Discussion

Robert Platt
McGill University
Seattle Symposium on Healthcare Data Analytics
Is Observational Research Useful for Safety Surveillance?

- Madigan: recognize the limitations
  - Operating characteristics derived from RCTs are inappropriate.
  - How much can good design matter?
    - “Clinical judgment” vs. design principles
    - Map observational design to RCTs
    - Time is critical

- Gruber: what is the alternative?
  - Improve data quality
  - Bias analysis, much more generous bounds
Cook: need *appropriate* methods for signal detection

» Use principles from good sequential RCT methods

React early but not too early

» Cost/benefit (both clinical and $)

What is precise research question?

Need for validation/confirmatory studies?
“Canadian mini-Sentinel” with some twists

Directed research questions from Health Canada
  » Validation, not detection
  » Usually generated based on initial safety signal
  » Methods specific to the research question

Distributed data; no common data model
  » Canadian provinces plus CPRD and US MarketScan

Common protocol/analysis plan
  » Allow for different bias adjustments (within reason) in different sites
  » Allow for understanding of heterogeneity

Meta-analysis if possible
PPIs and Pneumonia

- Conflicting evidence
  - Positive association with short treatment regimens
  - Disappears with longer treatment time

- Problem: subtle protopathic bias
  - Early symptoms similar to GERD

- Solution: restriction to PPI prescribed at same time as NSAID
  - Preventive rather than therapeutic
  - Unconfounded by symptoms
Example

Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis

Kristian B Filion,1 Dan Chateau,2 Laura E Targownik,3 Andrea Gershon,4 Madeleine Durand,5 Hala Tamim,6 Gary F Teare,7 Pietro Ravani,8 Pierre Ernst,1 Colin R Dormuth,9 the CNODES Investigators

➢ Very restricted sample
➢ Conclusion: no association
   » Associations re-appear in unrestricted cohort

<table>
<thead>
<tr>
<th>Site</th>
<th>OR (95% CI)</th>
<th>Weight (%)</th>
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<tbody>
<tr>
<td>Alberta</td>
<td>0.93 (0.50, 1.74)</td>
<td>7.32</td>
</tr>
<tr>
<td>Manitoba</td>
<td>1.09 (0.44, 2.69)</td>
<td>3.47</td>
</tr>
<tr>
<td>Ontario</td>
<td>0.96 (0.72, 1.30)</td>
<td>32.60</td>
</tr>
<tr>
<td>Quebec</td>
<td>1.08 (0.46, 2.56)</td>
<td>3.86</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>3.73 (1.12, 12.36)</td>
<td>1.97</td>
</tr>
<tr>
<td>MarketScan</td>
<td>1.21 (0.78, 1.87)</td>
<td>14.89</td>
</tr>
<tr>
<td>GPRD</td>
<td>1.03 (0.78, 1.37)</td>
<td>35.88</td>
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<tr>
<td>Overall</td>
<td>1.05 (0.89, 1.25)</td>
<td>100.00</td>
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Bottom Line

- We need to learn from observational data
- But we need to better recognize the limitations
  - More work on operating characteristics in controlled conditions
  - Better practice at the *design* stage
  - Better estimation of the *true* uncertainty
Questions

- What CAN we do?
- No choice but to make observational studies better
  - Learn the operating characteristics
  - Or make our conclusions more appropriate?
- Should we do more or different trials?
  - Seems like David’s arguments apply to them too…
  - Can we make them large enough to learn about safety?
  - Pragmatic trials?
  - Registry trials?
    - Rigor of a trial, speed and efficiency of an observational data analysis
    - Feasibility? Cost?
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