WHY MODERN CDISC DATA VISUALIZATION MATTERS IN CLINICAL TRIALS.

Valerie Nedbal, PhD, SAS Institute GmbH
Egbert Van Der Meulen, PhD, Ferring Pharmaceuticals

INTRODUCTION TO RISK BASED MONITORING

- Clinical Trials are performed at different sites (hospitals) where patients are undergoing treatment with a particular drug. Those patients are followed for drug efficacy and safety. In some cases, because of the drug, patients are having severe adverse events, are withdrawing, are other non-wished effects or events. This can happen at particular sites and those sites must be monitored very closely. Those sites are flagged as underperforming.

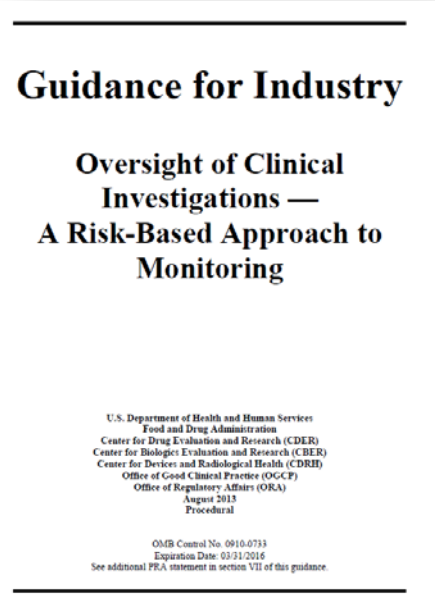
- Current operational practices used in clinical trials are expensive and do not guarantee data quality. Such as “Source Data Verification”, track CRFs from data source for completeness, accuracy, and verifiable. This is done by on-site monitoring from medical doctors that monitors on site the performance of the different sites.

- Through modernization, including use of technology enablers, efficiencies can be gained without impacting subject safety by implementing quality risk management approaches to clinical trial oversight.

- There is movement of on-site monitoring to centralized risk based monitoring

RISK BASED MONITORING

REGULATORS GUIDANCE since 2011



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.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 August 2011
EMA/INS/GCP/394194/2011
Compliance and Inspection

Reflection paper on risk based quality management in clinical trials
Draft

It has been suggested that a statistical approach to central monitoring can “help improve the effectiveness of on-site monitoring by prioritizing site visits and by guiding site visits with central statistical data checks,”

INTRODUCTION TO RISK BASED MONITORING

How well does the sites performing, can enable life sciences companies to target and prioritize resources around identifiable risks with a more centralized risk based monitoring approach?

Risk based monitoring is all about

- Patient Safety is of paramount concern
- Eligible patients are being enrolled
- Protocol procedures are being followed
- Accurate data are being collected

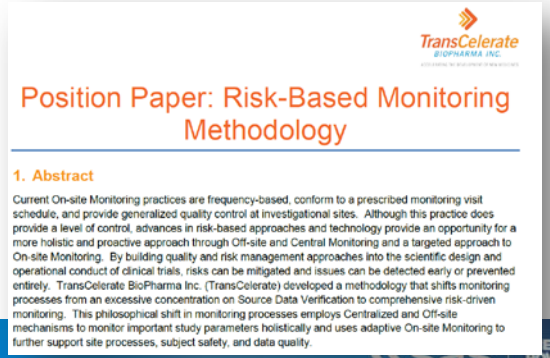
- **Advantages**:
  - Site performance
  - Protocol compliance
  - Monitoring standards

- **The outcome of RBM:**
  - Up to 30% of a clinical trial cost is site monitoring
  - Average cost of phase III trial depends on therapeutic area and varies between $10M to $30M.
  - RBM could reduce clinical trial cost by 10%, perhaps more.

TRANSCELERATE

- Ten biopharmaceutical companies announced Sept. 19 **2012** the formation of TransCelerate BioPharma Inc., a nonprofit intended to accelerate new medication development. Nowadays, 18 members

- TransCelerate BioPharma Inc. (TransCelerate) developed a methodology that shifts monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk-driven based monitoring.



TransCelerate BIOPHARMA INC.

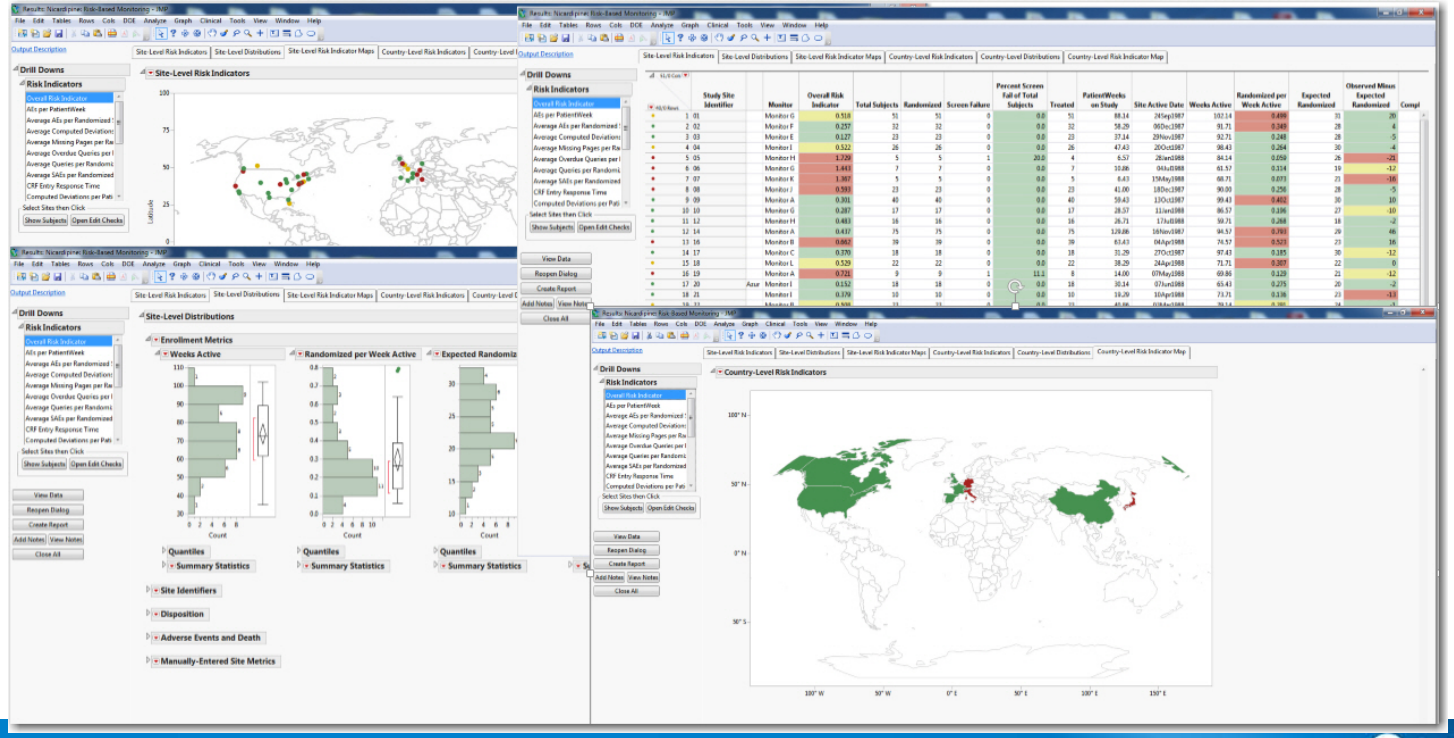
Position Paper: Risk-Based Monitoring Methodology

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. By building quality and risk management approaches into the scientific design and operational conduct of clinical trials, risks can be mitigated and issues can be detected early or prevented entirely. TransCelerate BioPharma Inc. (TransCelerate) developed a methodology that shifts monitoring processes from an excessive concentration on Source Data Verification to comprehensive risk-driven monitoring. This philosophical shift in monitoring processes 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.

EXAMPLE RISK-BASED MONITORING METHODS

- Employ risk indicators to rate potentially problematic sites for further follow-up



Agenda

- What is Central Statisticial Monitoring (CSM) ?
- What should be top-priorities?
- How are we presently implementing CSM
- A demonstration of the resulting **SAS JMP Clinical template for CSM (beta version)**
- Practical aspects
- Questions

What is CSM, Central Statistical Monitoring ?

FERRING PHARMACEUTICALS

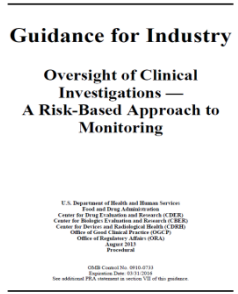
Quotes from FDA 2013 Guidance on Risk-Based Monitoring *

FERRING PHARMACEUTICALS

" Conduct statistical analyses to identify data trends not easily detected by onsite monitoring, such as …
checks for unusual distribution of data within and between study sites, such as too little variance …

"… routine review of submitted data to identify and follow-up on missing data, inconsistent data, data outliers, and …
that may be indicative of systemic or significant errors in data collection and reporting at a site"

"… focusing on the most critical data elements, are more likely than routine visits to all clinical sites and 100% data verification to ensure subject protection and overall study quality"


Guidance for Industry

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

* FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM269919.pdf

Ferring's Definition of Central Statistical Monitoring

FERRING PHARMACEUTICALS

Statistical analyses conducted in real time

1. **to detect, at the site level**, poor performance, **data errors, or fraud** by finding anomalous data patterns, such as

   - lack of variation,
   - odd correlation structures,
   - high or low incidences,
   - digit preferences,
   - and incorrect/clustered dates/times

2. to identify **general 'scientific' data trends** not easily detected by on-site monitoring

FERRING PHARMACEUTICALS

WHAT SHOULD BE TOP-PRIORITIES: FURTHER PRIORITIZED

1. **Fraud by particular sites**

2. **Generally ’poor’ recruitment by many sites**

Fraud in clinical trials

Detecting it and preventing it

FERRING PHARMACEUTICALS

Fraud is surprisingly hard to conceal. If you make up or alter the data in a clinical trial you will leave a trail that a good statistician can follow. **Christopher Weir** and **Gordon Murray** tell would-be detectives where the clues will be.

If a man defrauds you one time, he is a rascal; if he does it twice, you are a fool.
(Author unknown)

Clinical trials are important. Much hangs on their results – for the patients, new and better treatments; for the clinicians, prestige, promotion, pay. A trial that leads to negative results gets little thanks or credit within the medical profession – name-making academic papers do not follow. Given all that, the incentive to fabricate or to

fraud in clinical research is uncommon. Of the 22 cases from clinical trials recorded in the Committee for Publication Ethics database between 1997 and 2011, more relate to ethical review and only three to investigat. of potential data fabrication. Other estimates sugge that fraud occurs in rather less than 1% of publicly an commercially supported medical research. This may of course be an underestimate; by its nature undetected fraud is unrecorded fraud. Box 1 summarises two widely publicised fraud cases.

and *forging* (inventing data). Allegations of data tampering have been made against Ptolemy, Galileo, Newton, Dalton, Mendel, and Burt, to name just a few. R.A. Fisher's reanalysis of Gregor Mendel's data

INTRODUCTION

Go to:

Scientific fraud reappears with alarming consistency from paleontology to nanotechnology. Several studies have found that more than 40% of surveyed researchers were aware of misconduct but did not report it. Sheehan *et al*. reported in 2005 that 17% of surveyed authors of clinical drug trials reported that they personally knew of fabrication in research occurring over the previous 10 years.[1] Quality at sites is usually judged by audits and inspections. There has been as high as 23% (official action indicated) for cause inspections conducted by US Food and drug Administration (USFDA) over the last several years.[2] These kinds of results indicate that there exists a substantial problem. Fraud/misconduct can lead to study losing its entire credibility. Moreover, it can lead to ineffective or harmful treatment being available or patients being denied of effective treatment. This article discusses the difference between fraud and

1% ?

Table 2.3.2 : χ^2 value of deviation from expected and probability ($\chi^2 \geqslant$ observed value) for each group of experiments conducted by Mendel (Source : R. A. Fisher, *Annals of Science*, 1, 1936)

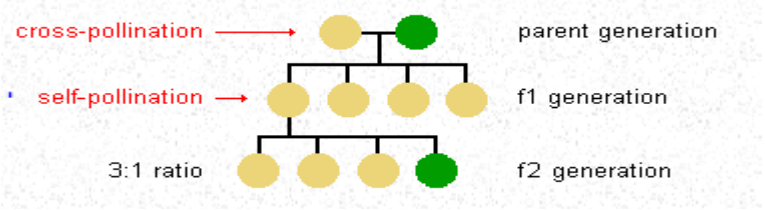
Experiments to test hypothesis	degrees of freedom	χ_0^2 (observed)	$P(\chi^2 > \chi_0^2)$
3 : 1 ratios	7	2.1389	0.95
2 : 1 ratios	8	5.1733	0.74
bifactorial	8	2.8110	0.94
gametic ratios	15	3.6730	0.9987
trifactorial	26	15.3224	0.95
Total	64	29.1186	0.99987
Illustrations of plant variation	20	12.4870	0.90
Total	84	41.6056	0.99993

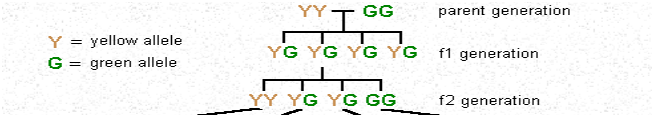
We see that the probabilities are extremely high in each case indicating that "data are probably faked to show a remarkably close agreement with theory". The overall probability of such good agreement is

$$1-.99993 = \frac{7}{100000}$$

which is very small. Fisher commented on this rare chance as follows :

> "Although no explanation can be expected to be satisfactory, it remains the possibility among others that Mendel was deceived by some assistant who knew too well what was expected. This possibility is supported by independent evidence that the data of most, if not all, of the experiments have been falsified so as to agree closely with Mendel's expectations".





Source: Statistics and Truth, Putting Chance to Work by C.R. Rao (1989)

Poor Recruitment as reflected by artifically inflated baseline values used for eligibility

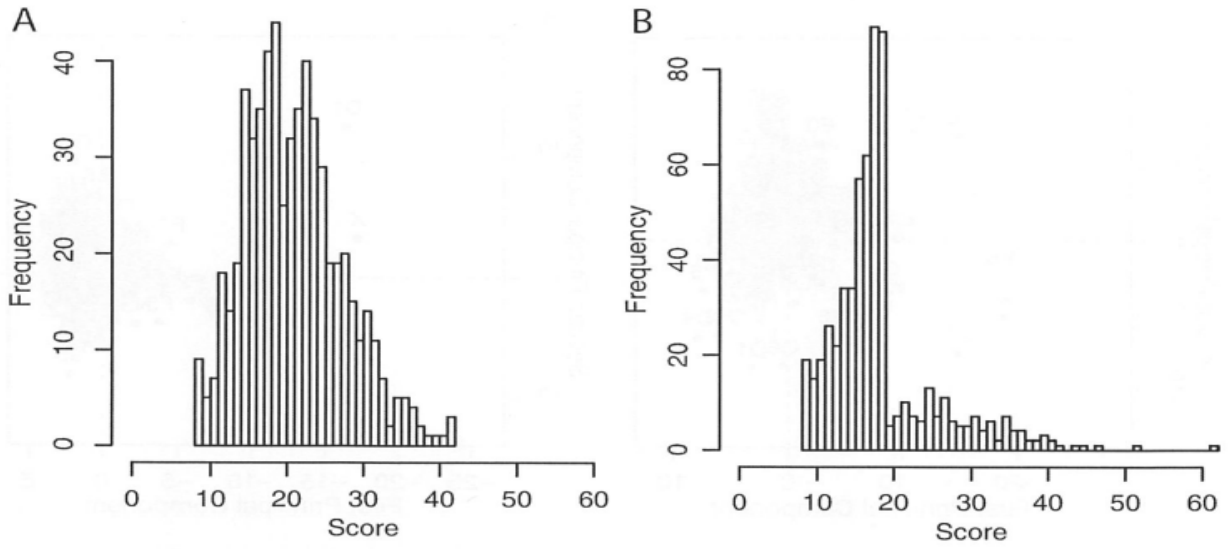
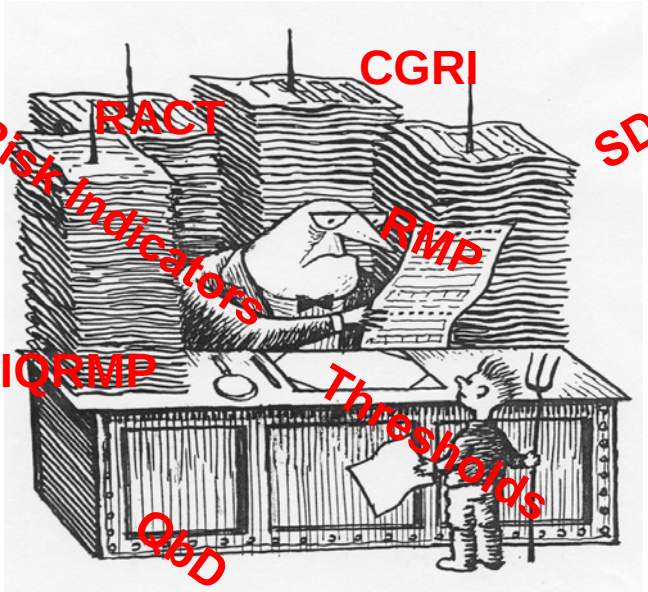
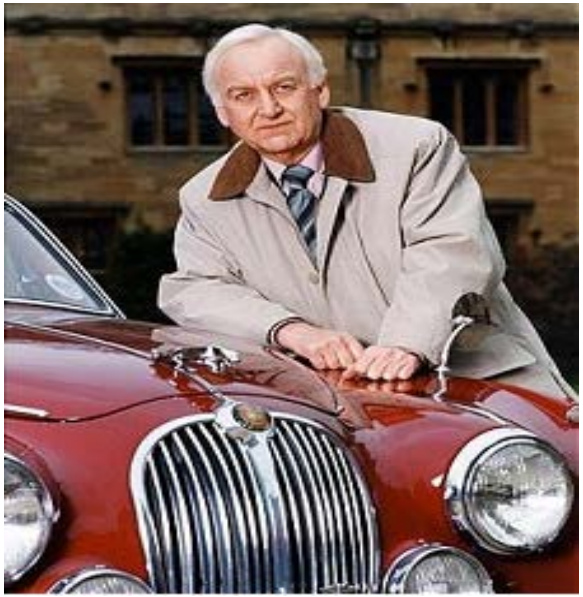


Figure 1. Distribution of psychiatric scores at entry in open-label phase (panel A) and prior to randomization (panel B). Patients with a psychiatric score below 20 were eligible.

An observed trend I worry about slightly



Careful not to turn into burocrates and stare at automated blinking lights



The core should be true detective work

”SAS JMP Clincial template”

Source: TransCelerate PP

HOW ARE WE PRESENTLY IMPLEMENTING CSM

- **Central Statistical Monitoring: SAS JMP Clinical**

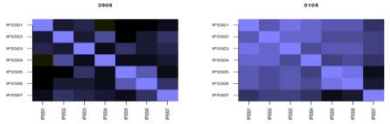
  Jointly with SAS (Denmark) have build a template (beta version) that a.o.

  (1) Allows evaluating site performance using statistical inference (p-values!)

  (2) Enables evaluation overall performance, particularly with regard to Recruitment Quality

- **Ferring is front runner**
  - **Template feeds back into future SAS JMP Clinical release**
  - **Collaboration with SAS JMP Cl in US (Richard Zink cs)**
  - **Yearly platform to share experiences with Roche/Novo a.o.**

Kasper Munck
Business Delivery Manager
SAS Institute A/S, Denmark



Richard ZInk

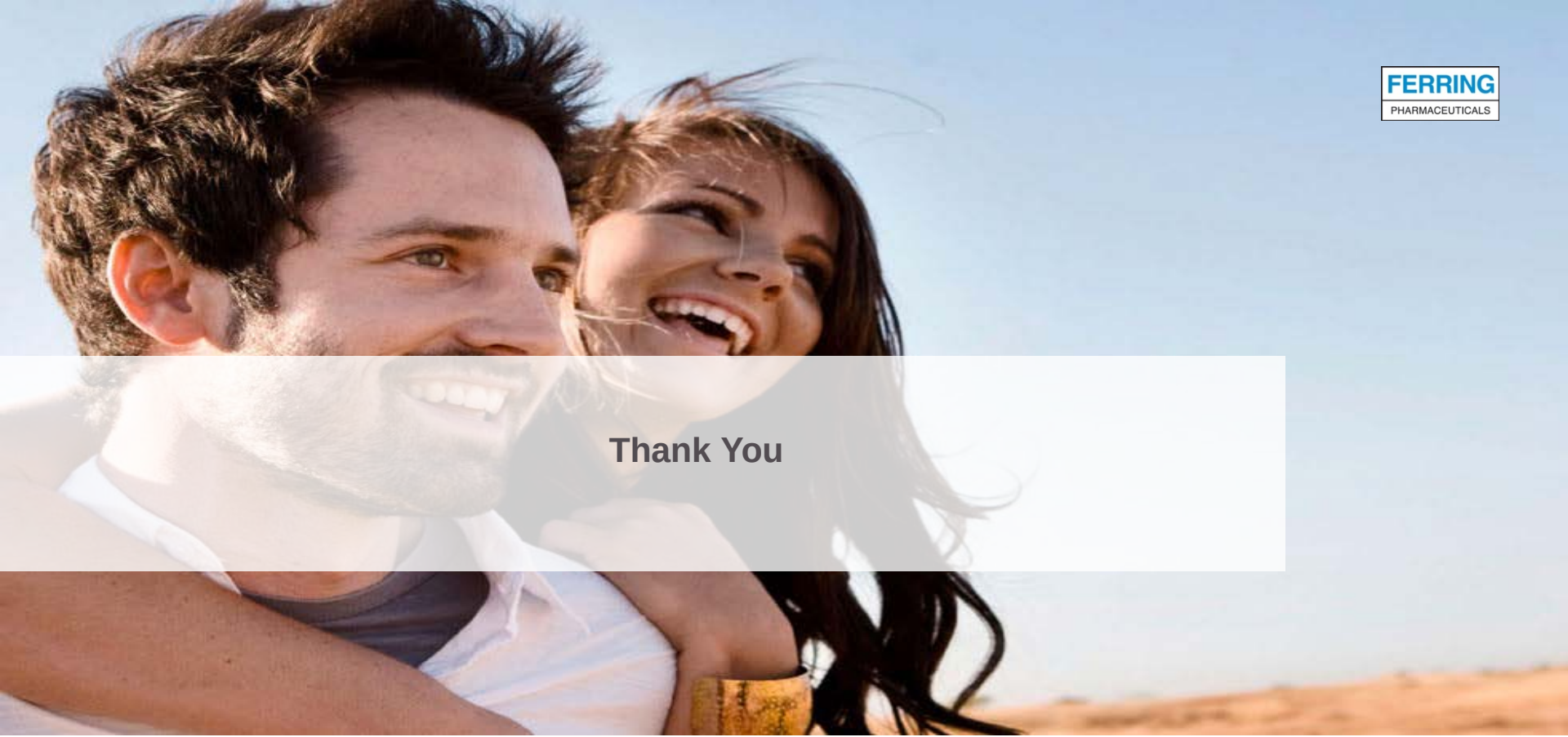
FERRING
PHARMACEUTICALS

A DEMONSTRATION OF THE SAS JMP CLINICAL TEMPLATE FOR CSM

sas THE POWER TO KNOW.

PRACTICAL ASPECTS

- Requires instant availability of SDTM/ADaM (from FPFV onward). Having eCRF and CDISC standards this is doable
- Additional routine role for trial statistician: data-mine the data from CSM perspective and discuss during clinical trial team meetings while trial is ongoing
- Have to dealing with ”Ongoingness” of the data
- Document: standard (push-on-one-button) auto-reporting during the meeting
- Define follow-up action as needed (e.g. re-train site, site- audit, stop trial, etc)
- Requires new SOP(s) on CSM only (after process has taken more shape)



FERRING
PHARMACEUTICALS

Thank You

PhUSE SDE, June 15, 2016

sas THE POWER TO KNOW.

QUESTIONS

BACK UP

CSM - AmsterdanTrial - JMP

File Edit Tables Rows Cols DOE Analyze Graph Clinical Tools View Window Help CentralStatisticalMonitoring

GLOBAL BIOMETRICS

PEOPLE COME FIRST AT FERRING

FERRING PHARMACEUTICALS

Centralized Statistical Monitoring

Trial:AmsterdanTrial

Overview | General Scientific | Site Performance | Actions

Study Options

Select Study: AmsterdanTrial

Save Report: Save RTF

Last Update: 09-11-2015 15:25:40 Update Analysis

Update Study Metadata Update Metadata

Overview of Study: AmsterdanTrial

Status

Analysis Completed

Demographics

Medical History

Analysis Missing

Primary End Points

Secondary End Points

Key Safety Report

Recruitment Trends

Reporting Dates & Times

PCA Analysis on PRO

Digit Preferences

Constant Findings

Duplicate Records

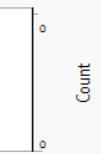
Inliers & Outliers

Birthdays & Initials

Site Variation

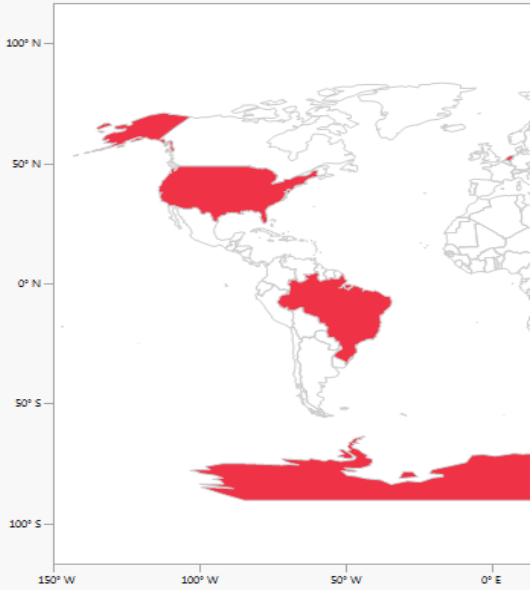
Count of Significant sites from Analysis

Site



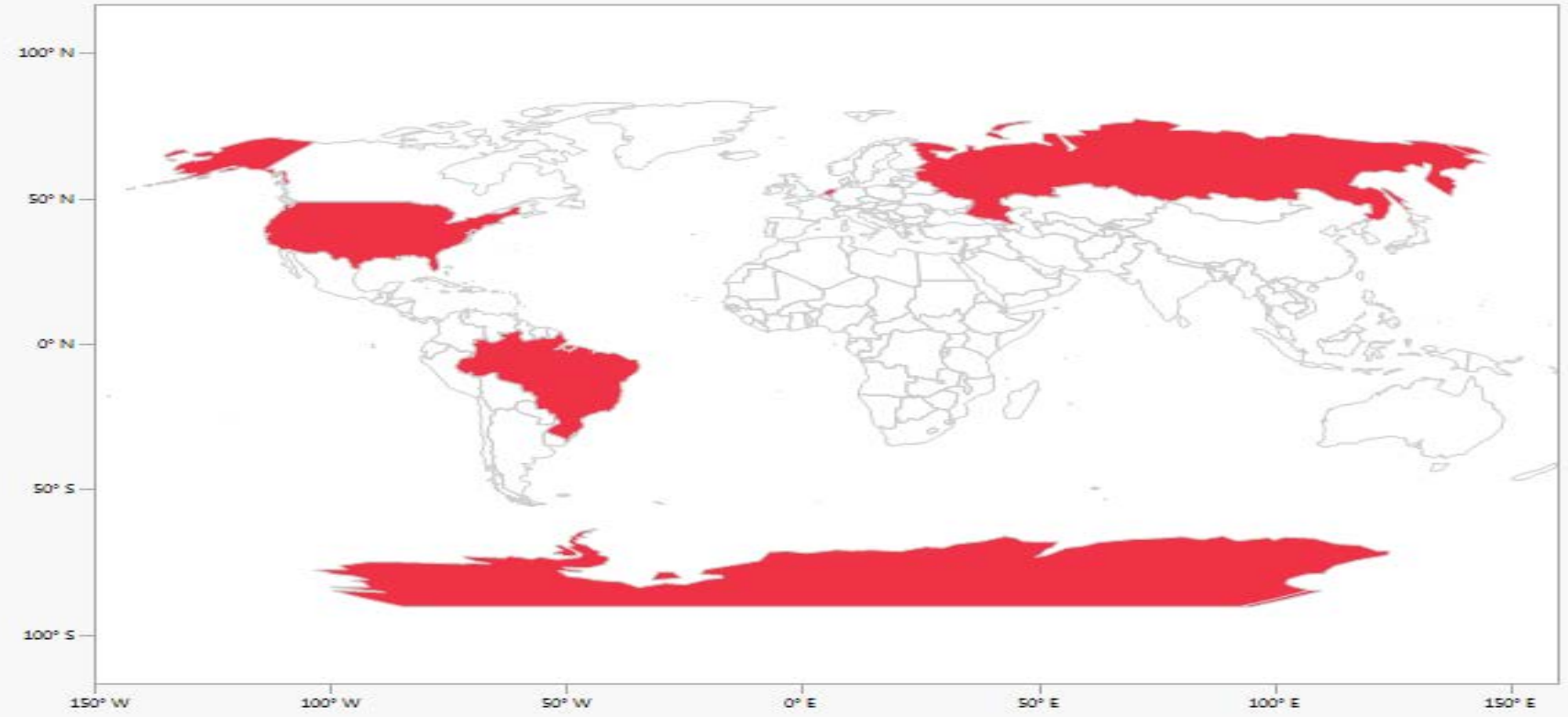
Min. number of Subjects required pr Site to be included in End Point Analysis: 2 Rerun End Point Analysis Must be integer and >=2

Country-Level Data



Trial:AmsterdanTrial

Country-Level Data



PEOPLE COME FIRST AT FERRING

Centralized Statistical Monitoring

Trial:AmsterdanTrial

Overview | General Scientific | Site Performance | Actions

General Scientific

Primary

Define Primary End Points

Key Secondary

Define Secondary End Points

Key Safety

Standard Safety Report

Treatment Emergent Adverse Event Listing
Table 7.1.3.2.1 of the GRP

Trial	Center	Patient	Age (YR)	Sex	Planned Treatment for Period 01	Time (days)	Body System	Preferred Term
NICSA01	10	101001	65	F	Placebo	2	GASTROINTESTINAL DISORDERS	Vomiting
NICSA01	10	101001	65	F	Placebo	28	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia
NICSA01	10	101001	65	F	Placebo	28	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pyrexia
NICSA01	10	101002	66	M				Vasoconstriction
NICSA01	10	101002	66	M				Hydrocephalus
NICSA01	10	101002	66	M				Pulmonary oedema
NICSA01	10	101002	66	M				Alveolitis
NICSA01	10	101002	66	M	NSC 17	10	INFECTIONS AND INFESTATIONS	Urinary tract infection
NICSA01	10	101003	31	F	Placebo	12		
NICSA01	10	101003	31	F	Placebo	1		
NICSA01	10	101003	31	F	Placebo	1		
NICSA01	10	101003	31	F	Placebo	12		
NICSA01	10	101004	48	F	NSC 17	1	NERVOUS SYSTEM DISORDERS	Coma

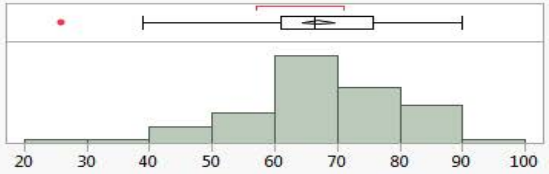
NO DATA
OR
ANALYIS NOT RUN

Update Report Data

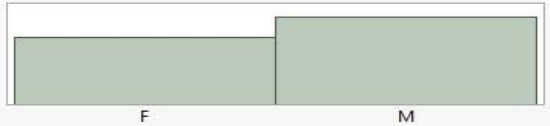
Demographics

Distributions

Age



Sex



Distribution

The Following Parameter(s) are signigficant regarding Study Site: {"Ethnicity"}

Centralized Statistical Monitoring

Overview | General Scientific | Site Performance | Actions

Site Performance

Subject Population by Study Site

	Count							
	Study Site Identifier							
	ATA01	BRA01	BRA02	NLD01	RUS01	RUS02	USA01	All
	9	27	10	6	7	22	7	88

Primary

Primary End Points

Time to death up until day 30 (days)

Define analysis for Primary End Point | Modify Primary End Points selection

Key Secondary

Please Define End Points

Centralized Statistical Monitoring

Trial:AmsterdanTrial

Site Performance

Subject Population by Study Site

	Count							
	Study Site Identifier							
	ATA01	BRA01	BRA02	NLD01	RUS01	RUS02	USA01	All
	9	27	10	6	7	22	7	88

Primary

Primary End Points

Time to death up until day 30 (days)

Define analysis for Primary End Point | Modify Primary End Points selection

Key Secondary

Please Define End Points

Reporting Dates & Times | Medical History | PCA Analysis of Patient Report Outcome (PRO)

Select Analysis - JMP

File Edit Tables Rows Cols DOE Analyze
Graph Clinical Tools View Window Help
CentralStatisticalMonitoring

Specifiy End Point Analysis

Time to death up until day 30 (days) Kaplan-Meier

Done

Site Performance

Subject Population by Study Site

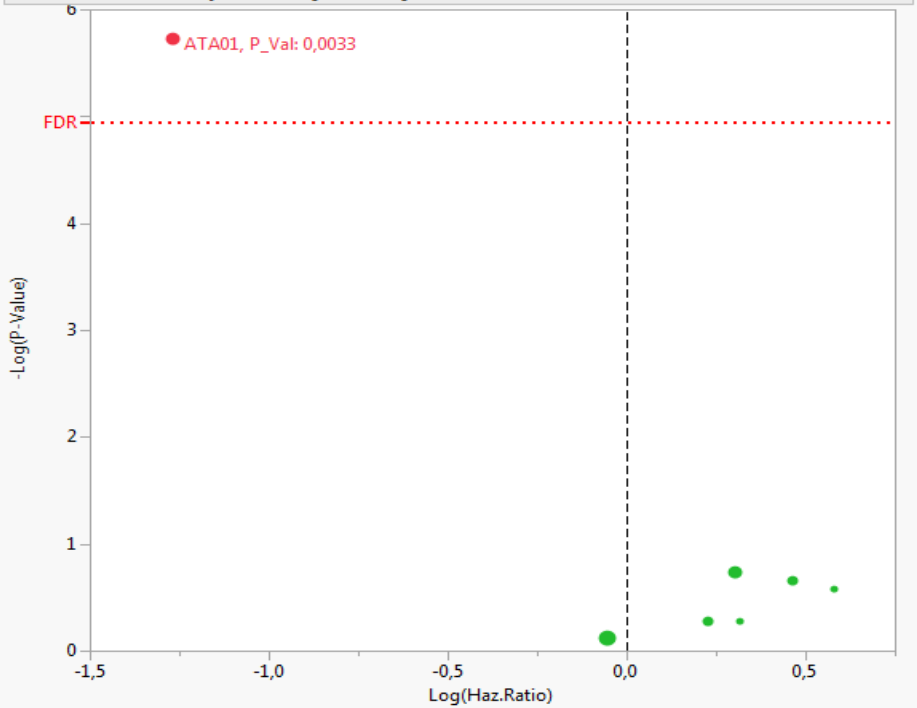
	Count							
	Study Site Identifier							
	ATA01	BRA01	BRA02	NLD01	RUS01	RUS02	USA01	All
	9	27	10	6	7	22	7	88

Primary

Primary End Points

Time to death up until day 30 (days)

Time to death up until day 30 (days)



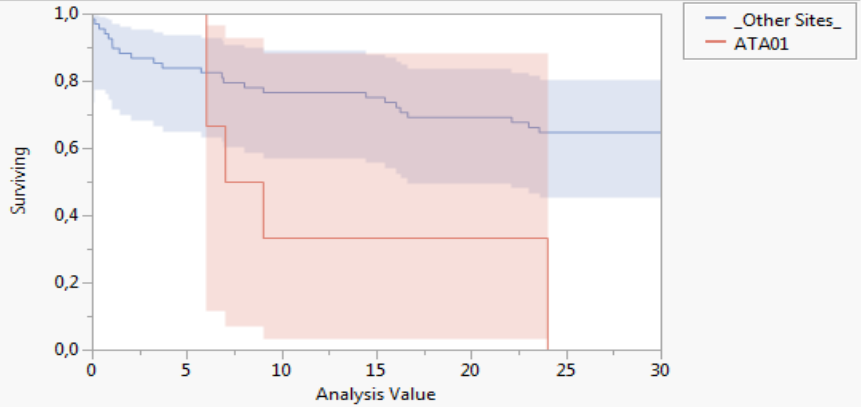
FDR is the Bonferroni adjustment

Bubblesize is based on # of Events

Kaplan-Meier

Product-Limit Survival Fit

Survival Plot



Time to event: Analysis Value

Censored by Censor

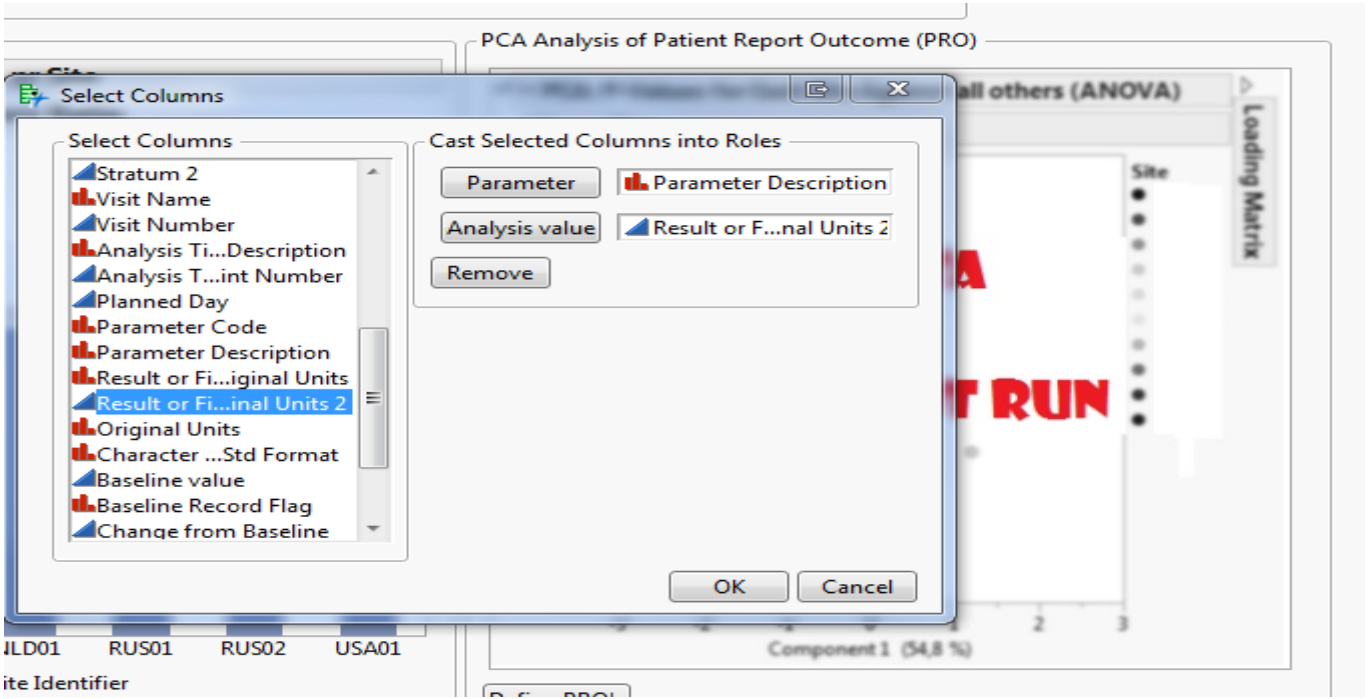
Censor Code 1

Grouped by Group

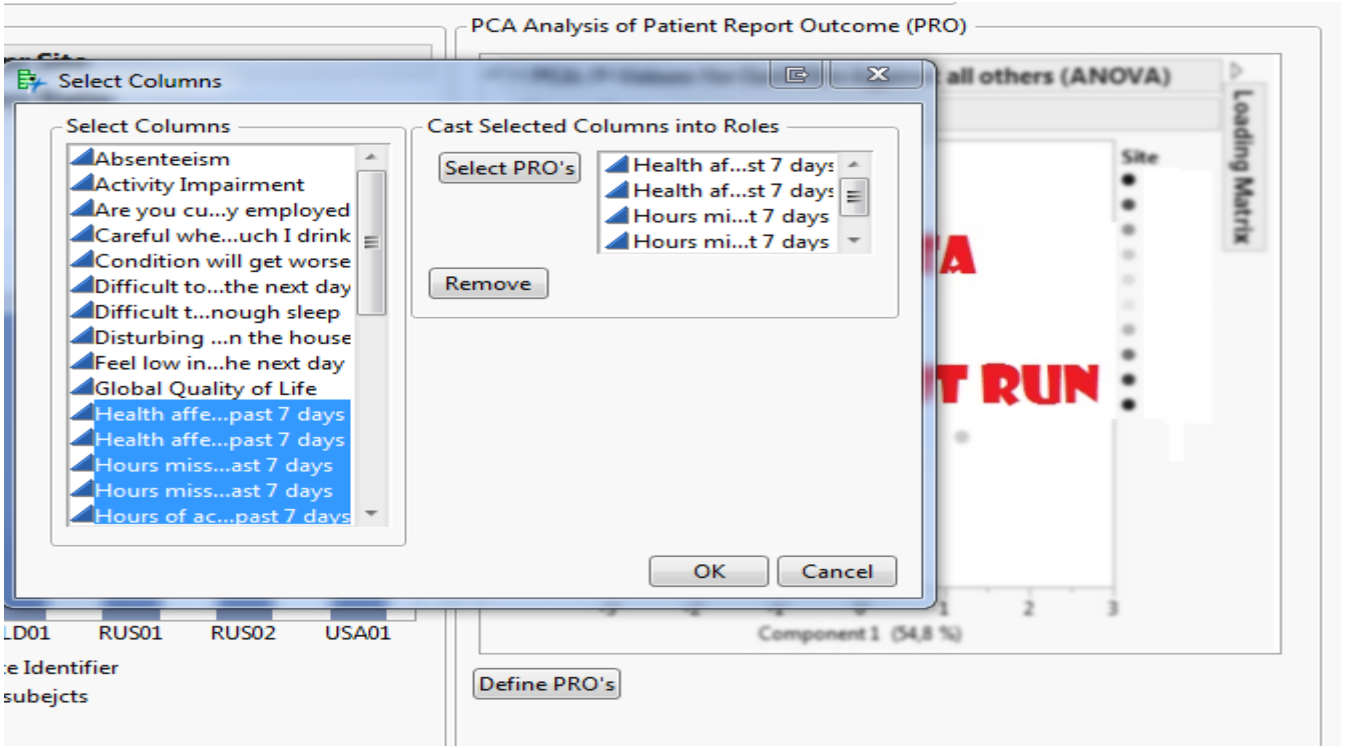
Tests Between Groups

Test	ChiSquare	DF	Prob>ChiSq
Log-Rank	8,6556	1	0,0033*
Wilcoxon	5,7433	1	0,0166*

SCREENSHOTS OF SAS JMP CSM TEMPLATE



SCREENSHOTS OF SAS JMP CSM TEMPLATE

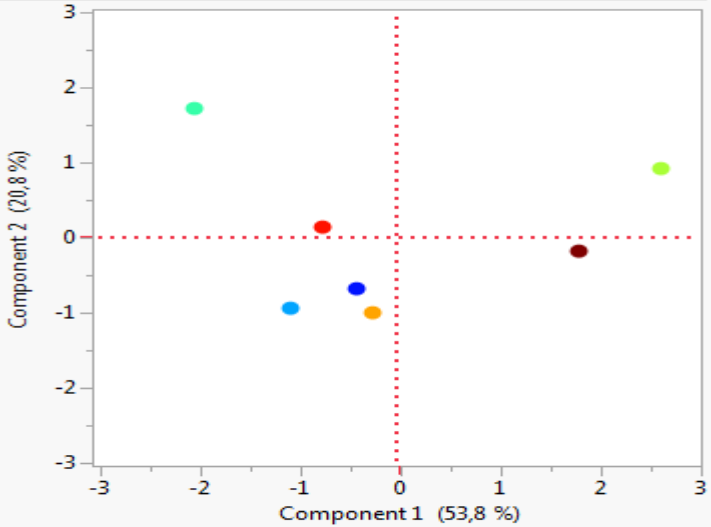


SCREENSHOTS OF SAS JMP CSM TEMPLATE

PCA Analysis of Patient Report Outcome (PRO)

PCA: -Log(P-Values) for Each Site Against all others (ANOVA)

Score Plot

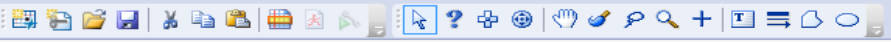


Delete PRO's

Loading Matrix

	Prin1	Prin2
Health affect activities past 7 days	0,82021	0,20619
Health affect productivity past 7 days	0,87600	0,18650
Hours missed due to health past 7 days	-0,50910	0,48270
Hours missed other to health past 7 days	-0,28802	0,83742
Hours of actual work past 7 days	0,95388	0,16190

File Edit Tables Rows Cols DOE Analyze Graph Clinical Tools View Window Help CentralStatisticalMonitoring



GLOBAL BIOMETRICS

PEOPLE COME FIRST AT FERRING

FERRING PHARMACEUTICALS

Centralized Statistical Monitoring

Trial:AmsterdanTrial

Overview | General Scientific | Site Performance | Actions

Actions

Action	Created by	Date of Creation	Status	Date of Completion	Comment	Option

Create Action

sas THE POWER TO KNOW.

Centralized Statistical Monitoring

Overview | General Scientific | Site Performance | Actions

Study Options

Select Study: AmsterdanTrial

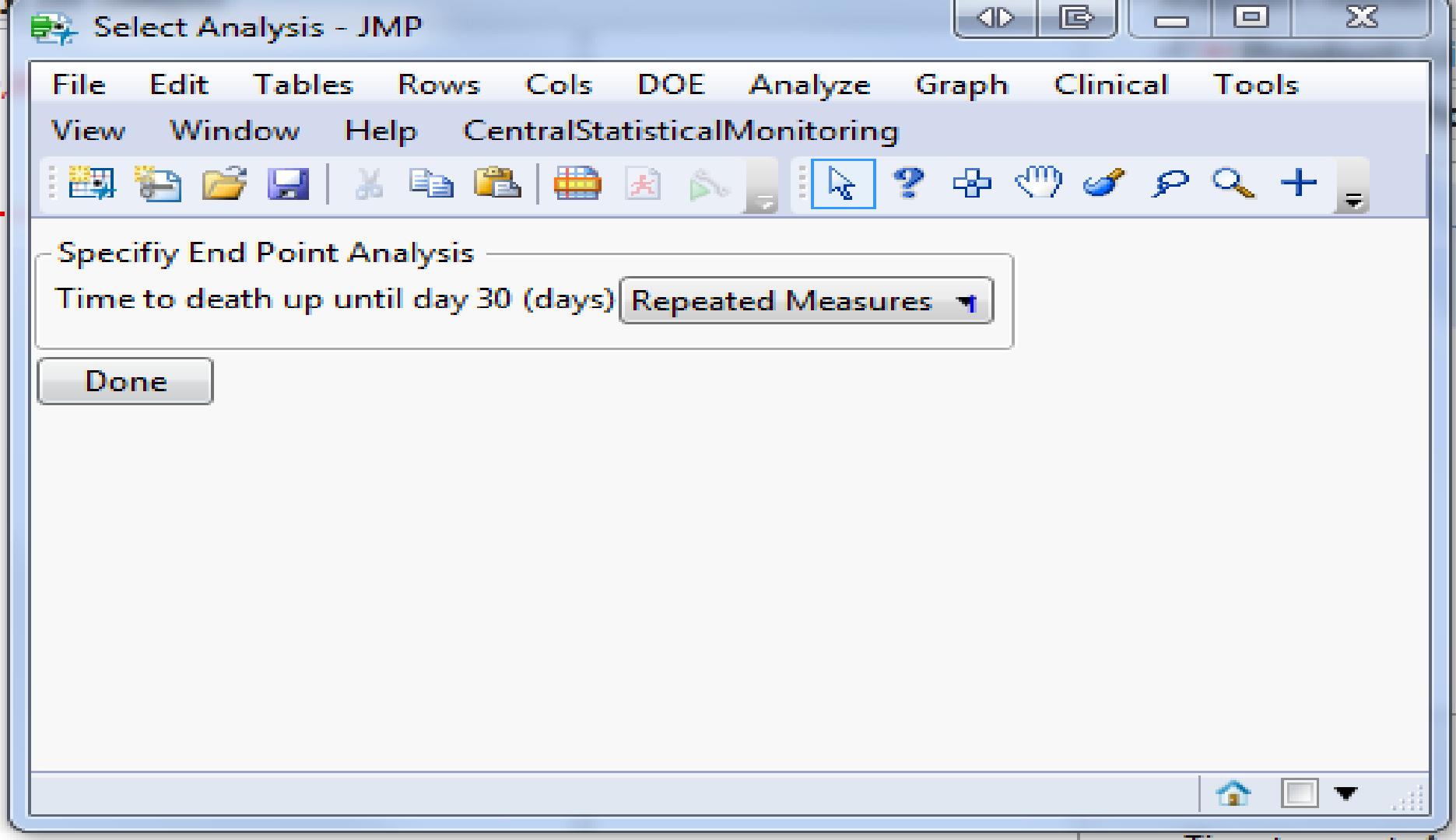
Last Update: 09-11-2015 15:25:40 Update Analysis

Save Report: Save RTF

Update Study Metadata Update Metadata

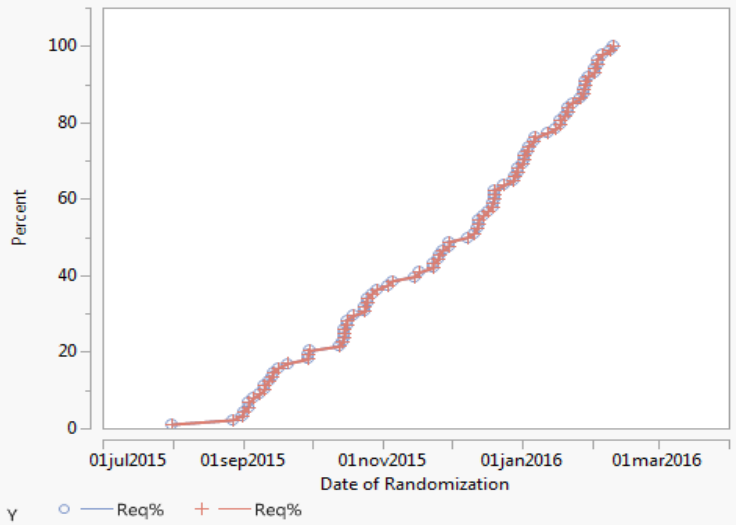
Overview of Study: AmsterdanTrial

Status


Select Analysis - JMP
File Edit Tables Rows Cols DOE Analyze Graph Clinical Tools
View Window Help CentralStatisticalMonitoring
Specifiy End Point Analysis
Time to death up until day 30 (days)
Repeated Measures
Done

Recruitment Trends

Recruitment Speed/Quality



Data Filter

Clear | Start Over | Favorites

Select | Show | Include

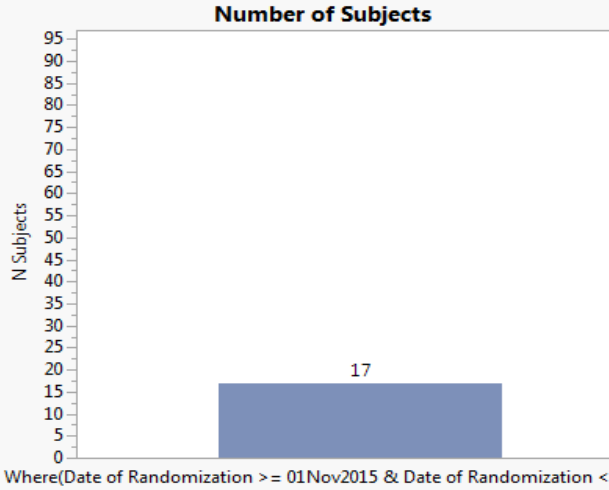
17 matching rows

Inverse

01nov2015 ≤ Date of Randomization ≤ 16dec2015

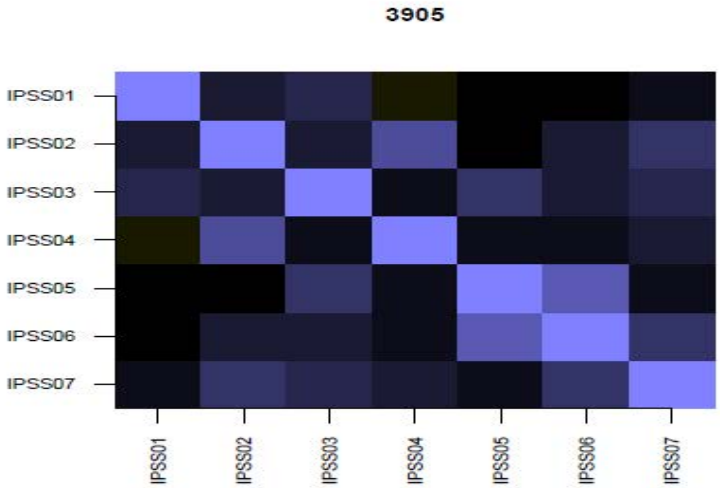
AND | OR

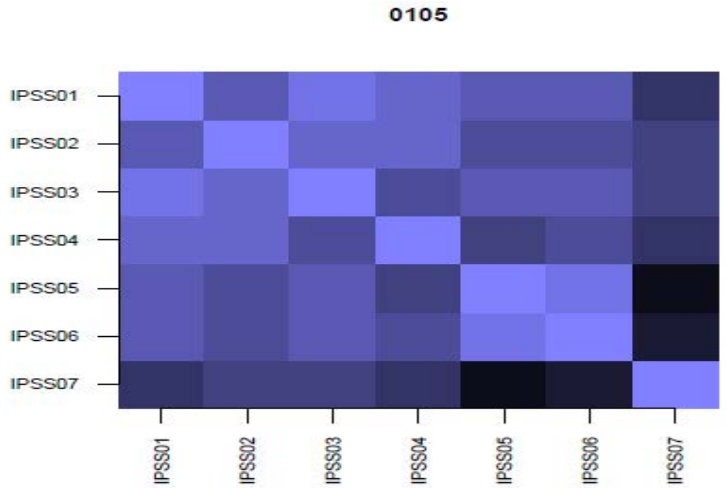
Graph Builder



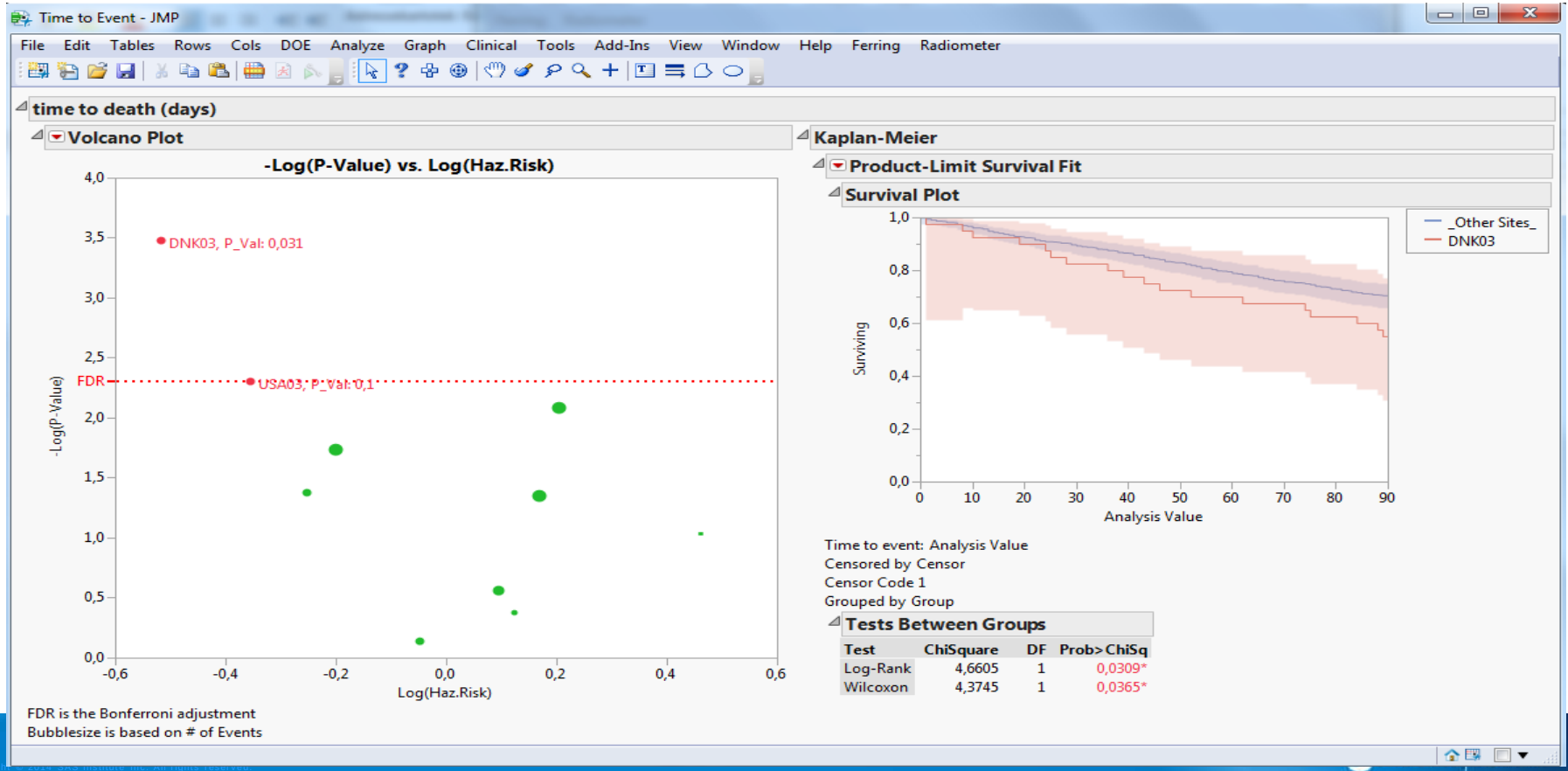
Ad –hoc Programming in R (instead of SAS)

EXAMPLE (CS36, IPSS ITEMS): CORRELATION MATRIX PLOTS BY SITE

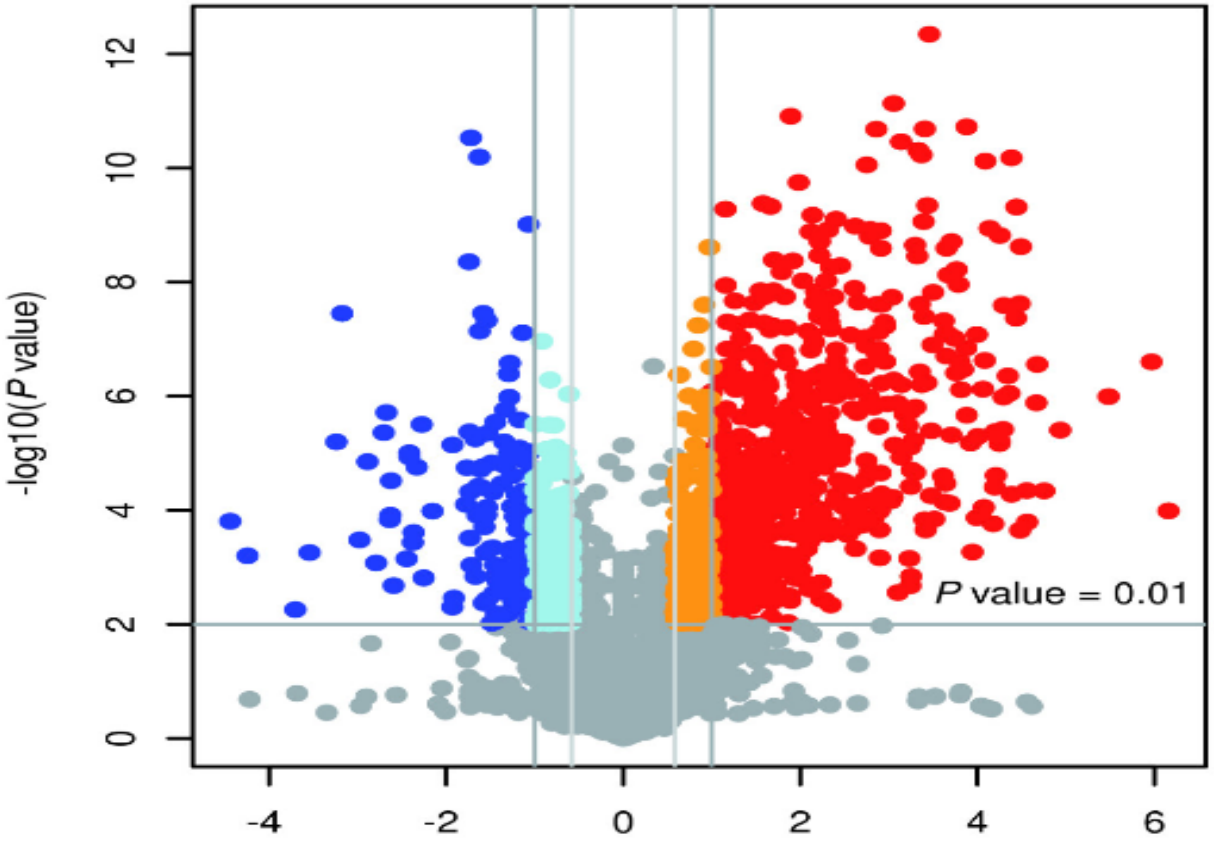




A first impression: Volcano plots – statistically signficantly and clinically relevantly outlying sites



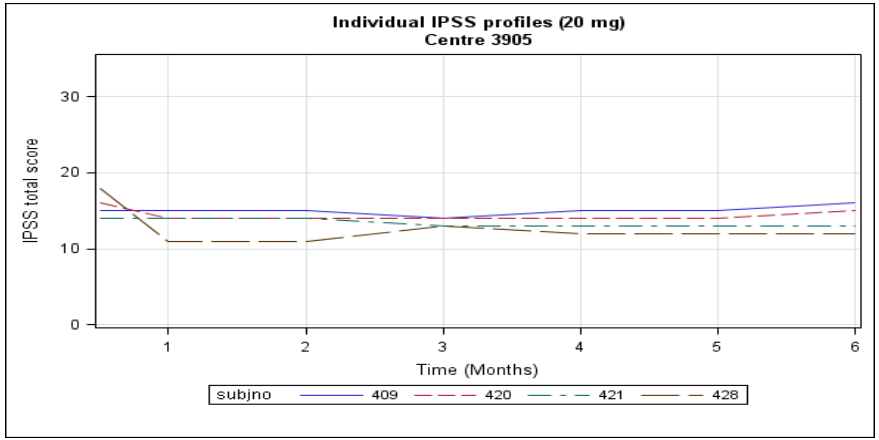
Example of Volcano plot (genomebiology)



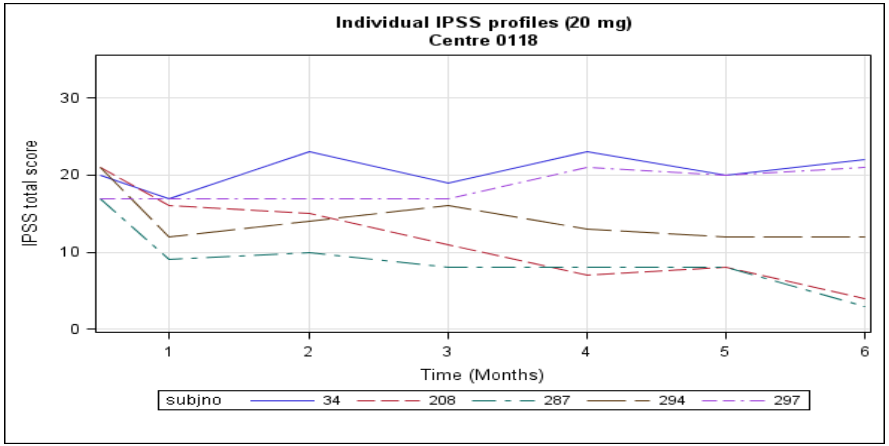
Ad –hoc Programming in R (instead of SAS)

EXAMPLE (CS36, DEGARELIX IN BPH): LACK OF WITHIN–SUBJECT VARIATION

Hmmm ??



What you would expect



A few stories from the past

From a Ph III, Global HRT trial

Hector ’s method of
”adhering to the ITT principle (complete data)”