Real World Evidence: Use, Misuse, and Ensuring High-Quality Output from Databases

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Disclosures

• None
Observational Data

- **Epidemiology**
  - Increasing incidence of colorectal cancer among young adults

- **Clinical outcomes**
  - Association of neoadjuvant chemotherapy and complications after resection of colorectal liver metastases

- **Care delivery research**
  - Racial disparities in receipt of adjuvant chemotherapy in stage III colon cancer

- **Cost-effectiveness**
  - Cost effectiveness analysis of DCD kidney transplantation

- **Comparative effectiveness**
  - Adjuvant chemotherapy is associated with improved OS in pancreatic cancer
What is *real world data*?
Real World Data

• “Data related to patient health status and/or the delivery of health care routinely collected from EHRs, claims and billing data, data from product and disease registries, patient-generated data including home settings, and data gathered from other sources that can inform on health status, such as mobile devices.”

Real World Evidence

• Real world data are analyzed to create real world evidence (RWE), or clinical evidence about “the usage, and potential benefits or risks, of a medical product derived from analysis of RWD.”

**Randomized Controlled Trials**

**Advantages**
- Gold standard
- High internal validity
  - Clearly defined inclusion/exclusion criteria and outcome measures
- Randomization diminishes confounding

**Disadvantages**
- Cost $$$
- Slow to accrue/complete
- Some research questions may not be practical/ethical
- Stringent eligibility → limited generalizability
  - Disparities
## Real World Evidence

### Advantages
- Generalizable data reflective of clinical practice setting
- Expanded inclusion criteria
- Cost effective
- Timely

### Disadvantages
- Concerns about validity
- Confounding/Bias
  - Confounding by indication or selection bias
- Limited information
  - Performance status, treatment intent, duration, compliance, subsequent tx
## Sources of Real World Data

<table>
<thead>
<tr>
<th>Real World Data Source</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Administrative Data</td>
<td>Longitudinal medical history</td>
<td>• Not collected for research purposes</td>
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<tr>
<td></td>
<td></td>
<td>• Loss to follow-up</td>
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<td></td>
<td></td>
<td>• Important clinical endpoints not available (i.e. progression, death)</td>
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<tr>
<td>EHR</td>
<td>Granular data</td>
<td>• Often limited to single facility</td>
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<tr>
<td></td>
<td></td>
<td>• Time intensive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Difficult to abstract unstructured data</td>
</tr>
<tr>
<td>Patient-generated Data</td>
<td>Provides patient perspective</td>
<td>• Not always validated tool</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Lacks clinical data/context</td>
</tr>
<tr>
<td>Patient Registries</td>
<td>Standardized data collection</td>
<td>• Missing data very common</td>
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<tr>
<td></td>
<td></td>
<td>• Lack of uniform assessment of response/progression</td>
</tr>
<tr>
<td>Social Media</td>
<td>Information about patient adherence and experience</td>
<td>• Limited to qualitative data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Selection bias</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Verification is challenging</td>
</tr>
</tbody>
</table>

RWE in Cancer

• Only 2-3% of patients with cancer are enrolled in clinical trial → no data for 97% of patients with characteristics outside clinical trial eligibility

Correlation between Observational Studies & RCTs

# Outcomes of 5-FU for LN+ Colon Cancer

<table>
<thead>
<tr>
<th>Fluorouracil versus none (Referent category)</th>
<th>Mortality from colon cancer</th>
<th>Mortality from other causes</th>
<th>All cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>0.74</td>
<td>0.67–0.82</td>
<td>0.35</td>
</tr>
<tr>
<td>Adjusted †</td>
<td>0.78</td>
<td>0.70–0.87</td>
<td>0.48</td>
</tr>
<tr>
<td>Cox regression adjusted for age and propensity score</td>
<td>0.80</td>
<td>0.72–0.89</td>
<td>0.48</td>
</tr>
</tbody>
</table>

CAUTION

- Use of RWD to demonstrate efficacy when prior RCT have shown lack of efficacy
  - Effectiveness in this situation most likely artifact!
  - Example: Adjuvant chemotherapy for stage 2 CRC
- Be very careful about new therapies based on RWE in isolation

Karim S and Booth C. JCO. 2019.
How do we ensure high-quality output from real world data?
Choosing a dataset

- Clearly define study question and primary endpoint
- Ensure that database is equipped to answer the question
  - Is endpoint available?
    - Select intermediate/short-term endpoint if possible
  - Are the key covariates included?
- Assess limitations of dataset
  - Extent of missing data
  - Rigor of data abstraction
Oncology databases

- **SEER**
  - No chemotherapy data; includes cancer specific survival & overall survival
- **NCDB**
  - Overall survival only
- **SEER Medicare**
  - Only > 65 yrs old
- **Limitations of all:** no recurrence or progression data (RFS/PFS)
How do we address RWD limitations?

• Choose appropriate dataset to answer study question
• Statistical analysis can mitigate bias
  – Examples: multivariable regression, propensity, instrumental variable analysis, matching, stratification
  – BUT - only controls for variables that are known & measurable
• Avoid overinterpretation
• Acknowledge limitations of dataset and methodology
How *should* we define RWD?

- Highly reliable data sets derived from multiple centers
- Data abstracted according to validated protocols
- Data obtained using robust quality assurance and verification

How can we best utilize RWD?

• Identify deficiencies that can guide future trials
  – Rare diseases/excluded populations
• Hypothesis-generating
• Cost of care, resource use, PRO, care delivery
• Comparative effectiveness
  – Can be used to follow-up RCT data: confirm efficacy in “real world population”
  – Expand on efficacy of underpowered RCTs or within subgroups
  – Use intermediate/short-term outcomes if at all possible
  – Proceed with caution


