

Enhancing Visual Analytics Approaches in Safety Monitoring

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Abstract

Safety data present many challenges with regard to analysis and interpretation. Safety outcomes have high variability in measurements and are multidimensional and interrelated in nature. The use of tabular outputs for safety data often results in large volumes of output leading to problems in generation, assessment, validation, assembly, comprehension and communication of safety findings. It is well recognized that visual analytics present a useful alternative to tabular outputs for exploring safety data and present a great opportunity to enhance evaluation of drug safety. Graphs can play a big role in facilitating communication of safety results with regulators, investigators, data monitoring committee, and other stakeholders and help convey multiple pieces of information concisely and more effectively than tables. This paper will consider the role of graphical methods in safety monitoring and show how to get maximum gain from using visual analytics in safety monitoring and reporting, taking into account some considerations that must be borne in mind for effective visualization. We will show via some examples how visual analytics play a critical role in the ongoing evaluation of a drug during study conduct and discuss some enhancement that can be applied to visual analytic tools to help in the assessment of safety monitoring and risk-benefit.

Key Words: Safety monitoring.

1. Introduction

Safety data present many challenges with regard to analysis and interpretation. Safety outcomes have high variability in measurements and are multidimensional and interrelated in nature. The typical clinical study is generally not powered to detect safety signals. The use of tabular outputs for safety data often results in large volumes of output leading to problems in generation, assessment, validation, assembly, comprehension and communication of safety findings. It is well recognized that visual analytics present a useful alternative to tabular outputs for exploring safety data and present a great opportunity to enhance evaluation of drug safety. Graphs can play a big role in facilitating communication of safety results with regulators, investigators, data monitoring committees, and other stakeholders and help convey multiple pieces of information concisely and more effectively than tables. In this discussion, we will consider the role of visual analytics in safety monitoring. We will then consider some current practices and show how to get maximum gain using visual analytics in safety

monitoring and reporting, taking into account some considerations that must be borne in mind for effective visualization. We will show via some examples how visual analytics play a critical role in the ongoing evaluation of a drug during study conduct. We will also consider some enhancements of current.

2. Complexity of Safety Data

In comparison to efficacy data, safety data tend to be much more complex from an analysis perspective. Analyzing safety data with conventional statistical methods is difficult because many of the standard assumptions may not necessarily be satisfied. Further, there are many pathological features frequently seen in safety data, including, non-normal data, high variability, and heterogeneous sub-populations. For example, patients are differentially prone to adverse events depending on their prognosis and two patients with the same prognosis can exhibit differences in their safety response and experience to treatment. Differences in the standard of care and clinical assessment can also contribute to high variability in a clinician's reporting and assessment of safety data. A further complication factor is that one often needs to look across several data domains and across difference studies to assess safety. The core safety data domains include adverse events, clinical laboratory data, vital signs, and electrocardiograms. Other specialty safety data based on indication and class of medication may also be collected to help assess specific drug adverse effects or adverse events of special interest. All these considerations add to the data complexity equation. Figure 1 is an illustration of the complexities in terms of the safety data that are collected on a given study and also illustrate a cross-study component.

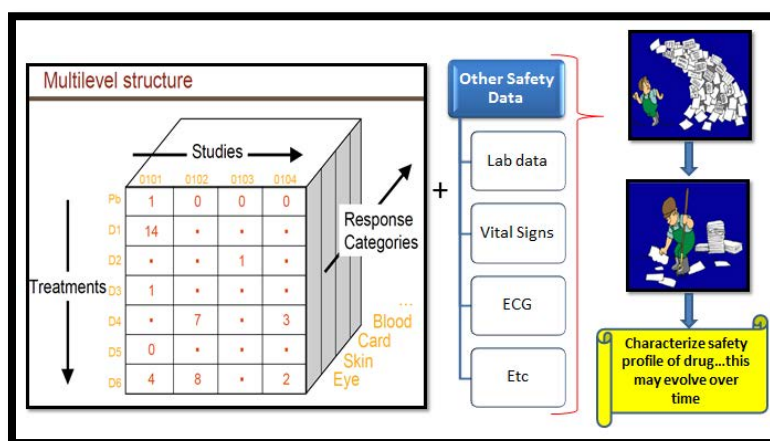


Figure 1: Complexity of Safety Data, adapted from Kerman et al (2007)

A further complicating factor is that certain specific adverse conditions may manifest themselves in different ways, or may require several pieces of related safety information to conclusively ascertain harm and causal effects. Based on the standard analyses of safety data in clinical trial reports, it is evident that although a lot of safety data are collected, the overall treatment of safety data is not reflective of this and it is probably and not necessarily the most appropriate data upon which to conclusively base safety decisions. In essence, the appropriate data to demonstrate the safety of a product will depend on the proposed indication, life-threatening potential, or quality of life enhancement, intended duration of use (one time versus short-term versus long-term versus intermittent versus recurrent use) and diversity of the patient population (age, race,

gender, disease history, medication history, concomitant medication, concomitant disease, standard of care, genetic disposition, and many other factors). The resulting status quo is massive amounts of tabular outputs which may not render themselves useful in a thorough assessment of the safety profile of a drug. Using tabular formats for safety data analysis leads to large volumes of output. As noted by Wittes (1996), a plethora of tables that describe safety may bury some true signal in a cacophony of numbers.

3. The Case for Visual Analytic in Safety Monitoring

The above discussion points out to a need to improve how safety data are analyzed. One well widely and recognized approach is through the use of visual analytics to present safety data as an alternative to tabular outputs. Visualization of safety data can help convey multiple pieces of information concisely and more effectively than tables. Graphical exploration can substantially improve information gain from safety data. Visual analytics methods are useful for exploring safety data and they present a great opportunity to enhance evaluation of drug safety. For example, Harrell (2005) pointed out that it is difficult to see patterns in tables and substituting graphs for tables can help increase efficiency of review. McKain, Jackson, and Elko-Simms (2015) argued that traditional case reviews and use of tables and listings are not sufficient for safety surveillance principles. Vlachos (2015) argued that despite their potential, visual analytics methods are an underutilized resource in safety analysis. Graphs can be used to aid in inference and communicating safety results and to help display large amounts of safety data coherently and maximize the ability to detect unusual features or patterns. They can also play a big role in facilitating communication of safety results with regulators, investigators, data monitoring committee, and other stakeholders. Additionally, many guidance documents on the analysis and review of safety data do recommend the use of visual analytics tools when looking at safety data, see for example ICH-E3 and FDA Safety Review Guidance (2005).

In the context of safety monitoring and reporting, many variables are considered and many safety analyses are performed and as a result it can be challenging to come up with a coherent understanding of the safety profile without the help of visualizations techniques. With the mix of data from safety, visual analytics arguably play a central role in the ongoing evaluation of a drug both during study conduct in a blinded fashion and in surveying a set of studies – completed or ongoing.

4. Principles of Visualization and Graph Creation and Asking the Right Question and Graph Complexity and Tools

In order to get maximum gain from using visual analytics in safety monitoring and reporting, a couple of considerations must be borne in mind. These include taking into account principles for data visualization, posing to frame the right questions to interrogate safety data, and the use of visualization tools. Principles for construction of graphs to aid safety interpretation of data have been discussed in the literature, for example, Duke (2014) and Duke et al (2015). Some of these principles include considerations for graph content, communication, information, annotation, axes, and style. It is ideal to have graphs adhere to Tuf's principles including, tell the truth (graphical integrity), do it effectively with clarity, precision (data ink ratio, data density, design principles color rules) and so on. Successful visualization of data can best be summarized in the context of information, a story, goal, and a visual form, as exemplified

in Figure 3 below. All these are important to ensure that we have good visualization and successful visualization of the data, especially in the context of safety monitoring.

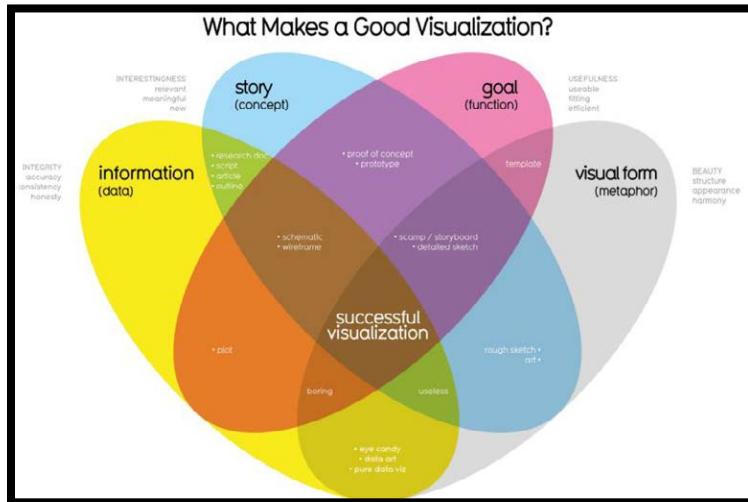


Figure 2: What makes a good visualization.

Source: <http://www.informationisbeautiful.net/visualizations/what-makes-a-good-data-visualization/>.

In general, data needs to be put into context with the concepts of safety profiles. Likewise, the goal of detecting safety issues early and accurately and the form of visualization should match with the data and the idea of what safety monitoring does. Along the same lines, to effectively use visual analytics in safety monitoring and reporting, it is a good idea to begin with some questions with regards to safety data under consideration. More specifically, safety monitoring and reporting should be driven by asking the right question(s) of safety data. Some examples of questions associated with adverse events that one may ask are outlined below:

- Which adverse events (AEs) are elevated in treatment versus control?
- What is the constellation of AEs that come with the drug?
- Is there any evidence of a dose-response-relationship?
- Is the potential AE of interest increasing over time?
- Is there a difference in the time to the first event across treatment groups?
- Which AEs are elevated in patient subgroups?
- What are the risk factors of the AE?

When one considers the many questions that one can ask in the safety monitoring setting to help in effective visualization of data and hence identify potential concerns, the more evident it becomes to see that visualization types and settings can fit many subcategories. These subcategories range from graph types, graph complexity, graph usage, graph information type, and static and dynamic aspects for the graphs. Figure 3 below is an illustration of these considerations.

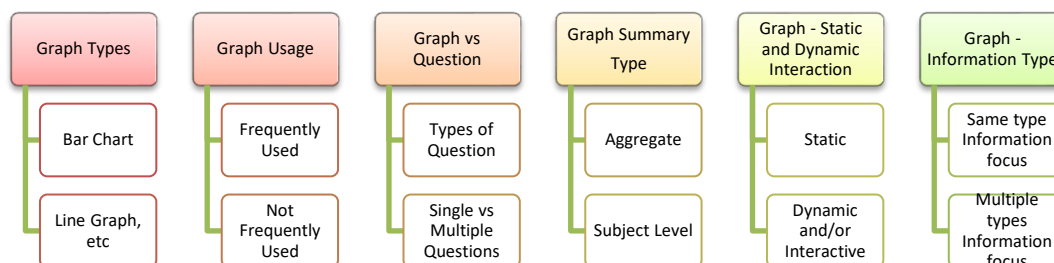


Figure 3: Graph complexity considerations

Ultimately, the safety question and graph type will dictate the right tool to use for SMR. There are many tools available that can be used to aid in visual analytics in SMR. These include R, R Shiny, Splus, Spotfire, SAS, JMP, JMP Clinical, Tableau, and J-Review, to mention a few. All these visual analytics tools have different functionality, and hence the choice of tool should consider tool functionality. For example, static versus interactive and/or dynamic visualization, drill down to patient level data, and the graph types most effective for SMR question. Clearly, the safety question and ultimately the graph type will determine the choice of the visual analytics that will be used. Selection of the visual type or graph type may also be driven by the nature of the event in terms of adverse event tier category, see for example Crowe *et al* (2009). A good guide for the most appropriate graph type is available at: <https://blogs.fda.gov/fdavoices/index.php/2015/09/seeing-is-believing-making-clinical-trial-statistical-data-from-medical-product-testing-easy-to-understand>.

5. Some Visualization Resources

There have been many outstanding and commendable efforts, both individual and through collaborations, towards visualization of safety data. Below is a small sampling of these efforts focussing on those that pertain to clinical safety data. There are many other similar resources.

Source/Author	URL/Source Details
Frank Harrel	http://biostat.mc.vanderbilt.edu/wiki/pub/Main/FHHandouts/gksafety.pdf http://biostat.mc.vanderbilt.edu/wiki/Main/RCTGraphics
Shi-Tao Yeh	http://www.lexjansen.com/pharmasug/2007/po/PO10.pdf http://www2.sas.com/proceedings/forum2007/164-2007.pdf http://www.lexjansen.com/nesug/nesug07/po/po23.pdf http://www2.sas.com/proceedings/sugi31/181-31.pdf
Jonathan Levine	http://www.gersonides.com/r/
CTSpedia	https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome
PhUSE	https://github.com/phuse-org/phuse-scripts/wiki/Standard-Script-Index
Andreas Krause, Michael OConnell	http://www.elmo.ch/doc/life-science-graphics/

In looking at the many visualization efforts and in light of graph complexity and usage from the various sources, one can classify these graphs for brevity purposes into the following broad buckets:

- “Main stream graphs” in the sense that these graphs are used frequently

- “Not so main Stream graphs” in the sense that these are graphs are not used frequently

Using the above dichotomy, we can classify some of the safety graphs that have been proposed into one of these two buckets. We can also think of these graphs as noted earlier as addressing a specific safety question.

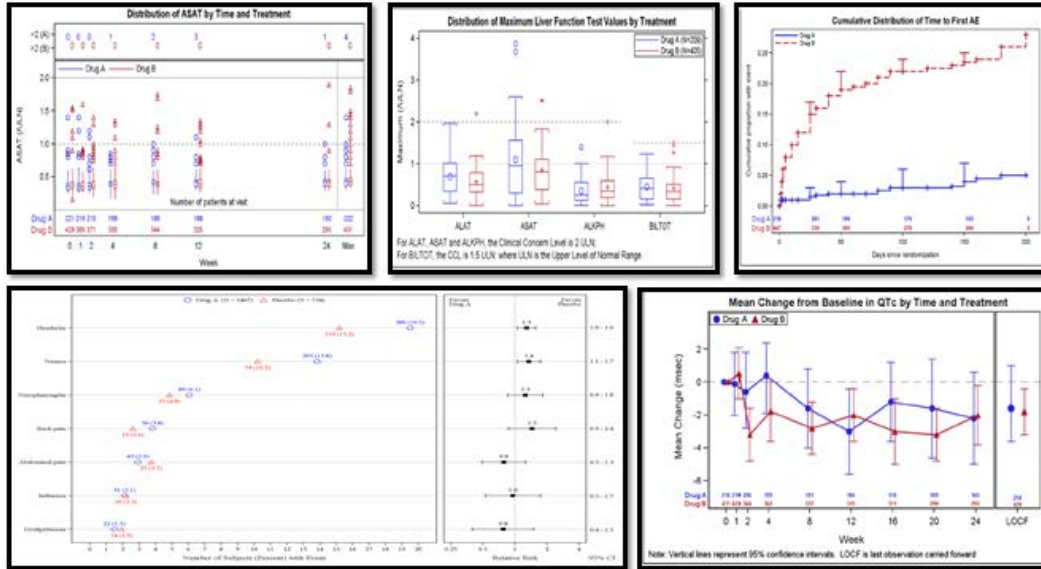


Figure 4a: Main stream graphs in the analysis of safety data

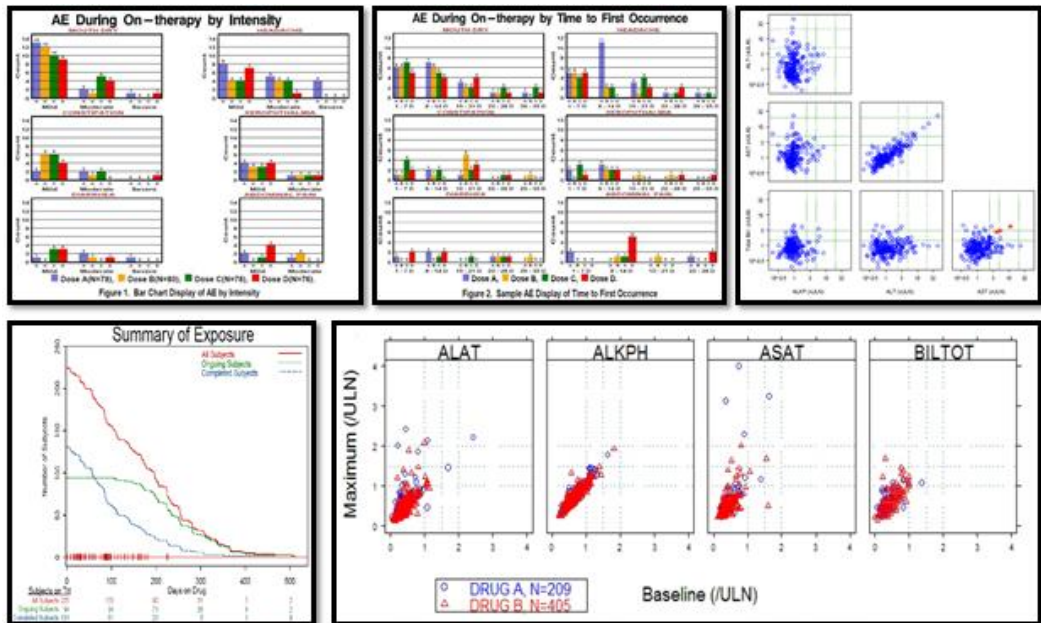


Figure 4b: Main stream graphs in the analysis of safety data

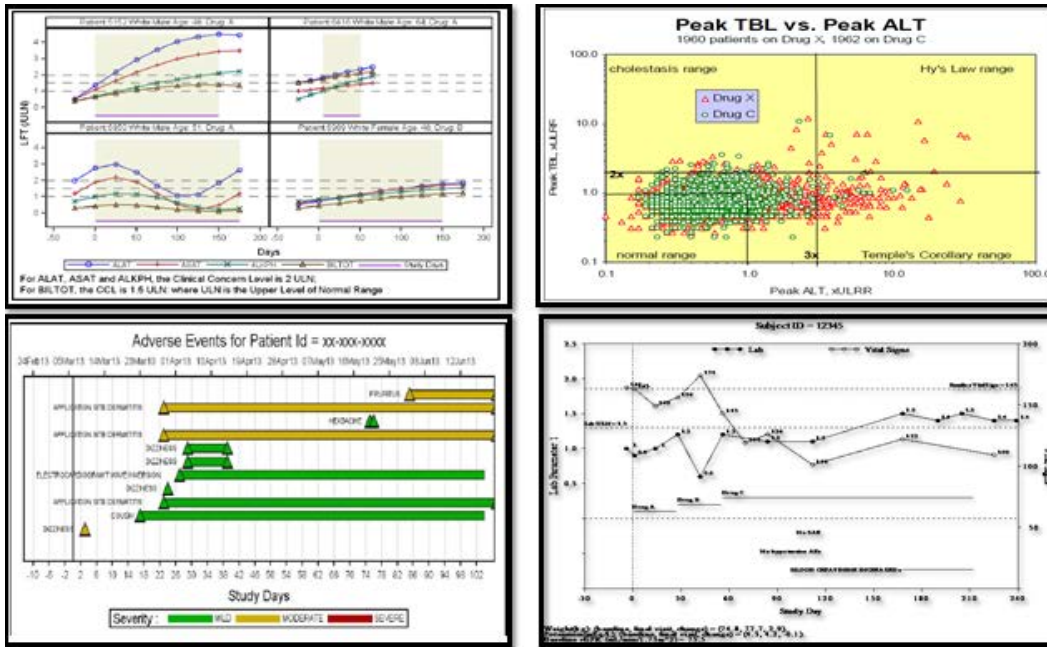


Figure 4c: Main stream graphs in the analysis of safety data

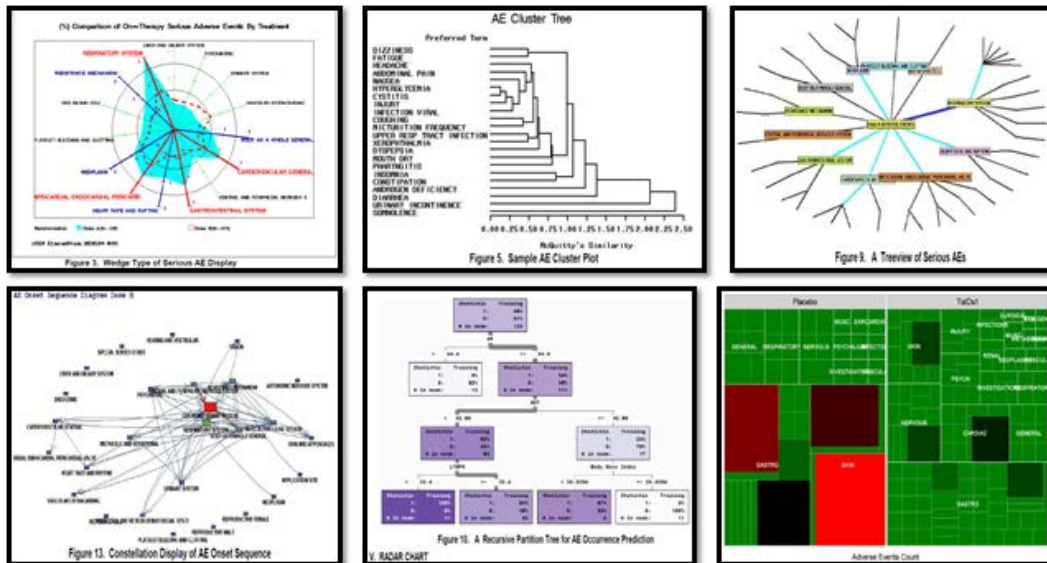


Figure 4d: No so main stream graphs in the analysis of safety data

6. Enhancing Visual Analytics

There are many outstanding and commendable efforts on visual analytics for safety data. These present as excellent resource and starting point for anyone wanting to harness the power of visualization in safety analyses. A natural question to ask therefore is, can we enhance the visualization presented in these initial commendable efforts and resources and efforts by making use of available tools? The term enhancement here is used to point out to the question as to *can we make theses graphs even more useful to the various end users and stakeholders?* We can consider several types of enhancement including:

- Making the graphs more useful in some way such as incorporating functionality for interactivity, a dynamic aspect, animation, drill down, connectivity, flexibility, and integration with a narrative
- Consideration for incorporating Bayesian ideas in graphs, where applicable
- Consideration for new types of visualization by borrowing newer and informative visualizations and tools, for example, visual analytics from big data, for example, D3.js: <https://github.com/d3/d3/wiki/Gallery>
- Using safety monitoring method based graphs, that is, graphs that we can associate with the various safety monitoring methods.

Enhancing various graphical outputs, especially via making the graphs more useful in some way such as through interactivity, making them dynamic, through animation, and allowing for drill down is not a new idea and this has been discussed by various authors, for example, Southworth (2012). Indeed, many commercial software tools such as Spotfire, SAS JMP Clinical, and J-Review, to mention a few have made commendable efforts to allow graph enhancement by including functionality that allows for interactivity, animation, and drill down. There are many available open software tools that can also be customized and allow for different graph enhancement to any desired degree, including building applications. One such software tool is the R Shiny which has found increasing use in visual analytics. It incorporates considerable functionality, including an integrated development environment, reproducibility, application development, and had lots of shared resources online. It additionally allows for many types of outputs including integration of the narrative with the code out and output. The various output and reporting options include:

- R Markdown document: <http://rmarkdown.rstudio.com>
- R Notebook: http://rmarkdown.rstudio.com/r_notebooks.html
- R Flexdashboard: <http://rmarkdown.rstudio.com/flexdashboard>
- R Bookdown: <https://bookdown.org/yihui/bookdown>
- R Shiny App: <https://shiny.rstudio.com>
- R Html Widgets: <http://www.htmlwidgets.org>
- R Crosstalk: <http://rstudio.github.io/crosstalk/using.html>

A very interesting functionality of R Shiny is that it brings the best of JavaScript data visualization to R and allows for use of JavaScript visualization libraries at the R console. R Shiny also allows one to embed widgets in R Markdown documents and Shiny web applications and one can develop new widgets using a framework that seamlessly bridges R and JavaScript, linking multiple HTML widgets within an R Markdown page or Shiny application. Below we consider three examples of graph enhancements including interactivity and Bayesian approaches.

6.1 Enhancement: Example 1 - Interactivity in the Kaplan-Meir Plot

In this first example of an enhancement, we consider the setting in which we want to allow the user to interact with the graph so that additional information may be made available by using a mouse. This is not a new idea. In fact Shi-Tao using SAS and Java considered a similar idea in which he tried to create functionality to allow an end user to obtain individual subject-level information from a Kaplan-Meir plot thereby changing the plot from a simple static plot to one which the user can interact with the graphic. This functionality is illustrated below in Figure 5.

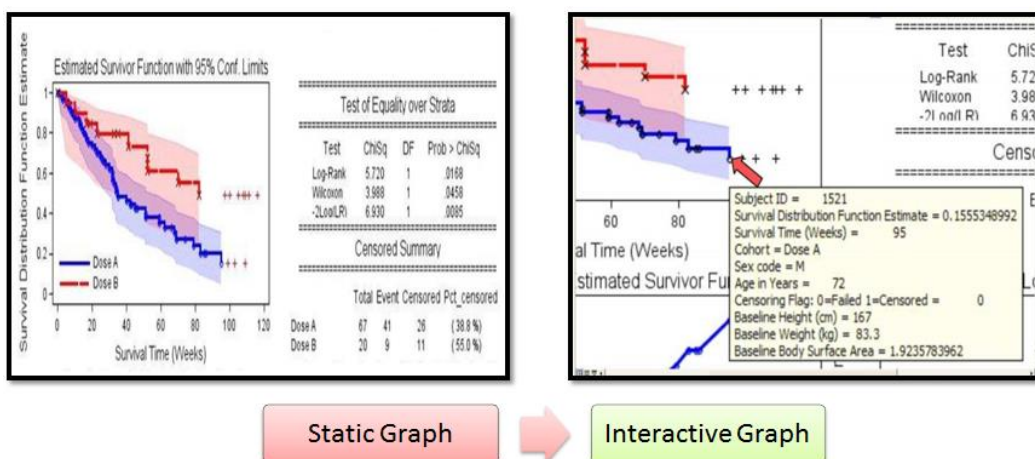


Figure 5: Interactive Kaplan-Meier Graph

Similar ideas that try and attempt to create interactive Kaplan-Meier plots can be seen at: <https://sachsmc.github.io/interactive-KM> and <https://github.com/selcukorkmaz/geneSurv>.

6.2 Enhancement: Example 2 - Interactivity and Drill Down in a Risk Difference Plot

In this second example of an enhancement of the static risk plot (see example, <http://www.ctspedia.org/do/view/CTSpedia/ClinAEGraph000>). Some enhancements of this plot have been implemented in the following resources:

- R Package: <https://www.rdocumentation.org/packages/HH/versions/3.1-34/topics/AEdotplot>
- R Shiny Tool: <https://becca-krouse.shinyapps.io/aetableapp/>
- Java Tool: <https://rhoinc.github.io/viz-library/examples/0008-safetyExplorerer-default/ae-table/>

The last two URLs share some similar functionality. We will therefore only discuss some of the functionality in the first two enhancements of the risk plot forest in the first two URLs. The first enhancement is based on the R package HH. Enhancements are available in the HH package that provide static graphic versions are provided in sample code Appendix A. One can alternatively execute the R Shiny version of the code that allows for interactions with the risk plot using mouse dropdown menus and a check box. We only discuss some of the enhancements here. Once you execute the R Shiny code below, you should see a figure similar to Figure 6 below. The red arrows indicate the various options that one can use to interact with the plot. These include removing the tabular part, applying different sort orders, obtaining different subgroupings, among others. One can use the various available options to address different questions, such as the most common adverse events within each body system, or to obtain a different sort order for the risk plot.

```
shiny::runApp(system.file("shiny/AEdotplot", package="HH"))
```

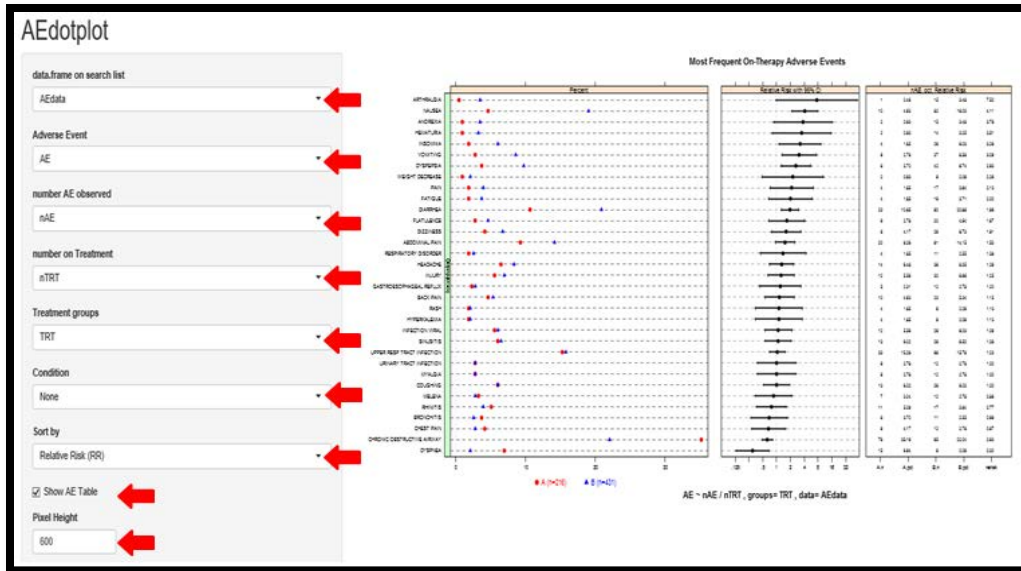


Figure 6: Interactive risk difference plot using the HH R package

The second R Shiny enhancement makes use of the safetyexploreR package. The safetyexploreR R package has many more options (see Figure 7 below) than the HH R package, and also allows for more functionality, including drilldown and use of other data domains. The R Shiny code for the R Shiny version of the safetyexploreR R Shiny is as follows:

runSafetyApp()

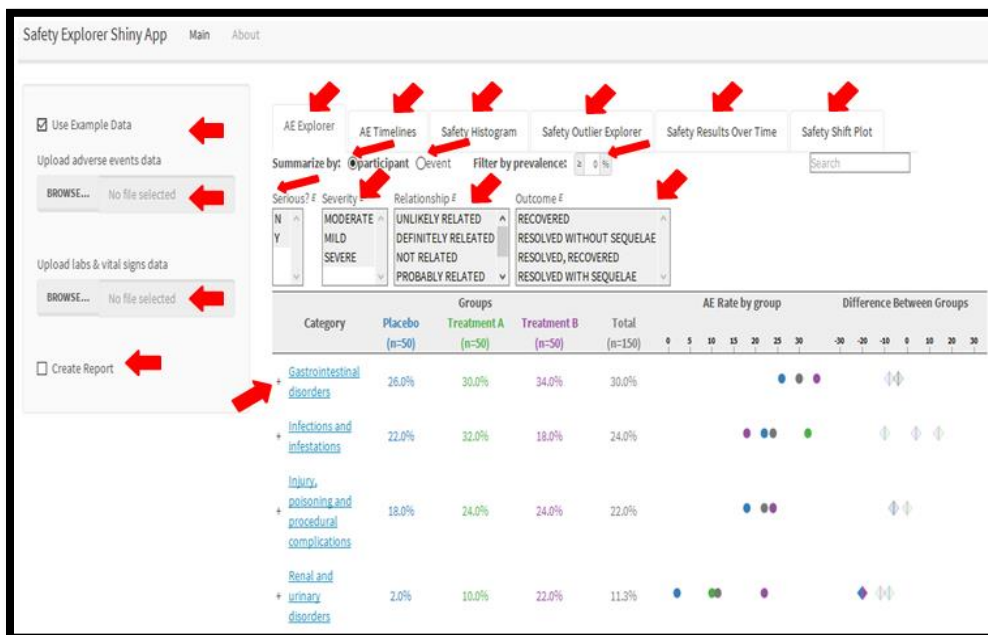


Figure 7: Interactive risk difference plot using the safetyexploreR R package

Both enhancements of the risk difference plot above provide the end user the ability to perform interactive explorations of the risk plot to help address various questions of interest.

6.3 Enhancement: Example 3: Incorporating Bayesian Thought

In this enhancement, we consider the setting in which Bayesian methods are incorporated into graphs to help address various inferential questions. Bayesian approaches provides a single coherent framework in which diverse elements of the data can be modeled. Through this approach, we can handle multiplicity issues, and incorporate prior information. This approach in addition does not rely on asymptotic properties in dealing with rare events. As pointed by Chi, Hung, and O'Neill (2002), *Safety assessment is one area where frequentist strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise.*

The first Bayesian example we consider is that of Confidence Interval vs. Credible Interval. The frequentist confidence interval is by definition based on the idea of a large number of repeated samples in which 95% of times the true value of the parameter will fall within the range of lower confidence limit and upper confidence limit. In contrast, the credible interval is a Bayesian term, also called 'Bayesian Posterior Interval'. The Bayesian credible intervals incorporate information from the prior distribution into the estimate, while confidence intervals are based solely on the data. In essence a 95% credible interval essentially means that the posterior probability that the parameter lies within the interval from lower confidence limit and upper confidence limit is 95%. In the meta-analysis example below, we can see that since the frequentist interval relies solely on the data, we may not be able to define the lower and upper intervals in the case of zero events, without modifying the data in some form or shape such as adding correction factors. In contrast, this is not a problem for credible intervals, see Figure 8.

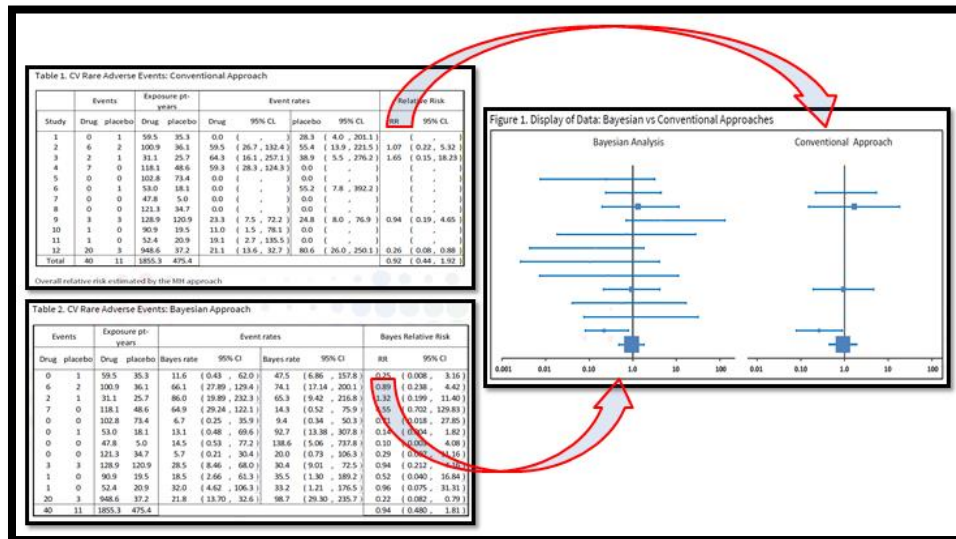


Figure 8: Confidence Interval vs. Credible Interval in Meta-Analysis rare event setting
 Source: https://www.kjcstatistics.com/wp-content/uploads/2016/07/KJC_Meta-Analysis-for-Rare-Adverse-Events.pdf

The second Bayesian example we consider is that of Volcano Plot using P-value (frequentist) versus use of the odds ratio (OR) (Bayesian, see, Xia, Ma, Carlin (2011), see Figure 9. Bayesian inference on volcano plot AE_{bj} is flagged if $Pr(\theta_{bj} > d^* | \text{Data}) > p$,

where θ_{bj} is log-OR in Binomial models d^* and p are pre-specified. Using the frequentist version of the volcano plot, we can see that a number of adverse events can be identified as concerning. On the other hand, using the ORs ratio suggests that perhaps the events in question are not so concerning and perhaps not signals at all, see Figure 9.

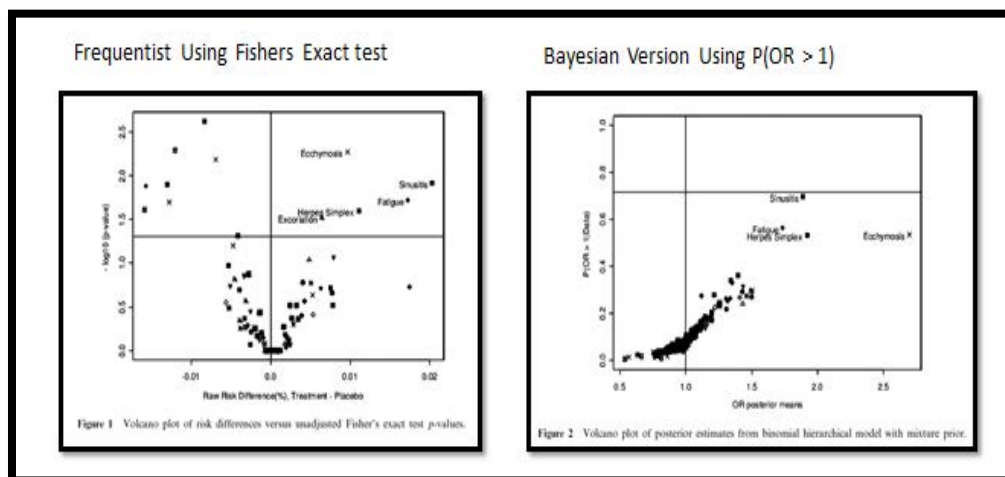


Figure 9: P-value (frequentist) versus use of the odds ratio (OR) (Bayesian)
Source: Xia, Ma, Carlin (2011)

7. Conclusion and Recommendations

Safety data present many challenges with regard to analysis and interpretation. Safety outcomes have high variability in measurements and are multidimensional and interrelated in nature. Visual analytics can help in safety monitoring and in safety data analysis in general. Utilizing visualization tools can help exploration and substantially improve information gain for safety monitoring activities. One should however take into consideration important principles of graph construction in order to render them visuals useful in safety monitoring. Ultimately, the visual type and tool used will depend on the question or questions under consideration in the safety monitoring activity. By considering various enhancements, one can select visualizations and tools that are most useful for the end-user and reporting to address various questions with a wide range of functionality to allow for efficient safety monitoring

Acknowledgements

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Appendix**Sample Code for HH package**

This code assumes you already have installed the HH package.

```

data(AEdata)
head(AEdata)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT, data = AEdata)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata, sortByVar="PCT")
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata, sortByVar="PCT",
  sortByVarBegin=2)
AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata, sortByRelativeRisk=FALSE)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT, data = AEdata,
  sortByVar="ase.logrelrisk")
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups = TRT,
  data = AEdata[c(AEdata$OrgSys %in% c("GI","Resp")),])
ABCD.12345 <- AEdata[1:12,]
head(ABCD.12345)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups=TRT, data=ABCD.12345)
AEdotplot(AE ~ nAE/nTRT | OrgSys, groups=TRT, data=ABCD.12345, sort=FALSE)
#suppress third panel
tmp <- AEdotplot(AE ~ nAE/nTRT, groups = TRT, data = AEdata)
print(tmp, ATable=FALSE)
shiny::runApp(system.file("shiny/AEdotplot", package="HH"))

```

Sample Code for HH package

This code assumes you already have installed the safetyexploreR package

```

runSafetyApp()
aeExplorer(data=ADAE)
aeExplorer(data=ADAE, group_col="ARM", filters_ptcpt_col = c('SEX','RACE'))

```