

Interactive Data Visualization: A Tool for Common Clinical Study Figures and SAP Figure Shells

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ABSTRACT

Figures are essential and critical elements in clinical trial data analysis and reporting. We propose a tool for the interactive generation of mock-up biostatistical figures using Excel and SAS. An excel file holds sample preset data and figure attributes, such as title, axis labels, tick definitions, groups, group attributes, etc. Actual values of data or attributes could be modified following the samples. The SAS program code for each type of figure can be generated automatically from the Excel file utilizing Visual Basic for Application (VBA) scripts, thus producing the sample outputs. The figures produced by this tool could help statisticians choose the right type of figures for visualizing different data, tailor figure details, generate mock-up shells, and quickly generate additional figures for reporting/presentation purposes if needed. The SAS code generated in the designing stage could be shared with programmers to produce the figures for study reports later.

INTRODUCTION

In clinical study data reporting and analysis, figures are unique and essential in that they help visualize critical changes within a treatment group or comparisons among treatment groups easily. But usually, it is not as easy for statisticians to produce figure shells for the Statistical Analysis Plan (SAP). They first need to determine the types of figures to utilize for the best presentation of different data types and the details within the figures. Then the next challenge is to convey that information clearly in the figure shell. To accomplish the SAP figure shell task, a tool that can generate different types of figures quickly with easily adjustable attributes would be of great help. This paper will demonstrate a tool we developed for various common figure types in clinical trials.

USER INTERFACE AND WORKFLOW

As shown in Figure 1, this tool is based on Microsoft® Excel. Each type of figure utilizes two tabs: one for figure attributes (panel a) and another for data (panel b). Both are pre-filled with example data, and users can adjust the values according to their needs.

CreateSAS		GRPN	GRP	XAXIS	AVISIT	SUBJID	AVAL
Program Name	Line_plot.sas	1	Placebo	0	Visit0	subject1	69.58725952
		1	Placebo	1	Visit1	subject1	54.78350426
		1	Placebo	2	Visit2	subject1	94.00402323
		1	Placebo	3	Visit3	subject1	86.01699959
		1	Placebo	4	Visit4	subject1	32.25982649
		1	Placebo	5	Visit5	subject1	10.64659983
		1	Placebo	6	Visit6	subject1	33.35206467
		1	Placebo	7	Visit7	subject1	71.51830263
		1	Placebo	8	Visit8	subject1	68.99222199
		2	Active	0	Visit0	subject1	44.18230896
		2	Active	1	Visit1	subject1	39.02700043
		2	Active	2	Visit2	subject1	28.36096957
		2	Active	3	Visit3	subject1	57.06303083
		2	Active	4	Visit4	subject1	49.81380613
		1	Placebo	0	Visit0	subject2	28.63763025
		1	Placebo	1	Visit1	subject2	74.10678884
		2	Active	0	Visit0	subject2	17.74684439
		2	Active	1	Visit1	subject2	82.09512845
		2	Active	2	Visit2	subject2	84.25153311
		2	Active	3	Visit3	subject2	39.44259654
Title1	Figure 15.3.1.4	1	Placebo	0	Visit0	subject3	94.95361337
		1	Placebo	1	Visit1	subject3	65.25623591
		1	Placebo	2	Visit2	subject3	68.26368227
		1	Placebo	3	Visit3	subject3	31.02560933
		1	Placebo	4	Visit4	subject3	42.29118724
		1	Placebo	5	Visit5	subject3	27.7320462
		1	Placebo	6	Visit6	subject3	27.85536921
		1	Placebo	7	Visit7	subject3	94.57521177
		1	Placebo	8	Visit8	subject3	41.44087346
		1	Placebo	9	Visit9	subject3	18.44607918
Title2	Mean (± SE) of Liver Function Tests	1	Placebo	10	Visit10	subject3	23.57574898
		1	Placebo	11	Visit11	subject3	55.80207708
Title3	Safety Population	2	Active	0	Visit0	subject3	60.06465837
Title4	Parameter: Alanine Aminotransferase (U/L)						
xlabel	Study Visits						
ylabel	Alanine Aminotransferase (U/L)						
legendlabel	Treatment						
legendoption	location=inside haligh=left valign=bottom border=false						
Colors	blue red green						
Symbols	CircleFilled TriangleFilled Triangle						
xtick	(0 1 2 3 4 5 6 7 8 9 10 11)						
ytick	(10 20 30 40 50 60 70 80 90 100)						

a. Attributes Tab

b. Data Tab

Figure 1. User Interface

After setting the input, a simple click on the 'Create SAS' button on the top of the attributes tab will generate and store the SAS program for the corresponding figure at the same location as the tool under the program name specified in the excel. In our example shown In Figure 1, the output program name is Line_plot.sas.

The code generated contains three parts: a) attributes setup; b) data read-in (only partially shown for simplicity); c) post-processing and graph generation.

```
a. %let title1 = Figure 15.3.1.4;
%let title2 = Mean ( $\pm$  SE) of Liver Function Tests;
%let title3 = Safety Population;
%let title4 = Parameter: Alanine Aminotransferase (U/L);
%let xlabel = Study Visits;
%let ylabel = Alanine Aminotransferase (U/L);
%let legendlabel = Treatment;
%let legendoption = location=inside halign=left valign=bottom border=false;
%let colors = blue|red|green;
%let symbols = CircleFilled|TriangleFilled|Triangle;
%let xtick = (0 1 2 3 4 5 6 7 8 9 10 11);
%let ytick = (10 20 30 40 50 60 70 80 90 100);

b. data final;
length GRP $200.;
length AVISIT $200.;
length SUBJID $200.;
GRP=1; GRP="Placebo"; XAXIS=0; AVISIT="Visit0"; SUBJID="subject1"; AVAL=69.5872595231049; output;
GRP=1; GRP="Placebo"; XAXIS=1; AVISIT="Visit1"; SUBJID="subject1"; AVAL=54.7835042630322; output;
GRP=1; GRP="Placebo"; XAXIS=2; AVISIT="Visit2"; SUBJID="subject1"; AVAL=94.0040232324973; output;
GRP=1; GRP="Placebo"; XAXIS=3; AVISIT="Visit3"; SUBJID="subject1"; AVAL=86.0169995897449; output;

c. proc sort data = final; by grpn grp xaxis avisit; run;
proc univariate data = final noprint;
by grpn grp xaxis avisit;
var aval;
output out=final2 mean=yaxis stdmean=interval;
run;
data final3; set final2; yaxisl=yaxis-interval; yaxish=yaxis+interval; run;
proc sort data = final2(where=(grpn > .)) out = grps nodupkey; by grpn; run;
data _null_;
set grps end=eof;
call symput ('grps'||compress(put(_n_,best12.)), trim(put(grp,$100.)));
if eof then call symput ('tot_grp', compress(put(_n_, best12.)));
run;
%macro mcl;
proc template;
define statgraph LinePlot;
dynamic TITLE1 TITLE2 TITLE3 TITLE4 TITLE5;
beginninggraph / border=false designwidth=9in designheight=4.8in;
discreteattrmap name="grp" / ignorecase=true;
%do i = 1 %to &tot_grp.;
value "&grps&i.." / markerattrs=GraphData&i(color=%scan(&colors, &i,|) symbol=%scan(&symbols, &i,|) size=7)
lineattrs=GraphData&i(color=%scan(&colors, &i,|) fillattrs=(color=%scan(&colors, &i,|) textattrs=(color=%scan(&colors, &i,|)));
%end;
enddiscreteattrmap;
discreteattrvar attrvar=grp var=grp attrmap="grp";
entrytitle TITLE1; entrytitle TITLE2; entrytitle TITLE3; entrytitle TITLE4; entrytitle TITLE5;
layout overlay /
xaxisopts=(LABELATTRS=(SIZE=8pt) label="&xlabel." type=linear lineopts=(tickvaluelist=&xtick. tickvaluefitpolicy=rotate ))
yaxisopts=(LABELATTRS=(SIZE=8pt) label="&ylabel." lineopts=(tickvaluelist=&ytick. ));
seriesplot x=xaxis y=yaxis / group=grp name='a' includemissinggroup=false;
scatterplot x=xaxis y=yaxis / group=grp name='b' YerrorLower=yaxisl YerrorUpper=yaxish ;
MERGEDLEGEND 'a' 'b' / title="&legendlabel." down=2 &legendoption.;
endlayout;
endgraph;
end;
run;
%mend mcl; %mcl;
proc sgrender data=final3 template=LinePlot;
dynamic TITLE1=&title1 TITLE2=&title2 TITLE3=&title3 TITLE4=&title4;
run;
```

Figure 2. Excerpts of Output SAS Codes

The last step is simply submitting the SAS codes to generate the figure. In our example, the output line plot is shown in Figure 3.

Figure 15.3.1.4
Mean ($\pm$ SE) of Liver Function Tests
Safety Population
Parameter: Alanine Aminotransferase (U/L)

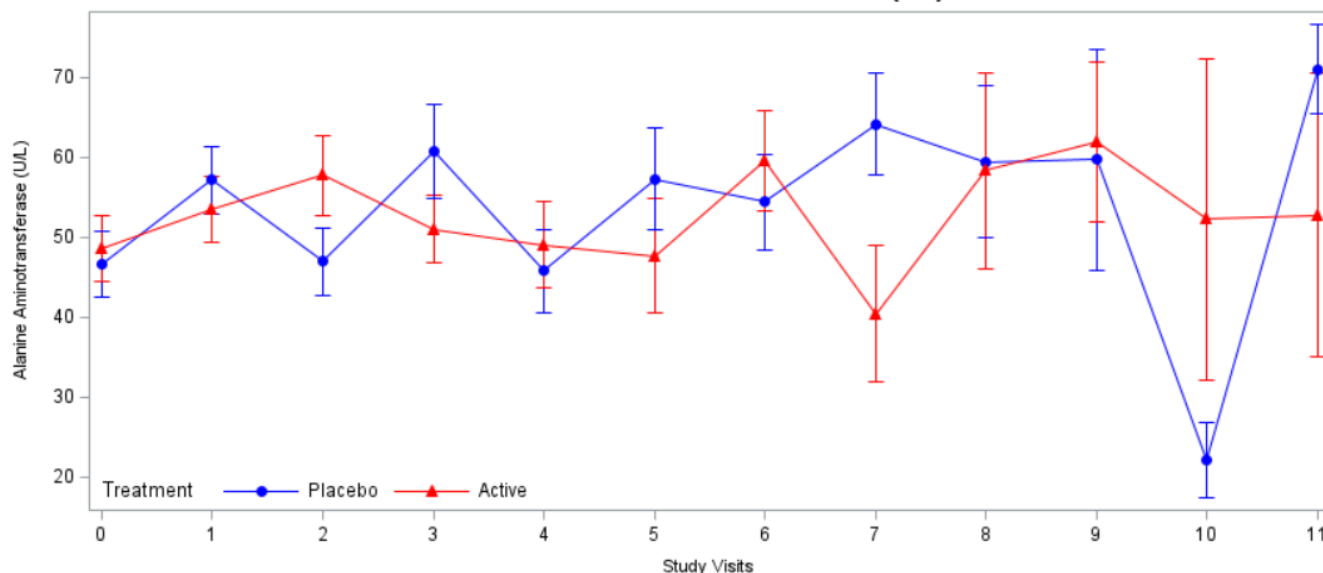


Figure 3. Line Plot Example

The straightforward process for the creation of sample figures by this tool is summarized in the flow chart below:

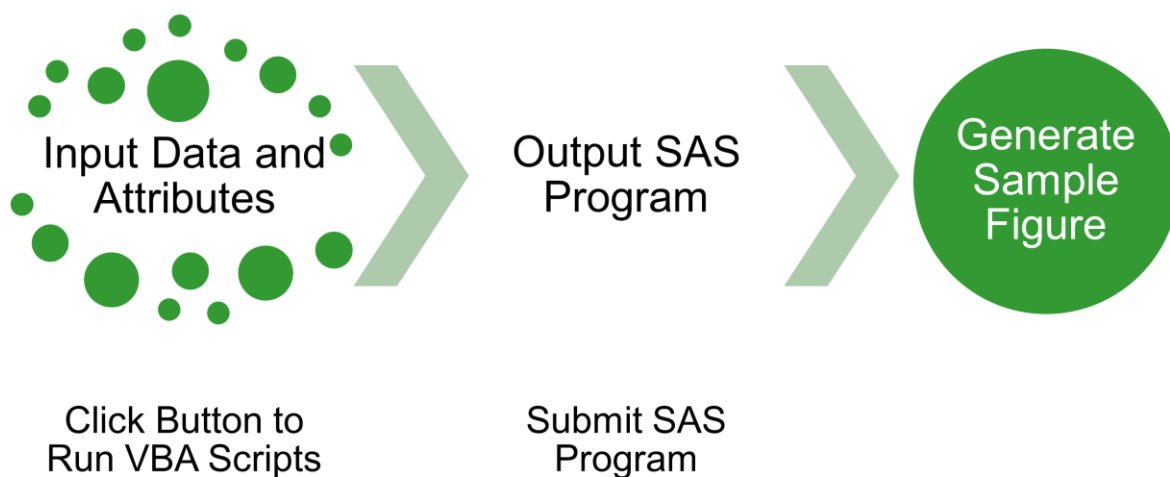


Figure 4. Sample Figure Creation Process

BEHIND THE SCENES: USE VBA TO GENERATE SAS PROGRAM

The one-click generation of the figure SAS program is realized by VBA scripts. We will briefly discuss the mechanisms below.

INITIATE VBA MACRO AND ADD CREATE SAS BUTTON

- 1) In the excel file that holds the figure attributes and data, press ALT+F11 to launch the VBA editor. Double-click on 'This Workbook' on the left and enter scripts 'Sub Demom() End Sub' to initiate a macro named ThisWorkbook.Demom for this whole excel workbook.
- 2) To add a button in the attributes tab, go to Files-> Options-> Customize ribbon to add the 'Developer' tab to the display ribbon. Then insert a button by going to the developer tab -> insert -> select a Form Controls button. Place it in the same column as the attribute values (in our case, cell B1).

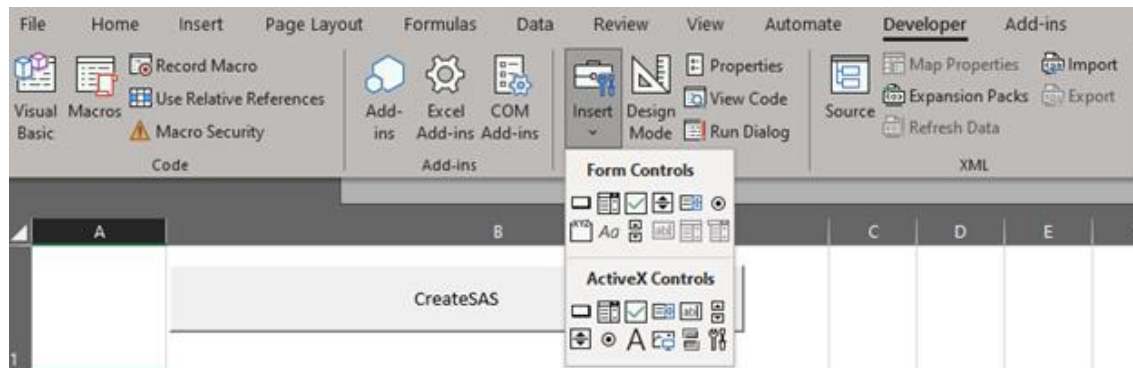


Figure 5. Insert the 'Create SAS' Button

- 3) A dialog window will prompt the user to assign a macro to the button. Or the macro 'ThisWorkbook.Demom' could be assigned to the button from the right-click menu. The text on the button could also be edited from the right-click menu.

READ THE ATTRIBUTES TAB INFORMATION WITH VBA

- 1) Use the following code to find the column of the attributes:

```
With ActiveSheet.Buttons(Application.Caller).TopLeftCell
ProgCol = .Column
End With
```

Then find each row of desired information with the following code as an example:

```
Rowa = Cells.Find(What:="Program Name", After:=ActiveSheet.Cells(1, 1), LookAt:=xlPart,
LookIn:=xlValues, SearchOrder:=xlByRows, SearchDirection:=xlPrevious, MatchCase:=False).Row
```

With the current values of ProgCol and Rowa, the 'Program Name' information can be read by VBA at Cells(Rowa, ProgCol).

- 2) Get the path of the current workbook and prepare the output for SAS programs.

```
Set pgm = Cells(Rowa, ProgCol)
path = ThisWorkbook.path & "\" & pgm
Open path For Output As FileNum
```

Then use the following code to output the SAS program. The example below only output the first row in Figure 2. Notice to use 'Chr(34)' to replace all double quotation marks going into SAS codes when creating the VBA code.

```
Print #FileNum, "%let title1 = " & title1 & ";"
```

READ THE DATA TAB INFORMATION WITH VBA

- 1) 'Activate' data tab to switch the active sheet from the attributes tab to the data tab.
- 2) Find the total number of columns and rows in the data region.
- 3) For each column, detect the variable data type as string or numeric. If the variable type is string (VarType returns 8), set the variable length to \$200 in the output SAS code. Otherwise, a variable is set as numeric.
- 4) Read through each row of data. Any numeric variable with a missing entry is set to the value "."; any string variable with a missing entry is set to the value "****", otherwise we output the entry value as is.

Sample VBA scripts for this part can be found in Appendix 1.

FEATURE HIGHLIGHT: INTERACTIVE VISUALIZATION

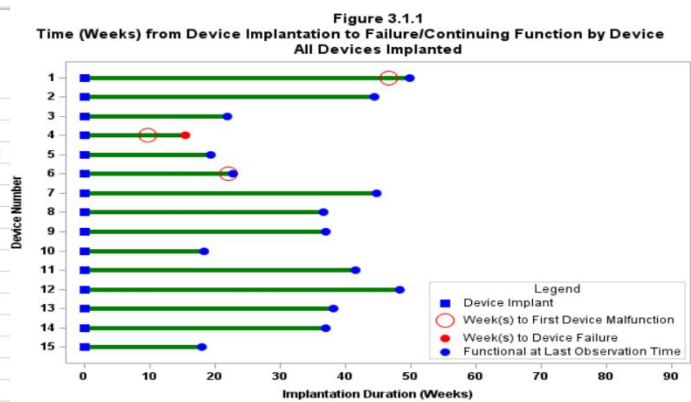
Now let's take a closer look at the key feature of our tool: interactive adjustments of the figure output. Figure 6 compares the swimmer plot outputs before and after attribute adjustments. In this example, all attributes, including titles, axis labels, legend labels, legend options, axis tick values, marker shapes, marker sizes, marker colors, line colors, and line thickness, are modified to illustrate the flexibilities of the tool. Although there is no change to the data, the resulting presentations are very different. Comparing panels b and d, we would like to point out some key differences that impact the completeness and clarity of the output. Firstly, the location of the legend. Placing the long legend inside the graph area saves space vertically, so each page could fit more rows of data or show more clearly. But this also requires adjustments in the x-axis values. The device implantation duration values in the data are only up to about 50 weeks. To avoid the overlap of the legend with the data line,

the maximum x-axis value is set to 90. The x-axis tick interval is decided by the range. For a range of 90, an interval of 10 is clear; whereas for a range of 50, an interval of 5 works better. Secondly, the marker symbols and colors. For device number 6, the time points for the first malfunction and the last observation time are close, so the two symbols overlap. It is clear from the comparison that the symbol pair in panel b is easier to see than that in panel d.

The flexibility of our tool is beyond quick visual checks on varying attributes. Changes in the input data could also be well accommodated. Looking back at Figures 1 and 3, we can see that the default values for 'colors' and 'symbols' are set up for three groups, but the data and output only have two groups. Still, the tool runs smoothly. On the other hand, if more groups are needed in the data, they will be properly presented by simply assigning new symbols and colors (see Figure 7 below).

	CreateSAS		
Program Name	Swimmer_plot.sas		
Title1	Figure 3.1.1		
Title2	Time (Weeks) from Device Implantation to Failure/Continuing Function by Device		
Title3	All Devices Implanted		
xlabel	Implantation Duration (Weeks)		
ylabel	Device Number		
legendlabel	Legend		
legendoption	border=on valign=bottom halign=right location=inside		
xtickvalue	xmin=0 xmax=90 xtick=10		
x1attr	SYMBOL=squarefilled size=8pt color=blue		
x2attr	SYMBOL=circle size=13pt color=red		
x3attr	SYMBOL=circlefilled size=8pt color=red		
x4attr	SYMBOL=circlefilled size=8pt color=blue		
lineattr	color=green thickness=4pt		

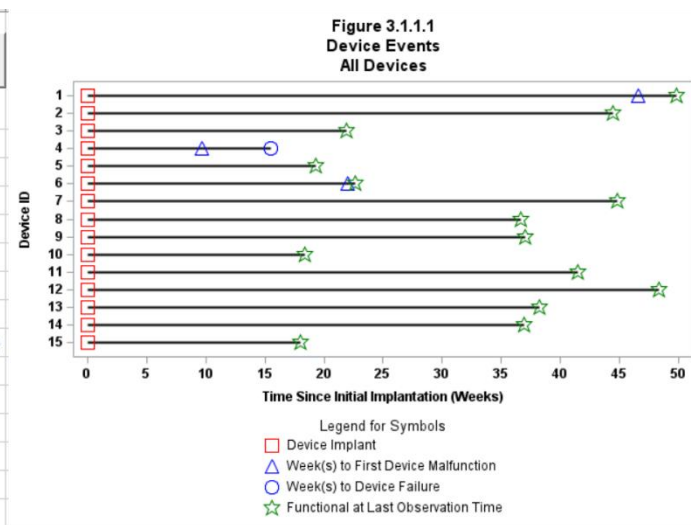
a. Default Attributes



b. Swimmer Plot Output with Default Attributes

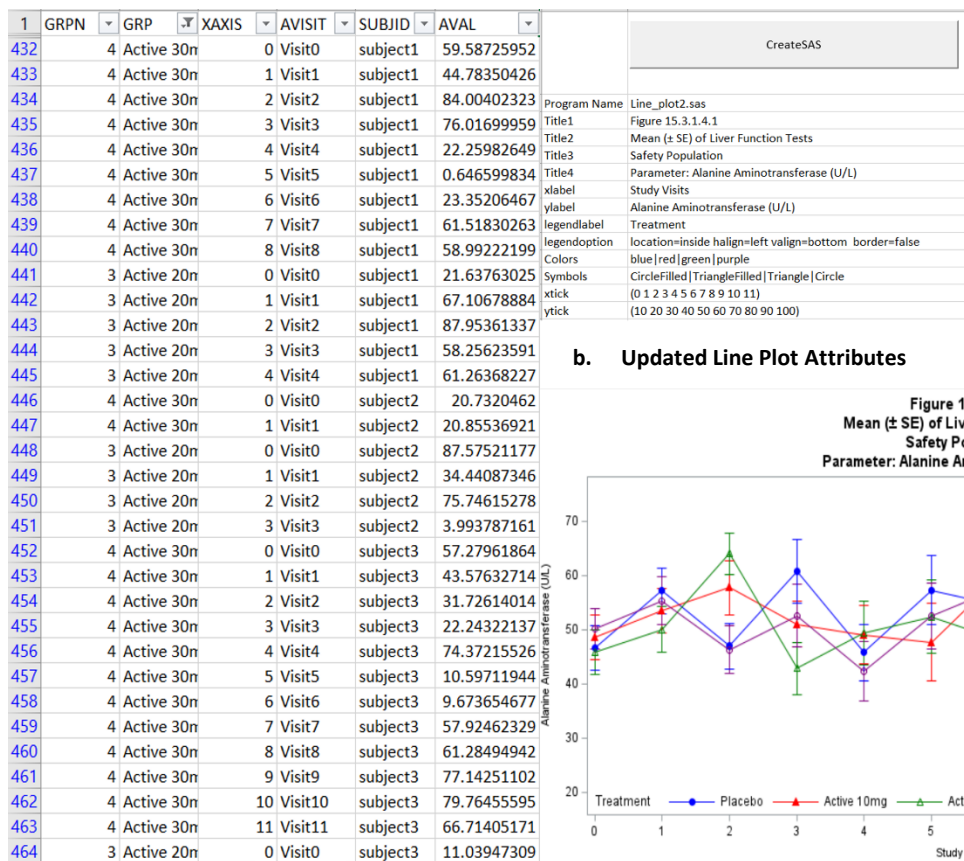
	CreateSAS		
Program Name	Swimmer_plot2.sas		
Title1	Figure 3.1.1.1		
Title2	Device Events		
Title3	All Devices		
xlabel	Time Since Initial Implantation (Weeks)		
ylabel	Device ID		
legendlabel	Legend for Symbols		
legendoption	border=off valign=bottom halign=center location=outside		
xtickvalue	xmin=0 xmax=50 xtick=5		
x1attr	SYMBOL=square size=10pt color=red		
x2attr	SYMBOL=triangle size=10pt color=blue		
x3attr	SYMBOL=circle size=10pt color=blue		
x4attr	SYMBOL=star size=10pt color=green		
lineattr	color=black thickness=2pt		

c. Adjusted Attributes

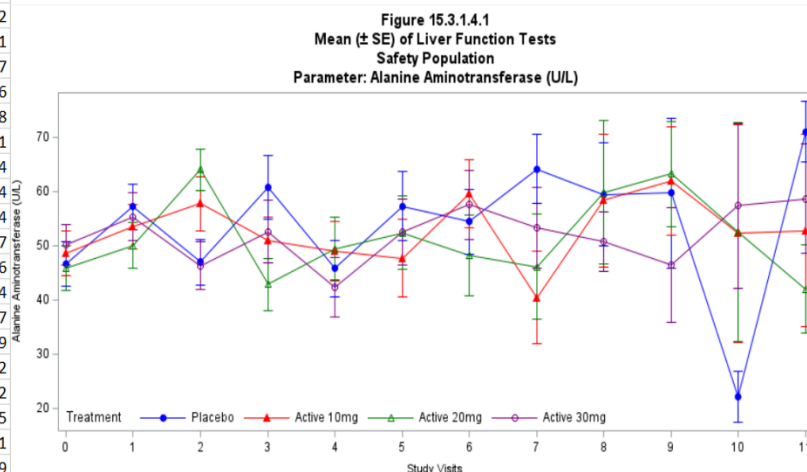


d. Swimmer Plot Output with Adjusted Attributes

Figure 6 Interactive Attributes Adjustment Example: Swimmer Plot



b. Updated Line Plot Attributes



c. Updated Line Plot Output

a. Updated Line Plot Data

Figure 7 Interactive Data/Attributes Adjustment Example: Line Plot

DEMONSTRATION: SAMPLE FIGURE LIBRARY

In the first tab of our tool, the Table of Contents is included, which shows the eight types of figures currently in our library (Figure 8). The selection of figure types and sample figures for those not shown already are detailed below.

Table of Contents
Line Plot
Box Plot
Scatter Plot
KM Plot
Forest Plot
Waterfall Plot
Swimmer Plot
Heatmap

Figure 8 Table of Contents of Current Figure Types

By surveying all 77 reports of randomized controlled trials in five general medical journals from November 2006 to January 2007, Pocock SJ et al. have found that the types of figures mostly used in clinical trials reports are flow diagrams, Kaplan-Meier plots, forest plots, and repeated measures plots [1]. The flow diagram is an integral part of the CONSORT guidelines, adopted by most major journals. Its aim is to display the flow of participants through each stage, specifically for each randomized group reporting the numbers randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome [1]. Since it is usually not part of the figure output defined by the clinical study SAP, it is not

included in the tool. Kaplan-Meier plots are commonly used to present time-to-event results. Forest plots are typically used for displaying subgroup analysis results. Sample figures for these two types are in Figure 9 lower panels.

Repeated measures plots display observed measurement values at multiple time points, typically the baseline and follow-up time points, or changes from baseline at different time points. In the paper from Pocock SJ et al. [1], the repeated measure plots referred to line plots, but other formats could be used too. Box plots at different time points, sometimes also connected with a line through the mean values, could visualize the same information about the trend of changes, with additional information for data distribution and outlier at each time point. Similarly, box plots at each time point could be replaced by scatterplots, which show the complete information on data distribution. The sample line plot has been shown above, and the sample box plot and scatter plot are in Figure 9 upper panels. Besides visualizing repeated measures data, scatter plots can also visualize X-Y relationships, for example, the relationship between estimated changes and actual changes.

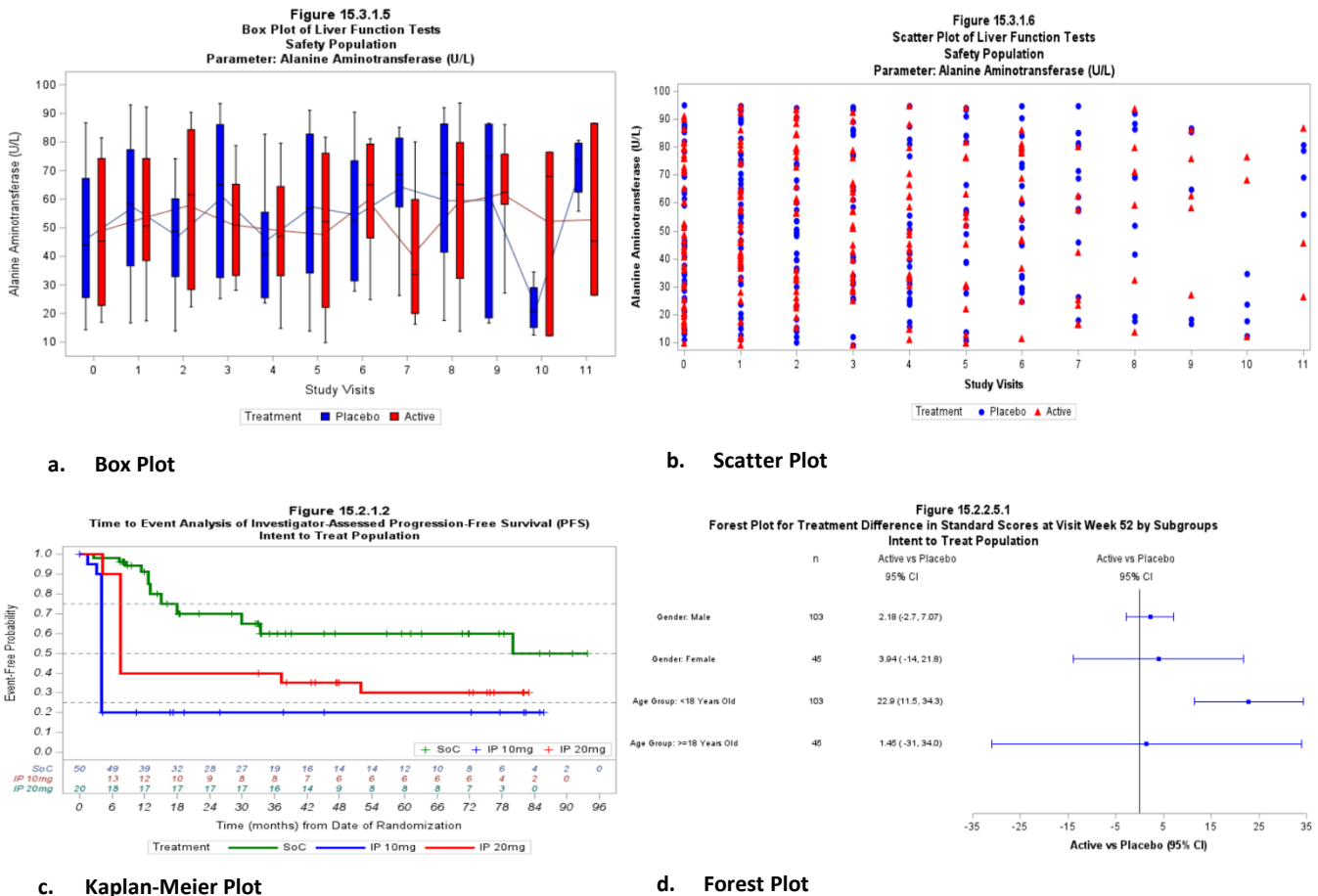


Figure 15.2.2.3.1
Waterfall Plot of BIRC-Assessed Best Percentage Change from Baseline in the Target Lesion
Sum by Best Confirmed Response
Intent to Treat Population
Arm A IP

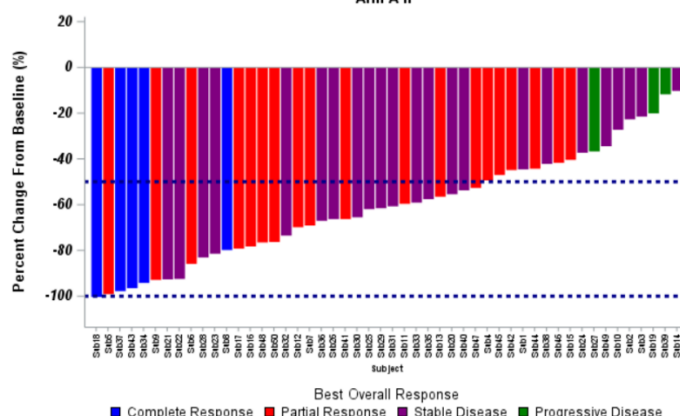


Figure 15.3.2.1
Heatmap of Mutations in Genes by Subject at Baseline
Safety Population

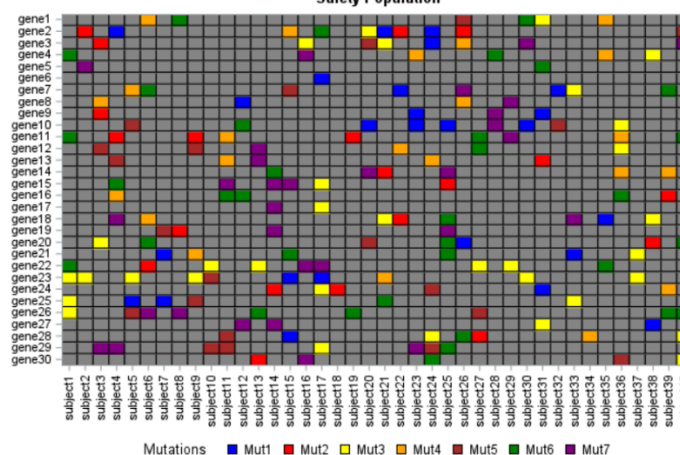


Figure 10 Waterfall Plot and Heatmap Samples From the Tool

DISCUSSION

Now we know the workflow and features of this tool, let's discuss more how it helps with clinical trials, including the generation of SAP figure shells and actual data analysis.

CHOOSE THE RIGHT FIGURE TYPE

For some study data, the decision on figure types is straightforward; for example, the Kaplan-Meier plot for time-to-event data, as discussed earlier in the paper. But for other data, it may require more effort for such decisions. In the case of repeated measures data, line plots, box plots, and scatter plots could be potential options. The choice in each study depends on the sample size, the number of treatment groups and time points, the endpoint measure, etc., to make the output figure as informative as possible but be clear and succinct at the same time. With the tool, if a dummy dataset tailored to the specific study is input into the data tab, sample outputs in different figure types could be quickly generated and facilitate the statistician to land on a confident decision.

DECIDE ON FIGURE DETAILS AND CONVEY THE INFORMATION IN THE SHELL

It is better to display the desired figure attributes as expected in figure shells, although the sample graphs are not reflecting actual data. Otherwise, plenty of explanations will be required in the programming notes or other communications. From our experience, we have received shells with lengthy text descriptions of the figure only, a minimal figure with just the axes paired with text descriptions, or a sample figure borrowed from similar studies with text for the desired changes. We also took the approach of borrowing sample figures from other studies for the task of figure shell generation. With those shells, the client often asked our team to generate a draft figure and then commented to make changes to the attributes. Now that we have this new tool, the details can be tried out during the interactive process to achieve a satisfactory presentation, as discussed above in the feature highlight section, and illustrated in Figure 6. Then a sample graph according to study-specific expectations could be generated and put into the shell. This could greatly simplify the back-and-forth process for the outputs review and update and shorten the timeline.

REUSE SAS CODE TO FACILITATE ANALYSIS

Figure 2 above demonstrates the SAS program output from the data and attributes settings in Figure 1. When it is time to produce the figure output, the programmer can replace the dummy data (panel b) with actual study data and reuse the rest of the codes. Slight modifications might be necessary to account for the differences in the data, for example, data ranges, or repeat the figure for multiple parameters. But overall, the saving in effort and time is significant.

CONCLUSION

In summary, in this paper, we demonstrated a tool to interactively visualize data and adjust attributes as needed in a user-friendly interface. Besides the types of figures showcased in this paper, this tool is extensible to other figures following the same idea. For statisticians, this tool will help decide the type and details for figures to use, and the sample figure output could be used to generate mock-up shells with exact expectations. For programmers, the output SAS program code from the designing stage could be a time-saver for output generation. Also, this tool could help quickly generate additional figures for reporting/presentation purposes if needed.

REFERENCES

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APPENDIX 1

```
Sheets("LineData").Activate
datarow = Cells.Find(What:="", After:=ActiveSheet.Cells(1, 1), LookAt:=xlPart,
LookIn:=xlValues, SearchOrder:=xlByRows, SearchDirection:=xlPrevious, MatchCase:=False).Row
datacol = Cells.Find(What:="", After:=ActiveSheet.Cells(1, 1), LookAt:=xlPart,
LookIn:=xlValues, SearchOrder:=xlByColumns, SearchDirection:=xlPrevious,
MatchCase:=False).Column
ReDim Header(0 To datacol)
Set dataheader = ActiveSheet.Range(Cells(1, 1), Cells(1, datacol))
Set datarange = ActiveSheet.Range(Cells(2, 1), Cells(datarow, datacol))
For l = 1 To datarange.Columns.Count
    If VarType(datarange.Cells(1, l)) = 8 Then
        Print #FileNum, "    length " & dataheader.Cells(1, l) & " $200.;"
        Header(l) = 8
    ElseIf VarType(datarange.Cells(1, l)) = 0 Then
        For lc = 1 To datarange.Rows.Count
            If VarType(datarange.Cells(lc, l)) = 8 Then
                Print #FileNum, "    length " & dataheader.Cells(1, l) & " $200.;"
                Header(l) = 8
                Exit For
            ElseIf VarType(datarange.Cells(lc, l)) = 5 Then
                Header(l) = 5
                Exit For
            End If
        Next lc
    Else
        Header(l) = 5
    End If
Next l
For j = 1 To datarange.Rows.Count
    For k = 1 To datarange.Columns.Count
        If VarType(datarange.Cells(j, k)) = 0 And Header(k) = 5 Then
            LineText = IIf(k = 1, "    ", LineText) & dataheader.Cells(1, k) & "=.; "
        ElseIf VarType(datarange.Cells(j, k)) = 0 And Header(k) = 8 Then
            LineText = IIf(k = 1, "    ", LineText) & dataheader.Cells(1, k) & "=" & Chr(34)
            & Chr(34) & "; "
        Else
            LineText = IIf(k = 1, "    ", LineText) & dataheader.Cells(1, k) & "=" &
            IIf(Header(k) <> 8, "", Chr(34)) & datarange.Cells(j, k) & IIf(Header(k) <> 8, "", Chr(34)) &
            "; "
        End If
    Next k
    Print #FileNum, LineText & " output;"
Next j
```