Using R Shiny to Explore Clinical Trial Data

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ABSTRACT

Shiny is an R package that makes it easy to build interactive web apps straight from R. It provides the framework to explore and analysis the clinical trial data in a more efficient way. Compatible with other packages(e.g. DT, echarts4r), listing, table and figure can be displayed dynamically which is customized to simplify filtering and visualizing the data. After the set-up process completed, R shiny app could be deployed under both local disk and public disk so that the whole team could review the results. In this paper, an example will show how to develop the R shiny app by statistical programmers who have no experience on the frontend website development.

Key Words: R shiny, echarts4r, deployment, data visualization, clinical trial data

BACKGROUND

R is a programming language and free software environment for statistical computing and graphics supported by the R Foundation for Statistical Computing. In clinical trial industry, the R language is widely used among statisticians. As of July 2021, R ranks 12th in the TIOBE index, a measure of popularity of programming languages [1]. Shiny is an R package that helps to build interactive web apps directly from R. It provides the framework to explore and analysis the clinical data in a more efficient way. Apache ECharts is a free, powerful charting and visualization library offering an easy way of adding intuitive, interactive, and highly customizable charts to your commercial products [2]. Package echarts4r is the R package converted from ECharts. With “ggplot2” knowledge, echarts4r is easy to learn.

With the increasing need for exploring data in a timely and visualized manner, developing the R shiny app is a smart choice.

R SHINY APP STRUCTURE

A simple R Shiny app is divided into two parts: the User Interface (UI) and the Server. The UI is responsible for the app presentation, while the server is responsible for the app logic. Here is the sample code of a simple R shiny app.

```r
library(shiny)
u <- fluidPage()
s <- function(input, output){}
shinyApp(ui = u, server = s)
```

The UI controls what is being displayed on the application page and how the components are laid out, including defining the webpage layout, defining static HTML display information, defining HTML controls that receive user input, and defining HTML controls that output information when responding to users.
The Server controls the data that will be displayed through the UI. The server will be where you load and analyze data, then define the outputs using input from the UI.

Both of two parts can be defined in one file, but it is a good practice to separate these into three files to simplify any future changes or maintenance on the app. It means you need to set up three files: *ui.R* to define the app presentation, *server.R* to define the app logic, and *app.R* to combine the former two files.

**R SHINY APP EXAMPLE**

Following is the introduction on a Shiny app in clinical trial data. You can click the [URL](URL) to browse the webpage, the app was deployed to the shiny cloud. For the sample code of the shiny app, please refer to the [github](github) or [gitee](gitee).

The shiny app contains five main pages: *Data Listing, Summary Table, Plot, Efficacy* and *About*, which is shown on Figure 1. Specially, the sidebar on the right is developed to filter and download data. This sidebar automatically works on all pages by default. Generally, core variables or baseline character variables are implemented in the right sidebar, Figure 2 shows the example of the sidebar.

![Figure1: The whole page of shiny app](Image1)

![Figure2: Right sidebar](Image2)

*Data Listing* page is designed to display patient line listings which is popularly used in clinical trials as Figure 3 shows. Multiple datasets can be selected in the selectinput. The variables in selectinput will be changed dynamically according to the dataset selected. A search box also can be used to search the data. As mentioned above, the data table will be responded immediately if the right sidebar worked.
The R package “DT” provides an R interface to the JavaScript library “DataTables”. R data object can be displayed as tables on HTML pages, it provides filtering, pagination, sorting, and many other features in the table \[3\]. *Output() and render*() functions work together to add R output to the UI. *Output() is used in ui.R and render*() is used in server.R. For example, to output the data listing, package “DT” provides function DTOutput() and renderDT().

```r
ui <- fluidPage(
  DTOutput("listing1")
)
server <- function(input, output){
  output$listing1 <- renderDT()
}
```

Summary Table page is designed to display basic statistical summaries such as frequency count and descriptive statistics. Figure 4 shows the summary of data from subject level analysis dataset ADSL. The package “gtsummary” is used to generate this table. Function gt_output() is used in ui.R, correspondingly, render_gt() is used in server.R. The “gtsummary” package provides an elegant and flexible way to create publication-ready analytical and summary tables using the R programming language \[4\]. Figure 5 shows the summary of adverse events and Figure 6 is the table generated from datasets with CDISC basic data structure implemented. The package “arsenal” is applied to develop the summary table of this kind of data. tableOutput() in ui.R and renderTable() in server.R are used to output summary tables in Figure 5 and Figure 6.

![Figure 3: Example of data listing](image)

![Figure 4: Table of subject level data](image)
Plot page is designed to display statistical charts. Package “echarts4r” is a powerful data visualization package in R. Figure 7 shows the bar plot using “echarts4r”, with a message box showing the count number. On the upper right corner, there are five click buttons to support saving image, zooming in/out of the data, viewing the data and restoring figure from left to right respectively. Varieties of plots could be generated by using “echarts4r”, such as, line chart, pie chart, scatter chart, box plot, heatmap, treemap and 3D map [5], etc. Here is the sample code for generating bar chart by using “echarts4r”.

```r
# Sample code for generating bar chart using echarts4r
library(echarts4r)

# Data preparation
data <- data.frame(
  x = c(9, 13, 16, 18, 21, 24, 25, 25, 21, 21, 41),
  y = c(771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781)

# Plotting
plot <- echart()
plot <- plot + chart_bar(
  x = x, y = y,
  tooltip = list(trigger = "axis", axisType = "category"),
  toolbox = list(feature = list(saveAsImage = TRUE))
)
```

![Figure 7: Bar chart used echarts4r](image-url)
In addition to basic charts, plots used in oncology studies could also be generated by using "echarts4r". Here is the example of swimmer plot. A message box shows the overall response of the selected patient on the relative day by the selecting timepoint. Data zoom in x axis or y axis could be used to zoom in/out the plot. Following shows the snapshot of swimmer plot by “echarts4r”, also with the sample code.

```
tmpplotds %>% count(get(input$plotvariables)) %>% arrange(n) %>%
  e_charts(get(input$plotvariables)) %>%
  e_bar(n, legend = FALSE) %>%
  e_datazoom(
    x_index = 0,
    toolbox = FALSE
  ) %>%
  e_datazoom(
    y_index = 0,
    toolbox = FALSE
  ) %>%
  e_tooltip(trigger = "item") %>%
  e_labels(position = "top") %>%
  e_x_axis(splitLine = list(show = FALSE)) %>%
  e_color(c('#dda0dd', '#eeeeee', '#59c4e6', '#edafda')) %>%
  e_toolbox_feature(feature = "saveAsImage") %>%
  e_toolbox_feature(feature = "dataZoom") %>%
  e_toolbox_feature(feature = "dataView") %>%
  e_toolbox_feature(feature = "restore")
```

Figure 8: Swimmer plot used echarts4r

```
tmpplotds2 %>%
  arrange(TRTA, treat) %>%
  e_charts(x = USUBJID) %>%
  e_bar(treat, legend = FALSE, name = "Treatment duration") %>%
  e_scatter(CR, name = "CR", symbol = "circle", symbol_size = 8) %>%
  e_scatter(PR, name = "PR", symbol = "diamond", symbol_size = 8) %>%
  e_scatter(SD, name = "SD", symbol = "roundRect", symbol_size = 8) %>%
  e_scatter(PD, name = "PD", symbol = "triangle", symbol_size = 8) %>%
  e_datazoom(
    x_index = 0,
    type = "slider",
```
toolbox = FALSE
) %>%
e_datazoom(
y_index = 0,
type = "slider",
toolbox = FALSE
) %>%
e_tooltip() %>%
e_flip_coords() %>%
e_y_axis(splitLine = list(show = FALSE)) %>%
e_x_axis(show = TRUE) %>%
e_add("itemStyle",color) %>%
e_color(c('#dda0dd', '#eeeeee', '#59c4e6', '#edafda')) %>%
e_toolbox_feature(feature = "saveAsImage") %>%
e_toolbox_feature(feature = "dataZoom") %>%
e_toolbox_feature(feature = "dataView") %>%
e_toolbox_feature(feature = "restore")

In the similar way, waterfall and spider could also be generated by using “echarts4r”. The syntax of “echarts4r” is similar to “ggplot2” which is more widely used by the users, it is very easy to learn the “echarts4r” if you are familiar with “ggplot2”. echarts4rOutput() is used in ui.R and renderEcharts4r() in server.R.

**Efficacy** page is designed to display analysis of efficacy data. Survival analysis is essential when talking about an oncology study, “survminer” is a useful package for the survival analysis, K-M curve could be generated by using the package. Figure 9 shows the km curve by using “survminer”, following is the sample code.

```
fit <- survfit(as.formula(paste("Surv(AVAL, CNSR)~", str1)),
              data = adtte)

ggplot1 <- ggsurvplot(fit,
                      pval = TRUE, conf.int = FALSE,
                      risk.table = TRUE,
                      risk.table.col = "strata",
                      linetype = "strata",
                      surv.median.line = "hv",
                      gghtheme = theme_gray(),
                      xlab = "Time (days)"
```

![Figure 9: KM plot used survminer](image-url)
axes.offset = T,
legend.labs = c("Placebo", "Xanomeline High Dose", "Xanomeline Low Dose")

By summarizing all functions mentioned above, Table 1 shows the summary of common output objects in shiny.

<table>
<thead>
<tr>
<th>Object</th>
<th>Function in <code>ui.R</code></th>
<th>Function in <code>server.R</code></th>
</tr>
</thead>
<tbody>
<tr>
<td>Data table</td>
<td><code>DTOuput()</code></td>
<td><code>renderDT()</code></td>
</tr>
<tr>
<td>Summary table(gt)</td>
<td><code>gt_output()</code></td>
<td><code>render_gt()</code></td>
</tr>
<tr>
<td>Summary table(data frame)</td>
<td><code>tableOutput()</code></td>
<td><code>renderTable()</code></td>
</tr>
<tr>
<td>Plot(echarts4r)</td>
<td><code>echarts4rOutput()</code></td>
<td><code>renderEcharts4r()</code></td>
</tr>
<tr>
<td>Plot(ggplot2)</td>
<td><code>plotOutput()</code></td>
<td><code>renderPlot()</code></td>
</tr>
</tbody>
</table>

About page is designed to provide the information of the packages. There are three parts in About page: the study data, about packages used and about me. This is a pilot study from the CDISC website, source data can be downloaded from the link. Since ADTR and ADRS are not available in this data source, the two datasets are dummed by paper author. Many packages are used in the shiny app but not limited to the ones listed in Figure 10.

![Figure 10: Packages used](image)

R SHINY APP DEPLOYMENT

When talking about the deployment of the R shiny app, it could be deployed to the cloud, such as shinyapps.io, but the free accounts are limited, so the better choice is to deploy on local disk or public disk. Here is the method on the deployment of the R shiny app.

1. Create a folder named `R_shiny/`.
2. Download firefox portable, R portable and install them under the folder `R_shiny/`.
3. Create a folder under `R_shiny/`, named `shiny3`, so the folder is like following

```
R_shiny/
  +- Firefox portable
  +- R-portable
  +- shiny3/
```
4. Modify the R-Portable/App/R-Portable/etc/Rprofile.site, add below codes to the bottom of the file.

```r
.First = function()
{
    .libPaths(.Library)
}
```

5. Start R-Portable and install core package dependencies.


```r
message('library paths:
', paste('...', .libPaths(), sep='', collapse='\n'))
# if want to use ie browser
ie=file.path('C:/Program Files (x86)/Internet Explorer/iexplore.exe')
firefox=file.path(getwd(),'../Firefox 70.0 32bit/App/Firefox/firefox.exe')
options(browser = firefox)
shiny::runApp('./', launch.browser=TRUE)
```

7. Create a vb script, named `run.vbs`, below codes added.

```vb
Rexe = "..\R-Portable\App\R-Portable\bin\Rscript.exe"
Ropts = "--no-save --no-environ --no-init-file --no-restore --no-Rconsole"
RScriptFile = "runShinyApp.R"
Outfile = "ShinyApp.log"
strCommand = Rexe & " " & Ropts & " " & RScriptFile & " 1>" & Outfile & " 2>&1"
intWindowStyle = 0
bWaitOnReturn = False
With CreateObject("Wscript.Shell")
    .CurrentDirectory = "programs"
    .Run strCommand, intWindowStyle, bWaitOnReturn
End With
```

8. Finally, the folder can be created shown as Figure 11, 12 and 13. Double click the run.vbs, finish the deployment.

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**Figure 11:** Folder under R_shiny

**Figure 12:** Folder under R_shiny/shiny3
CONCLUSION

With the help of R shiny, we can quickly develop a visual and interactive web page to explore clinical trial data, after the deployment on public disk, the whole team can review the results. After setting-up the apps, statisticians can quickly validate the study results without developing complex SAS codes and the results can be displayed in a more visualized manner to medical or other functions to illustrate the results. In addition to the basic analysis, R shiny app is also helpful for the exploratory analysis, varieties of plots/tables could be generated to meet the requirements of varieties roles from other functions. For example, heat maps could be used to explore the incidence rate of specified adverse events.

DISCUSSION

During the development, two points can be improved in the future. One is `ui.R`, knowledge about HTML/CSS/JavaScript can be helpful to make the R shiny app look crisp and usable. Another is the big data, the R package “data.table” is powerful when dealing with big data, it provides a high-performance version of base R’s data frame with syntax and feature enhanced for ease of use and with programming efficiency improved [7].

REFERENCES

[1]: https://www.tiobe.com/tiobe-index/
[3]: https://rstudio.github.io/DT/
[4]: https://www.danielsjoberg.com/gtsummary/
[7]: https://github.com/Rdatatable/data.table/
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