Update on progress of ASA Biopharm Safety Monitoring Working Group

ICSA Conference

June 28, 2017 Chicago, IL

Susan Duke, MS, MS

Consultant
Drug Safety Counts LLC

BIOPHARMACEUTICAL SECTION

Safety Monitoring Working Group is sponsored by Biopharmaceutical Section of the American Statistical Association

Why Safety?

More details emerge on fateful French drug trial

The study was halted on Monday, and all six patients who had taken the drug were hospitalized; one is brain-dead, four others have neurological symptoms of varying severity, while one is under observation but without symptoms,

Cardiovascular News

Withdrawal of Posicor From Market

Early in June 1998, Roche Laboratories of Nutley, NJ, abruptly and voluntarily withdrew its novel T-channel

drugs), the drug's problems are viewed as an unreasonable risk to consumers."

Diabetes Drug Rezulin Pulled Off the Market

Health: Medication has been linked to 63 deaths. FDA faced strong criticism for approving treatment.

March 22, 2000 | DAVID WILLMAN | TIMES STAFF WRITER

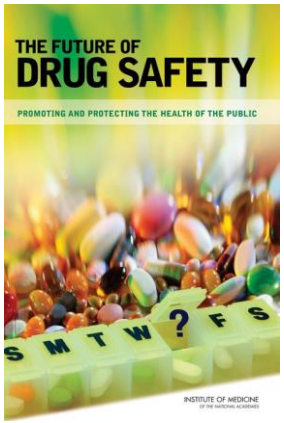
JAMA | Original Investigation

Postmarket Safety Events Among Novel Therapeutics Approved by the US Food and Drug Administration Between 2001 and 2010

RESULTS From 2001 through 2010, the FDA approved 222 novel therapeutics (183 pharmaceuticals and 39 biologics). There were 123 new postmarket safety events (3 withdrawals, 61 boxed warnings, and 59 safety communications) during a median follow-up period of 11.7 years (interquartile range [IQR], 8.7-13.8 years), affecting 71 (32.0%) of the novel therapeutics. The median time from approval to first postmarket safety event was 4.2 years (IQR, 2.5-6.0 years), and the proportion of novel therapeutics affected by a postmarket safety event at 10 years was 30.8% (95% CI, 25.1%-37.5%). In multivariable

Some history

2005 Formation of the Drug Safety Board, consisting of FDA, NIH and VA staff. The Board will advise CDER on drug safety issues and work with the agency in communicating safety information to health professionals and patients.



- 2007 report, Institute of Medicine

https://www.nap.edu/catalog/11750/the-future-of-drug-safety-promoting-and-protecting-the-health

The beginnings of Safety Statistics

- George Rochester, FDA statistician
  - Served as FDA's Expert Lead Statistician for Quantitative Safety in the Office of Biostatistics, developed the Quantitative Safety Program, renamed the Division of Biometrics VII
- Now lead by Mark Levenson

Mark Levenson

SPERT and Program Safety Analysis Plan

Amy Xia

Amy Xia, Amgen
Brenda Crowe, Lilly

Brenda Crowe

Safety Monitoring Working Group Goals

Established in 2015 by the ASA Biopharm Safety Statistics Working Group

Initial Goal

- To empower the biostatistics community to play a more proactive role and better enable quantification in safety monitoring

Stage 2 Goal beginning 2017

- To empower the broader cross-disciplinary, cross-regional community to discover and promote practical quantitative solutions for safety monitoring during clinical development

	Presentations	Short Courses	Publications
2016	DIA Annual Meeting JSM Biopharm Section DIA China Quantitative Science Forum	Deming (1/2 day)	JSM Proceedings (WS1, WS2)
2017	Global Safety Congress Midwest Biopharm Statistics Workshop DIA Annual Meeting JSM Biopharm Section	ICSA (full day) Deming (1/2 day, methods)	Regulatory review (TIRS) Industry survey

BIOPHARMACEUTICAL SECTION

ASA Safety Monitoring Working Group

William Wang, Chair

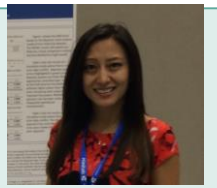
WS1: Industry Practice & Regulation

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† (Qscicon)
- 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 (Theravance)
- Yueqin Zhao (FDA)

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

Safety Monitoring WG Statistical Advisors

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

One of our deliverables was achieved here at ICSA!

Quantitative Sciences for Safety Monitoring during Clinical Development

An ICSA Short Course from the ASA Biopharm Safety Monitoring Working Group

June 25, 2017 Chicago, IL

Instructors: Ed Whalen, Susan Duke, Krishan (KP) Singh and Wenquan Wang

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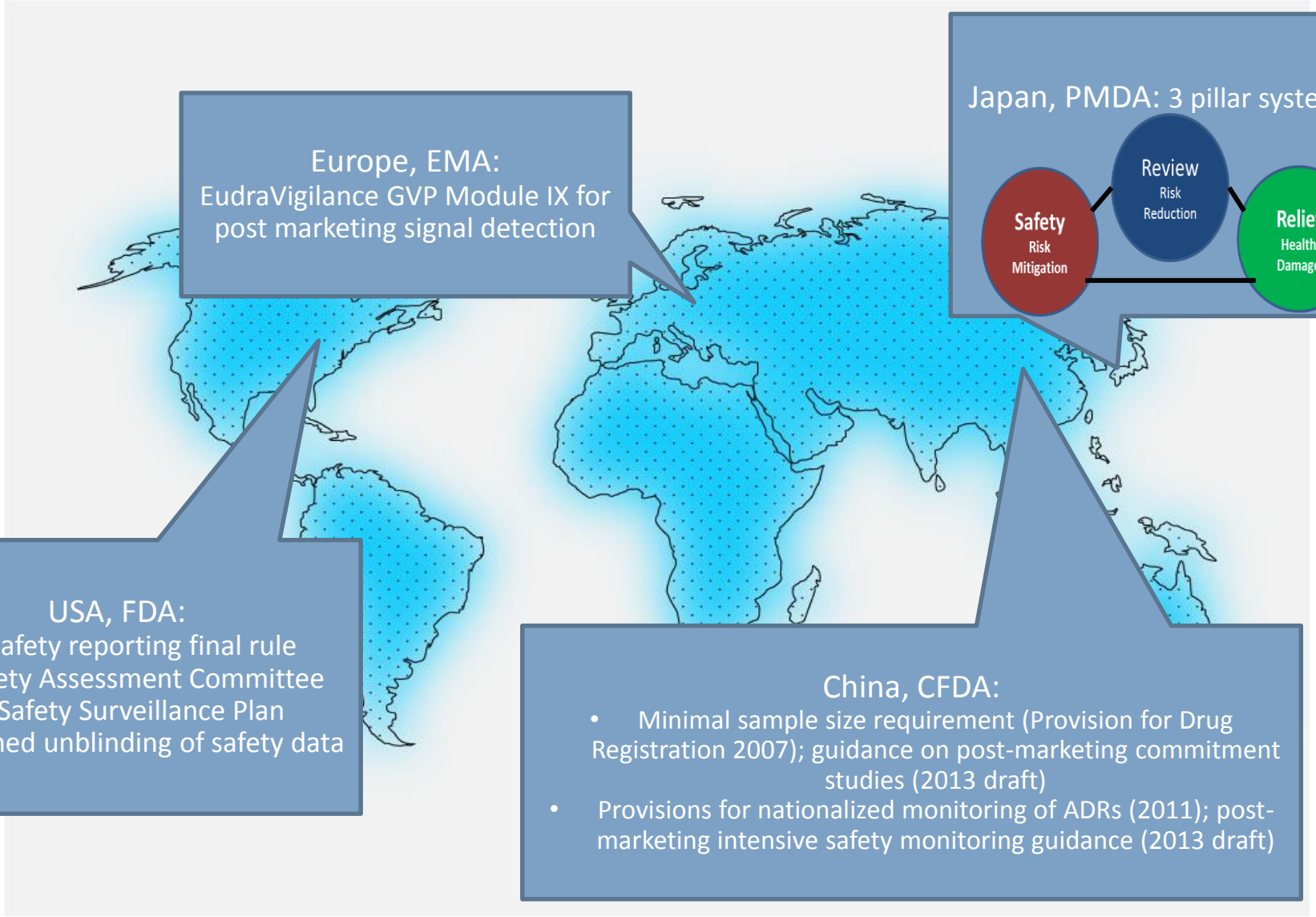
An Overview of the Regulatory Environment for Safety

- CIOMS / ICH
- FDA / EMA / Japan / China

Regulatory Motivation: Unique Regional Safety Regulations



Regulatory Motivation: CIOMS Working Groups on Safety

CIOMS WG	Descriptions	Resulting Regulatory Guidance
VI	Management of Safety Information from Clinical Trials (2005)	IND Safety Reporting
VII	Development Safety Update Report (DSUR) (2006)	ICH E2F
VIII	CIOMS Working Group on Signal Detection (2006)	GVP Module IX
IX	Practical Approaches to Risk Minimisation for Medicinal Products (2010)	
X	Considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process (2016)	

Work Stream 1: Pulse of the Industry

Thought 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 (Qscicon)
- Lily Krasulja* (Janssen)
- Mark Levenson (FDA)
- Mondira Bhattacharya* (AbbVie)
- Olga Marchenko (Quintiles)
- Steve Snapinn (Amgen)
- Valerie Simmons* (Eli Lilly)
- Walter Offen (AbbVie)

* Physicians

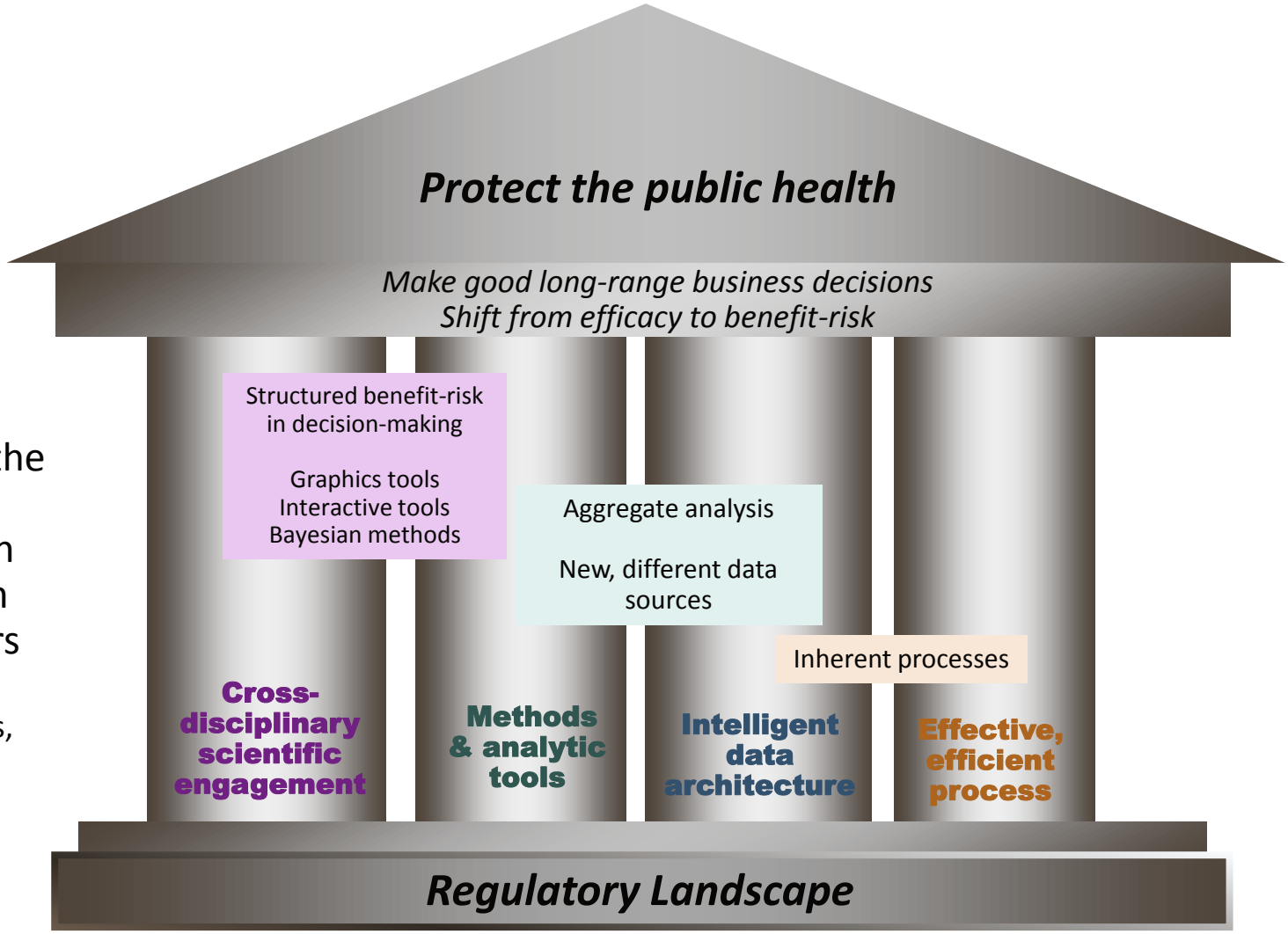
We are indebted to the 18 thought leaders who each spent at least an hour with us discussing their views on quantitative assessment of safety monitoring

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

From the thought leaders:
How is analysis of safety different from that of efficacy?

Feedback from the survey* was consistent with feedback from thought leaders

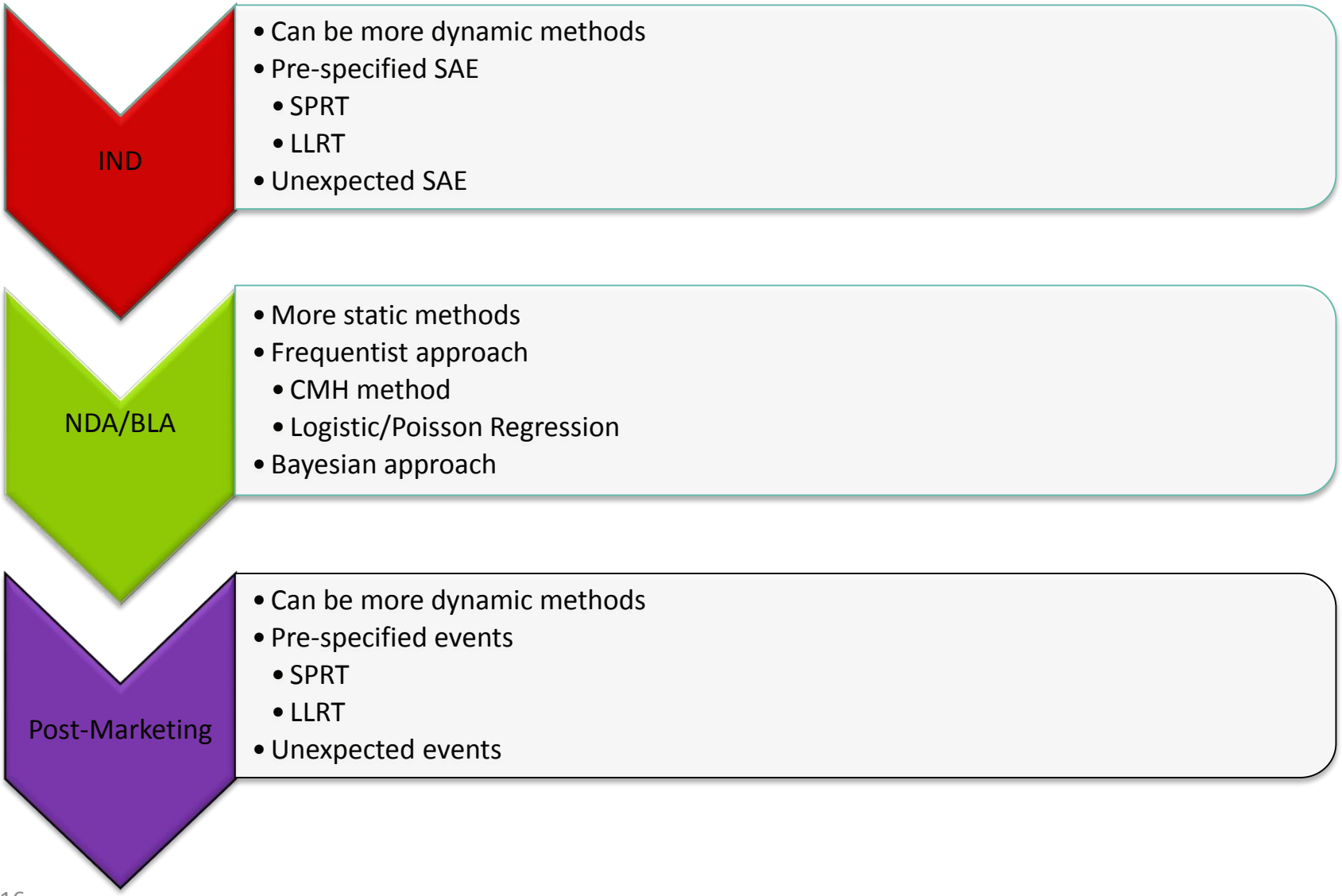
* Out of 35 companies, 24 responded



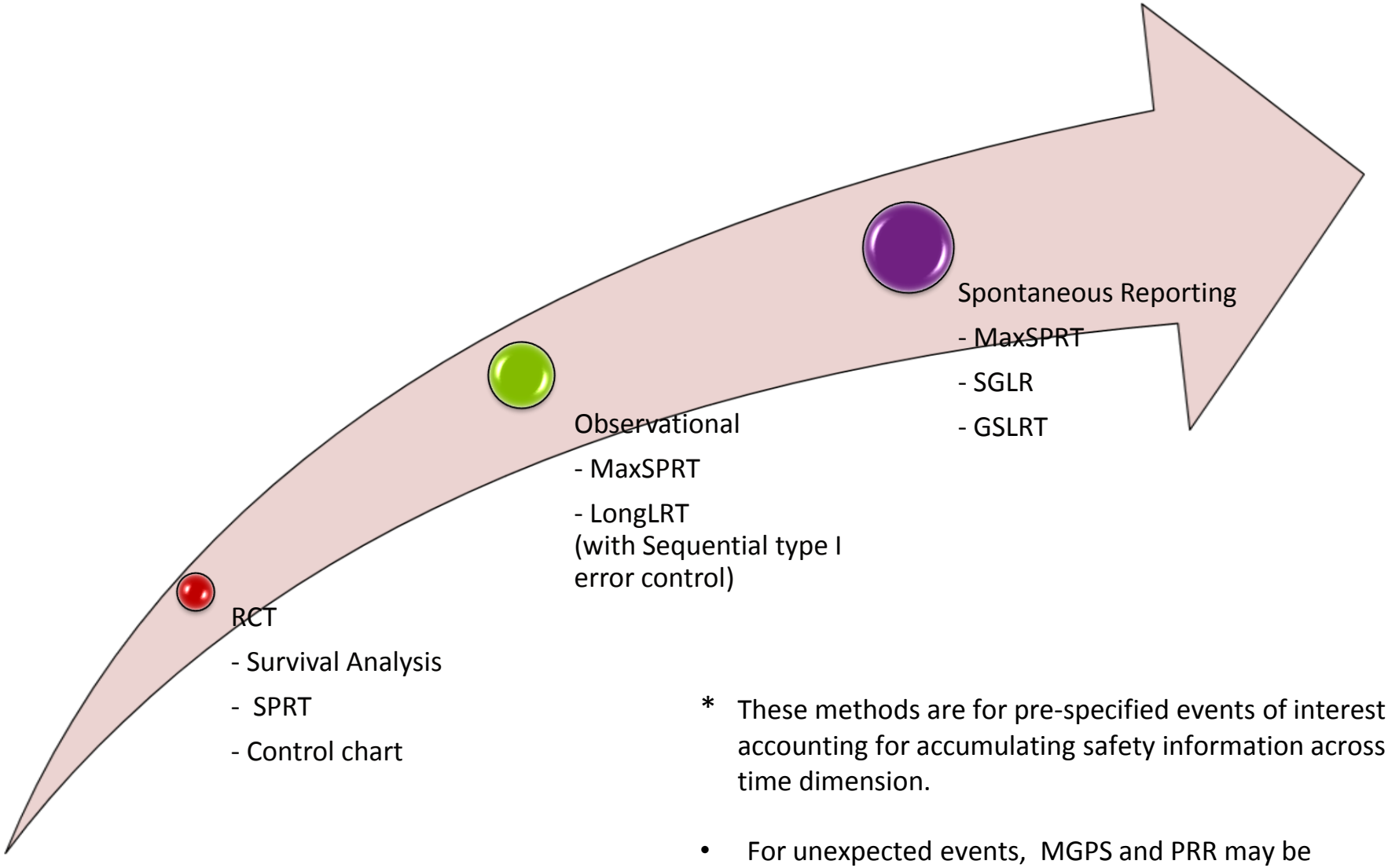
Workstream 2: Safety Statistics Methods in action

- Static and dynamic methods
- Meta-analysis
- Visual analytics
- Quantitative frameworks

Static vs Dynamic Evaluation During the Life Cycle



From Randomized Control Trial to Spontaneous Reporting: Dynamic Methods for Safety Evaluation*



* These methods are for pre-specified events of interest accounting for accumulating safety information across time dimension.

- For unexpected events, MGPS and PRR may be used to account for type I error.

17

Safety Statistics Methods in action

- Static and dynamic methods
- Meta-analysis
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Meta-Analyses Timeline

1999 Rosiglitazone approved for Type II Diabetes in US (EU in 2000)

2007 Dr. Nissen reports 43% increase in myocardial infarction.

Rosiglitazone prescribed to 11.3 million patients

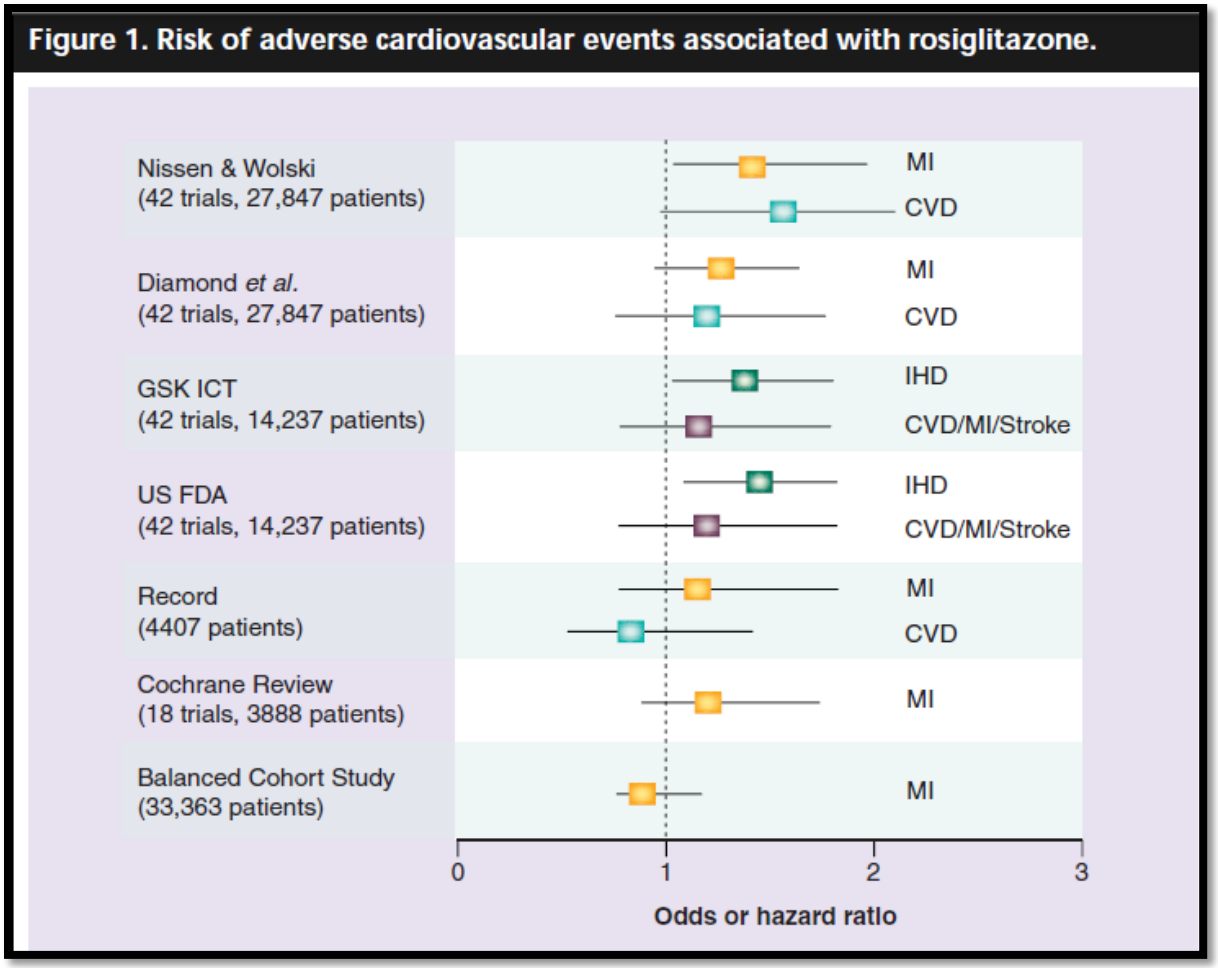
Numerous meta-analyses and obs. studies follow

2008 FDA issues safety guidance for antidiabetic drugs

2010 Rosiglitazone withdrawn in EU and **restricted in US**

2013 **FDA removed label restrictions**

Differences in Results (Kaul & Diamond, 2008)



CIOMS-X - Evidence Synthesis and Meta-Analysis for Drug Safety

- Provides background of synthesis research and need to synthesize
- Important considerations for research synthesis based on document flow
- Considerations in
  - Planning and preparing for meta-analysis
  - Analysis and Reporting
  - Interpretation of the Results
- Four case studies (including rosiglitazone)
- Regulatory Criteria for Evaluating Evidence from a Meta-Analysis
- Best practices (under FDA consideration)

Safety Statistics Methods in action

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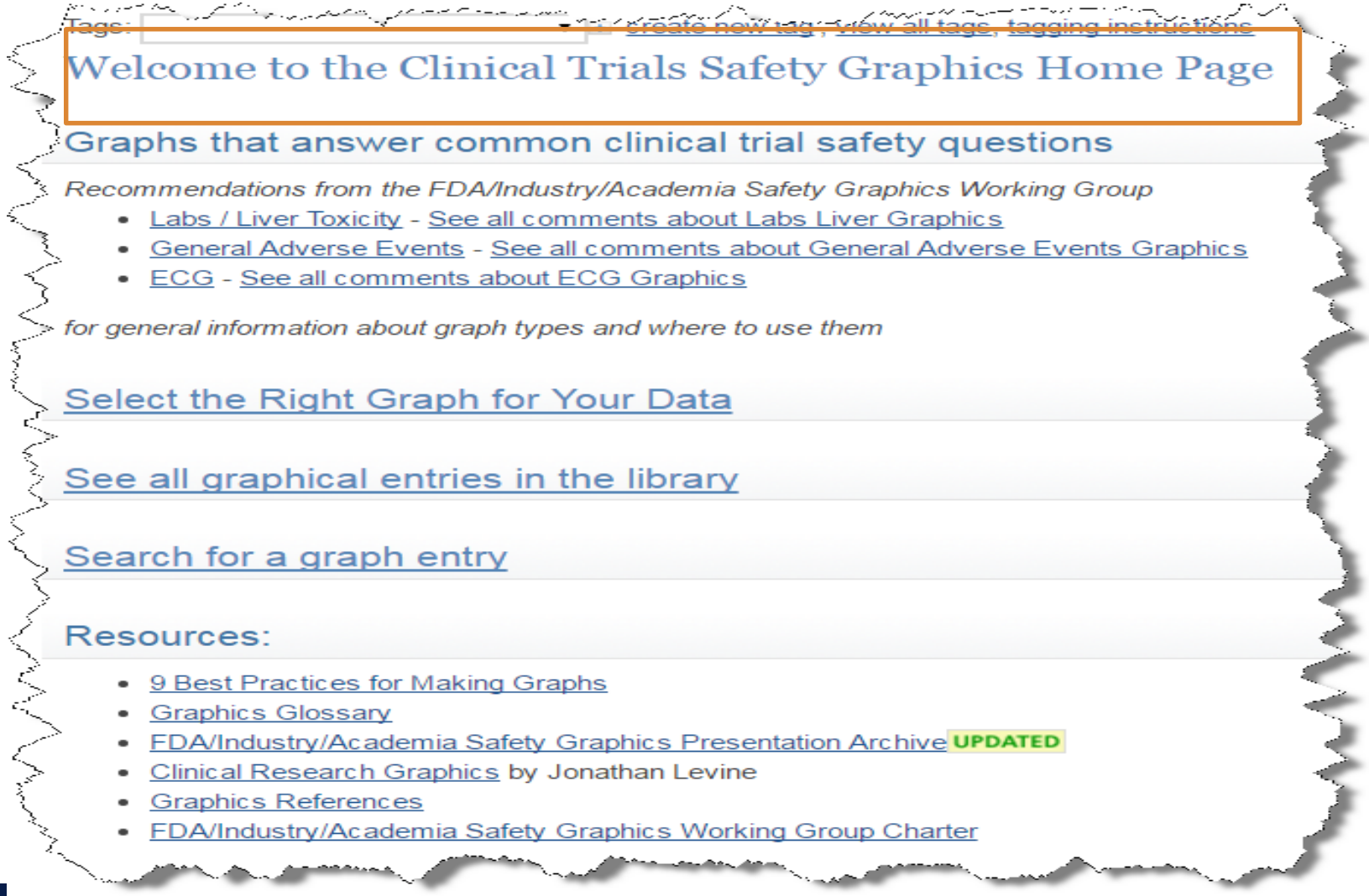
Visualization Efforts

Safety graphics on CTSpedia http://www.ctspedia.org/do/view/CTSpedia/StatGraphHome



Tags: create new tag , view all tags, tagging instructions

Welcome to the Clinical Trials Safety Graphics Home Page

Graphs that answer common clinical trial safety questions

Recommendations from the FDA/Industry/Academia Safety Graphics Working Group

- Labs / Liver Toxicity - See all comments about Labs Liver Graphics
- General Adverse Events - See all comments about General Adverse Events Graphics
- ECG - See all comments about ECG Graphics

for general information about graph types and where to use them

Select the Right Graph for Your Data

See all graphical entries in the library

Search for a graph entry

Resources:

- 9 Best Practices for Making Graphs
- Graphics Glossary
- FDA/Industry/Academia Safety Graphics Presentation Archive UPDATED
- Clinical Research Graphics by Jonathan Levine
- Graphics References
- FDA/Industry/Academia Safety Graphics Working Group Charter

Each Safety Category has common safety questions

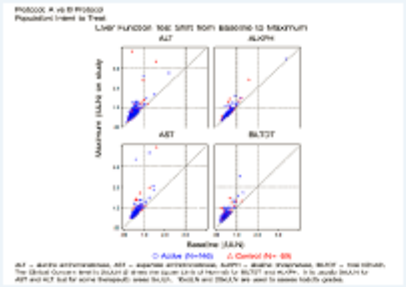
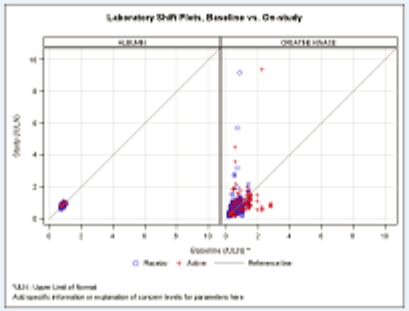
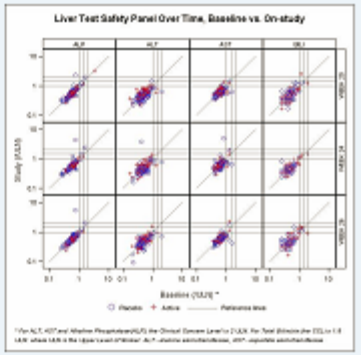
The graph thumbnails within each question include a usage description and the SAS or R code used to create it

Labs and Liver Toxicity Clinical Questions

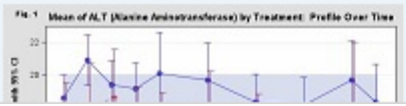
Return to Safety Graphics Home

Baseline and Trending over Time

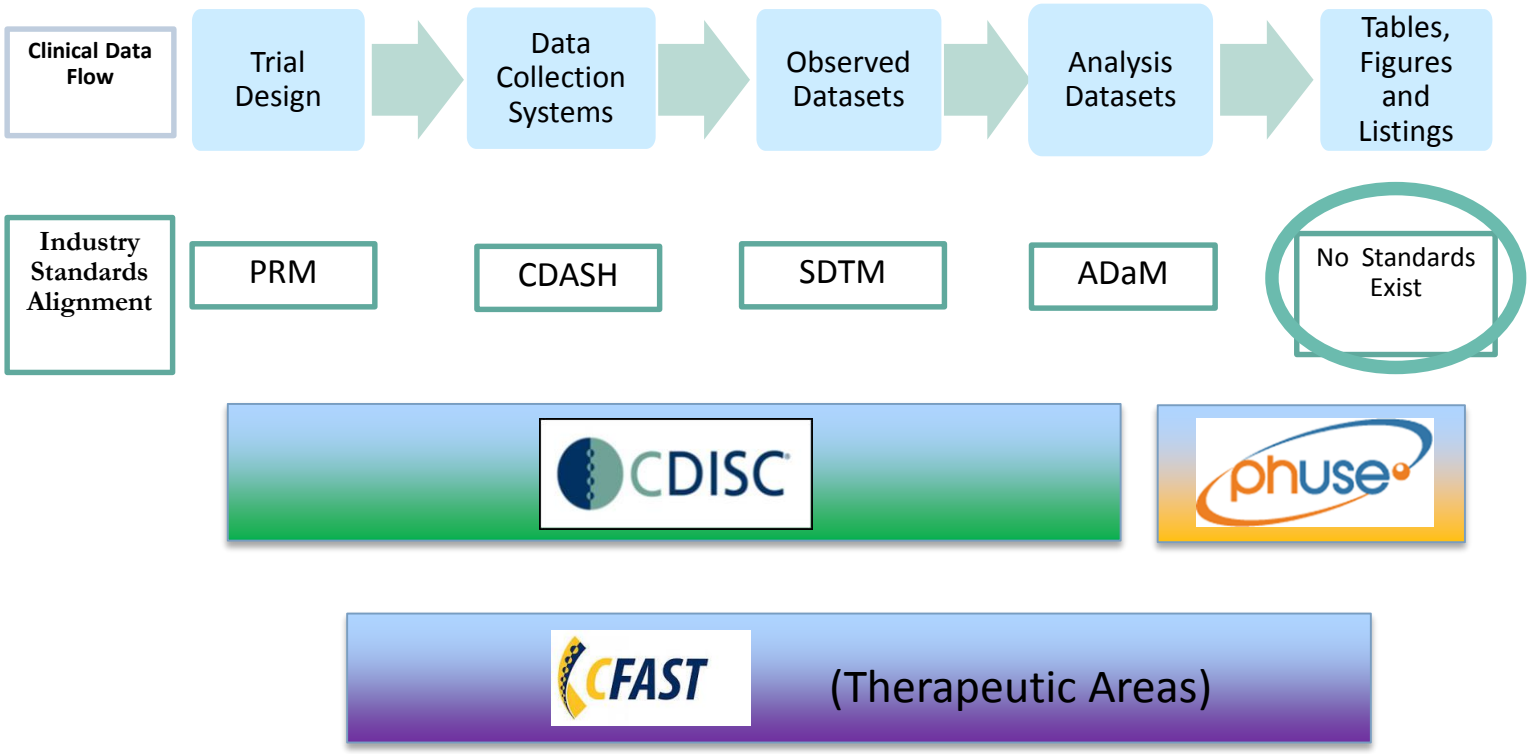
1. What are the changes and percent changes from baseline over time? ie, are abnormal lab values a result of an abnormal baseline or have values changed on study?

EG: Lab Shift Plots	EG Lab Parameter Shift Plots	EG Liver Test Safety Panel
		
Click here for Lab Shift Plots Data	Click here for Lab Parameter Shift Plots Data	Click here for Liver Test Safety Panel Data
Comment on Lab Shift Plots	Comment on Lab Parameter Shift Plots	Comment on Liver Test Safety Panel

2. Is there a temporal relationship between treatment and lab values?

EG Mean of ALT	EG Cumulative Incidence	EG Distribution of ALT
		

Vision: Fill the Gap on Analysis and Display Standards



CS Working Group White Papers

How to find final white papers: Go to www.phuse.eu, Click on Working Groups, Click on CS Deliverables Catalog

7 White Papers Finalized

- Vital Signs, ECGs, Labs - Central Tendency (2013)
- Non-Compartmental Pharmacokinetics (2014)
- Demographics, Disposition, Medications (2014)
- Vital Signs, ECGs, Labs – Outliers and Shifts (2015)
- Thorough QT/QTc Studies (2016)
- Adverse Events (2017)
- Screen Shots of the Displays Created Using Scripts Contributed by the FDA (2017)

Computational Science Working Groups

phuse

Safety Statistics Methods in action

- Static and dynamic methods
- Meta-analysis
- Visual analytics
- Quantitative frameworks

Example of IND Reporting: Case Study Monitoring Tool

Materials developed by Robert Gordon, Janssen of J&J

. 28

Stage 1: Identification and Definitions

ASMP includes 2 threshold criteria:

1. When to conduct an aggregate analysis. Ad-hoc analysis can be supported based upon findings during the clinical review of AE data
2. When a disproportionate value / imbalance vs. placebo/historical control identified in Stage 2 requires a medical review the analysis moves to Stage 3.

ASMP Contents

Contacts, study timing and duration, review period

List of events as MedDRA PTs and MedDRA codes

List of event groups, if applicable

Thresholds for each event / group

Embedded instructional document

Safety Monitoring with Simulation

Monitoring Rule:
frequency

Number of times of monitoring visit
2

Monitor Timepoints (weeks)
(26, 52)

Threshold
4

Assumptions:

Background Parameter:
Background Event Rate (per patient year)

Background Parameter Value
(0.025, 0.05, 0.075, 0.1)

Relative Difference between treatment group and background
(0, 0.5, 1)

Dropout Rate (per patient year)
0.005

Enrollment Period (weeks)
78

Simulation:

Number of simulations
1000

Randomization Seed
12345

Treatment Group Size:
200

Go!

Introduction:

This tool evaluate different rules for anticipated AE monitoring thru simulation. Users can change variable values according to their own study features. It output a simulation result and a graph to present the probability of safety alerts.

Monitoring Rule: Frequency

There is no control group in study; Number of patients with anticipated AEs in the treatment group will be compared with a threshold given by user for safety monitoring. If the number of patients with anticipated AEs in treatment group >= threshold at any visit, it will trigger alert.

Assumptions:

1) Enrollment Pattern:
   Assume linear enrollment pattern and use uniform distribution to generate enrollment time.
2) AE and dropout events generation:
   exponential distribution with parameters given by user.
3) AE after dropout:
   AEs occurred > 30 days after dropout will not be counted.
4) Alert count:
   if safety alert is triggered at any single monitoring visit, the whole trial will be counted as having safety alert.

Probabilty Table

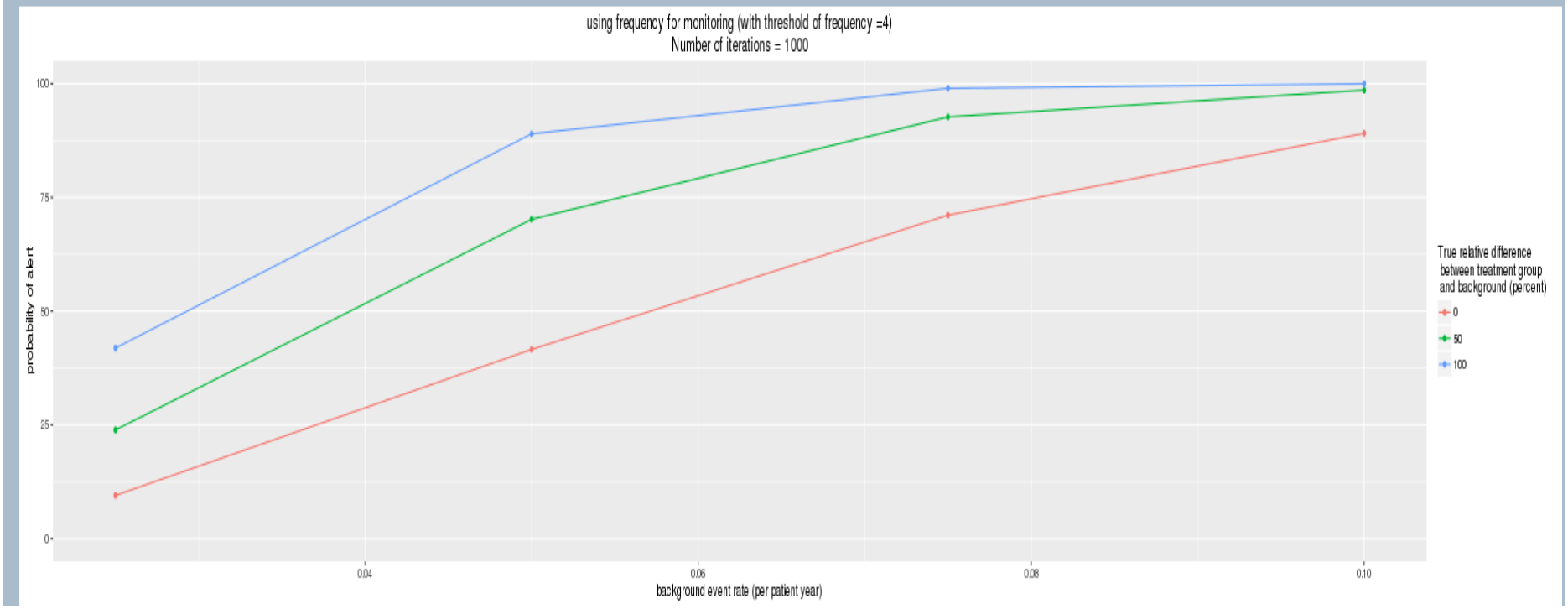
Simulation Parameters

Probabilty Table

background parameter	relative diff between trt and background	Probability
0.025	0	9.5
0.025	0.5	23.9
0.025	1	41.9
0.05	0	41.6
0.05	0.5	70.2

Simulation Parameters

Parameter	Value
Monitoring Rule	frequency
Monitoring Timepoints	(26, 52)
Threshold	4
Dropout rate (Per patient year)	0.005
Enrollment Period	78



General Messages

Safety has distinct differences from efficacy statistics

1. Cross-disciplinary scientific engagement: **Safety Mindset**
2. Effective, efficient process: **Extended PSAP, process (WS 1)**
3. Methods and analytic tools: **See the whole elephant (WS 2)**
4. Intelligent data architecture: **Safety data integration**
5. Encapsulated and enriched by the **Regulatory Landscape**