

ASSESSING NEW CFDA REQUIREMENTS ON DATA INTEGRITY USING RISK-BASED MONITORING AND ENROLLMENT PATTERNS

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PHUSE
OCT. 2017



OUTLINES

- **CFDA Announcements:**
 - **Assess and Ensure Quality**
- **Efficient Approaches**
 - **RBM**
 - **Enrollment Pattern**
- **Conclusions**

CFDA ANNOUNCEMENTS: ENSURE QUALITY



July 22, 2015



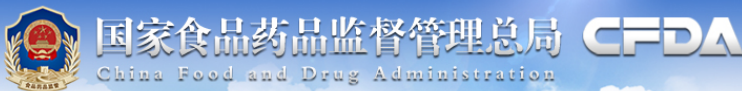
Dec. 17, 2015



April 1, 2016



June 3, 2016



May 19, 2017



Sept. 13, 2017

总局关于药物临床试验数据自查核查注册申请情况的公告（2017年第109号）

DATA SELF-EXAM AND AUDIT



食品药品审核查验中心

药物临床试验数据核查工作要求

4. 药物临床机构抽查原则。多中心临床试验抽查2-3个临床试验机构，必要时，可扩大核查范围，适当增加抽查机构数。临床试验场点抽查风险考虑因素包括：

- (1) 有效性结果明显高于其他中心或者同类临床试验结果的临床试验中心； **Efficacy**
- (2) 安全性数据（不良事件、预期的严重不良事件）明显低于/高于其它中心或者同类临床试验结果的临床试验中心； **Safety: AE and SAE**

DATA SELF-EXAM AND AUDIT



食品药品审核查验中心

药物临床试验数据核查工作要求

(3) 试验入组速度明显快于其他中心的临床试验中心; Enrollment Speed

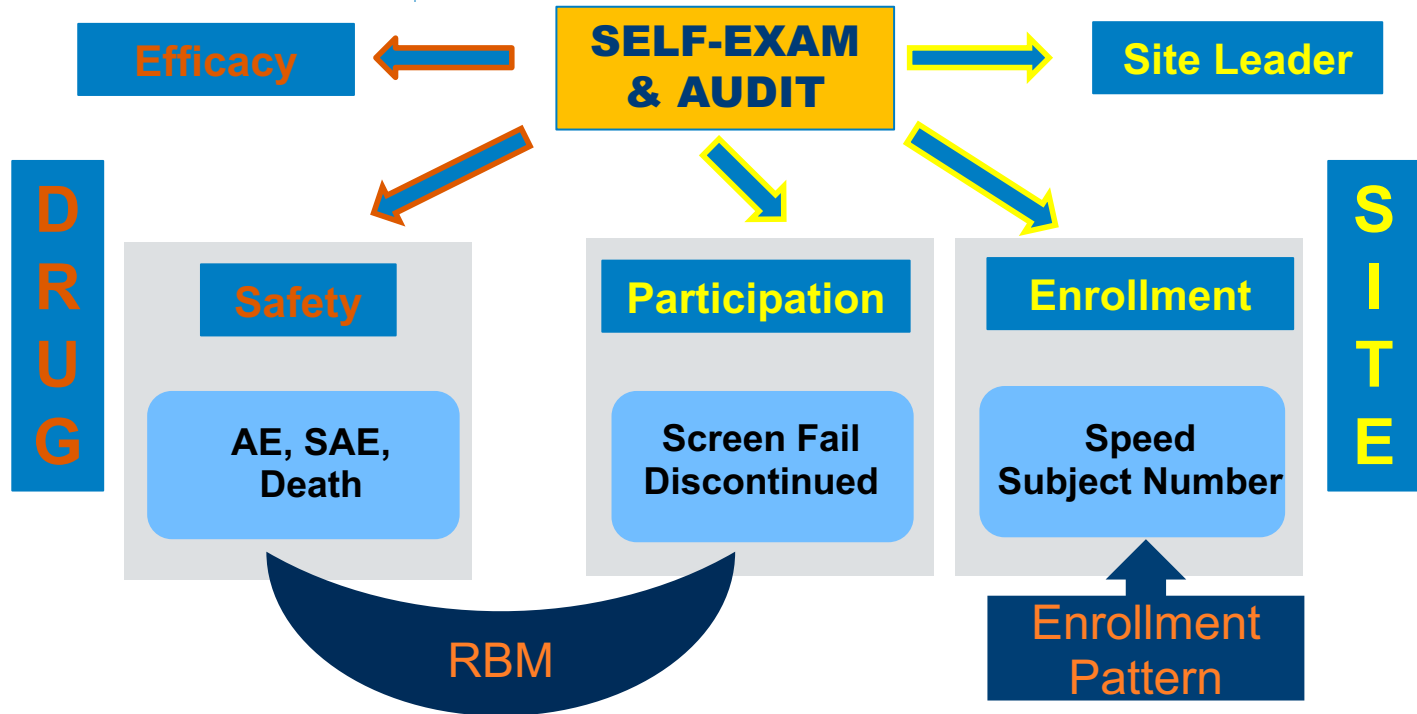
(4) 试验筛选成功率明显高于常规的临床试验中心; Screen Success Rate

(5) 试验脱落率明显高于常规的临床试验中心; Discontinued Rate

(6) 试验入组人数最多的临床试验中心; # Enrollment

(7) 担任组长单位的临床试验中心。Leader's Site

DATA SELF-EXAM AND AUDIT





RISK-BASED MONITORING

RBM



Members of Transcelerate BioPharma Inc.

abbvie



AMGEN



Johnson & Johnson



MERCK & CO., INC.
Kenilworth, N.J., U.S.A.



Oct. 2017: <http://www.transceleratebiopharmainc.com/about/meet-the-members/>

RISK-BASED MONITORING (RBM)



Position Paper: Risk-Based Monitoring Methodology

1. Abstract

Current On-site Monitoring practices are frequency-based, conform to a prescribed monitoring visit schedule, and provide generalized quality control at investigational sites. Although this practice does provide a level of control, advances in risk-based approaches and technology provide an opportunity for a more holistic and proactive approach through Off-site and Central Monitoring and a targeted approach to On-site Monitoring. RBM employs **Centralized and Off-site** mechanisms to monitor important study parameters **holistically** and uses adaptive On-site Monitoring to further support site processes, subject safety, and data quality.

TRADITIONAL VS RISK-BASED MONITORING

TM

- Expensive^[1-3]
25~ 30% Trial Cost
- Local data
- Human Capacity^[3]

RBM

- ❖ Efficiency and accuracy
- ❖ data trends across time, patients, and clinical sites ^[4, 5]
- ❖ 95% identified from database ^[6]

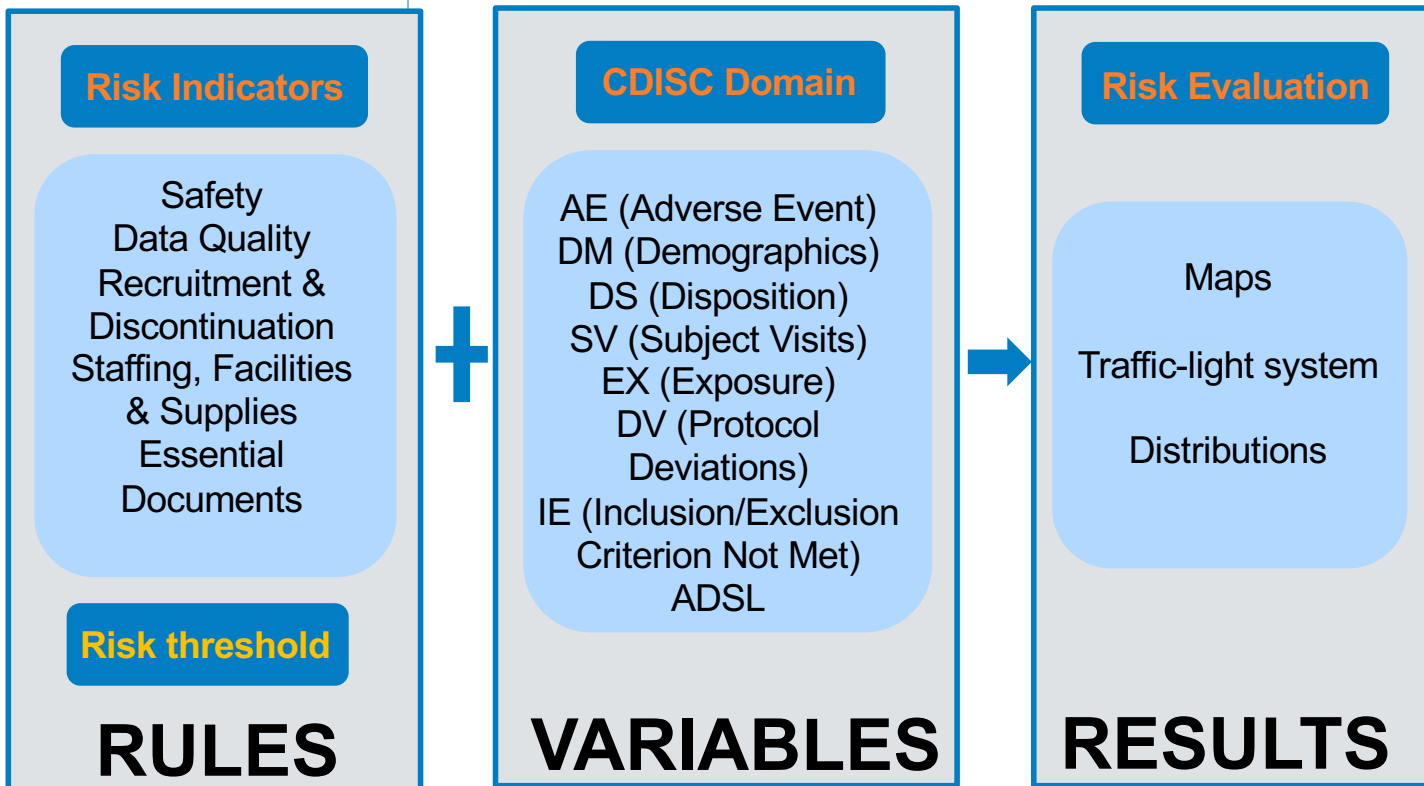
Quality ↑

Risk ↓

1. Eisenstein EL et al (2005). *American Heart Journal* 149: 482–488.
2. Funning S et al (2009). *The Quality Assurance Journal* 12: 3-7.
3. Tantsyura V et al (2010). *Drug Information Journal* 44: 745-756.

4. TransCelerate BioPharma Inc. (2013). <http://transceleratebiopharmainc.com/>
5. Zink RC. (2014). ISBN-13: 978-1612909912,, Cary, NC: SAS Institute.
6. Bakobaki JM et al. (2012). *Clinical Trials* 9: 257-264.

RISK-BASED MONITORING (RBM)



RISK-BASED MONITORING (RBM)

I. RISK THRESHOLD SETUP

Risk Indicators

Safety
Data Quality
Recruitment &
Discontinuation
Staffing, Facilities
& Supplies
Essential
Documents

Risk threshold

RULES

Risk Threshold Data Set - JMP

Default Risk Threshold

Variable	Label	Category	Yellow Percent of Center	Yellow Magnitude	Red Percent of Center
1 TOTAL	Total Subjects	Enrollment	*	*	*
2 RAND	Randomized	Enrollment	*	*	*
3 SCRNFALL	Screen Failure	Enrollment	*	*	*
4 PCTSCRNFALL	Percent Screen Fail of Total Subjects	Enrollment	5	0	15
5 TREATED	Treated	Enrollment	*	*	*
6 PATWEEKS	PatientWeeks on Study	Enrollment	*	*	*
7 MISSCONSENT	Missing Informed Consent	Enrollment	*	*	*
8 WEEKSACTIVE	Weeks Active	Enrollment	*	*	*
9 SITERATE	Randomized per Week Active	Enrollment	5	0	15
10 EXPRAND	Expected Randomized	Enrollment	*	*	*
11 DIFFRAND	Observed Minus Expected Randomized	Enrollment	*	5	*
12 TARGETRAND	Target Randomized	Enrollment	*	*	*
13 TARGETDIFFRAND	Observed Minus Target Randomized	Enrollment	*	5	*
14 COMPLETE	Completed	Disposition	*	*	*
15 PCTCOMP	Percent Completed of Randomized Subje...	Disposition	*	*	*
16 ONGOING	Ongoing	Disposition	*	*	*
17 PCTONGOING	Percent Ongoing of Randomized Subjects	Disposition	*	*	*
18 DISCON	Discontinued	Disposition	*	*	*
19 PCTDISCON	Percent Discontinued of Randomized Sub...	Disposition	15	3	30
20 DISCDEATH	Discontinued due to Death	Disposition	*	*	*
21 DCAE	Discontinued due to AE	Disposition	*	*	*
22 LTFU	Lost to Followup	Disposition	*	*	*
23 WITHDREW	Patient Withdrew from Study	Disposition	*	*	*
24 DCOth	Discontinued Other	Disposition	*	*	*
25 TOTIE	Total Inclusion or Exclusion Not Met	Disposition	*	*	*
26 AVGIE	Average Inclusion or Exclusion Not Met p...	Disposition	5	0	15
27 TOTDV	Total Protocol Deviations	Disposition	*	*	*
28 AVGDV	Average Deviations per Randomized Subj...	Disposition	5	0	15
29 DEATH	Death	Safety	*	*	*
30 PCTDEATH	Percent Deaths of Randomized Subjects	Safety	5	0	10
31 PWDEATH	Deaths per Patient/Week	Safety	5	0	10
32 TOTAE	Total AEs on Study	Safety	*	*	*
33 AVGAE	Average AEs per Randomized Subject	Safety	5	0	15

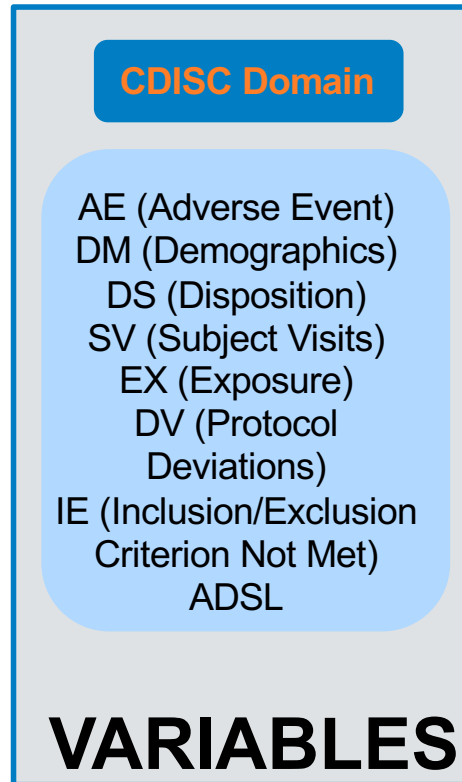
*NOTE: The table structure should not be altered. Do not add/remove rows or columns and do not change the data type of any column.

¹Position Paper: Risk-Based Monitoring Methodology. TransCelerate Biopharma Inc, 2013

²Risk-Based Monitoring and fraud detection in clinical trials using JMP and SAS. Richard Zink 2014

RISK-BASED MONITORING (RBM)

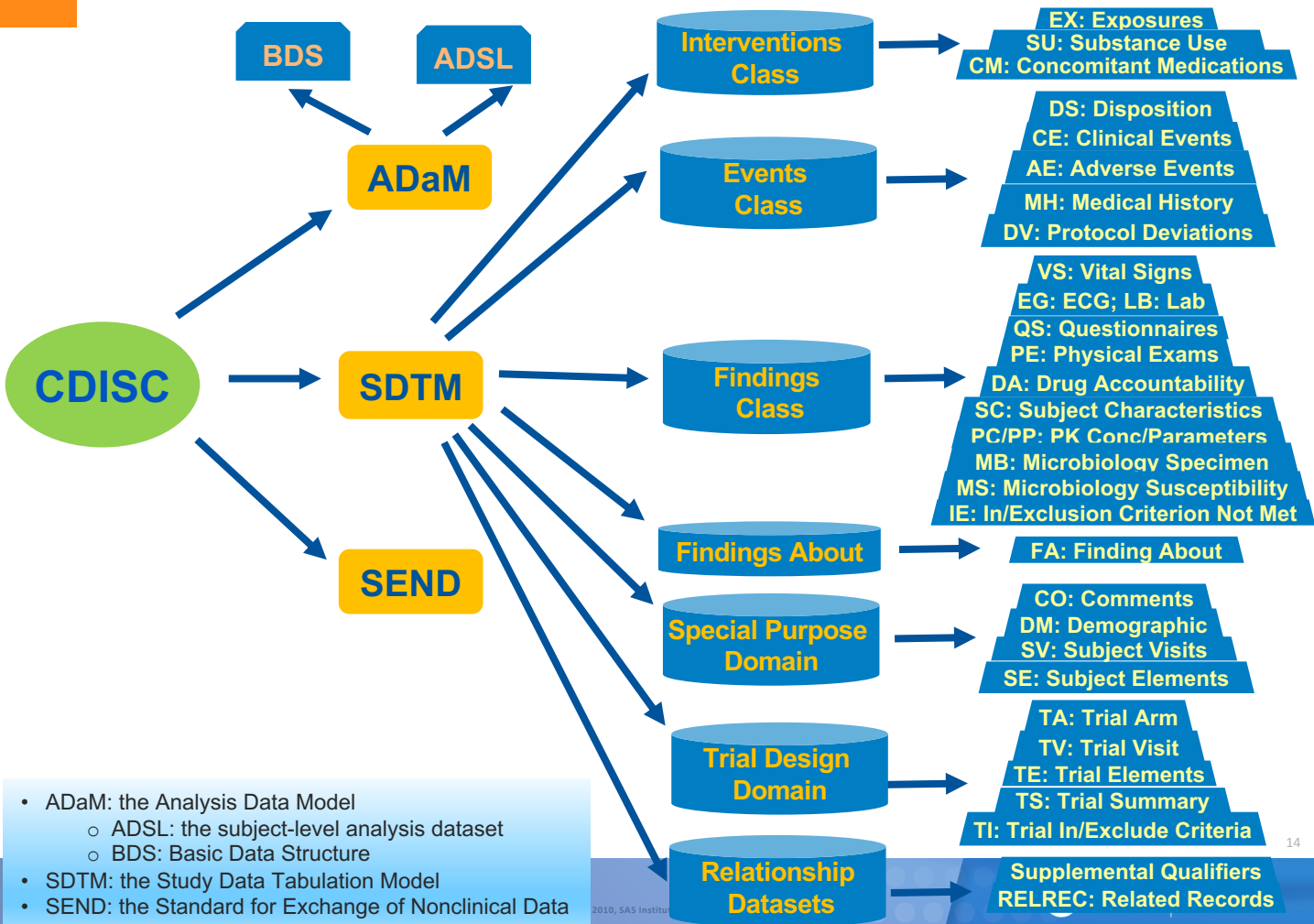
II. CDISC DOMAIN FOR INFO



¹Position Paper: Risk-Based Monitoring Methodology. TransCelerate Biopharma Inc, 2013

²Risk-Based Monitoring and fraud detection in clinical trials using JMP and SAS. Richard Zink 2014

CDISC: Clinical Data Interchange Standards Consortium



RISK-BASED MONITORING (RBM)

III. RESULTS DISPLAY

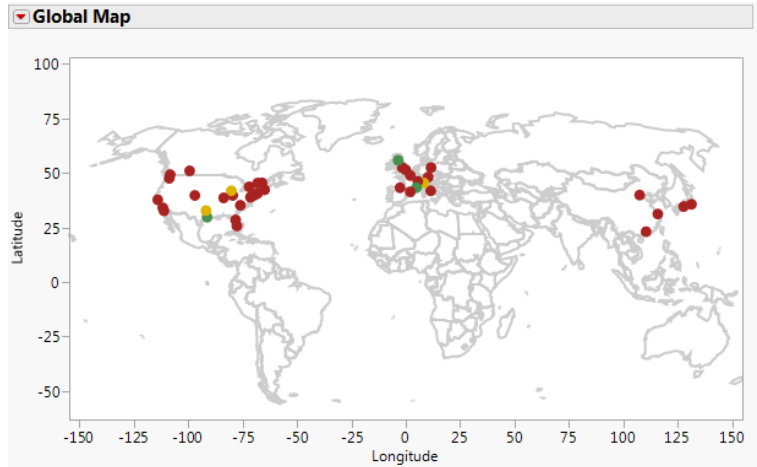
Risk Evaluation

Maps

Traffic-light system

Distributions

RESULTS



Site-Level Data

Site-Level Distributions

Site-Level Map

Country-Level Data

Country-Level Distributions

Country-Level Map

Applying risks defined in Default Risk Threshold.

10/0 Rows

Country

Overall Risk Indicator

Overall Risk Indicator Adverse

Overall Risk Indicator...

Overall Risk Indicator...

Overall Risk Indicator Manually

Total Sites

Total Subjects

Randomized

Screen Failure

1

CAN

0.283

0.388

0.267

0.897

0.029

5

221

221

1

2

CHE

0.202

0.482

0.023

0.185

0.098

1

24

24

0

3

CHN

0.307

0.415

0.181

0.000

0.376

3

33

33

0

4

DEU

0.360

0.213

0.724

0.000

0.493

2

24

24

0

5

ESP

0.171

0.193

0.032

0.000

0.240

2

23

23

0

6

FRA

0.317

0.430

0.045

0.000

0.412

2

44

44

0

7

GBR

0.315

0.112

0.060

0.322

0.457

3

81

81

0

8

ITA

1.766

2.028

2.915

1.595

1.501

2

10

10

2

9

JPN

0.628

1.421

0.711

0.443

0.280

2

43

43

1

10

USA

0.073

0.100

0.023

0.068

0.069

18

403

403

0

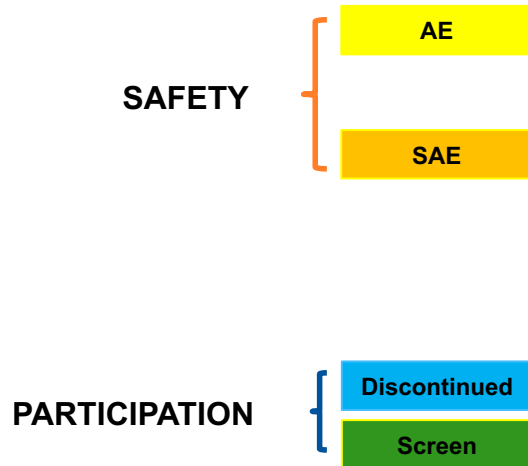


¹Position Paper: Risk-Based Monitoring Methodology. TransCelerate Biopharma Inc, 2013

²Risk-Based Monitoring and fraud detection in clinical trials using JMP and SAS. Richard Zink 2014

ER
NOW.

RISK BASED MONITORING (RBM)



Risk Indicators	
Overall Risk Indicator	
Overall Risk Indicator Adverse Events	
Overall Risk Indicator Disposition	
Overall Risk Indicator Enrollment	
Overall Risk Indicator Manually Entered	
AEs per PatientWeek	
Average AEs per Randomized Subject	
Average Computed Deviations per Randomized Subject	
Average Missing Pages per Randomized Subject	
Average Overdue Queries per Randomized Subject	
Average Queries per Randomized Subject	
Average SAEs per Randomized Subject	
CRF Entry Response Time	
Computed Deviations per PatientWeek	
Deaths per PatientWeek	
Missing Pages per PatientWeek	
Observed Minus Expected Randomized	
Overdue Queries per PatientWeek	
Percent Deaths of Randomized Subjects	
Percent Discontinued of Randomized Subjects	
Percent Screen Fail of Total Subjects	
Queries per PatientWeek	
Query Response Time	
Randomized per Week Active	
SAEs per PatientWeek	

Self-check and Audit for the sites related to RBM:

- Sites with more AE and/or SAE
- Sites with more discontinued subjects
- Sites with more screen fail

RBM: AE AT COUNTRY LEVEL

[Output Description](#)

Site-Level Data

Site-Level Distributions

Site-Level Map

Country-Level Data

Country-Level Distributions

Country-Level Map

Drill Downs

Risk Indicators

Overall Risk Indicator
Overall Risk Indicator Adverse Events
Overall Risk Indicator Disposition
Overall Risk Indicator Enrollment
Overall Risk Indicator Manually Entered

AEs per Patient/Week

Average AEs per Randomized Subject
Average Computed Deviations per Randomized Subject
Average Missing Pages per Randomized Subject
Average Overdue Queries per Randomized Subject
Average Queries per Randomized Subject
Average SAEs per Randomized Subject
CRF Entry Response Time
Computed Deviations per Patient/Week
Deaths per Patient/Week
Missing Pages per Patient/Week
Observed Minus Expected Randomized
Overdue Queries per Patient/Week
Percent Deaths of Randomized Subjects
Percent Discontinued of Randomized Subjects
Percent Screen Fail of Total Subjects
Queries per Patient/Week
Query Response Time
Randomized per Week
SAEs per Patient/Week

[Output Description](#)

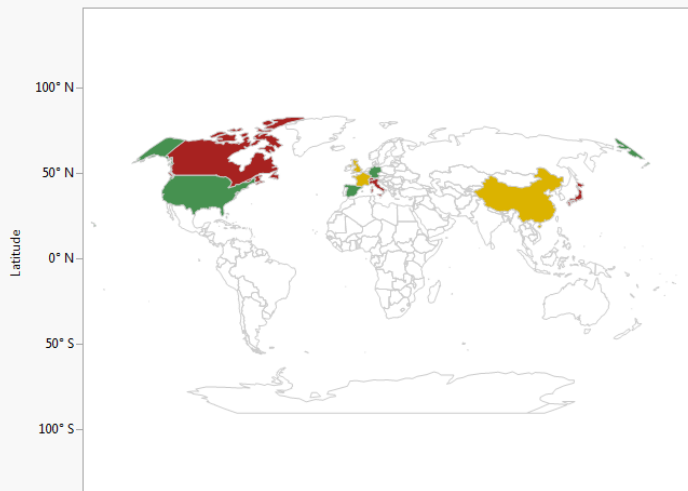
Drill Downs

Risk Indicators

Overall Risk Indicator
Overall Risk Indicator Adverse Events
Overall Risk Indicator Disposition
Overall Risk Indicator Enrollment
Overall Risk Indicator Manually Entered
AEs per Patient/Week
Average AEs per Randomized Subject
Average Computed Deviations per Randomized Subject
Average Missing Pages per Randomized Subject
Average Overdue Queries per Randomized Subject
Average Queries per Randomized Subject
Average SAEs per Randomized Subject

Country-Level Data

Local Data Filter



Site-Level Data

Site-Level Distributions

Site-Level Map

Country-Level Data

Country-Level Distributions

Country-Level Map

Applying risks defined in Default Risk Threshold.

Country	Overall Risk Indicator	Overall Risk Indicator Adverse	Overall Risk Indicator...	Overall Risk Indicator...	Overall Risk Indicator Manually	Total Sites	Total Subjects	Randomized	Screen Failure
1 CAN	0.283	0.388	0.267	0.897	0.029	5	221	221	1
2 CHE	0.202	0.482	0.023	0.185	0.098	1	24	24	0
3 CHN	0.307	0.415	0.181	0.000	0.376	3	33	33	0
4 DEU	0.360	0.213	0.724	0.000	0.493	2	24	24	0
5 ESP	0.171	0.193	0.032	0.000	0.240	2	23	23	0
6 FRA	0.317	0.430	0.045	0.000	0.412	2	44	44	0
7 GBR	0.315	0.112	0.060	0.322	0.457	3	81	81	0
8 ITA	1.766	2.028	2.915	1.595	1.501	2	10	10	2
9 JPN	0.628	1.421	0.711	0.443	0.280	2	43	43	1
10 USA	0.073	0.100	0.023	0.068	0.069	18	403	403	0

RBM: SAE AT SITE LEVEL

Perform Additional Analyses

☐ Monitor ?

☐ Vendor ?

Analyze Selected Sites

Clear

Select Sites ?

Analyze Selected Site Categories

Clear

Select Site Categories

Country-Level Maps

Where(Uppercase(:Country)) == "USA"

▷ **Site-Level Risk Indicators in the United States**

Where(Uppercase(:Country)) == "CAN"

▷ **Site-Level Risk Indicators in Canada**

Where(Uppercase(:Country)) == "FRA"

▷ **Site-Level Risk Indicators in France**

Where(Uppercase(:Country)) == "DEU"

▷ **Site-Level Risk Indicators in Germany**

Where(Uppercase(:Country)) == "GBR"

▷ **Site-Level Risk Indicators in Great Britain**

Where(Uppercase(:Country)) == "ITA"

▷ **Site-Level Risk Indicators in Italy**

Where(Uppercase(:Country)) == "ESP"

▷ **Site-Level Risk Indicators in Spain**

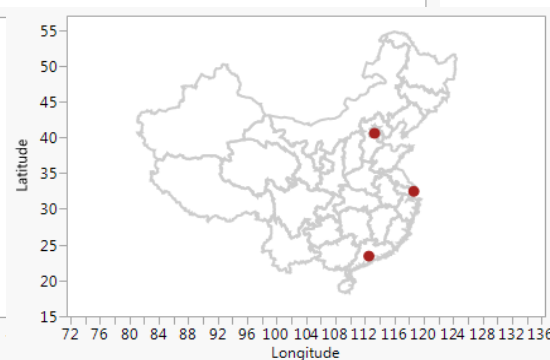
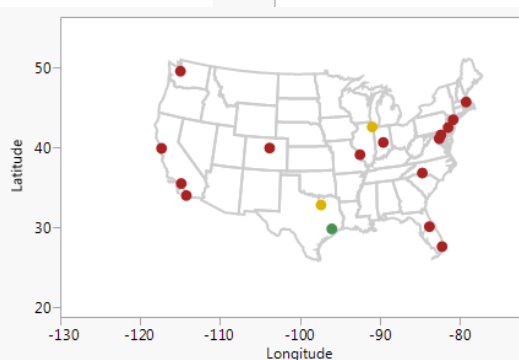
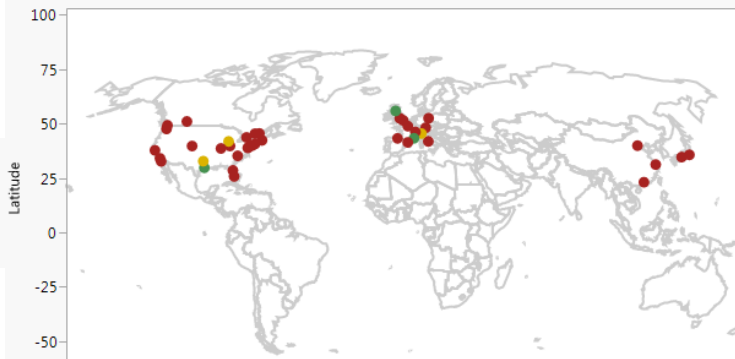
Where(Uppercase(:Country)) == "CHN"

▷ **Site-Level Risk Indicators in China**

Where(Uppercase(:Country)) == "JPN"

▷ **Site-Level Risk Indicators in Japan**

Global Map



RBM: ACTION SUGGESTION BY RISK INDICATORS

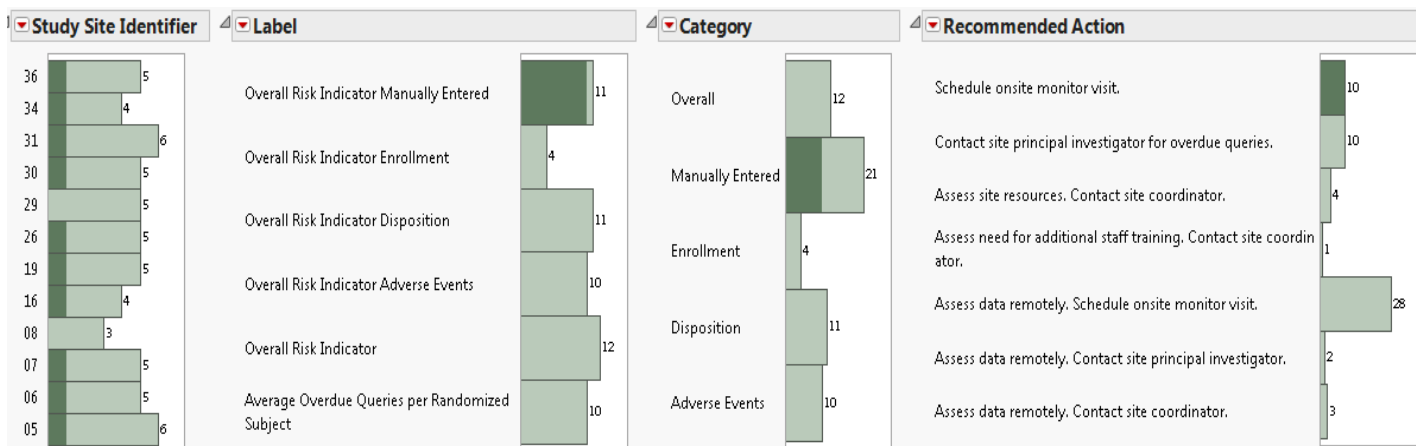
Study Site Identifier	Country	City	State or Province	Monitor	Site Category	Vendor	Overall Risk Indicator	Overall Risk Indicator ...	Overall Risk Indicator ...	Overall Risk Indicator ...	Overall Risk Indicator ...
01	USA	New York	NY	Monitor G	Veteran	Vendor A	0.518	0.441	0.056	0.607	0.603
02	USA	Orlando	FL	Monitor F	Experienced	Vendor A	0.257	0.637	0.448	0.218	0.047
03	USA	Indianapolis	IN	Monitor E	Experienced	Vendor A	0.127	0.205	0.497	0.000	0.069
04	FRA	Paris	Ile-de-France	Monitor I	Experienced	Vendor C	0.522	0.535	0.027	0.000	0.773
05	ITA	Milano	Lombardia	Monitor H	Novice	Vendor C	1.729	1.288	3.660	2.120	1.498
06	USA	Philadelphia	PA	Monitor G	Experienced	Vendor A	1.443	2.481	1.289	0.000	1.431
07	CHN	Guangzhou	Guangdong Sheng	Monitor K	Experienced	Vendor B	1.367	1.682	1.107	0.000	1.709
08	GBR	Birmingham	Birmingham	Monitor J	Novice	Vendor C	0.593	1.149	1.052	0.000	0.435
09	CAN	Montreal	Quebec	Monitor A	Veteran	Vendor A	0.301	0.400	0.629	0.356	0.178
10	USA	Baltimore	MD	Monitor G	Experienced	Vendor A	0.287	0.687	0.432	0.000	0.158
12	DEU	Berlin	Berlin	Monitor H	Experienced	Vendor C	0.483	0.881	1.346	0.008	0.299
14	CAN	Toronto	Ontario	Monitor A	Veteran	Vendor A	0.437	0.552	0.850	1.368	0.000
16	USA	Seattle	WA	Monitor B	Experienced	Vendor A	0.662	0.597	1.282	0.669	0.589
17	USA	Los Angeles	CA	Monitor C	Experienced	Vendor A	0.370	1.072	0.327	0.000	0.151
18	JPN	Osaka	Osaka	Monitor L	Novice	Vendor B	0.529	0.548	1.155	0.109	0.556
19	CAN	Ottawa	Ontario	Monitor A	Experienced	Vendor A	0.721	0.368	0.682	1.178	0.752
20	FRA	Marseille	Provence-Alpes-Cote d'Azur	Monitor I	Veteran	Vendor C	0.152	0.286	0.382	0.027	0.088
21	ESP	Barcelona	Cataluna	Monitor I	Experienced	Vendor C	0.379	0.420	0.169	0.000	0.520
22	CAN	Calgary	Alberta	Monitor B	Experienced	Vendor A	0.508	1.209	0.058	0.067	0.381
23	USA	Chicago	IL	Monitor E	Veteran	Vendor A	0.174	0.136	0.095	0.225	0.188
24	CHN	Shanghai	Shanghai Shi	Monitor K	Veteran	Vendor B	0.243	0.221	0.838	0.002	0.235
25	USA	Miami	FL	Monitor F	Experienced	Vendor A	0.538	0.936	1.107	0.000	0.424

Perform Additional Analyses

☐ Monitor ?

☒ Vendor ?

RBM: ACTION SUGGESTION BY RISK INDICATORS



Choose Risk Levels

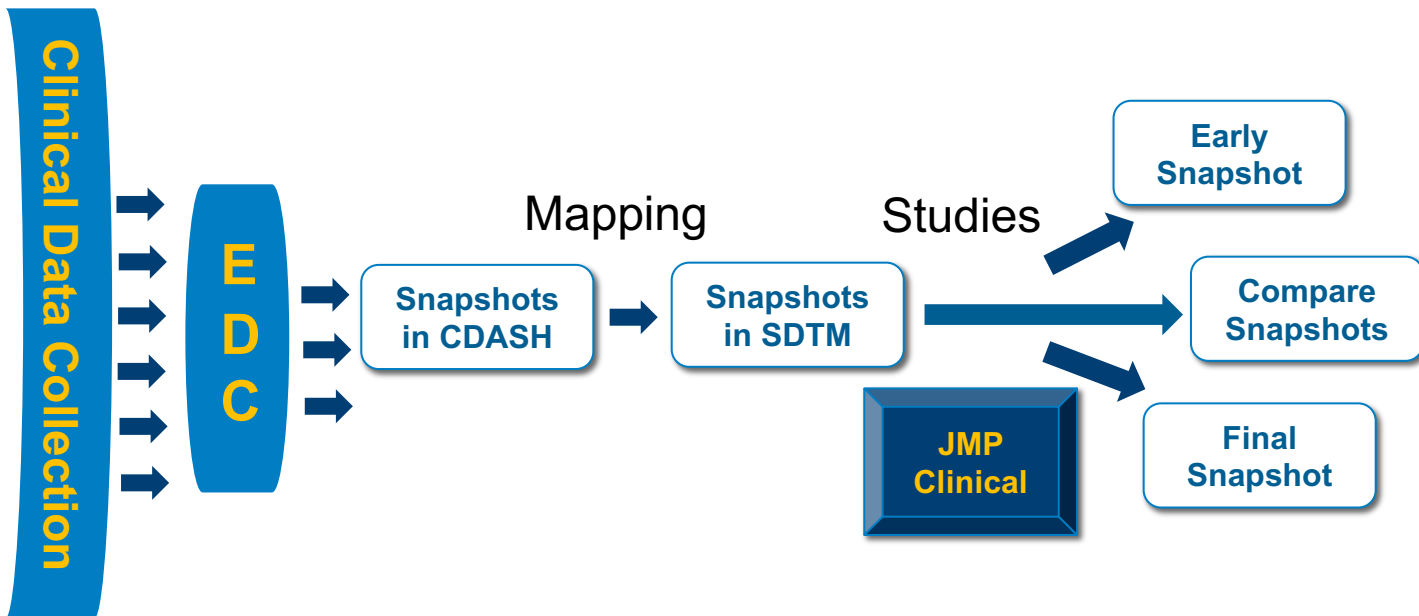
- ☐ Green
- ☒ Yellow
- ☒ Red



REAL TIME RBM



REAL TIME RBM



TWO SNAPSHOT EXAMPLES

	Early Snapshot	Final Snapshot
Trial Year	1987	1987, 1988, 1989
Subjects	43	902
Sites	10	40
Countries	1	10

ADD SNAPSHOTS AS TWO STUDIES

Add Study from Folders - JMP

General

* Study Name
Nicardipine1987 Clear [?](#)

SDTM or SEND Folder
P:\Wenjun\Clinical\Data\Nicardipine1987\ Choose Open [?](#)

ADaM Folder
Choose Open [?](#)

☐ Import SAS Transport Files (If Available) [?](#)

☒ Enable Future Snapshot Comparisons [?](#)

Options

Selected SDTM Domains
Clear Select SDTM Domains [?](#)

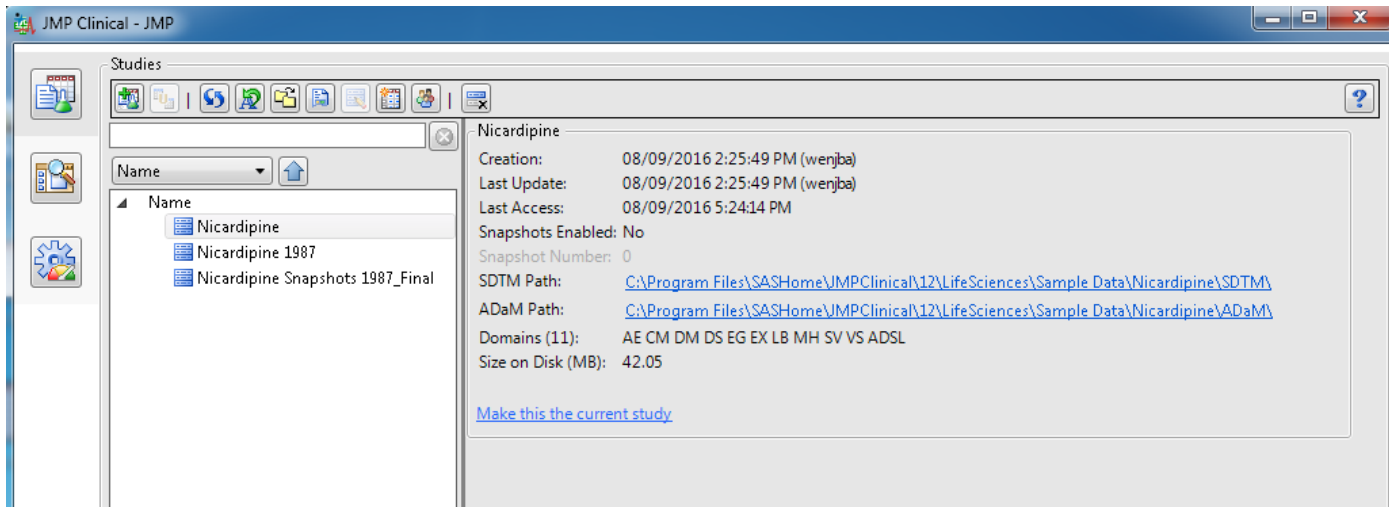
Selected ADaM Domains
Clear Select ADaM Domains [?](#)

* Required Parameter

☒ Make this the current study

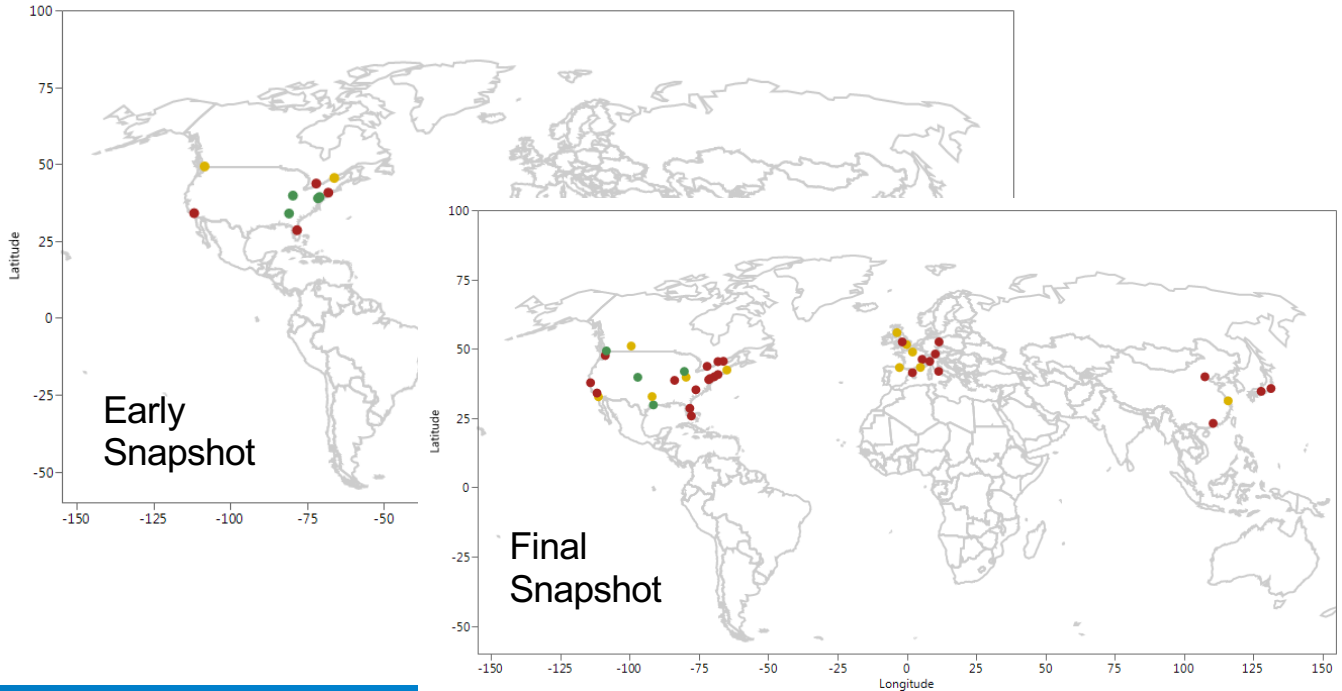
Run Settings... Close

ADD SNAPSHOTS AS TWO STUDIES



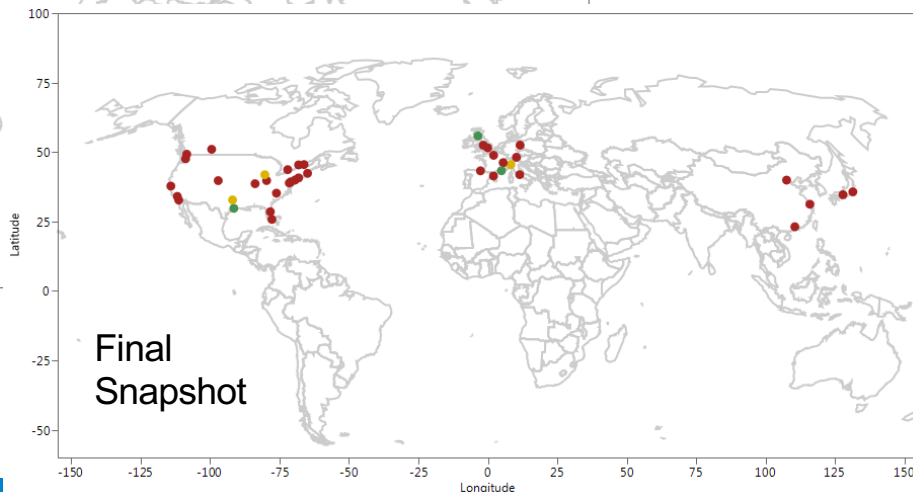
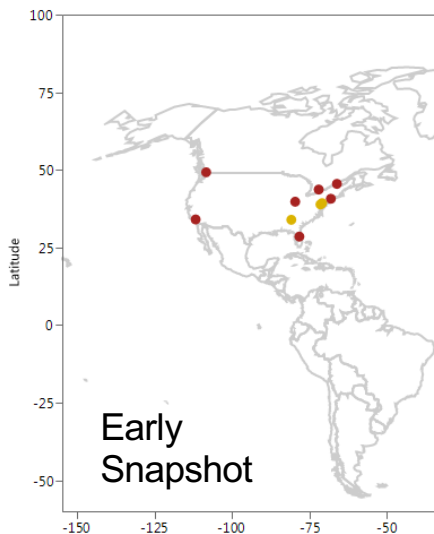
REAL TIME RBM

AEs per PatientWeek



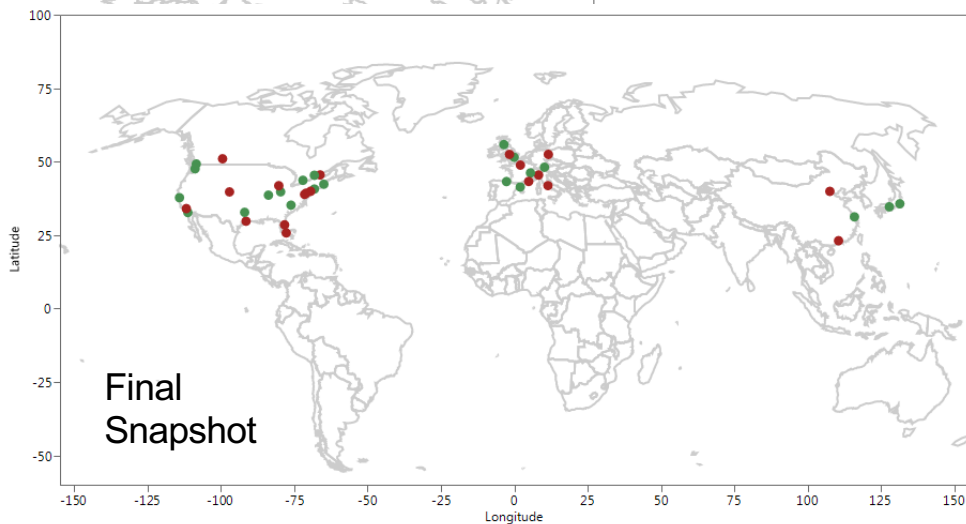
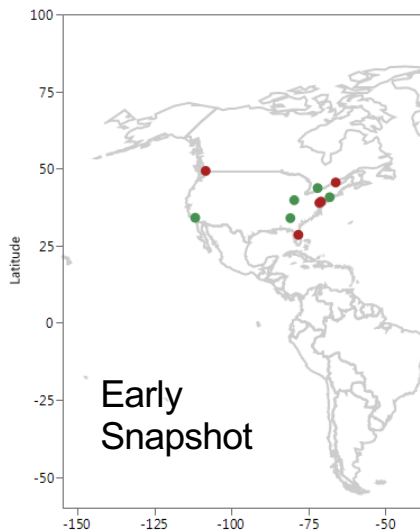
REAL TIME RBM

SAEs per PatientWeek



REAL TIME RBM

Death per PatientWeek



RISK-BASED MONITORING

Risk	↓
Cost	↓
Quality	↑
Efficiency	↑

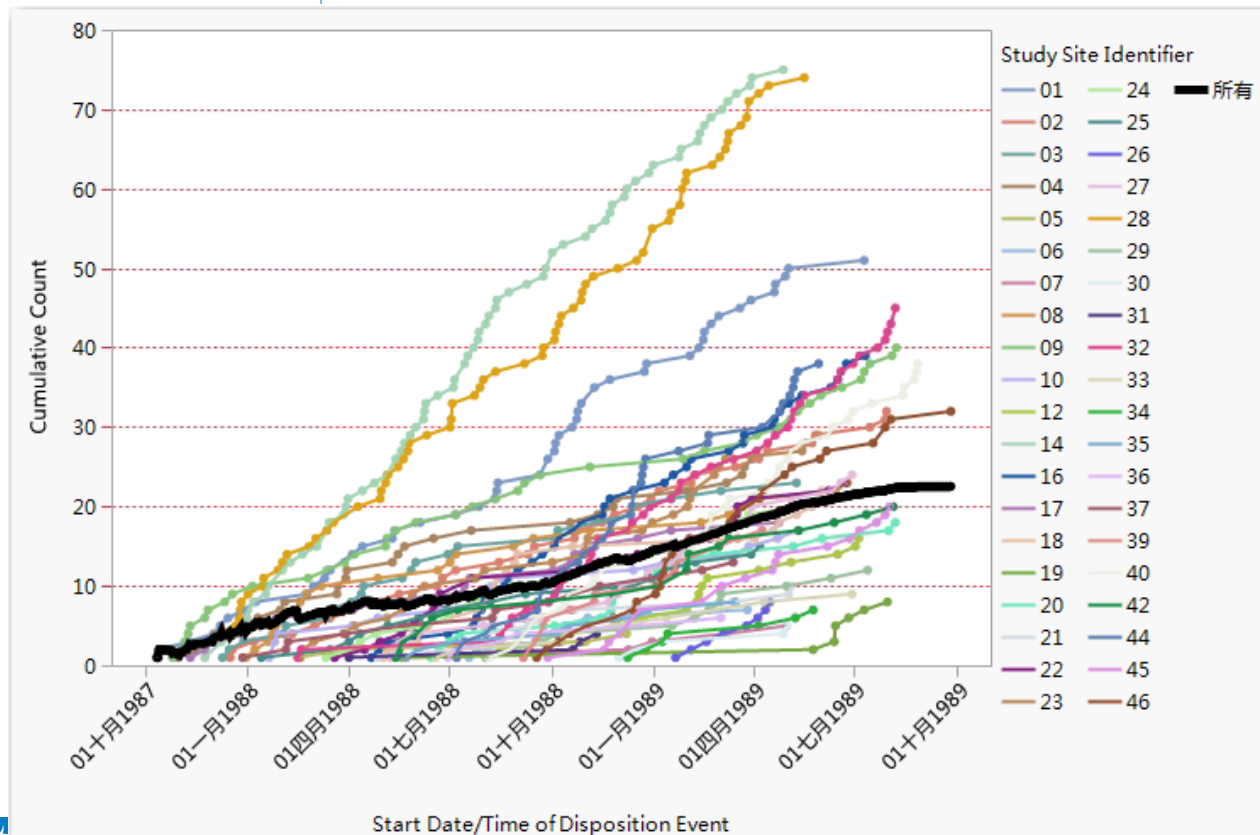


ENROLLMENT PATTERN



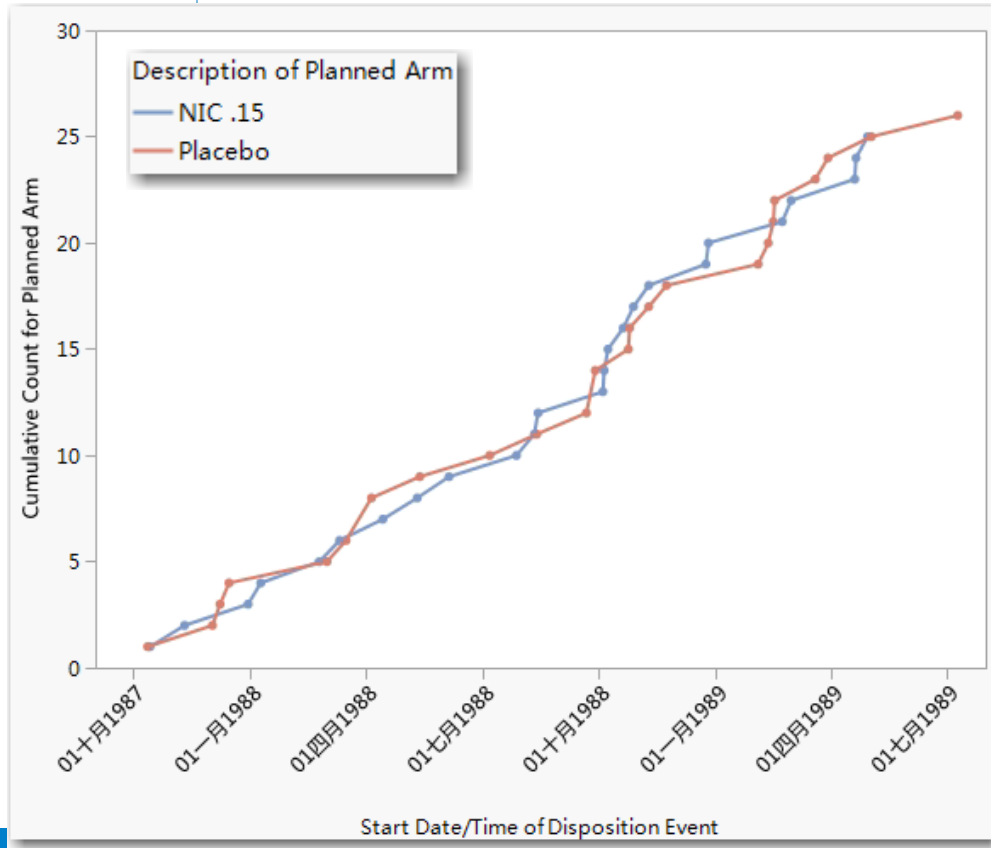
ENROLLMENT

ENROLLMENT SPEED AND NUMBER OF SUBJECTS



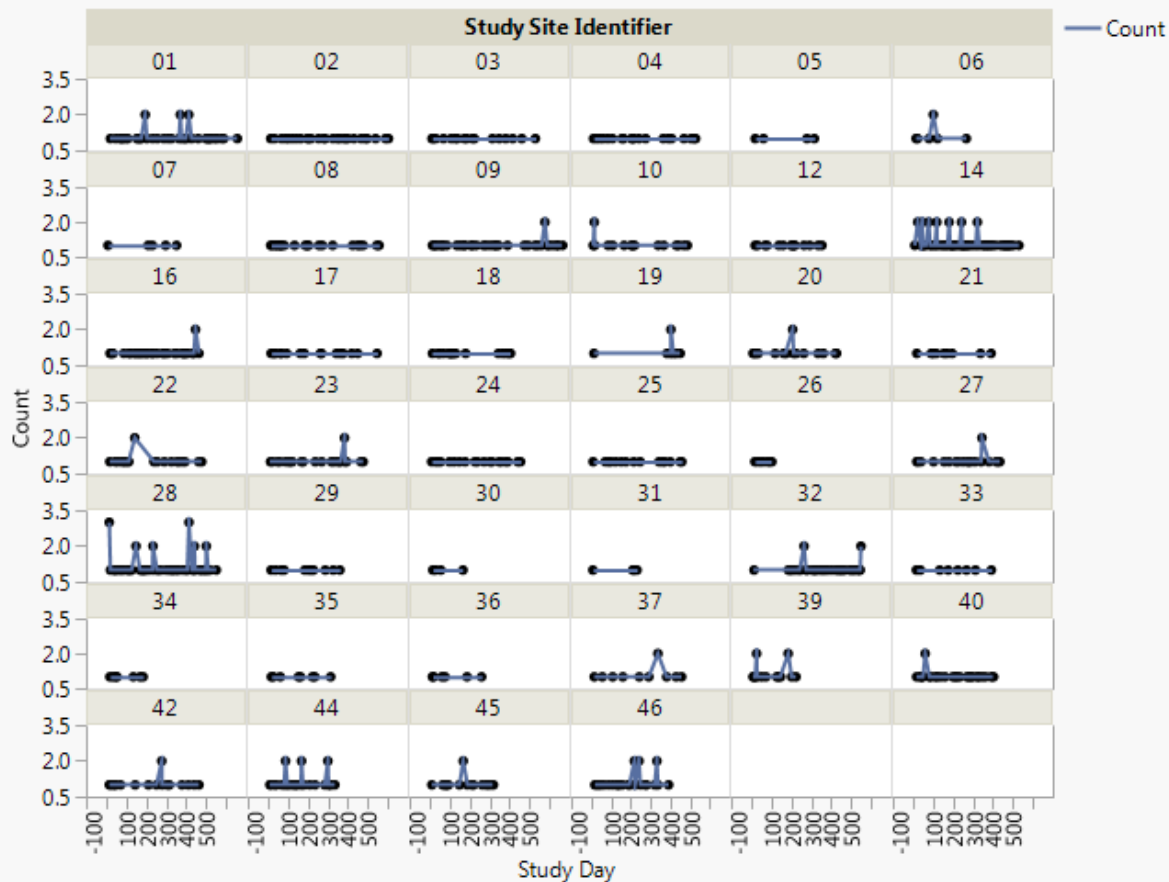
ENROLLMENT

COMPARISON OF TREATMENT AND PLACEBO GROUPS



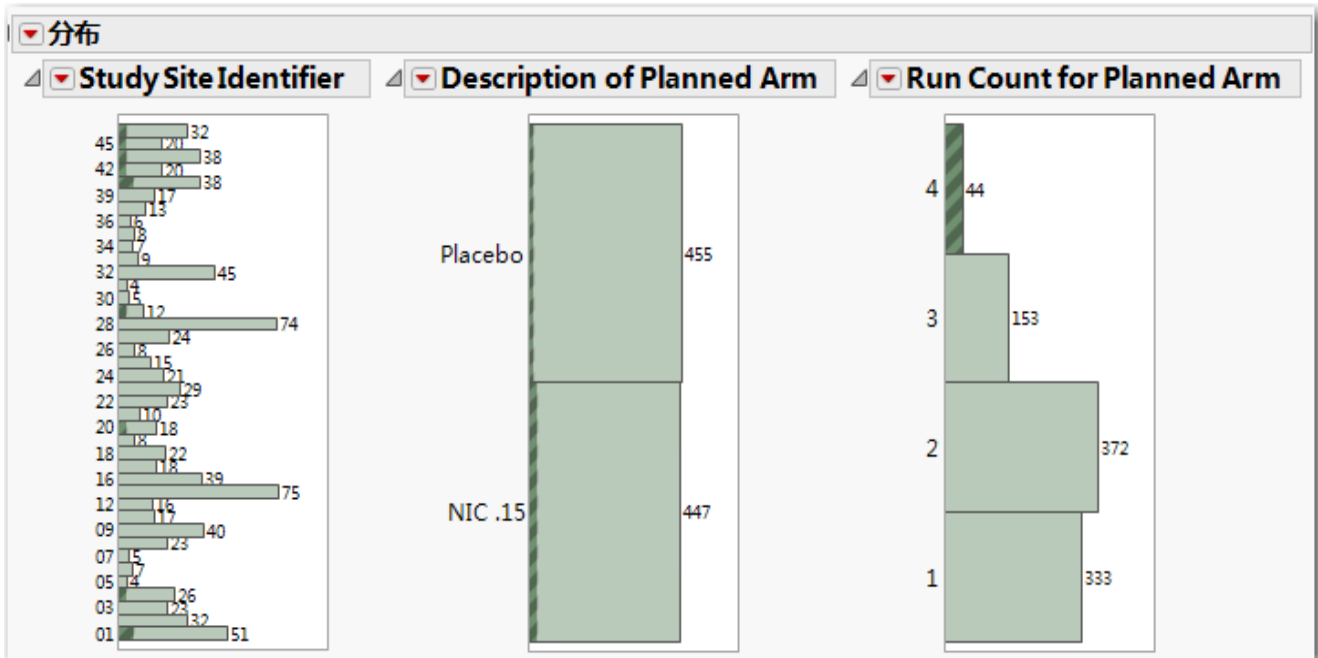
ENROLLMENT

COUNTS SUBJECTS BY STUDY DAY



ENROLLMENT

RANDOMIZATION FOR EACH SITE



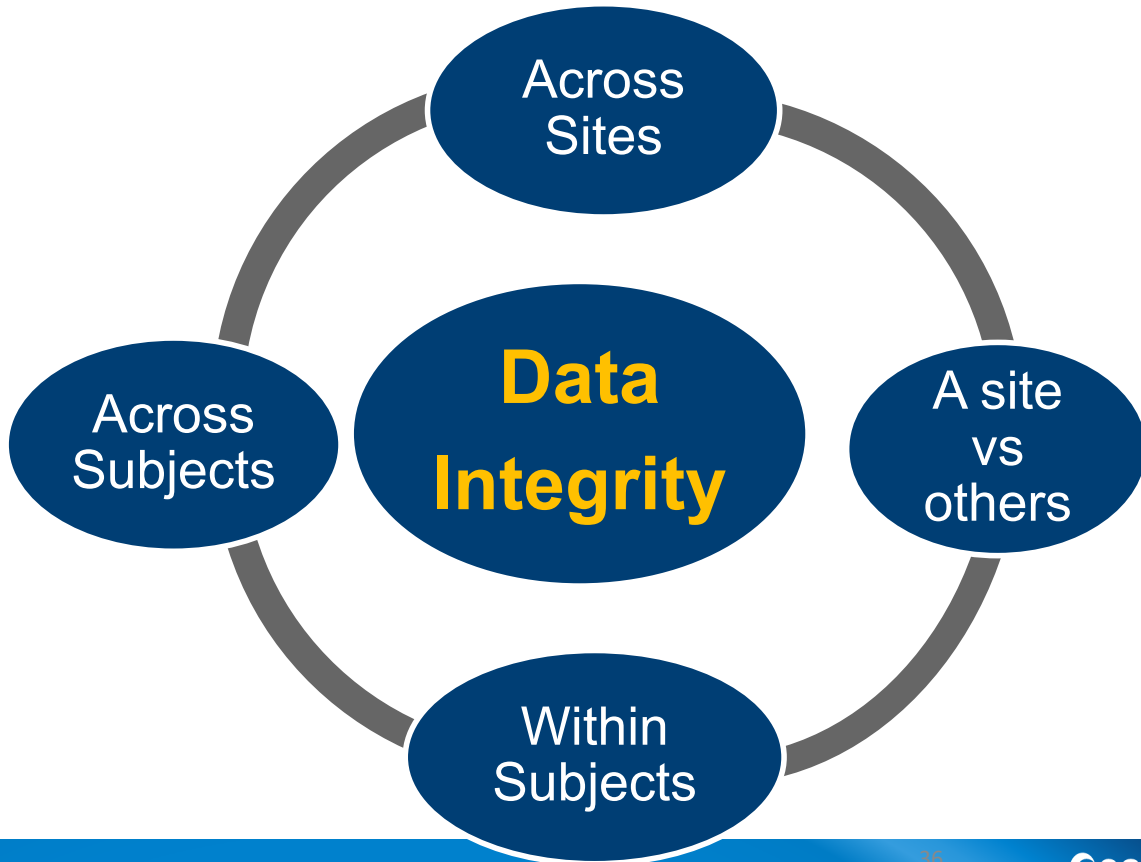
CENTRALIZED STATISTICAL MONITORING



FRAUD AND PROBLEM DETECTION



DATA INTEGRITY ANALYSIS



DATA INTEGRITY

Sites

Across Sites

- Risk-Based Monitoring
- Enrollment
- **Birthday and Initial**
- Cluster subjects across study sites
- **Multivariate Inliers and Outliers**

A Site and/or A Site vs Others

- Correlated Findings
- **Digit Preference**
- Frequencies
- **Missing Value**
- Outliers
- Perfect Scheduled Attendance
- Screen Bias
- Weekend and Holidays

Subjects

Within a Site between Subjects

- **Birthday and Initial**
- Cluster subjects Within study sites
- **Duplicate Records**

Subject Records

- Constant Finding
- **Duplicate Record**
- **Multivariate Inliers and Outliers**
- Visit Orders

CONCLUSIONS

- **CFDA new requirements can use RBM and Enrollment pattern to assess.**
- **More centralized statistical monitoring Methods are available to further assess the data quality.**

JMP Clinical: Combination of SAS & JMP



- **Base SAS**
- **SAS/STAT**
- **SAS/GRAPH**
- **SAS/IML**
- **SAS/Secure**
- **SAS/Secure Windows**
- **SAS/Genetics**
- **SAS/ACCESS PC Files**
- **SAS/IML Studio**

