Safety Analyses: The Cinderella of Biostatistics?

Industry Perspective

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Topics

- Current state
- Anticipated need for change and current initiatives
- Considerations for managing change
- Statistics vs. Decision Making

Asymmetry between Analyses of Efficacy and Safety

- The broad aim of the process of clinical development of a new drug is to find out whether there is a dose range and schedule at which the drug can be shown to be **simultaneously safe and effective**, to the extent that the risk-benefit relationship is acceptable.
- In most trials the **safety implications** are best addressed by applying **descriptive statistics** of the safety data, **supplemented by confidence intervals** wherever this aids interpretation.
- **Hypothesis tests are sometimes useful** either as an aid to evaluating a specific difference of interest, or as a “flagging” device applied to a large number of safety variables to **highlight differences worth further attention**.

Statistical Principles for Clinical Trials (ICH E9)

Status Quo

- Historically**, planning for safety** assessment has **not always been done** in a defined, coordinated fashion program-wide
- As individual trials complete, data may be looked at in isolation
- Data from multiple studies are typically **summarized** in a Summary of Clinical Safety **just prior to submission** of the new product application
- Concept: **Opportunity** to respond to evolving safety/tolerability profile may be **missed by waiting**
- Could result in an **avoidable gap in knowledge** of the safety profile at time of submission

Crowe et al., 2009

Overlapping Stages of Safety

- Safety monitoring during clinical development
  - Focus: Case reviews and quantitative methods for **signal detection**
- Safety specification at submission (and other key milestones)
  - Focus: Characterization of safety profile (**quantification**)
- Post-marketing safety surveillance
  - Individual Case Safety Reports (ICSRs)
  - Safety Studies
  - Registries
  - Pharmaco-epidemiological studies

Not all Safety Endpoints / Risks are Equal

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed.

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest.

Safety concern

An important identified risk, important potential risk or missing information.

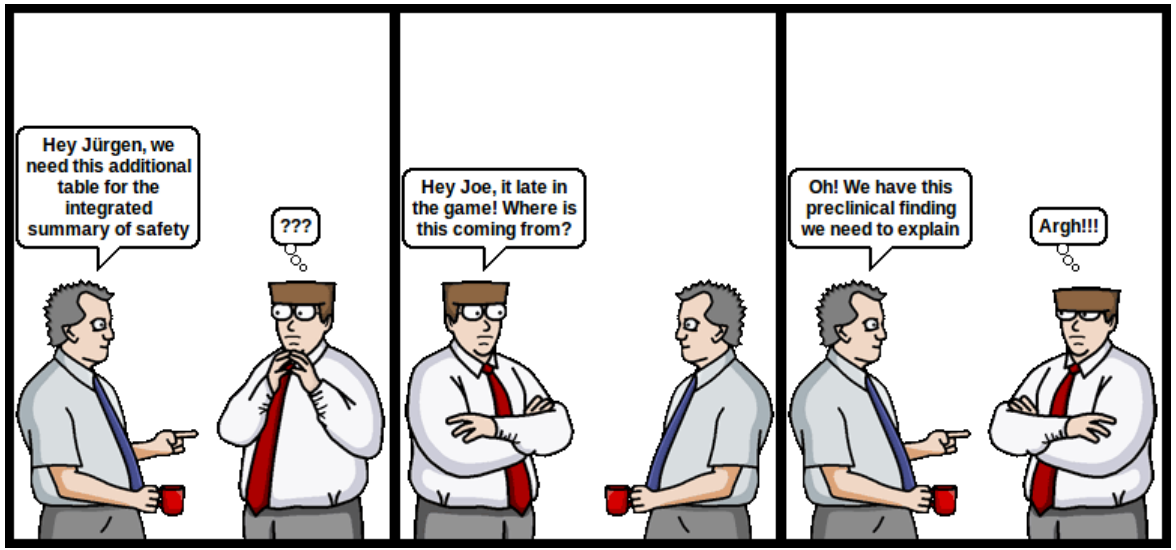
Important identified risk and important potential risk

Limited number of endpoints!

An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.

GVP – Module V

Does this sound familiar?



Proactive Approach

- Look early, look at regular intervals
- Develop initial objectives (related to, e.g., risk quantification, hypothesis testing, signal detection)
- Consider data standardization issues early, to facilitate ongoing integration and interpretation
- Adjust objectives as new safety information emerges

Relevant Initiatives

- CIOMS VI, 2005: Management of Safety Information from Clinical Trials
- PhRMA, 2009: Safety Planning, Evaluation and Reporting Team (SPERT)
- ASA-DIA Interdisciplinary Safety Evaluation Scientific Working Group, since 2015

ASA-DIA Interdisciplinary Safety Evaluation Scientific Working Group

- Offspring of the ASA Biopharm Safety Monitoring Working Group (since 2015)
- Co-sponsored by ASA and DIA since 2017
- Goal is to empower cross-regional, interdisciplinary Safety Management Teams (SMTs) to discover and promote practical quantitative solutions for safety monitoring during clinical development and for safety planning throughout the lifecycle

Partnership Between Clinical and Statistical Scientists

Workstreams

Workstream	Sponsored by
1. Safety Evaluation and Best Practice a. Regulations, Framework and Aggregate Safety Assessment Plan (ASAP)	ASA Biopharm / DIA Interdisciplinary Safety Evaluation SWG
b. Safety Monitoring, Evaluation and Identification of Risk via Interactive Safety Graphics	
c. Communication, Training and Fan-Club	
2. Safety Methods	ASA Biopharm Safety Monitoring WG
3. Integrating and Bridging RCT and RWE for Safety Decision Making	

Benefit-Risk Assessment Plan (BRAP) Taskforce

- As part of the American Statistical Association (ASA) Safety Evaluation Working Group, the **Benefit-Risk Assessment Plan (BRAP) Taskforce** was created at the beginning of 2019 to supplement the ASAP with a BRAP that will incorporate planning for benefit-risk assessments

- The BRAP Taskforce intends to connect the safety and benefit-risk planning activities together for high-level considerations for regulatory interactions and internal planning

Potential Elements of a BRAP

- A document or template incorporating points-to-consider, checklists, and process flow charts for high-level planning purposes
- Defines a process of benefit-risk assessment planning throughout the life cycle of a medical product, which is iterative as needed
- Modularized so that users can pick and choose parts of the BRAP to utilize
- Serves to facilitate interactions between regulatory agencies and industry sponsors at key points in the development and approval process
- Flexible to incorporate special considerations on areas such as patient preference, patient experience of side effects/tolerability, COA/PRO data, REMS, Real World Data, …
- Facilitates early planning and global regulatory considerations

Trends Identified in the Regulatory Landscape

- Globally, there is a trend to use structured frameworks for qualitative evaluation of benefit-risk in regulatory decision-making for medical product approvals
- For some medical devices and diagnostics, the benefits and risks may be more clearly defined; some quantitative decision-making
- Regulatory agency viewpoints are evolving, and trends show consideration of real world data and patient preference information as supplementary information in decision-making
- Regulated industry may integrate global regulatory agencies' benefit-risk framework considerations in their development lifecycle, but there are challenges to alignment

ASAP: Key Value Propositions

- Puts safety issues that arise during clinical development in perspective:
  - Compare to background rates with help of quantitative scientists
  - Redefine target patients for optimal risk-benefit
  - Provide framework for exploring, adjustment and decision making
  - Better characterization of safety profile vs ISS at NDA
- Transparently define and track AESIs
  - Ensure proper data collection of all AESIs
- Provide operational smoothness
  - Consistent, up-front analysis definitions
  - Provides operational details of review of cumulative safety data
- Pave way for future activities at submission and into post-marketing stage
- Document and archive continuous efforts along the developmental journey

What is Needed for a Successful Change

- Readiness of internal environment
- Statisticians with safety mindset
- *"Goal is to empower cross-regional, interdisciplinary Safety Management Teams (SMTs) to discover and promote practical quantitative solutions for safety monitoring during clinical development and for safety planning throughout the lifecycle"*
  (ASA-DIA Working Group)

Is there a Role for Statisticians as Decision Makers?

- Scenario 1
  - Team presents data on a safety observation regarding risk of *X:*
    - Plausible Mode of Action
    - Dose trend in pre-clinical data
    - Dose trend in Phase I study (related lab parameter)
    - Dose trend for event *X* in Phase II study
    - None of the above was statistically significant, however, studies were not powered for this question
  - Decision?
- Scenario 2
  - Risk *Y* is elevated to 'important identified risk'
  - Suggested action: 'further monitor'
  - Recommended activities?
- Scenario 3
  - Important identified risk *Z* with mounting number of deaths in the post-marketing phase
  - Role of statistician on safety board?

Final word

Years ago a statistician might have claimed that statistics deals with the processing of data... to-days statistician will be more likely to say that statistics is concerned with decision making in the face of uncertainty.

Herman Chernoff