



**Analyses and Displays
Associated with Laboratory
Analyte Measurements in
Phase 2-4 Clinical Trials
and Integrated Submission
Documents – Update to
Recommendations**

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Revision History

Version	Date	Summary
1.0	2022-Jun-16	This is the first version specifically for laboratory analyte measurements. Two previous white papers (PHUSE 2013, PHUSE 2015) included recommendations for laboratory analyte measurements and are precursors to this white paper, but this white paper does not supersede these previous white papers.



1. Overview: Purpose of this document

This white paper provides updated recommendations for tables, figures, and listings (TFLs) used to analyze and display laboratory measurement data, with a focus on Phase 2-4 clinical trials and integrated summary documents. Two previous white papers containing recommendations for laboratory measurements were published by the PHUSE Analysis and Display white papers project team (PHUSE 2013, PHUSE 2015). The Analyses and Displays for Laboratory Data project team has gathered shared learning and has recommendations to improve the TFLs. Discussion topics (e.g., central vs. local laboratories) described in the previous white papers will remain foundational for this white paper and not reiterated in this white paper. Thus, we recommend users refer to all 3 white papers for useful information on laboratory analyses and displays.

As noted in the two previous white papers containing recommendations for analyses and displays for laboratory data (PHUSE 2013, PHUSE 2015) and additional analysis-related white papers (PHUSE 2017, PHUSE 2018, PHUSE 2021), the development and maintenance of standard TFLs and associated analyses will lead to improved and harmonized product lifecycle management across therapeutic areas by ensuring that reviewers receive clinically relevant and meaningful analyses of safety for benefit-risk assessment. While this white paper reflects recommendations that would lead to more consistent TFLs, the recommendations should not be interpreted as “required” by any regulatory agency.

2. Scope

This white paper is intended to provide advice to sponsors who are developing the analysis plan for Phase 2-4 clinical trials and integrated summary documents, or other documents in which analysis of laboratory measurements are of interest. The advice pertains to analyses that are generally relevant across all therapeutic areas for routine safety displays (tables and figures) and are likely to be included in a study report or integrated summary document.

The focus of this white paper is on study level Phase 2-4 controlled clinical trials and integrated analysis for regulatory submissions. However, some of the content may apply to Phase 1 studies, single-arm studies, ongoing aggregate safety evaluations, or other types of medical research such as observational studies. Similarly, this white paper discusses mainly laboratory data, but the suggested updates may also apply to vital signs and ECGs.

Detailed variable specifications for TFLs or dataset development are out of scope.

The following are also out of scope for this white paper, but are planned for future deliverables:

- *Recommendations for laboratory-related safety topics of interest:* We use safety topics of interest as a catch-all term that includes identified or potential risks that need to be further characterized, potential toxicities that all products should consider (e.g. laboratory measures that pertain to hepatic safety), potential findings based on drug class, or topics anticipated to be requested by a regulatory agency for any reason. A laboratory analyte measurement may become of special interest based on findings from the routine analyses, such as described in this white paper. Additional and/or different tables and figures might be warranted for these analytes, and a future deliverable with these recommendations is planned.
- *Updates to laboratory-related discussion topics:* In PHUSE 2013 and PHUSE 2015, several topics were discussed that continue to be relevant (e.g., central versus local labs, reference limits). Updates to these discussion topics based on shared learning is planned. In the meantime, we encourage referring to previous white papers for a greater understanding of multiple topics associated with analyzing and displaying data.
- *Methods of analyses when the observation time is different between treatment groups:* The recommended routine analyses generally assume relatively equal observation time between treatment groups, which is usually the case for most short-term clinical trials. When observation time is substantially different between treatment groups (e.g., when participants in one treatment arm discontinue at a greater rate than another treatment arm), different methods are required. We plan to provide recommendations for this situation in the future.
- *Interactive displays for laboratory analyte measurements:* We encourage broad use of interactive capabilities for safety review. Future deliverables and/or collaboration with other groups (e.g., Interactive Safety Graphics task force within the DIA-ASA Interdisciplinary Safety Evaluation working group) to facilitate implementation of interactive capabilities is planned.

3. Definitions

Acronyms and Abbreviations

Term	Definition
ADaM	Analysis Data Model
AE	adverse event
AESI	adverse event of special interest
ADR	adverse drug reaction
ALT	alanine aminotransferase
ASA	American Statistical Association
AST	aspartate aminotransferase
CDASH	Clinical Data Acquisition Standards Harmonization
CI	confidence interval
CSR	clinical study report
CSS	Computational Science Symposium
DIA	Drug Information Association
ECG	Electrocardiogram
FDA	Food and Drug Administration
ICH	International Conference on Harmonization
IQR	interquartile range
LLN	lower limit of normal
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
SDTM	Study Data Tabulation Model
SI	Système International
STD	standard deviation
TFL	tables, figures, and listings
TRT	Treatment
ULN	upper limit of normal

4. Problem Statement

Industry standards for data collection and storage have evolved over time: Clinical Data Acquisition Standards Harmonization (CDASH), observed data (SDTM), and analysis datasets (ADaM). However, creating industry standards for analyses and displays has only started recently (e.g., PHUSE 2013, PHUSE 2015, PHUSE 2017, PHUSE 2018, PHUSE 2021). Crowd-sourcing standardization efforts, instead of each organization maintaining their own standards, should lead to more optimal and consistent displays for medical reviewers, health authorities, ethics committees, and drug development teams. While individual organizations with mature standardization in place may be hesitant to change, the idea is that, over time, the overall review of safety data will be improved by implementing recommendations developed through collaborations. Using the recommendations in this white paper, along with other deliverables providing cross-collaborative recommendations, should lead to more effective and clear communication for all stakeholders.

5. Background

The PHUSE Computational Science Collaboration is an initiative involving PHUSE, the FDA, and industry that identifies computational science priorities that could be addressed by collaboration, crowd sourcing, and innovation. Several working groups have been created to address many of these challenges. The working group titled “Safety Analytics” has led the development of this white paper.

Members of the Analyses and Displays for Laboratory Data project team shared their learning when drafting this white paper. Contributors to this white paper included industry statisticians, industry physicians, FDA clinical reviewers, and a clinical pathologist with laboratory medicine specialty. The white paper was then posted in the PHUSE environment for public comments.

6. Recommended Tables and Figures

6.1 Individual Studies

Throughout this section, recommended displays for individual studies are provided. The displays show examples in which there are 2 treatment arms, low dose and high dose, and a placebo arm, and can be modified as needed to fit different scenarios. The displays in this white paper do not include headers/footers with the program name, output name, date, etc. Although not included in the example displays, their inclusion is recommended as a general practice. See the “General Output Tips and Considerations” PHUSE white paper (PHUSE 2020).

Figure 6.1 is a three-panel display showing laboratory measures at each time point. The top part of the display is a box plot of the observed values at each visit. The box plot includes the mean (white dots) and median (horizontal bar in the box) and the 25th and 75th percentile as the edges of the box, and the whiskers are the 5th and 95th percentiles. There are symbols of individual measures overlaid on top of the box plot. The color of the symbol indicates if the measure is above (red) or below (blue) the reference limit. The limits can vary across age, gender, etc. The same value can be a “high”/ “low” value for one participant but is a “normal” for another participant. Therefore, in Figure 6.1, some gray symbols are higher than the red symbols.

Below the box plot, there are three lines of text showing the number of observations available for each of the time points, and the numbers of observations that are above or below the lab reference limits. The colors in the text correspond to the colors in the graph and represent the different treatment arms.

The bottom part of the display is a line plot showing the average of measures at each visit with 95% confidence intervals (CIs).

The following table summarizes the changes between the previous recommendations and the new recommendations, with rationale:

Current Recommendation (2022)	Previous Recommendation (2013/2015)	Rationale for Change
Whiskers in the box plot are the 5th and 95th percentiles	Whiskers in the box plot are the max/min values within an invisible fence that is defined by 1.5 times of the interquartile ranges above and below the edges of the box	Easier to understand and interpret The “invisible fence” to define statistics-based outliers is difficult to interpret and can cause a lot of confusion for clinical reviewers. The statistical outliers are not always clinically meaningful. Distinguishing statistical outliers from the abnormal lab findings was not critical.
Include line plot with group average over time below the box plot	Not included	Easier to see group average over time across different treatments
The summary table below the box plot includes N, #highs, #lows	The summary table below the box plot includes N, min, median, max, mean, standard deviation at each time point*	Accommodates more time points on one page The data included in the summary table is flexible. Excluding data that takes a lot of column space (e.g., mean) allows more time points on one page. Keeping the rows to a minimum allows the box plot and line plot to stay close together. Including N is strongly recommended. However, #highs and #lows can be excluded, or other summary statistics can be included instead.

* The use of a detailed summary table recommended in the 2013 white paper often limited the number of time points included on a page. Keeping as many time points on a page is important for the overall purpose of the display. Creating a table with the summary statistics (e.g. mean, std, min, max) in text may still be needed as a source but does not necessarily need to be included in the Clinical Study Report (CSR).

Figure 6.2 is very similar to Figure 6.1 but shows change over time. For changes, there are no established reference limits. Therefore, there aren't “high” or “low” values indicated by color in the top panel. Similarly, there are no lines for number of “high” values and number of “low” values.

We consider both observed values and changes from baseline box plots useful. Of note, it is important to understand any imbalances in baseline labs when interpreting changes from baseline.

The following summarizes the changes between the previous recommendations and the new recommendations, with rationale:

- The changes and rationale described above for Figure 6.1 are also applicable to Figure 6.2.
- We recommend removing change from baseline to last observation from the box plot of change values. As

described in PHUSE 2019 [2019 CSS Workshop], change from baseline to last observation has limited value in signal detection. We now recommend its exclusion from individual study displays and integrated summaries for simplification. Change from baseline to last observation can be added but interpreted with caution. As noted in the 2019 CSS Workshop, group-level summaries are very unreliable for any transient versus persistent assessments.

For displaying shift from baseline to post baseline, we recommend Figure 6.3 (maximum values) and Figure 6.4 (minimum values). In Figure 6.3, the scatter plot shows, for each participant, the maximum measure during baseline versus the maximum measure during post baseline. Results from participants with a maximum baseline measure that is below ULN and a maximum post baseline measure above ULN are displayed with a star symbol to distinguish them from the other participants. In Figure 6.4, the scatter plot is similar but with minimum values.

The following summarizes the changes between the previous recommendations and the new recommendations, with rationale:

Current Recommendation (2022)	Previous Recommendation (2013/2015)	Rationale for Change
Separate panels of scatter plots are created for the different treatment groups with x and y axis in the same scale	One scatter plot with different symbols and colors for treatment groups	Most clinicians find it easier to review data when plots are side by side for different treatment arms.
There are no reference lines for ULN and LLN. Different symbols and shapes are used to show those patients who shift from normal/low (or normal/high) baseline to high (or low) values at post baseline.	There are reference lines for ULN and LLN; the ULN and LLN that apply to most of the analysis population are used.	ULN and LLN reference lines removed because they vary across demographics (e.g., gender and age group); sometimes there is large variability.

Table 6.1 is recommended for displaying the percentage of participants shifting from low/normal to high and normal/high to low. The table shows summary statistics for the number of patients falling into each of the shift categories and the comparison metrics, including 95% confidence interval for each pair of treatments. Related lab analytes are grouped together to help clinical reviewers to review the related labs together.

The following summarizes the changes between the previous recommendations and the new recommendations, with rationale:

Current Recommendation (2022)	Previous Recommendation (2013/2015)	Rationale for Change
One table includes all pertinent laboratory analytes. The lab analytes are grouped by the types of analyte, such as metabolic, renal, etc.	Each laboratory analyte has two shift tables: shift from normal/low to high; shift from normal/high to low. This table and the matrix table below are presented along with the scatter plot as the complete set of outlier/shift analysis.	With the previous recommendation, the idea was to have all data for an analyte displayed together. However, feedback has indicated some difficulty in implementation. Having all lab analytes summarized in one table with related analytes grouped together makes it easier for clinicians to go through related labs together. The scatter plot is sometimes implemented through an interactive package, making a stand-alone table for shifts to high/low more practical.
No matrix table	The matrix table of baseline categories (low, normal, high, missing) versus post baseline (low, normal, high, missing).	The scatter plot in Figure 6.3 provides similar, but more detailed, information.

Some laboratory analyte measurements are collected in a qualitative manner that is usually binary (e.g., Elliptocytes: normal/abnormal) or ordinal (e.g., Spherocytes: 0 [imply by lack of reporting], +, ++, +++, +++++). Some analytes have a numeric value when present but are better treated as qualitative data (e.g., atypical lymphocytes, a type of abnormal white blood cell seen with some viral infections, should be treated as present/not present). For these laboratory measures, a table similar to Table 6.1 is recommended. Instead of categories for shift from baseline normal/low to post baseline high and shift from baseline normal/high to post baseline low for each analyte, we only have baseline normal to post baseline abnormal. This is consistent with the recommendation we gave for qualitative lab analysis in the previous white paper.

For those patients who do not have a baseline measure for a lab analyte, we need a way for clinical reviewers to review for any abnormal post baseline findings. This is something not covered by the scatter plots and the summary table for the outlier and shift analysis. We recommend the listing display shown in Listing 6.1. This listing display includes all of the post baseline measures for those patients who do not have a baseline measure for a lab analyte as long as that patient has at least one abnormal measure for that analyte.

Figure 6.1. Laboratory Analysis – Box plot of Observed Values Over Time



** Box shows median, interquartile range (IQR, edge of the bar), 5% & 95% (ends of the whisker) and mean (white dot).

Figure 6.2. Laboratory Analysis – Box plot of Changes from Baseline Over Time



** Box shows median, interquartile range (IQR, edge of the bar), 5% & 95% (ends of the whisker) and mean (white dot).

Figure 6.3 Scatter plot of Maximum Baseline versus Maximum Post baseline – Lab xxxx (unit)

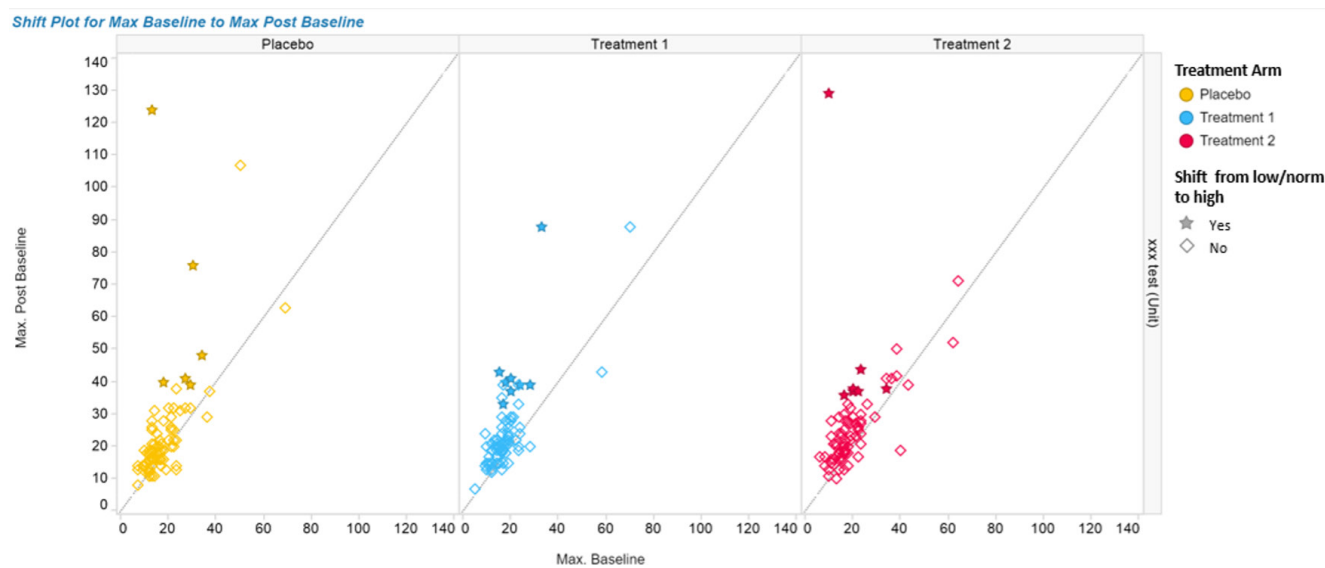


Figure 6.4 Scatter plot of Minimum Baseline versus Minimum Post Baseline– Lab xxxx (unit)

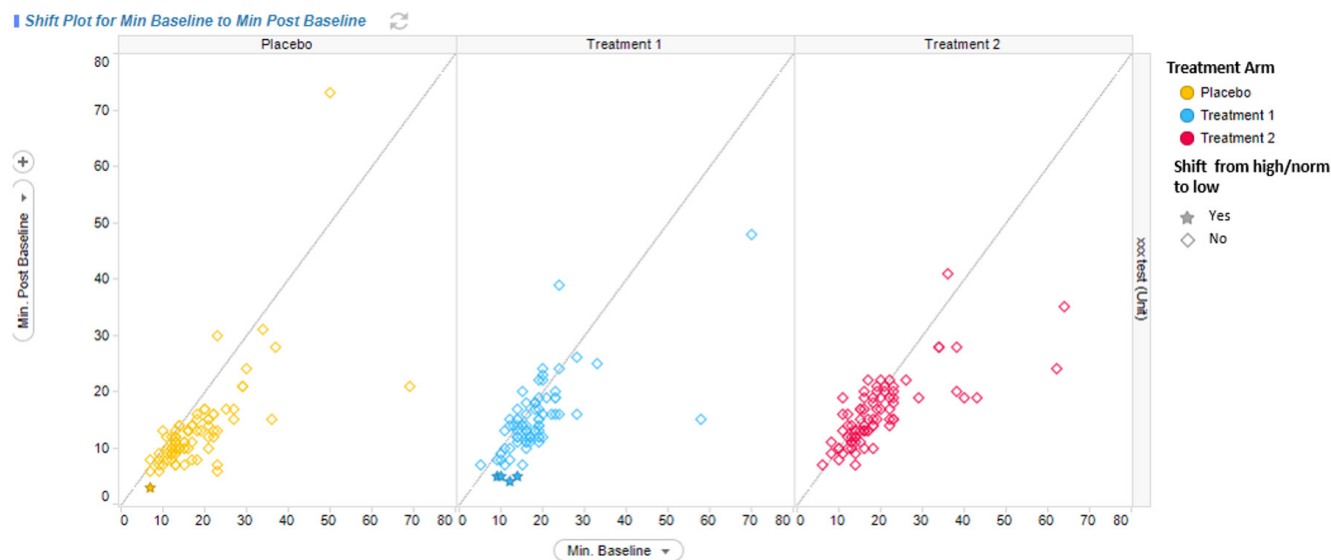


Table 6.1. Shift to High/Low – Laboratory Analysis

Metabolic labs:

Lab Analyte	Baseline	Post Baseline	PL n, N (%)	T1 n, N (%)	T2 n, N (%)	T1 & T2 n, N (%)	Comparison Metric ^a T1-PL (95% CI)	Comparison Metric ^a T2-PL (95% CI)	Comparison Metric ^a T1&T2-PL (95% CI)
Cholesterol	Low/ Norm	High	xx, xxx (xx.x)	xx, xxx (xx.x)	xx,xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	High/ Norm	Low	xx, xxx (xx.x)	xx, xxx (xx.x)	xx,xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
LDL	Low/ Norm	High	xx, xxx (xx.x)	xx, xxx (xx.x)	xx, xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Renal labs:

Lab Analyte	Baseline	Post Baseline	PL n, N (%)	T1 n, N (%)	T2 n, N (%)	T1 & T2 n, N (%)	Comparison Metric ^a T1-PL (95% CI)	Comparison Metric ^a T2-PL (95% CI)	Comparison Metric ^a T1&T2-PL (95% CI)
Urea Nitrogen	Low/ Norm	High	xx, xxx (xx.x)	xx, xxx (xx.x)	xx,xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
	High/ Norm	Low	xx, xxx (xx.x)	xx, xxx (xx.x)	xx,xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Serum Creatinine	Low/ Norm	High	xx, xxx (xx.x)	xx, xxx (xx.x)	xx, xxx (xx.x)	xx, xxx (xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Footnotes:

N=number of patients meeting baseline criteria and with at least one post baseline measures; n=number of patients fulfill both baseline and post baseline criteria. Percentages are calculated relative to the treatment group N;
 Low:<LLN; Norm=Normal (>=LLN and <=ULN); High:>ULN
 a[insert comparison metric and the relevant method].

Listing 6.1 Listing of Lab Measures Over Time for Subjects without Baseline Measures and at >=1 Abnormal Post Baseline Findings

Subject ID	Lab test name (units)	Visit	Actual Treatment	Study Day*	LLN,ULN	Value	Normality flag
xxx-xx-xxxx-xxx-xxxxx	Lab test 1 (xxx)	3.00	Treatment n	xxx	xxx,xxx	xxx.x	N
		4.00	Treatment n	xxx	xxx,xxx	xxx.x	N
		4.01	Treatment n	xxx	xxx,xxx	xxx.x	N
		5.00	Treatment n	xxx	xxx,xxx	xxx.x	N
		6.00	Treatment n	xxx	xxx,xxx	xxx.x	L
		7.00	Treatment n	xxx	xxx,xxx	xxx.x	N
xxx-xx-xxxx-xxx-xxxxx	Lab test 3 (xxx)	3.00	Treatment n	xxx	xxx,xxx	xxx.x	N
		3.01	Treatment n	xxx	xxx,xxx	xxx.x	H
		3.02	Treatment n	xxx	xxx,xxx	xxx.x	H

*Study Day derived relative to start date of study treatment

6.2 Integrated Summaries

Throughout this section, recommended displays for integrated analyses are provided. The displays show examples in which there is a treated arm and a placebo arm, but can be modified as needed under different scenarios. The displays in this white paper do not include headers/footers with the program name, output name, date, etc. Although not included in the example displays, their inclusion is recommended as a general practice. See the PHUSE white paper titled “General Output Tips and Considerations” (PHUSE 2020). During the review of integrated analysis, we recommend that the clinical review also examine study level results since both form the complete signal detection package.

Table 6.2. is a summary table for the minimum and maximum measures during baseline and during post baseline, as well as the changes between the baseline and post baseline. The summary statistics include mean and standard deviation. In addition, treatment comparison metrics (adjusted for study effect) with 95% confidence interval are also reported. In the table shell, change was used as outcome measures in the model. Another alternative is to use minimum or maximum postbaseline instead of change. Related lab analytes are grouped together to aide in reviewing the related lab values together. As noted in Section 6.1, box plots and line plots over time are recommended for individual studies as the central tendency approach, whereas a focus on minimum and maximum summaries are recommended for integrated summaries. If the visit schedule is consistent across studies within the integration, box plots can be considered for integrated summaries but additional statistics may need to be added to address potential misinterpretation (PHUSE 2013). Similarly, the summary table of minimum and maximum values and associated changes can be created for individual studies. However, in order to right-size the number of displays created, including figures of data over time for individual studies and minimum/maximum tables for integrated summaries provides a complementary package of safety for general laboratory assessment.

The following summarizes the changes between the previous recommendations and the new recommendations, with rationale:

Current Recommendation (2022)	Previous Recommendation (2013/2015)	Rationale for Change
One table includes all pertinent laboratory analytes. The lab analytes are grouped by the types of analyte, such as Metabolic, Renal, etc.	Each laboratory analyte has four sets of box plots displays shows the minimum to maximum, baseline and post baseline measures and changes. The box plots show individual study data first and then pooled result.	Since we have box plots for individual studies, the integrated box plots do not add much more value than the summary table and in certain situations provide a confounded view. The summary table is easy to review and serves the purpose of identifying at the integrated level any imbalance in the group average for the changes from min/ max baseline to min/ max post baseline.

For shifting from low/normal to high and normal/high to low analysis we recommended a single table display (see Table 6.3).

The following summarizes the changes between the previous recommendations and the new recommendations, with rationale:

Current Recommendation (2022)	Previous Recommendation (2013/2015)	Rationale for Change
One table includes all pertinent laboratory analytes. The lab analytes are grouped by the types of analyte, such as Metabolic, Renal, etc.	Each laboratory analyte has two sets of displays for: <ul style="list-style-type: none"> • Shift from normal/ low at baseline to high post baseline • Shift from normal/ high at baseline to low post baseline Each set has two sections: <ul style="list-style-type: none"> • Scatter plot for shift by study and integrated • Table for the shift 	We already have a scatter plot for shift in the individual study package. We feel having a crude pooled scatter plot for shift does not add a lot of value and in certain situations provide a confounded view. Therefore, we do not recommend them in the integrated analysis. The summary table including all of the lab analytes is easy to review and serves the purpose of identifying any imbalance at integrated level.

For laboratory measures that are collected qualitatively, a table similar to Table 6.3 is recommended. Instead of having categories for shift from baseline normal/low to post baseline high and shift from baseline normal/high to post baseline low for each lab analyte, we only have baseline normal to post baseline abnormal. This is consistent with the recommendation we gave to qualitative lab analysis in the previous white paper.

Table 6.2. Summary of Min and Max Measures at Baseline and Post Baseline and the Changes

Metabolic labs:

		PL N=xxx	TRT N=xxx	
Lab Analyte		Mean (SD)	Mean (SD)	Lsmeans Difference ^a TRT-PL (95% CI)
Cholesterol (mmol/dl)	n	xxx	xxx	
	Max.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Max.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
	Min.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Min.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
LDL (mmol/dl)	n	xxx	xxx	
	Max.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Max.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
	Min.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Min.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)

Renal labs:

		PL N=xxx	TRT N=xxx	
Lab Analyte		Mean (SD)	Mean (SD)	Lsmeans Difference ^a TRT-PL (95% CI)
Urea Nitrogen (mmol/dl)	n	xxx	xxx	
	Max.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Max.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
	Min.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Min.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
Creatinine (mmol/dl)	n	xxx	xxx	
	Max.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Max.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
	Min.Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Min.Post Baseline	xx.x (xx.x)	xx.x (xx.x)	
	Change	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x, xx.x)
			

Footnotes:

N= number of patients in the safety population; n=number of patients with at least one baseline and at least one post baseline measures; ^aLeast square Means difference and 95% CI is from an ANCOVA model change = baseline + treatment+ study.

Table 6.3. Shift to High/Low – Laboratory Analysis**Metabolic labs:**

Lab Analyte	Baseline	Post Baseline	PL n, N (%)[adj%]	TRT n, N (%)[adj%]	Comparison Metric ^a TRT-PL (95% CI)
Cholesterol	Low/Norm	High	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)
	High/Norm	Low	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)
LDL	Low/Norm	High	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)

Renal labs:

Lab Analyte	Baseline	Post Baseline	PL n, N (%)[adj%]	TRT n, N (%)[adj%]	Comparison Metric ^a TRT-PL (95% CI)
Urea Nitrogen	Low/Norm	High	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)
	High/Norm	Low	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)
Creatinine	Low/Norm	High	xx, xxx (xx.x)[xx.x]	xx, xxx (xx.x)[xx.x]	xx.x (xx.x, xx.x)

N=number of patients meeting baseline criteria and with at least one post baseline measures; n=number of patients fulfill both baseline and post baseline criteria. Percentages are calculated relative to the treatment group N; %=n/N; adj%=study size adjusted percent. Low:<LLN; Norm: Normal (>=LLN and <=ULN); High:>ULN

a:[insert comparison metric and the relevant method].

7. Example Language for Statistical Analysis Plans

7.1 Individual Studies

The planned analyses of laboratory analyte measurements are based on the recommendations provided in white papers produced by a PHUSE working group (available in the PHUSE Deliverables catalog). The white papers include justifications for the choices. Specifically, the following white papers pertain to laboratory analyte measurements:

- Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2 to 4 Clinical Trials and Integrated Submission Documents (PHUSE 2013)
- Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2 to 4 Clinical Trials and Integrated Summary Documents (PHUSE 2015).
- Analyses and Displays Associated with Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents – Update to Recommendations (PHUSE 2022)

Not all displays described in this plan will necessarily be included in the clinical study report. Not all displays will necessarily be created as a “static” display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display. Any display described in this plan and not provided would be available upon request.

Laboratory tests include all planned analytes as defined in the protocol, excluding those collected in a reflex manner (only collected under certain circumstances). ALT, AST, alkaline phosphatase, and total bilirubin will not be included in this analysis because they will be analyzed as described in the hepatotoxicity section.

Table 7.1 Tables and Figures Produced to Support Clinical Laboratory Evaluations for Individual Studies

Analysis Type	Analysis Details	Sample
Box plots for observed values by visit	<ul style="list-style-type: none"> Includes participants who have both a baseline and a post baseline measurement from a planned visit. Only planned measures will be included. Unplanned measurements will be excluded. Last baseline will be used. Original-scale data will be used. Both SI and conventional units will be provided in the axis within a single plot. Summary statistics (N, number of observations above the reference limit, and number of observations below the reference limit) will be included in a table below the box plot. A line plot showing the average of the measurements at each visit with 95% confidence intervals will be displayed below the summary statistics. <p>See also: <i>Figure 6.1 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Indiv. Studies – Controlled
Box plots for change from baseline values by visit	<ul style="list-style-type: none"> Includes participants who have both a baseline and a post baseline measurement from a planned visit. Only planned measures will be included. Unplanned measurements will be excluded. Last baseline will be used. Summary statistics (N) will be included in a table below the box plot. A line plot showing the average of the change in measurements at each visit with 95% confidence intervals will be displayed below the summary statistics. <p>See also: <i>Figure 6.2 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Indiv. Studies – Controlled
Scatter plots of baseline-by-maximum values and baseline-by-minimum values	<ul style="list-style-type: none"> Includes participants who have both a baseline and post baseline observation. Both planned and unplanned measurements will be included. Max vs Max : Maximum baseline versus maximum post baseline Values from participants with a maximum baseline measure that is below ULN and maximum post baseline measure above ULN will be displayed using a star symbol to distinguish them from the other participants. Min vs Min: Minimum baseline versus minimum post baseline (same as above, except with minimum values). <p>See also: <i>Figures 6.3 and 6.4 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Indiv. Studies – Controlled
Summary tables for shifts to high/low	<ul style="list-style-type: none"> Excludes analytes collected qualitatively. Normal/high to low: Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum post baseline result is low. <ul style="list-style-type: none"> Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 result during the treatment period. Normal/low to high: Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum post baseline result is high. <ul style="list-style-type: none"> Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period. A comparison metric and 95% confidence interval will be included for each pair of treatments. For laboratory analyte measurements collected qualitatively, a similar table of percentages will be created except for each lab analyte, shifts from baseline normal to post baseline abnormal will be displayed. <p>See also: <i>Table 6.1 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Indiv. Studies – Controlled Indiv. Studies – Uncontrolled
Listing of abnormal laboratory findings for participants without baseline measurements	<ul style="list-style-type: none"> For laboratory analyte measurements collected qualitatively, a listing of measurements over time will be created for participants missing all baseline measurements and having at least one abnormal post baseline measurement. The listing will include patient ID, treatment group, laboratory collection date, analyte name, and analyte finding. <p>See also: <i>Listing 6.1 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Indiv. Studies – Enrolled Population

Abbreviations: Controlled = analysis set with a comparator; Indiv. = individual; Max = maximum; Min = minimum; Uncontrolled = analysis set without a comparator.

7.2 Integrated Summaries

The planned analyses of laboratory analyte measurements are based on the recommendations provided in white papers produced by a PHUSE working group (available in the PHUSE Deliverables catalog). The white papers include justifications for the choices. Specifically, the following white papers pertain to laboratory analyte measurements:

- Analyses and Displays Associated with Measures of Central Tendency – Focus on Vital Sign, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2 to 4 Clinical Trials and Integrated Submission Documents (PHUSE 2013)
- Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2 to 4 Clinical Trials and Integrated Summary Documents (PHUSE 2015).
- Analyses and Displays Associated with Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Submission Documents – Update to Recommendations (PHUSE 2022)

Not all displays described in this plan will necessarily be included in the Summary of Clinical Safety. Not all displays will necessarily be created as a “static” display. Some may be incorporated into interactive display tools instead of or in addition to a static display. Any display described in this plan and not provided would be available upon request.

Laboratory tests include all planned analytes as defined in the protocol, excluding those collected in a reflex manner (only collected under certain circumstances). ALT, AST, alkaline phosphatase, and total bilirubin will not be included in this analysis because they will be analyzed as described in the hepatotoxicity section.

Table 7.2 Tables Produced to Support Clinical Laboratory Evaluations for Integrated Summaries

Analysis Type	Analysis Details ^w	Sample
Summary for maximum and minimum, observed and change values	<ul style="list-style-type: none"> • Includes participants who have both a baseline and a post baseline measurement. • A table for the minimum and maximum values during baseline and during post baseline, and well as changes between baseline and post baseline will be created. • The summary statistics include mean and standard deviation. • Treatment comparison metrics with 95% confidence interval based on ANCOVA model change = baseline + treatment+ study will also be provided. <p><i>See also: Table 6.2 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Integrated – Controlled
Summary tables for shifts to high/low	<ul style="list-style-type: none"> • Excludes analytes collected qualitatively. • Normal/high to low: Includes the number and percentage of participants by treatment whose minimum baseline result is normal or high and whose minimum post baseline result is low. <ul style="list-style-type: none"> ◦ Denominator equals participants whose minimum baseline result is normal or high and who have at least 1 result during the treatment period. • Normal/low to high: Includes the number and percentage of participants by treatment whose maximum baseline result is normal or low and whose maximum post baseline result is high. <ul style="list-style-type: none"> ◦ Denominator equals participants whose maximum baseline result is normal or low and who have at least 1 result during the treatment period. • A comparison metric (with adjustment for study effect) and 95% confidence interval will be included for each pair of treatments. • For laboratory analyte measurements collected qualitatively, a similar table of percentages will be created except for each lab analyte, shifts from baseline normal to post baseline abnormal will be displayed. <p><i>See also: Table 6.3 from the Analyses and Displays Associated with Laboratory Analyte Measurements – Update to Recommendations white paper (PHUSE 2022)</i></p>	Integrated – Controlled Integrated – Uncontrolled

Abbreviations: Controlled = analysis set with a comparator; Indiv. = individual; Max = maximum; Min = minimum; Uncontrolled = analysis set without a comparator.

8. Disclaimer

The opinions expressed in this document are those of the authors and should not be construed to represent the opinions of PHUSE members; respective companies/organizations or Regulator's views or policies. The content in this document should not be interpreted as a data standard and/or information required by Regulatory Authorities.

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11. References

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