BASS XIX Presentation

Statistical Analysis of Safety Data – A Survey of Some Analysis Methods

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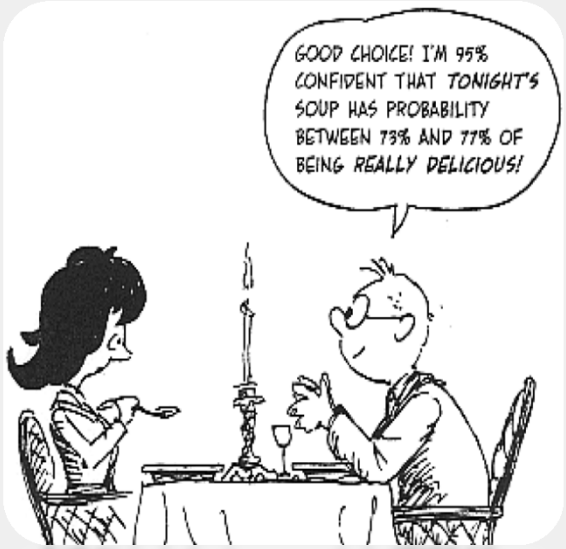
Outline

- Introduction
- Scope of Safety Data
- Guidance on the Analysis of Safety Data
- Thoughts on Safety Data
- Thoughts on Safety Analysis
- Analysis Approaches
- Conclusion



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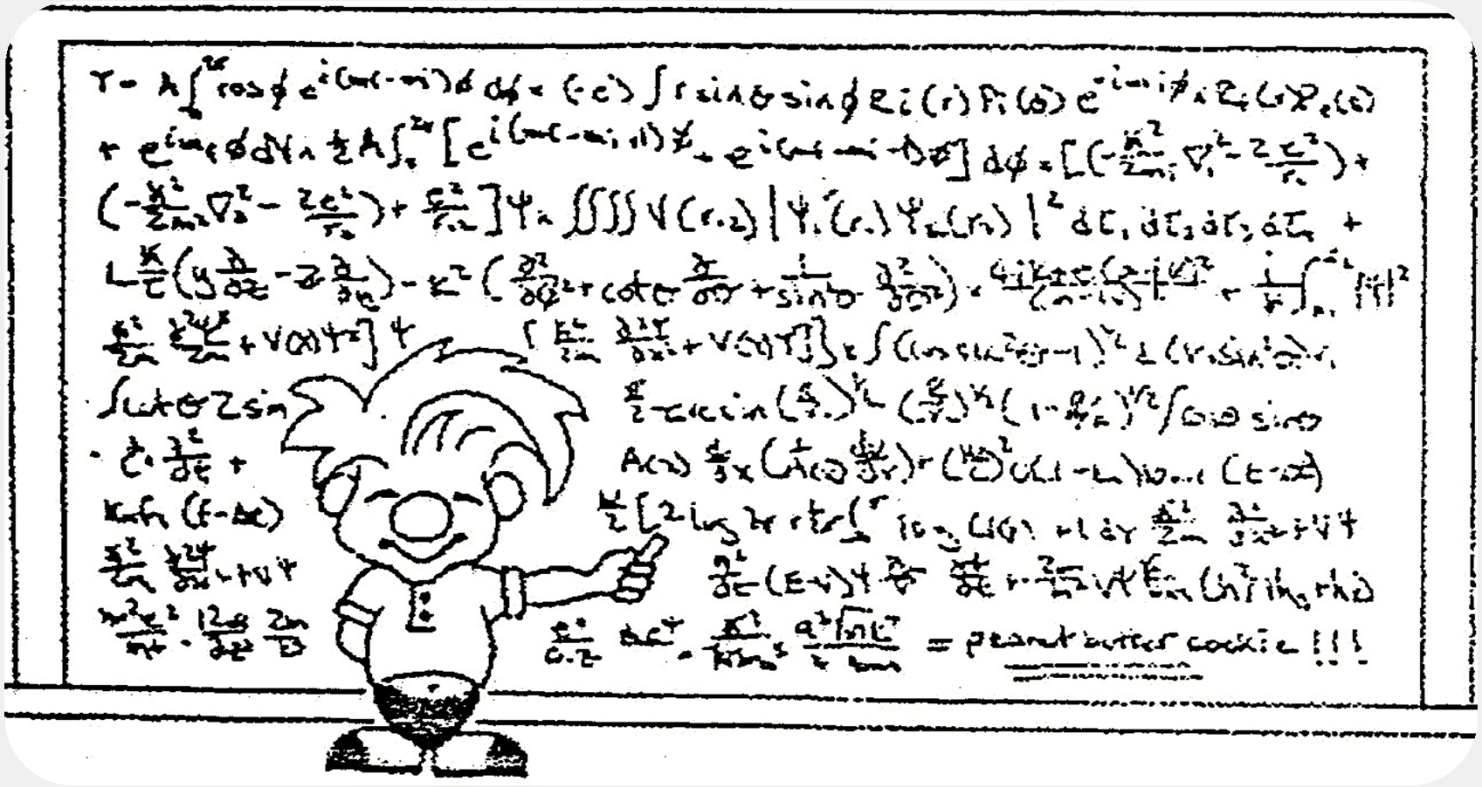


Introduction

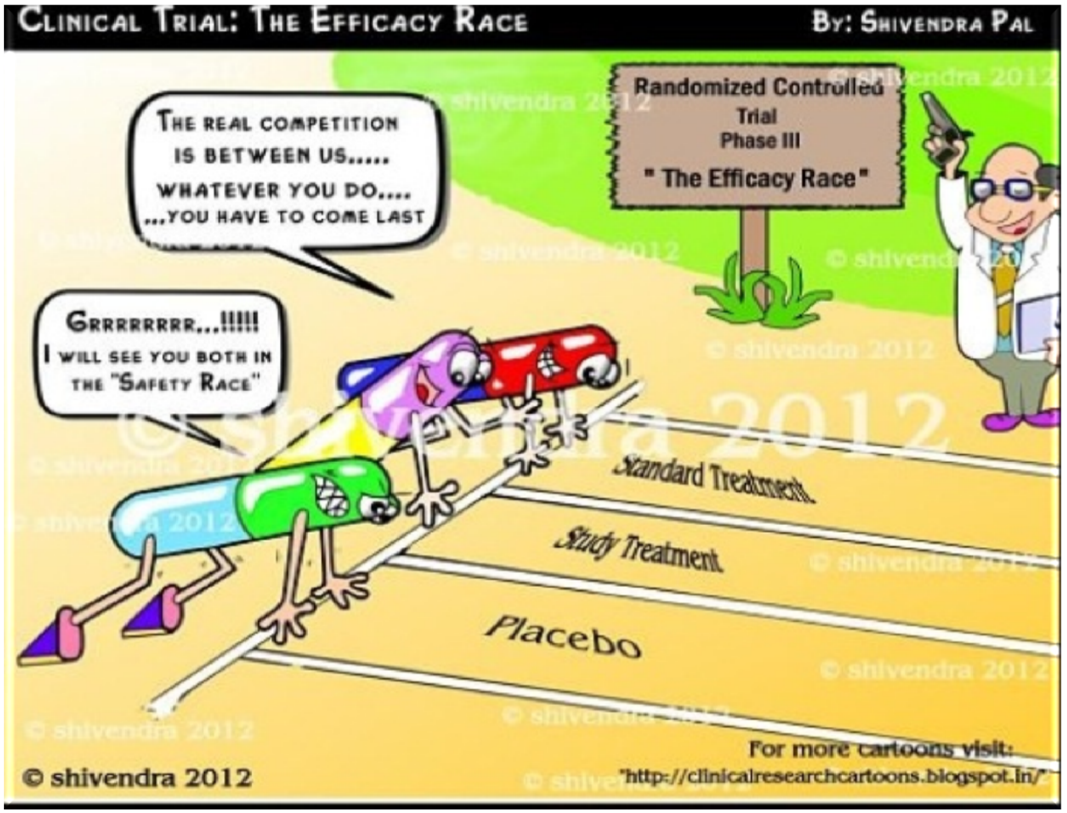
Safety - *"a reasonable certainty that a substance is not harmful under the intended conditions of use"* - Green

Did My Drug Cause This? a Biostatistical Perspective Mark S. Von Tress, Drug Information Journal October 1992 vol. 26 no. 4 565-572

- Much is written in older and recent literature with a ***safety headline or implication or connotation or implication for clinical safety data***
- Questions have been raised regarding completeness and inadequacies in the analysis and reporting of safety data
- General acknowledgement
  - There is room for improvement in the analysis and reporting of safety data from clinical trials
  - Safety data are not assessed appropriately - more focus on efficacy and often selective reporting for safety data
  - Insufficient methodological approaches for safety data – efficacy is given a more rigorous treatment than safety
  - Currently more scrutiny on safety, both pre- and post approval

Introduction

Efficacy versus safety race in clinical trials?



Introduction

Drug Safety Reporting- now and then
David J. Garbutt 2008 PhUSE 2008 Paper RA08

This paper is about the now and then of safety reporting, about its future and where it can, and should, go. safety…is vital to marketing, drug screening, approval, and continued existence on the market

Safety Analysis: Too Much? Not Enough? and How?
Christy Chuang-Stein
Biopharmaceutical Report, Volume 1, No.2, 1992

What constitutes an appropriate safety analysis for a given trial…are conducting too many comparisons, or is what we are doing (if we know what we are doing) enough? Are we doing the right thing?...

Challenges and Opportunities to Improve Premarketing Safety Planning, Evaluation and Reporting
DIA/FDA/PhRMA Drug Safety Conference
Robert T. O'Neill Ph.D.
2008

A lot of emphasis on efficacy evaluation of clinical outcomes in individual studies… Not much on quantification or summarizing safety data… Rigorous ascertainment of safety outcomes is essential

Some Concerns about Adverse Event Reporting in Randomized Clinical Trials
Yusuf Yazici, M.D.
Bulletin of the NYU Hospital for Joint Diseases 2008;66(2):143-5

Reporting of AEs is often lacking and with limited application in the real world,… It is not surprising that new and unexpected safety concerns emerge with any new drug after it has been launched and used by many more patients.

Perspectives of Safety Issues in Drug Development
Industry Statistical Perspective
Timothy Costigan, Ph.D Wei Shen, Ph.D
2003 FDA/Industry Statistics Workshop

Objectives of the safety data analysis should be to: Identify and understand safety issues as early as possible. Identify risk factors related to increased toxicity and lack of efficacy. ….Special safety data should be analyzed and interpreted differently than standard safety data…

Rethinking Statistical Approaches to Evaluating Drug Safety
Jen-pei Liu[1,2] Yonsei Med J 48(6):895 - 900, 2007

The current methods used to evaluate the safety of drug products are inadequate.

Introduction

Safety, Can You Paradigm? A Statistical Lament
Janet Turk Wittes
VII Graybill Conference on Biopharmaceutical Statistic, 2008

Because we find safety boring…we don't look at preclinical and early Phase data. We don't ask about: Chemistry, Biology, what PK/PD studies show. Safety part of analysis plan is an afterthought

Discovering adverse reactions: Why does it take so long?
Raymond L. Woosley, MD, PhD Clinical Pharmacology & Therapeutics, Volume, 76, 2004

Unfortunately, we continue to be shocked by reports of unexpected toxicity associated with some drugs after many years, sometimes after decades, of clinical use

SAFETY ANALYSIS IN CONTROLLED CLINICAL TRIALS
CHRISTY CHUANG-STEIN, PHD
Drug Information Journal, Vol. 32, pp. 1363S–1372S, 1998

Improve protocol considerations for adverse event recording….Improve the data analysis, event summarization and reporting. Bring adverse event analysis to the level of efficacy evaluation…There remains many amateur, naïve views of safety summarization, event rates, and reporting - these impact risk management

The Analysis of Adverse Drug Reactions in Clinical Trials: A Basis for Communicating and Managing Risk
Robert T. O'Neill Ph.D. 2001

The question that must be considered is whether the analysis that is currently being performed is relevant and whether safety data are being summarized in a way most beneficial ….in understanding the safety outlook of a new treatment….

The bottom line is that safety analysis, both pre- and post- marketing, needs more statistical input. The time for statisticians to answer this challenge is NOW…

Need a carefully crafted SAP which serves as a coherent framework for sponsors and regulators to characterize safety endpoints

Planning for Safety Assessment Throughout the Lifecycle of a Regulated Product
2007 International Biometrics Society
George Rochester, Ph.D.

Analysis of Safety Data Is More Enough?
Marc Andersen 2006

Adverse Events: After 58 Years, Do We Have it Right Yet?
Joel C. Scherer and Curtis G. Wiltse
Biopharmaceutical Report, Volume 4, 1996

Hiding safety signals: 5 easy lessons
Janet Wittes
MBSW, 2011

Introduction

CLINICAL TRIAL ADVERSE EVENTS: THE CASE FOR DESCRIPTIVE TECHNIQUES

Drug Information Journal, Vol. 25, pp. 447–456, 1991

William J. Huster, PhD

The manner in which safety information is collected implies that formal statistical inference is invalid.

Challenges and Opportunities to Improve Premarketing Safety Planning, Evaluation and Reporting

Robert T. O'Neill Ph.D. 2008

Culture change is needed for prospective planning for safety evaluation that improves our quantification of risk and uncertainty. Safety evaluation is hard…the pre-market process, the post-approval process and the life-cycle perspective all need to be considered

Life-cycle Planning for Product Safety Evaluation in Support of Benefit-Risk Activities

C. George Rochester, M.A., Ph.D., 2009

The Quantitative Safety Analysis Plan

C. George Rochester, M.A., Ph.D., RAC 2009

Methods….time to onset, time-to-resolution, dropout and AEs preceding discontinuation, injury repair models, event history, competing risks, risk factor identification - logistic, hazard, or Poisson regression models, time dependent covariates, propensity models, methods for sparse data, information synthesis methodology, multilevel models, methods to handle indirect comparisons

Emerging Trends in Regulatory Biostatistics - What might be their impact ?

Robert T. O'Neill Ph.D.

VII Graybill Conference on "Biopharmaceutical Statistics" 2008

Methods…causal analysis, propensity score matching, cumulative meta-analysis, rare events, multiple recurrent event, time-to-event, visual graphics

Pre-Market Safety Must Balance Statistics With Clinical Discernment – FDA

"The Pink Sheet" Nov. 10, 2008, Vol. 70, No. 045

Safety evaluation is probably much harder than efficacy evaluation because in many ways it's reading the tea leaves. It's a lot of multiplicity, a lot of false discovery, a lot of it-it-real or is-it-not-real…But nonetheless, you can't even approach that discussion if you can't quantify it in a reasonable way…statisticians for the most part have not been involved in safety evaluations…The sophistication is out, it just has not bee brought to bear on routine safety assessment for chronically used drugs.

Introduction

Bayesian Applications in Clinical Trial Safety Assessment — Topic Contributed Papers

Biopharmaceutical Section 2012 JSM

Recent Developments of Bayesian Meta-Analysis for Safety Evaluation in Randomized Clinical Trials — **Karen Price, Eli Lilly and Company**

Identifying Potential Adverse Events Dose-Response Relationships via Bayesian Indirect and Mixed Treatment Comparison Models — **Haoda Fu** ; Karen Price, Eli Lilly and Company ; Mary E. Nilsson, Eli Lilly and Company ; Stephen J. Ruberg, Eli Lilly and Company

Bayesian Meta Experimental Design: Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes — **H. Xia, Amgen, Inc.** ; Joseph Ibrahim, The University of North Carolina at Chapel Hill ; Ming-Hui Chen, University of Connecticut ; Thomas Liu, Amgen, Inc.

Applications of Bayesian Model Selection for Clinical Safety Data — **Bradley McEvoy, FDA/CDER** ; Rajesh R Nandy, University of California at Los Angeles ; Ram C. Tiwari, FDA/CDER/OTS/OB

Discussant: George Rochester, FDA

Using Advanced Visual Analytics to Improve Safety Assessment and Decisionmaking in Drug Development — Invited Papers

Section on Health Policy Statistics , ENAR , Section on Risk Analysis , Scientific and Public Affairs Advisory Committee

Safety Graphics: Graphical Approaches for Identifying Safety Signals — **Janelle Charles, U.S. Food and Drug Administration/OTS/CDER** 2011

Creating Effective Visual Tools for the Assessment and Characterization of Pharmaceutical Product Safety: General Principles, Illustrations, and Public Access — **Kenneth J. Koury, Merck Research Laboratories**

Visualization Tools and the Evaluation of Safety Data in Pharmaceutical Industry Clinical Trials — **Qi Jiang, Amgen Inc.**

Visually Displaying Benefit:Risk:Uncertainty in Safety Assessments — **Mark O. Walderhaug, U.S. Food and Drug Administration** ; Richard A. Forshee, U.S. Food and Drug Administration/CBER ; Arianna Simonetti, U.S. Food and Drug Administration/CBER ; Anne Fernando, Norfolk State University

Floor Discussion

BASS XIX

Tutorial Topics

Modeling, Bayesian, Comparative Effectiveness and Safety Assessment of Pharmaceuticals

Short Courses

1. *Targeted Maximum Likelihood Methods with Applications to Safety Data*
Speakers: Mark van der Laan, Susan Gruber, Sherri Rose

2. *Monte Carlo Clinical Trial Simulations for Pharmaceutical Industry: Concepts, Algorithms, Implementation and Case Studies*
Speakers: Mark Chang, Sandeep Menon, Gheorghe Doros

3. *Advanced Safety Data Analysis and Handling Nonrandom Missing Data*
Speakers: Russ Wolfinger, Craig Malincrodt, Richard Zink

4. *Data Safety Monitoring Boards: Planning and Execution*
Speakers: Janet Wittes, Ruth McBride, April Slee, Matt Downs

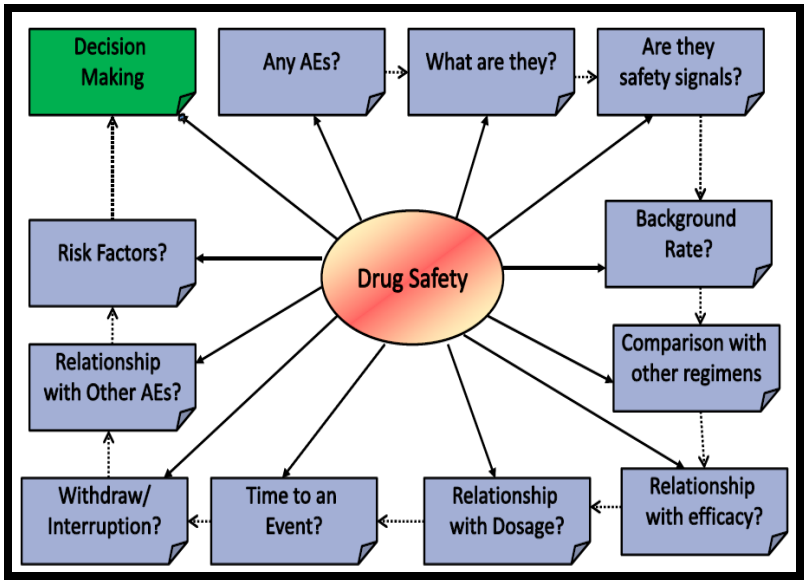
Introduction

In order to better assess drug safety, identify potential harms earlier than later, minimize risks to patients, and reduce late attrition due to safety issues – need to:

- Raise the bar on establishing acceptable safety profile of drugs
- Apply appropriate and/or develop formal statistical methodology to help identify signals and provide a better characterization of safety profile
- Monitor safety on both ongoing basis and also post-submission
- Make use of software tools that can help in safety profiling of drug
- Need more thorough safety analyses taking into account many considerations – need to address a variety of questions

A safety analysis should provide information on safety profile of the drug, one that is reasonable or acceptable, show the drug has no safety concerns, at a minimum point out what risks are associated with the drug:

- ***Under what circumstances they are important to the patient***
- ***The constellation of AEs that come with the drug***
- ***The incidence dose or exposure relationship***
- ***Relationship to concomitant medications***
- ***Identify any particular-prone patient subsets***
- ***Address any surprises in the data***



Source: Jiang and Huang, 2012

Introduction

Otherwise…

The New York Times

Painkiller Can Harm Liver, F.D.A. Warns

February 11, 1998

Long Labels Help Drug Firms, But Can Obscure What Matters

THE WALL STREET JOURNAL. JUNE 28, 2005

The New York Times February 23, 2010

A Face-Off on the Safety of a Drug for Diabetes

By GARDINER HARRIS

Bad Pharma: How drug companies mislead doctors and harm patients

Ben Goldacre

Scope of Safety Data

Core : **AE, lab data, vital signs, ECG**

Other: **PE, exposure, concomitant medications, concurrent disease, etc**

About Safety data

- **May not be appropriate to analyze via conventional statistical methods because many of the standard assumptions may not be fulfilled**
- **Typical clinical trial generally not sufficient to detect safety signals, unless study is specifically powered for safety - zero observed events does not mean drug is safe**
- **Pathological features leading to - asymmetric non-normal distributions, heterogeneous subpopulations, etc**
- **High variability in measurements**
- **Data are multidimensional and inter-related in nature**
- **Safety endpoints of concern may not be known prior to trial - unexpected**
- **Large volume of output - problems in generation, assessment, validation, assembly and last, and worst comprehension and communication of safety and challenging to interpret**
- **Simple descriptive summary tables and review of individual patient data**
- **Rarely analytical - lots of exploration and estimation**

Scope of Safety Data

AEs	Labs
▪Often presented as counts but complicated by the large number of possible events and placebo response ▪Large number of possible events means potential for false positives ▪Analysis approaches challenging due to many zero counts on placebo treatment ▪Subjective assessment of relation to drug and severity ▪Possible relationships with other AEs ▪AEs can occur in any body system	•Abnormal laboratory data from clinical trials are considered precursors of potential organ dysfunction •Multivariate, non-normal, correlated time series •Typically assessed based on raw data or as categories via comparisons to normal ranges or custom cut-off points •Missing data •Different units •Exact occurrence time for concerning values not known

Guidance on the Analysis of Safety Data

On AEs…

ICH-E3	FDA Clinical Review Template	CIOMS
•AEs occurring after initiation of study treatment, including changes in vital signs and any laboratory changes that were considered SAEs •Listing of AEs by Patient •Listing of Deaths, Other SAEs, and Other Significant AEs	•Incidence of common AEs •Common AE tables •Identify common and DRAEs •Additional analyses and explorations - age, gender, etc •Etc	•Rates of AEs •RR and OR •CIs •Time to Event Methods

Guidance on the Analysis of Safety Data

On Labs…

ICH-E3	FDA Clinical Review Template	CIOMS
• Listing of individual labs and abnormal lab values •Evaluation of each lab parameter Laboratory values and changes from baseline over time (descriptive and categorical based abnormal values) •Shift tables •Graphs comparing initial value and on-treatment values •Individually clinically significant abnormalities	•Laboratory findings •Analyses focused on measures of central tendency •Analyses focused on outliers or shifts from normal to abnormal •Marked outliers and dropouts for laboratory abnormalities •Additional analyses and explorations - dose dependency, time dependency, and also drug-demographic, drug disease, and drug-drug interactions	•Analyze lab data using ANCOVA with baseline value as covariate with observed value or change from baseline or maximum value (most severe value) •Analyze binary values of lab data based on various cutoffs •Graphical displays - scatter plots of baseline versus post-baseline

Thoughts on Safety Data

Tremmel (1996) – know type of AE you are looking at…

Event Type	Example	Question
Absorbing	Death	Will I get it
Absorbing	Blindness	When will get it
Repeating	Seizure	How often will get it
Repeating	Seizure	Will I develop tolerance
Long Duration	Depressive Disorder	How much time
Long Duration	Neutropenia	How much time

And hence the measure or metric you should be looking at…

Measure of Risk for Absorbing Events	*Measure of Risk for Recurrent Events of Short Duration*	*Measure of Risk for Recurrent Events of Long Duration*
•Crude Incidence rate •Events per unit time •Survival rate (cumulative rate) •The hazard as a function of rime	•Number of events per unit time •Expected number of events as a function of the hazard •Hazard - simple AG Model •Modeling the effect of preceding events •Heterogeneity among subjects	•Long Term Duration •Prevalence Rates •Markov Models •Hazard - Simple Anderson-Gill Model •Modeling the Effect of Preceding Events •Heterogeneity Among Subjects

Thoughts on Safety Data

Use meaningful measures/metric of risk by AE type…

Type of Trial	Type of AE	Meaningful Measure
Short Term	All	Crude rate
Short Term	All	Cumulative rate
Long Term	Absorbing	Hazard function
Long Term	Recurring	Hazard function
Long Term	Long Duration	Prevalence

But exercise caution…for example,

- Exposure adjusted incidence rate and exposure adjusted event rate may be more appropriate measures to account for the potential difference in the duration of drug exposure or the follow-up time among individuals, and to capture the multiple occurrences of certain adverse events for a subject
- Also, when an event is (or is believed to be) likely to occur at any stage during continuous treatment with a drug then an event rate with a time component (e.g., rate per-person-year, etc) has a true meaning …but
- If there are relatively rare idiosyncratic drug reactions that occur early in the treatment and in only a few individuals…further apart from a few with AEs, remaining patients who are prescribed drug will never get these AEs however long they use the drug

Events per person-time (incidence rate): A misleading statistic?
Helena Chmura Kraemer *Statist. Med.* (2009)

Events per person year—a dubious concept Jurgen Windeler, Stefan Lange **BMJ, 1995**

Thoughts on Safety Analysis

On the question of SOC vs HLT vs. PT?

- **Pearson *et al* (2009) compared results of analyses using three different algorithms, when AEs are identified using PT vs. HLT vs SMQs**
- **Concluded that use of HLT and SMQ groupings prove better information safety**

Influence of the MedDRA® hierarchy on pharmacovigilance data mining results

INTERNATIONAL JOURNAL OF MEDICAL INFORMATICS 78 (2009) e97–e103

Ronald K. Pearson[a], Manfred Hauben[b,c,d], David I. Goldsmith[e], A. Lawrence Gould[f], David Madigan[g], Donald J. O'Hara[a], Stephanie J. Reisinger[a], Alan M. Hochberg[a,]*

Another challenge in generating the most accurate and useful information is deciding what level of terminology (e.g., Lower Level or Preferred term from a coding dictionary) should be used in presenting AE data (for example, in summary tables).

The CIOMS VI Working Group suggests that AE data should generally be presented as Preferred Terms (e.g., from MedDRA®), organized within the relevant System Organ Classes (SOCs). However, due to the high granularity of MedDRA®, there may be several Preferred Terms describing different AE/ADR cases that involve the same medical concept within one SOC. Therefore, under some circumstances, it might be useful to include data at more than one level of the hierarchy within a SOC (e.g., High Level Terms (HLT) as well as Preferred Terms).

One approach to overcoming the various shortcomings discussed above has been undertaken by a separate CIOMS Working Group on "Standardized MedDRA® Queries (SMQs)." It has been operating for several years as a collaboration between senior

Thoughts on Safety Analysis – *which one to use?*

Chatfield

- ***The goal of statistical analysis is to present the data in such a way that most readers will believe the conclusion drawn***

- ***The force of the conclusion is roughly inversely proportional to the complexity and number of methods used to exhibit it. The simplest techniques should be used***

Cox

- ***Most real-life statistical problems have one or more nonstandard features. There are no routine statistical questions; only questionable statistical routines***

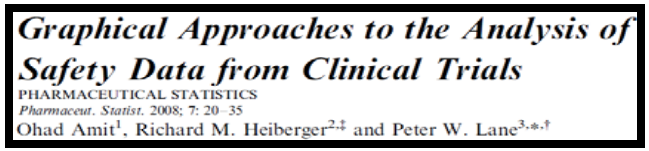
Thoughts on Safety Analysis

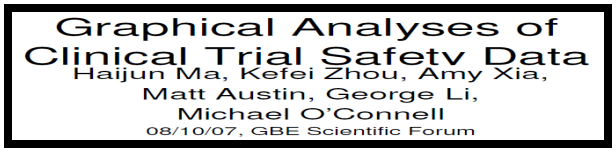
Analysis Methods

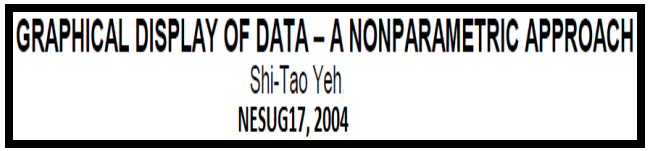
Widely Used	Not So Widely Used
AEs	
•Descriptive	•Competing risks
•Fisher Exact Test	•Recurrent Events
•Odds Ratio	•Bayesian Methods
•Risk ratio	•Multivariate Methods
•Risk Difference	•Advanced Graphical Methods
•Time-to-Event	•Multistate Models
•Chi-Square	•Disease State Models
•Mantel-Haenszel	•Meta Analysis
•Simple Graphical Methods	•Etc
Lab Data	
•Descriptive	•Recurrent Events
•Shift Tables	•Bayesian methods
•Analysis of 'Outliers‘	•Multivariate Methods - cluster analysis, etc
•Time-to-Event	•Modeling
•Fishers exact test	•Advanced Graphical Methods
•Chi-Square	•Meta Analysis
•Mantel-Haenszel	
•Simple Graphical Methods	

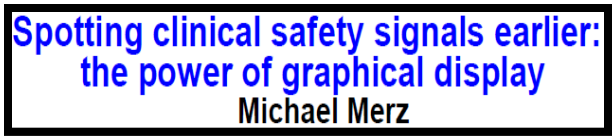
Analysis Approaches – Graphical Approaches

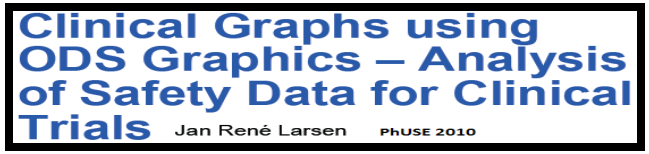
Much has been written on the use of graphs for safety data…

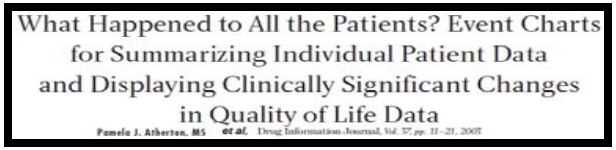












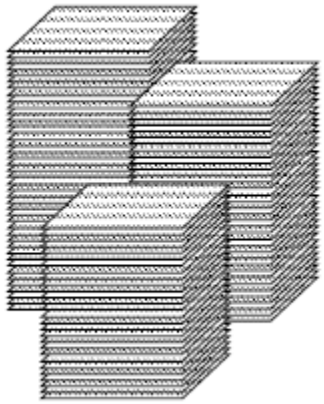
Analysis Approaches – Graphical Approaches

- Useful for exploring data
- Aid in inference and communicating results
- Display large data coherently
- Maximize ability to detect unusual features or patterns
- Can help facilitate communication with regulators, investigators, DMC, etc
- Present a great opportunity to enhance evaluation of drug safety
- Can convey multiple pieces of information concisely and more effectively than tables
- Combine multiple data
- Utilizing graphical exploration can substantially improve information gain from safety data, e.g.,
  - Which AEs are elevated in treatment vs. placebo?
  - Any special patterns of AE onset?
  - What is the trend of treatment effects on safety outcomes over time?
  - Which patients have abrupt changes in lab tests? Is there temporal causality of drug intake?
  - Group level information display
  - Individual level information display and drill down
- Graphs are not complete solution - should be used with other analyses
- Much information on graphs becoming publicly available, e.g., CTSpedia website - www.ctspedia.org

Analysis Approaches – Graphical Approaches

Harrell (2005)

- **Graphs, Not Tables!** ***(But really you also need tables)***
  - ***Have pity on statistical and medical reviewers***
  - ***Difficult to see patterns in tables***
  - ***Substituting graphs for tables increases efficiency of review***

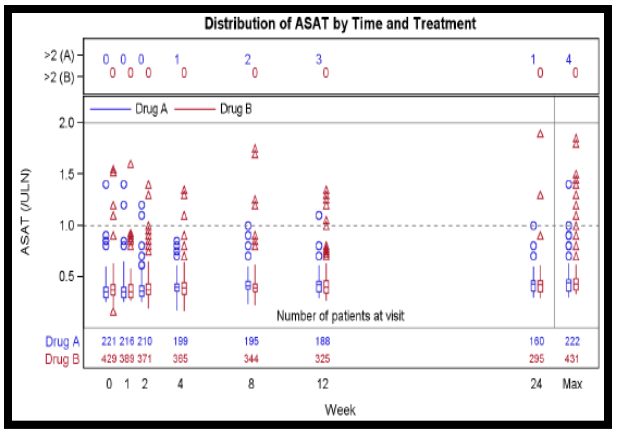


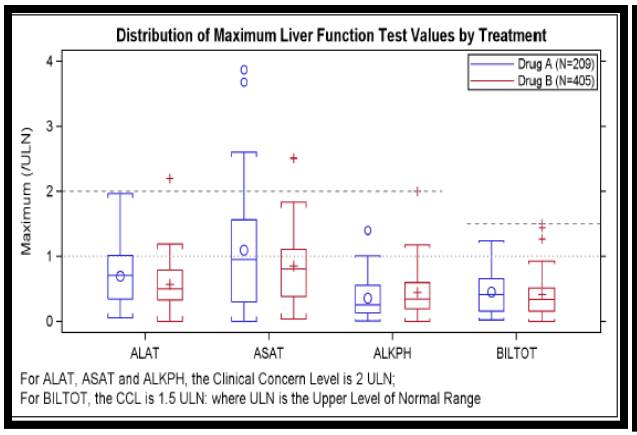
A Statistical Perspective on Adverse Event Reporting in Clinical Trials
Janet Wittes Biopharm Report, Fall 1996

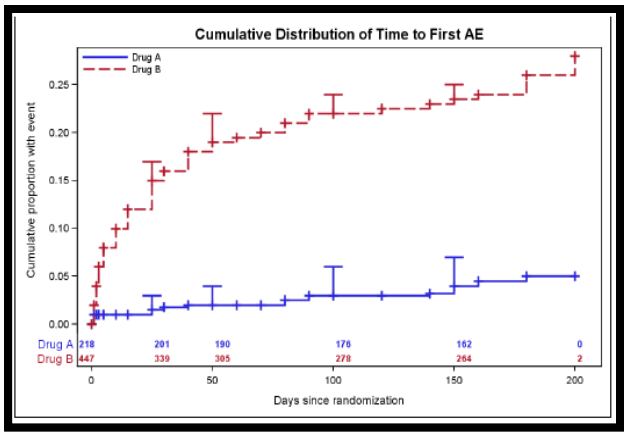
A plethora of tables and graphs that describe safety may bury some true signal in a cacophony of numbers.

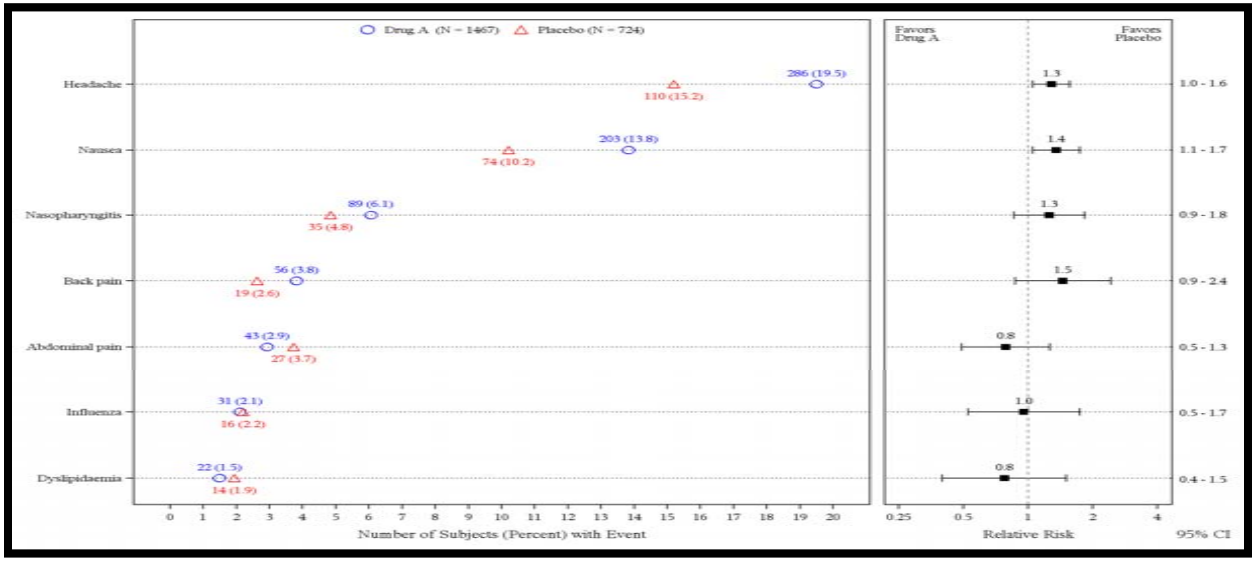
Analysis Approaches – Graphical Approaches

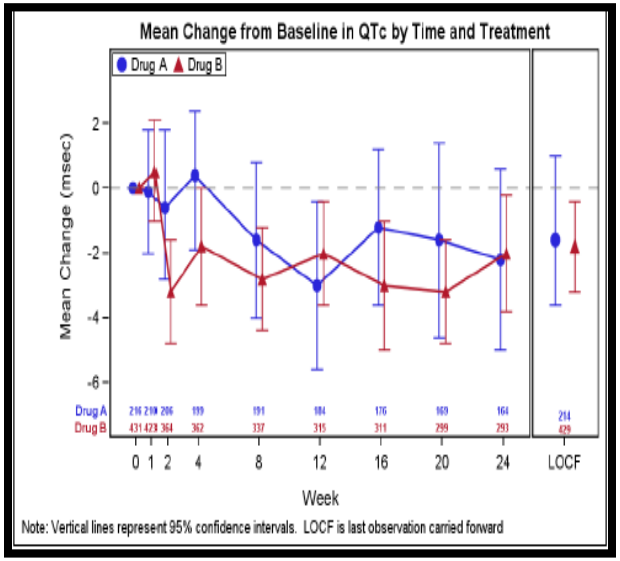
Main Stream Graphs in the Analysis of Safety Data











Analysis Approaches – Graphical Approaches

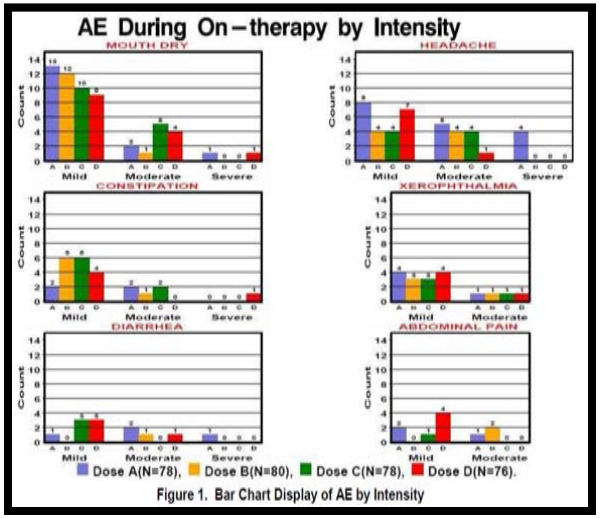


Figure 1. Bar Chart Display of AE by Intensity

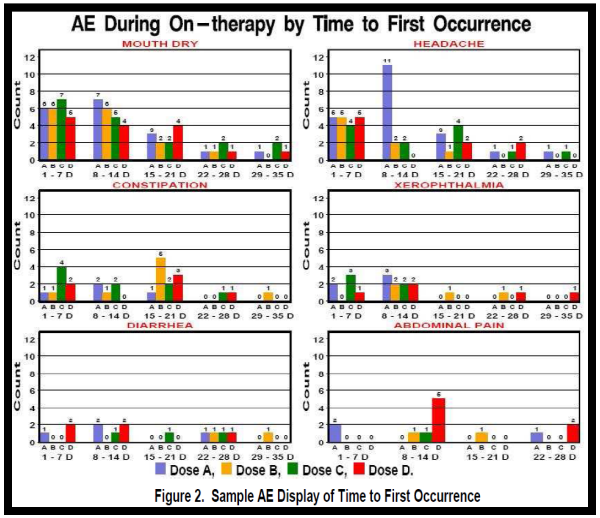
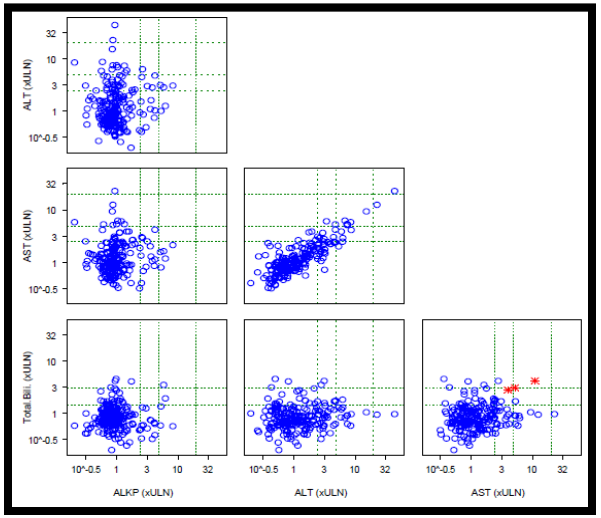
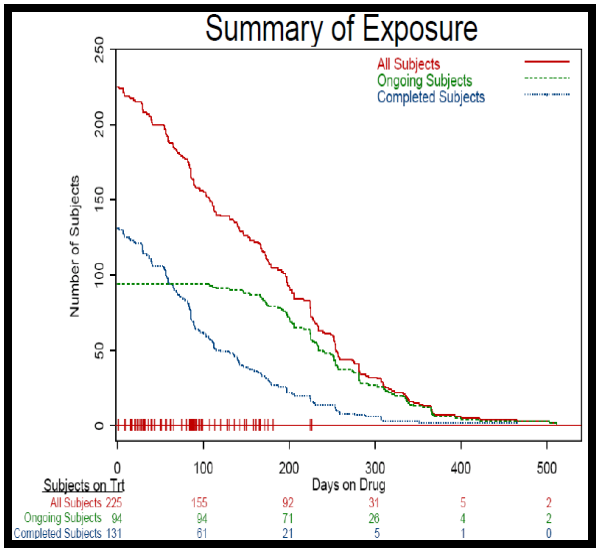
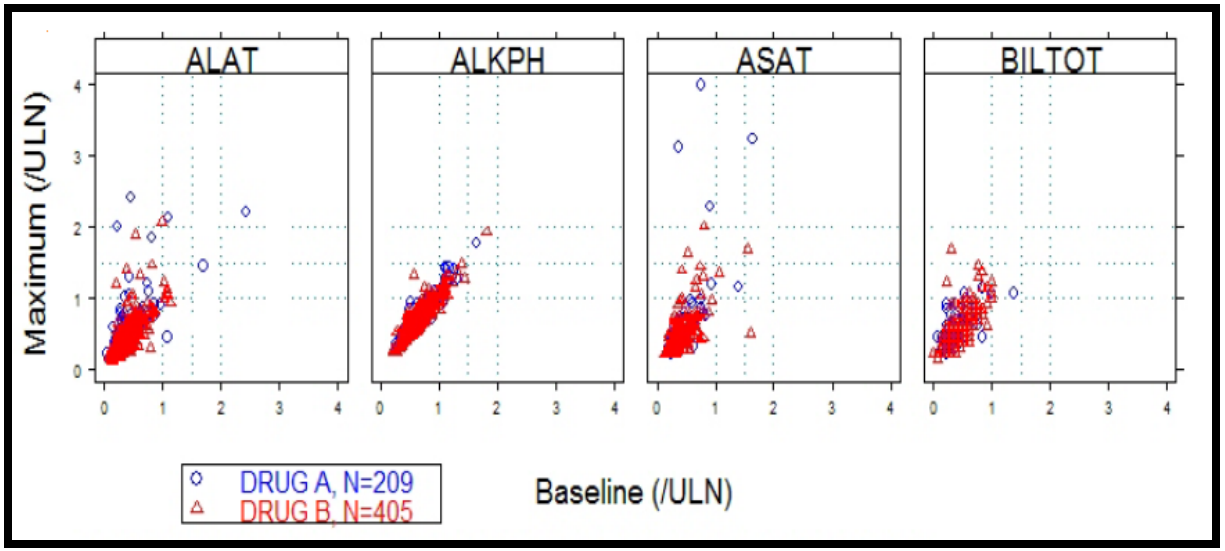


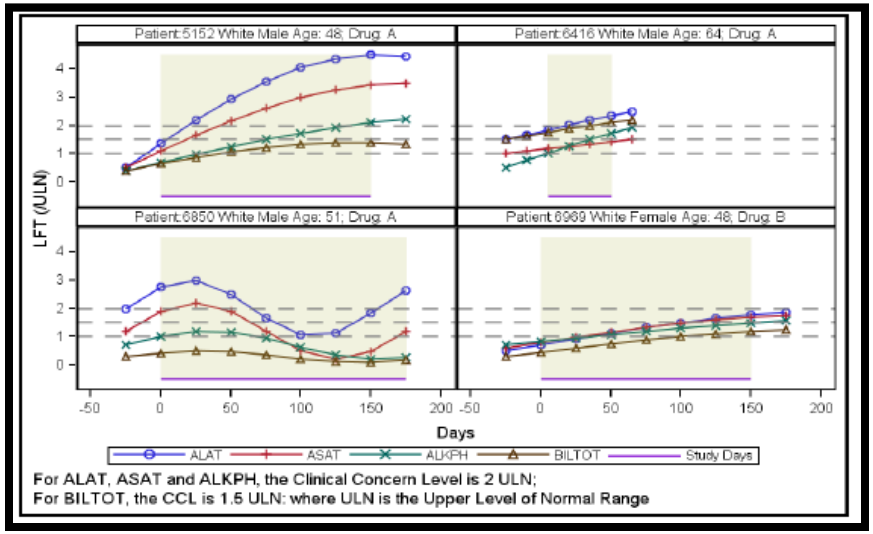
Figure 2. Sample AE Display of Time to First Occurrence

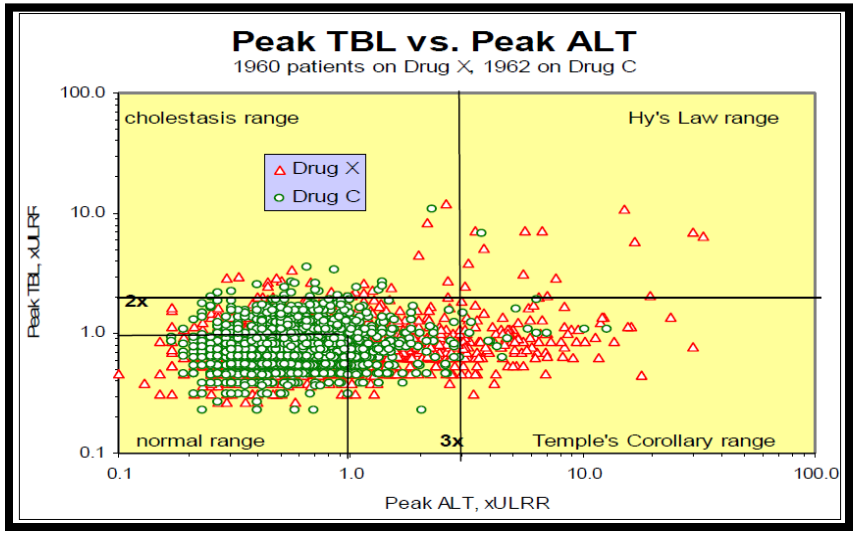


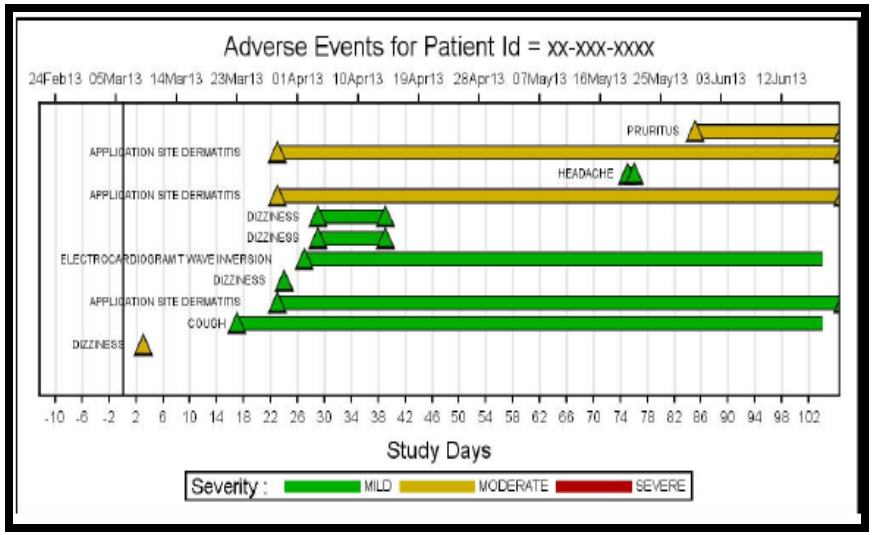


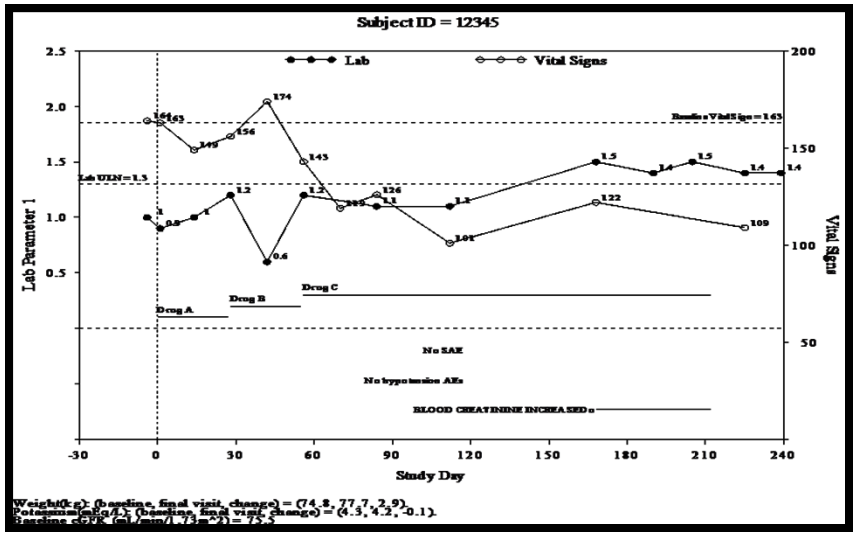


Analysis Approaches – Graphical Approaches









Analysis Approaches – Graphical Approaches

- **Not so main stream graphs in the analysis of safety data**

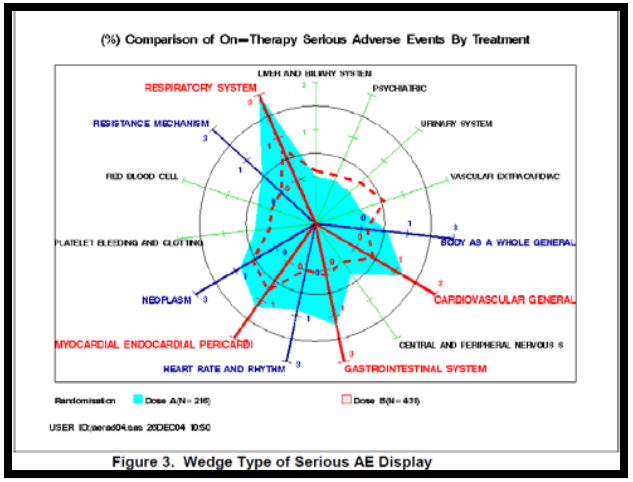


Figure 3. Wedge Type of Serious AE Display

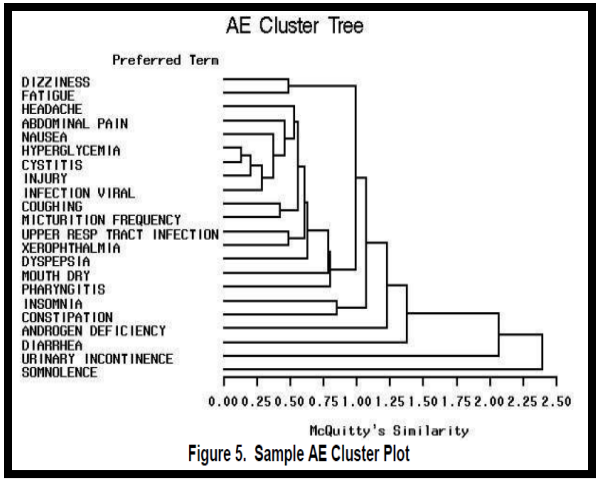


Figure 5. Sample AE Cluster Plot

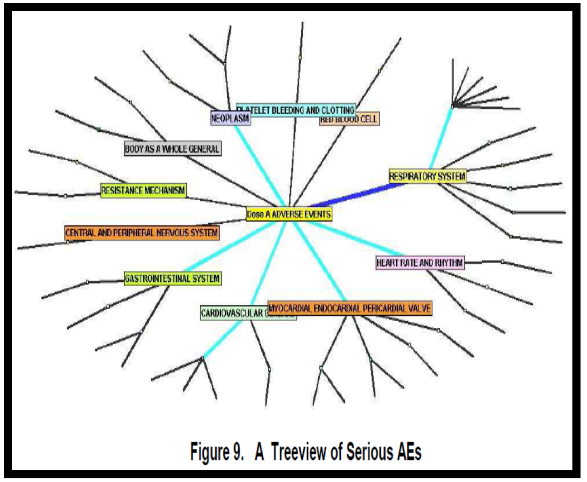


Figure 9. A Treeview of Serious AEs

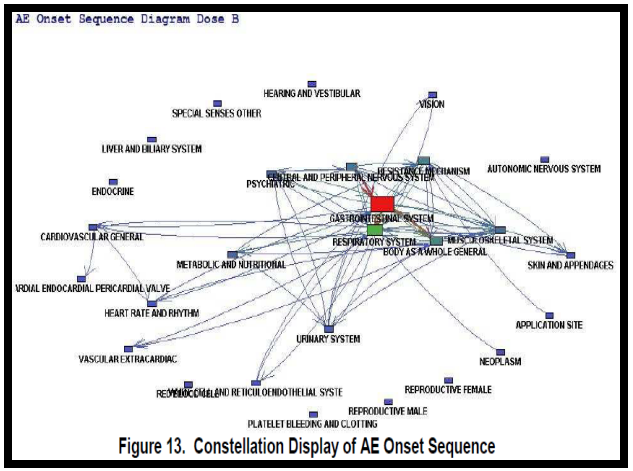


Figure 13. Constellation Display of AE Onset Sequence

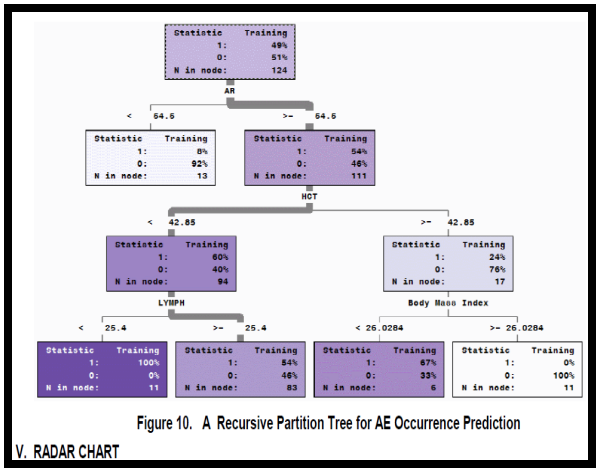
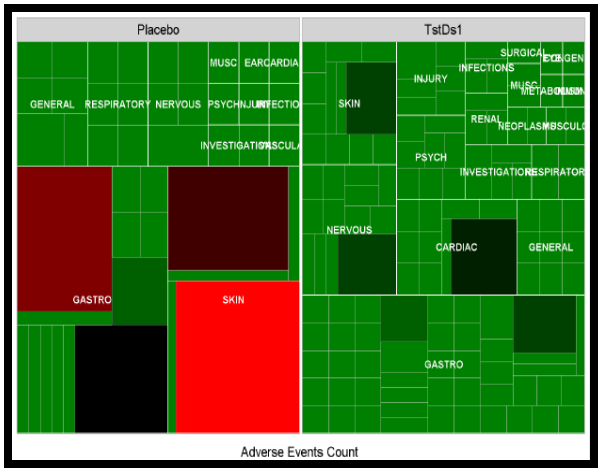


Figure 10. A Recursive Partition Tree for AE Occurrence Prediction

V. RADAR CHART



Analysis Approaches – Formal Analysis

- Many formal methodological approaches have been discussed for safety data
- Common inferential analyses are those noted earlier, including Fisher's Exact test, KM time-to-event analysis, etc
- Typically formal analyses focused on some specific concern
- Variety of methods proposed to address various questions
- But for the most part, safety analyses still based on crude rate and sometimes on exposure adjusted analyses
- Crude rate - total number of people treated divided by the number of people who experience AE
  - Crude rate index has several disadvantages – for example, it ignores frequency of adverse events and factors which may affect the occurrence of adverse events

Analysis Approaches – Recurrent Events

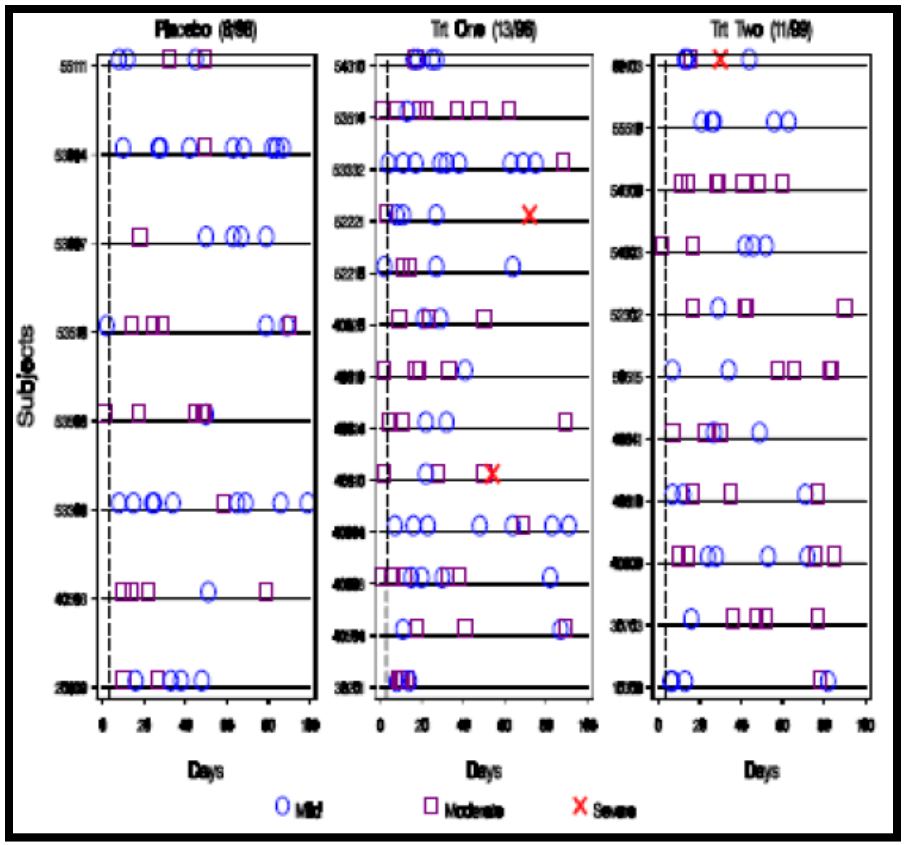
- When analyzing time to event for safety data, typically use:
  - The Kaplan-Meier (KM) method: estimate the survival function
  - The Nelson-Aalen method - estimate the cumulative hazard function
  - Cox proportional hazards models – evaluate effects of explanatory variables on hazard ratio
- Problem - All these methods usually focus on time to the first AE, and they are not appropriate for recurrent data which is a typical characteristic of AEs or other characteristics of data - *Tremmel (1996)*

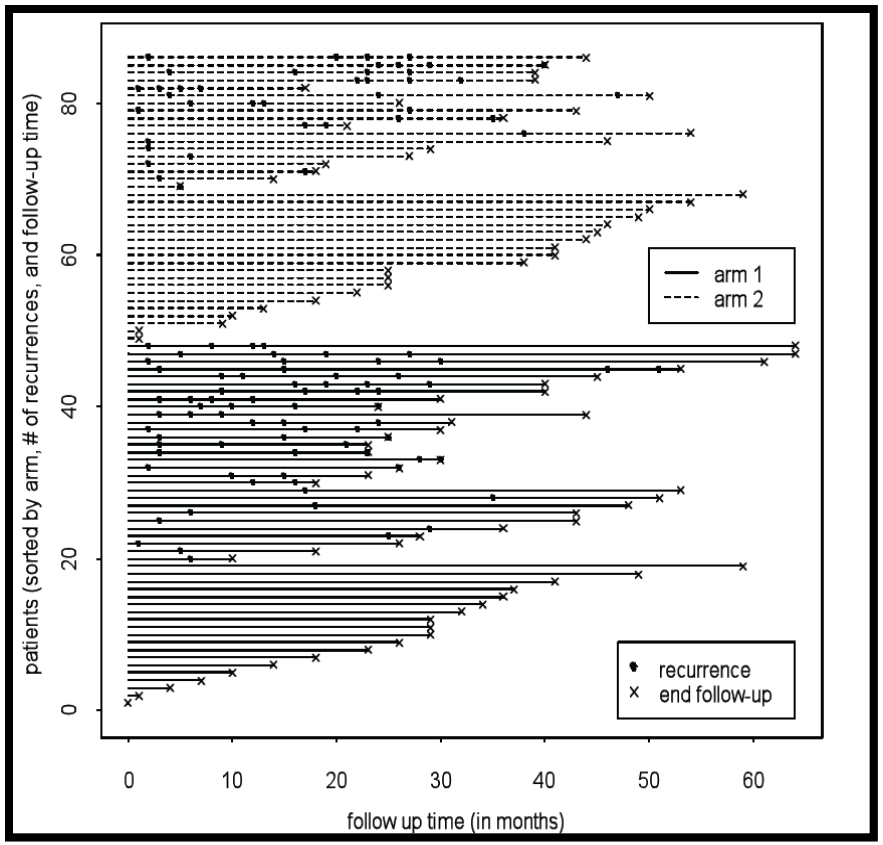

DEFINING, MONITORING AND COMBINING SAFETY INFORMATION IN CLINICAL TRIALS Gregory G. Enas[1], David J. Goldstein[2]
Statistics in Medicine 1995 Volume 14, Issue 9, 1099–1111

Also, when evaluating overall safety, one needs to assess all available information by combining information from many trials and other sources

Analysis Approaches – Recurrent Events

For example AEs can be recurring





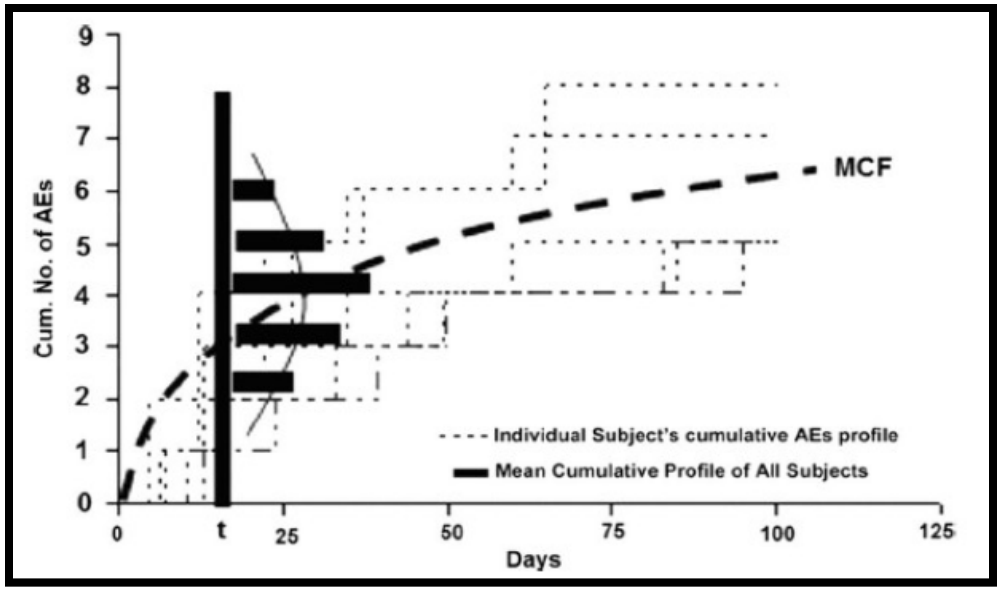
An Useful Chart to Display Adverse Event Occurrences in Clinical Trials
Chuanchieh Hsu Zhongwei Zhou, J. Michael Hardin SUGI 27 Paper 119-27

Visualization of Titrated Dose and recurrent Events Using R/ggplot2
Yue Shentu 2010

Event Charts for the Analysis of Adverse Events in Longitudinal Studies: An Example from a Smoking Cessation Pharmacotherapy Trial
Joel A. Dubin[*1] and Stephanie S. O'Malley[2] *The Open Epidemiology Journal*, 2010, 3, 34-41

Analysis Approaches – Recurrent Events

- Need to use alternative approaches similar to those for first event, but which take into account recurring nature of AEs
- Use Mean Cumulative function and regression models for recurrent data – Nelson (2003)
- Implemented in SAS Proc Reliability (can also get in Proc Phreg)



STATISTICAL METHODS TO ANALYZE ADVERSE EVENTS DATA OF RANDOMIZED CLINICAL TRIALS
Journal of Biopharmaceutical Statistics, 19: 889–899, 2009
Ohidul Siddiqui

Statistical Analysis of Adverse Events in Randomized Clinical Trials Using SAS Dongsun Cao, Xiaomin He PharmaSUG2011 - Paper SP07

Analysis Approaches – Recurrent Events

Regression models for recurrent data

- Consider a recurrent event process starting at $t = 0$, let $T_1 < T_2 \cdots$ denote the event times, where T_k denotes the time of the kth event.
- Let $N(t) = \sum_k I(T_k \le t)$ denote the cumulative number of events occurring over the time interval $[0, t]$.
- Let $H(t) = \{N(s) : 0 \le s \le t\}$ denote the history of the process at time t.
- For a short time interval $[t, t + \Delta t)$, the instantaneous probability of an event occurring at t, conditional on the process history, is given by the *intensity function*,

$$\lambda(t \mid H(t)) = \lim_{\Delta t \to 0} \frac{Pr\{N(t + \Delta t) - N(t) = 1 \mid H(t)\}}{\Delta t}.$$

- Unconditional Models: the events are "incidental" that their occurrence does not alter the process itself.
- Examples include mild epileptic seizures or asthmatic attacks.
- A Poisson process can be used to describe the number of events in time $(s, t]$, which is defined as $N(s, t)$:
  - → 1. $N(s, t)$ has a Poisson distribution.
  - → 2. If $(s_1, t_1]$ and $(s_2, t_2]$ are nonoverlapping intervals, then $N(s_1, t_1)$ is independent of $N(s_2, t_2)$.
- The intensity function is given by $\lambda(t \mid H(t)) = \rho(t)$: the probability of an event in $(t, t + \Delta t]$ may depend on t but is independent of $H(t)$.
- The process is *homogeneous* if $\rho(t) = \rho$ is a constant; otherwise it is *nonhomogeneous*.

On reporting results from randomized controlled trials with recurrent events *BMC Medical Research Methodology* 2008, 8:35

Lisa Kuramoto*[1], Boris G Sobolev[2] and Meghan G Donaldson[3]

Analysis Approaches – Recurrent Events

- Let x_i denote the indicator for treatment, and let λ_o denote the baseline intensity.
- Poisson model:

$$\lambda_i = \lambda_o \exp(\beta x_i).$$

- This model assumes λ_i is a constant over time, and it does not depend on either the event history or time t.

- Independent-Increment model:

$$\lambda_i(t) = Y_i(t)\lambda_o(t)\exp(\beta x_i),$$

where $Y_i(t) = \begin{cases} 1 & \text{if subject i is under observation at time t} \\ 0 & \text{if subject i is censored by time t} \end{cases}$

- $\lambda_o(t)$ is the baseline rate function that can vary over time, but is independent of the event history.

- Gamma-Poisson model:

$$\lambda_i = \mu_i \lambda_o \exp(\beta x_i).$$

- Independent-Increment frailty model:

$$\lambda_i(t) = Y_i(t)\mu_i\lambda_o(t)\exp(\beta x_i).$$

- Here, μ_i is a frailty parameter that measures heterogeneity of the subjects and allows for overdispersion. A convenient choice for μ_i is gamma distribution,

$$f(\mu) = \frac{\mu^{1/\theta - 1}\exp(-\mu/\theta)}{\Gamma(1/\theta)\theta^{1/\theta}}.$$

- Under the assumption of time homogeneous models, the marginal distribution of the total number of events is negative binomial.

Analysis Approaches – Recurrent Events

- Conditional Models: the events may substantially affect the event process in the future.
- Examples include myocardial infarction and stroke in cardiovascular studies.
- Conditional model:

$$\lambda_{ij}(t - T_{N(t^-)}) = Y_{ij}(t)\lambda_{oj}(t - T_{N(t^-)})\exp(\beta x_i),$$

where $T_{N(t^-)}$ is the time of the event just prior to time t.

- $Y_{ij}(t) = \begin{cases} 1 & \text{if } (j-1)\text{th event occurred by time } t \text{ and } j\text{th event has not} \\ 0 & \text{if otherwise or censored at time } t \end{cases}$
- Thus a subject is considered at risk at time t only if the previous event occurred before that time, and if he is under observation.
- The intensity function depends on both time t and the event history.

Analysis Approaches – Recurrent Events

- ***Simulated data***

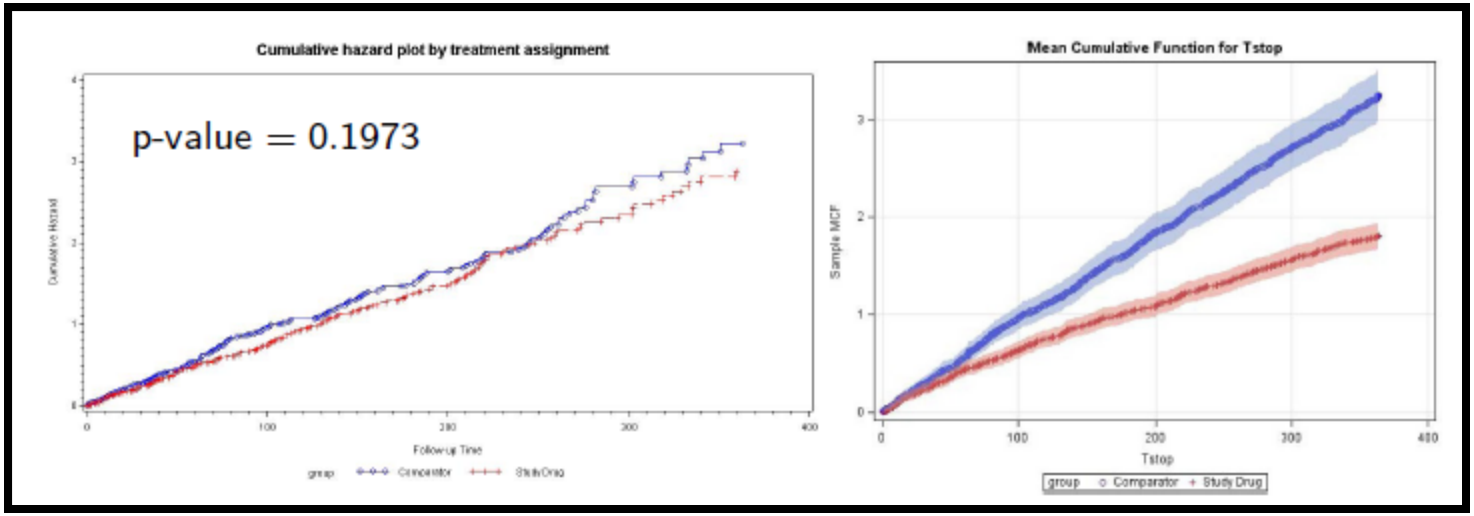


Table : Effect of treatment on adverse events

Model	Parameter	*p* value	Hazard Ratio	95% CI
Cox	-0.1179	0.1986	0.889	(0.742, 1.064)
Poisson	-0.4154	<0.0001	0.660	(0.600, 0.726)
Gamma-Poisson	-0.2665	<0.0001	0.766	(0.682, 0.860)
Independent-increment	-0.5880	<0.0001	0.555	(0.495, 0.623)
Conditional	-0.5255	<0.0001	0.585	(0.524, 0.654)

Analysis Approaches – Bayesian Methods

Bayesian Analysis Approach…

"Safety assessment is one area where frequentist strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise." (Pharmaceutical Report, 2002) – G.Chi, H.M. Hung, R. O"Neill

BAYESIAN HIERARCHICAL MODELING FOR DETECTING SAFETY SIGNALS IN CLINICAL TRIALS
Journal of Biopharmaceutical Statistics, 21: 1006–1029, 2011
H. Amy Xia[1], Haijun Ma[1], and Bradley P. Carlin[2]

BayesWeb: A USER-FRIENDLY PLATFORM FOR EXPLORATORY BAYESIAN ANALYSIS OF SAFETY SIGNALS FROM SMALL CLINICAL TRIALS
Journal of Biopharmaceutical Statistics, 21: 1030–1041, 2011
John A. Scott[1], Austin L. Hand[1,2], and Layla S. Sian[3]

Bayesian Modeling with S-PLUS® and the S+flexBayes Library
Andrew Jack, Dawn Woodard, Joel Hoffman, Michael O'Connell PhUSE 2007

Multivariate Bayesian Logistic Regression for Analysis of Clinical Study Safety Issues[1] William DuMouchel
Statistical Science
2012, Vol. 27, No. 3, 319–339

Detecting Potential Safety Issues in Clinical Trials by Bayesian Screening
Biometrical Journal **50** (2008) 5, 837–851
A. Lawrence Gould*

Safety analysis using Bayesian simulation methods in SAS® 9.2 Armin Gemperli
Pharmaceutical Programming 2010

Bayesian Applications in Drug Safety Evaluation
Amy Xia, 2010

Bayesian Hierarchical Models for Detecting Safety Signals in Clinical Trials
H. Amy Xia and Haijun Ma 2009

A Bayesian Modeling Approach for Safety Data Analysis in Drug Development Y. Gu, K. Zhang, and L. Yang, 2010

Applied Bayesian Approaches in Safety and Pharmacovigilance
Andy Grieve 2011

Analysis Approaches – Bayesian Methods

Why use a Bayesian approaches?

- Offers many advantages in monitoring or analyzing safety data
- Can handle multiplicity question
- Ability to incorporate prior information
- Provides a single, coherent framework in which diverse elements of the data can be modeled
- Does not rely on asymptotic properties in dealing with rare events
- Straightforward and flexible to assess clinically important differences
- Can be as simple as performing a simple Bayesian computation applied to safety data – see for example Scott (2011 and http://bayesweb.com/)
- Can also be used in the modeling and prediction

Analysis Approaches – Bayesian Methods

- ***Berry and Berry Model (2004)***

B body systems

k_i adverse effects within body system i

For AE_{ij}, $i = 1, \ldots, B$, $j = 1, \ldots, k_i$

Control: x_{ij} events in n_C patients

Treatment: y_{ij} events in n_T patients

H_0: $c_{ij} = t_{ij}$, where c_{ij} & t_{ij} are event rates

$\text{logit}(c_{ij}) = \gamma_{ij}$

$\text{logit}(t_{ij}) = \gamma_{ij} + \theta_{ij}$

θ_{ij} are log odds ratios

$\theta_{ij} = 0$ => Pr(subject has AE_{ij}) is same for trt and ctl

$\gamma_{ij} \sim N(\mu_{\gamma i}, \sigma_\gamma^2)$

$\theta_{ij} \sim \pi_i I\{0\} + (1-\pi_i) N(\mu_{\theta i}, \sigma_{\theta i}^2)$

π_i is probability that the treatment has no effect on an AE in body system i

$\pi_i \sim \text{Beta}(a_\pi, b_\pi)$, $i = 1, \ldots, B$

Priors on a_π, b_π are chosen to be symmetric

=> Prior Pr($\theta_{ij} = 0$) = prior Pr(no trt effect on AE_{ij}) = 0.5

=> Addresses multiple comparisons issue directly

$\mu_{\gamma i}$, σ_γ^2 $\mu_{\theta i}$, $\sigma_{\theta i}^2$ π_i are same for PTs within SOCs

=> Borrow strength within SOCs

$\mu_{\gamma i}$, $\mu_{\theta i}$, π_i are modeled as random effects

=> Borrow strength across SOCs

Source: McConnell (2004)

Analysis Approaches – Bayesian Methods

- ***Sample Results***

Table 3

Two-sided Fisher-exact-test p-values compared with the probability of a treatment effect $p(\theta > 0)$ from a "one-stage" solo Bayesian model (see text) and from the three-stage hierarchical model

Type of adverse event	Fisher $2p$	Solo Bayesian	Hierarchical Bayesian
Diarrhea	0.029	0.885	0.231
Irritability	0.003	0.984	0.780
Rash	0.021	0.923	0.190
Rash, measles/ rubella-like	0.039	0.889	0.126

- *Code available in SAS, Splus, and R for Berry and Berry Model*

Analysis Approaches – Bayesian Methods

Gu, Zhang, and Yang Model (2010)

- Bayesian logistic mixed-effect model to analyze safety data
- Like Berry model, SOC is considered in the model so information within the same SOC can be borrowed to help model AE rate
- Risk factors can be easily added in the model

logit(p)=Treatment + SOC + AE+ Interaction Terms + Other Covariates

- p= AE rate
- prior information will be specified on the coefficients
- posterior of p = prior * likelihood of observed data
- Pr(RR> threshold |observed data)=?
- posterior predictive distribution of Y=posterior of p * likelihood of Y

- For AE_{bj}
- -- X_{bj}: number of reported AEs among N_c patients in control arm
- -- Y_{bj}: number of reported AEs among N_t patients in treatment arm

where SOC b=1,2,…, B, AE j=1,…, n1

- Suppose X_{bj} ~ Binomial (Nc, c_{bj}) Y_{bj} ~ Binomial (Nt, t_{bj})
- Where c_{bj} and t_{bj} are the event rates in control and treatment arms, respectively
- Mixed effect model with interaction

Model is

where p= X_{bj} /Nc or Y_{bj} /Nt, $\beta_{2b} \sim N(0,\sigma_2^2)$, $\beta_{3j} \sim N(0,\sigma_3^2)$, $\beta_{4b} \sim N(0,\sigma_4^2)$, $\beta_{5j} \sim N(0,\sigma_5^2)$, priors on β_0, β_1, σ_2^2, σ_3^2, σ_4^2, σ_5^2

$$\text{logit}(p) = \beta_0 + \beta_1 * T_i + \sum_b \beta_{2b} * SOC_b + \sum_j \beta_{3j} * AE_j + \sum_b \beta_{4b} T_i * SOC_b + \sum_j \beta_{5j} T_i * AE_j$$

Slide from authors

Analysis Approaches – Bayesian Methods

- Criteria of flagging AE are based on the posterior probability of the question with clinical meaning
- Any clinical questions that can be expressed in the function of AE rates can be answered directly
  - What is the Pr(RR >1 | Data)?
  - What is the Pr(Difference of AE rates > 10%|Data)?
  - What is the Pr(RR>1 and AE rates in both treatment and control arms > 5%|Data)?

AE	Fisher exact test (p-value)	Post prob of θ>0	Post prob of RR>1
Diarrhea	0.029	0.231	0.991
Irritablility	0.003	0.780	1.000
Rash	0.021	0.190	0.994
Rash, measles/rubella-like	0.039	0.126	0.994

Analysis Approaches – Formal Analysis

Some considerations/thoughts

- Rare AE or no AE
- AEs of Special Interest
- Multiplicity
- Meta Analysis
- Integrated analysis
- Safety Pharmacology

Meta-analysis of rare and adverse event data
A. J. Sutton, et al
Expert Rev. Pharmacoeconomics Outcomes Res. 2(4), 367–379 (2002)

Meta-Analysis of Rare Binary Adverse Event Data
Dulal K. Bhaumik, et al, JASA 2012

Meta-analysis of incidence of rare events
Peter W. Lane
Statistical Methods in Medical Research 2011

Meta-analyses of safety data: a comparison of exact versus asymptotic methods
Ben Vandermeer, et al
Statistical Methods in Medical Research 2009; **18**: 421–432

Estimating With Confidence the Risk of Rare Adverse Events, Including Those With Observed Rates of Zero
A. M-H. et al,
Regional Anesthesia and Pain Medicine, Vol 27, No 2 (March–April), 2002: pp 207–210

Calculating the probability of rare events: why settle for an approximation?
Brown, Byron Wm. Jr.; Luft, Harold S.
Health Services Research 1993

Planning for the Identification, Data Collection, and Integration of Adverse Events of Special Interest (AESI)
Manfred Oster, MD
DIA/FDA/PhRMA Drug Safety Conference, October 14-15, 2008

Applying SMQs to Adverse Event Data
John van Bemmelen, PhUSE 2008 Paper TU05

Current State of Special Safety Analyses for Clinical Trials
Miganush Stepanians, 2008

Use of the false discovery rate for evaluating clinical safety data
Devan V Mehrotra and Joseph F Heyse
Statistical Methods in Medical Research 2004; **13**: 227–238

Accounting for Multiplicities in Assessing Drug Safety: A Three-Level Hierarchical Mixture Model
Scott M. Berry and Donald A. Berry
Biometrics 60, 418–426 2004

Multivariate time-to-event analysis of multiple adverse events of drugs in integrated analyses
Achim Güttner[1,*,†], Jürgen Kübler[1,‡] and Iris Pigeot[2,3,§]
Statist. Med. 2007; **26**:1518–1531

An Approach to Integrated Safety Analyses From Clinical Studies
Gerd K. Rosenkranz
Drug Information Journal, *Vol. 44, pp. 649–657, 2010*

Modelling and Simulation of the incidence of adverse events in clinical trials
Filip De Ridder[1], An Vermeulen[2], Vladimir Piotrovskij[2]

Pharmacokinetic-Pharmacodynamic Modelling of Adverse Effects of Nitrendipine
I. Locatelli, et al, 2003

Analysis Approaches – Formal Analysis

Specific to AEs…

Analysis Approaches – Formal Analysis

Specific to lab data…

DETECTING OUTLIERS IN MULTIVARIATE LABORATORY DATA

Journal of Biopharmaceutical Statistics, 18: 1178–1183, 2008

Harry Southworth

A comparison of multivariate outlier detection methods for clinical laboratory safety data

Kay I. Penny and Ian T. Jolliffe *The Statistician* (2001) 50, *Part* 3, *pp.* 295–308

MULTIVARIATE OUTLIER DETECTION APPLIED TO MULTIPLY IMPUTED LABORATORY DATA

KAY I. PENNY[1*] AND IAN T. JOLLIFFE[2] *Statist. Med.* **18**, 1879–1895 (1999)

Extreme value modelling of laboratory safety data from clinical studies

Harry Southworth[a*] and Janet E. Heffernan[b] *Pharmaceut. Statist.* **2012**

Assessing a vector of clinical observations

Morris L. Eaton[a], Robb J. Muirhead[b,*], Eve H. Pickering[c]

Journal of Statistical Planning and Inference 136 (2006) 3383–3414

Multivariate statistical interpretation of laboratory clinical data

Agelos Papaioannou[1*], Vasili Simeonov[2], Panagiotis Plageras[1], Eleni Dovrikil and Thomas Spanos[3]

Central European Journal of Medicine 2007 319–334

Modeling laboratory data from clinical trials

Gerd K. Rosenkranz Computational Statistics and Data Analysis 53 (2009) 812–819

Analysis of longitudinal laboratory data in the presence of common selection mechanisms: A view toward greater emphasis on pre-marketing pharmaceutical safety

Jonathan S. Schildcrout[1,*,†], Cathy A. Jenkins[1], Jack H. Ostroff[2], Daniel L. Gillen[3], Frank E. Harrell[1] and Donald C. Trost[2] *Statist. Med.* (2007)

Vector Analysis to Detect Hepatotoxicity Signals in Drug Development

Donald C. Trost, James W. Freston, Drug Information Journal, Vol. 42, pp. 27–34, 2008

Dissimilarity Measures for Detecting Hepatotoxicity in Clinical Trial Data*

Matthew Eric Otey Srinivasan Parthasarathy Donald C. Trost

Multivariate Probability-Based Detection of Drug-Induced Hepatic Signals

Donald C. Trost Toxicol Rev 2006; 25 (1): 37-54

Bayesian modelling of the dynamics of hepatotoxicity

Q. Li[1], X. Shen[2,*,†] and D. K. Pearl[1] *Statist. Med.* 2007; **26**:3591–3611

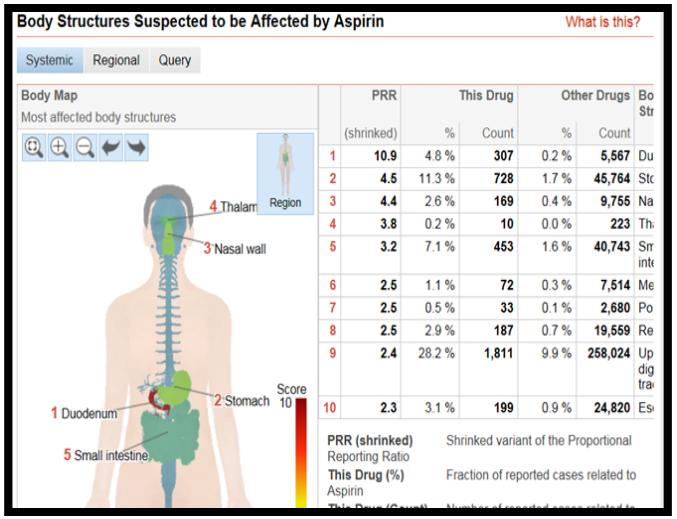
Analysis Approaches – Final Thoughts

- ***The future of safety data analysis…?? Combine tables analysis and graphs…***

Using Avatars to Understand Adverse Drug Reactions

POSTED BY: ROBERT CHARETTE / TUE, MARCH 06, 2012

nhumi Drug Safety beta



	PRR (shrinked)	This Drug %	This Drug Count	Other Drugs %	Other Drugs Count	Bo Str
1	10.9	4.8 %	307	0.2 %	5,567	Du
2	4.5	11.3 %	728	1.7 %	45,764	Sto
3	4.4	2.6 %	169	0.4 %	9,755	Na
4	3.8	0.2 %	10	0.0 %	223	Th
5	3.2	7.1 %	453	1.6 %	40,743	Sm int
6	2.5	1.1 %	72	0.3 %	7,514	Me
7	2.5	0.5 %	33	0.1 %	2,680	Po
8	2.5	2.9 %	187	0.7 %	19,559	Re
9	2.4	28.2 %	1,811	9.9 %	258,024	Up dig tra
10	2.3	3.1 %	199	0.9 %	24,820	Es

http://drugsafety.nhumi.com/drugsafety/

Closing Remarks

- There is room to improve safety reporting
- Need to make safety analysis more formal..also race for safety
- Plan safety analyses similar to efficacy analyses
- Consider using the various formal analyses methods that have been discussed in the literature and use graphs
- Methods used should be well thought prior to use
- Need to make more use of graphs to help enhance safety reporting
- Heed recommendations from Safety Planning, Evaluation, and Reporting Team
- Consider benefit risk

Planning and core analyses for periodic aggregate safety data reviews

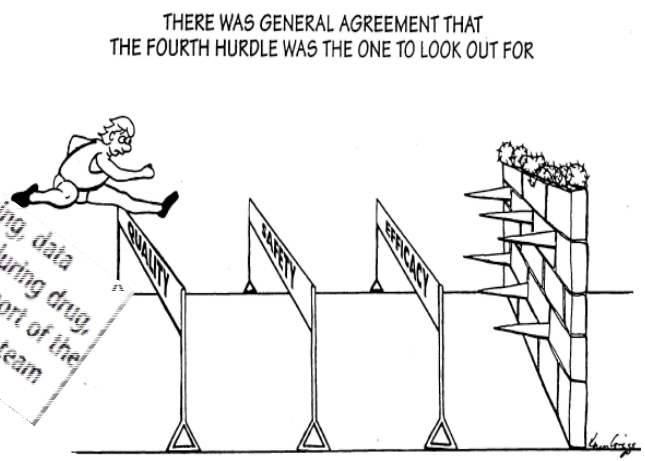
Clinical Trials 2011; 8: 175–182

H Amy Xia¹, Brenda J Crowe², Robert C Scherer³, Manfred Ockert⁴ and Donald S Hall⁵

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 2009; 6: 430–440

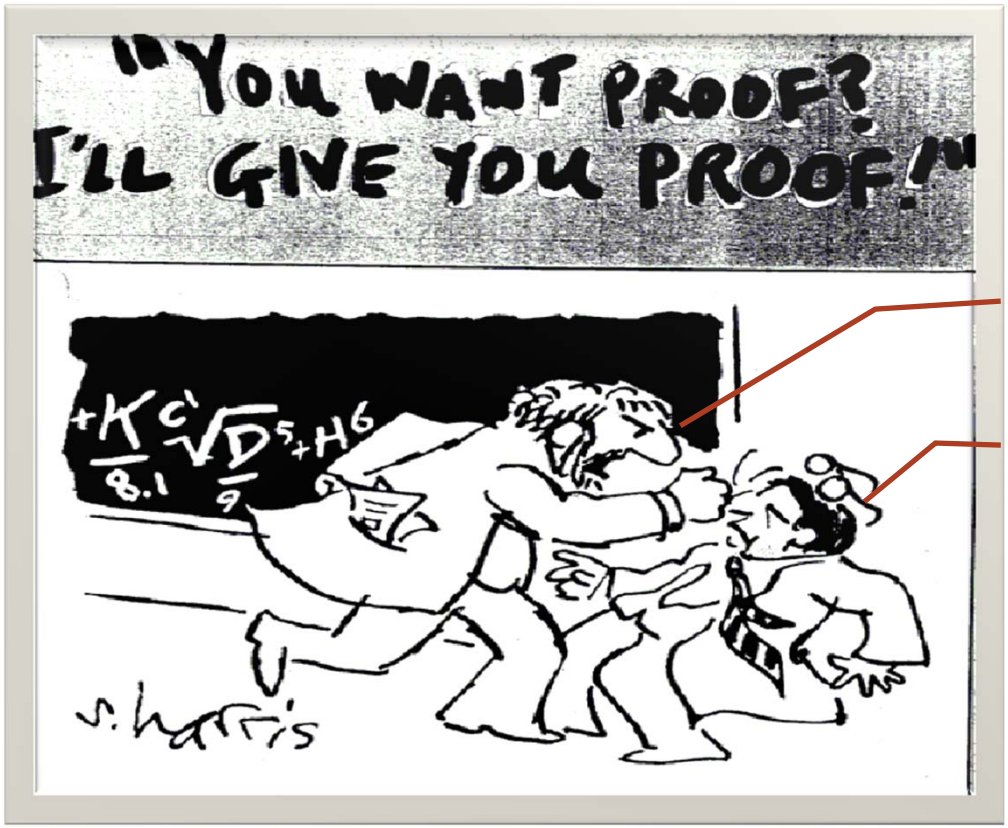
B. J. Crowe, et al



Slide from C. Chung-Stein

Some things that I have learned!

- Try to understand where the other person is coming from…know the science as much you can



What do we really know about safety?

Donald Rumsfeld on Knowledge

As we know,
There are known knowns.
There are things we know we know.

We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.

But there are also unknown unknowns,
The ones we don't know
We don't know.

Feb. 12, 2002, Department of Defense news briefing

Slide from J. Hung

Thank You!

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??Questions??

References

Plenty! – see references noted in the 'boxes' in the slide deck