

Interactive Clinical Data Review for Safety Assessment and Trial Operations Management

M. O'Connell, PhD
Sr. Director, Analytics
Spotfire Clinical Practice

October, 2010



- **Clinical Stakeholders & Use Cases**
 - Clinical, Safety, Medical Monitoring, Study Operations
 - Data Management, Statistics, Programming

- **Clinical Data Review – Safety Assessment & Operations Management**
 - Medical Monitoring and Safety Assessment
 - Clinical Operations Analysis

- **Summary and Resources**
 - Information and Technical Resources

Acknowledgements

- ❑ **Ohad Amit, Peter Lane, Susan Duke, Mike Durante, Will Bushnell, GSK**
 - Safety graphics + graphics standardization implementation
- ❑ **Karina Stender, *H. Lundbeck***
 - Graphics standardization implementation
- ❑ **Amy Xia, Kefei Zhou, Haijun Ma, Matt Austin, *Amgen***
 - Safety graphics
- ❑ **Mat Soukup, George Rochester, *FDA***
 - Safety graphics
- ❑ **Kye Gilder, *Biogen IDEC***
 - Efficacy graphics
- ❑ **Andreas Krause, *Actelion***
 - PKPD graphics
- ❑ **Michaela Jahn, Josh Haznedar, Xavier Logier, *Roche***
 - Interactive exploratory graphics
- ❑ **Michael Merz, *Novartis***
 - Interactive exploratory graphics
- ❑ **Harry Southworth, Ian Taylor, Paula Johansson, *AstraZeneca***
 - Safety graphics and interactive exploratory graphics
- ❑ **Mohan Beltangady, Joan Demers, Meghan Fajardo, *Pfizer***
 - Safety graphics and workflows

Industry Trends - Challenges

❑ Drug Development is expensive

- Need to reduce cost, improve productivity

❑ Regulatory bar is high

- Safety issues must be addressed

❑ Time to market must be reduced

- Medicines to patients, maximize patent life, delay generic pressure

⇒ Simplify and Streamline

- Safety Analysis (clinical, safety, stats)
- Efficacy Analysis (M&S, DMPK, clinical, stats)
- Operations (enrollment, site/resource mgt)
- Protocol Adherence (medical monitoring)
- Data Cleaning (data management)

⇒ Data Visibility is a hot issue

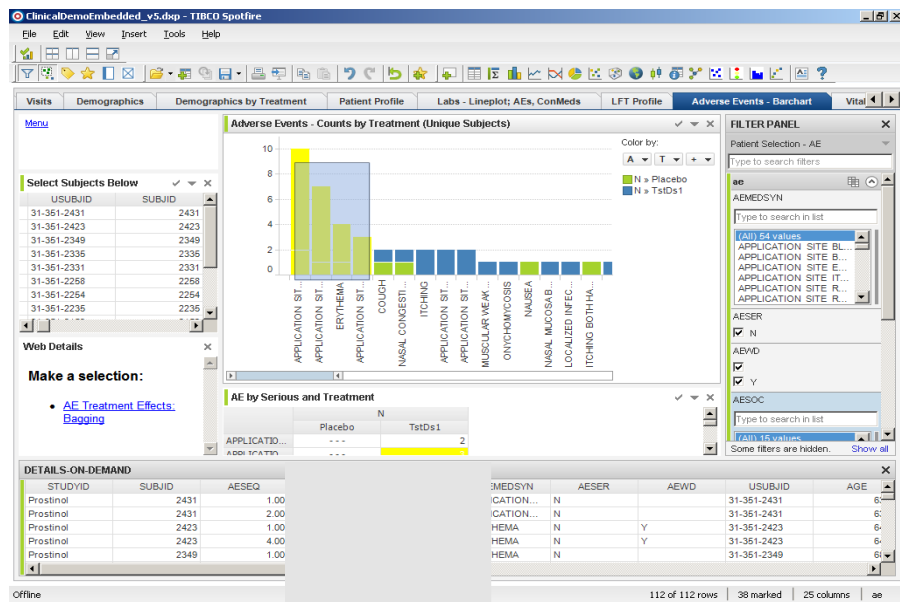
- Old way of working doesn't work !
- Its 2010 - look at data early and often !!



Clinical Study Team

	User	Need	Objective
	CT Mgr	<i>Site Scorecard/Dashboard/KPIs Resource Forecasting</i>	<i>Trial Management</i>
	Pharm Mgr	<i>Dosing, ICH Stability, Reg/Manuf Milestone Mgt</i>	<i>Compound Management</i>
	CRA	<i>Issue Detection Protocol Adherence</i>	<i>Data Driven Monitoring</i>
	Data Mgmt	<i>Data Issue ID / Query Mgt</i>	<i>Data Cleaning</i>
	Biostatistics Programming	<i>Visual / Stat Analysis Trends / Outliers</i>	<i>Data Analysis (Exploratory/Report)</i>
	Med / DMPK	<i>Multivariate Visualization Variable Relationships</i>	<i>Dosing, Exposure-Response</i>
	Safety	<i>Patient Data Visualization Data Cross-Referencing</i>	<i>Signal Detection Risk Minimization</i>
	PI / Clinician	<i>Patient Data Visualization Data Cross-Referencing</i>	<i>Clinical Results Risk Minimization</i>
	Med Writing	<i>Data Visualization Data Cross-Referencing</i>	<i>Write CSR, Presentations</i>

Case Study #1: Clinical Trial Safety Analysis and Review



Highlight Subjects
- AEs, Labs, QTc
Define Sub-Population
Drill to Subject Data

Trial / Sub-Population / Subject Data at Fingertips

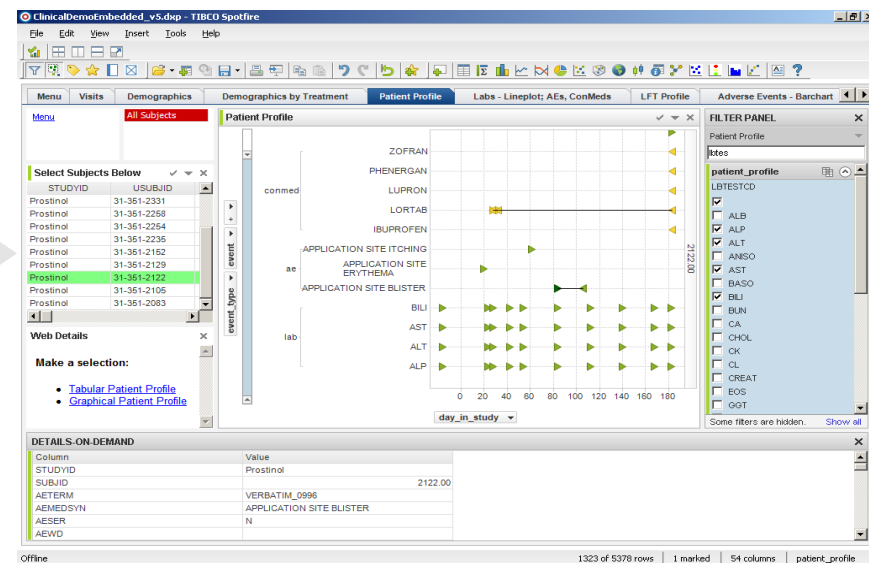
SUCCESS STORY

Novartis
Operating in 140 countries with global headquarters in Basel, Switzerland, Novartis offers a wide range of healthcare products through Pharmaceuticals, Vaccines and Diagnostics, Sandoz and Consumer Health Divisions. Nearly 100,000 people are working at Novartis.

Using TIBCO Spotfire for Exploratory Data Analysis in Preclinical and Clinical Safety

"Interactive graphical data exploration provides an efficient, powerful and flexible tool to improve both detection and systematic assessment of safety signals,"

**Michael Merz, Clinical Pharmacologist and Head of Safety Networks
Preclinical Safety, Novartis.**



Safety Data Analysis – Summary for Today

□ Lots of data

- Many variables (labs, AE' s, vitals, ...)

□ Statistics / Analytics – FDA

- “P-values can provide some evidence of strength of the finding, but unless trials are designed for hypothesis testing (rarely the case), these should be thought of as descriptive...

- “It should be appreciated that exploratory analyses... are a critical and essential part of a safety evaluation....”



Safety Data Analysis – Summary for Today

□ Lots of data

- Many variables (labs, AE' s, vitals, ...)

□ Statistics / Analytics

- p-values are descriptive !
- Statistics: analyze data at subject level e.g. machine learning to prioritize AE/lab signals

□ Graphics – the key to success

- Targeted statistical graphics: AE' s, labs, vitals at population and patient level
- Interactive data review – patient profiles
- Graphical Review – early and often !!



□ **Labs**

- Which patients have changes in lab tests during trial
- Is there temporal causality of drug / conmed intake
- Liver labs and FDA DILI Guidance – Hy's Law

○ **Adverse Events**

- Review the TME's and DME's (e.g. cardio events)
- Are adverse events related to treatment or conmeds?
- Patterns of AE onset

□ **Vitals and QT prolongation**

- Which patients have elevation in QTc during trial (FDA E14 Guidance)
- How do these subjects fare re. QTc and other safety issues

□ **Combinations of data**

- Con meds, demographics, medical history, exposure
- Review subjects with AE and lab combinations e.g. rhabdomyolysis
- Patient level analysis – Patient Profiling

DEMO



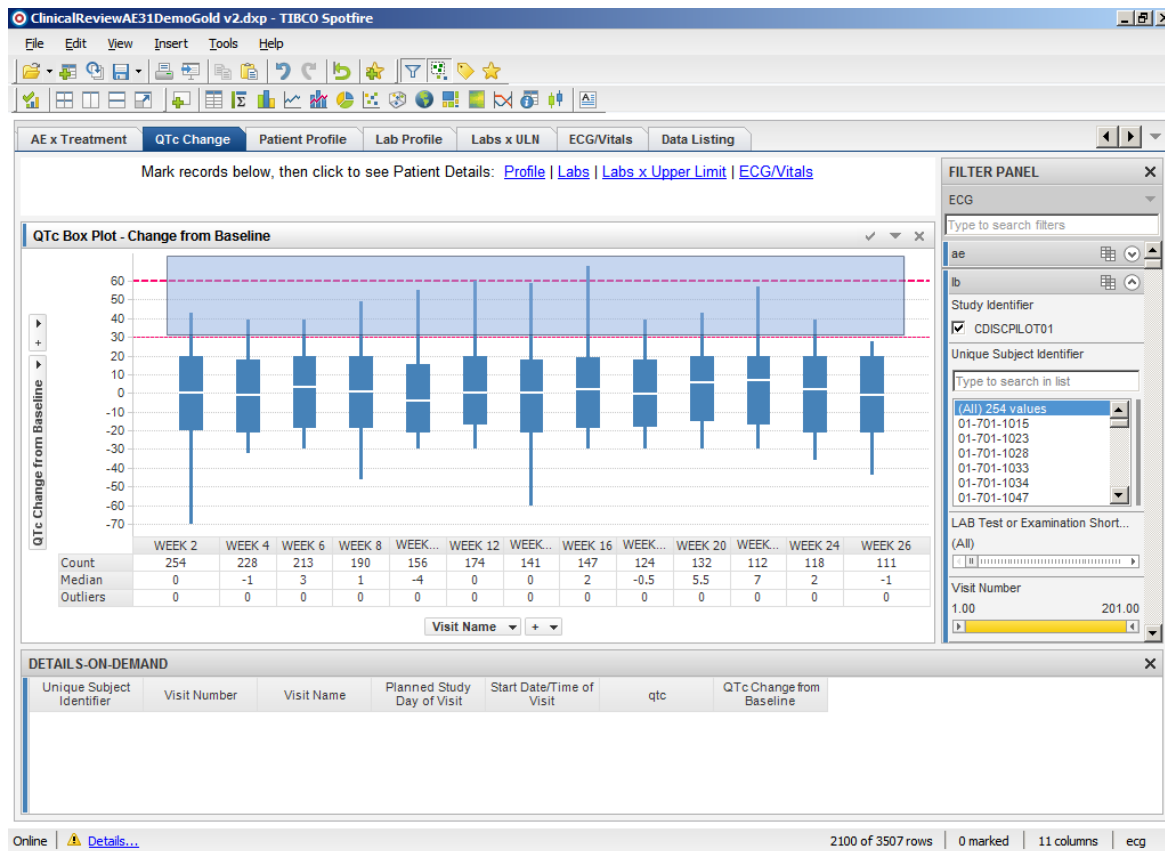
QT/QTc Prolongation – Subject and Population Analysis

Guidance for Industry

E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

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)

October 2005
ICH



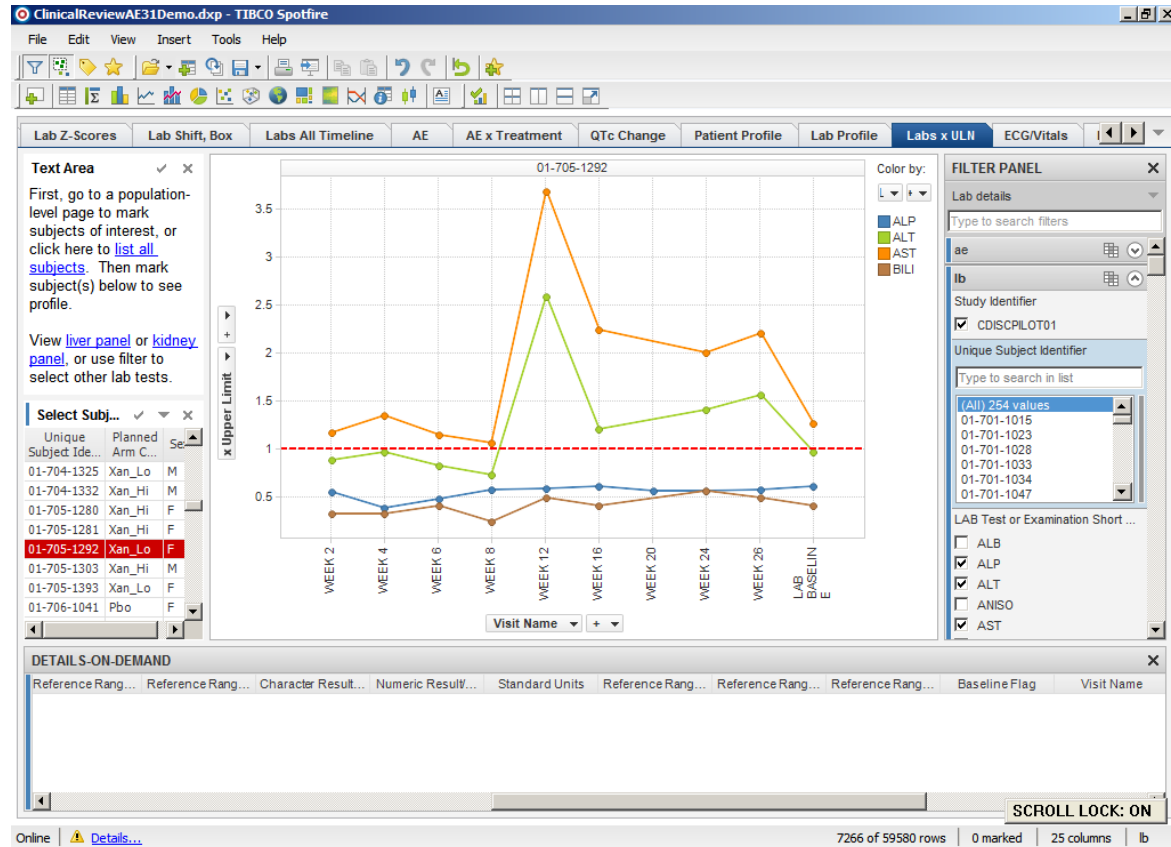
Clinical Trials: Guidance for Liver Injury: Hy's Law

Hyman Zimmerman's criteria for evaluating drug induced liver injury (DILI)

Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation

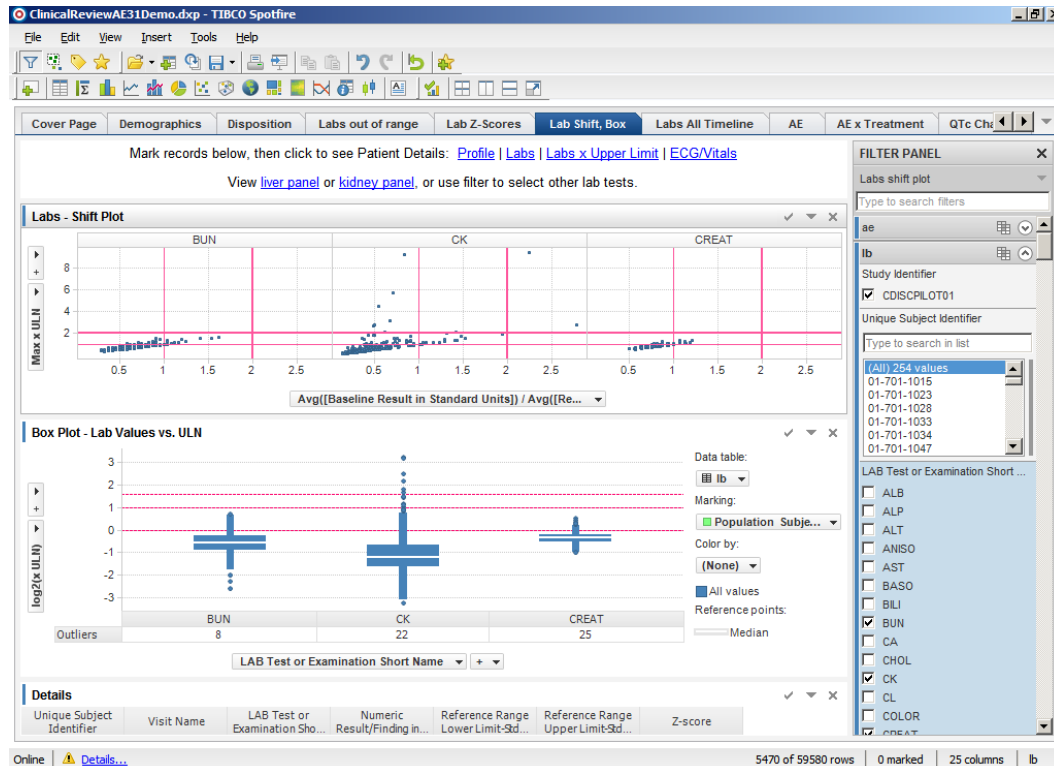
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety



Clinical Trials: Industry Best Practice - Analysis of Safety Data

Amit, Heiberger and Lane (2008) Graphical Approaches to the Analysis of Safety Data from Clinical Trials. *Pharm. Stat*



PHARMACEUTICAL STATISTICS
Pharmaceut. Statist. (in press)
Published online in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/pst.254



Graphical Approaches to the Analysis of Safety Data from Clinical Trials

Ohad Amit¹, Richard M. Heiberger^{2,†} and Peter W. Lane^{3,*†}
¹ Oncology Medicine Development Center, GlaxoSmithKline, USA
² Department of Statistics, Temple University, USA
³ Research Statistical Unit, GlaxoSmithKline, UK

Patient safety has always been a primary focus in the development of new pharmaceutical products. The predominant method for statistical evaluation and interpretation of safety data collected in a clinical trial is the tabular display of descriptive statistics. There is a great opportunity to enhance evaluation of drug safety through the use of graphical displays, which can convey multiple pieces of information concisely and more effectively than can tables. Graphs can be used in an exploratory setting to help identify emerging safety signals, or in a confirmatory setting as a tool to elucidate known clinical risks. This paper discusses the use of graphical displays in clinical trials, including the QT interval from electrocardiograms, laboratory measurements for detecting hepatotoxicity, and adverse events of special interest. We discuss in detail the statistical and graphical principles underlying the production and interpretation of the displays. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: graphics; dotplot; boxplot; trellis display; hepatotoxicity; QT interval; adverse experience

*Correspondence to: Peter Lane, GlaxoSmithKline, NPSP South, Third Avenue, Harlow CM19 5AW, UK.
E-mail: peter.w.lane@gsk.com
†Richard M. Heiberger participated in the study reported here while on research leave from the Department of Statistics at Temple University.

1. INTRODUCTION

Graphical approaches to the analysis of safety data are underused. The statistical evaluation and interpretation of safety data is predominantly

Clinical Trials: Industry Best Practice - Analysis of Safety Data

Southworth and O'Connell (2009).
Data Mining and Statistically Guided
Clinical Review of Adverse Event
Data in Clinical Trials, *J Biopharm
Stat* 19, 803-817

CIOMS VI. Management of
Safety Information from
Clinical Trials. WHO Press

SPERT: Crowe, Xia, Berlin.,
Watson, Shi, Lin et al. (2009).
Recommendations for safety
planning, ... *Clinical Trials* , 6
(5), 430-440.

Journal of Biopharmaceutical Statistics, 19, 803-817, 2009
Copyright © Taylor & Francis Group, LLC
ISSN: 1054-3406 print/1528-5711 online
DOI: 10.1080/10543409.2010.5232



DATA MINING AND STATISTICALLY GUIDED CLINICAL REVIEW OF ADVERSE EVENT DATA IN CLINICAL TRIALS

H. Southworth¹ and M. O'Connell²

¹AstraZeneca

²Tibco

Some approaches to the analysis of adverse event data arising from clinical trials are presented. These include (a) an inside-out data mining method where the adverse events are used as explanatory variables, classifying the treatment allocation, (b) a support method where we fit separate regression models to each adverse event with and without a treatment effect, and (c) a three-level hierarchical Bayesian mixture model for analysis of adverse event counts. The problem of understanding treatment-emergence of the adverse events is formulated as one of data mining rather than hypothesis testing. Our approaches provide an ordering of the adverse events by the strength of evidence of a treatment effect, rather than p values for pre-specified hypotheses. The three methods produce intuitive graphical summaries showing the treatment effect on adverse event incidence. These graphs can be readily linked to relevant supportive information such as reports summarizing predicted risks for (demographic) subpopulations of interest and

Key
words

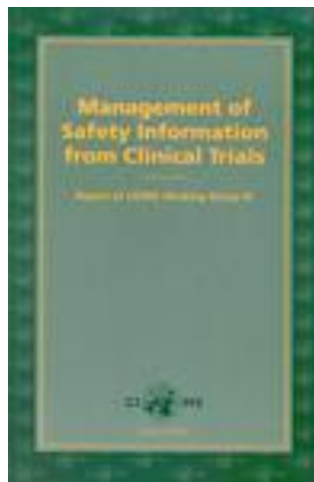
**AstraZeneca
TIBCO (Spotfire)**

of interest to evaluate which, if any, are related to the treatment. There are two key statistical issues with these data: (a) It is common for a clinical trial to report many, e.g., hundreds, of different types of adverse events, and there are additional measures of drug safety recorded, e.g., laboratory data and vital signs; and (b) many of the adverse event types have low incidence in any particular trial. These issues of endpoint multiplicity and data sparseness make a classical hypothesis testing approach problematic.

In what follows we describe some alternatives to hypothesis testing and apply these to clinical trial data. The outputs from the analysis are simple plots and summaries that are easy to interpret and that provide visibility into potential safety signals. These graphs can be readily linked to relevant supportive information such

Received November 11, 2008; Accepted January 16, 2009
Address correspondence to H. Southworth, Parklands, Alderley Park, Macclesfield SK10 4TG,
UK; E-mail: Harry.Southworth@astrazeneca.com

803



Recommendations for Safety Planning, Data Collection, Evaluation and Reporting During Drug,
Biologic and Vaccine Development: A Report of the Safety Planning, Evaluation and Reporting
Team (SPERT)

Authors:

1. Brenda J. Crowe, PhD, Eli Lilly and Company, Indianapolis, IN, USA
2. H. Amy Xia, PhD, Amgen Inc., Thousand Oaks, CA, USA
3. Jesse A. Berlin, ScD, Johnson & Johnson Pharmaceutical Research and Development, Titusville, NJ, USA
4. Douglas J. Watson, PhD, MSPH, Merck & Co., Inc., North Wales, PA, USA
5. Hongliang Shi, MS, Millennium Pharmaceuticals Inc., Cambridge, MA, USA
6. Stephen L. Lin, MD, sanofi-aventis, Bridgewater, NJ, USA
7. Juergen Kuebler, PhD, Novartis Pharma AG, Basel, Switzerland
8. Robert C. Schriver, MS, GlaxoSmithKline, King of Prussia, PA, USA
9. Nancy C. Santanello, MD, MS, Merck & Co., Inc., North Wales, PA, USA
10. C. George Rochester, PhD, RAC, US Food and Drug Administration, Silver Spring MD
11. Jane B. Porter, MS, Millennium Pharmaceuticals, Inc. Cambridge, MA, USA
12. Manfred Oster, MD, sanofi-aventis, Bridgewater, NJ, USA
13. Devan V. Mehrotra, PhD, Merck & Co., Inc., North Wales, PA, USA
14. Zh
15. El
16. Er
17. Da

Background
by the Pha
Purpose: S
data collec
continuing
Methods:
consensus
Results: Al
early in di
cumulativ
within the
special in
We descri
highlight
sponsors
the devel
Limitation
Conclusion
and health
time of ne

**Lilly Amgen
J&J Merck
Millenium
SanofiAventis
Novartis
GSK BMS
P&G BI**

* Disclaimer

2

X variables (explanatory variables)

Y variable

Subject	AE-1	AE-2	...	AE-n	Treatment
1001	...	...	...	...	Placebo
1002	...	...	...	...	Treated
...	...	...	...	...	...
1200	...	...	...	...	Placebo

One Model in Southworth and O'Connell (2009) is

$$Y = f(X, b) + e$$

f is forest of classification trees (bagging)

- Resample data matrix (bootstrap, with replacement)
- Fit tree to each sample; average (vote) over all trees

Calculate **Variable Importance** for each **AE** from forest

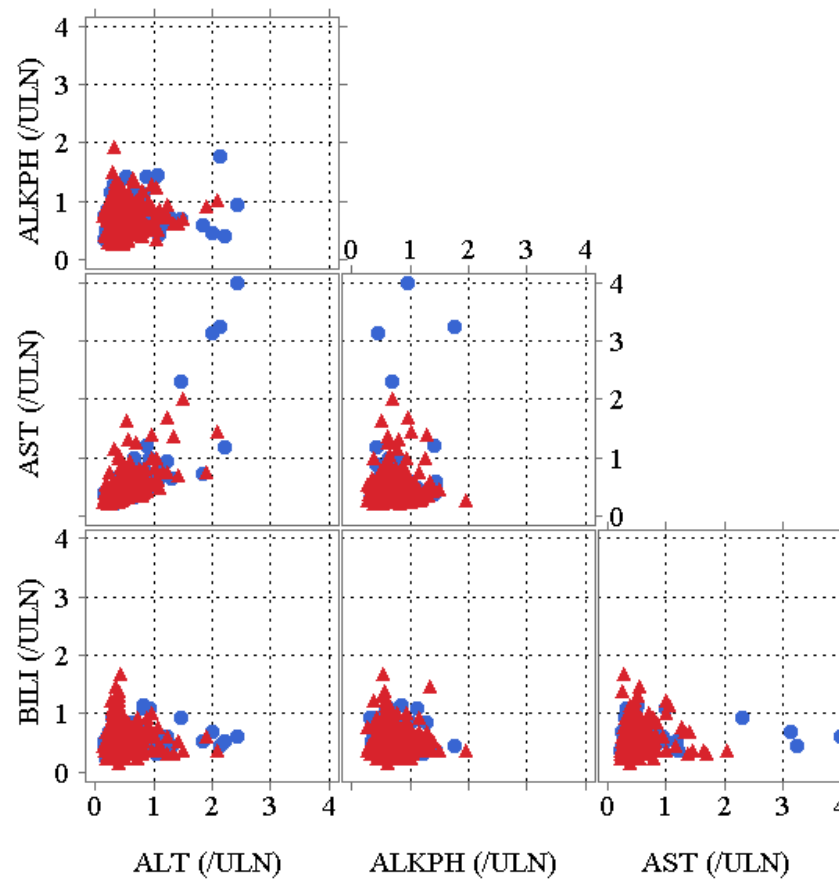
- High Variable Importance => potential treatment-emergence

S+ libraries on statistics server – called from Spotfire

- cdiscsplus, arbor, forest and FlexBayes, brlr

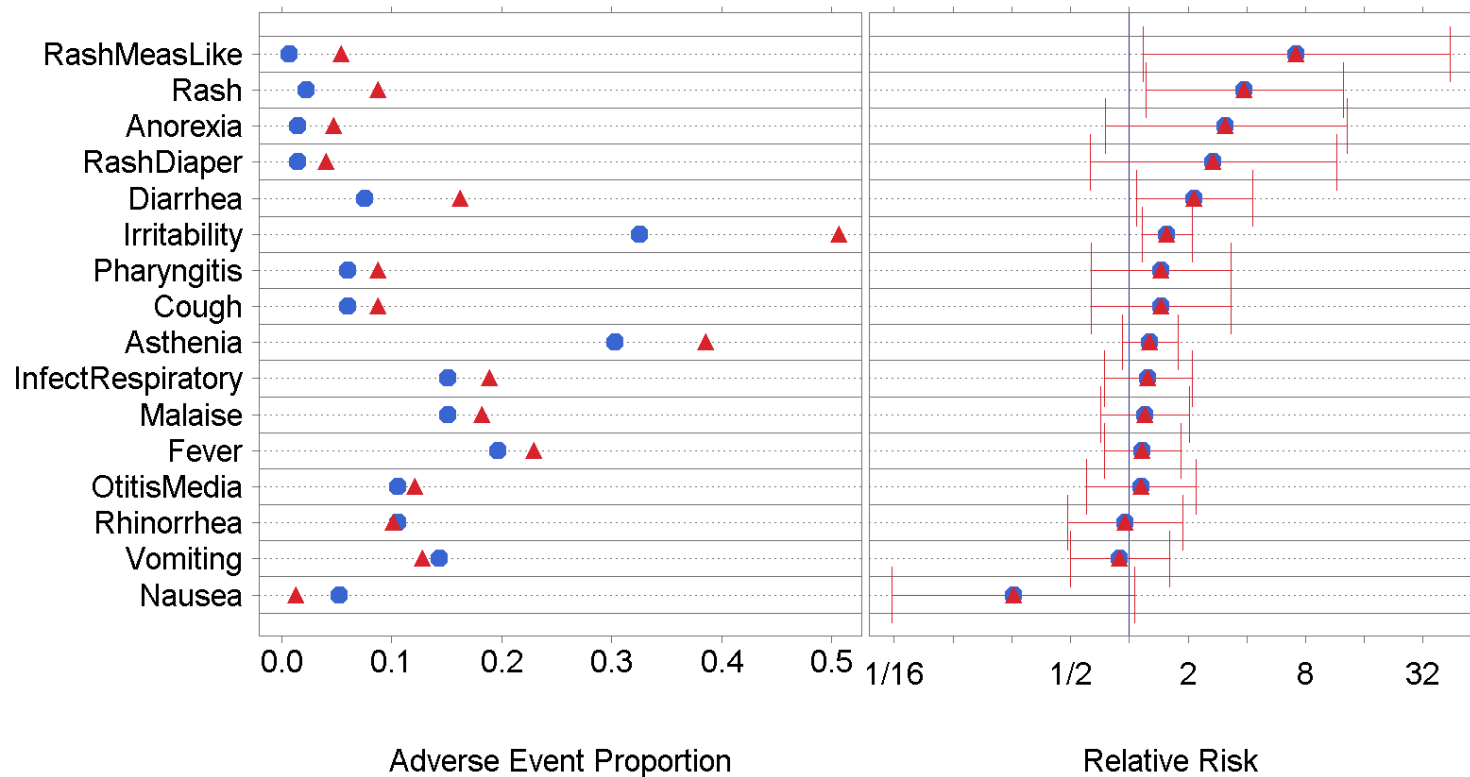
lft5.unstack.endpt.csv

Matrix Display of LFT (/ULN)



DRUG A ●
DRUG B ▲

Adverse Events sorted by Relative Risk



Placebo (N=132)
Treatment (N=148)



Data: http://PCKPIETZKO01197:8080/SplusServer/webdav/tscg/files/DataSources/Examples/double_dot_data.csv

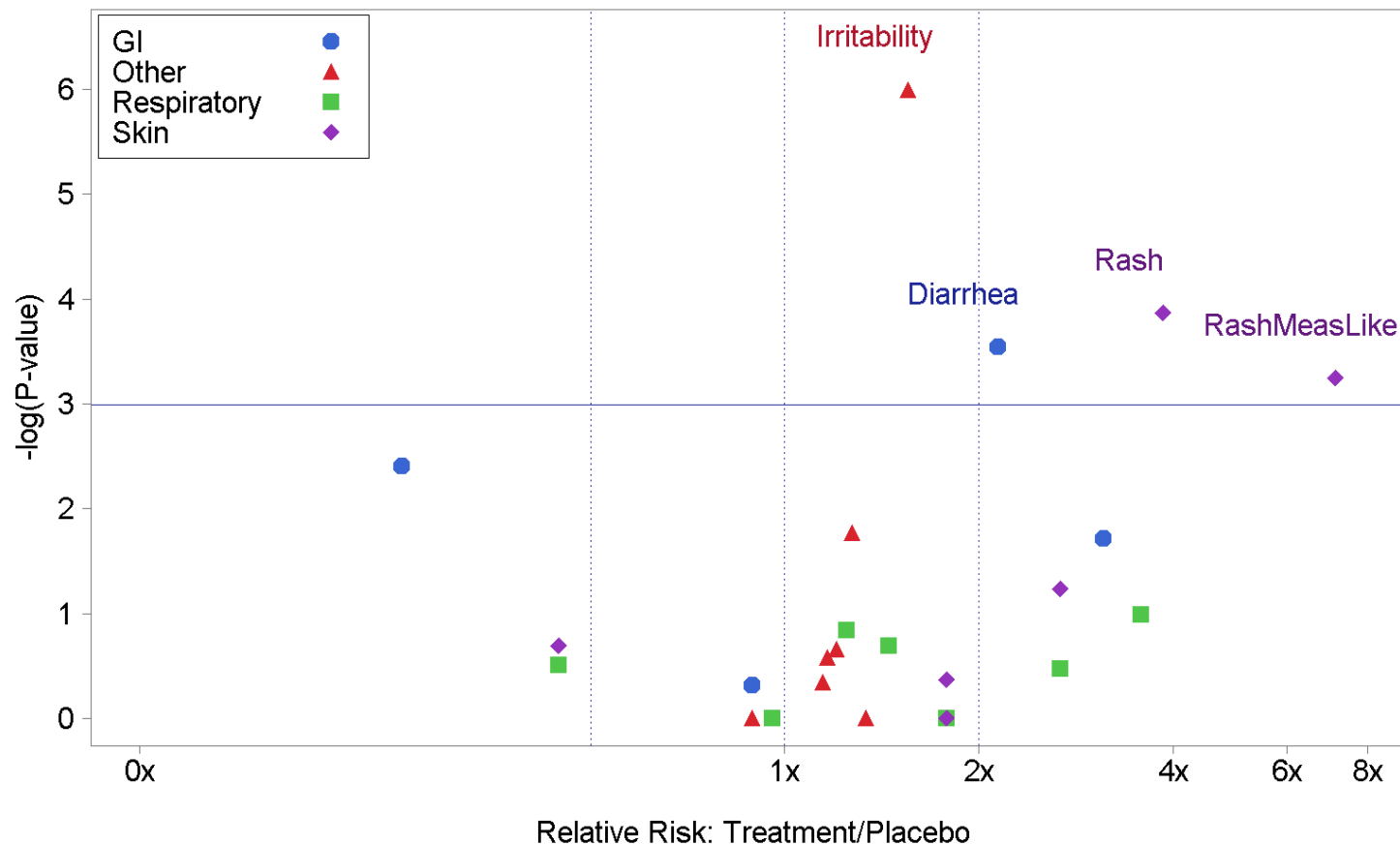
Author: kpietzko

Last Modified: 2009-08-20T10:08:38.2771152+02:00

Version: 2.0.3; Validation: Not Validated

Data: Mehrotra and Heyse
Graph: Amit, Lane, Heiberger

Risk Plot of Adverse Events Rates



Data: <http://PCKPIETZKO01197:8080/SplusServer/webdav/tscg/files/DataSources/Users/kpietzk/heyseDataFig2.xls>

Author: kpietzk

Last Modified: 2009-08-21T09:26:24.6093750+02:00

Version: 2.0.3; Validation: Not Validated

Data: Mehrotra and Heyse

Case Study #2: Clinical Trial Operations Analysis and Review

□ Live, interactive analysis – scorecards for management

- KPI's e.g. Protocol to 1st Patient by country, site
- Planned and actual comparisons

□ Enrolment and cross trial analysis

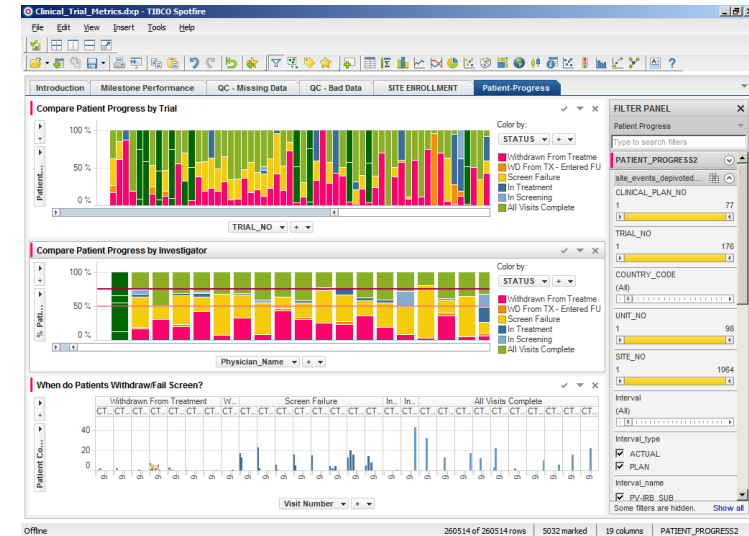
- Understand recruitment patterns across countries, sites and trials
- Discrepancies (queries) analysis
- Drill to root cause
- Identify and retain best performing sites

□ Link to clinical / safety data

- Sites with disproportionate AE frequencies etc.

□ Efficient clinical trial operations

- Identify sites that aren't performing eg PI's with good screen rates but poor enrolment
- Data-driven monitoring saves trial expense
- Resource management based on enrolment projections



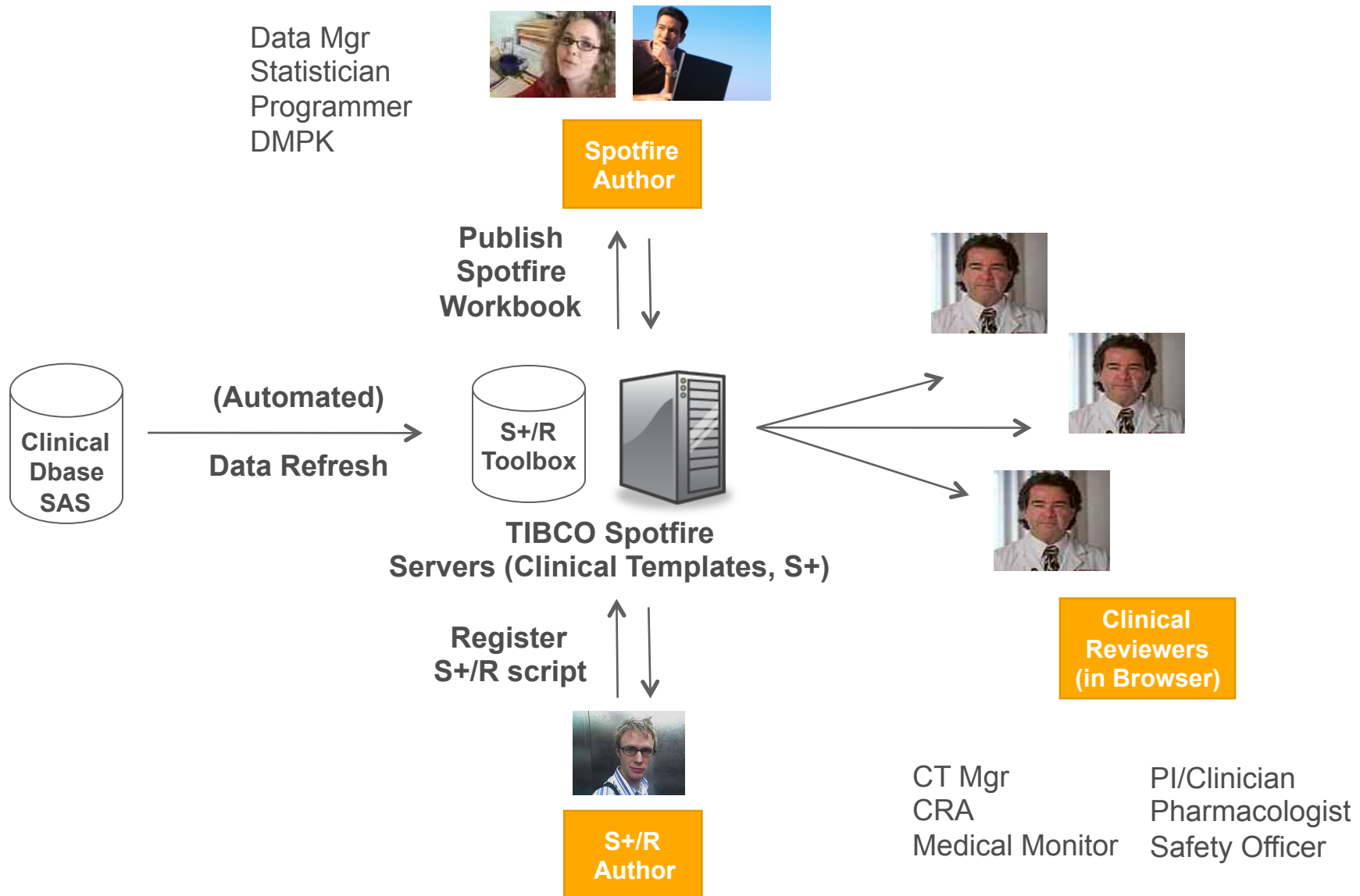
Implementations with OPX2, IMPACT, Siebel CTMS data sources

Implementations with Inform and Medidata EDC data sources

DEMO



Spotfire Clinical - Analytic Workflow



❑ Clinical Review – Medical Monitoring

- Safety Assessment
- Protocol Adherence
- Data Cleaning

❑ Clinical Trial Operations

- Management KPIs re trial progress
- Enrolment
- Resource Management

❑ Combinations

- Sites with high AE rates
- Sites with data quality or protocol adherence issues

Its 2010 – Look at the Data – Early and Often !!

Michael O' Connell, Ph.D.

Sr Director, Analytics

TIBCO Software

moconnel@tibco.com

+1 919 7401560

References

- Amit, O. (2007). *Understanding Patients Safety Through Use of Statistical Graphics*. TIBCO webcast. Available on request.
- Amit, O., Heiberger, R. and Lane, P. (2008). Graphical approaches to the analysis of safety data in clinical trials. *Pharmaceut. Stat.*
- Bushnell, W. (2007). *Graphical Analysis of Oncology Data*. JSM. Available on request.
- Cleveland, W. (1993): *Visualizing Data*. Hobart Press.
- Crowe, B. J., Xia, H. A., Berlin, J. A., Watson, D. J., Shi, H., Lin, S. L., et al. (2009). Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clinical Trials* , 6 (5), 430-440.
- Duke, S. (2008) *Graphics Standardization at GSK*. FDA Statistics Workshop. Available on request.
- Gilder, K. (2007). S-PLUS graphics in medical research. TIBCO webcast. TIBCO Available on request
- Krause, A, and O'Connell, M. (2007) *Statistical Graphics for Clinical Data Analysis*, Deming Conference Tutorial. Available on request.
- Ma, H., Zhou, K., Xia, A., Austin, M., Li, G., and O'Connell, M. (2007). *Graphical Analyses of Clinical Trial Safety Data*. JSM. Available on request
- O'Connell, M. (2008). *Statistical Graphics for Clinical Development Studies*. 44th DIA annual meeting. Available on request
- O'Connell, M and Pietzko, K (2009), Statistical Graphics for Exploration Presentation, Publication and Submission in Clinical Development TIBCO Whitepaper, available on request.
- Soukup, M. (2008). *Visual Representations of Clinical Data during the NDA Review Cycle*. 44th DIA annual meeting. TIBCO Spotfire website or available on request
- Southworth, H. (2007). S-PLUS Data Review Tools for Clinical Data. Insightful User Conference. Available on request.
- Stender, K, (2009) Graphics Deployment and Production in Drug Development at H. Lundbeck A/S, PSI, Available on request.
- Tufte, E. R. (1983). *The Visual Display of Information*, Graphics Press.
- Tukey, J. W. (1977). *Exploratory Data Analysis*. Addison-Wesley.
- Zimmerman, HJ, (1978), Drug-Induced Liver Disease, In: Hepatotoxicity, *The Adverse Effects of Drugs and Other Chemicals on the Liver*, 1st ed., pp. 351-3, Appleton-Century-Crofts, NY