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# Aggregate Safety Analysis for Causality Assessment of SAEs

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**Presented at BASS, October 2019. Version 10/17/2019**

# ASA Safety Working Group (Q4 2017 … )

Co-chairs: Judy Li (Regeneron), William Wang (Merck)

**Mission: Empower the biostatistics community and interdisciplinary safety management partnerships to better enable qualitative and quantitative safety evaluation throughout drug development life cycle**

| | |
|---|---|
| WS1: Interdisciplinary Safety Evaluation (Joint with DIA new in 2019) | • Task Force 1a: Regulatory context, industry survey, planning framework<br>• Review paper on the global regulatory landscape and underlying quantitative principles<br>• Task Force on Aggregate Safety Assessment Planning (ASAP) Points to Consider<br>• Task Force on Interactive Safety Graphics<br>• Task Force on Benefit Risk Assessment Planning (BRAP) |
| WS2: Safety Monitoring Statistical Methodology | • Bayesian vs Frequentist Approach<br>• Blinded vs Unblinded Analyses<br>• Static and dynamic methods<br>• Visual analytics<br>• Meta-analysis<br>• Safety Enabled Benefit Risk Evaluation (new task force) |
| WS3: Integration and Bridging the RWE and RCT for Safety Decision Making | • Statistical and Design Consideration for RWE<br>• Statistical and Design Consideration for RCT<br>• Advanced Analytical and Machine Learning Methodologies for Qualitative or Quantitative Integration of the Multi-Source Safety Data |

**Advisors**

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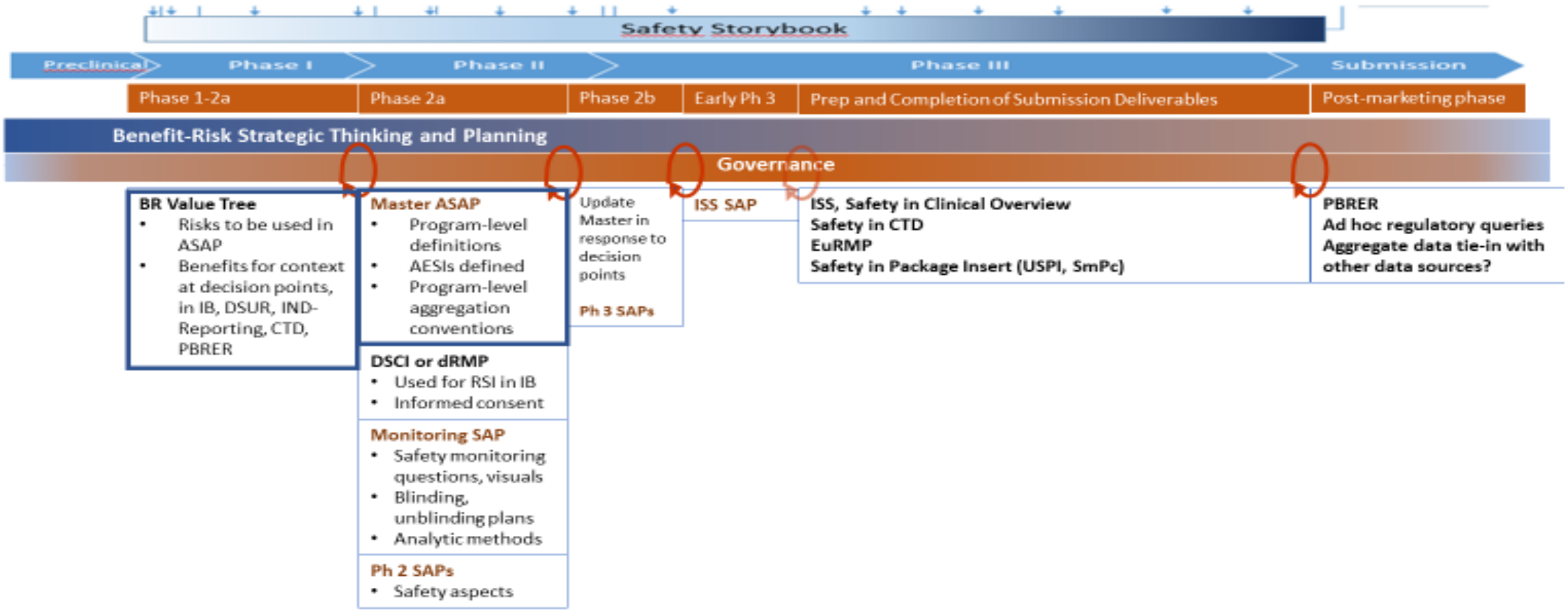
# Pre-Marketing Safety Surveillance

- Why?
- What is required?

# Drug Development has become as complex as putting a man on the moon!

….. much so because of Safety Regulations



# Influencers of the Global Regulatory Landscape

CIOMS

CIOMS

ICH

harmonisation for better health



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# CIOMS is one important driver of safety regulations

- “Council for International Organizations of Medical Sciences”
- Founded in 1949 by WHO and UNESCO
- NGO “Think Tank” about clinical trials.
- Mission:

“*to advance public health through guidance on health research including ethics, medical product development and safety*.”

Source: https://cioms.ch/

# CIOMS Working Group Reports

| Number: Issuing Year | Title | Regulatory Alignment |
|---|---|---|
| I: 1987 | International Reporting of Adverse Drug Reactions | ICH E2A |
| II: 1993 | International Reporting of Periodic Drug-Safety Update Summaries | ICH E2C |
| III: 1995 | Guidelines for Preparing Core Clinical-Safety Information on Drugs | |
| IV: 1998 | Benefit-Risk Balance for Marketed Drugs | ICH E2C (R2) |
| V: 2001 | Current Challenges in Pharmacovigilance | |
| VI: 2005 | **Management of Safety Information From Clinical Trials** | FDA IND Safety Reporting Final Rule |
| VII: 2006 | Development Safety Update Reports (DSUR) | ICH E2F |
| I: 1987 | Practical Aspects of Signal Detection in Pharmacovigilance | EMA GVP Module IX |
| IX: 2014 | Practical Approaches to Risk Minimization for Medicinal Products | |
| X: 2016 | Evidence Synthesis and Meta-Analysis for Drug Safety | |

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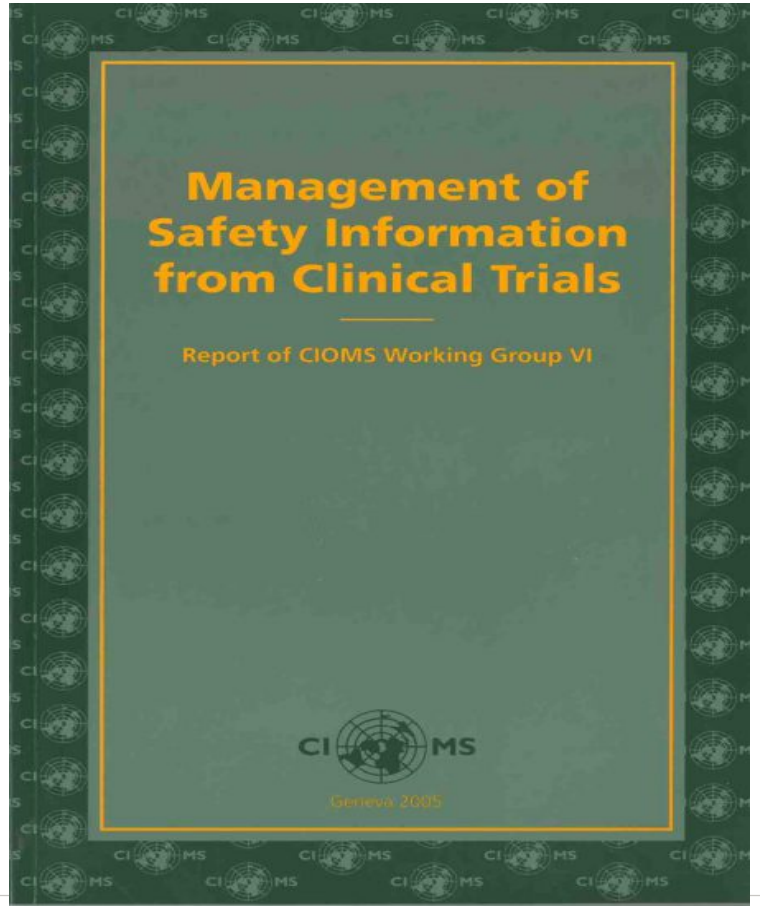
# Of particular interest, CIOMS VI is concerned with safety monitoring in Clinical Trials



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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 “pre” and “post” approval activities to understand and manage risk

- Paradigm shift from management of post-marketing safety information and spontaneous reports to the management of clinical trial information

- Discusses the importance of having a systematic approach to managing risk during development

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

Ongoing aggregate evaluation of safety during clinical development serves several important purposes

- To protect human subjects participating in clinical trials
- To gain an understanding of the safety profile of the drug as early in its development as possible
  - Terminate a program early when new risks are felt to be unacceptable
  - Avoid premature termination of a program that shows promise of value even in the face of certain risks
  - Introduce proper risk minimization actions

# ICH – International Conference of Harmonization


- Formed in 1990 to standardize global drug registration and approval process
- Original members: USA, EU, Japan
- Recent new members: Switzerland, Brazil, China, Singapore, Korea

# ICH Guidances on SAFETY

| Code: Issuing Date | Title |
|---|---|
| **E1: October 1994** | The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions |
| **E2A: October 1994** | Clinical Safety Data Management: Definitions and Standards for Expedited Reporting |
| **E2B (R3): February 2014** | Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide – Data Elements and Message Specification |
| **E2C: November 1996** | Periodic Safety Update Report (PSUR) |
| **E2C (R2): December 2012** | Periodic Benefit-Risk Evaluation Report (PBRER) |
| **E2D: November 2003** | Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting |
| **E2E: November 2004** | Pharmacovigilance Planning |
| **E2F: August 2010** | Development Safety Update Report (DSUR) |
| **M4E: September 2002** | The Common Technical Document for the Registration of Pharmaceuticals for Human Use |
| **M4E (R2): June 2016** | Revision of M4E Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH |

# ICH guidance on SAE reporting in Clinical Trials

- AEs need to be reported if they are
  - Serious
  - Unexpected
  - Possibly Related
- SUSAR = Suspected Unexpected Serious Adverse Reaction
- “unexpected” = not consistent with Reference Safety Information (IB or drug label)
- “possibly related” = EU: As *judged* by sponsor or investigator.
  - FDA: Sponsor has some empirical evidence (more about that later)

# FDA – Key guidances related to safety in clinical trials

| Issuing Date | Title |
|---|---|
| July 1988 | Format and Content of the Clinical and Statistical Sections of an Application |
| February 2005 | Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review |
| March 2005 | Pre-Marketing Risk Assessment |
| September 2010 | **FDA IND Safety Reporting Final Rule** |
| December 2012 | Guidance: Safety Reporting Requirements for INDs and BA/BE Studies |
| December 2015 | Draft Guidance: Safety Assessment for IND Safety Reporting |

*Original Research*

DIA

Therapeutic Innovation
& Regulatory Science
1-15

DOI: 10.1177/2168479019841314
tirs.sagepub.com

# Global Regulatory Landscape for Aggregate Safety Assessments: Recent Developments and Future Directions

**Greg Ball, PhD[1], Raffael Kurek, MD[2], Barbara A. Hendrickson, MD[3], James Buchanan, PharmD[4], William W. Wang, PhD[5], Susan P. Duke, MS[6], Amit Bhattacharyya, PhD[7], Mengchun Li, MD[8], Dennis O'Brien, MD[9], Judith Weigel, MS[10], Wenquan Wang, PhD[11], Qi Jiang PhD[12], Faiz Ahmad, MS[13], Jonathan H. Seltzer, MD[14], Esteban Herrero-Martinez, PhD[15], and Lothar Tremmel, PhD[16]**

# FDA's 2010 Final Rule on IND Safety Reporting

March 2003: Proposed rule published

Sept 2010: Final Rule published, plus draft guidance

Dec 2012: Final Guidance published

Dec 2015: Follow-on final guidance published

# The Spirit of the Rule

**The revision of the long standing IND Safety Reporting Rule was intended to address unnecessary reporting of large number adverse events that were:**

- Probable manifestations of the underlying disease
- Adverse events common in the study population independent of drug exposure (e.g., heart attacks or strokes in older people)
- Study endpoints

From Temple's presentation at March 8 2018 Duke Margolis workshop on IND Safety Reporting

# Potential Serious Risks that Require IND Safety Reporting

## 3 easy and 1 hard

### Individual Events

- **Uncommon and strongly associated with drug exposure (e.g., Stevens Johnson Syndrome)** (312.32(c)(1)(i)(A))
- **Not commonly associated with drug exposure but uncommon in population (e.g., tendon rupture)** (312.32(c)(1)(i)(B))

### Aggregate Analyses

**Events/findings that:**

- **An unexpected adverse event that occurs more frequently in drug treatment group than control** (312.32(c)(1)(i)(C))
- **Suspected adverse events (in the IB) that occur at a clinically important increased rate above that listed in protocol or IB** (312.32(c)(1)(iv))

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From Temple's presentation at March 8 2018 Duke Margolis workshop on IND Safety Reporting

# FDA IND Safety Reporting Final Rule

- Sponsors should have a systematic approach to safety surveillance to comply with IND safety reporting requirements and to improve overall quality of safety reporting
  - ➢ An aggregate analysis of specific events that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group
- Sponsors should periodically review accumulating safety data collected across multiple studies (completed and ongoing), analyze the data in the aggregate, and make a judgment about the likelihood that the drug caused any SAEs [E2]

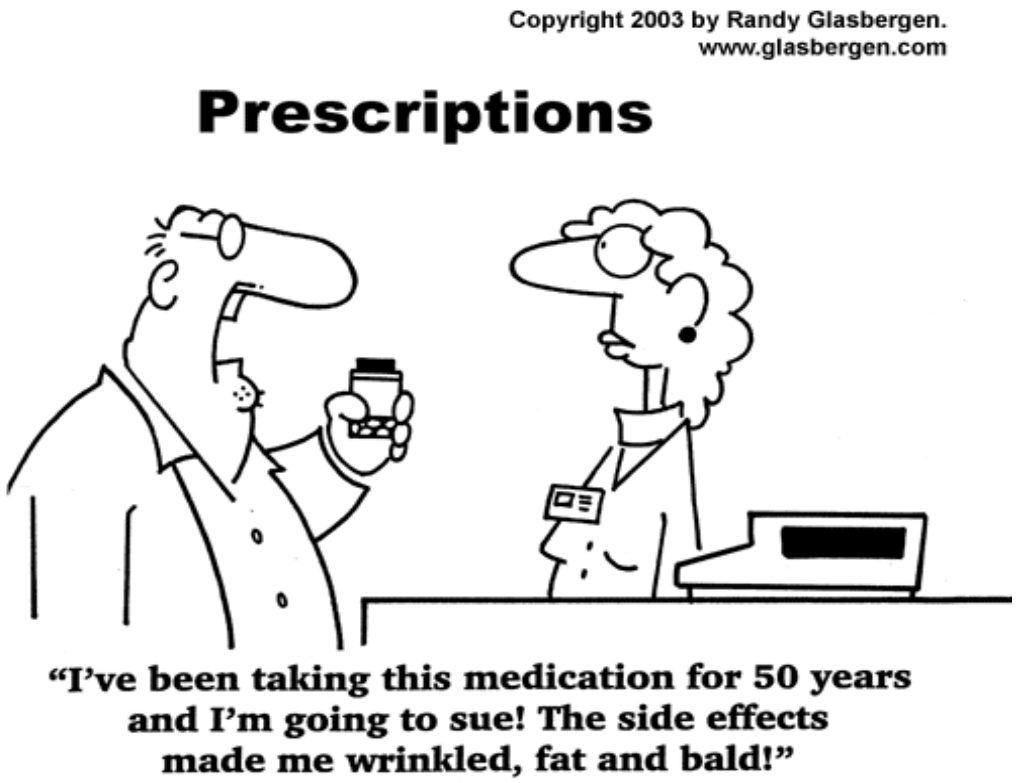
# Aggregate Safety Analysis for Pre-Marketing Safety Surveillance

- What to report and what not to report?

# FDA “Final Rule“: Further Guidance

- 2012 Guidance “Safety Reporting Requirements for INDs and BA/BE studies”
  - “Anticipated events” should not be reported individually even though they are “unexpected”.
    - Only report those events if an aggregate analysis shows increased frequency
  - Blinded analyses could be performed by DMC or independent sponsor safety team
  - BA/BE studies: Report all SAEs.

# Why the concept of “anticipated events” is so important




Expected vs anticipated:

- Expected = Property of the drug
- Anticipated = Property of the population

(Wittes in Duke Margolis 2018 workshop)

# FDA “Final Rule“: Further Guidance

## 2015 Draft Guidance “Safety Assessment for IND Safety Reporting”

- Pushes for unblinded analyses to be done by a “Safety assessment committee” (SAC)
- Perceived as too detailed and heavy handed; under debate

# Aggregate Safety Analysis for Pre-Marketing Safety Surveillance

- Who will decide?

# Who will do the unblinded aggregate Safety Review?

| | PROs | CONs |
|---|---|---|
| SAC | Will typically know data from all trials | Added complexity (yet another firewalled team) |
| DMB | Already in place | Focus on benefit-risk<br><br>Typically review only 1 trial |

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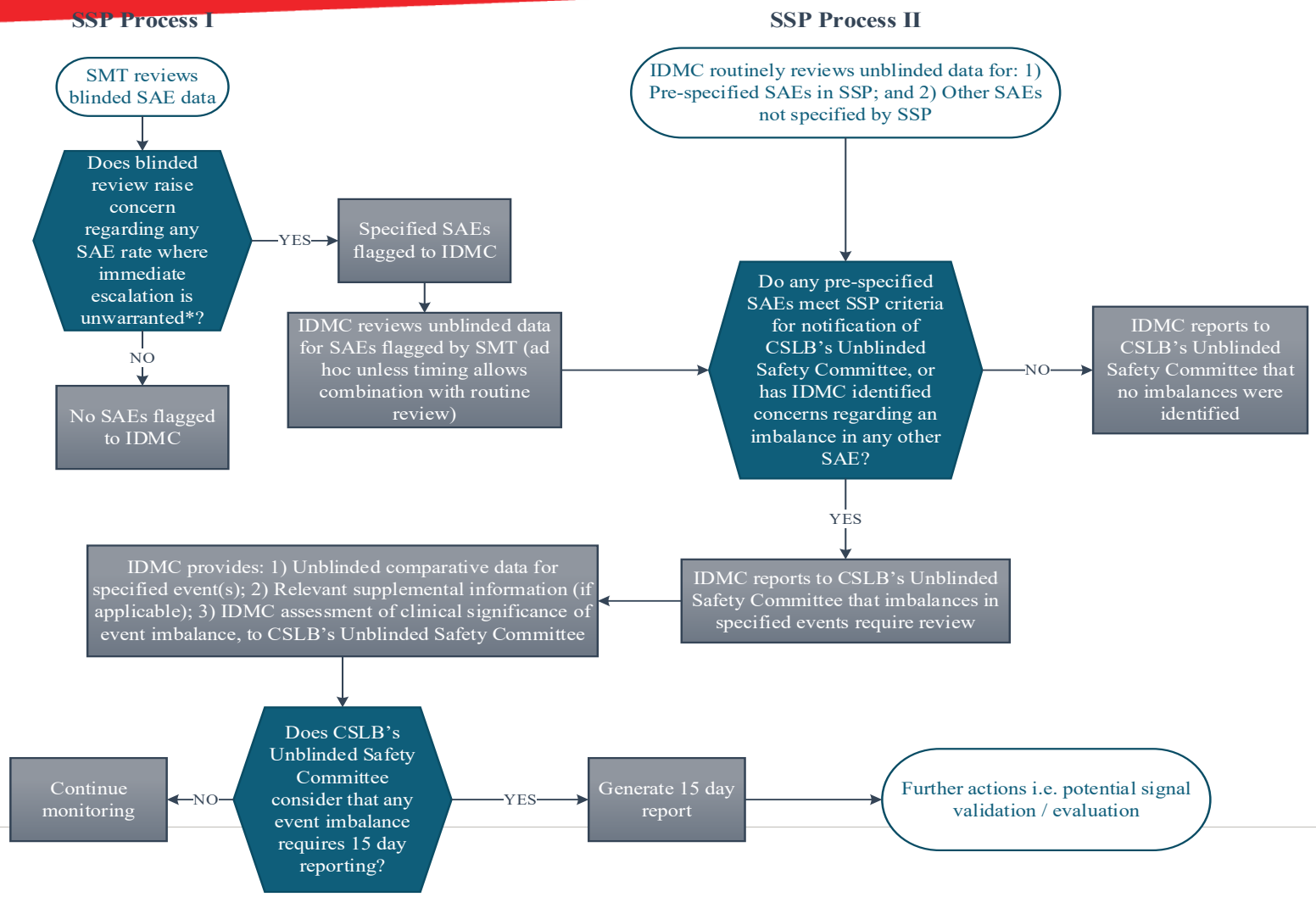
# Case study: One large Cardiovascular Outcomes Trial

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# Aggregate Safety Analysis for Pre-Marketing Safety Surveillance

- How to plan for it up-front, systematically and comprehensively?

# Safety Planning, Evaluation, and Reporting Team (SPERT)

Formed in 2006 by the PhRMA to recommend a standard for safety planning, data collection, evaluation, and reporting.

Heavily influenced  by CIOMS VI

In their key 2009 publication*, recommended:

- Multi-disciplinary Safety Management Teams (SMT), referencing CIOMS VI
- Program Safety Analysis Plan (PSAP)

* Crowe et al: Recommendations for safety planning, data collection, evaluation, and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clinical Trials 2009; 6:430-440.

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# SPERT Recommendations (2009)

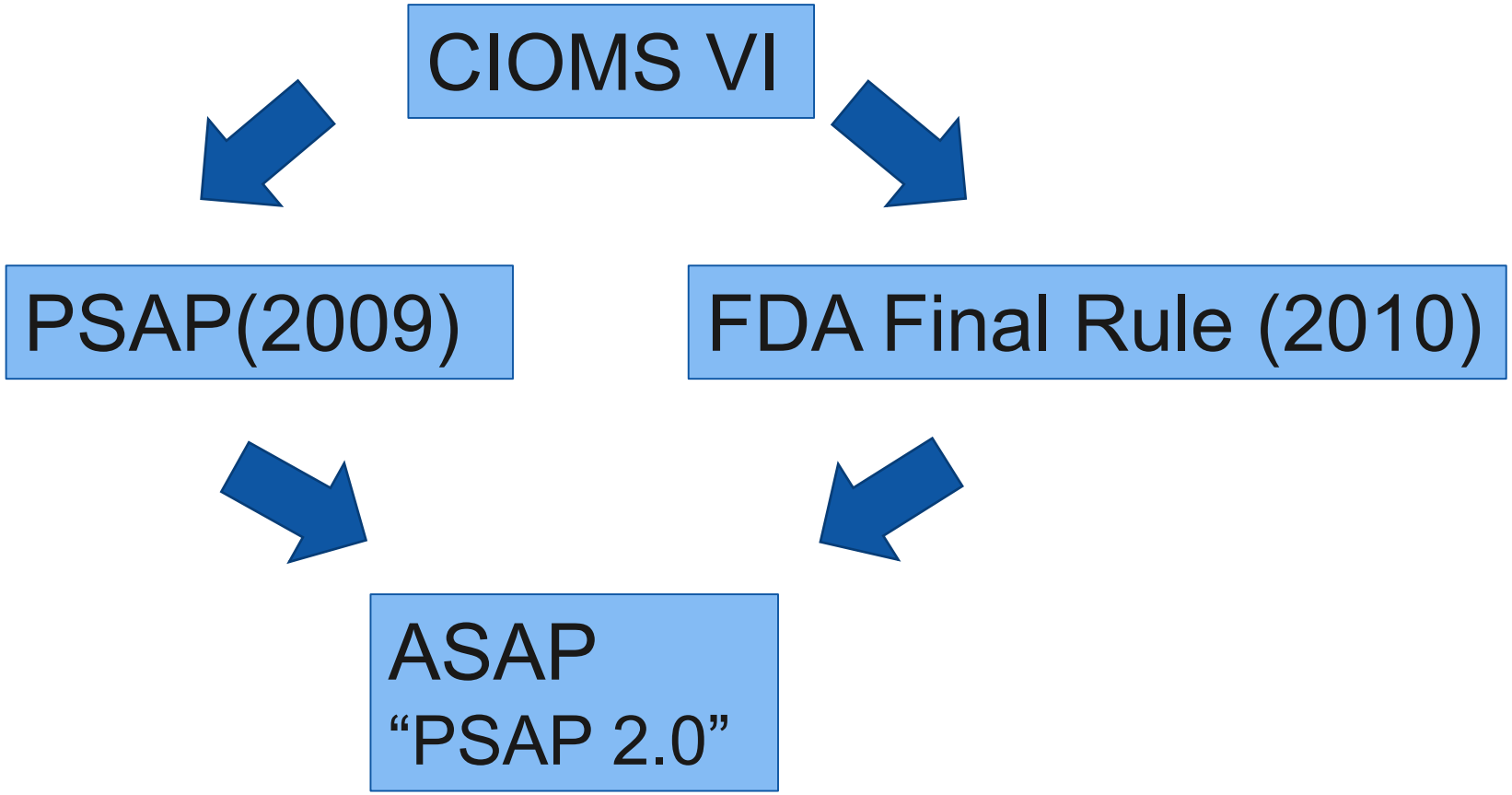
## A proactive approach:

- Create a Program Safety Analysis Plan early in development
- Plan repeated, cumulative meta-analyses of the safety data
- Implement a 3-tier system for signal detection and analysis of adverse events (AEs):
    1. Pre-specified hypothesis testing – AESIs
    2. Signal detection of common events
    3. Descriptive analysis (rare AESIs & others)
- Review aggregated safety data on an ongoing basis throughout the development program, rather than waiting until submission

# Program Safety Analysis Plan (PSAP)

- The 2009 SPERT Publication was important and pre-saged future developments.
- Issued before the FDA Final Rule; focused mainly on cumulative meta-analysis with less emphasis on ongoing trials.
- The publication was more a list of points to consider without giving a detailed document structure.
- Influence was limited; only some large companies took steps towards concrete implementation.

# OUR PROPOSAL: THE ASAP



# ASAP Value Proposition

***Consistency***

***-> Fewer operational wrinkles***

# Standardization of Product Level Statistical Analyses

# ASAP Value Proposition

***Preparedness***

***-> Look for signals via pre-specified databases and methods***

***-> but also provide context for interpreting signals***

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# Executing Aggregate Safety Monitoring and Safety Communications – Ongoing Trials

# Case study 1:
# A signal hits without preparedness

# FEDRATINIB, JAK2 selective inhibitor

- Studied for indication of Myelofibrosis (MF), a rare bone marrow disease
- In the phase III studies JAKARTA I and JAKARTA II, results indicated clinical benefit for the majority of patients not responding to standard therapy.
- However development was discontinued after FDA placed a clinical hold in 2013 due to reported cases of Wernicke's encephalopathy
- These events were not expected based on the MOA; however similar events were not seen with similar molecules, such as Incyte's Jak inhibitor.
- A putative mechanism was identified only *a posteriori*.

# FEDRATINIB (continued)

In 2017, a  re-examination of the data from 670 subjects across 5 trials revealed the following *:

- Not all of the 8 / 670 potential cases withstood closer diagnostic scrutiny; only 3-5 cases were confirmed

- The background rate of this event is elevated in the disease population

- The observed incidence rate was below the background rate.

- For the 5 potential WE cases:
  - 1 subject had malnutrition related to protracted nausea/vomiting
  - 2 subjects recovered without a fedratinib dose interruption.
  - Remaining 2 subject had an unclear diagnosis with 2 of 3 experts believing the data were either inconclusive or not supportive of WE (with one patients not on fedratinib at time of symptoms).

Harrison *, CN et al. Blood 2017 130:4197

# ASAP Emphasizes the Importance of Interdisciplinary Collaboration

Maximizes use of the team's expertise
Minimizes disconnected decision making

- Statistics / Statistical programming
- Pharmacovigilance / Patient Safety
- Clinical development
- Epidemiology

- Others as needed: e.g. Regulatory Affairs, Pharmacokinetics, Preclinical

# Proposed ASAP Structure

**(1) ASAP Value Proposition and Governance**

**(2) Current Safety Profile:**
"Knowns" and "Known unknowns"; AESIs

**(3) Data Analysis Rules**

**(4) Gap Analysis**

**(5) OASE (Ongoing Aggregate Safety Evaluation)**

**(6) Communication of safety data**

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# Section 2: Current Safety Profile (example)

| Area of Safety Interest | Basis for Inclusion | Identification of Events* | Use of event adjudication ^ | Special data collection (form or study) | Relevant restrictions# |
|---|---|---|---|---|---|
| **Identified Risks** | | | | | |
| **Thrombocytopenia** | Decreased Plt count with product dosing<br>In clinical studies | Haematopoietic thrombocytopenia SMQ (Narrow) AEs<br>Any Plt counts reported as <75,000/ml | N/A | Supplemental event CRF (all studies):<br>• AEs identified by SMQ<br>• Occurrence of Plt ct <75,000/μl | Study exclusion criteria:<br>Plt ct <75,000/μl |
| **Potential Risks** | | | | | |
| **A. Serum Sickness** | Reported in products of same class | Hypersensitivity SMQ (Narrow) | External Adjudication (see Charter for details) | Supplemental event CRF (all studies) | Study exclusion criteria: Prior h/o serum sickness |
| **Other Areas of Interest** | | | | | |
| **A. Major Adverse CV Events (MACE)** | Increased risk in study X population | Adjudicated<br>CV death<br>Nonfatal MI<br>Nonfatal stroke | External Adjudication (see Charter for details) | Supplemental event CRF for CV events (indication X only) | Study exclusion criteria: No h/o MI or stroke in previous 3 mo. |

*e.g. PT, specified PT grouping, HLT, SMQ Broad/Narrow. Laboratory, Vital sign or ECG Value outliers

^ e.g. CV Endpoints Committee or Hepatic Event Adjudication Committee

# e.g. protocol exclusion criteria limiting data on certain patient populations

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# Section 3: Data Analysis Rules: Key content

**(A) Computational rules**

- definition of treatment emergent Aes
- Exposure adjusted incidence rates
- rules for clinically significant outliers
- event severity grading scales

**(B) Specifications of estimands for safety topics of interest**

# Estimands for Safety Topics of Interest

ICH guidance E9(R1): An estimand has 4 defining characteristics:

- *the population, that is, the patients targeted by the scientific question;*
- *B. the variable (or endpoint), to be obtained for each patient*
- *the specification of how to account for intercurrent events, such as treatment interruption, rescue medication, discontinuation, death, …*
- *the population-level summary for the variable which provides a basis for the estimation of the estimand.*

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# Example: Crude Incidence Rate

(A) All patients while exposed

(B) binary: Patient did or did not experience the event of interest

(C) ignore intercurrent events

(D) # patient affected / # patients exposed.

| Features / Assumptions | Estimand | Estimate |
|---|---|---|
| Short exposure time<br>Fixed f-u time<br>Risk is relatively constant<br>Repeat events not important | Crude rate | # patients affected / # patients exposed |
| Individual f-u time<br>Risk is relatively constant<br>Time is continuous<br>Repeat events not important | Exposure-adjusted incidence rate | Counts per total person-time at risk |
| Risk is relatively constant<br>Repeat events are important | Poisson parameter | # events / exposure |
| Individual f-u time<br>Risk can vary over time | Kaplan-Meier Cumulative rate | Counts accumulating over time intervals of exposure |
| Individual f-u time<br>Risk can vary over time but hazard ratios is constant<br>Covariates are important | Hazard ratio | Ratio of two hazard rates |
| Average time to failure up to the specified time<br>Well defined irrespective of risk pattern over time | Restricted mean survival time | Area under the survival curve |

# Section 4: Gap analysis

Purpose: Highlight the “Known unknowns”

What are the safety risks that need to be further characterized?

*Based on preclinical findings; MOA; class effects; ….*

What additional data will be needed to generalize to target population?

*e.g. renal / hepatic studies; pediatric study*

# Case study 2: A pre-clinical signal was insufficiently explored in the clinic

# REBINYN, Pegylated Factor IX for Hemophilia

- Efficacy demonstrated (Trial 3747 randomized 74 patients to low and high doses of prophylaxis) -> 60% reduction in annualized bleeding rate (ABR).
- 2017 FDA review and AdComm: Concerns raised about preclinical signal of PEG accumulation and vacuolation in the choroid plexus with repeat dosing
- Per FDA review, unclear whether monitoring of neurologic function was adequate to detect all clinically important neurologic signs or symptoms
- Although no safety issues identified in the clinical trials, both quality and quantity of clinical data deemed insufficient to debunk preclinical signal
- Given the duration of exposure and total dose necessary, prophylaxis indication was not endorsed; FDA favored marketing approval only for short-term use (on-demand treatment and perioperative management)

Appendix B: REBINYN Clinical Review Memo:
https://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM564340.pdf

# Section 5: OASE (Ongoing aggregate Safety Evaluation)

Specifies methods and decision criteria for signal detection:

- Signal assessment based on the totality of data
- Maintaining study integrity

Provides context

- Background rates for known safety topics
- A database+algorithm to provide background rate on short notice if anything new comes up

# OASE: Some approaches for signal detection

Properties:

- Bayesian vs. Frequentist rules
- Unblinding required vs. not required
- Static vs Dynamic:

  *Proper for detecting "unknown unknowns" vs. proper for monitoring "known unknowns"*

# A Frequentist Rule for Static Analysis of Unblinded Data

Q1: Does  one-sided 80% CI of difference between observed and control include zero?

Q2: RR compared to control <2?

Q3: Does “lumping” similar events make the signal disappear?

All 3 “Yes”: Insufficient evidence of balance

All 3 “No”: Clear increase; send 15-day report

Otherwise: Consider sending, depending on circumstance

Wittes et al: The FDA’s Final Rule on Expedited Safety Reporting: Statistical Considerations. Statistics in Biopharmaceutical Research, 2015

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## Ball 2011: A Bayesian rule for static analysis of blinded data

Bayesian approach (Ball 2011) allows you to express the background rate as a Prior distribution, centered around a plausible value, say 2.00 events per pat. year.

Under H0, the rate should be the same in control and treatment,
so the pooled, blinded rate should follow that distribution.

You update the distribution based on the blinded AE rate.

You flag the event if the updated distribution shifts to the right so
that you get a high probability that the combined rate is higher than
the expected rate (2.00 in our example)

Ball, Greg: Continuous safety monitoring for randomized controlled clinical trials with blinded treatment Information. Contemporary Clinical Trials 32, 511-517

# The Sequential Probability Ratio Test (SPRT)

An Oldie but Goodie! (developed by Wald in the 1940's)

You analyze *after each additional data point* (event)

May be quite appropriate for safety monitoring

You compare

$$\frac{\text{probability(data under alternative)}}{\text{Probability (data under H0)}} = \text{"Likelihood ratio"}$$

to boundary values

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# SPRT: Boundary values

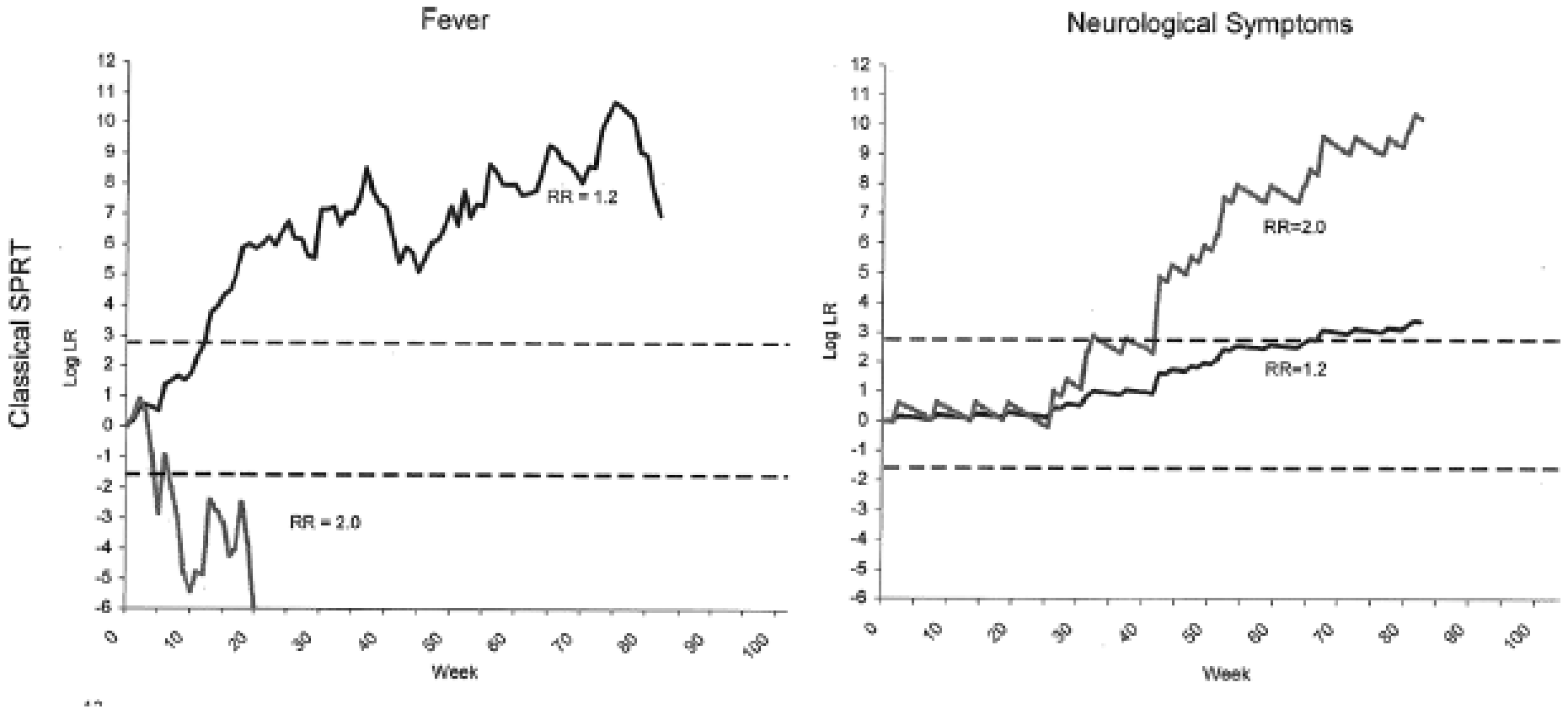
Shockingly simple formulae for boundaries:

- Reject H0 if Likelihood ratio $\geq$ (1- beta) / alpha

- Accept H0 if Likelihood ratio $\leq$ beta / (1 – alpha)

# The issue with the traditional SPRT

Behavior of the traditional SPRT depends on what you choose as H1:




Kulldorff et al. 2011

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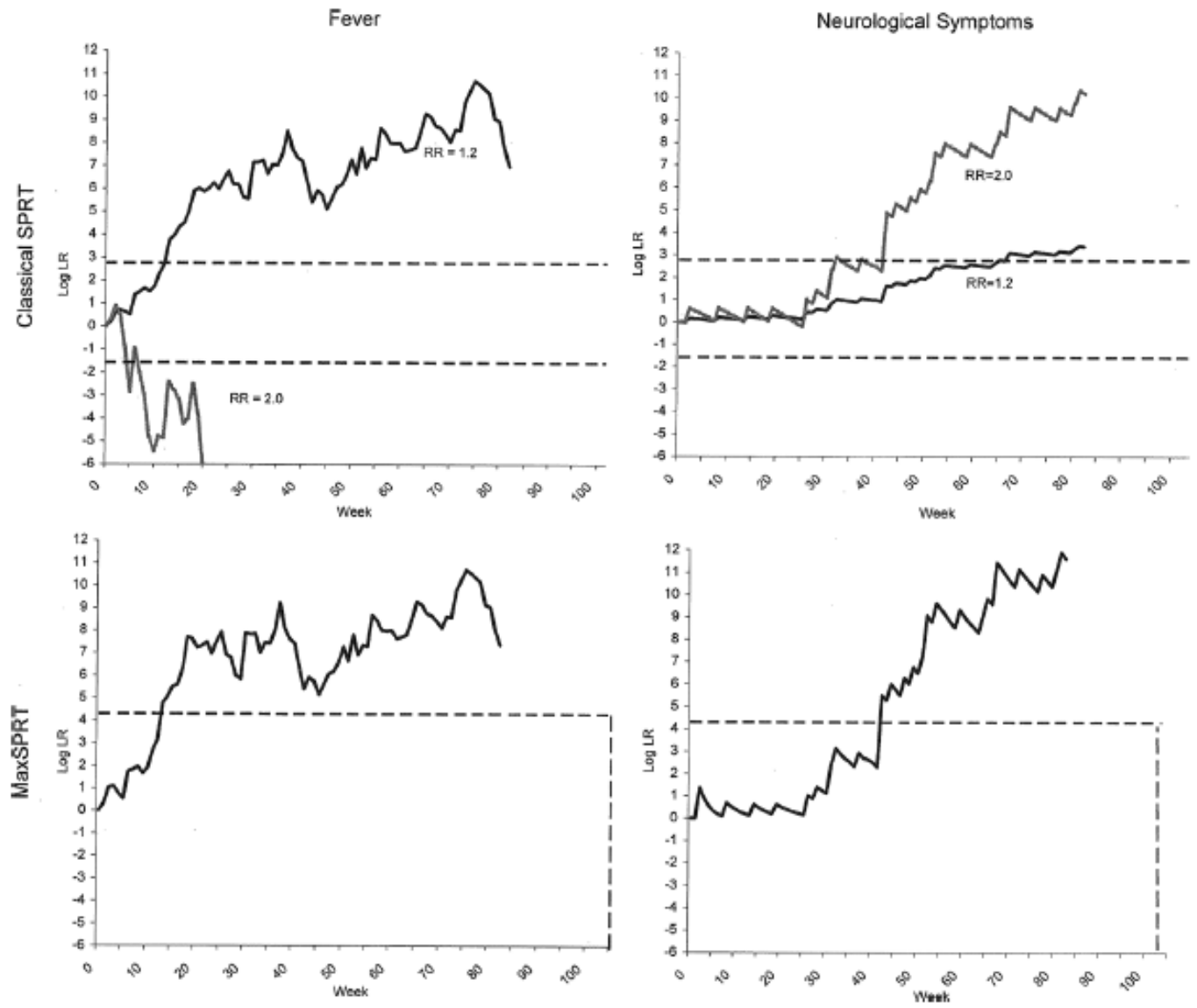
# Maximized SPRT (Kulldorff et al. 2011)

Idea: Base decisions on the maximized likelihood ratio:

$$\text{Likelihood ratio} = \frac{\text{probability (data under H1)}}{\text{probability (data under H0)}}$$

As H1 you choose a value that maximizes this ratio.

# Behavior of SPRT (upper row) vs MaxSPRT (lower row)

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# Approaches for Determining Background Rates

- Literature / Meta-analysis
- RWE
- “Natural history” study

- **EHR /Health Claims Databases may present issues for extrapolation to clinical trial databases**

- MedDRA coding (clinical trials) versus International Classification of Disease (ICD) coding (EHR/Claims)

- Questions about the matching of patient characteristics in the external database to the clinical study population

- Approach to recording diagnoses leading to hospitalization may be different for claims databases versus clinical trials

- Events meeting clinical trial seriousness criteria other than hospitalization may be difficult to identify in EHR/Claims

From Dr. Hendrickson's presentation at March 8 2018 Duke Margolis workshop on IND Safety Reporting

# Section 6: Safety Communications

- **ASAP outputs may be used to:**
  - Facilitate decision making during clinical development
  - Investigations of Safety Topics of Interest
  - Support safety related discussions in the:
    - Investigator Brochure (IB)
    - Developmental Safety Update Report (DSUR)
    - Periodic Benefit Risk Evaluation Report (PBRER)
    - Risk Management Plans (RMPs)
    - Regulatory submissions, Ad hoc regulatory responses
    - Publications

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# Review

- Safety regulations (with thought history)
- FDA 2010 “Final Rule”
- Implementation
- Importance of a planned approach (PSAP; ASAP)
- Some statistical rules for signal detection or monitoring of AESI

# Thank you for your kind attention


- Lothar Tremmel, Head Biostatistics and Medical Writing, CSL Behring

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