Exposure-Response Analysis User Manual

Document Version:00

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1. OVERALL DESCRIPTION

1.1 Description

The ER Visualization function is intended to allow the user to plot Exposure-Response relationship of summary of Concentration-Emergent Adverse Events by treatment.

1.2 Operating Environment

The function will be used with R Version 4.0.2 and RStudio.

1.3 Parameters

Parameters	Required	Usage
data	Y	Name of input SAS dataset for scatter plot and logistics regression analysis
data_stat	Y	Name of input SAS dataset for bar plot
ftitle	Y	Name of input Excel filename of footnotes and titles
fname	Y	Name of file in "ftitle" indicating which file should be chosen
xlab	Y	Name of X-axis label
ylab	Y	Name of Y-axis label
user	Y	User's name

Note:

1. data should include at least the following variables:

USUBJID: Unique Subject Identifier

TRT01A: Actual Treatment

PARAMCDR: Parameter Type (eg: AE or SAE)

PARAMCD: Parameter Code

AVAL: Analysis Value

AVALR: Event Indication (Binary)

TRT: Treatment Flag Including Number of Patients in Each Group

2. data_stat should include at least the following variables:

QTR: Quartiles Sequences

N: Number of Patients in Each Quartile

MEAN: Mean Probability of The Adverse Event at Interest of Each Quartiles

UPPER: The Upper Confidence Interval for Mean Probability of The Adverse Event of Each Quartiles

LOWER: The Lower Confidence Interval for Mean Probability of The Adverse Event of Each Quartiles

AVAL: The Mean Concentrations of Each Quartile

1.4 Required Packages

Package	Usage
haven	Import and Export 'SPSS', 'Stata' and 'SAS' Files
ggplot2	Create Graphics
readxl	Read Excel Files
rtf	Rich Text Format (RTF) Output

Packages should be installed in advance by **install.packages("package name")**

1.5 Constraints

The exposure and response variables should only be "AVAL" and "AVALR".

2. EXAMPLE

2.1 Sample Data Used in Following Examples

Sample data 1 is an analysis ready data set for scatter plot and logistics regression analysis:

	TRT	TRTA	USUBJID	PARAMCD	AVAL	PARAMCDR	I	AVALR
1	Xanomeline Medium Dose (N=72)	Xanomeline Medium Dose	01-701-1015	AST	21	SAE	1	0
2	Xanomeline High Dose (N=56)	Xanomeline High Dose	01-701-1028	AST	28	SAE	1	1
3	Xanomeline High Dose (N=56)	Xanomeline High Dose	01-701-1034	AST	26	SAE	1	1
4	Xanomeline Low Dose (N=60)	Xanomeline Low Dose	01-701-1097	AST	18	SAE	1	1
5	Xanomeline Low Dose (N=60)	Xanomeline Low Dose	01-701-1115	AST	25	SAE	1	0
6	Xanomeline Medium Dose (N=72)	Xanomeline Medium Dose	01-701-1118	AST	18	SAE	1	1
7	Xanomeline Medium Dose (N=72)	Xanomeline Medium Dose	01-701-1130	AST	18	SAE	1	0
8	Xanomeline High Dose (N=56)	Xanomeline High Dose	01-701-1133	AST	19	SAE	1	0
9	Xanomeline High Dose (N=56)	Xanomeline High Dose	01-701-1148	AST	26	SAE	1	1
10	Xanomeline Medium Dose (N=72)	Xanomeline Medium Dose	01-701-1153	AST	21	SAE	1	1
11	Xanomeline Low Dose (N=60)	Xanomeline Low Dose	01-701-1192	AST	23	SAE	1	1
12	Xanomeline Medium Dose (N=72)	Xanomeline Medium Dose	01-701-1203	AST	19	SAE	1	0

Sample Data 1. Analysis Ready Data Set (1)

Sample data 2 is an analysis ready data set for bar plot:

	QTR	N	MEAN	UPPER	LOWER	AVAL
1	Q1	40	0.450000	0.611000	0.289000	16.15
2	Q2	53	0.472000	0.611000	0.333000	19.962
3	Q3	42	0.381000	0.534000	0.228000	23.548
4	Q4	52	0.442000	0.582000	0.303000	30.788

Sample Data 2. Analysis Ready Data Set (2)

2.2 Example1: Summary of Treatment-Emergent Adverse Events

Sample Call:

```
#Import Useful Packages
library(haven)
library(ggplot2)
library(readxl)
library(rtf)
library(extrafont)
library(r2rtf)
library(dplyr)


subsetting=function(data,data_stat,ftitle,fname,xlab,ylab,min,max,int,user){
    #Read SAS Data Sets Into RStudio
    er <- read_sas(data)
    er_stat <- read_sas(data_stat)


    #Extract Statistical Coefficients
    fit<-glm(AVALR~AVAL,data=er,family=binomial(link="logit"))
    pval<-round(coef(summary(fit))[2,4],4)
    #Get Statistical Results
    summary(fit)


    #Import Excel Dataset
    titfoot <- read_excel(ftitle)
    View(titfoot)
    titfootf<-titfoot[which(titfoot$Outfile_Name==fname),]
    datetime<-Sys.time()


    #Plotting And Statistical Analysis
    #Scatter Plot
    p<-ggplot()+
        geom_point(data=er,aes(x=AVAL,y=AVALR,shape=TRT,color=TRT),
```

```r
                    position=position_jitter(width=0.3,height=0.03),size=1.5,alpha=0.5)+
      scale_shape_manual(values=c(0,1,2))+
      scale_color_manual(values=c("red","green","blue"))
   print(p)


   #Logistics Regression
   p<-p+geom_smooth(data=er,aes(x=AVAL,y=AVALR),formula = y~x,
      method = "glm",level=0.95,method.args=list(family="binomial"))
   print(p)


   #Bar Plot for Quartile Analysis
   p<-p+geom_errorbar(data=er_stat,aes(x=AVAL,ymin=LOWER,ymax=UPPER),
      width=2,size=1,color="green")+

geom_point(data=er_stat,aes(x=AVAL,y=MEAN),alpha=0.8,shape=21,size=1.5,fill="white")


   #Figure Appearance
   p<-p+theme_bw()+theme(panel.border = element_rect(colour = "black",size=0.8))+
      labs(x=xlab,y=ylab,title=paste0(titfootf[1,4],"\n",titfootf[1,5],"\n",titfootf[1,7]))+
      theme(legend.position = "bottom",legend.direction = "horizontal",
            legend.title = element_blank(),legend.text = element_text(size=7),
            legend.key.size = unit(1,"lines"),
            text=element_text(family = "Times New Roman"),
            plot.title=element_text(family="Times New Roman",size=(12),hjust = 0.5))


   #RTF Package
   rtf<-RTF(paste0(fname,".rtf"),width=11,height=8.5,omi=c(1,1,1,1),font.size=10)
   addPlot(rtf,plot.fun=print,width=9,height=5.6,res=1000,p)
   addHeader(rtf,title="",subtitle=paste0(titfootf[1,10],"\n","(",user," ",datetime," R 4.0.2)."))
   done(rtf)
}


   #Call Function
   subsetting(data="C:/Users/kgvk524/Desktop/er_dataset.sas7bdat",
```
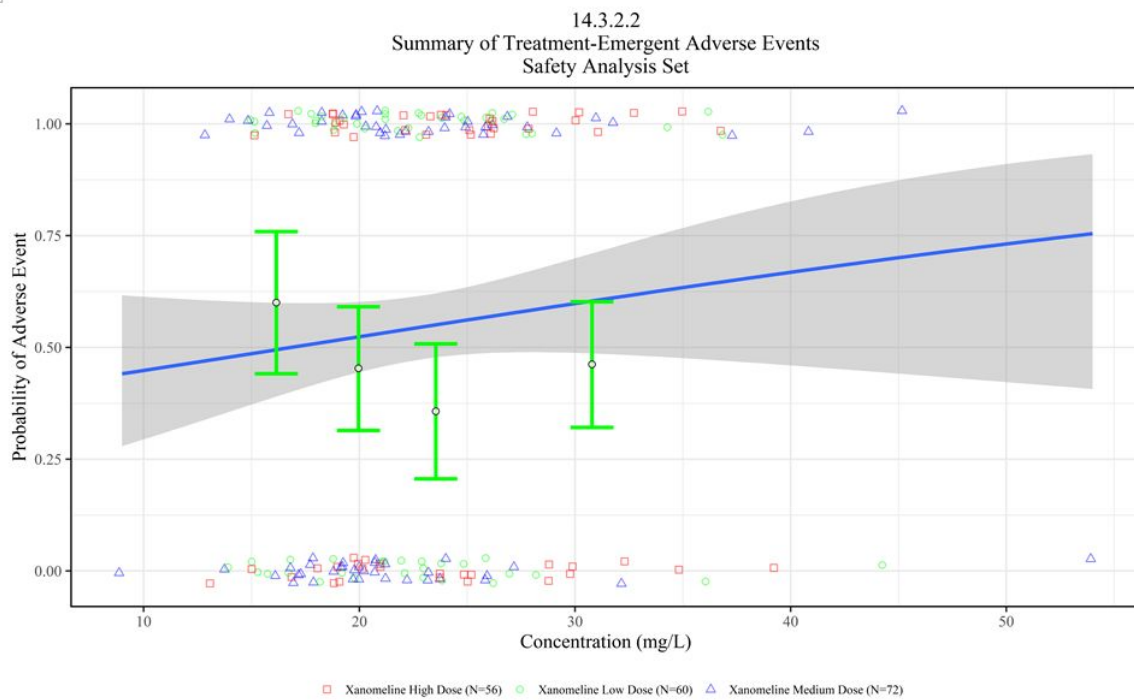
```
data_stat="C:/Users/kgvk524/Desktop/er_stat.sas7bdat",

ftitle="C:/Users/kgvk524/Desktop/m_titles_rpt.xlsx",

fname="T_AE",

xlab="Concentration (mg/L)",

ylab="Probability of Adverse Event",

user="Pinyan.Liu")
```

Sample Output:

14.3.2.2
Summary of Treatment-Emergent Adverse Events
Safety Analysis Set

Abbreviation: n = number of subjects in the specified category.
(Pinyan.Liu 2020-08-13 09:15:29 R 4.0.2).

3. NOTE

3.1 Install R Packages

All R packages should be installed when first used by install.packages(). After that, every time if users want to use it, packages should be imported by library().

3.2 Capital Letters in R

R is sensitive to uppercase and lowercase letters.