Modification History:

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| --- | --- | --- | --- | --- |
| **Unique Identifier for this Version** | **Date of the Document Version** | **Author** | **Significant Changes from Previous Version** |  |
|  |
| 1 | 16-Jun-2017 | Mike Schembri |  |  |
|  | 28 June 2017 | Alan Hopkins | Adapted for R Functions |  |
|  | 25-July-2017 | Mike Schembri | Add Introduction, General Description |  |
|  | 8/21/2917 | Mike Schembri | Edits from 7/26 meeting |  |
|  | 08-Nov-2017 | Gustav Bernard | Updates with Andy and Nancy |  |

# Outliers or Shifts from Normal to Abnormal White Paper Requirements Specification

## Figure 11.1 Scatter Plot – Quantitative Safety Measures Assessing Low Value

## Introduction

#### Purpose

The purpose of this program is to produce the following scatter plot of minimum baseline vs minimum post-baseline value, as described in the white paper:

*Analyses and Displays Associated with Outliers or Shifts from Normal to Abnormal: Focus on Vital Signs, Electrocardiogram, and Laboratory Analyte Measurements in Phase 2-4 Clinical Trials and Integrated Summary Documents*

Figure 11.1 Scatterplot and Shift Summary for Quantitative Safety Measures Assessing Low Value: Individual Study

#### Scope

The macro will be run in SAS 9.4 TS Level 1M2 or higher.

#### Definitions

## General Description

#### Perspective

This will be one of several macros used to produce the displays described in the white paper.

#### Functions

This will produce one scatter plot of minimum baseline vs minimum post-baseline value, stratified by treatment arm, with a diagonal reference line for zero change, and vertical and horizontal reference lines for high/low ranges.

#### Assumptions and Dependencies

* ADaM BDS data structure is required
* Requires the PhUSE CS macro library:   
   <https://github.com/phuse-org/phuse-scripts/tree/master/whitepapers/utilities>
* User must ensure that SAS can find PhUSE CS macros in the SASAUTOS path.

## Specific Requirements

### SAS Script or R Function Specifications

#### Specific Output Requirements

* Basic script functionality (user options)
* ***data display features***
* Scatter plot, as described in [SAS/STAT 9.4 Graph Template Language: Reference (Scatterplot Statement)](https://support.sas.com/documentation/cdl/en/grstatgraph/69718/HTML/default/viewer.htm#p08qhdljvzthmnn1vkbule00ad6r.htm) or R ggplot function
* X-Axis: Minimum Baseline Value [min(AVAL) where Flag = Y or ABLFL = Y(if this presents the Minimum baseline value) ]
* Flag = Minimum Baseline Value per Subject per Test.
* Both Standard and Conventional Unit needs to be displayed.
* Variable with Conventional unit per test.
* Variable with Conversion Ration per test from SI to Conventional unit.
* Y-Axis: Minimum Post-Baseline Value [min(AVAL) where Flag = Y]
* Flag = Flag for Minimum Post Baseline Value per Subject per Test.
* Both Standard and Conventional Unit needs to be displayed.
* Variable with Conventional unit per test.
* Variable with Conversion Ration per test from SI to Conventional unit.
* Grouped by treatment [TRTP/TRTA/TRTPGy/TRTAGy]
* reference ranges - options to draw reference lines for various scenarios (based on values found in data [(ANRLO and ANRHI) or (AyLO and AyHI)]
* **uniform:** DEFAULT. If all reference range values are uniform for a set of measures, draw those uniform low/high reference range line.
* **narrow:** If the limits vary across the population , the limits that apply to the majority of the subjects are displayed in the scatter plot.
* **all:** Discouraged by white paper authors – draw all reference lines relevant to the set of measures.
* **none**
* **Manually specify numeric value(s):** draw exactly these specific reference lines (e.g., a zero (0) line for change from baseline boxplots.
* Diagonal reference line for no change from baseline to follow-up
* X and Y axis both use the same value range – AVAL
* ***User variability (arguments for R function)***
* location and name of each input data sets
* output location (user-specified path)
* parameterize core variables required for analysis & display:
* "Treatment name" which could be planned or actual [TRTP/TRTA/TRTPGy/TRTAGy]
* "Treatment number" used for display order of Treatment Names [TRTPN/TRTAN/TRTPGyN/TRTAGyN]
* Baseline visit value for AVISITN
* Follow-up visit value for AVISITN
* AVAL (measured outcome)
* ANRLO (lower limit of reference range)
* ANRHI (upper limit of reference range)
* AVISITN (Analysis Visit)
* Record set selection (Optional)
* Analysis Flags, e.g.:
* FASFL (full analysis set population flag)
* SAFFL (population flag)
* ANL01FL (analysis flag)
* Time point selection: ATPT
* Where statement criteria

#### General Output and Formatting Requirements

See the specification document *CS\_GeneralOutputandFormattingRequirements.docx.*

It is recommended that displays use unique plot symbols (or line patterns) for each data series so that they are interpretable by readers with color blindness.

### Usage Requirements

#### Required Input\*

##### Laboratory Domain

* Dataset: ADLBC or ADLBH or ADLBHY or ADLB
* Variables: STUDYID, USUBJID, FASFL/SAFFL/ANY OTHER POPULATION FLAG, [(TRTP and TRTPN) or (TRTA and TRTAN)], PARAM, PARAMCD, AVAL, [(ANRLO and ANRHI) or (AyLO and AyHI)], Flag variables to Identify Minimum Baseline and Post-Baseline observations.
* Three BDS approaches
* If Baseline for the study is the Minimum Baseline Value Then Flag will be ABLFL to identify Baseline Result.
* If Baseline for the study is different than the Minimum baseline value the:
* Create Separate ADLB file with Minimum Baseline Value as Baseline Definition Use ABLFL to identify baseline observation
* Create Separate rows in the ADLB file where BASETYPE = “MIN” for use of the additional Baseline Criteria, use BASETYPE = “MIN” and ABLFL = “Y” to identify baseline observation.
* Record selection
* Population Flag
* Flag = Minimum Baseline Value per Subject per Test.
* Flag = Flag for Minimum Post Baseline Value per Subject per Test.
* Subject will require to have both a Minimum Baseline and Post Baseline value.

##### Vital Signs Domain

* Dataset: ADVS
* Variables: STUDYID, USUBJID, FASFL/SAFFL/ANY OTHER POPULATION FLAG, [(TRTP and TRTPN) or (TRTA and TRTAN)], PARAM, PARAMCD, AVAL, [(ANRLO and ANRHI) or (AyLO and AyHI)], Flag variables to Identify Minimum Baseline and Post-Baseline observations.
* Three BDS approaches
* If Baseline for the study is the Minimum Baseline Value Then Flag will be ABLFL to identify Baseline Result.
* If Baseline for the study is different than the Minimum baseline value the:
* Create Separate ADVS file with Minimum Baseline Value as Baseline Definition Use ABLFL to identify baseline observation
* Create Separate rows in the ADVS file where BASETYPE = “MIN” for use of the additional Baseline Criteria, use BASETYPE = “MIN” and ABLFL = “Y” to identify baseline observation.
* Record selection
* Population Flag
* Flag = Minimum Baseline Value per Subject per Test.
* Flag = Flag for Minimum Post Baseline Value per Subject per Test.
* Subject will require to have both a Minimum Baseline and Post Baseline value.

##### ECG Domain

* Variables: STUDYID, USUBJID, FASFL/SAFFL/ANY OTHER POPULATION FLAG, [(TRTP and TRTPN) or (TRTA and TRTAN)], PARAM, PARAMCD, AVAL, [(ANRLO and ANRHI) or (AyLO and AyHI)], Flag variables to Identify Minimum Baseline and Post-Baseline observations.
* Three BDS approaches
* If Baseline for the study is the Minimum Baseline Value Then Flag will be ABLFL to identify Baseline Result.
* If Baseline for the study is different than the Minimum baseline value the:
* Create Separate ADEG file with Minimum Baseline Value as Baseline Definition Use ABLFL to identify baseline observation
* Create Separate rows in the ADEG file where BASETYPE = “MIN” for use of the additional Baseline Criteria, use BASETYPE = “MIN” and ABLFL = “Y” to identify baseline observation.
* Record selection
* Population Flag
* Flag = Minimum Baseline Value per Subject per Test.
* Flag = Flag for Minimum Post Baseline Value per Subject per Test.
* Subject will require to have both a Minimum Baseline and Post Baseline value.

\* Digits in red may be substituted for appropriate index (02, 03, etc).

### Test Data

* Data sets from <https://github.com/phuse-org/phuse-scripts/tree/master/data/adam/cdisc>
* Domain data
  + ADVS – Vital signs
  + ADLBC, ADLBH, ADLBHY, ADLB – Laboratory measures
  + ADEG – ECG measures

### Sample Output

**Scatterplot and Shift Summary for Quantitative Safety Measures Assessing Low Value: Individual Study**



### Reference Documents:

White paper: <http://www.phusewiki.org/wiki/images/4/48/CSS_WhitePaper_CentralTendency_v1.0.pdf>

Programming Guidelines: <http://www.phusewiki.org/wiki/index.php?title=WG5_P02_Programming_Guidelines>

For R:

Wickham, H. (2015) R Packages: Organize, Document, and Share Your Code. Sebastapol, CA: O’Rielly. or online at <http://r-pkgs.had.co.nz/>

Google R Style Guide. <https://google.github.io/styleguide/Rguide.xml>

CS\_General\_OutputandFormattingRequirements.docx: <https://github.com/phuse-org/phuse-scripts/blob/master/whitepapers/specification/CS_General_OutputandFormattingRequirements.docx>