Real-World Data Integration for Causal Inference: Benefits, Costs, and Case Studies

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Michael Grabner, PhD
Principal Scientist
Carelon Research

Edward Yu, ScD
Director
Bristol Myers Squibb

Ruth Dixon, PhD
Sr Researcher
Carelon Research

Patricia Lloyd, PhD, ScM
Health Statistician
U.S. Food and Drug Administration

Disclosures

Michael Grabner is an employee of Carelon Research and stockholder of Elevance Health.

Edward Yu is an employee and stockholder of Bristol-Myers Squibb.

Ruth Dixon is an employee of Carelon Research.

Patricia Lloyd is an employee of the U.S. Food and Drug Administration.

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The views expressed here are those of the authors and not necessarily those of Carelon Research, Bristol-Myers Squibb, or the U.S. Food and Drug Administration.

This workshop is a team effort

Michael Grabner
Carelon Research

Edward Yu
BMS

Ruth Dixon
Carelon Research

Patsy Lloyd
U.S. Food and Drug Administration

Nathan Hill
BMS

Dawn Flick
BMS

Stephan Lanes
Carelon Research

Katherine Harris
Carelon Research

Agenda

1. Basics of integrated data, causal inference, and their interplay (~15 min, Mike)
2. Case Study 1: External Control Arm (ECA) in multiple myeloma (~10 min, Ed)
3. Case Study 2: Directed Acyclic Graphs (DAGs) in colorectal cancer (~10 min, Ruth)
4. Case Study 3: COVID-19 vaccine safety in the *BEST* Initiative; Conclusions (~15 min, Patsy)

Audience polls will be conducted throughout; Q&A at the end.

Learning objectives

Participants will be able to…

1. List and describe the benefits and challenges of integrating RWD
2. Understand the relationships between integrated data and observational study biases
3. Reference and discuss multiple case studies
4. Critique studies using integrated data for causal inference

Part 1

What are Real World Data & Real-World Evidence?

Real-World Data

Data on the effects of health interventions that are routinely collected, outside the scope of conventional randomized controlled trials

- EHR
- Claims
- Wearables
- Mortality data
- Census data

Real-World Evidence

Insights derived from the analysis of RWD

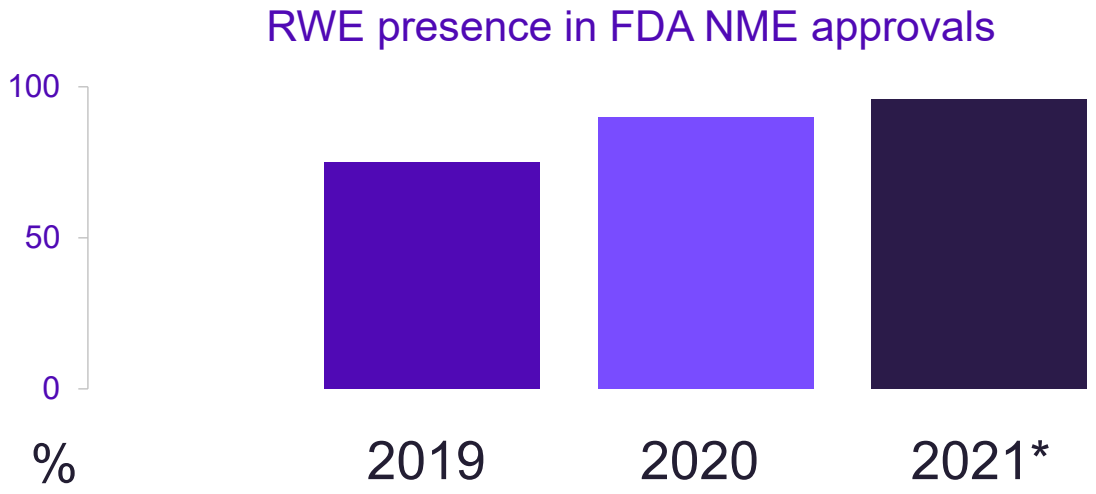
https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

RWD & RWE have many advantages…

- Less time and cost compared with a clinical trial
- May be able to perform research that wouldn't be possible in a clinical trial
- Detection of less frequent side-effects
- Possibility of understanding therapeutic journeys in very large patient groups

And regulating agencies recognize the value

From 2019 – 2021*, 116 out of 136 new molecular entity (NME) approvals from the FDA featured RWE – and the use of RWE increased over time[1]



*Data included first half of 2021

Purpura, C.A., Garry, E.M., Honig, N., Case, A., & Rassen, J.A. (2022). The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clinical Pharmacology & Therapeutics*, 111(1), 135-144.

What is integrated RWD?

Integrated RWD

Datasets produced by linking or cross-referencing two or more sources of RWD

- EHR
- Claims
- Wearables
- Mortality data
- Census data

Why is integrated RWD especially useful?

When it comes to RWD, the whole is greater than the sum of its parts

Integrated RWD can…

Give us a longitudinal view of the patient journey	Cover for blind spots in individual RWD data sets	Enhance existing analytical/ methodological processes	Enable brand new approaches

RWD integration does come with challenges

Collaboration	Security, ethics and compliance
Finding common ground across stakeholders	Protecting data and patient privacy

Data interoperability	Data quality	Data availability
Communicating, exchanging, and using data	Ensuring accurate integration and reliability of measures	Establishing feasible sample sizes

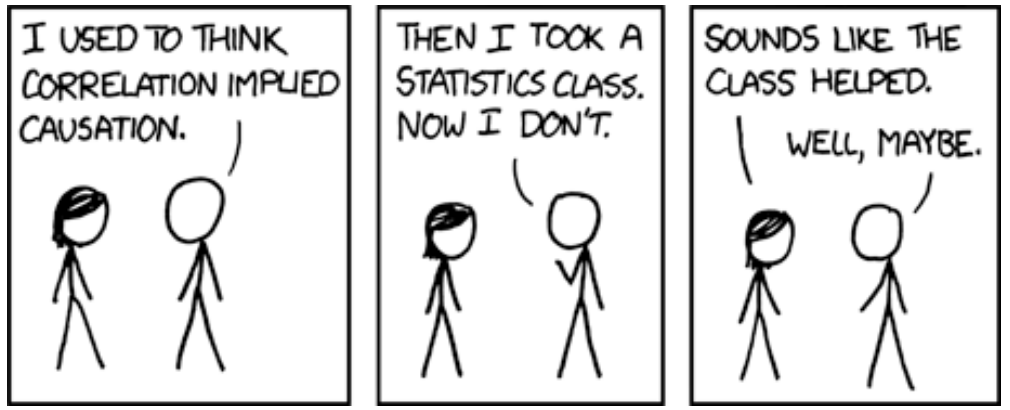
What is causal research?

Association | Intervention | Counterfactual

Modern causal research in healthcare aims to **quantify** causal effects of an intervention in order to improve decision-making

Human behavior seeks to optimize outcomes, and observed relationships rarely reflect causal relationships

Most research intends to uncover causal effects and our language should reflect that (Hernan 2018)



xkcd: Correlation

PEARL, J. (2000). Causality: Models, Reasoning, and Inference. Cambridge University Press, New York. 2nd edition, 2009 | Hernán MA. The C-Word: Scientific Euphemisms Do Not Improve Causal Inference From Observational Data. Am J Public Health. 2018 May;108(5):616-619

Common biases in observational study designs

Confounding	Variables that affect both exposure and outcome induce spurious correlation
Measurement	Observed values deviate from underlying true value
Selection	Study sample selection is related to both exposure and outcome
Time-related	Follow-up time and exposure status are inadequately taken into account

Prada-Ramallal G, Takkouche B, Figueiras A. Bias in pharmacoepidemiologic studies using secondary health care databases: a scoping review. BMC Med Res Methodol. 2019 Mar 11;19(1):53

Using integrated RWD sources can increase confidence in the estimated causal relationships

Confounding	More covariates allow for better adjustment of our causal estimate for confounding
Measurement	Information from multiple sources can help estimate and reduce missingness and misclassification of exposures, outcomes, and covariates
Selection	Trade-off: ➕ Effect robustness can be assessed across multiple databases ➖ Higher potential for introducing selection bias (e.g., subgroup with labs)
Time-related	Neutral (design-driven)

Part 2

Disclosures

- **Edward Yu is an employee and stockholder of Bristol-Myers Squibb.**

RWE is a major regulatory priority for health authorities globally, with interest accelerated following COVID-19

FDA

2016: 21st Century Cures Act

2018: FDA RWE Framework

2019: Draft Guidance on Submissions Containing RWE

2021:

- Draft Guidance on EHR/Claims Data
- Draft Guidance on Registry Data
- Draft Guidance on RWD Standards
- Draft Guidance on Considerations for RWD/E

2022:

- Final Guidance on Submitting RWE
- Advancing RWE Pilot Program

2023:

- Advancing RWE Pilot Program
- Draft Guidance on RW External Controls
- Draft Guidance on RCTs leveraging RWD Elements
- Draft Guidance on Non-Interventional Studies
- Draft Guidance on using RWE to support regulatory decision-making for medical devices

EMA

2017: EMA/HMA Big Data TF Initiated

2018: EMA Regulatory Science to 2025 Initiated

2020: EC Pharmaceutical Strategy for Europe Adopted

2021: Multiple Big Data Workshops

2021: Registry-Based Studies Final Guideline

2022:

- DARWIN EU Launched
- Draft Data Quality Framework
- Draft Good Practices Guide for the Use of the Metadata Catalogue for RWD Sources

2023: RWE framework for decision-making

PMDA

2019: Registry Consultation Pathway

2020: Database Consultation Pathway

2021: PMDA Final Guidance on Basic Principles on the Use of Registries

2021: PMDA Final Guidance on Reliability Assurance of Registry Data

2021: PMDA/Trade Association RWE Working Group Established

2022: Guidance for using registry and medical databases for drug approvals

2023: Guidance for using registry and medical databases for regenerative medical product approvals

Rest of World

Taiwan

- **2020:** Final TFDA Guidance on Basic Consideration for RWE
- **2021:** Final TFDA Guidance on Relevance and Reliability of RWD; Final Guidance on Submitting RWE

Canada

- **2019:** HC Notice Optimizing RWE
- **2022:** Joint CADTH/HC Draft Guidance on Reporting RWE

Australia

- **2021:** TGA Holding Paper on RWE

Brazil

- **2021:** AVNISA RWE Workshops

Switzerland

- **2022:** Swiss medic RWE Position Paper

MHRA

2021: MHRA Final Guideline on RWD to Support Regulatory Decisions

2021: MHRA Final Guideline on RCTs Generating RWE

NMPA

2020: Final Guideline on Using RWE in Drug Evaluation; Final Guideline Pediatric RWE

2021: Final Guideline on Data Considerations with RWD

2022: Draft Guideline on RWE Protocol Development; Draft Guideline on CDE RWE Meetings)

International

ICH – 2022: Plan for Guidance on Safety Pharmaco-epi RWE

ICRMA – 2022: ICRMA Joint Statement on International Collaboration to Enable RWE for Regulatory Decision-Making

Overview of results by guidance category

Most major health authorities have released frameworks on RWE

US FDA, EMA, Health Canada, Japan PMDA, China NMPA, and Taiwan FDA

Data quality guidance and fit for use standards is often an important next step

NMPA and PMDA released dedicated guidance on data quality in 2021. Additional HAs released guidance spanning multiple topics including data quality. Multiple FDA guidance documents in 2022.

Methods guidance

Countries are now releasing methods guidance largely focused on RCTs incorporating RWE or guidance discussing multiple topics including general study methods (FDA, EMA, China, Japan, and Taiwan)

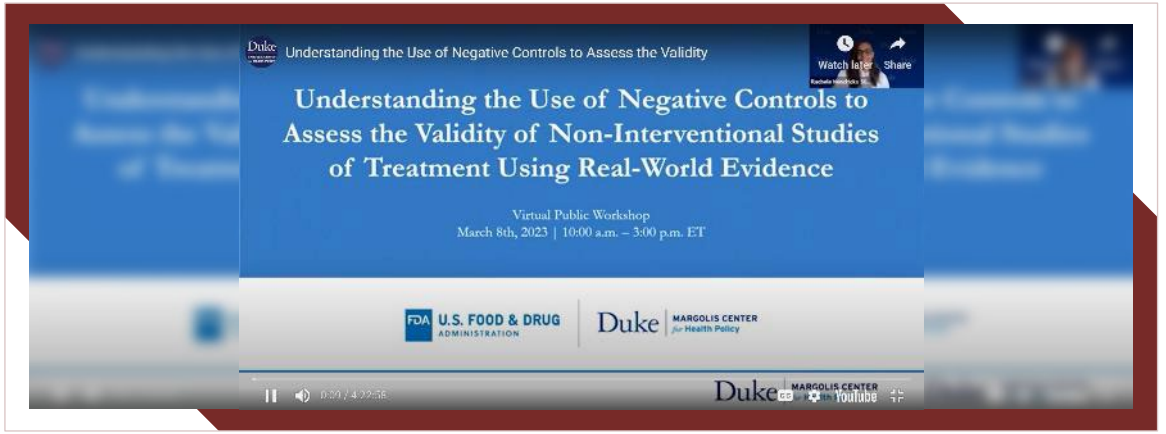
FDA Guidance on Externally Controlled Trials

What is in-scope?

- Considerations for the design and analysis of externally controlled trials to study the effectiveness and safety of drugs
- Risks to the validity of trial results from potential bias
- Focuses on the use of patient-level data from other clinical trials or from Real-world Data (RWD) sources, e.g., registries, EHR, claims
- Considerations related to communicating with FDA and ensuring access by FDA to data from an externally controlled trial

Addressing potential bias

- Unmeasured confounding, lack of blinding, and other sources of bias cannot be eliminated in externally controlled trials
- Critically important in the conduct of such trials to:
  - Assess the extent of confounding and bias
  - Use of analytic methods to reduce the impact of such bias

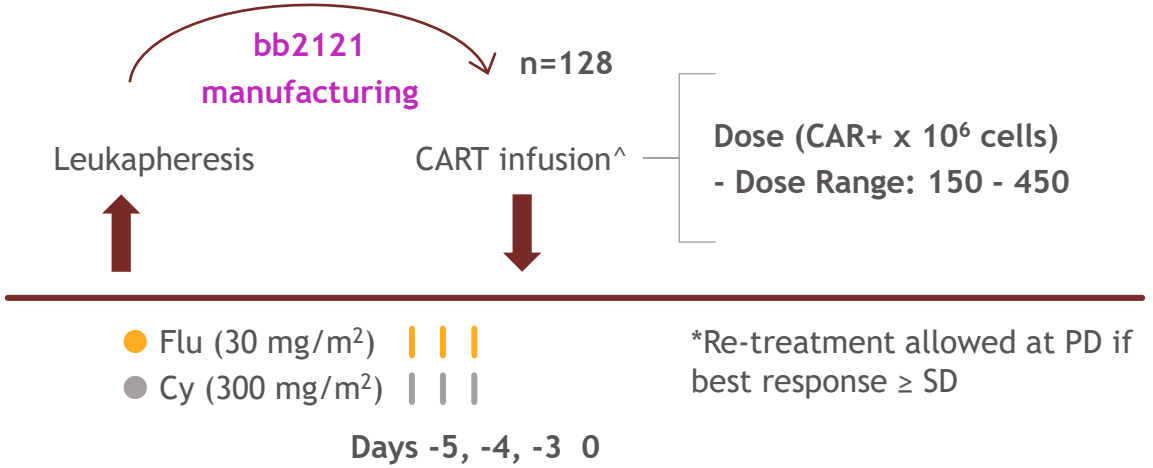


External Control in RRMM as part of EMA filing
(Aug-2021 EMA Approval)[1]

Abecma (idecabtagene vicleucel)

KarMMa (MM-001) was a single arm trial investigating Abecma in Relapsed Refractory Multiple Myeloma (RRMM):

RRMM:
- Received ≥3 prior MM treatment regimens
- Received ≥2 consecutive cycles of each regimen
- Received an immunomodulatory
- agent, PI and anti-CD38 mAB
- Refractory to last treatment regimen



- **Primary endpoint:** ORR
- **Secondary endpoints:** CT, TTR, DoR, PFS, TTP, OS, MRD, HRQoL

PRIME EMA meeting (2018)

- Main limitation of KarMMa is the single arm design, with lack of control/comparator arm
- ***Due to number of products approved, EMA recommended to consider an External Control Group to demonstrate significant benefit***
  - The Agency acknowledged plan for Systemic Literature Review (SLR), but noted that without an external control arm with patient-level data, the approach may result in difficulties quantifying the magnitude of benefit

1. EPAR Assessment Report. EMEA/H/C/004662/0000. CHMP. EMA. 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/abecma-epar-public-assessment-report_en.pdf

EMA Feedback on submitted RWE (EPAR)
(Aug-2021 EMA Approval)[1]

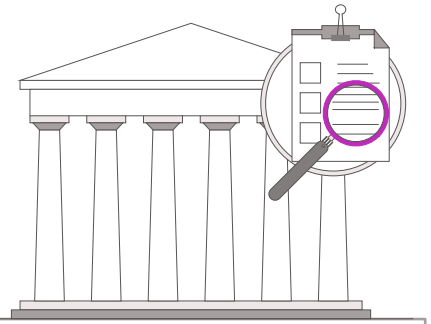
Abecma (idecabtagene vicleucel)

- **Results of External Comparison**
  - The comparison showed *"**clinically relevant and statistically significant benefit** for ide-cel across all pre-defined efficacy endpoints"*
  - The efficacy results compared *"favourably to those in the matched RW historical cohort as well as those reported in the literature"*
- **Limitations**
  - *"Despite extensive efforts to match the patient population, the comparison was limited by several factors including:*
    - *"long time period (up to 60 days from the index date) allowed for collection of baseline data"*
    - *"overlapping recruitment periods of the RWS and the MM-001 at the same study centers"*
    - *"large proportion of **missing data** (up to 30%) for some included co-variates and **several co-variates excluded** from the PS model due to >30% missing data"*
- **Conclusions**
  - *"**Despite the limitations** of the indirect treatment comparisons, the results indicate that ide-cel treatment is associated with responses that are well above those reported with current standard of care"*

ABECMA granted Conditional Approval as the first cell therapy authorized for the treatment of RR MM in the EU

1. EPAR Assessment Report. EMEA/H/C/004662/0000. CHMP. EMA. 2021. Available at: https://www.ema.europa.eu/en/documents/assessment-report/abecma-epar-public-assessment-report_en.pdf

Regulators are leading in RWE guidance – and payors are starting to follow suit



Ultimately, payors…

Care about high quality evidence

Recognize the value of measuring outcomes in the covered population

NICE National Institute for Health and Care Excellence

NICE real-world evidence framework

"Real-world data can be used to **contextualise randomised trials**, to **estimate effects of interventions** in the absence of trials, or **to complement trials** to answer a broader range of questions about the impacts of interventions in routine settings."[1]

1. NICE real-world evidence framework, June 2022. Available at: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

Part 3

Case study 2 – Directed Acyclic Graphs (DAGs) in colorectal cancer

Ruth Dixon, PhD
Senior Researcher
Carelon Research

Disclosures & acknowledgments

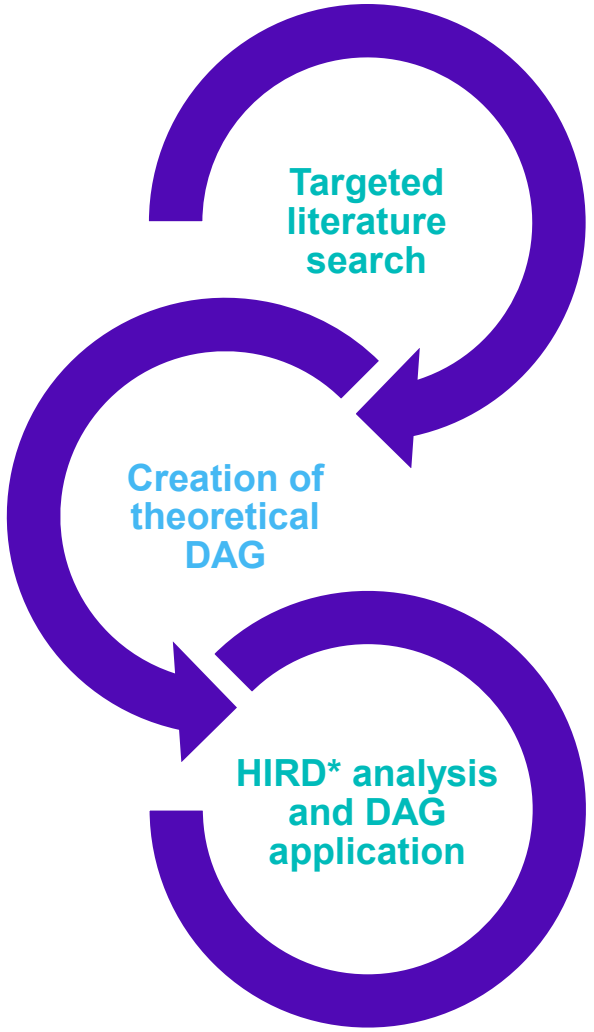
Ruth Dixon is an employee of Carelon Research.

Carelon Research received funding from Bristol-Myers Squibb (BMS) for the conduct of this study.

Overview

Study objective: to systematically build a directed acyclic graph (DAG) to depict causal pathways between first-line (1L) treatment and survival among patients with metastatic colorectal cancer (mCRC)

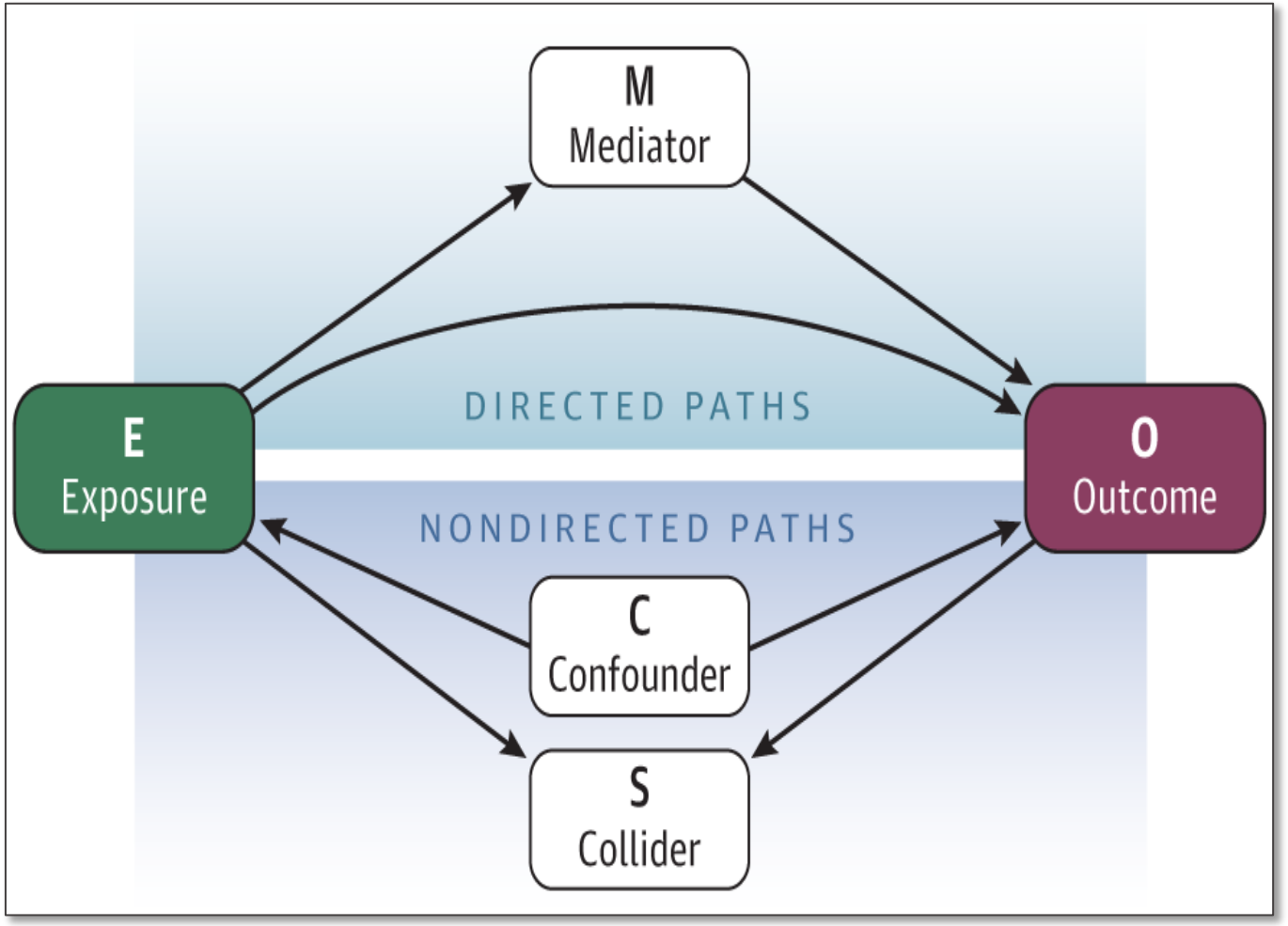
Study design: Two targeted literature searches; plausibility assessments to create a theoretical DAG; analysis of integrated data to distinguish measured from unmeasured confounders, estimate bivariate relationships, and calculate DAG-implied unconditional independencies.



*Carelon Research's *Healthcare Integrated Research Database*

What are DAGs?

- DAGs are graphical models used to encode assumptions about the data-generating process
- DAGs depict relationships between variables and are used to study causal relationships between exposures and outcomes
- The nodes/vertices correspond to variables of potential interest in a study
- Edges/arrows depict hypothesized direct causal effects



Lipsky AM, et al. JAMA. 2022;327(11):1083-1084

Variables (i.e., nodes)

Age

ECOG* performance status

Prior chemotherapy

Location of primary tumor

Surgery of primary tumor

Number of metastatic sites

Liver-only metastasis

Intrahepatic tumor burden

Surgical/resection of metastases

Synchronous versus metachronous metastases

KRAS and BRAF mutation status

Microsatellite instability/mismatch repair status (MSI/MMR status)

Number of prior treatment lines (N/A)

Biological sex

Race/ethnicity

Prior radiotherapy

Stage at first diagnosis

Tumor differentiation

Initially resectable metastatic disease

Lung-only metastases

Metastasis to peritoneum

Comorbidities

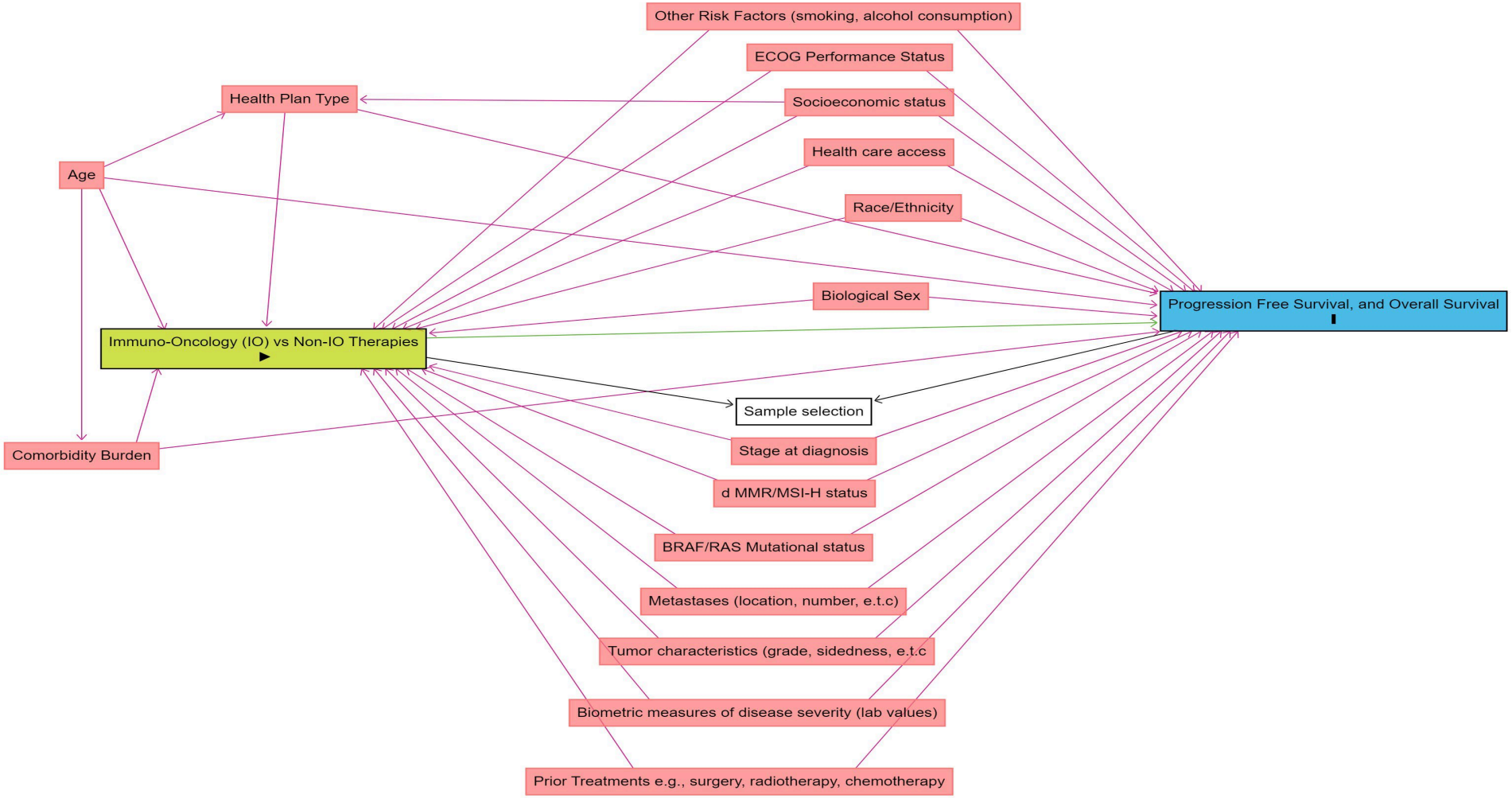
Biometric measures of disease severity (laboratory values)

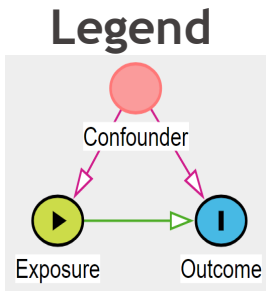
- Lactate dehydrogenase (LDH)
- Alkaline phosphatase (ALP) albumin
- platelet count
- Carcinoembryonic antigen (CEA)

Two targeted literature searches identified 94 RCTs and 22 RWD studies, from which 28 variables were extracted.

*The ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability; Goey KKH, et al. Eur J Cancer. 2018;100:35-45

The theoretical DAG





All 28 variables considered as potential confounders (e.g., race/ethnicity) or colliders (e.g., sample selection) relative to the treatment-outcome relationship were built into the DAG. The DAG was created using the free online tool DAGitty (https://www.dagitty.net/); Textor J, et al. Int J Epidemiol. 2016;45(6):1887-1894

Real-world data application

Healthcare Integrated Research Database (HIRD®): integrated enrollment files, medical and pharmacy claims, clinical EHR and cancer care quality program data, SDoH, mortality, from a large US payer.

We applied our DAG to the HIRD in order to:

- Distinguish measured from unmeasured confounders (feasibility assessment)
- Calculate bivariate associations between exposure, outcome, and each confounder to assess the relative strength of the relationships: a weak relationship, combined with other supporting information, may allow researchers to remove/reverse arrows
- Calculate DAG-implied unconditional independencies between confounders: a strong relationship may indicate that arrows must be added

Patient characteristics

Demographics and clinical characteristics of metastatic colorectal cancer patients in the HIRD from 2014-01-01 to 2023-05-31			
	All patients	**IO**	**Non-IO***
Sample size	9,046	213	8,866
Age (years), median (IQR)	57 (50-63)	60 (50-71)	57 (50-63)
Age ≥ 65 years, n (%)	1,795 (19.8%)	71 (33.3%)	1,730 (19.5%)
ECOG performance status grouping, n (%)			
0	2,890 (46.0%)	58 (32.6%)	2,842 (46.3%)
1	3,021 (48.1%)	104 (58.4%)	2,932 (47.8%)
2	330 (5.3%)	15 (8.4%)	317 (5.2%)
3	41 (0.65%)	<5	41 (0.67%)
4	<5	0	<5
Prior chemotherapy, n (%)	2,391 (26.4%)	55 (25.8%)	2,362 (26.6%)

ECOG, Eastern Cooperative Oncology Group; the ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability. The scores are derived from the CCQP data and integrated in the HIRD. IO, immuno-oncology.
*IO and non-IO populations are not mutually exclusive. There are 33 patients in the non-IO cohort that also had a claim for an IO therapy in the 30 days pre/post mCRC case start.

Bivariate associations

Potential confounders	Directed arrows	Sample size	Measure of association (odds ratio)	95% CI	p-value	Notes and interpretation
Age *(≥65 years vs. <65 years)*	Exposure (IO therapy vs non-IO therapies)	9046	2.35	1.74 – 3.16	<0.01	Strong evidence for relationship
	Overall Survival	9046	1.61	1.43 – 1.81	<0.01	Strong evidence for relationship
ECOG performance status *(0 vs 1+)*	Exposure (IO vs non-IO therapies)	6283	1.87	1.33 – 2.61	<0.01	30% Data Missing; Strong evidence for relationship
	Overall Survival	6283	1.67	1.47 – 1.9	<0.01	30% Data Missing; Strong evidence for relationship
Prior chemotherapy *(Yes vs No)*	Exposure (IO vs non-IO therapies)	9046	0.60	0.41 – 0.87	<0.05	Strong evidence for relationship
	Overall Survival	9046	1.63	1.47 – 1.82	<0.01	Strong evidence for relationship

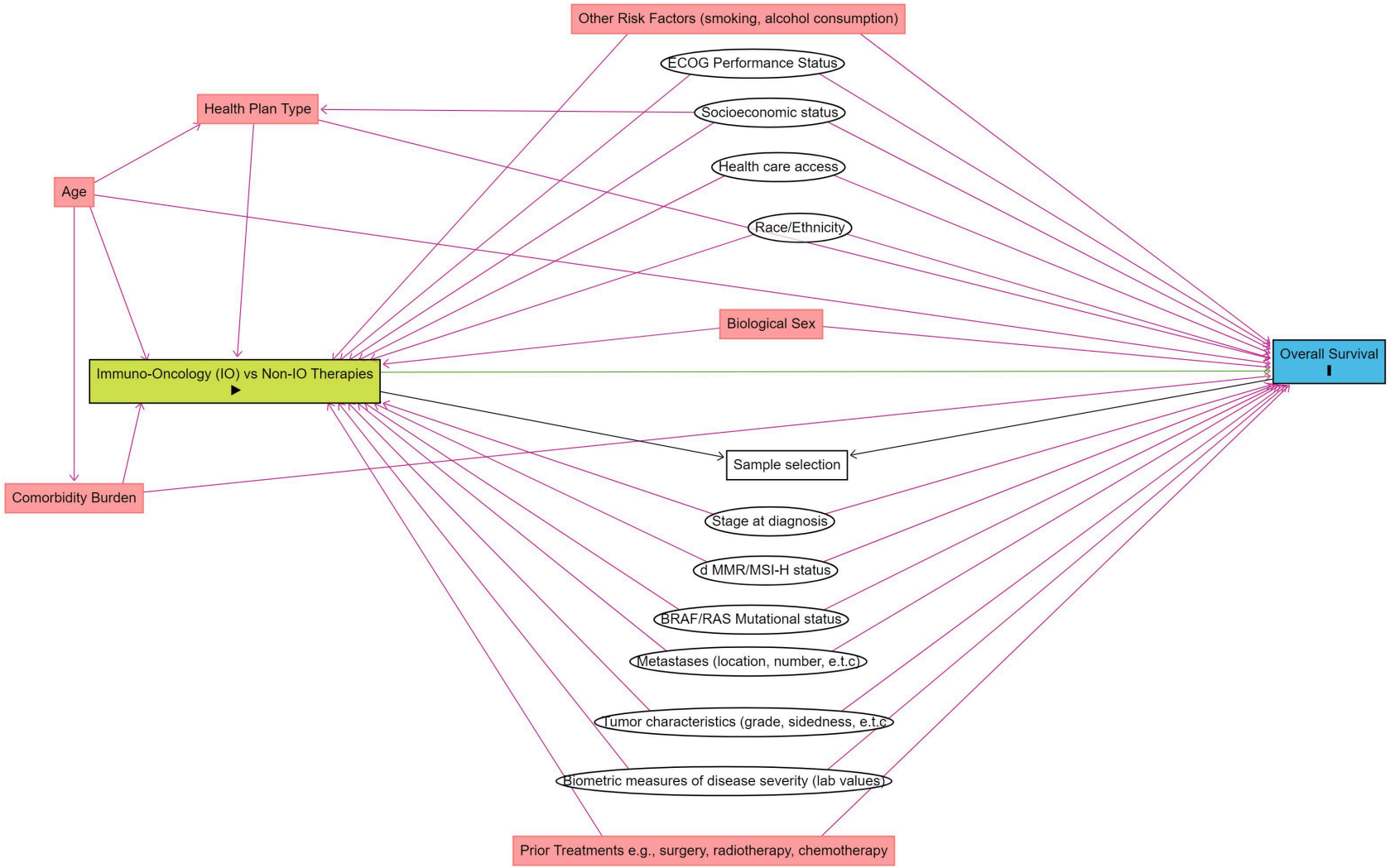
ECOG, Eastern Cooperative Oncology Group; the ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability. The scores are derived from the CCQP data and integrated in the HIRD. IO, immuno-oncology

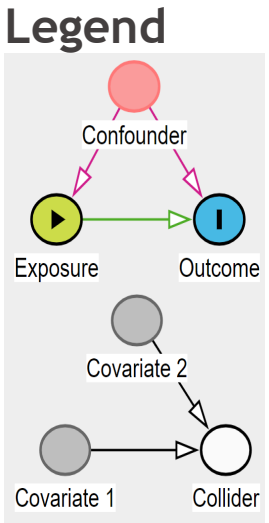
DAG-implied independencies

Variable	DAG-implied independency	Sample size	Measure of association (odds ratio)	95% CI	p-value	Notes and interpretation
ECOG performance status (*0 vs 1+)*	ECOG ⊥ Age*	6283	1.84	1.62 - 2.09	<0.01	strong evidence for relationship; older members much more likely to have worse ECOG. Causal directionality can go both ways
Prior chemotherapy (*Yes vs No*)	Prior chemotherapy ⊥ Age	9046	0.94	0.83 – 1.05	0.27	Weak evidence for relationship

ECOG, Eastern Cooperative Oncology Group; the ECOG Performance Status Scale describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability. The scores are derived from the CCQP data and integrated in the HIRD.
*Defined as ≥65 years vs. <65 years

Claims-only DAG – Any single data source will lack important confounders

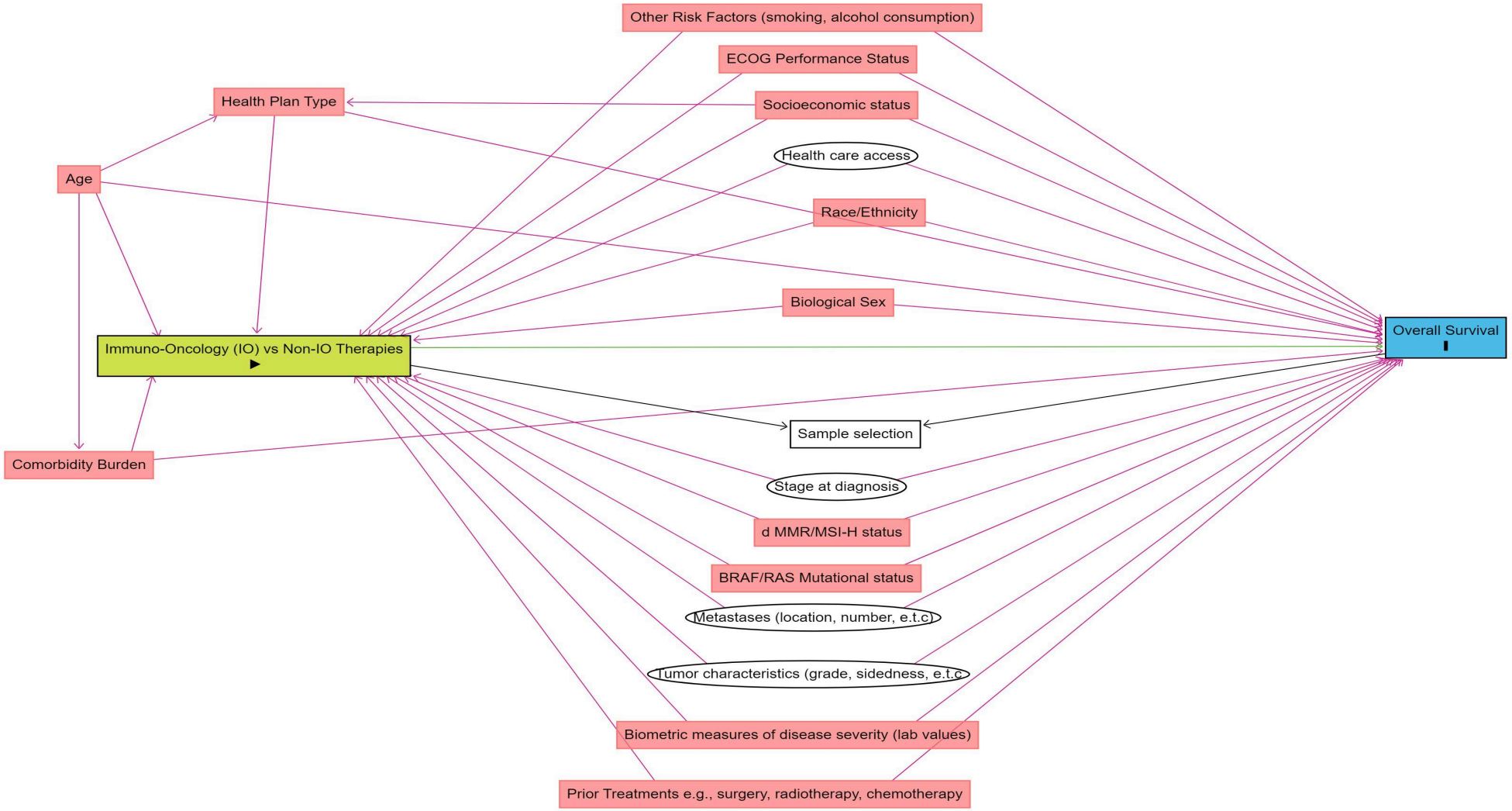


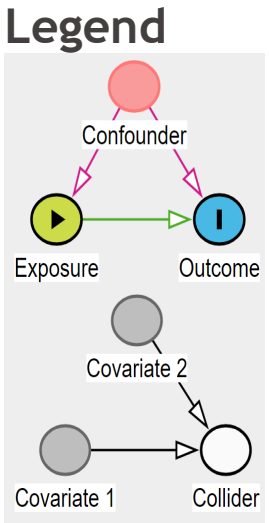


Created using the free online tool DAGitty (https://www.dagitty.net/)

Textor J, et al. Int J Epidemiol. 2016;45(6):1887-1894

Integrated RWD DAG – Example of unmeasured variables





Created using the free online tool DAGitty (https://www.dagitty.net/)
Textor J, et al. Int J Epidemiol. 2016;45(6):1887-1894

Conclusions

- Creating DAGs in a systematic and efficient manner, informed by existing literature and plausibility assessments, provides transparency when estimating causal effects from RWD and can reduce bias in the chosen statistical model.
- DAGs do not provide guidance on the appropriate functional form of the exposure-outcome relationship, how to deal with missing or misclassified data, how to quantify biases, or how to identify effect measure modifiers.
- To learn more about the mCRC case study, I invite you to the "Novel outcomes Research Data Methods" Podium session (P55) on Wednesday 08 May 2024, 8:45am – 9:45am.

References

1) Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). *Ann Oncol*. 2016;27(1):121-127. doi:10.1093/annonc/mdv491

2) Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. *Ann Oncol*. 2018;29(7):1528-1534. doi:10.1093/annonc/mdy140

3) Datta SS, Ghosal N, Daruvala R, et al. How do clinicians rate patient's performance status using the ECOG performance scale? A mixed-methods exploration of variability in decision-making in oncology. *Ecancermedicalscience*. 2019;13:913. Published 2019 Mar 28. doi:10.3332/ecancer.2019.913

4) Ferguson KD, McCann M, Katikireddi SV, et al. Evidence synthesis for constructing directed acyclic graphs (ESC-DAGs): a novel and systematic method for building directed acyclic graphs [published correction appears in Int J Epidemiol. 2020 Feb 1;49(1):353]. *Int J Epidemiol*. 2020;49(1):322-329. doi:10.1093/ije/dyz150

5) Goey KKH, Sørbye H, Glimelius B, et al. Consensus statement on essential patient characteristics in systemic treatment trials for metastatic colorectal cancer: Supported by the ARCAD Group. Eur J Cancer. 2018;100:35-45. doi:10.1016/j.ejca.2018.05.010

6) Lipsky AM, Greenland S. Causal Directed Acyclic Graphs. JAMA. 2022;327(11):1083-1084. doi:10.1001/jama.2022.1816

Part 4

Real-World Data Integration for Causal Inference

Case Study for COVID-19 Vaccine Safety Surveillance

ISPOR May 6, 2024

Patricia C. Lloyd, PhD, ScM
U.S. Food and Drug Administration (FDA)
Center for Biologics Evaluation and Research (CBER)

Disclosure

- The views expressed here are those of the authors and not necessarily those of the U.S. Food and Drug Administration.

- The U.S. Food and Drug Administration funded this study.

- No personal or financial relationships relevant to this presentation existed during the past 12 months or during the conduct of the study.

CBER Surveillance Program

CBER-Regulated Products


Vaccines (preventative and therapeutic)


Blood (components and derived)


Human Tissues and Cellular Products


Gene Therapies


Xenotransplantation Products

FDA CBER Mission Focus

Ensure biologic-product safety and effectiveness

CBER Surveillance Program's Vision

To create and utilize an effective national post-market surveillance system for CBER-regulated products to provide data for evidence-based regulatory decisions

FDA CBER Active Surveillance Program Collaborative

Through multiple contracts and partnerships, CBER works with a diverse group of epidemiologists, clinicians and data scientists to conduct active surveillance studies.

BEST: Biologics Effectiveness and Safety

Federal Partner and BEST Initiative Data Sources

Data Source*	Database Type	Number of Patients Covered (Millions)	Time Period Covered
CMS - Medicare	Claims	105	2005 - present
Blue Health Intelligence	Claims	46	2012 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	30	2017 – present
Carelon Research	Claims	69	2010 – present
CVS Health	Claims	37	2018 – present
Optum EHR	EHR	102	2007 - 2020
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 - 2020

*Data lag varies for different databases.

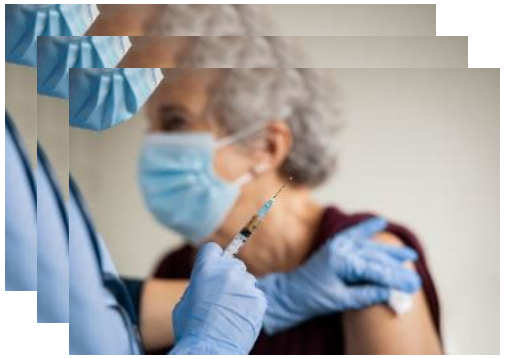
COVID-19 Vaccine Safety Surveillance

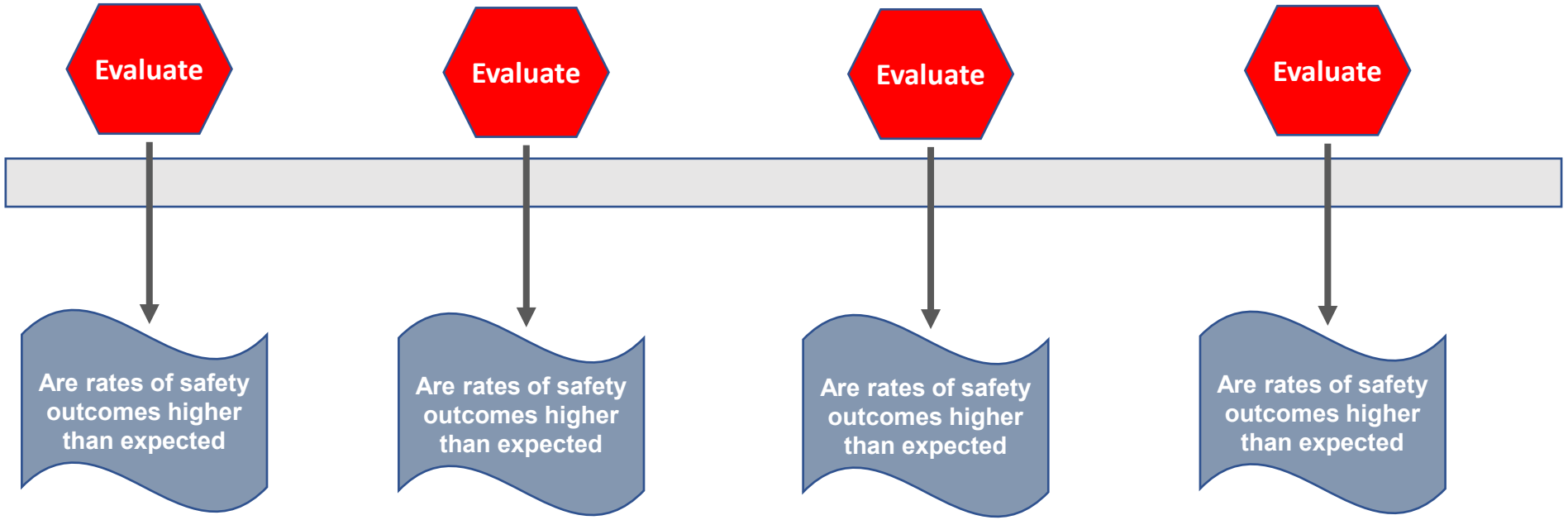
- **Signal Detection**
  - Near Real-time Surveillance

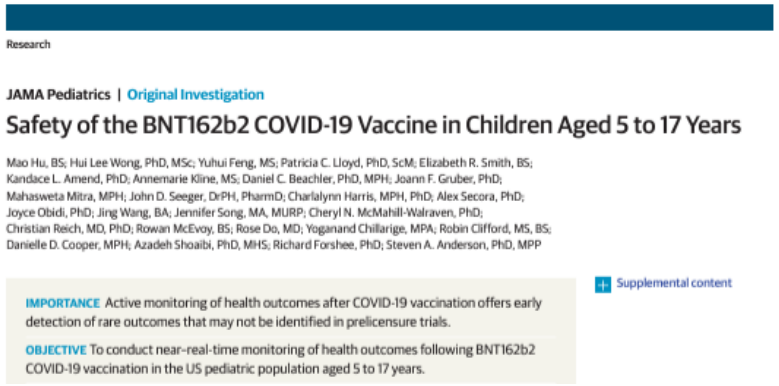
- **Signal Evaluation**
  - Cross-check with other federal surveillance systems
  - Additional Analysis
  - Fully adjusted epidemiologic studies

COVID-19 Vaccine Safety Surveillance

Signal Detection







Research

JAMA Pediatrics | Original Investigation

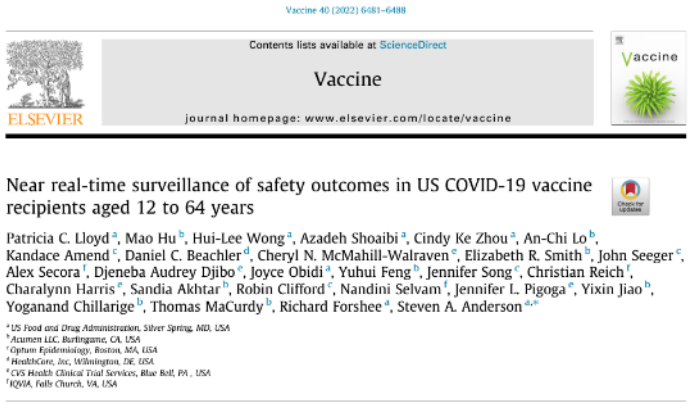
Safety of the BNT162b2 COVID-19 Vaccine in Children Aged 5 to 17 Years

Mao Hu, BS; Hui Lee Wong, PhD, MSc; Yuhui Feng, MS; Patricia C. Lloyd, PhD, ScM; Elizabeth R. Smith, BS; Kandace L. Amend, PhD; Annemarie Kline, MS; Daniel C. Beachler, PhD, MPH; Joann F. Gruber, PhD; Mahasweta Mitra, MPH; John D. Seeger, DrPH, PharmD; Charlalynn Harris, MPH, PhD; Alex Secora, PhD; Joyce Obidi, PhD; Jing Wang, BA; Jennifer Song, MA, MURP; Cheryl N. McMahill-Walraven, PhD; Christian Reich, MD, PhD; Rowan McEvoy, BS; Rose Do, MD; Yoganand Chillarige, MPA; Robin Clifford, MS, BS; Danielle D. Cooper, MPH; Azadeh Shoaibi, PhD, MHS; Richard Forshee, PhD; Steven A. Anderson, PhD, MPP

Supplemental content

IMPORTANCE Active monitoring of health outcomes after COVID-19 vaccination offers early detection of rare outcomes that may not be identified in prelicensure trials.

OBJECTIVE To conduct near-real-time monitoring of health outcomes following BNT162b2 COVID-19 vaccination in the US pediatric population aged 5 to 17 years.



Vaccine 40 (2022) 6481–6488

Contents lists available at ScienceDirect

Vaccine

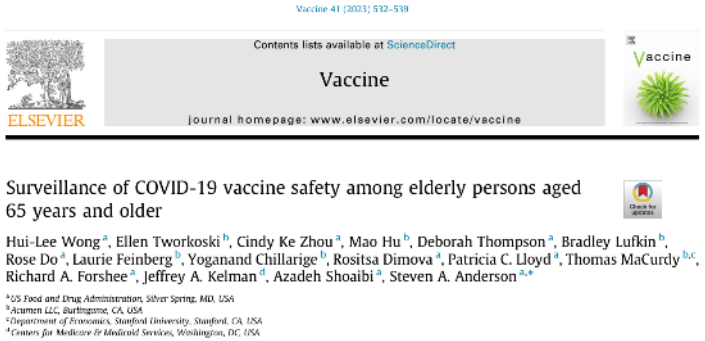
journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years

Patricia C. Lloyd [a], Mao Hu [b], Hui-Lee Wong [a], Azadeh Shoaibi [a], Cindy Ke Zhou [a], An-Chi Lo [b], Kandace Amend [c], Daniel C. Beachler [d], Cheryl N. McMahill-Walraven [e], Elizabeth R. Smith [b], John Seeger [c], Alex Secora [f], Djeneba Audrey Djibo [c], Joyce Obidi [a], Yuhui Feng [b], Jennifer Song [c], Christian Reich [f], Charalynn Harris [e], Sandia Akhtar [b], Robin Clifford [c], Nandini Selvam [f], Jennifer L. Pigoga [e], Yixin Jiao [b], Yoganand Chillarige [b], Thomas MaCurdy [b], Richard Forshee [a], Steven A. Anderson [a,*]

[a] US Food and Drug Administration, Silver Spring, MD, USA
[b] Acumen LLC, Burlingame, CA, USA
[c] Optum Epidemiology, Boston, MA, USA
[d] HealthCore, Inc, Wilmington, DE, USA
[e] CVS Health Clinical Trial Services, Blue Bell, PA, USA
[f] IQVIA, Falls Church, VA, USA



Vaccine 41 (2023) 532–539

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

ELSEVIER

Surveillance of COVID-19 vaccine safety among elderly persons aged 65 years and older

Hui-Lee Wong [a], Ellen Tworkoski [b], Cindy Ke Zhou [a], Mao Hu [b], Deborah Thompson [a], Bradley Lufkin [b], Rose Do [a], Laurie Feinberg [b], Yoganand Chillarige [b], Rositsa Dimova [a], Patricia C. Lloyd [a], Thomas MaCurdy [b,c], Richard A. Forshee [a], Jeffrey A. Kelman [d], Azadeh Shoaibi [a], Steven A. Anderson [a,*]

[a] US Food and Drug Administration, Silver Spring, MD, USA
[b] Acumen LLC, Burlingame, CA, USA
[c] Department of Economics, Stanford University, Stanford, CA, USA
[d] Centers for Medicare & Medicaid Services, Washington, DC, USA

Limitations of Signal Detection Studies

- Results with an historical comparator may be sensitive to the time period
- Vaccinated individuals may differ from individuals from an historical comparator group
- Data on potential confounders may not be available in claims data

COVID-19 Vaccine Safety Surveillance

Signal Evaluation

Example: Potential Adverse Events Following COVID-19 Ancestral Monovalent mRNA Vaccination Among Adults Aged 65 Years and Older

Analysis Specifications	Primary Series Study	Booster Study
Study Period	December 11, 2020 – Spring 2021	August 12, 2021 – Spring 2022
Data Sources	U.S. Center for Medicare and Medicaid Services (CMS) - Medicare Administrative Claims	
Study Design	Self-Controlled Case Series (SCCS)	
Study Population	U.S. CMS beneficiaries aged 65+ with ≥ one dose of the vaccine and an identified Adverse Event (AE)	
Exposures	BNT162b2 (Pfizer-BioNTech), mRNA-1273 (Moderna)	
Adverse Events (AE)	• Acute Myocardial Infarction (AMI) • Pulmonary Embolism • Immune Thrombocytopenia • Disseminated Intravascular Coagulation	• Acute Myocardial Infarction (AMI) • Pulmonary Embolism • Immune Thrombocytopenia • Bell's Palsy • Myocarditis/Pericarditis

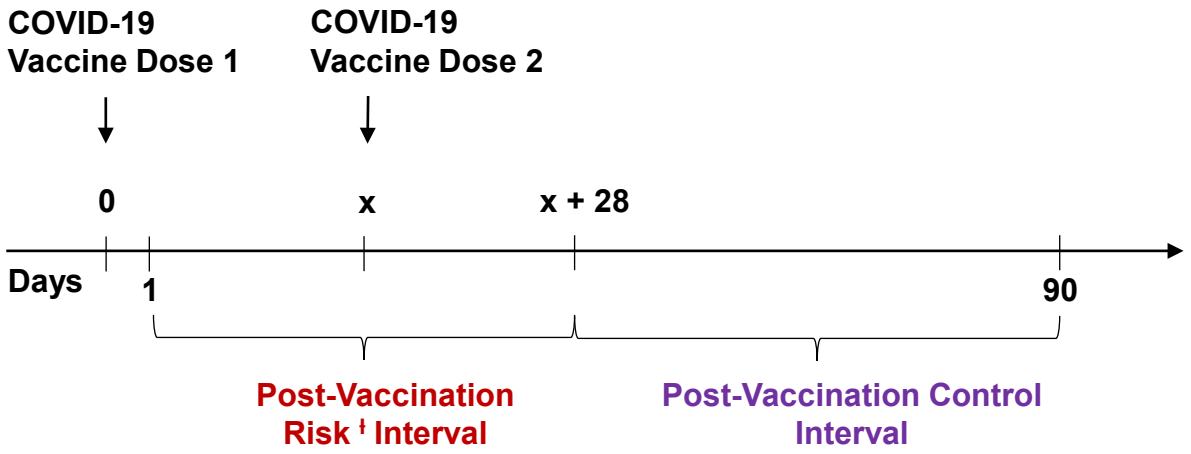
Citation: Shoaibi A, Lloyd PC, Wong HL, Clarke TC, Chillarige Y, Do R, Hu M, Jiao Y, Kwist A, Lindaas A, Matuska K, McEvoy R, Ondari M, Parulekar S, Shi X, Wang J, Lu Y, Obidi J, Zhou CK, Kelman JA, Forshee RA, Anderson SA. Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the U.S. Vaccine. 2023 Jul 19;41(32):4666-4678. doi: 10.1016/j.vaccine.2023.06.014. Epub 2023 Jun 14. PMID: 37344261; PMCID: PMC10266501.

COVID-19 Vaccine Safety Surveillance

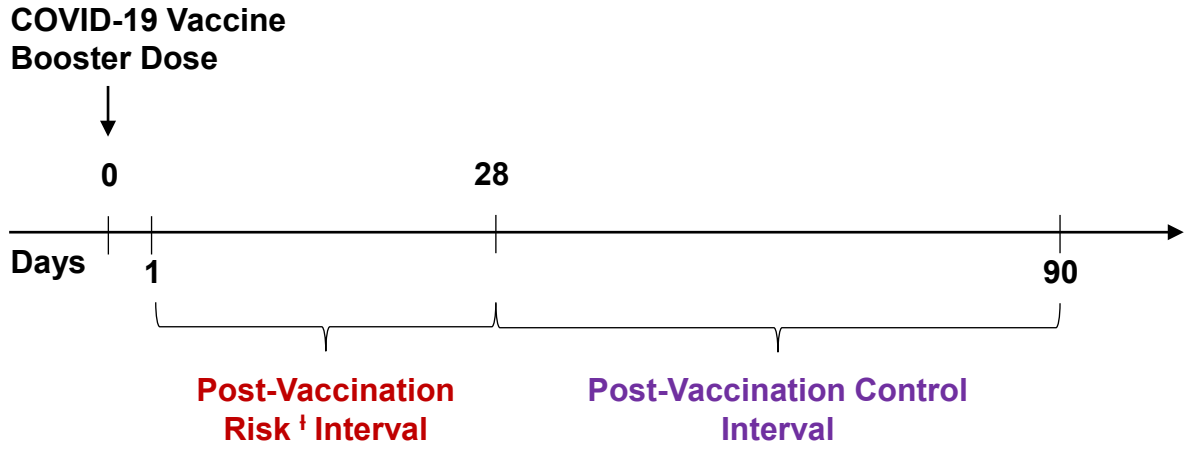
Signal Evaluation

Example: Potential Adverse Events Following COVID-19 Ancestral Monovalent mRNA Vaccination Among Adults Aged 65 Years and Older

Primary Series Study



Booster Study



Population Inclusion Criteria

- Enrolled in Medicare FFS from *clean window* prior to AE occurrence
- At least 65 years of age at the time of COVID-19 vaccination
- Contributed follow-up times to risk and control intervals
- Did not have an AE diagnosis during AE-specific clean window

Population Exclusion Criteria

Primary series study

- Less than 17 days between first and second doses
- Received different brands of COVID-19 vaccines for first and second dose observation

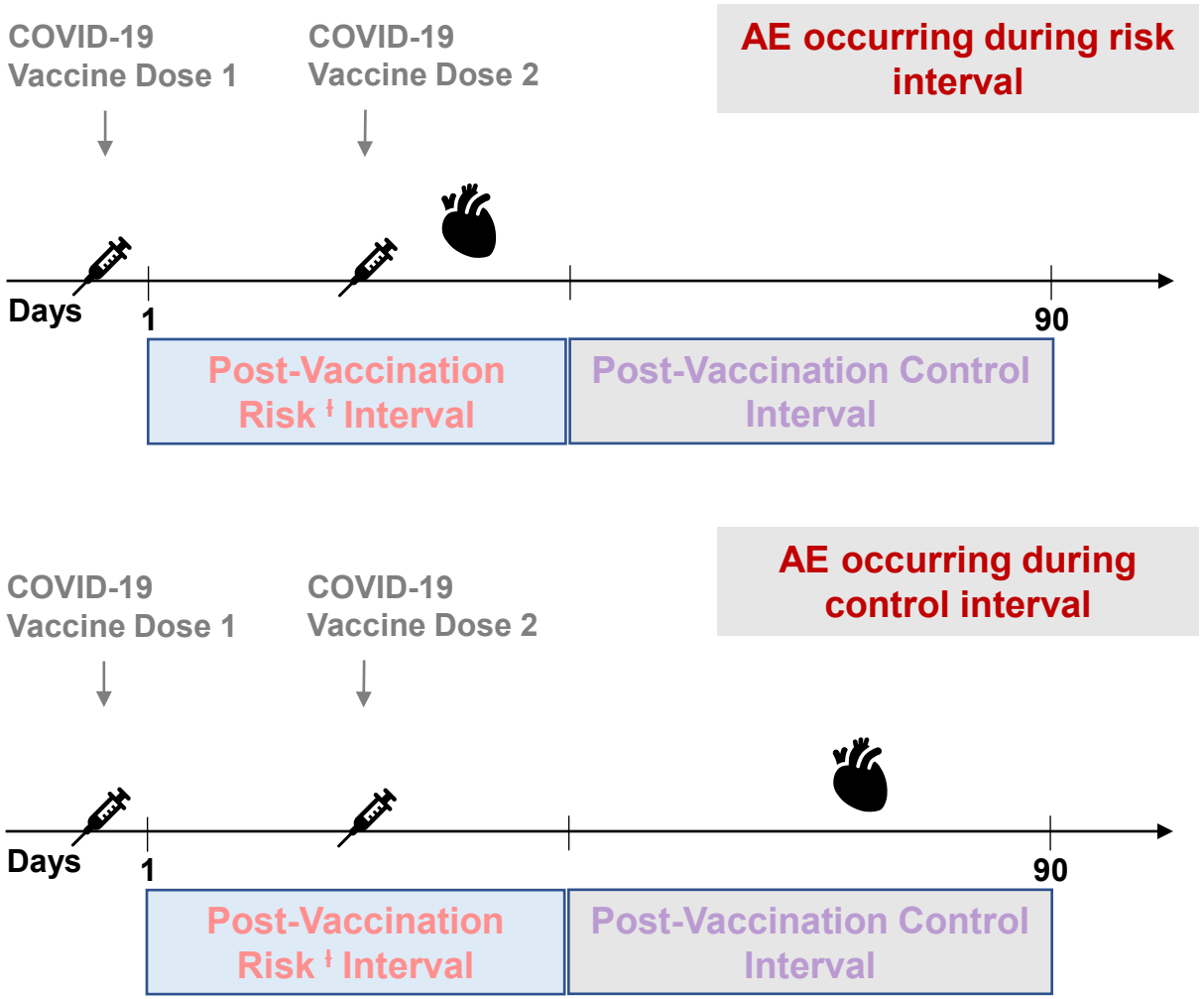
Booster study

- Received different brands of COVID-19 vaccines for the booster dose compared to the primary series vaccine

ǂ Risk Intervals: AMI : 1-28 days

COVID-19 Vaccine Safety Surveillance

Self-Controlled Case Series (SCCS) Design



SCCS design

The risk of the AE following any dose is compared in the risk and control intervals using a conditional Poisson regression model.

Strengths

- Ability to control for time-invariant confounders
- Each case serves as their own control, eliminating the need to identify unvaccinated comparators

Limitations

- The assumptions may not be met in each exposure – outcome scenario
- Does not control for time-varying confounders

COVID-19 Vaccine Safety Surveillance

Signal Evaluation

Example: Potential Adverse Events Following COVID-19 Monovalent mRNA Vaccination Among Adults Aged 65 Years and Older

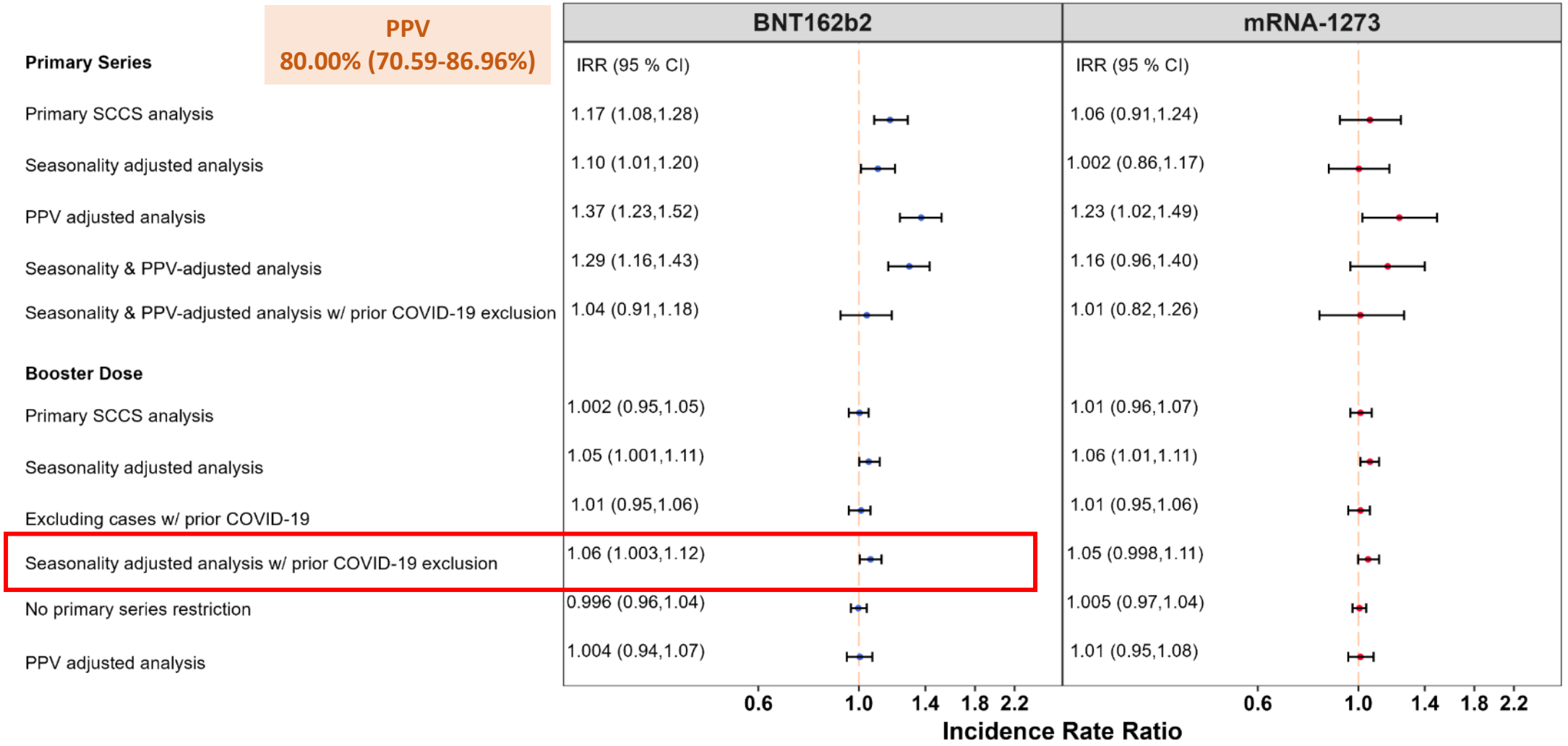
<table>
<tr><th>Analysis Specifications</th><th>Primary Series Study</th><th>Booster Study</th></tr>
<tr><td>Statistical Analyses</td><td colspan="2">• Incidence Rate Ratio (IRR)
• Absolute Risk: Attributable Risk
• Medical Chart Review: Positive Predictive Values (PPVs), Quantitative Bias Analyses</td></tr>
<tr><td rowspan="2">Adjustments</td><td colspan="2">• Seasonality adjustment
• PPV-adjusted analysis</td></tr>
<tr><td>• Seasonality and PPV-adjusted analysis
• Seasonality, PPV-adjusted, and prior COVID-19 exclusion analysis</td><td>• Prior COVID-19 exclusion analysis
• Seasonality and prior COVID-19 exclusion analysis
• Removal of restriction for population with primary series vaccine analysis</td></tr>
</table>

Case Counts for Acute Myocardial Infarction

Primary Series Study (n=3.36 M individuals; 6.34 M doses)		Booster Study (n=6.12 M individuals; 6.12 M doses)	
BNT162b2	**mRNA-1273**	**BNT162b2**	**mRNA-1273**
2,783	870	8,101	7,941

Inferential Results: Acute Myocardial Infarction

PPV
80.00% (70.59-86.96%)



Statistically significant results (increased risk) related to the most adjusted analysis are highlighted.
PPV=positive predictive value.

Discussion

Strengths

- SCCS study design provides adjustment for potential time-invariant confounding
- Large population-based database facilitates more precise evaluation of AE
- Study findings are generalizable to the U.S. population aged 65 years and older

Limitations

- Potential exposure and outcome misclassification in real world data
- Low PPV for some AE
- Potential misspecification of risk and control intervals
- Potential for residual confounding

Conclusion

- COVID-19 vaccine safety surveillance requires rapid detection while ensuring accurate assessments of risk following vaccination
- The objective of signal detection studies are to rapidly identify potential safety signals while data are still accruing
- The SCCS design with sensitivity analyses enable evaluation of safety outcomes while accounting for time-invariant confounding and adjusting for various forms of bias

Thank You!

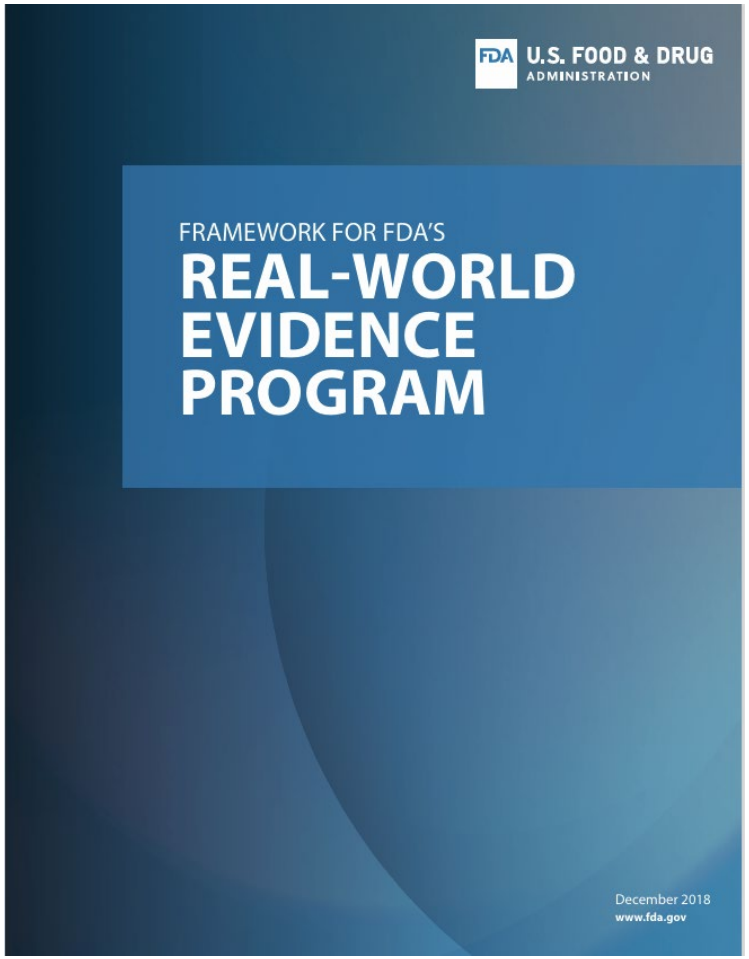
- **<u>U.S. FDA CBER:</u>**
  - Joann Gruber, PhD
  - Tainya C. Clarke, PhD, MPH
  - Carla Zelaya, PhD
  - Richard A. Forshee, PhD
  - Steven A. Anderson, PhD, MPP
- **Acumen LLC**
- **CMS**

Conclusions

FDA considerations for the use of RWE

1. Are the data fit for use (relevant and reliable)?
2. Can the study design used to generate RWE provide adequate scientific evidence?
3. Does study conduct meet FDA regulatory requirements?

Integrating multiple sources of RWD increases both the opportunities and the challenges



Upcoming RWD Sessions at the Conference

Tuesday, May 7

8:30AM - 9:45AM PLENARY SESSION

200: Missing Link for HEOR: A Path Forward for HEOR Data Integration

10:15AM - 11:15AM CONCURRENT BREAKOUT SESSION 4

205: Instrumental Variables: Revolutionizing Evidence Generation Using Real-World Data

12:15PM - 12:45PM EXHIBIT HALL THEATER

220: Innovative Strategies for Fit-for-Purpose RWE Research: Maximizing Data Completeness and Accuracy

1:45PM - 2:45PM CONCURRENT BREAKOUT SESSION 5

225: Bridging Real-World Data and Regulatory Decision-Making: The Role of AI in External Control Arm Development

227: Revolutionizing Regulatory Pathways: Unleashing the Power of Real-World Evidence, Adaptive Trials, and Synergistic Collaboration for Expedited FDA Device Approval, Breakthrough Designation, and CMS Reimbursement

Wednesday, May 8

8:00AM - 9:00AM CONCURRENT BREAKOUT SESSION 7

303: Real-World Evidence for Crossover Adjustment: Challenges, Opportunities, and Newly Proposed Methods

Q&A

Thank you!

Please reach out with any questions and comments to:

rwe@carelon.com