Identifying and Addressing Safety Signals In Clinical Trials

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Illustration: Cancer Risk with Vytorin in Slowing progression of Aortic-Valve Stenosis

- **SEAS Trial**

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Relative Risk: 1.55  1.78
95% C.I.: (1.13, 2.12)  (1.03, 3.11)

Challenge:

Interpreting safety signals from exploratory analyses
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Primary Goal

Identifying **effective** interventions that are **safe**

⇒ An important objective:

 Obtaining a Timely & *Reliable* Assessment of *Benefit-to-Risk*

 ... Detecting **long** & short term risks...

 ... Detecting **rare** & frequent risks...

 Enabling one to *rule out*

 unacceptable increases in safety risks
Approaches to Pre- and Post-Marketing Evaluation of Safety

I  Passive Surveillance Systems
II Active Surveillance Systems
III Large Randomized Clinical Trials

- Surveillance for new safety signals
- Exploration of existing signals
Passive Surveillance Systems

AERS:
(based on voluntary submission of MedWatch forms for serious AEs caregivers believe might be drug related)

+ Timely information
+ Uniformity of reporting procedure

- Not randomized; no comparator group
- Lack of denominator
- Voluntary submission ⇒ underreporting
Active Surveillance Systems

Large Prospective Cohorts & Linked Databases:

+ Information on a defined population
+ Complete numerators & denominators
+ Fast & inexpensive

– Not randomized
– Confounder information often unavailable
– Outcome sensitivity
– Outcome specificity

… is stated event truly an event?
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Celebrix, Vioxx, Bextra            | CV Death / Stroke / MI RA, OA and Alzheimers | 10            | 1.5                           | 5                    |
| **Long Acting β-Agonists**
Salmeterol, serevant               | Asthma-related Death Severe Asthma | 0.5           | 4                             | 1.5                  |
| **Anti-psychotics**
Ziprasidone                          | QTc related CV Events Schizophrenia | ?             | ?                             | ?                    |
| **Tysabri**                         | Progressive Multifocal Leukoenceph Multiple Sclerosis & Crohn’s Dis. | <0.001?       | 1000                          | 1                    |
| **Rotavirus Vaccine**              | Intussusception High Risk for Rotavirus | 0.1           | >10                           | >1                   |
| Muraglitazar Rosiglitazone         | CV Death / Stroke / MI Type 2 Diabetes | 20            | 1.5 - 2                       | 10-20                |
| Erythropoietin                     | Thrombosis, Death Renal Disease, Oncology | ?             | 1.1-1.15                      | ?                    |
| **ADHD Psychostimulants**
Adderall, Ritalin in Adults         | CV Death / Stroke / MI ADHD Adult Setting | 10            | 2.5                           | 15                   |
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Safety Assessments: Advantages provided by Randomized Prospective Cohorts

- Randomization removes systematically occurring imbalances in baseline characteristics
  ~ Pts/caregivers don’t start/stop treatments “at random”
  ~ Known & recorded covariates are the “tip of iceberg”

- Need to conduct an ITT evaluation
  ⇒ Need ability to define a time 0 cohort
  ~ Assess risk over specified time interval, even if intervention is stopped earlier in time
  ~ Risk cannot be assumed to be independent of duration of exposure
Illustration: Cancer Risk with Vytorin in Slowing progression of Aortic-Valve Stenosis

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95% C.I.: (1.13, 2.12)  

Challenge:

Interpreting safety signals from exploratory analyses

...Hypothesis Confirmation vs. Hypothesis Generation, keeping in mind “random high” type bias
Can Efficacy or Safety Signals Discovered in Exploratory Analyses Be Viewed to be Reliable Results?

• Criteria to be simultaneously satisfied:

✓ << P-values (e.g., Tysabri & PML)

✓ Biologically plausible effect

   ➢ Ezetimibe blocks the absorption of phytosterols and other phytonutrients linked to protection against cancer, which provides some biologic plausibility that the drug could have an effect on the growth of cancer cells

✓ Confirmed by external results
Illustration: Cancer Risk with Vytorin in Slowing progression of Aortic-Valve Stenosis

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Interpreting the SEAS, IMPROVE-IT & SHARP Trials Regarding Cancer Risk with Vytorin

✔ Peto et. al. (NEJM, 2008)
  “The available results from these 3 trials do not provide credible evidence of any adverse effect of ezetimibe on rates of cancer.”

✔ However, safety is established by ruling out unacceptable increases in safety risks…
  …i.e. by what you can say, not what you can’t say…
  Fleming (NEJM, 2008)
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- A relative increase of as much as 84% in cancer deaths with the use of Vytorin cannot be excluded
- IMPROVE-IT and SHARP are ongoing trials:
  - Reduced reliability of interim nature of data
  - The Integrity of these two trials can be disturbed by the release of interim data on safety or efficacy
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- An important safety signal has been identified for Vytorin ...evidence of efficacy is limited to effects on biomarkers
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The PRECISION Trial: 
*Ruling out* Excess Rates of 
CV Death / Stroke / MI

Pain Medications in Patients with 
Osteoarthritis & Rheumatoid Arthritis 
With or at Hi Risk for CV Disease 

Celecoxib 
Ibuprofen 
Naproxen
Using the Proportional Hazards Model for the rate of “CV Death/Stroke/MI”

Naproxen : $\lambda_0(t)$  
Celecoxib : $\lambda_1(t) = \lambda_0(t)r$

Note: With 10 events / 1000 p.y. in the control arm, then $r = 1.333 \Rightarrow 3.33$ add’l events / 1000 p.y., offsetting ↓ in GI ulceration & ↑ analgesic effects

Then $L = 508$ events are required, if one sets:

✓ $H_0 : r = 1.333$  &  $H_1 : r = 1.00$
✓ (one-sided) 2.5% false positive error rate, and
✓ 10% false negative error rate (i.e., 90% power)
“CV Death / MI / Stroke” Events

Celecoxib compared with Naproxen

- **Celecoxib better**
- **Naproxen better**

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Based on analysis at \( L = 508 \) Events

- **A** CEL: superior
- **B** CEL: ruling out unacceptably inferior
- **C** CEL: neither ruling out to be unacceptably inferior, nor establishing as inferior
- **D** CEL: inferior
Performance Standards in Non-inferiority Safety Trials

- **Enrollment Rate**
  - need timely result

- **Target Population / Ineligibility Rate / Event Rate**
  - need to address settings where excess risk is most plausible
  - need sufficiently high risk to achieve targeted number of events

- **Adherence**
  - must at least match adherence in prior trials with safety signal
  - include frequency/timing of withdrawal from rand. treatment

- **Cross-ins**
  - minimize by: careful screening; educating caregivers & patients
    …Very challenging in a post-marketing setting...

- **Retention**
  - critical to maintaining integrity of randomization
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Consequences of Reliance on Surrogate Endpoints For Accelerated or Full Regulatory Approval

- Less reliable evidence regarding Efficacy
- Less reliable evidence regarding Safety

...The stronger the efficacy evidence, the greater the resilience regarding uncertainties about safety...

Recent Experiences:

- Tysabri: PML in Crohns Disease & Multiple Sclerosis
- Erythropoiesis Stimulating Agents: Chemo-Induced Anemia & Hemodialysis in CHF
- Muraglitazar & Rosiglitazone: Type 2 Diabetes
- Simvastatin/Ezetimibe (Vytorin): Aortic Stenosis
Conclusions

An important objective:
Obtaining a Timely & Reliable Assessment of the Benefit-to-Risk Profile...

✓ ...establishing substantial evidence of efficacy
✓ ...enabling one to rule out unacceptable increases in safety risks

“Absence of Evidence is not Evidence of Absence”