Assessing and minimizing bias in observational comparisons

What is known and what questions remain?

Jessica Franklin
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Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine, Brigham & Women’s Hospital and Harvard Medical School
When and How Can Real World Data Analyses Substitute for Randomized Controlled Trials?

Jessica M. Franklin¹ and Sebastian Schneeweiss¹

Regulators consider randomized controlled trials (RCTs) as the gold standard for evaluating the safety and effectiveness of medications, but their costs, duration, and limited generalizability have caused some to look for alternatives. Real world evidence based on data collected outside of RCTs, such as registries and longitudinal healthcare databases, can sometimes substitute for RCTs, but concerns about validity have limited their impact. Greater reliance on such real world data (RWD) in regulatory decision making requires understanding why some studies fail while others succeed in producing results similar to RCTs. Key questions when considering whether RWD analyses can substitute for RCTs for regulatory decision making are WHEN one can study drug effects without randomization and HOW to implement a valid RWD analysis if one has decided to pursue that option. The WHEN is primarily driven by externalities not controlled by investigators, whereas the HOW is focused on avoiding known mistakes in RWD analyses.
New user design

* Like in RCTs, a new-user design ensures that all patient characteristics are measured (and balanced) before the drug exposure starts. A washout period ensures no use of the study drug and outcomes before cohort entry. The clearly defined inception point of the new use of a drug makes it possible to study drug effects dependent on duration of use and reduces the risk of immortal time bias.

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Claims-based studies of oral glucose-lowering medications can achieve balance in critical clinical variables only observed in electronic health records

Elisabetta Patorno MD¹ ✧ | Chandrasekar Gopalakrishnan MD¹ ✧ |
Jessica M. Franklin PhD¹ | Kimberly G. Brodovicz DrPH² | Elvira Masso-Gonzalez PhD³ |
Dorothee B. Bartels PhD³,⁴ | Jun Liu MD¹ | Sebastian Schneeweiss MD¹

<table>
<thead>
<tr>
<th>Covariate (%)</th>
<th>Lina</th>
<th>DPP-4</th>
<th>Lina</th>
<th>Sulf</th>
<th>Lina</th>
<th>Pio</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7.8</td>
<td>7.9</td>
<td>7.8</td>
<td>8.1</td>
<td>8.0</td>
<td>8.2</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>11.3</td>
<td>10.7</td>
<td>10.8</td>
<td>12.6</td>
<td>12.5</td>
<td>16.4</td>
</tr>
<tr>
<td>Obese</td>
<td>35.8</td>
<td>37.3</td>
<td>36.5</td>
<td>40.3</td>
<td>34.1</td>
<td>35.2</td>
</tr>
<tr>
<td>Duration of diabetes &lt; 3 years</td>
<td>23.8</td>
<td>25.1</td>
<td>29</td>
<td>30.2</td>
<td>23.9</td>
<td>29.7</td>
</tr>
<tr>
<td>Current smoker</td>
<td>8.8</td>
<td>8.9</td>
<td>10.8</td>
<td>10.1</td>
<td>9.7</td>
<td>7.9</td>
</tr>
</tbody>
</table>

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Avoidable methodological mistakes are common

<table>
<thead>
<tr>
<th>Methodological issue</th>
<th>Cohort studies (N=100)</th>
<th>Case-control (N=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immortal Person-Time</td>
<td>66%</td>
<td>58%</td>
</tr>
<tr>
<td>Over-Adjustment</td>
<td>37%</td>
<td>87%</td>
</tr>
<tr>
<td>Inappropriate comparator</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Compared with non-diabetic patients</td>
<td>13%</td>
<td>11%</td>
</tr>
<tr>
<td>2. Compared with non-treated diabetic patients</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>3. Compared with any combination group that includes either 1 or 2.</td>
<td>44%</td>
<td>78%</td>
</tr>
</tbody>
</table>


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Process

Candidate RCTs

Select target RCTs

Set up scalable RWD analytics platform

Reproduce RCTs with RWD

Products

List of RCTs to be reproduced with RWD

Document exclusions:
Limited RWD, Key measurements missing, Extremely strong confounding etc. ...

RWD study infrastructure:

Scalable RWD infrastructure

Quantify accuracy of RWD studies

Expert group guidance
RWD Implementation Process

- Is data quality fit for purpose?
  - Statistical analysis plan shows feasibility/validity.
- Initial analyses show feasibility/validity.
- BWH implements analysis.
- Is setting appropriate for RWD analysis?
- Is data quality fit for purpose?
- RWD analytics platform with audit trail to show what analyses were done at what time.
- Regulator checks and re-analyses.
- Plan for additional analyses.
- Regulatory and HTA consideration.
- Analysis.
- Structured reporting.

Options:
- Yes
- No
- RCT
Thanks!

• JMFranklin@BWH.Harvard.edu
• www.drugepi.org/faculty-staff-trainees/faculty/jessica-franklin/