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Standard Safety Visualization Set-up Using Spotfire

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ABSTRACT

Stakeholders are requesting real-time access to clinical data to explore the data interactively and get a deeper understanding. An initiative at Roche to address these requests led to the Core Safety Visualization (CoreSV) - a set of standard safety data visualizations. The intended primary users of the CoreSV are Roche Safety Scientists, who are responsible for the review and interpretation of safety data from Roche clinical trials. CoreSV enables the customers to access and gain insights from data via self-service. The CoreSV has been developed with Tibco Spotfire® version 6.5 by Statistical Programmers at Genentech, a member of the Roche group.

Different types of outputs from a dummy phase III study are included in this Paper to get an overview of available templates. Tables, listings, and graphs are presented for Demographics, Adverse Events, and Laboratory data. In addition, possibilities to explore data in more detail are described.

INTRODUCTION TO CORE SAFETY VISUALIZATION (CORESV)

Spotfire was chosen since there is an existing infrastructure at Roche and Safety Scientists are familiar with the tool.

The CoreSV includes summary tables, listings, and graphs to enable Safety Scientists to explore baseline safety data, study drug intake, adverse events, concomitant medication use, vital signs, and laboratory data. The CoreSV is set-up in agreement between Safety Scientists and Statistical Programmers for new or already ongoing studies. For all visualizations the analysis datasets produced for clinical study reports are used.

All Roche Statistical Programmers were trained in Spotfire in face to face interactive sessions. Further training for CoreSV is given when the Statistical Programmers need to upload their study data. Drop-in sessions and super-user support is available for all Statistical Programmers.

Joint sessions are scheduled for Statistical Programmers and Safety Scientists to get further information about the CoreSV and to build-up a good relationship for further collaboration.

Safety Scientists get access to the CoreSV for their corresponding study data via a web-player.

CORESV TABLE OF CONTENTS

The CoreSV home page contains a Table of Contents which shows all available standard safety templates (Figure 1). Since the safety analysis datasets within the different studies have a similar structure, study data can be uploaded to the CoreSV templates with minimal or no changes. Furthermore, additional visualization(s) can be added according to study needs.
Statistical Programmers will replace the dummy analysis data within the CoreSV with the analysis data of the respective study. They access the CoreSV as authors. Authors can modify and/or add visualizations and upload data to the CoreSV.

Safety Data Domain	Summary Tables/Plots	Listings / By-Patient Plots
Demographics	Demographics 1 (Discrete) Demographics 2 (Continuous)	Listing: Demog
AE	AE Graph Time to AE Onset AE Table by PT AE Table by SOC and PT AE Table by Highest Grade	Listing: AE
Patient Profile	Patient Profile	
Lab	Lab Summary Lab Summary (Chg Fr BL)	Lab By-Patient Plot Listing: Lab Tests
Vital Sign	VS Summary VS Summary (Chg Fr BL)	VS By-patient Plot Listing: VS
Study Drug		Study Drug by-Patient Plot Listing: Dose Exposure
Concomitant Medication	Conmed Summary	Listing: Conmed
Medical History		Listing: Medical History

Figure 1

Figure 1 shows the table of contents of the CoreSV – these are the standard visualizations available. The arrows mark the visualizations, which are further explained in this paper.

FILTERING OF VISUALIZATIONS

Filters in Spotfire can be used to select a specific subgroup. For example, users (e.g. Statistical Programmers, Safety Scientists) can select only the female population and patients with a concomitant diagnosis of hypertension (Figure 2, arrows 1).
Within the CoreSV the filters are shown on the right side of every page. Applying the selection of this subgroup, 10 female patients with hypertension are found in the data (Figure 2, arrow 2).

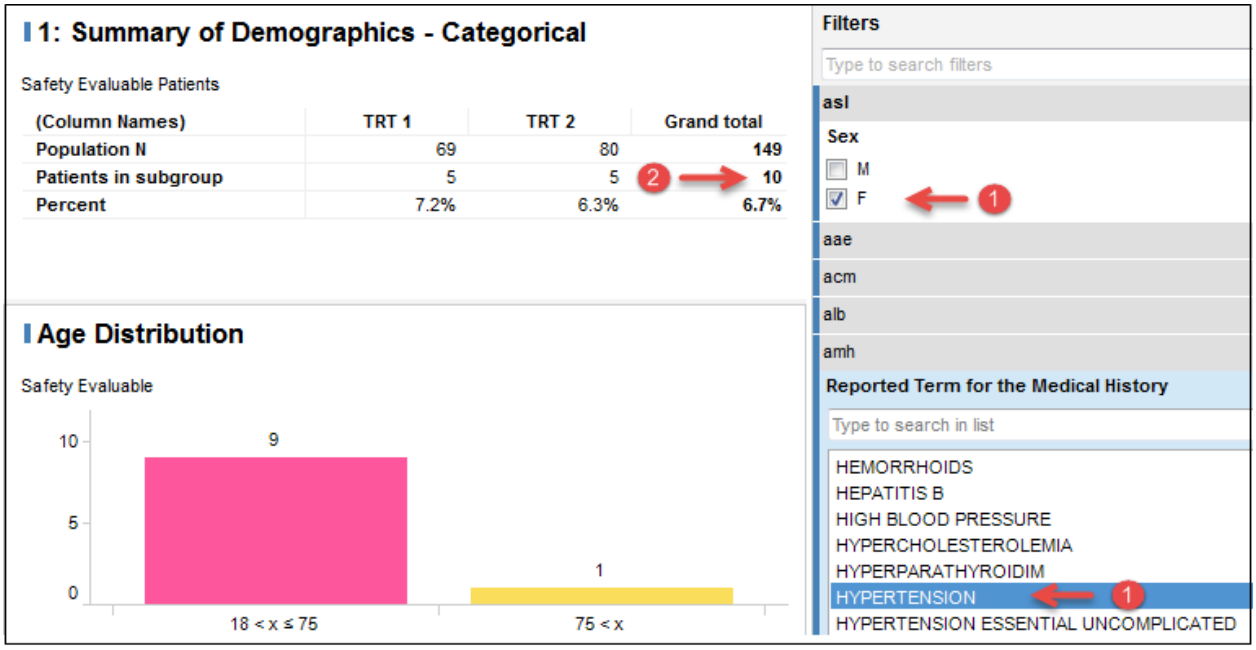


Figure 2

Filters selected across multiple variables are subject to an AND constraint, in this example female patients with hypertension. Multiple filters selected on one variable are subject to AND/OR constraints, for example, if 'HIGH BLOOD PRESSURE' and 'HYPERTENSION' Medical History reported terms are selected, then all patients with either would be displayed.
All visualizations in the CoreSV have the button 'Reset Filters and Markings' (Figure 3). If the user presses this button, new filters can be selected.

The 'ShowModifiedFilters' button will give the information of the selected filters the user has chosen, if any. In this example (Figure 2), the female patients with hypertension as medical history are selected (Figure 3).

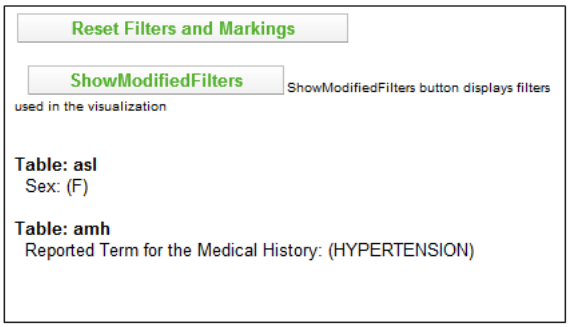


Figure 3

The selection of a subgroup applies to all visualizations in the CoreSV. Figure 4 shows the mean plot for systolic blood pressure for these 10 patients.

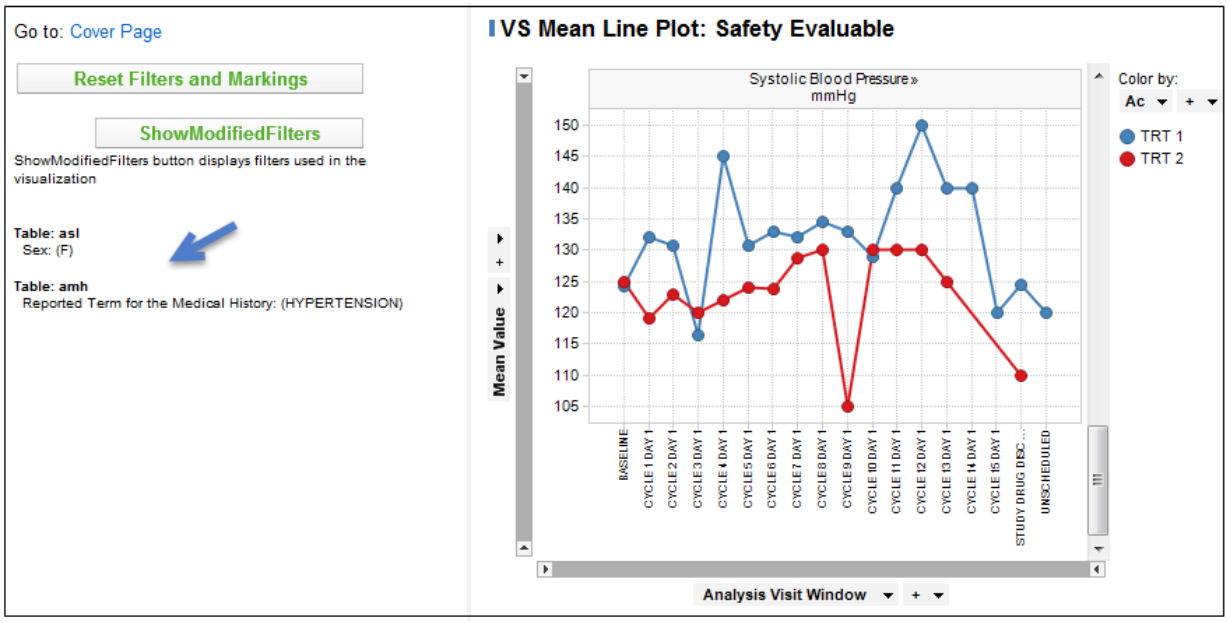


Figure 4

WEB PLAYER

Users (e.g. Safety Scientists) have access to CoreSV via a web player. The web player provides controlled access and new visualizations cannot be created by users.

Key variables from the datasets are selected by the author to be included in the filters panel after discussion with the user. The data, which has been made available by the author, can be reviewed and filtered. All visualizations can be downloaded and tables and listings can be exported as Excel files.

Filter selections can be bookmarked. Figure 5 shows the time to onset of treatment emergent adverse events for the female patients. This subgrouping can always be selected using the bookmark for female patients (arrows 1). Also a bookmark for the male population was created. These bookmarks are saved and usable when the web player link is opened again.

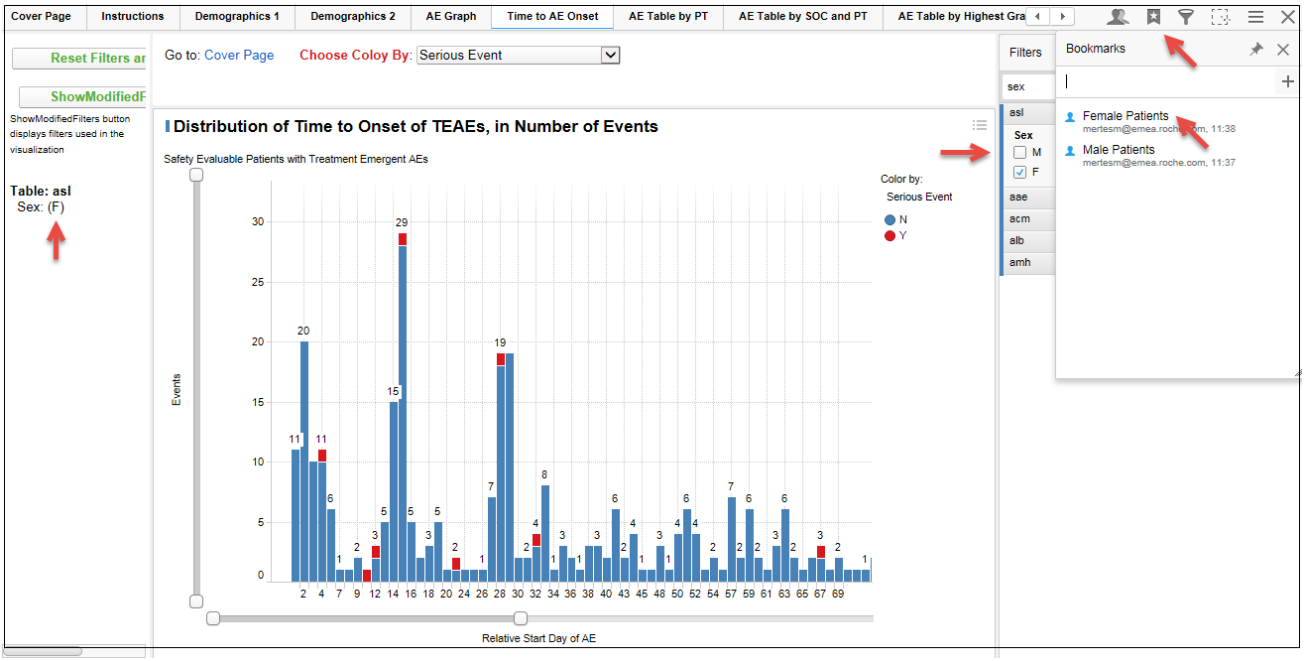


Figure 5

DEMOGRAPHICS 1 (DISCRETE)

Users can navigate between the different visualizations either using the links in the table of contents (Figure 1) or choosing one of the pages at the top row of the CoreSV.
The first demographic page Demographics 1 (Figure 6) shows discrete demographic variables. Sex, age group, race, and region are graphically displayed with either a bar or a pie chart and in a table, together with ethnicity and discontinuation information.

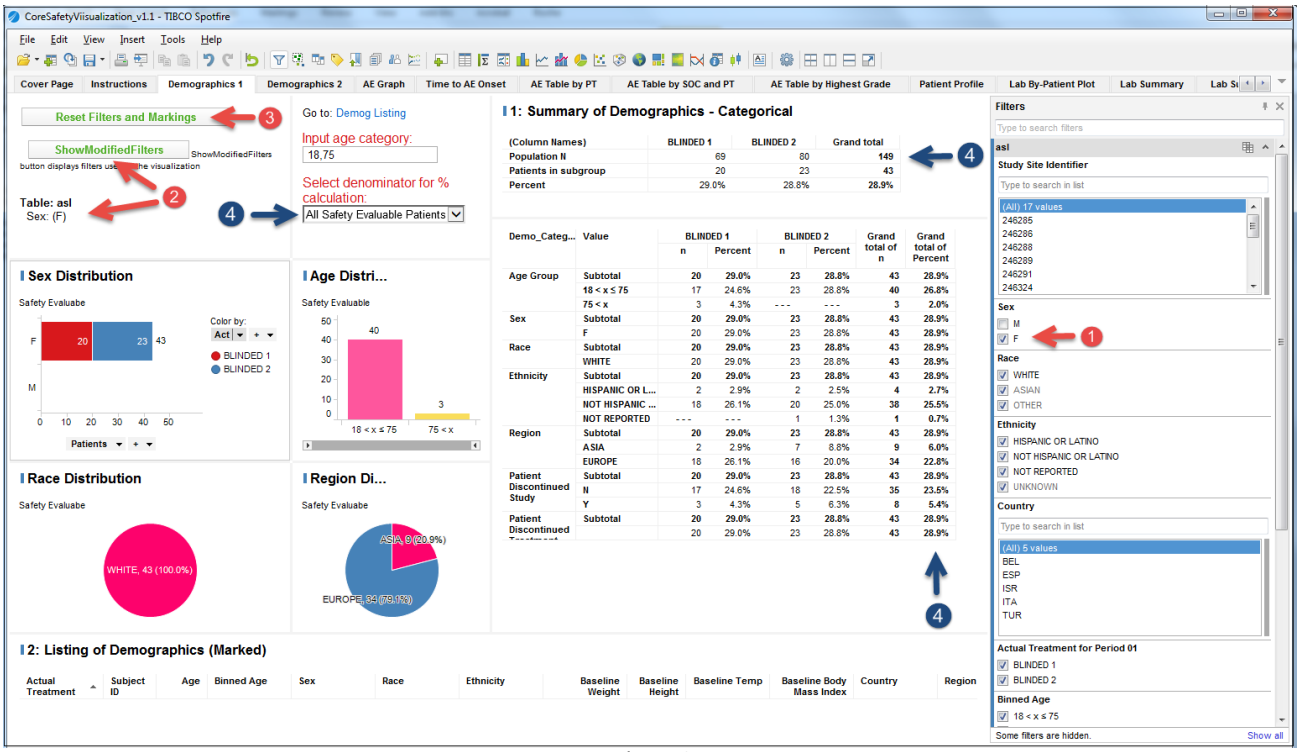


Figure 6

In figure 6 only the female population is chosen (arrow 1). With the button 'ShowModifiedFilters' on the top left always the actual selected filtering is shown (arrow 2); with the button 'Reset Filters and Markings' a new selection can be started (arrow 3).

For the summary table the calculation of percentage is according to all safety evaluable patients (Figure 6, arrows 4). The subgroup, in this example the female population, can be selected for the calculation of percentages in the summary table (Figure 7). The percentage calculation of the summary table is updated automatically (Table 1).

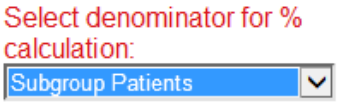


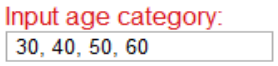
Figure 7

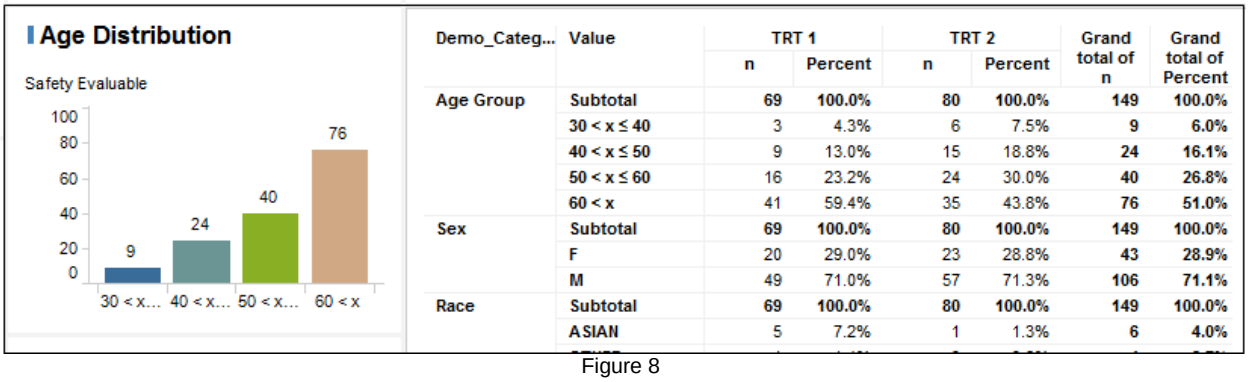
1: Summary of Demographics - Categorical

(Column Names)		TRT 1		TRT 2		Grand total	
Population N		69		80		149	
Patients in subgroup		20		23		43	
Percent		29.0%		28.8%		28.9%	
Demo_Categ...	**Value**	**TRT 1**		**TRT 2**		**Grand total of n**	**Grand total of Percent**
		n	**Percent**	**n**	**Percent**		
Age Group	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	18 < x ≤ 75	17	85.0%	23	100.0%	**40**	**93.0%**
	75 < x	3	15.0%	---	---	**3**	**7.0%**
Sex	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	F	20	100.0%	23	100.0%	**43**	**100.0%**
Race	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	WHITE	20	100.0%	23	100.0%	**43**	**100.0%**
Ethnicity	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	HISPANIC OR L...	2	10.0%	2	8.7%	**4**	**9.3%**
	NOT HISPANIC ...	18	90.0%	20	87.0%	**38**	**88.4%**
	NOT REPORTED	---	---	1	4.3%	**1**	**2.3%**
Region	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	ASIA	2	10.0%	7	30.4%	**9**	**20.9%**
	EUROPE	18	90.0%	16	69.6%	**34**	**79.1%**
Patient Discontinued Study	**Subtotal**	**20**	**100.0%**	**23**	**100.0%**	**43**	**100.0%**
	N	17	85.0%	18	78.3%	**35**	**81.4%**
	Y	3	15.0%	5	21.7%	**8**	**18.6%**

Table 1

Within the input field ‘Input age category’ the user can create own age categories (Figure 8). Entering this, the bar chart and the variable ‘Age Group’ in the summary table will be updated automatically. By default it is 18, 75 as shown in Table 1. Using the age categories 30, 40, 50, 60, bar chart and summary table are updated accordingly (Figure 8).





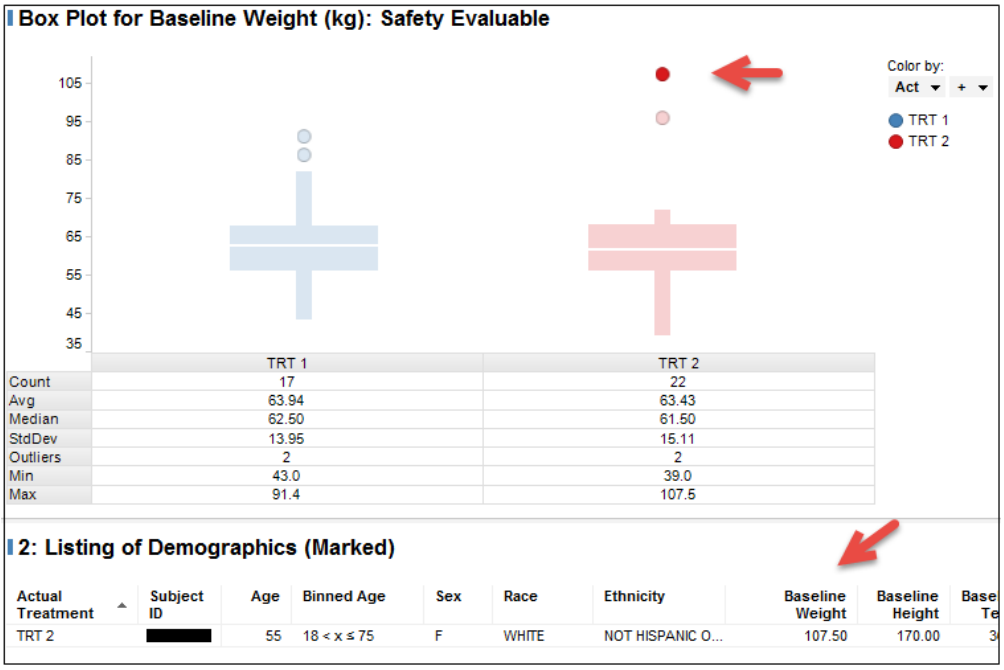
Demo_Categ...	Value	TRT 1		TRT 2		Grand total of n	Grand total of Percent
		n	Percent	n	Percent		
Age Group	**Subtotal**	**69**	**100.0%**	**80**	**100.0%**	**149**	**100.0%**
	30 < x ≤ 40	3	4.3%	6	7.5%	**9**	**6.0%**
	40 < x ≤ 50	9	13.0%	15	18.8%	**24**	**16.1%**
	50 < x ≤ 60	16	23.2%	24	30.0%	**40**	**26.8%**
	60 < x	41	59.4%	35	43.8%	**76**	**51.0%**
Sex	**Subtotal**	**69**	**100.0%**	**80**	**100.0%**	**149**	**100.0%**
	F	20	29.0%	23	28.8%	**43**	**28.9%**
	M	49	71.0%	57	71.3%	**106**	**71.1%**
Race	**Subtotal**	**69**	**100.0%**	**80**	**100.0%**	**149**	**100.0%**
	ASIAN	5	7.2%	1	1.3%	**6**	**4.0%**

Figure 8

DEMOGRAPHICS 2 (CONTINUOUS)

Using the link Demographics 2 (Continuous) within the table of contents the second demographics page will be displayed. Users will get a summary table of baseline information of age, height, weight, temperature, and body mass index. Weight

and body mass index are visualized with box plots. If the user wants to look into outliers, they can be marked/ticked and further information is displayed in the Listing of Demographics (Marked) at the bottom of the page (Figure 9).



	TRT 1	TRT 2
Count	17	22
Avg	63.94	63.43
Median	62.50	61.50
StdDev	13.95	15.11
Outliers	2	2
Min	43.0	39.0
Max	91.4	107.5

Figure 9

ADVERSE EVENTS

Figure 10

Navigating to the page AE Graph displays a bar chart of incidence of all treatment adverse events by System Organ Class (SOC) on the left side (Figure 10) for all female patients, since the female patients, selected in the demographic analysis data set, are still considered (Figure 10, arrow 1).

The color of the bars can be chosen (Figure 10, arrow 2). In this example the color is different if either the event is serious or not. The serious adverse events of 'Gastrointestinal Disorders' are marked, e.g. the user ticked at that section of the bar (Figure 10, arrow 3). Therefore within this system organ class the number of patients per preferred term with serious events are shown at the bar chart on the right side. Further information of all serious adverse events for these 3 patients is listed at the bottom of the page (Figure 10, arrows 4).

Within the listing some variables are color coded. This is already defined in the CoreSV template. For example, within the column of serious adverse events 'Serious Events' are colored red (Figure 10, arrow 5). Non-serious events are not colored.

In addition, summary table AE Table by SOC and PT gives the exact numbers of serious events in the female population (Table 2).

MedDRA System Organ Class	MedDRA Preferred Term	TRT 1 Events	TRT 2 Events	Grand total
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Subtotal	---	2	2
	MALAISE	---	1	1
	SUDDEN DEATH	---	1	1
GASTROINTESTINAL DISORDERS	Subtotal	2	1	3
	DIARRHOEA	1	---	1
	ILEUS PARALYTIC	---	1	1
	PANCREATITIS ACUTE	1	---	1
BLOOD AND LYMPHATIC SYSTEM DISORDERS	Subtotal	---	2	2
	FEBRILE NEUTROPENIA	---	1	1
	NEUTROPENIA	---	1	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Subtotal	2	1	3
	PULMONARY EMBOLISM	2	---	2
	PULMONARY OEDEMA	---	1	1
INFECTIONS AND INFESTATIONS	Subtotal	1	1	2
	GASTROENTERITIS	---	1	1
	SEPSIS	1	---	1
VASCULAR DISORDERS	Subtotal	1	---	1
	JUGULAR VEIN THROMBOSIS	1	---	1

Table 2

LABORATORY

LAB SUMMARY

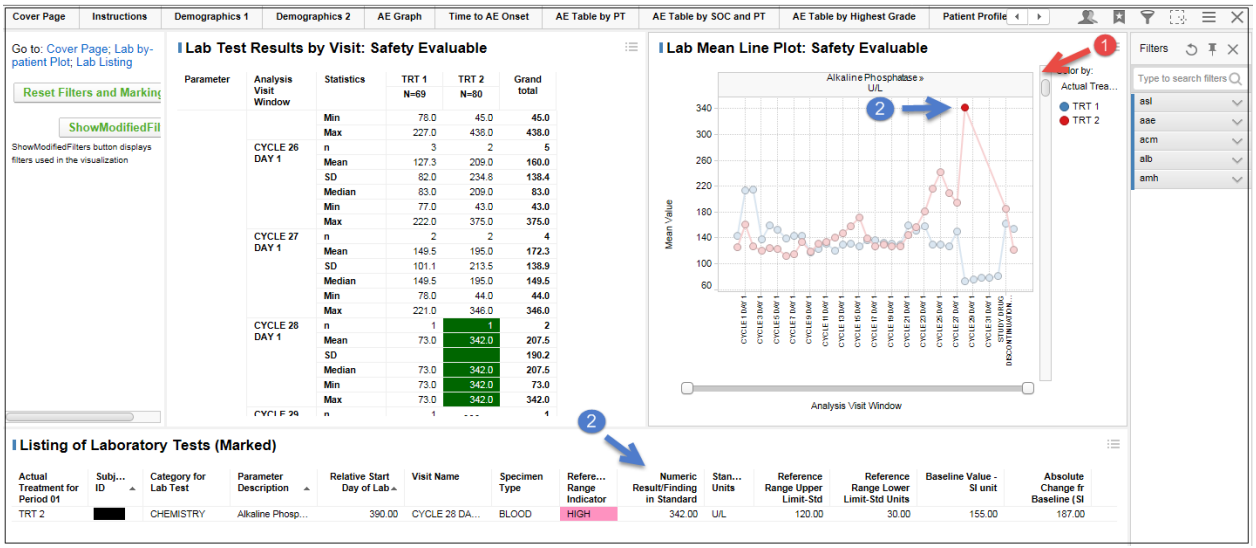


Figure 11

The Lab Summary (Figure 11) shows mean line plots of laboratory values, in this example Alkaline Phosphatase. All laboratory parameters can be looked at by just scrolling down (Figure 11, arrow 1). The corresponding summary table gives the exact numbers. One high value is marked within the line plot (Figure 11, arrows 2). You can see further details of all values available for the calculation of the mean value in the listing at the bottom of the page. In this example it is only one patient listed corresponding to that mean value.

LAB BY-PATIENT PLOT

The Lab By-Patient Plot visualization can be used to look into one patient in more detail.

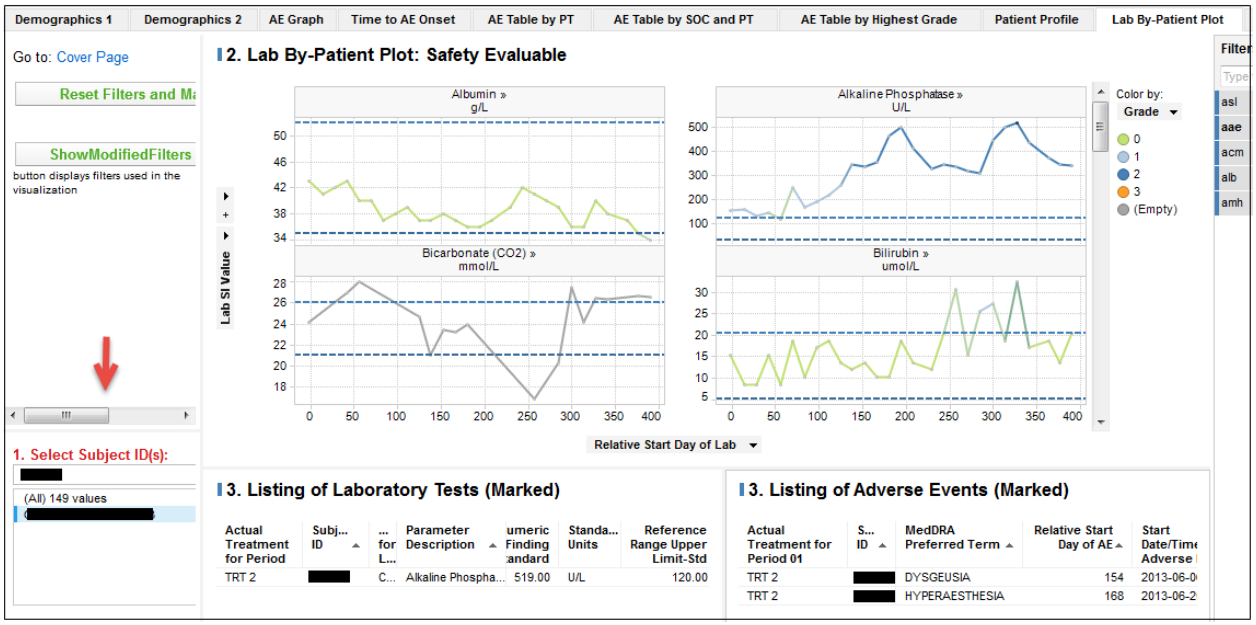


Figure 12

The Lab By-Patient Plot shows line plots of the actual values per study day for the selected patients together with adverse event information (Figure 12). The patient is chosen by entering the patient number in the selection panel and clicking the number.

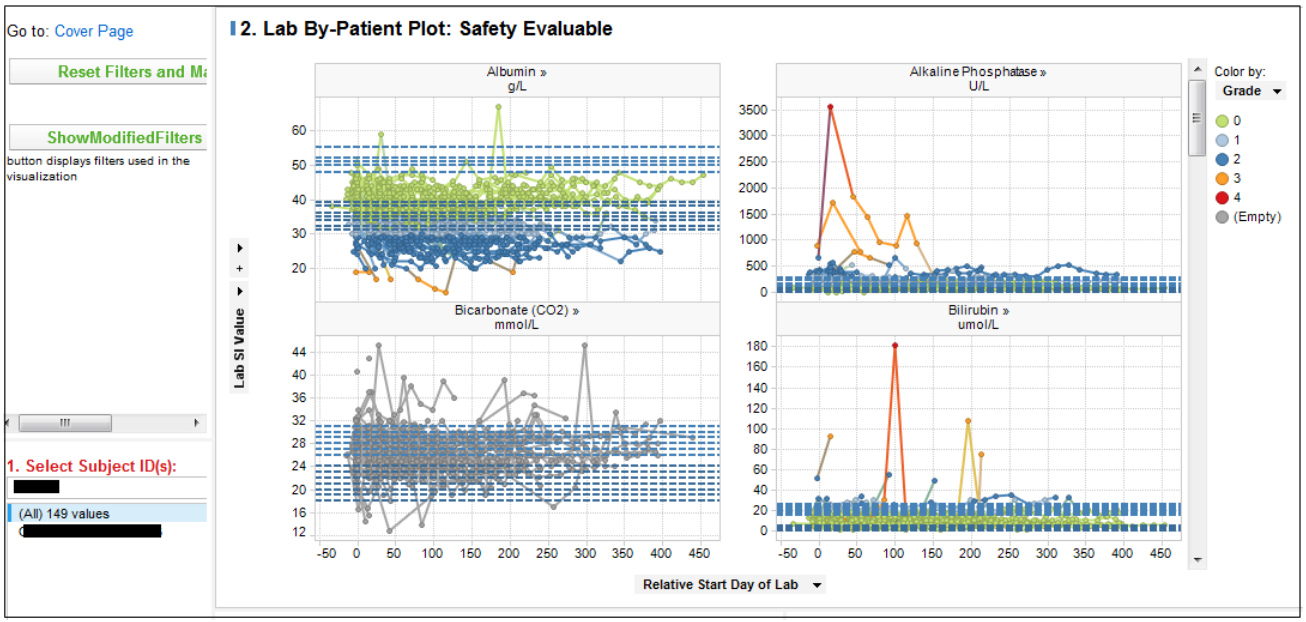


Figure 13

If you choose all patients, line plots for all values for all patients are displayed (Spaghetti Plots). The lines are colored according to the CTC grade (Figure 13).

STUDY DRUG PLOT

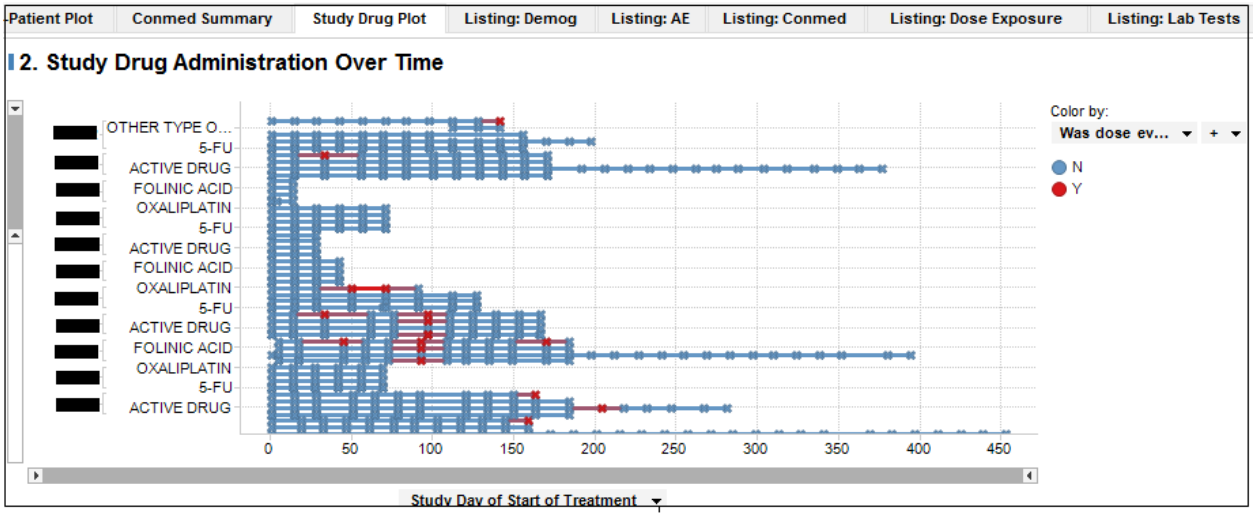


Figure 14

The Study Drug Plot gives a quick overview of the study drug intake pattern (Figure 14). Red colored lines mark dose entries, if the dose was modified.

FEEDBACK FROM STAKEHOLDERS

Feedback from the first users is very encouraging. With minimal resource investment, Statistical Programmers were able to build and maintain the CoreSV. Our primary customers (Safety Scientists) appreciate the ability to gain insights from the data with a user-friendly tool. It was noted that some support is needed to ensure the correct understanding of how to use the filters to subset data accordingly.

Furthermore,

- Multiple internal presentations have been created using CoreSV Spotfire visualizations.
- For one project the Statistical Programmers had to do fewer official safety outputs as Safety Scientists had a faster and more complete insight to the data using the CoreSV.
- The requests of additional outputs from Safety Science were more specific after the initial exploration of the data within CoreSV.
- On the other side questions came up like: “Why should Safety Scientists take more time to explore the data themselves and do the work of Statistical Programmers?”, “What, if Safety Scientists would get to a conclusion using the wrong numbers from their own exploratory analysis?” “What, if Safety Scientists think the selection was not important and do not look further into it at all?” These concerns can hopefully be solved with a good dialogue between Statistical Programmers and Safety Scientists.

CONCLUSION

- With visually displayed data one can often get better insights into the data than merely comparing numbers. The coloring of contents of variables (e.g. serious adverse events) enables much easier interpretation of the data.
- CoreSV enables non-programmers to get easy access to and insights from clinical data.
- Due to the standardization of the safety data, it is easier for the Statistical Programmers to upload their own study data and Safety Scientists do have similar visualizations between the studies.
- By using the analysis datasets, the visualizations are consistent with the outputs in the clinical study reports.
- Statistical Programmers can use CoreSV to cross-check and validate safety outputs created for the clinical study report.
- During the phase of customization of the CoreSV according to study needs, Statistical Programmers and Safety Scientists have the opportunity to build up a good relationship and they can learn from each other.

Statistical Programmers are often asked to share the data with other parties. At Roche this is the first step towards this goal to give Safety Scientists the opportunity to explore the analysis data themselves. Statistical Programmers are still responsible for the creation of all needed regulatory or exploratory outputs.

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