The Flexible Ways to Create Graphs for Clinical Trial
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ABSTRACT
Without a doubt, SAS® programming can create high-quality graphics. In SAS language, PROC TEMPLATE with SGRENDER procedure is a powerful and commonly used tool to create a customized figure. PROC TEMPLATE allows any figure type to overlay in one plotting space, lattice any figure type side by side, and control every visual aspect of the graphical field. However, the R language's more flexible tools have gained popularity recently by using the ggplot2 package, especially combined with the patchwork package. The combination of patchwork and the ggplot2 package can provide you with a more powerful and effective tool to create all kinds of graphs in clinical trial reports[1,2].

This paper will introduce the R package patchwork combined with the ggplot2 using typical graphs in the clinical trial as examples. This paper will also include PROC TEMPLATE with SGRENDER procedure of SAS, as the comparison. In summary, patchwork combined with the ggplot2 package in R opens a new window for you to customize your graphs, especially combining different graphs or text content on one page or across the page.

KEYWORDS
Graphics, R language, Graph Template Language (GTL), ggplot2, patchwork, clinical trial, visualization

INTRODUCTION
When we work with a large and diverse amount of data for clinical trials, data visualization can help us to make data more understandable. A well-designed, informative graph should be essential to analyze these complex data better and have a concise visual presentation to show statistical results for reporting. High-quality graphs help us analyze and understand the data from different clinical trial domains.

In this paper, the SAS data set named "adtl" is the example data set to generate graphs by SAS language and the R package. The data set contains made-up data with one patient record per test date, to simulate a clinical patient study where the outcome of interest is the evaluation of target lesion tumor size in the solid tumor during a study. The variable 'BASE' is the baseline of tumor size, 'AVAL' is the tumor size value at that test date, 'CHG' is the difference between 'AVAL' and 'BASE', 'PCHG' is the percentage change, and the 'mean', 'std', 'median' is based on the treatment. Below are the first 12 observations in the example data ADTL.
Graph Template Language (GTL) in SAS and ggplot2, together with the patchwork package in R, provides many possible combinations of statements to create graphs. This paper will discuss the visual presentation of data in clinical trials using two tools, especially for combining different plots into one page using ggplot2 together with the patchwork package in R. We will take a couple of boxplot graphs as examples to describe how to accomplish the goal. Through the illustrations, we will recommend a few valuable options that help the customization. We will also demonstrate how to generate the same graphs using SAS language for comparison. The three boxplots as examples for combination in one page include as following:

- Percent changes for tumor size (Sum of diameter, SOD) from baseline by treatment over time.
- The baseline value of tumor size (Sum of diameter, SOD).
- Percent changes for tumor size (Sum of diameter, SOD) from baseline by treatment.

**CREATING GRAPHS BY USING GTL**

**Key Syntax of GTL**

In the SAS application, we can define the graph template with the TEMPLATE procedure as follows:

```
proc template;
    define statgraph <template-name>;
    begingraph / <options>;
        <GTL statements>;
    endgraph;
end;
run;
```

The TEMPLATE procedure defines and saves the Graph's structure as a template for later usage. This code alone will not create the Graph. The BEGINGRAPH and ENDGRAPH statements define the outermost container for the Graph and must contain all the GTL statements. Produce the Graph with the SGRENDER procedure:

```
proc sgrender data = <data> template = <template-name>;
run;
```

The SGRENDER procedure will associate data with the predefined template and create the Graph[2]. The same template can be used with multiple, compatible data sets to create additional graphs if necessary.

**Example of using GTL to create graphs**

GTL is a useful tool for programmers to create graphs through SAS, however, it is difficult and even impossible for you to remember all statements and options of SAS GTL. GTL is still an efficient way to enable the user to generate complex, advanced, and customized figures. As figure 1 shows below, three boxplots are created on one page. The SAS codes are also listed below. This approach shows that SAS GTL would require a significant programming effort.

```
**Define the graph’s structure as a template;**
proc template;
    define statgraph sgdesignb;
    dynamic _AVISIT _PCHG _TRT01A _TRT01A2 _BASE _TRT01A3 _MEAN;
    begingraph/border=true;
    layout lattice/rows=2 rowgutter=10 rowweights=(0.6 0.4);
    **First row;**
    layout lattice/rowdatarange=data columndatarange=data rowgutter=10;
    layout overlay/xaxisopts=(label='Analysis Visit')
```
**Generate graphs;**

```sas
proc sgrender data=adtl template=sgdesignb;
dynamic _PCHG="PCHG" _AVISIT="AVISIT" _TRT01A="TRT01A"
_TRT01A2="TRT01A" _BASE="BASE"
_TRT01A3="TRT01A" _MEAN="MEANVAL"
run;
```

Figure 1. Plots for Sum of Diameters of Tumor (SOD) for Baseline Value and Percent Changes from Baseline

If we want to change the above figure’s structure or add some new features, we have to write the complicated TEMPLATE procedure again to define a new Graph’s structure template. However, we can add new features and re-arrange the graph’s structure by using R functions straightforwardly.

**CREATING GRAPHS BY USING GGPlot2 AND PATCHWORK PACKAGE**

**Key Syntax of R packages ggplot2 and patchwork**

The basic grammar of ggplot2 package is as the following:
The patchwork package is a great "composer" of plots, with primary functions listed in table 1 below. The reference document is available online[3].

<table>
<thead>
<tr>
<th>Function name</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>area</td>
<td>Specify a single area in a rectangular grid that should contain a plot. Objects constructed with the area() can be concatenated together with c() to specify multiple areas.</td>
</tr>
<tr>
<td>guide_area</td>
<td>Add an area to hold collected guides.</td>
</tr>
<tr>
<td>inset_element</td>
<td>Create an inset to be added on top of the previous plot.</td>
</tr>
<tr>
<td>multipage_align</td>
<td>Align plots across multiple pages.</td>
</tr>
<tr>
<td>plot_annotation</td>
<td>Annotate the final patchwork.</td>
</tr>
<tr>
<td>plot_arithmetic</td>
<td>Plot arithmetic. In addition to the + operator known in ggplot2, patchwork defines logic for some of the other operators, such as &quot;/&quot; or &quot;</td>
</tr>
<tr>
<td>plot_layout</td>
<td>Define the grid to compose plots in. In order to control how different plots are laid out, you need to add a layout specification. If you are nesting grids, the layout is scoped to the current nesting level.</td>
</tr>
<tr>
<td>plotSpacer</td>
<td>Add a completely blank area.</td>
</tr>
<tr>
<td>wrapElements</td>
<td>Wrap arbitrary graphics in a patchwork-compliant patch.</td>
</tr>
<tr>
<td>wrapGgplotGrob</td>
<td>Make a ggplot created from a ggplot object patchwork compliant. This function converts a ggplot, as produced by ggplot2::ggplotGrob(), and makes it ready to be added to a patchwork. In contrast to passing the ggplot to wrap_elements(), wrapGgplotGrob() ensures proper alignment as expected. On the other hand, major restructuring of the ggplot will result in an object that doesn't work properly with wrapGgplotGrob().</td>
</tr>
<tr>
<td>wrapPlots</td>
<td>Wrap plots into a patchwork. While the use of + is a natural way to add plots together, it can be difficult to string together multiple plots programmatically if the number of plots is not known beforehand. wrapPlots makes it easy to take a list of plots and add them into one composition, along with layout specifications.</td>
</tr>
</tbody>
</table>

The ggplot2 and patchwork package in the R library use a layered approach. The programmer can view the work in progress without completing the final Graph. The code can be developed and executed one layer at a time and adjusted as needed. On the other hand, the patchwork package makes it extremely simple to combine
separate plots from `ggplot2` into the same graphic. As such, it does the same job as `gridExtra::grid.arrange()` and `cowplot::plot_grid`. It helps you easily assemble plots, define layout, add an annotation on one page and align graphs across pages.

Here are the examples of the basic syntax of the `ggplot2` and `patchwork` packages:

```r
library(ggplot2)
library(patchwork)
p11 <- ggplot(mtcars) + geom_point(aes(mpg, disp))
p22 <- ggplot(mtcars) + geom_boxplot(aes(gear, disp, group = gear))
Figure 2.1: p11 + p22
```

```r
p33 <- ggplot(mtcars) + geom_smooth(aes(disp, qsec))
p44 <- ggplot(mtcars) + geom_bar(aes(carb))
Figure 2.2: (p11 | p22 | p33) / p44
```
Example of using ggplot2 and patchwork to create graphs

Below are the R libraries and functions used in this paper.

```r
library(tidyverse)
library(haven)
library(ggplot2)
library(gridExtra)
library(devtools)
library(patchwork)
```

We will use dummy SAS data sets `adtl` as an input data frame in ggplot2 for the following examples.

First, we need to read SAS data into RStudio.

```r
adtl <- read_sas("adtl.sas7bdat")
```

Second, we will create the single box plot one by one using the ggplot2 package:

```r
p1 <- adtl %>%
  ggplot(aes(x=AVISIT, y=PCHG, fill=TRT01A))  +
  geom_boxplot(shape=3, outlier.size=3, outlier.shape=18, outlier.color="red")  +
  stat_summary(fun = mean, geom = "point", col = "green")    +
  labs(#x ="Analysis Visit"
       x="Analysis Visit 
       (Red points indicate outliers, Green points indicate means)" ,
       y ="Percent Change From Baseline",  axis.text.x = element_text(angle = 45, hjust = 1))   +
  theme(legend.position ="top", legend.title=element_blank(), axis.text.x =
  element_text(angle = 45, hjust = 1))    +
  ylim(-100, 100)

p2 <- ggplot(adtl, aes(TRT01A, BASE)) + geom_boxplot() +
  labs(x = " ", y = "Baseline Value \n (SOD)") +
  coord_cartesian(ylim=c(0, 400))

p3 <- ggplot(adtl, aes(TRT01A, PCHG)) + geom_boxplot() +
  labs(x = " ", y = "Percent Change from Baseline \n (SOD)") +
  coord_cartesian(ylim=c(-100, 100))
```

Finally, we can use the patchwork R package to combine three separate plots into one page. The patchwork package combines plots by:

- Using a ggplot2 syntax for the grammar of plot-layout operations.
- Extending the amazing ggplot2 package.

Patchwork has a straightforward syntax where we can create layouts super easily. Here is the general syntax that combines:

- Two-Column layout using the Plus Sign `+`
- Parenthesis `()` to create a subplot group.
- Two-Row layout using the Division Sign `\`

```r
```
The code is listed below, which patchwork through an operator such as "/" and "|" does the same as the grid.arrange and grid.grob do. Now we use the very simple code to create the same effect output (figure 3) as the above plot (figure 1) which is created by GTL:

\[ p1/(p2|p3) \]

**Figure 3. Plots for Sum of Diameters of Tumor (SOD) for Baseline Value and Percent Changes from Baseline**

![Figure 3: Generated by R packages, combined from three boxplots](image)

The composer of ggplot2 and patchwork can combine separate plots into the same graphic and rearrange plots into a grid and add figures, labels, and annotations very simply.

**More examples of flexible features for ggplot2 and patchwork packages**

You can change the position for the Graph on the top in figure 3 to the bottom and assign a tag to it as "Fig c", and put the two figures on the bottom in figure 3 to the top and place the tag "Fig a and Fig b" to them respectively. Also, patchwork can add space among graphs on the top and bottom. It has the options such as plot_spacer, plot_layout, and plot_annotation. The code listed below generates the output of figure 4.

```r
p01 <- ((p2|plot_spacer () |p3) + plot_layout(widths = c(4.5, 0.2 ,4.5)))/
(pl + plot_spacer()+ plot_layout(heights = unit(c(3, 0.2), c('cm', 'cm'))))
```

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We can also add the non-plot content by combining the ggplot2 and the patchwork package. Below is the example code, and figure 5 is the output.

```r
adtla <- adtl %>% select(TRT01A, mean, median, std) %>% distinct()
colnames(adtla) <- c("Treatment", "Mean", "Median", "Standard Deviation")

pc <- gridExtra::tableGrob(adtla)
p03 <- ((p2|plotSpacer()|p3) + plot_layout(widths = c(4.5, 0.2, 4.5))/pc/p1 +
    plot_annotation(tag_levels = list(c('Fig a', 'Fig b', " ", "Fig c")))
```

**Figure 4: Based on Fig 3, changed position, added space individual graphs, and added tags**

Figure 4. Plots for Sum of Diameters of Tumor (SOD) for Baseline Value and Percent Changes from Baseline
CONCLUSION

SAS is a powerful statistical analysis software and has made many significant improvements to match industry needs. Still, the programming for graphs is complicated, hard to learn, and difficult to debug, especially since SAS GTL requires a significant amount of programming effort. On the other hand, R is an open-source software environment, and the latest functionality is updated more frequently. R also provides a wide variety of statistical and graphical techniques to create complex graphs with less programming effort, such as ggplot2 and patchwork package. The syntax of R is simple and easy to debug. Since R has already built many statistics and output programming packages for your use, the amount of R coding skills you need to learn is fairly minimal. The return on this investment of effort can be great - access to thousands of additional analytical and graphical methods.

In conclusion, SAS GTL provides data visualization features and awesome technical support, however, R offers tons of packages to create graphs more efficiently and straightforwardly. Both technologies can improve data analysis and visualization capabilities in clinical trials. It is the winning solution to start combining both technics of SAS and R and get maximum benefits.
REFERENCES


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