

# *The biostatistics workgroup on the FINAL RULE*

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# Participants

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# FDA 15-day reports: Investigational products

- Former rule – reported by investigator
  - Serious
  - Unexpected (not in the investigator brochure)
  - Associated with study drug
    - i.e., investigator could not rule out association
- Sent to FDA/IRBs/ECs/DSMBs/Investigators

# The problem: FDA 15-day reports

- Many were sent....
- Few were read...
- Fewer were interpretable

# The change: FDA 15-day reports

- Properties
  - Serious
  - Unexpected (not in the investigators brochure)
  - “Associated with study drug”
    - Some evidence of a causal relationship
    - Determined by investigator or Sponsor

The challenge:

Want to separate wheat from chaff



Send fewer reports  
But don't miss signals

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

- Two influential papers in Clinical Trials

Crowe et al. (2009) 6:430-40.

Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development.

Xia et al. (2011) 8:175-82.

Planning and core analyses for periodic aggregate safety data reviews.

# Our charge

- How to quantify harms
- How to assess risk (not vs. benefit)
- So Sponsors will know what to report in 15 days



# Statistical topics: 15 day reporting

- How to set trigger (threshold) for reporting
  - New events
  - Increased frequency of events
- Should we worry about blinding (if so, why?)
- Most of the issues not statistical

# We are looking for events to report

- Not necessarily a known harm
- Something that is a potentially a harm
  - A signal
  - “Reasonable possibility” of being real: **NEW**
    - Small studies – overreporting not a burden
    - Large studies (e.g., CV studies) – want specificity

# Classes of events

- A. Single occurrence of event known to be strongly associated with drug exposure (Stevens-Johnson Syndrome, hepatic injury...)
- B. A few (1? 2? 3?) events not commonly associated with drug exposure but otherwise uncommon in the population exposed to the drug
- C. Common events that occur more frequently than expected in the treatment group

# A. Rare but associated with drugs

- Not a statistical issue

## B. A few surprising events

- Examples
  - Tendon rupture in any population
  - Myocardial infarction in young women
- When to report
  - Small trials: each one
  - Large trials: ??

## C. Aggregate of specific events

- This is the most difficult – no one case a surprise
- Study of the elderly – strokes and MIs
- Study in kids - infections

# What are the issues?

- Who is looking at the data?
  - To whom do they report?
- How do we deal with coding (e.g., MedDRA)?
  - Lumping or splitting
  - What do verbatim terms mean?
    - Huge cultural differences in symptoms recognized and called
    - Remember “hysteria”?

# Issues, continued

- Who is looking at the data?
- Do we lump or split?
- How do we look at ongoing trials?
- How do we look at completed trials?



## B. Analysis of a Single Type of Outcome Based on Observing Increased Frequency Relative to Expectation

Is Imbalance (IMB) Clear?		
Yes: No IMB	Unclear	Yes: IMB
<b>DO NOT REPORT</b>	<b>REPORT IF...</b>	If CI excludes 0 AND Rel Risk > 3 AND Lumping similar events doesn't make signal disappear THEN imbalance CLEAR Therefore, REPORT
	Other safety outcomes support causality	
	Mech of action and labs support causality	
	Investigators need info to manage patient	
	Info might affect pt's willingness to continue	
	Pooling similar outcomes strengthens signal	
	Even if potentially fatal or disabling	
	<b>OTHERWISE: DON'T REPORT</b>	

# But of course there are problems..

- Multiplicity
- Rel risk  $>3$ ?
- What if it almost excludes 0?
- Answer: we are not looking for proof, just reasonable probability, so REPORT

## C. Analysis of a Single Type of Outcome Based on Observing Increased Frequency Relative to Control

Is Imbalance (IMB) Clear?		
Yes: No IMB	Unclear	Yes: IMB
DO NOT REPORT	REPORT IF...	80% CI exclude 0
	Other safety outcomes support causality	AND
	Mech of action and labs support causality	Rel Risk > 2
	Investigators need info to manage patient	AND
	Info might affect pt's willingness to continue	Lumping similar events doesn't make signal disappear
	Pooling similar outcomes strengthens signal	
	Even if potentially fatal or disabling	THEN imbalance CLEAR, so REPORT
	OTHERWISE: DON'T REPORT	

# But of course there are problems..

- Multiplicity
- What if the control is not placebo?
  - Oral anti-diabetic with rosiglitazone as a control
  - Omega-3 fatty acid with other oils as control
- Answer: we are not looking for proof, just reasonable probability, so go to B's tree

# How we learned to stop worrying and love multiplicity\*

- Recall, we are detecting signals
- Trying to cut out a host of false signals
- But a few false ones are acceptable

\*With thanks to Dr. Strangelove

# Ongoing struggles

- Role of the DMC
  - DMCs: traditionally thought about risk vs benefit
  - Cautious about reporting new associated events
- Role of internal pharmacovigilance group
- Who should be unblinded?
- What does meta-analysis tell us

# Appeal to the FDA

- FDA review team must buy into the Final Rule
- FDA should develop a regulatory guidance
- Need harmonization with other reg bodies

# Conclusion

- Stay tuned....more coming in July.....