GLOBAL REGULATORY LANDSCAPE FOR SAFETY MONITORING: A QUANTITATIVE PERSPECTIVE

12 October 2017

Greg Ball (Merck), Judy Li (Regeneron), Bill Wang (Merck)
and Brenda Crowe (Eli Lilly) on behalf of the
ASA Biopharm Safety Monitoring Working Group

Agenda

- Global Regulatory Landscape and Pulse of the Industry
  - Safety Monitoring Working Group
  - Industry Survey
  - Global Regulatory Landscape
  - Key Opinion Leader Interviews
  - 2017 Deep Dive Deliverables
- Safety Monitoring Methodology: From a Bayesian Perspective
  - Bayesian Thinking in Safety Monitoring
  - Under the Blinded Setup
  - Dynamic Safety Monitoring
  - Static Safety Monitoring
  - Under the Post-Marketing Setup

Global Regulatory Landscape and Pulse of the Industry

Global Regulatory Landscape and Pulse of the Industry

1 Safety Monitoring Working Group

2 Industry Survey

3 Global Regulatory Landscape

4 Key Opinion Leader Interviews

5 2017 Deep Dive Deliverables

ASA Biopharm Safety Monitoring Working Group

- Established in 2015, part of the ASA Biopharm Safety Statistics Working Group
- Goal
  - To empower the biostatistics community to play a more proactive role and better enable quantification in safety monitoring
- Key activities
  - Review safety regulations, survey industry, and interview key opinion leaders
  - Review statistical methodologies
- 2016 deliverables
  - Jun: DIA Annual
  - Aug: JSM Biopharm Section (2 manuscripts in the proceedings), DIA China
  - Dec: Deming Conference (1/2 day)
- 2017 deliverables
  - May: World Drug Safety Americas
  - Jun: DIA Annual, ICSA Tutorial (full day)
  - Jul: JSM Biopharm Section
  - Aug: DIA China, ISBS
  - Dec: Deming conference (1/2 day)
  - 3 manuscripts (1 submitted)

BIOPHARMACEUTICAL SECTION

ASA Biopharm Safety Monitoring WG


Greg Ball


Susan Duke


William Wang, Chair

WS1: Industry Practice & Regulation

- Faiz Ahmad (Galderma)
- Greg Ball (Co-lead, Merck)
- Amit Bhattacharya (ACI Clinical)
- Brenda Crowe (Lilly)
- Susan Duke (Co-lead, Drug Safety Counts)
- Michael Fries (CSL Behring)
- Robert (Mac) Gordon (Janssen)
- Barbara Hendrickson* (AbbVie)
- Esteban Herrero-Martinez¥ (AbbVie)
- Juergen Kuebler† (Consultant)
- Qi Jiang (Amgen)
- Dennis O'Brien* (BI)
- Lothar Tremmel (AstraZeneca)
- Wenquan Wang (Morphotek)
- William Wang (Chair, Merck)

WS2: Methodology

- Michael Colopy (UCB)
- Michael Fries (CSL Behring)
- Karolyn Kracht (AbbVie)
- Judy Li (Co-lead, Regeneron)
- Li An Lin (Merck)
- Yong Ma (FDA)
- Melvin Munsaka (Co-lead, Takeda)
- Matilde Sanchez (Arena)
- Sourev Santra (Cytel)
- Krishan Singh (GSK)
- Ed Whalen (Pfizer)
- William Wang (Chair, Merck)
- Brian Waterhouse (AbbVie)
- Kefei Zhou (Amgen)
- Yueqin Zhao (FDA)


Judy Li


Melvin Munsaka

Special guest members:
* Safety physician.
¥ Regulatory affairs PV specialist.
† European statistician.

Key Trends in Safety Regulation

- Global Trend of ICH (and CIOMS influence) on Safety Monitoring and Evaluation, moving from…
  - Individual case review to aggregate analysis and reporting
  - Snap-shot submission to continual aggregate review
  - Separate processes to continuum for pre- and post-marketing safety surveillance
  - Safety evaluation to benefit-risk assessment
- Region Specific Safety Initiatives (go beyond ICH)
  - FDA: IND safety reporting
  - EMA: EudraVigilance (Module V)
  - PMDA: Electronic healthcare data (MIHARI/MID-NET)
  - CFDA: New guidance on PMR and key intensive monitoring

Causalities are difficult to determine by individual case safety report (ICSR) assessment, therefore aggregate safety assessment planning is important

Regulatory Motivation:
Unique Regional Safety Regulations

Europe, EMA:

EudraVigilance GVP Module IX for post marketing signal detection

Japan, PMDA: 3 pillar system

USA, FDA:

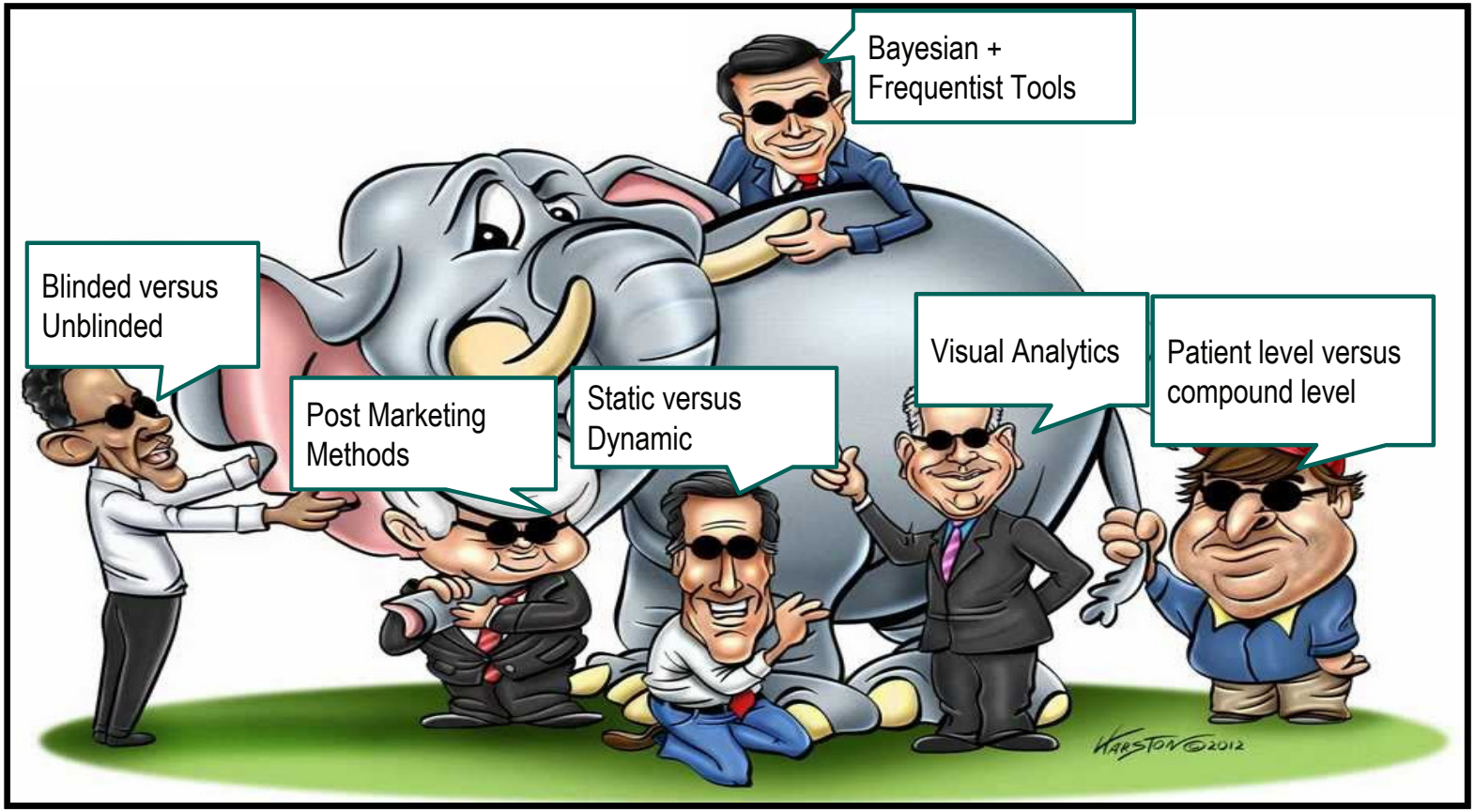
IND safety reporting final rule

- Safety Assessment Committee
- Safety Surveillance Plan
- Planned unblinding of safety data

China, CFDA:

- Minimal sample size requirement (Provision for Drug Registration 2007); guidance on post-marketing commitment studies (2013 draft)
- Provisions for nationalized monitoring of ADRs (2011); post-marketing intensive safety monitoring guidance (2013 draft)

WS2: Safety Monitoring Methodology- the Elephant Metaphor



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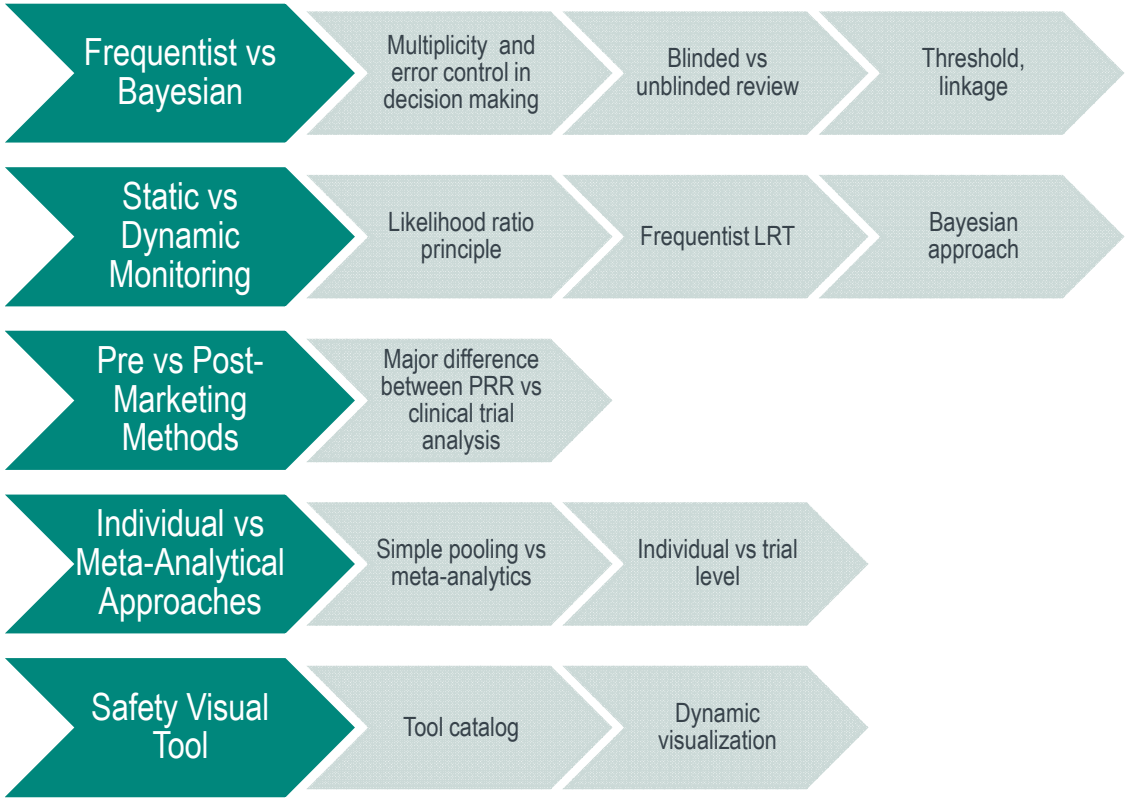
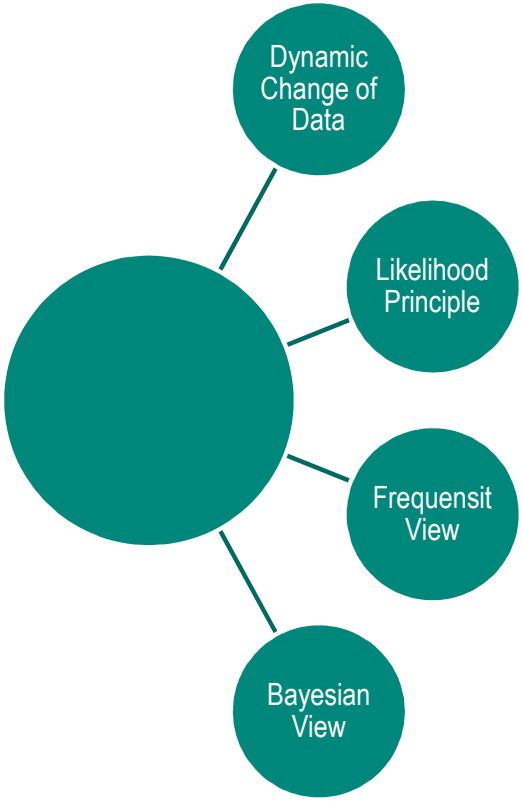
WS2: Key Methodology Deep Dives



WS2 Deep Dive: From Static to Dynamic Safety Monitoring



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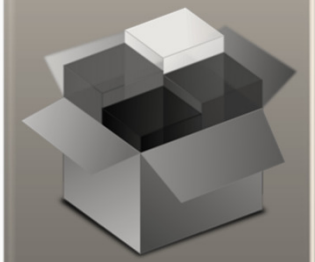


Industry Survey:
Statisticians & Safety Professionals

- Requested participation from 35 companies of all sizes
- 1 survey per company (no company names collected)
- 24 responders (69% response rate)
- Goals, to assess:
  - Levels of involvement statisticians have in a wide range of quantitative safety analyses
  - Alignment of operational processes with regulatory guidance
  - Various types of new & traditional approaches being used today
  - Areas where statisticians want & need training

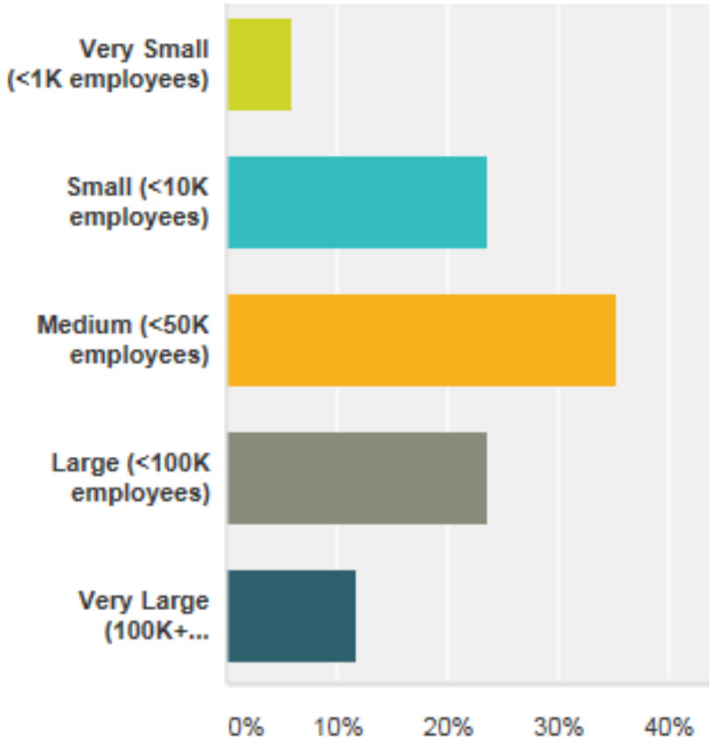
Industry Survey Summary

- 24 responders across industry, majority medium to large organizations
- 75% (18) worked in Biostatistics, 42% (10) worked in Drug Safety (few solely dedicated), majority supported safety activities
- Representation across numerous therapeutic areas
- Trial statistician responsible for most activities except unblinded reviews
- Broad involvement in background rate characterization (stats, clinical, epi, safety)
- Most have active or planned SOPs for safety monitoring, outside of meta-analysis of completed studies

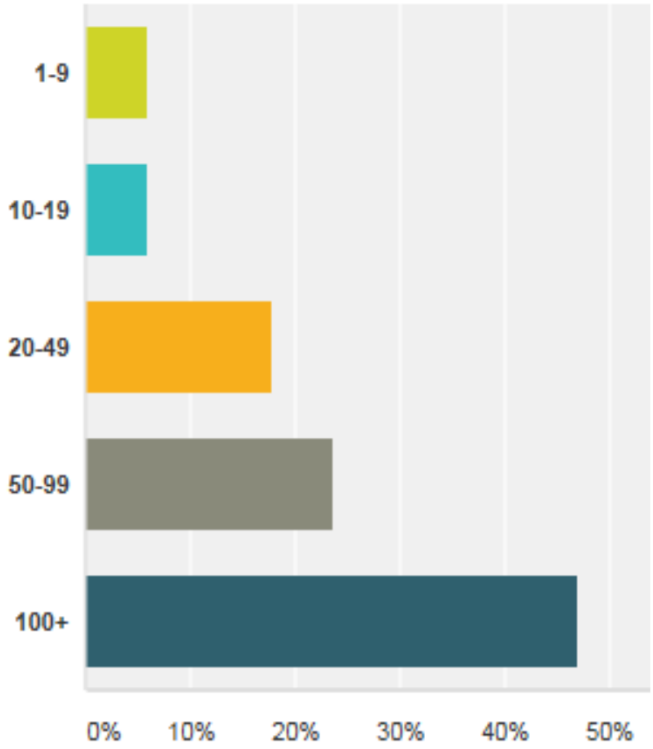
Industry Survey: Statisticians & Safety Professionals

Response Rate: 69% (24/35 Organizations)

Size of Company



Number of Statisticians



Statisticians Dedicated to Safety

Answer Choices	Responses	
0	50.00%	12
1	12.50%	3
2	0.00%	0
3-5	8.33%	2
6-9	12.50%	3
10+	16.67%	4
Total		**24**

Statistical Safety Methods

	Former	Latter	Both	Total	Weighted Average
Patient profiles vs. Summary statistics	0.00% 0	31.58% 6	68.42% 13	19	2.68
Individual vs. Aggregated studies	10.53% 2	21.05% 4	68.42% 13	19	2.58
Blinded vs. Unblinded data	5.26% 1	21.05% 4	73.68% 14	19	2.68
Tabular vs. Graphical displays	42.11% 8	5.26% 1	52.63% 10	19	2.11
Descriptive vs. Inferential statistics	63.16% 12	0.00% 0	36.84% 7	19	1.74
Frequentists vs. Bayesian approaches	78.95% 15	0.00% 0	21.05% 4	19	1.42
Predictive vs. Statistical modeling	11.11% 2	38.89% 7	50.00% 9	18	2.39
Study-level vs. Product-level analyses	21.05% 4	5.26% 1	73.68% 14	19	2.53
Qualitative vs. Quantitative Benefit-Risk Assessment	57.89% 11	10.53% 2	31.58% 6	19	1.74

- Key opinion leader alignment: 3 areas KOLs considered of high importance for advancement are Bayesian approaches, Benefit Risk assessments and graphical displays. The next slide reinforces the industries alignment/goals

Importance for Advancement

	No importance	Low	Medium	High	Total
Exploring electronic healthcare databases	16.67% 3	11.11% 2	38.89% 7	33.33% 6	18
Text mining of unstructured data	27.78% 5	44.44% 8	22.22% 4	5.56% 1	18
Predictive modeling	11.76% 2	17.65% 3	29.41% 5	41.18% 7	17
Standards for safety biomarker validation	11.11% 2	33.33% 6	27.78% 5	27.78% 5	18
Ways of communicating risk	5.26% 1	15.79% 3	31.58% 6	47.37% 9	19
Graphical displays / Data visualization	5.26% 1	21.05% 4	21.05% 4	52.63% 10	19
Benefit-risk assessment	5.26% 1	5.26% 1	10.53% 2	78.95% 15	19
Treatment discontinuation	5.56% 1	11.11% 2	50.00% 9	33.33% 6	18
Handling rare events	5.26% 1	5.26% 1	42.11% 8	47.37% 9	19
Criteria for handling early or rare safety signals	5.26% 1	5.26% 1	42.11% 8	47.37% 9	19
Bayesian approaches, including prior probabilities	15.79% 3	21.05% 4	42.11% 8	21.05% 4	19

- Encouraging to see the alignment within industry concerning the areas of improvement needed and the importance with graphics/benefit risk and Bayesian approaches

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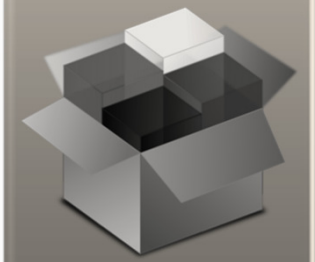

Global Regulatory Landscape

CIOMS

CIOMS

ICH

harmonisation for better health

ICH Harmonization of Safety Monitoring

- Inherent risks for patients during drug development
  - All marketed drugs have associated risks; investigational drugs have more uncertainty
  - Need proactive safety assessment to enable effective risk management
  - To deliver effective drugs with favorable benefit-risk profiles to the right patients
- Three overlapping stages (same across all regions)
  - Premarketing safety monitoring
  - Safety specification at submission
  - Postmarketing pharmacovigilance (PV)

Premarketing Safety Monitoring

ICH E2A Clinical Safety Data Management (October 1994)

- Serious and unexpected adverse drug reactions (ADRs) are subject to expedited reporting
  - Reasonable causal relationship judged by investigator and/or sponsor
  - Seriousness (not severity) guides reporting obligations
  - Unexpected: nature or severity is not consistent with source documents
- Premarketing and postmarketing safety reporting concepts/practices are interdependent
- Clinically important increases in the rate of expected serious ADRs is subject to expedited reporting
  - How to make aggregate safety assessments in ongoing studies (especially without unblinding study personnel) has not been described in ICH guidance

Safety Specification at Submission

ICH M4E(R2): The CTD — Efficacy (June 2016)

- Clinical Overview should provide an evaluation of benefits and risks based on conclusions of relevant clinical studies
  - How findings support proposed dose and target indication
  - How prescribing information will optimize benefits and manage risks
- Summary of Clinical Safety should summarize safety in the intended patient population, integrating results of individual clinical study reports
  - Grouping studies and pooling results to improve precision of estimates and sensitivity to differences should generally be considered
  - Extensive safety analyses may be presented in a separate report and summarized here (for example, FDA Integrated Summary of Safety)
- Reports of efficacy and safety studies should include reports of all clinical studies (this is where the ISS usually goes)

Postmarketing Pharmacovigilance

ICH E2E Pharmacovigilance Planning (November 2004)

- PV planning activities for early postmarketing of a new drug
  - Improve benefit-risk balance by reducing risks
- Safety specification should be a summary of important identified risks, potential risks, and missing information
  - Should also address potentially at-risk populations and likely uses that have not been studied preapproval
- PV plan should include actions to address special concerns
- Pharmacovigilance should be a continuing process

CIOMS Is a Think Tank for Advancing International PV Practices

CIOMS WG	Descriptions	Resulting Regulatory Guidance
I	International Reporting of Adverse Drug Reactions (1990)	ICH E2A
II	International Reporting of Periodic Drug-Safety Update Summaries (1992)	ICH E2C
III	Guidelines for Preparing Core Clinical-Safety Information on Drugs (1999)	
IV	Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals (1998)	ICH E2C R2 (PBRER)
V	Current Challenges in Pharmacovigilance: Pragmatic Approaches (2001)	

CIOMS Is a Think Tank for Advancing International PV Practices

- Divergence and disharmony on two recent reports
  - Natural part of healthy life-cycle management
  - Go beyond ICH technical requirements
- CIOMS VIII (2006): Signal Detection
  - Early adopter: EMA Good Pharmacovigilance Practices (2012)
  - Moving toward a new equilibrium at a higher level
    - FDA Sentinel system
    - Japan GVP and good postmarketing study practices
- CIOMS VI (2005): Management of Safety Information From Clinical Trials
  - Early adopter: FDA IND Safety Reporting Final Rule (2010)
  - Has not been adopted in other regions

CIOMS Is a Think Tank for Advancing International PV Practices

CIOMS WG	Descriptions	Resulting Regulatory Guidance
VI	Management of Safety Information From Clinical Trials (2005)	IND Safety Reporting
VII	Development Safety Update Report (DSUR) (2006)	ICH E2F
VIII	CIOMS Working Group on Signal Detection (2006)	GVP Module IX
IX	Practical Approaches to Risk Minimization for Medicinal Products (2010)	
X	Considerations for Applying Good Meta-Analysis Practices to Clinical Safety Data Within the Biopharmaceutical Regulatory Process (2016)	

Management of Safety Information From Clinical Trials: Report of CIOMS Working Group VI

- One goal of CIOMS VI is to help bridge the gap between preapproval and postapproval activities to understand and manage risk
  - Mentioned in ICH E2A but has not been developed
- Also discusses the importance of having a systematic approach to managing risk during development
  - To ensure earliest possible identification of safety concerns
  - To take appropriate risk minimization steps
- A systematic, reproducible approach to detect, classify, and document adverse events (AEs) would enable investigators to develop clinical as well as statistical understanding of the safety profile

Management of Safety Information From Clinical Trials: Report of CIOMS Working Group VI

- Safety monitoring during clinical development requires a partnership between clinical and statistical scientists
  - Requires thorough understanding of existing safety data, the patient population and relevant sub-populations, and risk factors for particular AEs
  - A meta-analytic review should be a routine part of the process so that ADRs, and differences in ADR rates, can be detected as readily as possible
- As the database increases, aggregate analysis becomes more important for detection and evaluation of signals
  - Mentioned in ICH E2A but not developed
  - Higher incidence for experimental compared control
  - Increased frequency of previously recognized SAR

Management of Safety Information From Clinical Trials: Report of CIOMS Working Group VI

- A special challenge in ongoing aggregate evaluation of safety data is the application of appropriate statistical techniques with a safety mindset
  - Exploration; medical judgment and decision-making within a quantitative framework
  - As opposed to strict statistical inference, with an emphasis on testing and confirming

FDA Safety Guidance Documents That Go Beyond ICH Technical Requirements

- Format and Content of the Clinical and Statistical Sections of an Application (1988)
- Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review (2005)
- Premarketing Risk Assessment (2005)
- Format and Content of Proposed Risk Evaluation and Mitigation Strategies, REMS Assessments and Proposed REMS Modifications (2009)
- FDA IND Safety Reporting Final Rule (2010)
  - Safety Reporting Requirements for INDs (2012)
  - Safety Assessment for IND Safety Reporting (2015)
- Determining the Extent of Safety Data Collection Needed in Late-Stage Premarket and Postapproval Clinical Trials (2016)

Safety Reporting Requirements for INDs: Guidance for Industry (December 2012)

- To improve the overall quality of safety reporting and to comply with requirements for IND safety reports based on data in the aggregate, "the sponsor should have in place a systematic approach for evaluating the accumulating safety data"

- "Reasonable possibility" for IND safety reporting
  A. "A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure"
  B. "One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug"
  C. "An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group"

Cross-Disciplinary Scientific Engagement

- The FDA IND Safety Reporting Final Rule highlights the importance of aggregate analyses for determining reasonable possibility of an association with study drug for serious adverse events (for anticipated and expected events)
  - Safety physicians have been strong qualitative thinkers, focused on individual case review and case series
  - The new guidance will require them to think more about quantitative methods, especially for disease-related events
  - Statisticians have a lot to offer in this area
  - Successful implementation will require collaboration between qualitative and quantitative thinkers

Safety Assessment for IND Safety Reporting: Draft Guidance for Industry (December 2015)

- Sponsors should periodically review accumulating safety data
  - Integrated across multiple studies (completed and ongoing)
  - Provide a quantitative framework for measuring the evidence of an association (for unexpected events) or a clinically important increase (for expected events)
  - Make a judgment about "reasonable possibility" for IND safety reporting
- "It is critical for sponsors to detect and report, as early as possible, serious and unexpected suspected adverse reactions and clinically important increased rates of previously recognized serious adverse reactions"
  - Focusses on reporting requirements for SAEs that are not interpretable as suspected ADRs when observed as single events (become interpretable only via aggregate analysis)

Cross-Disciplinary Scientific Engagement

- FDA is calling for
  - A multidisciplinary approach
  - Frameworks around aggregate review and level of evidence (not statistical decision rules)
  - Assessments that are product specific and decisions that are driven by medical judgment
- FDA clearly states a preference for unblinded safety analyses of ongoing clinical trials
  - An alternative approach is to only perform an unblinded comparison of event rates across treatment groups if the overall rate for all treatment groups of a specific event is substantially higher than a predicted rate

Cross-Disciplinary Scientific Engagement

- Opportunity to partner with FDA to champion safety issues
- To protect human subjects participating in clinical trials
  - Terminate programs when unacceptable risks are discovered
- To gain an understanding of the aggregate safety profile of drugs as early in their development as possible
  - Avoid premature termination of a program that shows promise even in the face of certain risks
  - Improve the way we identify patients at higher risk so that we can better position a medicine

Quantitative Frameworks and Medical Judgment

- Statisticians can help multidisciplinary SMTs to think more quantitatively
  - By providing quantitative frameworks for medical judgment
  - Success will depend on dynamic, interactive, cross-disciplinary scientific engagement
- ASA Biopharm Safety Monitoring working group is developing…
  - Aggregate safety assessment planning process
  - ASA / DIA inter-disciplinary working group

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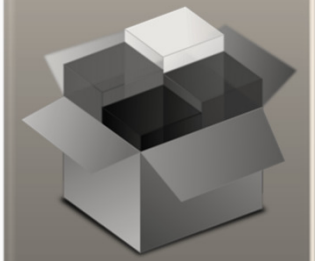


Key Opinion Leader Interviews

- Aloka Chakravarty (FDA)
- Bob Temple* (FDA)
- Brenda Crowe (Lilly)
- Christy Chuang-Stein (Consultant)
- Conny Berlin (Novartis)
- Dave DeMets (UW)
- Frank Rockhold (Duke)
- Frank Shen (AbbVie)
- Janet Wittes (Statistics Collaborative)
- Jose Vega* (Merck)
- Juergen Kuebler (Consultant)
- Lily Krasulja* (Janssen)
- Mark Levenson (FDA)
- Mondira Bhattacharya* (AbbVie)
- Olga Marchenko (Quintiles)
- Steve Snapinn (Amgen)
- Valerie Simmons* (Eli Lilly)
- Walter Offen (AbbVie)

We are indebted to the 18 key opinion leaders who each spent at least an hour with us discussing their views on quantitative assessment of safety monitoring

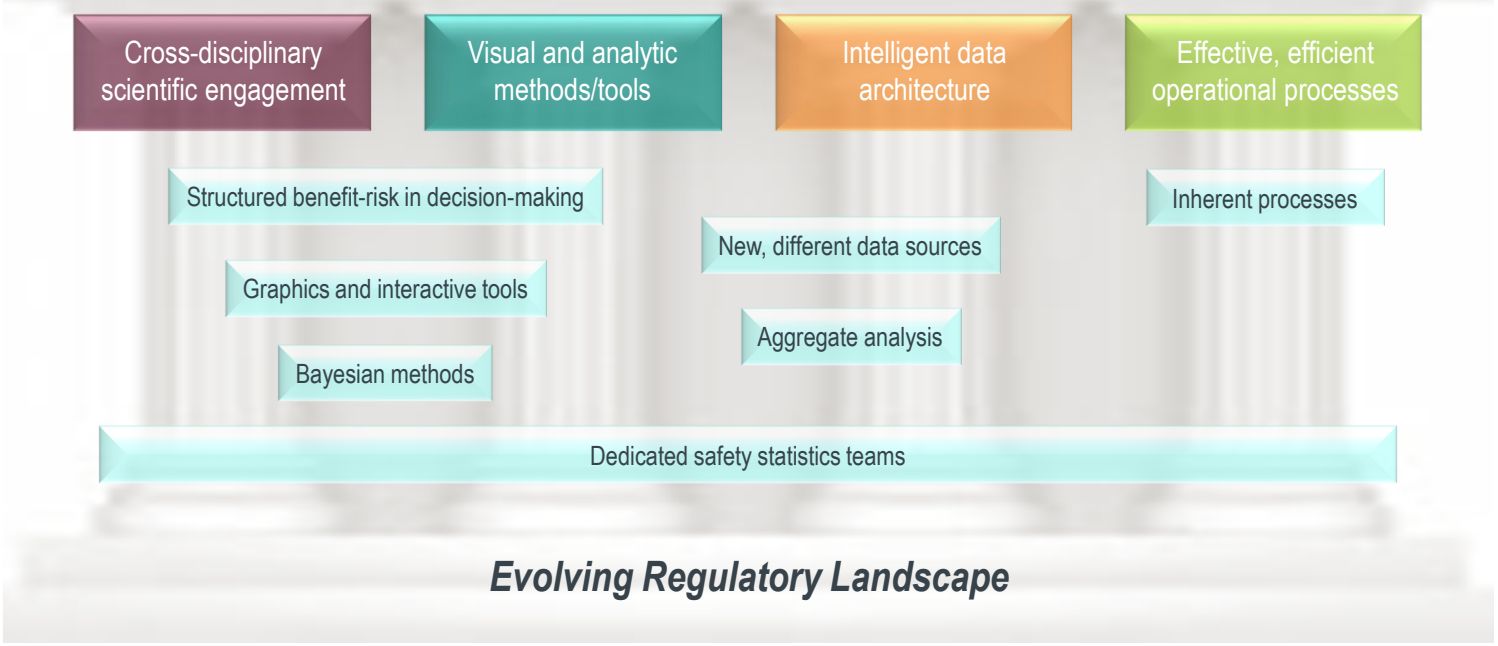
Interviewed by Greg Ball, Susan Duke, Mac Gordon, and Bill Wang

* Physicians.

Summary of Interviews with Key Opinion Leaders: Four Pillars of Safety Statistics

Moving from…

- Individual case review to aggregate analysis and reporting
- Snap-shot submission to continuous aggregate review
- Separate processes to continuum for pre- and post-marketing safety surveillance
- Safety evaluation to benefit-risk assessment



Key Opinion Leader Interviews: Cross-Disciplinary Scientific Engagement

- "Safety is the new efficacy" – a public health issue
  - No longer just PV and spontaneous reports
  - Requires experienced statisticians to interact with other departments
- Statisticians need a safety mindset and need to closely engage other disciplines (eg, safety physicians) to increase our impact
- Safety physicians need to rely heavily on quantitative expertise for aggregate data analysis and interpretation
- Siloed discussions of safety and efficacy are not in the patients' best interest
- We need to understand about "why" before jumping into "how"

Pulse of the Industry: Wrap Up and Future Path

- Interviews stressed importance of graphics, Bayesian approaches, benefit risk, aggregate analyses, dedicated teams and inherent safety assessment processes.
- Survey results indicate general alignment

Current Use Widespread or Planned	Current Use Not Widespread BUT Importance Acknowledged	Little Current Use
Inherent processes	Graphics and interactive tools	Dedicated safety teams
Different data sources	Bayesian approaches	
	Incorporation of benefit risk	
	Aggregate analyses	

- We aren't there yet, but goals and vision of the KOLs seemed representative of the desired future path/pulse of industry
- Safety statisticians are needed to help multi-disciplinary safety management teams to think more quantitatively
  - To provide quantitative frameworks for medical judgment
  - Success will depend on dynamic, interactive, cross-disciplinary collaboration

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2017 Deep Dive Deliverables: Aggregate Safety Assessment Plan (ASAP)

Key Components of the ASAP:

1. Safety endpoint characterization
2. Consistent collection of safety data
3. Ongoing aggregate safety evaluation
4. Preparation for regulatory deliverables

Value of the Aggregate Safety Assessment Plan

- Captures the emerging safety story through safety monitoring and scientific evaluation of accumulating safety data
- Provides a dynamic planning document that governs how aggregate safety data are to be collected, monitored and analyzed in a systematic and consistent way
- Supports and facilitates a collaborative effort among safety-related disciplines
- Provides an operational framework to ensure that various safety-related documents communicate the same safety profile and risk information (IB-RSI, DSUR, IND-Reporting, ISS, CTD, RMP, PBRER)
- Makes aggregate safety monitoring process congruent with regulatory safety reporting
- Promotes periodic benefit-risk evaluation

ASA Biopharm/DIA Scientific Working Group: Safety Monitoring for Clinical Development

- Objective: to empower the broader cross-disciplinary, cross-regional community to discover and promote practical quantitative solutions for safety surveillance during clinical development.

- Safety Clinicians: James Buchanan (Covilance LLC), Mary Furnari (Celgene), Barbara Hendrickson (AbbVie), Mengchun Li (TB Alliance), Dennis O'Brien (Behringer-Ingleheim), Jonathan Seltzer (ACI Clinical)

- Statisticians: Greg Ball (Merck), Brian Cohen (ACI Clinical), Susan Duke (Drug Safety Counts LLC), Bill Wang (Merck)

Conclusions

- Drug development paradigm shift and evolving regulatory landscape are calling for aggregate safety monitoring and evaluation earlier in the development process
- This requires cross-disciplinary process, framework and methodology innovation
- The ASA Safety Monitoring working group is developing specific deliverables to better enable quantification in safety monitoring

Safety Monitoring Methodology: From a Bayesian Perspective

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1 Bayesian Thinking in Safety Monitoring

2 Under the Blinded Setup

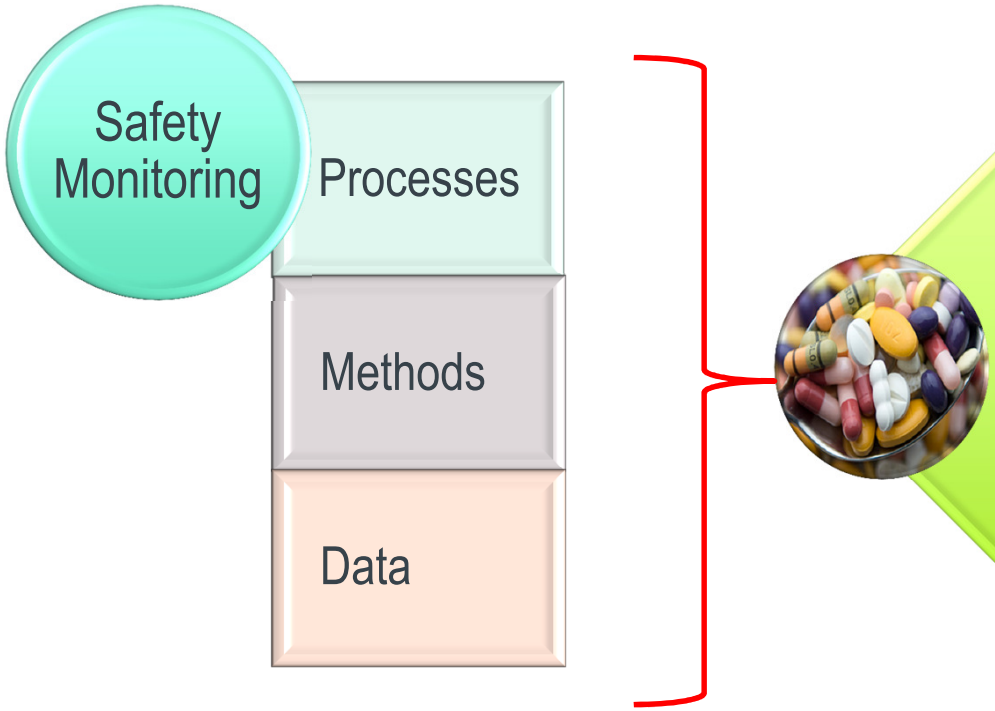
3 Dynamic Safety Monitoring

4 Static Safety Monitoring

5 Under the Post-Marketing Setup

Image adapted from: http://gureckislab.org/blog/?p=165

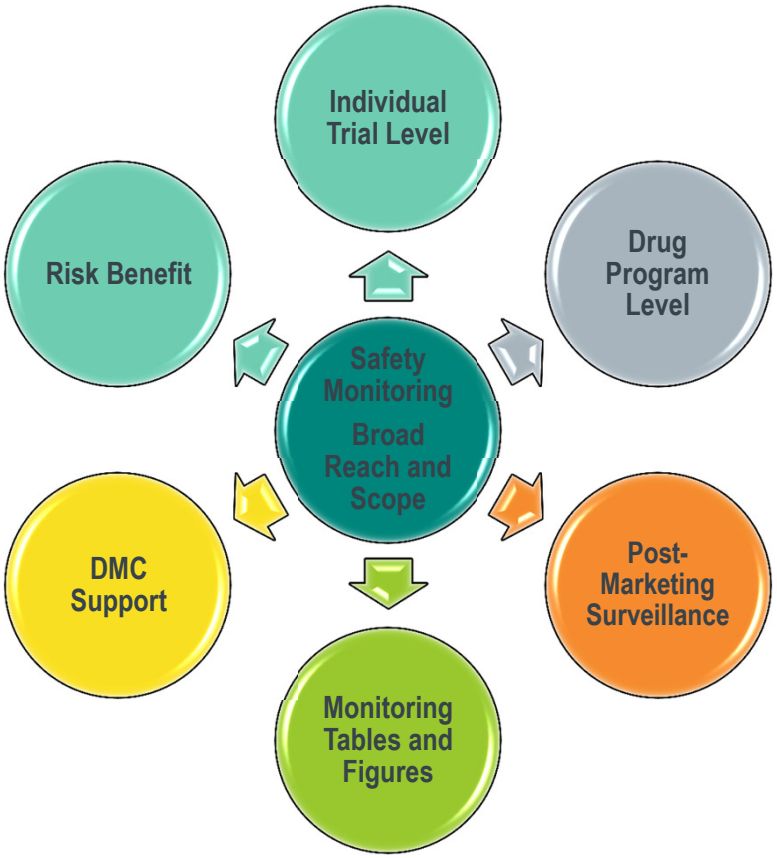
What is Safety Monitoring?

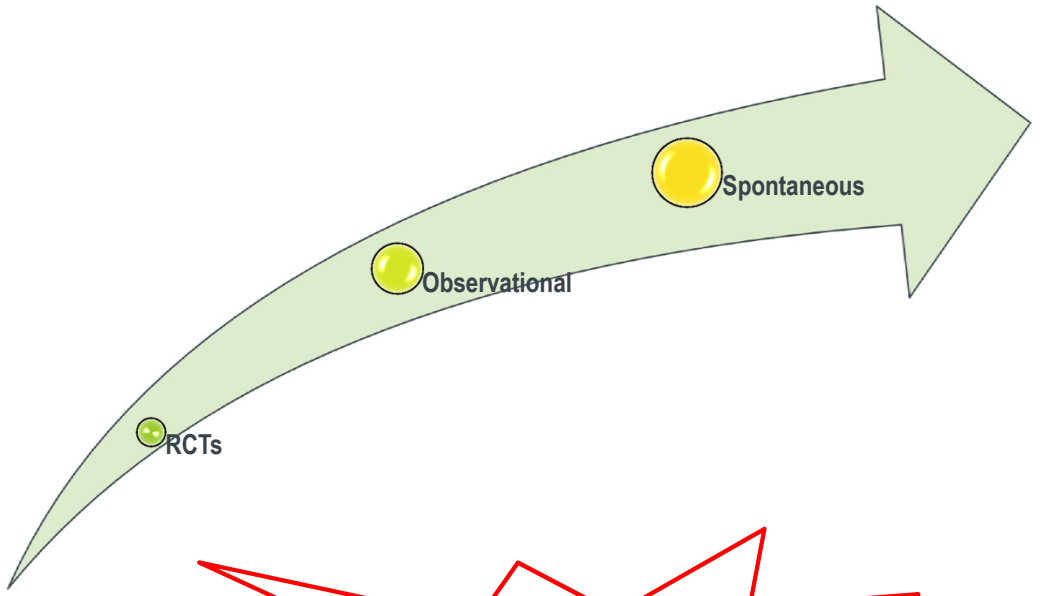


To assess both the frequency and magnitude of the safety concerns, ranging from easily detected to rarely occurring, but of potential high impact on patient well-being

Serves to lay out the foundation for Integrated Analysis of Safety preparation and benefit-risk analysis in the Clinical Overview and possible Advisory Committee Meeting

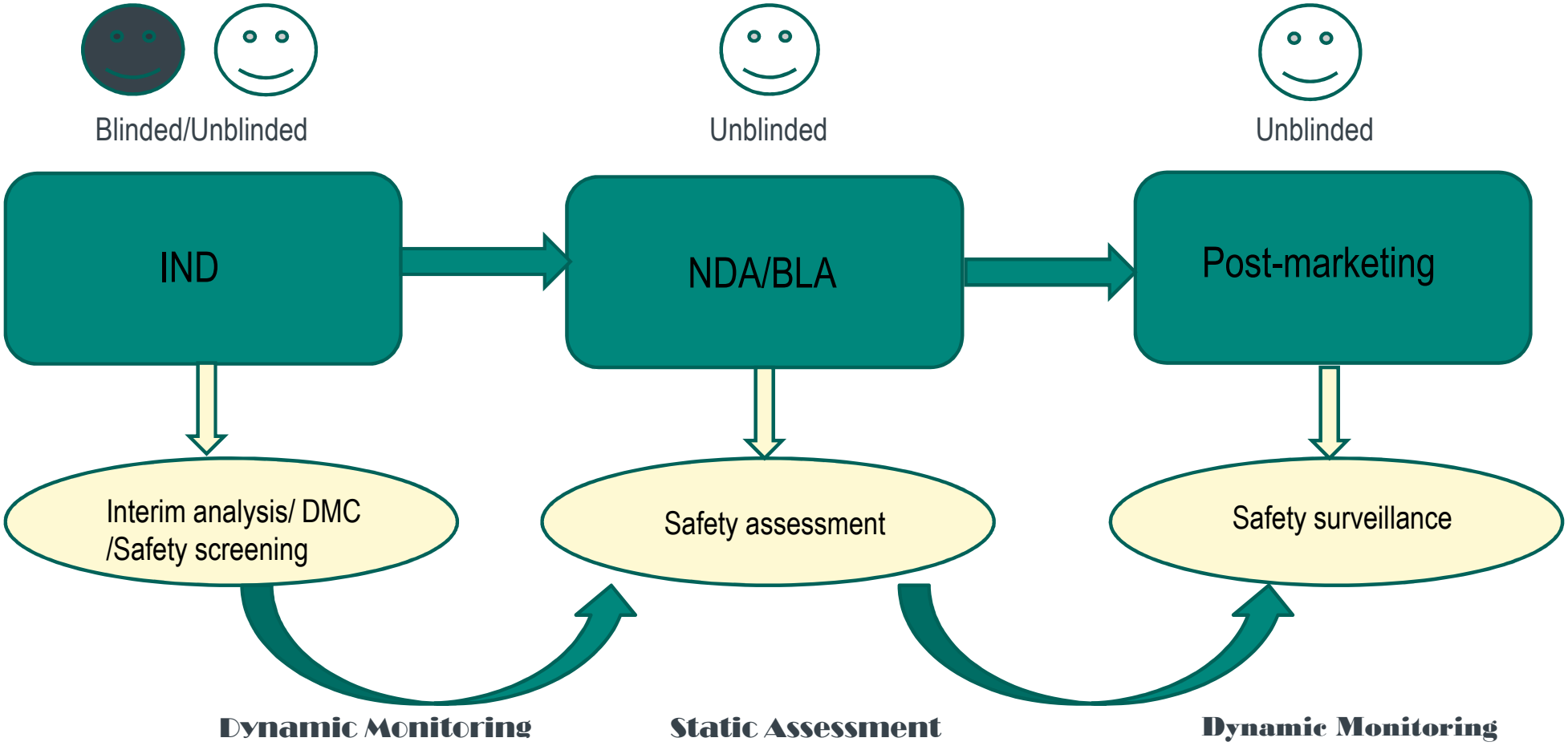
Safety Monitoring: What does it entail and where is it done?





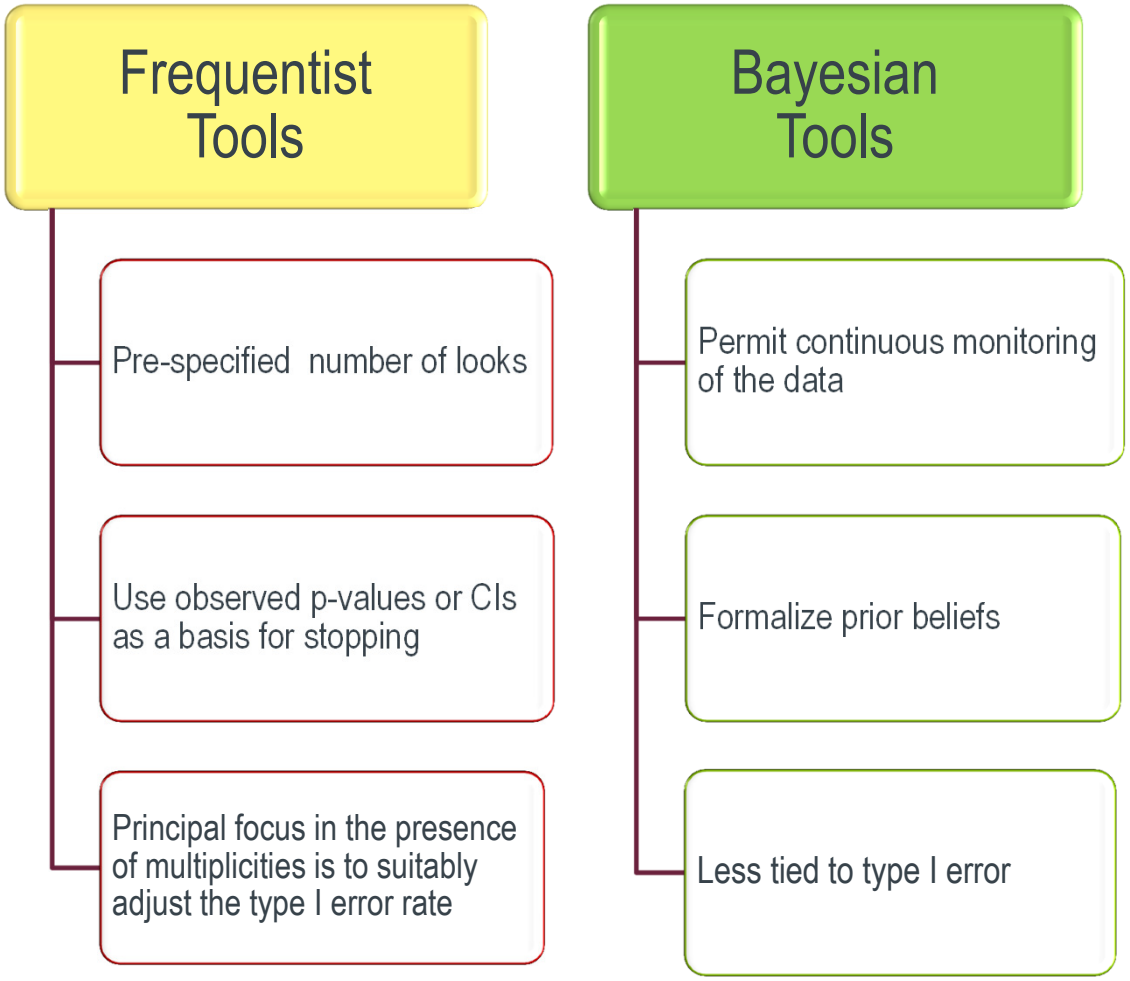
Lots of literature! The Elephant!

Safety Monitoring in the Process of Drug Development



Defining Safety Monitoring

Safety Monitoring From a Bayesian Perspective (Broadly Speaking)



"*Safety assessment is one area where frequentist strategies have been less applicable. Perhaps Bayesian approaches in this area have more promise*"

Chi, Huang and O'neil (2002)

Bayes Theorem and Bayesian Decision Rule

- Bayes Theorem

$P(H)$ is the pre-study opinion(prior probability)

$P(data|H)$ is the likelihood of obtaining the observed data

$P(H|data)$ is the revised opinion (posterior probability)

$$P(H|data) \propto P(data|H)P(H)$$

- Bayesian Decision Rule
  - Using either blinded or un-blinded data, pre-marketing or post- marketing data
  - Based on the posterior distribution
  - Threshold such that if posterior probability of exceeding a certain value is greater than threshold, then halt trial.
  - Could be dynamic monitoring or static assessment

Safety Monitoring Methodology : From a Bayesian Perspective

1 Bayesian Thinking in Safety Monitoring

2 Under the Blinded Setup

3 Dynamic Safety Monitoring

4 Static Safety Monitoring

5 Under the Post-Marketing Setup

Image adapted from: http://gureckislab.org/blog/?p=165

Defining Blinded Safety Monitoring?

- Blinded safety monitoring – looking at safety data without any knowledge of the treatment assignments
  - Can include masked treatment, e.g., Treatment A versus Treatment B without knowledge of what A and B are
- Blinded safety monitoring can be limited to one or more studies
- Since drug development programs continue for long periods of time, some safety information on the drug may be known from completed studies. It is important that this information is accounted for in some way
- Similarly, historical control information from the same class or population should also be accounted for in some form in blinded safety monitoring

Pros and Cons of Blinded Monitoring

Advantages and Disadvantages of Maintaining Study Blind in Safety Monitoring Setting	
Advantages	Disadvantages
- Identify potential safety issues ahead of scheduled DMC meetings - Identify safety issues that are, or have potential to become a key concern - Drive decisions regarding an unblinded analysis or a decision to setup a DMC, or even stopping a trial or development altogether	- It may not be as informative and efficient as in an unblinded analysis - It will inevitably raise logistical questions regarding monitoring patient safety while at the same time maintaining the study blind - Might provide less informative treatment effect estimate

Blinded Safety Monitoring and Reporting (SMR) Based on Pooled Data

- The general idea is to make some inference about the rate (or an exposure adjusted-rate) θ of a safety concern, for example, that of an adverse event of special interest.
- By incorporating the prior knowledge about safety profile of the control group or background adverse event (AE) rate, Bayesian method provides a framework to identify early safety signal from the accrued blinded data
- θ can be a derived metric, such as Risk Ratio, Risk Difference, Odds Ratio and etc.
- Convenient to keep updating knowledge using cumulative data
- The decision can be made on the basis of posterior density function or the credible intervals

Some Published Bayesian Approaches for Blinded Safety Monitoring

Likelihood based method (Ball, 2011)	– Likelihood based method – Designed objective early stopping rules that act as continuous safety screens for randomized clinical trials with blinded treatment information, under Bayesian framework
Bayesian Method (Wen, Ball, and Dey, 2015)	– Assess blinded safety monitoring within a Bayesian framework – Can be applied to one or more event – Key idea is to evaluate probability that a clinical parameter of interest exceeds a pre-specified critical value, given observed blinded data. – Critical value is selected based on historical data or medical judgment. – If probability meets criteria “big enough”, this would signal a potential safety concern, leading to other additional investigations
Bayesian Method (Gould, and Wang, 2015, 2016)	– Bayesian approach to determining likelihood of elevated risk suitable for binomial or Poisson likelihoods – Description is for a single trial, but method can be extended to multiple trials. – Can be applied regardless of the metric used to express the difference. – Suggest method is more appropriate when the AEs are not ‘rare’. – Some suggestions on determining prior distribution – Discusses decision rules that can be applied on the basis of posterior probability – Statistical properties provided

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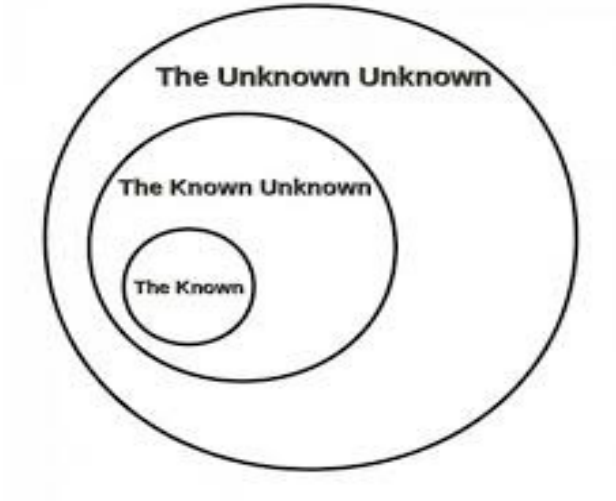
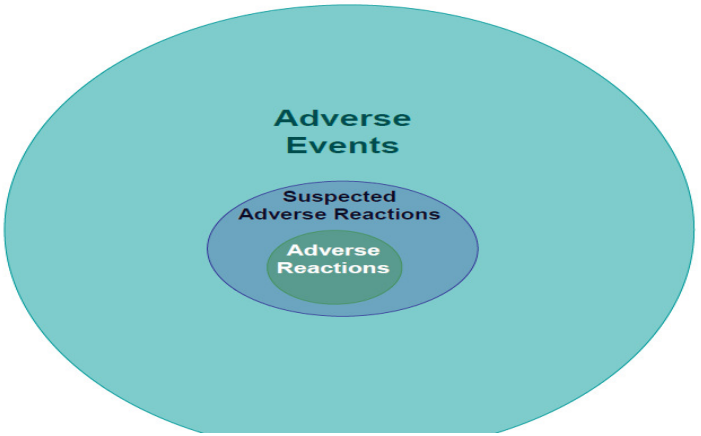
Dynamic Safety Evaluation

- Safety monitoring is a process of continuous learning: from unknown to known, from general AE to suspected adverse reaction (see figure)
- Lachenbruch et al (2007) paper provides a statistical framework for identifying the first or the first few sentinel events to trigger a formal monitoring plan on those events
- These methods can apply either to rare events or to common events not expected to occur at an elevated rate in the treated group





Dynamic Safety Evaluation

- Due to limited sample size, rare AEs are often impossible to detect during clinical development
- Use of continuous monitoring of patients as they receive the drug or vaccine is needed, generating an AE signal if and when the number of AEs are so great that they are unlikely to be due to chance alone
- For continuous sequential safety monitoring, Wald (1945) was the first to develop a sequential probability ratio test (SPRT)
- Bayesian dynamic safety monitoring has its own advantage

Bayesian Stopping Rule & Dynamic Monitoring

- Bayesian stopping rule based on the posterior distribution
  - Beta-Binomial Model (Tarone 1982; Thall and Simon 1994; Resnic et al. 2004; Yao et al 2013; Xia et al 2013)
    - Assume the prior distribution for the treatment event rate π_t and the control rate π_c
    - Posterior distribution of π_t and π_c can be obtained through Bayes theory
    - Pre-specify constant δ which represents an unacceptable safety concern margin
  - Poisson/Gamma model (Kashiwabara 2014)
- Parameters keep being updated as data are being collected
- Threshold such that if posterior probability of exceeding a certain rate is greater than threshold, then considerations should be given to sopping the trial, otherwise continue.

Bayesian Group Sequential Approach to Signal Detection

- Chen (2013) proposed a sequential approach to provide Bayesian evidence on the excessive AE occurrence in the treatment group as compared to the control group
- This is done in the framework of the Berry and Berry model (Berry & Berry 2004)
- It is assumed that once a signal is detected (posterior probability > threshold) it will be considered a signal for the remainder of the trial
  - The signal would be detected as early as possible with predefined posterior probability
  - Provides timely safety information for justification of any adjustment of the trial (e.g. change of patient allocation, extra safety monitoring and mitigation measures, or stopping the trial)

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Static Safety Evaluation

- ICH-E9 recommends descriptive methods supplemented by confidence intervals; P-values useful to evaluate a specific difference of interest
- Three-tiered approaches (Crowe et al, 2009)
  - Tier 1: Associated with specific hypotheses (p-value)
  - Tier 2: AEs with certain frequency (CI)
  - Tier 3: Rare events that require clinical evaluation
- P-values sometimes useful as a “flagging” device
  - While familywise error rate (FWER) control is commonly used for efficacy; False discovery rate (FDR) control is more appropriate in the context of safety, especially for Tier 2 AEs
  - Mehrotra & Heyse (2004) and Mehrotra & Adewale (2012) proposed a double FDR (DFDR) procedure to flag body systems/specific AEs
  - Berry & Berry (2004), Xia, Carlin & Ma (2011) proposed alternative Bayesian hierarchical mixed models to account for multiplicities in AE assessment

Bayesian Hierarchical Model –Berry & Berry Model

- Four important considerations when flagging a type of AE
  - Actual significance levels
  - Total number of types of AEs being considered
  - Rates for those AEs not considered for flagging
  - Biological relationships among the various AEs
- First 2 considerations are standard considerations in the frequentist approach to multiple comparisons, second 2 considerations are not, but are relevant in the Bayesian approach
- Berry and Berry (2004) proposed an explicit method for simultaneously addressing many types of AEs that are categorized into body system, which allows borrowing across types of AEs

Bayesian Hierarchical Model –Berry & Berry Model (Cont)

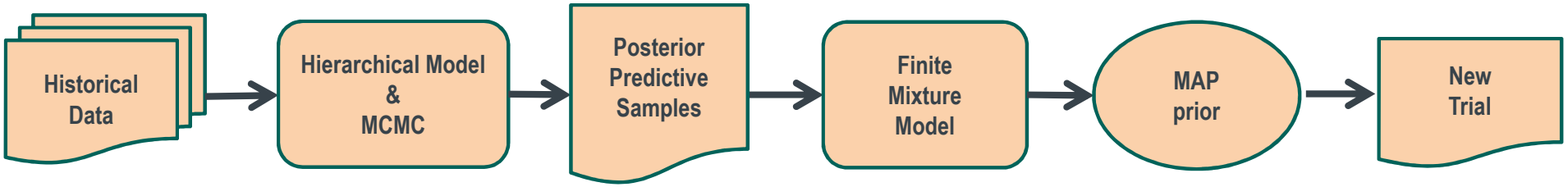
- A three-level hierarchical mixed model to account for multiplicities in AE assessment (Berry and Berry 2004):
  - Basic level: individual AE
  - Second level: body system which contains a number of types of possibly related AEs
  - Highest level: collection of all body systems
- Assume that AEs in the same body system are exchangeable and rates of AEs are more likely to be similar within than across body systems
- Hierarchical nature of the model gives rise to regression effect—which is appealing in the context of multiplicities because it modulates extremes
- Decision is based on the posterior probability that the event rate of the treatment group is greater than that of the control

Bayesian Hierarchical Model –Extended Berry & Berry Model

- Xia, Carlin, Ma (2011) extended B&B method to the hierarchical Poisson mixture model
  - accounts for the length of the observation of subjects and improves the characteristics of the analysis for rare events.
  - provides guidance on how to choose a signal detection threshold to achieve a fair balance between false positive error rates and false negative error rates via simulation study.
- They considered 5 different approaches.
  - Model 1a: three-stage model with normal prior on log-OR.
  - Model 1b: three-stage model with mixture prior on log-OR.
  - Model 1c: nonhierarchical one-stage Bayesian mixture model.
  - Model 2a: three-stage model with normal prior on log-RR.
  - Model 2b: three-stage model with mixture prior on log-RR.

Meta-Analytic Predictive Prior (MAP) Approach

- Weaver et al. (2016) introduced meta-analytic predictive prior approach (Schmidli et al. 2014) to access pre-specified adverse event
- Historical safety information could be incorporated into the analysis of the new trial data by using a mixture conjugate priors



Robust MAP and Empirical MAP Prior Approach

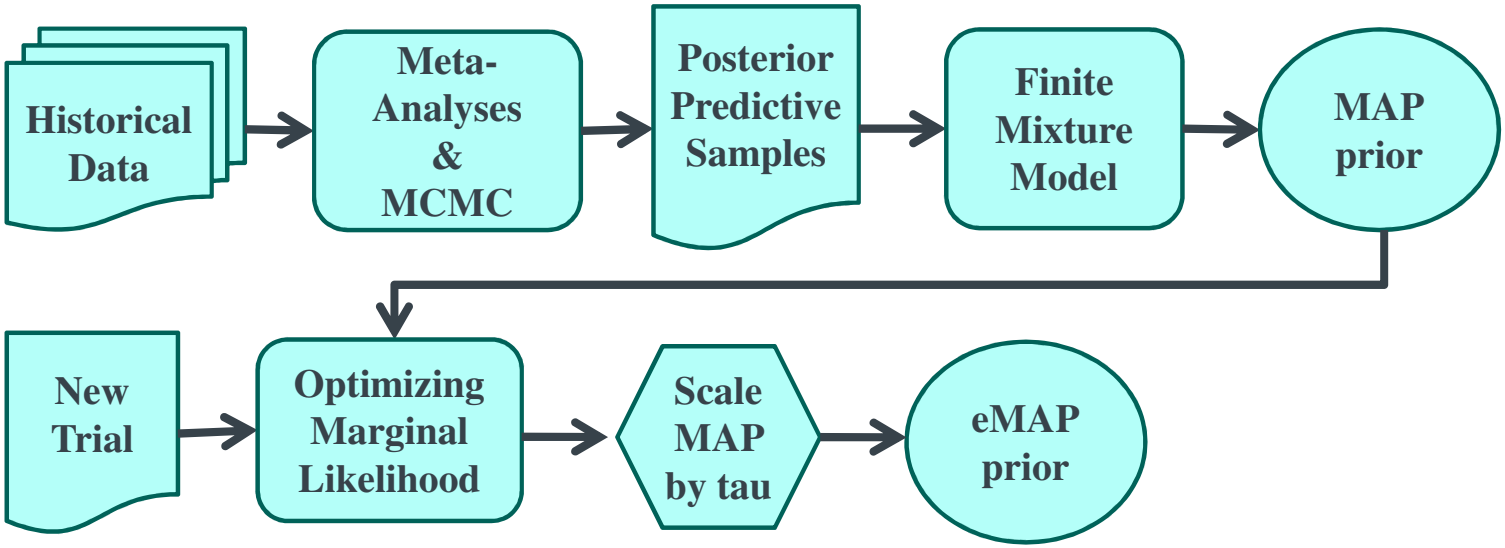
When prior-data conflict arises between historical informative prior and the data from current study

- Robust MAP prior approach (Schmidli et al. 2014):
  - A robust mixture prior incorporates a robust parameter and a weakly-informative component to the MAP prior, which allows for a discounting of the informative prior
  - The robust parameter is the probability that the new trial differs systematically from the historical trials

- Empirical MAP prior approach (Li et al. 2016):
  - An empirical mixture prior incorporates an empirical parameter that controls the borrowing of the information

Empirical MAP Approach

The empirical mixture parameter controls the borrowing of the information from the historical data when there is a prior-data conflict. The more heterogeneous the prior and the new trial data, the less the borrowing



Multivariate Bayesian Logistic Regression (MBLR)

- A compromise between separate analyses of finely distinguished events and a single analysis of a pooled event (DuMouchel, 2012)
  - Proposed a MBLR method to analyze safety data when there are rare events and sparse data from a pool of clinical studies
- Method: multivariate Bayesian logistic regression (MBLR)
  - As the Berry and Berry model, assumes events are classified into similar medical groupings in order to use a shrinkage model to allow borrowing strength across similar events
  - Requires selection of a set of medically related issues, potentially exchangeable with respect to their dependence on treatment and covariate
  - Exploratory in nature and examines the relationship of the adverse event frequencies to multiple covariates and to treatment by covariate interactions
  - To detect possibly vulnerable subgroups that might react different to the treatment

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Safety Monitoring Under the Post-marketing Setup

- A process from RCT, observational studies, to spontaneous reporting
- Lots of challenges with high volumes of data & multiple sources of data
- Post-marketing surveillance methods
  - Used on observational data (claims, FAERS, VAERS …)
  - May not have a denominator

- Methods that look for signals, exploratory
  - Development of new methods continues
  - Focus here on a few established ones

Origin of Bayesian Confidence Propagation Neural Network(BCPNN)

- Developed to analyze large spontaneous report datasets (WHO original)
- WHO database is analyzed regularly to find new drug safety signal, then communicate back to the nation centers for further analysis for possible regulatory decision
- Spontaneous report data accumulate continually over time, are sparse and only a few of the possible drug-event combinations occur
- BCPNN implement Bayesian statistics in a neural network architecture:

  Information Component (IC) for each drug - adverse drug reaction (ADR) combination in the database, where IC is a logarithmic measure of disproportionality
- U.S. FDA also uses disproportionality methods to identify statistical associations between products and events in the databases of safety reports

Proportional Reporting Ratio(PRR) and BCPNN

	Reports with drug of interest, j	***Reports of all other drugs in database***	***Total***
Reports with AE of interest, i	*a*	*b*	*a+b*
Reports of all other AEs in database	*c*	*d*	*c+d*
Total	*a+c*	*b+d*	*a+b+c+d*

PRR = [a/(a+c)] / [b/(b+d)]

PRR>1: greater than expected frequency of the report

IC = $\log_2$\{[a/(a+c)] / [(a+b)/(a+b+c+d)]\}

IC>0: unexpectedly frequency

BCPNN incorporates a Bayesian framework to PRR (Bate et al 1998, 2009)

Multi-Item Gamma Poisson Shrinker: MGPS(DuMouchel,1999)

- Very popular use with spontaneous report data
- Adjust for small observed or expected numbers of reports of the product-event pair of interest
- Considers the ratio of the observed drug-event combination to expected
- Models the rate with a prior that is a mixture of two gamma
- Incorporates Bayesian “shrinkage” and stratification to produce disproportionality scores toward the null, with advantages for cases the data is limited with only a small numbers of cases
- By diminishing the effect of spuriously high PRR values, MGPS approach provides a more stable estimate of the relative reporting rate of an event for a particular product with a reduced number of false-positive safety signals.

Other Bayesian Approaches

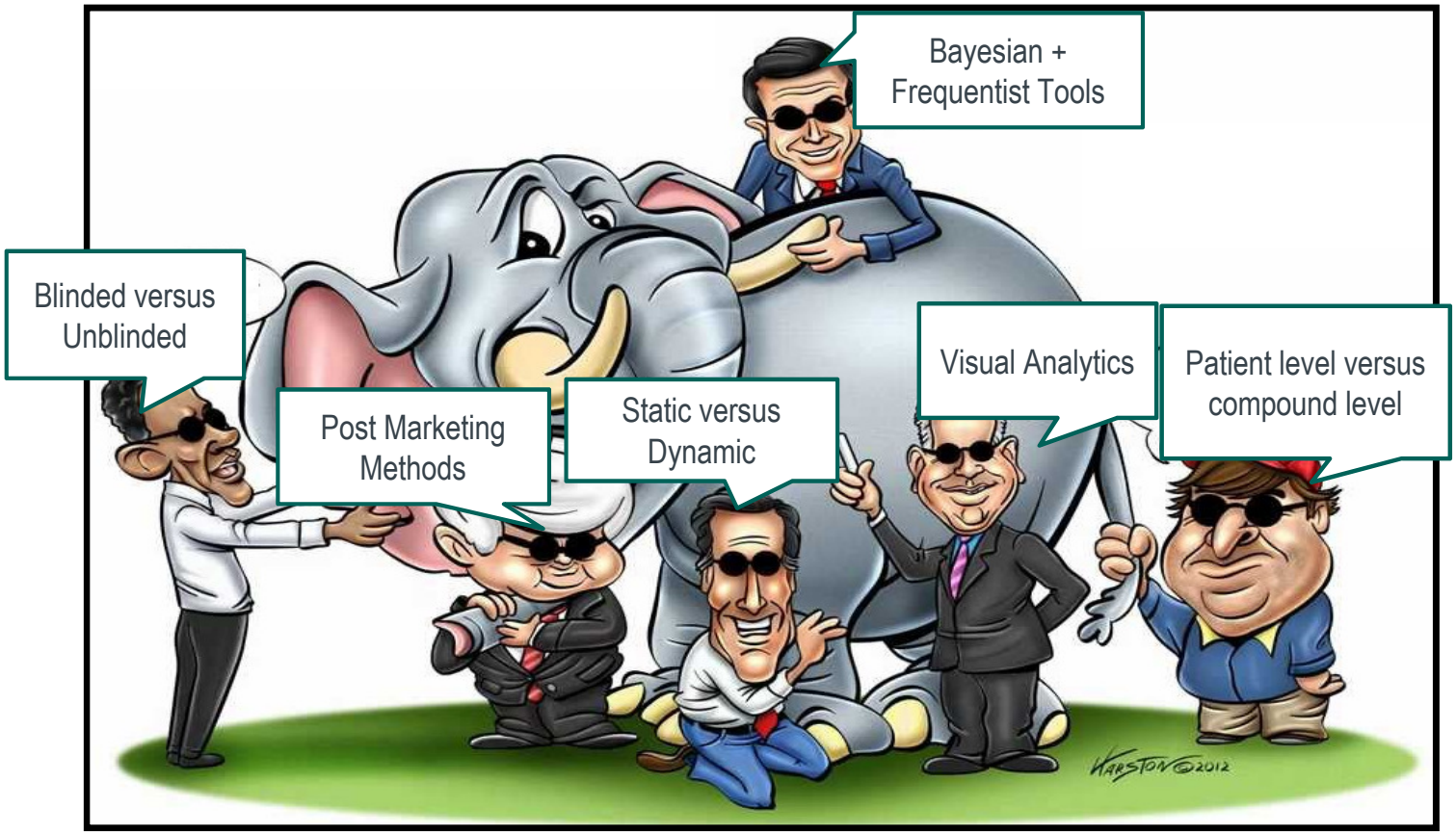
- Empirical Bayes Gamma Mixture method:
  - Screening very large, sparse frequency tables to identify cells showing drug-event associations (DuMouchel, 1999)
  - The parameter of the prior distribution is determined as the values that maximize the product of the marginal densities of the counts for each drug-event pair

- Nonparametric(hierarchical) Bayesian model:
  - The common prior, for the reporting rates, is the Dirichlet process (DP), an extension of simplified Bayes (sB) and MGPS (Hu, Huang, Tiwari 2015)
  - Use DP priors for AE reporting rates where sB uses a single Gamma distribution

Summary

- Due to time limitation, not all Bayesian safety monitoring approaches are discussed here, the literature keeps going on and on….
- Safety monitoring method should be chosen tailoring to:
  - The safety questions to be answered
  - The source of data
  - Other related historical information
  - Logistics
  - …..

Safety Monitoring: The Elephant Metaphor



Adapted from: https://www.youtube.com/watch?v=ygT-UwgEaSo

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Panel Discussion

Panel Questions

1. Thinking of drug development and life cycle management as a whole, how should we enhance the planning of safety data collection and integration from different sources, pre-marketing and post-marketing? What are the opportunities and challenges?

2. What do you see as the value of Bayesian methodology and/or machine learning in ongoing aggregate safety evaluations?

3. What are the pros and cons for ongoing blinded safety monitoring vs performing unblinded comparisons across treatment groups to detect numerical imbalances in anticipated events?

4. How can the ASAP better enable and align with overall benefit-risk assessment?