Healthcare Database Healthcare Data Science to Quantify Adverse Health Effects

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Conflicts of Interest

PI, Harvard-Brigham & Women’s Hospital Drug Safety Research Center (FDA); Co-Chair, Methods Core of the FDA Sentinel System; Consulting in past year: WHISCON LLC, Aetion Inc. (incl. equity); PI of research contracts to the Brigham & Women’s Hospital: Bayer, Genentech, Boehringer Ingelheim; Grants/contracts from NIH, AHRQ, PCORI, FDA, IMI, Arnold Foundation; Advising FDA, EMA, PCORI, PMDA, Health Canada.
Effectiveness Research with Healthcare Databases

RCT data

Non-interventional data

10%

Research data
- Data collected PRIMARILY for research

- For purpose
  - Data specifically for study purpose

- Other purpose
  - Data intended for other studies

90%

Transactional data
- Data used SECONDARILY for research

- Other purpose
  - Clinical documentation
    - EHR-based studies
    - NDI linkage
    - Lab test databases
    - Some registries

  - Administrative
    - Claims data studies
    - Geocoding/census

Example
- Framingham Study
- Cardiovas Health Study
- Slone Birth Defects Study
- Some registries

Nurses’ Health Study 1
Some registries

Franklin J, Schneeweiss S CPT 2017
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Database Studies

Franklin J, Schneeweiss S CPT 2017
From transactional data to study implementation

A. Dynamic database that records an ongoing stream of new healthcare records in Calendar Time for all enrolled patients:

B. Stabilized data snapshot for research purposes

C. Individual-patient data has arrived in episodes and from various sources

D. Study rules are applied and arranged by Event Time
In-hospital safety examples **blinded** with respect to RCT findings:

**Database Study**

Aprotinin during Coronary-Artery Bypass Grafting and Risk of Death

Sebastian Schneeweiss, M.D., Sc.D., John D. Seeger, Pharm.D., Dr.P.H., Joan Landon, M.P.H., and Alexander M. Walker, M.D., Dr.P.H.

**Risk of death (7d)**

HR = 1.78 (1.56 - 2.02)

**RCT**

A Comparison of Aprotinin and Lysine Analogues in High-Risk Cardiac Surgery

Dean A. Fergusson, M.H.A., Charles MacAdams, Ramiro Arellano, M.D., M.Sc., Raymond Martineau, M.D., Jennifer Clín, and the BART Investigators

**Risk of death (30 d)**

HR = 1.53 (1.06 - 2.22)
CV safety example **blinded** with respect to RCT findings:

**Database Study**

**ARTHRITIS & RHEUMATOLOGY**

Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients With Rheumatoid Arthritis

A Multi-Database Cohort Study

Seoyoung C. Kim,1 Daniel H. Solomon,1 James R. Rogers,1 Sara Gale,2 Micki Klearman,2 Khaled Sarsour,3 and Sebastian Schneeweiss1

**Risk of composite CV outcome**

HR = 0.85 (0.61-1.19)

<table>
<thead>
<tr>
<th>TCZ</th>
<th>No. of subjects</th>
<th>No. of events</th>
<th>Person-years</th>
<th>IR (95% CI)†</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>As-treated analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicare</td>
<td>2,531</td>
<td>17</td>
<td>1,841</td>
<td>0.92</td>
<td>0.70</td>
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<tr>
<td>PharMetrics</td>
<td>2,614</td>
<td>10</td>
<td>2,061</td>
<td>0.49</td>
<td>1.00</td>
</tr>
<tr>
<td>MarketScan</td>
<td>4,073</td>
<td>9</td>
<td>2,999</td>
<td>0.30</td>
<td>1.03</td>
</tr>
<tr>
<td>Combined</td>
<td>9,218</td>
<td>36</td>
<td>6,901</td>
<td>0.52</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**RCT**

**ABSTRACT NUMBER: 3L**

Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multicenter, Noninferiority, Phase 4 Clinical Trial

Jon T. Giles1, Naveed Sattar2, Sherine E. Gabriel3, Paul M. Ridker4, Steffen Gay5, Charlotte C. White3, David Musselman7, Laura Brockwell6, Emma Shittu6, Micki Klearman7 and Thomas F. Meursing8

**Risk of composite CV outcome**

HR = 1.05 (0.77-1.43)

<table>
<thead>
<tr>
<th></th>
<th>Etanercept N = 1542</th>
<th>Tocilizumab N = 1538</th>
<th>Tocilizumab vs Etanercept</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Events, n</td>
<td>78</td>
<td>83</td>
<td>1.05</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.77, 1.43</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Effectiveness Example **blinded** with respect to RCT findings:

**Database Study**

Cardiovascular outcomes associated with canagliflozin versus other non-gliflozin antidiabetic drugs: population based cohort study

Elisabetta Patomo, Allison B Goldfine, Sebastian Schneeweiß, Brett Green, Robert J Glynn, Jun Liu, Seoung C Kim

**Prevention of heart failure hospitalization**

HR = 0.61 (0.47-0.78)

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**RCT**

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, MB, ChB, PhD, Vlado Perkovic, MB, BS, PhD, Kenneth W. Mahaffey, MD, Dick de Zeeuw, MD, PhD, Greg Fulcher, MD, Ngozi Erondu, MD, PhD, Wayne Shaw, DSc, Gordon Law, PhD, Mehul Desai, MD, and David R. Matthews, DPhil, BM, BCCh

**Prevention of heart failure hospitalization**

HR = 0.67 (0.52-0.87)
Safety Example **after** RCT findings were released: **Confirming signal**

**Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes**

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erik Rudefer, Ph.D., Stefano Hanetl, Ph.D., Michaela M. Vlachavakis, M.D., Ph.D., Odd Erik Johansen, M.D., Kari C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

**Empagliflozin and risk of DKA**

1 / 2,333 vs. 3 / 2,345

HR = 2.9 (0.4-20.0)

**SGLT-2 and risk of DKA**

26 / 38,045 vs. 55 / 38,045

HR = 2.2 (1.4-3.6)**
Effectiveness Example after RCT findings were released:

**RCT** followed by **Database Study**

**The NEW ENGLAND JOURNAL of MEDICINE**

*Re-Ly*

Dabigatran versus Warfarin in Patients with Atrial Fibrillation

Safety and effectiveness of dabigatran and warfarin in routine care of patients with atrial fibrillation

Stroke prevention
HR = 0.66 (0.53-0.82)

Stroke prevention
HR = 0.77 (0.54-1.09)
Key information components

❖ **Accurate assessment of Exposure:**
  ▪ Completeness of repeated uses
  ▪ Prescribing vs. dispensing vs. use of drugs
  
❖ **Accurate assessment of Outcome:**
  ▪ High specificity of outcome assessment when estimating relative effect measures: risk ratio, rate ratio, hazard ratio
  ▪ Reasonable sensitivity to preserve event counts

❖ **Complete assessment of Confounders:**
  ▪ Reduced unobserved confounding
  ▪ Pre-exposure measurement to avoid adjustment for intermediates

Interview
Pill counter
How were data generated?

What does that tell us about the quality of data?

For our study? (Fit-for-Purpose)
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Prospective data collection

Retrospective data collection

Blinded regarding study question

Outcome validation studies

Clinical documentation

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Framingham Study (cohort)

Major: **Biennial examination** procedures with extensive examination + interview

Additional: NDI linkage

<table>
<thead>
<tr>
<th>Drug exposure assessment</th>
<th>Current or past use of estrogen @ biennial exam; <strong>No start date, no stop date</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome assessment</td>
<td>Physician review of clinical notes, hospital and physician records and death certificates. New Q waves in ECG since last visit. Stroke confirmed by review panel w/ neurologists</td>
</tr>
<tr>
<td>Confounder assessment</td>
<td>Very detailed, pre-exposure</td>
</tr>
<tr>
<td>Population size</td>
<td>5k – 20k</td>
</tr>
</tbody>
</table>

Nurses’ Health Study (cohort)

Major: Biennial self-administered questionnaires

Additional: Endpoint validation with medical records; NDI linkage

| Drug exposure assessment | “Are you currently taking any of the following medications at least once a week”  
|---|---
|   | No start date, no stop date (Consequences: Hernan et al) |
| Outcome assessment | Non-fatal events: permission for medical records review (exposure blinded)  
|   | Fatal events: Family + Med Records + NDI linkage |
| Confounder assessment | Very detailed, pre-exposure |
| Population size | 100k |


## Fundamental difference between primary vs. secondary data

<table>
<thead>
<tr>
<th>Control over:</th>
<th>Primary (research) data: <strong>Investigator defines measurements</strong></th>
<th>Secondary (transactional): <strong>Business purpose defines measurement</strong></th>
</tr>
</thead>
</table>
| **Which items will be measured** | Targeted measurements for research study  
-> little unobserved factors | Information necessary to get the business done |
| **How items will be measured** | Measurement methods designed by investigator  
-> sufficient accuracy | Measurement good enough for business purpose |
| **What surveillance will be in place to measure items?** | Measurements actively scheduled  
-> high completeness | Measurements tied to healthcare encounters  
-> informative missingness  
(sicker patients with more encounters have more opportunity to have Dx recorded) |

Secondary data work best if business interests are serendipitously aligned with research interests
Examples: Outcome assessment

<table>
<thead>
<tr>
<th>Event surveillance</th>
<th></th>
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<tbody>
<tr>
<td>Medial records review</td>
<td></td>
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<tr>
<td>Death certificate</td>
<td></td>
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<tr>
<td>Ultrasound</td>
<td></td>
</tr>
</tbody>
</table>
Summary (Example)

<table>
<thead>
<tr>
<th>Drug exposure assessment</th>
<th>Research data</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>For purpose</td>
</tr>
<tr>
<td></td>
<td>Data collected PRIMARILY for research</td>
</tr>
<tr>
<td></td>
<td>C (A-)</td>
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<table>
<thead>
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<td></td>
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<tr>
<td></td>
<td>A</td>
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<tr>
<td>5k – 20k</td>
<td>100k</td>
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<table>
<thead>
<tr>
<th>0.1% exposed</th>
<th>Research data</th>
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<td>For purpose</td>
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<tr>
<td></td>
<td>Data specifically for study purpose</td>
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<tr>
<td>5-20</td>
<td>100</td>
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<table>
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<th>1% exposed</th>
<th>Research data</th>
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<tr>
<td>50-200</td>
<td>1k</td>
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Conclusion

❖ There is no single perfect data source or study character

❖ Fit-for-purpose considerations
  ▪ Exposure assessment
  ▪ Endpoint assessment
  ▪ Risk factors assessment before MRI exposure

❖ Clinical data do well
  ▪ In detailed risk factor assessment
  ▪ Outcome assessment

❖ Clinical data struggle:
  ▪ Size
  ▪ Prescription drug assessment