WHITE PAPER

Transforming Clinical Development

revvity signals

OPPORTUNITY

The estimated cost of bringing a drug to market in the U.S. according to JAMA is $1 billion.[1] The extreme cost of clinical trials urge biopharmaceutical, medical device and diagnostics manufactures to identify failures early, in order to minimize costs, and to complete clinical trials as safely, efficiently and quickly as possible, while maintaining high quality, accuracy, completeness and integrity of the clinical data.

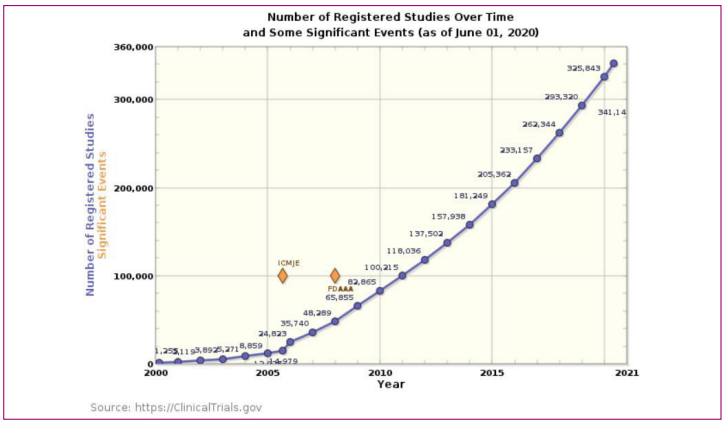

Figure 1: *Number of registered trials as of June 2020.*

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. This data is 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. This model serves as a prime example of why emerging technology that allow 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 increased steadily worldwide with over 342,489 federally and privately supported trials posted on ClinicalTrials.Gov as of June 2020 (See Figure 1). 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.

Each corporation collects data in various systems either in-house, at a collaborator corporation or at a CRO. The data in these systems typically lives in individual silos, in their own data formats and their own reporting environments making it challenging to integrate the information together for analysis. 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.

LEVERAGING TRANSLATIONAL RESEARCH DATA TO IMPROVE STUDY DESIGN

Biopharmaceutical companies are scrambling to improve efficiency and reduce costs of the drug development process, and one modern, emerging approach is to use translational medicine techniques to better match drugs with patients.

Several recent clinical studies used biomarkers to stratify patients for treatment, resulting in improved therapeutic response and smaller, more efficient trial designs. Thus, translational medicine holds the promise not only to improve drug development efficacy and safety, but also to reduce clinical trial cost and increase success.

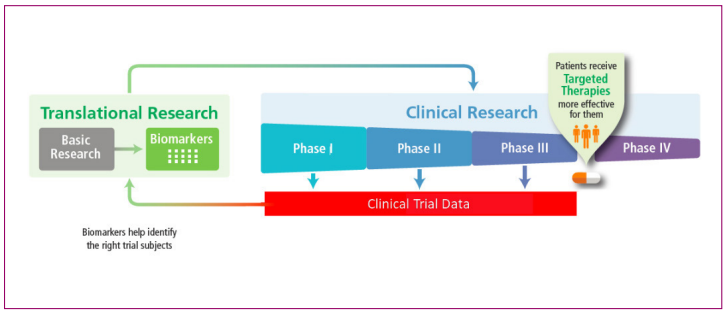

Figure 2: *Leveraging clinical data for biomarker discovery and patient selection for improved clinical trial success.*

At Revvity Signals we are taking action to provide the best solutions to enable clinical and translational researchers to drive change and shape the future of medicine. Revvity Signals provides a translational medicine platform where research data is seamlessly integrated with clinical data (Figure 3). Our objective is to enhance the capability of clinical development programs by integrating a wide variety of biomarker-based datasets such as genetic variants, gene expression, copy number variation, immunohistochemistry, multiplex enzyme-linked immunosorbent (ELISA) assays to the analysis of clinical data.

To achieve this, we have designed Revvity Signals™ Translational, a unifying data platform that enables search, aggregation and analytics in a fully integrated manner empowering researchers to perform cross-study biomarker analysis for their clinical trials (Figure 4).

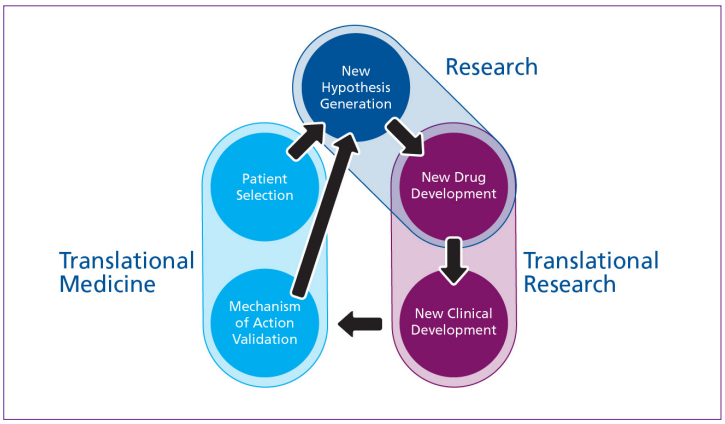

Figure 3: *Translational Research Cycle.*

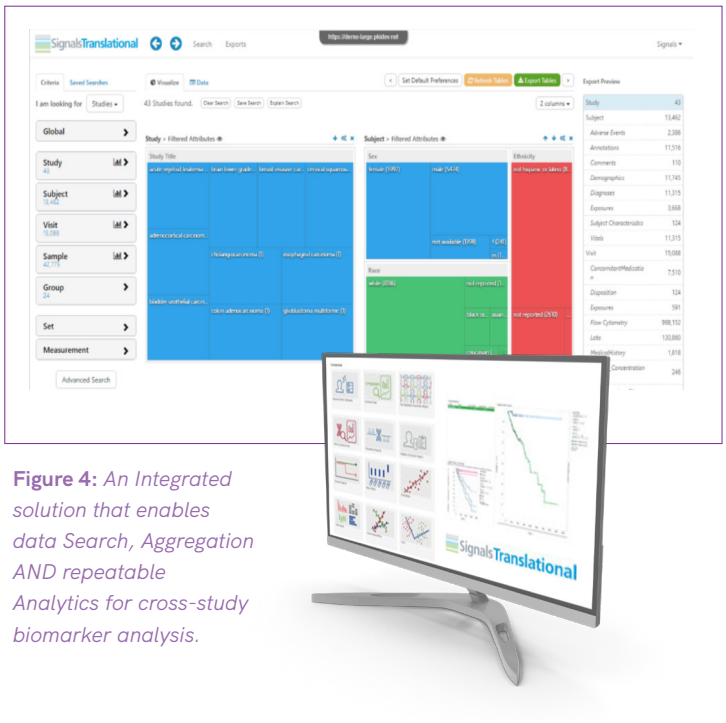

Figure 4: *An Integrated solution that enables data Search, Aggregation AND repeatable Analytics for cross-study biomarker analysis.*

With visual analytics powered by Spotfire®, Revvity Signals Translational provides all the necessary tools to harmonize, manage, search, aggregate and analyse studies consistently across large datasets for use in translational research in a highly scalable manner. This delivers novel insights that cannot otherwise be achieved when examining biomarker and clinical datasets in isolation. Thereby, providing researchers with the capacity to rapidly develop and test hypotheses, stratify their patient populations, and expedite the discovery and development of new therapeutics.

REVVITY INFORMATICS SOLUTIONS FOR CLINICAL DEVELOPMENT

One of the main challenges in clinical development is information is typically pulled in from multiple data sources making it difficult to associate data, observe trends and identify issues quickly and easily. Moreover, answering important questions from clinical, operational and safety data proves to be time-consuming and expensive as data integration and aggregation are necessary before analysis. This effort is compounded as the number of trials increases.

Leveraging Revvity Signal's solutions for clinical development, team members can perform self-service data discovery in the areas of in stream safety assessment, protocol adherence, data cleaning, site reports, patient enrollment, study budgeting, etc. in a way that complements Development IT and Biostatistics.

Clinical trials are thus enhanced by:

1. Exploration of the key aspects of the protocol for specified follow-up. This enables a deeper understanding of the salient aspects of the data.
2. Ensures protocol adherence by identifying drop-outs and violations early; this enables subjects with missing data to be fixed or replaced quickly, saving money and keeping trials progressing as designed.
3. Providing views on all the data early and often which facilitate rapid data cleaning and ensures data quality
4. Reduces the churn and rework from static reports and listings leveraging self-service exploratory analysis.
5. Allows for the re-use of workflows for multiple trials/ therapy areas saving time and money in development and validation efforts.

Revvity Signals' clinical solutions 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. Revvity Signals has solutions to address the following clinical development use cases:

SOLUTION	VALUE
Study Design	• Patient Stratification • Accelerate Biomarker Projects • Optimize Cross Study Analysis
Data Management Operations	• Speed Database Lock • Reduce Unfrozen Databases
Data Review	• Manage Safety Risk in Portfolio • Faster Medical Review • Improved Data Quality
Trial Monitoring	• Meet Study Milestones • Ensure Proper Site Management
Risk-Based Monitoring	• Enhance Subject Protection • Improve Operations and Data Quality • Reduced Study Costs
Pharmacovigilance	• Accelerate Response to Safety Issues • Enhance Protection of Patients • Maintain Good Standing with Regulators
Project and Portfolio Management	• Accurate Portfolio Prioritization • Optimized Capacity Management • Improved Resource Forecasting
Supply Management	• Maintain Targeted Supply Levels at Sites • Reduce Dropouts Due to Supply Issues

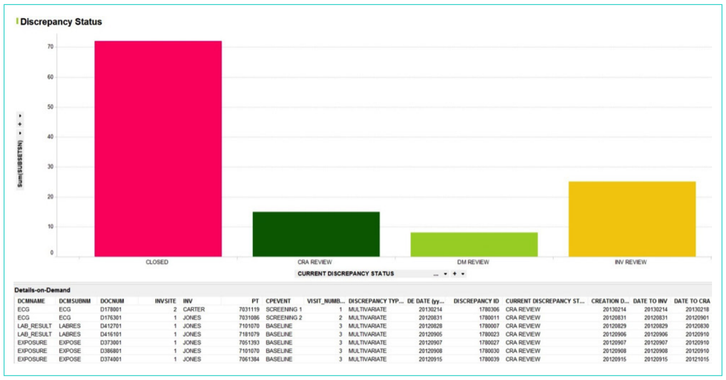

Figure 5: *Discrepancy Management.*

DATA MANAGEMENT

Analytics can facilitate optimal monitoring of data quality during the capture of clinical data with the ability to quickly spot outliers. Data management can be optimized by reducing discrepancy lag times as seen in Figure 5. Poor performing sites with high discrepancy counts and missing pages can be identified. CRFs with high discrepancy counts can be identified as seen in Figure 6. Data management staff performance can be more efficiently monitored. This can help facilitate faster data cleaning and database lock. This also enables the avoidance of problems being picked up in the data post database lock which can lead to significant trial delays. Customers have reported a significant reduction in data quality issues with a reduction in database lockdown preparation time and a decrease of unfrozen databases.

Spotfire® helps users identify trends earlier and provide the ability to dig deeper into the data without the need for biostatistics groups to create additional charts and reports.

DATA REVIEW

Revvity Signals offers solutions to analyze in stream safety biomarker data to understand safety risks earlier in development. And that is the basic value of PKI's customers in clinical pharmacology: they can identify trends earlier and have the ability to dig deeper into the data without the need for their biostatistics group to create additional charts and reports. A Phase 1 interdisciplinary project team consisting of biostatistics, clinical, safety and others at a top 10 global pharmaceutical company won an internal award for their innovative approach to clinical review on a very high priority project.

Other top 10 pharmaceutical companies have deployed globally across all of clinical pharmacology where they look at dose adjustment decisions, interactively in a team environment and can quickly interrogate the data. This enables actionable decisions to be made quickly.

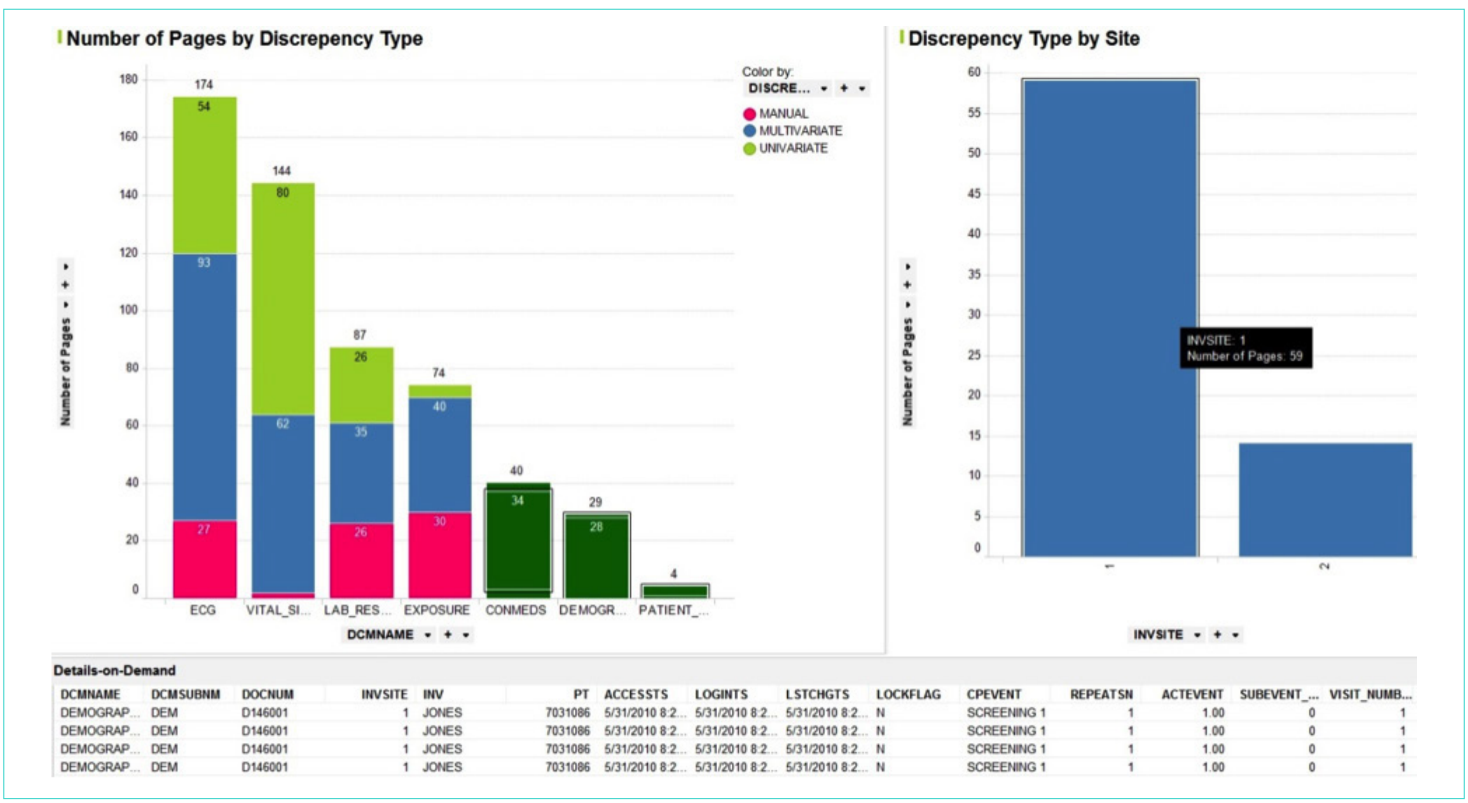

Figure 6: *CRFs with associated Discrepancy Counts.*

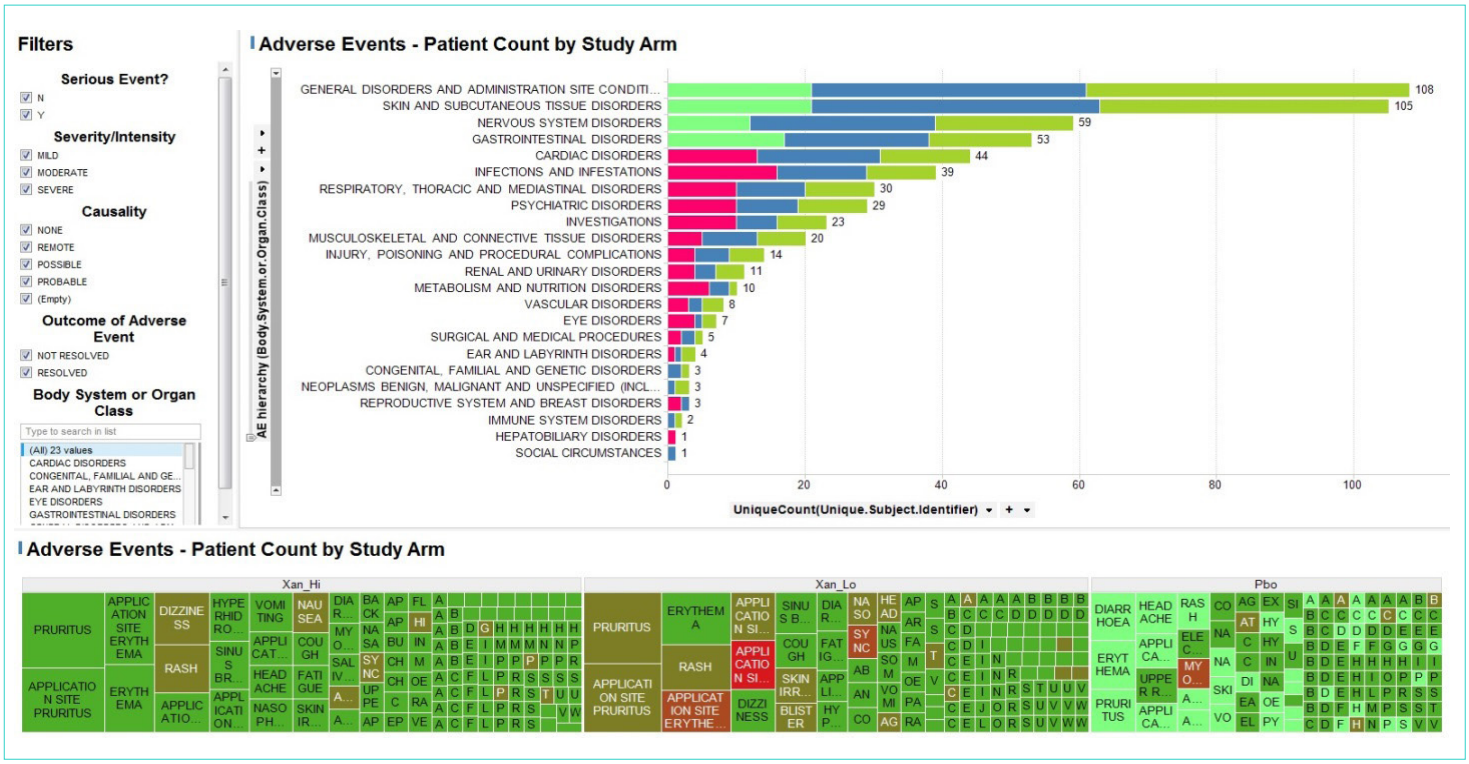

Figure 7: *In-Stream Safety Review.*

CLINICAL TRIAL MONITORING

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. Advanced visualization-based data discovery 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. The graph below shows withdrawal / drop rates versus screen failure rates for each site across all trials.

Information on trial progression (enrollment, budget and milestones) can be readily available to study management teams along with data to assess protocol violations, site performance and dropouts.

The largest single staffing commitment to large clinical studies is clinical research associates - CRAs (or Monitors). Customers have obtained a 30% decrease in CRA monitoring visits and related expenses via data-driven monitoring utilizing site dashboards with KPIs.

Other top 30 pharmaceutical company customers have experienced a 50% decrease in site time to data entry. Optimal site management has been proven to save $20K+ per problem patient along with a 50% reduction in protocol violations.

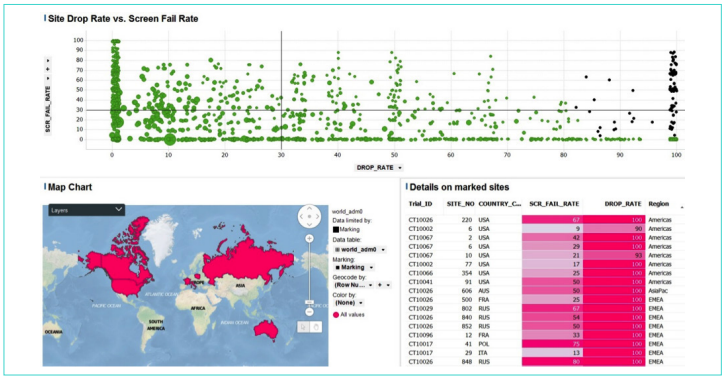

Figure 8: *Drop Rate vs. Screen Failure Rate.*

This explains how Program Managers can perform proper Portfolio management, analyze regional / study trends, and monitor performance metrics using live, interactive scorecards based on KPIs.

Country Managers can keep a good handle on regional performance, perform regional comparisons, and analyze site performance metrics.

Study Managers can perform optimal study management utilizing visual analysis capabilities to identify trends and outliers, perform budget management and analyze country and site performance

CRAs benefit from the ability to prioritize their work via data driven monitoring which enables issue detection and the identification of protocol violations.

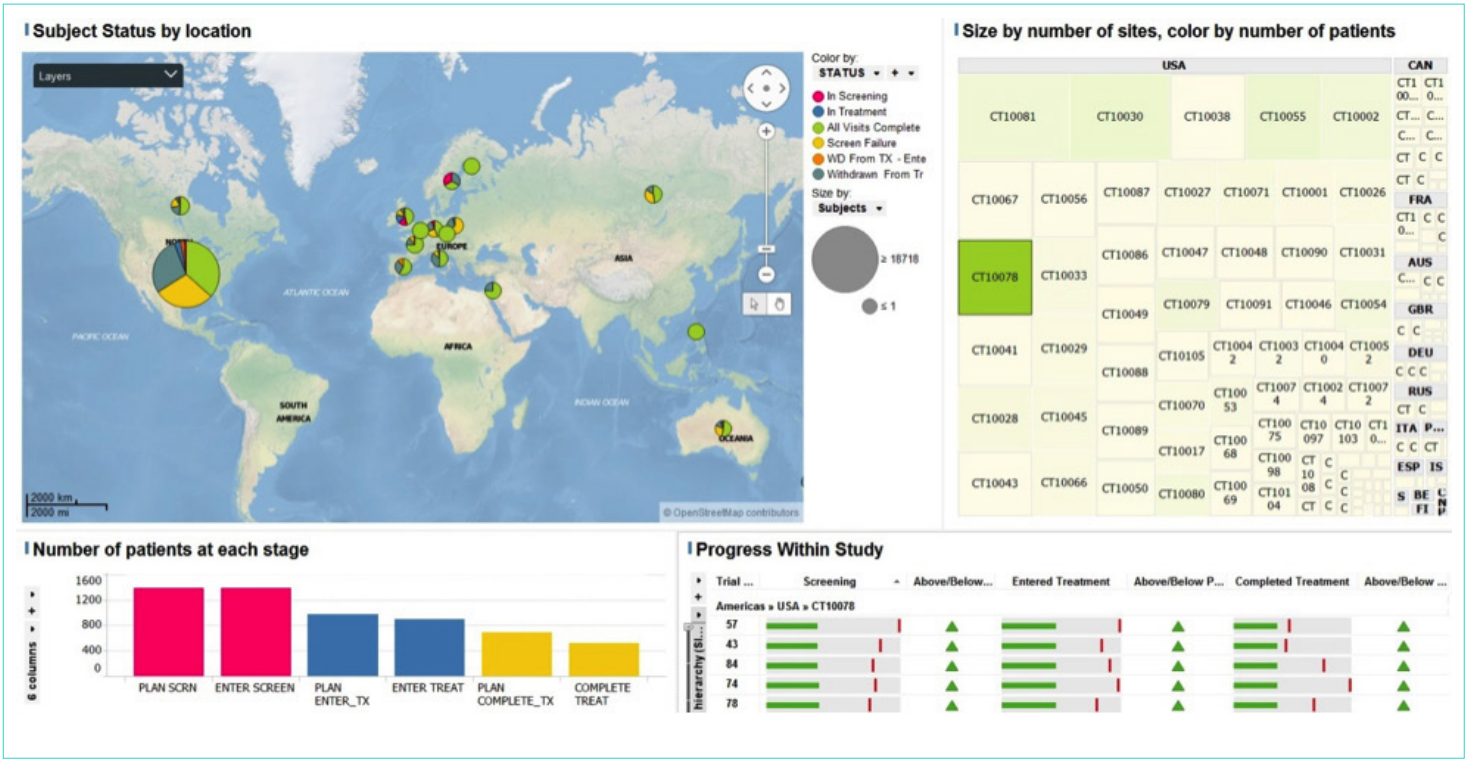

Figure 9: *Progress Within Studies.*

Advanced data analysis can help mitigate common problems such as:

- Protocol violations
- Identify studies that are failing operationally or medically
- Investigator fraud
- Reduce the number of underperforming sites on a study

Advanced visualization-based data discovery makes it easy to evaluate data from multiple sites, and identify differences early on.

RISK-BASED MONITORING

Data aggregation from multiple sources is typical in risk-based monitoring, where data integration and analysis is essential for monitoring the overall performance of each site. The data resides in individual silos, such as EDC and CTMS systems, with different data formats and reporting environments, which makes data aggregation difficult. The power of world-class visual analytics can be used to proactively monitor clinical trial data from a variety of source systems contributing to more efficient trial execution and the timely identification of issues related to patient safety and data quality.

Real-time advanced analytics on captured data can provide an end-to-end holistic approach to maximize the efficiency and safety of clinical trials. PKI's solution follows the industry's best practices, such as those of the TransCelerate BioPharma framework. As the key performance indicators are adapted from study to study and from one therapeutic area to another, the software provides flexibility that allows for those indicators to be updated as well as the algorithms that contribute to the overall risk score. This flexibility of the platform, coupled with interactive visualization and statistical modelling help deliver an industry leading Risk-Based Monitoring solution.

This flexibility of the Spotfire® platform, coupled with interactive visualization and statistical modelling help deliver an industry leading Risk-Based Monitoring solution.

Figure 10: *Overall Risk Score Across Sites.*

PHARMACOVIGILANCE

Data aggregation from multiple sources is typical in risk-he world of pharmacovigilance is a complex one that is undergoing a shift in focus as evidenced by the change from things like Periodic Safety Update Report (PSUR) to Periodic Benefit Risk Evaluation report (PBRER) and the increased complexity that comes with that shift.

Current off the shelf safety solutions provide robust data collection and reporting futnctionality but lack the visualization and analytic capabilities required to understand the data and efficiently work with the bigger picture.

Revvity Signals pharmacovigilance solutions built on the Spotfire® platform provide a new way to work with pharmacovigilance data, find insights and drive operational efficiency. Activities that relate to compliance monitoring such as measuring timeliness to ensure compliance to company and global regulatory reporting requirements and identifying case processing workflow challenges can be enhanced. Our customers report that with pharmacovigilance solutions they are able to dramatically improve their process as seen below:

TASK	OLD METHODS	REVVITY SOLUTIONS
Prepare for Safety Team Review	3 Days	10 minutes
Pivot from cases to events	New data extracted, 1-2 days	<1 minute
Answer the 'next' question	1 week	In the room

Figure 11: *Case Seriousness Overview.*

> Emerging technology that allows for the consolidation and rapid analysis of clinical and non-clinical data is critical.

PROJECT AND PORTFOLIO MANAGEMENT

In order to successfully manage a portfolio of clinical candidates, a holistic view into all projects and studies with the needed clinical trial subjects and other resource requirements is required. Resource constraints for major study events and manpower estimates for the current portfolio can be visualized along with "what-if" scenario testing. With information for all projected studies managed and updated in real-time, accurate study information can drive patient enrollment projections and associated clinical and non-clinical resources. As seen below in Figure 12, the broader impact on the pipeline from attrition-adjusted projects currently in the portfolio, new discovery derived efforts, line extensions and in-licensed assets can be determined.

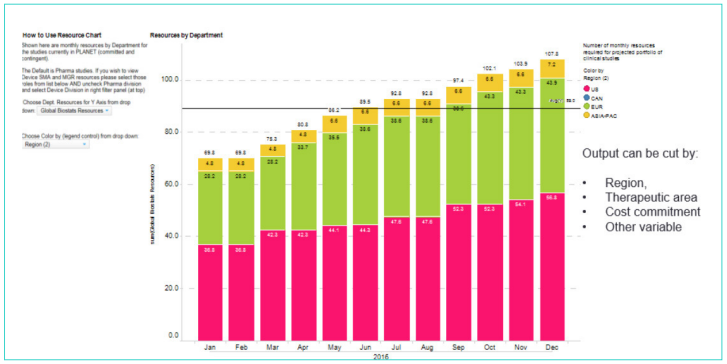

Figure 12: *Number of Resources Required for Projected Portfolio.*

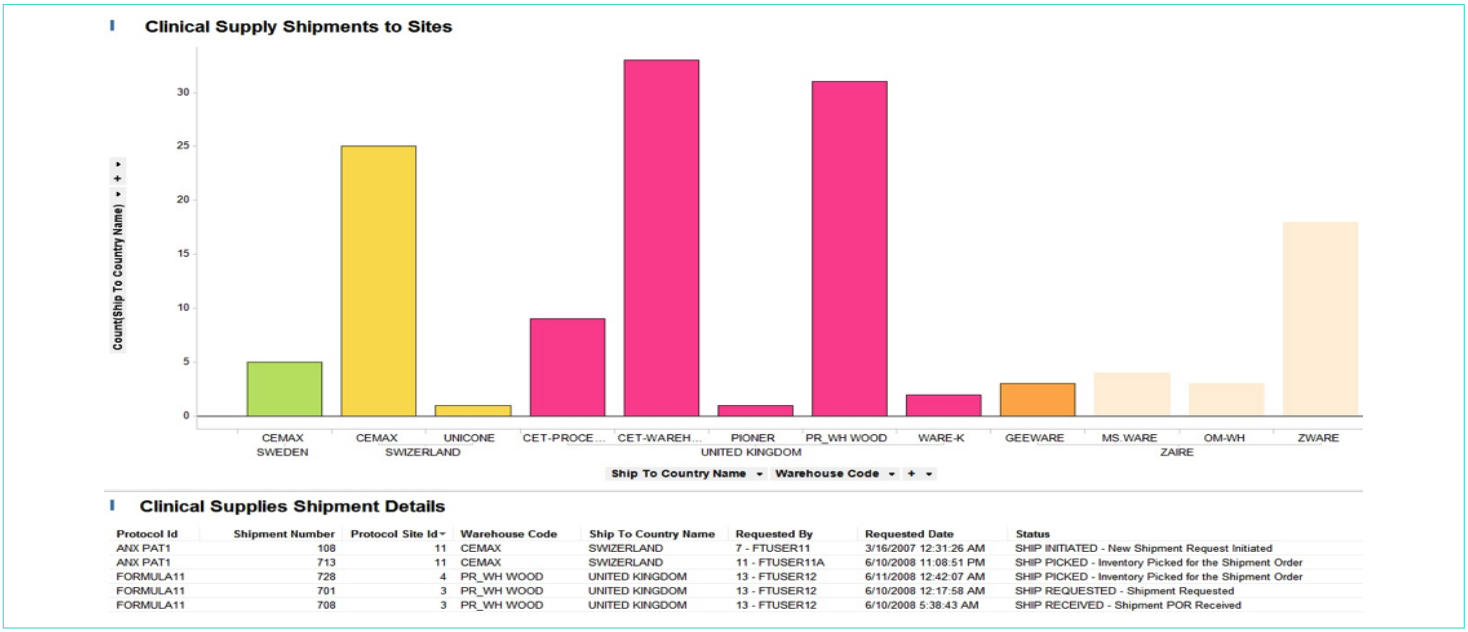

Figure 13: *Clinical Supply Tracking of Shipments to Sites.*

CLINICAL SUPPLY MONITORING

The accurate tracking of clinical supplies at internal and external locations is fundamental in making sure clinical supplies are in place at sites to keep patients dosed and trails moving forward. Clinical supply monitoring analytics enable the oversight of packaging, distribution, returns, reconciliation and quality management of clinical kits. Understanding aggregate demand across different protocols for clinical kits provides an overall demand view at an enterprise level. The solution replaces numerous planning spreadsheets that require manual input from all stages of clinical development and complements a forecasting scenario modeling tool so that clinical supply organizations are more proactive vs. reactive with each study. Data is loaded on demand for each study to prepare for the impact of:

- Various enrollment rates / patterns
- Drop percentages
- Drop limits
- Countries starting studies at different times
- Addition or removal of treatment arms
- Protocol amendments
- Lost, stolen, destroyed kits
- Changing randomization schemes

HEALTH ECONOMICS AND OUTCOMES RESEARCH

Life science companies are spending more and more on health economics and outcomes research but struggling with

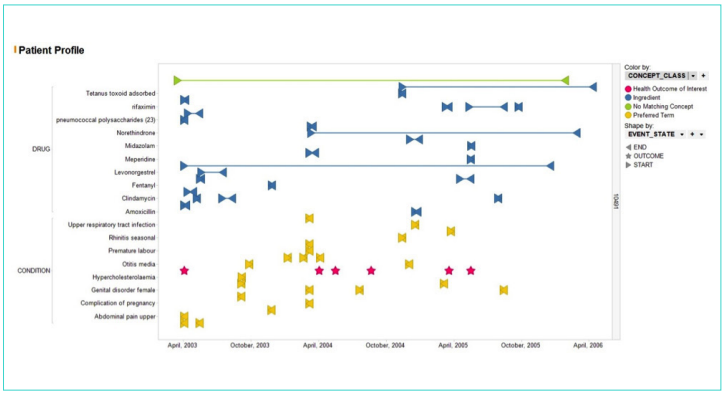

Figure 14: *Disease atnd drug prevalence analysis using patient profile outcomes data.*

data volumes, data integration, long-running analyses and visualization.

Combining Revvity Signals expertise in the area of health economics and outcomes research with Teradata® and Spotfire® technology, users are empowered to quickly discover insights through meaningful visualizations, interactively visualizing outcomes data without requiring structural or semantic changes to that data. In addition, life science companies can dynamically aggregate, filter and access micro-level data details to produce near-real-time analytic visualizations that highlight where the data value can be found. Teradata® and Spotfire® guarantee high performance and linear scalability as data volume and complexity grow.

SUMMARY

Revvity Signals empowers a broad spectrum of individuals in life science companies from executives managing an entire portfolio of clinical candidates to those involved with translational medicine and health economics and outcomes research with insight leading to actionable decisions that enhance patient safety, streamline clinical development and enable faster launches leading to better medical outcomes for patients.

REFERENCES

1. BIOPHARMADIVE. March 3, 2020. Accessed at: https://www.biopharmadive.com/news/new-drug-cost-research-development-market-jama-study/573381/

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.

Revvity Signals enables companies to significantly reduce the validation burden for initial installation and upgrades of Spotfire®, the operation of the software 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. Revvity Signals also provides documentation for our clinical offerings that can accelerate the validation process.

It is the responsibility of the end user to install and validate Spotfire® within the end users quality systems in accordance with their policies and standard operating procedures.

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