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Statistical Evaluation of Drug Safety Data

Amy Xia and Qi Jiang

Global Biostatistical Science, Amgen, Inc.

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Complete List of Authors:	Xia, Amy; Amgen, Inc, Global Biostatistical Science Jiang, Qi; Amgen, Global Biostatistical Science
Keywords:	PSAP , Bayesian methods for signal detection, meta-analysis, safety graphics, benefit-risk assessment
Abstract:	There has been growing awareness of the importance of the statistical evaluation of drug safety data, both in the pre-marketing and post-marketing settings. Careful and comprehensive approaches are warranted in safety evaluation. This paper offers a high-level review of some key issues and emerging statistical methodologic developments. Specifically, we discuss the following topics: prospective program-level safety planning, evaluation and reporting; the impact of adverse event grouping on statistical analysis; the applications of Bayesian methods in safety signal detection and safety monitoring; meta-analysis for analyzing safety data; and safety graphics. In addition, we cover aspects related to benefit-risk assessment.

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Outline

- Introduction
- Special topics for statistical evaluation of safety data
 - Impact of AE grouping on statistical analysis
 - Bayesian applications in safety signal detection
 - Meta-analysis for analyzing safety data
 - Program safety analysis plan (PSAP)
 - Safety graphics
 - Benefit-risk assessment
- Closing remarks

Introduction

- There has been growing awareness of the importance of statistical evaluation of drug safety data
- Traditional statistical approaches for analyzing safety data are often descriptive and perhaps oversimplified, and knowledge of and experience with proper methods may be inadequate
- A well-planned, systematic, and consistent approach including use of comprehensive statistical methods for assessing safety during drug development is warranted
- There were numerous guidance documents issued from regulatory authorities in the past decade

Some Statistical Challenges in Quantitative Safety Analyses

- Power
- Multiplicity
- Medical classification
- Complexity of safety data with multi-dimensional elements
- Impact of a new signal must be weighted in the context of the benefit-risk profile of the drug

Special Topics

- **Impact of AE grouping on statistical analysis**
- Bayesian applications in safety signal detection
- Meta-analysis for analyzing safety data
- Program safety analysis plan
- Safety graphics
- Benefit-risk assessment

Impact of AE Grouping on Statistical Analysis

- Signal detection and evaluation can be obscured by
 - Lack of standard definition of AEs
 - Lack of standard coding conventions and terminology usage
 - Lumping and splitting of terms without prospective plans
- One of challenges that DMCs are generally facing in assessing safety during clinical trials
- Grouping AEs into categories can pose statistical challenges

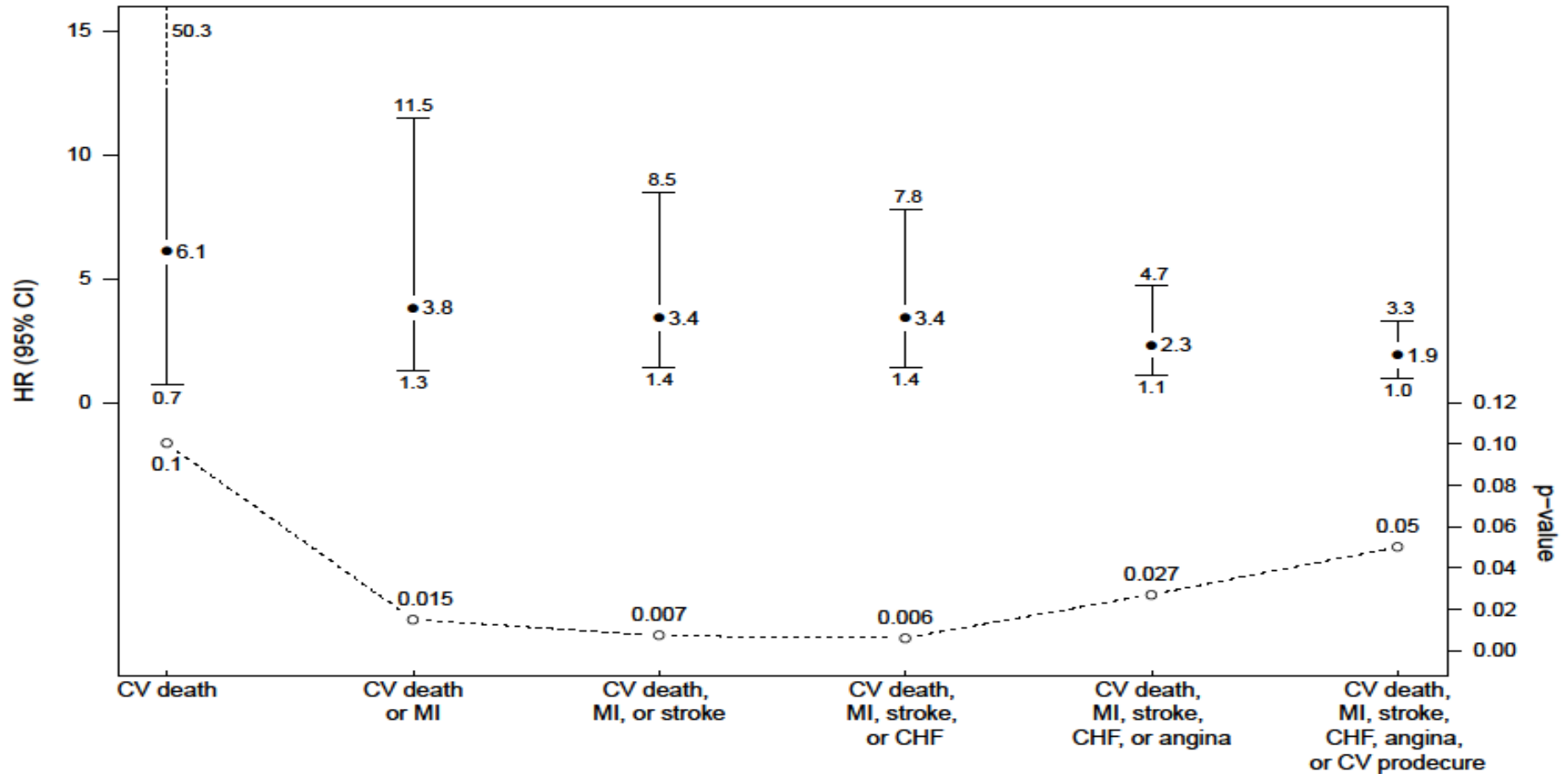
Broad vs Narrow Classification

- Historically, broad search is viewed as conservative in the sense that it minimizes the risk of missing an event of interest
- However, it can lead to non-differential misclassification and bias the relative risk estimate towards null
 - Treatment effect can be diluted
 - Signal can be masked

- O'Neill RT, (Marcel Dekker, 1988)
- Crowe B, Xia A, Berlin, J, et al (2009)

Hierarchical Outcome Classification

– An Example with CV Events



- Proschan MA, Lan KKG, Wittes JT. Statistical Monitoring of Clinical Trials, 2006
- Solomon SD, McMurray JJV, Pfeffer, MA, et al. NEJM, 2005

MedDRA Terminology

- A difficulty arises in deciding whether groupings of different terms can be formally regarded as a medical concept
 - Two or more Preferred Terms (PTs) may stand for the same medical concept
 - Some terms may be more general than others
 - Inconsistencies in event classification and codification are common
- Standardized MedDRA Queries (SMQs) should be used when available
- It is important to obtain agreement on customized endpoint definitions (a PSAP could be used as a tool)

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Three-Tier System for Analyzing Adverse Events in Drug Safety Data

- Tier 1 AEs -- events for which a hypothesis has been defined
- Tier 2 AEs -- events that are not pre-specified and “common”
- Tier 3 AEs – events that are not pre-specified and infrequent

Detection of safety signals from routinely collected, not pre-specified AE data is a critical task in drug development

Some Challenging Statistical Issues in Safety Signal Detection

- Multiplicity
 - Without multiplicity adjustment, there is a potential for an excess of false positive signals
 - Traditional ways of adjusting for multiplicity such as Bonferroni may lead to an excessive rate of false negatives
 - The challenge is to develop a procedure for flagging safety signals which provides a proper balance between 'no adjustment' versus 'too much adjustment'
- Rare events

Advantages of Bayesian Methods in Safety Signal Detection

- Bayesian hierarchical modeling provides a useful tool to address multiplicity by explicitly modeling AEs with the existing AE coding structure
 - Strength can be borrowed among ‘similar’ AEs
 - Provides ‘partial correction’ when it is crucial but does not overdo it when it is not
- Bayesian approach is attractive statistically in dealing with rare events
 - Model adaptively modulates the extremes
 - Inferences are based on the full posterior distributions, without the need to assume normality (which may not be sensible in the rare events setting)

Advantages of Bayesian Methods in Safety Signal Detection (Con't)

- Ease of interpretation
 - Straightforward and flexible to assess clinically important difference with different scales
 - Avoid detecting medically unimportant signals (an AE could have high $\Pr(\text{OR or RR} > 1 \text{ or RD} > 0 \mid \text{Data})$, but medically unimportant)
- Models the entire AE dataset and makes efficient use of all the data
 - Distinction of Tier 2 and Tier 3 events is not necessary

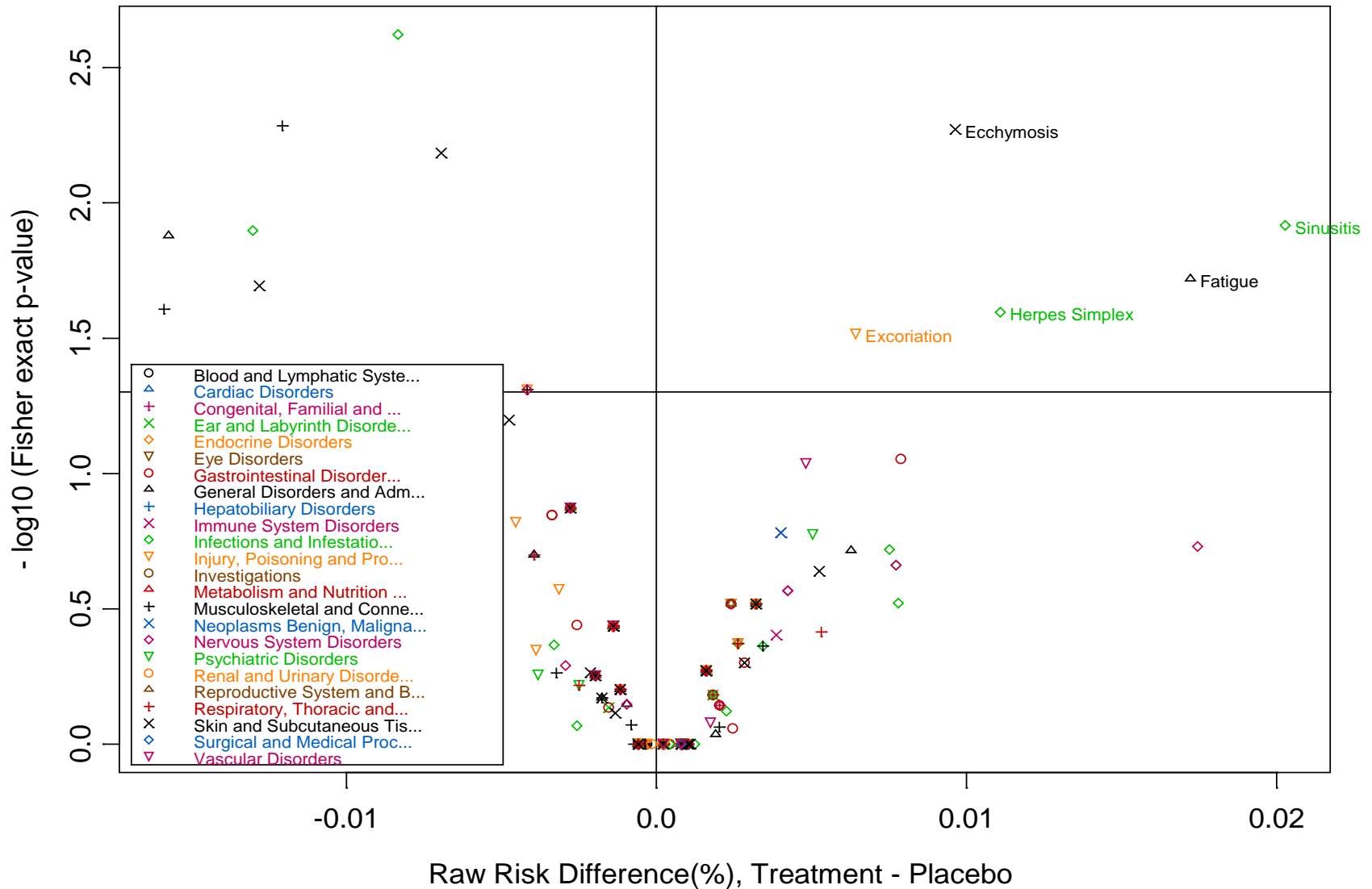
Bayesian Methods Have Been Commonly Used for Signal Detection in Data from Various Sources

- Clinical trial AE data
 - **Bayesian hierarchical modeling** [Berry & Berry, 2004; Xia, et al. 2011]
 - Bayesian screening [Gould, 2008]
 - Multivariate Bayesian logistic regression [DuMouchel, 2011]
- Spontaneous adverse drug reaction reports
 - Gamma Poisson Shrinker on FDA AERS database [DuMouchel, 1999]
 - Bayesian Confidence Propagation Neural Network on WHO database [Bate, et al. 1998]
- Electronic medical records and administrative claims databases
 - Longitudinal Gamma Poisson Shrinker and Longitudinal Evaluation of Observational Profiles of AEs Related to Drugs [Schuemie, 2011]
 - Temporal Pattern Discovery [Norén, et al. 2010]

Bayesian Approach for Flagging Adverse Events in Clinical Trials – A Case Study

- A three-level binomial (Berry & Berry 2004) or Poisson hierarchical mixture model can be constructed by accounting for the biologic relationship among various types of AEs through modeling data with AE coding structure (e.g. system organ class/preferred term)
- Bayesian inferences: flag AE_{ij} (AE type j within body system i) if $\Pr(\theta_{ij} > c \mid \text{Data}) > p$, where θ_{ij} is $\log(\text{OR})$ in Binomial models or $\log\text{-RR}$ in Poisson model (c and p are all pre-specified constants)

Fisher's Exact Test 2-sided P-values



Data source: pooled AEs from 4 trials

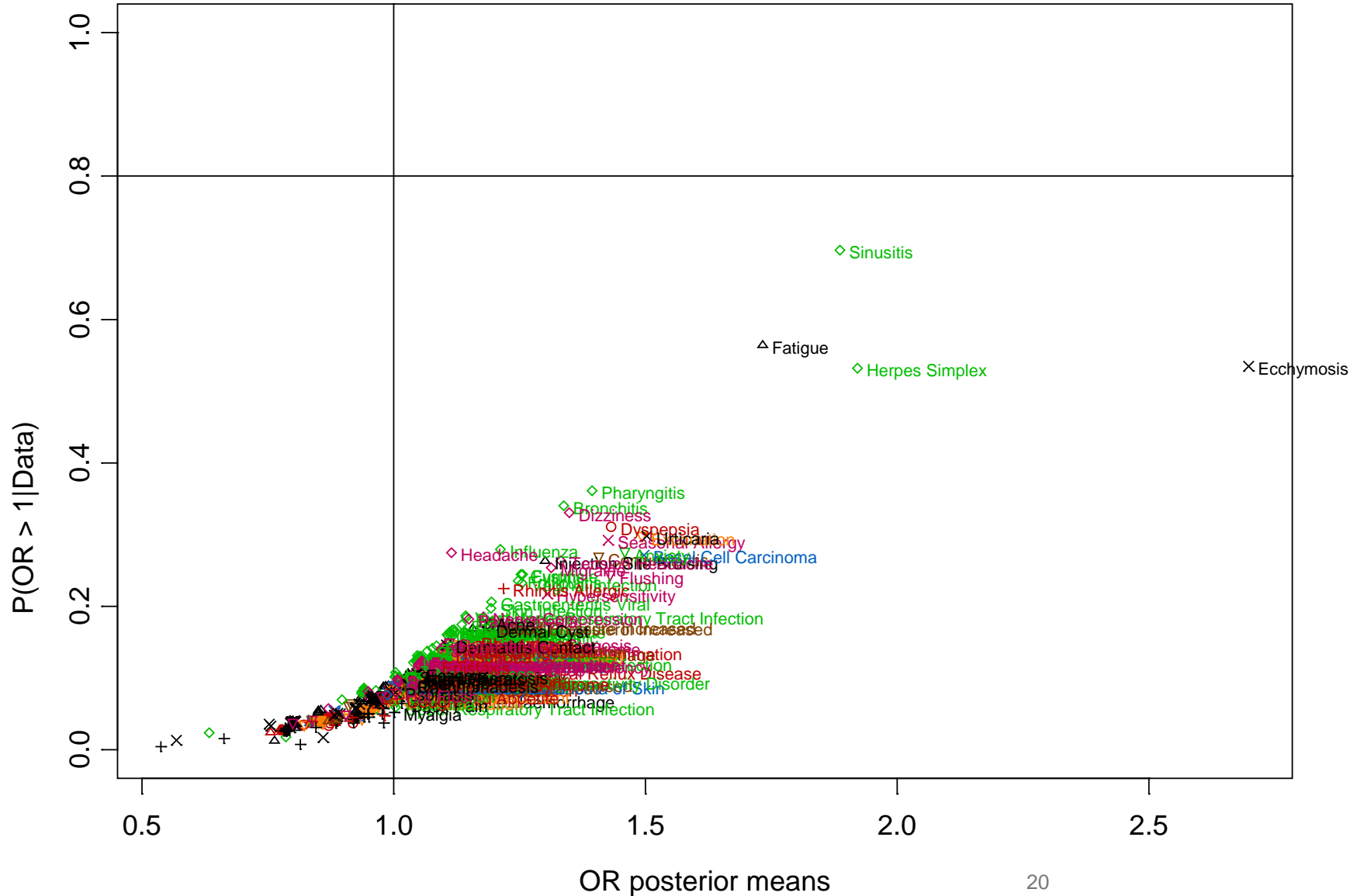
- Treatment = drug X (N = 1245); Control = placebo (N = 720)
- 465 AE types (PTs) under 24 body systems (SOCs)

Inferences of Binomial Hierarchical Model with Mixture Prior

			Posterior Exceedance Probability for:				
SOC	PT	Unadjusted p-value	OR>1.0	OR>1.2	OR>2	RD>2%	RD>5%
General Disorders & Administration Site Conditions	Fatigue	.019	.56	.55	.32	.10	.00
Infections and Infestations	Herpes Simplex	.025	.53	.51	.36	.00	.00
	Sinusitis	.012	.70	.69	.42	.28	.00
Injury, Poisoning & Procedural Complications	Excoriation	.030	.30	.28	.18	.00	.00
Skin & Subcutaneous Tissue Disorders	Ecchymosis	.005	.54	.52	.44	.00	.00

OR = odds ratio (drug:placebo), RD = risk difference (drug - placebo)

Binomial Hierarchical Model with Mixture Prior



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Statistical Considerations for Meta-analysis of Safety Data Using RCTs

- Scale of measures
- Heterogeneity assessment
- Fixed effect vs random effects models
- Statistical methods for analyzing rare event meta-analysis
- Individual patient data (IPD) meta-analysis
- Multiplicity

Absolute Measure (Risk Difference) vs Relative Measure (Odds Ratio or Relative Risk)

Measure	Pros	Cons
Absolute measure	<ul style="list-style-type: none">• Easy to interpret;• Always well defined so it allows the inclusion of studies with zero events• Knowledge of absolute risks is important in clinical decision making	<ul style="list-style-type: none">• Clinical importance may depend on the underlying baseline event rate, but it is less an issue for rare events
Relative measure	<ul style="list-style-type: none">• Typically analyzed in logarithm scale; more stable on average than absolute measures• Good statistical modeling property	<ul style="list-style-type: none">• Undefined when control rate is zero, so it does not allow the inclusion of studies with zero events

In the rare event setting, RD has an appeal!

Heterogeneity

- Clinical
 - Patient selection (e.g., severity of disease)
 - Interventions (e.g., duration, dosing, control)
 - Outcomes (e.g., definitions of endpoints)
- Methodological, e.g.,
 - Mechanism of randomization
 - Allocation concealment
 - Handling of withdrawals
- Statistical
 - Numerical variability in results, beyond random error

Heterogeneity Assessment

- Graphical (e.g. forest plots)
- Statistical tests (e.g. Cochran's Q with χ^2 test; I^2 statistics)
 - Absence of statistical heterogeneity does not necessarily mean absence of clinical heterogeneity or the absence of differential treatment effects
 - The *global* statistical test of heterogeneity may fail to detect differing treatment effects due to lack of power, especially when the number of studies included is small or the event is rare.
 - Conversely, large studies with clinically small variability can yield spuriously high *statistical* heterogeneity

The guiding principle should be to evaluate the association of clinical differences among studies with treatment effects, rather than to rely on an overall global statistical test of heterogeneity.

Fixed-effect vs. Random-effects Models

- Fixed effect = common effect across all studies
 - Inference is to the studies at hand
 - Reasonable to expect (?) when designs and populations are similar across studies
- Random-effects models: true underlying population effects differ from study to study and that the true individual study effects follow a statistical distribution
 - The analytic goal is then to estimate the overall mean and variance of the distribution of true study effects

Fixed-effect vs. Random-effects Models (Con't)

- Although random-effects models gained wider acceptance recently, it may result in misleading results in the rare event setting
- It might be generally useful to conduct meta-analysis with both models
 - Results that vary substantially between these two approaches should be examined carefully to understand the clinical reasons behind the observed differences
- Some analytical approaches may be helpful to understand the heterogeneity
 - Stratification by patient characteristics
 - Models of IPD using treatment by covariate interactions
 - Meta-regression methods

Statistical Methods for Rare Event Meta-analysis

- The choice of method in a sparse event meta-analysis is important since certain methods perform poorly; especially when group imbalances exist
 - Bias is greatest using the I-V and D-L methods, and M-H method with continuity correction (CC) of 0.5
- The M-H method using the alternative CC provides the least biased results for all group imbalances
- At event rates below 1%, the Peto method provides least biased , most powerful estimate and best CI coverage for balanced groups but bias increases with greater group imbalance and larger treatment effect
- Logistic regression performs well and generally unbiased and reliable
- The Bayesian fixed-effect model performs consistently well irrespective of group imbalance
- Alternative CCs perform better than a constant CC

Advantages of Individual Patient Data (IPD) Meta-analysis

- Enables to use common definitions, coding and cut-points, and produces consistent analyses across multiple studies
 - E.g., age categories may have been defined using different category boundaries
 - Different threshold hemoglobin values may have been used to define 'anemia'
- Allows specification of a common set of patient-level covariates so subgroup analyses across trials can be performed
- Permits the investigation of additional hypotheses (those related to individual patient characteristics)

Advantages of Individual Patient Data (IPD) Meta-analysis (Con't)

- Permits time-to-event analyses and allows to evaluate acute or long latent outcomes
 - Flexibility in defining time periods of interest for analyses, e.g., events occurring during “short-term” or “long-term” follow-up
 - Definitions of censoring events may also be standardized
- Can define outcomes based on combinations of variables defining specific events but that may indicate a common mechanism
 - e.g., a combination of weight loss or appetite reduction

Meta-analysis based on IPD (although not always available) is regarded as the gold standard, and whenever feasible, should be considered

Multiplicity

– Complicated in the Safety Context

- Adjustment for multiplicity is not commonly done in the safety context and there is no consensus among the scientific community
- Complicated by having multiple looks over time and multiple (and unknown number of) endpoints
- Whether to adjust for different types of multiplicity should tie with the analytical goals
 - For Tier 1 events, generally, should consider performing formal adjustment for multiple looks
 - Goal is to risk quantification; e.g. to rule out an effect of a certain magnitude for assessing a particular risk (a noninferiority test – as for diabetes drugs)
 - For non-Tier 1 events, should consider multiplicity adjustment for multiple endpoints
 - Goal is signal detection, but initial detection is not the same as proving the causality between a given drug and a given event

Special Topics

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- Meta-analysis for analyzing safety data
- **Program safety analysis plan**
- Safety graphics
- Benefit-risk assessment

Safety Analysis Planning

- Safety assessment planning is a process throughout the life-cycle of the product
- Program Safety Analysis Plan (PSAP) provides a framework for planning, analysis, and reporting of clinical trial safety information throughout the lifecycle of drug development
 - An emerging industry standard recommended by both PhRMA SPERT (Safety Planning, Evaluation and Reporting Team) and George Rochester at FDA *

* FDA/Industry Statistics Workshop, September, 2009

Safety Analysis Planning (Con't)

- What Is A PSAP?

- A plan for program-associated activities
- Provides analytical plan for the assessment of prospectively defined safety outcomes as well as identification of safety signals
- It has two aspects
 - Prospective
 - Retrospective
- A 'living' document, amended as needed
- Recommend it be discussed with FDA and other regulatory agencies at milestone meetings (e.g., end-of-phase 2 meetings)

Safety Analysis Planning (Con't)

- Elements of A PSAP Template

- Background
 - Regulatory agreements
 - Definition of safety outcomes
- General Plan
 - Part I: Prospective AESI
 - Part II: Retrospective emerging issues
- Data Generation
 - Adequacy of safety database
 - Size and type of studies (submission or program based analysis)
 - Safety populations
 - Proper duration of exposure
 - Major toxicities
 - Data collection methods
 - Adjudication procedure
 - Safety monitoring algorithms
 - Data safety monitoring board
- Data Structure and Content
 - Data quality and integrity assurance
 - CDISC-SDTM, ADaM
 - Terminology: WHODrug, MedDRA
 - Concordance of AE and laboratory defined abnormalities
- Methods for Analysis, Presentation and Reporting
 - Major analyses of SAEs and AESIs
 - Dropouts, discontinuations and adequacy of follow-up and monitoring
 - Biomarker validation
 - Drug Interactions: concomitant illness, demographic, geography, substance interactions, medical systems
 - Analytical methods for information synthesis for rare/uncommon events
 - Tables and Graphs
- Problem oriented summary for AESIs

Safety Analysis Planning (Con't)

- Benefits of Developing a PSAP Including

- Being proactive and planning early for safety assessment at the program level
- Facilitate communications with regulatory agencies in safety evaluation for products in Phase 2/3 development
- Consider data standardization issues early, to facilitate ongoing integration and interpretation
- Potential risks may be identified earlier in the drug development process, allowing data collection strategies to be modified in time to collect additional data for further understanding of a safety issue
- Facilitate ongoing safety assessment throughout the lifecycle of drug development

Safety Analysis Planning (Con't)

- Timing of the PSAP

- The PSAP development should be initiated during phase 2 product development in preparation for the end-of phase 2 portal
- Key components of the PSAP with question(s) pertaining to the PSAP may be included in the end of phase 2 package to elicit a response/review from the regulatory agency
- One of the main purposes of the PSAP is to allow teams to plan early and be proactive, therefore full benefits of PSAP are realized when PSAP is developed at the right time

Safety Analysis Planning (Con't)

- PSAP and Other Documents

- PSAP complements the risk management plan (RMP) and specifies the analysis of the safety data in more detail
- PSAP serves as a basis for development of the iSAP (Statistical Analysis Plan for Integrated Summary of Safety), but there are some distinctions from the iSAP
 - The PSAP is a planning, strategic document, has a 'longitudinal' feature, is being maintained throughout a product lifecycle, unlike iSAP which in general will be done once the filing is over
 - once PSAP is approved, individual study protocols and SAPs can reference the PSAP for key elements of safety data collection and analysis
 - The PSAP development could be initiated during phase 2 product development. In contrast, iSAP in general is put together when P3 studies are being conducted

Special Topics

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- **Safety graphics**
- Benefit-risk assessment

Where Is the Safety Signal?

Event	Drug A (%)	Drug B (%)	5.5%	Low5%	Up5%
ARTHRALGIA	3.5	0.5	7.0	1.0	31.5
NAUSEA	10.0	4.6	4.1	2.5	6.0
ANOREXIA	3.5	0.9	3.9	1.2	13.1
HEMATURIA	3.2	0.9	3.6	1.0	12.2
INSOMNIA	6.0	1.9	3.3	1.3	7.9
VOMITING	8.6	2.8	3.1	1.5	6.2
DYSPEPSIA	9.7	3.7	2.6	1.4	4.9
WEIGHT DECREASE	2.1	0.9	3.3	0.8	9.0
PAIN	3.9	1.9	2.1	0.0	5.3
DIARRHEA	20.9	10.6	2.0	1.4	2.9
FATIGUE	3.7	1.9	1.9	0.7	5.1
FLATULENCE	4.6	2.8	1.6	0.7	3.7
DIZZINESS	6.7	4.2	1.6	0.8	3.1
ABDOMINAL PAIN	14.2	9.3	1.5	1.0	2.4
RESPIRATORY DISORDER	2.6	1.9	1.4	0.5	4.0
HEADACHE	8.4	5.8	1.3	0.7	2.9
INJURY	7.0	5.6	1.2	0.7	2.9
GASTROESOPHAGEAL REFLUX	2.6	2.3	1.3	0.4	3.3
BACK PAIN	5.3	4.5	1.2	0.6	2.9
HYPERKALEMIA	2.1	1.0	1.1	0.4	3.4
RASH	2.1	1.9	1.1	0.4	3.4
SINUSITIS	6.5	8.0	1.1	0.8	2.0
INFECTION VIRAL	6.0	5.8	1.1	0.8	2.1
UPPER RESP TRACT INFECTION	15.8	15.3	1.0	0.7	1.6
NYALGIA	2.8	2.9	1.0	0.4	2.8
URINARY TRACT INFECTION	2.8	2.8	1.0	0.4	2.8
COUGHING	6.0	5.0	1.0	0.5	1.9
MELEHA	2.8	3.2	0.9	0.9	2.2
RHINITIS	3.9	5.1	0.8	0.4	1.7
BRONCHITIS	2.6	3.7	0.7	0.9	1.8
CHEST PAIN	2.6	4.2	0.7	0.9	1.6
CHRONIC OBSTRUCTIVE AIRWAY	22.0	35.2	0.6	0.5	0.8
DYSPNEA	2.1	6.9	0.3	0.1	0.0



How to Achieve This?



By: David Walker

Visualization of Safety Data

By Using Effective Graphics

- Makes safety results more understandable
- Increases the likelihood of detecting key safety signals and improves the ability to make clinical decisions
- Conveys information more efficiently and meets regulatory requirement for ongoing safety evaluation

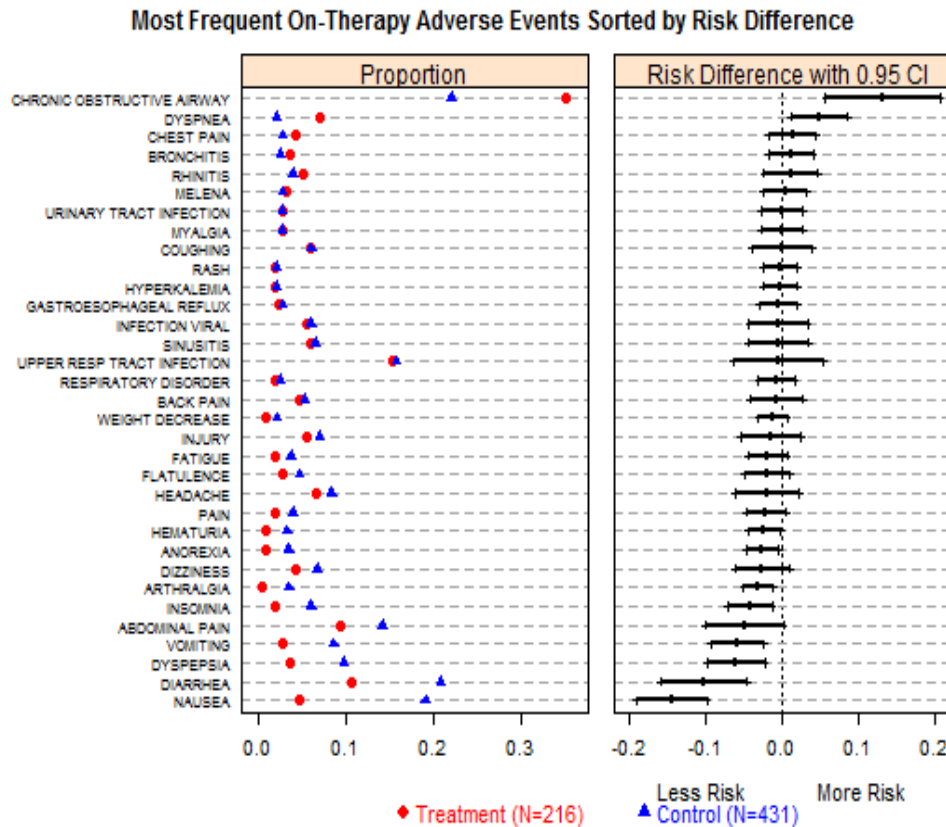
Safety Review Activities

Potential Use of Graphics

- AEs and SAEs
 - Dot plots, volcano plots , create a 3-tier system to reduce "false positive" findings (by SPERT)
- Events of interest (EOIs)
 - Kaplan-Meier curves, forest plot, risk over time plot
- Laboratory assessments
 - Mean changes vs extreme values, matrix plots to display multiple lab parameters, time course of laboratory values, patient profile to depict subject-level data
- Minimum Critical Toxicities
 - Graphs of relationship between QT correction and drug concentration, individual values over time, corrected QT vs RR Interval
- Discontinuations and adequacy of follow-up
 - Kaplan-Meier graph

Example: Potential Improvement Through Graphical Approach

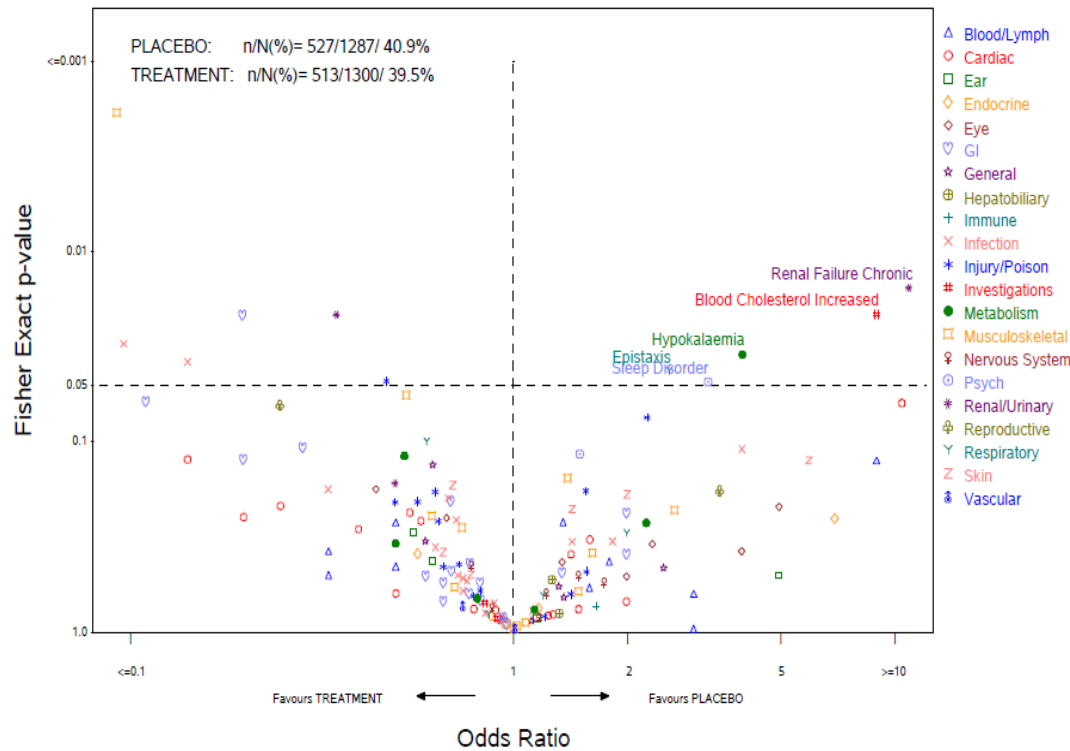
- Adverse Event Double Dot Plot



Example: Potential Improvement Through Graphical Approach (Con't)

- Volcano Plot for AEs

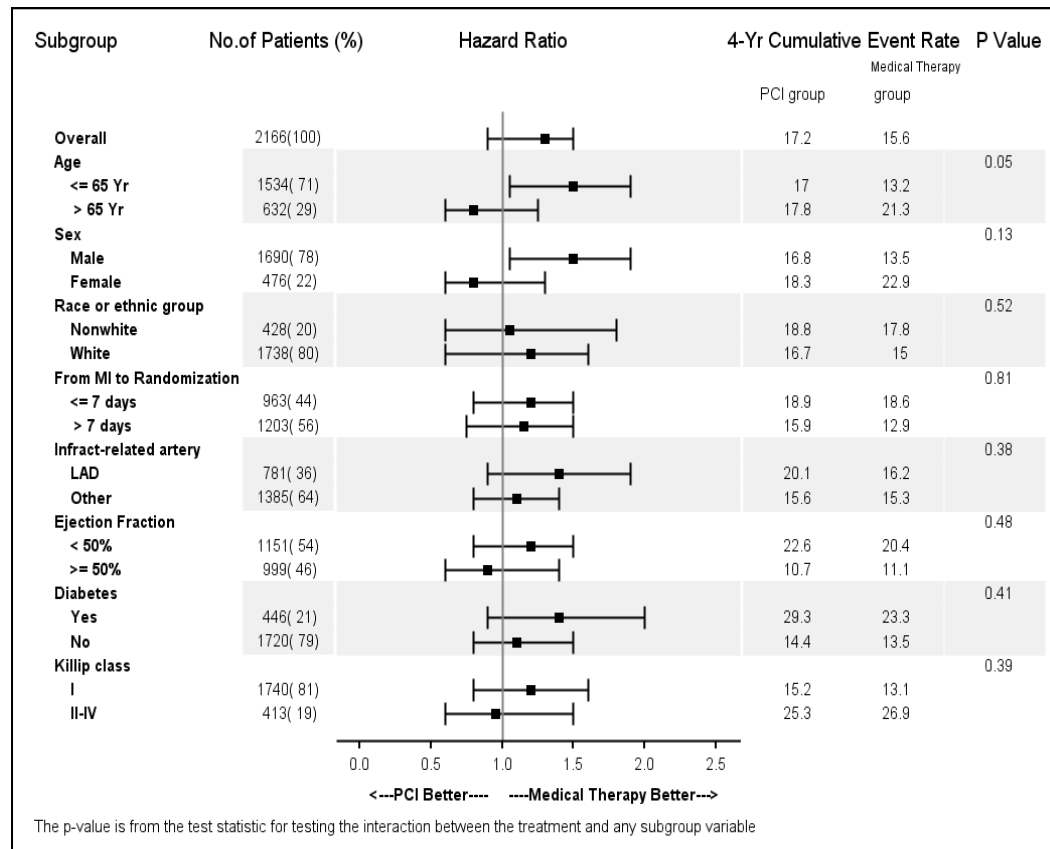
P-risk (Odds Ratio) Plot of Treatment Emergent Adverse Events at PT Level



<https://www.ctsmedia.org/ClinAEGraph003>

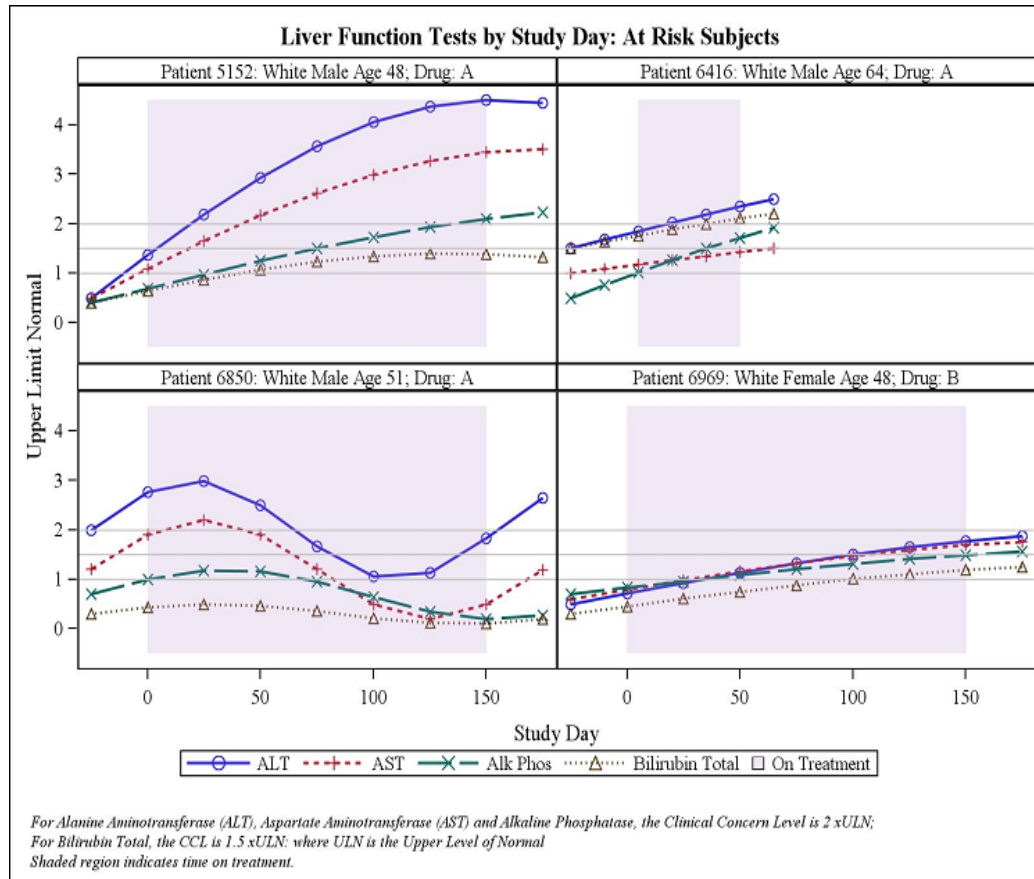
Example: Potential Improvement Through Graphical Approach (Con't)

- Forest plot for subgroup analysis of percutaneous coronary intervention (PCI, commonly known as angioplasty) versus medical therapy



Example: Potential Improvement Through Graphical Approach (Con't)

- Lab Specific Patient Profile



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Background

- Increasingly, companies, regulatory agencies, and other governance bodies are using structured benefit-risk (B-R) assessment approaches
- Assessment of B-R is challenging
- Important to have systematic B-R assessments that incorporate a thorough understanding of evolving methodologies

Key B-R Assessment Initiatives

US

- FDA internally-piloted framework with intention to provide a structured benefit:risk assessment approach
- FDA Draft PDUFA V Implementation Plan on Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making
- PhRMA BRAT Framework
- Quantitative Sciences in the Pharmaceutical Industry Benefit:Risk Working Group (QSPI BRWG) (among US statisticians)

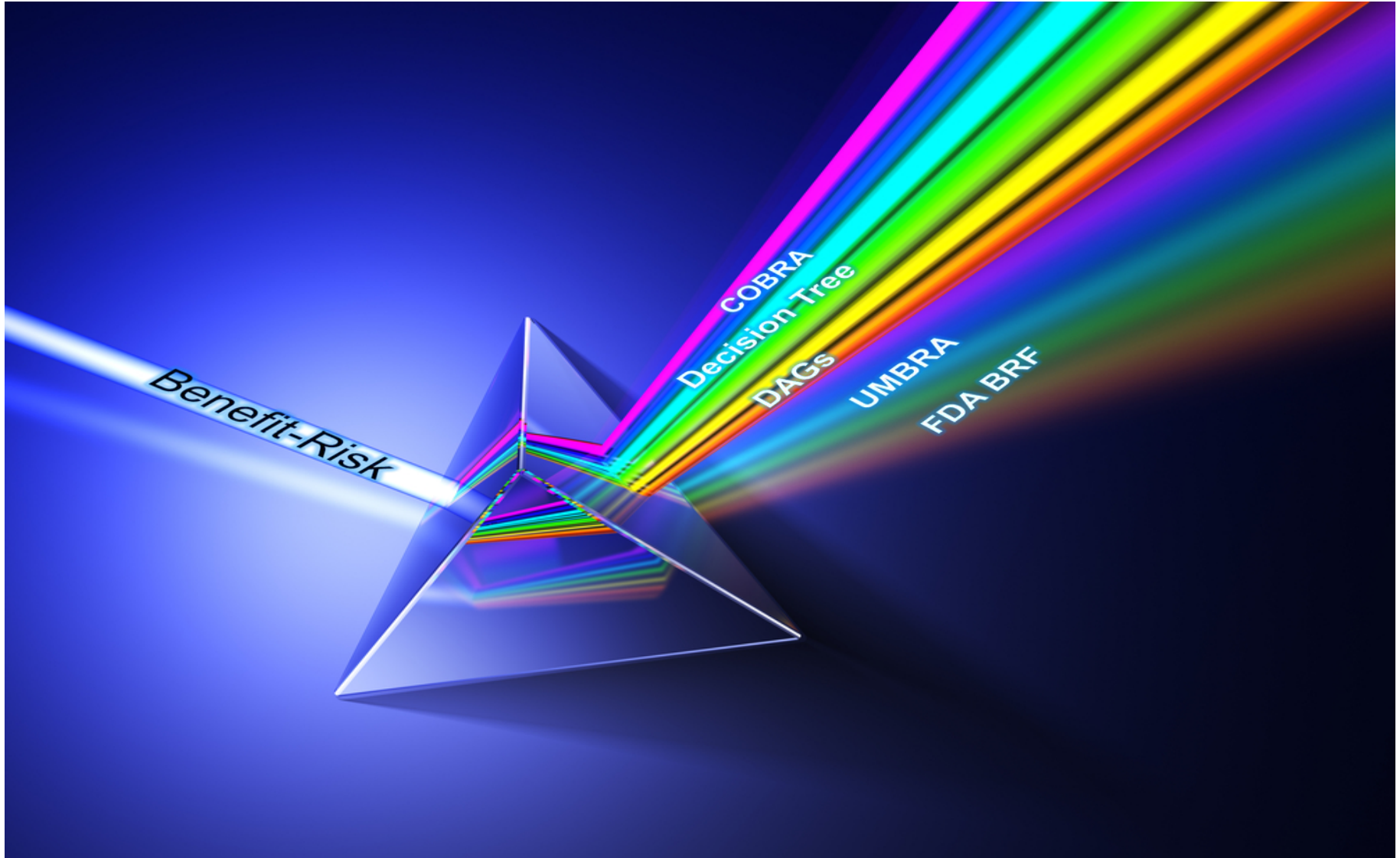
EU

- EMA B-R methodology project
- Innovative Medicines Initiative (IMI) PROTECT

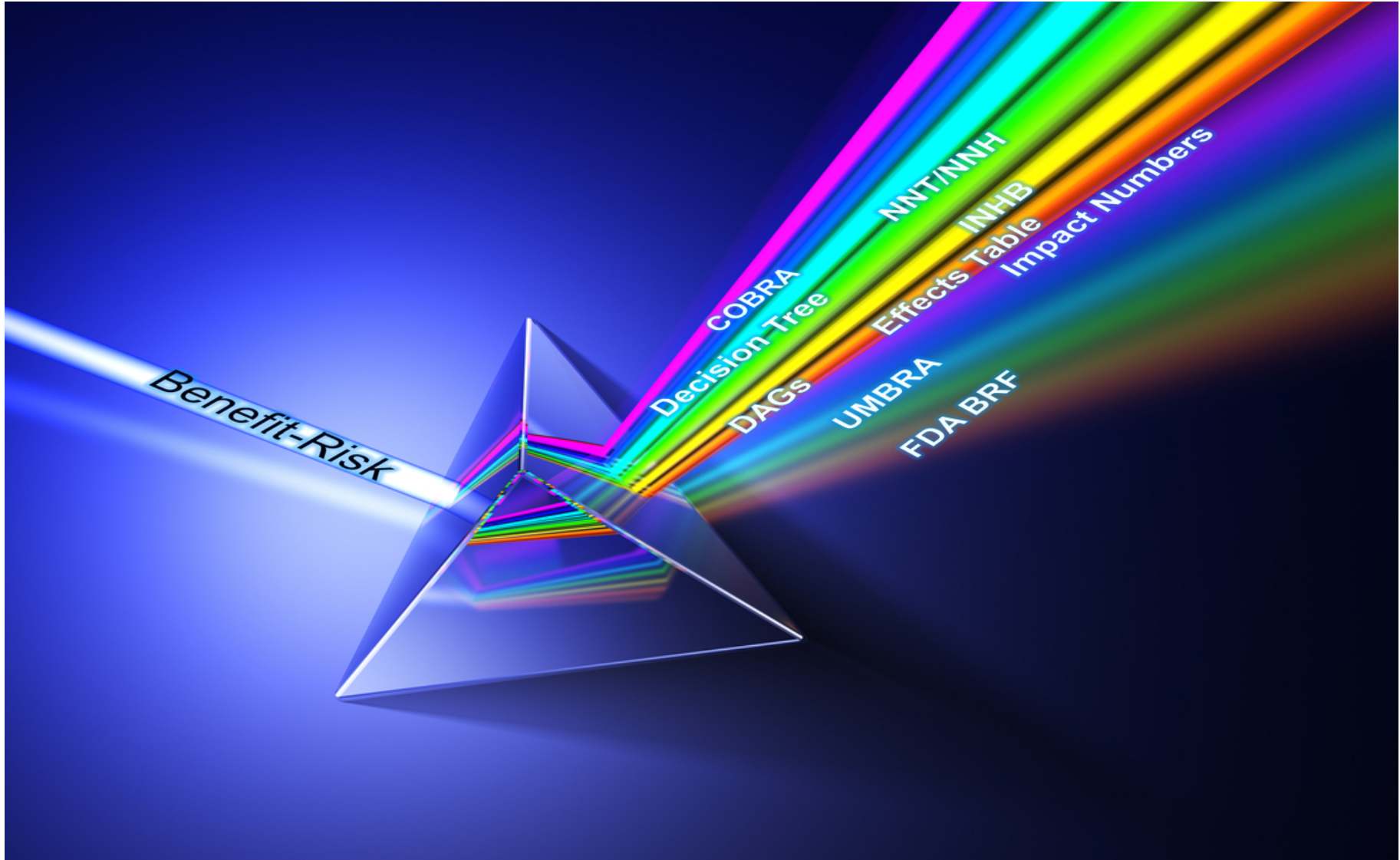
Global

- ICH E2C Draft Guidance: B-R requirements in the revised PSUR (PBRER)
- CIRS unified methodology for benefit-risk assessment (UMBRA)

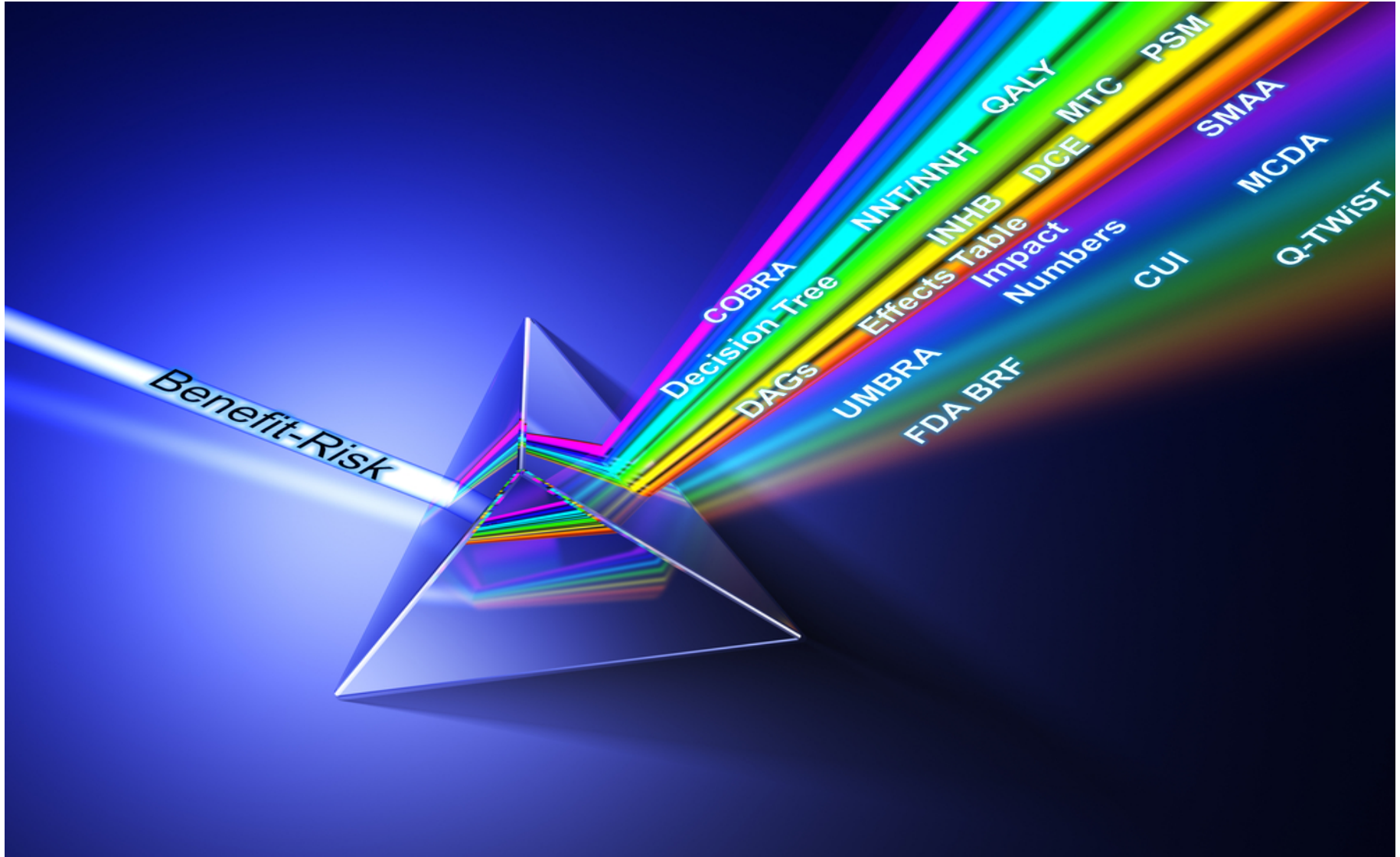
A Spectrum from Qualitative to Quantitative




A Spectrum from Qualitative to Quantitative



A Spectrum from Qualitative to Quantitative



FDA BRA framework



Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making
Draft FDORA V Implementation Plan - February 2013
Fiscal Years 2013-2017

FDA

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FDA Benefit-Risk Framework

- Qualitative framework will be implemented that relies on expert judgment
- Clinical review templates will be provided to reviewers to perform the assessments
- Benefit-risk assessments will be publicly available
- Benefit-risk Advisory Group with CDER/CBER leadership will review process/templates and assessments across review divisions
- Many outstanding questions exist, including:
 - How the patient perspective will be incorporated into the assessment
 - How assessments will be communicated to sponsors
 - How the benefit-risk assessment will impact regulatory decision making for REMS programs and labeling

FDA BRA Framework

- FDA released its structured framework and implementation plan in early 2013

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk		
Risk Management		
Benefit-Risk Summary Assessment		

Benefit:Risk Assessment

- The benefit-risk landscape is currently changing. Many regulatory and industry-wide activities will enhance structured systematic Benefit-Risk assessments
- Qualitative approaches may be sufficient for simple benefit-risk assessment. Quantitative approaches could be useful for more complicated ones
- Transparency in decision making is beneficial
- It is critical to determine appropriate endpoints for benefit:risk assessment, select weights, and utilize graphical presentation
- Requires cross functional collaboration and input from all stake holders

Closing Remarks

- Safety evaluation is important with many challenges
- Grouping AE presents statistical challenges which potentially can lead to misclassification and impact statistical power
- Bayesian methods are useful for safety signal detection
- Meta-analysis of AE data based on RCTs is a powerful tool but poses a series of methodological challenges that require due attention and action
- A PSAP can encourage proactive safety planning and evaluation
- Graphics can make safety results more understandable and facilitate effective safety evaluation
- Benefit-risk landscape is evolving and enhanced structured benefit-risk assessment is important

Acknowledgment

- PhMRA SPERT Committee
- FDA/Industry/Academia Safety Graphics Workstream
- Amgen PSAP Working Group
- Amgen Benefit:Risk Taskforce

