

Statistical Graphics for Review and Reporting in Clinical Development

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Introduction

Clinical trials are complex.

There are many safety and efficacy endpoints and much information to be summarized and communicated to a variety of stakeholders.

Graphics promote better science and more effective communication. In clinical trials, graphics can be effectively used to both explore data and report data. Examples of exploratory analysis include instream review, medical monitoring and safety assessment. Examples of graphics for reporting include presentations, publications, clinical study reports and regulatory submissions. Exploratory and reporting graphics are quite different. Report graphics typically need to be self-contained and documented with source data and output file references. They stand as static summaries of an analysis and need to be reproducible. Exploratory graphics are typically interactive and not self-contained. They are best when they allow the user to explore points/regions of a graph through brushing and drill-down. This enables viewing of population trends with subsequent detailed exploration of interesting individual subjects.

Graphics for Reporting

Graph must be self-contained

- In-text figures should have an explanation in the caption

Graph must be documented

- Log file, time stamp
- Source data and output file references

Examples

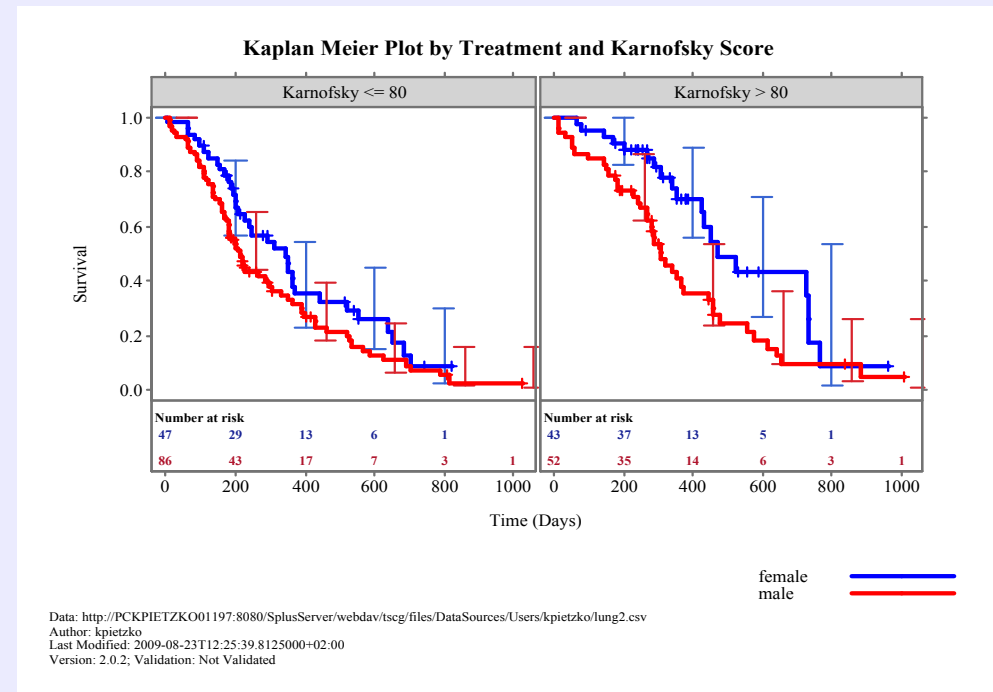
- NDA Submission
- Scientific Publication
- Clinical Study Report and Presentation

Color and Format

- Interpretable in black and white
- High Quality, Resizable

Device

- WMF, PNG, PDF, PS



Graphics for Review

Graph may not be self-contained

- Often interactive display

- Brushing and metadata

Graph may not be documented

- Data analyst produces to explore data
- Date/Time stamps can be useful

Examples

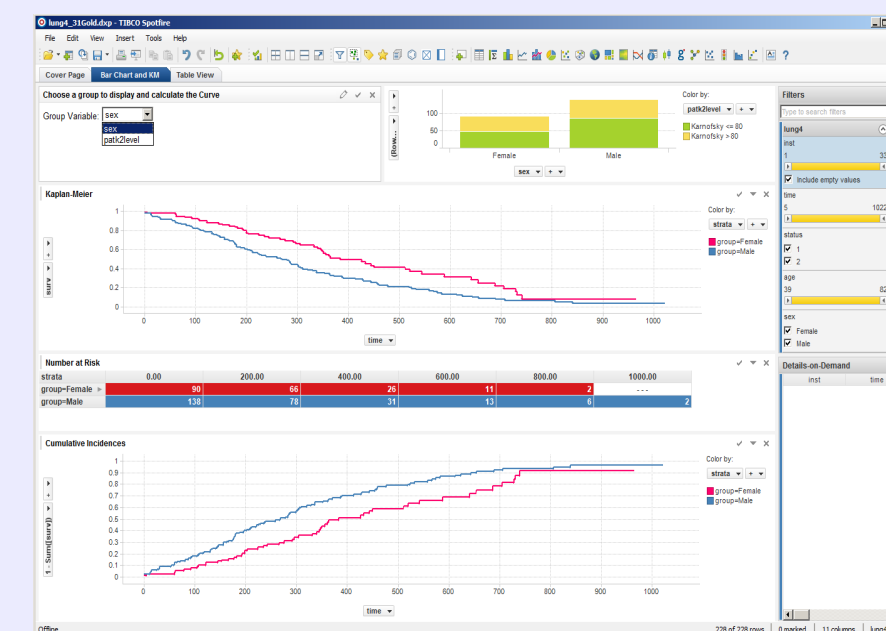
- Clinical data review by/with clinician
- Viewing all data – data cleaning
- Model diagnostics

Color and Format

- Few pre-defined rules
- Just make it clear and easy to interpret

Device

- Interactive



Illustrations

The illustrations show the use of some graph types through the analysis of safety data including adverse events, laboratory measurements and combined patient profiles, using the TIBCO Spotfire Clinical Graphics software product for reporting graphics and the TIBCO Spotfire software product for exploratory graphics. The examples show how appropriate statistical graphics elements may be used to extract and highlight salient safety information in the clinical study data.

In clinical trial research there are two key areas where statistical graphics provide value:

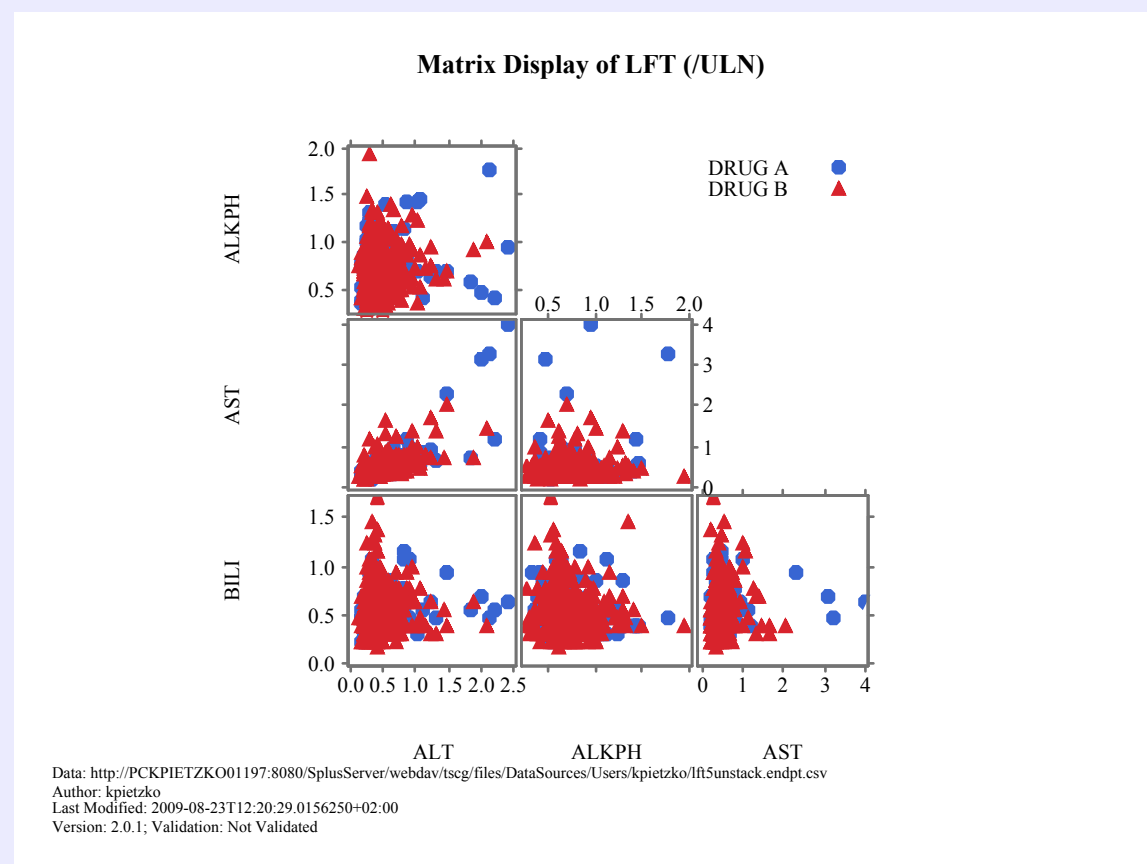
- (1) exploratory data analysis and clinical review of results by clinicians and management, and (2) formal clinical study reports, scientific papers, presentations and submission.

In exploratory analysis and data review, the goals are to quickly extract, display and review the salient safety and efficacy information in the data.

In clinical study reports, papers, presentations and submissions, graphics must adhere to company or journal style guides and/or regulatory (e.g. FDA) reporting standards.

Labs - Interpretive Goals

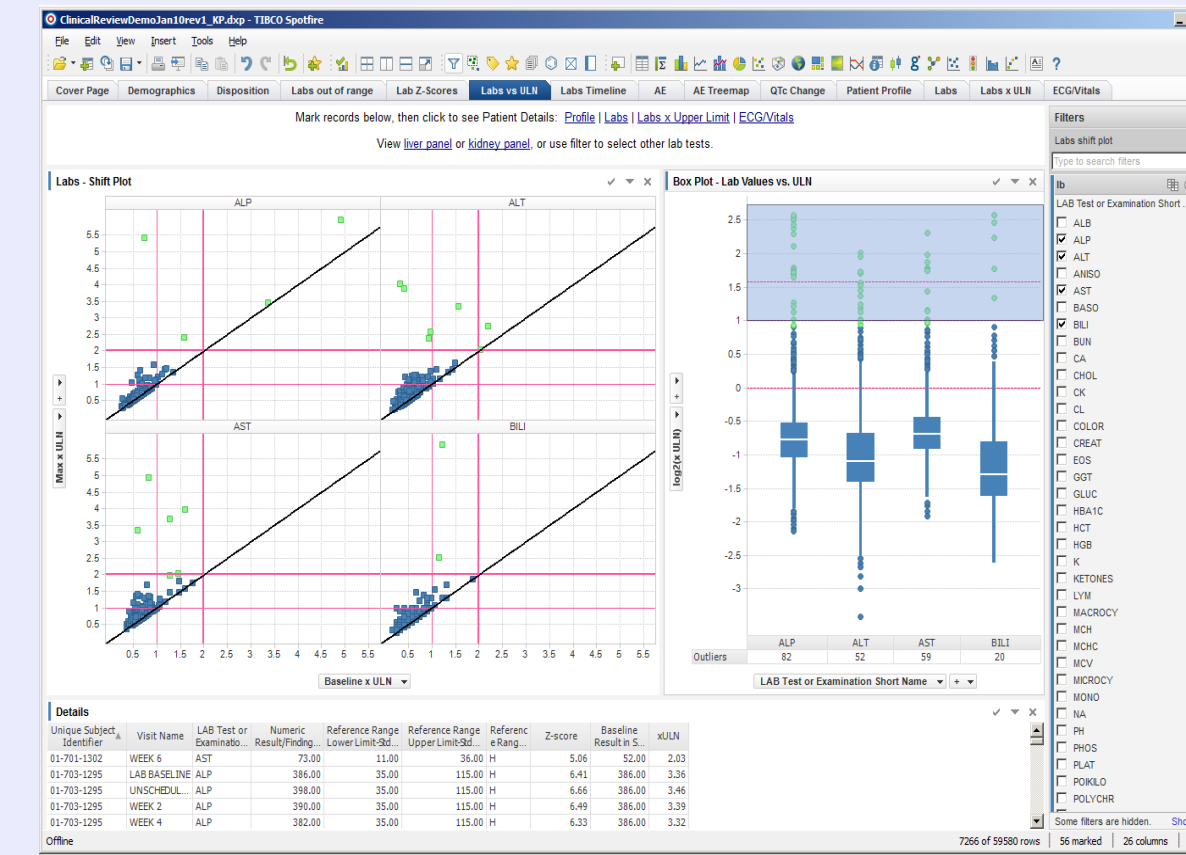
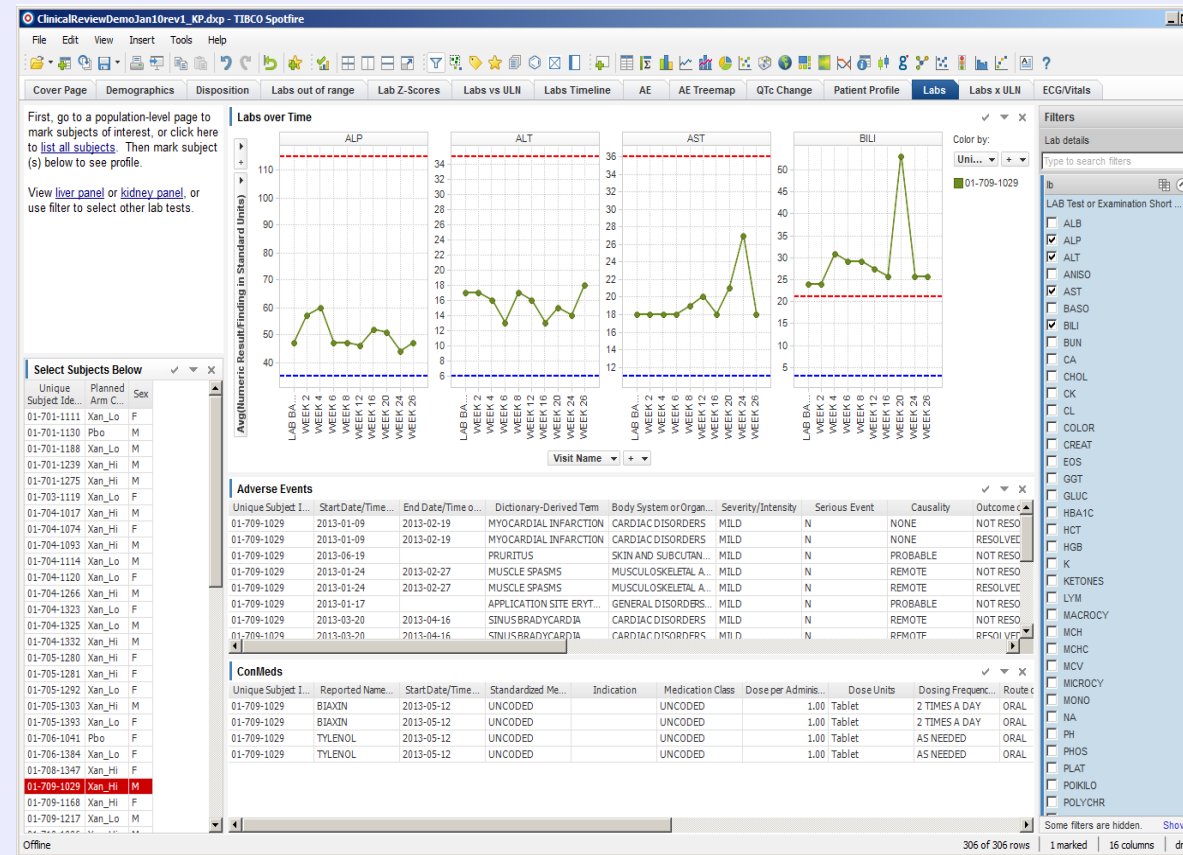
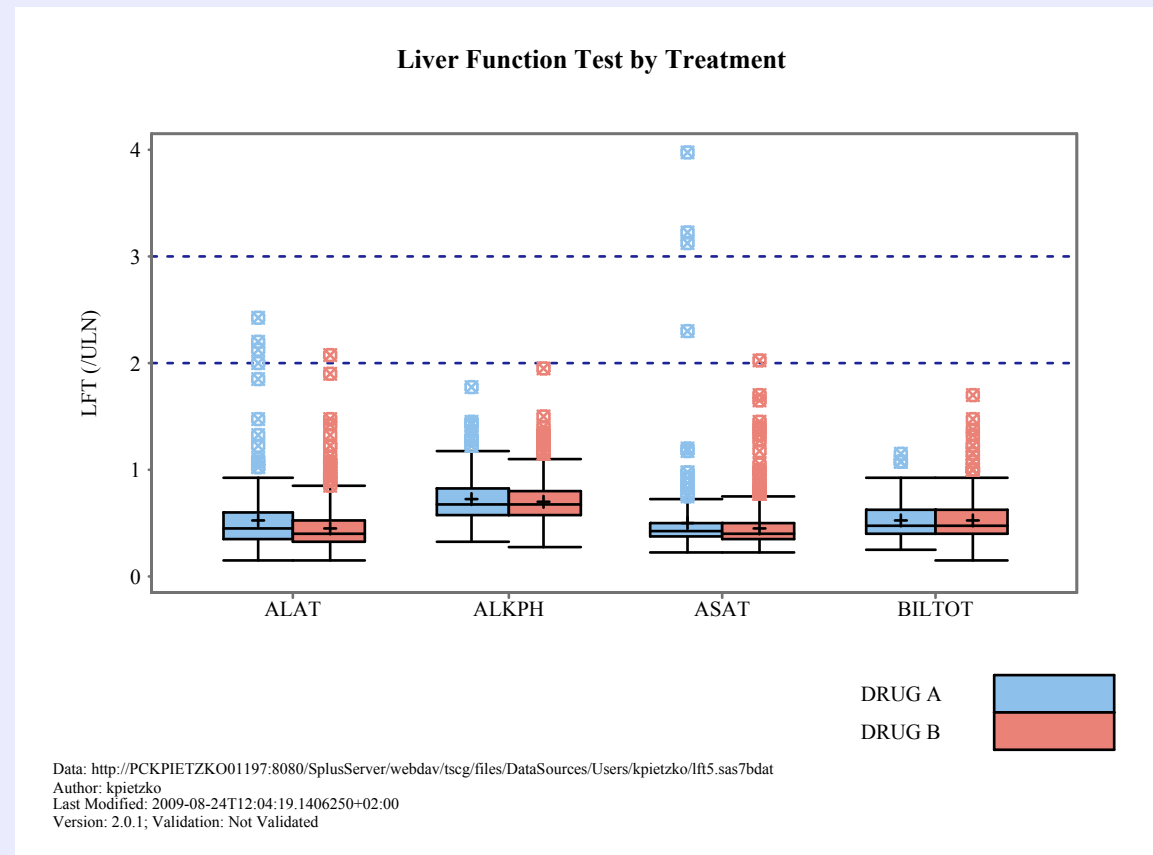
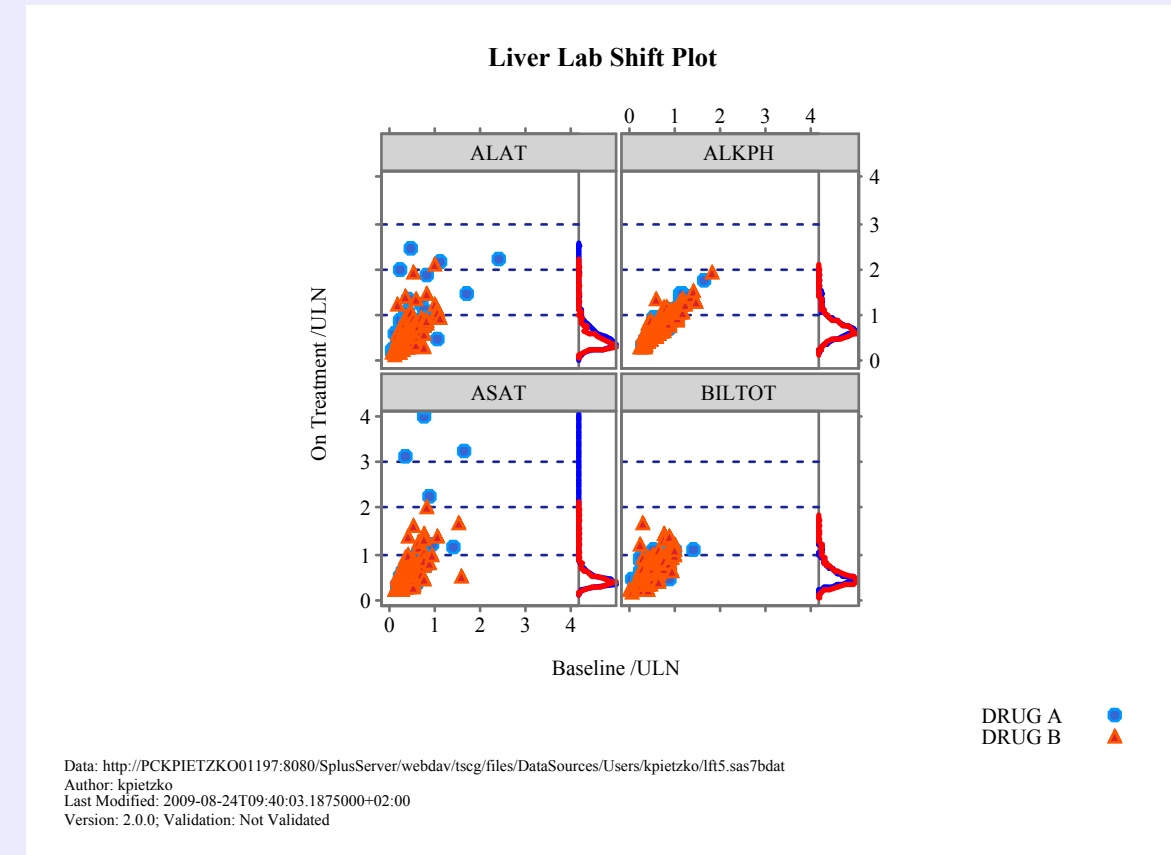
- Which subjects have elevated (liver) labs?
- Are there subjects with elevation on multiple labs?
- Do ALT and AST track together?
- Are there simultaneous elevations in ALT/AST and Bilirubin?
- What is the time-course of the elevations?
- What is pattern of treatment effects across time and dose?



“Hy’s Law” was developed by Hyman Zimmerman as criteria for evaluating drug induced liver injury. Potential for severe drug-related hepatotoxicity signaled by three components:

- Subjects with elevations of ALAT or ASAT above 3xULN
- Simultaneous elevation of Bilirubin above 2xULN
- No elevation of ALKP above 3xULN

“Hy’s Law” can be evaluated as part of the scatter matrix by generating different symbols for subjects who meet the criteria.



Adverse Events – Analysis Questions

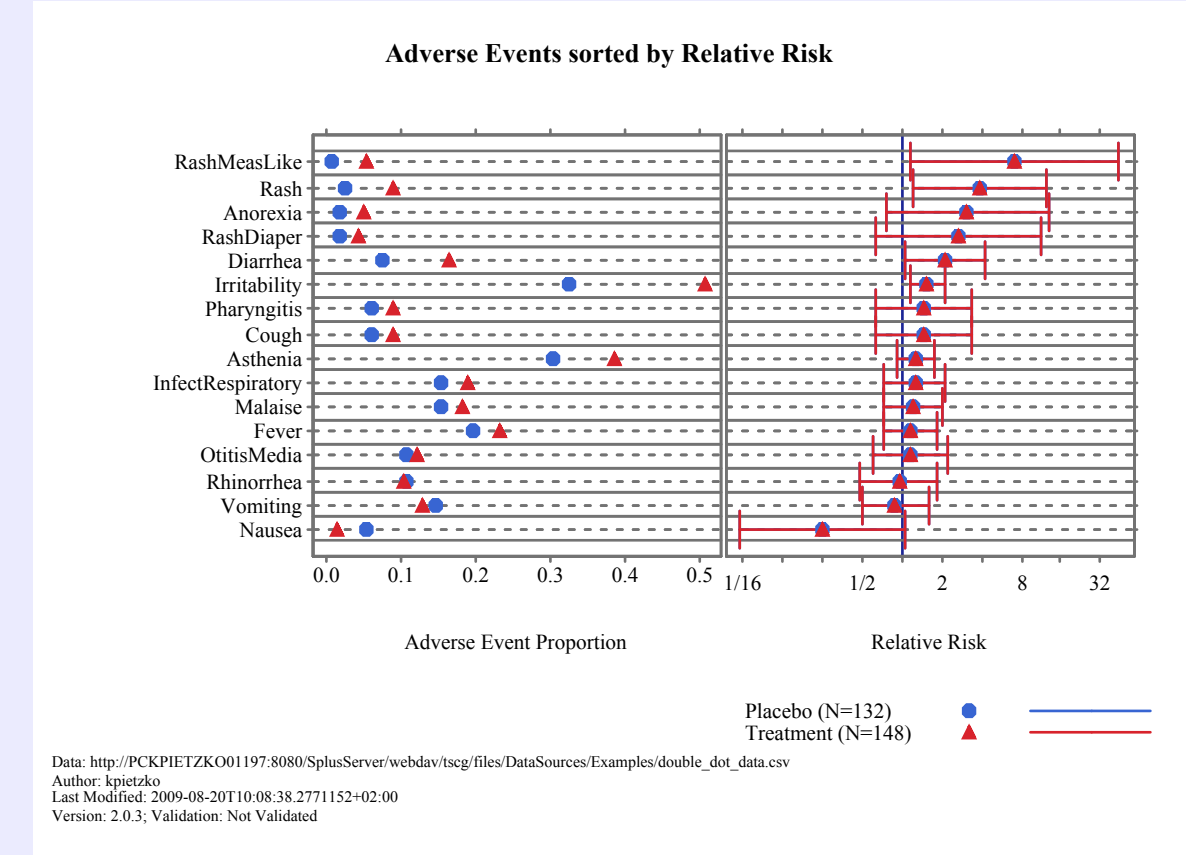
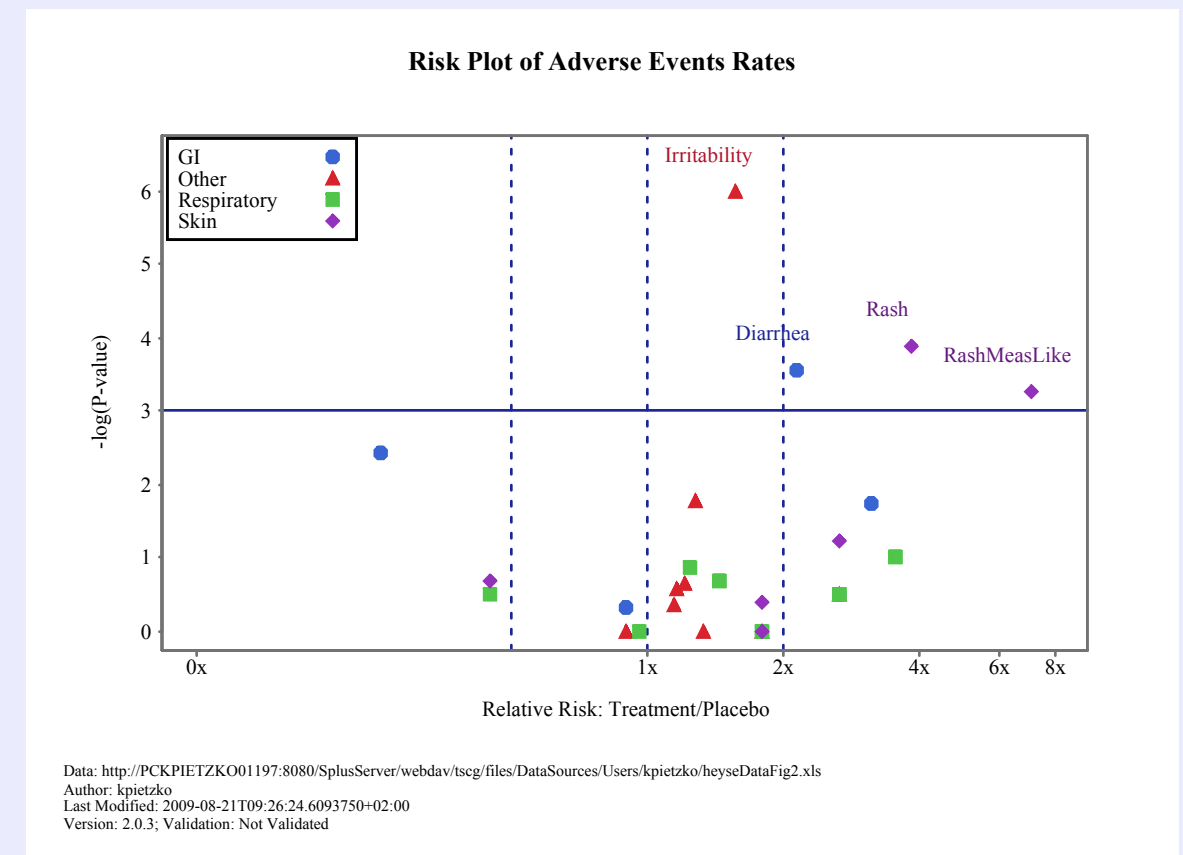
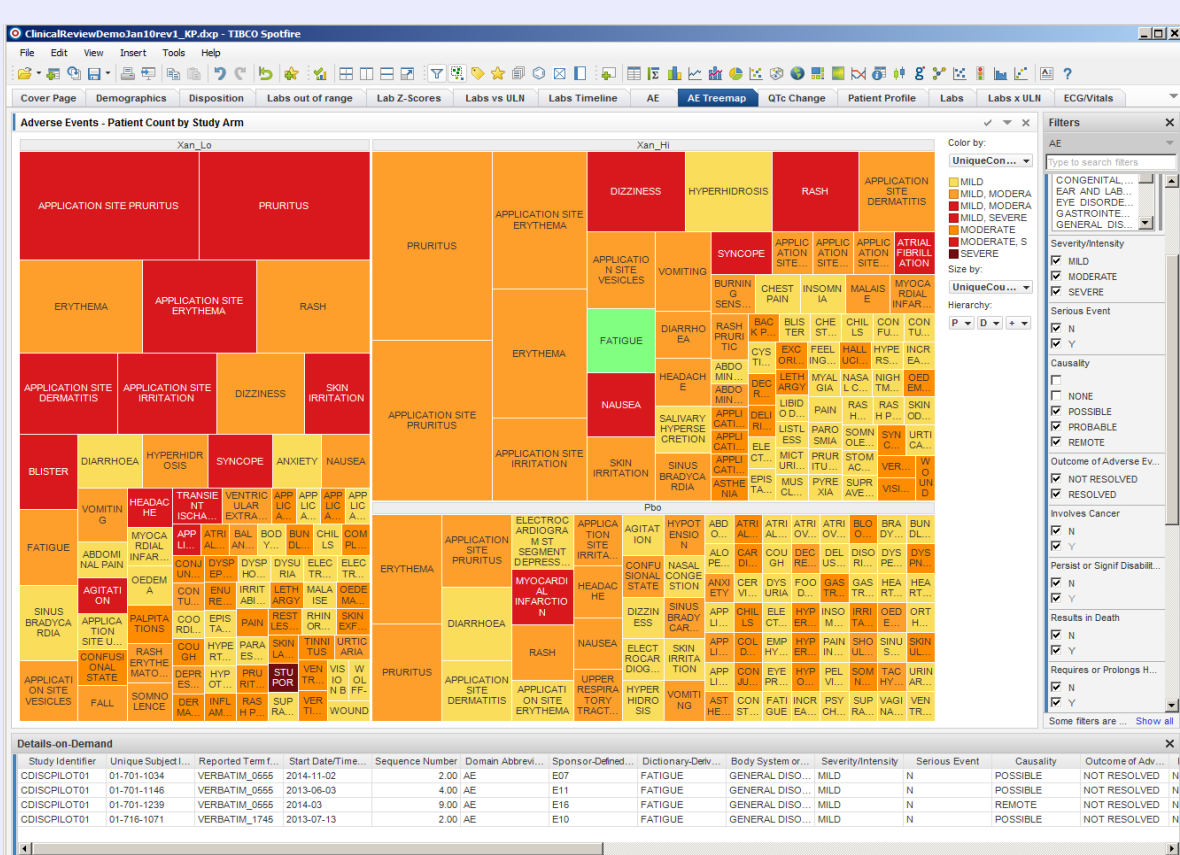
- Which adverse events are elevated in treatment vs. placebo?
- Patterns of AE onset in treatment vs. placebo?
- Relationship to concomitant medications?

Adverse Events by Relative Risk

- attributable risk can be used to provide a simple estimate of the number at risk at a large population.
- RR can be estimated from a Bayes model that borrows strength i.e. within and across body systems for sparse data.

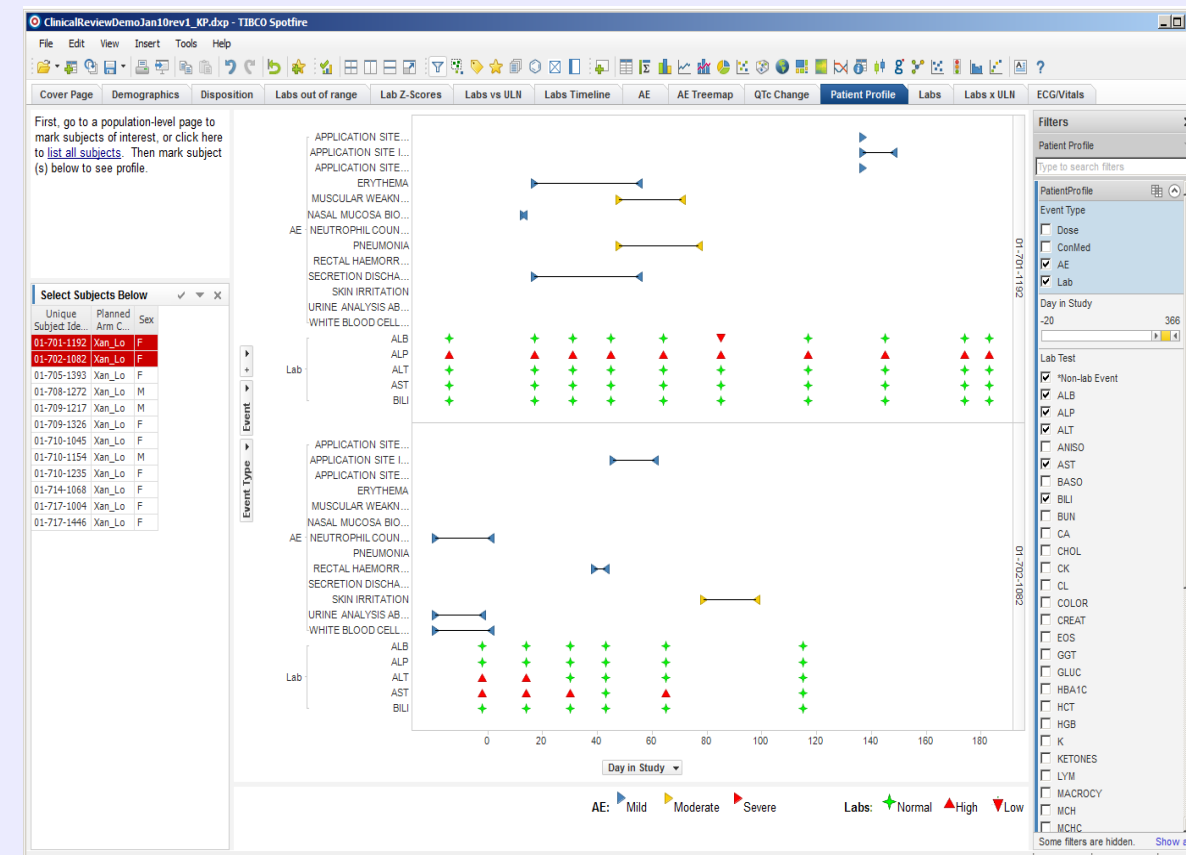
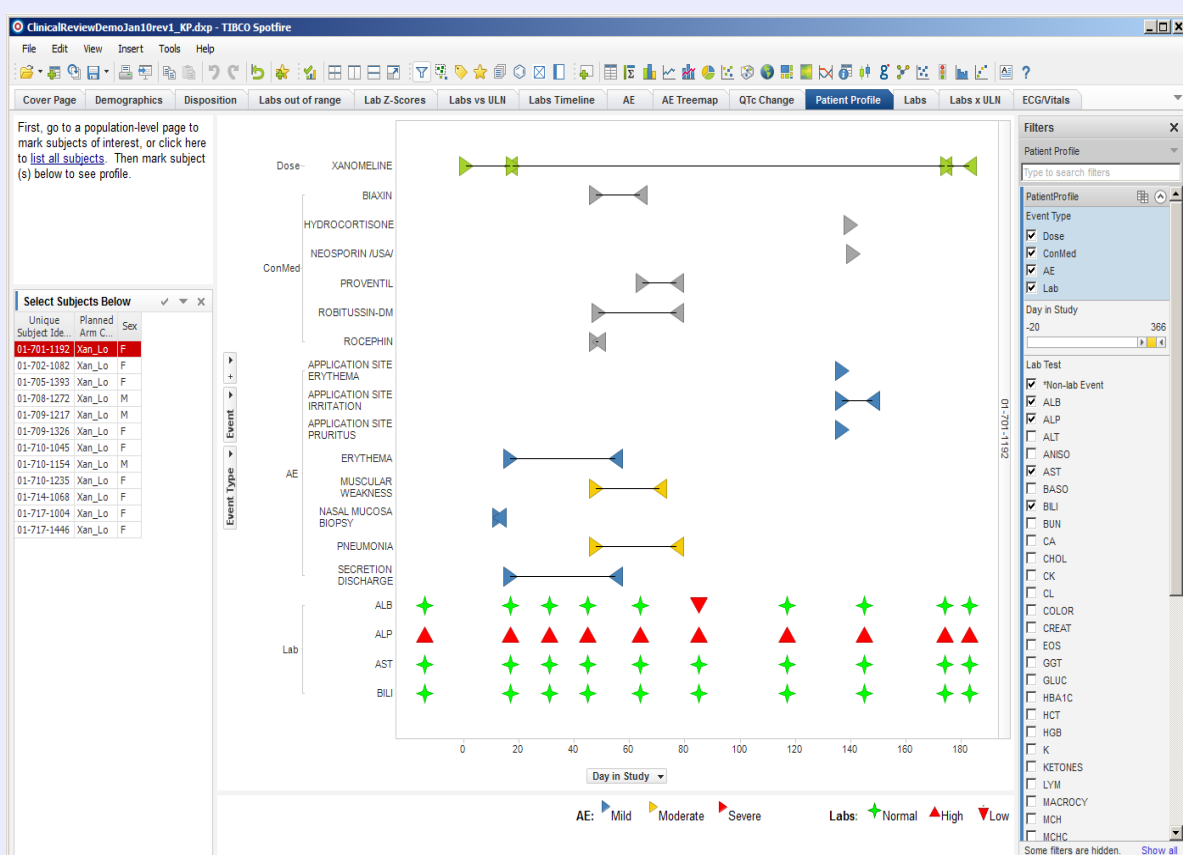
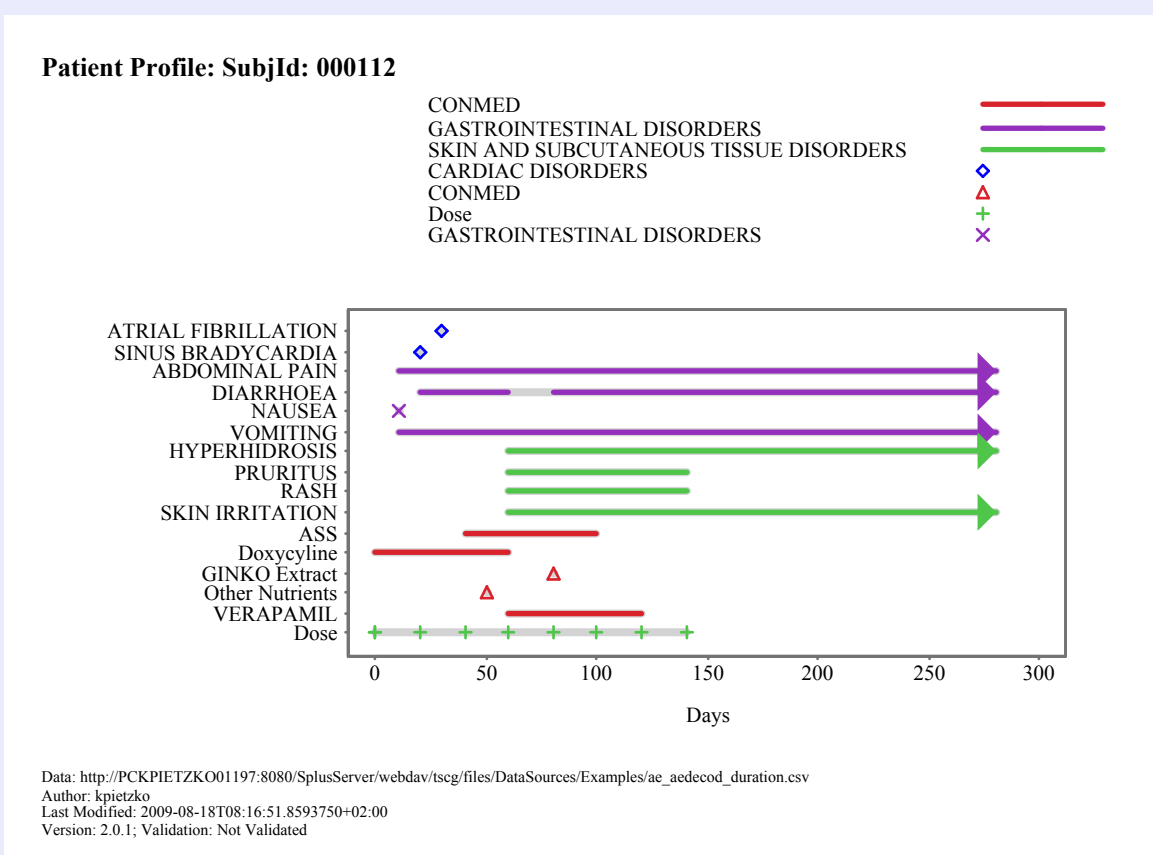
Double Dot Plots present relative risk along with the frequency of adverse event occurrence

- the relative risk is shown in an additional panel to the original dot plot
- the adverse events are sorted by the relative risk
- the first x-axis (Adverse Event Proportion) is on a linear scale
- the second x-axis (Relative Risk) is on a log2 scale



Patient Profile

- Are conmds related to AE's
- Are lab elevations related to AE's
- Are lab elevations and AE's related to treatment



Conclusion

Better graphics lead to better science and more effective communication of information. Statistical graphics are critical for the efficient and accurate analysis and interpretation of clinical data.

Statistical graphics enable:

- Rapid and accurate comparative analysis of treatment effects
- Exploratory analysis, cleaning and understanding of safety and efficacy data
- Efficient, electronic data browsing and clinical data review
- Clarity in safety and efficacy messaging in clinical study reports
- Clear and effective presentation of study results in scientific presentations, publications and marketing applications
- Clear presentation of trial and program results in regulatory submissions.