Blinded Ongoing Aggregate Safety Evaluation

ASA (CT and Boston Chapters) and Boehringer Ingelheim Academic Webinar Series

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Disclaimer

The opinions provided here are those of the presenters and are not necessarily reflective of the positions, policies or practices of their employer.

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Agenda

- Global Trends in Regulatory Landscape for Safety Monitoring during Clinical Development
  - ICH E2A Clinical Safety Data Management (1994)
  - Management of Safety Information from Clinical Trials (CIOMS VI 2005)
- FDA IND Safety Reporting Final Rule (2010)
  - Safety Reporting Requirements for INDs (2012)
  - Safety Assessment for IND Safety Reporting (2015)
- Quantitative Frameworks and Medical Judgment
  - Blinded Ongoing Aggregate Safety Evaluation (Blinded-OASE)
- ASA Biopharm Safety Monitoring Working Group

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Safety Monitoring during Clinical Development: Fundamental Framework

- Inherent risks for patients
  - All marketed drugs have associated risks; investigational drugs have more uncertainty
  - Need proactive safety assessment to enable effective risk management
  - Ultimate goal is to deliver effective drugs with favorable benefit-risk profiles to the right patients

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Global Regulatory Landscape

CIOMS

CIOMS

ICH

harmonisation for better health

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ICH Technical Requirements for Safety Monitoring during Clinical Development

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
- Clinically important increase in rate of expected serious ADRs is subject to expedited reporting
- Premarketing and postmarketing safety reporting concepts/practices are interdependent
- How to make aggregate safety assessments in ongoing studies (especially without unblinding study personnel) has not been described in ICH guidance

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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 not 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

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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

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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

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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)

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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"

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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
  - Safety physicians have been strong qualitative thinkers, focused on individual case review and case series
  - New guidance requires more 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

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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"

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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

Inter-Disciplinary Aggregate Safety Assessment Enables Effective Risk Management

- 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

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

- A safety assessment committee (SAC) and safety surveillance plan (SSP) are key elements
- FDA's preferred approach: SAC should regularly perform unblinded comparisons across treatment groups to detect numerical imbalances
  - Anticipated SAEs prespecified in the SSP (anticipated events)
  - Previously recognized SARs listed in the IB (expected events)
  - Appropriate steps should be taken to maintain overall study blinding
- Alternative approach: only perform unblinded comparison of event rates across treatment groups if the overall rate for all treatment groups of a specific SAE is substantially higher than a predicted rate
  - Sponsors should prespecify (in the SSP) predicted rates of anticipated events and expected events and guidelines for determining when an observed rate has exceeded the predicted

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Key Questions to Answer

- Have more events occurred than were expected? (yes or no)
- What is the magnitude of this relative risk elevation? (how much)

Quantitative framework to stimulate SMT discussions and improve conversations about safety monitoring of accumulating blinded data, these are not a decision rules

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Quantitative Framework: Bayesian Posterior Probabilities of Risk Elevation for AESI

Safety Monitoring Requires Flexibility

- Bayesian approach
  - Accommodates uncertainty
  - Natural for learning and decision making
  - Leverage prior information from earlier trials and related treatments
  - Unified framework for continual safety monitoring using all of the available data
  - Probability statements that are easy to interpret
- Operating characteristics can be used to tune the probability threshold boundaries

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Quantitative Framework: Probability Threshold Boundaries

Probability (pooled rate > critical rate / data) ≥ probability threshold

- Parameters
  - Critical rate
  - Probability threshold
- Data
  - Overall number of events = x
  - Overall number of patients = n
  - Pooled rate = x/n

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Bayesian Approach for Blinded Safety Monitoring

- Bayesian approach for blinded safety monitoring has been well established (Ball, 2011)
  - Given current information, an alert can be given if the posterior probability exceeds a threshold boundary

$$\Pr(P > P_c|\text{data}) \geq \theta_T$$

where P is pooled event rate in the trial population, P_c is pre-defined critical event rate, and θ_T is threshold boundary

  - Critical event rate can be obtained from the literature, a historic trial, or regulatory perspective; if P_c is uncertain, it could be replaced by an informative prior (beta distribution)

  - To adjust exposure times, event rate P can be replaced by incidence density

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Bayesian Approach for Blinded Safety Monitoring

- Schnell and Ball (2016) developed a full Bayesian method with a strong prior on the control rate and a separate weak prior on the treatment rate (updated with pooled blinded data).
  - Binomial model

Combined Arms $Z = Y_0 + Y_1$	
Control Arm	**Treatment Arm**
$Y_0 \mid M_0, \theta_0 \sim \text{Bionomial}\,(M_0, \theta_0)$	$Y_1 \mid M_1, \theta_1 \sim \text{Bionomial}\,(M_1, \theta_1)$
$M_0 \sim \text{Bionomial}\,(N, 1-r)$	$M_1 = N - M_0$
$\theta_0 \sim \text{Beta}\,(a, b)$	$\theta_1 \sim \text{Beta}\,(c, d)$

  - Poisson model

$$
\begin{aligned}
Y_i \mid a_i,\ \lambda_0,\ \lambda_1 &\sim Poisson(\lambda_{a_i}),\ i = 1, \ldots, N \\
a_i &\sim Bernoulli(r),\ i = 1, \ldots, N \\
\lambda_0 &\sim Gamma(\alpha_0,\ \beta_0) \\
\lambda_1 &\sim Gamma(\alpha_1,\ \beta_1)
\end{aligned}
$$

where α_0, β_0, α_1, and β_1 are elicited hyperparameters.

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Collaborative Process: Characterize Background Rates

Study incidence: not annualized (ADNI is 2 years, and other studies are 1.5 years)

Study	Description	N	Year	Age	Female	MMSE	Range	Syncope
Semagacestat	76-week phase 3 study (stopped early)	501	2008	73.2 (8.2)	53	20.8 (3.5)	16-26	1.4†
ADNI	2-year natural history, nontreatment study	190	2004	75.2 (7.5)	47.9	23.3 (2.0)	20-26	4.2‡
Bapineuzumab	18-month published trial	110	2005	67.9 (9.4)	59.8	20.7 (3.1)	16-26	1.8
Bapineuzumab	78-week phase 3 study	524	2007	71.9 (10.1)	50.3	21.2 (3.2)	16-26	2.5
Solanezumab	Two 18-month phase 3 studies	1025	2009	73.4 (7.9)	55.9	21 (3)	16-26	2.1

MMSE=Mini-Mental State Examination is used to test for complaints of problems with memory or other mental abilities, with higher scores indicating better cognitive function. †Stopped early; ‡2-year study of different patient population.

Henley DB, Sundell KL, Sethuraman G, Dowsett SA, May PC. Safety profile of semagacestat, a gamma-secretase inhibitor: IDENTITY trial findings. *Curr Med Res Opin*. 2014;30(10):2021-2032.

Henley DB, Sundell KL, Sethuraman G, Siemers ER. Safety profile of Alzheimer's disease populations in Alzheimer's Disease Neuroimaging Initiative and other 18-month studies. *Alzheimers Dement*. 2012;8(5):407-416.

Salloway S, Sperling R, Fox NC, et al. Two phase 3 trials of bapineuzumab in mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):322-333.

Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370(4):311-321.

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Collaborative Process: Calibrate Operating Characteristics

Operating characteristics of probability threshold boundaries for syncope with a critical treatment rate of 3.0%

True Control Rate	True Treatment Rate	True Pooled Rate	Probability Threshold Boundary (percent of trials crossing the boundary)		
			70%	80%	90%
2.0%	2.0%	2.00%	9.6%	4.0%	0.9%
	3.0%	2.67%	63.7%	47.9%	26.8%
	4.0%	3.33%	98.9%	96.6%	91.7%
	5.0%	4.00%	100.0%	100.0%	100.0%
3.0%	2.0%	2.33%	30.1%	16.7%	5.8%
	3.0%	3.00%	90.6%	82.2%	64.3%
	4.0%	3.67%	100.0%	99.8%	99.0%
	5.0%	4.33%	100.0%	100.0%	100.0%

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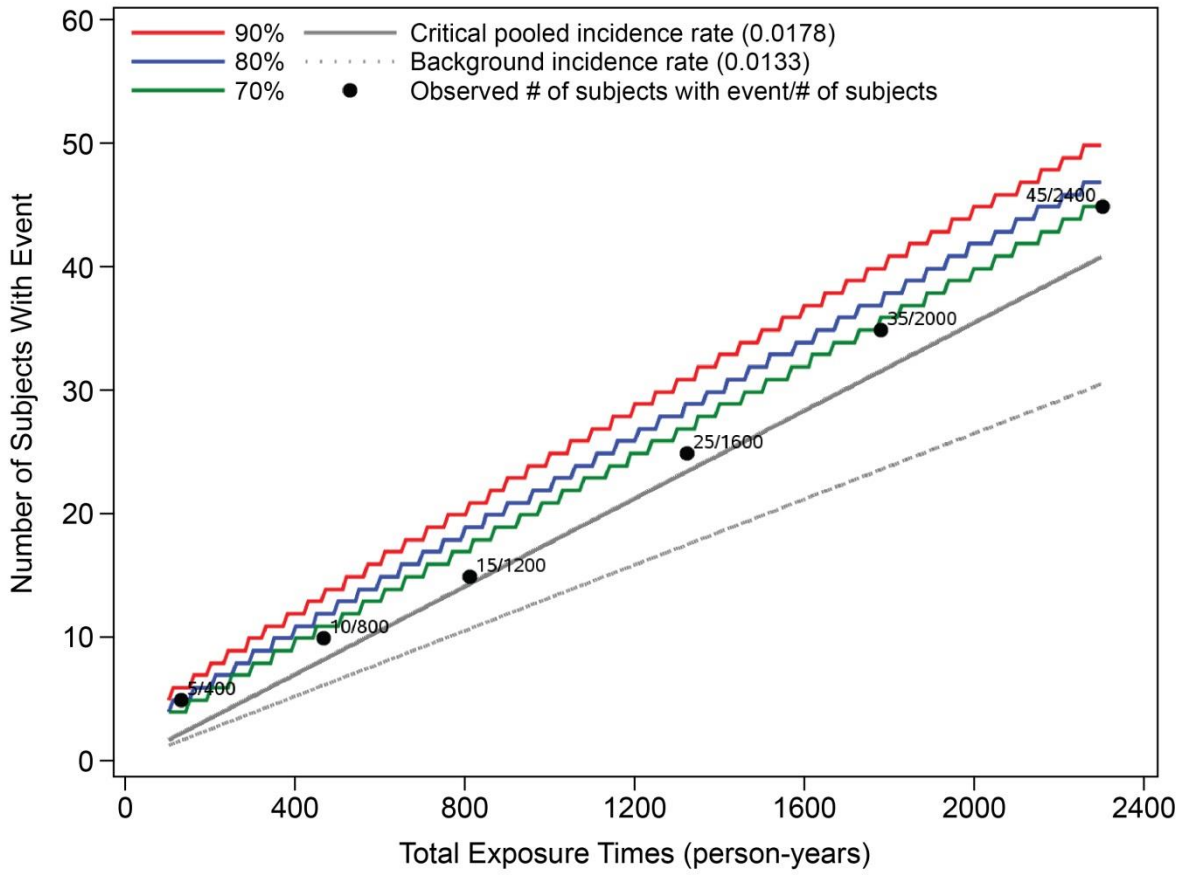
Blinded Ongoing Aggregate Safety Evaluation (Blinded-OASE)

Probability threshold boundaries for aggregate blinded safety monitoring: exposure-adjusted incidence rate (mock data)



Bayesian Approach for Blinded Safety Monitoring

- Likelihood of risk elevation can be expressed by a risk metric (for example, risk difference or ratio) (Gould and Wang, 2017)
  - Given the current information, alert could be given if posterior probability of the treatment effect metric value M exceeding a critical value M_{crit} is at least γ_{crit}

$$\Pr(\mathrm{M} > \mathrm{M}_{crit} | \mathrm{data}) \geq \gamma_{crit}$$

    where M is risk metric, γ_{crit} is threshold boundary

  - Need to specify prior distribution for the metric and the control group event

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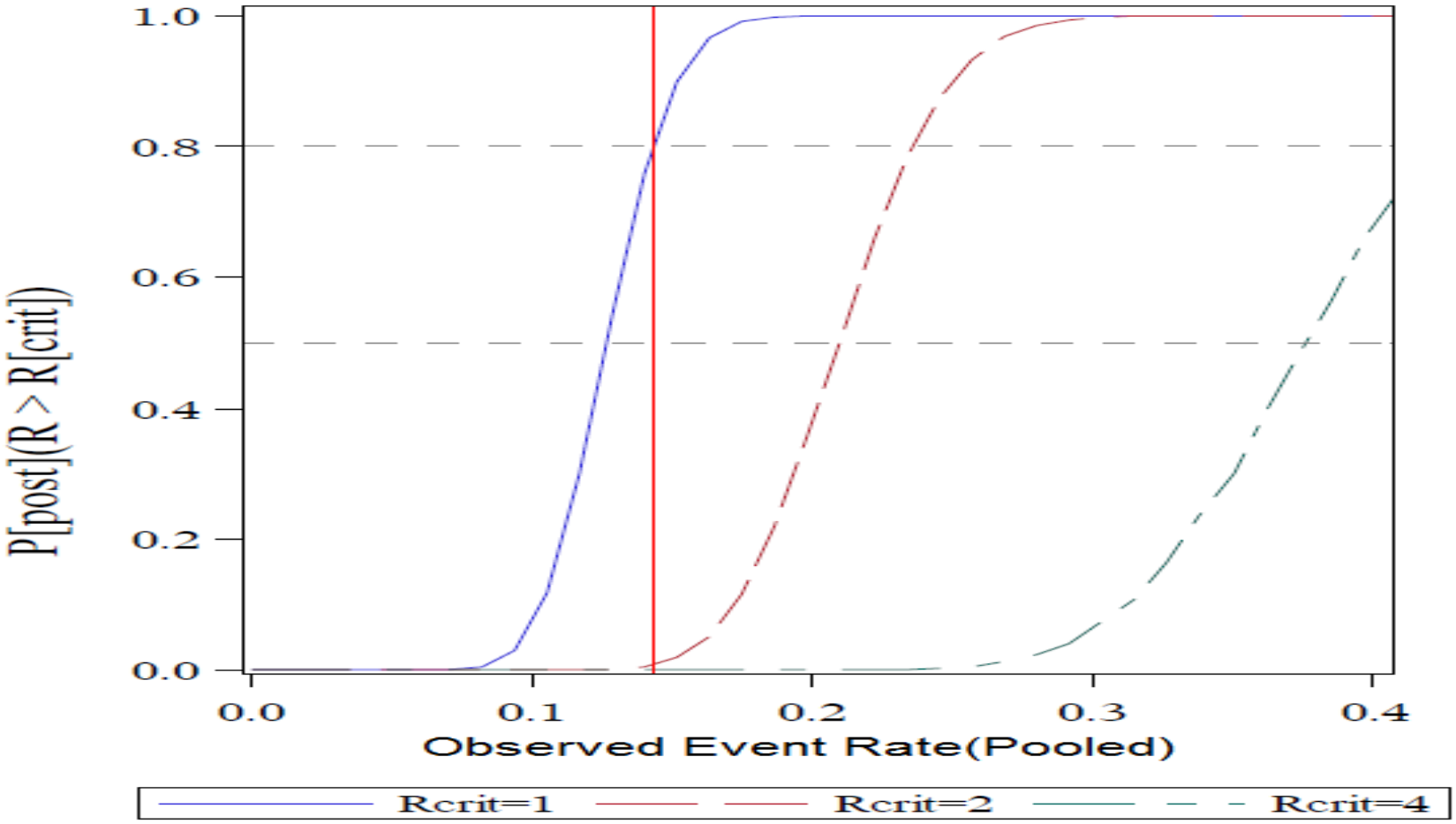
Quantitative Framework: Estimates of Relative Risk Elevation

Assessment of Relative Risk Elevation for Rash (n = N)



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Summary of Aggregate Safety Monitoring With Ongoing Blinded Studies

An alternative approach for anticipated events

- Collaborative process facilitates engagement with safety, clinical, epidemiology, and statistics
  - Characterize background event rates
  - Calibrate probability threshold boundaries
- Quantitative framework helps guide medical review and safety monitoring of the accumulating blinded data
  - General summary of aggregate safety profile
  - Bayesian posterior probabilities of risk elevation
- SMT uses medical judgment to decide on next actions
  - Have more events occurred than were expected?

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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)

ASA Biopharm Safety Monitoring WG


William Wang, Chair

WS1: Industry Practice & Regulation


Greg Ball


Susan Duke

- Faiz Ahmad (Galderma)
- Greg Ball (Co-lead, Merck)
- Amit Bhattacharya (ACI Cli
- 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


Judy Li


Melvin Munsaka

- Michael Colopy (UCB)
- Michael Fries (CSL Behr
- Karolyn Kracht (AbbVie)
- Judy Li (Co-lead, Regen
- 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)

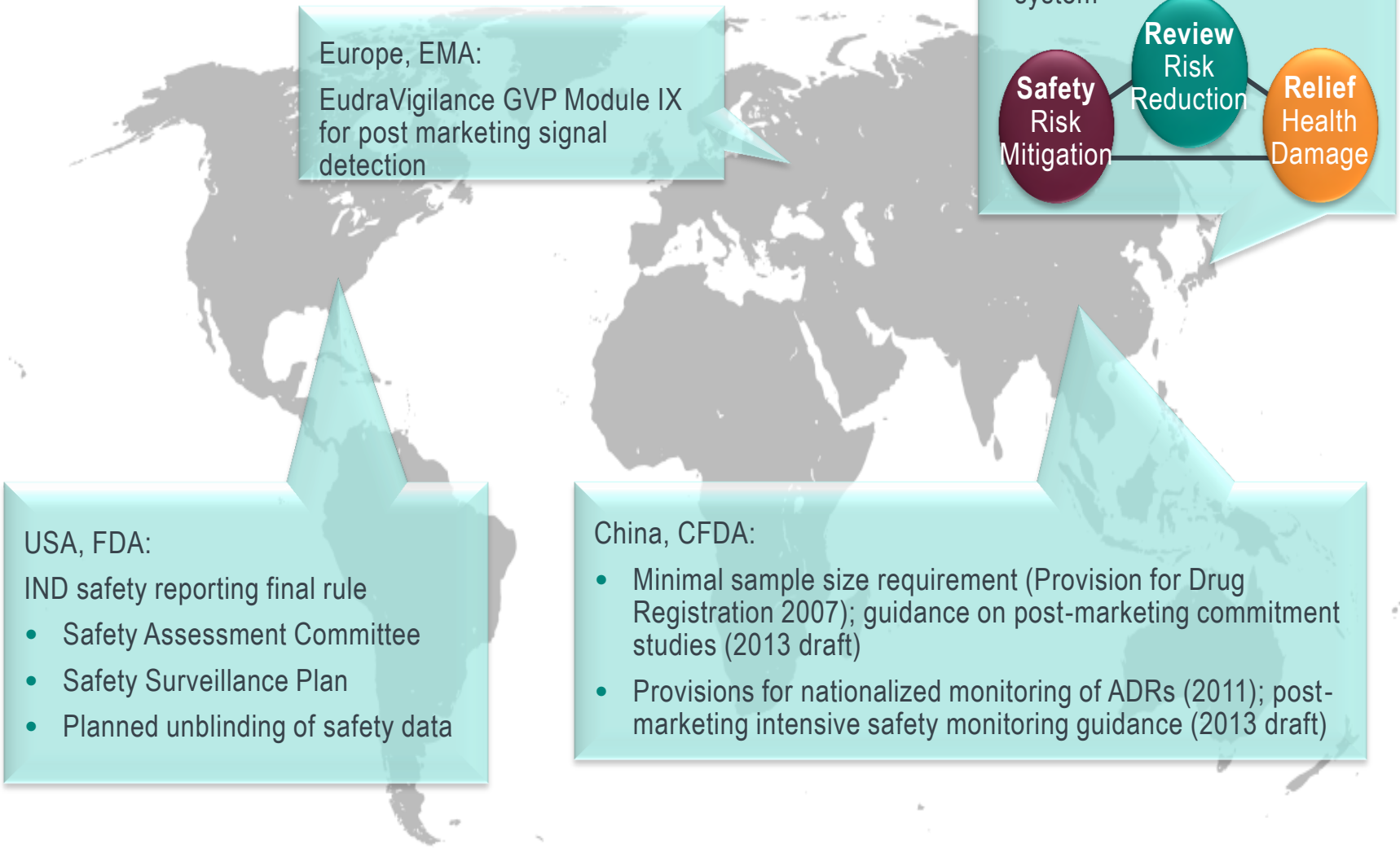
* Safety physician.
¥ Regulatory affairs PV specialist.
† European statistician.

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:

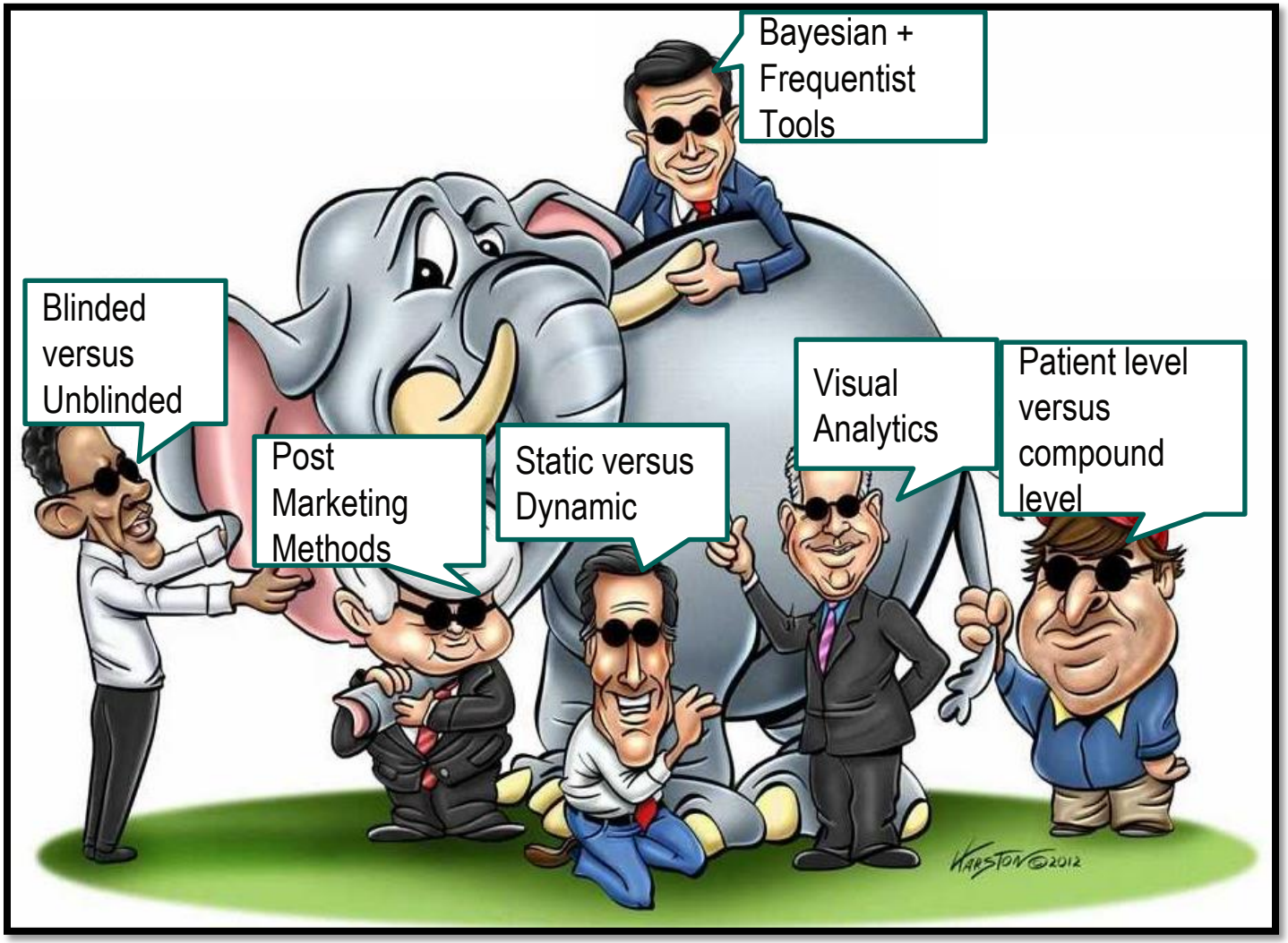
IND safety reporting final rule

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

China, CFDA:

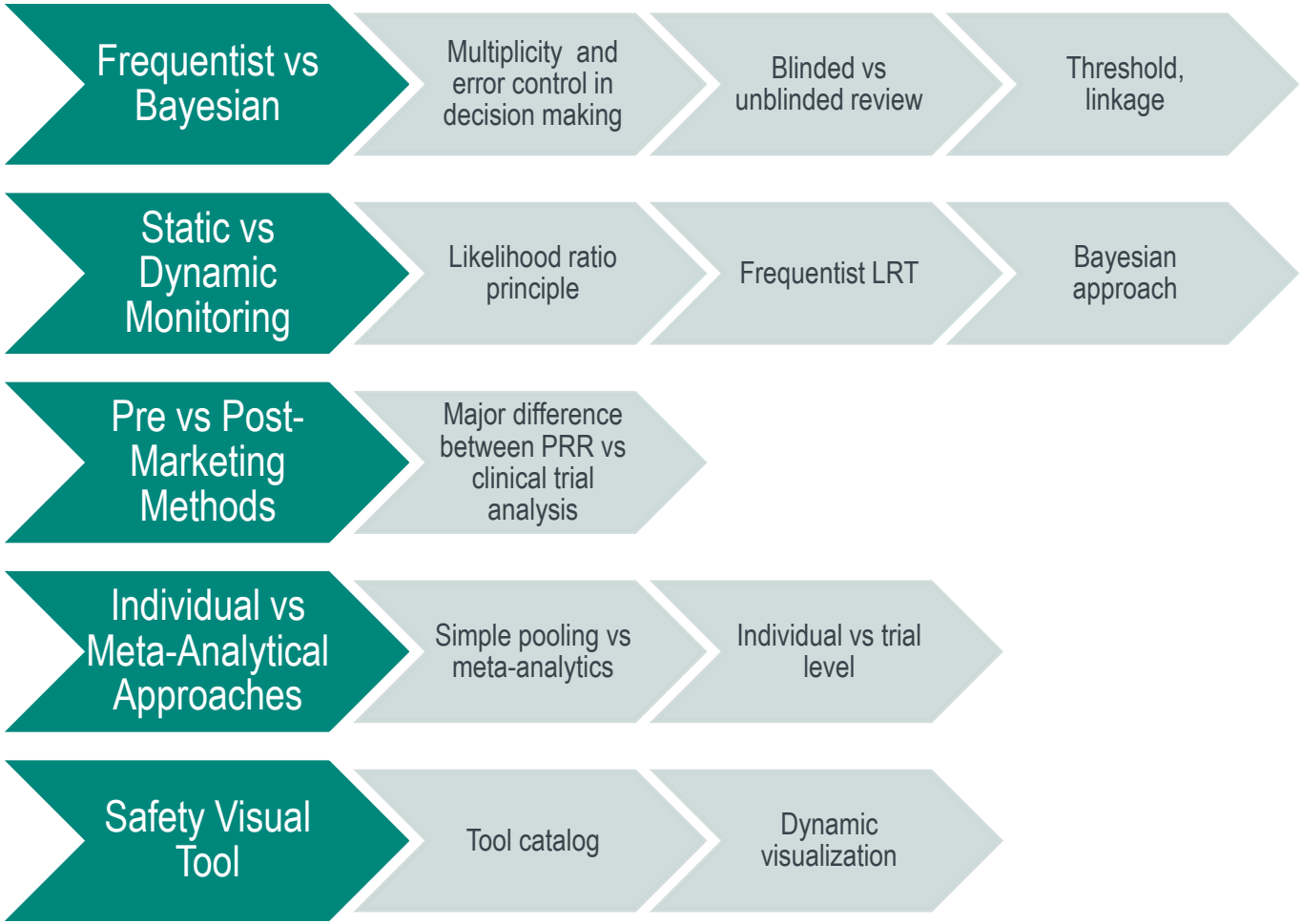
- Minimal sample size requirement (Provision for Drug Registration 2007); guidance on post-marketing commitment studies (2013 draft)
- Provisions for nationalized monitoring of ADRs (2011); post-marketing intensive safety monitoring guidance (2013 draft)

Safety Monitoring Methodology: Elephant Metaphor



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

WS2: Key Methodology Deep Dives



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