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Interactive Clinical Data Review for Safety Assessment and Trial Operations Management

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ABSTRACT

Clinical trial data are complex with thousands of safety and efficacy measurements collected on many subjects, often over a considerable period of time. For clinical development to proceed faster, clinical development organizations are simplifying and streamlining data management and analysis processes. They are deploying software to provide meaningful data views to people who need them quickly - to medical monitors, clinicians and safety officers for instream review and safety analysis; and to trial managers and research associates for protocol adherence and operations metrics, monitoring and management. They are moving to a framework of proactive, data-responsive decision making – rather than retrospective tracking of results.

The drive for productivity in drug development translates directly in to simplification and speed of clinical data management, analysis and reporting. The modern clinical development organization is striving to optimize trial progression, site performance and protocol adherence; while simultaneously managing safety risk, maintaining data quality and continuously monitoring medical data across a portfolio of clinical programs. Such proactive decision making shortens the time between critical development gates and enables key milestones to be met sooner, while simultaneously managing safety risk.

This presentation includes (a) an outline and live analysis of a phase 2 clinical trial including interactive review/analysis of adverse events, labs, vitals and in-built statistical analysis for assessing AE treatment emergence; and (b) an analysis of a portfolio of clinical trials from a study management and operations perspective. This includes assessment of trial enrolment across trials, sites and countries; and assessment of key performance indicators (KPIs) for management of trial sites and operations.

The instream, interactive data analyses are illustrated using the TIBCO Spotfire® platform; and the seamless connection between Spotfire and S+®/R for statistical analysis and predictive modeling is discussed in context.

1. INTRODUCTION

Clinical trials are complex, representing many years of research, and comprising data from the many dimensions associated with a clinical study. Clinical and medical data are the focus of much attention during the trial: with interim analyses, and with the final analytic and reporting effort. Safety assessment is large and ongoing task including analysis of adverse events, lab measurements, medical history and concomitant medications. Efficacy analyses, including exposure-response, dose-response, biomarker assessment and endpoint analyses are also an intensive effort. Some key use-cases involving instream and exploratory review of clinical data include:

- Medical review / monitoring of clinical and safety data
- Instream data quality assessment
- Selection of drug dose in adaptive and dose-ascending studies during early phase development
- Assessment of pharmacodynamic response data and biomarkers in terms of drug exposure, demographics and other patient-visit covariables
- Safety monitoring to enable timely decisions on dose adjustment, supplementary data collection and/or early termination of trials

- Protocol adherence monitoring to enable timely replacement of subjects or collection of required data
- Incorporation of emerging data sources such RNA expression and medical images into the clinical data analysis process

Analysis of trial operations data is also a large effort and goes hand in hand with the clinical/medical analyses. Some key use-cases for operational data analysis include

- Live scorecards for management e.g. KPI's such as Protocol-to-First-Patient by country/site.
- Enrolment and cross-trial analysis; understanding recruitment patterns across countries, sites and trials
- Assessment of discrepancies and queries status/resolution
- Data-driven monitoring to identify sites that aren't performing to plan
- Resource projections e.g. by function – understanding recruitment patterns across countries, sites, trials; and planning resources accordingly

There are many stakeholders responsible for all of these aspects of medical and operational data analysis. A summary of these stakeholders and use-cases is provided in Table 1.

User	***Need***	***Objective***
Operational Data Analysis		
Clinical Trial Study Manager	Dashboards/ KPIs/ sites Resource forecasting	Trial Management
Clinical Research Associate	Issue detection Protocol adherence	Data-Driven Monitoring
Clinical Data Analysis		
Data Manager	Data issue identification Query management	Data Cleaning
Biostatistician	Exploratory analysis Trends and outlier analysis	Data Analysis
Modeler: DMPK / M&S	Multivariate visualization Variables relationships	Exposure-Response Analysis Dose Selection
Clinician	Aggregate and patient-level visualization, medical review and safety assessment	Clinical results Risk minimization
Safety Officer	Aggregate and patient-level safety assessment	Signal Detection Risk Minimization
Medical Writer	Data visualization Data cross-referencing	Clinical Study Reports Presentations, publications

Table 1. Stakeholders and use-cases in Clinical and Operational data analysis.

In this paper we describe some of the basic use-cases and workflows outlined in Table 1, as addressed by interactive data analysis using TIBCO Spotfire. The paper is structured in two primary sections outlining analyses and workflows for (a) instream medical review, and (b) trial operations analysis and reporting.

The analyses are highly graphical and interactive, featuring exploration of points/regions of a graph through brushing and drill-down. This enables viewing of population trends with subsequent detailed exploration of interesting individual subjects and/or trial sites/PIs. The analyses are illustrated using TIBCO Spotfire software. This software enables 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.

2. MEDICAL / SAFETY REVIEW

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 during or at the conclusion of clinical programs.

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 clinicians, research associates and study managers want to identify safety signals as early as possible in order to (a) reassign or withdraw subjects from a trial, (b) gather supplemental data on emerging medical events, and/or (c) stop a trial and/or prioritize the portfolio of drug candidates in development.

Some medical / adverse events are of special interest (AESI's) e.g. (a) targeted medical events: events known or suspected to be associated with the therapy under study, (b) designated medical events: events known to be of interest to regulatory agencies e.g. liver and cardio events, (c) spontaneous events: events of note arising during the course of the study.

Interactive exploratory analysis and medical review enables rapid and ongoing safety assessment e.g. AESI's, data cleaning, and efficacy analysis e.g. exposure/dose – response. In what follows, we describe a safety assessment of a 3-arm Phase 2 clinical trial using interactive TIBCO Spotfire software for the medical review.

ADVERSE EVENTS

Some goals of unblinded 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 both population-level and subject-level analysis are important.

The PhRMA SPERT group, comprising senior safety analysts from across all major Pharma companies, recently released its initial report/manuscript (Crowe et al., 2009) including the following recommendations:

- creation of a Program Safety Analysis Plan early in development.
- a 3-tier system for signal detection and analysis of adverse events and highlight proposals for reducing "false positive" safety findings.
- recommendation that sponsors review the aggregated safety data on a regular and ongoing basis throughout the development program, rather than waiting until the time of submission.

The 3-tier system is readily implemented through the medical review framework described herein. The combination of visualization and predictive analysis enables identification and management of adverse events of special interest (AESI's); and leads to informed, proactive, responsive decision making.

Figure 1 shows a stacked Barchart and Treemap of Adverse Events in Spotfire; with unique counts (across subject) of Adverse Event preferred terms. Note the filter panel on the right hand side where the user may filter the display based on various columns in the adverse event datatable e.g. AE Severity (Mild, Moderate, Severe), Serious Event (Yes, No), Causality (None, Possible, Probable, Remote). The Barchart is colored by treatment (Placebo, Low Dose, High Dose). It is a simple matter to color or Trellis™ (Cleveland, 1993), the display on any variable in the filter panel by dragging the variable on to the graph and dropping it in the appropriate position.

Two preferred terms are highlighted (Vomiting and Nausea); these markings form a sub-population of subject IDs that may be used to drill down to detailed displays at the subject-level. The drill-down is achieved by clicking on the hyperlinks in the top panel (Patient Profile, Labs, Labs * Upper Limit, ECG/Vitals) or navigating to the appropriate drill-down page in the Spotfire workbook.

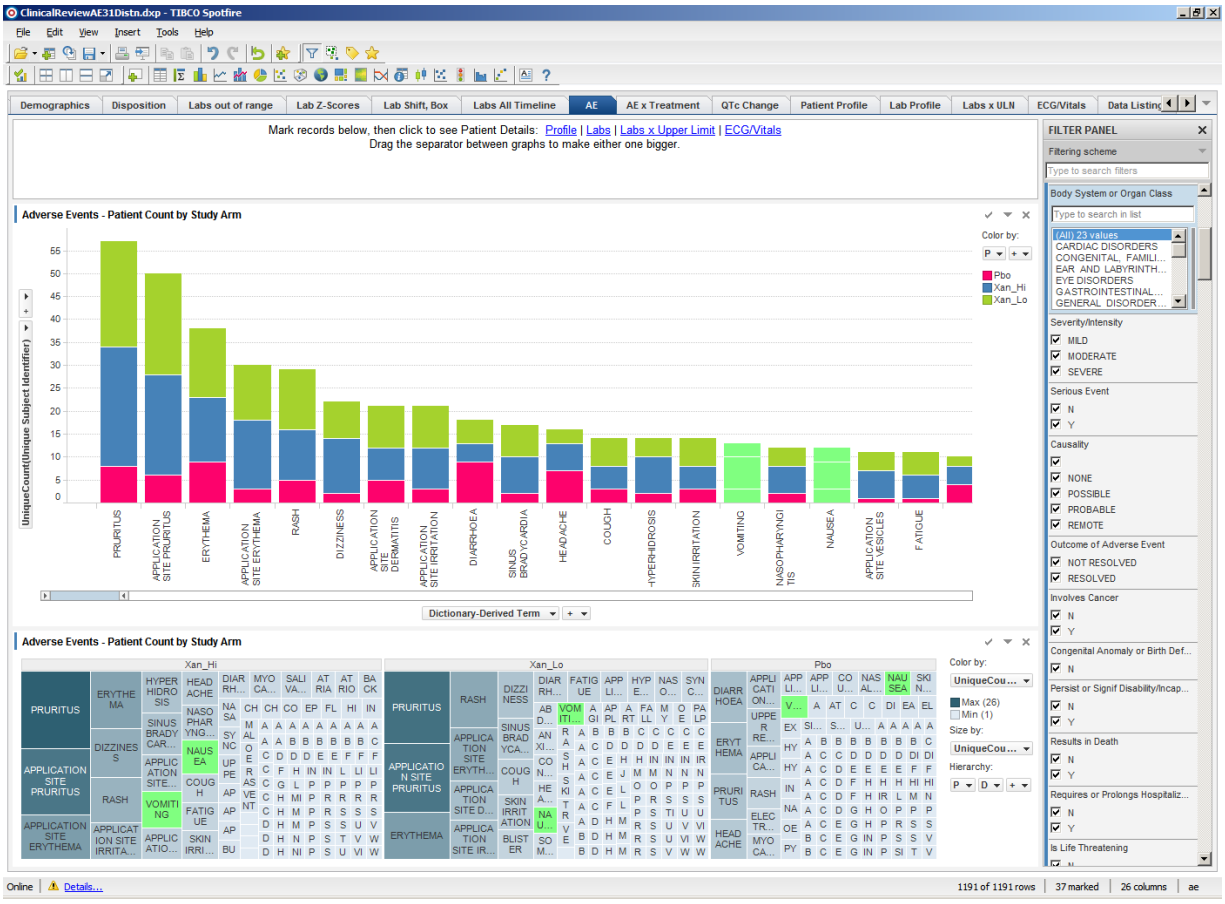

Figure 1. Barchart and Treemap of Adverse Events in Spotfire; unique counts (across subject) of Adverse Event preferred terms

In the Treemap, each rectangle represents a preferred term, with size and color proportional to the unique count of subjects with that adverse event. The treatment is ordered High Dose, Low Dose and Placebo, left to right. Note that the overall area is larger for high/low dose than placebo; these are dominated by skin irritation events e.g. pruritis, application site pruritis, erythema, application site erythema. This is expected since the drug was administered transdermally in this trial.

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 2 shows a shift plot and box plot of liver lab measurements, ALP, AST, ALT and BILI (left to right). 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 BILI and > 3x ULN for AST, ALT and ALP. The horizontal and vertical reference lines on the plot provide thresholds for these CLCs. In Figure 2, subjects with elevations beyond 2x ULN on-therapy are highlighted.

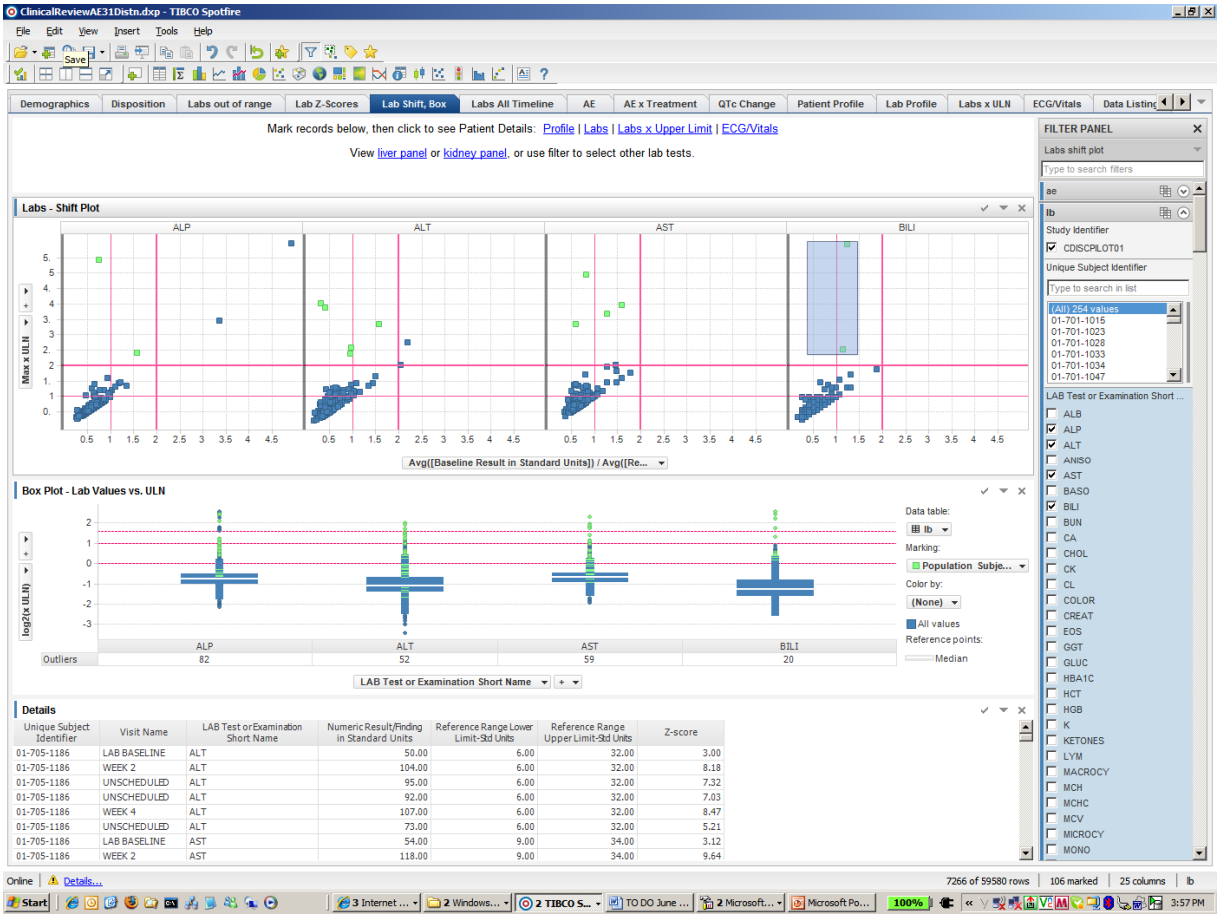

Figure 2. Shift plot and box plot of liver lab measurements, ALP, AST, ALT and BILI (left to right). Each lab measurement is normalized to the upper limit of normal (lab / ULN). Reference lines are included at clinically meaningful values including critical levels of concern e.g 2x ULN.

This act of marking defines a new sub-population that can be taken in to the drill-down graphs e.g. Patient Profile (see Figure 6), Labs, Labs * Upper Limit, ECG/Vitals; as defined in the text area above the shift plot. Note that the text area also includes a link to both liver panel and kidney panel plots; these links set the filters on the right hand side to include just the labs defined for the organ of interest.

Figure 3 shows a drill-down from Figure 2 to the Labs * Upper Limit graph. This graph shows a time course for each of the liver labs, with all labs scaled by dividing by the upper limit of normal (/ ULN). There are a total of 7 subjects with elevation on one of the 4 liver labs shown in Figure 2; these subjects appear in the Select Subjects text box on the left hand side of the graph in Figure 3. Five of these subjects are receiving placebo. The first of these is highlighted in the display; this subject has elevations in all liver labs beyond 3X ULN. If this analysis were being done during the trial, this subject would likely be violating protocol and would be removed from the trial. The line representing BILI values across time is highlighted. The individual lab values for these tests on this subject then appear in the details-on-demand panel below the graph. Note that it is simple to view other labs e.g. a kidney panel, by selecting these labs from the filter panel, or via pre-defined links in the left hand text area.

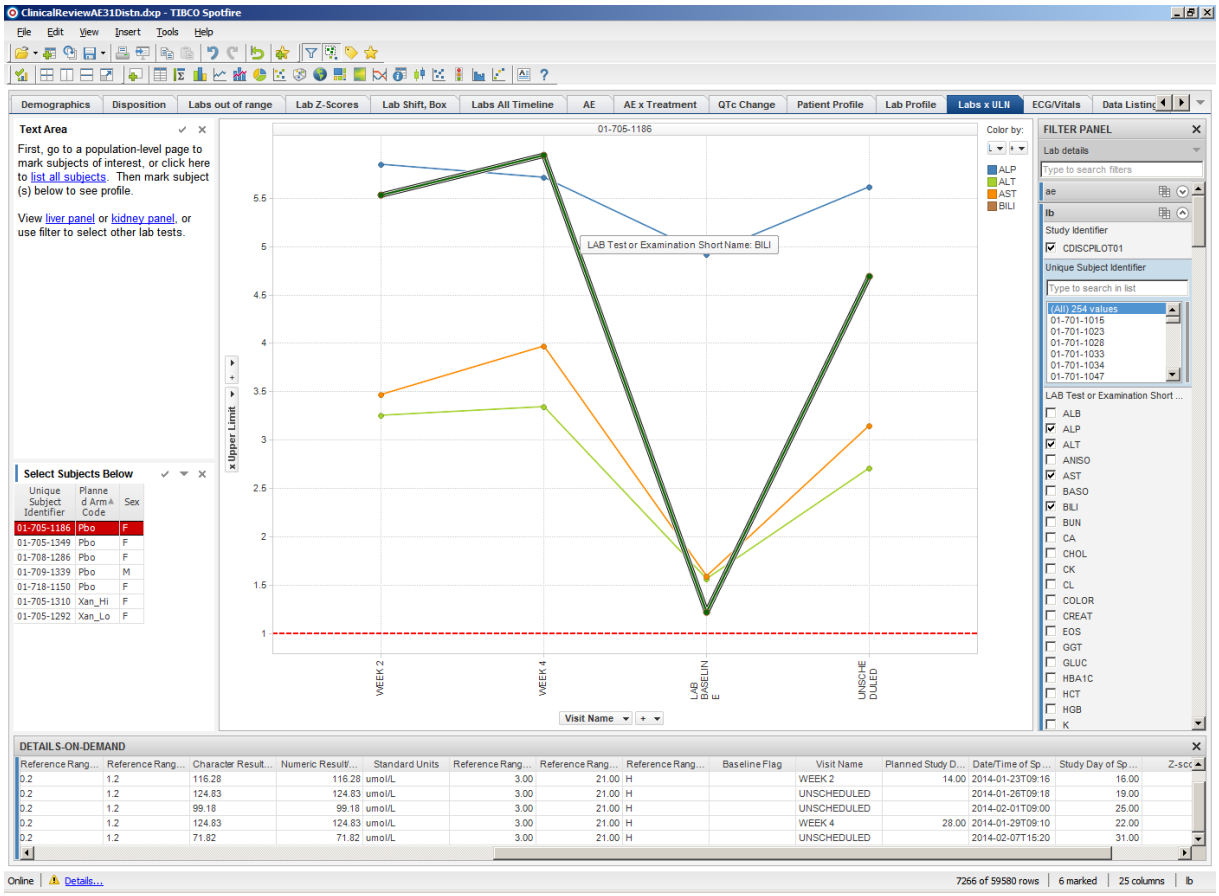

Figure 3. Drill-down from Figure 2 to the Labs * Upper Limit graph. This graph shows a time course for each of the liver labs, with all labs scaled by dividing by the upper limit of normal (/ ULN).

The presentation in Figures 2-3 enables assessment of Hy's Law for drug induced liver injury (DILI), which draws attention to subjects with elevation of ALT or AST above 3X ULN and simultaneous elevation of BILI above 2X ULN, and with no elevation of ALP 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, 2009).

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 milliseconds (ms) providing critical levels of concern, (b) elevation of QTc v BaseQTc, for the drug treatment, of more than 30 or 60 ms, and (c) elevation of QTc(Drug) v QTc(Placebo) of more than 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 4 shows a boxplot of change in QTc from baseline versus time. Guidance values of 30 and 60 ms are shown as dotted reference lines. Note that these data are randomly generated as the study analyzed did not include such data.

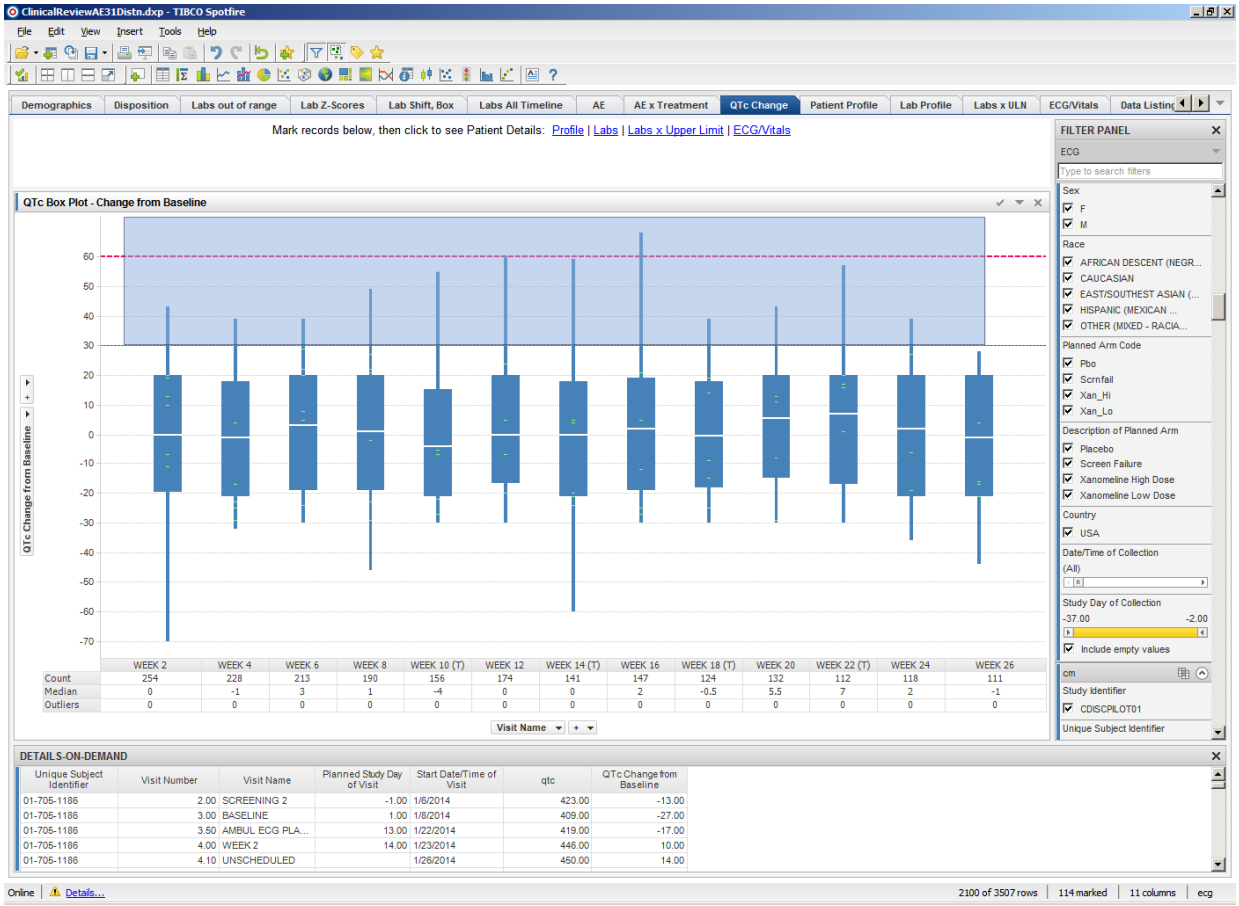

Figure 4: Boxplot of change in QTc from baseline. Reference lines are added at 30 and 60 ms in accordance with the FDA guidance. Subjects with QTc greater than 30 ms have been highlighted. This automatically forms a subpopulation in Spotfire which can be explored with drill down graphs such as that shown in Figure 5.

For subjects with delta QTc greater than 30 ms, the clinical reviewer may be interested to review those subjects with absolute QTc values greater than 500 ms. The subjects highlighted in the boxplot in Figure 4 are presented as a drill-down list in Figure 5. The QTc profile of these subjects may then be explored in Figure 5. Subjects with both delta QTc greater than 30 or 60 ms, and QTc greater than 500 ms are typically explored, especially those receiving drug treatment.

The subject highlighted in Figure 5 has delta QTc greater than 30 ms and QTc greater than 500 ms. The vitals line chart in the lower panel presents systolic and diastolic blood pressure for the same subject over time.

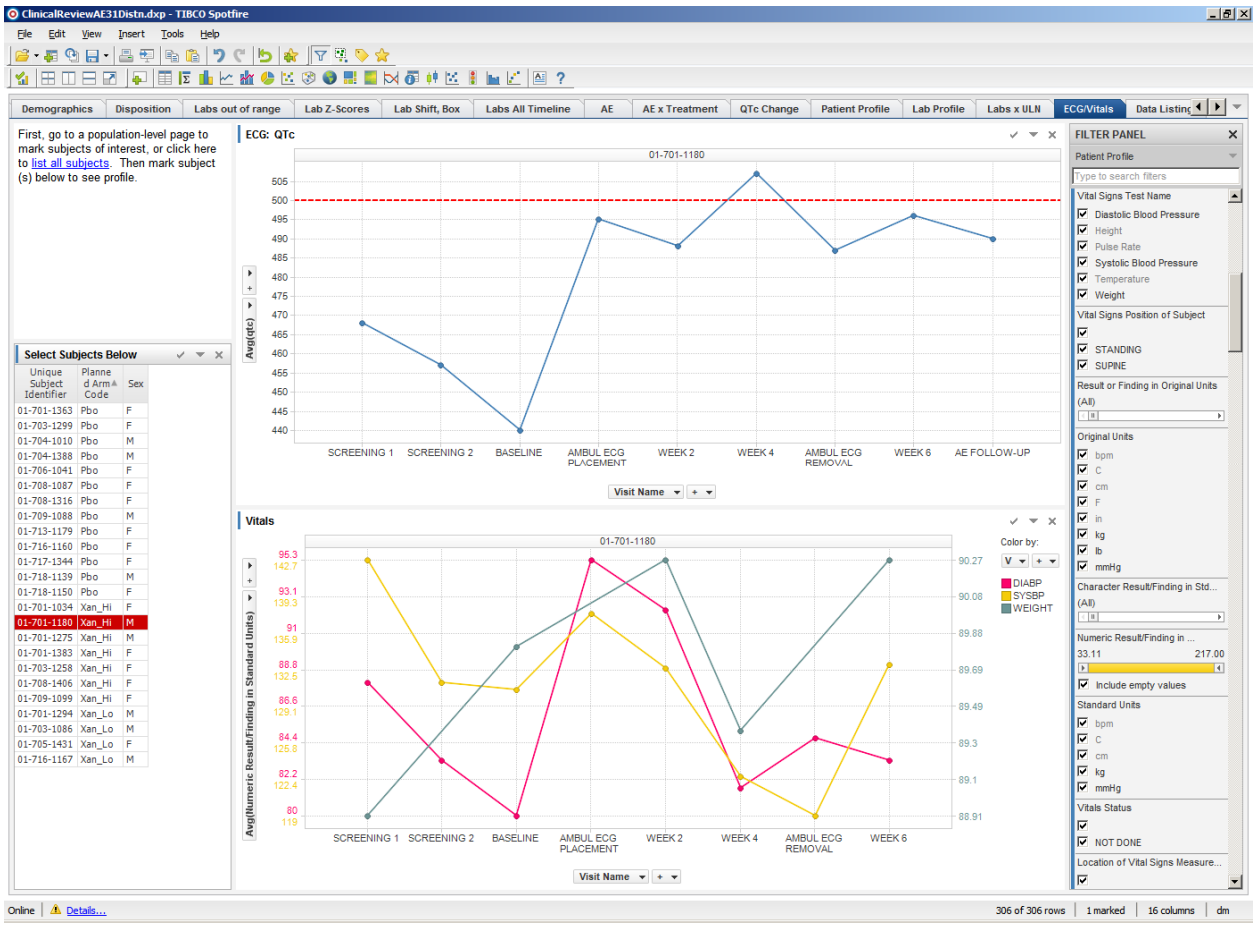

Figure 5. Line plot of QTc, along with vitals (lower panel). The list of subjects are those highlighted in the delta-QTc plot shown in Figure 4.

PATIENT PROFILES

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

Such patient profiles are particularly useful as drill down graphics from the population-level graphics described above. For example, highlighting subjects with a particular adverse event, lab elevation or QT prolongation, can be followed by a drill-down to a patient profile showing multiple data domains together.

Figure 6 shows a patient profile for subjects chosen in Figure 1, subjects with vomiting or nausea adverse events. 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. The Adverse Events are colored by severity: blue=mild, yellow=moderate, red=severe. The Lab Test values in green star symbols represent a normal lab value, whereas the red up or down arrow represent a value above the upper limit of normal or below the lower limit of normal.

A comparison of two or more patients on a common time scale is possible by multiple marking of patients in the left table of Figure 6. The Dosage, ConMeds, AEs or labs can be added/removed using the filter panel. Individual labs can be added/removed using the filter panel.

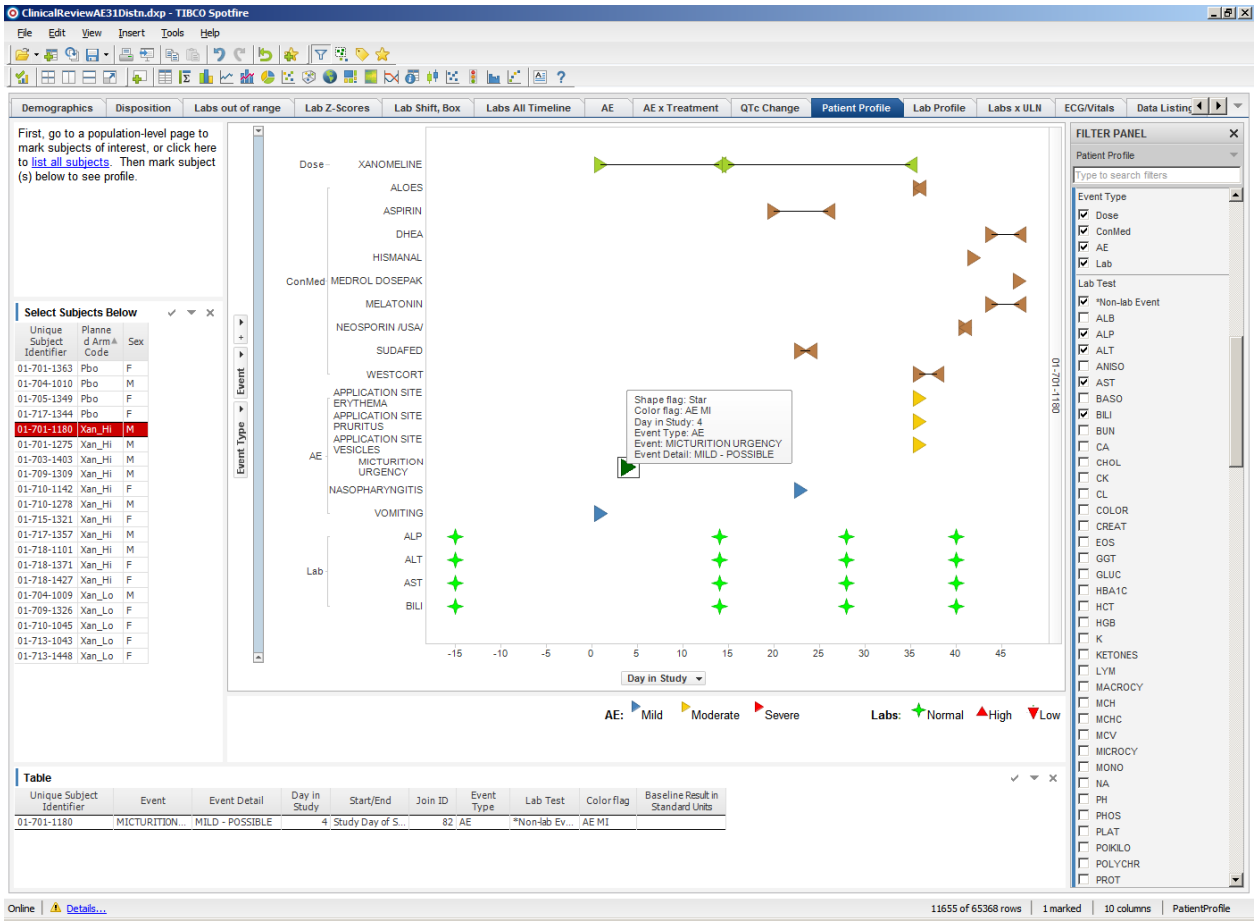

Figure 6. Patient profile for subjects marked in Figure 1. The list of subjects with either nausea or vomiting adverse events is shown in the list on the left panel. Drug dose, concomitant medication, adverse event and lab values are shown on the y-axis and time (days on study) on the x-axis. Adverse events are coded by severity : blue=mild, yellow=moderate, red=severe. Lab results are coded green=normal, red up arrow=high (above ULN), red down arrow=low (below ULN). The data domains can be turned off and on using the filter panel on the right hand side ; individual lab results can be similarly added/subtracted from the graph using the filter panel.

The same subpopulation patient profiles can be viewed with more detail on the lab values, as shown in Figure 7. Figure 7 shows an interactive line chart for liver lab values including upper and lower bounds per selected patient. By selecting one of the subpopulation patients the Lab profile line plot shows the liver lab values for the selected patient along with tables for adverse events and concomitant medication for the subject. The filter panel on the right side allows the reviewer to choose lab tests of interest.

Figure 7 allows the reviewer to assess time course sequences of lab values along with related data on adverse events. This enables exposure-response assessments including effects of drug treatment on salient lab response measurements. Such analyses include assessments of toxicity biomarkers, PD measures indicating therapy effects, PD measures related to targeted medical events and a range of lab responses of interest across the course of the trial / treatment.

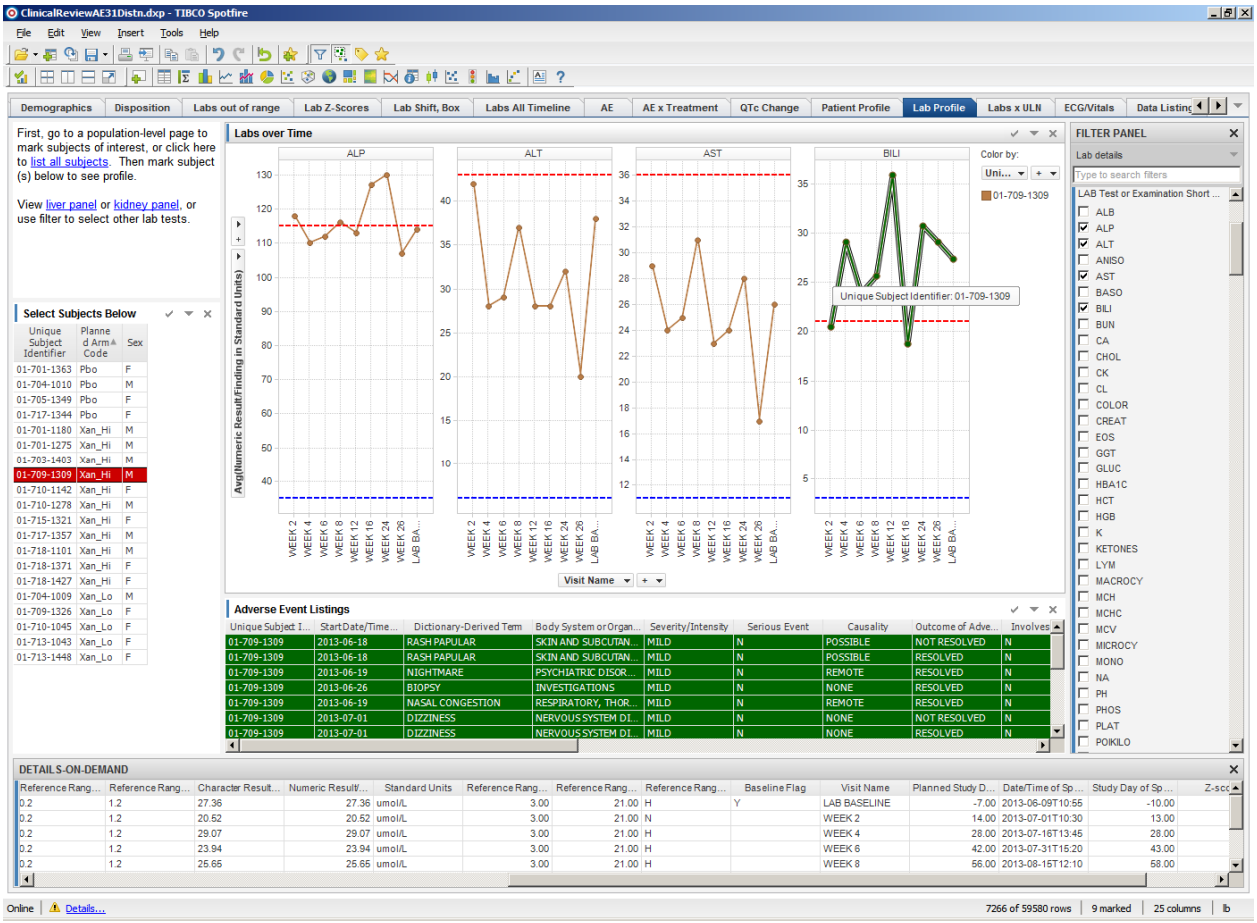

Figure 7. Interactive line plot for liver lab values including upper and lower bounds per selected patient. By selecting one of these patients the Lab profile plot shows the lab values for the corresponding patient along with tables of adverse events and concomitant medications. The filter panel on the right side allows the reviewer to choose lab tests of interest. This subpopulation was selected as a drilldown from the adverse event graphic in Figure 1.

3. TRIAL MANAGEMENT AND OPERATIONS

Managing trial operations, patient enrolment, supplies and resources is a crucial function in keeping trials on track and enabling milestones to be met. This is particularly important when managing a portfolio of compounds and trials across multiple global sites. Some key use-cases for operational data analysis are:

- Live scorecards for management e.g. KPI's such as Protocol-to-First-Patient by country/site.
- Enrolment and cross-trial analysis - recruitment patterns across countries, sites and trials
- Assessment of discrepancies and queries status/resolution
- Data-driven monitoring to identify sites that aren't performing to plan
- Resource projections - e.g. by function – understanding recruitment patterns across countries, sites, trials; and resource planning

Figure 8 shows planned versus actual number of patients screened in a portfolio of clinical trials. Individual trials are sized by number of sites; trials below plan are below the line; trials meeting or exceeding plan are colored in bright green. The trial in the lower right colored in dark green is marked, and details on each site – #screened vs expected #screened – are shown in the table. The graph may be filtered by country from the filter panel.

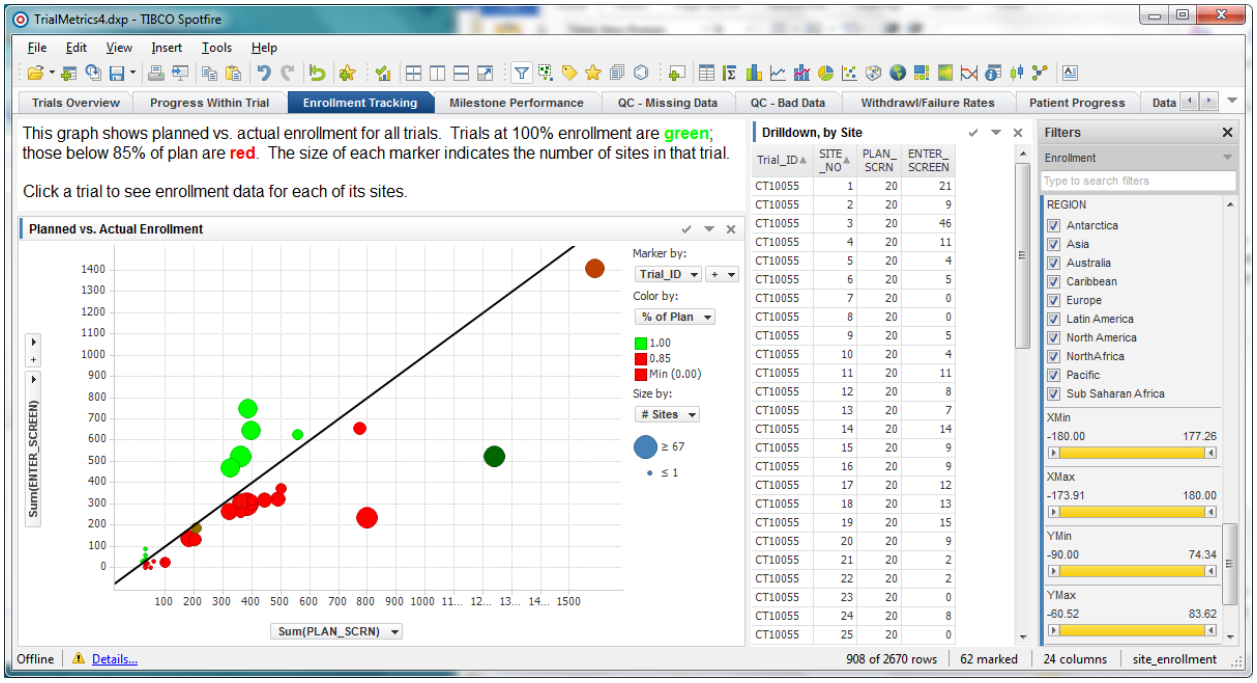

Figure 8. Planned versus actual number of patients screened in a portfolio of clinical trials. Individual trials are sized by number of sites; trials below plan are below the line; trials meeting or exceeding plan are colored in bright green. The trial in the lower right colored in dark green is marked, and details on each site – #screened vs expected #screened – are shown in the table on the right hand side. The graph may be filtered eg by country in the filter panel on the right.

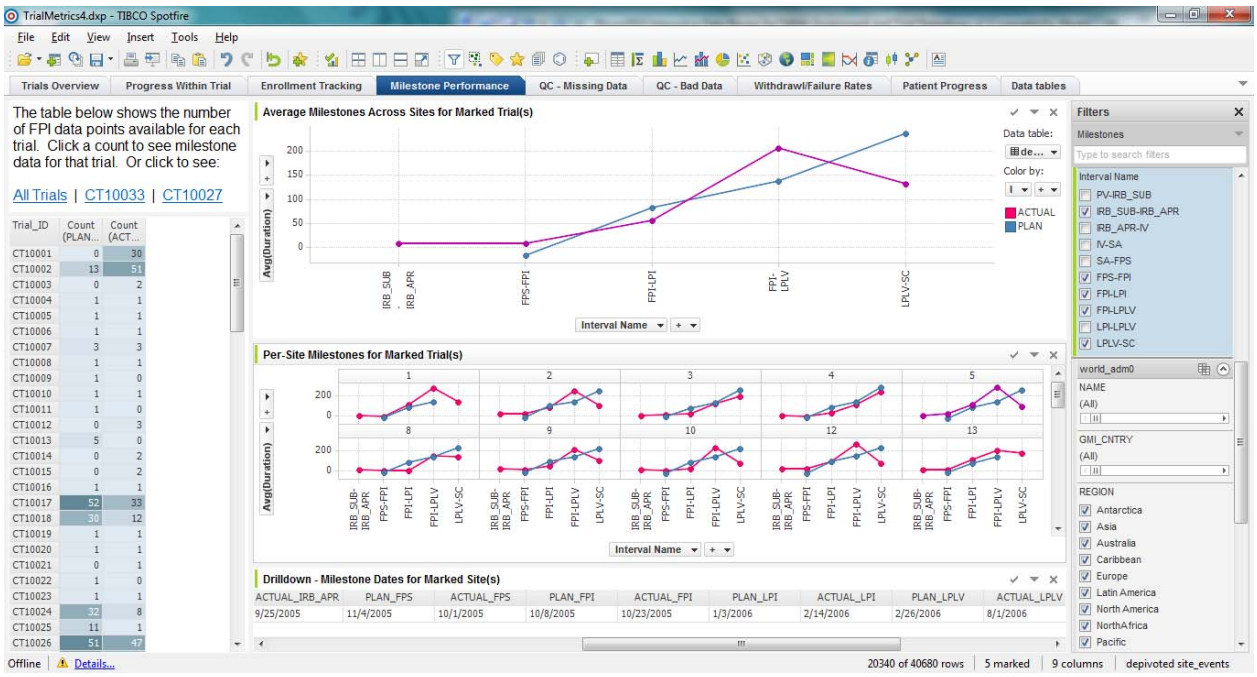

Figure 9. KPIs for trial management. Each trial in the portfolio is evaluated (actual vs. plan at any point in time) on a number of milestones including IRB submission (IRB_SUB), IRB approval (IRB_APR), first patient screened to first patient in (FPS-FPI), first patient in to last patient in (FPI-LPI), first patient in to last patient last visit (FPI-LPLV), last patient last visit to study closed (LPLV-SC).

Figure 9 shows a number of key performance indicators re trial progression. In this visualization, each trial in the portfolio is evaluated (actual vs. plan at any point in time) on a number of milestones including IRB submission (IRB_SUB), IRB approval (IRB_APR), first patient screened to first patient in (FPS-FPI), first patient in to last patient in (FPI-LPI), first patient in to last patient last visit (FPI-LPLV), last patient last visit to study closed (LPLV-SC). Again, the visualization may be filtered on country, indicator or other variables.

Figure 10 evaluates trials and sites based on multiple metrics i.e. dropout rate and screening failure rate as shown in the scatter plot. Trials and sites with low dropout and screening failure may be highlighted in the lower left corner of the scatter plot and visualized on the map; these are valuable sites for use in multiple trials. In Figure 10, we have actually highlighted trials/sites with low dropout rate and high screening failure rate. These sites may be investigated to understand the high screening failure rate.

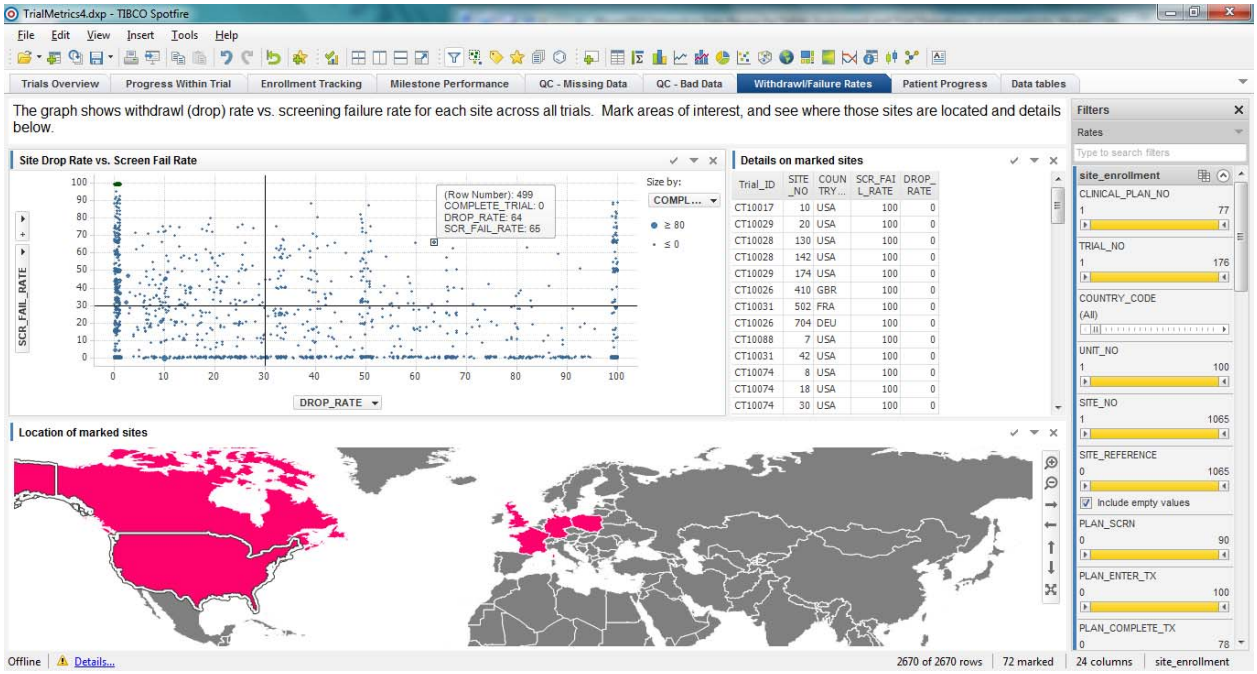

Figure 10. Evaluation of trials and sites re. dropout rate and screening failure rate. Trials/sites with low dropout rate and high screening failure rate have been marked on the scatter plot. These sites may be investigated to understand the high screening failure rate.

4. CONCLUSION

Medical monitors, clinicians and safety officers perform instream and end-of-study review of clinical data for exploratory analysis and safety assessment. Trial managers, research associates and data managers review data for protocol adherence, operations metrics/monitoring and data/query management. As the examples illustrate, different datatables can be linked together in a workbook to enable population, sub-population and patient level / trial site analysis, across all salient data domains. This feature enables the reviewer to move from a study level overview to underlying subpopulations of patients or trial sites to assess underlying mechanisms and root-causes e.g. population adverse event analysis with drill-down to a patient level lab values and patient profiles for assessment of underlying medical issues e.g. rhabdomyolysis. The Integration of Spotfire S+ ® or R language into TIBCO Spotfire allows sophisticated statistical analysis and computation from within the interactive Spotfire Workbook.

This paper shows an interactive medical review of safety data, and an analysis of a clinical trial portfolio from a study management and operations perspective. The medical review includes analysis of adverse events, labs and vitals including assessment of targeted, designated and spontaneous events. The operations analysis includes assessment of trial enrolment across sites and countries; and review of key

performance indicators (KPIs) re. trial progress.

The Spotfire environment has seamless connections to S+/R. This enables deeper analytic insight to be obtained at any point in the trial. For example, adverse event treatment emergence can be assessed by inside-out machine learning methods or bias-reduced logistic regression as proposed by Southworth and O'Connell (2009). These analyses return a barchart of adverse events and their relationship to treatment. The barchart is just another interactive visualization in Spotfire and can be used for subsequent drill-down and detailed exploration. Similarly, trial enrolment can be analyzed using a Poisson-Gamma hierarchical model as proposed by Anisimov and Federov (2007). This enables confidence intervals on completion of trial milestones to be obtained at any point during the study and for corrective course of action to be determined and implemented.

In summary, TIBCO Spotfire ® software offers a deep, interactive, analytic platform for exploratory data analysis. This interactive clinical and operational data review shortens the time between critical development gates and enables key milestones to be met sooner, while simultaneously managing safety risk.

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