



## PODCAST

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# an early read on data

**MICHAEL O'CONNELL**, Clinical Practice Manager for TIBCO Spotfire, discusses the drive for simplicity and speed in drug development; and how visualization and predictive analysis of clinical data enable trial milestones to be met sooner while minimizing risk

**Future Pharmaceuticals** What are some key challenges faced by clinical development organizations?

**MICHAEL O'CONNELL** Clinical development organizations are the engines of pharmaceutical revenue and growth. In order to meet revenue and profit goals, pharmaceutical companies need to file more new drug applications each year and get them approved. For the clinical development organization, this translates into a massive and continuous push — drug candidates through the pipeline and submissions to regulatory agencies — while managing risk in a hyper-sensitive drug safety environment.

Clinical trial data are complex with thou-

sands 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 need to simplify and streamline data management and analysis processes. They need to get meaningful data views to people who need them quickly — 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 need to move to a framework of proactive, data-responsive decision making rather than retrospective tracking of results.

The drive for productivity in drug development translates directly into 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.

**FP** How are clinical development organizations responding to these challenges? What are they doing to simplify and speed drug development?

**MO** The pharmaceutical industry has very solid processes and organizations for advancing candidates in clinical development. Pharma companies are focusing on clinical development while research is shifting to academia and biotech companies. Pharma companies are outsourcing and

cutting spending upstream and moving these resources into clinical development.

Clinical development organizations are supplementing their internal processes and organizations with external services, hosted data capture applications and outsourcing. They are focusing resources on consolidating disparate clinical data sources and providing visibility into clinical data for the clinical development team — for ongoing medical review, safety analysis, enrollment tracking, trial operations analysis and portfolio/project management.

Recent advances in clinical software, including comprehensive electronic data capture services, integrated back-end data environments like Oracle's LSH, end-user access portals, and sophisticated visualization and predictive analysis software; are enabling broader data visibility — and, in turn, this push to simplification and speed in clinical development.

Clinical development organizations are essentially tuning their clinical development engines for faster throughput of their most promising molecules. This means faster early phase proof-of-concepts and faster late phase confirmatory trials.

Bringing integrated data together with visualization and predictive analysis software is helping to drive this faster throughput. Our Spotfire Clinical platform — including Spotfire visualization and S+/R predictive analytics — combines visualization and predictive analysis to enable proactive, responsive decision making, rather than retrospective tracking or results.

Such proactive, responsive decision making — based on visualization and predictive analytics — can shorten the time between critical development gates and enable key milestones to be met sooner, while simultaneously managing safety risk.

**FP How have eClinical, electronic data capture (eDC) and business process automation delivered value to clinical development organizations? Has the increased use of eDC been leveraged through accompanying improvements in downstream clinical and operational informatics processes and the business value they deliver?**

**MO** eClinical and eDC have made it faster to get trials set up and move data from trial sites into a central database. Solutions like Medidata's RAVE are providing convenient hosted solutions for

rapid data capture in clinical trials.

Pharma companies have invested significantly in eClinical and eDC. However this investment is not being fully realized due to the often slow downstream processes for analysis and reporting on the data. Companies are hiring us to take it the last mile to the end-users.

Our Spotfire Clinical platform puts all the clinical data domains together enabling end-users to interactively review clinical data in real-time, while incorporating predictive analysis and reporting for responsive decision making and communication of results.

Clinical end-users can filter, group and slice the multivariate clinical data looking for outliers and missing data. They can line up different data domains on a common timescale as patient profiles, for example adverse events, labs, drug dosing and concomitant medications. They can obtain statistical analysis of adverse event treatment emergence and survival — on a regular basis as study data are refreshed. Clinical data managers are able to identify possible data errors and clean the data faster and with better quality — during the trial. This cuts down on the data cleaning effort for lockdown at the end of a trial and prevents the need to unfreeze frozen databases after the fact.

Operational end-users can obtain live, interactive scorecards for trial management including planned versus actual comparisons of key performance indicators by country and site, as well as enrollment and cross-trial analysis. They can understand recruitment across countries, trials, sites and obtain statistical predictions of study progress and completion times. These analyses enable drill to root cause and identification/retention of the best sites.

The Spotfire Clinical platform enables this review and analysis multiple clinical data sources together and in a common application framework. For example, operational and clinical data can be analyzed together to identify sites with disproportionate adverse event frequencies, missing or dirty data. Project management, resource and financial data can also be analyzed in this framework for cross-functional assessment of operations cost, program progress and portfolio priorities.

The combined suite of ongoing analysis, interactive review and reporting capabilities enables rapid, intelligent drug development and informed communication of results with regulatory agencies.

**FP How is the safety data landscape evolving? Are the congressional mandates and regulatory agency involvement affecting clinical development organizations?**

**MO** Drug safety is a significant public perception issue and, as you note, is now a congressional mandate! As such, obtaining an early read on safety data is crucial in this current world of clinical development. Each subject's data, each week of a trial can help discharge risk. And if potential signals emerge, supplementary data can be collected and analyses done to better understand the safety profile. There is nothing worse for the fate of a drug than a regulatory agency asking probing questions around the safety profile, and the Pharma sponsor scrambling to address the questions. The sponsor needs to understand the complete safety profile of the drug better than anyone else. And they need to communicate the safety profile, with comprehensive and relevant explanatory information, to the relevant regulatory agencies on a timely basis.

Ongoing predictive analysis of adverse events and elevated labs plays a crucial role in risk management and optimal drug development. In the Spotfire Clinical platform, sophisticated statistical analysis of AEs and labs can be readily set up in S+/R and incorporated in to an interactive report for viewing by end-user clinicians. Supervised learning methods can provide an assessment of adverse event treatment emergence. These analyses can be done each time the data are refreshed in to the interactive report. And it is self-service, in that the predictive analyses are embedded and updated so that all clinical stakeholders see the current assessment of the safety profile, the current predictions of trial enrolment — all whenever they have a little time to check in to the portal.

This enables ongoing proactive decision making on a timely basis. For adverse events that appear to be elevated in the treatment, supplementary data can be collected and analyses done to better understand the safety profile. With elevations of adverse events or labs of special interest (e.g. cardiac events, liver toxicity, QT prolongation, immunogenicity and bone marrow toxicity), a trial may be terminated early. If a trial is to fail, you want to fail early if you are to fail at all. Ongoing assessment of adverse event treatment emergence on a regular basis enables these proactive decisions to



# “OUR PLATFORM... COMBINES VISUALIZATION AND PREDICTIVE ANALYSIS TO ENABLE PROACTIVE, RESPONSIVE DECISION MAKING, RATHER THAN RETROSPECTIVE TRACKING OR RESULTS.”

be made regarding data capture/analysis and/or trial termination.

The PhRMA SPERT group, comprising senior safety analysts from across all major Pharma companies, recently released its initial report/manuscript. Some of its conclusions include:

- creation of a Program Safety Analysis Plan early in development;
- a three-tier system for signal detection and analysis of adverse events and highlight proposals for reducing “false positive” safety findings; and
- 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 three-tier system is readily implemented through the framework outlined above. The combination of visualization and predictive analysis enables identification and management of adverse events of special interest (AESI's) and informed, proactive, responsive decision making.

This ongoing analysis recommendation is a theme that more and more Pharma companies are picking up upon. The sophisticated statistical analysis of AEs and labs can be readily incorporated in to an interactive Spotfire report. The AE treatment emergence analysis may then be triggered with data refresh. Outputs of the analysis can be drilled to additional sub-group and patient-level analyses of the treatment emergent cases.

## **FP** How can the informatics advances you have described improve drug development team processes, communication and collaboration?

**MO** There are many stakeholders and contributors in clinical development teams. Clinical research associates, medical monitors and safety officers are involved in clinical and safety data review; trial managers with trial management and oversight; statistics and programming in exploratory analysis; data managers in data cleaning; clinical development and therapy area heads in managing a portfolio of assets through the development process; and portfolio managers in understanding and managing the entire set of entities and assets.

These stakeholders need rapid access to current data with visualizations and predictive analysis to enable informed, proactive, responsive decision making.

Unfortunately, some current business processes involve analysts e.g. statistics, programming and business performance analysts, providing ad hoc data listings and canned BI reports to the clinical development team. This approach to clinical and operational data analysis and review is incredibly slow - analysts are in a churn and rework cycle and can't produce results for clinical development stakeholders fast enough. The static reports and listings also make it difficult for clinical stakeholders to ask *ad-hoc* questions of the data, like drilling down

to relevant data about a patient or about similar patients with the same condition or combination of clinical data. Or, drilling in to a site's data and understanding root causes regarding disproportionate queries, protocol non-adherence and missing data.

With our Spotfire Clinical platform, analysts can publish interactive reports that enable other functions to review the data themselves. The workflow streamlining facilitates a self-service model whereby the clinical development team is able to obtain clinical information themselves directly. This cuts down on *ad-hoc* requests and manual processes.

Most of us spend too much time in meetings, which can be burdensome to organize and manage. Meetings with static reports beget more meetings because you can't answer the questions you have in the first meeting with the static reports. Someone usually needs to go back to their desk and do some more reports then organize yet another meeting.

The new clinical informatics environment that I have outlined above allows all of the questions people have of the data to be answered 'on the fly.' This cuts out the rework entirely and can free up large amounts of time. It also leads to deeper understanding of the clinical and operational data. This translates in to significant savings across a clinical development portfolio over the course of a year; while providing an exciting environment and experience for the clinical development team. **FP**



**MICHAEL O'CONNELL** leads the clinical practice at TIBCO Spotfire. He has been working in the pharmaceutical, device and diagnostics arena for the past 15 years. Dr. O'Connell's background and graduate work was in applied statistics and he has published more than 40 papers and several software packages on statistical methods and life science applications. Recently he has been active in the analysis and visualization of safety data in clinical trials.