.

Example of the new display—Page 2

Scatterplot and Shift Table Summary of Absolute Lab Values - Lab Test 1
Maximum Baseline vs. Maximum Post-baseline

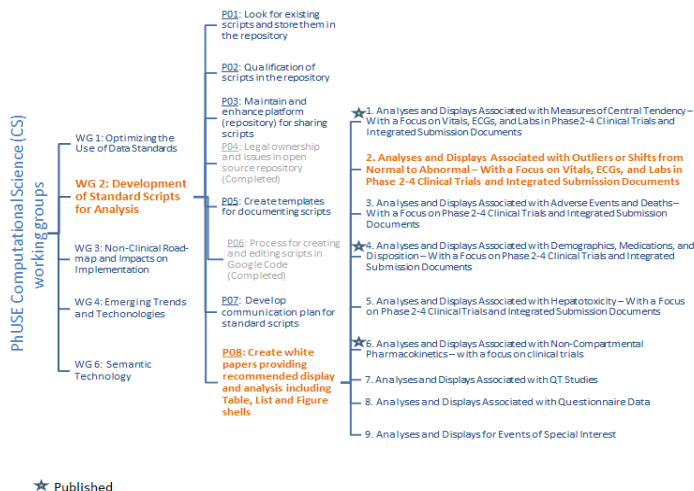
Shift from Normal/low to High				
Treatment	N	n	%	Study size adjusted %
A	xxx	xxx	xx.x	xx.x
B	xxx	xxx	xx.x	xx.x
Heterogeneity P value		OR	P value	
A	.xxx	x.xx	.xxx	
B				

N = number of subjects with Max baseline 'normal' or 'low' and at least one post baseline value; n = among the 'N', number of subjects with max post baseline 'high'.
CMH P-value = Cochran-Mantel-Haenszel (CMH) test stratified by study.
The denominator for Mantel-Haenszel odds ratio is treatment. A Heterogeneity P value is from Breslow-Day test.
High and low are determined using the reference limits based on the individual subject's demographics.

Study size adjusted percent in addition to the raw pooled percent.

Summary

- We are finalizing the version 1 of the white paper.
- Please continue providing us your review comments and recommendations.
- You can access the draft white paper in PhUSE wiki.



Draft 3 is available in PhUSE wiki

www.phusewiki.org/wiki/index.php?title=SS_P08_Outliers/Shifts_White_Paper

SS P08 Outliers/Shifts White Paper

White Paper Title and Lead

Title = Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal - With a Focus on Vitals, ECGs, and Labs in Phase 2-4 Clinical Trials and Integrated Summary Documents

Lead = Wei Wang

Status

Draft 3 of the white paper is out for broad review. Comments are due 01 December 2014. We encourage anyone to participate in this review, including statisticians, medical, medical writing, etc. Please provide your comments:

1. Enter your comments in Agilewords (If you do not have an account with Agilewords, you need to apply for one - it is free). Link to Agilewords Version of the white paper
2. Enter your comments in the Discussion tab on this wiki page
3. Provide comments to Wei Wang via email (wang_w@eillilly.com)

Reusable code for several tables and figures from the draft white paper is available in the Script Repository.

04 December 2014 Note: The review period has been extended to 16 January 2015. Thank you to those who have already provided comments. Receiving comments before 01 December 2014 was helpful so that we start working on the update. While we are working on the update, we are open to receiving additional comments before 16 January 2015.

Plan

Target February 2015 for a final white paper.

History

The draft paper (Old Outliers and Shifts Draft) was available for review by 28 February 2014. Old Agilewords links: Agilewords 0

Several topics were discussed during the PhUSE CSS March 2014 Meeting: See SS P08 18March2014 Standard Scripts Project 08 Meeting for meeting minutes.

Examples of Discussed Topics

- General Considerations
 - Whether to report P-values and Confidence Intervals
 - Handle of
 - Measures collected in reflex manner, repeated measures, unplanned measures, measurements post drug exposure
 - Baseline definition Multi-phase Clinical Trials'
 - Measurements After Stopping Study Medication
 - Measurements at a Discontinuation Visit
- Laboratory Analyte Measurements
 - Handling of central versus local laboratories
 - Choices of lab reference limits

