ASA Safety Monitoring Working Group Update for the JSM Safety Panel Session

July 2017

Greg Ball, Judy Li and William Wang

Agenda

- The ASA Safety Monitoring Working Group

- Panel Session: Quantitative Safety Monitoring
  - Intelligent Data Architecture
  - Visual and Analytic Methods/Tools
  - Effective, Efficient Operational Processes
  - Cross-disciplinary Scientific Engagement
  - Evolving Regulatory Landscape

ASA 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 thought leaders
- Review statistical methodologies

2016 deliverables

- June: DIA Annual
- August: JSM Biopharm Section, DIA China Quantitative Science Forum
- December: Deming Conference (1/2 day)

2017 deliverables

- May: World Drug Safety Americas
- June: DIA Annual, ICSA Tutorial (full day)
- July: JSM Biopharm Section

BIOPHARMACEUTICAL SECTION

ASA Safety Monitoring Working Group

William Wang, Chair

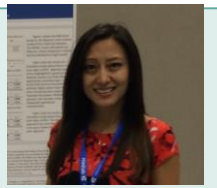
WS1: Industry Practice & Regulation

Greg Ball

Susan Duke

- 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



Judy Li

Melvin Munsaka

- 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)

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

Key Opinion Leaders

- 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)

* Physicians

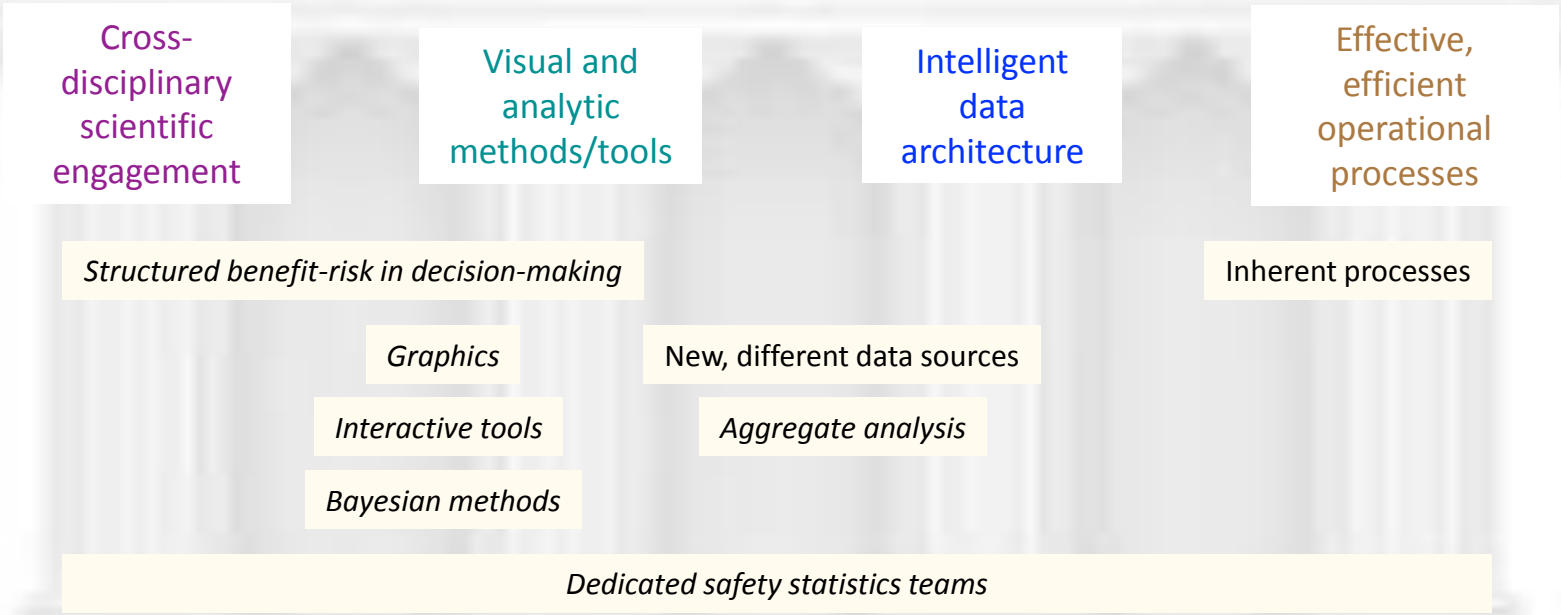
We are indebted to the 18 thought leaders who each spent at least an hour with us discussing their views on quantitative assessment of safety monitoring

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

Summary of Interviews with Thought Leaders: Four Pillars of Safety Statistics

Moving from…

- Individual case review to aggregate analysis and reporting
- Snap-shot submission to continuous aggregate review
- Safety evaluation to benefit-risk assessment



Evolving Regulatory Landscape

Key Trends in Safety Regulation

- Global Trend of ICH (and CIOMS) on Safety Monitoring and Evaluation, Moving from…
  - Individual case review to aggregate analysis and reporting
  - Snap-shot submission to continuous aggregate review
  - 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.

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

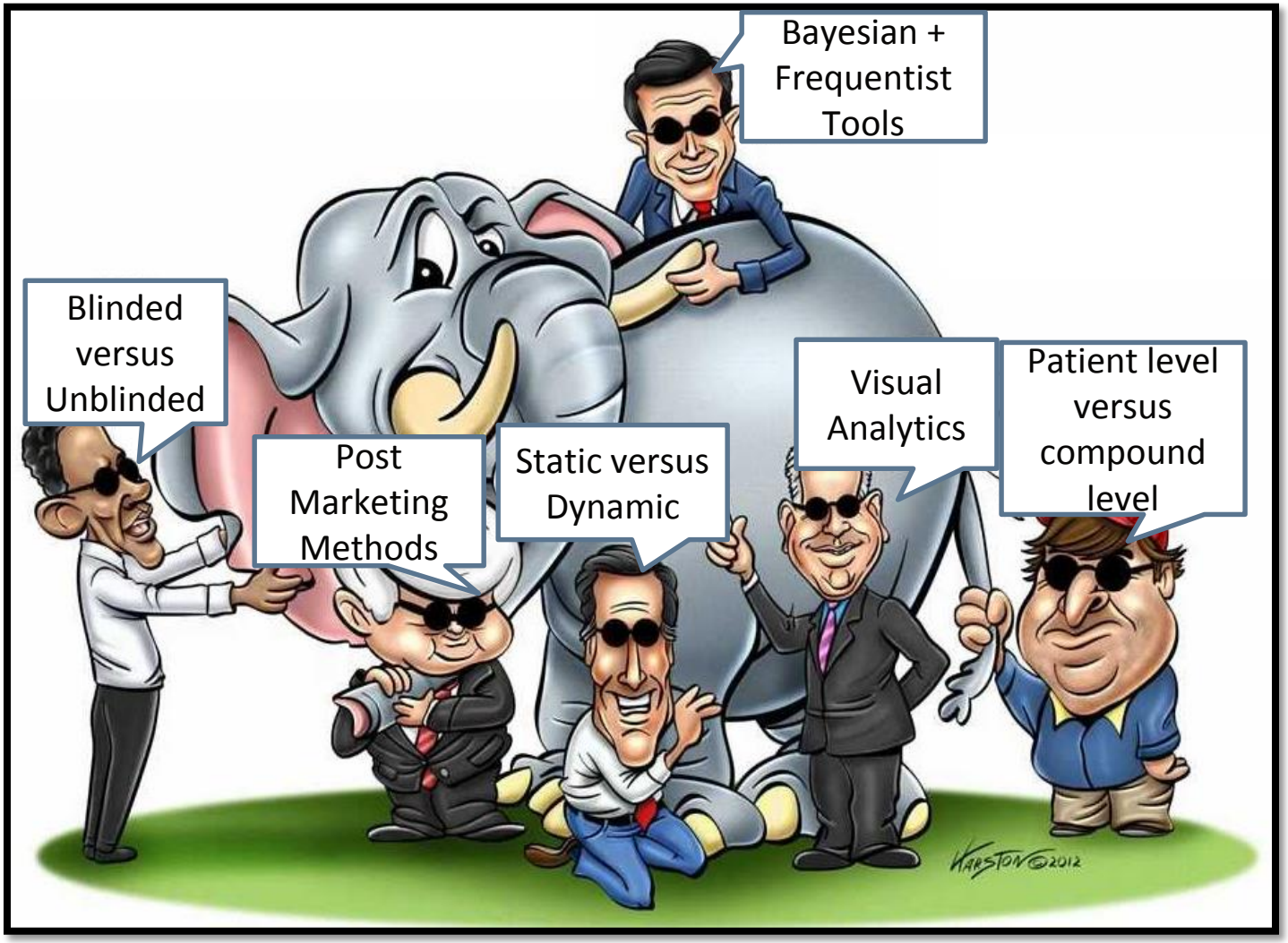
2017 Deep Dive Deliverable: ASAP-Driven Cross-Disciplinary Process

- How to create and maintain the ASAP
- Linkage to other processes
  - Both as input and as output
- Linkage to other regulatory documents and deliverables
- Linkage to benefit-risk process
  - Early planning: value tree, CTD, PBRER

2017 Deep Dive Deliverable: Key Components of the ASAP

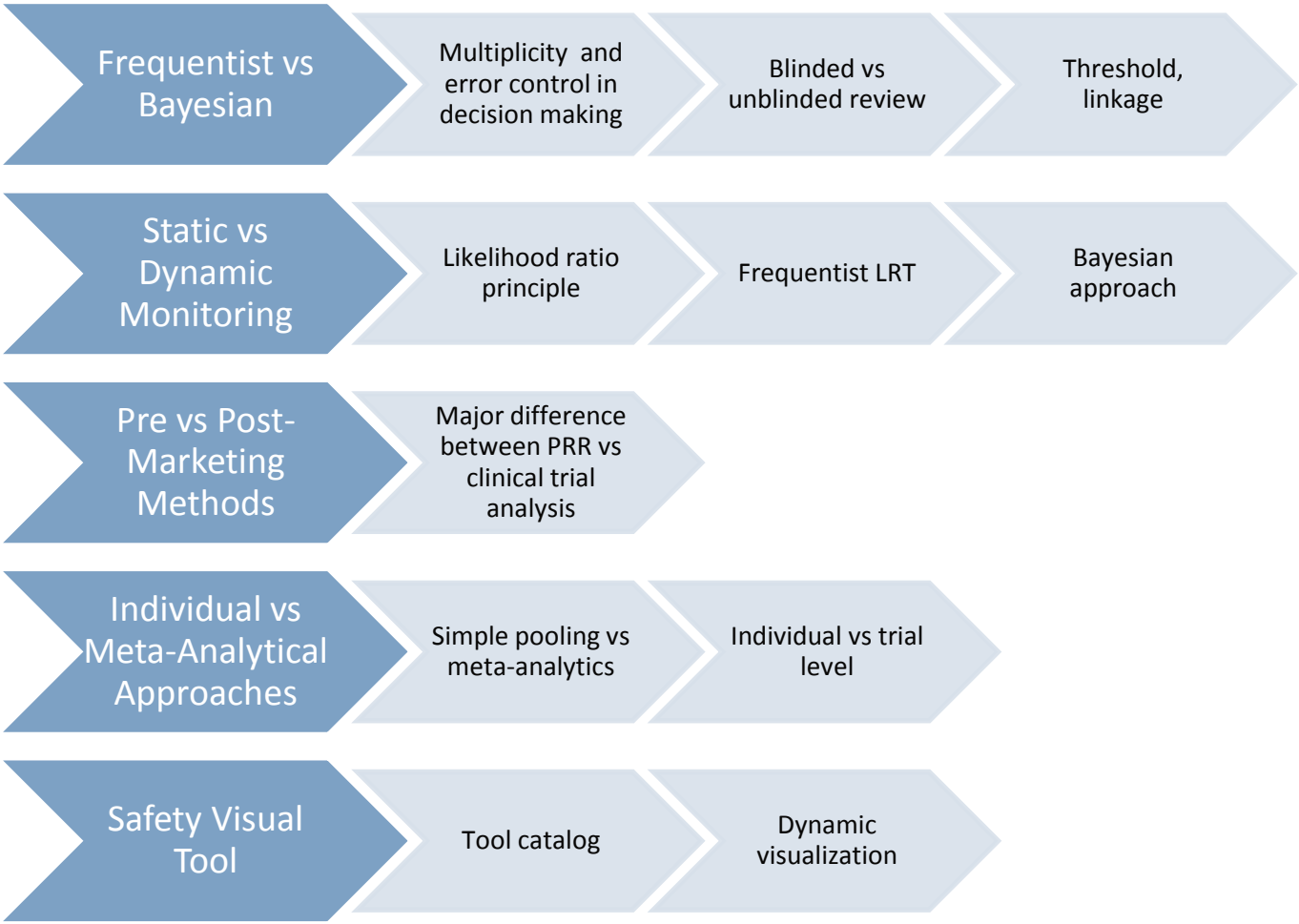
1. Safety endpoint characterization
2. Consistent collection of safety data
3. Ongoing aggregate safety evaluation
4. Preparation for regulatory deliverables

Looking at Safety Monitoring Methods: Elephant Metaphor

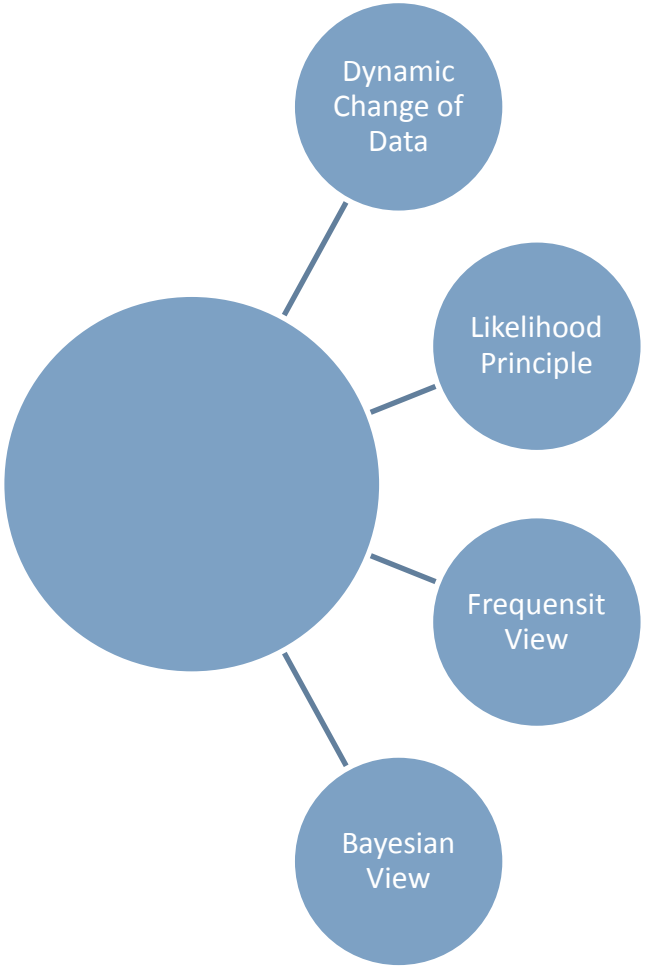


Adapted from: https://www.youtube.com/watch?v=ygT-UwgEaSo

Key Methodology Deep Dives



From Static to Dynamic Safety Monitoring

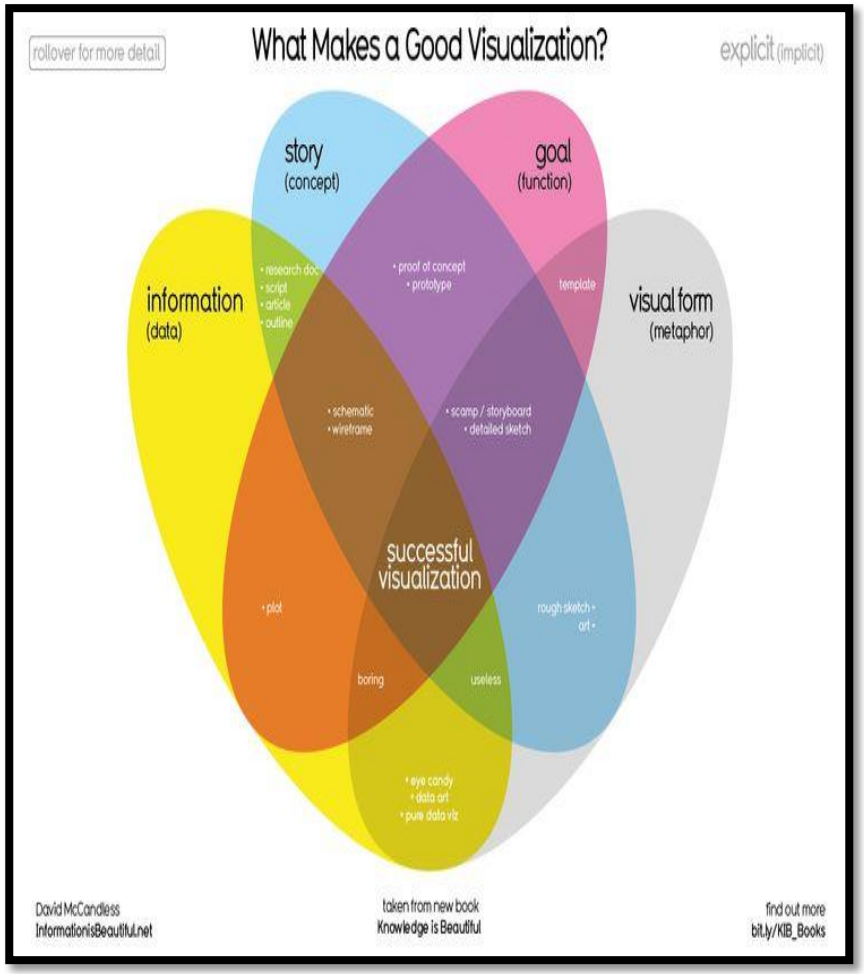


Safety Visualization: Static to Interactive

- The safety question and graph type will dictate the right tool to use in safety monitoring (Duke et al, 2015)
  - Static versus interactive and/or dynamic visualization
  - Drill down to patient level data
  - Graph types most effective for SMR question

- There are many tools available that can be used to aid in visual analytics in safety monitoring. Examples:
  - R, R Shiny
  - Splus/Spotfire
  - SAS, JMP, JMP Clinical
  - Tableau
  - J-Review

- Develop a catalog of question-graphics-tool selection



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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

Agenda

- The ASA Safety Monitoring Working Group

- Panel Session: Quantitative Safety Monitoring
  - Intelligent Data Architecture
  - Visual and Analytic Methods/Tools
  - Effective, Efficient Operational Processes
  - Cross-disciplinary Scientific Engagement
  - Evolving Regulatory Landscape

Panel Session: Quantitative Safety Monitoring

- Organizers/Chairs:
  - Greg Ball: Principal Statistician, Merck Research Labs
  - Judy Li: Associate Director, Regeneron Pharmaceuticals
- Panelists:
  - Frank Rockhold: Professor of Biostatistics, Duke University
  - Ana Szarfman: Medical Officer, CDER, FDA
  - Ram Tiwari: Division Director, CDRH/OSB, FDA
  - William Wang: Executive Director, Merck Research Labs
  - Janet Wittes: President, Statistics Collaborative

Intelligent Data Architecture

1. Dr Wittes: What should we do in safety data design, collection and analysis in order to monitor drug safety more efficiently and effectively?
2. Dr Rockhold: How should we enhance the pre-thinking of safety data collection and integration from different sources? What are the opportunities and challenges?

Visual and Analytic Methods/Tools

3. Dr Wang: What do you see as the value of Bayesian methodology and/or machine learning in ongoing aggregate safety evaluations?
4. Dr Rockhold: 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?

Effective, Efficient Operational Processes

5. Dr Wittes: Conditional on having a DMC, what could a DMC do and what could its role be for safety monitoring and IND safety reporting? If you don't have a DMC, what could you do? In particular, how do you maintain the integrity of the data?

Cross-disciplinary Scientific Engagement

6. Dr Wang: How can the PSAP be used, not only as a statistical planning document, but also as a dynamic tool to engage multi-disciplinary safety management teams in safety monitoring and scientific evaluation of safety data? How can statisticians be an integral part of the conversation?
7. Dr Rockhold: How can the PSAP better enable and align with overall benefit-risk assessment?

Evolving Regulatory Landscape

8. Dr Wittes: ICH E2A amendment on SAE reporting: Should E2A cover aggregate SAE reporting?
9. Dr Wang: Safety endpoint collection (ICH E19): Are we collecting too much or not enough?

Backup Questions

A. Intelligent Data Architecture: What pathways are there to take advantage of recent developments in data transparency for developing historical comparator databases?

B. Visual and Analytic Methods/Tools: How does the emerging safety profile characterized by the multi-disciplinary safety management teams using interactive safety monitoring tools align with Bayesian blinded and unblinded review? How does it align with DMC and/or SAC review? Can dynamic analyses ever be confirmatory, or should they always be exploratory?

Backup Questions

C. Effective, Efficient Operational Processes: How can we leverage the scientific expertise and medical judgment of multi-disciplinary safety management teams for aggregate IND safety reporting?

D. Cross-disciplinary Scientific Engagement: The IND safety reporting final rule embraces CIOMS VI. The PhRMA SPERT team has advanced the ideas of CIOMS VI to include the PSAP. How does the PSAP fit into a systematic approach for evaluating the accumulating safety data? How do the SSP and PSAP fit together?

Backup Questions

E. Evolving Regulatory Landscape: The FDA goes beyond the ICH technical requirements for safety monitoring during clinical development (with the well-established ISS and the more recent IND safety reporting final rule). What can be done to better harmonize safety monitoring across regions?