Exploration des données d'essais cliniques en utilisant le standard CDISC

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AGENDA

- Outcomes of using CDISC standards
- Case study: how standards can help with visualizations and analyses in a controlled and reproducible manner.
  - Nicardipine study for the treatment of subarachnoid hemorrhage
  - Particular focus on Safety, Signal Detection, Risk-Based Monitoring, Fraud Detection and Delta Review

STANDARDS: WHY?

- Enhance human subject protection
- Enhance quality of clinical trial data
- A large number of people are involved in clinical trials.
  - People who are doing the analysis: they need to communicate easily the data
  - People involved in the different phases : Data are complex

DATA EXPLORATION

- New challenges to clinical trial oversight:
  - More variability in clinical investigator experience
  - More treatment choices
  - More standard of health care
  - Geographic dispersion
- Increasing use of electronic systems and records:
  - Improve quality and efficiency of sponsor
  - Better understanding of data.

MONITORING OF DATA

- Drug safety assessment critical in Clinical Trials
- Do It EARLY and OFTEN
  - Continuous monitoring of data to ensure patient safety, efficacy and data quality
- Clear graphical summaries that drill down to subject level details
- Provide out-of-the-box reports by leveraging CDISC data standards
- Regulatory agencies use the standard
  - FDA
  - CFDA (China)
  - PMDA (Japan)
  - EMA (Europe)

WHO IS INVOLVED – THE ORGANIZATIONS

- Drug and Medical Device Companies (Sponsors)
- Contract Research Organizations (CROs)
- Regulatory Agencies

WHO IS INVOLVED – THE PEOPLE

- Different groups of people (with different roles) involved at each phase of the clinical trial
  - Medical Monitors/Reviewers/Clinicians/Medical Writers
    - Typically Clinicians/MDs
    - View clinical safety data in ongoing reviews. Adverse events (AE), concomitant medications (CM), lab/findings trends (LB, EG, VS, FA), patient profiles, AE narratives are typical areas of interest
  - Operational Data Managers/Monitors (Clinical Operations)
    - Risk-based monitoring: site performance evaluation through centralized data and risk signal detection methods
    - Data quality/fraud detection: Assess potential fraud/misconduct/data quality in clinical trials in data
  - Biostatisticians/Statisticians (Biometrics)
    - Signal Detection, safety + efficacy analysis, time-to-event, repeated measures, Bayesian Hierarchical modeling
    - Prediction methods and cross-validation for clinical trials, biomarker analysis

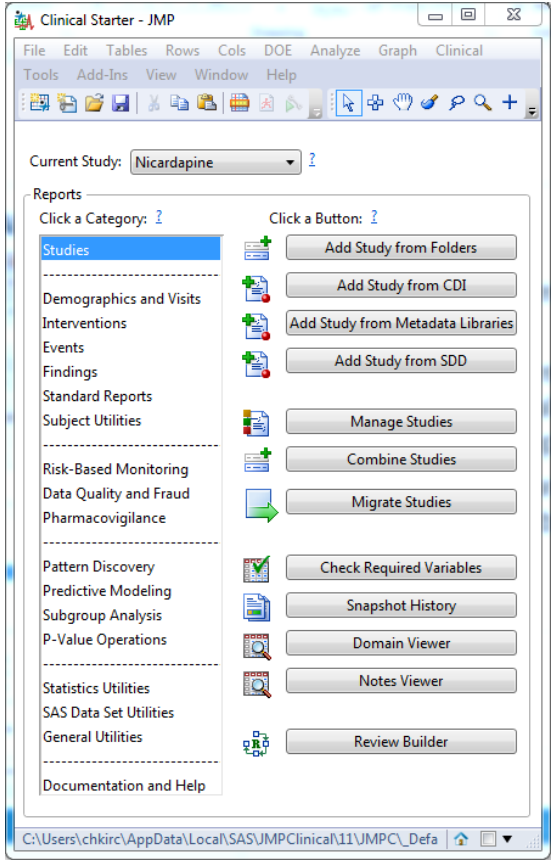
Case Study

Data Analysis Workflow
Live Demonstration

THE STUDY DESIGN

- Information about Clinical Study Used :
  - Nicardipine treatment of 902 subjects that had Subarachnoid Hemorrhage.
  - All the patients were included in a randomized double-blind placebo-controlled study; 449 patients received Nicardipine while 457 received the placebo.
  - Patients in each group were balanced with regard to prognostic factors for overall outcome.
  - Nicardipine and the placebo were delivered continuously at 0.15 mg for up to 14 days and patients were followed for up to 120 days following administration of the drugs.
  - Results are formatted according to the CDISC Study Tabulation Data Model (STDM) with Demographic data (ADSL) from ADaM

ENABLING OF AUTOMATED REPORTS



- JMP Clinical has processes / templates in place to go through a standard clinical review process
  - Based on the availability of the different data domains, able to graphically review :
    - Interventions, Events, Findings, Special Domains
- In addition, Data Monitoring tools simplified
  - Data Integrity Views and Analyses
  - Risk-Based Monitoring of Sites
- Helps with linking graphics the data, with drill-down options and patient profiles/automated narratives

SAFETY REVIEWS

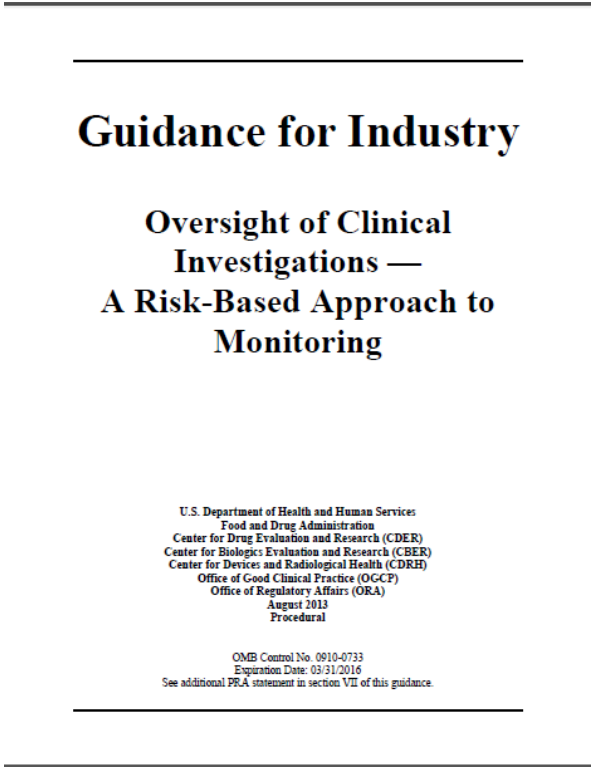
- Demographics
- Interventions
  - Reports on CM, EX, etc.
    - Distributions
    - Incidence Screen
- Events
  - Adverse Events
    - Distribution
    - Incidence Screen
- Findings
  - Shift Plots
  - Time Trends
  - Hy's Law Review

DATA INTEGRITY

- Using data in CDISC standards simplifies checking for data quality and fraud:
  - Able to look across domains for outliers in data
  - Look for findings that may be constant for subjects
  - Look for duplicate records with findings domains
  - Biases in Findings measurements (LB, EG, VS, etc.)
  - Assess Study Visits or Demographic data for inconsistencies

RISK-BASED MONITORING

- FDA recommends that each sponsor design a monitoring plan that is tailored to the specific human subject protection and data integrity risks of the trial
- Risk-based plan include a mix of centralized and on-site monitoring practices
- **Risk-Based Monitoring (RBM):**
  - **Identify Critical Data and Processes to be Monitored**
  - **Risk Assessment**
  - **Factors to Consider when Developing a Monitoring Plan**



Guidance for Industry

Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring

U.S. 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)
Office of Good Clinical Practice (OGCP)
Office of Regulatory Affairs (ORA)
August 2013
Procedural

OMB Control No. 0910-0733
Expiration Date: 03/31/2016
See additional PRA statement in section VII of this guidance.

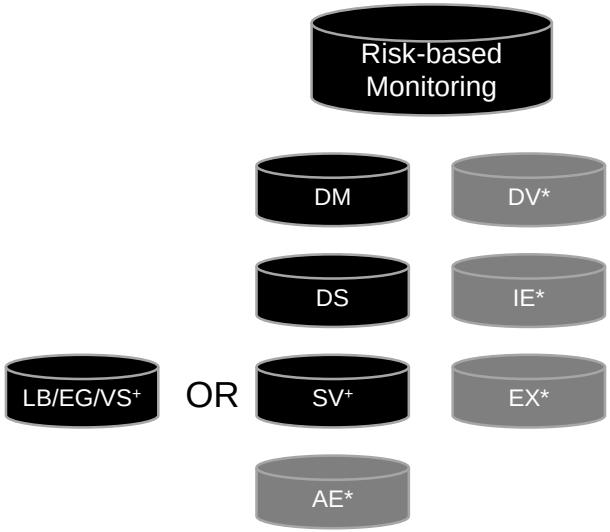
http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

RISK-BASED MONITORING

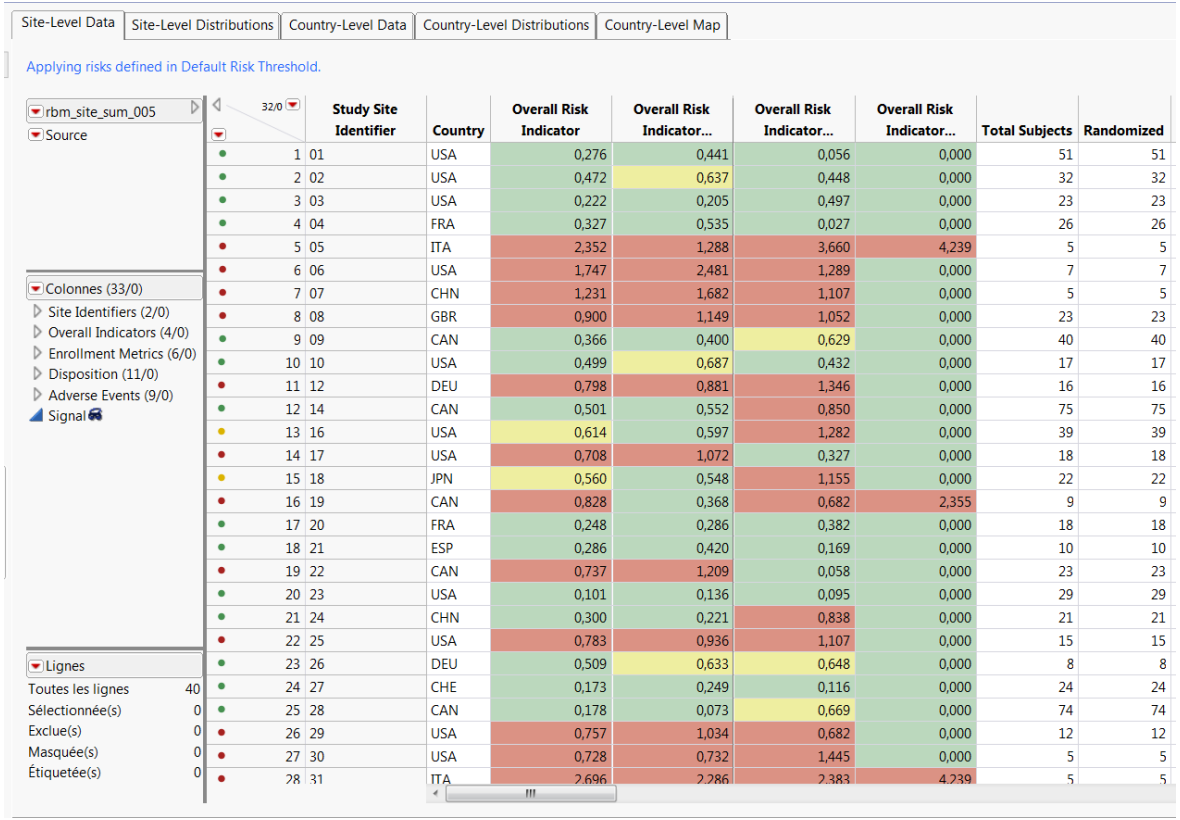
- Assess site performance based on safety and visit information
  - Overall risk score based on information from:
    - Adverse Events
    - Disposition
    - Enrollment
  - Time Trends to assess improvement or degradation of performance
  - Ability to drill down into patient level details for sites at risk

DOMAIN TABLES AND HOW THEY MAP: RBM/DATA QUALITY AND FRAUD

- Data Quality and Fraud will require different domains depending on the process/report.
- Risk-Based Monitoring requires a small set of domains and the rest are optional if one wants additional risk indicators to be generated
  - + If not available, then one or more Findings domain will work in place (needed for Date/Time of Measurements)
  - * Not required, but options for addition risk indicators



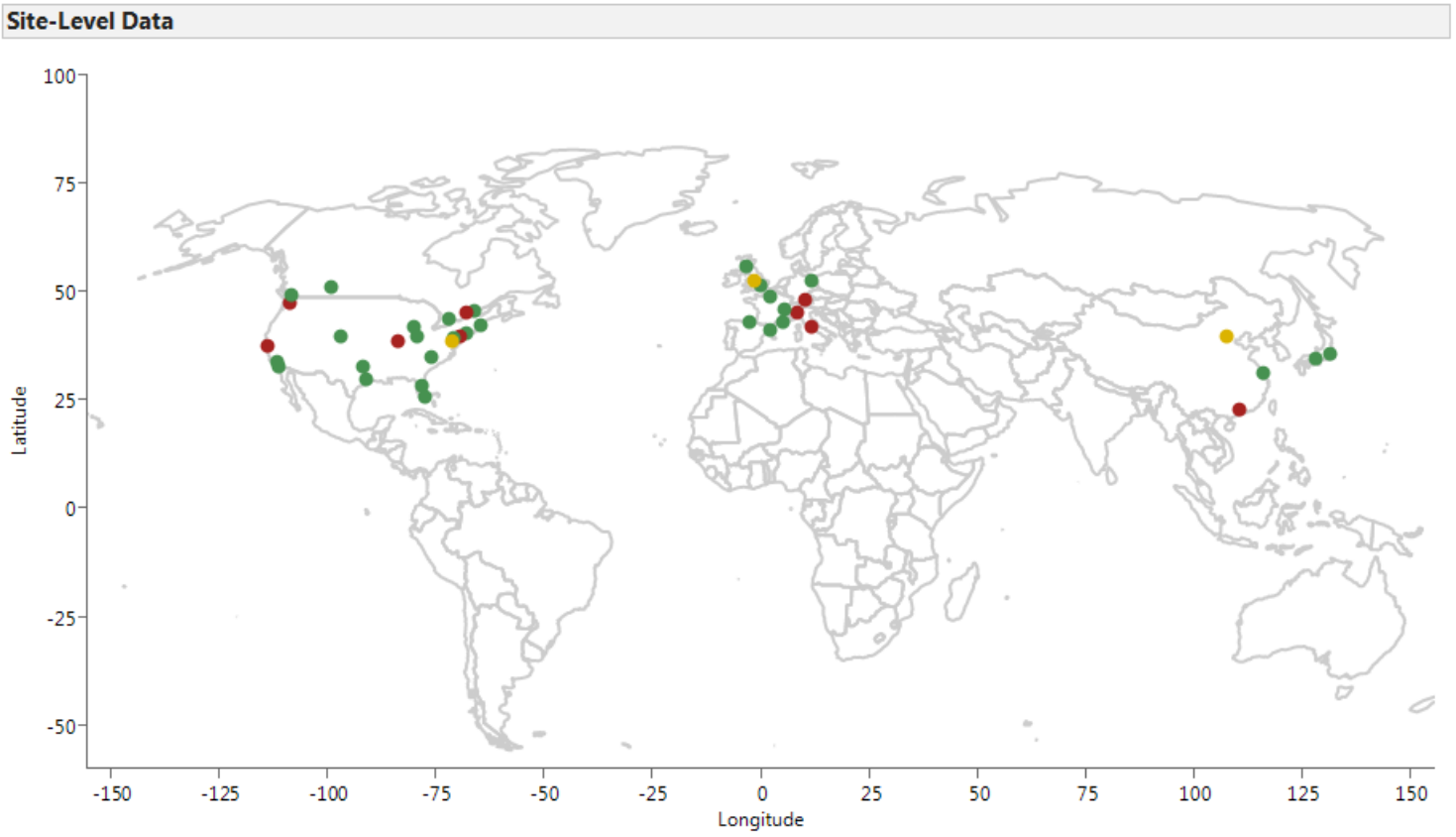
SITE LEVEL



	32/0	Study Site Identifier	Country	Overall Risk Indicator	Overall Risk Indicator...	Overall Risk Indicator...	Overall Risk Indicator...	Total Subjects	Randomized
●	1	01	USA	0,276	0,441	0,056	0,000	51	51
●	2	02	USA	0,472	0,637	0,448	0,000	32	32
●	3	03	USA	0,222	0,205	0,497	0,000	23	23
●	4	04	FRA	0,327	0,535	0,027	0,000	26	26
●	5	05	ITA	2,352	1,288	3,660	4,239	5	5
●	6	06	USA	1,747	2,481	1,289	0,000	7	7
●	7	07	CHN	1,231	1,682	1,107	0,000	5	5
●	8	08	GBR	0,900	1,149	1,052	0,000	23	23
●	9	09	CAN	0,366	0,400	0,629	0,000	40	40
●	10	10	USA	0,499	0,687	0,432	0,000	17	17
●	11	12	DEU	0,798	0,881	1,346	0,000	16	16
●	12	14	CAN	0,501	0,552	0,850	0,000	75	75
●	13	16	USA	0,614	0,597	1,282	0,000	39	39
●	14	17	USA	0,708	1,072	0,327	0,000	18	18
●	15	18	JPN	0,560	0,548	1,155	0,000	22	22
●	16	19	CAN	0,828	0,368	0,682	2,355	9	9
●	17	20	FRA	0,248	0,286	0,382	0,000	18	18
●	18	21	ESP	0,286	0,420	0,169	0,000	10	10
●	19	22	CAN	0,737	1,209	0,058	0,000	23	23
●	20	23	USA	0,101	0,136	0,095	0,000	29	29
●	21	24	CHN	0,300	0,221	0,838	0,000	21	21
●	22	25	USA	0,783	0,936	1,107	0,000	15	15
●	23	26	DEU	0,509	0,633	0,648	0,000	8	8
●	24	27	CHE	0,173	0,249	0,116	0,000	24	24
●	25	28	CAN	0,178	0,073	0,669	0,000	74	74
●	26	29	USA	0,757	1,034	0,682	0,000	12	12
●	27	30	USA	0,728	0,732	1,445	0,000	5	5
●	28	31	ITA	2,696	2,286	2,383	4,239	5	5

Coloured by risk level for each site

SITE LEVEL MAP



COUNTRY LEVEL

Coloured by risk level for each country

Site-Level Data | Site-Level Distributions | Country-Level Data | Country-Level Distributions | Country-Level Map

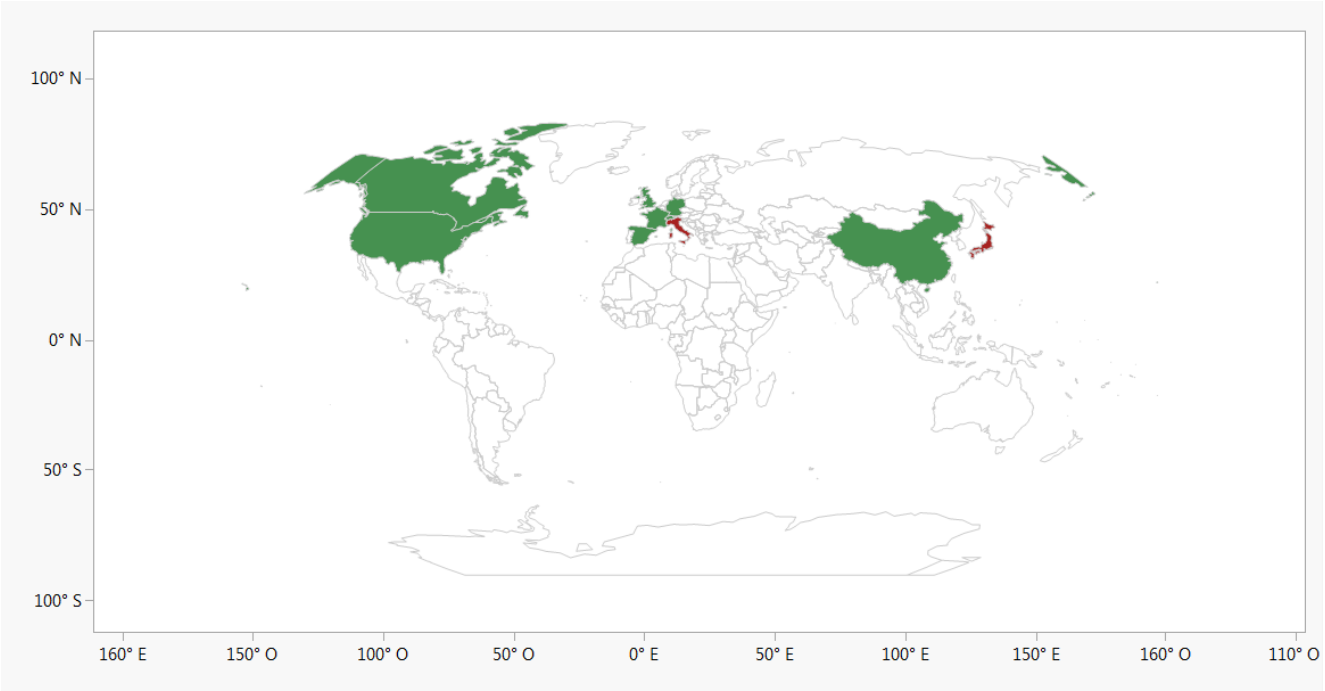
Applying risks defined in Default Risk Threshold.

rbm_country_sum_005
Source

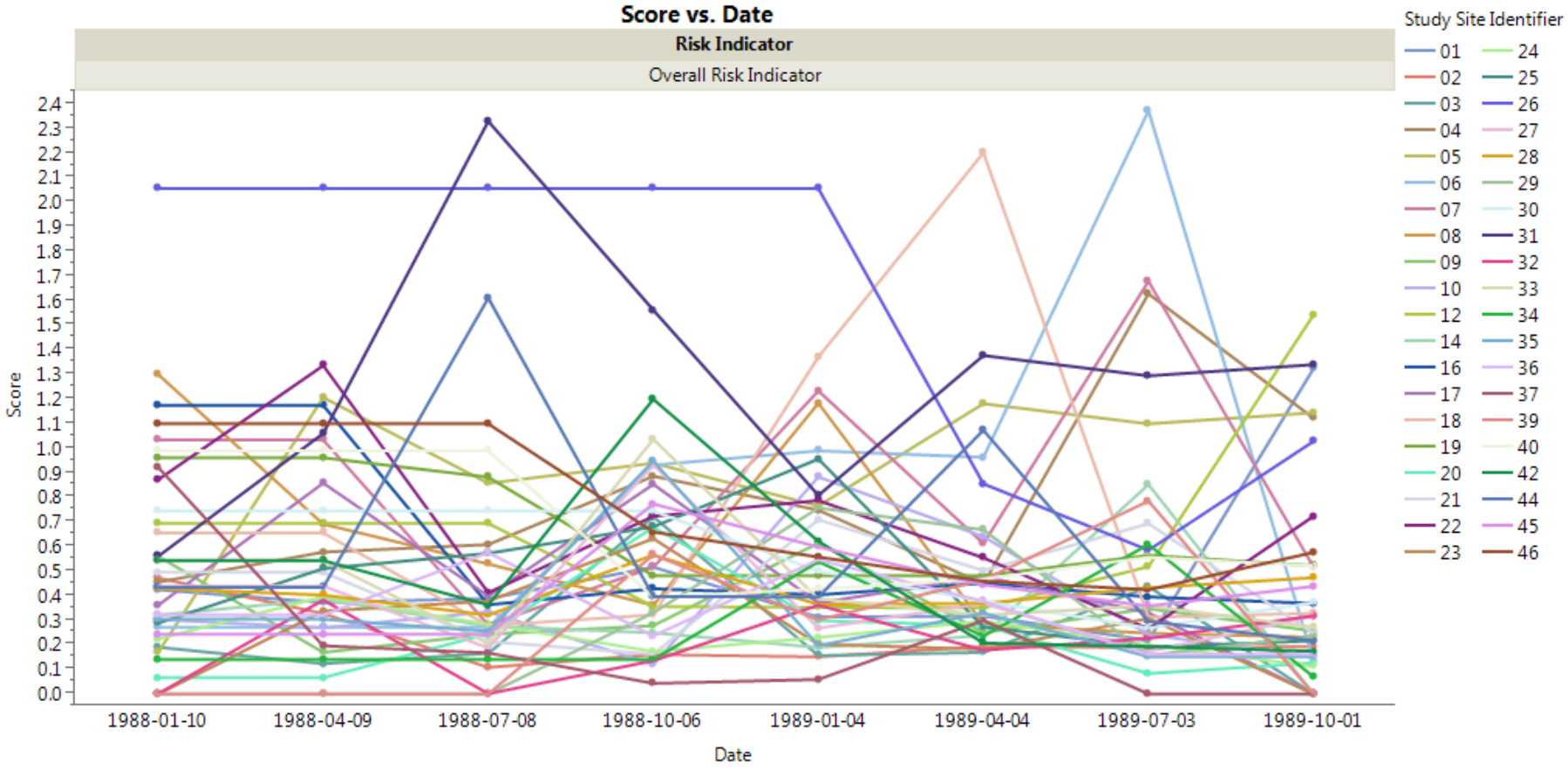
Colonnes (33/0)
Country
Overall Indicators (4/0)
Enrollment Metrics (7/0)
Disposition (11/0)
Adverse Events (9/0)
Signal

32/0	Country	Overall Risk Indicator	Overall Risk Indicator...	Overall Risk Indicator...	Overall Risk Indicator...	Total Sites	Total Subjects	Randomized	Screen Failure
1	CAN	0,301	0,388	0,267	0,072	5	221	221	1
2	CHE	0,294	0,482	0,023	0,000	1	24	24	0
3	CHN	0,285	0,415	0,181	0,000	3	33	33	0
4	DEU	0,273	0,213	0,724	0,000	2	24	24	0
5	ESP	0,122	0,193	0,032	0,000	2	23	23	0
6	FRA	0,267	0,430	0,045	0,000	2	44	44	0
7	GBR	0,079	0,112	0,060	0,000	3	81	81	0
8	ITA	2,438	2,028	2,915	3,190	2	10	10	2
9	JPN	1,069	1,421	0,711	0,371	2	43	43	1
10	USA	0,064	0,100	0,023	0,000	18	403	403	0

COUNTRY LEVEL MAP



TIME TRENDS



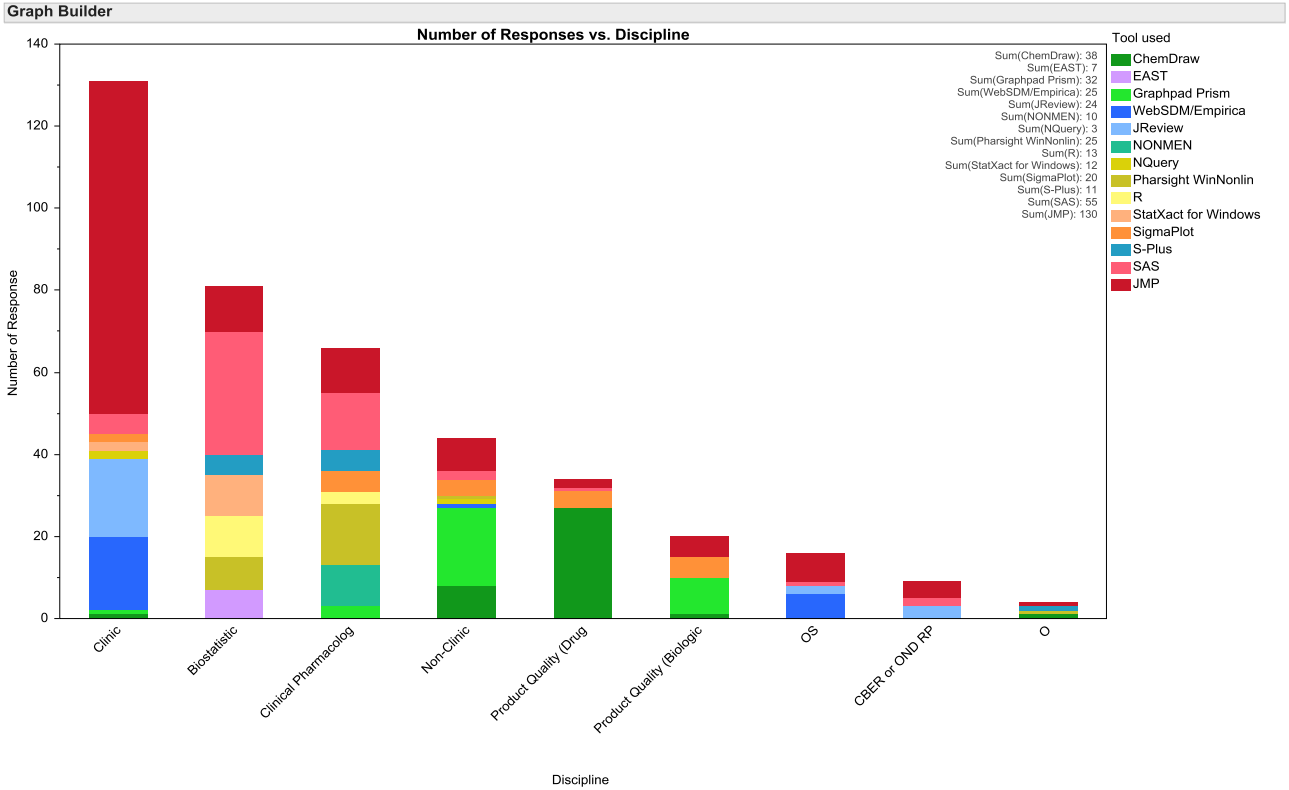
JMP® Clinical

Data Analysis Workflow
Live Demonstration

CONCLUSION

- Due to the use of standards from CDISC, JMP Clinical is able to be:
  - Intuitive, Interactive, Comprehensive, Highly Visual
  - Easy to use
  - Platform embraced at all levels of safety review process
  - Facilitates interpretation, communication and reporting
  - Helps users to improve the safety review process better, faster, cheaper

SOFTWARE USAGE AT FDA



http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM272444.pdf

JMP® CLINICAL IS THE DE FACTO STANDARD FOR CLINICAL DATA ANALYSIS

- It uses data standards (CDISC: SDTM & ADaM; SEND; AERS like)
- It follows standard reporting recommended by medical authorities reviewer guidance (ICH-E3)
- It is based on industry standard tools (JMP and SAS)
  - JMP is the most widely used review tool at the FDA (40% of medical reviewers at CDER/CBER)(*)
  - JMP is widely used in clinical groups at sponsors
  - SAS is the standard analysis and reporting tool of biostatistics groups at sponsors

(*) http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM272444.pdf

JMP® Clinical

Highly Visual
Interactive Graphics
Intuitive

Scalable
Validated Powerful Analytics

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