Safety Monitoring During Clinical Development

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- The authors are employed by Merck & Co., Inc. (known as MSD outside of the US and Canada)
- The opinions expressed are their own and do not necessarily reflect those of their employer

Agenda

- High level summary of safety monitoring during clinical development (from ASA Biopharm Safety Monitoring working group)
- Overview of new guidance on FDA IND safety reporting final rule
- Specific new method for blinded reviews of aggregate safety data that is being implemented in clinical trial programs

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Overview
ASA Safety Monitoring Working Group

Established in 2015 by the ASA Biopharm section Safety Statistics WG

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 thought leaders
- Review statistical methodologies

2016 deliverables

- August: JSM Biopharm Section, DIA China Quantitative Science Forum
- December: Deming Conference (tutorial)

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ASA Safety Monitoring Working Group

WS1: Industry Practice & Regulation

- Faiz Ahmad (Galderma)
- Greg Ball (Co-lead, Merck)
- Michael Colopy (UCB)
- Susan Duke (Co-lead, AbbVie)
- Robert (Mac) Gordon (Janssen)
- Qi Jiang (Amgen)
- Wenquan Wang (Morphotek)
- William Wang (Chair, Merck)

WS2: Methodology

- Michael Fries (Behring)
- Karolyn Kracht (AbbVie)
- Judy Li (Co-lead, FDA)
- Melvin Munsaka (Co-lead, Takeda)
- Matilde Sanchez (Arena)
- Krishan Singh (GSK)
- Ed Whalen (Pfizer)
- William Wang (Chair, Merck)
- Kefei Zhou (Amgen)

Safety Monitoring Statistical Advisors

- Aloka Chakravarty (FDA)
- Brenda Crowe (Lilly)
- Larry Gould (Merck)
- Qi Jiang (Amgen)
- Olga Marchenko (Quintiles)
- Amy Xia (Amgen)
- Janet Wittes (Statistics Collaborative)

We are indebted to the 18 thought 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

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Thought Leaders

- Aloka Chakravarty (FDA)
- Bob Temple (FDA)
- Brenda Crowe (Lilly)
- Christy Chuang-Stein (Pfizer)
- Conny Berlin (Novartis)
- Dave DeMets (UW)
- Frank Rockhold (GSK, now Duke)
- Frank Shen (AbbVie)
- Janet Wittes (Statistics Collaborative)

- Jose Vega (Merck)
- Juergen Kuebler (CSL Behring)
- Lily Krasulja (Janssen)
- Mark Levenson (FDA)
- Mondira Bhattacharya (AbbVie)
- Olga Marchenko (Quintiles)
- Steve Snapinn (Amgen)
- Valerie Simmons (Eli Lilly)
- Walter Offen (AbbVie)

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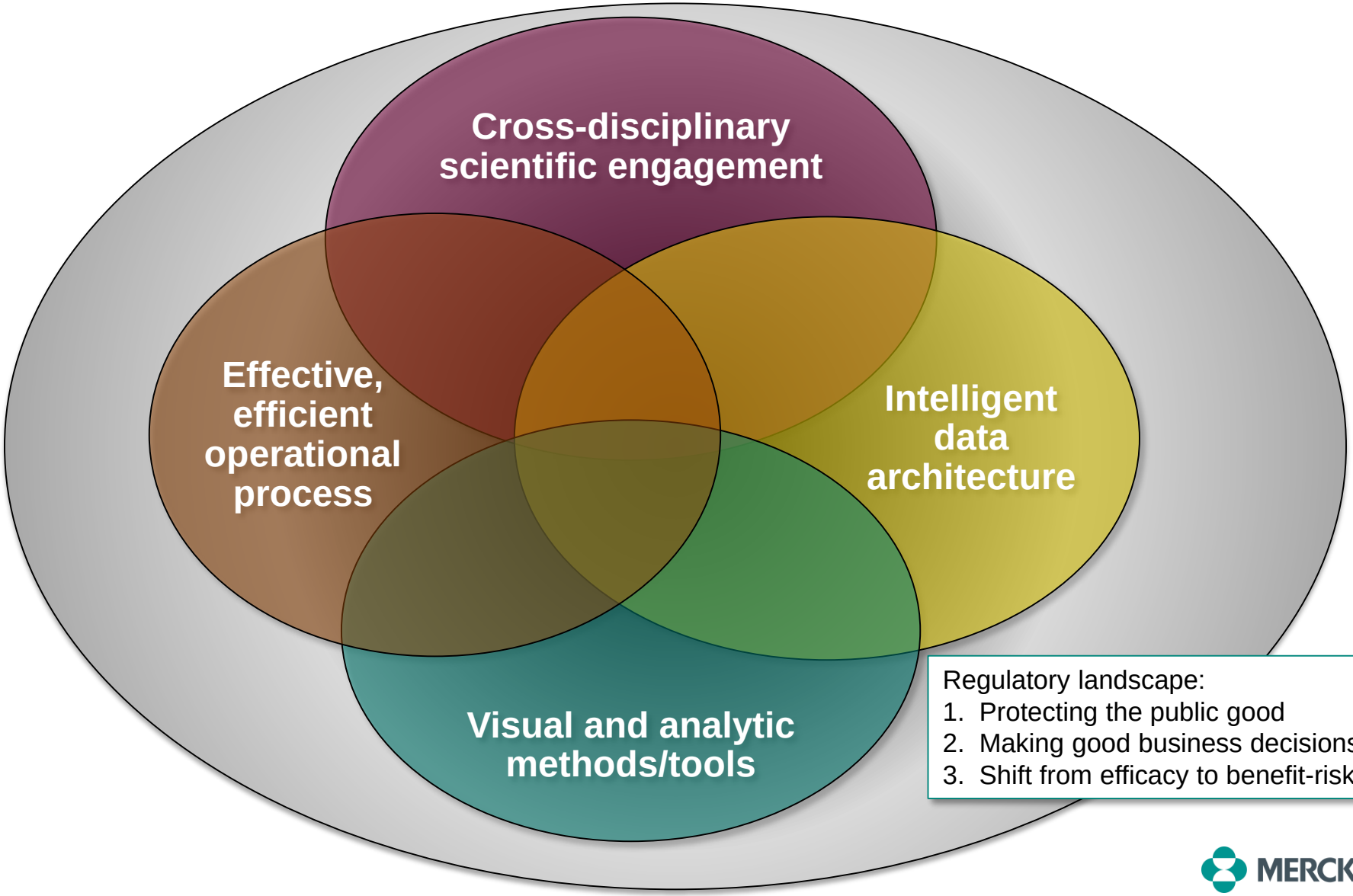
Four Pillars of Safety Statistics



Regulatory landscape:
1. Protecting the public good
2. Making good business decisions
3. Shift from efficacy to benefit-risk

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Thought 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 benefit are not in the patients' best interest
- Statisticians needs to understand about "why" before jumping into "how"

Reference: FDA Draft guidance on Safety Assessment Committees (SAC). Dec 2015.

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

- FDA recommends that sponsors develop a Safety Assessment Committee and a Safety Surveillance Plan as "key elements of a systematic approach to safety surveillance"
- Sponsors should periodically review accumulating safety data
  - Integrate 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"
- Opportunity for sponsors to partner with FDA to focus on important safety issues

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Aggregate Analyses for Comparison of Adverse Event Rates Across Treatment Groups

- 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
    - Considerable uncertainty of predicted rate in patient population
    - Substantial challenges for specifying a predicted rate for all events
  - Sponsors should prespecify, in the Safety Surveillance Plan

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Key Question to Answer

- Have more events occurred than were expected (yes or no)?

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

Collaborative Process and Quantitative Framework: Pilot Study

Evaluation, Not Implementation

- Based on SMT discussion, two AESI were selected for evaluation
  - Rash: Common, but not serious
  - Syncope: Serious, but not common
- Extensive literature search for background rates was conducted

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.

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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: Characterize Background Rates (continued)

Estimates for Background Rates Incorporating Clinical and Epidemiological Considerations

Estimate (%)	Syncope
Lower Background Rate	1.5
Upper Background Rate	3.0
Confidence Level	95
Expected Background Rate	2.0

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Collaborative Process: Characterize Treatment Rates

Estimates for Treatment Rates Incorporating Clinical and Epidemiological Considerations

Estimate (%)	Syncope
Lower Treatment Rate	1.5
Upper Treatment Rate	3.0
Confidence Level	85
Critical Rate	3.0

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 continuous 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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Quantitative Framework: Probability Threshold Boundaries (continued)

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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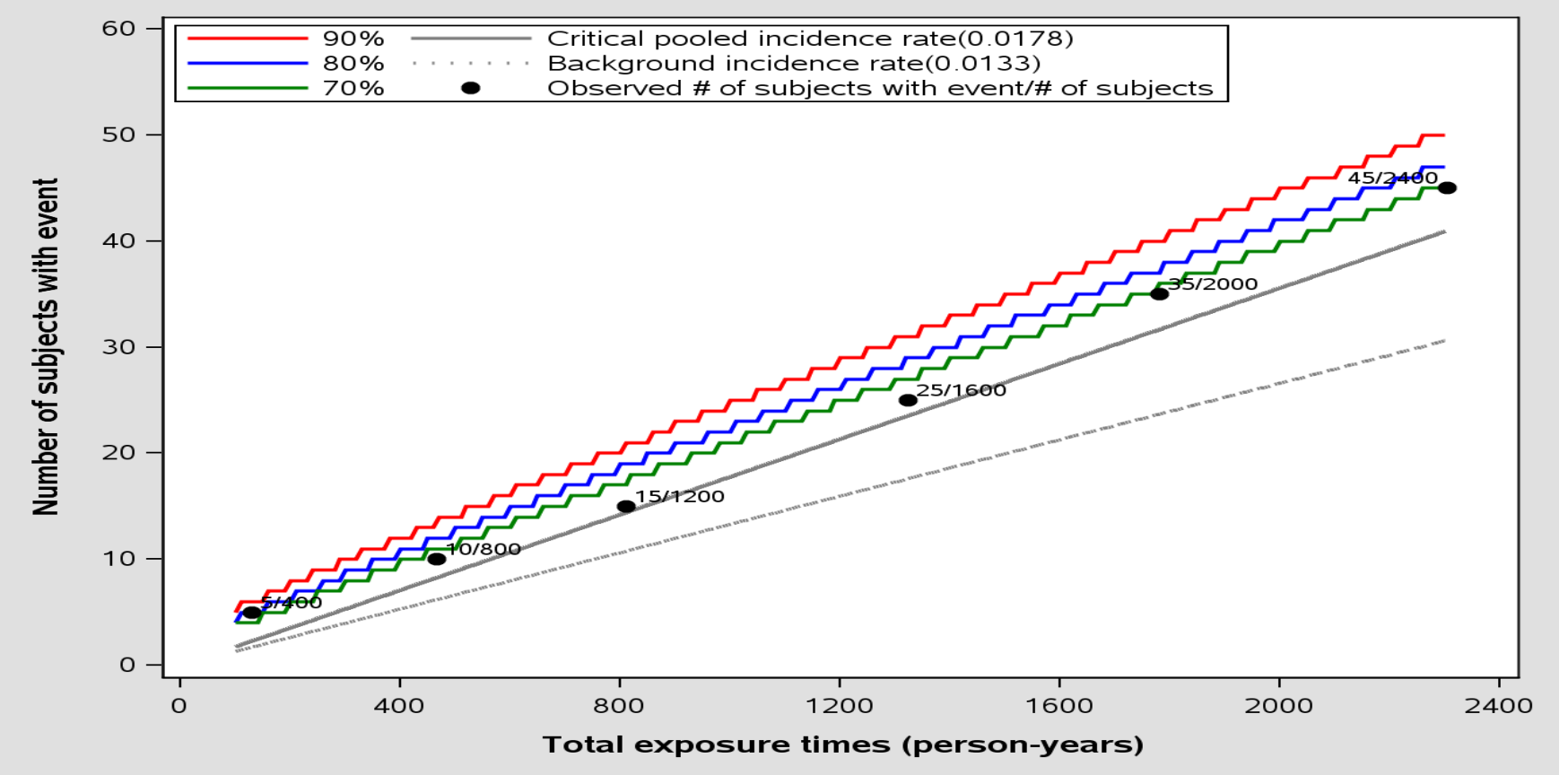
Quantitative Framework: Probability Threshold Boundaries (Mock Data)

Probability Threshold Boundaries for Syncope: Pooled Rate 2.67% (Critical treatment rate 3.0% and background rate 2.0%)



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Summary of Aggregate Safety Monitoring With Ongoing Blinded Studies

An Alternative Approach for Expected Events

- Collaborative process facilitates engagement with clinical safety, clinical development, epidemiology, and statistics
  - Characterize background event rates
  - Tune 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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