Paper AR04

Development of a Risk-Based Monitoring (RBM) Visualization Application Interface using JMP® Scripting Language (JSL)

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ABSTRACT

Risk-Based Monitoring (RBM) is a new initiative encouraged by the FDA. Successful implementation of RBM depends on many key factors, one of which is the availability of an efficient tool with capabilities for reviewing, analyzing, and visualizing ongoing data in an interactive manner. In this paper, we present the development of an add-in using JMP scripting language (JSL). The main features of this add-in include an interface to allow access to a snapshot of multiple studies simultaneously, a dashboard to provide information about the status of study sites related to the specified risk factors in the trial and individual KRI analysis functionalities at a more granular level, and the ability to drill down to the patient level. In addition, it provides graphical analyses to track changes in site overall risks over the course of a clinical trial, enabling Clinical Research Associates (CRAs) to follow up on the results of possible risk mitigation actions.

INTRODUCTION

Clinical trials involving human subjects are typically conducted in multiple sites. The global regulatory agencies require sponsors engaged in the clinical trials with an aim of submission to provide oversight to the sites in order to protect the well-being and safety of participants and to ensure data integrity. To meet the regulatory requirements, sponsors typically adopt an on-site monitoring approach where clinical research associates are sent to the sites every 4 to 6 weeks for 100% source data verification (SDV).

However, due to the increasing complexity and rising cost of clinical trials, the on-site monitoring approach has been proven to be cost-ineffective and inefficient. It is estimated that the cost spent on on-site visits account for 15% to 30% of total costs in a clinical trial (Eisenstein EL, 2005, 2008, NRC, 1999), which creates a huge financial burden on the sponsors and hinders the drug development. More importantly, on-site monitoring approach has been shown to have a minimal effect in ensuring the data quality. The rate of SDV-only discrepancies in critical clinical data is reported to be about 2.4%, indicating that SDV's contribution is minimal and negligible (TransCelerate, 2014). Moreover, Lienard et.al (2006) reported that monitoring sites had no effect on data quality (Lienard et.al, 2006). Getz (2012) reported that SDV does not significantly affect the outcome of clinical trials (Getz, 2012).

Growing evidence suggests that Risk-Based Monitoring (RBM) is more cost-effective and efficient than the traditional on-site monitoring approach (TransCelerate 2014). The key idea behind RBM is application of systematic quality risk management to clinical trials so monitoring activities and resources are focused on the sites with a potential risk rather than conducting on-site visits on all sites without taking into consideration site performances. Implementation of RBM involves three key steps 1). Identification of risks impacting the critical data and processes, 2). Assessment of risks represented by Key Risk Indicator (KRI), and 3). Design and execution of a comprehensive monitoring and risk mitigation plan. The core of RBM is the centralized monitoring where operational and clinical data are evaluated in a systemic and centralized manner. The risks identified in a centralized analysis are used to support or direct the on-site monitoring activities. Compared to traditional on-site monitoring approach, RBM not only reduces costs significantly but also has a potential to uncover data anomalies where 100% SDV fails to achieve. It is reported that centralized monitoring reduces the cost by 50% to 70% compared with SDV (Weir and Murray, 2011). RBM is shown to be as effective as on-site monitoring (Brosteanu et al, 2017). It should be noted that global regulatory agencies are aware of this development and recognized the need to improve current monitoring approach to speed up drug development. In 2013, both FDA and EMA published a guideline that encouraged sponsors to embrace RBM in their drug development.

As implementation of RBM requires monitoring the data in a continuous and real-time manner, it is essential to have the appropriate technologies in place to ensure that data from disparate sources are integrated, analyzed, and visualized in a timely manner. Dashboard monitoring is one of these key technologies that had been considered as an integral part in RBM. Dashboard is a graphic display of essential analytics results that provides a quick glimpse of a study status and allows for drilldown to additional details in a more granular level. Dashboard has been proven

effective in communicating findings or insights of analysis to stakeholders and documenting the evidence for monitoring activity.

JMP® is a statistical software developed by SAS institute. It integrates powerful statistical capability with interactive graphics, which makes data discovery extremely easy. In addition, with powerful scripting embedded, extended JMP® functionality can be utilized to make automation of customized data analysis a reality. Furthermore, JMP® can interact with other software such as SAS, R and MATLAB. All these advantages make it powerful and unique software to summarize, analyze, and visualize clinical data much more easily.

In this paper, we use JMP® scripting language(JSL) to develop a KRI analysis tool. The KRI Analyzer's user-friendly interface provides access to the snapshots of multiple studies simultaneously, provides an interactive monitoring dashboard allowing for quick glimpse of the status of study sites related to the specified risk factors in the trial and allows for drilldown to the detailed analysis of individual KRI. In addition, it provides graphical analyses to track changes in site overall risk over the course of a clinical trial, enabling CRAs to follow up on the results of possible risk mitigation actions.

METHODS

SDTM datasets are used as input to derive KRI datasets for analysis in the KRI Analyzer using SAS programs. KRIs are defined and derived with modifications based on methodology described in the TranCelerate paper (TransCelerate, 2014) and Overall Risk Ranking for each site is derived with modifications based on the method (Taylor, 2006). The details of derivation are beyond the scope of this paper and are not discussed here.

Development of JMP® Add-In: The KRI Analyzer is developed using JMP® scripting language and is deployed as an Add-In in JMP® Clinical v 6.1 as described in the JMP® scripting guide v12. The deployed Add-In KRI Analyzer will appear in the menu of JMP® Clinical.

STUDY SNAPSHOTS SELECTION

Monitoring is often performed on multiple studies in a continuous way, so, an effective application interface must allow users to access diverse data easily and be user friendly. In light of this idea, KRI analyzer is designed to empower users to freely and conveniently access any study and any snapshots with just a few mouse clicks.

Figure 1 Application Interface of KRI Analyzer

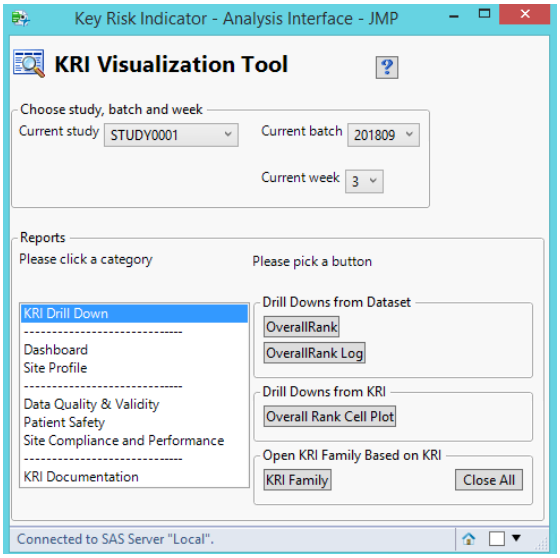


Figure 1 is a screen shot showing the access to the studies, snapshots. Assume that KRI Analyzer is installed in JMP Clinical, go to **Menu** and select **Add-Ins > KRI Analyzer**. The KRI analyzer interface window will appear as above.

In the panel **Choose Study, batch and week,** options are provided to choose studies. Once a study is selected, snapshots within the study identified by year, month, and week when they were generated are provided in drop down buttons dynamically for further selection. In our monitoring plan, analysis datasets are generated bi-weekly and the

Year- Month, batch are sorted in a way where the most recent batches appear on the top of the list to allow easy access. A drop-down button allows you to select any snapshot.

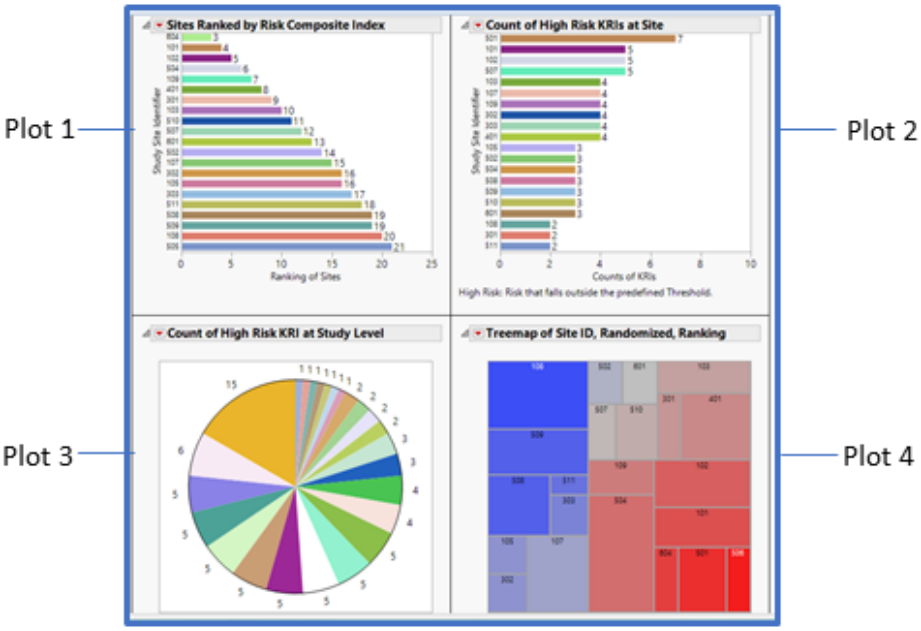
DASHBOARD MONITORING

OVERVIEW

KRI dashboard graphically provides a quick overview of site performance with regard to the overall risk ranking, KRIs being fired, and basic site information such as number of randomized subjects (Figure 2). As shown in Figure 2, Plot 1 shows overall risk ranking for each site based on the composite scores aggregated by individual KRIs and weighting scores. Plot 2 shows number of KRIs being fired at each site, in the descending order. Plot 3 shows a pie chart of counts of fired KRIs. Plot 4 is a tree map showing site overall risk rank in which the size of each sector is proportional to the number of randomized subjects. The sites are colored-coded using color gradient of blue-to-red, with red indicating a higher risk. In addition, the sites are ordered from left to right based on their overall risk rankings.

The graphics in JMP® based on the same underlying dataset are inherently dynamic, interactive, and cross-linked. The dashboard plots in the KRI Analyzer are created based on this idea. With all data in one dataset, you can click on any part of the four plots in the dashboard and view corresponding updates in the other three plots. For example, clicking site ID in the tree map Plot 4, the overall risk ranking, count of high risk KRIs, and KRI name will be easily read out by the highlights in the other three plots and enable users to get a quick idea about the particular site.

Figure 2 KRI Dashboard



The interactivity of KRI analyzer can also be realized using a filter box functionality in JMP. To take advantage of this function, a filter box containing site ID and KRI names is mounted on the right side of the dashboard. With the filter box, you can select a site or a KRI to view the graphics built on data extracted using the site ID or KRI names. The graphics are updated automatically once you have made selections, enabling users to focus on the information of interest (Figure not shown).

A user is often tempted to know additional details behind the summary data in the dashboard. But the interactivity by clicking the visualization elements in the graph and selection in filter box is limited by the underlying dataset, so, exploration of data behind the dashboard needs another must-have Drilldown tool which can only be customized using JSL. To extend the interactivity, KRI Analyzer takes advantage of JMP built-in functions and contains three buttons to enable users to further investigate the data in more depth. As shown in Figure 3, there are three functional buttons added to the dashboard on the side.

The button **Launch KRI Analysis** enable users to perform an individual KRI analysis at site level and drill down to the subject level. Detailed analysis will be illustrated in the section below.

Figure 3 Window for Drill Down

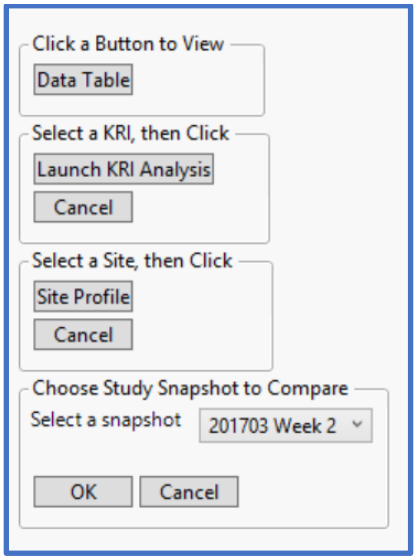
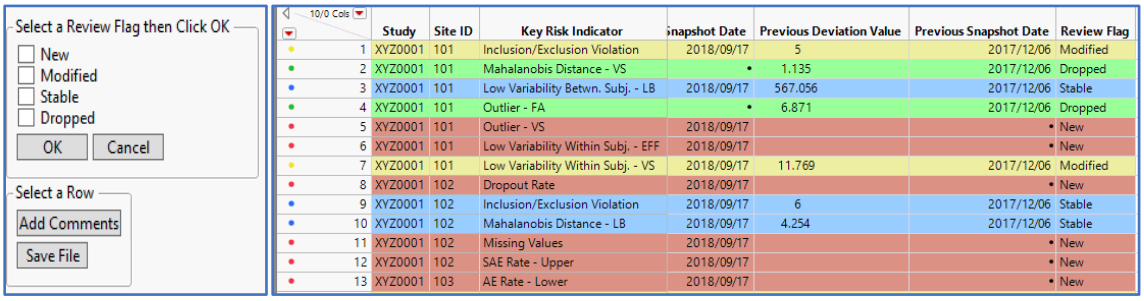


Figure 4 Site Profile

Clicking the button **Site Profile** in the panel **Select a Site, then Click** will present a plot showing changes in KRI risk classifications (high risk or low risk) over time for the site selected and for all KRIs (Figure 4). Row one shows the change of site overall risk rank across the visits while the remaining rows show the risk classification change over time for individual KRI in the selected site. With this plot, you can get a quick idea of how a site performs over time with regard to the KRIs being evaluated. On the right side of the profile plot, basic information about the site can be found, including number of screened and randomized subjects, and other demographic information.

In the panel box **Choose Study Snapshot to Compare**, you can select a previous snapshot and compare it with current data to examine which KRI is unchanged, modified, or new. The rows are color-coded based on the changes in KRI overall Ranking, presence or absence of KRIs in the current snapshot. Red means “New Record”; Yellow means “Modified due to a change in KRI ranking”; Blue refers to “Stable indicating no change in the ranking”; Green (“Dropped”) appears when a record does not exist in the current snapshot (Figure 5).

Figure 5 Comparison of Study Snapshots



	Study	Site ID	Key Risk Indicator	Snapshot Date	Previous Deviation Value	Previous Snapshot Date	Review Flag
1	XYZ0001	101	Inclusion/Exclusion Violation	2018/09/17	5	2017/12/06	Modified
2	XYZ0001	101	Mahalanobis Distance - VS	•	1.135	2017/12/06	Dropped
3	XYZ0001	101	Low Variability Betwn. Subj. - LB	2018/09/17	567.056	2017/12/06	Stable
4	XYZ0001	101	Outlier - FA	•	6.871	2017/12/06	Dropped
5	XYZ0001	101	Outlier - VS	2018/09/17		•	New
6	XYZ0001	101	Low Variability Within Subj. - EFF	2018/09/17		•	New
7	XYZ0001	101	Low Variability Within Subj. - VS	2018/09/17	11.769	2017/12/06	Modified
8	XYZ0001	102	Dropout Rate	2018/09/17		•	New
9	XYZ0001	102	Inclusion/Exclusion Violation	2018/09/17	6	2017/12/06	Stable
10	XYZ0001	102	Mahalanobis Distance - LB	2018/09/17	4.254	2017/12/06	Stable
11	XYZ0001	102	Missing Values	2018/09/17		•	New
12	XYZ0001	102	SAE Rate - Upper	2018/09/17		•	New
13	XYZ0001	103	AE Rate - Lower	2018/09/17		•	New

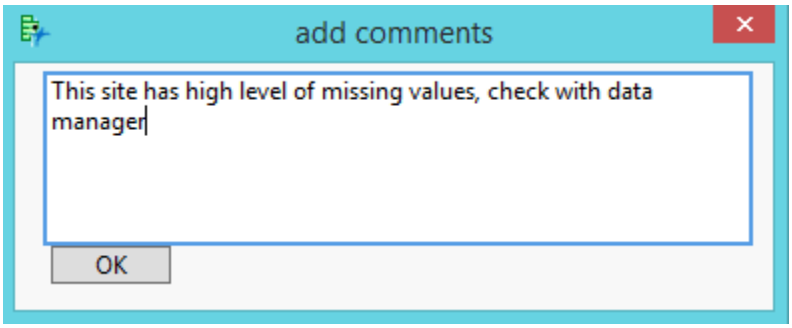
One the left side of snapshot comparison, a panel box is mounted to allow you to select records of interest in the comparisons dataset for a focused review. A subset of data will pop up based on the selection. For example, a user may want to visualize the data that only appears in the current batch and just select New and then click OK.

When you review the records, you may want to add your comments for future references. Use mouse to select a row then click button **Add Comments** (Figure 5). A small window will pop up and you can add comments then hit **OK** (Figure 6A). The comments will be added to the dataset (Figure 6B).

You can use **Save File** to save the dataset with your comments.

Figure 6 Add Review Comments

A.



B.

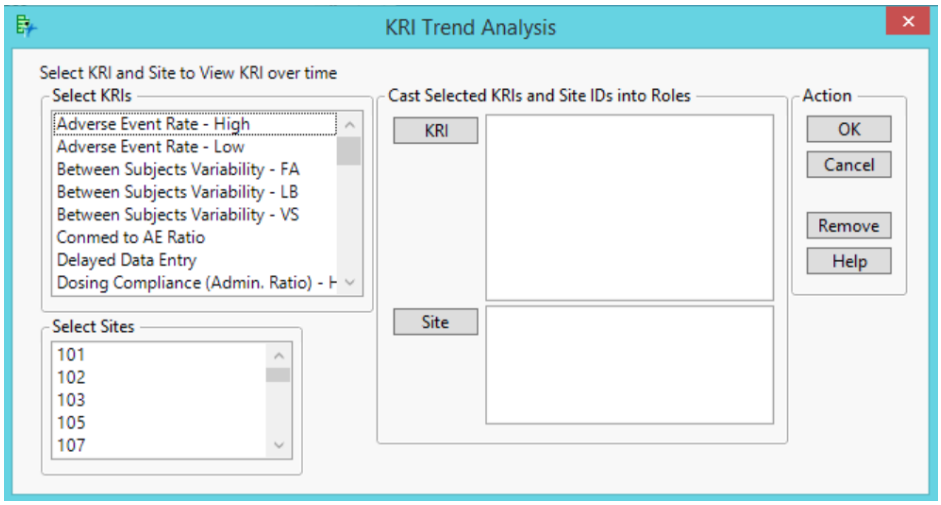
	Study	Site ID	Key Risk Indicator	Review Flag	Notes	Monitor	Note Date
4	XYZ0001	102	Missing Values	New	This site has high level of missing values, please check with Da...	Wendy S	2018-11-27
5	XYZ0001	102	SAE Rate - Upper	New			•

ANALYSIS OF KRI CHANGES OVER TIME

It is of interest to assess the effectiveness of monitoring. One way to achieve this goal for RBM is to follow the trend of a KRI as the clinical trial is advancing. The button **KRI Trend** allows users to perform this type of analysis.

Click on the button **KRI Trend**, a KRI Trend Analysis window will appear to allow for selection of KRIs and sites (Figure 7). To select KRI, select KRI names in the panel **Select KRIs**. If you need multiple KRIs, use **ALT** + mouse. (Figure 7). Then click button **KRI** and cast the selected KRIs to the list box in the middle. Site selection can be performed in a similar way.

Figure 7 Selection of KRIs and Sites for Trend Analysis



Once you click the button **OK,** graphs of KRI values vs. snapshot run time for each selected KRI will be stacked vertically. Figure 8 shows the trend of protocol deviation rates over time. The orange line in the graph represents a reference line of threshold. The data points above the threshold are marked with symbols of red upper triangles, indicating a risk requiring more attention (Figure 8).

Figure 8 Changes in PD Rates over Time

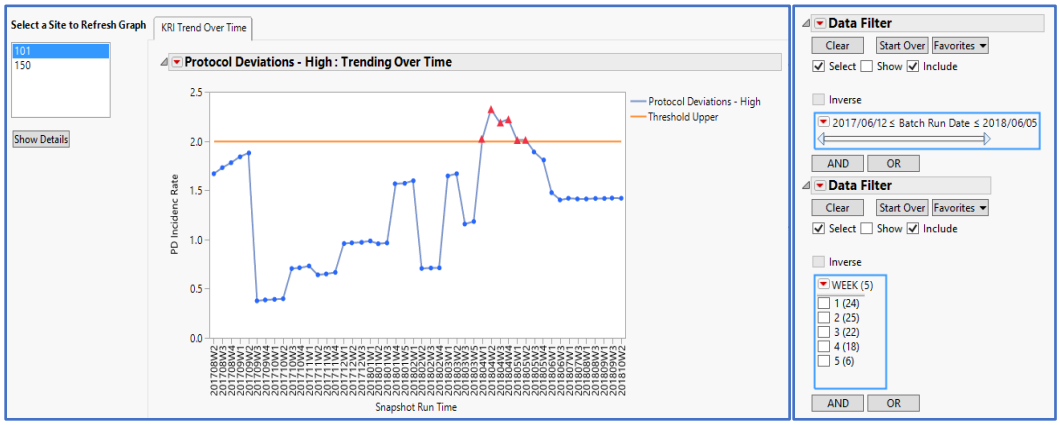
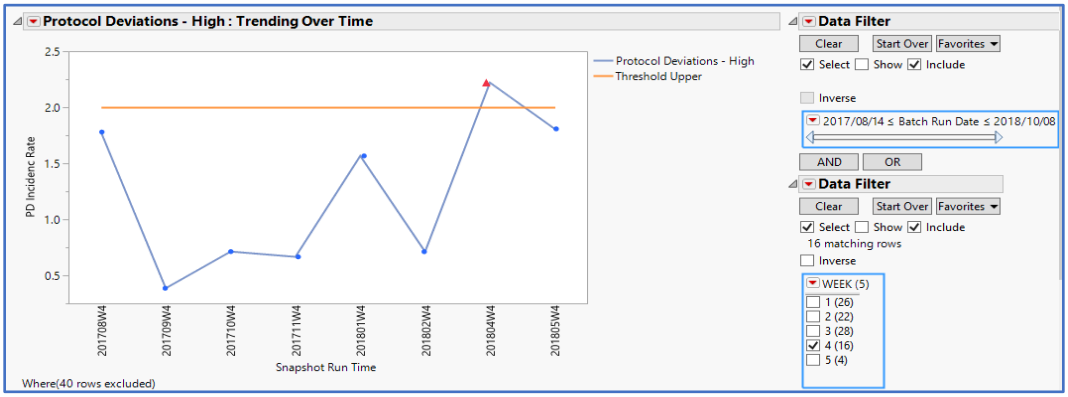


Figure 9 Change of PD Rate by Month

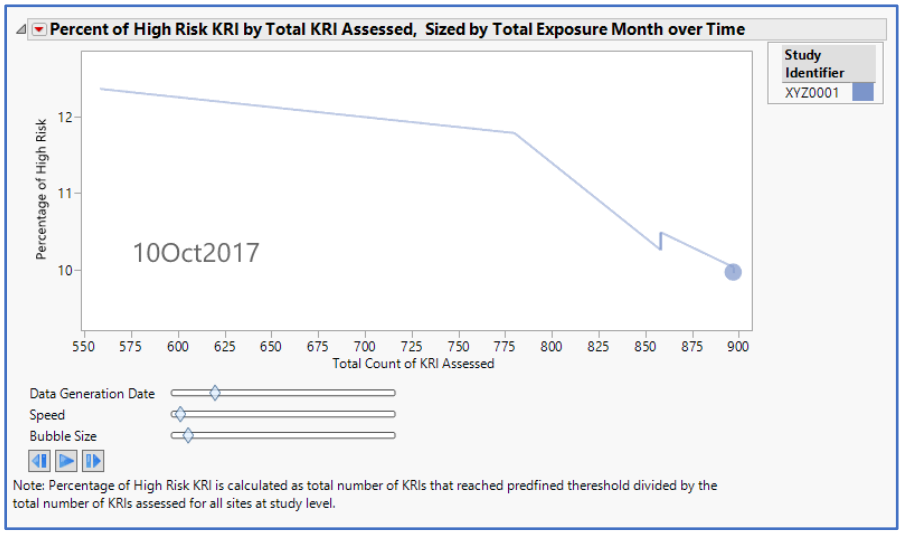


Since multiple sites are allowed for selections, a panel box with list of sites is mounted on the left side of graph window so that a site can be selected to view the graphs only related to the data from that site (Figure 8). The button **Hide Details** is a toggle button and has two states, **Hide Details** and **Show Details**. In the mode of **Show Details,** a box shows KRIs and sites selected and whether KRI has any events being reported in the dataset. On the right side, a filter box is added to allow for selection of a batch of snapshots (Figure 9). For example, you can view graphs that show monthly changes in KRI values simply by subsetting using filter **Week.** Figure 9 shows monthly changes in PD rate beginning from week 4 from one month to week 4 of next month.

PERCENT OF HIGH RISK KRI CHANGE OVER TIME

To assess study level monitoring activity at the study level, KRI Analyzer followed the trend of percentage of KRI fired over time during the clinical trial, Percent of High Risk KRI is derived as the number of KRIs that have reached predefined thresholds divided by the total number of KRIs assessed in the study. Click on the button **Percent of High Risk KRI Change Over Time** to reveal a bubble plot of Percent of High Risk KRI against Total KRIs Assessed in animated way. As shown in Figure 10, the Percent of High Risk KRIs show a decreasing trend as the clinical trial proceeds and becomes stable (Figure 10).

Figure 10 Percent of High Risk KRI Change over Time



ANALYSIS OF SPECIFIC KRI

It is important to perform a detailed analysis of individual risks so that specific issues can be pinpointed, addressed, and targeted for mitigation. In the KRI analyzer, analysis of each individual KRI is performed under three categories in the application interface below (Figure 11):

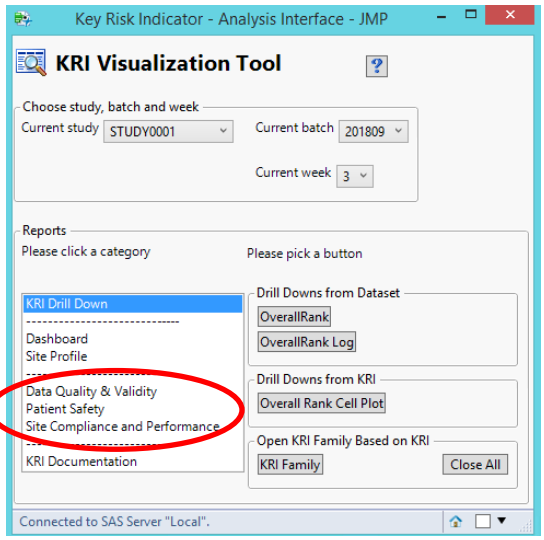
- Data Quality & Validity
- Patient Safety
- Site Compliance and Performance

Click on any of three KRI categories will bring out specific KRIs in the category on the right panel. Then clicking on any buttons to launch analysis for the selected KRI. For example, to visualize **Outliers,** click on **Data Quality & Validity** in the left panel, then click on the button **Outliers** on the right panel.

General Approach of KRI Analysis

Risk analysis driven by KRIs is performed on critical data and critical processes which are manifested in multiple aspects in a study. We are not going to present analysis for all the KRIs but to describe the general analysis approach and to use KRI Dropout as an example to illustrate how the customized analysis functions can be expanded and scaled up in this application software.

Figure 11 Categories of KRI Analysis



As expected, monitoring activities are typically done at the site level. In alignment with this practice, the landing page of specific KRI analysis is defaulted to be a graphic display of KRI values versus site ID, with risk of sites distinguished by two different colors. The sites with KRI values above predefined threshold are marked with warm colors such as red or orange while low risk sites are colored with cool colors such as blue or green. Along with the site-level graphs, functional buttons or lists are provided to allow for drilldown or exploratory analysis on the left side of the graph while a filter box is mounted on the right side of the graph to allow for slicing data for viewing a graph on the subset data.

If a KRI has multiple sub KRIs, radio buttons will be provided in a list box to allow the selection of one of the sub KRIs and site-level graph will be updated based on the selection. For example, Between/Within Subject Variability are derived from data in three different domains and each is used to classify the site risk separately, so, options to visualize each of these KRIs are provided by three radio buttons (Data not shown).

The site-level graph can be viewed in three ways with regard to the ordering of the following variables. The options are provided by radio buttons in the panel box **Click to Order.** Clicking on any radio button will switch the graph.

- Site ID
- KRI values
- Site Overall Risk

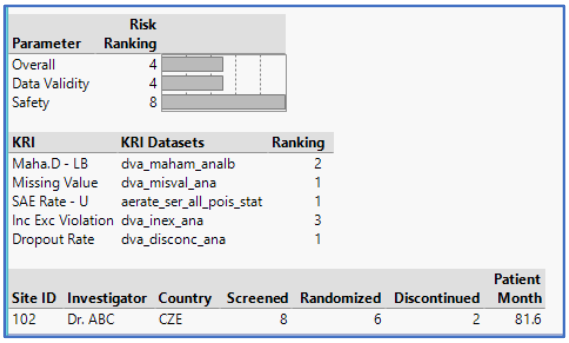
Panel box **Click a Button to View** is designed for viewing the dataset underlying the graph, customized analysis depending on the type of KRI.

Panel box **Select a Site then Click** is designed to allow users to explore data at a site level and to drill down to the subject level data. The button **Show Site Ranking** will display general information about the sites such as the overall ranking of the site, KRI being fired, number of subjects randomized, and exposure duration in months (Figure 12).

With each KRI, the associated **Help** button, when clicked, leads to a window to give a brief introduction of the KRI you are viewing. The information includes KRI variable, derivation algorithm, classifications, and links to open programming Data Definition Tables (DDT).

Number and type of KRIs to be monitored depends on the study. In the next section, we will use the KRI metric Dropout Rate as an example to illustrate how analysis of a specific KRI is carried out in this tool.

Figure 12 Site Ranking and KRIs Fired



Parameter	Risk Ranking
Overall	4
Data Validity	4
Safety	8

KRI	KRI Datasets	Ranking
Maha.D - LB	dva_maham_analb	2
Missing Value	dva_misval_ana	1
SAE Rate - U	aerate_ser_all_pois_stat	1
Inc Exc Violation	dva_inex_ana	3
Dropout Rate	dva_disconc_ana	1

Site ID	Investigator	Country	Screened	Randomized	Discontinued	Patient Month
102	Dr. ABC	CZE	8	6	2	81.6

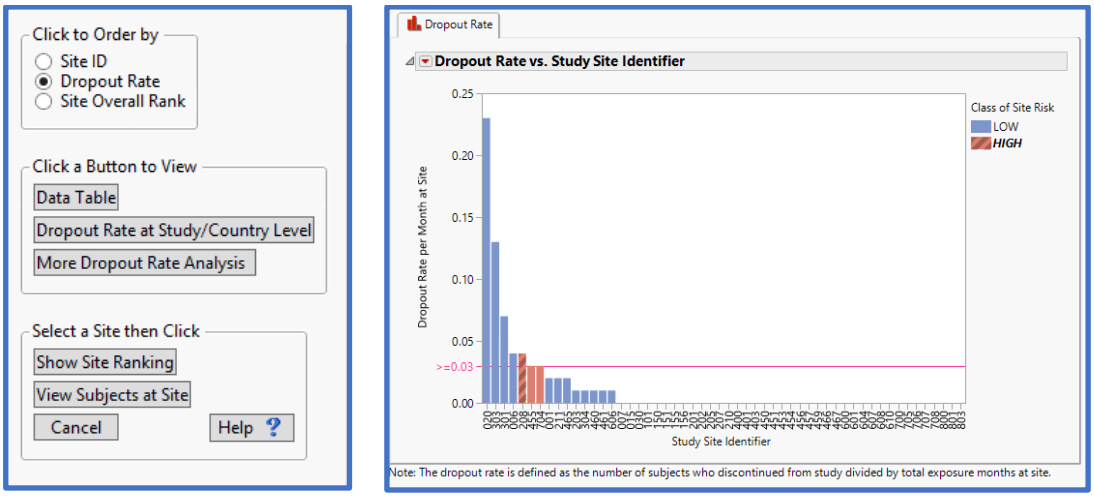
A KRI ANALYSIS EXAMPLE - DROPOUT RATES

It is known that patient compliance and retention are critical to the success of clinical trials. Excessive patient dropout rate results in costly delays and missing data that can compromise the study results. To perform a study dropout analysis, click on **Site Compliance and Performance > Dropout Rate** to show a bar graph of dropout rates at each site in the study (Figure 13). Note that the site dropout rate is calculated as number of dropouts divided by the total exposure months at the site.

As described in the section of **General Approach of KRI Analysis**, on the left side of the graph is the panel containing all the functional widgets that allow for interactions and drilldown. The radio buttons in the panel box provide options to order the bar in the graph according to the site ID, dropout rate, and site overall rank. The panel **Click a Button to View** allows you to open the data table underlying the graph, to view dropout rates at country and study levels, and to perform a customized analysis of dropout rates. The panel **Select a site then Click** contains action buttons to view basic site information, and table of subjects who discontinued from the study.

Note that it is assumed that a site with low enrollment rate does not provide sufficient information for identification of site risk. To identify sites with proper enrollments for analysis, a median value of randomized subjects in the study is used to classify sites into two categories, Low Enroller sites and High Enroller sites. If number of randomized subjects in a site is less than the study median, the site will be classified as Low Enroller, and it will not be evaluated for site risk.

Figure 13 Dropout Rates by Site ID

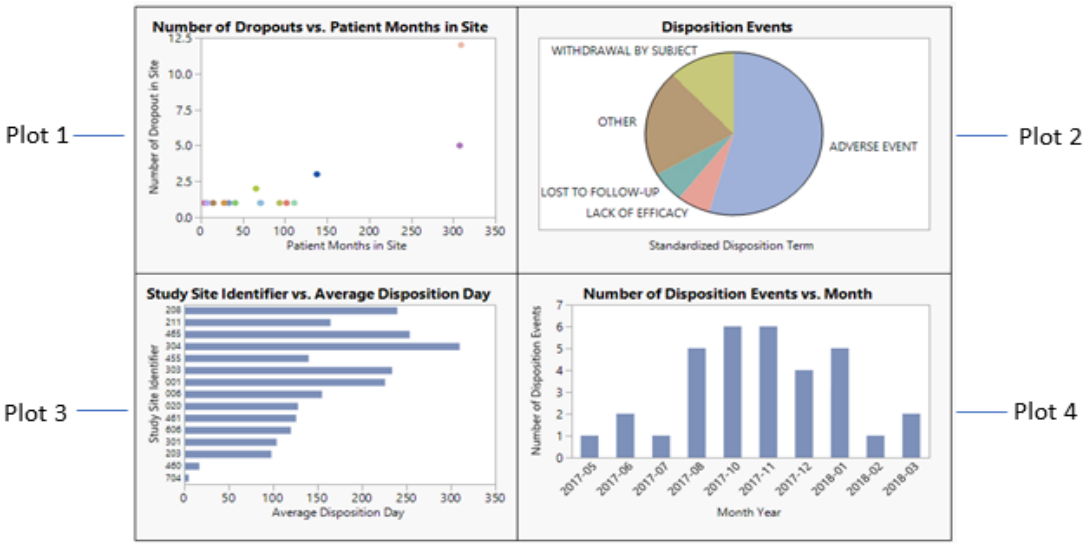


Each KRI is unique and may require customized analysis. The button **More Dropout Rate Analysis** contains custom analysis for dropout rates to provide more insight to the users. Once it is clicked, a window will pop up containing four

graphs created at a study level (Figure 14). The right side of the graphs contains a filter box of site IDs allowing to view data of a specified site and a button **View Subject Data**.

- Plot 1 is a scatter plot of Number of Dropouts and Patient Months in Site.
- Plot 2 is a pie chart displaying proportions of disposition events (standard terms)
- Plot 3 is a bar chart of Average Disposition Day for all sites in the study
- Plot 4 shows a bar chart of monthly dropouts

Figure 14 Exploratory Analysis of Dropout Rates



It should be pointed out that the Plot 1 is different from the other three plots because it is based on aggregated data in the dataset. A single dot in the graph may represent multiple data points because of overlaps. To select a complete set of data points underlying a dot in the graph, you need to use either **Arrow** to make a rectangular selection on a point or **Brush** in the JMP **Tools** menu.

Subset of information about dropouts can be viewed in two ways.

- From the graph, select data points in a scatter plot in Plot 1, or click on the slice of the pie graph to select the disposition event in Plot 2 or click on the bars on the Plot 3 or 4
- From filter box, select sites.

The difference between approach 1 and 2 is that making selections from a plot only highlights parts affected in the other plots and will not redraw graphs. The reason is that the underlying dataset is not subsetted. If you select a site or multiple sites from the filter box, the underlying dataset will be sliced based on the selection and graphs are redrawn on the sliced data automatically.

As four graphs are linked by one underlying dataset, information displayed in those plots triggered by a click on one of them reveal a great deal of information with regard to the sites, average disposition time of sites, disposition reason, and disposition month. For example, if you make a selection on Plot 1 where you can select a site with highest number of dropouts using **Tools > Arrow** or **Tools > Brush,** the dispositions events associated with the site are then highlighted in Plot 2, site ID can be read out in Plot 3, the month when disposition events occurred can be found in Plot 4 (Figure 15).

Likewise, if you want to know which sites have dropouts due to LOST TO FOLLOW-UP, click the LOST to FOLLOW-UP sector in the pie chart (Plot 2). Sites affected by the dispositions can be read out in Plot 3 with regard to patient months for the site (Plot 1), and time when LOST TO FOLLOW-UP occurred can be found in the Plot 4 (Figure 16, see the highlights with a stripped pattern).

Figure 15 Selection of a Data Point in Plot 1

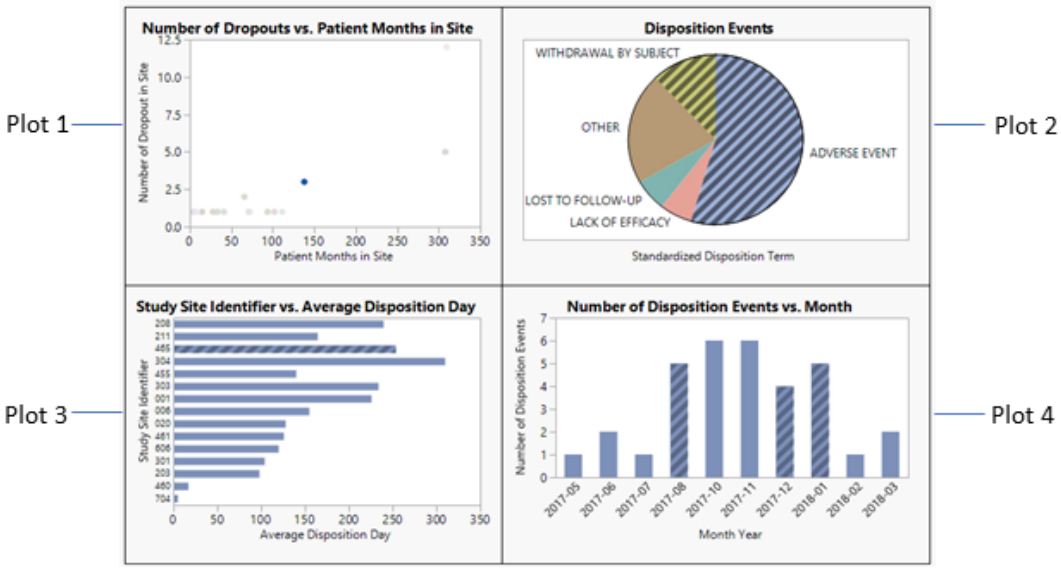
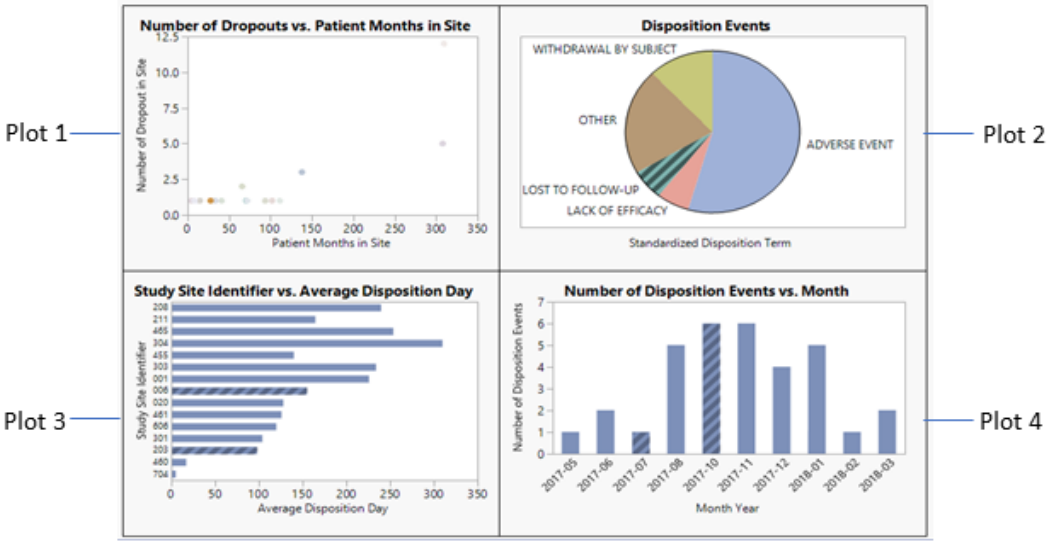


Figure 16 Selection of a Sector of Pie Chart in Plot 2

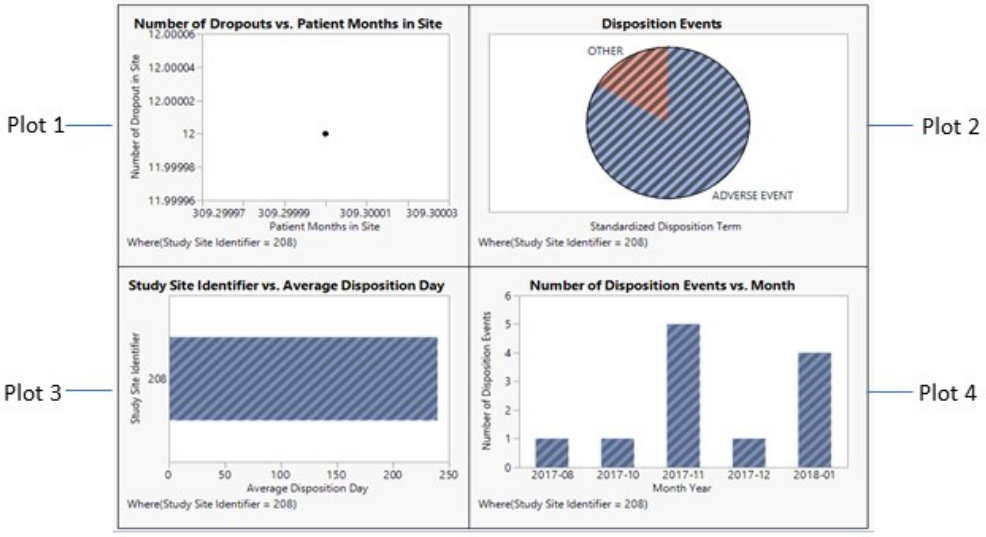


If you click on a bar in Plot 3 to select a site m then you can read out all disposition events associated with this site in Plot 2 and number of events and time of occurrence in Plot 4 (Figure not shown).

VIEW SITE-SPECIFIC GRAPHS

A click on the bar in the graph does not subset the data. To view the site-specific information, select a site or sites through the filter box mounted on the right side (Figure not shown). Information about number of dropouts, patient months, type of disposition events, average disposition day, and month when dropout occurred can be found on the site-specific graphs (Figure 17).

Figure 17 Selection of a Site from Filter Box



SUBJECT LEVEL DATA

Although graphs are very powerful to communicate the findings, tables and listings sometimes are preferred in some situations, for example, to show subject-level data. The end of data drilldown leads to showing of subject level data (Figure 18).

Figure 18 Subject Level Dataset to Show Disposition Events

Subject Data

Study Identifier	Unique Subject Identifier	Subject Identifier for the Study	Study Site Identifier	Investigator Name	Country	Number of Subjects Treated in Site	Category for Disposition Event	Reported Term for the Disposition Event	Standardized Disposition Term	Start Date/Time of Disposition Event	Day of Disposition Event
XYZ0001	XYZ0001-102-0001	00001	102	Dr. ABC	CZE	6	DISPOSITION EVENT	ADVERSE EVENT	ADVERSE EVENT	2018-01-29	316
XYZ0001	XYZ0001-102-0001	00002	102	Dr. ABC	CZE	6	DISPOSITION EVENT	ADVERSE EVENT	ADVERSE EVENT	2018-07-11	225

CONCLUSIONS

RBM is a process in which assessment and management of quality risks are at center stage with centralized monitoring as the foundation. Although risk-based approach has long been advocated for monitoring in the clinical investigations, it was not deemed feasible until a system of advanced technologies such as EDC and high speed internet are available. It is essential to have an analytic and visualization software in place to successfully implement the RBM.

In this paper, we take advantage of a platform provided by JMP® and report development of a user-friendly application interface KRI analyzer. It automates analysis of KRIs by integrating different sources of data from multiple studies, applying analytics to uncover the data patterns, anomalies, and trends in the studies, allowing for visualization of KRIs in a dynamical and interactive way. Specifically, it incorporates a dashboard concept to enable users to start from summary of study status with regard to risk at site level and allow for data exploration and drilldown to the bottom level of data. It is loaded with many functional and easy-to-use buttons and list boxes to ensure that the analysis of complex KRI data be conducted in an efficient and effective way. The value of KRI Analyzer lies in the ability to identify anomalies and data errors allowing improvement in the clinical data quality and optimization of on-site monitoring and reduction in the overall risk.

REFERENCES

Brosteanu O, Schwarz G, Houben P, Paulus U, Strenge-Hesse A, Zettelmeyer U, Schneider A and Hasenclever D, Risk-adapted monitoring is not inferior to extensive on-site monitoring: Results of the ADAMON cluster-randomized study, clinical trials, 1-13

Collins R, Cracknell BS, et al. Sensible approaches for reducing clinical trial costs. Clin. Trials 2008; 5: 75–84.

Eisenstein EL, Lemons II PW, Tardiff BE, et al. Reducing the costs of phase III cardiovascular clinical trials. Am Heart J 2005; 149: 482–88.

European Medicines Agency (EMA). Guideline for good clinical practice E6(R2). 2016. Available from: http://www.ema.europa.eu/docs/en_GB/ document library/Scientific_guideline/2009/09/WC500002874.pdf. Accessed June 2017.

Getz KA. Flying Blind on CRA workload, time demands, Appliced Clincal Trials, 21 (7) 22-24 (2012).

International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2). 2016. Available from: http:// www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/ E6/E6_R2__Step_4.pdf. Accessed on Feb 2017.

Lienard JL, Quinaux E, Fabre-Guillevin E, et al. Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer. Clin Trials 2006; 3: 486–92.

JMP® Scripting Guide, Version 12 Copyright © 2002 by SAS Institute Inc., Cary, NC, USA.

National Research Council. Assuring Data Quality and Validity in Clinical Trials for Regulatory Decision Making: Workshop Report. The National Academies Press, Washington, DC, 1999.

Taylor C, Composite Indicators: Reporting KRIs to Senior Management. *The RMA Journal 16-20* April (2006).

TransCelerate Biopharma Inc. Risk-based Monitoring Methodology Position Paper—RACT Tool. 2014. Available from: http://www.pdfpublications.com/ xls/the-risk-assessment-categorization-ract-tool-1449522.html.

US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). Guidance for industry oversight of clinical investigations – A risk-based approach to monitoring. OMB Control No. 0910-0733. Food and Drug Administration, Silver Spring, MD, August 2013.

ACKNOWLEDGMENTS

We would like to thank UCB Biosciences for consistently encouraging and supporting conference participation. We sincerely would like to thank Volker Schroder for his suggestions and making the participation in this year's conference possible.

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