# Assessing New CFDA Requirements on Data Integrity Using Risk-Based Monitoring and Enrollment Patterns

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To improve the quality of clinical trial data, China Food and Drug Administration (CFDA) has provided seven criteria for the assessment of submitted clinical trial data. These self-inspection and verification criteria can be divided into two groups: drug traits and clinical trial site quality. This presentation demonstrates how risk-based monitoring (RBM) techniques and the enrollment patterns analysis can efficiently assess the new CFDA requirement for safety and quality endpoints. RBM is used to evaluate performance of ongoing trials, offering pharmaceutical companies the potential to intervene and correct problems prior to study completion. RBM analyses can also be used to select appropriate sites for further review and potential audit by regulatory agencies like the CFDA. Further, these analyses provide regulators and sponsors with great insight into how aspects of safety and data quality vary by country and study sites. We provide several practical examples to illustrate the concepts, and describe how data and analysis standards enable an efficient review of safety and quality metrics.

## 1. INTRODUCTION

China Food and Drug Administration (CFDA) announced new self-checking and verification requirements for new and submitted clinical drug data in July 2015[1,2]. This self-inspection and verification includes seven criteria that can be divided into two groups: drug trait and clinical trial site quality. The drug trait group includes drug efficacy and safety. Drug safety focuses on serious adverse events and adverse events. The clinical trial site quality evaluation group includes evaluation of patient participation such as screen failure, discontinuation, and enrollments, and whether the principal investigator is also the study leader. While drug efficacy needs to be assessed according to the specific characteristics of each drug, the other six criteria can be assessed through Risk-Based Monitoring (RBM) methods and enrollment patterns.

TransCelerate proposed RBM methods for clinical trials in 2013[3]. RBM focuses on a centralized approach to monitor important site indicators while coordinating the necessary on-site clinical support to ensure data quality and the safety of study participants. The essential goal for RBM is to detect issues with the clinical sites, improve efficiency and reduce costs. Risk-based monitoring was suggested by the industry to periodically assess study data. For regulatory agencies, such as the CFDA, key indicators are assessed during routine examinations. Not only can RBM analyses be used to select appropriate sites for further review and verification, but they can also provide an overall assessment of safety and quality of by study sites and country.

CDISC (Clinical Data Interchange Standards Consortium) established a collection of standard models for clinical trial data, including data collection, analysis, exchange and submission[4]. CDISC has been become the required or recommended data format for drug submissions for regulatory agencies in many countries[5-10]: CDISC was required by US FDA in Dec. 2016 and recommended by Japan PMDA in Oct. 2016. CDISC was officially introduced into China in 2008 and has since attracted progressively more attention by CFDA and the industry[11]. CDISC was suggested by CFDA in July 2016. The CDISC models: Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) can be used directly in clinical trial data analysis. Using SDTM as an example, CDISC classifies the clinical trial data into different general observation classes according to different functions, such as Intervention, Events, and Findings. Each class can include multiple domains the Events class, for example, includes adverse events (AE), clinical events (CE), Disposition (DS), medical history (MH), and Protocol Deviations (PD) domains. CDISC clearly defines the content and format for each domain.

RBM and Enrollment pattern analyses in JMP Clinical[12,13] utilize the CDISC data contained in different domains such as Demographic (DM), AE, DS, PD, Exposure (EX) and Inclusion / Exclusion Criterion Not Met (IE). Enrollment pattern makes use of data available in the DM and DS domains.

This article describes how the RBM and enrollment pattern tools available in JMP Clinical can be used to meet the CFDA's new assessment requirement. RBM is able to assess data anomalies for patient safety and participation. Enrollment patterns can evaluate the speed of each site's enrollment, the number of patients enrolled, and highlight the performance of the site belonging to the principal investigator.

## 2. MATERIAL and METHODS

### 2.1 Data

Data is from a clinical trial for nicardipine hydrochloride[14,15], a calcium channel blocker that is used to treat hypertension, angina, and congestive heart failure. Since nicardipine also affects blood vessels in the brain, this trial was designed to observe whether patients on nicardipine (up to 15 mg / kg / hr) experienced a delay in cerebral vasospasm compared to placebo. The study included a total of 906 patients, including 447 and 455 patients treated with nicardipine hydrochloride or placebo, respectively. Patients were treated for up to 14 days.

### 2.2 Data Format and Data Analysis Software

Data is in CDISC format. Data analysis and results were generated using JMP Clinical 5.1 (http://www.jmp.com/en_us/software/jmp-clinical.html), a statistical tool developed at SAS Institute Inc. dedicated to the analysis and visualization of data from clinical trials. CDISC domains AE, DM, DS, SV, and EX were used for analysis.

### 2.3 Establish RBM risk indicators

According to TransCelerate recommendations, indicators are be classified as low, middle and high and displayed as green, yellow and red, respectively, to represent risk thresholds [3,12]. Using AE as an example, the risk threshold can be defined as:

- Low Risk (Green): site AE rate ≤ 5% of overall average,
- Moderate Risk (Yellow): site AE rate > 5 and ≤ 15% of overall average,
- Severe Risk (Red): site AE rate > 15% of overall average.

However, risk thresholds should be defined by the researchers themselves according to the characteristics of the drug, study population, and trial design.

## 3. RESULTS

### 3.1 Two aspects of self-inspection and verification

CFDA self-inspection and verification requirement can be divided into two groups (Figure 1): one is for drug traits to ensure drug efficacy and safety; the other is for clinical sites for comparing participation and enrollment to assess whether abnormal patterns occur for any site, especially the site of the principal investigator. Safety evaluation include serious adverse events (SAEs) and adverse events (AEs). Participation assessments include screen failure and discontinuation rates. Enrollment patterns examines the enrollment speed and the number of subjects enrolled at each site.

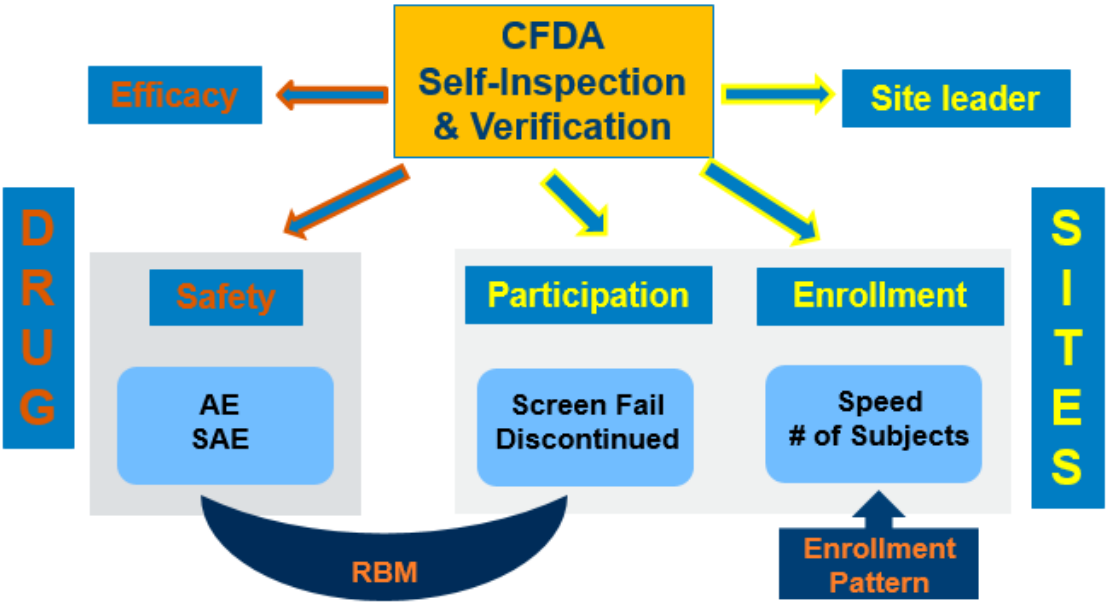


Figure 1. Self-inspection and verification of drugs safety and clinical sites.

3.2. Three components of RBM

RBM consists of three components (Figure 2). The first part is to define thresholds for risk indicators. Risk indicators can include information on safety, data quality, screening, enrollment, researchers, the site facilities, or whether necessary supplies and documents are maintained at the site. Each risk indicator divided risk into three levels with color to represent: low (green), medium (yellow), high (red) risk - aptly called traffic light system. The second component is the information for the study that can be extracted directly from the corresponding CDISC domains by the software. The third component shows the results. RBM displays results in a table with using the traffic-light colors or in a map (Figure 4-10). RBM can use risk thresholds and indicators suggested by TransCelerate, or researchers can customize or utilize additional risk indicators according to the specific circumstances of the clinical trial.

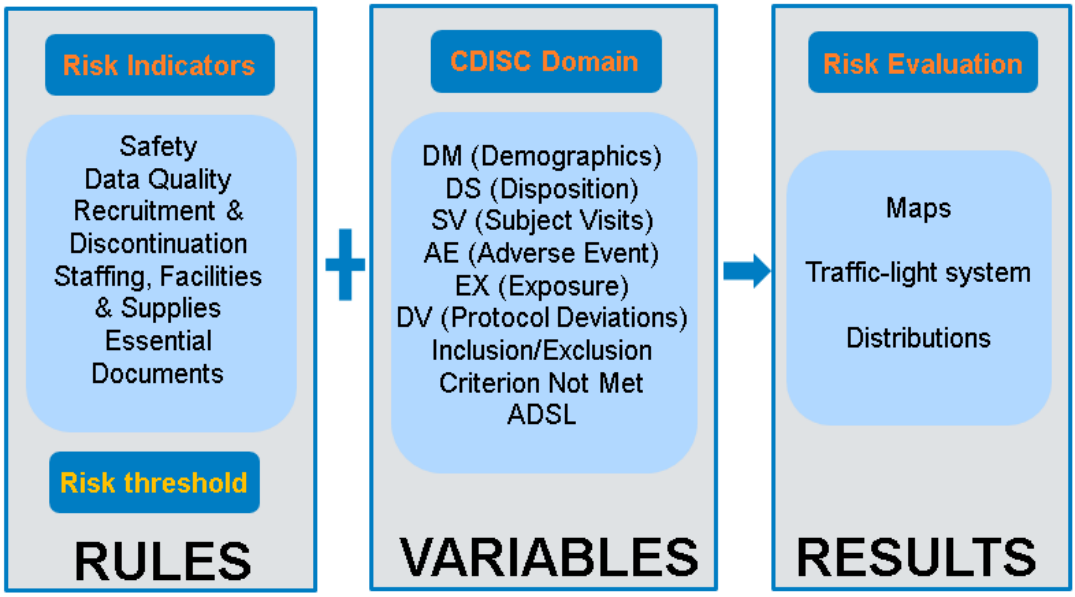


Figure 2. Three components of RBM: Risk indicators, CDISC domains and risk evaluation.

3.3. Four Types of RBM Result

Four types of RBM results are available: a series of risk indicators; risk assessment for each center; risk assessment for each country and the actions to be taken after assessment of proposals.

3.3.1. A Series of Risk Indicators

RBM results show a series of risk indicators (Figure 3) such as the AEs, SAEs, discontinuations and screen failures suggested by CFDA. In addition to the individual risk indicators, two or more risk indicators can be combined to generate overall risk indicators such as the overall adverse event risk indicators which combines information on AE, SAEs, and deaths.


Figure 3. A series of RBM risk indicators.

3.3.2. Evaluation Risk for Sites：

The site risk evaluated by RBM is presented in a tabular form with data highlighted according to the traffic light system. In the left panel of Figure 4, the overall risk index was selected which colors each row according to the risk observed for this indicator. When a different indicator is chosen in the left panel, the row marker changes accordingly.

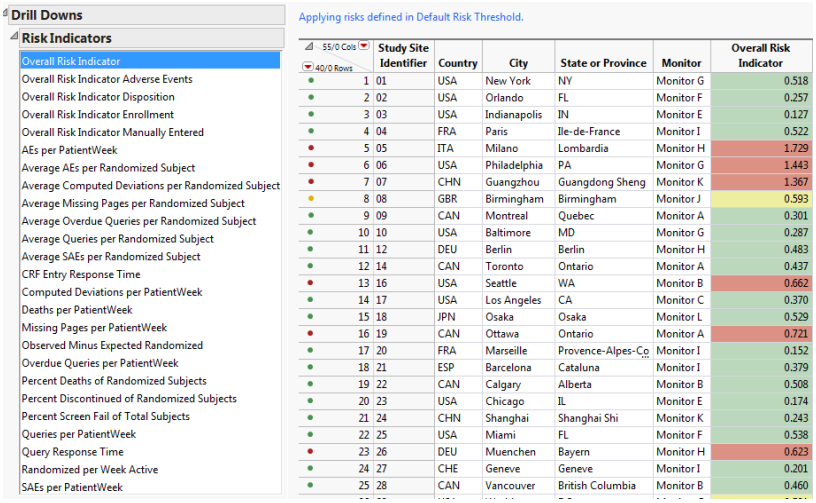


Figure 4. The RBM results for the site risk evaluated by traffic light system.

The site risk can also be displayed using a map so that risk can be interpreted geographically. In the left panel of Figure 5, the average SAEs per Randomized Subject was selected, which displays the degree of risk for the serious adverse event for each center in the map. As it can be seen from the figure, most centers worldwide are at high risk. Figure 6 displays the percentage of patients who were considered screen failures; most centers were of low risk.

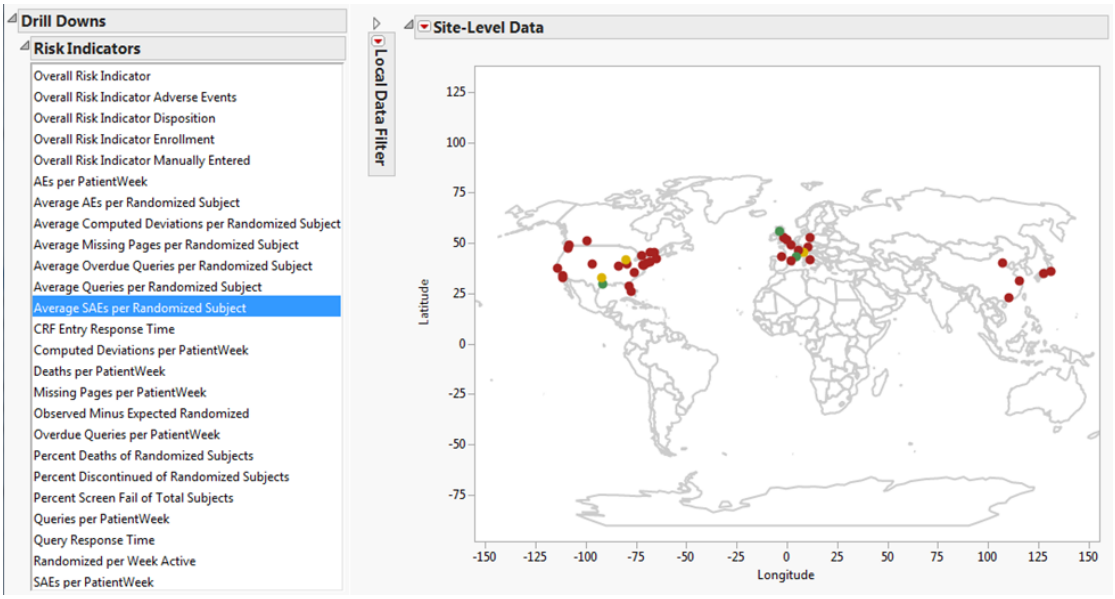


Figure 5. Risk indicators of serious adverse event to each site display on the map.

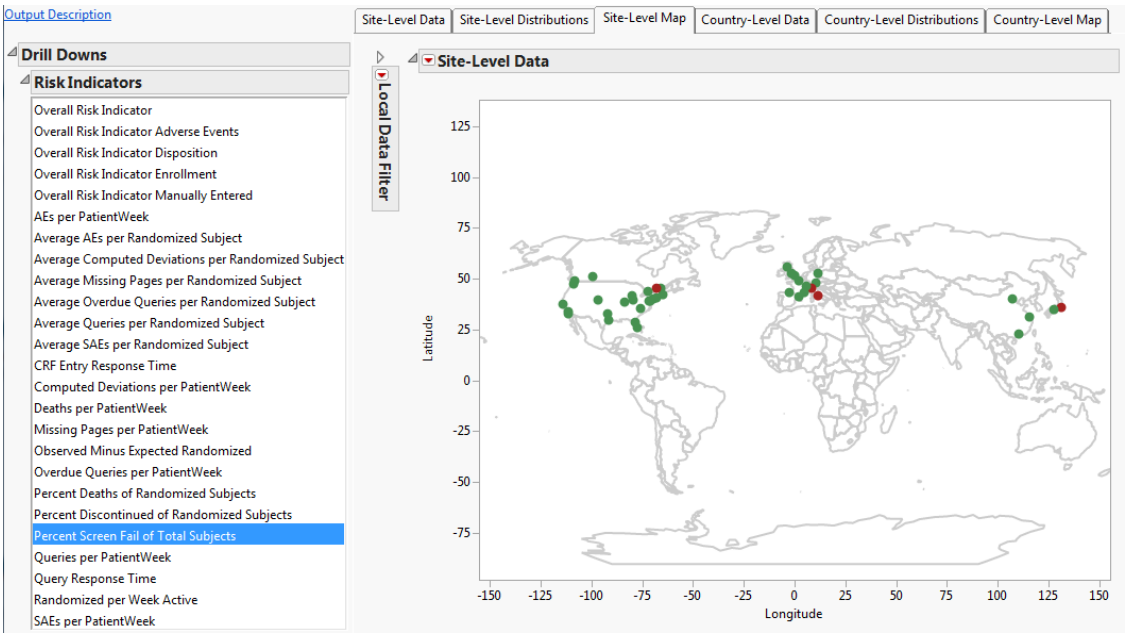


Figure 6. Risk indicators of each site display on the map

3.3.3. Evaluation Risk for Countries:

Country-level risk is also evaluated by RBM and presented in a tabular form with data highlighted according to the traffic light system. In the left panel of Figure 7, the overall risk indicator adverse event was selected (4th column of table) which colors each row according to the risk observed for this indicator.

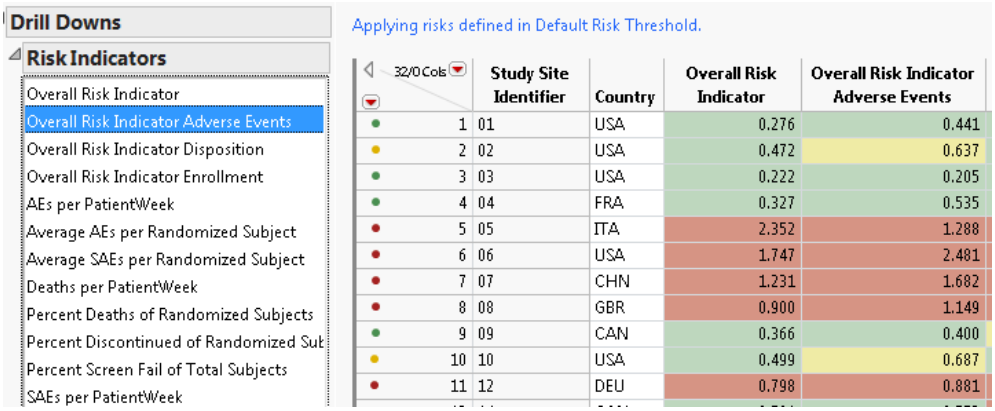


Figure 7. The RBM results for the country level risk evaluated by traffic light system.

Country-level risk can also be displayed geographically using maps. In the left panel of Figure 8, the AEs per PatientWeek was selected which highlights Canada as high risk, China at medium risk, and the United States at low risk for this study in the map in the right panel. Figure 9 displays the percentage of randomized patients who discontinued the study; most countries are at the low or moderate risk, with only a few European countries and Japan at high risk.

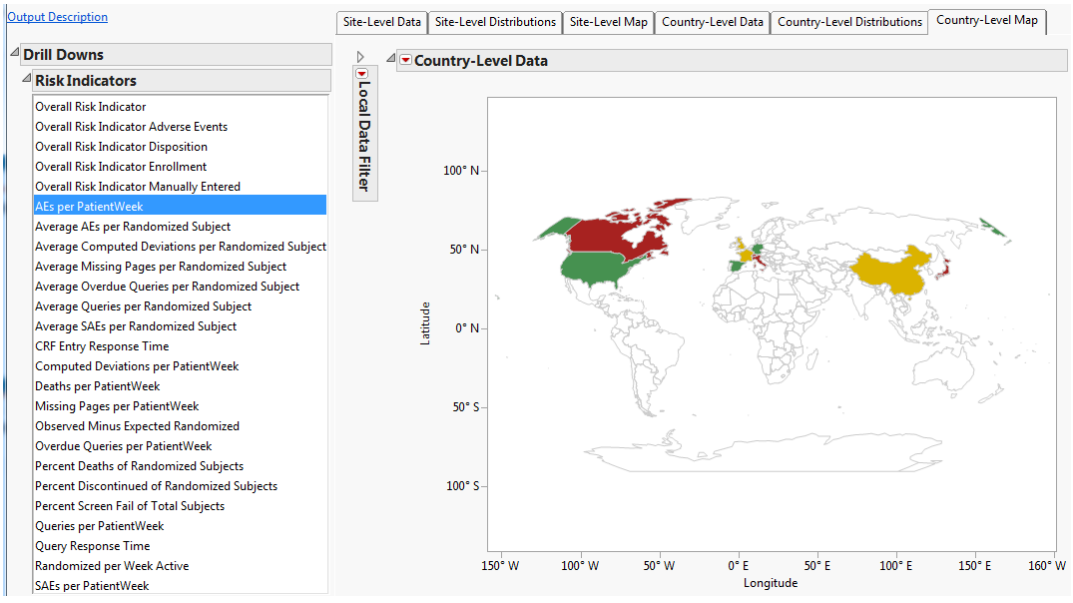


Figure 8. Risk indicators of AEs per PatientWeek at country level display on the map.

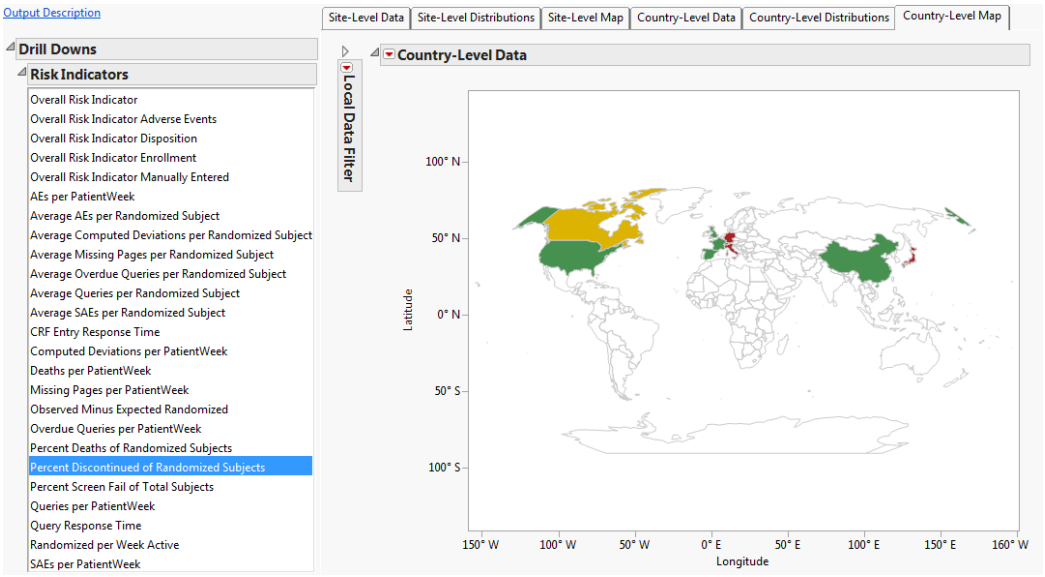


Figure 9. Risk indicators of discontinued at country level display on the map.

3.3.4. Action Suggestion：

Based on the comprehensive assessment of risk, RBM provides suggested actions for the study sites. Figure 10 highlights the sites with high risk for one or more indicators that require additional attention. Suggested actions include.: scheduling an onsite monitor visit; contacting the principal investigator for overdue queries; assessing site resources, contacting the site coordinator; assessing the need for additional staff training, contacting site coordinator; Assess data remotely, schedule onsite monitor visit; assess data remotely, contact site principal investigator; assess data remotely, contact site coordinator (Figure 10). Highlighting "Schedule onsite monitor visit" under the Recommended Action on the far right in Figure 10 shows the reason for the onsite visit was due to the manually entered items (second histogram). The sites that need to visit are highlight under Study Site Identifier on the left in the first histogram.

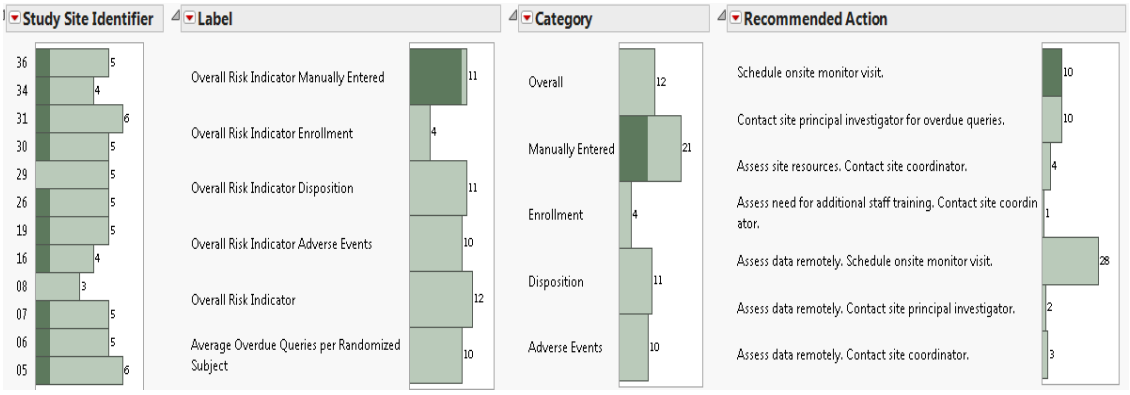


Figure 10. RBM's action suggestion.

Two forms of visualizing the data (tables and maps) are used to present the analysis of risk at the site and country level. Maps make it easier to identify different levels of risk for the sites and countries.

## 3.4. Five Displays for Enrollment Patterns

### 3.4.1. Cumulative number of subjects are calculated from the start date of the disposal of the event / time

Figure 11 shows the enrollment in the number of individual subjects in each site throughout the whole trial period. The black curve is the average across all sites. There are three sites, #16, #20 and #28, where the enrollment proceeded at a much faster rate than others. The speed at which these sites enrolled subjects could be due to many factors, such as poor adherence to study entry criteria, should be investigated further. Similarly, sites with much slower enrollment speed may also need investigated. The site of the principal investigator can also be examined for abnormality.

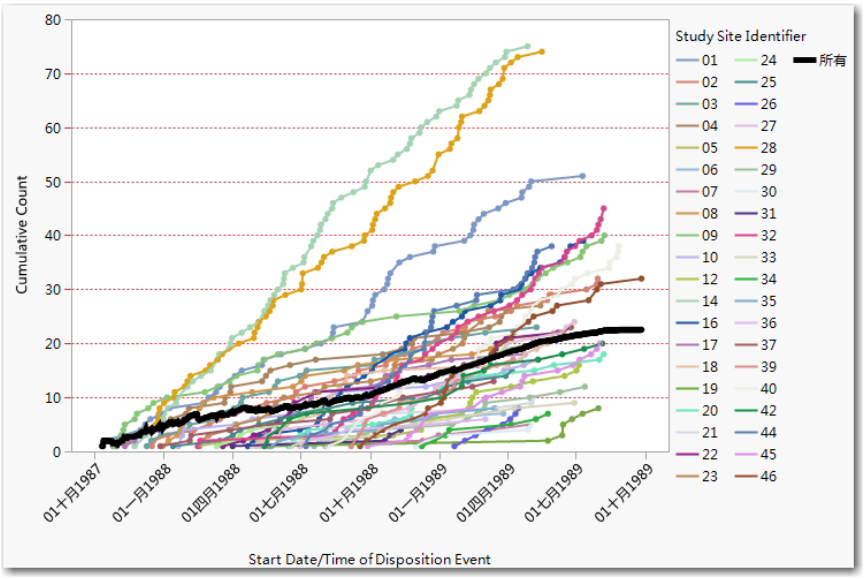


Figure 11. Cumulative count of subjects calculated by the start disposal date of the event / time.

### 3.4.2 Cumulative count of the subjects are calculated by the number of days

Subject's cumulative count numbers can also be presented by within-center study day, where dates are compared to when the site first began enrolling patients (Figure. 12). The same three groups, #16, #20 and #28, the enrollment speed are much faster than others.

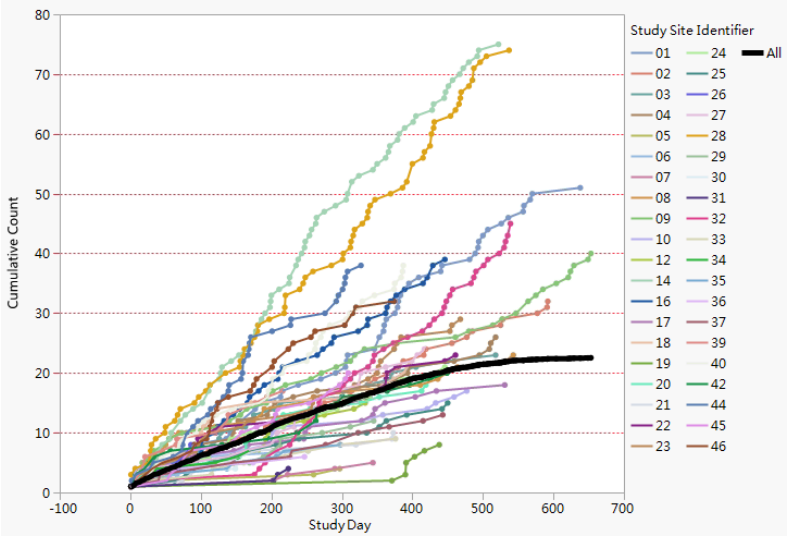


Figure 12. Cumulative count of the subjects calculated by study day within-site.

### 3.4.3. The number of daily enrollment of each center

The daily number of subjects enrolled into study of each group is shown in Figure 13. Each box of the grid represents a site. This graph clearly displays daily enrollment numbers at each center, which may help identify unusual enrollments or sites.

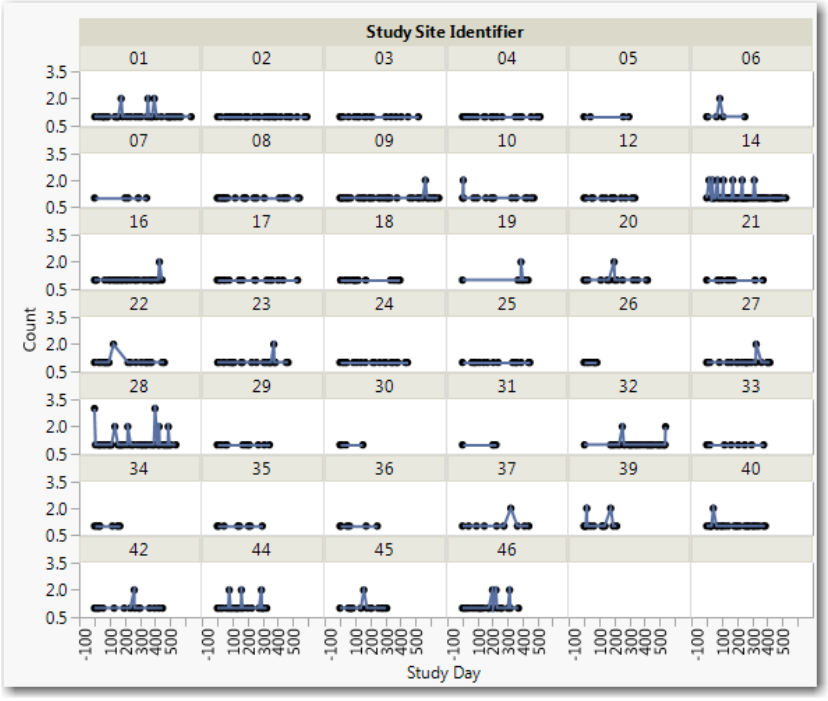


Figure 13. The number of daily enrollment of each site.

3.4.4. Comparison of enrollment velocity for treatment and control group per each site.

The cumulative count of subjects enrolled for the treatment (Blue) and control (Red) groups per each site is compared as shown in Figure 14. This site has almost the same enrollment velocity for the treatment and control groups which would be expected under 1:1 randomization.

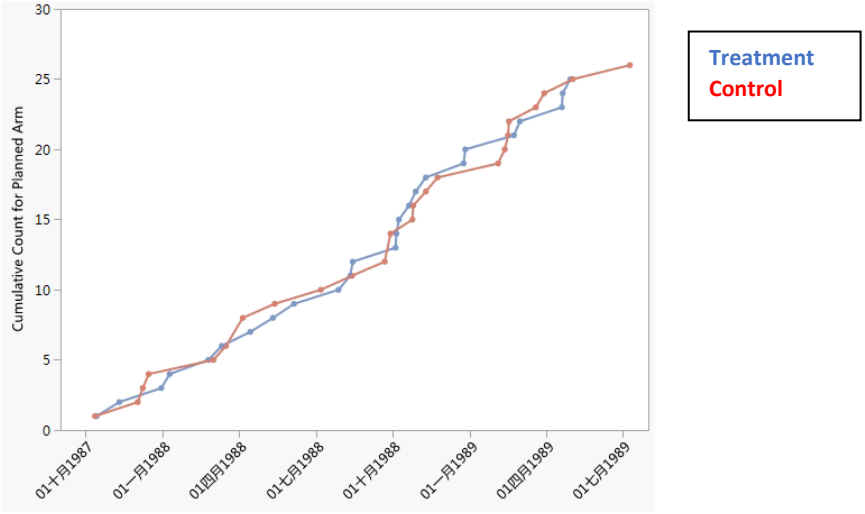


Figure 14. Comparison the enrollment velocity for treatment and control group per each site.

3.4.5 Randomization of Subject Enrollment:

Randomization of subject enrollment was evaluated in Figure 15. Figure 15 shows how many subjects were enrolled into same treatment group at adjacent times on the right site plot. For example, there were 44 instances where the same treatment was dispensed in a row (dark green) from nine centers (Left) with the treatment group (NIC.15) slightly more than the control group (Middle). Given a 1:1 randomization with a block size of 4, it would be impossible to see treatment runs greater than 4.

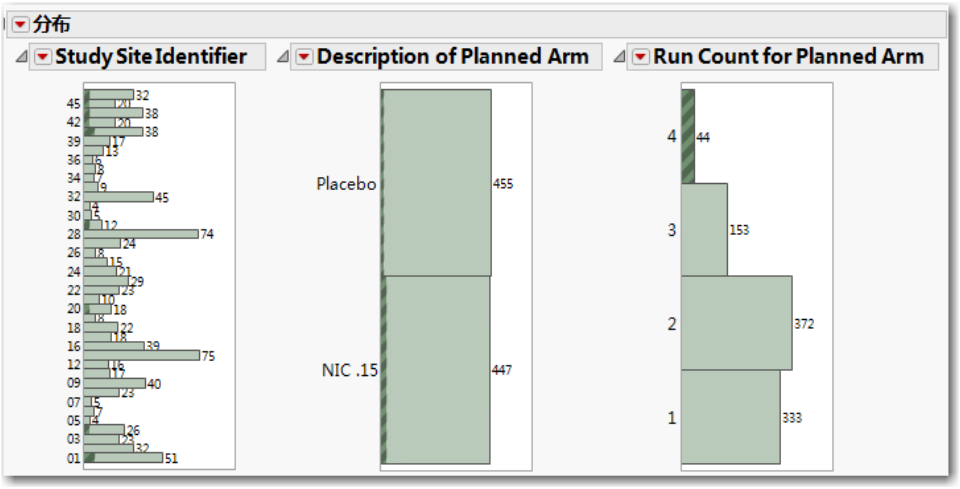


Figure 15. Randomization of Subject Enrollment.

## 4. DISCUSSION AND SUMMARY

Statistical analysis is an efficient and reliable way to evaluate the quality of clinical trial data and the safety and the efficacy of the drug. This article describes how to use RBM and enrollment patterns to complete the CFDA clinical data self-inspection and verification requirements efficiently. In addition to RBM, there are numerous methods for fraud detection to identify intentionally or unintentionally erroneous data. With proper assessment of data quality, the results of an analysis for drug safety and efficacy become more reliable and credible.

## 5. REFERENCES


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