Spotfire Analytics – Transforming Clinical Development
Despite the billions of dollars spent annually discovering and developing new drugs, the global output of innovative new medicines is at its lowest point in several decades. This is not as illogical as it first sounds. As an industry we have become accustomed to expecting that financial investment will equate to positive outcomes - this in spite of the fact that we have seen more breathtaking failures in drug launches in the past ten years than ever before.

All that money was not necessarily spent in vain. The completion of the Human Genome, the deciphering of more mechanisms of actions of diseases than ever before, the ability to analyze millions of samples a day and new sophisticated detection platforms, are all fundamental to how we discover and develop drugs today and will continue into the future.

Data Deluge
In the last ten years, with new and evolving methods of communication and processes of storing information, increasing amounts of electronic data have been generated and stored daily in multiple forms and locations in almost every market. Switzerland’s pharmaceutical giant, Roche, reported in 2010 that the company is producing so much data, that it is doubling every 15 months. These data are not just generated from internal research and development, but also from a networked clinical development model involving in-licensing, out-licensing, outsourcing, and collaborations with various contract research organizations, academia, pharmaceutical and healthcare partners. Their model serves as a prime example of why emerging technology that allows for the consolidation and rapid analysis of clinical and non-clinical data is so critical.

The Rapid Growth in Clinical Development:
The number of clinical trials underway each year has been increasing steadily, worldwide. In the last five years alone, over 75,000 federally and privately supported trials have been registered with the National Institute of Health’s Clinical Trials registry (See Figure 1), with a growing trend in trials being conducted in Brazil, Russia, India, and China. Trials executed in China are beginning to be filed with China’s State Food and Drug Administration (SFDA). Between 2006 and 2008, over 2,600 new trials were approved by the SFDA. The explosion of clinical trials in China indicates a major shift in clinical research and development to emerging markets and the need to support those markets (See Figure 2).

With a broad range of study designs, varying data collection methods and time points, efficient data analysis in clinical development has become more important than ever. The more effectively study data are managed, the faster the data can be extracted and analyzed. The analysis of the data is important for each trial stage as valuable insights can be gained. For example, during the early stages of a clinical trial, access to data is vital not only for patient safety, but for solving problems while they are still manageable and before they become costly.
TIBCO Spotfire Clinical Can Help
Clinical data collection, cleaning, analysis and reporting are time-consuming and expensive steps. This effort is compounded as the number of trials increases. Spotfire can streamline clinical trial data analysis with real time access to clinical data during all phases of clinical development, allowing the user to interact with the data as soon as it is collected (see Figure 2). What makes Spotfire unique and powerful is the ability to produce interactive visualizations that allow the user to easily explore the data and ask a multitude of what-if questions.

In an IDC Health Insights Perspective, entitled: “Familiar and User Friendly: TIBCO Spotfire owns the Front End in the Life Sciences”, TIBCO Spotfire was called: “the de facto end user interface of choice for the strategic assessment of clinical data.” This is why TIBCO Spotfire is being used by companies around the world for critical clinical development analytic tasks such as:

- Clinical data monitoring and review
- Medical / safety review
- Protocol adherence monitoring which is particularly important with complex protocols and therapy areas (i.e. oncology, neuroscience, metabolic, etc).
- Detailed data cleaning

Figure 1: Number of trials submitted to ClinicalTrials.gov by year.
- Exposure-response analysis and dose-finding in early-phase trials
- Clinical operations
  1. KPI analysis
  2. CRF completion and query management - across sites, countries, trials
- Pre-marketing safety analysis
- Post-marketing pharmacovigilance
- Portfolio/project management – risk-adjusted NPV analysis for compound prioritization across the portfolio
- Clinical data management operations
- Clinical trial supplies
- Pharmacometrics

In Spotfire, it is simple to adjust axes, symbols, text and export visualizations to PowerPoint for meetings and distributions. An example of this is users can modify patient profiles; add medical history, vital signs or other domains to the profile or as additional table/visualizations without IT intervention. Spotfire can call out to S+ graphics for inclusion in clinical study reports, presentations, publications, submissions.

Figure 2: In Stream Safety Review (shown in Chinese version of Spotfire)
Clinical Data Monitoring & Review
Assessing patient level and aggregated safety data at every stage is an essential aspect of running an effective clinical trial. Reviewing in-stream clinical data effortlessly can provide relief to busy medical reviewers and allow them to focus on the bigger questions at the heart of a trial.

In addition to analyzing patient level data, Spotfire can analyze operational or peripheral trial data. Review and analysis of this data can highlight site performance and study resources, allowing for improvement of trial operations. Addressing site or resource poor performances can increase data collection speed and patient recruitment pace, enabling shortened or on-time study timelines.

Figure 3: Spotfire in the Clinical Development Process

Figure 4: Clinical Data Management Operations
Faster Data Review, Quality Assessment and Process Improvement

The benefits of exploring crucial data (adverse events, lab values, demographics, drug exposure and response) early in the clinical trial process are numerous. They serve to reduce errors, improve quality, and increase productivity by 20-40%. Some specific benefits include:

- 3-4 days per month per trial saved in medical data review
- Better/faster data quality assessment
- Reduction of data quality issues – up to 30% reduction in lockdown prep time
- Decreased unfrozen databases by up to 50%
- Fundamental process improvements
- Early identification of protocol violations
- Early identification of drop-outs
- Better site management - can save $20K+ per patient
- Rapid implementation
- Shortest time to value of any system

Survival Analysis

One of the most important outcomes of clinical trials is the “time to event”, or the time it takes to reach an endpoint, such as cancer recurrence. TIBCO Spotfire Clinical has built-in survival analysis capabilities to perform these tasks, using S+ language. Survival designs provide detailed models for patient accrual, dropout and time-to-event.

Survival Analysis – marking in Spotfire drives S+ analysis

- Kaplan-Meier, cumulative incidence plots
- Graphics interact with rest of clinical analysis
- S+ RTF report run from Spotfire
- Kaplan-Meier or Cumulative Incidence Plot for inclusion in Clinical Study Report
- Survival library is state-of-art
Study Management/Trial Operations
Managers of clinical trials face supervision of site coordinators and other staff, sometimes in opposite ends of the globe. Problems within the trial may not be detectable in some sites, even with the best coordinators and research nurses on staff. TIBCO Spotfire Clinical makes it easy to evaluate data from multiple sites, and identify differences early on. For example, if withdrawal rates are higher in some sites than others, this can be easily explored. Some of the many advantages TIBCO Spotfire Clinical can offer for outstanding study management include:

- Identifying sites that aren’t performing
- Identifying subjects not adhering to protocol
- Data-driven monitoring saves much trial expense
- Live, interactive analysis – scorecards for management
- Protocol to 1st patient
- Enrollment actual versus plan and models
- Identify the root cause and perform cross trial analysis
- Identify signals before lockdown rollup – identify and retain best performing sites.

![Figure 5: Withdrawal Failure Rates](image-url)
Data management operations data can also be easily analyzed. The visualization of this data can provide key metrics and statuses that will greatly enhance the management of the data management data (See Figure 4). Examples of some of these data management metrics are below:

- Number of pages missing
- Outstanding discrepancies
- Discrepancy lag time
- Data entry status
- Number of terms to be coded
- Status of source document verification (EDC Studies)
- Status of Investigator approval (EDC studies)

**Pharmacometrics**

In the area of Pharmacometrics, TIBCO Spotfire provides:

- Inbuilt Trial Design Module – S+SeqTrial
- Group Sequential Design
- Survival Designs with detailed models for accrual, dropout, time-to-event
- Rapid evaluation of candidate designs
- Inbuilt Bayes Library – S+FlexBayes and Bayesian Response-Adaptive Design
- Inbuilt engine for hierarchical generalized linear models
- Connection to BUGS for other applications
- Validated for FDA submission

Figure 6 shows an example of how data can be expressed using pharmacometrics models. The left panel shows graphs representing how lab values have changed over time for 12 different patients. The right panel shows the S+ program that created the graphs. Many other forms of viewing patient level data are available.
**Pre Marketing Safety**

Viewing patient-level data is crucial to making decisions about changes. Identification of drop-outs, non-compliant participants, unexpected drug responses and any other common occurrences that could be causing fluctuations is critical to recognizing safety hazards, especially at the patient level. The head of Safety Networks at Novartis was recently quoted as saying “Interactive graphical data exploration in Spotfire provides an efficient, powerful and flexible tool to improve both detection and systematic assessment of safety signals”. One of the many strengths of Spotfire is the ability to stratify data, viewing by site, investigator, patient demographics and other categories to quickly locate problem areas. Interactions with the data are live, and can perform tasks that would normally take analysts days to accomplish. (See Figure 7)

![Figure 7: Pre Marketing Safety](image)

**Post Marketing Surveillance**

To ensure patient safety after medications are on the market, it is essential that unusual occurrences are quickly recorded and reported. Spotfire’s interactive graphical data exploration capability provides a flexible tool that improves detection, and systematic assessment of safety signals. The pharmaceutical industry has a responsibility to recognize these signals and act quickly to address them. For example, the lower graph on Figure 8 shows a spike in new cases in January for all three medications. This could be related to a cold weather effect, or possibly a data collection error or bias. To get a closer look, January can be viewed by day to examine exactly where the fluctuation appeared.
Clinical Graphics
A typical organization spends more time creating statistical graphics than they realize. Most organizations create graphs through an ad-hoc process of on-demand development by a statistical programmer, followed by extensive quality review, and finally coding the graph into a production process. When the customer wants even a simple change, the costly process starts all over again.

A typical trial contains 8-10 graphics created through this ad-hoc process. For a pharmaceutical company or CRO managing 150 trials, this equates to 30 full time employees; at $180,000 per employee, this represents a cost of $5.4 million. TIBCO Spotfire can help clinical development organizations create high quality statistical graphics for inclusion in clinical study reports: in 20% of the time compared with existing methods, without programming, and automated through integration into existing 21 CFR 11 compliant production processes.

The in-built gallery of graphics templates was built in collaboration with top industry thought leaders and the FDA—so you can quickly apply clinically-relevant views to your existing trial data. This allows you to quickly build graphical competency in your organization.
The graph templates in TIBCO Spotfire Clinical Graphics adapt to changes in trial data, allowing standardized graphical views to be applied across studies and therapeutic areas. By validating standardized graph templates, you save time by not having to QC every graph. Among the standardized graphics available are bar charts, box plots and contour plots. (See Figure 9)

Graphical displays of tabular data help pharmaceutical companies, CROs and biotechs improve communication across all of drug development. TIBCO Spotfire Clinical Graphics allows the export of statistical graphics for use in a variety of presentation, publication and submission formats, and customers have reported an 80% reduction in graph creation time compared with existing SAS processes. (See Figure 10)
The Validation Burden
In the life science industry, every software release must be validated. As such, up to half of application development time can be spent in validation. This typically causes companies to operate using older versions of software given the enormous investment of resources involved in implementing and upgrading to new technology.

Spotfire Qualification is an add-on to Spotfire 3.3, designed for software validation needs of regulated industries. With Spotfire Qualification, companies can significantly reduce the validation burden for initial installation and upgrades of Spotfire, the operation of Spotfire in different environments (e.g., Development, Test and Production), and changes to applications (.dxp files). This allows companies to focus manual qualification efforts on changes and anomalies.

Included in the product is an export tool which exports static snapshots of all data, visualizations and calculations, creating a directory of artifacts and produces an Export Report (HTML). The report contains hyperlinked thumbnails to all visualization and data artifacts (See Figure 11). The export tool reduces the documentation burden, since the output provides comprehensive details that can become the record for the quality assurance files. The comparison tool performs a “diff” on two sets of artifacts produced by the Export tool, produces a Comparison Report (HTML) and allows merging of approved variants into a “gold standard” export (See Figure 12). This comparison report tremendously reduces the time needed for onboard new visualizations. Also included is a qualification manual which provides a sense of the effort required to validate Spotfire in your environment. It describes an overview of the software qualification process and an indication of how the qualification tools support this process. Another addition is a gold standard example with an example .dxp file and example export.

Figure 11: Export Report
Figure 12: Export Report
The TIBCO Spotfire Clinical Solution - Making the IT Case

Business intelligence is about asking simple questions of the past — like a rear-view mirror for seeing where you’ve been. Analytic intelligence is about anticipating the future and determining best courses of action. Whereas business intelligence is about query and reporting against fixed data to deliver limited analysis about past events, analytic intelligence is about calculating the significance of the data to deliver informed inferences about the future and the best action plans to get there.

Despite the claims of many vendors, typical business intelligence tools are just not capable of providing true analytics. IT organizations that rely on such tools simply cannot provide the meaningful insights needed to better plan for the future in such critical areas as customer relationship management, revenue forecasting, quality improvement and process optimization. This means that many decisions are based on gut instinct, intuition and extrapolation.

The technology issues of today combine to make it difficult for IT to plan and maintain a strategy for cost-effectively providing intelligence in support of current and new business initiatives.

- How do you design architectures and process flows to tightly integrate modeling with operational information without affecting the performance of operational systems?
- Can one unified solution meet the diverse analytic requirements of all types of users, enabling them to share modeling results along with the tested models themselves while being open to business intelligence tools?
- What is the best way to model scenarios in complex contexts such as customer relationship management, revenue forecasting, quality improvement and process optimization — contexts in which most business intelligence applications fall short?

**What IT needs is a solution that:**

Combines specialized intelligence applications and tools into a cohesive enterprise wide foundation, transforms functional silos of data and modeling logic into a unified companywide knowledge base, strengthens ‘power’ users to perform analytics drawing on cleansed information from across functional areas, and enables information to be shared with business intelligence tools and many different types of users in a form that is meaningful to them.

- Clients can opt in based on the number of trials, number of users, or deploy across the enterprise.
- Core offering is based on the already robust TIBCO Spotfire Clinical Platform and is strengthened by the addition of S+/R as the underlying robust statistics engine
  - S+/R is well recognized in the clinical development world and has a strong user following
• Tight integration between TIBCO Spotfire Clinical and S+/R provides a very strong platform to build on
• TIBCO Spotfire Clinical will offer turnkey validation services in collaboration with a validation partner – Validation Master Plan, IQ/OQ/PQ, User Specification, Validation Summary Report

**TIBCO Spotfire Clinical Advantages**

What advantages does TIBCO Spotfire Clinical have over other clinical analytical applications? In comparison, Spotfire offers more capabilities, more flexibility and better efficiency. The format is user-friendly, and provides live, interactive visualizations. Among the top reasons for choosing TIBCO Spotfire Clinical are:

• Easily access and refresh real-time data from numerous clinical data sources such as: Clinical Data Management Systems, Electronic Data Capture Systems, SAS, SDD and SAS/SHARE, Clinical Trial Management Systems, Pharmacovigilance Systems, and Federated Clinical Development Systems.
• Multiple areas of use in addition to clinical data review and trial operations
• Superior graphics
• Easy to use by analysts, authors, reviewers
• Robust patient profiling capabilities
• Ad-hoc, on the fly, what-if analysis, drill downs and instantaneous filtering
• Interactive graphical data exploration providing an efficient, powerful and flexible method to improve both detection and systematic assessment of safety signals
• Simple to export all Spotfire Clinical graphics to PowerPoint for meetings and distributions
• Can easily integrate with various data warehouses
• Graphics are much better than competing products

To learn more about how TIBCO Spotfire can reduce clinical development costs for your organization, contact us by e-mail: mds@tibco.com