



JMP Clinical®

Visual Approaches for Safety Analysis and Review of Clinical Trials

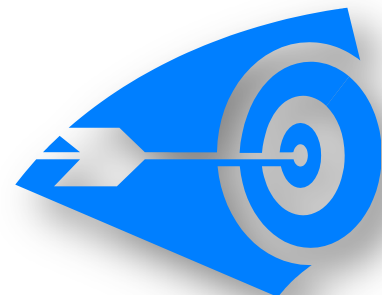


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AGENDA

- ❑ Introduction JMP Clinical
- ❑ Live demonstration
 - ❑ Nicardipine study for the treatment of subarachnoid hemorrhage
 - ❑ Particular focus on Safety, Signal Detection, Fraud Detection and Delta Review



JMP CLINICAL IS PARTS OF THE JMP FAMILY FOR STATISTICAL DISCOVERY

JMP



This is the JMP product you've known and loved for more than 20 years. It's the standard for visual data analysis right on the desktop. JMP links statistics with graphics, making information accessible in ways a spreadsheet never could. JMP empowers you to enjoy one breakthrough after another.

JMP Pro



JMP Pro includes everything you'll find in JMP, plus powerful new capabilities designed for advanced analytic users who need data mining techniques to create robust predictive models. If you have large data volumes, want to engage in data mining or build predictive models that generalize well, then JMP Pro is for you.

JMP Clinical



JMP Clinical software shortens the drug development process by streamlining safety reviews of clinical trials data. It helps clinicians and biostatisticians migrate into the modern review environment using CDISC data. Intuitive dashboards create a visual framework for rigorous statistical analysis.

JMP Genomics



The desktop solution for analysis and visualization of genomics data, JMP Genomics combines the power of the JMP statistical discovery platform with industry-leading SAS Analytics and customized applications tailored for vast genomic data sets.

INTRODUCTION TO JMP® CLINICAL

- JMP Clinical software from SAS shortens the drug development process by streamlining both internal safety reviews during preclinical, clinical trials and final evaluation by the Food and Drug Administration (FDA).
- JMP Clinical creates reports from standard Clinical Data Interchange Standards Consortium (CDISC) and Standard for Exchange of Non-Clinical Data (SEND) data, facilitating communication between (pre-) clinicians and biostatisticians at the sponsor organization and, subsequently, between sponsors and FDA reviewers.
- It targets Pharmacovigilance sector by using the 4 industry standards algorithms for signal detection in the disproportionality analysis
- It dynamically links advanced statistics and graphics, enabling sophisticated analysis in a user-friendly environment.
- Interactive graphs offer multiple views of patient profiles and reveal hidden patterns in drug-drug, drug-adverse events interactions.

JMP® CLINICAL IS THE *DE FACTO* STANDARD FOR CLINICAL DATA ANALYSIS SOFTWARE.

- It uses standard data (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>

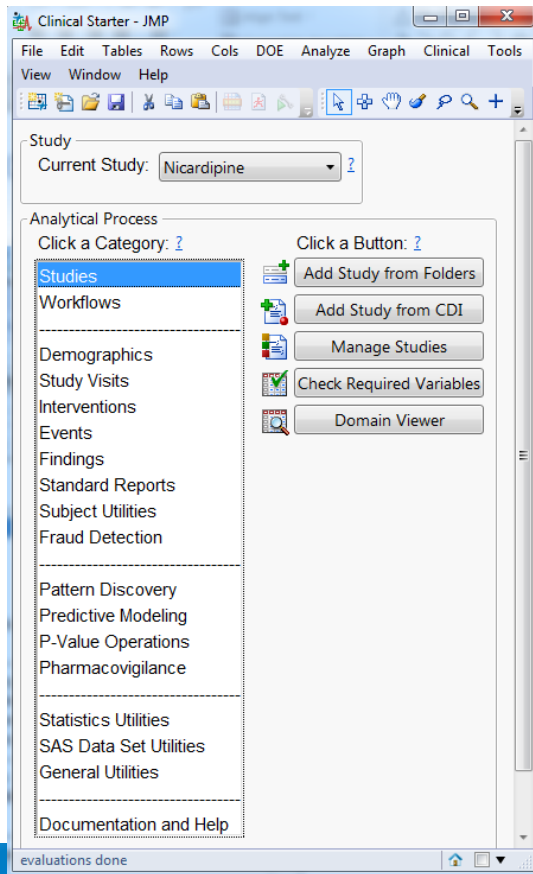
JMP® Clinical

Highly Visual
Interactive Graphics
Intuitive



Scalable
Validated Powerful Analytics

JMP® CLINICAL PROCESSES ON THE SHELF



- JMP Clinical has all processes / templates in place to go through a standard clinical review process.
- Based on the availability of the different data domains, you will be able to graphically review :
 - Interventions, Events, Findings, Special
 - All Graphics linked to the data, with drill-down options and patient profiles



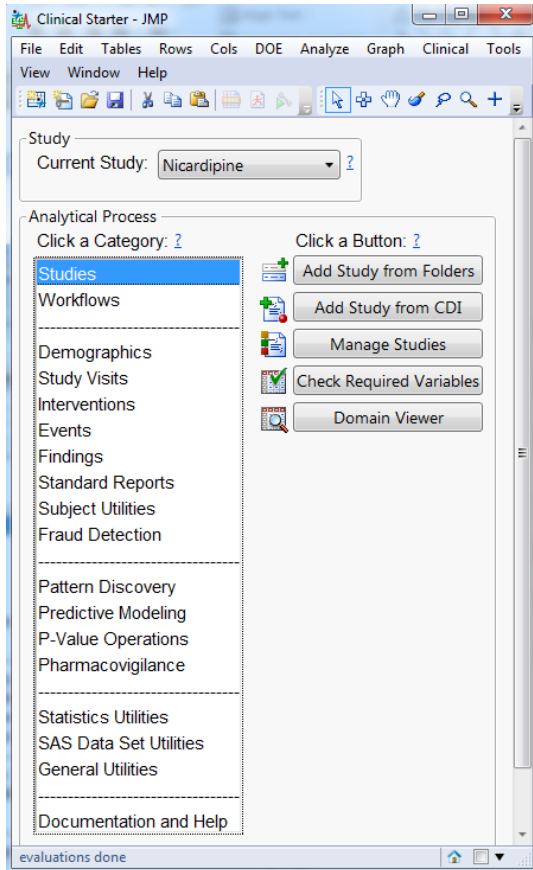
JMP[®] Clinical

Data Analysis Workflow
Live Demonstration



The Clinical Study used is the following:

- 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 Model.



JMP Clinical comes with its JMP Clinical Starter.

This dialog enables you to quickly view and access all JMP Clinical, workflows, and applications.

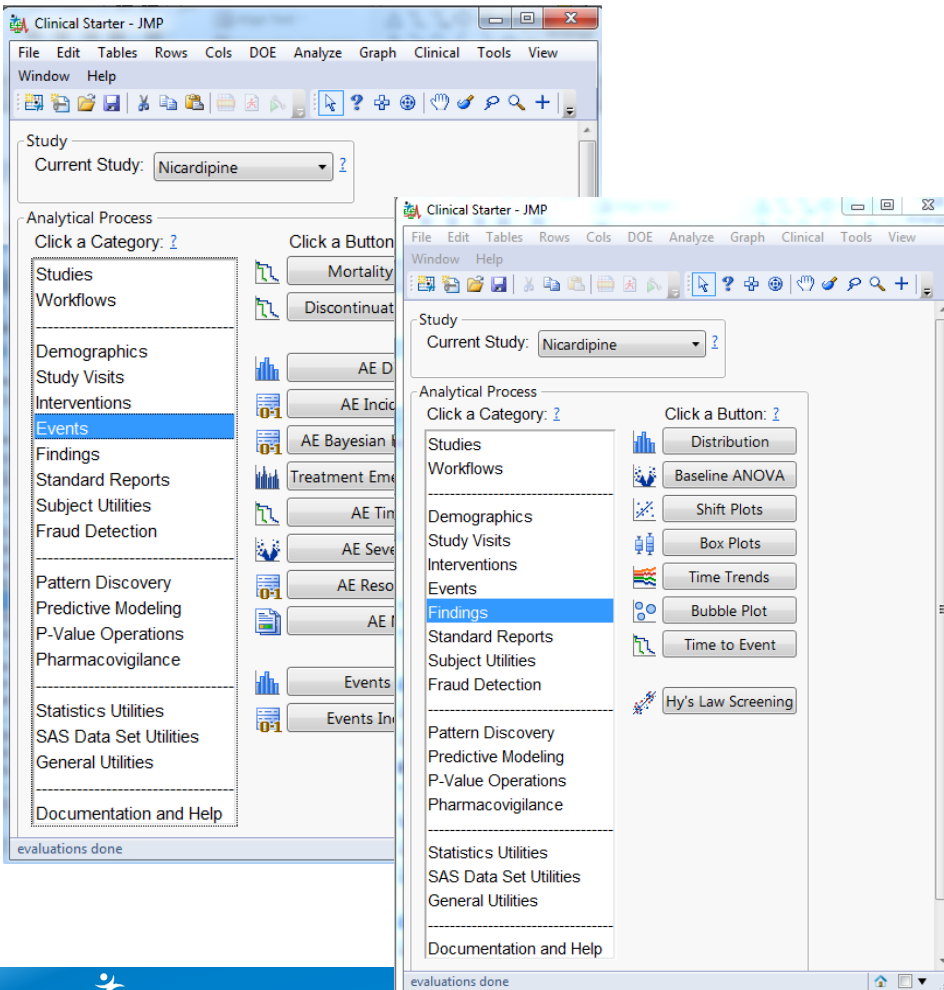
The order of this menu is important. It follows roughly the order described in the ICH-E3 reviewer guidance

JMP® CLINICAL STARTER MENU

JMP Clinical comes with its JMP Clinical Starter.

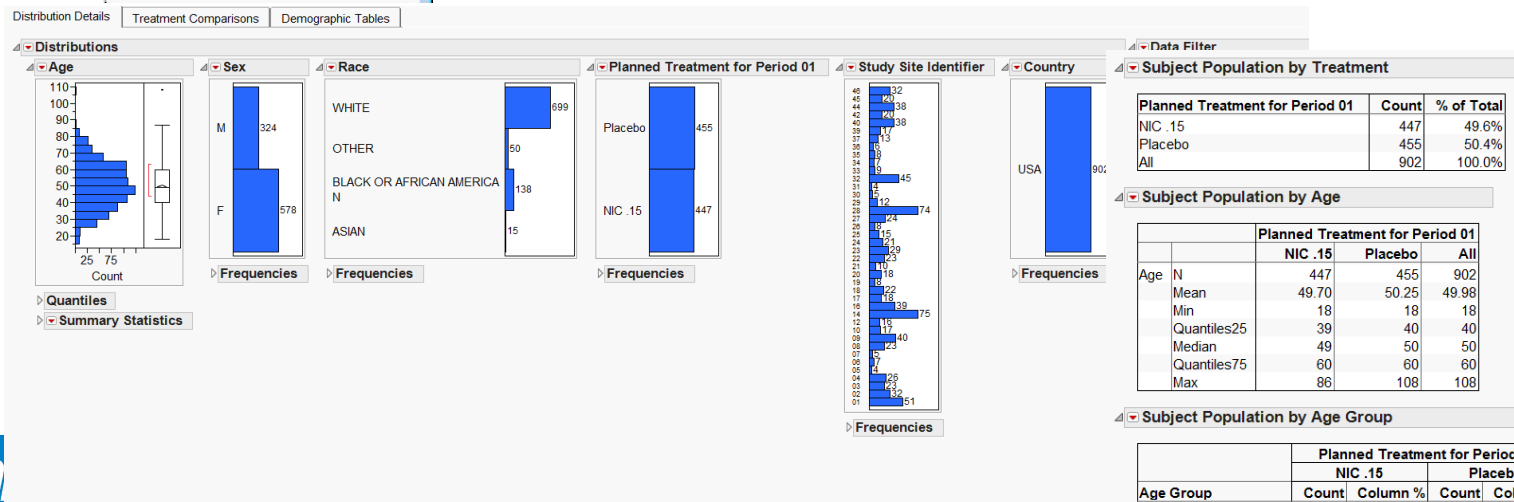
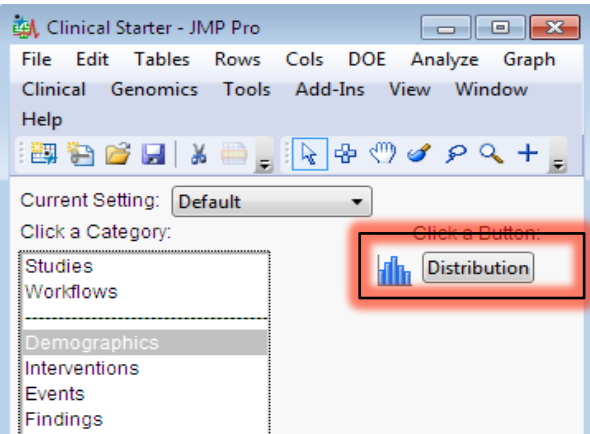
This dialog enables you to quickly view and access all JMP Clinical, workflows, and applications.

The Applications are ordered in categories and subcategories for the ease of use



Visualize relationships between demographic characteristics and treatment groups

One would need to check for consistency in the demographics distributions to evaluate any significant deviation among age, sex, race groups and sites within the different treatment groups



Output Description

Subjects

21025

Templates

Active Template: None

Create or Update a Template

Delete Templates

Domains

Data Tables

Findings

Axes

Create Report

Create Narratives

View Comments

Create Subject Filter

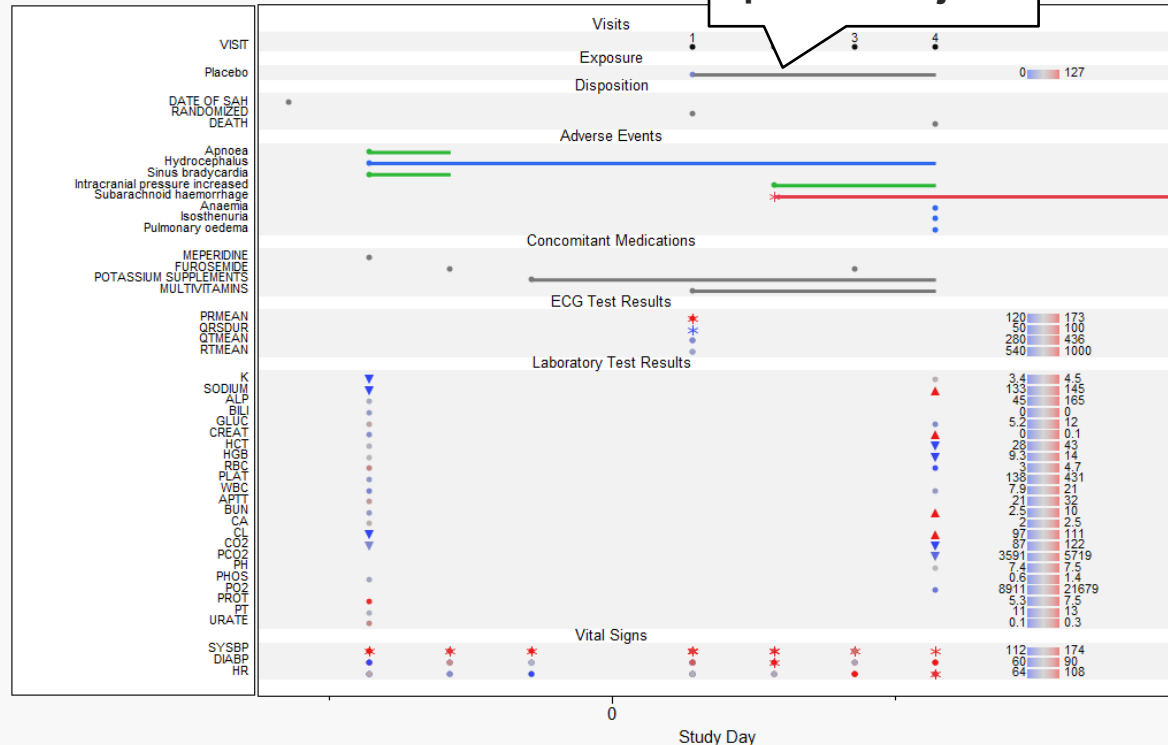
Add Notes View Notes

Close All

General

Demographics

Profile



Demographic Attributes

Review Status Notification

Demographics

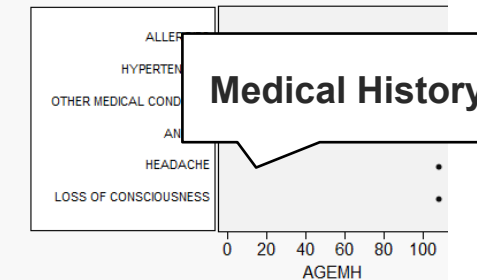
Subject Age

21025 108

Review Status

21025 Status: Unreviewed

Medical History



Legend

Adverse Events

Mild Moderate Severe
Not Serious

Numeric Findings with High or Low Reference Values

High
Normal
Low

Patient Narratives

Subject: 101001
Randomized Arm: Placebo
Investigator: 101A

Subject 101001 was a 63-year-old white female. Her medical history included headache associated with sah(1988), hypertension with t sah(1988), vomiting associated with sah(1988) and hypertension prior to sah(1981). She began dosing with 40 mg/h of placebo on 21JAN1988 (Day 1). The subject discontinued the trial on 18FEB1988 (Day 29) due to death.

Other Significant Adverse Event (coded term [reported term]): HYDROCEPHALUS [HYDROCEPHALUS]

On 21JAN1988 (Day 1) the subject experienced a hydrocephalus (mild) which was considered a significant adverse event. At the time of the event, the subject was taking 40 mg/h of placebo and had been at this dose for 1 day. The significant AE occurred on the first day of dosing with any study medication. Trial medication had an action of drug withdrawn as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a ± 3 -day window of the onset of the significant AE included vasoconstriction (moderate) and vomiting (mild). Concomitant medications taken at the onset of the significant AE included potassium supplements, codeine compound 1/2, docusate sodium and multivitamins.

The investigator considered the AE to be not related to study medication. The final outcome of the event was reported as recovered/resolved on 02FEB1988 (Day 13).

Other Significant Adverse Event (coded term [reported term]): PYREXIA [PYREXIA]

On 25JAN1988 (Day 5) the subject experienced a pyrexia (mild) which was considered a significant adverse event. At the time of the event, the subject was taking 40 mg/h of placebo and had been at this dose for 5 days. The significant AE occurred 4 days after the first dose of any study medication. Trial medication had an action of dose not changed as a result of the event. It is not known from the case report form if therapeutic measures were administered to treat the event.

Adverse events that occurred within a ± 3 -day window of the onset of the significant AE included vomiting (mild). Concomitant medications taken at the onset of the significant AE included potassium supplements, docusate sodium, multivitamins and codeine compound 1/2.

The investigator considered the AE to be not related to study medication. The final outcome of the event was reported as recovered/resolved on 31JAN1988 (Day 11).



JMP[®] Clinical

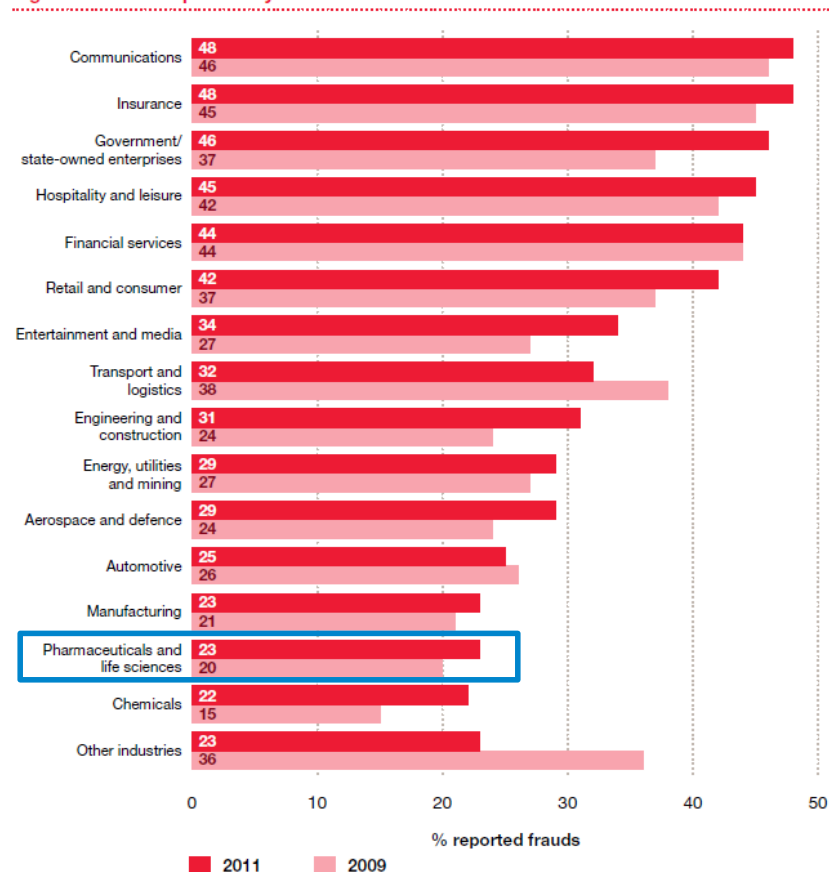
Fraud Detection



FRAUD DETECTION

- What is fraud? 'fraud' specifically to refer to data fabrication (making up data values) and falsification (changing data values).
- Recent cases of fraud in clinical trials have attracted considerable media attention: Fraud is a million-dollar business and it is increasing every year. The PwC global economic crime survey of 2009 suggests that close to 30% of companies worldwide have reported being victims of fraud in the past year.

Figure 9: Fraud reported by industries



% respondents representing individual industry sectors

PricewaterhouseCoopers LLP

FRAUD MOTIVATIONS

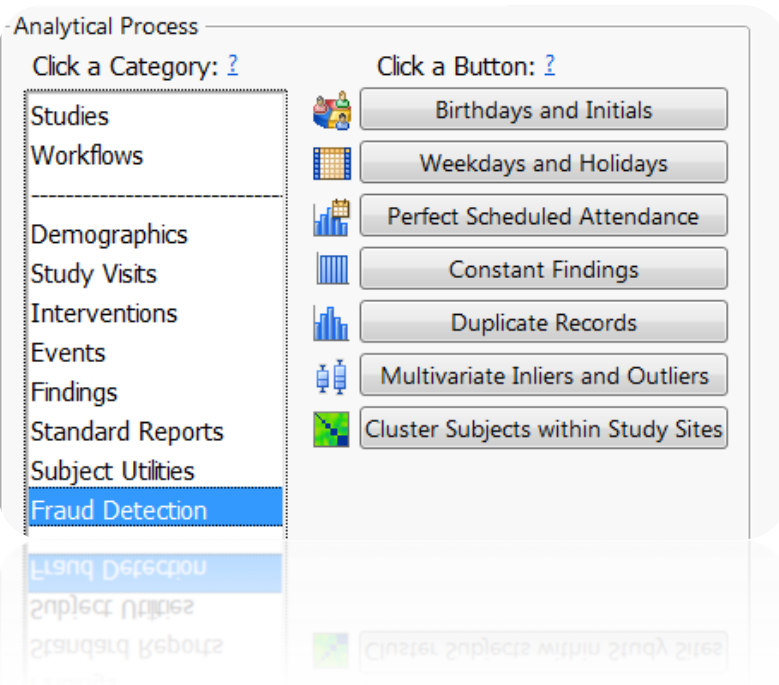
- Financial
- Progress one's career
- Overwork
- Conflicts of Interest



FRAUD IMPACTS

- Costs to the pharmaceutical sponsor because of additional resources for detecting fraud and eventually rework
- Pharmaceutical organisation reputation
- Dignity, rights, well-being and safety of research participants

JMP CLINICAL FRAUD DETECTION



- Identify

- Multiple enrolment of same subject
- Visits on weekends or holidays
- Constant labs, vital signs and ECG values
- Duplicate vital signs records
- Inliers and Outliers values within investigator sites
- Clusters of subjects with similar values within study sites

JMP CLINICAL FRAUD DETECTION

- Birthdays and Initials

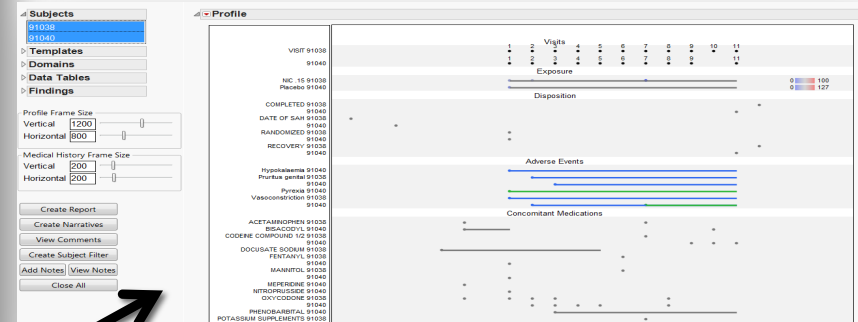
- Match subjects based on birthdates or initials to identify subjects that enroll in the study more than once and link to patient profiles for further investigations

List of Subjects with Duplicates for Birthday

Depending on birthday window or missing initials, subjects can appear in more than one matching bin.

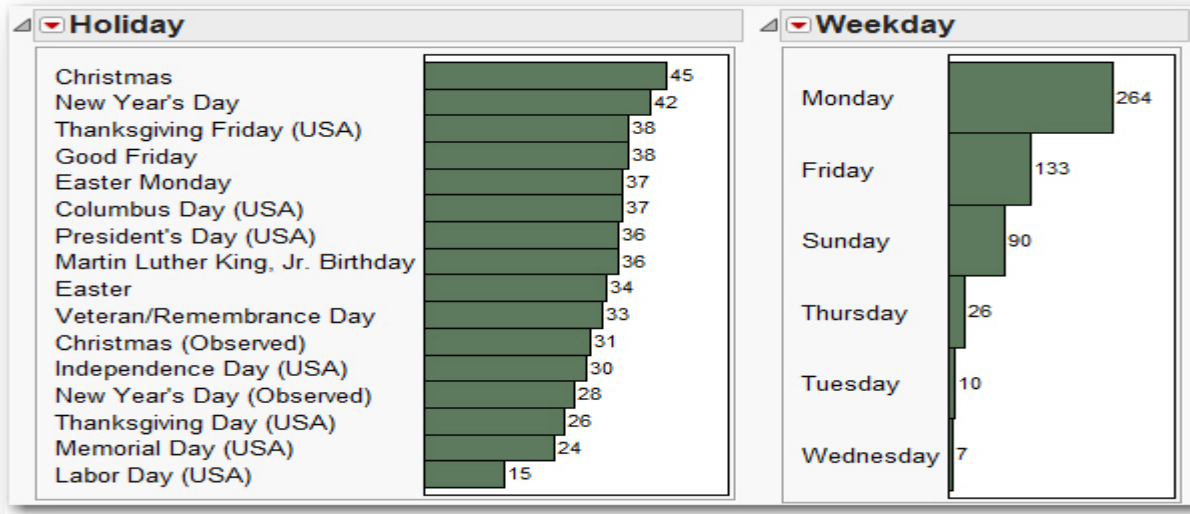
List of Subjects with Duplicates for Birthday

Matching Variable Value	Unique Subject Identifier	Study Site Identifier	Date/Time of Birth	Sex	Race	N
15Apr1915	141001	14	1915-04-15	M	WHITE	1
	442001	44	1915-04-15	F	WHITE	1
01Jan1917	392012	39	1917-01-01	F	OTHER	1
	41018	04	1917-01-01	M	WHITE	1
11Aug1925	221020	22	1925-08-11	M	BLACK OR AFRICAN AMERICAN	1
	282003	28	1925-08-11	F	WHITE	1
28Jul1928	241003	24	1928-07-28	F	WHITE	1
	81011	08	1928-07-28	F	WHITE	1
13Nov1935	141021	14	1935-11-13	F	OTHER	1
	231027	23	1935-11-13	F	WHITE	1
25Aug1937	31006	03	1937-08-25	M	WHITE	1
	31012	03	1937-08-25	F	WHITE	1
23Mar1938	171001	17	1938-03-23	M	WHITE	1
	271014	27	1938-03-23	F	WHITE	1
29May1939	11034	01	1939-05-29	F	WHITE	1
	161003	16	1939-05-29	F	WHITE	1
21Jan1941	282008	28	1941-01-21	F	BLACK OR AFRICAN AMERICAN	1
	351006	35	1941-01-21	M	WHITE	1
09Jul1941	11033	01	1941-07-09	F	WHITE	1
	392017	39	1941-07-09	F	WHITE	1
27Aug1943	11048	01	1943-08-27	F	WHITE	1
	291002	29	1943-08-27	F	ASIAN	1
22Feb1947	201018	20	1947-02-22	M	WHITE	1
	81023	08	1947-02-22	M	WHITE	1
23Jan1949	141013	14	1949-01-23	F	ASIAN	1
	461023	46	1949-01-23	M	WHITE	1
09Feb1954	161016	16	1954-02-09	F	WHITE	1
	241011	24	1954-02-09	F	WHITE	1
15Oct1955	141054	14	1955-10-15	F	WHITE	1
	551055	55	1955-10-15	F	WHITE	1
18Oct1956	91038	09	1956-10-18	F	BLACK OR AFRICAN AMERICAN	1
	91040	09	1956-10-18	F	BLACK OR AFRICAN AMERICAN	1



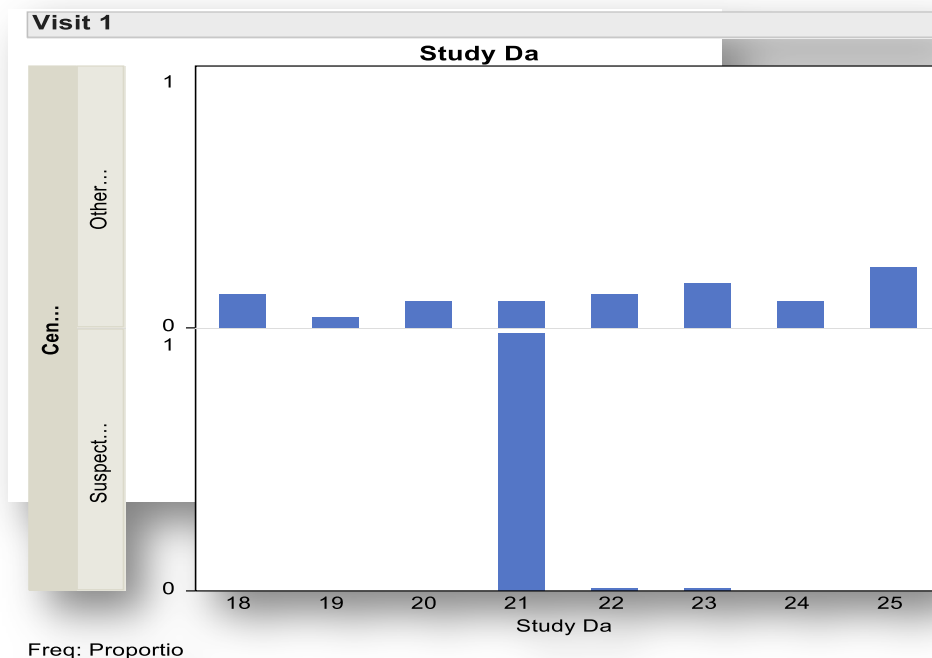
JMP CLINICAL FRAUD DETECTION

- **Holidays and weekdays**
 - Review visit dates to see if they occur on weekends or major holidays.



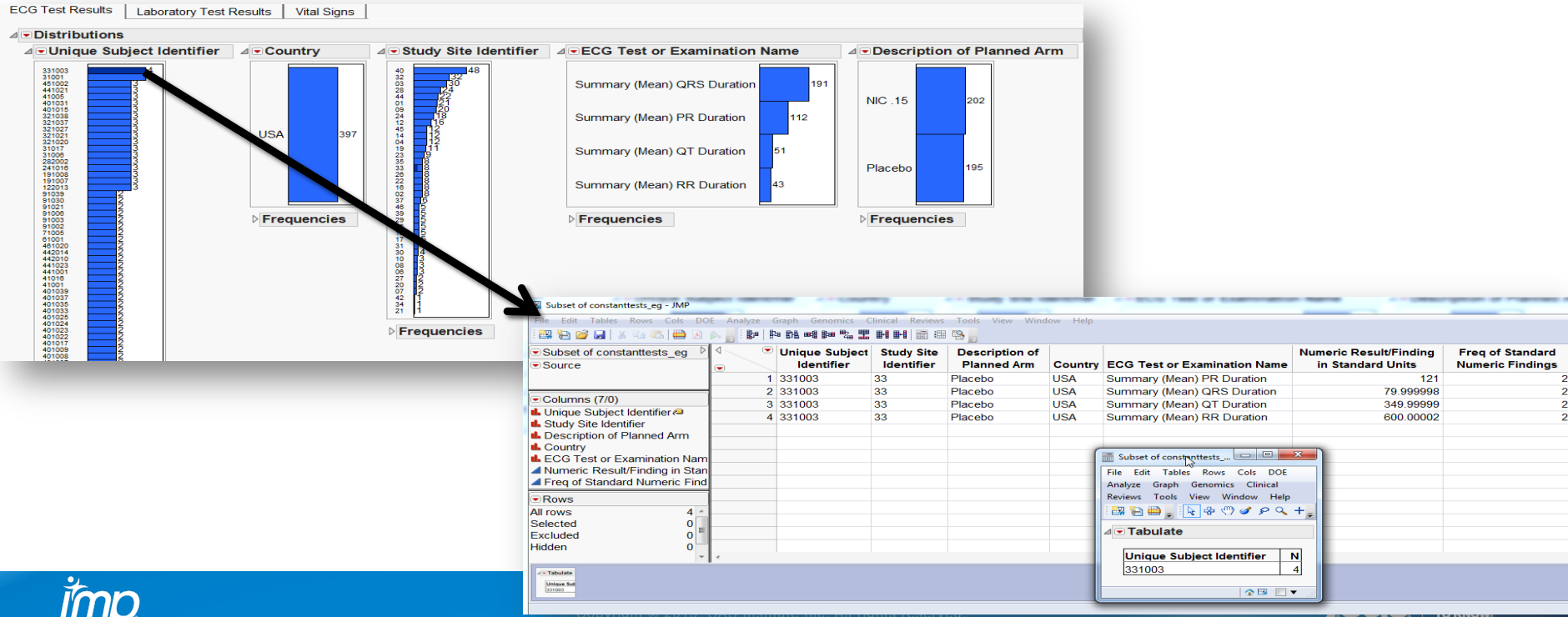
JMP CLINICAL FRAUD DETECTION

- **Perfect Schedule Attendance**
 - Perfect scheduling based on expected study visits may be too-good-to-be-true.



JMP CLINICAL FRAUD DETECTION

- Constant Findings
 - Let identify subjects with constant ECG, Laboratory and Vital Signs Tests.



- **Duplicate Records**

- ECG Test Results Laboratory Test Results Vital Signs

Duplicate records are based on numeric results in standard units.

▼ Distributions

▼ Duplicate ID

► Frequencies

▼ Unique Subject Identifier

► Frequencies

▼ Country

► Frequencies

▼ Study Site Identifier

► Frequencies

▼ Description of Planned Arm

► Frequencies

	Unique Subject Identifier	Study Site Identifier	Description of Planned Arm	Country	Date	Time	Vital Signs
1	441014	44	Placebo	USA	24Dec1988	0:10:00.00	
2	442004	44	NIC .15	USA	29Nov1988	0:14:00.00	

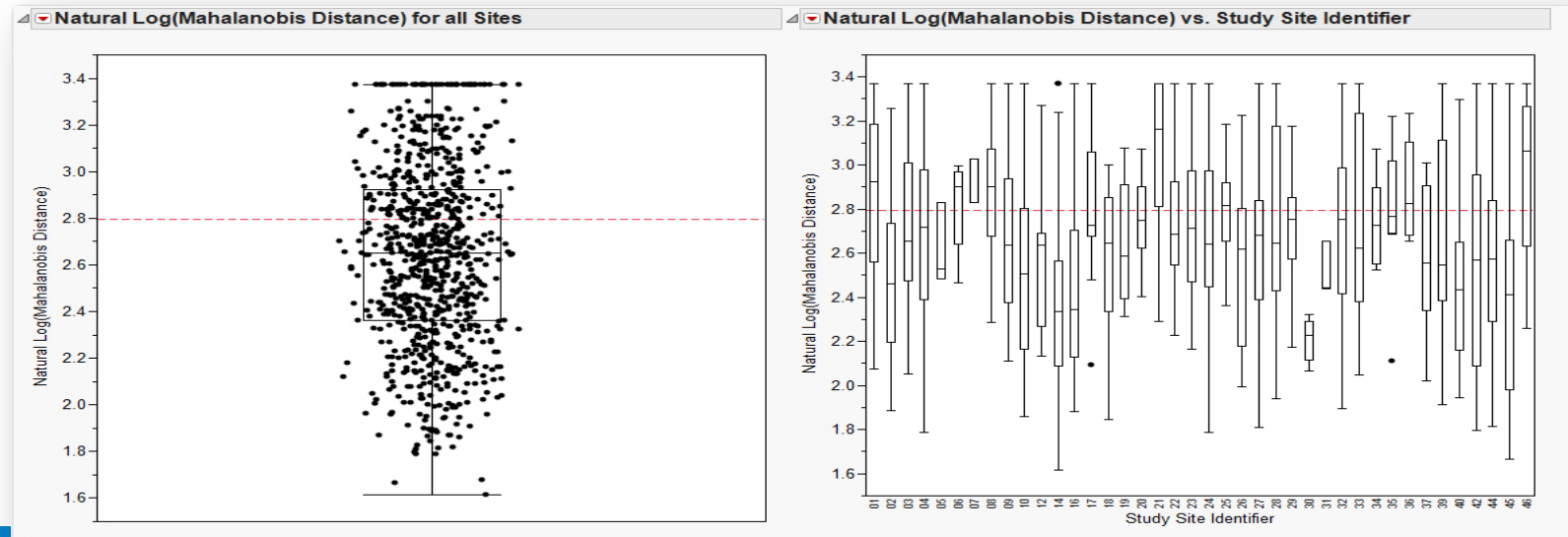
	Unique Subject Identifier	Study Site Identifier	Description of Planned Arm	Country	Date	Time	VISITNUM	Summary (Mean) PR Duration	Summary (Mean) QRS Duration	Summary (Mean) QT Duration	Summary (Mean) RR Duration	Duplicate ID
1	441014	44	Placebo	USA	24Dec1988	:0:10:00:00	14	180.00001	79.999998	360.00001	839.99997	18
2	442004	44	NIC. 15	USA	29Nov1988	:0:14:00:00	14	180.00001	79.999998	360.00001	839.99997	18

Subset of duplicate...

Unique Subject Identifier	N
441014	1
442004	1

JMP CLINICAL FRAUD DETECTION

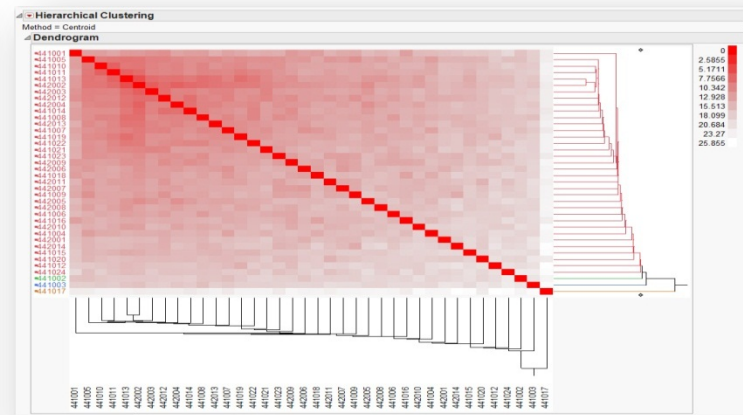
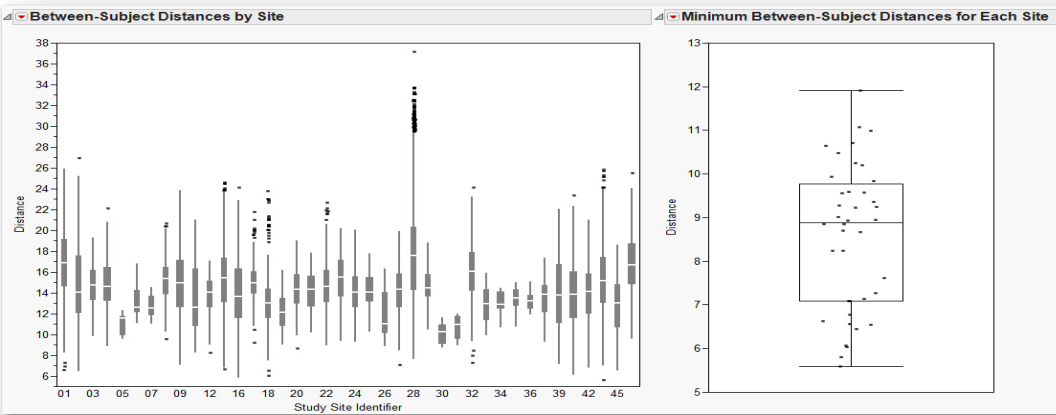
- **Multivariate outliers and inliers**
 - Multivariate outliers or inliers can identify subjects that are extreme compared to the center of the multivariate distribution of study variables. Inliers may be more important to identify fraud since these subject may be too-good-to-be-real.



FRAUD DETECTION

- **Cluster Subjects**

- Some of the previous analyses look for exact matches of study records between subjects. However, to identify potentially made-up subjects it is likely that values may be changed from one case report form to the next. The following analysis calculate pairwise distances of all subjects at a study site to determine how similar they are overall. Hierarchical clustering determines if they are very similar subsets of subjects within the study site.





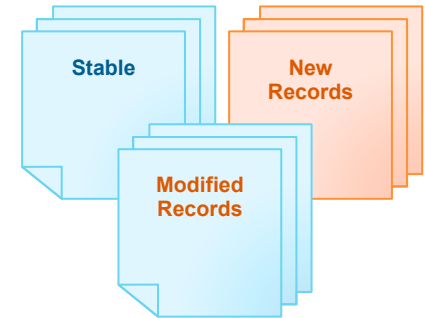
JMP[®] Clinical Snapshot Comparison



SNAPSHOT COMPARISONS

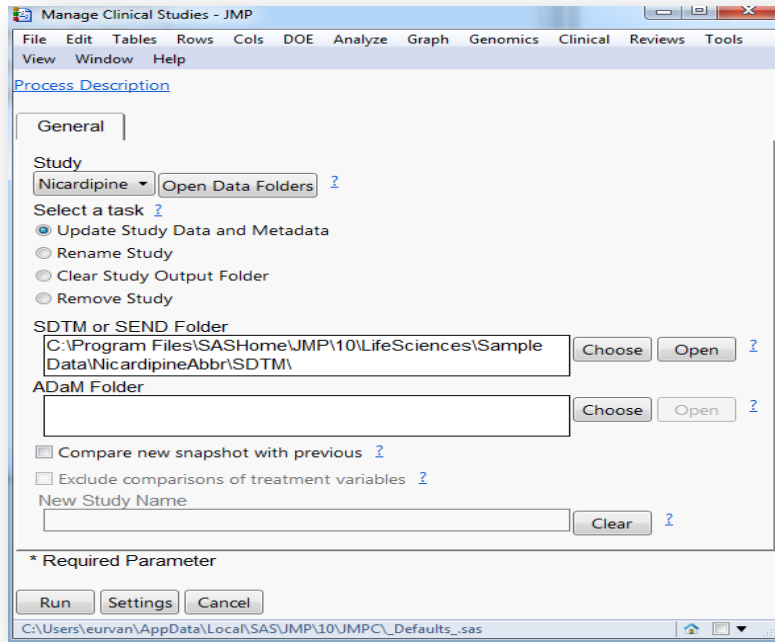
DATA REVIEW WITH SNAPSHOT COMPARISONS

- Can't you just show me the new data?
- Can't you just show me the modified data?
- Seriously, can't you just show me the new data?
- JMP Clinical Version 4.1 includes a snapshot comparison feature
 - Update study data to a new snapshot
 - Compares new and previous snapshot
 - Flag records
 - New
 - Dropped
 - Non-unique or duplicate
 - Modified records (creates a note for modification)
 - Flag subjects
 - Flags can be used to subset analyses or filter subjects that have new data
 - Nicardipine data cut off at 01Aug2009



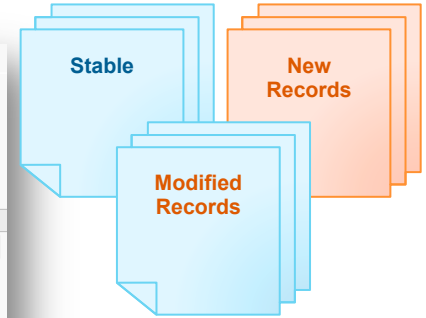
SNAPSHOT COMPARISONS

- Import different snapshots of clinical trial data into JMP Clinical



SNAPSHOT COMPARISONS

Status Distribution allows to track „Introduced“, „New Records“, „Modified Records“ and „Stable Records“



Distribution

Codes for subject-level review flags:

INTRODUCED: Subject is newly added to review. All records can be considered new.

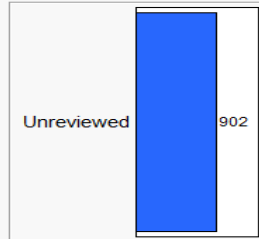
NEW RECORDS: Subject has new or modified records.

MODIFIED RECORDS: Subject has no new records, but previously available records have been modified.

STABLE: Subject has no new or modified records.

Distributions

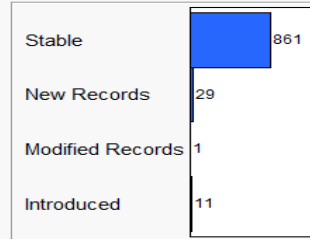
Review Status



Frequencies

Level	Count	Prob
Unreviewed	902	1.00000
Total	902	1.00000
N Missing	0	
1 Levels		

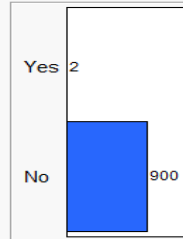
Review Flag



Frequencies

Level	Count	Prob
Introduced	11	0.01220
Modified Records	1	0.00111
New Records	29	0.03215
Stable	861	0.95455
Total	902	1.00000
N Missing	0	
4 Levels		

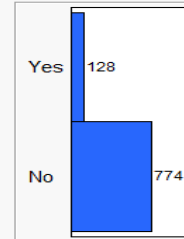
User Notes Available



Frequencies

Level	Count	Prob
No	900	0.99778
Yes	2	0.00222
Total	902	1.00000
N Missing	0	
2 Levels		

System Notes Available

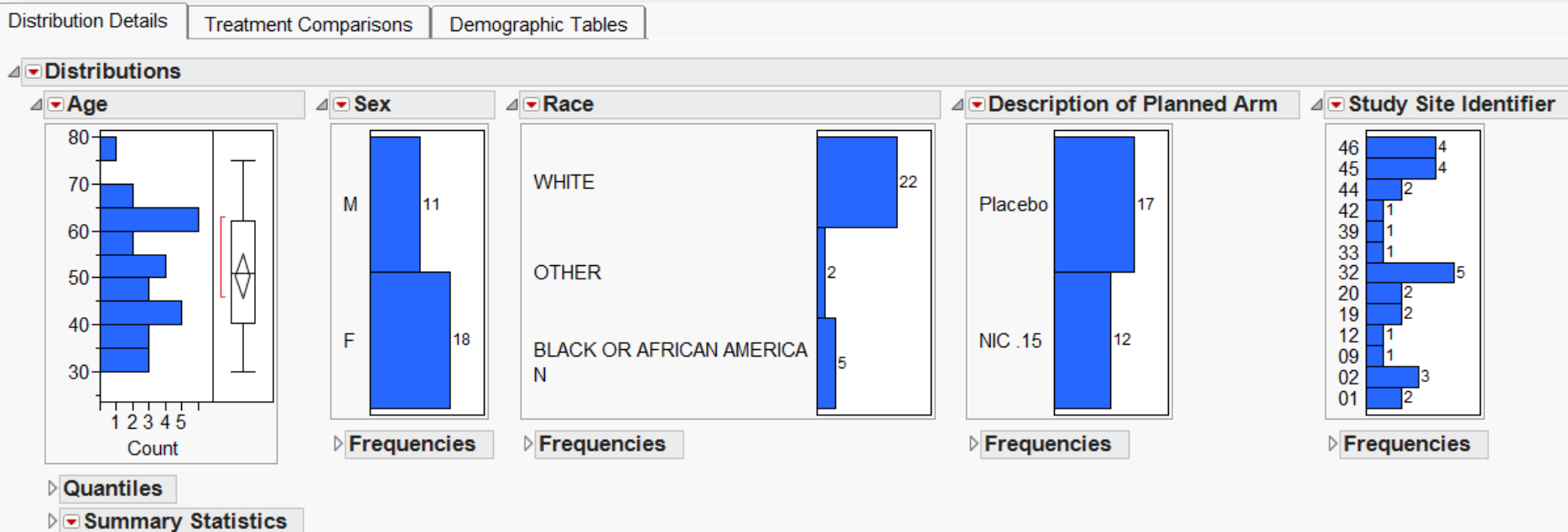


Frequencies

Level	Count	Prob
No	774	0.85809
Yes	128	0.14191
Total	902	1.00000
N Missing	0	
2 Levels		

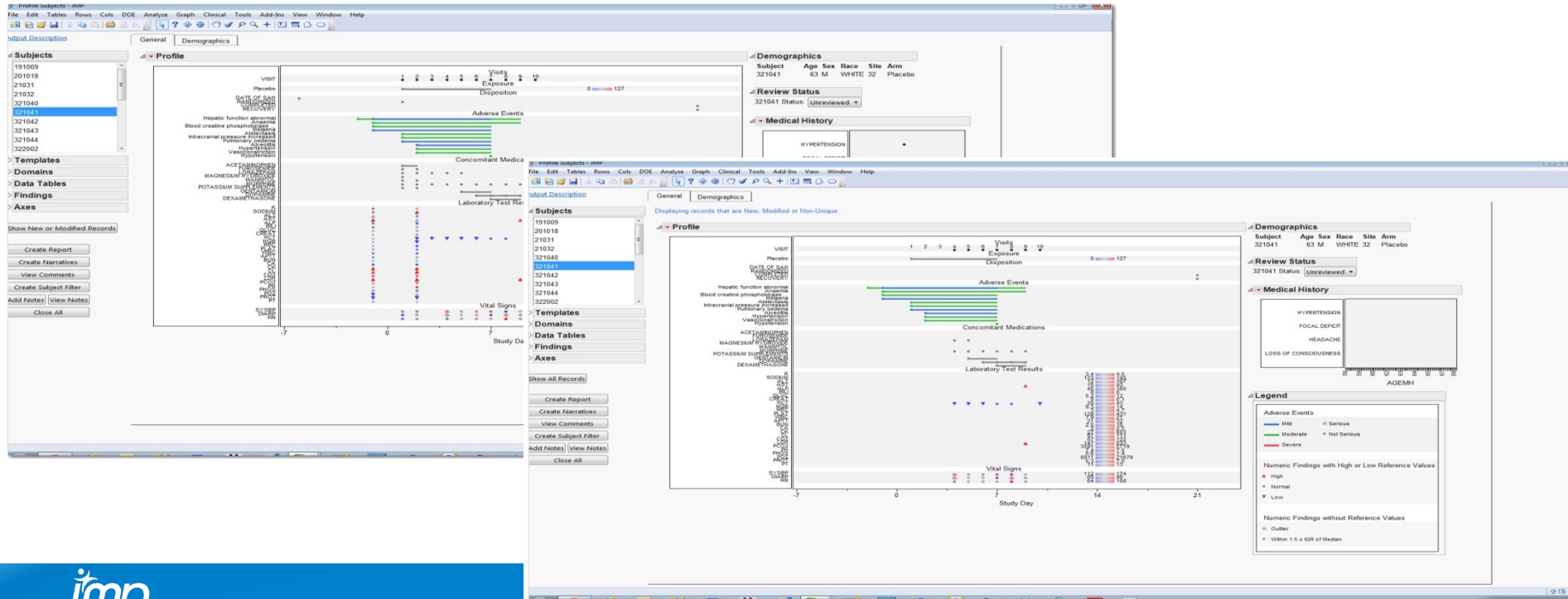
SNAPSHOT COMPARISON

- Report level review flags can be used to filter modified, new and stable records



SNAPSHOT COMPARISONS

- Subject level, review new, modified or all records



SNAPSHOT COMPARISONS

- Identify new or modified records in CDISC domain using the Domain Viewer

Output Description

Domains

AE

Drill Downs

Select a Domain Above then Click

View Domain

View Domain Notes

Show Dropped Records

Show Duplicates

Show Domain Keys

Select Records then Click

Profile Subjects

Create Subject Filter

Add Record-Level Notes

View Record-Level Notes

Domain Viewer

Codes for record-level review flags (merging based on domain keys):

NEW: Record was not previously available.

MODIFIED: Record was previously available, but data in one or more variables has changed.

STABLE: Record was previously available, no data has changed.

NON-UNIQUE: Record was previously available, but duplicates exist in the prior or current snapshot so that comparisons are not performed due to non-uniqueness of records.

DROPPED: Record was previously available, but does not exist current snapshot. Click 'Show Dropped Records' to view records for selected domain, if available.

Note: NEW records may include duplicates not considered among the records labeled NON-UNIQUE. Click 'Show Duplicates' to view all duplicates for selected domain, if available.

Note: All data is subset to the selected population and filtered subjects from the dialog.

The screenshot displays the JIMP software interface. The top section shows the 'Domain Viewer' with a list of domains and their associated records. The bottom section shows a detailed view of the selected records, including columns for Study Name, Keys, Keys Values of notes, Domain, Analytical Process, User, Note, and Date of Note.

Study Name	Keys	Keys Values of notes	Domain	Analytical Process	User	Note	Date of Note
Nicardipine Early Snapshot	STUDYID USUBJID	NICSAH1-321040	DM	ManageStudies	JMP Clinical	Value change in Subject Reference End Date/Time (RFPENDTC) from Missing to 1989-06-02T09:00:00	25Apr2013 4:33:21 PM
Nicardipine Early Snapshot	STUDYID USUBJID	NICSAH1-321041	DM	ManageStudies	JMP Clinical	Value change in Subject Reference End Date/Time (RFPENDTC) from Missing to 1989-06-04T12:30:00	25Apr2013 4:33:21 PM
Nicardipine Early Snapshot	STUDYID USUBJID	NICSAH1-321042	DM	ManageStudies	JMP Clinical	Value change in Subject Reference End Date/Time (RFPENDTC) from Missing to 1989-06-02T09:00:00	25Apr2013 4:33:21 PM

CONCLUSION

JMP® Clinical is

- 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



THE
POWER
TO KNOW.

For more information,
ask for a demo
or visit

[HTTP://WWW.JMP.COM/SOFTWARE/CLINICAL/](http://www.jmp.com/software/clinical/)