PhUSE 2018

Paper DV10

Safety Signal Detection Visualizations using Spotfire including R

Michaela Mertes, F. Hoffmann-La Roche, Ltd., Basel, Switzerland

ABSTRACT

The Safety Signal Detection Visualizations are a draft set of safety visualizations which were taken out of a PhUSE White Paper 'Analysis and Displays Associated with Adverse Events' and out of the presentation 'The Forest for the Trees Visualizing Adverse Events' held at the DIA 2011. It is primarily planned for the use of Safety Scientists at Roche. It enables the customers to access and gain insights from data via self-service. The Signal Detection Visualizations are developed with Tibco Spotfire® version 7.7 including R 3.4.2.
Different types of outputs from a phase III study are included in the live-demo to get an overview of available templates. The presented standard safety outputs are selected for Demographics and Adverse Events analysis data sets. They include listings, tables and graphs. In addition, possibilities for safety scientists or programmers are explained to dive into the data in more detail.

INTRODUCTION

Spotfire is an analytics platform where data can be explored inter-actively. Numerous in-built visualizations can be selected. With the ability to combine R programs into Spotfire a lot more can be added. Stakeholders do have access to a final combination of visualizations via a web-player to dig deeper into their data of interest. The web-player provides controlled access.

OVERVIEW OF SPOTFIRE VISUALIZATIONS

The idea for the set-up of the following visualizations is to try to implement different examples seen in various presentations and within own programming experience of adverse event data - to collect these together in one visualization package. All data / visualizations presented in this paper are from dummy data.

Percentages of Adverse Events

The first example is figure 1, a scatter plot done with Spotfire:

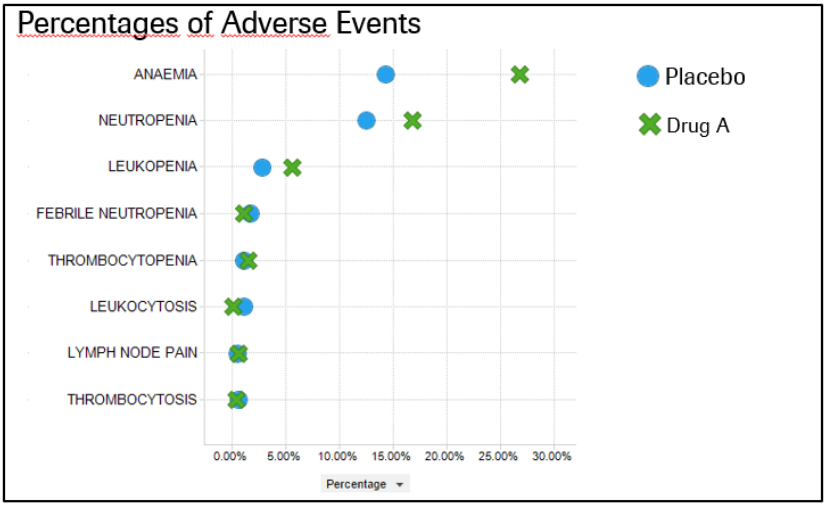


Figure 1

It shows the number of percentages per preferred term sorted by total frequency where it is easier to see where the percentage is higher in drug A group compared to placebo group, e.g. anaemia. This is much easier to detect than in summary tables, which is displayed in Table 1 showing anaemia in 26.8% of patients exposed to drug A compared to 14.3% in the placebo control group.

Summary of Adverse Events by Body System and Preferred Term

Body System or Organ Class	Dictionary-Derived Term	PLACEBO N	PLACEBO %	PLACEBO Events	DRUG A N	DRUG A %	DRUG A Events
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Subtotal	206	20.96	640	332	41.04	757
	ANAEMIA	141	14.34	230	217	26.82	321
	NEUTROPENIA	123	12.51	238	136	16.81	301
	LEUKOPENIA	28	2.85	51	45	5.56	79

Table 1

Percentages of Adverse Events within Severe Adverse Events

The next example, a scatter plot done with Spotfire, shows on the left also the percentages of adverse events, but where at least one adverse event is reported as severe. On the right only the percentage calculation of the severe adverse events is plotted.

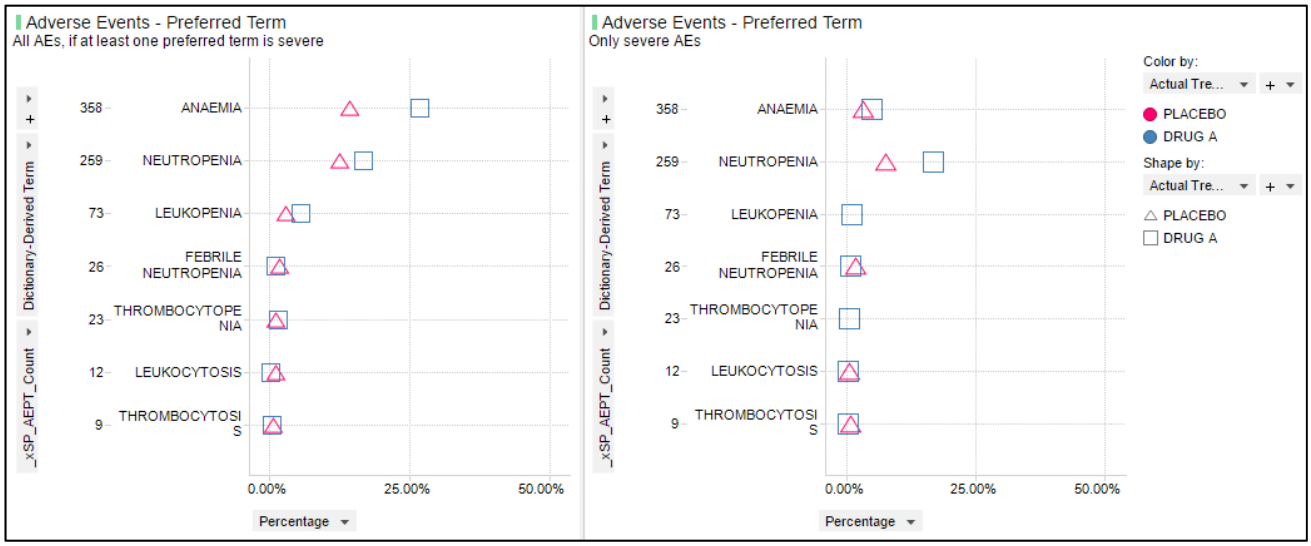


Figure 2

Figure 2 shows, that for anaemia the percentage of the severe adverse events are very similar, even if more adverse events of anaemia occur in within group drug A. However, for neutropenia patients receiving drug A do experience more severe events than in the placebo group.

Bar Chart of Percentages of Adverse Events

Figure 3 shows a bar chart done with Spotfire including an R script calculating the percentages per system organ class of adverse events. On the left the percentages within placebo group is displayed and on the right the percentage of the adverse events within group drug A. 20.96% of the patients receiving placebo do experience adverse events categorized within “Blood and Lymphatic System Disorders”, 41.04% of patients in the group drug A The more highlighted part of the bar shows the difference between the two groups: 20.08%. Only the percentage of the difference could be displayed in a bar chart as well.

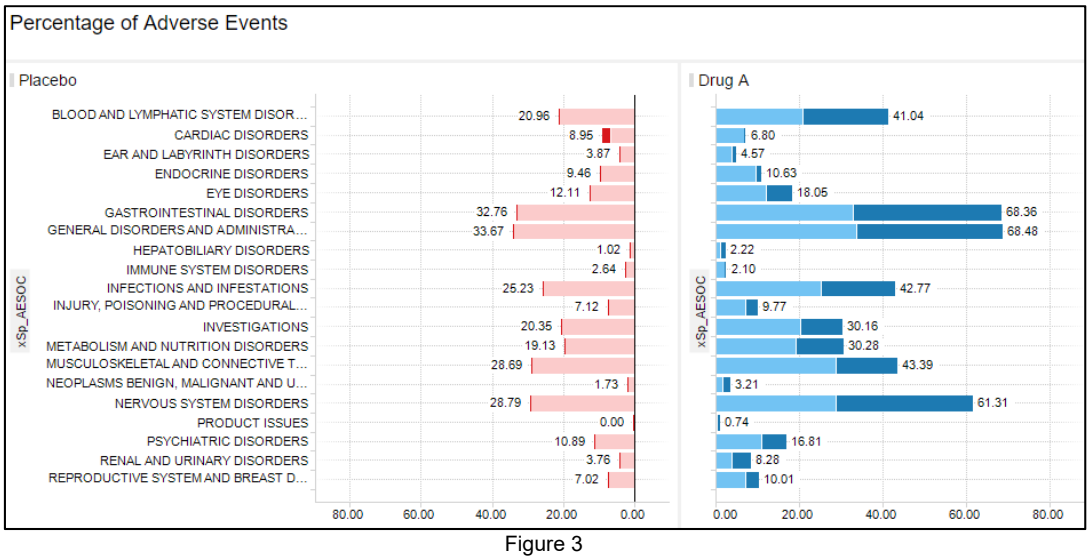


Figure 3

Bar Chart of Related Adverse Events

The next example, figure 4, a bar chart done with Spotfire including an R script, shows on the left the percentages of adverse events within drug A and on the right the percentage of the related adverse events within group drug A. 26.82% of patients in the group drug A do experience anaemia, and anaemia is reported as related to drug A for 10.75% of patients in group drug A. An R script is needed to also show the adverse events where no event is displayed as related to drug A, e.g. for leukocytosis. On the left of the Spotfire page the variable selection is displayed below "ShowModifiedFilters": drug A is chosen from the demographic data.

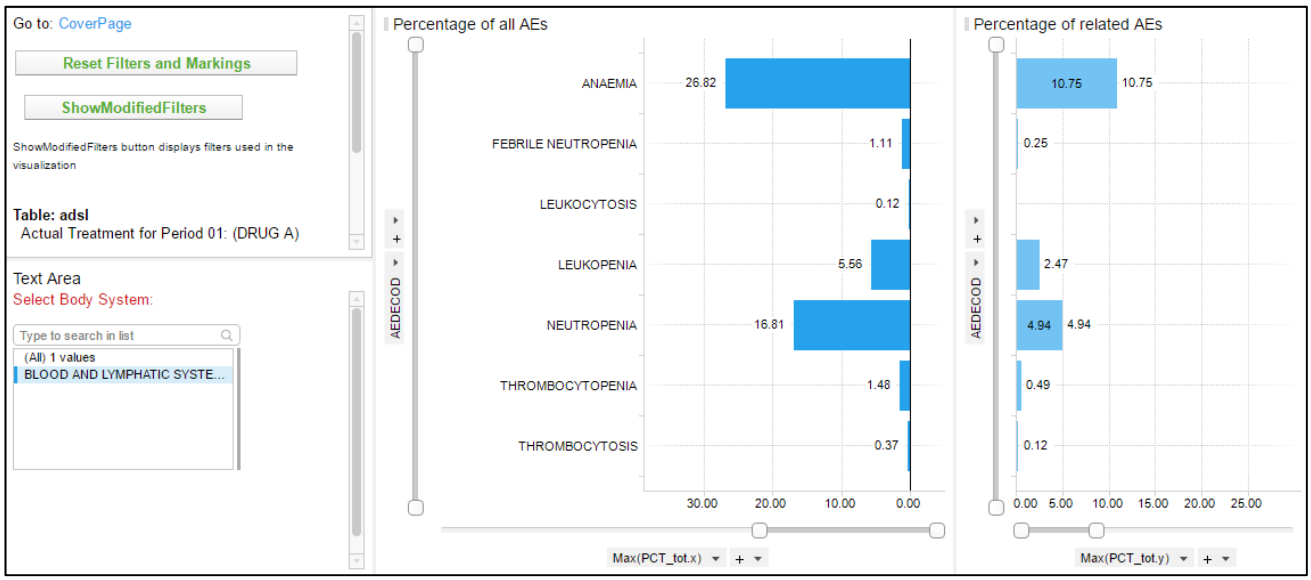


Figure 4

Percentage / Risk Difference (RD)

Figure 5 shows on the left again the percentages per adverse events displayed as a scatter plot and on the right the RR (Relative Risk) together with the 95% Confidence Interval calculated within an R script according to the following formulas for two groups:

	Group 1	Group 2
Number with positive outcome	a	c
Number with negative outcome	b	d
Total	a+b	c+d

Risk Difference (RR), Standard Error (SE), 95% Confidence Interval (95% CI)

$$RD = \frac{a}{a+b} - \frac{c}{c+d} \qquad \mathrm{SE}\{RD\} = \sqrt{\frac{a \times b}{(a+b)^3} + \frac{c \times d}{(c+d)^3}} \qquad 95\%\ \mathrm{CI} = RD - 1.96 \times \mathrm{SE}\{RD\} \quad \text{to} \quad RD + 1.96 \times \mathrm{SE}\{RD\}$$

Calculation of the Risk Difference for neutropenia:

	Drug A	Placebo
Number of patients with neutropenia	136	123
Number of patients without neutropenia	673	860
Total	809	983

RD for neutropenia = (136/809) – (123/983) = **0.043**

SE for neutropenia = (((136*673)/ (809)^3) + ((123*860)/ (983) ^3))^(1/2) = **0.0167**

95% CI for neutropenia = 0.043 +/– 1.96*0.0167 -> **0.010 to 0.076**

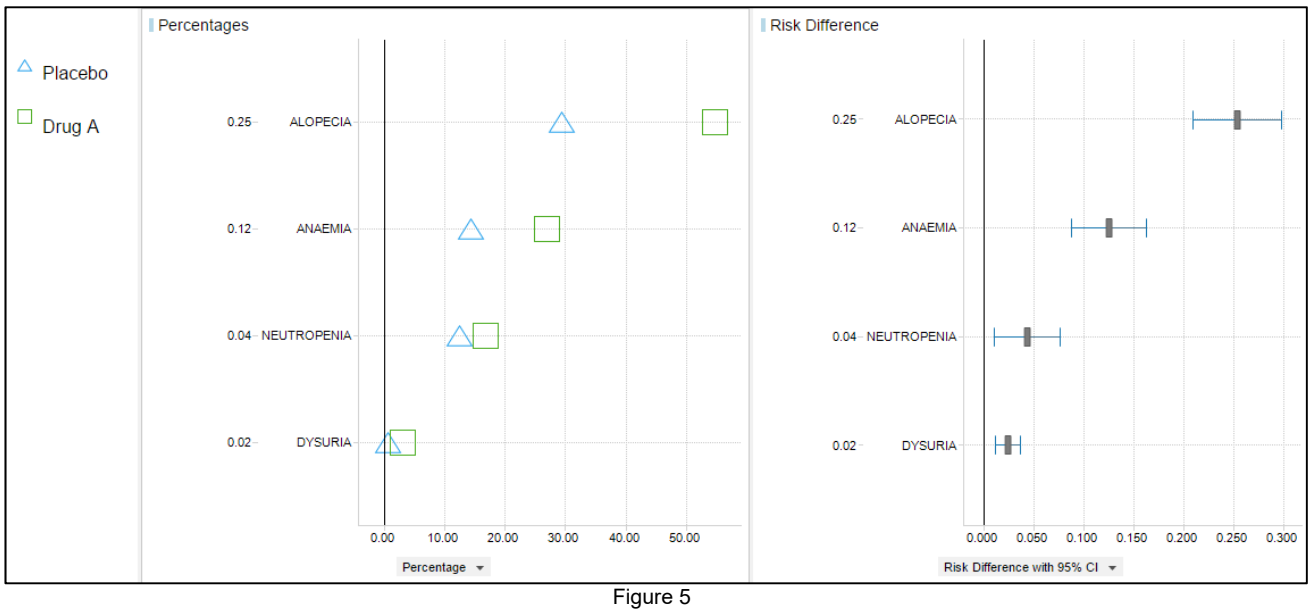


Figure 5

Volcano Plot

Example Figure 6 shows a P-risk plot, sometimes named volcano plot, because the plot can look like a volcano in certain circumstances. The higher the z-score the higher the probability to experience that adverse event (y-axis). The more to the left or the right on the x-axis (Relative Risk), the higher the probability to experience this adverse event in one group compared to the other. A relative risk of 1 means that there is no difference between the two groups.

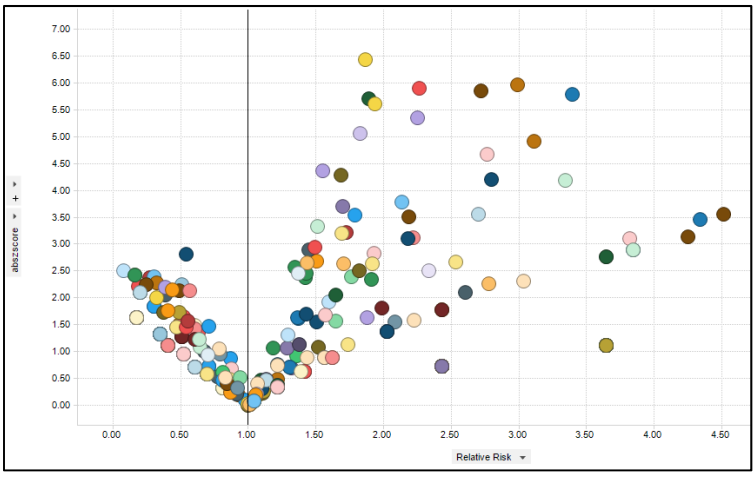


Figure 6

A Scatter plot is used within Spotfire to show the relative risk versus the absolute z-score in figure 6. An R script is doing the calculation of the z-score and the relative risk. The same dummy data are used as in Table 1. Within Spotfire the data points can be marked and shown in more detail to look for adverse events which are at a higher risk within the population, shown in Figure 7.

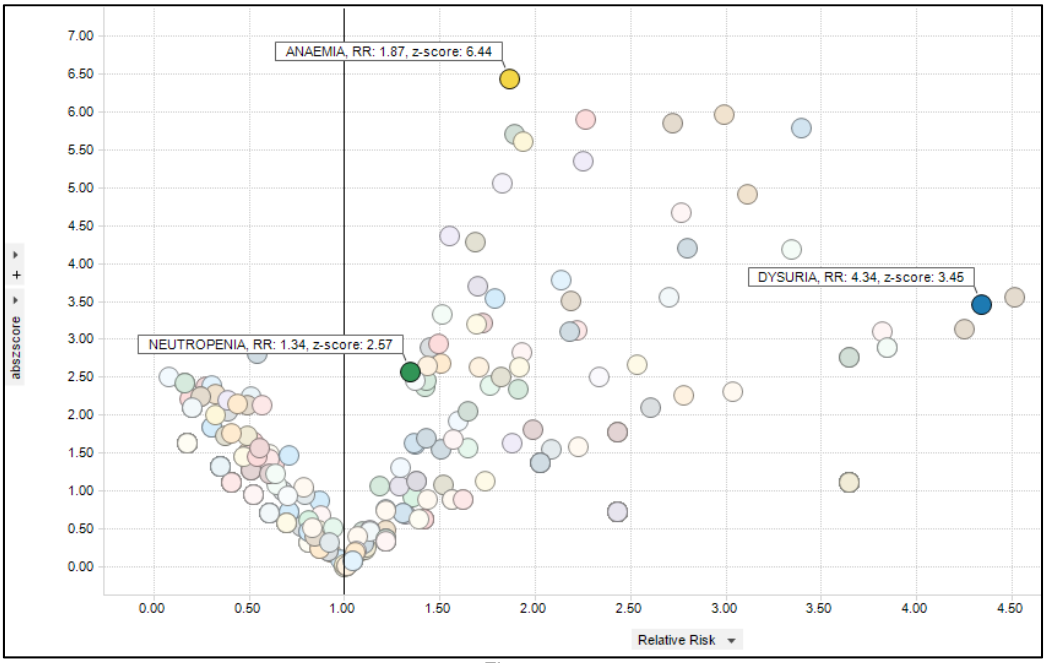


Figure 7

The relative risk or risk ratio (RR) is the ratio of the probability of an event occurring in one group versus the event occurring in the comparing group. The formula for RR is as following:

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

For neutropenia, we do have 123 patients with an event out of 983 patients in total for drug A. 809 patients do receive placebo and 136 patients experience neutropenia in the placebo group.
Relative Risk for Neutropenia: (136/809) / (123/983) = 1.34. Relative Risk of 1 means that there is no difference between the placebo and control group drug A. RR for dysuria is 4.34, which is displayed more on the right on the y-axis. It is a higher risk to experience dysuria in the control group drug A compared to the placebo group.

The z-score indicates how many standard deviations an element is from the mean.
A z-score of 0 is the average, meaning that the total number of patients having a specific adverse event with a z-score of 0 is the average number of patients having an adverse event in these study data. A z-score above 0 mean that the number of patients experiencing this adverse events is much higher than the average.

Time to Event

Time to Event curve points are calculated within an R script. A line chart from Spotfire displays the calculated values Within Spotfire the data can be filtered. The following Figure 8 shows the time to event curve only for the filtered adverse event neutropenia.

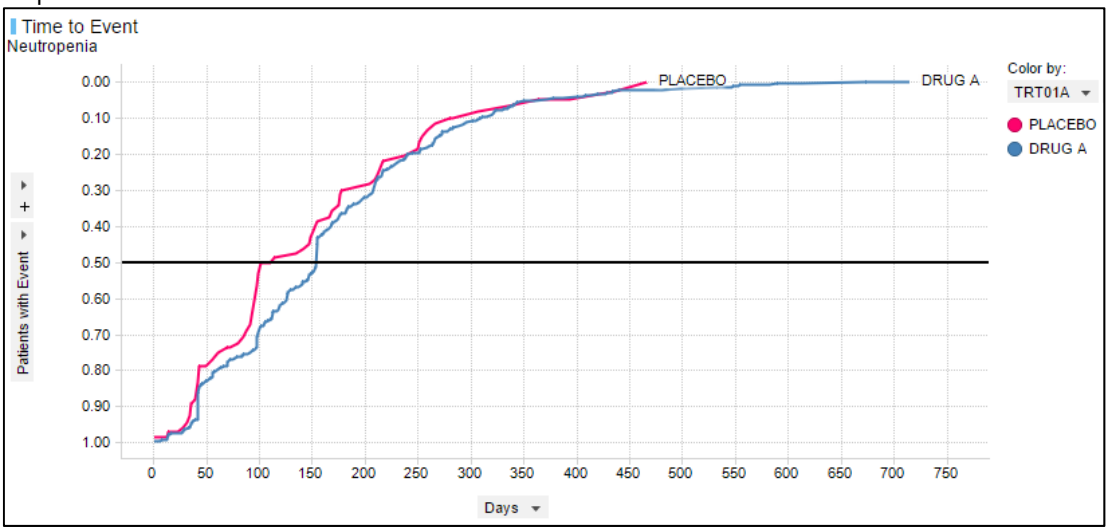


Figure 8

Patient Years at Risk Calculation

Go to: CoverPage

Reset Filters and Markings

ShowModifiedFilters

ShowModifiedFilters button displays filters used in the visualization

Table: adae
Dictionary-Derived Term: (NEUTROPENIA)

Patient Years at Risk

Summary Category	PLACEBO	DRUG A
N	983	809
Number of Patient with Event	123	136
Total Sum (Days)	131964	115209
Total Patient Years	361.30	315.43
Patient Years at Risk	2.94	2.32

Summary Category

Table 2

Table 2 shows the calculation of patient years at risk for the filtered adverse event neutropenia. All days from the start of the first treatment intake until the end of the study are summed up for patients without experiencing neutropenia, plus all days for patients with neutropenia until the first day the adverse event started the first time. This total sum of days is divided by 365.25 to have the total patient years. The total patient years are divided by the number of the patients with an event to get the patient years at risk.

Start and End Days of Adverse Event

Figure 9 shows start and end days of a specific adverse event if there would be any pattern. If this specific adverse event would start more often at the beginning of the study, or at a specific time point compared to the intake of the study drug. The duration is displayed by the length, as well if the event is serious or not (marked with a star).

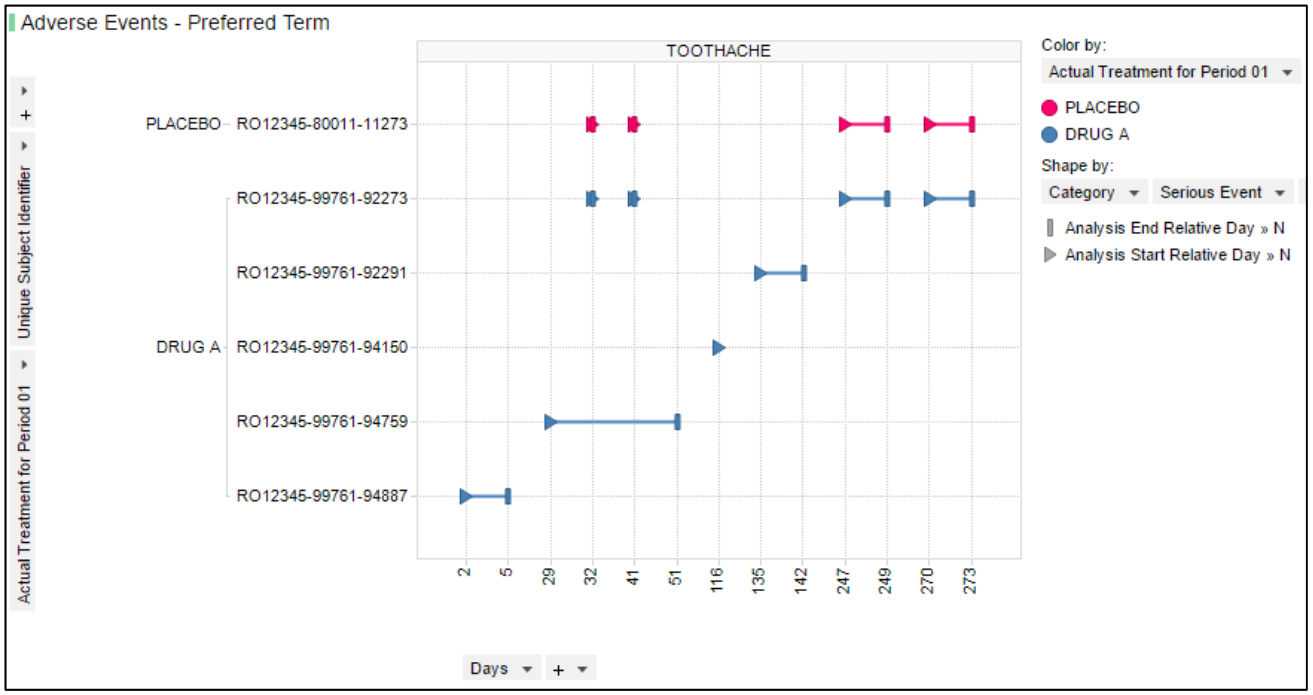
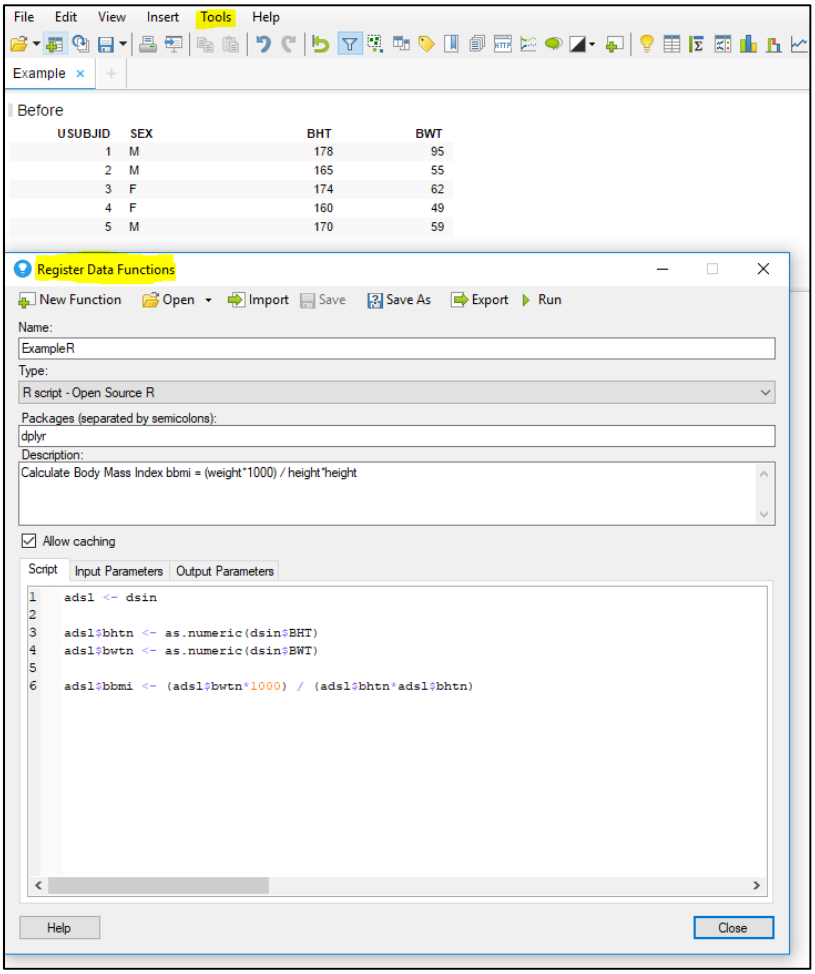


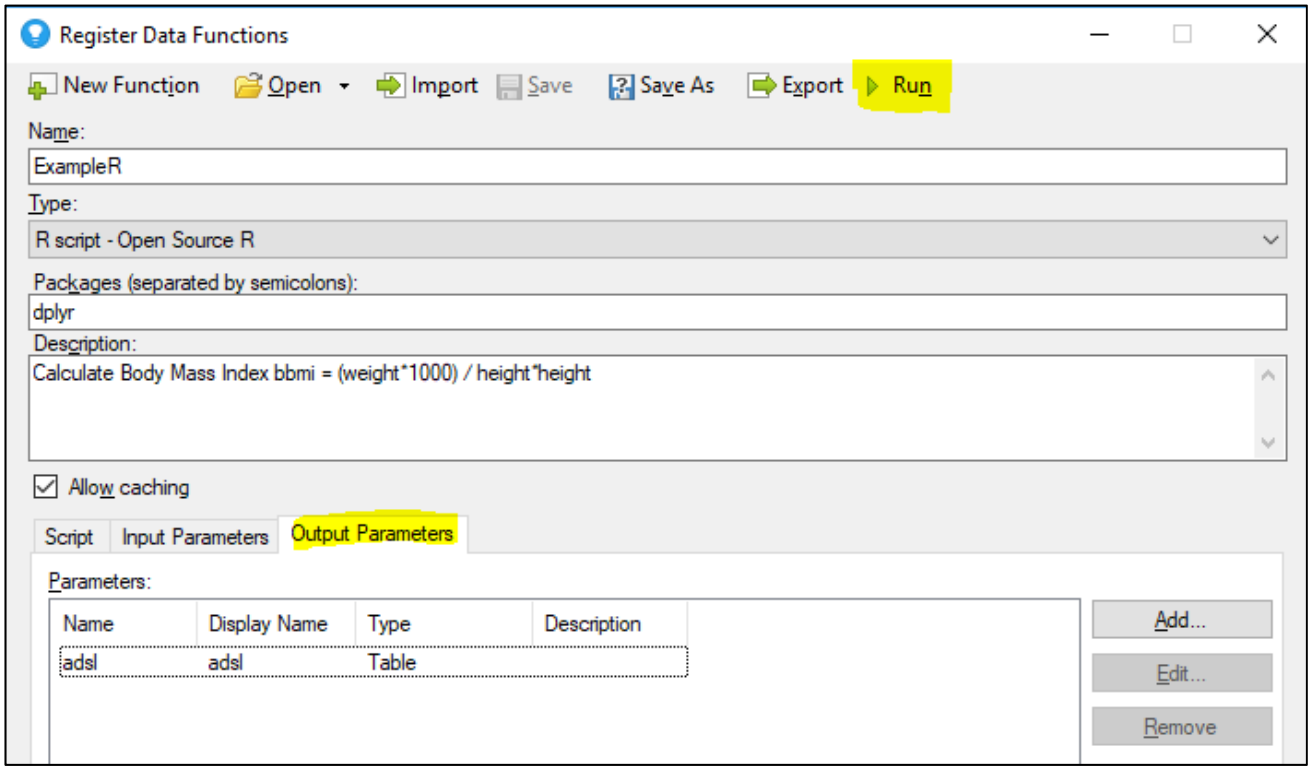
Figure 9

Spotfire: Including a simple R program

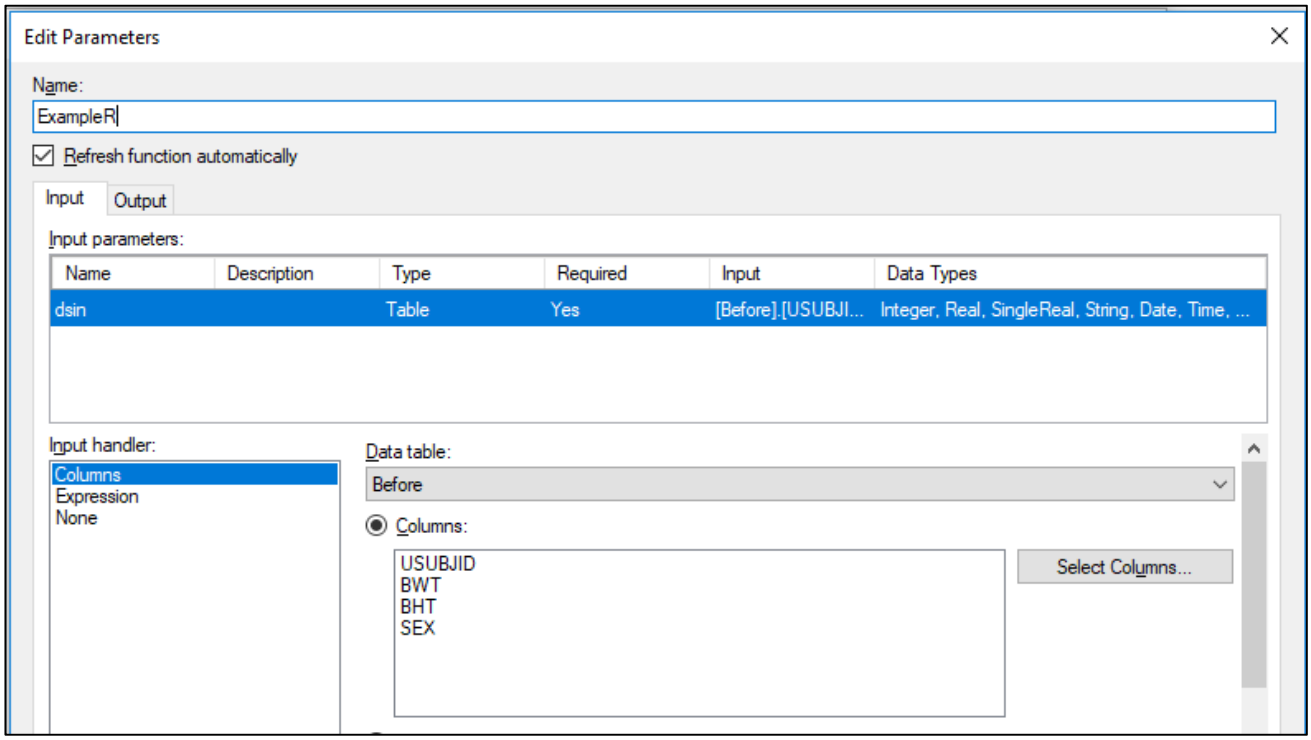
First the R program needs to be created. Then the script can be added within Spotfire going to **Tools -> Register Data Function**



In this example a simple R code is added to the Script panel. Within the “Input Parameters” panel the input needs to be specified. These are the parameters the R function needs as input to run. Here, R needs a table “dsin”. The output parameter needs to be specified as well, “adsl” is specified in the “Output Parameters” panel as type “Table”.



After that the program needs to be run. The user is asked to specify the Spotfire information for running the R code. In this example the “Input” parameter “dsin” will be specified in the Edit Parameters Panel. For “dsin” the Spotfire table “Before” is selected as input with all available columns. Scrolling down the filtering options can be selected.



The “Output” Panel needs to be edited as well. In this example “adsl” will be the name of the table within Spotfire as well. Table 3 shows the result after running the R function within Spotfire. Data table “adsl” is selected on the right for displaying the result data set.

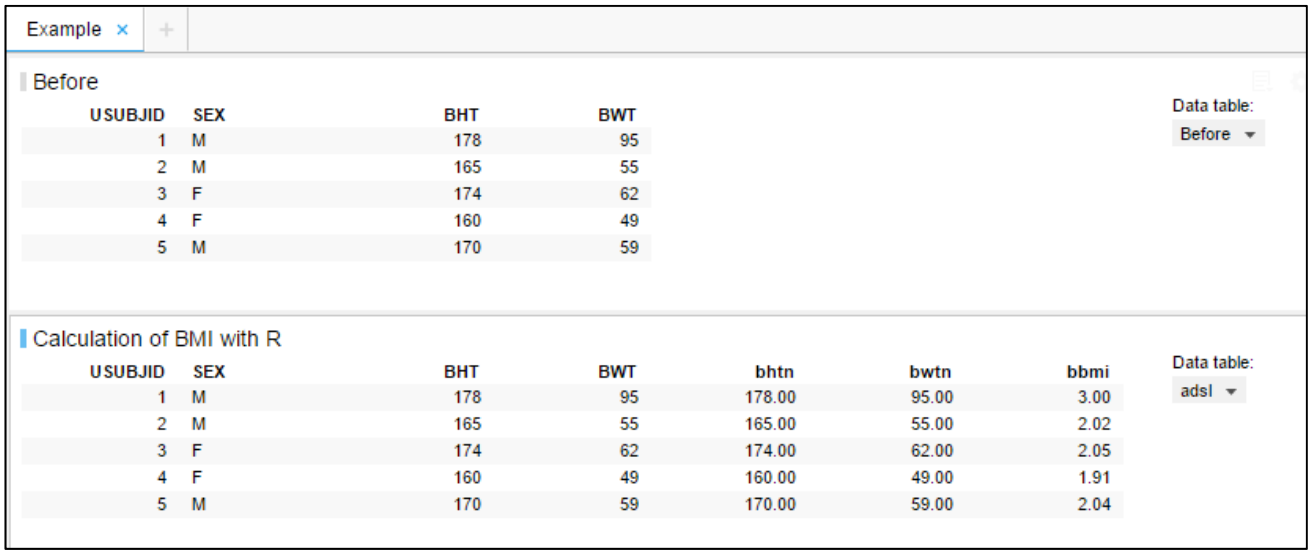


Table 3

CONCLUSION

Within Spotfire you can set-up a package of visualizations for adverse events. A filtering option is built in, therefore the visualization shown in this paper can start from a higher level of categorization of adverse events, e.g. from System Organ Classes or Body Systems terms, down to the preferred terms. Adverse events of special interest could be summarized together.

Filtering the data further down to look into specific patient subgroups, e.g. different countries or into the male/ female sub-population, is also possible. You can also dig into the data to select single patient data and/or corresponding adverse event information.

I aim to promote this idea to different stakeholders to implement real data, to find out if it is of interest and safety signals could be found.

REFERENCES

The Forest for the Trees Visualizing Adverse Events (DIA 2011), Andreas Bruckner, Bayer Healthcare
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ACKNOWLEDGMENTS

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:
Michaela Mertes
F. Hoffmann-La Roche, Ltd.
Email: michaela.mertes@roche.com