

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

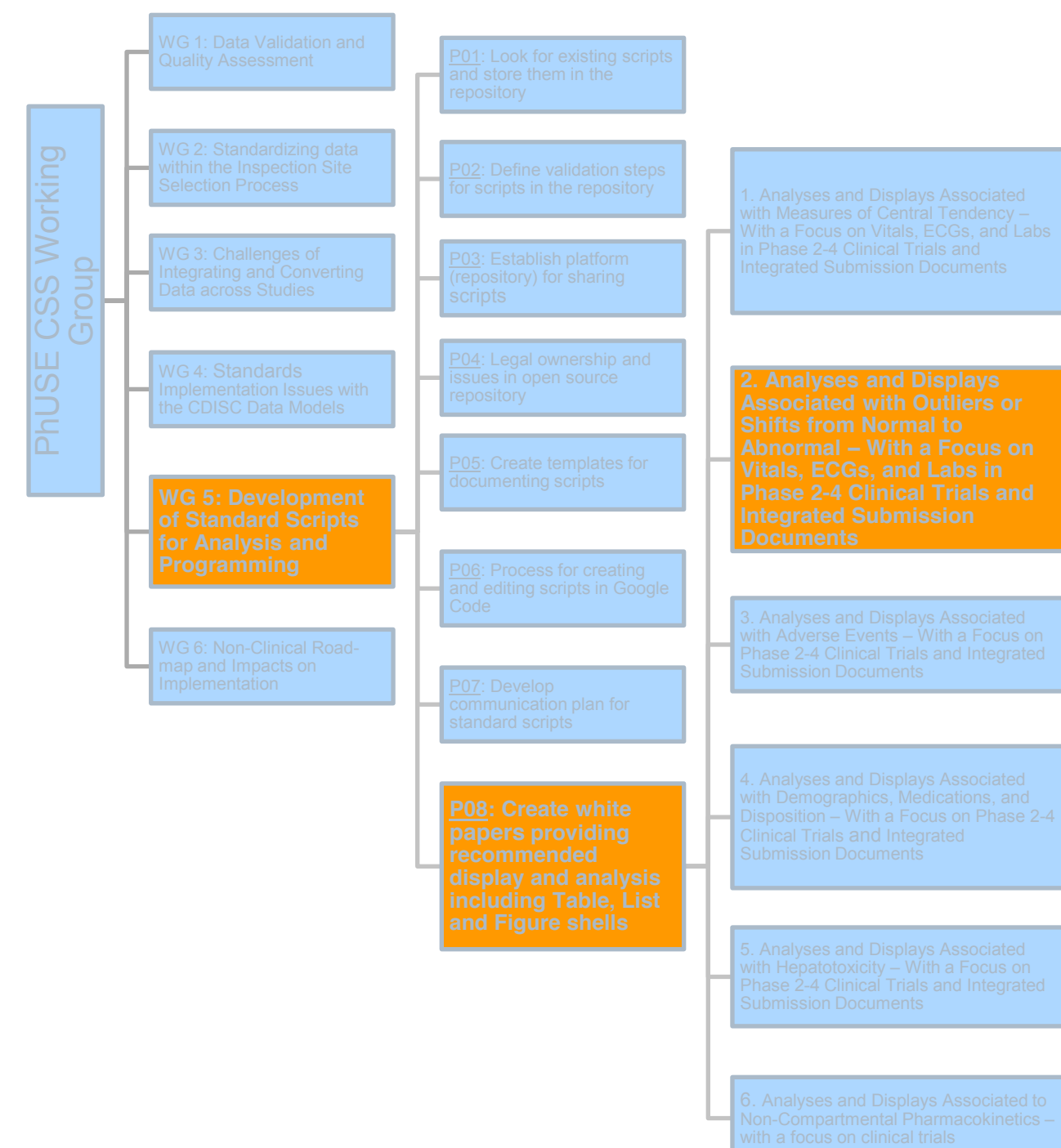
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INTRODUCTION

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 WG 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.

This poster will cover the recommended tables and figures associated with outliers or shifts from normal to abnormal, as outlined in a draft 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". The FDA Safety Reviewer Guidance includes a statement that the safety review of laboratory data should include a review that focuses on patients whose values deviate substantially from a reference range. They also recommend a similar approach for ECGs and vital signs. In addition to the final recommendations, this poster will cover reasons for the recommendations and various alternatives that were considered. Developing shared code to create the displays in this white paper is planned for the Script Repository.

Working Group



Draft is Under 1st Round of Review

1. 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

Version 1.0
Created xx XXXX 201x.

A White Paper by the PhUSE Computational Science Symposium Development of Standard Scripts for Analysis and Programming Working Group

This white paper does not necessarily reflect the opinion of the institutions of those who have contributed.

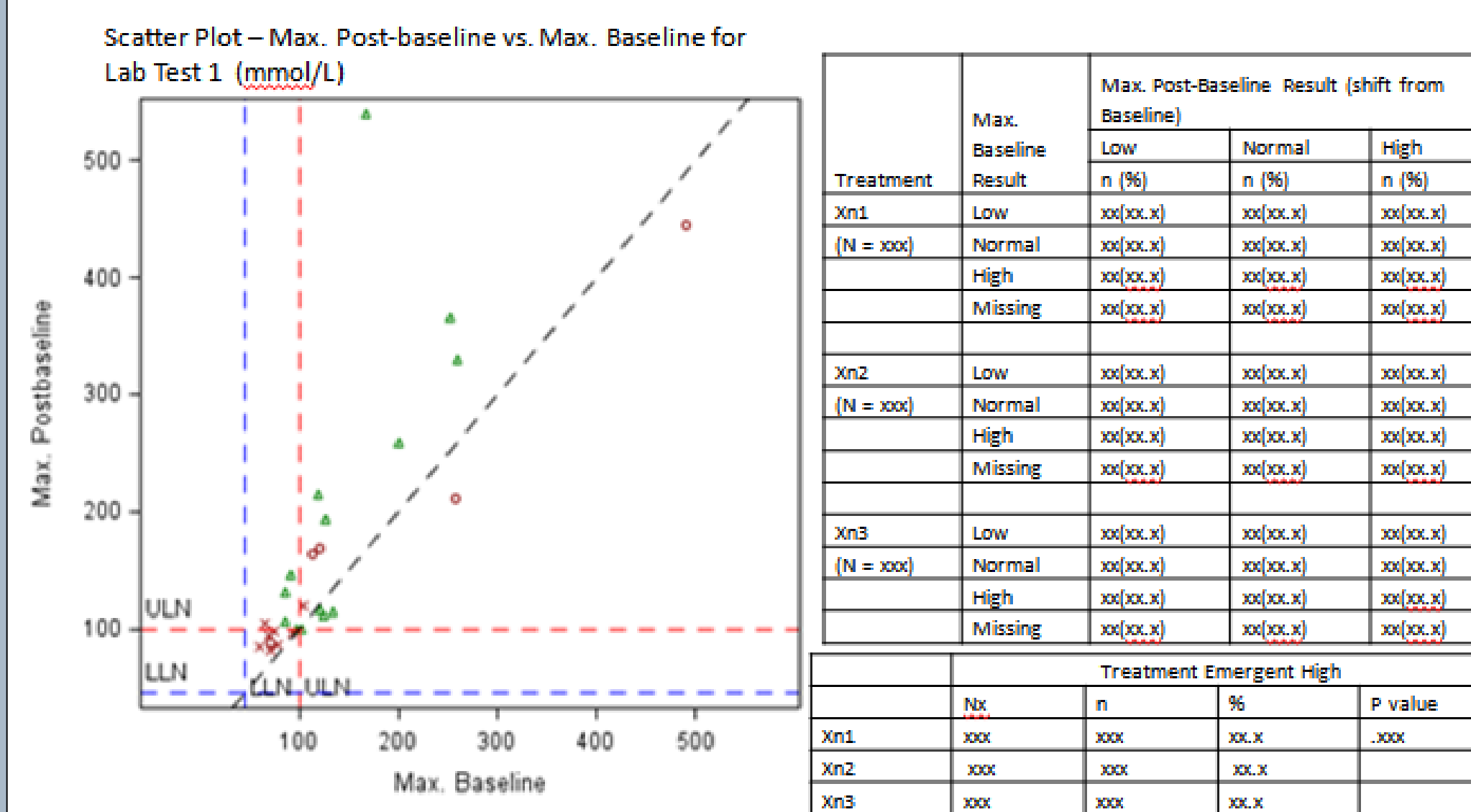
Examples of Discussed Topics

- General Considerations
 - Whether to report P-values and Confidence Intervals
 - Handling of
 - Measures collected in reflex manner*, repeated measures, unplanned measures, measurements post drug exposure
 - Baseline definition Multi-phase Clinical Trials
- Laboratory Analyte Measurements
 - Handling of central versus local laboratories
 - Choices of lab reference limits

Tables and Figures



Recommended for Quantitative Measures



Scatter plot: includes subjects with both a baseline and a post-baseline measure. Reference limits apply to most of the patients are used in the plot. N=number of subjects with at least one post-baseline measure; Nx=number of subjects with maximum baseline either normal or low and have at least one post-baseline measure. Summary tables used the reference limits applied to individual patients. P value is from the Fisher's Exact test. Reference limits: set 1 (Male, Age 18-65, LLN= xxx mmol/L/ ULN= xxx mmol/L) set 2 (Female, Age 18-65, LLN= xxx mmol/L/ ULN= xxx mmol/L).

- Outliers/shifts analysis for numeric safety measures
 - Labs, ECGs and Vital Signs
- Two pages per laboratory analyte
 - One for Max. baseline vs. Max. post-baseline (show on the left)
 - Another identical one for Min. baseline vs. Min. post-baseline

Three panels display:

- Scatter plot
 - Shows patient level information
 - Allows quick browsing through a large amount of information
- Shift table
 - Shows useful summary level statistics
- Treatment emergent high/low table
 - Shows concise summary level statistics
 - Allows for easy assessment of treatment difference

Traditional Tabulate Display

Treatment-Emergent Abnormal at Any Time Post Baseline – xxx Measures					
Laboratory Test	Abnormality Direction	Treatment	N	n (%)	P value*
Lab test 1	Low	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
	High	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
Lab test 2	Low	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
	High	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
Lab test 3	Low	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
	High	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
Lab test n	Low	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	
	High	Treatment A	xxx	xx (xx.x)	.xxx
		Treatment B	xxx	xx (xx.x)	

Abbreviations: N = number of subjects with a normal baseline and at least one post-baseline measure
n = number of subjects with an abnormal post-baseline result.
* – P values are from Fisher's Exact test.

- Lack of patient level information
 - Lack of patient baseline
 - Lack of magnitude of change from baseline

Lab Test Name					
Shifts from Baseline to Last Post-Baseline Result					
Treatment	Baseline Result	Post-Baseline Result			
		Low n (%)	Normal n (%)	High n (%)	Total n (%)
Comparator (N = xxx)	Low	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Normal	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	High	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Total	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
All LY (N = xxx)	Low	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Normal	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	High	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)
	Total	xx(xx.x)	xx(xx.x)	xx(xx.x)	xx(xx.x)

Abbreviations: N = number of subjects with a baseline and post-baseline result; n = number of subjects in category;

- Lack of information on patient level information
 - Lack of magnitude of shift
- Difficult to assess overall treatment difference
 - Very popular, however, users of the shift tables tend to count and create grouped percentages manually for those shifting to high from low/normal (or low from normal/high).



Recommended for Qualitative Measures

Table 7.1 Treatment-Emergent Abnormal Summary for Qualitative Safety Measures – Individual Study

Laboratory Test (unit)	Abnormality Direction	Treatment	N	n (%)	P value*
Lab Test 1	Abnormal	Control	xxx	xx (xx.x)	.xxx
		Treated	xxx	xx (xx.x)	
Lab Test 2	Abnormal	Control	xxx	xx (xx.x)	.xxx
		Treated	xxx	xx (xx.x)	
Lab Test n	Abnormal	Control	xxx	xx (xx.x)	.xxx
		Treated	xxx	xx (xx.x)	

Abbreviations: N = number of subjects with a normal baseline and at least one post-baseline measure, n = number of subjects with an abnormal post-baseline result.
* – P values are from Fisher's Exact test.

- One report for multiple Lab tests
- Outliers/shifts analysis for subjective lab measures

Why Outlier/Shift Analyses?

Reviewer Guidance

Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

February 2005
Good Review Practices

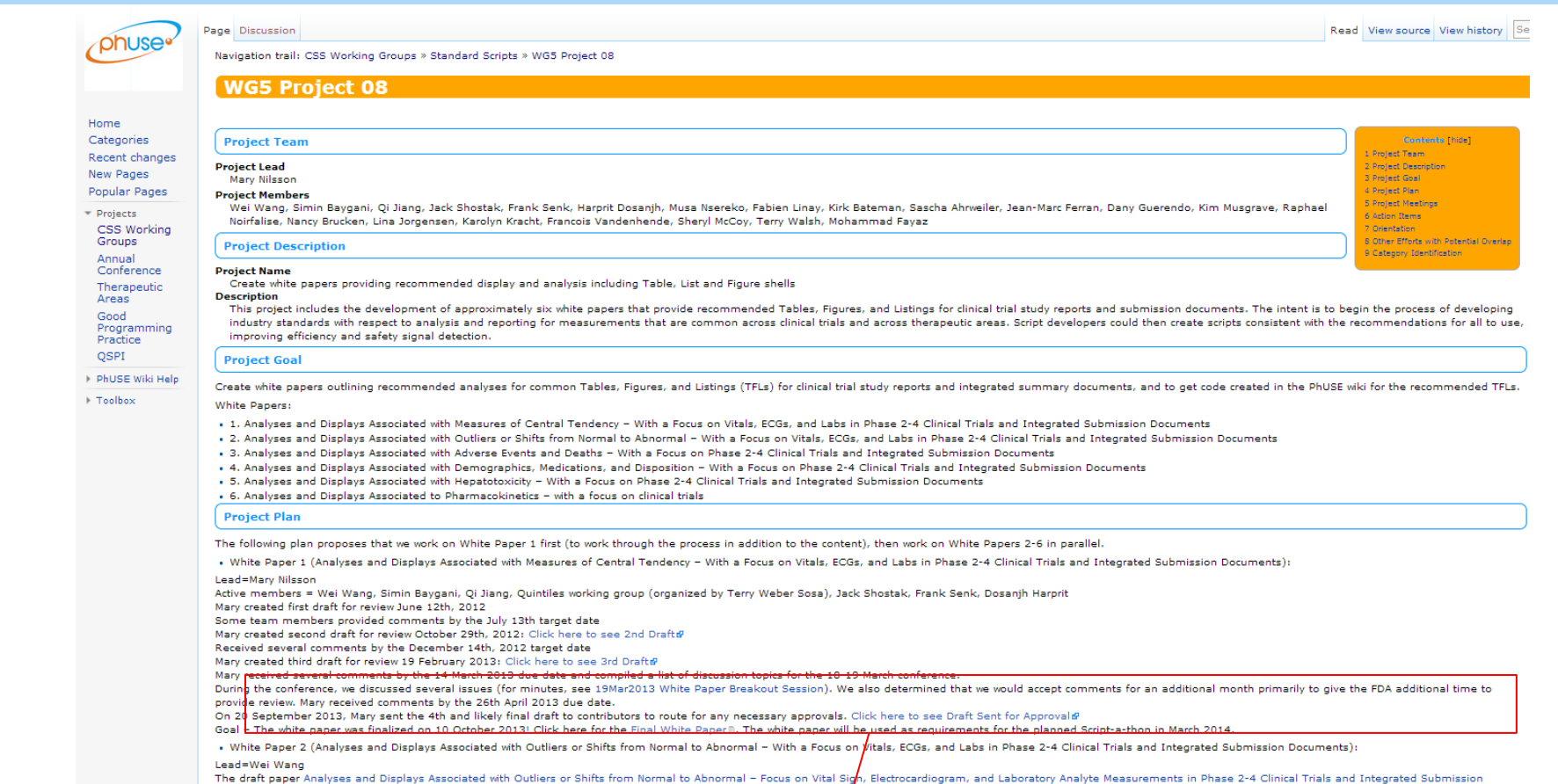
For Labs, ECG and Vital Signs, while at times a potentially important effect may be revealed only in analyses looking at differences in mean change from baseline:

'marked outliers are typically of greatest interest from a safety standpoint'

'The review should focus on patients whose laboratory values deviate substantially from the reference range.'

Want to Review the White Paper?

Visit PhUSE wiki at
http://www.phusewiki.org/wiki/index.php?title=WG5_Project_08



- White Paper 2 (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 Submission Documents):

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The draft paper Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal – Focus on Vitals, ECGs, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents is available for review by 28 February 2014. Review online: [Agilewords](#)

CONCLUSION

- Draft 1 of the white paper is currently under review.
- We are collecting feedback
- We also included in the white paper other displays that have been considered.
- This white paper provides guidance and foundation for the work in the Script-athon.