

Statistical Graphics for Review and Reporting in Clinical Development

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ABSTRACT

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.

This presentation shows a number of different graph types for exploratory analysis and reporting of safety data. Report graphics are illustrated using S+® and Clinical Graphics™, both part of the TIBCO® Spotfire® product family. Exploratory graphics are illustrated using TIBCO Spotfire. These products enable end-users to create their own graph templates from an inbuilt palette of graph types, and to share these for re-use on different clinical trial data across a variety of functional areas.

INTRODUCTION

Clinical trials are complex, representing many years of research, and comprising data from the many dimensions associated with a clinical study e.g. efficacy endpoint measurements, dosing, adverse events, lab measurements, medical history and concomitant medications. Statistical graphics play a crucial role in the interpretation of such complex clinical drug development data by enabling accurate and rapid interpretation of the multifaceted data.

In this paper we describe some primary elements of statistical graphics for the analysis of clinical data, and a graphics taxonomy whereby the graphics are categorized via data and metadata typing. This is followed by differencing of Reporting and Exploratory Graphics. We then illustrate the use of some graph types through the analysis of safety data including adverse events, laboratory measurements, vital signs and combined patient profiles, using the TIBCO Spotfire Clinical Graphics software product for reporting Graphics and the TIBCO Spotfire software product for exploratory Graphics. In the examples we show how appropriate statistical graphics elements may be used to extract and highlight salient safety information in the clinical study data. The exploratory graphics examples show the value of interactivity and drill-down capacity to shorten the time for finding safety issues and reduce the risk.

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

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

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 these settings there are minimal formatting restrictions and it is possible to use interactive plots to help facilitate interpretation and communication.

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. For example, strict standards regarding headers, footers, fonts, symbols, lines, axes, legends, annotations and the graphic file itself are typically enforced.

GRAPHICS FOR STATISTICAL ANALYSIS, DATA REVIEW AND STUDY REPORTING

Excellence in statistical graphics consists of complex ideas communicated with clarity, precision and efficiency (Tufte, 1983). The goal is to communicate the salient information in the data, and the channel is the viewer's perception of data values and data patterns. For correct viewer perception and retained information, data need to be presented accurately and the presentation needs to be rapidly interpreted.

Pattern perception from a graph involves three key tasks: (a) detection–recognition of geometry, (b) assembly–grouping of detected symbols; and (c) estimation–assessment of relative magnitudes.

Tufte (1983, and in his widely attended seminars) espouses key graphics principles for accurate and retained information extraction:

- Show all the data – multivariate data and metadata

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- Induce the viewer to think about the substance rather than the graphic design – maximize the data-to-ink ratio
- Avoid distorting what the data are saying
- Make large data sets coherent
- Encourage the eye to compare different pieces of data
- Leverage investment by showing multiple plots of same type (principle of small multiples)
- Reveal the data at several levels of detail, from a broad overview to the fine structure
- Serve a clear purpose: description, exploration, tabulation
- Be closely integrated with the statistical and verbal descriptions of a data set
- Use gray scale and color sparingly

Applying these graphics principles to clinical data analysis results in the following tips for comparative graphical analysis and presentation:

- Group data into interpretive categories e.g. treatment, dose, AE PT or SOC; applying different elements (color, symbol, line, fill) to groups for easy comparisons
- Use multi-panel Trellis displays, leveraging a reader's investment in the graphic being viewed
- Use dot plot, box plot, line plot rather than pie chart; thus maximizing the data-to-ink ratio. Or use bar chart when you want the ink to matter e.g. in presentation of efficacy results.
- Distinguish report v exploratory review graphics with appropriate graph elements, serving a clear purpose with the graphic
- Rotate data when curves are steep (Bland-Altman: $(Y-X) \vee (Y+X)/2$, rather than $Y \vee X$)
- Set a sound aspect ratio e.g. banking to 45 degrees for comparing slopes of lines, or showing the true slope in the data
- Include (feint) grid lines and reference lines as appropriate
- Sort categories e.g. on dot plots, Pareto plots
- Minimize use of legends by annotating the graph directly
- Try not to use more than 3 color hues
- Use contrast hues (e.g. blue-yellow) and avoid color-blind hues (red-green)
- Use colors that hold up to photocopying (e.g. black and gray) for 2-group and multi-group comparisons (treatment and control)
- Don't use too many dashed line types – they are difficult to distinguish
- Use metadata, brushing, drill-down (e.g. TIBCO Spotfire) to move from population to patient level data; revealing data at several levels of detail

GRAPHICS FOR REPORTING VS GRAPHICS FOR EXPLORATORY REVIEW

Exploratory and reporting graphics are quite different.

Reporting graphics typically need to be self-contained, in-text figures should have an explanation in the caption, footer, header and titles need to be added whereas exploratory graphics may not be self-contained because they are used by the data analyst for interactive display and should contain metadata information on demand and allow brushing, marking and filtering to ease the exploration of safety risks. Graphics for reporting should also be documented by log files, time-stamps, source data and output file references compared to exploratory graphs which are produced for exploration and may not be documented.

Another difference between reporting and exploratory graphics is the required color schemes and formats. Reporting graphics need to be interpretable in black and white so that different shapes of point and lines need to be used. They also need to be of a very high quality and resizable to fit into the submission reports and presentations – which also requires a compatible graphics device with Microsoft Word and PowerPoint. Exploratory graphics need to be interactive and easy and clear to interpret, but do not need to be aligned to some regulatory needs.

GRAPHICS FOR PRESENTATION OF SAFETY DATA

There has been much recent work on development of statistical methodology for clinical trial design and analysis methods for efficacy endpoints. In contrast, safety data are collected as concomitant information, typically analyzed as an afterthought, and reported as simple tables and listings. For example, large amounts of safety data are collected in clinical trials, but basic information such as which types of patients have adverse events or elevated lab values, is not well captured or summarized in statistical analyses and clinical study reports. Adverse event data are often presented in tables with stand-alone p-values and then much effort is spent explaining why adverse events with significant p-values are not important. In short, the current approach to safety data analysis in clinical trials is rudimentary at best.

The consumers of safety data analysis and clinical study reports need to rapidly and accurately interpret the safety content, and have short available time windows to do so. DSMBs typically have one-day meetings, and paging through tables is inefficient. Regulatory agencies such as the FDA want transparency of analysis and internal consistency of results; they are sensitive to any gaming of results through opaque modeling. Finally, internal stakeholders such as sponsors, CROs and partners want to identify safety signals as early as possible in order to (a) reassign or withdraw subjects from a trial, and (b) stop a trial and/or prioritize the portfolio of drug candidates in development.

Statistical graphics, combined with simple summary statistics such as relative risk or attributable risk (risk difference), enable clear and unambiguous presentation of safety information from clinical studies. In exploratory analysis and clinical review, statistical graphics enable rapid data cleaning and signal identification, since all of the data can be displayed efficiently. In clinical reporting, a well-formed statistical graphic can communicate the safety message in the data clearly and quickly. Such graphics can anchor the clinical study

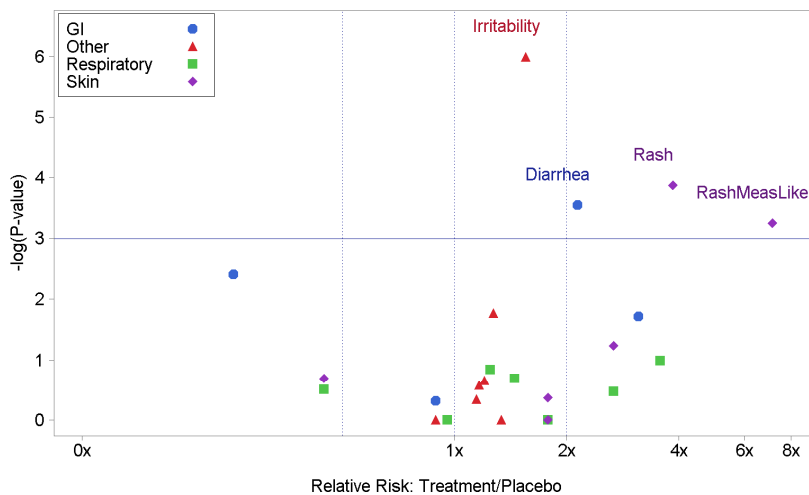
report from the safety perspective.

ADVERSE EVENTS

Some primary goals of adverse event analysis include identifying which adverse events may be elevated in treatment vs. placebo, and the rapidity of their onset in treatment vs. placebo. These are inferential questions relating to treatment effects and patterns; and population level analysis is important.

We illustrate some graphical analyses using data from a vaccine trial in babies from Mehotra and Heyse (2001).

Risk Plot of Adverse Events Rates

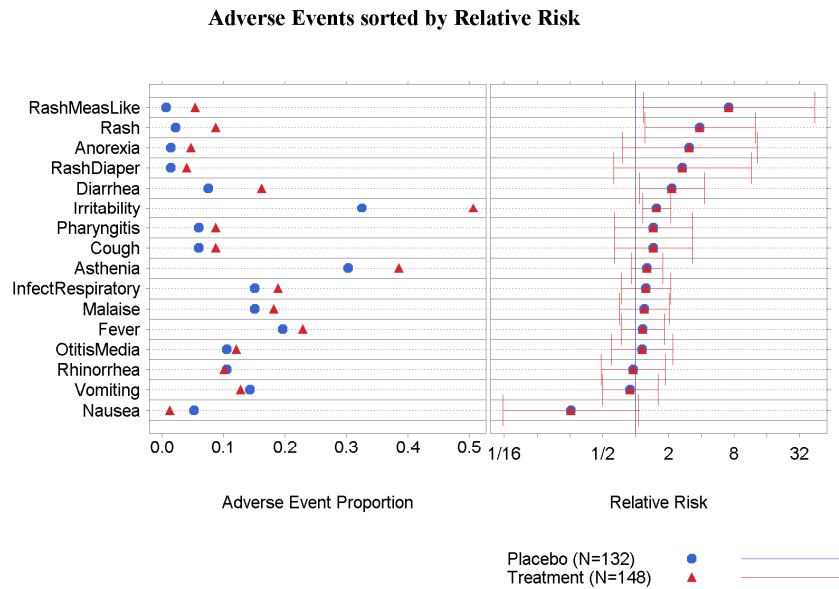


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Figure 1: p-Risk plot of adverse event rates in a vaccine trial (Mehotra and Hayes, 2001); grouped on system organ class (SOC).

Figure 1 shows a grouped p-Risk plot for the Mehotra and Heyse data. This graph was introduced in the analysis of adverse event data by O'Connell (2006) and shows the relative risk of the adverse events on the x-axis and the p-value comparing treatment and control rates on the y-axis. The combination of the p-value of the treatment effect, with the relative risk or risk difference, provides perspectives of a statistician and clinician in a single graph. Adverse events above the solid horizontal line are annotated with their preferred term. Note that Anorexia has a 3.5X risk but only 9 observed events, so its' point is below the line (blue circle at 3.5x). Diarrhea on the other hand only has a 2X risk, but with 34 observed events is a stronger potential signal than Anorexia (blue circle above the line at 2x). Variations on this plot include the use of the risk difference rather than relative risk on the x-axis; this has the nice interpretation of attributable risk i.e. the proportion of risk attributable to the treatment. Attributable risk can be used to provide a simple estimate of the number at risk in an at-large population. Also, one may estimate the RR from a Bayes model that borrows strength e.g. within and across body systems. This enables more reliable estimates of RR, especially in situations where data are sparse i.e. low counts for some/many AE's.

Figure 2 shows another way of presenting relative risk along with the frequency (percentage) of adverse event occurrence using a double dot plot (Amit et al., 2006). In this graph the relative risk is shown in an additional panel to the original dot plot. In Figure 3, the adverse events are sorted by the relative risk. The second x-axis (Relative Risk) is on a log2 scale, whereas the first x-axis (Adverse Event Proportion) is on a linear scale.



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Figure 2. Double dot plot of adverse event rates in a vaccine trial (Mehotra and Hayes, 2001).

Another graphic that is sometimes used to show adverse events is the Treemap. This shows areas for Treatment ARM and PTs in accordance with a chosen variable e.g. frequency or frequency difference between treatment groups; and a color scale in accordance with another variable e.g. severity. A treemap for a clinical trial dataset is shown in Figure 3.

Compared to the reporting graphs as shown above, the exploratory graphics can start at high-level overview of adverse events and then drill-down to a patient level overview. The treemap graph shown in Figure 3 is an interactive graph which displays a hierarchy ordered by treatment arm and preferred term. The size of the rectangles corresponds to the number of patient where this adverse event appeared. The adverse events are also sorted by the number of patients starting from the left top and going to the right bottom. The severity is shown by the color of the areas. By marking a specific adverse event a table at the bottom shows the corresponding patients to this preferred term. The tooltip displays some summary information about the respective area.

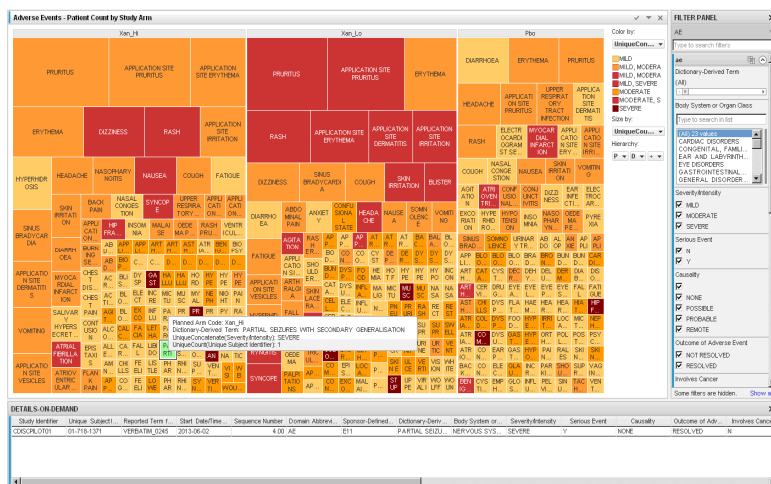


Figure 3: Treemap of adverse events, sized by patient count and colored by adverse event severity

The filters on the right hand side allow filtering of criteria like the severity or causality of adverse events. Figure 4 shows only those adverse events which have at least a causality of *possible* and a severity of *moderate* or *severe*. The green marking shows patients that have suffered from myocardial infarction in the treatment group. This subset of patients can be used to do further analysis of the corresponding lab values or vital signs.

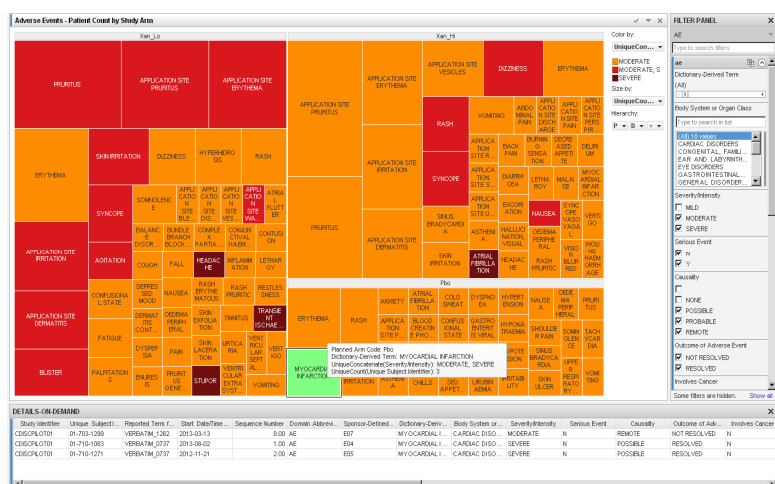


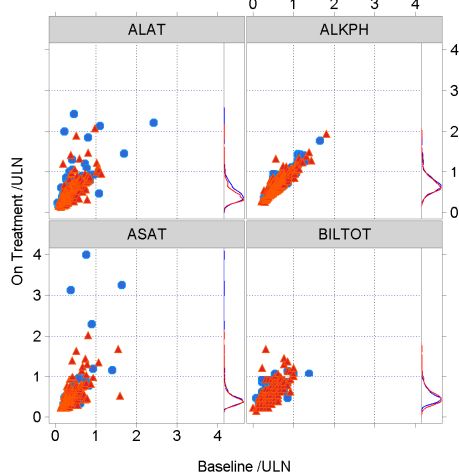
Figure 4: Treemap of adverse events, filtered data.

LABORATORY MEASUREMENTS

Some primary goals in the analysis of instream and unblinded lab data (e.g. liver panels) include (a) understanding patterns of effects on lab values across time and treatment, and (b) identifying which subjects have elevated (liver) labs and elevation on multiple labs. As such, both population and subject level analysis are important.

Figure 5 shows a shift plot of liver lab measurements, ASAT, ALAT, AlkPhos and Bilirubin. The plot is grouped on treatment, with blue and red symbols representing placebo and treatment. Note that each lab measurement is normalized to the upper limit of normal (lab / ULN). This presentation scale has the advantage of easy comparability among individual lab measures and assessment of elevation. The shift plot shows the baseline lab value on the x-axis and the on-therapy value on the y-axis. Values in the top left corner of the graph indicate subjects whose values were below the upper limit of normal at baseline and became elevated during the study. Typical critical levels of concern (CLC) are $> 2x$ ULN for Bilirubin and $> 3x$ ULN for ASAT, ALAT and ALKPH. The dotted horizontal and vertical lines on the plot provide thresholds for these CLCs. In the plot below, there are 3 subjects with elevations beyond the CLC for ASAT and no subjects above the CLC for the other labs.

Liver Lab Shift Plot

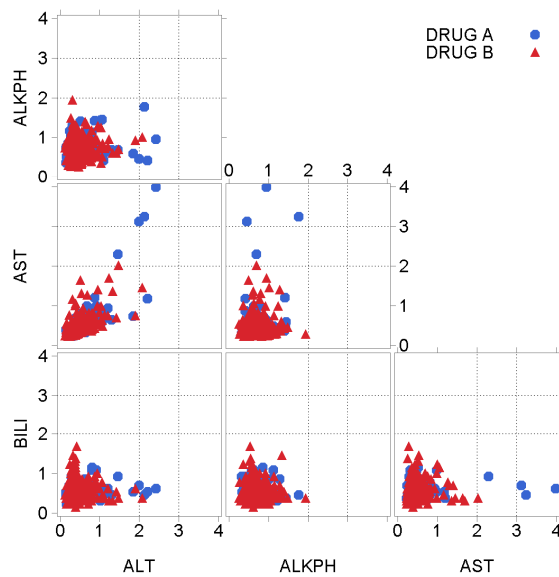


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Figure 5: Grouped shift plot of ASAT, ALAT, ALKPH and Bilirubin; grouped on Treatment (red points are drug and blue are placebo). The lab values are normalized to their upper limit of normal (/ULN). Reference lines are included at clinically meaningful values including critical levels of concern (3X ULN for ASAT, ALAT and ALKPH, and 2X ULN for Bilirubin).

Figure 6 shows a scatter plot matrix for the panel of four liver lab measurements from the same study. In this plot a subject has elevated results on two (AST and ALT) of the four liver labs (AST, ALT, Alkaline Phosphatase and Bilirubin). The presentation in Figure 6 enables assessment of Hy's Law for drug induced liver injury (DILI), which draws attention to subjects with elevation of ALAT or ASAT above 3X ULN with simultaneous elevation of Bilirubin above 2X ULN and no elevation of ALKPH above 3X ULN. Such subjects in the treatment group have potential drug-induced liver injury. A recent FDA guidance describes such assessment of DILI in some detail (US HHS, October 2007).

Matrix Display of LFT (/ULN)



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Figure 6: Scatter plot matrix for multiple liver labs: rows: Bili, AlkPhos, AST; cols: ALT, AST, AlkPhos

for same trial as in Figure 3. This graph allows assessment of Hy's law which highlights treated subjects with elevation of ALAT or ASAT above 3X ULN with simultaneous elevation of Bilirubin above 2X ULN and no elevation of ALKPH above 3X ULN, as having potential drug-induced liver injury.

Compared to reporting graphs, interactive graphs allow an immediate drill down to subjects at potential risk. Figure 7 shows Lab Shift Plots for selected lab values and also a Box Plot displaying lab test on- treatment value. By marking values higher than one in the box plot the same subjects also gets marked green on the shift plot and displayed on the details table at the bottom. This enables an immediate drill-down to a patient level view as shown in Figure 8.

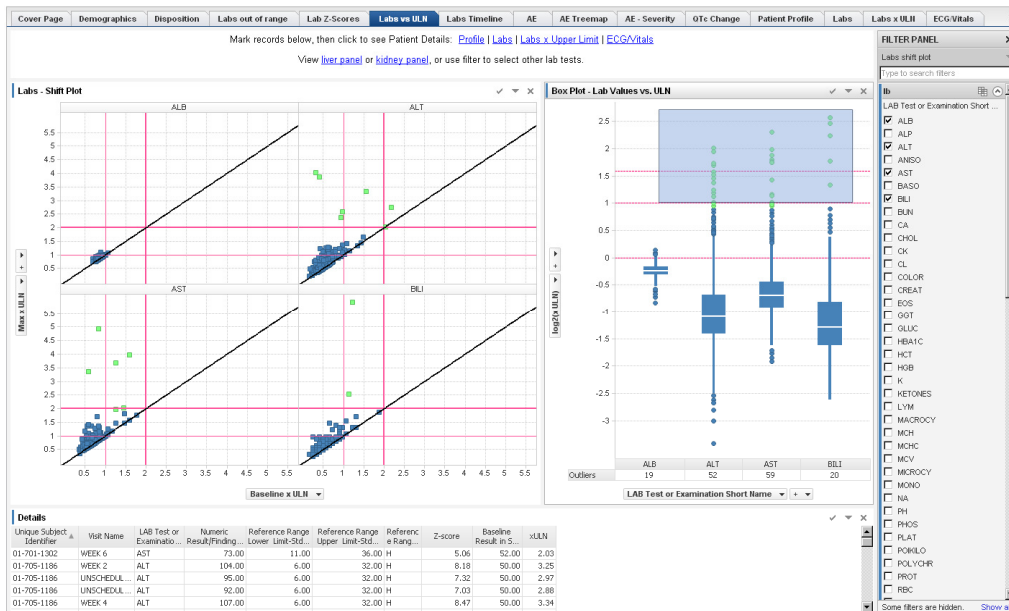


Figure 7: Lab Shift Plot and Box Plot for filtered Lab Tests. Marking (in green) shows patients with increased lab values during treatment. The Details on-demand table on the bottom displays these subjects.

Figure 8 shows an interactive line chart for liver lab values including upper and lower bounds per selected patient. In Figure 7 patients

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with increased lab test values during treatment were marked. These subjects automatically appear in the small table on the left hand side of Figure 8. By selecting one of these patients the *Lab over Time* chart shows the lab values for the corresponding patient and the tables for adverse events and concomitant medication provides additional information on this subject. The filter panel on the right allows to select lab tests of interest.



Figure 8: Lab Line Plot for selected patient and filtered Lab Values. Tables below show corresponding adverse events and ConMeds.

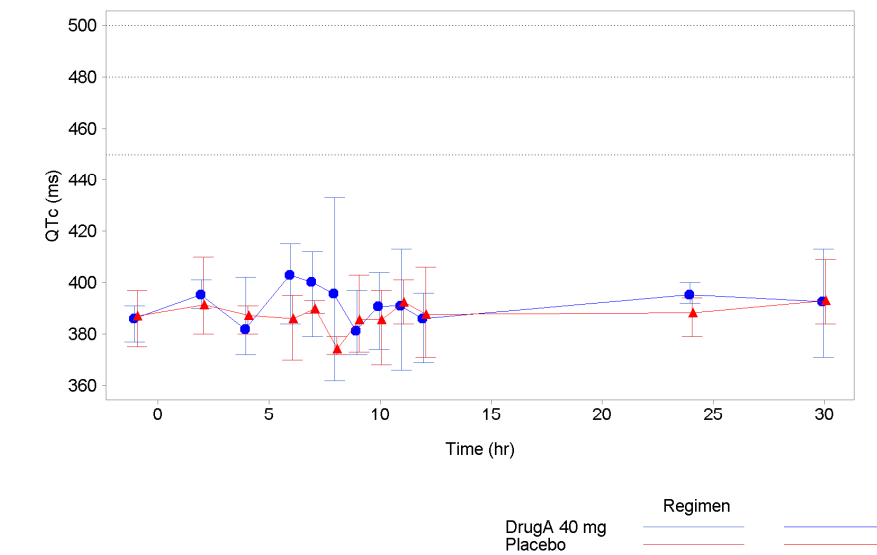
VITAL SIGN MEASUREMENTS

As outlined in a recent FDA guidance on clinical evaluation of QT/QTc prolongation (US HHS, 2004), some goals in the analysis of QT intervals include assessment of (a) elevation of corrected QT (QTc) for the drug treatment, with 450, 480, 500 ms providing levels of concern, (b) elevation of QTc v BaseQTc, for the drug treatment, of 30 or 60 ms, and (c) elevation of QTc(Drug) v QTc(Placebo) of 5 or 10 ms. Analysis of vital sign data involves both subject level and population level analysis, referred to as categorical and central tendency analysis in the guidance.

Figure 10 shows a *grouped line plot* of mean QTc, grouped on treatment. Guidance values of 450, 480 and 500 ms are shown as dotted reference lines. Note the confidence intervals around the mean are staggered to prevent overlap and allow assessment of both the point and interval estimates for the two treatments in the study.

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QTc Profile With BootStrap Confidence Intervals

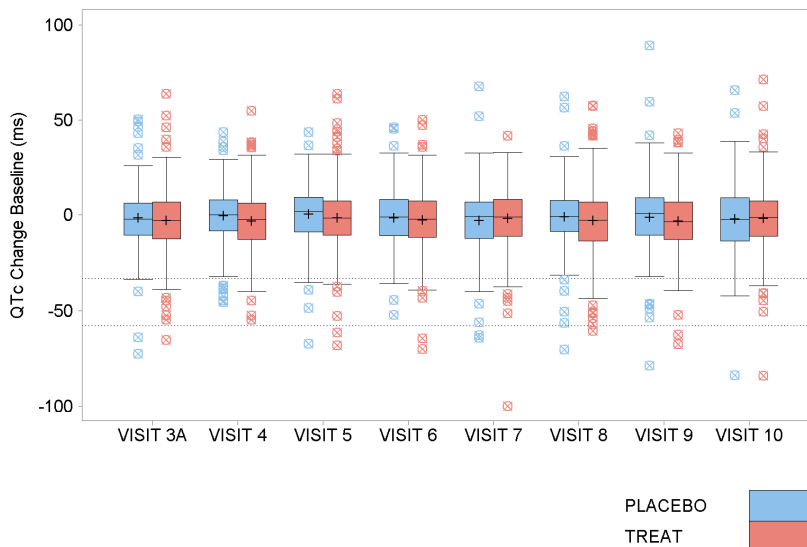


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Figure 9: Grouped line plot of QTc; grouped on treatment. Confidence intervals are staggered so as not to overlap. Reference lines are added at 450, 480 and 500 ms in accordance with the FDA guidance.

In addition to plotting the raw QTc values, we can plot the elevation of QTc versus baseline QTc and the elevation of QTc in the drug versus QTc in the placebo. Figure 10 shows a Boxplot of elevation of QTc versus baseline QTc, grouped by treatment. Guidance values of -30 and -60 ms are shown as dotted reference lines.

Box Plot - Baseline Change in QTc in Time and Treatment



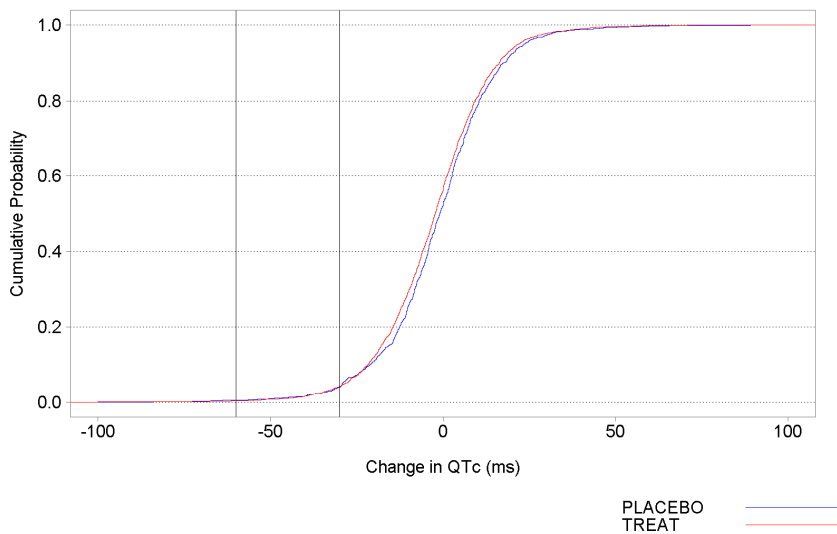
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Figure 10: Grouped Boxplot of QTc change from baseline versus time with levels of concern at -30 and -60 msec. There are some subjects with values exceeding the levels of concern at some visits.

Another way of graphing the QTc versus baseline QTc is an empirical CDF plot of the delta QTc, grouped by treatment. This is shown in Figure 11. One issue to consider in all QTc and lab value plots is whether to include all observations or just the maximum (or

maximum delta).

Empirical Distribution Function for Change in QTc



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Figure 11. Empirical CDF plot of the delta QTc, grouped on treatment with levels of concern shown as vertical lines at -60 and -30. The distributions of the delta QTc are very similar for placebo and treatment.

Figure 12 shows an interactive patient level view of vital signs for a particular subgroup of patients. The line graph on the top shows the QTc value over time for a particular subject. The dotted red line at 500 ms has been added in accordance to the FDA guidance. The vitals line chart below presents systolic and diastolic blood pressure and pulse values for the same subject over time. Other vital signs like temperature or weight can be added to the plot using the filter panel.

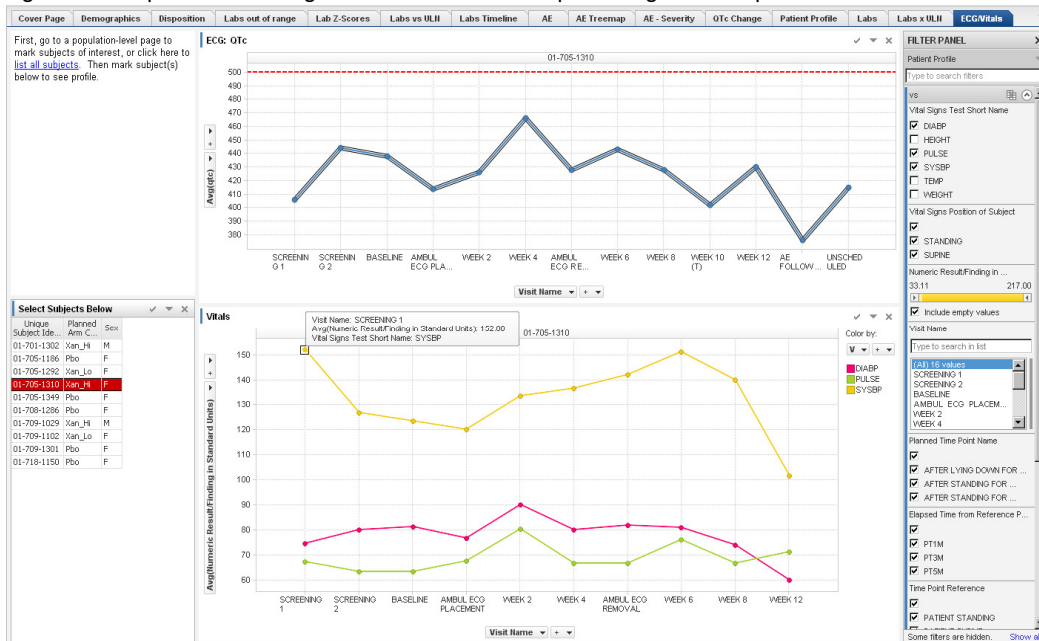


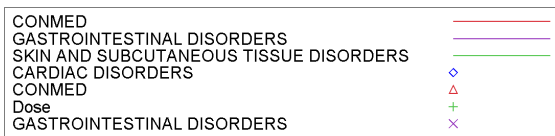
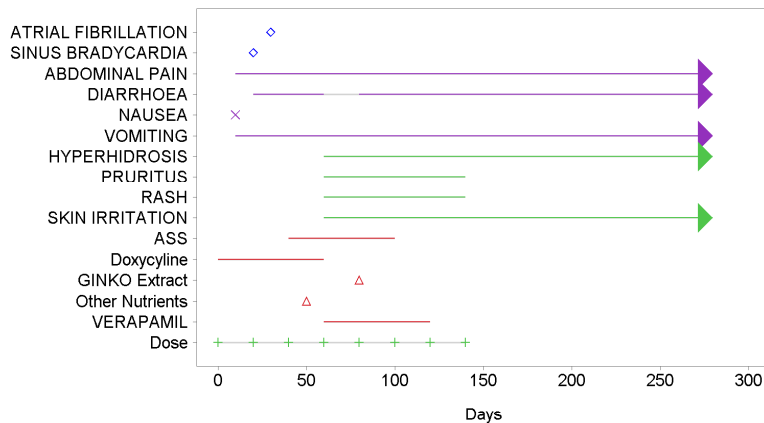
Figure 12. ECG and Vital signs for selected patient.

PATIENT PROFILES

Sometimes it is useful to visualize multiple data domains on a common timescale. For example, viewing lab measurements, adverse events, study drug dosing and concomitant medications can reveal patterns and associations between adverse events and elevated labs with study drug and/or concomitant medication administration.

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Patient Profile: SubjId: 000112



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Figure 13. Patient profile for particular patient in the Prostamol study. Note that adverse events, concomitant medications and study dosing are shown on a common time scale (days on study).

Figure 14 shows a patient profile for patients of interest. The table on the left can be configured to show all patients or just a subset of patients which were already identified to be potentially at risk. This Patient Profile shows a combination of Dosage, Concomitant Medication, Adverse Event and Lab Tests all aligned on a common time scale. The symbols used for Dose, ConMed and AE indicate the start and end date of the event and are colored by the event type group and adverse event severity. The Lab Test values represented as green stars stand for normal lab values, whereas the red up or down arrows indicate low or high values.

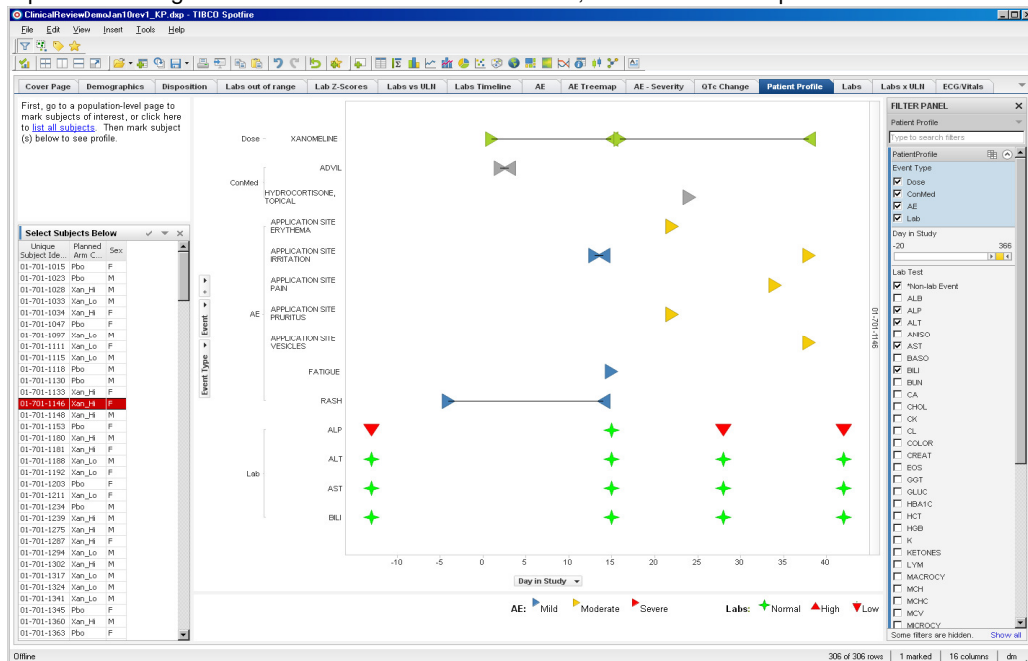


Figure 14. Patient profile for patient of interest. All events are shown on a common time scale (days on study).

CONCLUSION

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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.

Consistency in the deployment of statistical graphics principles and standards is vital to maintaining the value created by statistical graphics. Significant efficiencies are created throughout an organization when statistical graphics are specified consistently for clinical study reports, clinical data review, scientific presentation and publication, and regulatory submission.

Reliable and robust integration of statistical graphics with existing data management and analysis environments can multiply cost savings across the drug development lifecycle. The deployment of statistical graphics standards and libraries across clinical functional areas provides built-in quality control through the elimination of graphics reworking and other manual processes.

As illustrated in this paper, TIBCO Spotfire® Clinical Graphics software has a rich palette of clinical graphs available through a point-click environment. As detailed graphs are constructed, they can be saved as central templates that can be re-used in clinical data during a trial and applied to data from other trials. The graph types and templates can also be run from within the SAS environment for regulatory submissions.

This includes detailed specification of graph elements directly from within SAS. Finally, the graph types and templates are also available from the Spotfire environment as part of the exploratory review process.

The simple point-click creation of a rich set of clinical graphs for safety and efficacy, their re-use as scripts from Spotfire S+® and SAS production environments and from the Spotfire exploratory review environment, saves much time, while driving consistency and best practices throughout all pharmaceutical development functional areas.

TIBCO Spotfire® software offers an interactive platform for exploratory data analysis. As the examples illustrate, different tables can be linked together in a workbook to enable filtering on patient level over the entire workbook independent of the tables. This feature allows the start from a study level overview of adverse events and subsequent drill-down to patient level lab values and patient profiles. The Integration of Spotfire S+® or R language into TIBCO Spotfire allows sophisticated statistical analysis and computation from within the interactive Spotfire Workbook.

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ABOUT TIBCO, SPOTFIRE AND S-PLUS

TIBCO Software Inc. (NASDAQ:TIBX) is a provider of data management, predictive analytics and reporting solutions. TIBCO products in the Spotfire division include TIBCO Spotfire, TIBCO Spotfire S+ and TIBCO Spotfire Miner™ and the S-PLUS programming language. These products allow companies to perform sophisticated statistical data analysis, data mining and create high-quality graphical analysis and reporting from numeric data. TIBCO Spotfire has been delivering industry-leading, high-ROI solutions to thousands of companies in financial services, life sciences, biotechnology, telecommunications, and manufacturing, plus government and research institutions, for

20 years.

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