Safety Monitoring in Pharma

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Abstract – 1) Overview of safety statistics in general for randomized controlled studies, observational studies, and spontaneous report data.
2) Examine recent changes in investigational new drug (IND) safety reporting.
3) Some questions illustrating the need for improved methods to evaluate important side effects, especially ones that occur rarely.

Who?

- Drug Sponsors
- Regulatory Agencies
  - FDA
  - EMA
- Large Health Organizations
  - Payors
  - World Health Organization
- Others
  - Research Groups
  - Concerned Parties

Where?

- Early development
  - Animal data
  - First in human
  - Early phase clinical trials
- Near submission for marketing approval
  - Phase III, larger clinical trials
- Post-approval
  - Continued review of clinical studies
  - Observational databases – FAERS, Insurers, EHRs

How?

- In Clinical Studies
  - Patient reports upon general questioning
  - Test measurements such as labs, ECGs, neuro exams
  - Specially defined or adjudicated endpoints
- In Observational Data Sources
  - Ongoing monitoring systems such as FAERS
  - Longitudinal data from insurers using index defining criteria

Adverse Events

- "*Adverse event* means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. "

Serious Adverse Events

- "*Serious adverse event* or *serious suspected adverse reaction.* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

For example: Steven-Johnson Syndrome

Safety Monitoring in Clinical Trials

Table AE 3
Incidence of Treatment Emergent Adverse Event by System Organ Class, Preferred Term, and Treatment
(Format 2)
All Randomized Subjects

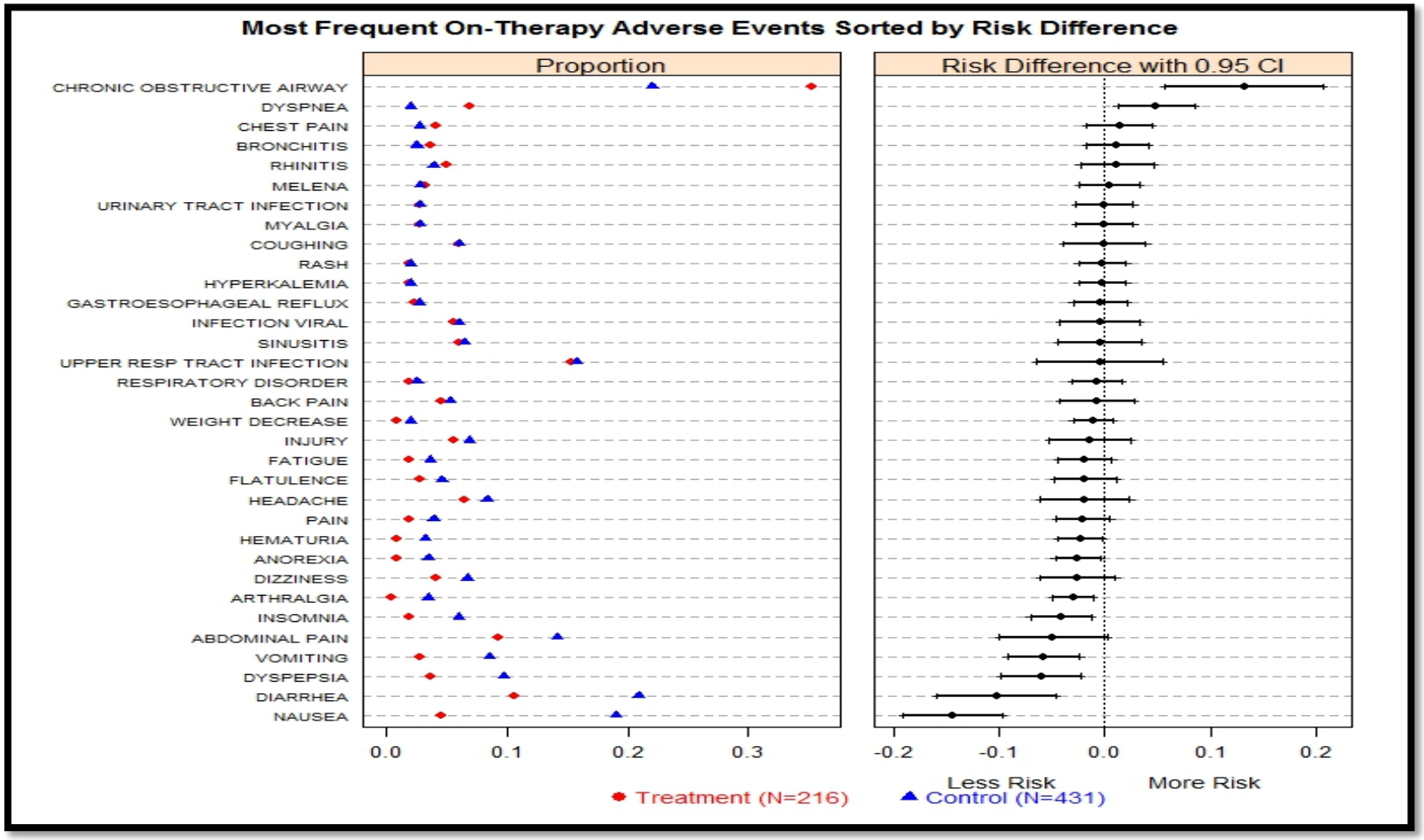
Body Class or System Organ Class	Preferred Term	Placebo N=xxx	Demo Dose 10 mg N=xxx	Demo Dose 30 MG N=xxx	Demo Dose 60 MG N=xxx
With Any Adverse Event	Overall	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 1		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
. . .		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 2		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
. . .		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
SOC Term 3		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 1	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 2	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
	Preferred term 3	xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)
. . .		xxx (xx)	xxx (xx)	xxx (xx)	xxx (xx)

Note: denominator of percentage is the number of subjects in the column
Percentage is based on the number of subjects who had event not the number of events.

Safety Monitoring in Clinical Trials

- Proportions or rates
  - Summary stats
  - Not so visual
- Multiplicity
- “hypothesis vs exploratory”
- Clinical Meaning
- High number of questions of interest

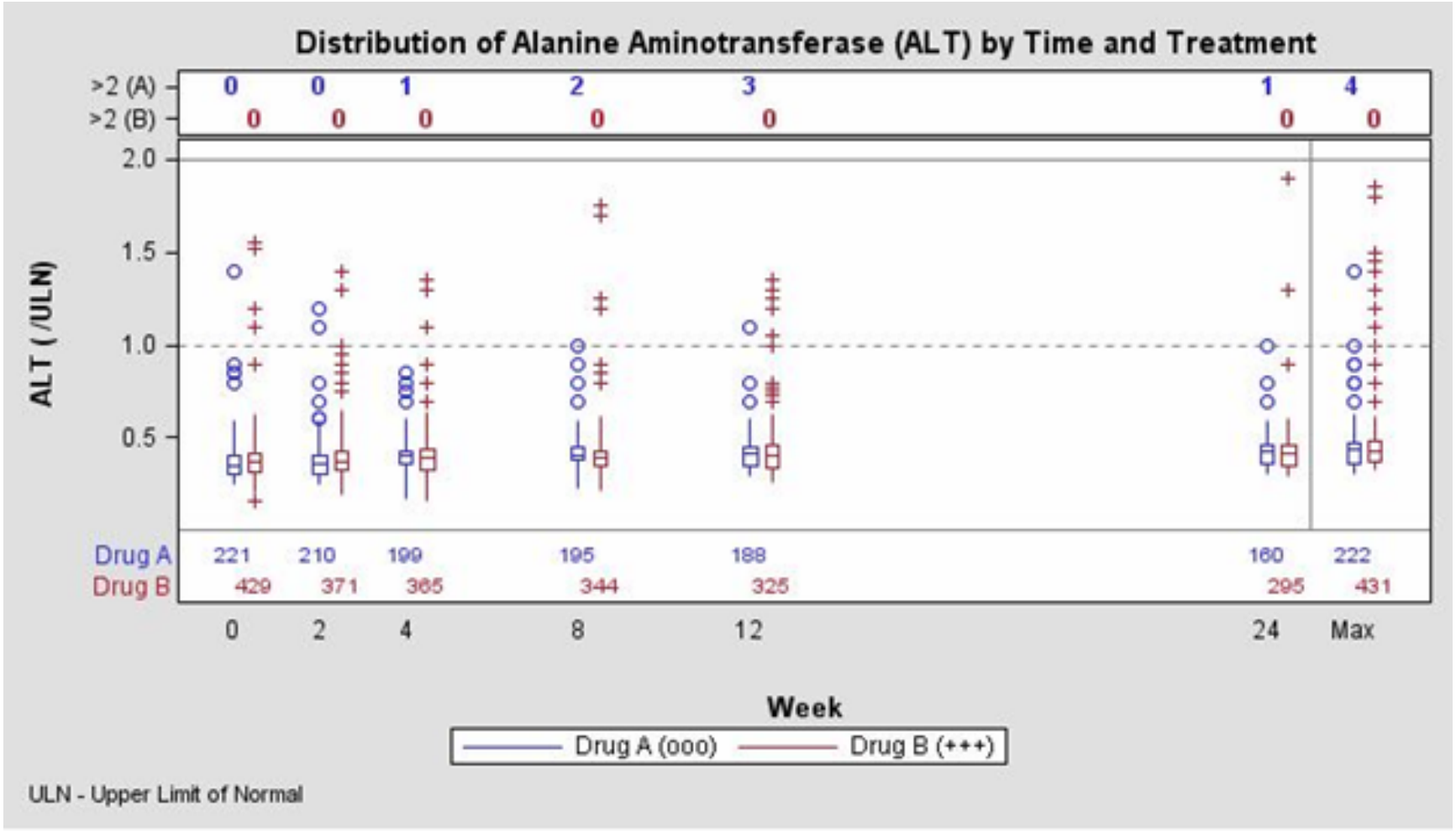
Safety Monitoring in Clinical Trials



https://www.ctspedia.org/do/view/CTSpedia/ClinAEGraph000

Safety Monitoring in Clinical Trials

Is there a temporal relationship between treatment and lab values?



https://www.ctspedia.org/do/view/CTSpedia/ListingsLabsLiverVetted

Safety Monitoring in Observational Data

- Sentinel https://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm
- OHDSI (OMOP data model) https://www.ohdsi.org/

Safety Monitoring in Observational Data

- Drug-Event Combination (DEC)

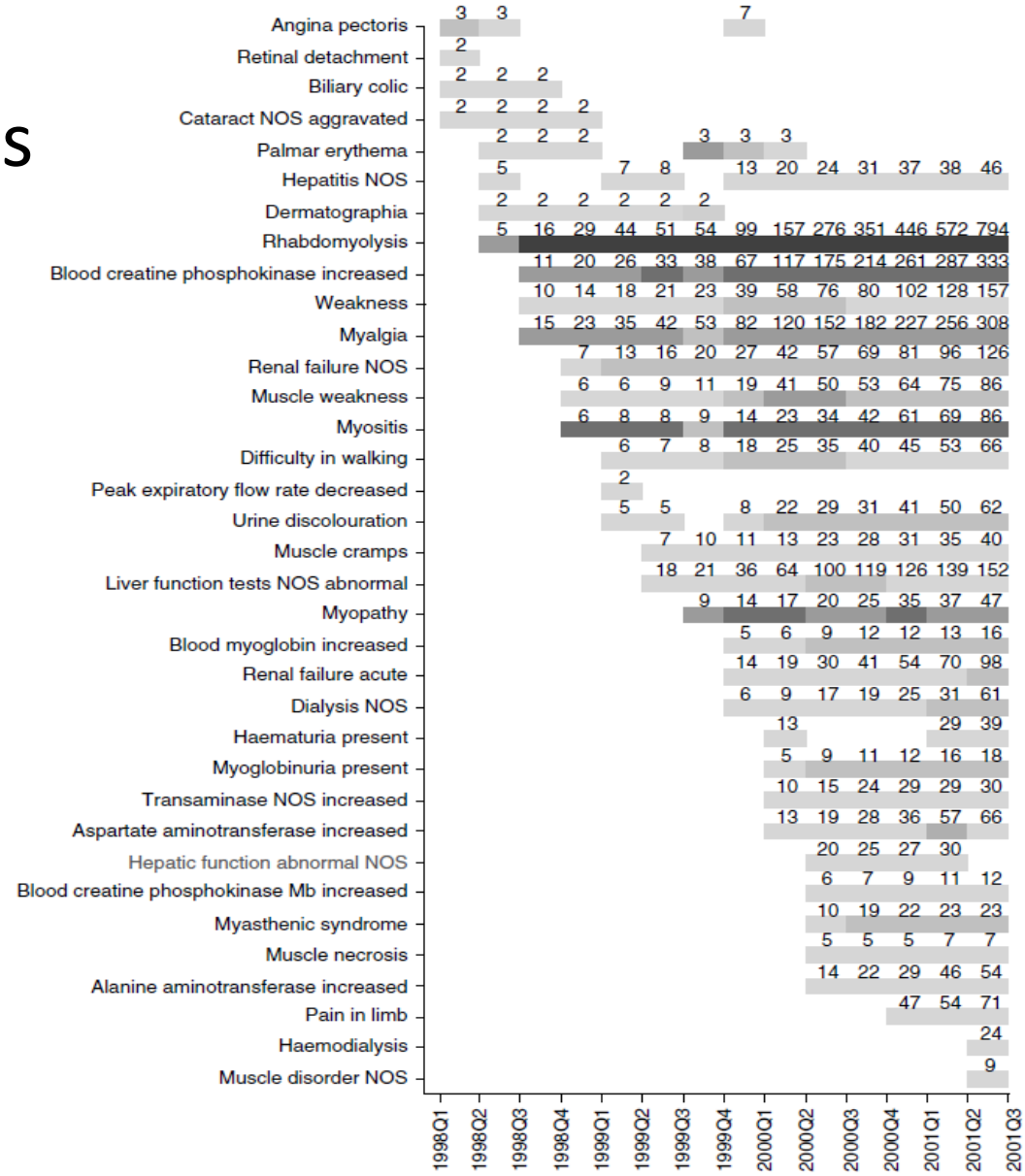
Table I. A 2×2 contingency table for adverse event evaluation.

	$Drug_j$	$Drug_{j-}$	Total
AE_i	n_{ij}	$n_{i.} - n_{ij}$	$n_{i.}$
AE_{i-}	$n_{.j} - n_{ij}$	$n_{..} - n_{i.} - n_{.j} + n_{ij}$	$n_{..} - n_{i.}$
Total	$n_{.j}$	$n_{..} - n_{.j}$	$n_{..}$

Table from Chen et al (2015), Evaluation of statistical methods for safety signal detection: a simulation stuy. Pharmaceut. Statist.

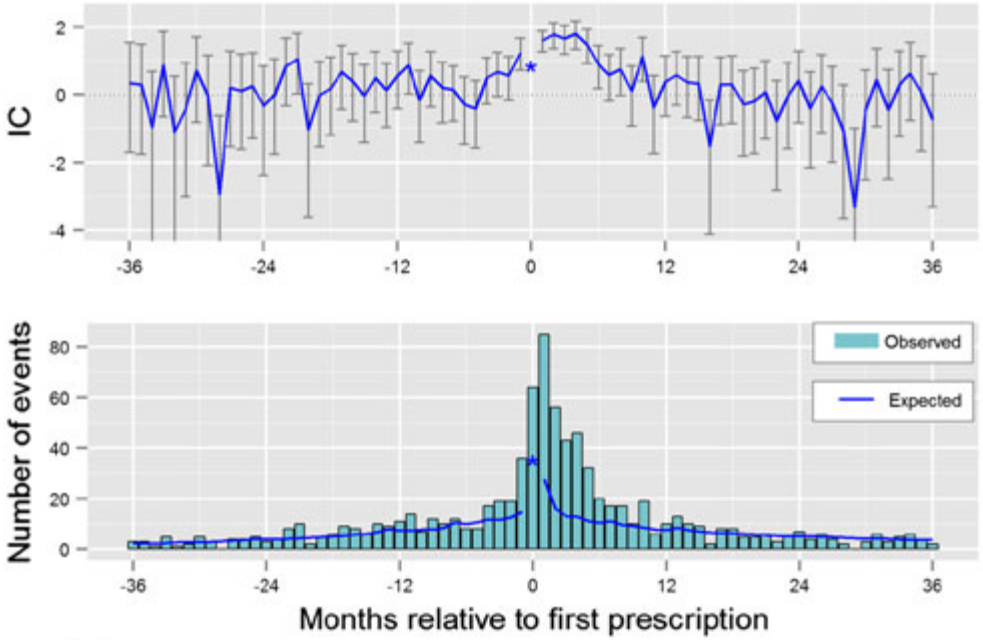
Where? Observational Data

- Spontaneous Reports
  - eg FAERS
  - Drug-Event pairs
  - MGPS and many more (EB05)

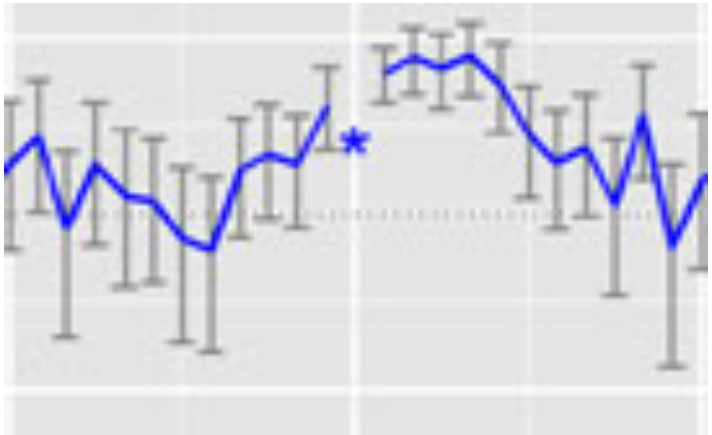


Where? Observational Data

- Claims, Provider Data
  - Cross-sectional
  - Longitudinal
  - Epidemiology
  - Large data methods
- EHRs
  - NLP on patient records
  - Also large data methods



(a) Isoniazid – true positive



Graphs from Noren (2013), Empirical Performance of the Calibrated Self-Controlled Cohort Analysis Within Temporal Pattern Discovery: Lessons for Developing a Risk Identification and Analysis System

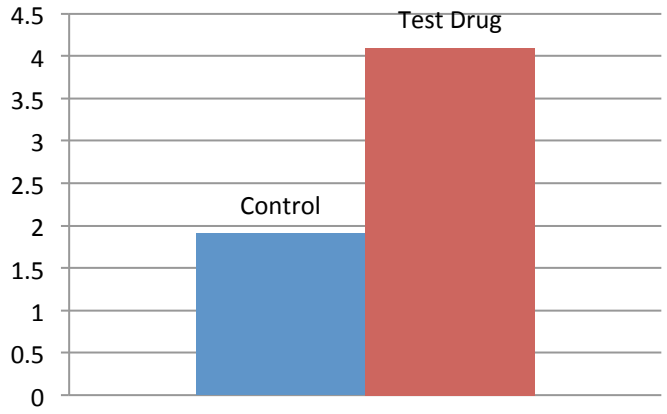
IND Safety Reporting: Safety Assessment for IND Safety Reporting Guidance for Industry

- In human clinical study data

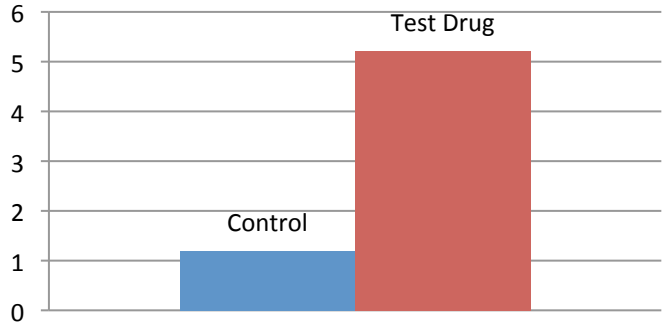
This guidance contains recommendations on the following: (1) the composition and role of a safety committee, (2) aggregate analyses for comparison of adverse event rates across treatment groups, assessment, (3) planned unblinding of safety data, (4) reporting thresholds for IND safety reporting, and (5) the development of a safety surveillance plan.

Focus on Serious Adverse Events

- Increase above expected rates for an events
  - Rate of pneumonia



- Unanticipated events
  - Rate of heart attack



General Questions

(no particular order or importance)

- How do we estimate “background” rates for determining if an SAE rate diff/ratio rises beyond clinical concern?

- Where and how do population characteristics come into play and/or bias estimates of both background rates and compartive rates?

General Questions

(no particular order or importance)

- What pharmacometric-like methods can we develop to integrate data sources across stages (eg animal data to model and update early phase study work …)?

- What do criteria look like that guide decisions on action/no action for rare event imbalances?

General Questions

(no particular order or importance)

- Which events (reports, lab values, ECGs, other tests) cluster together? Within patients? Among a subgroup(s) of patients?

- What predictive factors can we determine to identify the “right medicine” for a given patient? Relative to benefit-risk?

General Questions

(no particular order or importance)

- What does it take to design valid, meaningful, studies of a drug's safety?