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Interactive Adverse Event Data Visualization using R-Shiny

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ABSTRACT

AE data is critical data in drug discovery process, monitored for the patient safety and to take critical decisions regarding continuation of subjects in clinical trial. Reviewers look for parameter such as treatment emergent, seriousness, relatedness and toxicity grade. The traditional AE reports consist of basic summary tables and listings. It is difficult to detect AE patterns in a table presentation. Interactive visual analytics present a useful alternative to static outputs for exploring safety data and present a great opportunity to enhance evaluation of drug safety. In this paper we would use R-Shiny application to create interactive dashboards based on different parameters, which would help the statisticians to have comprehensive view of the Adverse events as well as they can also look at more granular level. Overall R-Shiny app would provide the detailed AE information at patient level/study level as interactive graphs and tables.

INTRODUCTION

For oncology clinical trials safety review meetings are conducted frequently and the purpose of these meetings are to perform comprehensive review of the patient safety data and identify potential safety concerns. Adverse events (AE), Laboratory (LB), ECG (EG) and Vital signs (VS) data form an important component of the safety review. Oncology trials are always done on patients and their safety is of prime concern for any new drug trial. Any abnormal lab findings or toxicity need to be reported to the concerned authorities to take quick decisions for patient's safety and wellbeing.

Safety analysis is primarily based on summary tables related to AE, LB, EG and VS. These reports are reviewed by statistician, safety lead and medical monitors, who will look for any potential risk for safety and also for any anomalies in data which would be queried with the site. These reports would also be part of Development Safety Update report (DSUR) which is the annual report for Safety. Tables for LB, EG and VS would consist of summaries of change from baseline and shift tables. For AE data adverse event term is recorded on CRF and coded using MedDRA dictionary to assign System Organ Class (SOC) and Preferred Term (PT). AE's are summarized based on occurrence in patients by SOC and PT. Summary table generally show the number of distinct patients having AE's or frequency of AE's within a subject. Percentages are also calculated based on number of subjects who have been given particular treatment. Below are the AE summary Tables which are generally used for Safety review.

1) Treatment Emergent Adverse events
2) Serious Adverse events
3) Related Adverse events
4) Adverse events with CTCAE Toxicity Grade>=3
5) Adverse events leading to Death
6) Adverse events of Special Interest

The data collected on CRF is mapped into SDTM's which are then converted to ADaM's based on SAP. These Analysis datasets are used to create Safety review outputs or sometimes outputs can be directly created from raw datasets. These activities are performed by SAS Programmers who provide the reports to Safety team. The Clinicians then analyze these static outputs and reach out to the SAS programmers in case of any re-run or any adhoc outputs required. This makes the process slow and highly inefficient.

In this paper, we discuss, how to create interactive R-Shiny application which generates AE dashboard for safety review meetings when provided with an analysis dataset or raw dataset. This application would give a

comprehensive view of AE data in the form of interactive graphs and tables. This dashboard would help us to find any AE pattern, signal or trend and then dig into data for more granularity.

DATA IMPORT AND USER INTERFACE

Datasets were created in excel and imported in R studio using **read.csv** function. User interface was created in a dynamic fashion and sidebar layout panel was adopted for this application (Figure. 1). The side bar would consist of drop downs for all the variables which would be used to filter data for the reports. Current side bar panel consists of Population flag, Treatment Emergent flag, Treatment groups, AE Seriousness, AE Relatedness, Toxicity grade, System organ class (SOC) and Preferred Term(PT) variables. Any other variable can be added or removed as per the requirement.

All the dropdown filters have distinct values of their respective variables along with “All” option in the case of SOC and PT. We can select any unique value or all the values together to generate graphs and tables as per the demand.

On left hand side of Figure 1 depicts the dropdown selection of variables and on right hand side code was used to make user interface (UI) dynamic, where all of the selections are dependent upon each other combination.

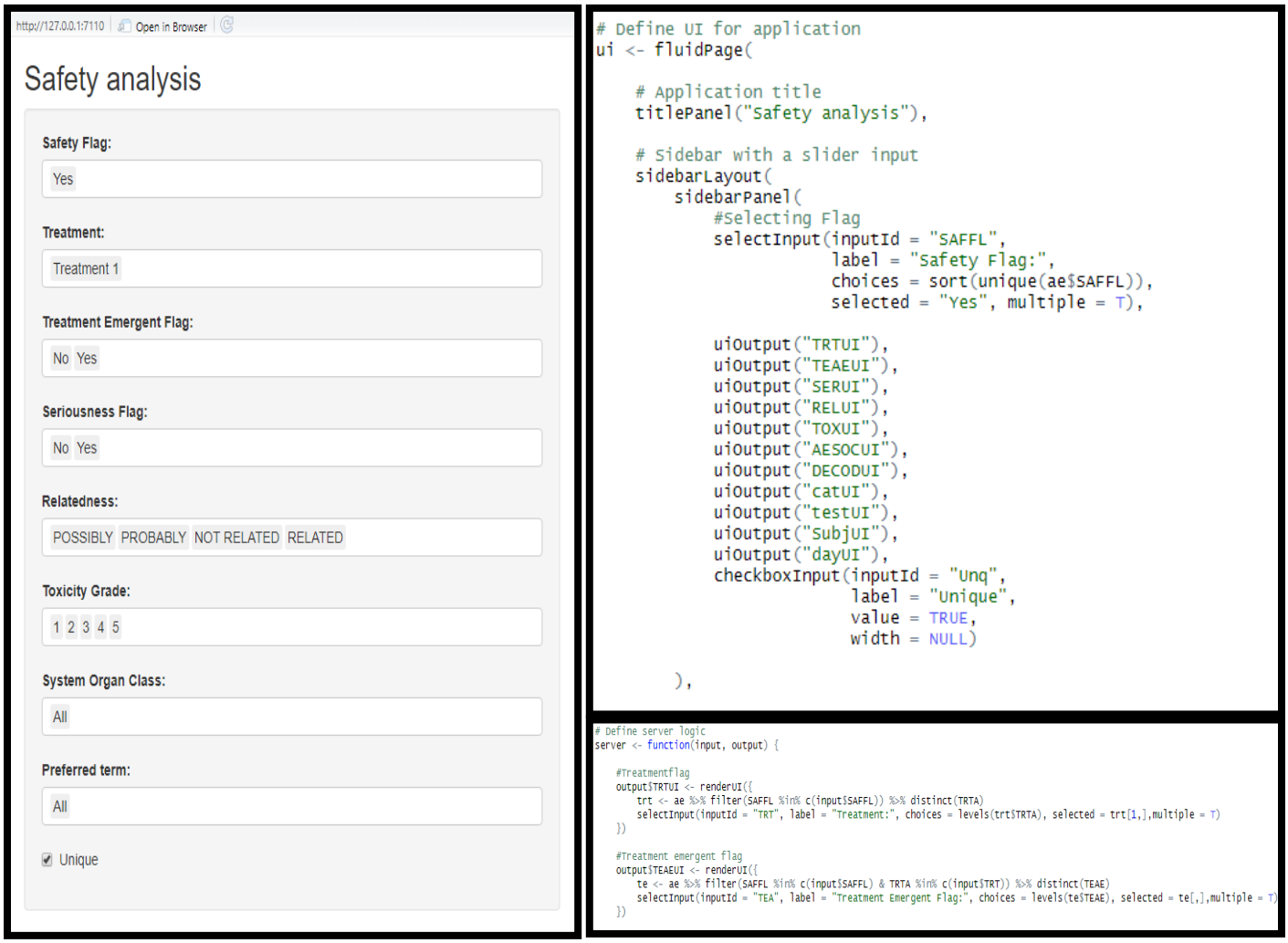
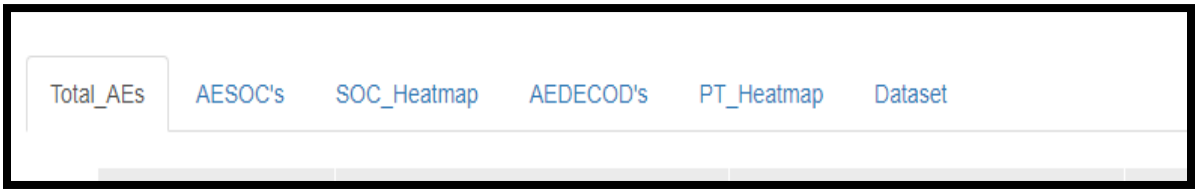


Figure 1

For the main panel in the below schematic different tabs were created to show “Total AE’s”, “AESOC’s”, “SOC_Heatmap”, “AEDECOD’s”, “PT_Heatmap” and “Dataset”. The tabs from main panel would interact with filters of side panel. Total AE’s tab would present data for overall AE’s, while AESOC’s and AEDECOD’s tabs would show subject data based on SOC’s and PT’s respectively. The code used to generate main panel tabs is given below the tab panel of Figure 2.




```
        # Tabsets
        mainPanel(
            tabsetPanel(type = "tabs",
                        tabPanel(title = "Total_AEs",
                          fluidRow(
                             column(12, plotlyOutput(outputId = "plot1")),
                             column(12, dataTableOutput(outputId = "tabl"))
                        )),


                        tabPanel(title = "AESOC's",
                                 fluidRow(
                                   column(12, plotlyOutput(outputId = "plot2")),
                                   column(12, dataTableOutput(outputId = "tabl2"))
                                 )),
                        tabPanel(title = "SOC_Heatmap",
                                 plotlyOutput(outputId = "plot4",height="850px", width = "1250px")),



                        tabPanel(title = "AEDECOD's",
                                 fluidRow(
                                   column(12, plotlyOutput(outputId = "plot3")),
                                   column(12, dataTableOutput(outputId = "tabl3"))
                                 )),

                        tabPanel(title = "PT_Heatmap",
                                 plotlyOutput(outputId = "plot5",height="850px", width = "1250px")),

                        tabPanel(title = "Dataset",
                                 br(),
                                 dataTableOutput(outputId = "data"))
            )
        )
    )
)
```

Figure 2

Dashboard tabs are described in the detail below:

TOTAL AE’s

Traditionally Adverse events are presented as summary tables and listings, which make it difficult to detect patterns. In this Shiny application we present adverse events as bar graphs and heat maps which makes it easier for statisticians and reviewers to get a glimpse of the data in short time.

Adverse events are generally fall in two categories, treatment emergent or not treatment emergent. To visualize the number of patients with treatment emergent AE's, we plotted data in the form of bar diagram. Figure. 3 shows number of unique patients in all the treatments based on treatment emergent flag. The table beneath the bar diagram shows the number in each treatment along with total of all treatments.

Figure 3

As we can see in figure 3 there are more patients with adverse events in Treatment 3 are not treatment emergent, while Treatment 2 and Treatment 4 have more subjects with treatment emergent AE's in comparison to non-treatment emergent

AESOC's

AE term collected on CRF is called Verbatim, this is classified into hierarchy based on coding dictionary called MedDRA (Medical Dictionary for Regulatory Activities) by data management team/Medical Coding team. MedDRA is an international Standardized terminology which is widely used for coding adverse events. Preferred term and System Organ Class are the 2 levels used for reporting Adverse Events.

SOC is the highest level of hierarchy which provides the broadest information of adverse event. SOC's are grouped by etiology, manifestation and purpose. To visualize number of patients in each SOC we plotted a bar graph. Figure 4 shows the unique patients in each SOC within a treatment. Each treatment is color coded differently. The table beneath the bar graph shows the counts of unique subjects per SOC within a treatment.

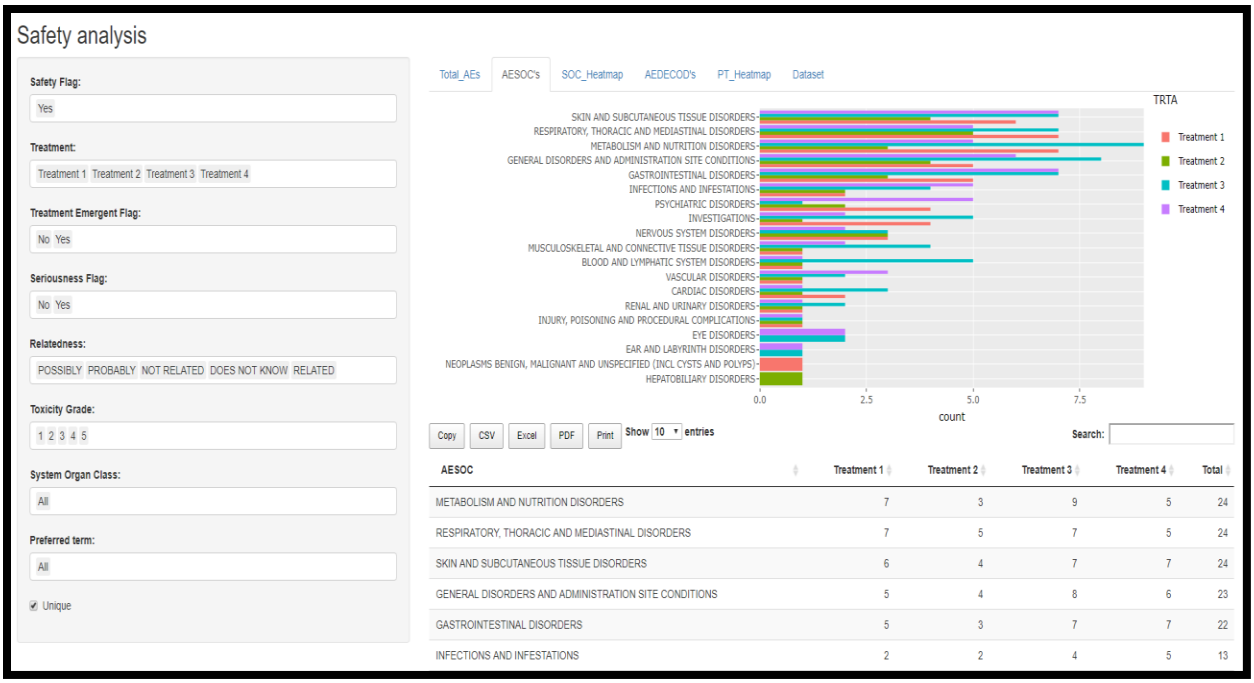


Figure 4

SOC are also summarized based on occurrence within each subject. For this we have created a check button unique which is shown in Figure 5. This button when checked would count the frequency of SOC within each subject.

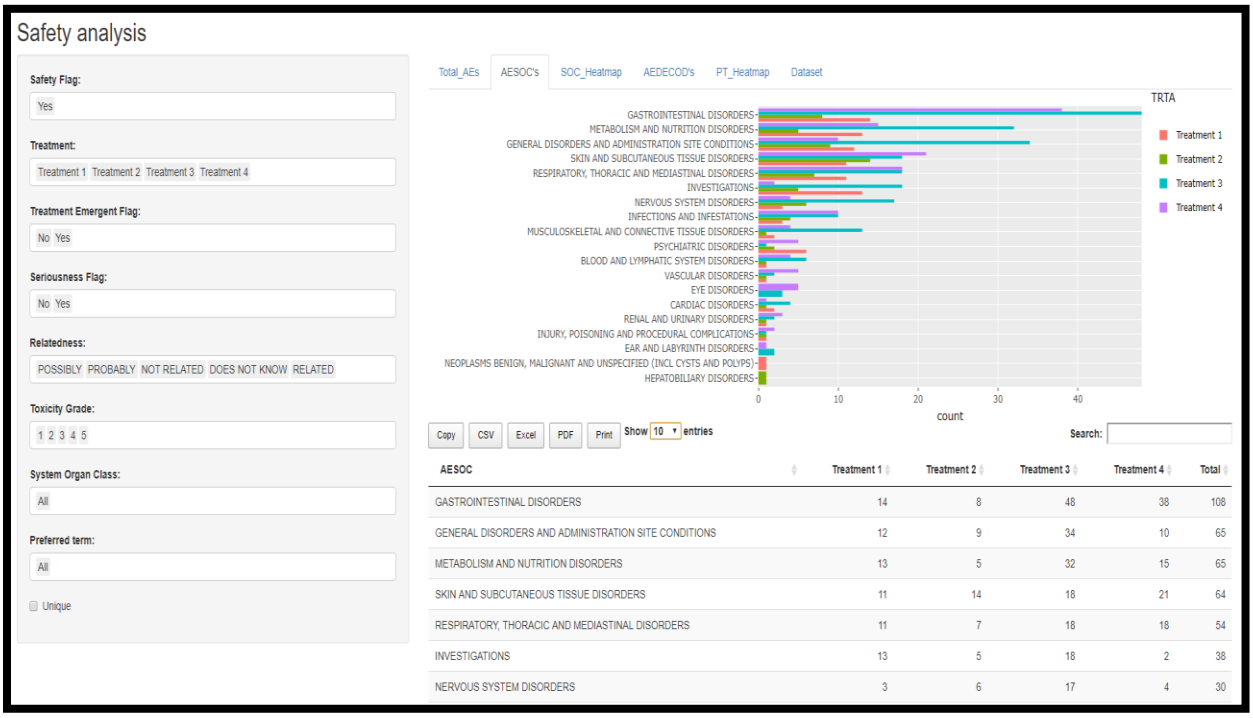


Figure 5

In AE outputs conventionally we show distinct SOCs in a subject or number of occurrences of SOCs for a subject. Figure 4 and 5 present an example which highlights on how counting unique SOCs per subject vs occurrence of

SOCs for a subject helps in understanding of the AE events. In both the figures the filter conditions are the same except for the “unique” check box. If the unique check box is selected this would count unique SOC within a subject else it would count occurrence of SOC within a subject.

As visible in the figure 4, when unique check box is selected “SKIN and SUBCUTANEOS DISORDER”, “RESPIRATORY THORAIC AND MEDIASTINAL DISORDER” and “METABOLISM AND NUTRITION DISORDERS” have the highest count but when it’s unchecked “GASTROINTESTINAL DISORDERS” have the highest count. This means more subjects have “SKIN and SUBCUTANEOS DISORDER”, “RESPIRATORY THORAIC AND MEDIASTINAL DISORDER” and “METABOLISM AND NUTRITION DISORDERS” but more frequently occurring SOC in subjects is “GASTROINTESTINAL DISORDERS”. The Table in Figure 5 shows “SKIN and SUBCUTANEOS DISORDER”, “RESPIRATORY THORAIC AND MEDIASTINAL DISORDER”, “METABOLISM AND NUTRITION DISORDERS” have same count but sorted in ascending order of SOC.

Below (Figure 6) is the code used which is used to count unique adverse events vs occurrence.

```
# Create barplot for total AEs
output$plot1 <- renderPlotly({

  if(input$Unq == TRUE) {

    data <- filtered_data() %>%
      select (SUBJID,TEAE,TRTA ) %>%
      group_by(TRTA, SUBJID, TEAE) %>% slice(1)


  } else {

    data <- filtered_data() %>%
      select (SUBJID,TEAE,TRTA ) %>%
      group_by(TRTA, SUBJID, TEAE)

  }

    p <- ggplot(data, aes(x = TRTA,  fill = TEAE)) +
        geom_bar(position = "dodge")

    ggplotly(p)
})
```

Figure 6

AEDECOD

Preferred term is a distinct descriptor for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure and medical social or family history characteristic. Each preferred term is assigned to one SOC. To visualize number of patients in each PT we plotted a bar graph. Figure 8 shows the unique patients in each PT within a treatment, each treatment is color coded differently. The table beneath the bar graph shows the counts of unique subjects per PT within a treatment.

In Figure 7 we are visualizing adverse events with CTCAE Toxicity Grade>=3. The side panel filters used for Toxicity Grade as 3, 4, 5 and all preferred terms were selected for preferred term filter. The table beneath has a total column which is sum of all treatment groups and it is sorted based on descending counts of the total column. Unique subject counts were used for bar diagram and table as the unique check box is selected.

Figure 7

Dataset

In this application the dataset used for visualization is available in last tab. This can be downloaded in CSV, Excel or PDF format. Figure 8 shows the dataset from application, this can be used by the reviewer to further investigate the data. The dataset also work interactively with side panel. Any specific text can be searched using the search option available on top.

Figure 8

HEAT Maps

A heat map is a graphical representation of data that uses a range of color-coding to represent different values. Heat maps are used in various forms of analytics but are most commonly used to show gene expression profile in biological sciences. Heat maps can give a more comprehensive overview of adverse events as per the treatment groups or in combination of all the treatments together.

In this paper, we are showing heat maps for the first time to represent the adverse events associated with body system organ class (SOC's). The intensity of the color is an indication of the number of AE's i.e. higher the value more intense will be the color. Figure below shows a heat map of SOC count in this study where Y axis reflect SOC's and X axis reflect treatments. Total on X axis refers to the patients from all the treatments. This heat map is made interactive with the filters on sidebar.

Figure 9

CONCLUSION

Interactive visualization provides insight into the data which would help reviewer's to identifying patterns leading to potential safety signal. This will help them to create any adhoc report of interest from the Shiny application directly thus reducing the dependency on programmers. Interactive visualization presents data in clear and concise manner than the traditional static outputs. This helps in interpreting the data and getting cues in a highly efficient way. The reports downloaded from the application can also be used in validation. Overall, R-Shiny visualization make whole procedure efficient and modern and can be adopted for future trials.

REFERENCES

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