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

Rebecca A. Snyder, MD, MPH
Assistant Professor of Surgery and Public Health
Brody School of Medicine at East Carolina University
@RSnyder_MD

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."

US FDA. Use of real-world evidence to support regulatory decision-making for medical devices. 2017.

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."*

US FDA. Use of real-world evidence to support regulatory decision-making for medical devices. 2017.

Randomized Controlled Trials

AAS Association for Academic Surgery

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

AAS Association for Academic Surgery

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

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

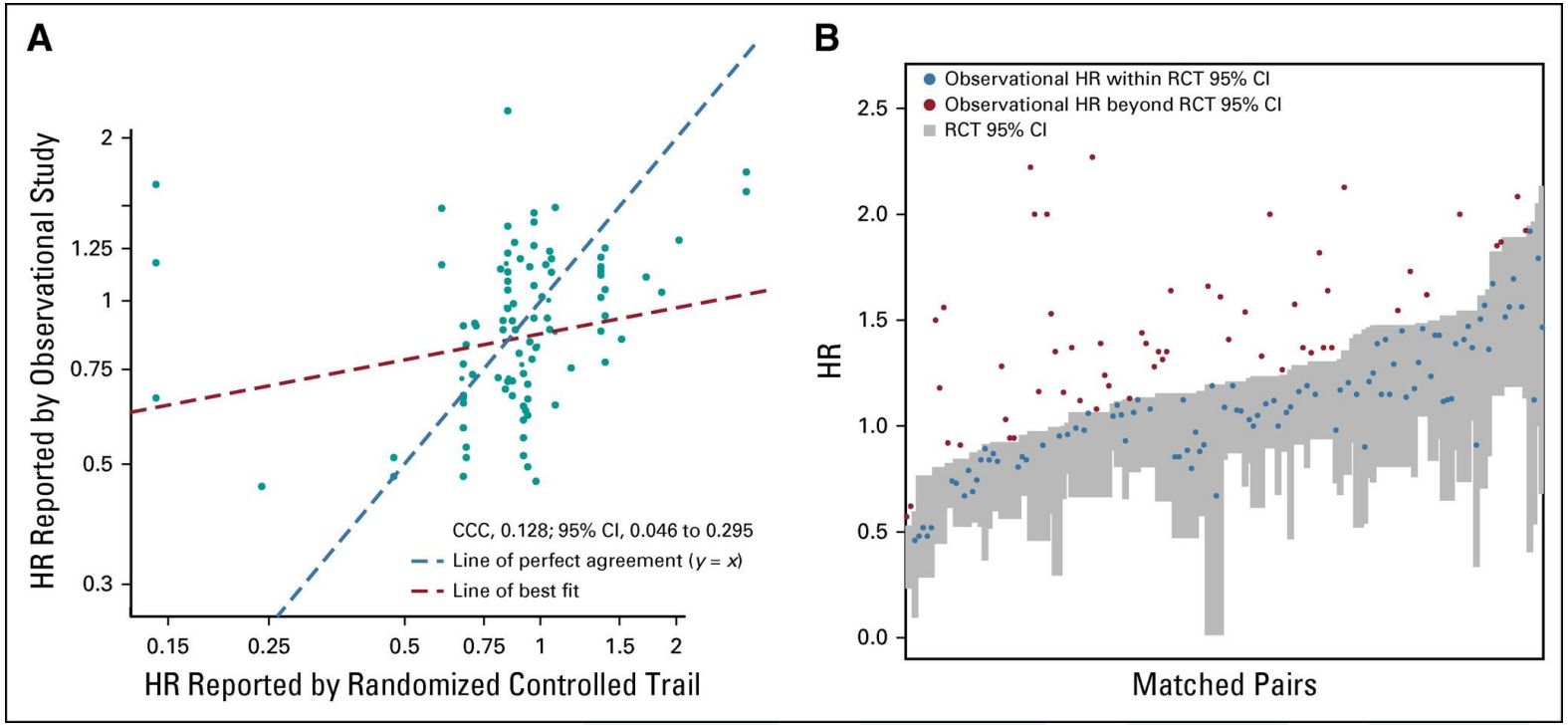
Nabhan et al. JAMA Oncol. 2019.

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

Nabhan et al. JAMA Oncol. 2019.
Sweetenham J. ASCO Connection. 2019.

Correlation between Observational Studies & RCTs



Soni P et al. Comparison of Population-Based Observational Studies with Randomized Trials in Oncology. *JCO.* 2019.

Outcomes of 5-FU for LN+ Colon Cancer

Fluorouracil versus none (Referent category)	Mortality from colon cancer		Mortality from other causes		All cause mortality	
	HR	95% CI	HR	95% CI	HR	95% CI
Unadjusted	0.74	0.67–0.82	0.35	0.31–0.41	0.57	0.53–0.62
Adjusted †	0.78	0.70–0.87	0.48	0.41–0.56	0.66	0.61–0.72
Cox regression adjusted for age and propensity score	0.80	0.72–0.89	0.48	0.41–0.56	0.67	0.62–0.74

Giordano S. Cancer. 2008.

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

Sweetenham J. ASCO Connection. 2019.

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

Key References

Bartlett VL et al. Feasibility of Using Real-World Data to Replicate Clinical Trial Evidence. *JAMA Network Open.* 2019.

Giordano SH. Limits of Observational Data in Determining Outcomes From Cancer Therapy. *Cancer.* 2008.

Karim S and Booth C. Effectiveness in the Absence of Efficacy: Cautionary Tales From Real-World Evidence. *JCO*. 2019.

Nabhan C. et al. Real-world Evidence- What Does It Really Mean? *JAMA Oncol*. 2019.

Soni P et al. Comparison of Population-Based Observational Studies with Randomized Trials in Oncology. *JCO.* 2019.

Stewart M et al. An Exploratory Analysis of Real-World End Points for Assessing Outcomes Among Immunotherapy-Treated Patients with Advanced Non-Small-Cell Lung Cancer. *JCO.* 2019.

Zauderer MG. Practical Application of Real-World Evidence in Developing Cancer Therapies. *JCO.* 2019.