Fifteenth Annual Sentinel Initiative Public Workshop

November 08, 2023
9:00 a.m. – 5:00 p.m. ET

FDA U.S. FOOD & DRUG ADMINISTRATION | Duke MARGOLIS CENTER for Health Policy

Welcome and Opening Remarks

Mark McClellan

Director, Duke-Margolis Center for Health Policy

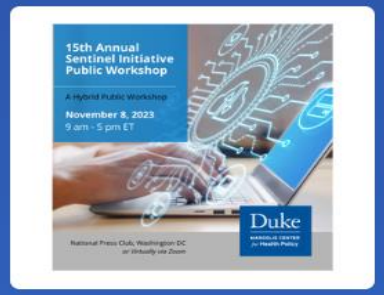
Workshop Agenda

9:00 AM	**Welcome and Opening Remarks**
9:10 AM	**Keynote Address**
9:30 AM	**Fireside Chat with Sentinel Initiative Leadership**
10:15 AM	**Break**
10:25 AM	**International Approaches to the Distributed Networks Data System**
11:00 AM	**Sentinel System and BEST Operations and Coordinating Center Perspectives**
11:50 AM	**Break for Lunch**
1:05 PM	**BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities**
1:50 PM	**Linked-Claims EHR Data: Sentinel System's Efforts at Improving Causal Inference & Broadening Queries**
2:35 PM	**Break**
2:50 PM	**Leveraging Lessons Learned to Move Beyond COVID-19**
3:50 PM	**Stakeholder Reflections on Sentinel**
4:50 PM	**Closing Remarks**

Statement of Independence

The Robert J. Margolis, MD, Center for Health Policy is part of Duke University, and as such it honors the tradition of academic independence on the part of its faculty and scholars. Neither Duke nor the Margolis Center take partisan positions, but the individual members are free to speak their minds and express their opinions regarding important issues.

For more details on relevant institutional policies, please refer to the Duke Faculty Handbook, including the Code of Conduct and other policies and procedures. In addition, regarding positions on legislation and advocacy, Duke University policies are available at http://publicaffairs.duke.edu/government.



Join at

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#Sentinel

Keynote Address

Janet Woodcock

Principal Deputy Commissioner, U.S. Food and Drug Administration

Fireside Chat with Sentinel Initiative Leadership

Moderator: **Mark McClellan,** Duke-Margolis Center for Health Policy

Speakers:

Steve Anderson, U.S. Food and Drug Administration

Gerald Dal Pan, U.S. Food and Drug Administration

Danica Marinac-Dabic, U.S. Food and Drug Administration

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Moderated Discussion and Q&A

Moderator: Mark McClellan

Duke-Margolis Center for Health Policy

Break

Workshop will resume at **10:25 a.m. EST**

December 14, 2023

12:30 PM – 5:00 PM

A Virtual Public Workshop

Visit healthpolicy.duke.edu/events

International Approaches to the Distributed Networks Data System

Moderator: **Rachele Hendricks-Sturrup,** Duke-Margolis Center for Health Policy

Speakers:

Daniel Morales, European Medicines Agency (EMA)

Melissa Kampman, Health Canada

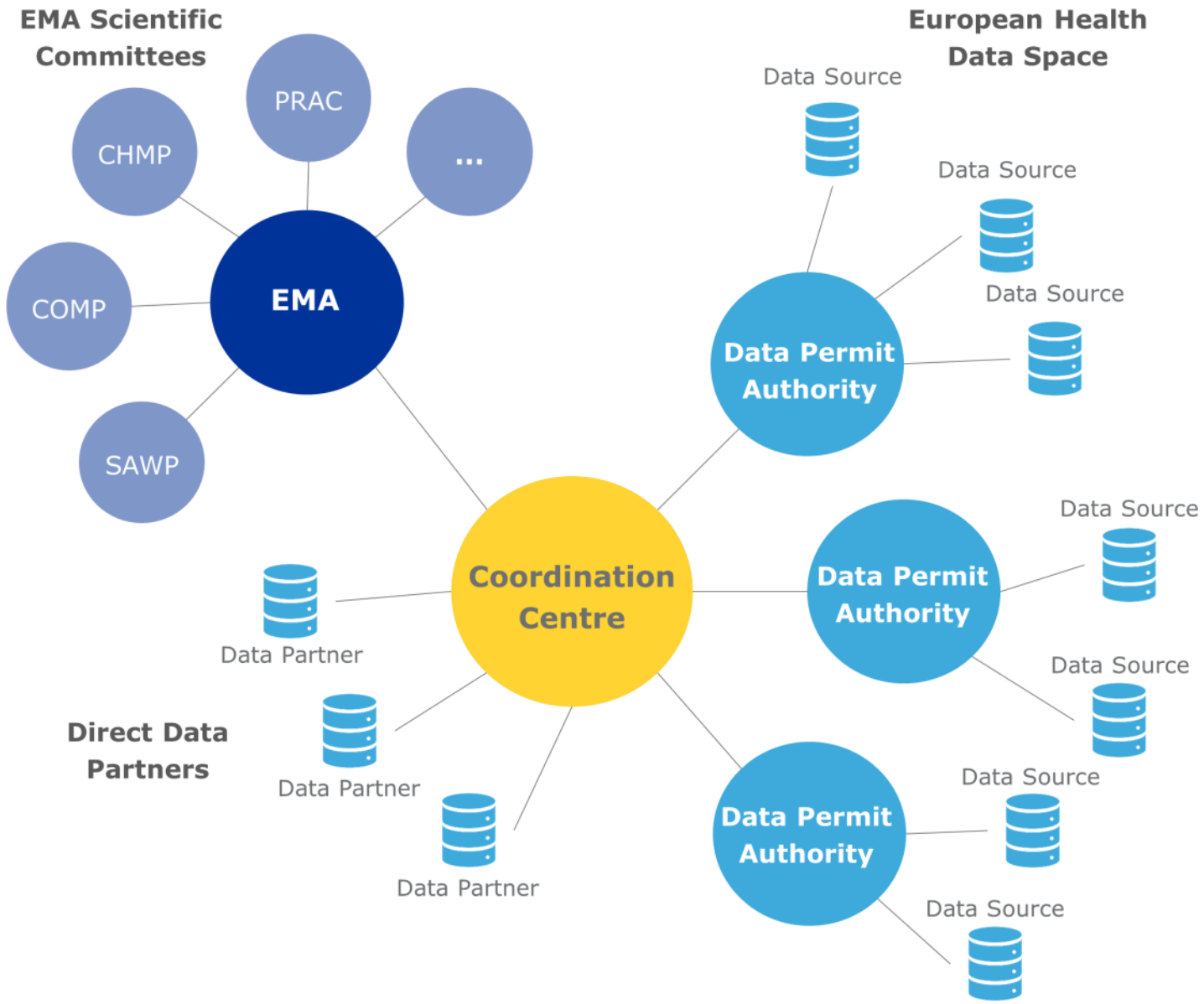
David Moeny, U.S. Food and Drug Administration

Scaling-up Real-World Evidence Generation for Regulators in Europe: DARWIN EU

15th Annual Sentinel Initiative Public Workshop 8th November 2023

Presented by Dr Daniel Morales
European Medicines Agency, Data Analytics and Methods Taskforce – Real World Evidence

DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



FEDERATED NETWORK PRINCIPLES

- Data stays **local**
- **Use of OMOP Common Data Model** (where applicable) to perform studies in a timely manner and increase consistency of results

Data Partners – Phase I

UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

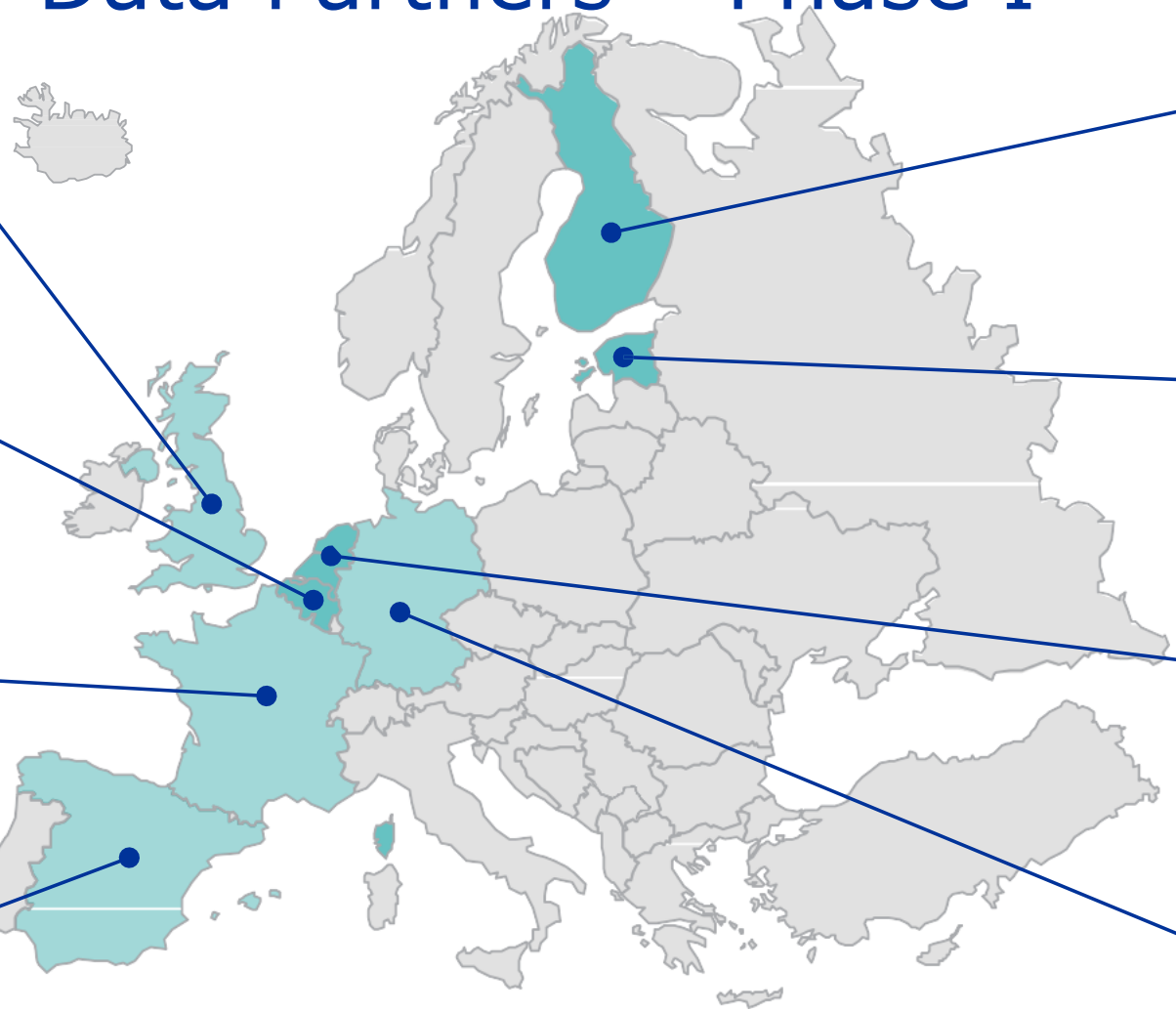
2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)



Finland

6. Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)

Estonia

7. University of Tartu (Biobank)

Netherlands

8. Integrated Primary Care Information
9. Netherlands Comprehensive Cancer Organisation

Germany

10. IQVIA Germany Disease Analyser

~26 million active patients

Currently **selecting Phase II DPs** via open call of interest, then Phase III to follow

Main areas where RWE will support regulatory decision-making

1 Support the planning and validity of applicant studies

- Design and feasibility of planned studies
- Representativeness and validity of completed studies

2 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

- Safety and effectiveness studies
- Impact of regulatory actions

Ongoing studies

Background all-cause **mortality rates in patients with severe asthma aged ≥12 years** old [EUPAS103936]

CHMP
Complex

EHDS coagulopathy of COVID-19

EC/EHDS
Complex

Effectiveness of **COVID-19** vaccines against severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection.

ECDC/VMP
Complex

Drug utilisation study on co-prescribing of **endothelin receptor antagonists** (ERAs) and **phosphodiesterate-5 inhibitors** (PDE-5is) in pulmonary arterial hypertension. [EUPAS106052]

CHMP
OTS

Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022 [EUPAS105033]

HTA/Payers
OTS

Drug utilisation study of **medicines with prokinetic properties** in children and adults diagnosed with gastroparesis

NCA
OTS

Naloxone use in treatment of opioid overdose. [EUPAS105644]

CHMP
OTS

Drug utilisation study of prescription **opioids**. [EUPAS105641]

PRAC
OTS

OTS = off-the-shelf study

Challenges of DARWIN EU network

Related to the databases content

- Differences in the underlying health care systems;
- Different methods of data generation & coding schemes;
- Differences in data quality

Related to the organisation of a network

- Different ethical and governance requirements
- Implementing quality controls procedures
- Speed

Importance of feasibility assessment & an iterative approach to learning

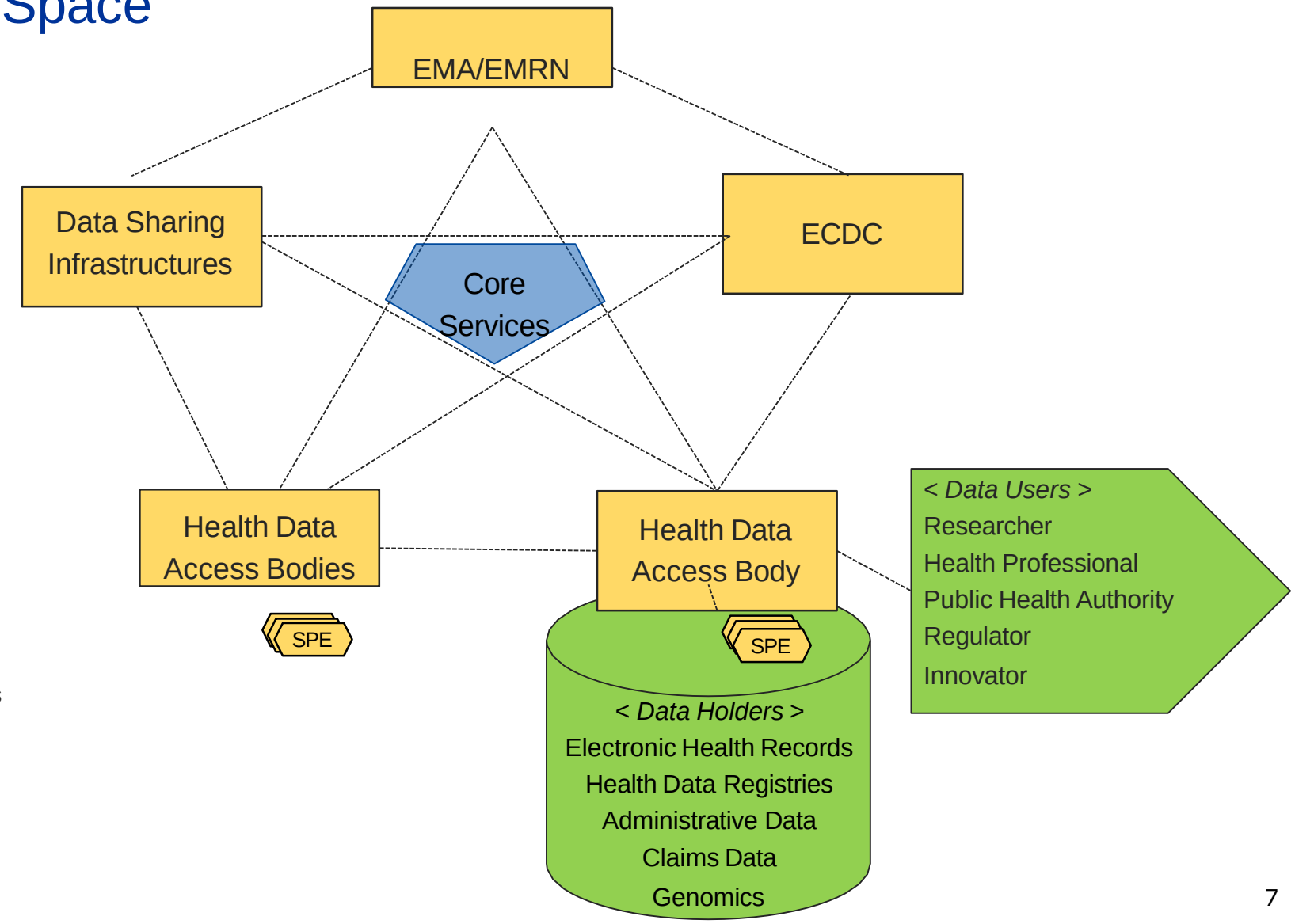
Future perspectives

- ✓ 2nd year of establishment in progress, delivery on target and according to plan
- ✓ Focus on selection of further Data Partners and study conduct (various use cases)
- ✓ Establishment of standard analytical pipelines and codes

		Phase I	Phase II	Phase III	Option I	Option II
Studies	Off the shelf	2	6	30	60	60
	Routine repeated	1	6	30	60	60
	Complex study	1	4	12	24	24
	Very complex	0	0	0	1	1
Data Partners (total)		10	20	30	40	40

European Health Data Space

- **New infrastructure for secondary uses of health data**
- Connecting health data access bodies and data sharing infrastructures
- Several health data access bodies are established, or in the process, across Member States



CORE Services provided by EC

GENERIC Services provided by authorized participants

SPE Secure Processing Environments

LOCAL Services provided by/to local partners

Further information

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Send us a question Go to www.ema.europa.eu/contact

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International Approaches to the Distributed Networks Data System

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Moderated Discussion and Q&A

Moderator: Rachele Hendricks-Sturrup

Duke-Margolis Center for Health Policy

Sentinel System and BEST Operations and Coordinating Center Perspectives

Moderator: **Gerrit Hamre,** Duke-Margolis Center for Health Policy

Speakers:

Margaret Anderson, Deloitte

Darren Toh, Harvard Medical School and Harvard Pilgrim Health Care Institute

Yoganand Chillarige, Acumen LLC

John Seeger, Optum Epidemiology

Sentinel

15th ANNUAL SENTINEL INITIATIVE PUBLIC WORKSHOP

Sentinel's Community Building and Outreach Center (CBOC) Updates and Enhancements

NATIONAL PRESS CLUB | WASHINGTON, DC

November 8, 2023

Introducing Our Speaker

Margaret Anderson

Margaret is a Managing Director at Deloitte and serves as a Principal Investigator for the Sentinel Program. She is a leader in Deloitte's Strategy and Analytics Diversity, Equity, and Inclusion efforts and the Chief Marketing Officer of the firm's Federal Health Sector.

Presentation Agenda

CBOC engages and educates a community of health professionals to advance objectives related to Sentinel

The Journey

The Community

The Impact

Sentinel as a National Resource

What is the Sentinel CBOC?

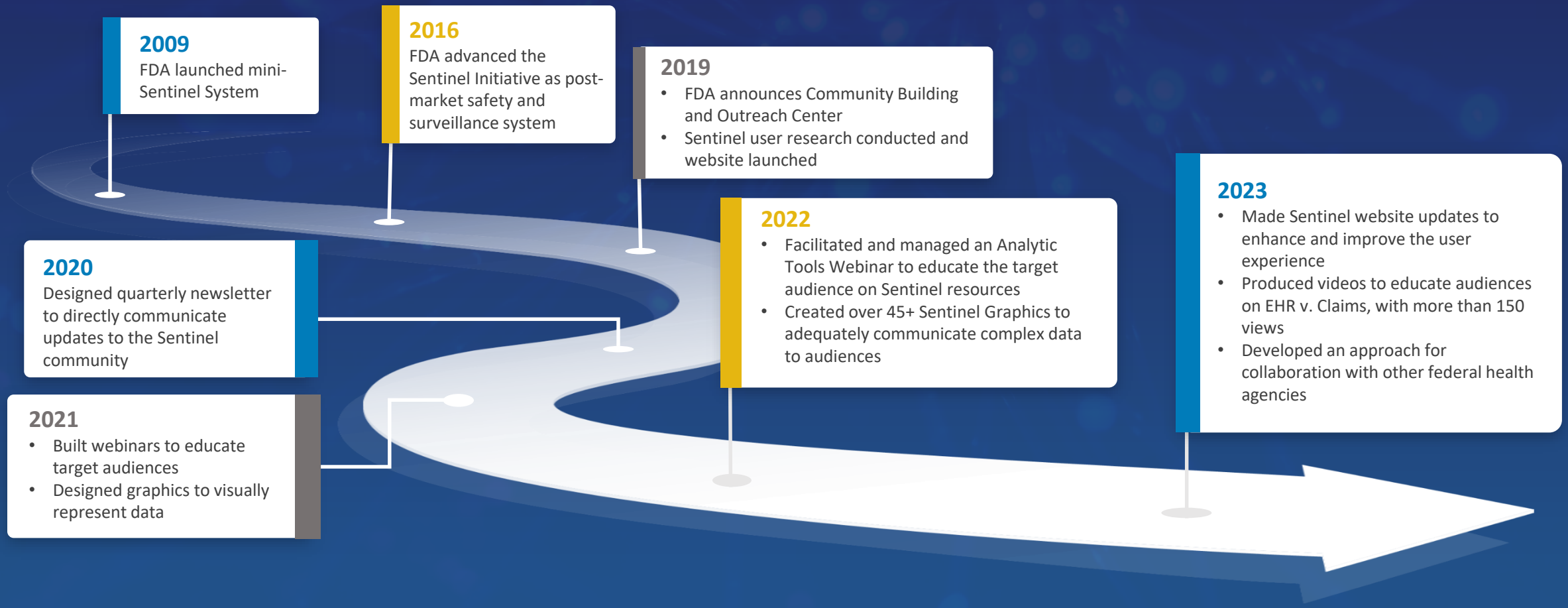
The Sentinel Community Building and Outreach Center (CBOC) was created to **broaden and activate a strong scientific community to advance the U.S. Food and Drug Administration's (FDA) Sentinel Initiative.** The CBOC supports FDA in accomplishing three of the strategic aims outlined in "*The Sentinel System Five Year Strategy (2019 – 2023)*." These aims are reflected in the recommendations and projects outlined in the CBOC Master Plan.

SENTINEL'S STRATEGIC AIMS
supported by CBOC

- Use the Sentinel System to **accelerate access to** and **broaden the use** of Real-World Data (RWD) for Real-World Evidence (RWE).
- Broaden the Sentinel System's userbase **to pursue the vision of a national resource.**
- Disseminate knowledge and advance regulatory science to **encourage innovation** and meet the Agency's scientific needs.

What the CBOC Sentinel Journey looked like

Since 2019, CBOC has positioned the Sentinel brand with several stakeholder and audience groups. The CBOC has and continues to implement outreach tactics and deliver communication products to expand the reach of Sentinel and relationships with those groups.



Spotlight: Quarterly Newsletter

11
Newsletters sent

9%
Subscriber growth

5,750
Subscribers to date

1. Clear calls to action

2. Visual organization

3. Consolidation of content

CBOC is building and growing the Sentinel community

COMMUNITY-BUILDING OUTREACH

Focusing on the tools and services that audiences need and want

Expanding Sentinel outreach to academia and other government officials

Keeping audiences engaged with interactive content and experiences

ENGAGEMENT AND IMPACT

- Managed 5+ Sentinel webinars, providing audiences with information to better serve their people and patients
- Created a multi-channel resource for audiences to understand EHR and claims data sources, such as slides and an informational video

- Cultivated a subscriber network, with 14% of quarterly newsletter readers or receivers being academia and 7% being from government agencies
- Increased government and academia subscriber newsletter opens by 86% and 113% respectively, from 2021 to 2023

- Designed over 45 downloadable key database graphics to enhance the user experience on the website
- Provided enhancements to Sentinel website functionality, to include designing and maintaining the site

SENTINEL AUDIENCES

Researchers and Research Institutions

Academics and Universities

Epidemiologists

Federal Health Care Partners

Public Health Professionals

We created a network of channels to engage stakeholders

The CBOC set many goals to accomplish in the future, to build on accomplishments to date. Below are some of those goals centered on trainings, partnerships, and several communications activities to expand the Sentinel Program's reach.

Training

- Continue to think of innovative ways to engage and educate audiences, with on demand information

Partnerships

- Identify collaboration opportunities with agencies that could benefit from Sentinel data
- Engage partners in sharing content on and promoting Sentinel, to their networks

Videos

- Produce educational videos that focus on scientific studies
- Promote videos through push and pull communications channels, such as the newsletter and FDA social media

Newsletter

- Increase subscribers and readers of the newsletter by improving layout and streamlining content
- Produce mini-monthly updates on Sentinel activities and progress
- Send promotional newsletters for trainings and webinars

Website

- Update and improve website design while continuing to perform routine maintenance
- Improve user experience and access to all resources on the Sentinel site

We are cultivating

collaborations

to earn trust from the people we strive to serve

The CBOC evaluated federal health partnerships and identified several opportunities for collaboration. Next, the CBOC will work to establish relationships with those potential partners.

WHY PUBLIC HEALTH PARTNERSHIPS?

- Rapid advances in emerging technologies are helping government organizations, especially federal health care agencies, share information and practices that can holistically impact public health
- Collaborations between federal health care partners can bring in new perspectives, resources, and expertise
- Promotes transparency and good communication, which can lead to increased trust in government
- Creates opportunities for researchers to examine complex public health problems in innovative ways

POTENTIAL OUTCOMES FOR SENTINEL

- Sentinel's investment in tools, analytics packages, data, and models can be leveraged by other health care agencies
- Joint research and development opportunities, including expanding EHR data sources and creating linkages to identify safety signals and study health outcomes
- Co-creation of new products, services, or experiences

The path ahead based on public health communication trends

The CBOC aims to help the Sentinel program expand by educating those interested, empowering individuals to use the tools offered, and elevating the program's position as a cutting-edge reservoir of knowledge. Future activities will be aligned to lessons learned to date, specific to Sentinel, and aligned to trends in public health communications.

Trends in Public Health Communications

Spur action in communities using digital channels

- Embrace social marketing campaigns through content
- Create a marketing mix to reach your audience
- Engage your audience through multiple touchpoints

Push the needle on effective communication

- Develop creative partnerships and collaboration channels – partnerships vary from co-creation to innovation labs
- Create room for risk-taking

Use technological progress to optimize communications

- Take advantage of the unprecedented opportunities, like new technology that helps reach and connect with audiences
- Establish meaningful connections through content that fits into audience needs and wants
- Proceed with (some) caution

Sentinel

Sentinel Operations Center

15th Annual Sentinel Initiative Public Workshop

November 8, 2023

Disclaimers

- The views expressed in this presentation represent those of the presenter and do not necessarily represent the official views of the U.S. Food and Drug Administration (FDA)

- This Sentinel Operations Center is funded by the U.S. FDA through the Department of Health and Human Services (HHS) contract number 75F40119D10037

Collaborating Institutions

DEPARTMENT OF POPULATION MEDICINE
HARVARD MEDICAL SCHOOL
Harvard Pilgrim Health Care Institute

CVSHealth
aetna™
Aetna, part of the CVS Health Family of companies.

carelon
Elevance Health

Optum

HealthPartners® Institute

Humana
Healthcare Research

TN Division of TennCare

CMS
CENTERS FOR MEDICARE & MEDICAID SERVICES

KAISER PERMANENTE®
Colorado
Hawaii
Mid-Atlantic
Northwest
Washington

TriNetX

Marshfield Clinic
Research Institute

HCA Healthcare

merative

VANDERBILT UNIVERSITY
MEDICAL CENTER

UF College of Pharmacy
Department of Pharmaceutical Outcomes and Policy
UNIVERSITY of FLORIDA

SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

UMass Chan MEDICAL SCHOOL

MHCI Meyers Health Care Institute

healthverity

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

Department of Population Health Sciences
Duke University School of Medicine

Brigham and Women's Hospital
Founding Member, Mass General Brigham

CCEB

Perelman School of Medicine
University of Pennsylvania

FY2023 Sentinel Analyses

Analysis Type	Total
Sentinel Distributed Database	
Descriptive	34
Inferential	15
Signal Identification	3
Additional EHR Data Sources	
Descriptive	12
Total	**64**

51 reports posted to the Sentinel website

14 analytic packages shared with the public on the Sentinel website

15 manuscripts published

33 posters / presentations presented

Analyses are assigned to years based on analytic package distribution date

Sentinel Analyses Meeting Requirements of FDCA Section 505(o) Prior to Requiring a Sponsor Postmarket Requirement (PMR)

Product	Approval Date	# Ongoing/Completed ARIA Analyses	Status
Sinuva (mometasone sinus implant)	12/08/2017	8	☑
Ablysinol (dehydrated alcohol)	06/21/2018	3	☑
Stelara (ustekinumab)	09/23/2016	4	📊
Invokana (canagliflozin)	10/29/2018	1	📊
Annovera (segesterone estradiol)	09/10/2018	3	🔍
Gimoti (metoclopramide nasal spray)	06/19/2020	1	🔍
Tremfya (guselkumab)	07/13/2017	2	🔍
Ilumya (tildrakizumab)	03/20/2018	2	🔍
Skyrizi (risankizumab)	04/23/2019	2	🔍
Siliq (brodalumab)	02/15/2017	2	🔍
Ibsrela (tenapanor)	09/12/2019	1	🔍

Status Key

☑ = Complete

📊 = Inferential Analysis Phase

🔍 = Monitoring Ongoing

FDCA = Federal Food, Drug, and Cosmetic Act

Planned Sentinel Analyses Identified During Approval (1 of 3)

Rinvoq (upadacitinib) & Myocardial Infarction, Acute Stroke, Deep Vein Thrombosis, and Pulmonary Embolism, for Crohn's Disease

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate Rinvoq (upadacitinib) in the Sentinel System. We have determined that Sentinel's Active Postmarket Risk Identification and Analysis System, established under section 505(k)(3) of the FDCA, is sufficient to identify unexpected serious risks (myocardial infarction, acute stroke, deep vein thrombosis, and pulmonary embolism) possibly related to upadacitinib dose during long-term use for Crohn's disease.

FDCA = Federal Food, Drug, and Cosmetic Act

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/211675Orig1s015ltr.pdf

Planned Sentinel Analyses Identified During Approval (2 of 3)

Rinvoq (upadacitinib) & Myocardial Infarction, Stroke, and Thrombosis, for Ulcerative Colitis

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

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FDCA = Federal Food, Drug, and Cosmetic Act

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/211675Orig1s007ltr.pdf

Planned Sentinel Analyses Identified During Approval (3 of 3)

Olumiant (baricitinib) & Myocardial Infarction, Stroke, and Thrombosis, for Alopecia Areata

SENTINEL/ARIA NOTIFICATION

The Food and Drug Administration Amendments Act of 2007 (FDAAA) required FDA to establish a national electronic system to monitor the safety of FDA-regulated medical products. In fulfillment of this mandate, FDA established the Sentinel System, which enables FDA to proactively monitor drug safety using electronic health data from multiple data sources that contribute to the Sentinel Distributed Database.

FDA plans to evaluate Olumiant (baricitinib) tablets in the Sentinel System. We have determined that Sentinel's Active Postmarket Risk Identification and Analysis System, established under section 505(k)(3) of the FDCA, is sufficient to identify unexpected serious risks (myocardial infarction, stroke, and thrombosis) possibly related to baricitinib dose during long-term use for alopecia areata.

FDCA = Federal Food, Drug, and Cosmetic Act

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/207924Orig1s007ltr.pdf

Sentinel's Support of FDA's Signal Identification Efforts (1 of 3)

Product	Design	Determination
Ozempic (semaglutide): Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin?	Cohort design with PS matching	All alerts observed were either labeled adverse events or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None required further follow-up.

https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide

Signal Identification for Ozempic (semaglutide)

Background

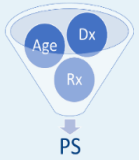
Ozempic

VS.

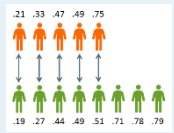
Sitagliptin

Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin use?

Methods



1:1 PS Match & hdPS match

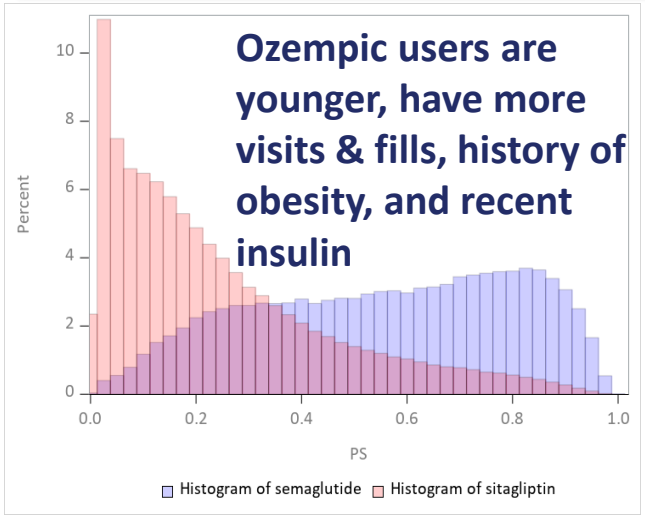


Analysis and Findings

Sentinel Distributed Database

- Scanned ~83,000 non-pregnancy and non-cancer outcomes
- Sensitivities based on encounter setting

Jan. 2018 – Feb. 2022



n=134,007 1:1 Matched Pairs with Conventional PS
n=118,161 1:1 Matched Pairs with Conventional + hdPS

Ozempic users less adherent, more likely to stop treatment after a single dispensing

Significant Alerts: nausea/vomiting, diarrhea, constipation, GI distress / pain, obesity, abnormal weight loss, metabolic issues, sleep apnea

Conclusions: All of the alerts observed were either labeled adverse events, or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None of the alerts required further follow-up.

https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2

Sentinel's Support of FDA's Signal Identification Efforts (2 of 3)

Product	Design	Determination
Ozempic (semaglutide): Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin?	Cohort design with PS matching	All alerts observed were either labeled adverse events or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None required further follow-up.
Zarxio (filgrastim-sndz): Is there any difference in medical product safety profiles between the biosimilar the and originator product?	Cohort design with PS matching	No follow-up needed

https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide
https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz

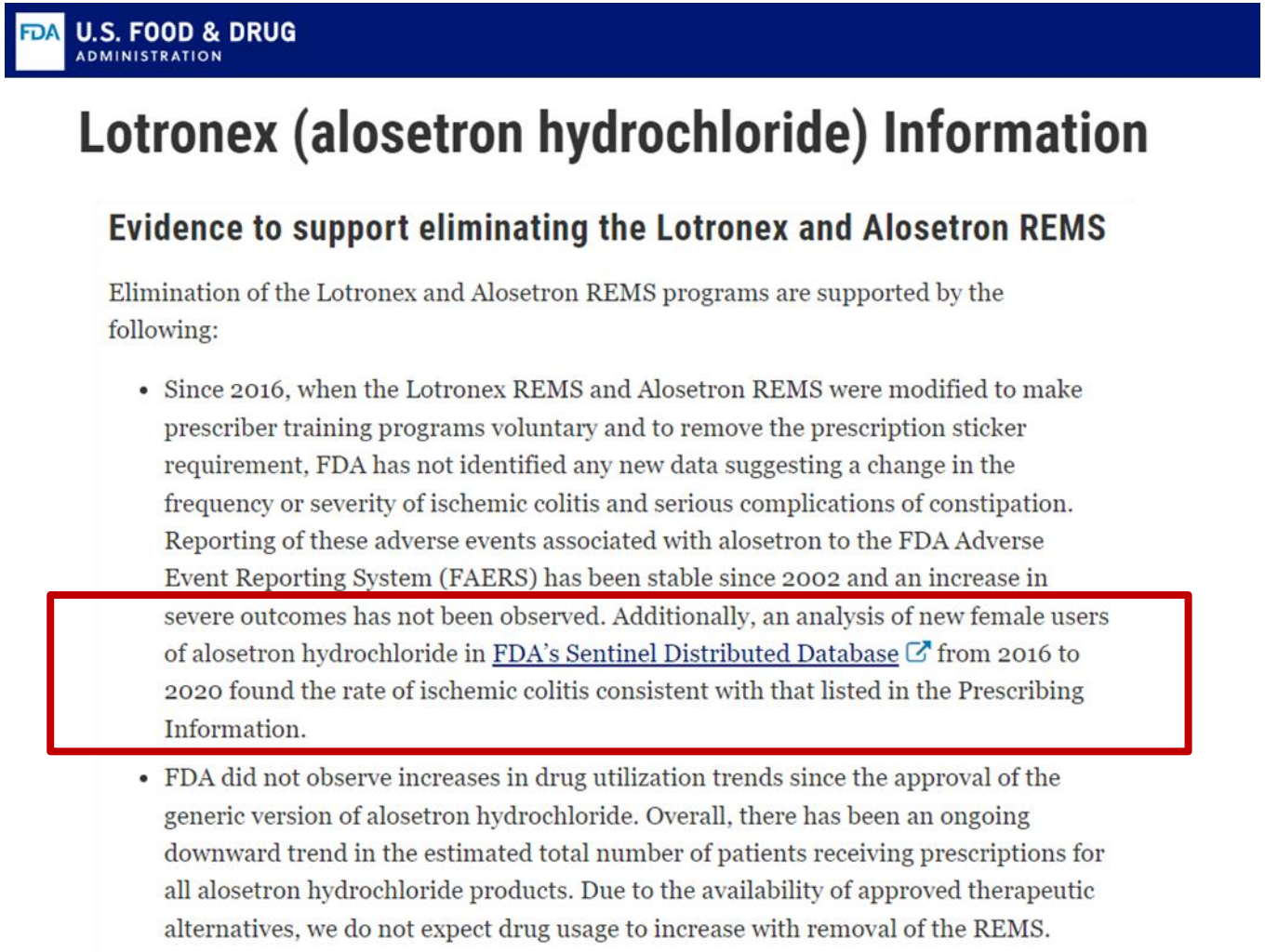
Sentinel's Support of FDA's Signal Identification Efforts (3 of 3)

Product	Design	Determination
Ozempic (semaglutide): Is there an increase in frequency of adverse events during Ozempic use as compared to sitagliptin?	Cohort design with PS matching	All alerts observed were either labeled adverse events or comorbid conditions of people likely using Ozempic not only for glucose control but also for weight loss. None required further follow-up.
Zarxio (filgrastim-sndz): Is there any difference in medical product safety profiles between the biosimilar the and originator product?	Cohort design with PS matching	No follow-up needed
Aimovig (erenumab): Is there an increase in frequency of adverse events during erenumab risk period compared to control period?	Self-controlled risk interval design	The alert for "Other specified cerebrovascular disease" required follow-up with a Patient Episode Profile Retrieval. Upon review of patient entries FDA determined there was low suspicion that diagnoses were related to erenumab exposure

Summary: No statistical alerts were determined to be newly identified safety signals

https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide
https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz
https://www.sentinelinitiative.org/studies/drugs/aimovig-erenumab-0

Support for Eliminating REMS for Lotronex and Alosetron



FDA U.S. FOOD & DRUG ADMINISTRATION

Lotronex (alosetron hydrochloride) Information

Evidence to support eliminating the Lotronex and Alosetron REMS

Elimination of the Lotronex and Alosetron REMS programs are supported by the following:

- Since 2016, when the Lotronex REMS and Alosetron REMS were modified to make prescriber training programs voluntary and to remove the prescription sticker requirement, FDA has not identified any new data suggesting a change in the frequency or severity of ischemic colitis and serious complications of constipation. Reporting of these adverse events associated with alosetron to the FDA Adverse Event Reporting System (FAERS) has been stable since 2002 and an increase in severe outcomes has not been observed. Additionally, an analysis of new female users of alosetron hydrochloride in FDA's Sentinel Distributed Database from 2016 to 2020 found the rate of ischemic colitis consistent with that listed in the Prescribing Information.
- FDA did not observe increases in drug utilization trends since the approval of the generic version of alosetron hydrochloride. Overall, there has been an ongoing downward trend in the estimated total number of patients receiving prescriptions for all alosetron hydrochloride products. Due to the availability of approved therapeutic alternatives, we do not expect drug usage to increase with removal of the REMS.

https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/lotronex-alosetron-hydrochloride-information

ARTICLE

Six Years of the US Food and Drug Administration's Postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for Real World Evidence Generation

Judith C. Maro[1,*], Michael D. Nguyen[2], Joy Kolonoski[1], Ryan Schoeplein[1], Ting-Ying Huang[1], Sarah K. Dutcher[2], Gerald J. Dal Pan[2] and Robert Ball[2]

CLINICAL PHARMACOLOGY & THERAPEUTICS doi:10.1002/cpt.2979

Six Years of the US Food and Drug Administration's Postmarket Active Risk Identification and Analysis System in the Sentinel Initiative: Implications for Real World Evidence Generation

Judith C. Maro[1,*], Michael D. Nguyen[2], Joy Kolonoski[1], Ryan Schoeplein[1], Ting-Ying Huang[1], Sarah K. Dutcher[2], Gerald J. Dal Pan[2] and Robert Ball[2]

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Table 4 Reasons for determinations of ARIA insufficiency

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Inability of ARIA tools to perform required analysis	82	Insufficient signal identification tool	ARIA has integrated signal identification abilities (**Figure 1**)[16–18]
Study requires data elements captured in unstructured clinical data, such as clinical notes	73	Lack of radiology or pathology findings in notes	Addressable with development of feature engineering capabilities to extract and structure these data[37]
Absence of validated code algorithm	72	No gold-standard chart review was performed for outcome of interest	Sentinel has performed several gold standard chart validations[38–42] but these require substantial resources. Efforts underway to investigate rapid silver standard reviews.
Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate	60	Codes do not exist for concept or validated performance characteristics are inadequate	Potentially addressable with added EHR elements but if outcome is not well-defined or new (e.g., long COVID), there may be substantial hurdles to identification
Inadequate sample size	57	Low uptake of drug	Non-actionable as ARIA is the largest system of its kind
Requires linkage to additional data source that is unavailable	52	Inability to ascertain cause of death	Additional linkages are possible with significant financial resources
Insufficient observation time available	44	Inability to follow patients across healthcare plans or systems	Actionable with substantial further research and development and resolution of data governance issues[43]
Insufficient mother-infant linkage	24	Lack of ability to connect mothers and infants	Resolved with 2018 integration of Mother-Infant Linkage table[15]
Insufficient inpatient data	18	Inability to access granular inpatient pharmacy information	Resolved with partnerships with inpatient healthcare systems[10]
Inability to identify over-the-counter medication use	8	Over-the-counter medication use not captured	Inherent limitation of both claims and EHR data
Insufficient race capture of information on race	3	Race is not well-captured	FDA is working with Data Partners to understand approaches for better capture of this data
Insufficient representation of the population of interest	1	Limited generalizability based on commercial claims data	Sentinel added Medicare data in 2018 and Medicaid in 2022

ARIA, Active Risk Identification and Analysis; COVID, coronavirus disease; EHR, electronic health record; FDA, US Food and Drug Administration.

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Master Plan of the Sentinel Innovation Center

Current Sentinel System limitations

Inability to identify certain study populations of interest from insurance claims

Inability to identify certain outcomes of interest from insurance claims

Other limitations (inadequate duration of follow-up, the need for additional signal identification tools)

Sentinel Innovation Center Initiatives

Data infrastructure (DI)

Feature engineering (FE)

- Emerging methods including machine learning and scalable automated natural language processing (NLP) approaches to enable computable phenotyping from unstructured EHR data

Causal inference (CI)

- Methodologic research to address specific challenges when using EHRs such as approaches to handle missing data, calibration methods for enhanced confounding adjustment

Detection analytics (DA)

- Development of signal detection approaches to account for and leverage differences in data content and structure of EHRs

Sentinel Innovation Center Vision

A query-ready, quality-checked distributed data network containing EHR for at least 10 million lives with reusable analysis tools

2020 → **2024**

Desai et al. npj Digital Medicine (2021) 4:170

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Table 3 Distribution of safety concerns insufficient for assessment in ARIA attributed to capture of health outcome, by regulatory approval stage (*N*=132 safety concerns)

Health outcome (MedDRA system organ class)	Safety concerns identified pre-approval	Safety concerns identified postapproval	Total
Pregnancy, puerperium and perinatal conditions	42	3	45
Neoplasms benign, malignant and unspecified (including cysts)	9	1	10
General disorders and administration site conditions	9	0	9
Cardiac disorders	6	0	6
Infections and infestations	4	2	6
Injury, poisoning and procedural complications	1	4	5
Nervous system disorders	4	1	5
Psychiatric disorders	4	1	5
Immune system disorders	4	0	4
Hepatobiliary disorders	2	2	4
Respiratory, thoracic, and mediastinal disorders	2	1	3
Surgical and medical procedures	3	0	3
Blood and lymphatic system disorders	2	0	2
Musculoskeletal and connective tissue disorders	2	0	2
Renal and urinary disorders	2	0	2
Skin and subcutaneous tissue disorders	2	0	2
Vascular disorders	2	0	2
Gastrointestinal disorders	0	1	1
Metabolism and nutrition disorders	0	1	1
Product issues	0	1	1
Other[a]	12	2	14
Total	112	20	132

[a]A recording of "Other" indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.
ARIA, Active Risk Identification and Analysis; MedDRA, Medical Dictionary for Regulatory Activities.

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Snapshot of Sentinel Distributed Database, 2000-2023

463 million unique patient identifiers (2000-2023)

1.1 billion person-years of data*

113 million members currently accruing data*

20 billion pharmacy dispensing*

20 billion medical encounters*

11 million deliveries with mom-baby linkage

https://www.sentinelinitiative.org/about/key-database-statistics

* Among individuals with both medical and drug coverage

Sentinel's Prescription Drug User Fee Act (PDUFA) VI Commitments

Sentinel System fulfilled PDUFA VI commitments to enhance and modernize FDA's drug safety system

K. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will continue to use user fees to enhance and modernize the current U.S. drug safety system, including adoption of new scientific approaches, improving the utility of existing tools for the detection, evaluation, prevention, and mitigation of adverse events, standardization and integration of REMS into the healthcare system, enhancing communication and coordination between postmarketing and pre-market review staff, and improving tracking, communication and oversight of postmarketing safety issues. Enhancements to the drug safety system will improve public health by increasing patient protection while continuing to enable access to needed medical products.

1. Advancing Postmarketing Drug Safety Evaluation Through Expansion of the Sentinel System and Integration into FDA Pharmacovigilance Activities

a. FDA will work toward expanding the Sentinel System's sources of data and enhancing the system's core capabilities.

b. FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.

c. FDA will evaluate additional ways to facilitate public and sponsor access to Sentinel's distributed data network to conduct safety surveillance.

d. By the end of FY 2019, FDA will hold or support a public meeting engaging stakeholders to discuss current and emerging Sentinel projects and seek stakeholder feedback and input regarding gaps in the current system to facilitate the further development of Sentinel and its system of Active Risk Identification and Analysis (ARIA).

e. By the end of FY 2020, FDA will establish policies and procedures (MAPPs and SOPPs) to facilitate informing sponsors about the planned use of Sentinel to evaluate a safety signal involving their respective products. These MAPPs and SOPPs will address what types of evaluations and what information about the evaluations will be shared with sponsors, and the timing of such communications.

f. By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPs, as needed.

g. By the end of FY 2020, FDA will develop a comprehensive training program for review staff (e.g., epidemiologists, statisticians, medical officers, clinical analysts, project managers, and other review team members) to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistently participate in use of Sentinel to evaluate safety issues.

h. By the end of FY 2022, FDA will analyze, and report on the impact of the Sentinel expansion and integration on FDA's use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs.

https://www.fda.gov/media/99140/download

October 1, 2017 – September 30, 2022

Looking Ahead: PDUFA VII

October 1, 2022 – September 30, 2027 (Fiscal Years 2023 – 2027)

Focus on Pregnancy Safety

FDA committed to optimizing the Sentinel System not only through maintenance, but also through guidance on pregnancy postmarket safety studies. The goal of these studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manneer.

> "FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of postmarket studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects."
>
> *Prescription Drug User Fee Act VII: Fiscal Years 2023-2027 Commitment Letter (I)(M)(2)(b)(i)*

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

PDUFA VII: Focus on Pregnancy Safety

i. Pregnancy Safety

The goal of pregnancy safety post-market requirements and commitments studies is to inform labeling on the safety of use in pregnancy and to detect or evaluate safety signals in a timely manner.

(1) FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of post-market studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects. The framework would consider factors such as, but not limited to, purpose of study, types of post-market studies, anticipated exposure in females of reproductive potential (FRP) and pregnant women, potential toxicity of the drug and proposed risk mitigation, benefits of the drug, and magnitude and type of risk to be detected. The framework would specifically address the use of pregnancy registries and electronic healthcare data sources including Sentinel, with a goal of ensuring the most efficient means of obtaining highest quality safety data available.

(a) FDA will review published literature and conduct a review of types of post-market pregnancy data that have been included in pregnancy labeling.

(b) By September 30, 2023, FDA will hold a public workshop on post-market safety studies in pregnant women to facilitate determination of the ideal post-market study design(s), including industry experience and use of Sentinel Initiative and other real-world data resources.

(c) By September 30, 2024, FDA will publish a workshop report describing the proposed framework.

(2) Incorporating feedback from (1), conduct 5 demonstration projects to address gaps in knowledge about performance characteristics of different study designs. FDA will initiate the following demonstration projects which may be modified as needed, before September 30, 2024:

(a) Assess the performance of pregnancy registries versus electronic healthcare database studies to detect a signal when the exposure to medication in pregnancy is relatively common.

(b) Assess the performance of single arm safety studies versus signal identification methods using electronic healthcare data to detect a signal when the exposure to medication in pregnancy is anticipated to be low.

(c) Assess the performance of pregnancy registries versus electronic healthcare database studies to evaluate a signal when the exposure to medication in pregnancy is relatively common.

(d) Assess the performance of major congenital malformations (MCM) as a composite outcome in signal detection and evaluation when there is true risk for some but not all specific malformations.

(e) Assess the performance of an algorithm using electronic health record (EHR) and claims-linked healthcare data for a pregnancy-related outcome, or composite of outcomes (e.g., spontaneous abortion, stillbirth, congenital malformations), after use of vaccines in pregnant women. The parameters of the pregnancy-outcome algorithm will be developed to have general usability with therapeutic products.

(3) By September 30, 2027, based on the results of demonstration projects in (2) update the proposed framework and develop a guidance or MAPP/SOPP as appropriate to implement a standardized process for determining necessity and type of pregnancy postmarketing studies including PMRs.

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

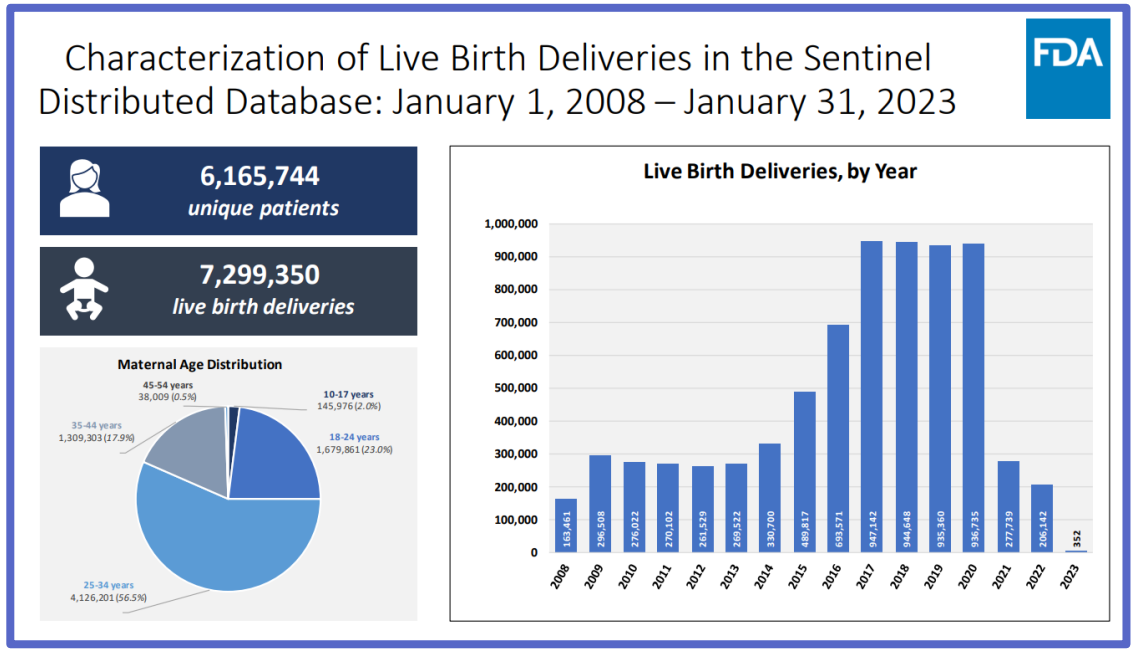
Workshop: Optimizing the Use of Postapproval Pregnancy Safety Studies

September 18, 2023 – September 19, 2023

Session 3: FDA's Considerations for Constructing a Pregnancy Safety Study Framework

Presenters:

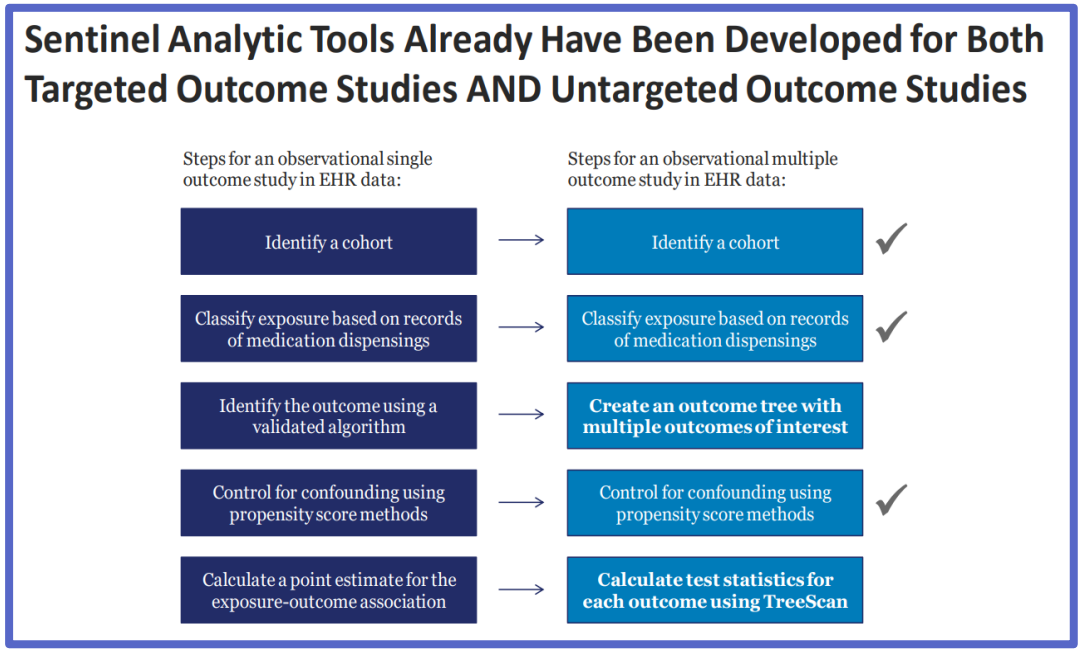
- Wei Hua, CDER
- Adebola Ajao, CDER
- Aida Kuzucan, CDER
- José J. Hernández-Muñoz, CDER



Session 5: Filling the Known Gaps for a Comprehensive Pregnancy Safety Study Framework

Presenters:

- Patricia Bright, CDER
- Judith Maro, Harvard Pilgrim Health Care Institute / Harvard Medical School
- Joann Gruber, CBER



https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/optimizing-use-postapproval-pregnancy-safety-studies-two

PDUFA VII: Focus on Negative Controls

FDA also committed to expanding methodologies in support of real-world evidence (RWE) initiatives. This commitment involves development of an empirical method to automate the negative control identification process in the Sentinel System, as well as development of a method to use a double negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines in CBER's BEST System.

"FDA will develop new methods to support causal inference in Sentinel/BEST that could address product safety questions and advance our understanding of how RWE may be used for studying effectiveness."

Prescription Drug User Fee Act VII: Fiscal Years 2023-2027
Commitment Letter (I)(M)(2)(b)(ii)

https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

PDUFA VII: Focus on Negative Controls

ii. Use of Real-World Evidence – Negative Controls

FDA is building Sentinel/BEST methodology to improve understanding of robustness evaluations used to address the consistency of RWE with respect to study design, analysis, or variable measurement. FDA will develop new methods to support causal inference in Sentinel/BEST that could address product safety questions and advance our understanding of how RWE may be used for studying effectiveness.

(1) By September 30, 2023, FDA will hold a public workshop on use of negative controls for assessing the validity of non-interventional studies of treatment and the proposed Sentinel Initiative projects.

(2) FDA will initiate two methods development projects by September 30, 2024 to 1) develop an empirical method to automate the negative control identification process in Sentinel and integrate it into the Sentinel System tools; and 2) develop a method to use a double negative control adjustment to reduce unmeasured confounding in studying effectiveness of vaccines.

(3) By September 30, 2027, FDA will publish a report on the results of the development projects.

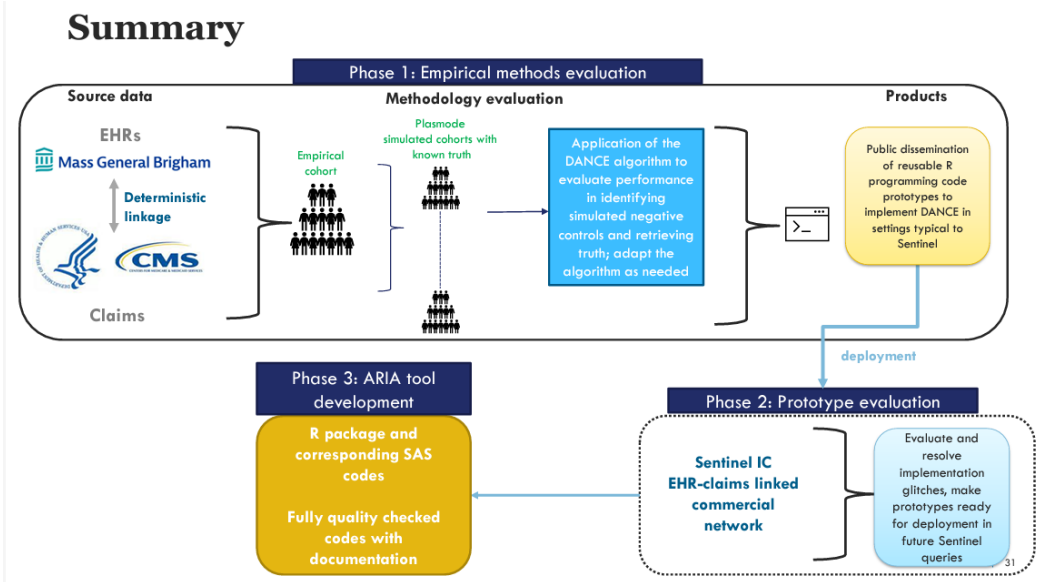
https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vii-fiscal-years-2023-2027

Workshop: Understanding the Use of Negative Controls to Assess the Validity of Non-Interventional Studies of Treatment Using Real-World Evidence

March 8, 2023

Session: Utilizing Negative Control in Safety and Effectiveness: Methods Development and Key Considerations

Presenter: Richard Wyss, Brigham and Women's Hospital



https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/understanding-use-negative-controls-assess-validity-non

Received: 3 March 2021 | Revised: 25 March 2021 | Accepted: 26 March 2021

DOI: 10.1002/pds.5240

REVIEW

WILEY

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

Noelle M. Cocoros[1] | Candace C. Fuller[1] | Sruthi Adimadhyam[1] | Robert Ball[2] | Jeffrey S. Brown[1] | Gerald J. Dal Pan[2] | Sheryl A. Kluberg[1] | Vincent Lo Re 3rd[3] | Judith C. Maro[1] | Michael Nguyen[2] | Robert Orr[2] | Dianne Paraoan[2] | Jonathan Perlin[4] | Russell E. Poland[1,4] | Meighan Rogers Driscoll[1] | Kenneth Sands[1,4] | Sengwee Toh[1] | W. Katherine Yih[1] | Richard Platt[1] | And the FDA-Sentinel COVID-19 Working Group

Utilization of Potential Paxlovid Interactors

among Paxlovid-eligible COVID-19 Patients or Patients with a Paxlovid Exposure

RETROSPECTIVE COHORT STUDY

Sentinel

Objective: Estimate the magnitude of the "at-risk" population using drugs that interact with Paxlovid to inform the Division of Antiviral's labeling decision

Rapid Sentinel Distributed Database

December 2021 – December 2022

1. **Individuals with outpatient diagnosis of COVID-19 and no prior evidence of severe renal or hepatic impairment**
2. **Individuals with use of Paxlovid**

	COVID among Patients ≥65 years or High-risk		COVID among Patients ≥50 years or High-risk		Paxlovid Users	
Total number of patients	1,228,761		1,450,712		551,482	
Any Drug that Interacts with Paxlovid	**695,320**	**56.6%**	**763,727**	**52.6%**	**310,012**	**56.2%**
Any Drugs Contraindicated for use with Paxlovid	89,916	7.3%	95,400	6.6%	37,929	6.9%
Any Drugs to be avoided with paxlovid	354,035	28.8%	379,286	26.1%	167,996	30.5%
Any Other Drug Drug Interactor	508,854	41.4%	557,654	38.4%	211,257	38.3%

- **>50% of Paxlovid eligible users could have taken drugs that could interact with Paxlovid***
- **Commonly used Paxlovid interactors are unlikely to prevent Paxlovid use**
- **7% of Paxlovid users may have used contraindicated drugs and 31% may have used drugs that should be avoided with Paxlovid***

Query results were included in Paxlovid NDA review.

* Health insurance claims data do not capture if concurrent medications were withheld or had their dose adjusted due to Paxlovid

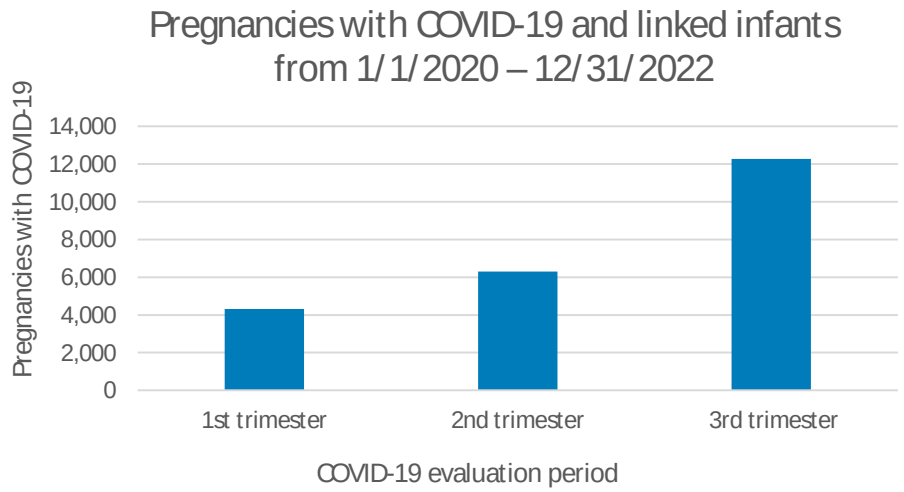
CONSIGN (COVID-19 Infection and Medicines in Pregnancy) Study

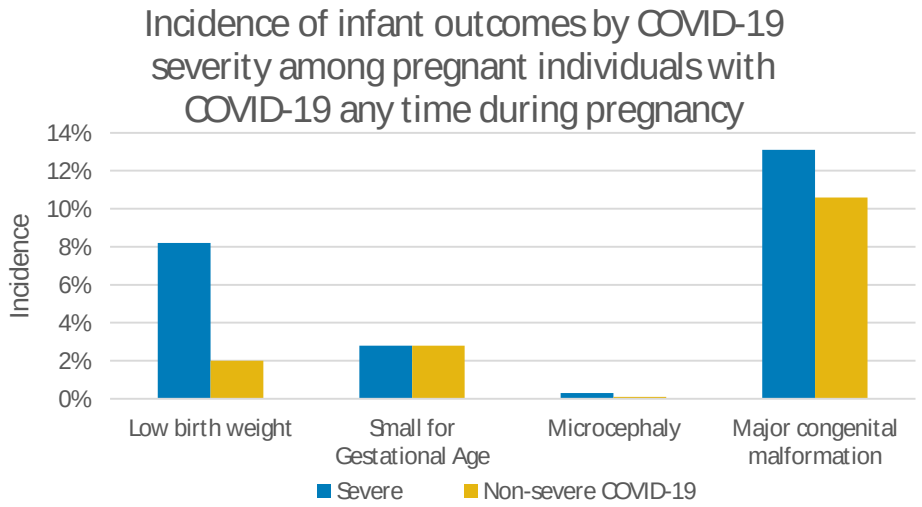
Objective: To evaluate the impact of COVID-19 on adverse infant outcomes in pregnant individuals with COVID-19 compared to those without COVID-19

Live-birth deliveries in U.S. FDA's Sentinel System

Pregnant individuals with and without COVID-19

Estimated pregnancy start date within +/-14 days, similar pregnancy duration





Key Takeaways: No increased risk of infant outcomes was observed comparing pregnant individuals with COVID-19 to those without COVID-19 but a slightly higher number of infants with congenital malformations and low birth weight was observed among severe COVID-19 pregnant individuals

Acknowledgements (1 of 2)

Aimovig

U.S. Food and Drug Administration

Blum, Michael
Herity, Leah
Hernandez, Jose
Kidd, James
Ma, Yong
Mundkur, Mallika
Munoz, Monica

Sentinel Operations Center

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Kanani, Xhulia
Mai, Xiaodan Melody
Maro, Judy
Marshall, Jim
Peters, Alexander
Siranosian, Liz

Sentinel Data Partners

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- Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
- Carelon Research/Elevance Health, Wilmington, DE
- Humana Healthcare Research Inc., Louisville, KY
- OptumInsight Life Sciences Inc., Boston, MA

Ozempic

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- OptumInsight Life Sciences Inc., Boston, MA
- Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN

Zarxio

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Sentinel Data Partners

- CVS Health (Aetna), Blue Bell, PA
- Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
- Carelon Research/Elevance Health, Wilmington, DE
- Humana Healthcare Research Inc., Louisville, KY
- OptumInsight Life Sciences Inc., Boston, MA

Acknowledgements (2 of 2)

CONSIGN Study

U.S. Food and Drug Administration

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Sentinel Operations Center

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- Humana Healthcare Research Inc., Louisville, KY
- Kaiser Permanente Colorado Institute for Health Research, Aurora, CO
- Kaiser Permanente Northwest Center for Health Research, Portland, OR
- Kaiser Permanente Washington Health Research Institute, Seattle, WA
- OptumInsight Life Sciences Inc., Boston, MA

Paxlovid Utilization Among COVID-19 Patients

U.S. Food and Drug Administration

Greene, Patty
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Hua, Wei
Mistry, Kusum
Perez-Vilar, Silvia
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- HealthPartners Institute, Minneapolis, Minnesota
- Humana Healthcare Research Inc., Louisville, KY
- Kaiser Permanente Colorado Institute for Health Research, Aurora, CO
- Kaiser Permanente Northwest Center for Health Research, Portland, OR

Sentinel

Thank you!

FDA Biologics Effectiveness and Safety (BEST) Coordinating Center Perspectives

Yoganand Chillarige
Acumen LLC
November 2023

Outline

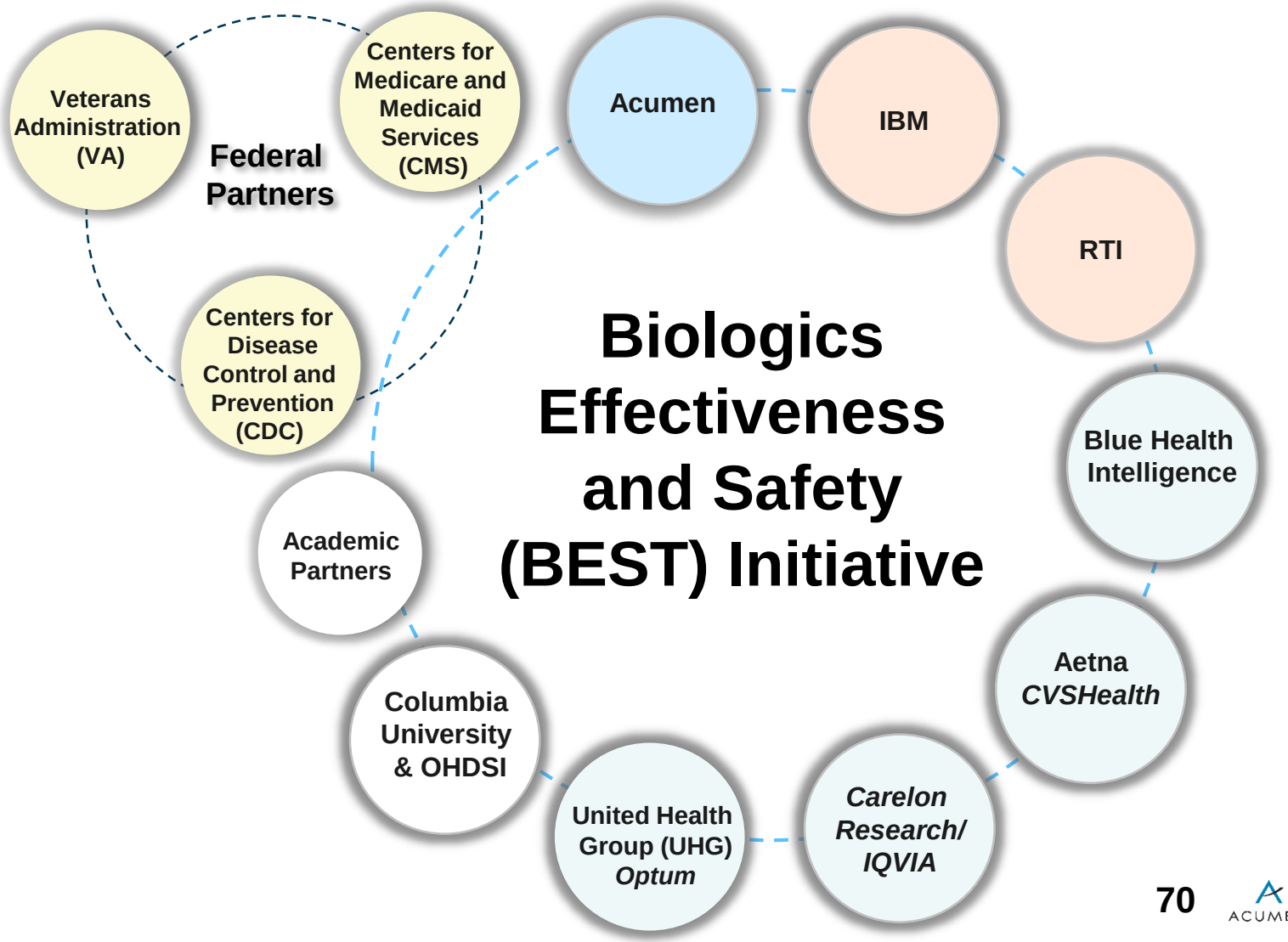
- Introduction to CBER BEST
- Expansion of Network Capacities in FY23
- Surveillance Activities in FY23
- Planned Activities for FY24

Outline

- **Introduction to CBER BEST**
  - CBER Active Surveillance Program
  - BEST Claims-Based Distributed Data Network
- Expansion of Network Capacities in FY23
- Surveillance Activities in FY23
- Planned Activities for FY24

CBER Active Surveillance Program

- Long history of federal partner collaboration, with CMS involvement since 2008
- BEST Initiative launched in 2018
- Distributed Data Network (DDN) with a common data model (CDM) established in 2020



BEST Claims-Based Distributed Data Network

- Collaborators maintain data in an adapted version of the Observational Medical Outcomes Partnership (OMOP) Common Data Model

- In the absence of a CDM, Acumen works with the collaborating partner to build study-specific research analytic files

- Databases are updated monthly, or more frequently

Outline

- Introduction to CBER BEST
- **Expansion of Network Capacities in FY23**
  - Enhancing Data Access and Network Infrastructure
  - Improving Capacity for Analysis Implementation
- Surveillance Activities in FY23
- Planned Activities for FY24

Enhancing Data Access and Network Infrastructure

- Expanded linkage of data from immunization information systems (IIS) registries with BEST data partners (DP) databases
  - Increased the number of IIS jurisdictions sharing data with partners
  - Expanded information received to include new vaccines (e.g., mpox)

- Improved processes for expedited retrieval of medical records
  - Modified outreach process to increase response rate and time
  - Received over 50% of records within two weeks of request

Improving Capacity for Analysis Implementation

- Implemented the BEST Pregnancy Algorithm and Mother-Infant Linkage across entire network
  - Successfully validated linkage of mothers and infants

- Expanded the suite of analytical methods available for the distributed data network
  - Earlier years focused on building the capacity for active surveillance methods
  - Developed and implemented packages to conduct cohort studies, propensity score methods, and self-controlled analyses

Outline

- Introduction to CBER BEST
- Expansion of Network Capacities in FY23
- **Surveillance Activities in FY23**
  - Overview of Surveillance Activities
  - COVID-19 Surveillance Activities
  - Other Biologics Surveillance
- Planned Activities for FY24

Overview of Surveillance Activities in FY23

- Maintained primary focus of surveillance on COVID-19 products, while expanding scope of activities to monitor other biologics

- Responded to emerging situations, as required
  - Monitoring safety of vaccines to prevent mpox

- Disseminated findings through publications, pre-prints, and presentations at scientific conferences and advisory committees

COVID-19 Related Surveillance Activities

- Vaccine Safety:
  - Near real-time monitoring of pediatric and bivalent formulations of mRNA vaccines
  - Follow-up studies responding to signals identified in FDA surveillance or through other active surveillance systems in the U.S.

- Vaccine Effectiveness (VE):
  - Evaluated effectiveness in preventing severe outcomes in the elderly Nursing Home-dwelling Medicare population
  - Evaluated effectiveness of the primary series and monovalent boosters in preventing severe outcomes and infection in the community-dwelling population, ages 5-64

COVID-19 Related Surveillance Activities

- Conducting studies to contextualize the risk and benefit profile of the COVID-19 vaccines by evaluating the short-term and long-term risks associated with the disease
  - Evaluating the risk of adverse events after COVID-19
  - Validation of algorithms to identify multisystem inflammatory syndrome in children (MIS-C)
  - Characterization of long-COVID among U.S. Medicare beneficiaries using claims data

Other Biologics Surveillance Activities

- Evaluation of influenza vaccine safety for the 2022-23 season:
  - Used a self-controlled case series analysis to evaluate the risk of adverse events in the elderly (65+) population

- Monitoring vaccines to prevent mpox in the adult population below the age of 65
  - Monitored vaccine uptake and incidence rates of adverse events following vaccine administration

Outline

- Introduction to CBER BEST
- Expansion of Network Capacities in FY23
- Surveillance Activities in FY23
- **Planned Activities for FY24**

Looking Ahead: FY24

- Vaccine Surveillance for influenza, COVID-19, and RSV vaccines
  - Vaccines are approved for specific age groups:
    - Influenza**:** Ages 6 months and older
    - COVID-19**:** Ages 6 months and older
    - RSV**:** Ages 60 and older; pregnant individuals at 32-36 weeks gestational age
  - Evaluating safety and effectiveness of all three vaccine-types, both individually and in combination with one another

- Utilize the expanded scope of the data network:
  - Evaluating safety and effectiveness of maternal vaccines

- Continue to advance methods for safety surveillance in a distributed data network

Thank You

Optum

Perspectives on FDA BEST from the Ground Up

John D. Seeger, PharmD, MPH, DrPH, FISPE
Chief Scientific Officer, Optum Epidemiology
Adjunct Assistant Professor, Epidemiology,
Harvard T.H. Chan School of Public Health

2023

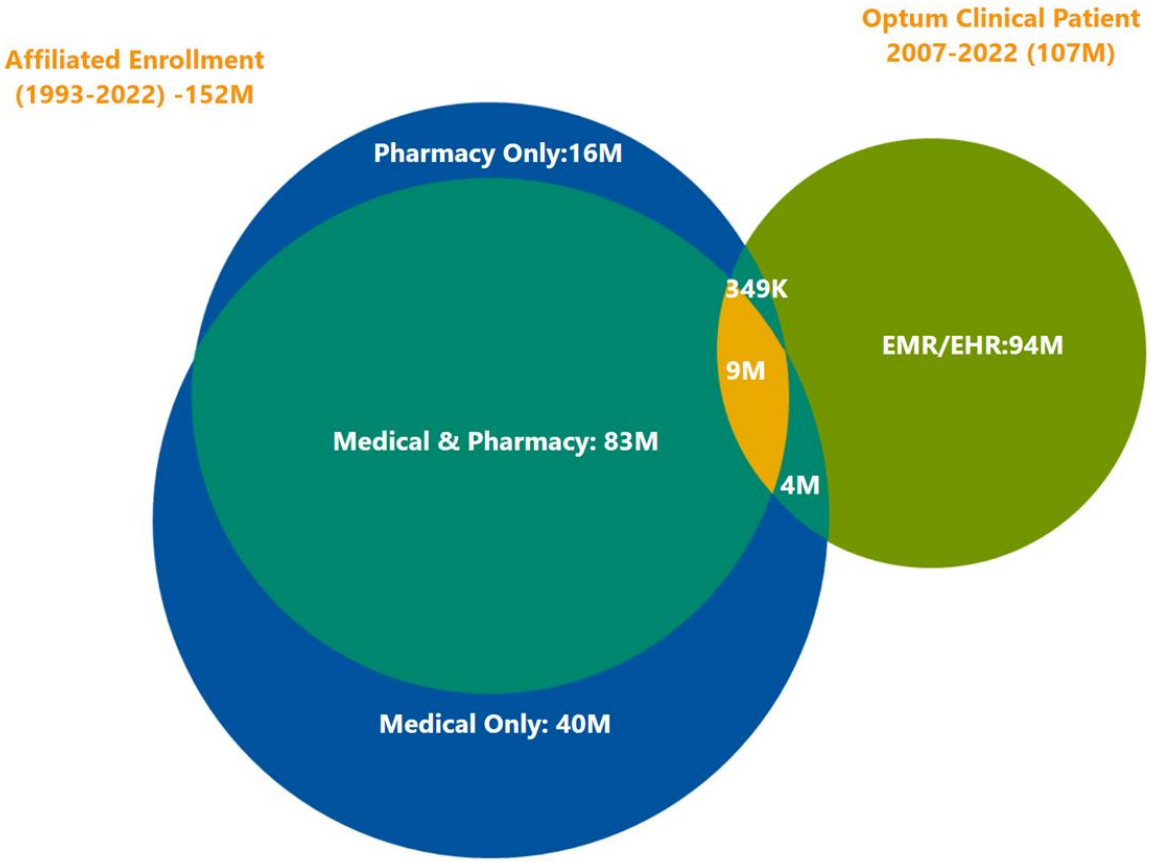
FDA BEST Through the Optum Lens

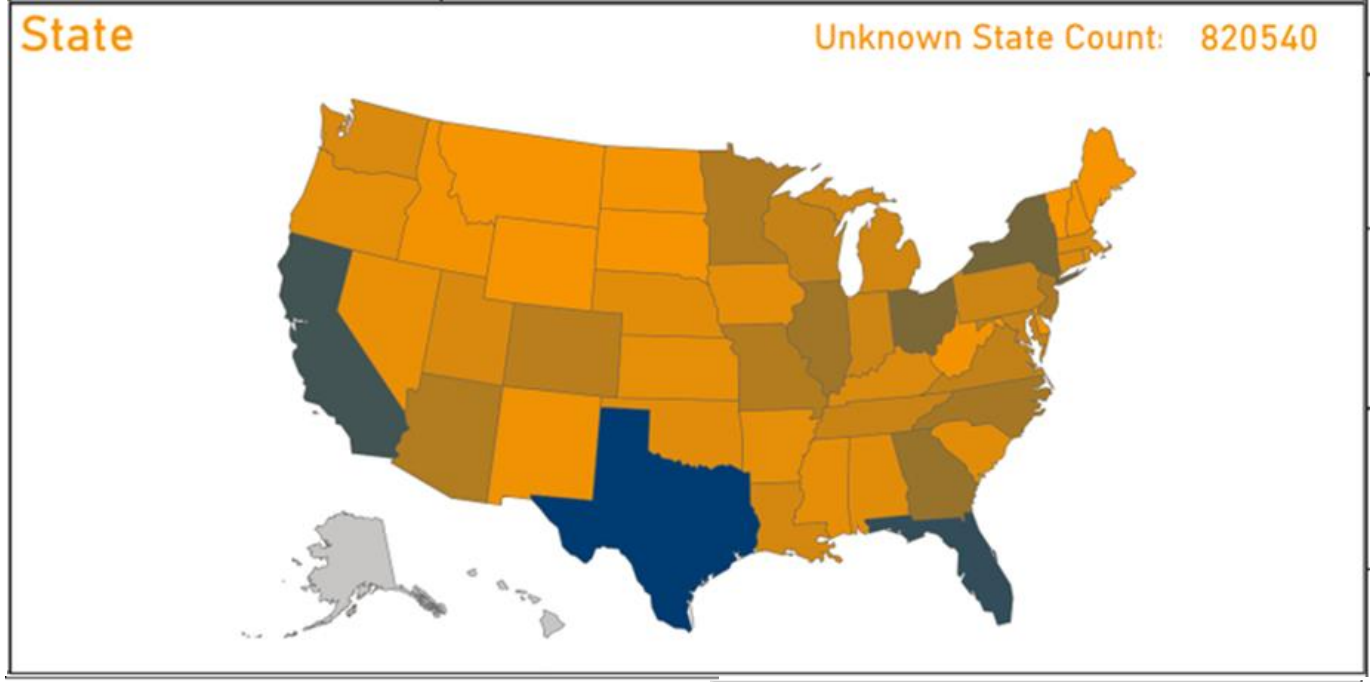
- Claims data have become a standard within pharmacoepidemiology
- Paradigm shift: questions and answers framed in the language of claims
- Claims data provide both strengths & challenges
  - Unlimited combinations of codes (drugs/biologics, diagnoses, procedures)
  - Specific codes along with their co-occurrence and relative timing
  - Represent metadata of complex medical encounters
  - Between patients and the healthcare system (byproduct of routine care)
- Optum and other claims data sources offer distinctly American dialects of medical care – coded in ways that reflect the billing practices in the US

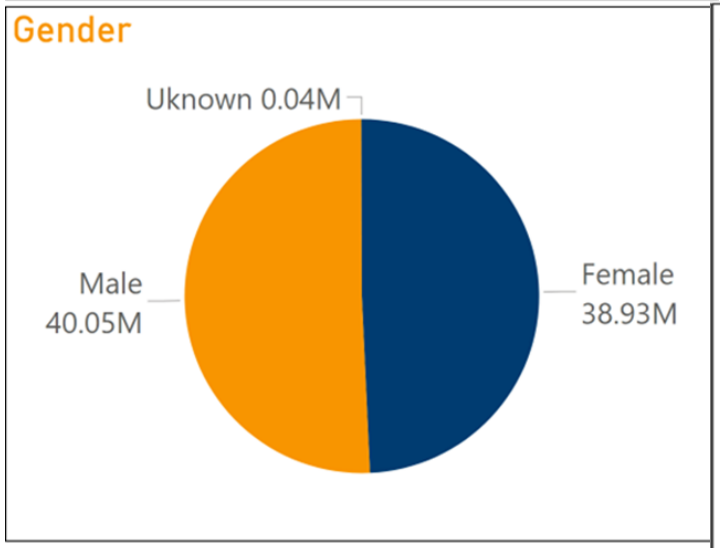
What Does Optum Bring to FDA BEST

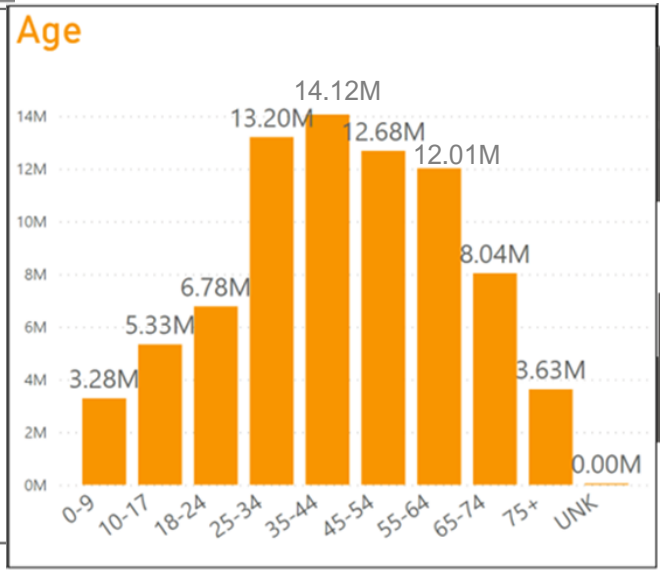
- Pharmacoepidemiology expertise (25+ years drug and vaccine research)
  - Large team (~40 people across EPI, OS, and Data teams)
- Situated within the Optum data ecosystem
- Providing a human user interface to the Optum data
  - Applied Epidemiology methods
  - Protocol development and adherence
  - Regulatory-grade analytic programming
  - Facility with Optum data in its native format and privileged data access
- “Data with benefits”

Optum Data Ecosystem

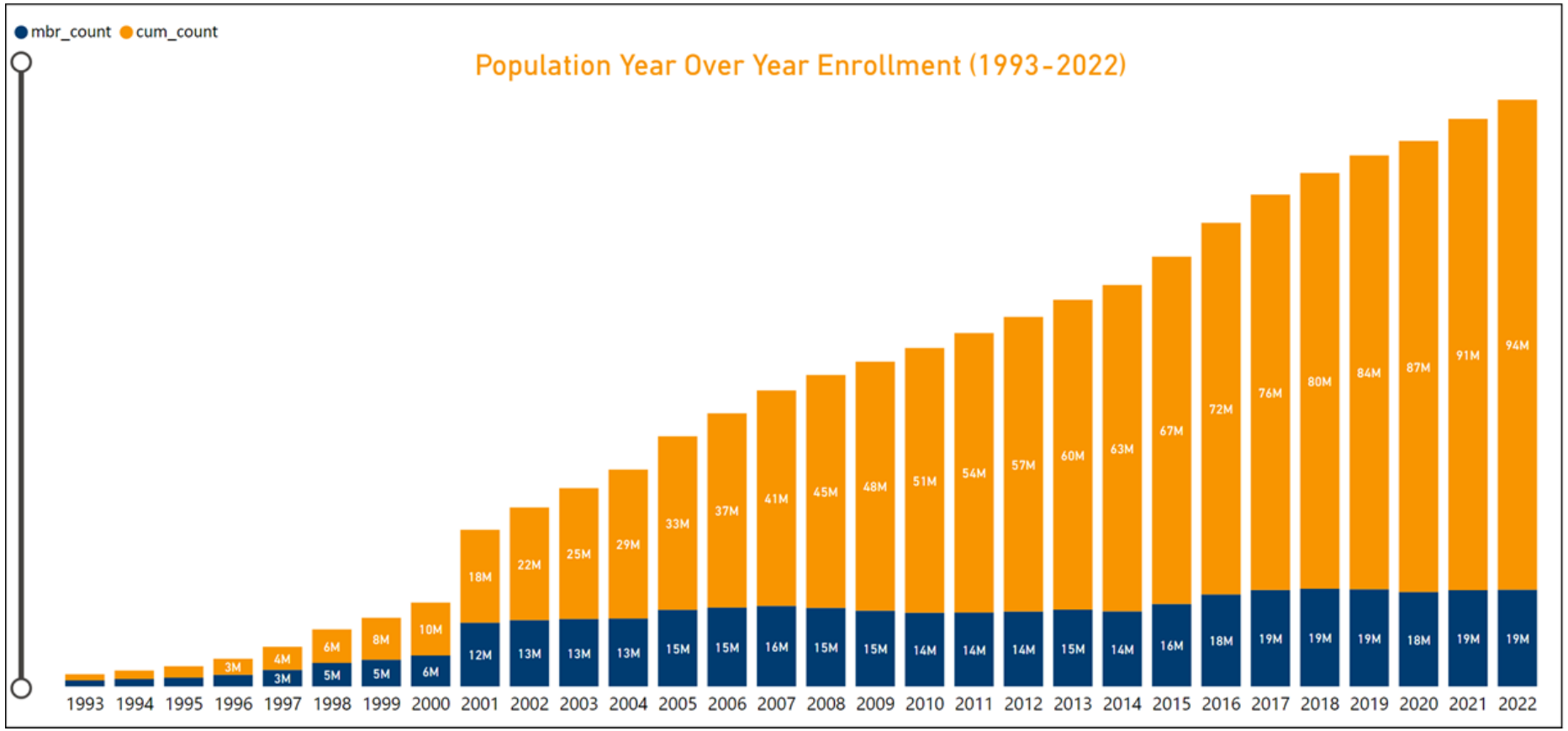








Growth and Evolution



- Constant updates – data ecosystem
- Healthcare services to millions – any billed transaction, current & historical
- Ability to go beyond – indexing system linked to sources (charts/EHR)
- Anything that can happen…

Optum

Conclusions for Optum and FDA BEST

- Optum provides boots on the ground
- Founded in science (epidemiology)
- Connected to source data (Optum bridges the “rift”*)
- Facilitates translation of RWD to RWE
- Foundation for fact-based decision-making

* Rothman KJ. The growing rift between epidemiologists and their data. Eur J Epidemiol 2017;32:863–865.

Optum

Thank You!

John D. Seeger, PharmD, MPH, DrPH, FISPE

Chief Scientific Officer, Optum Epidemiology

Adjunct Assistant Professor of Epidemiology, Harvard T.H. Chan School of Public Health

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Optum

Join at
slido.com
#Sentinel

Moderated Discussion and Q&A

Moderator: Gerrit Hamre

Duke-Margolis Center for Health Policy

Break for Lunch

Workshop will resume at **1:05 p.m. EST**

BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

Moderator: **Christina Silcox,** Duke-Margolis Center for Health Policy

Speakers:

Joann Gruber, U.S. Food and Drug Administration

Mao Hu, Acumen LLC

Patricia Lloyd, U.S. Food and Drug Administration

Lauren Peetluk, Optum Epidemiology

BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

Patricia C. Lloyd, PhD[1]
Joann F. Gruber, PhD[1]
Mao Hu, BS[2]
Lauren Peetluk, PhD[3]

[1]U.S. FDA CBER, [2]Acumen, LLC, [3]Optum Epidemiology

15th Annual Sentinel Initiative Public Workshop
November 8, 2023

Disclaimer

- The BEST Initiative and its studies are funded by the U.S. Food and Drug Administration (FDA)
- There are no potentially conflicting relationships to disclose
- The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, Acumen, LLC, or Optum Epidemiology

Outline

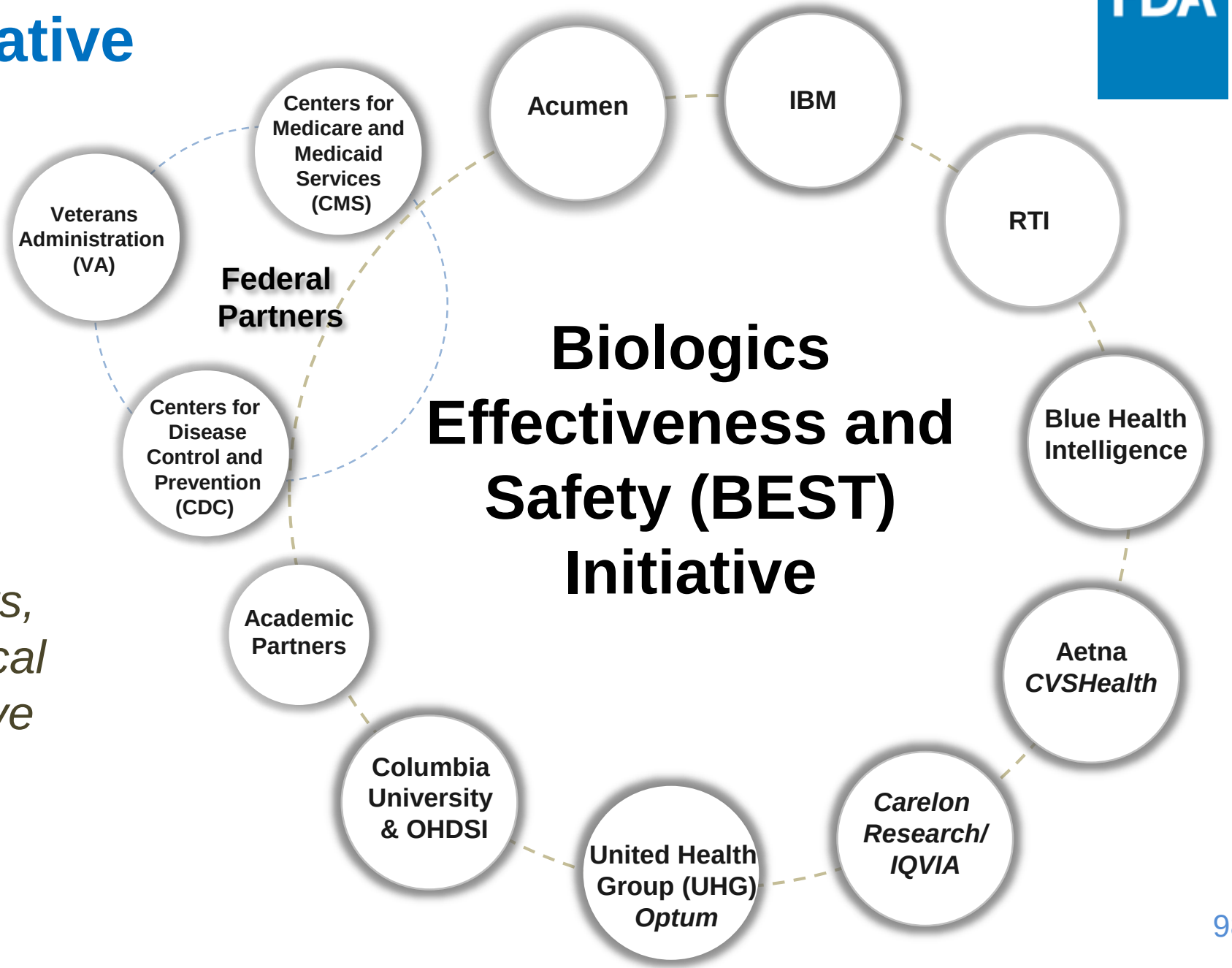
- Introduction & Enhancements to the BEST Infrastructure
- Safety Surveillance Activities for Fiscal Year 2023
- Self-Controlled Studies for Fiscal Year 2024 Safety Surveillance Activities
- COVID-19 Vaccine Effectiveness

Introduction & Enhancements to the BEST Infrastructure

Patricia C. Lloyd, PhD
U.S. FDA CBER

CBER Active Surveillance Program Collaborative

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



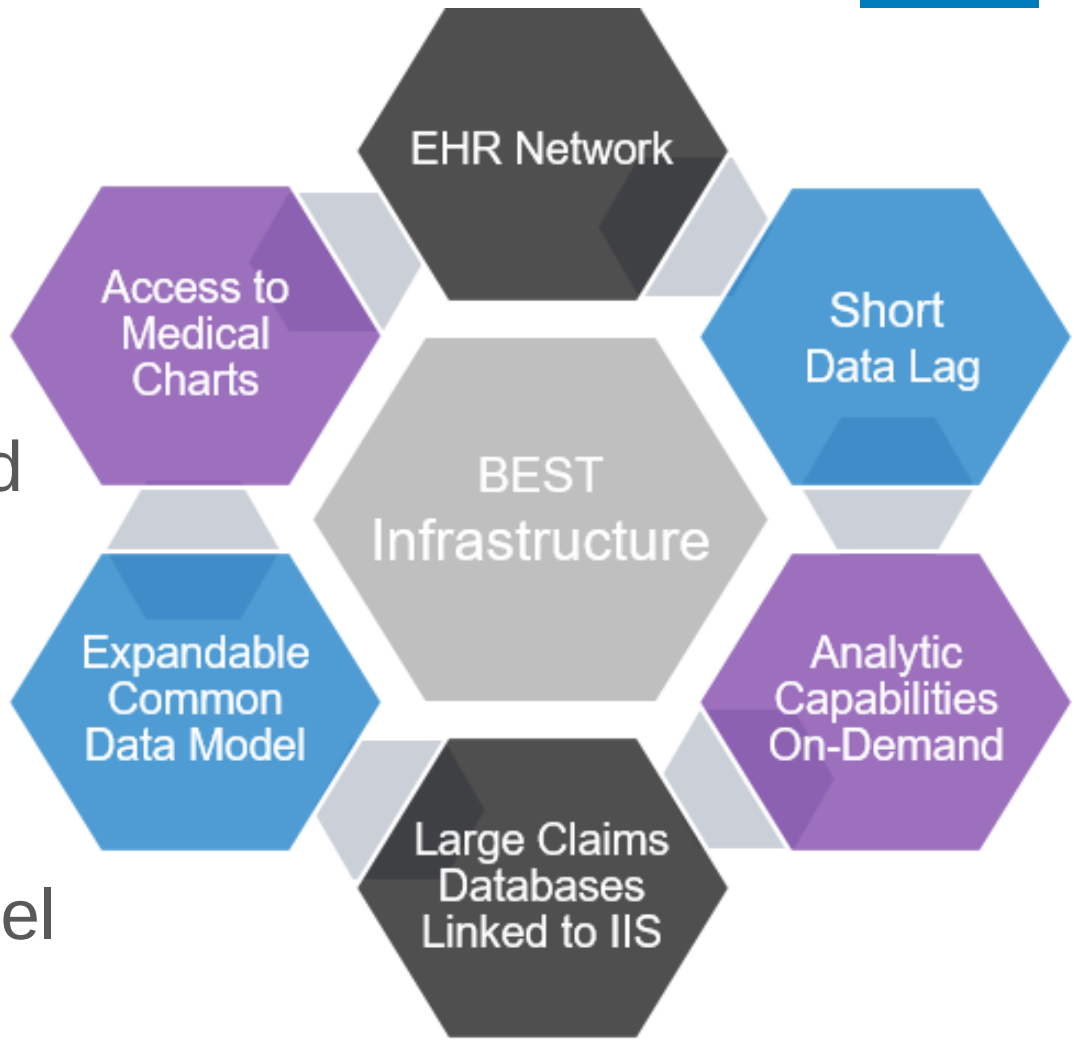
Data Network

Distributed data network

- No central repository
- Data are maintained and reside behind firewall of each data contributor

Data are standardized

- Transformed into a common data model (CDM)



BEST Initiative Data Sources

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS–Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
Blue Health Intelligence	Claims	33.6	2012 - present
Optum–Adjudicated	Claims	66	1993 - present
Optum–Pre adjudicated	Claims	22	2017 - present
Carelon Research	Claims	76	2006 - present
CVS Health	Claims	26	2018 - present
OneFlorida Clinical Research Consortium–Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium–EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6.0	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims–EHR	Linked EHR Claims	25	2007 - 2020
OneFlorida Clinical Research Consortium–Linked EHR Claims	Linked EHR Claims	1.5	2012 - present

*Data lag varies for different databases from a few days to a few months.

Enhancements to the BEST Infrastructure

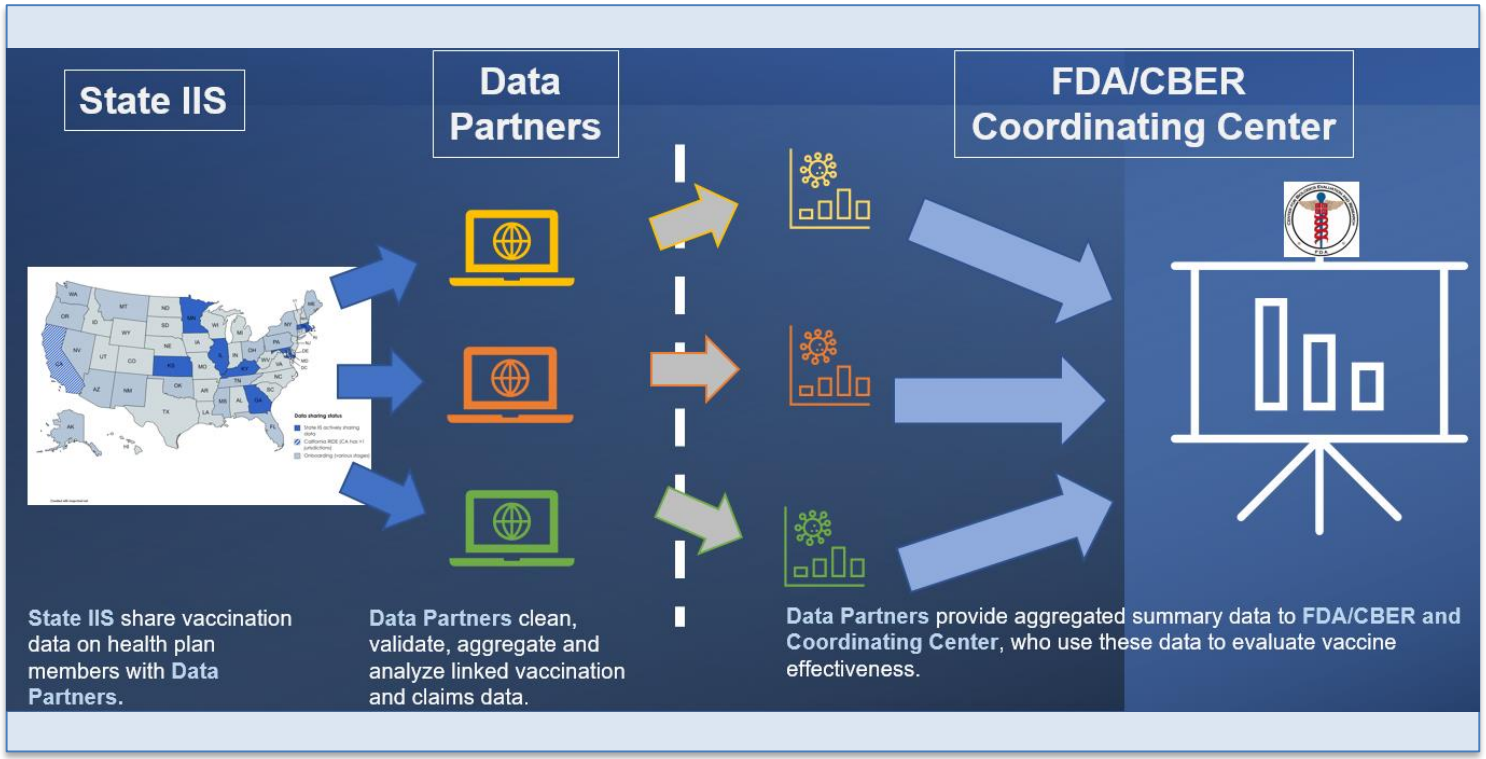
- **Data Sources**
  - Large claims databases with shorter data lag and more frequent data refresh for timely monitoring of rare events

- **Infrastructure**
  - Augmenting vaccination capture in claims data bases with external data sources, such as Immunization Information Systems (IIS)
  - Developing algorithms for linking mothers to infants in claims data

Immunization Information System (IIS)

IISs provide crucial vaccine data and enhances FDA BEST safety and effectiveness surveillance

- IIS data are used to conduct more robust, accurate safety and effectiveness studies
- Contribute to regulatory decision making
- Input for benefit risk assessment
- Improved public communication



IIS data have been linked to claims databases from BEST data partners and used in:

- COVID-19 vaccine safety surveillance studies
- COVID-19 vaccine effectiveness work
- Mpox safety surveillance

Linkage of pregnant individuals and infants within BEST databases

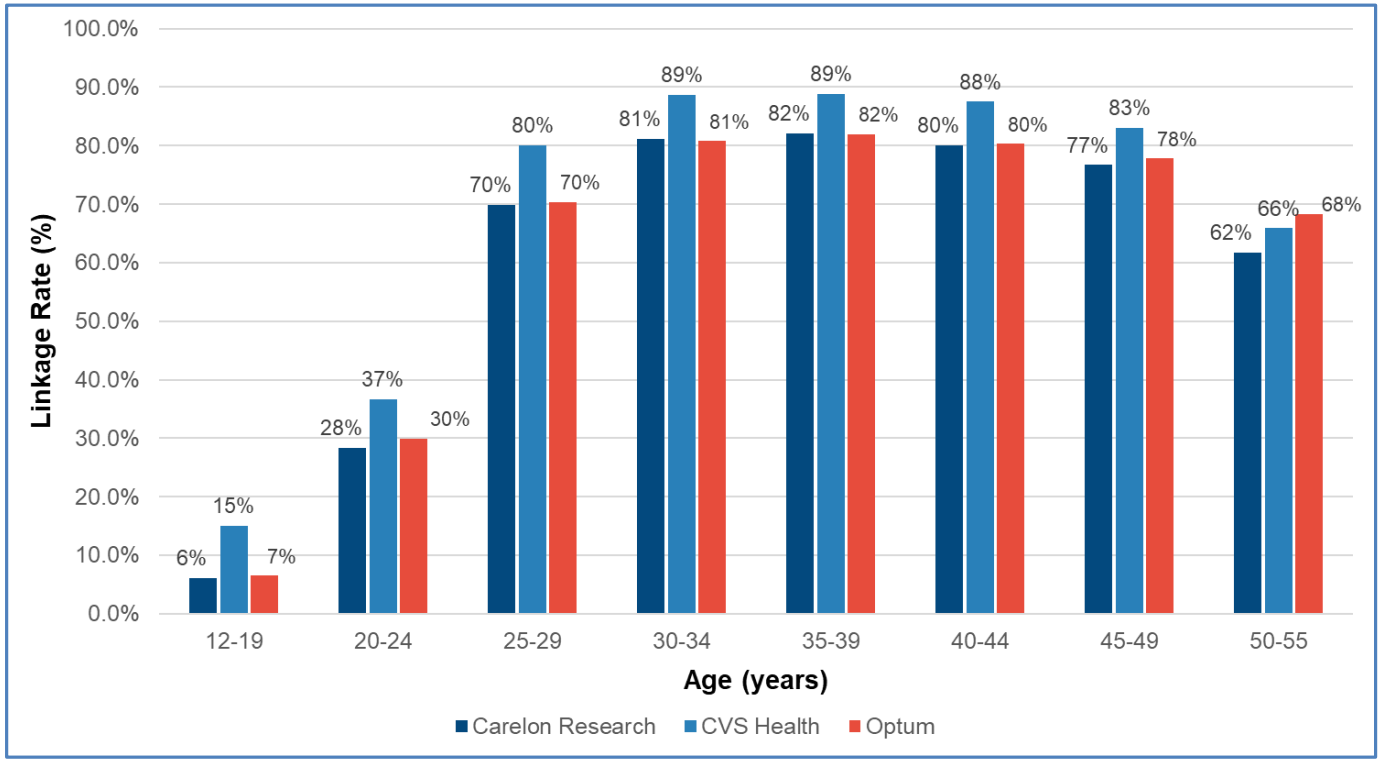
Enhances BEST's ability to conduct safety surveillance of biologics during pregnancy and on the health of infants

- Identify pregnancy outcomes and gestational ages using claims-based algorithms
- Link live deliveries and infants in claims databases

Next Steps

- Develop and execute processes to compare linked vs. non-linked mothers and infants
- Evaluate pregnancy and infant outcomes following exposure to biologics

Linkage rates by mother's age, BEST databases



Session Roadmap

- Safety Surveillance Activities for Fiscal Year 2023
- Future Safety Surveillance Activities: Shifting near-real time surveillance to self-controlled studies
- COVID-19 Vaccine Effectiveness

Safety Surveillance Activities for Fiscal Year 2023

Joann F. Gruber, PhD
U.S. FDA CBER

Safety Surveillance Activities for Fiscal Year 2023

- COVID-19
  - Pediatric Population
  - Bivalent Booster
- Other Vaccine Safety Studies
  - Vaccines to Prevent Mpox
  - Influenza Vaccines

Safety of COVID-19 Vaccines in Pediatric Populations

Near-real time monitoring with monthly sequential testing

- **Initially**: Pfizer-BioNTech in populations 5–17 years
- With new authorizations, **expanded** monitoring to:

Vaccine	Age Group
Pfizer-BioNTech (BNT162b2)	6 months–17 years
Moderna (mRNA-1273)	6 months–17 years
Novavax (NVX-CoV2373)	12–17 years

Near Real-Time Monitoring: Pediatric Populations

Design	Near Real-Time Sequential Testing
Data Sources	CVS Health/Aetna, Carelon Research, Optum
Study Population	Health plan members receiving original monovalent doses of: • Pfizer-BioNTech, 6 months–17 years • Moderna, 6 months–17 years • Novavax, 12–17 years
Study Period	Earliest EUA date by age group through February–April 2023
Health Outcomes	21 pre-specified AEs • 15 assessed with sequential testing • 6 monitored descriptively
Statistical Analysis	• Monthly sequential testing • Statistical signals when observed AE rates exceeded expected

Results and Conclusion

~8.4 million doses

Of the 15 AEs sequentially tested:

13 did not meet threshold for statistical signal

2 met the threshold for statistical signal

Anaphylaxis	Common site TTS	Encephalitis or encephalomyelitis	Immune thrombocytopenia	Non-hemorrhagic stroke
Appendicitis	Deep vein thrombosis	Guillain-Barré syndrome	Myocarditis/ pericarditis	Pulmonary embolism
Bell's palsy	Disseminated intravascular coagulation	Hemorrhagic stroke	Narcolepsy	Seizures or convulsions

Conclusion: The signal for **myocarditis/pericarditis** in children 12–17 years is consistent with existing literature. A new signal for **seizures/convulsions** in children 2–4 years is being further evaluated. FDA still believes the known and potential benefits of COVID-19 vaccination outweigh the known and potential risks of COVID-19 infection.

Dissemination & Follow-Up

Interim Results	JAMA Pediatrics | Original Investigation Safety of the BNT162b2 COVID-19 Vaccine in Children Aged 5 to 17 Years
Final Results	medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES Safety of Monovalent BNT162b2 (Pfizer–BioNTech), mRNA–1273 (Moderna), and NVX–CoV2373 (Novavax) COVID–19 Vaccines in US Children Aged 6 months to 17 years
Follow-up Study	FDA Evaluation of a Preliminary Seizure Safety Signal from Rapid Surveillance of Children Ages 2 – 4/5 yrs. following COVID-19 mRNA Vaccination BEST Prelim Seizure Safety Signal Ages 2-5 2023 (pdf)

Near Real-Time Monitoring: Bivalent Booster

Design	Near Real-Time Sequential Testing
Data Sources	CVS Health/Aetna, Carelon Research, Optum, Medicare
Study Population	Health plan members ≥ 6 months receiving bivalent doses of: • Pfizer-BioNTech • Moderna
Study Period	Earliest approval/EUA date by age group through mid-2023
Health Outcomes	18–21 pre-specified AEs monitored descriptively or with sequential testing
Statistical Analysis	• Monthly sequential testing • Statistical signals when observed AE rates exceeded expected

Results and Conclusion

~13.9 million doses

Of the 18 AEs sequentially tested in at least one age group:

16 did not meet threshold for statistical signal

2 met the threshold for statistical signal

Acute myocardial infarction	Bell's palsy	Disseminated intravascular coagulation	Hemorrhagic stroke	Narcolepsy	Seizures or convulsions
Anaphylaxis	Common site TTS	Encephalitis or encephalomyelitis	Immune thrombocytopenia	Non-hemorrhagic stroke	Transverse myelitis
Appendicitis	Deep vein thrombosis	Guillain-Barré syndrome	Myocarditis/ pericarditis	Pulmonary embolism	Unusual site TTS

Conclusion: The identified signals are consistent with existing literature.

This study supports the safety profile of bivalent COVID-19 mRNA vaccines.

Dissemination & Follow-Up

In Prep.

Safety Monitoring of Bivalent COVID-19 mRNA Vaccines Among Recipients 6 months and Older in the United States

VRBPAC Meeting: January 26, 2023

- Reported interim results of the bivalent booster monitoring with a particular focus on the population ≥65 years for the outcome non-hemorrhagic stroke

medRχiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

Evaluation of Stroke Risk Following COVID-19 mRNA Bivalent Vaccines Among U.S. Adults Aged ≥65 Years

Other Completed/Ongoing COVID-19 Studies

Submitted

Risk of Adverse Events Following Monovalent Third or Booster Dose of COVID-19 mRNA Vaccination in U.S. Adults Ages 18 Years and Older

Evaluating the Risk of Adverse Events After COVID-19 Diagnosis

BEST Post COVID-19 AE Protocol 2023 (pdf)

Validation of Algorithms to Identify Multisystem Inflammatory Syndrome in Children (MIS-C) in Administrative Claims Data

BEST MIS-C Validation Protocol 2023 (pdf)

Other Vaccine Studies

Monitored 11 AEs following JYNNEOS vaccines in adults 18–64 years with monthly analyses

In Prep.

Safety Monitoring of Vaccines used to Prevent Mpox Administered to U.S. Adults Aged 18–64 Years

Monitored 4 AEs following seasonal influenza vaccination among those ≥65 years an end-of-season analysis

medRxiv
THE PREPRINT SERVER FOR HEALTH SCIENCES

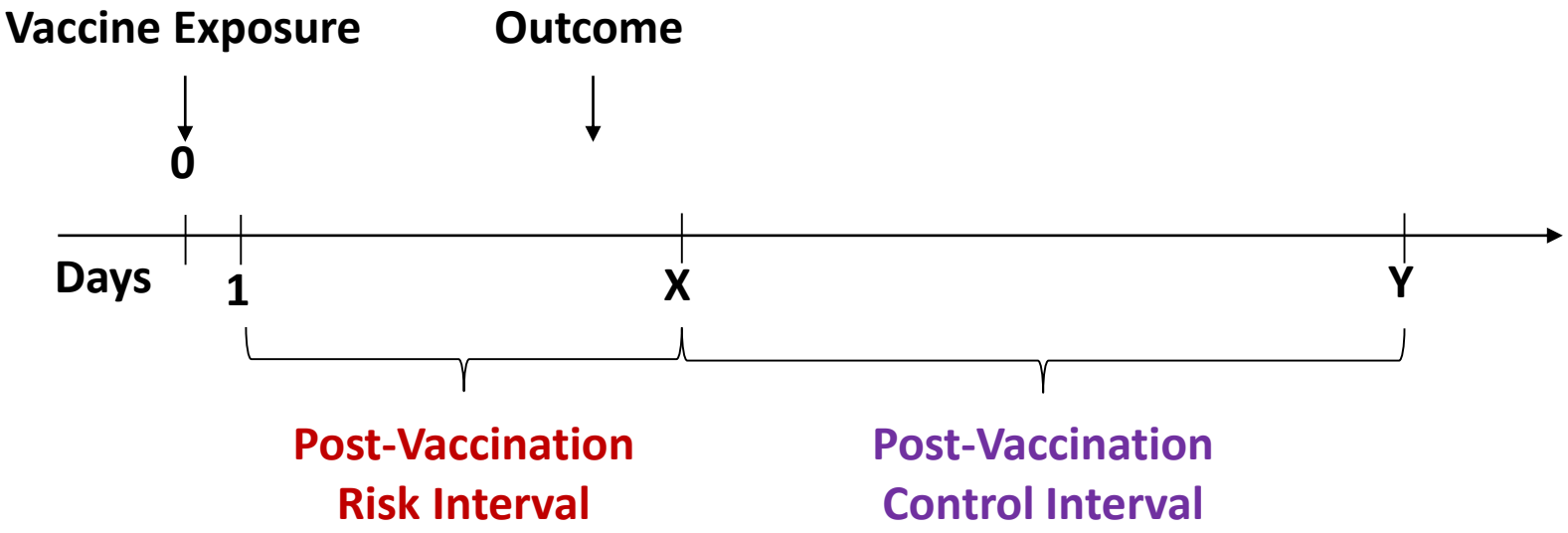
Assessment of Potential Adverse Events Following the 2022–2023 Seasonal Influenza Vaccines Among U.S. Adults Aged 65 Years and Older

Self-Controlled Studies for Fiscal Year 2024 Safety Surveillance Activities

Mao Hu
Acumen, LLC

Self-Controlled Studies for Future Safety Surveillance

- Self-controlled studies (self-controlled case series, self-controlled risk interval) are commonly used to assess outcome risk post-vaccination[1]
- Future safety surveillance will primarily rely on self-controlled study designs where exposed patients serve as their own controls



1. Weldeselassie, Y. G., H. J. Whitaker, and C. P. Farrington. "Use of the self-controlled case-series method in vaccine safety studies: review and recommendations for best practice." *Epidemiology & Infection* 139, no. 12 (2011): 1805-1817.

Self-Controlled Studies

Strengths

- Availability of adjustments for:
  - Time-fixed confounding
  - Quantitative Bias Assessment
  - Seasonality adjustment
  - Event-dependent observation period adjustment [1]
- Appropriate for evaluating rare adverse events in large population-based databases
- Provide estimates of effect size and precision

Limitations

- Potential misspecification of risk and control intervals
- Potential for residual confounding
- Less rapid identification of elevated risk compared to sequential monitoring

1. Farrington, P., et al., *Self-Controlled Case Series Analysis With Event-Dependent Observation Periods.* Journal of the American Statistical Association, 2011. **106**: p. 417-426.

Implementation of Self-Controlled Studies in Safety Surveillance

- **Descriptive monitoring:** Continuous monitoring of vaccination and outcome counts to assess feasibility of self-controlled studies
- **Inferential analysis:** Self-controlled analysis conducted with all appropriate adjustments to provide comprehensive assessment of outcome risk following exposure
  - Early-period analyses may be conducted based on regulatory need or availability of cases for analysis

Examples of Self-Controlled Studies

Guillain-Barré Syndrome After High-Dose Influenza Vaccine Administration in the United States, 2018–2019 Season

- **Exposure:** High-dose, adjuvanted, and other influenza vaccines
- **Outcome:** Guillain-Barré Syndrome (GBS)
- **Population:** ≥65 years in Medicare Fee-for-Service
- **Study design:** Self-controlled risk interval
  - Early-season analysis (data through March 15, 2019)
  - End-of-season analysis (data through September 27, 2019)
- **Findings:** Following high-dose vaccinations, no statistically significant increased risk of GBS
  - Findings consistent between early and end-of-season analysis

Perez-Vilar, Silvia, Mao Hu, Eric Weintraub, Deepa Arya, Bradley Lufkin, Tanya Myers, Emily Jane Woo et al. "Guillain-Barré syndrome after high-dose influenza vaccine administration in the United States, 2018–2019 season." *The Journal of infectious diseases* 223, no. 3 (2021): 416-425.

Examples of Self-Controlled Studies

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.

- **Exposure:** Monovalent COVID-19 vaccine
- **Outcomes:** acute myocardial infarction, pulmonary embolism, immune thrombocytopenia, disseminated intravascular coagulation, Bell's Palsy, and myocarditis/pericarditis
- **Population:** ≥65 years in Medicare Fee-for-Service
- **Study design:** Self-controlled case series
- **Findings:** No safety concern identified for five outcomes; inconsistent evidence of elevated risk for pulmonary embolism

Shoaibi, Azadeh, Patricia C. Lloyd, Hui-Lee Wong, Tainya C. Clarke, Yoganand Chillarige, Rose Do, Mao Hu et al. "Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the US." Vaccine (2023).

Upcoming Safety Studies

- Influenza Vaccine (2023-24 Formula)
- RSV Vaccine in Older Adults
- COVID-19 Vaccine (2023-24 Formula)

Optum

COVID-19 Vaccine Effectiveness

BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

Presented by: Lauren Peetluk, PhD, MPH
Optum Epidemiology

November 8, 2023

Disclosures

This research was funded by the US Food and Drug Administration.

I am an employee at Optum and own stock in UnitedHealth Group.

FDA BEST: Vaccine Effectiveness (VE) Studies

Protocol available at
https://bestinitiative.org/vaccines-and-allergenics
or by scanning this QR code:

Objective: To evaluate brand-specific effectiveness of COVID-19 vaccines in preventing **medically diagnosed COVID-19 and hospital/emergency department (ED)-diagnosed COVID-19** among cohorts of vaccinated and unvaccinated individuals aged less than 65 years in the United States

Pediatric VE
5 to 17 years

Adult VE
18 to 64 years

Booster VE
12 to 64 years

Optum

Objectives

Pediatric VE

5 to 17 years

Adult VE

18 to 64 years

Booster VE

12 to 64 years

Primary objective

Evaluate effectiveness of receiving a complete primary series of COVID-19 vaccination vs. being unvaccinated

Secondary objectives

VE in age subgroups
VE in variant eras

VE in age subgroups and variant eras
Time-specific VE
VE of single dose of 2-dose primary series
Comparative effectiveness of complete vaccine series of different vaccine brands

Primary objective

Evaluate effectiveness of receiving an additional dose or booster dose vs. not receiving an additional dose or booster dose, **among individuals with a complete primary series of COVID-19 vaccine**

Secondary objectives

VE in subgroups of interest
VE in variant eras
VE by homologous/heterologous status

Optum

Objectives

Pediatric VE

5 to 17 years

Adult VE

18 to 64 years

Booster VE

12 to 64 years

Primary objective

Evaluate effectiveness of receiving a complete primary series of COVID-19 vaccination vs. being unvaccinated

Secondary objectives

VE in age subgroups
VE in variant eras

VE in age subgroups and variant eras
Time-specific VE
VE of single dose of 2-dose primary series
Comparative effectiveness of complete vaccine series of different vaccine brands

Primary objective

Evaluate effectiveness of receiving an additional dose or booster dose vs. not receiving an additional dose or booster dose, **among individuals with a complete primary series of COVID-19 vaccine**

Secondary objectives

VE in subgroups of interest
VE in variant eras
VE by homologous/heterologous status

Optum

Study Design

Data Sources, Study Population, Study Period

Data Sources

Optum database
- Enrollment
- Adjudicated prescription drug claims
- Pre-adjudicated hospital and physician claims

CVS Health data
- Aetna enrollment
- Adjudicated prescription dispensings, hospital and physician claims

+

IIS repositories

16 unique IIS jurisdictions included in VE analyses from Optum and CVS

Study Design

Matched, retrospective cohort design

Study Population

- Continuous enrollment for at least 365 days
- Within authorized age range for vaccination
- Reside in catchment area of linked IIS-claims data
- Exclusions related to previous COVID-19 diagnoses or long-term care residence
  - **Booster VE:** Complete primary series of COVID-19 vaccination with BNT162b2, mRNA-1273, JNJ 7836735

Study Period

- **Adult/Pediatric VE:** 11 December 2020
- **Booster VE:** 12 August 2021

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- **Booster VE:** 12 August 2021

Optum

Study Methods and Analysis

Matching

- Calendar date
- Age group
- Sex
- County of residence
- Immunocompromised status
- Influenza vaccine receipt
- Comorbidity increasing risk of COVID-19

Adult/Pediatric VE:
- Pregnancy status
- Previous COVID-19 diagnosis

Booster VE:
- Brand of primary series
- Time since primary series completion

Propensity Score Weighting

Standardized Inverse Probability Weights (sIPTW) from propensity score model with all matching characteristics + pre-specified baseline covariates

Study Follow-up

Time 0 (cohort entry) until earliest of:
- COVID-19 diagnosis
- End of study period
- Disenrollment from health plan

Adult/Pediatric VE:
- Deviation from vaccine pattern at Time 0

Booster VE:
- Any additional COVID-19 vaccine

Analysis

- Cox proportional hazards regression to estimate Hazard Ratio (HR)
- VE = 1-HR * 100%
- Quantitative bias analysis
- Subgroup and sensitivity analyses

Study Methods and Analysis

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- Calendar date
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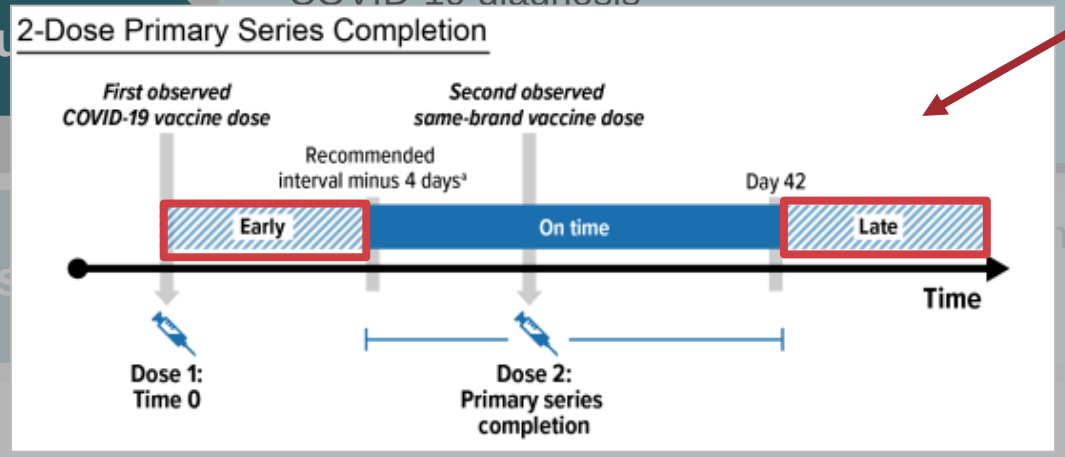

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Optum

Results

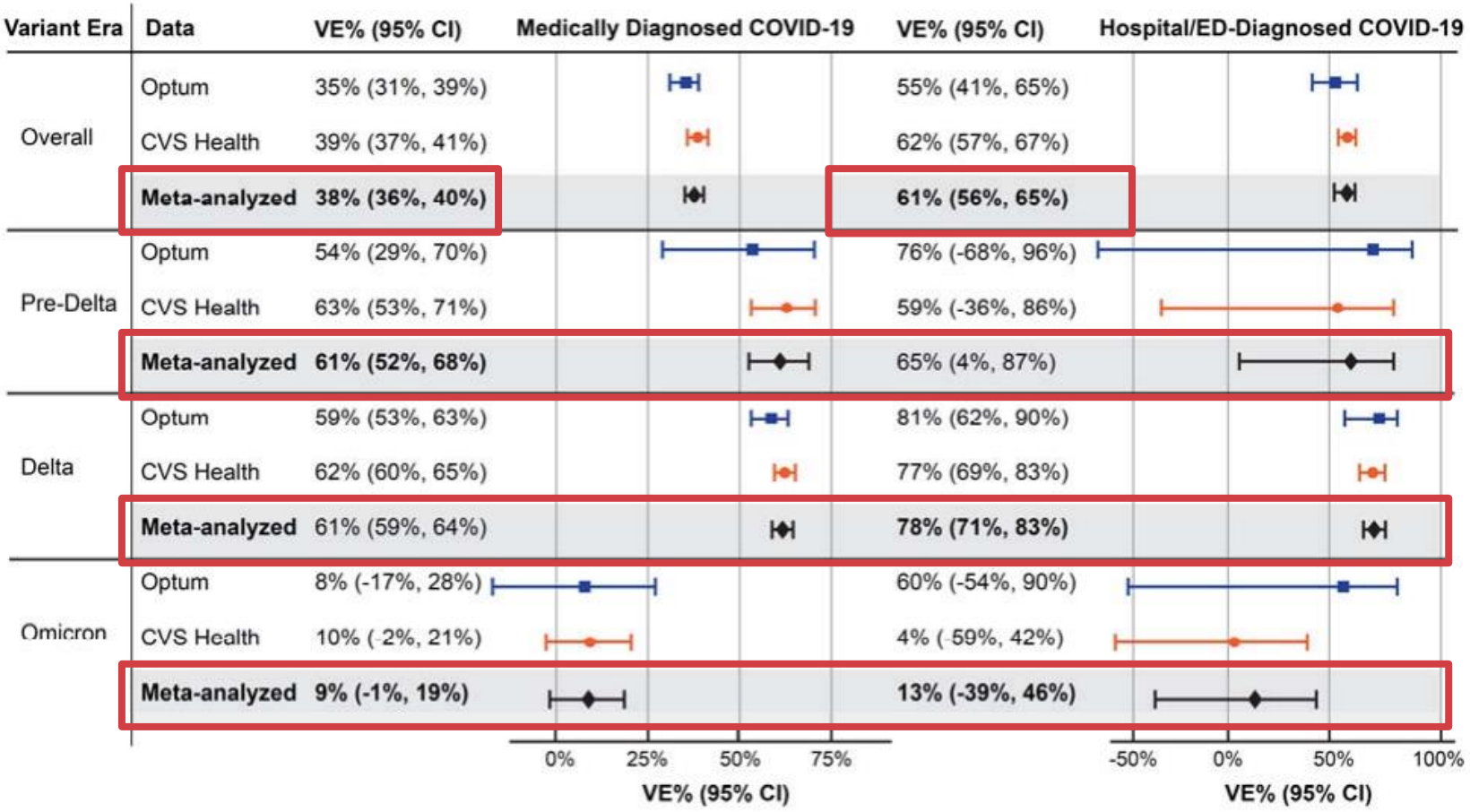
Pediatric VE Preprint: Ogilvie RP, Layton JB, Lloyd PC, et al. Effectiveness of BNT162b2 COVID-19 Vaccination in Children Aged 5–17 Years in the United States. medRxiv. 2023:2023.09.06.23294426. doi:10.1101/2023.09.06.23294426

Booster VE Poster at ICPE 2023: Layton JB, Peetluk LS, Wong H, et al. Effectiveness of monovalent COVID-19 booster/additional vaccine doses in the United States. Presented at the 39th ICPE Annual Conference; August 27, 2023. Halifax, Canada.

Pediatric VE Results

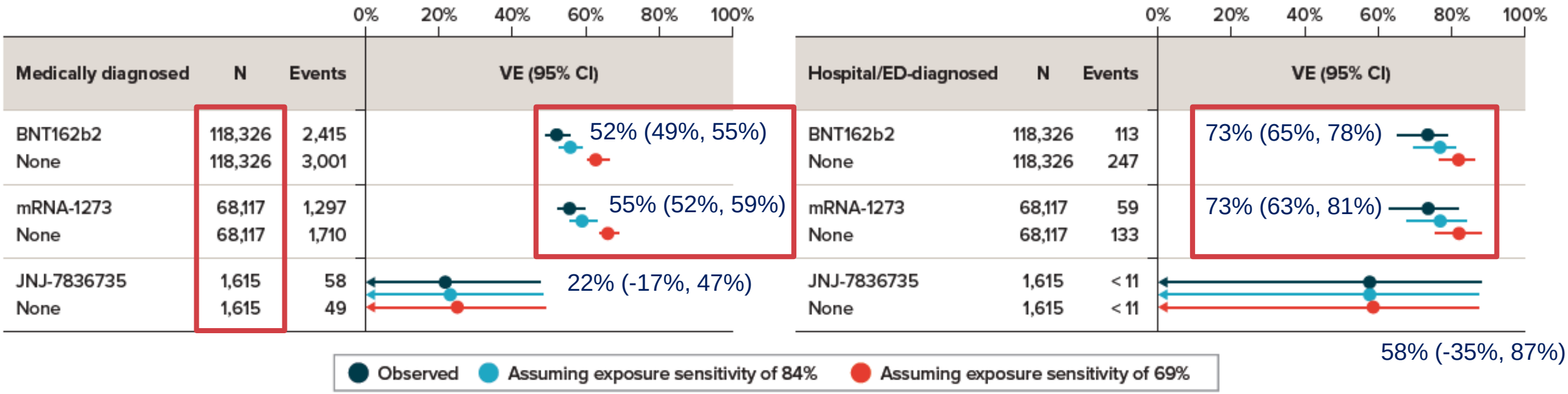
Matched populations
Optum: N=92,338
CVS: N=361,317
Total: 453,655

Rate of hospital/ED-diagnosed COVID-19
Optum: 41.2 per 100,000 PY
CVS: 44.1 per 100,000 PY



Rachel PO, Layton JB, Patricia CL, et al. Effectiveness of BNT162b2 COVID-19 Vaccination in Children Aged 5–17 Years in the United States. medRxiv. 2023:2023.09.06.23294426. doi:10.1101/2023.09.06.23294426

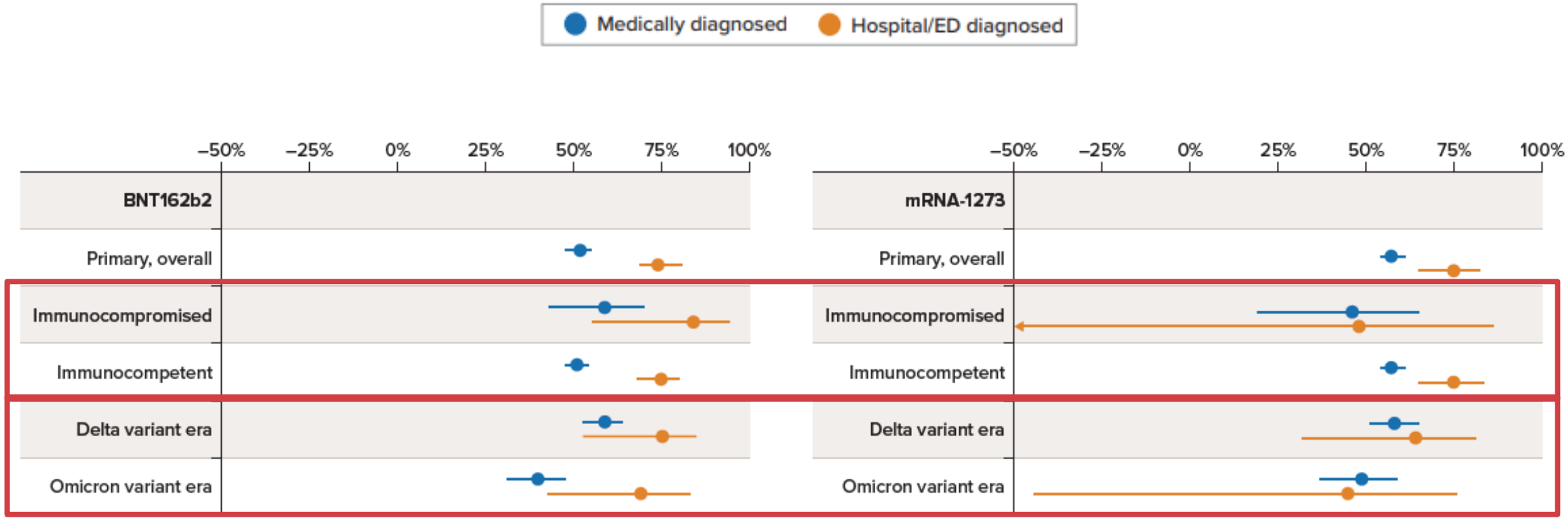
Booster VE Results



Presented by Bradley Layton at ICPE 2023

Optum

Booster VE Results



Presented by Bradley Layton at ICPE 2023

Conclusions

- FDA BEST Initiative is a robust infrastructure for studying vaccine effectiveness
- Common protocol carried out by multiple data partners
- Large study population enabling evaluation of multiple secondary objectives
- Results emphasize effectiveness of COVID-19 vaccines, especially against hospital/ED-diagnosed COVID-19

Stay tuned for more VE results coming soon!

Optum

Acknowledgements

FDA/CBER/OBPV	
Patricia C. Lloyd, PhD, ScM	Richard A. Forshee, PhD
Tainya C. Clarke, PhD, MPH, MSc	Steven A. Anderson, PhD, MPP
Joann F. Gruber, PhD	Azadeh Shoaibi, PhD, MHS
Hui-Lee Wong, PhD	
RTI International	
J. Bradley Layton, PhD	Xabier Garcia de Albeniz Martinez, MD, PhD
Dora Illei, MSc	Sarah Harris, MA
Christine Bui, MPH	Melissa McPheeters, PhD
Alison Kawai, ScD, ScM	Mary S. Anthony, PhD
Optum	
Rachel P. Ogilvie, PhD, MPH	Lauren Peetluk, PhD, MPH
Ron Parambi, MBBS, MPH	Elizabeth J. Bell, PhD, MPH
Jie Deng, MS	Grace Yang, MPA, MA
Michael Miller, MS	Kandace Amend, PhD, MPH
Jennifer Song, MA, MURP	John D. Seeger, DrPH, PharmD
Lisa Weatherby, MS	
Acumen, LLC	
Yixin Jiao, MPP	Blair Cha, BA
An-Chi Lo, MS, MPH	Wenxuan Zhou, BS
Kathryn Matuska, BA	Jessica Hervol, MPH
Yoganand Chillarige, MPA	Nirabh Koirala, BA
Michael Wernecke, BS	John Hornberger, MD, MS
Shanlai Shangguan, MPH	Thomas MaCurdy, PhD
Zoe Wu, MS	
CVS Health	
Cheryl N McMahill-Walraven, MSW, PhD	Yi Liu, MDA, MS
Djeneba Audrey Djibo, PhD	Xun Zhang, MMS
Anne Marie Kline, MS CHES	Ralph Webber, BS
Nancy B Shaik	Arka Pal, MCA
Eugenio Abente, PhD	Raman Kumar, BP
Jonathan DeShazo, PhD MPH	Anuj Saini , MBA-IT
Smita Bhatia, MCA	Gaurav Bohra, BT
Ana M Martinez-Baquero, MA	Steve Magill, BS
Vaibhav Sharma, MS	Harpreet Kaur Dhillon, MCA
Aparna Srikanti, MSc	Wuan M Head, BA
Carla Brannan, BA	Charlalynn Harris, PhD, MPH

Acknowledgements

- Steven A. Anderson
- Richard Forshee
- CBER Surveillance Team: Tainya C. Clarke, Joann F. Gruber, Patricia C. Lloyd, Carla Zelaya
- CBER OBPV
- Federal Partners: CMS, VA, CDC
- FDA Partners: Acumen, CVS Health, Carelon, IQVIA, OHDSI, Optum, RTI Health Solutions

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#Sentinel

Moderated Discussion and Q&A

Moderator: Christina Silcox

Duke-Margolis Center for Health Policy

Linked-Claims EHR Data: Sentinel System's Efforts at Improving Causal Inference &Broadening Queries

Moderator: **Rachele Hendricks-Sturrup,** Duke-Margolis Center for Health Policy

Speakers:

Sebastian Schneeweiss, Harvard Medical School and Brigham and Women's Hospital

Jennifer Nelson, Kaiser Permanente Washington Health Research Institute

Richard Wyss, Harvard Medical School and Brigham and Women's Hospital

Robert Ball, U.S. Food and Drug Administration

Sentinel

Sentinel Innovation Center

Integrating innovation for a strategic objective

November 8, 2023

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine
Brigham and Women's Hospital, Harvard Medical School, Boston

Sentinel *EHR+claims* network development

Commercial *EHR+claims* Network
20 million linked lives

healthverity
TriNetX

Deriving variables,
Phenotyping,
Outcome validation,
Adv. confounding control

EHR toolkit deployment
EHR algo deployment
EHR algo transportability check

Development Network

- BRIGHAM HEALTH — BRIGHAM AND WOMEN'S HOSPITAL
- Duke Clinical Research Institute
- VANDERBILT UNIVERSITY MEDICAL CENTER
- KAISER PERMANENTE — Kaiser Permanente Washington Health Research Institute

~3 million EHR+claims linked lives

Quarterly patient-level data updates

Innovation Center analyses

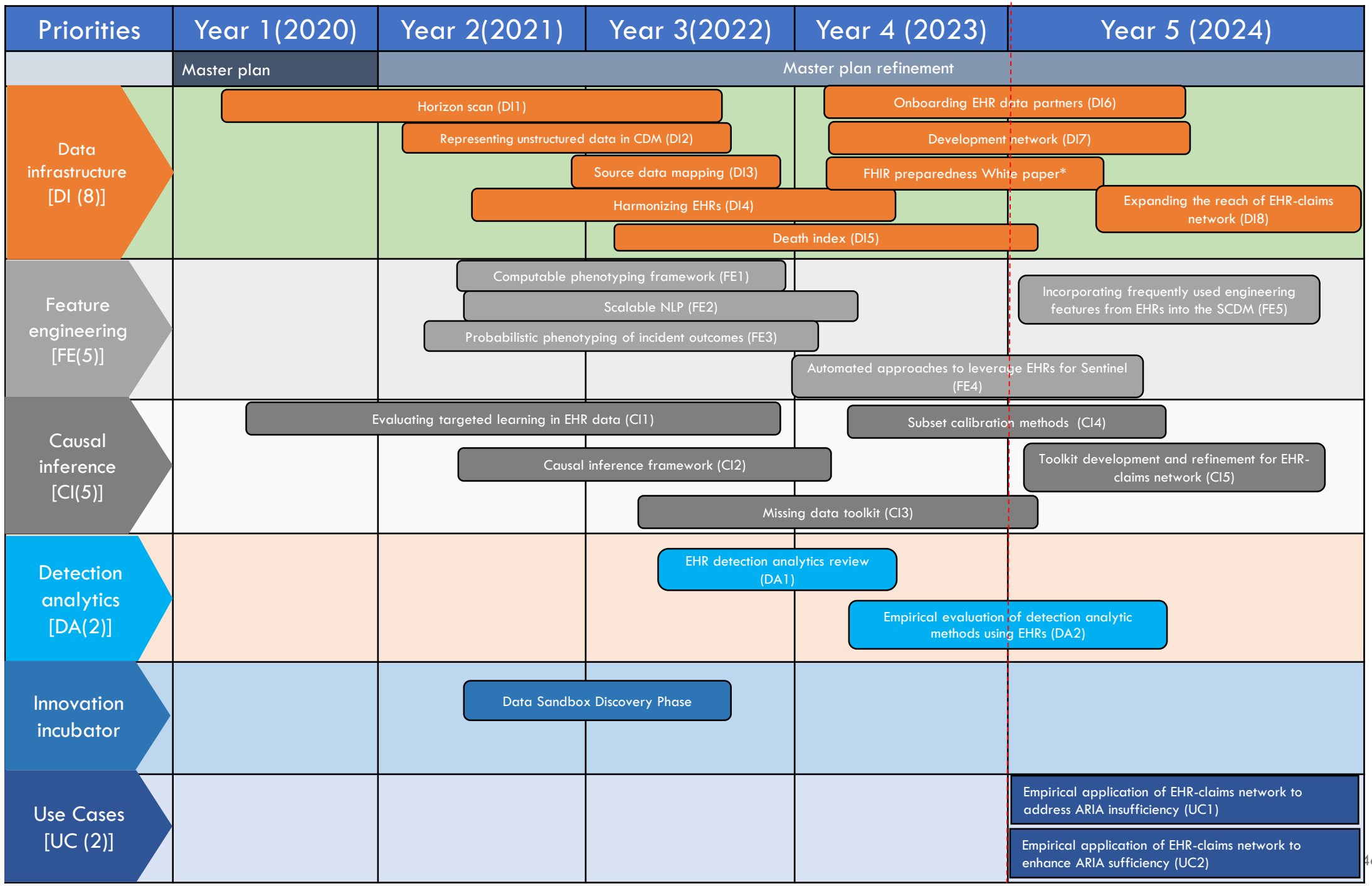
EHR-claims linked analyses:
- Data QA
- Query development
- Query execution
- Interpretation

Example use cases:
- Use and adaptation of existing SOC tools
- Comparison of EHR+claims vs. claims only
- Validation of claims algorithms for outcomes
- Phenotyping using EHR and claims
- Unmeasured confounder balance check in EHR
- Advanced confounding adjustment using EHR

Active participation by SOC staff

DI6: Onboarding of commercial DP– Year 4 project

DI7: Development network Year 4 project



*ASPE supported project

The Sentinel *EHR+claims* network:

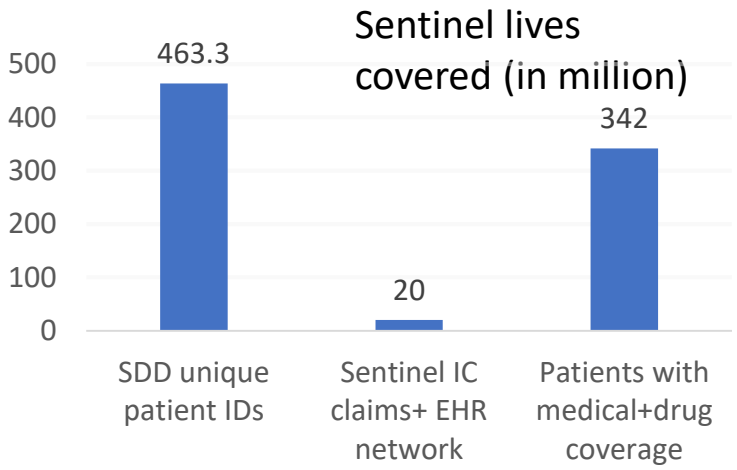
Value Add Part 1:

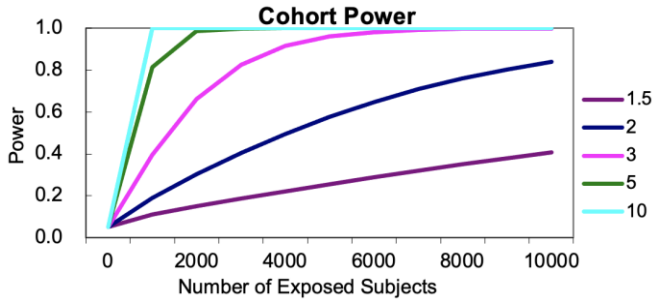
Reducing ARIA insufficiencies

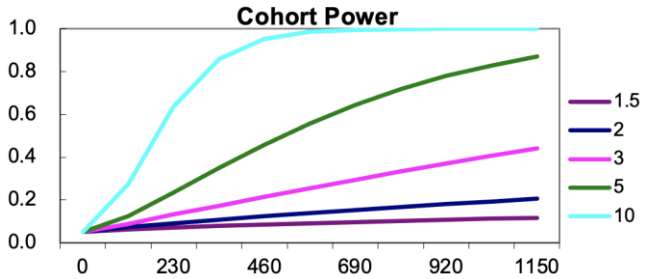
If sample size allows, analyses can be performed using data from the network containing 20 million lives to leverage additional EHR based data on outcomes or confounders not available in claims

Safety/RWE studies in the Sentinel EHR + claims network:

What is achievable with the expected 20 million lives?







	Expl 1: **High prevalence conditions** e.g., diabetes	Expl 2: **Low prevalence conditions** e.g., rheumatoid arthritis
Starting sample, total subjects TriNetX + HealthVerity	20,000,000 people	20,000,000 people
N with condition (T2DM or RA) based on prevalence estimate per CDC	1,530,000 (7.6%)	170,000 (1%)
Prevalence of a recently approved drug e.g., canagliflozin*	26,010 (1.7%)	2,890 (1.7%)
Meet typical study requirements e.g., new users, continuous enrollment, other inclusion criteria	10,404 (40%)	1,156 (40%)
Common safety outcome: e.g., rate 5/100 for **genital infections** assuming average follow-up of 6 months	260 events	29 events
Rare safety outcome: e.g., rate 2/1000 for **diabetic ketoacidosis** assuming average f-u of 6 months	10 events	1 events

* Based on prevalence reported in Horizon scan queries

The Sentinel *EHR+Claims* Network:

Value Add Part 2:

Strengthening ARIA sufficient analyses

Further strengthening ARIA sufficient analyses via the Sentinel

EHR+claims network: 5 key use cases

1. Rapid balance evaluation of patient characteristics in EHRs and not measured in claims data
(DI6)

2. Routinely apply corrections for unmeasured confounding through subset calibration toolkit
(CI4)

3. NLP assisted validation of claims-based algorithms for outcomes to inform quantitative bias analysis
(DI7)

4. Routinely expand claims-based analyses with deep clinical information on outcomes, confounders and inclusion criteria
(CI1, FE2, FE4)

5. Expanding signal detection capabilities by incorporating EHR data elements
(DA1, DA2)

Identifiers in the bracket indicate upcoming or ongoing IC projects that aim to demonstrate proof of concept for these enhancements

1. Rapid confounder balance evaluation of factors unmeasured in Sentinel claims data

1. Rapid balance evaluation of patient characteristics in EHRs and not measured in claims data (DI6)

Evaluating patient characteristics between treatment groups in EHR-based variables that are unmeasured in claims data

	Before PS-matching		After PS-matching	
	Linagliptin (*N* = 243)	Other DPP-4 inhibitors (*N* = 3041)	Linagliptin (*N* = 240)	Other DPP-4 inhibitors (*N* = 271)
Median (IQR) laboratory test results[c]				
HbA1c, %	7.8 (7.0-9.0)	8.1 (7.1-9.5)	7.8 (7.0-9.0)	7.9 (7.1-9.1)
Creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.7-1.0)	0.9 (0.8-1.1)	0.9 (0.7-1.1)
eGFR, mL/min/ 1.73 m^2	98 (84-108)	102 (92-115)	101 (92-115)	103 (92-116)
Total cholesterol level, mg/dL	168 (146-197)	171 (147-201)	168 (146-196)	171 (152-200)
HDL, mg/dL	40 (34-49)	42 (35-50)	40 (34-49)	42 (36-49)
LDL, mg/dL	100 (76-122)	95 (73-120)	100 (76-121)	97 (70-120)
Triglycerides, mg/dL	171 (110-233)	156 (105-226)	171 (109-233)	156 (103-216)

Provides quantitative evidence on the threat of unmeasured confounding in ARIA sufficient analysis conducted in Sentinel DD

Year 5 plan: To be applied throughout the Development Network

Patorno et al. *Diabetes Obes Metab*. 2018

2. Correcting claims analyses for unmeasured confounding using subset calibration tools

2. Routinely apply corrections for unmeasured confounding through subset calibration toolkit (CI4)

PS calibration

Requires a validation study that includes gold standard measure of the variables in addition to the error-prone measurements already available in the main study.

- Validation study could be conducted in a data source with linked EHR+claims

Steps:

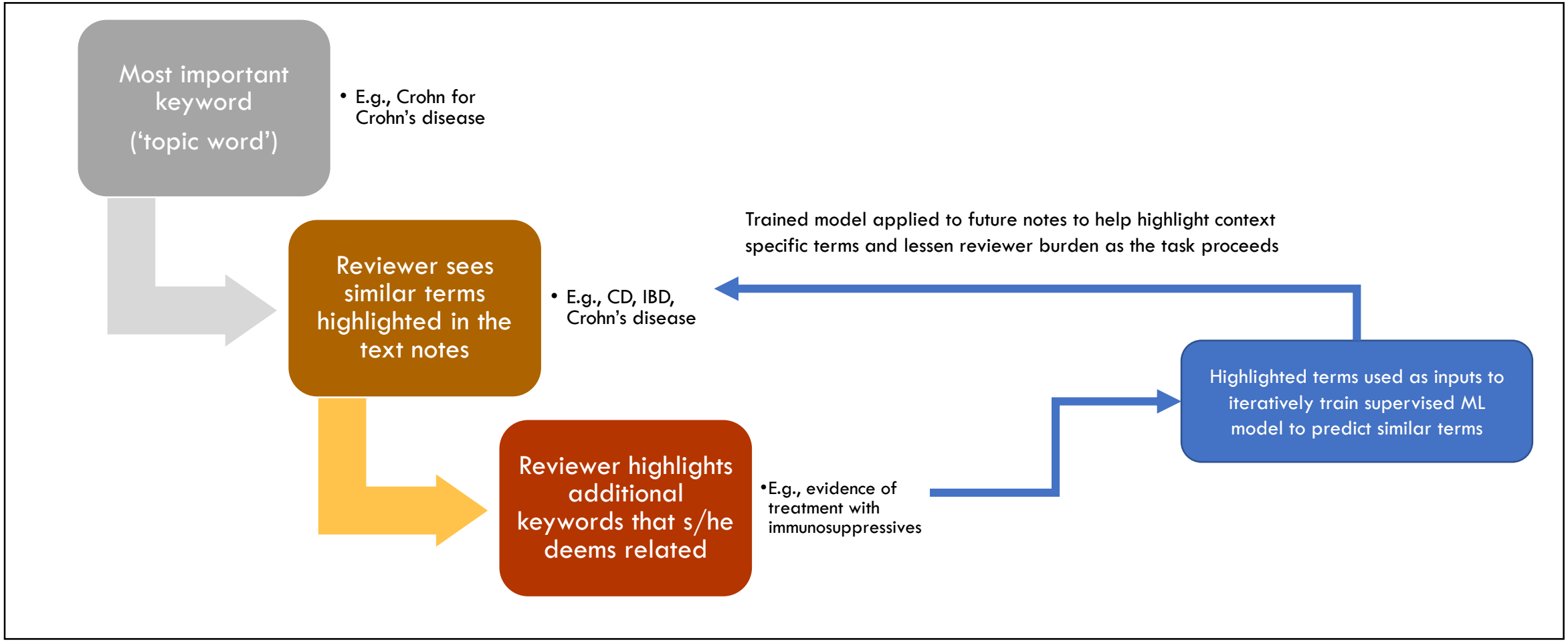
1. Estimate the error-prone PS in validation study (i.e., using only information available in the claims data)
2. Estimate the gold standard PS in validation study (i.e., using information from both claims and EHR data)
3. Estimate the treatment effect after correcting for measurement error in the error-prone PS.

Year 5 plan: To be applied throughout the Development Network

3. NLP-assisted chart validation using EHR data from Development Network for efficient gold standard development (free text and structured)

3. NLP assisted validation of claims-based algorithms for outcomes to inform quantitative bias analysis (DI7)

Medical context vector space: an approach to assist with information retrieval by efficient query expansion

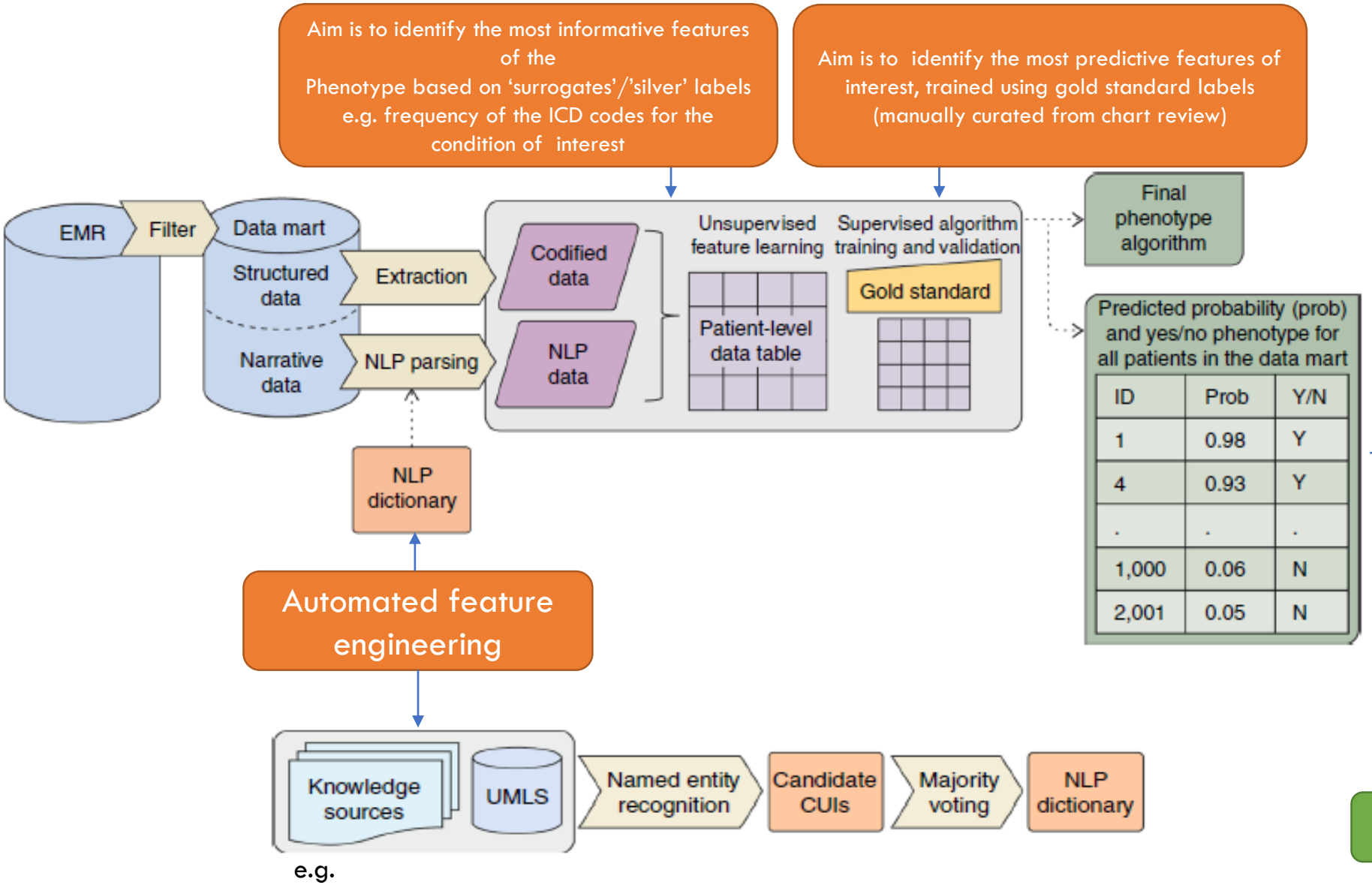


Tool currently available at VUMC, KPWA, and MGB; Year 5 plan includes validation exercises

Ye *et al. BMC Medical Informatics and Decision Making. 2021*

4. Expand claims-based analyses with deep clinical information on outcomes, confounders and inclusion criteria using scalable phenotyping

4. Routinely expand claims-based analyses with deep clinical information on outcomes, confounders and inclusion criteria (CI1, FE2, FE4)



Include derived variables into SCDM: Development Network and commercial data partners

Year 5 plan: Implementation at KP, VUMC, MGB

e.g.

MERCK MANUAL Professional Version

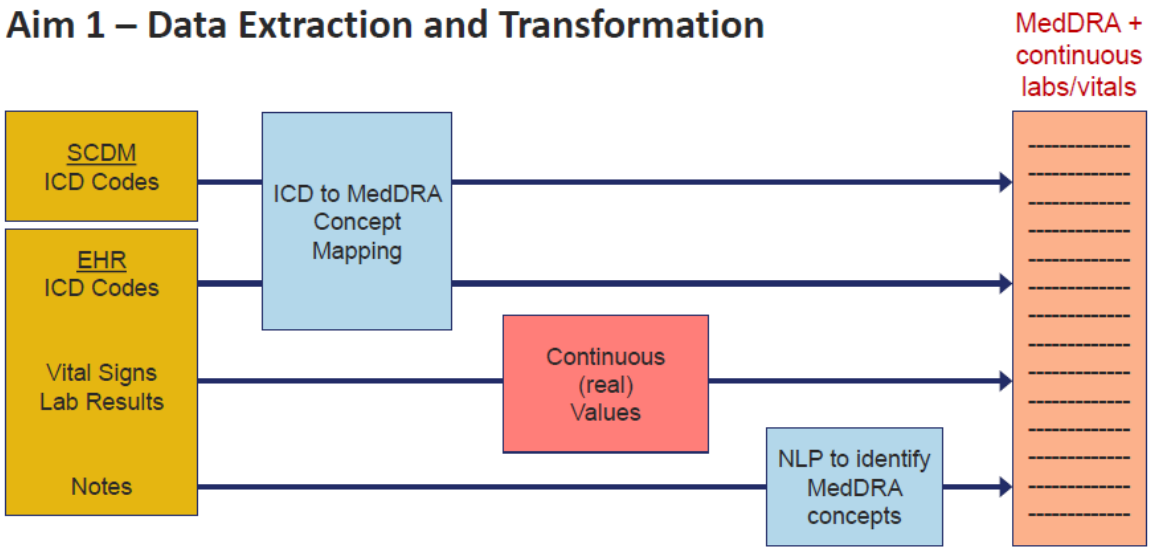
Zhang et al. *Nat protocols*. 2019

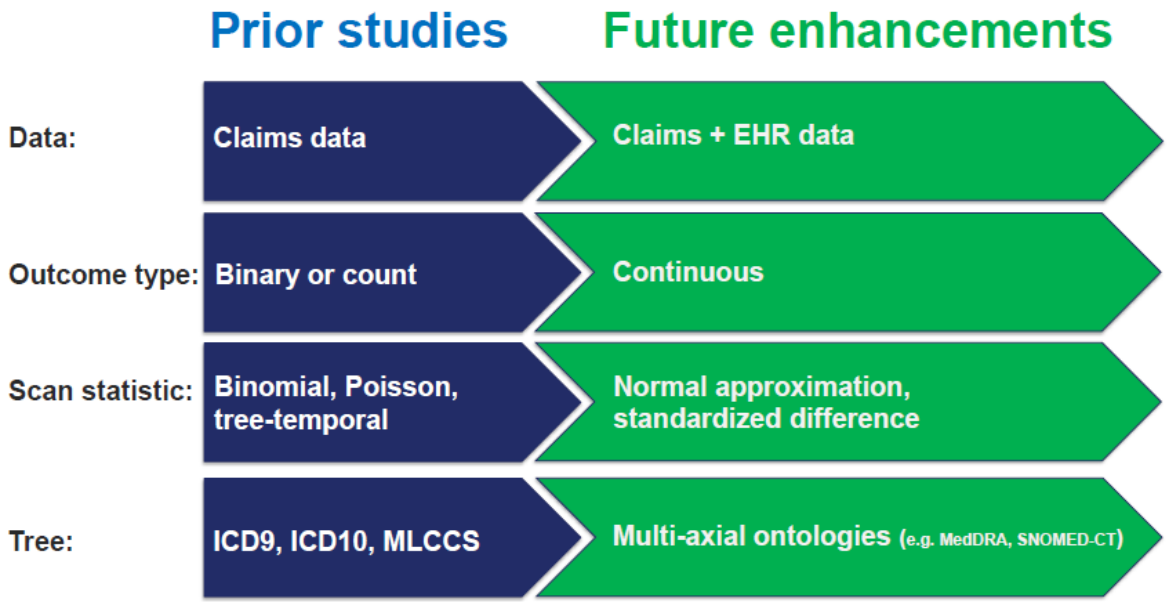
5. Expand signal detection capabilities incorporating EHR data elements

Empirical evaluation of detection analytic methods using EHRs (DA2)

Developing a portable pipeline to create an outcome table combining structured + pre-processed unstructured data elements

Adapting Treescan methodology to conduct signal identification based on the enhanced outcome table





IC lead: Josh Smith; Shirley Wang (project kicked off Jan 2023)

Year 5 Plans

A series of use cases emulating ARIA requests

The expansion of ARIA sufficiency will be tested by applying the 5 use cases discussed above to potential ARIA questions

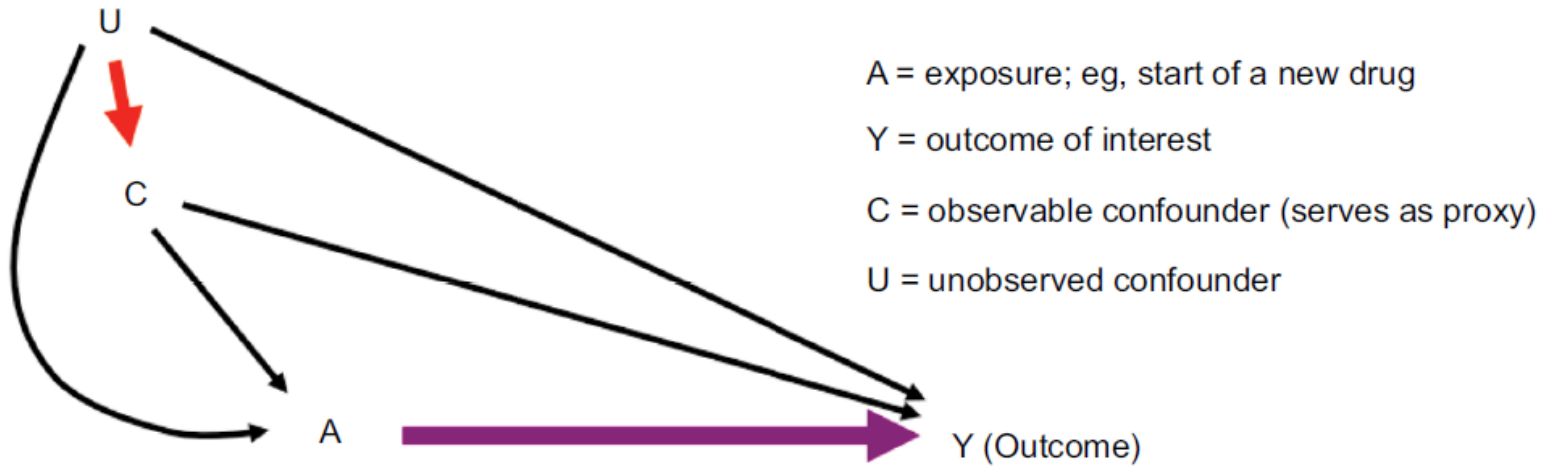
Improving Confounding Control in RWE Studies

- Confounding arising from non-randomized treatment choices remains a challenge for extracting causal inference on treatment effects that supports regulatory decisions.

- Standard approaches to confounding adjustment typically rely on adjusting for few investigator-specified variables, however:
    - Some confounders are unknown at the time of drug approval
    - Many confounders are not directly measured in routine-care databases.

The Idea of Proxy Confounder Adjustment

Healthcare databases may be understood and analyzed as a high-dimensional set of "proxy" factors that indirectly describe the health status of patients (Schneeweiss 2009, 2017).



Unobserved confounder	Observable proxy measurement	Coding examples
Very frail health	Use of oxygen canister	CPT-4
Sick but not critical	Code for hypertension during a hospital stay	ICD-9, ICD-10
Health-seeking behavior	Regular check-up visit; regular screening examinations	ICD-9, CPT-4, #PCP visits

Leveraging Unstructured EHRs for Large-Scale Proxy Adjustment

Table. Example data structure for 2 cohort studies that include linked claims with NLP generated EHR features

	Sample Size			Outcome	Baseline Covariates		
Cohort	N_{Total}	$N_{Treated}$	$N_{Comparator}$	N_{Total}	N_{Total}	$N_{Predefined}$	$N^{**}_{Proxies}$
Study 1:[A]	21,343	13,576	7,767	899 (4.2%)	14,937	91	**14,846**
Study 2:[B]	35,031	12,872	22,159	251 (0.7%)	12,464	91	**12,373**

[A] Study 1: Effect of NSAIDs versus opioids on acute kidney injury

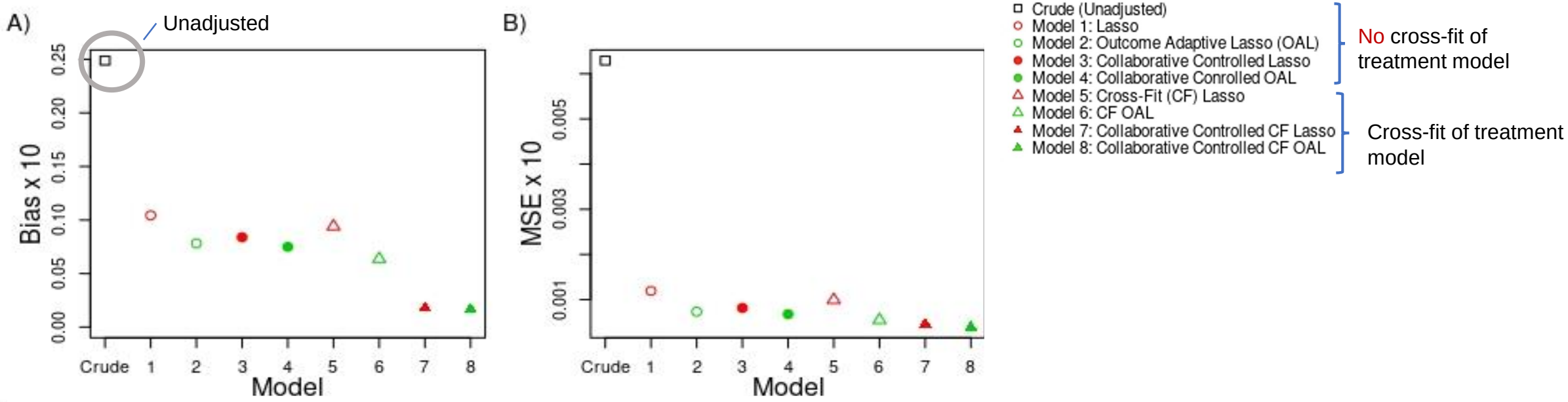
[B] Study 2: Effect of high vs low-dose proton pump inhibitors (PPIs) on gastrointestinal bleeding

** Number of claims and EHR features after screening those with prevalence <0.001

** N_{total} = total sample size, total number of outcomes, and total number of baseline covariates, respectively.

*** $N_{predefined}$ = Number of prespecified variables

Results for Plasmode Simulations



General Findings:

- Established feature generation methods to build ultra high-dimensional covariate spaces
- Some degree of undersmoothing (overfitting) the treatment Lasso model is desirable to capture more confounding factors

Franklin et al. 2014

Next steps

- Linking large-scale EHR features with claims data creates ultra high-dimensional data structures. **Further improve how to optimally identify and adjust for confounder information** in this setting:
  - In comparative safety research, outcome events are often rare.
  - Some overfitting by regularized PS models can improve confounding control but can also cause problems of non-overlap (Ju et al. 2019).

- How to best decide on the amount of overfitting in large-scale regularized PS models to improve confounding control?

- Can principles of targeted learning improve large-scale covariate adjustment in ultra high-dimensional RWE studies involving linked claims data with EHR records?

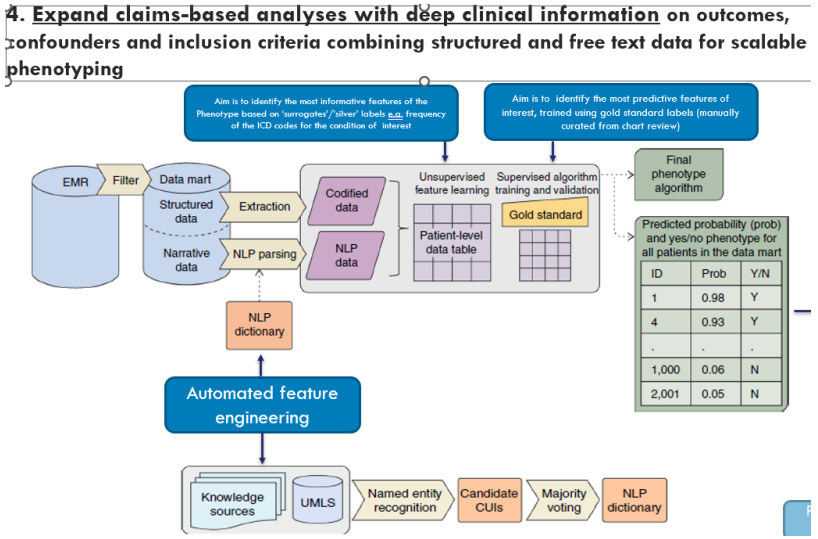
2. Correcting claims analyses for unmeasured confounding using subset calibration tools

2. Routinely apply corrections for unmeasured confounding through subset calibration toolkit (CI4)

- **Key challenge for Active Risk Identification and Analysis (ARIA) system**
  - Incomplete confounder capture in claims data → BIAS
  - Example: Confounding by frailty for influenza vaccine effectiveness estimation
- **Promising solution** to both reduce ARIA insufficiency & strengthen ARIA sufficient analyses
  - Obtain more detailed confounder data on a subset using Innovation Center (IC) EHR data
  - Use EHR confounders (on a subset) to reduce bias in (calibration of) claims estimates
  - Can also think of this as a "missing data" problem (EHR data are not available on everyone)
- **Ongoing aims for Subset Calibration (Causal Inference project 4 or CI4)**
  - Build on Sentinel's Missing Data Toolkit (CI3) framework to assess "why" data are missing
  - By studying a wider range of subset calibration methods
    - ✓ Common methods in practice: complete case, inverse weighting, multiple imputation
    - ✓ Newer methods w/robustness & precision gains: survey calibration, targeting learning
  - Focus is on simulation evaluations to compare methods under known conditions
- **Subset Calibration (CI4) deliverables**
  - Evidence-based guidance on selecting suitable method(s) for Sentinel applications
  - Reusable analyses tools for Sentinel to implement the novel methods that are tested

Year 5 plan: To be applied throughout the Commercial Data Partner network

4. Expand claims-based analyses with deep clinical information on outcomes, confounders & inclusion criteria



- **Key challenge for Active Risk Identification & Analysis (ARIA)**
  - Some outcomes are inaccurately captured in claims → BIAS
  - Examples: Anaphylaxis, acute pancreatitis
- **Promising solution** to reduce ARIA insufficiencies is to use NLP
  - Extract structured features from rich unstructured clinical text in EHR
  - Build more accurate outcome-identifying machine-learned models using these NLP features
  - Simple, automated, and reusable
- **Completed aims & deliverables for Feature Engineering project 1 (FE1) Scalable Phenotyping Framework**
  - 2 validation studies using IC EHR data
  - 2 NLP model development studies to ↑ claims-based positive predictive value (PPV)
  - 1 NLP study to find missing cases (↑sensitivity)
  - 1 general framework guidance
    - ✓ To facilitate future effective & scalable use of these methods in Sentinel

Identification and Validation of Anaphylaxis Using Electronic Health Data in a Population-based Setting

Maralyssa A. Bann,[a] David S. Carrell,[b] Susan Gruber,[c] Mayura Shinde,[d] Robert Ball,[e] Jennifer C. Nelson,[b] and James S. Floyd[f]

Validation of Acute Pancreatitis Among Adults in an Integrated Healthcare System

Floyd, James S.; Bann, Maralyssa A.; Felcher, Andrew H.; Sapp, Daniel; Nguyen, Michael D.; Ajao, Adebola; Ball, Robert; Carrell, David S.; Nelson, Jennifer C.; Hazlehurst, Brian Less

Epidemiology. 34(1):33-37, January 2023.

Vol. 192, No. 2
https://doi.org/10.1093/aje/kwac182
Advance Access publication: November 4, 2022

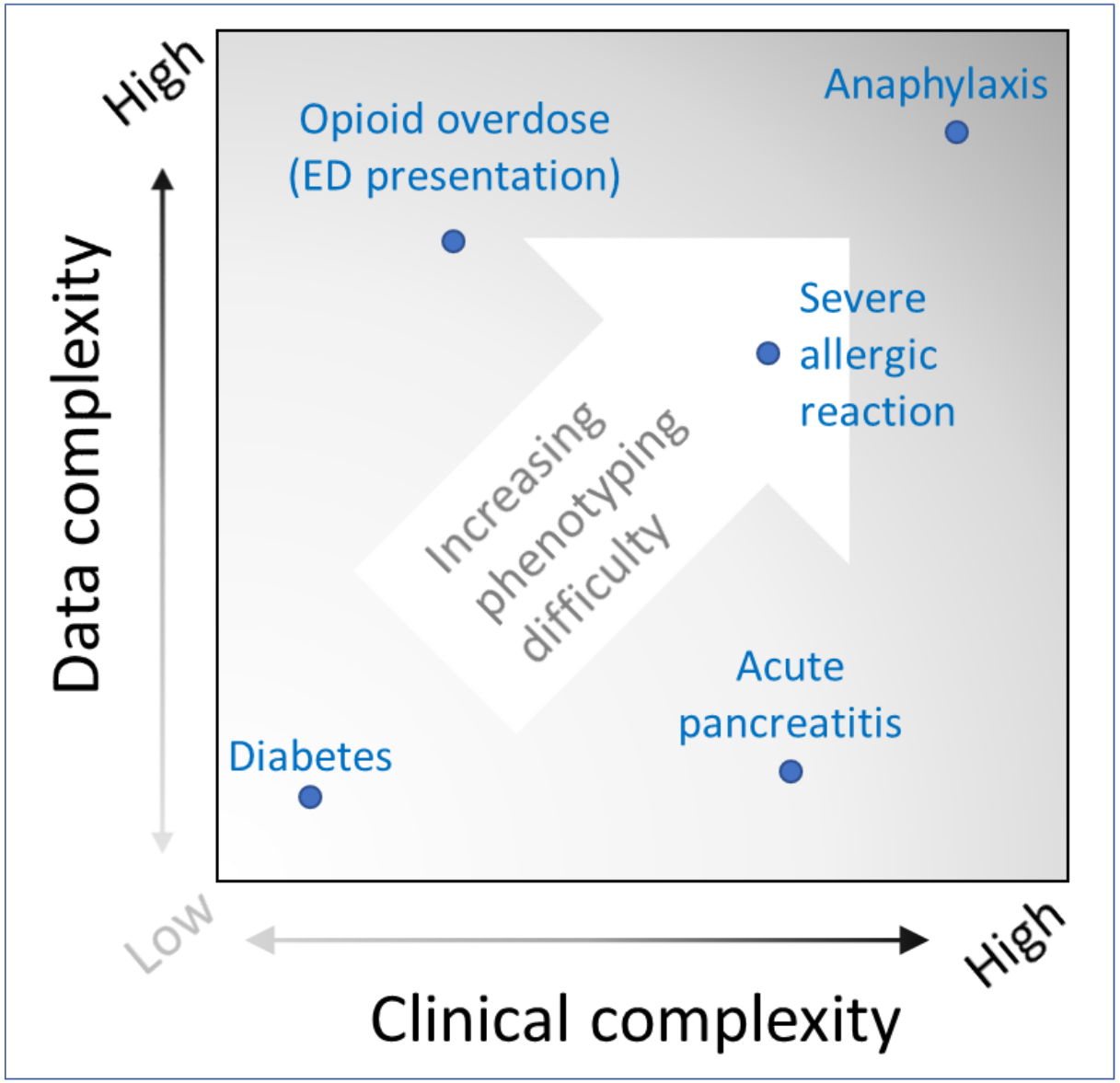
Practice of Epidemiology

Improving Methods of Identifying Anaphylaxis for Medical Product Safety Surveillance Using Natural Language Processing and Machine Learning

Assessing Fitness for Purpose - Complexities

Data complexity:

- Heterogeneity of data (settings, systems, customs)
- Obscurity of data ("needles in haystacks")
- Imprecise recording of data
- Instability (ICD9→ICD10)
- Lack of structure (chart notes)



Clinical complexity:

- Lack of agreement about diagnostic criteria
- Lack of definitive diagnostic tests
- Presence of competing diagnoses
- Diagnostic resource constraints (time, tech.)

Slide courtesy of David Carrell

Kaiser Permanente Washington

Sentinel

Thank you

Linked-Claims EHR Data: Sentinel System's Efforts at Improving Causal Inference & Broadening Queries

Moderator: **Rachele Hendricks-Sturrup,** Duke-Margolis Center for Health Policy

Speakers:

Robert Ball, U.S. Food and Drug Administration

Sebastian Schneeweiss, Harvard Medical School and Brigham and Women's Hospital

Jennifer Nelson, Kaiser Permanente Washington Health Research Institute

Richard Wyss, Harvard Medical School and Brigham and Women's Hospital

Join at
slido.com
#Sentinel

Moderated Discussion and Q&A

Moderator: Rachele Hendricks-Sturrup

Duke-Margolis Center for Health Policy

Break

Workshop will resume at **2:50 p.m. EST**

November 14, 2023

12:30 – 4:30 PM

National Press Club

or

Virtually Via Zoom

Visit healthpolicy.duke.edu/events

Leveraging Lessons Learned to Move Beyond COVID-19

Moderator: **Christina Silcox,** Duke-Margolis Center for Health Policy

Speakers:

Richard Forshee, U.S. Food and Drug Administration

Silvia Perez-Vilar, U.S. Food and Drug Administration

Susan Winckler, Reagan-Udall Foundation for the FDA

FDA Benefit-Risk Assessment of COVID-19 Vaccines and Use of Real-World Data & Evidence

Richard Forshee

Office of Biostatistics and Pharmacovigilance,
Center for Biologics Evaluation and Research, FDA

15th Sentinel Annual Meeting
November 8, 2023

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA's views or policies.

Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Comirnaty) for Age 16-29 years

Patrick R. Funk, Osman N. Yogurtcu, Richard A. Forshee, Steve A. Anderson, Peter W. Marks, Hong Yang

Vaccine, March 2022

Analysis of Condition

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

- 208 million COVID-19 cases and 4.3 million deaths worldwide by August 2021
- 90% cases among age 16 + years of age

Treatment Options in the US

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

At time of analysis (August 2021)

- No licensed vaccines or anti-viral drugs for COVID-19

- Emergency Use Authorizations of three vaccines:
  - Pfizer-BioNTech Vaccine for 16+ years of age
  - Moderna Vaccine for 18+ years of age
  - Janssen for age 18+ years of age

Considerations for Benefits

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

- Vaccine efficacy against confirmed symptomatic and severe COVID-19 illness after Dose 2 are 90% and 95%, respectively
- Real-world vaccine protection against disease depends on COVID-19 incidence and circulating virus strains
- Post vaccination immunity is waning

Risks and Risk Management

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition		
Current Treatment Options		
Benefit		
Risk and Risk Management		
Conclusions Regarding Benefit-Risk		

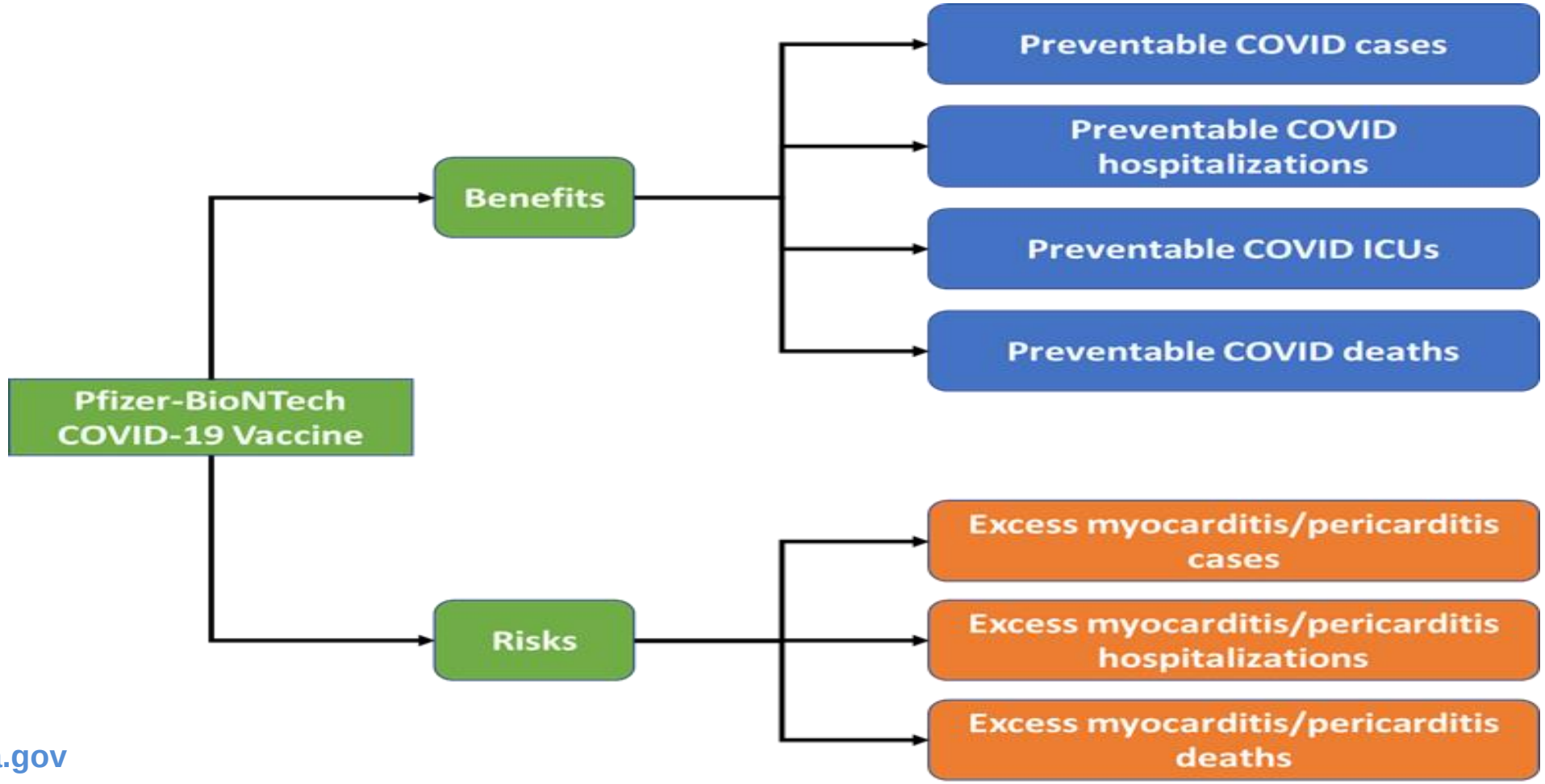
- No notable serious adverse events and deaths related to vaccination reported in clinical trials
- Elevated myocarditis/pericarditis case rate identified by post-EUA safety surveillance
  - Clinically significant risk
  - Higher risk among male adolescents
- Risk management options:
  - Product label
  - Post-market safety surveillance
  - Post-market requirement/commitment

Whether Benefits of COMIRNATY Outweigh the Risks for Age 16-29 years?

- Uncertainty in Benefits
  - Uncertain dynamic of pandemic (greater vaccination benefit when the disease incidence is higher)
  - Emerging Delta variant (unknown vaccine effectiveness)
  - Waning of vaccine protection
- Clinically significant risk of myocarditis/pericarditis
  - Higher risk among male adolescents

Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Comirnaty) for Age 16-29 years, *Vaccine, March 2022*

Per million individuals with two-doses of vaccine



What RWDs/RWEs Were Used?

Benefits
(Prevented COVID-19 cases)

COVID-19 incidence (cases, hospitalizations, ICUs and deaths)	CDC COVID NET
Vaccination rate	CDC DataTracker
Vaccine effectiveness & wanning of protection	US and international epidemiology studies

Risks
(Excess myo/pericarditis cases)

Myo/pericarditis rate attributable to vaccine (cases, hospitalization, deaths)	• CBER Biologics Effectiveness and Safety (BEST) System • CDC vaccine safety data link (VSD)

RWD/RWE Challenges and Opportunities

- **Most RWD/RWE not generated for a specific study**
  - Varied data collection protocols
  - Inconsistent data definitions
  - Bias in data reporting
  - Missing data/information
- **Evaluate the strength of RWD/RWE**
  - Fit for use?
  - Any way to reduce the bias?
- **Use sensitivity analysis to evaluate the uncertainty**
- **Acknowledge limitations**

Model Scenarios for Age 16-29 years

Seven model scenarios evaluating the impact on benefits and risks of uncertain **vaccine effectiveness**, **pandemic dynamic** and **myocarditis case/death rates**

Common Model Inputs

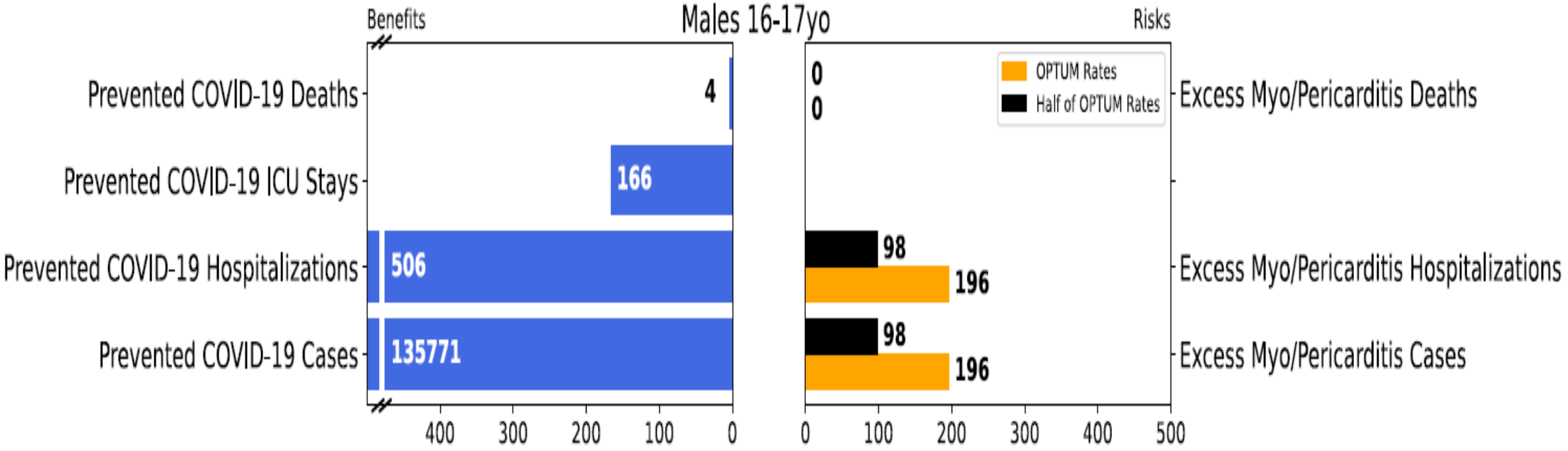
- Protection period[1]: 6 months
- Vaccine effectiveness[2] against
  - Cases: 70%
  - Hospitalization: 80%
- Myo/pericarditis rate: FDA BEST/OPTUM

Two Major Scenarios

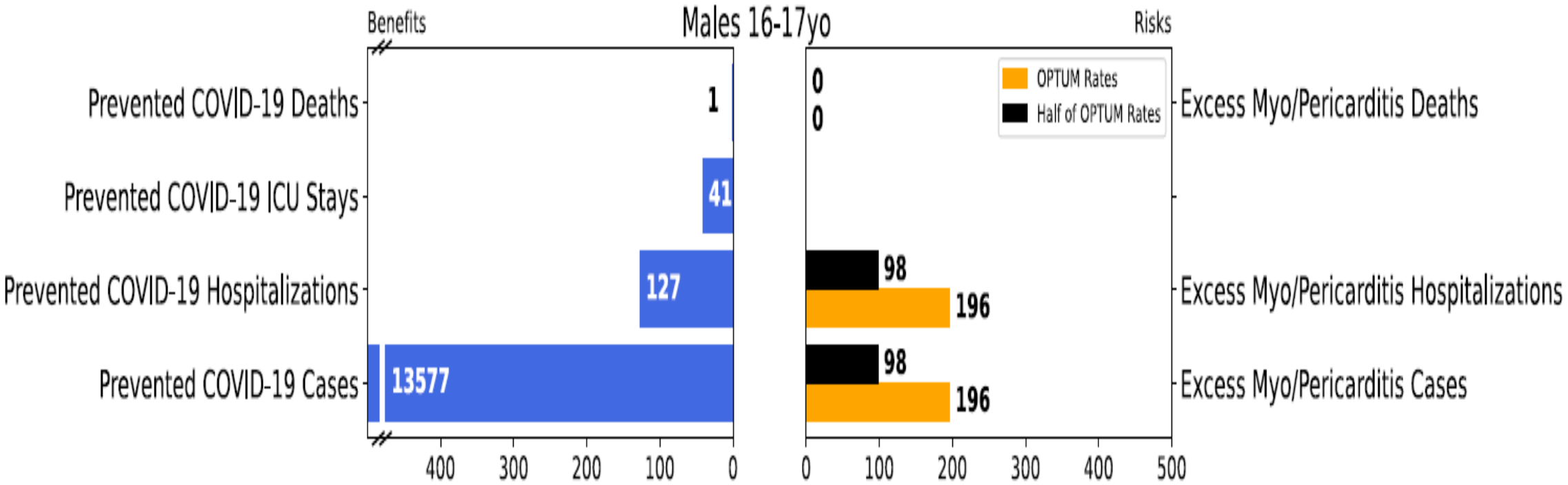
	COVID-19 case incidence[3]	COVID-19 hospitalization incidence[3]	Vaccine attributable myo/pericarditis death rate[4]
Pessimistic Scenario	July 10, 2021 rate	July 10, 2021 rate	0.002%
Most Likely Scenario	10x July 10, 2021 rate	4x July 10,2021 rate	0%

[1]Assumption, [2]Real-world evidence, [3]CDC COVID NET & DataTracker, [4]VAERS data & assumption

Result- Most Likely Scenario (per Million)



Result- Pessimistic Scenario (per Million)



Conclusion Regarding Benefit-Risk

Benefits/uncertainty

- Direct benefits: reduces COVID-19 cases, hospital stays, ICUs, deaths and long-term effects
- Indirect benefits: reduce disease transmission, economic and societal impacts
- Uncertainty in dynamic of pandemic, new virus strain, protection waning, protection for subpopulation with comorbidity

Risks/uncertainty and risk management

- Myocarditis and pericarditis risk
- Uncertainty on risk among age groups and its long-term effect
- Post-market requirements/commitments for risk management: post-market studies and active surveillance on myocarditis/pericarditis

Trade-off conclusion & decision

- Known and potential benefits outweigh the known and potential risks
- FDA approved licensure of COMIRNATY for individuals 12y+ in Nov. 2021

Acknowledgment

- Drs. Patrick Funk and Osman Yogurtcu contributed to benefit-risk modeling
- Comirnaty BLA review team
- FDA BEST partners Acumen and Optum provided data on myocarditis/pericarditis cases
- CDC Vaccine Task Force shared COVID-19 data and information

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Richard Forshee, Ph.D.
FDA/CBER

Richard.Forshee@fda.hhs.gov

FDA U.S. FOOD & DRUG ADMINISTRATION

U.S. FOOD & DRUG ADMINISTRATION

Leveraging Lessons Learned to Move Beyond COVID-19

15th Annual Sentinel Initiative Public Workshop

November 8, 2023

Silvia Perez-Vilar, PhD, PharmD
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Disclaimer

The views expressed represent those of the presenter and do not necessarily represent the official views of the U.S. Food and Drug Administration

Agenda

1	COVID-19 Sentinel Surveillance System
2	Contributions
3	Strengths
4	Weaknesses
5	Opportunities
6	Challenges
7	Closing Remarks

COVID-19 Surveillance System


PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

REVIEW | Free Access

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

Noelle M. Cocoros, Candace C. Fuller, Sruthi Adimadhyam, Robert Ball, Jeffrey S. Brown, Gerald J. Dal Pan, Sheryl A. Kluberg, Vincent Lo Re 3rd, Judith C. Maro, Michael Nguyen, Robert Orr, Dianne Paraoan, Jonathan Perlin, Russell E. Poland, Meighan Rogers Driscoll, Kenneth Sands, Sengwee Toh, W. Katherine Yih, Richard Platt, And the FDA-Sentinel COVID-19 Working Group ... See fewer authors

First published: 02 April 2021 | https://doi.org/10.1002/pds.5240

Members of the FDA-Sentinel COVID-19 Working Group: Catherine Corey, MSPH; Grace Chai, PharmD; Sarah K. Dutcher, PhD; Wei Hua, MD; Brian Kit, MD; Silvia Perez-Vilar, PhD; Danijela Stojanovic, PhD; Corinne Woods, MPH.

A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System - Cocoros - 2021 - Pharmacoepidemiology and Drug Safety - Wiley Online Library

Common Data Model Enhanced

- SARS-CoV-2 laboratory test results

New Data Sources Incorporated

- Outpatient and inpatient Electronic Health Record (EHR) data

Rapidly refreshed distributed database (RAPID COVID)

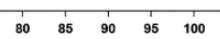
- Shortened data lags (4-6 weeks vs. 4-6 months from time of care)

Sentinel Contributions

Methods development

- Validation of Diagnosis Codes for Identifying Patients Hospitalized with COVID-19

	Positive Predictive Value (95% CI)		Patient Counts	
	PPV (95% CI)		PPV Numerator: NAAT+	PPV Denominator: NAAT+ or NAAT-
Overall (2/2/2020-10/17/2020*)				
Algorithm 1	84.7% (84.0-85.4)		8,070	9,527
Algorithm 2	84.8% (84.0-85.5)		8,536	10,071
Algorithm 3	84.3% (83.6-85.0)		8,570	10,163
Algorithm 4	84.3% (83.5-85.0)		8,598	10,205
Algorithm 5	87.5% (86.8-88.2)		7,095	8,108
Time A (2/2/2020-3/31/2020)				
Algorithm 1	94.1% (92.3-95.5)		869	924
Algorithm 2	92.3% (90.8-93.6)		1,328	1,439
Algorithm 3	90.7% (89.1-92.1)		1,352	1,491
Algorithm 4	90.6% (89.0-92.0)		1,371	1,514
Algorithm 5	92.9% (91.4-94.3)		1,220	1,313
Time B (4/1/2020-4/30/2020)				
Algorithm 1	88.5% (87.3-89.6)		2,637	2,979
Algorithm 2	88.2% (87.0-89.3)		2,640	2,993
Algorithm 3	87.9% (86.7-89.1)		2,647	3,011
Algorithm 4	87.8% (86.6-88.9)		2,651	3,020
Algorithm 5	89.6% (88.3-90.7)		2,291	2,558
Time C (5/1/2020-10/17/2020*)				
Algorithm 1	81.2% (80.1-82.2)		4,564	5,624
Algorithm 2	81.0% (80.0-82.0)		4,568	5,639
Algorithm 3	80.8% (79.7-81.8)		4,571	5,661
Algorithm 4	80.7% (79.6-81.7)		4,576	5,671
Algorithm 5	84.6% (83.5-85.7)		3,584	4,237



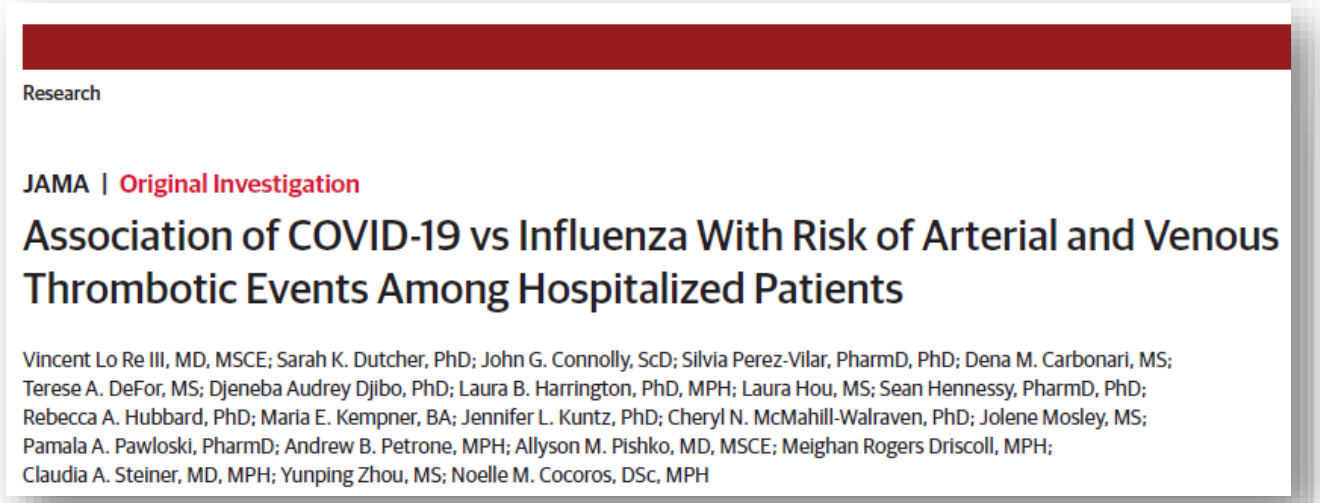
Positive predictive value (PPV) of five diagnosis code-based algorithms for COVID-19 relative to laboratory diagnosis, Sentinel Distributed Database, September 15, 2020, to October 17, 2020

Validation of diagnosis codes to identify hospitalized COVID-19 patients in health care claims data (wiley.com)

Sentinel Contributions

Natural history of COVID-19

- Risk of Arterial or Venous Thromboembolism in Patients with COVID-19 Vs Patients Hospitalized with Influenza

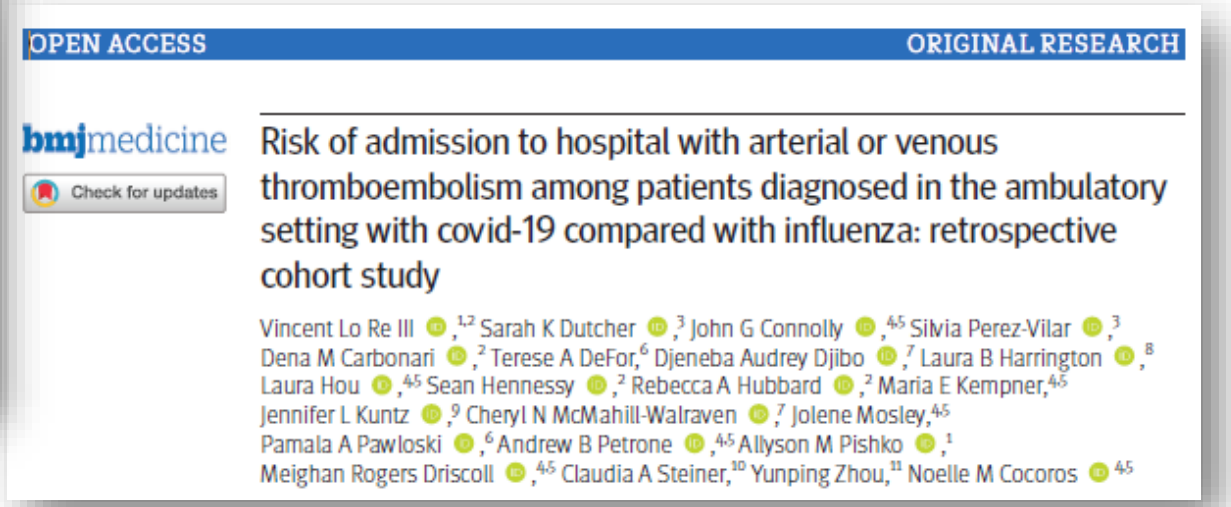


Research

JAMA | Original Investigation

Association of COVID-19 vs Influenza With Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients

Vincent Lo Re III, MD, MSCE; Sarah K. Dutcher, PhD; John G. Connolly, ScD; Silvia Perez-Vilar, PharmD, PhD; Dena M. Carbonari, MS; Terese A. DeFor, MS; Djeneba Audrey Djibo, PhD; Laura B. Harrington, PhD, MPH; Laura Hou, MS; Sean Hennessy, PharmD, PhD; Rebecca A. Hubbard, PhD; Maria E. Kempner, BA; Jennifer L. Kuntz, PhD; Cheryl N. McMahill-Walraven, PhD; Jolene Mosley, MS; Pamala A. Pawloski, PharmD; Andrew B. Petrone, MPH; Allyson M. Pishko, MD, MSCE; Meighan Rogers Driscoll, MPH; Claudia A. Steiner, MD, MPH; Yunping Zhou, MS; Noelle M. Cocoros, DSc, MPH



OPEN ACCESS ORIGINAL RESEARCH

bmjmedicine

Check for updates

Risk of admission to hospital with arterial or venous thromboembolism among patients diagnosed in the ambulatory setting with covid-19 compared with influenza: retrospective cohort study

Vincent Lo Re III [1,2] Sarah K Dutcher [3] John G Connolly [4,5] Silvia Perez-Vilar [3] Dena M Carbonari [2] Terese A DeFor,[6] Djeneba Audrey Djibo [7] Laura B Harrington [8] Laura Hou [4,5] Sean Hennessy [2] Rebecca A Hubbard [2] Maria E Kempner,[4,5] Jennifer L Kuntz [9] Cheryl N McMahill-Walraven [7] Jolene Mosley,[4,5] Pamala A Pawloski [6] Andrew B Petrone [4,5] Allyson M Pishko [1] Meighan Rogers Driscoll [4,5] Claudia A Steiner,[10] Yunping Zhou,[11] Noelle M Cocoros [4,5]

Association of COVID-19 vs Influenza With Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients | Coronavirus (COVID-19) | JAMA | JAMA Network

Risk of admission to hospital with arterial or venous thromboembolism among patients diagnosed in the ambulatory setting with covid-19 compared with influenza: retrospective cohort study | BMJ Medicine

Sentinel Contributions

Emergency Response

- Systemic Corticosteroid Use among Non-Hospitalized Patients with COVID-19

Research Letter

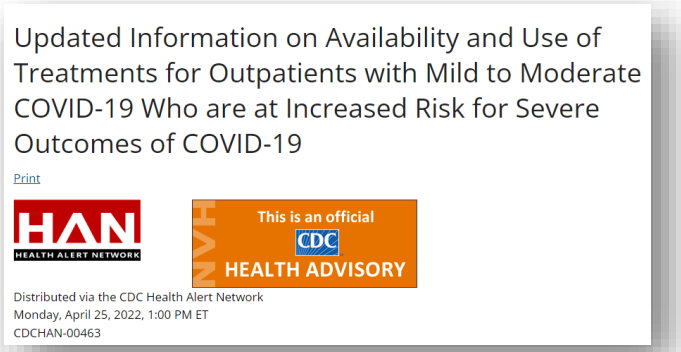
April 8, 2022

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021

Marie C. Bradley, PhD, MPharm, MScPH[1]; Silvia Perez-Vilar, PhD, PharmD[1]; Yoganand Chillarige, MPA[2]; Diane Dong, RN, MPH[3]; Ashley I. Martinez, PharmD, PhD[4]; Andrew R. Weckstein, BA[5]; Gerald J. Dal Pan, MD, MHS[1]

Author Affiliations | Article Information

JAMA. 2022;327(20):2015-2018. doi:10.1001/jama.2022.4877



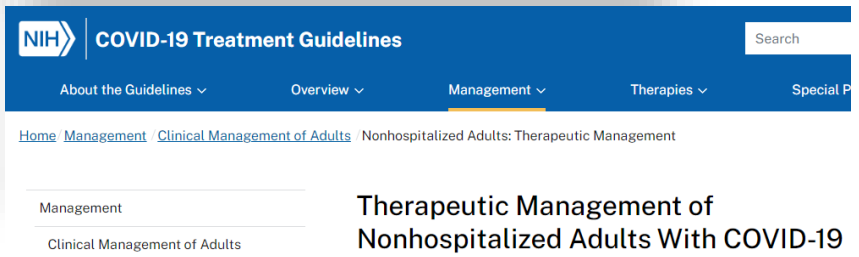
Updated Information on Availability and Use of Treatments for Outpatients with Mild to Moderate COVID-19 Who are at Increased Risk for Severe Outcomes of COVID-19

Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
Monday, April 25, 2022, 1:00 PM ET
CDCHAN-00463



NIH COVID-19 Treatment Guidelines

Search

About the Guidelines | Overview | Management | Therapies | Special P

Home / Management / Clinical Management of Adults / Nonhospitalized Adults: Therapeutic Management

Management

Clinical Management of Adults

Therapeutic Management of Nonhospitalized Adults With COVID-19

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021 | Critical Care Medicine | JAMA | JAMA Network

HAN Archive - 00463 | Health Alert Network (HAN) (cdc.gov)

National Institutes of Health (NIH)'s COVID-19 Treatment Guidelines updated on August 8, 2022, Nonhospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines (nih.gov)

Sentinel Contributions

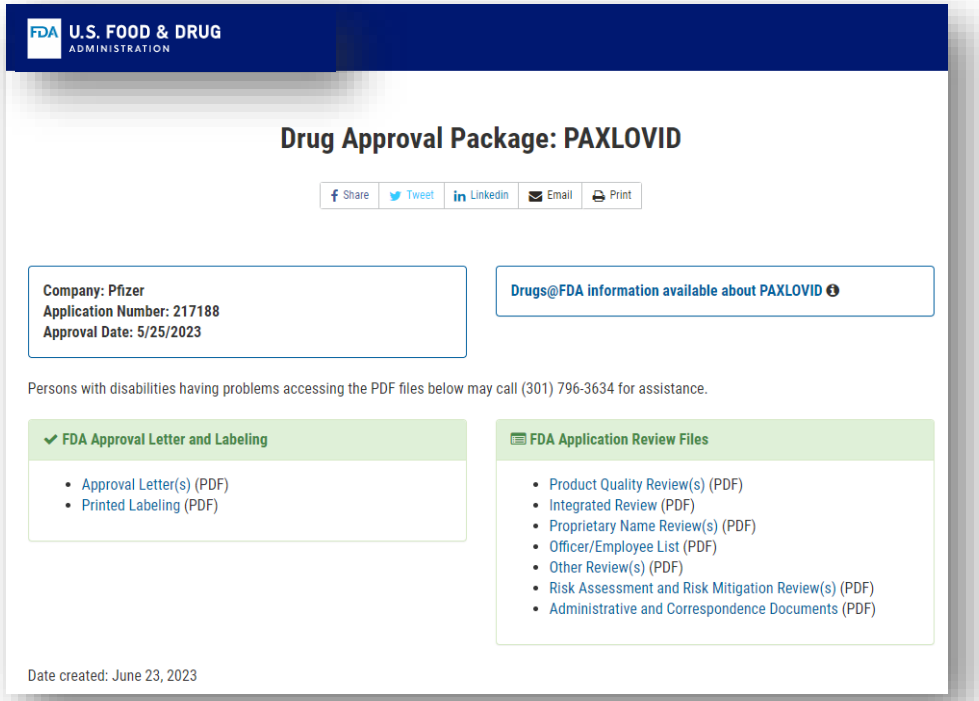
Regulatory Decision-Making

- Estimate Magnitude Of The "At-risk" Population Using Drugs that Interact with Paxlovid to Inform Labeling Decisions

	COVID among Patients ≥65 years or High-risk		COVID among Patients ≥50 years or High-risk		Paxlovid Users	
Total number of patients	1,228,761		1,450,712		551,482	
Any Drug that Interacts with Paxlovid	**695,320**	**56.6%**	**763,727**	**52.6%**	**310,012**	**56.2%**
Any Drugs Contraindicated for use with Paxlovid	89,916	7.3%	95,400	6.6%	37,929	6.9%
Any Drugs to be avoided with paxlovid	354,035	28.8%	379,286	26.1%	167,996	30.5%
Any Other Drug Drug Interactor	508,854	41.4%	557,654	38.4%	211,257	38.3%

- >50% of Paxlovid-eligible users could have taken drugs that interacted with Paxlovid*

*** Health insurance claims data do not capture if concurrent medications were withheld or had their dose adjusted due to Paxlovid**

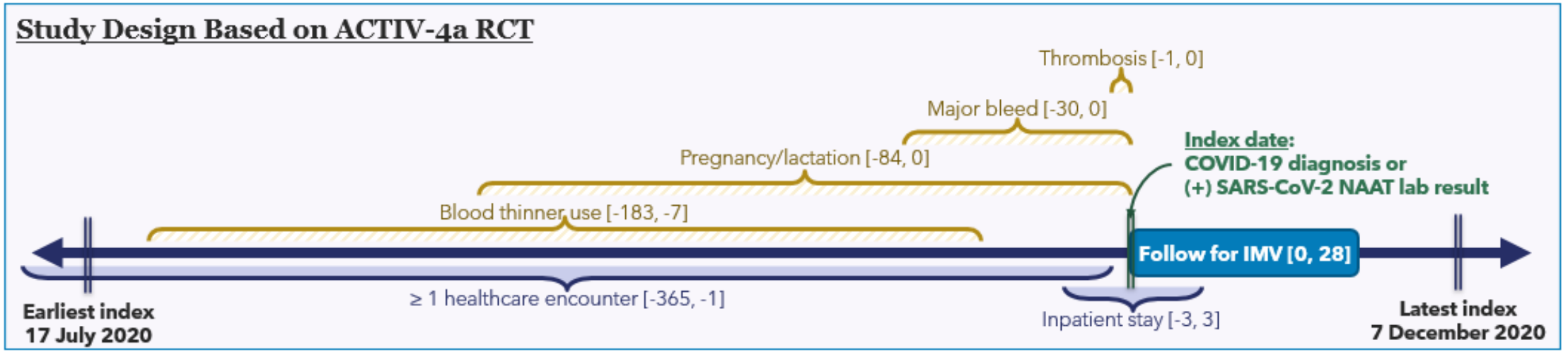


Drug Approval Package: PAXLOVID (fda.gov)

Sentinel Contributions

Support Other Federal Agencies

- NIH-funded Clinical Trials to Investigate Effectiveness and Safety of Antithrombotic Therapy in The Context of COVID-19 (Sample Size Re-estimation)



Accelerating COVID-19 Therapeutic Interventions and Vaccines 4 ACUTE | ClinicalTrials.gov

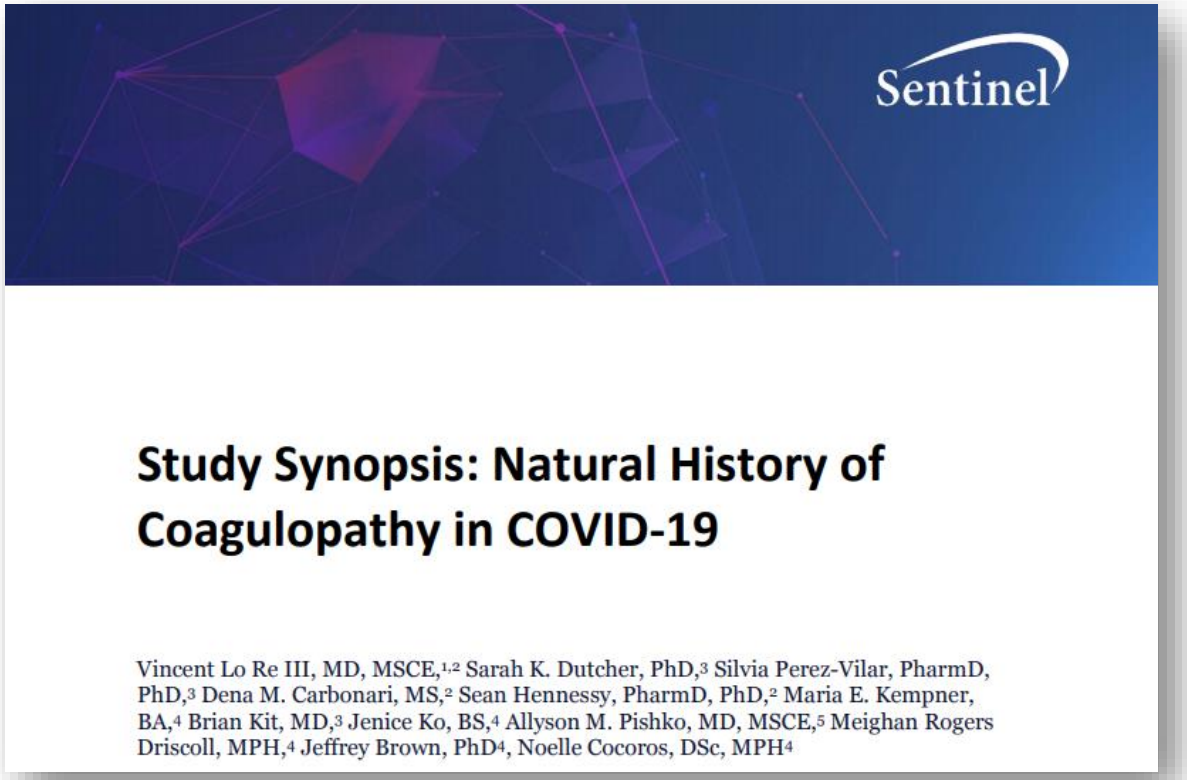
Abstracts of the 37th International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Virtual, August 23, 2021. Pharmacoepidemiol Drug Saf. 2021 Aug;30 Suppl 1:3-439

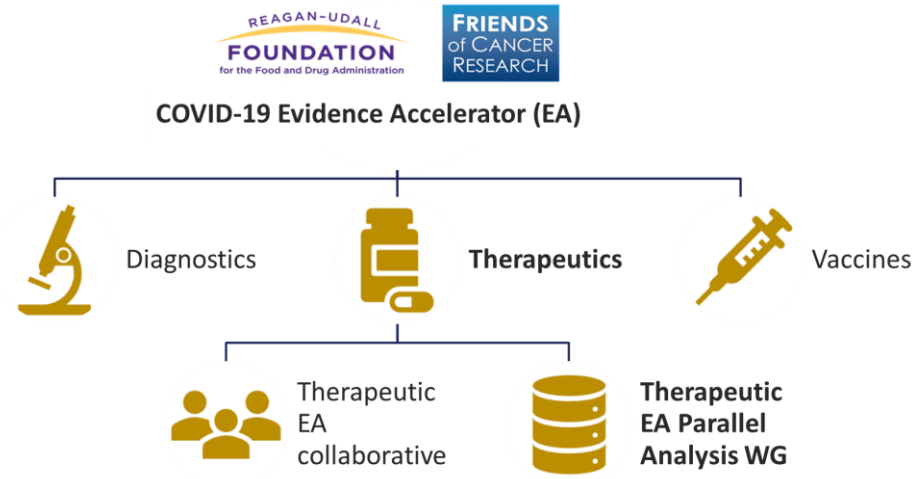
- Comparing outcomes in trial-eligible vs real-world COVID-19 patients: The case of invasive mechanical ventilation. Martinez A.I., Perez-Vilar S., Shinde M., Kempner M.E., Kolonoski J., Dutcher S.K., Kit B.
- Outpatient-identified COVID-19 and subsequent hospitalized thrombotic events. Perez-Vilar S., Martinez A.I., Shinde M., Kempner M.E., Kolonoski J., Dutcher S.K., Kit B.

Sentinel Contributions

Collaboration with other U.S. Stakeholders

- Share Real-World Data and Generate Innovative Responses on COVID-19





What We've Learned, Where We're Headed (Public Meeting) | Evidence Accelerator

Sentinel Contributions

Collaboration with other Regulatory Agencies

- International Coalition of Medicines Regulatory Authorities (ICMRA)

International Meta-Analyses

Under review

Natural history of coagulopathy (led by FDA)

- England, Germany, Italy, The Netherlands, Spain, Canada, United States

Ongoing

Pregnancy Observational Studies (led by EMA)

- Italy, France, Spain, UK, Norway, Sweden, Canada, United States

Search Covid-19 infectiON and medicineS In preGNancy (zenodo.org)
COVID-19 Pregnancy Study Implementation | Sentinel Initiative

Sentinel Contributions

FDA Sentinel System's Coronavirus (COVID-19) Activities | Sentinel Initiative

Strengths: What Did We Do Well?

- Expanded Sentinel capabilities early in the pandemic
- Provided recognized expertise in pharmacoepidemiology
- Led and shaped development and implementation of master protocols
- Characterized drug utilization and trends
- Supported regulatory decision-making (drug safety)
- Collaborated with internal and external stakeholders

Weaknesses: What Prevented Us From Doing Better?

Critical data elements

- Infecting variant, COVID-19 vaccination status, capture of supplemental oxygen, disease onset date identification, disease severity, race

Timeliness

- Data lag, query turnaround, approval and clearance processes

Nationally representative data sources with EHR inpatient data

Limited experience with newly incorporated EHR databases

- HCA, TriNetX

Research availability not always in step with rapidly evolving pandemic

- Questions no longer relevant, shifting priorities

Opportunities: What Could Give us an Advantage to Prepare For a Future Pandemic?

- Fresher data
- Nationally-representative EHR databases with inpatient data
- Further enhancement of the Common Data Model
- EHR-claims linked databases
- Artificial intelligence

Opportunities: What Could Give us an Advantage to Prepare for a Future Pandemic?

- Streamlined and more affordable access to medical records for validation of case definitions for outcomes, exposures, and covariates
- Data standards/integration
- Foster and maintain internal, national, and international collaborations
- Streamlined processes for approval, query turnaround, and clearance

Challenges: What Are Potential Barriers to Prepare for a Future Pandemic?

- Data completeness, reliability, relevance
- Inconsistent access to validated and sufficiently large databases
- Privacy/security standards
- Slow development and incorporation of expanded capabilities
- Competing interests/priorities
- Unpredictability of future pandemics
- Maintaining consistent funding

Closing Remarks

Strengths

- Master protocols
- Emergency response
- Regulatory-decision making

Weaknesses

- Missing critical data elements
- Timeliness
- Insufficient EHR inpatient data, EHR-claims linked databases

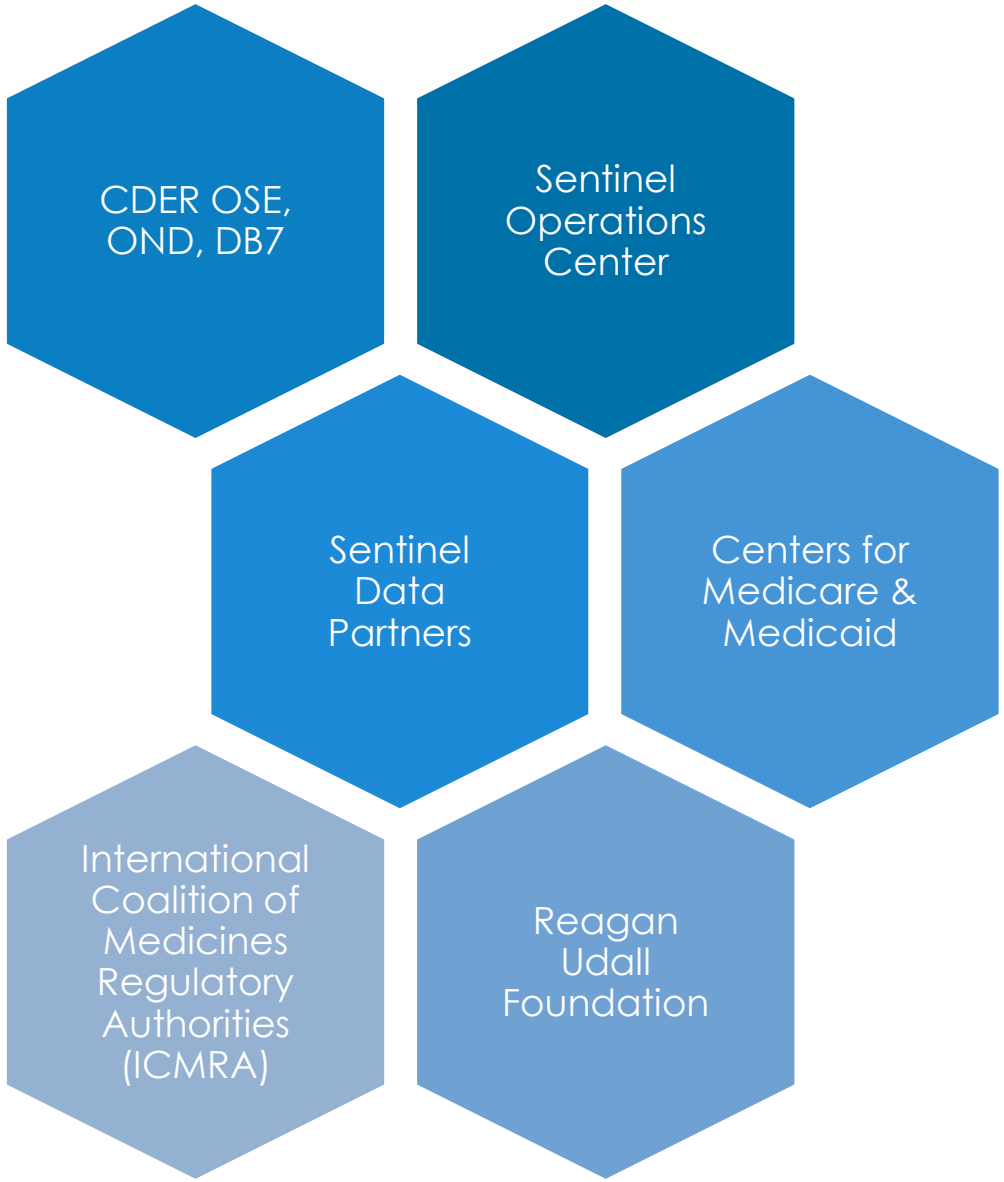
Opportunities

- Incorporate additional reliable and relevant data sources
- Foster and maintain collaborations
- Streamline processes

Challenges

- Competing interests/priorities
- Unpredictability of future pandemics
- Maintaining consistent funding

Acknowledgments



U.S. FOOD & DRUG ADMINISTRATION

Thanks

Leveraging Lessons Learned to Move Beyond COVID-19

Susan C. Winckler, RPh, Esq
CEO

Fifteenth Annual Sentinel Initiative Public Workshop
Nov. 8, 2023
Washington, DC

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COVID-19 EVIDENCE ACCELERATOR PRINCIPLES

Together, we will **create** and **lead**.

C **CONTEXT** — tie data to the question, address bias, explain validation strategies.

R **RESPECT** — for patient privacy and the patient voice is paramount.

E **EARN TRUST** — show processes, analytic approaches, and comparisons. Be open to input. Challenge with productive intent.

A **ACT FAST AND DO GOOD WORK** — act with a sense of urgency, but not at the expense of quality or credibility.

T **TRANSPARENCY** — ruthless transparency.

E **EMBRACE AND EXPLORE** —convergence and discordance to facilitate understanding and generate knowledge.

L **LEARN** — continually integrate best practices from **sharing** process, limitations, pitfalls, and successes.

E **EXERCISE PATIENCE** — state when a question can't be answered right away and institute action to answer it.

A **ACCESSIBILITY AND TRACEABILITY** — document data generation, processing, curation, and analytics.

D **DISSEMINATE WORK** — to show what good looks like. *Teach, Don't Preach.*

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FRIENDS of CANCER RESEARCH

Lesson Learned: We can (and must) improve the collection of real-world data to power the generation of real-world evidence

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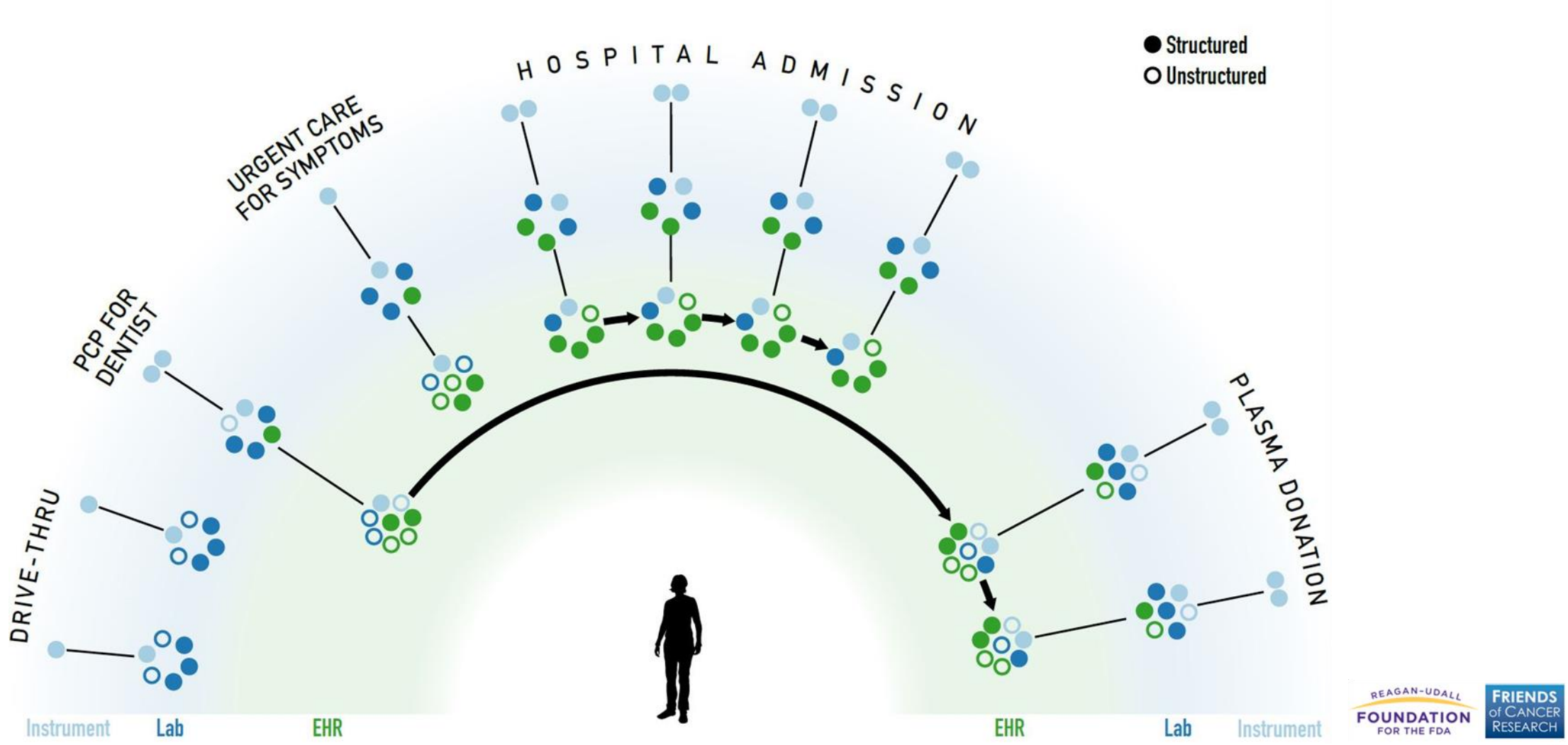
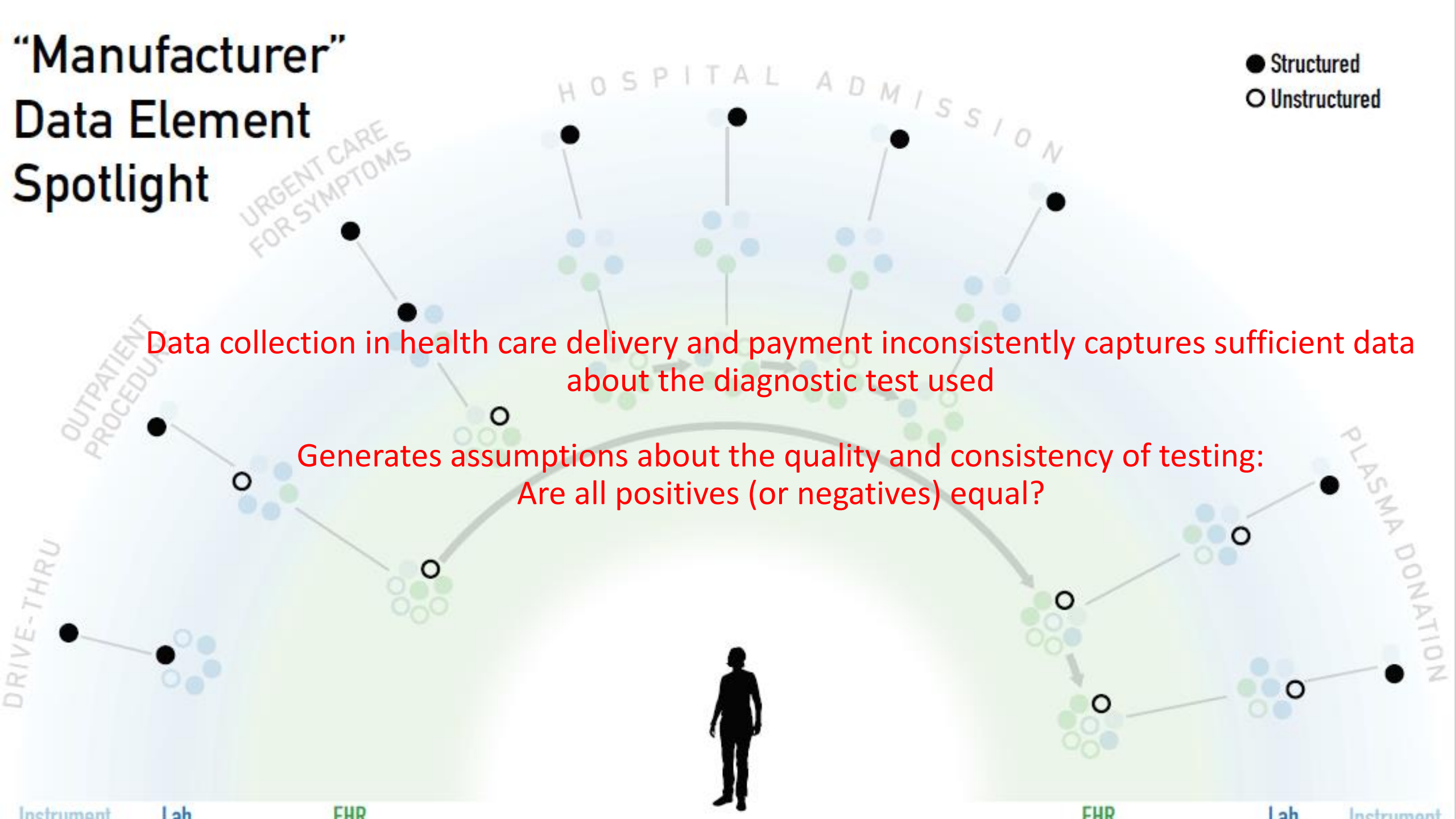
One Individual's Clinical Journey: Diagnostic Testing Data



Credit to then-FDA team members R.J. Andrews and Gina Valo

"Manufacturer" Data Element Spotlight



Data collection in health care delivery and payment inconsistently captures sufficient data about the diagnostic test used

Generates assumptions about the quality and consistency of testing:
Are all positives (or negatives) equal?

Race and Ethnicity Data

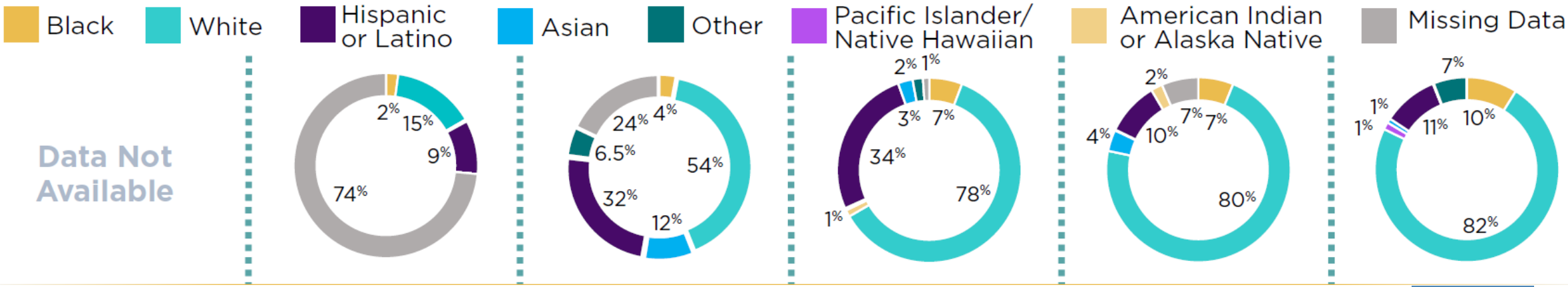
Despite the known racial disparity of COVID-19, race data was routinely missing in real-world data repositories

- **65%** of confirmed cases reported to the CDC had complete race and ethnicity reported[1]

[1]*Kaiser Family Foundation (COVID-19 Cases and Deaths by Race/Ethnicity: Current Data and Changes Over Time | KFF)*]

- In the COVID-19 Evidence Accelerator/Diagnostics Parallel Analysis, race data was largely missing in one-third of contributing Accelerators (Figure 4)[2]…

FIGURE 4: Race/Ethnicity Data Among Those Serotested



[2]*Rodriguez-Watson CV, Sheils NE, Louder AM, Eldridge EH, Lin ND, et. al. Real-world utilization of SARS-CoV-2 serological testing in RNA positive patients across the United States. PLoS One. 2023 Feb 10;18(2):e0281365. doi: 10.1371/journal.pone.0281365. PMID: 36763574; PMCID: PMC9916659*

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We can do better…

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RAISE

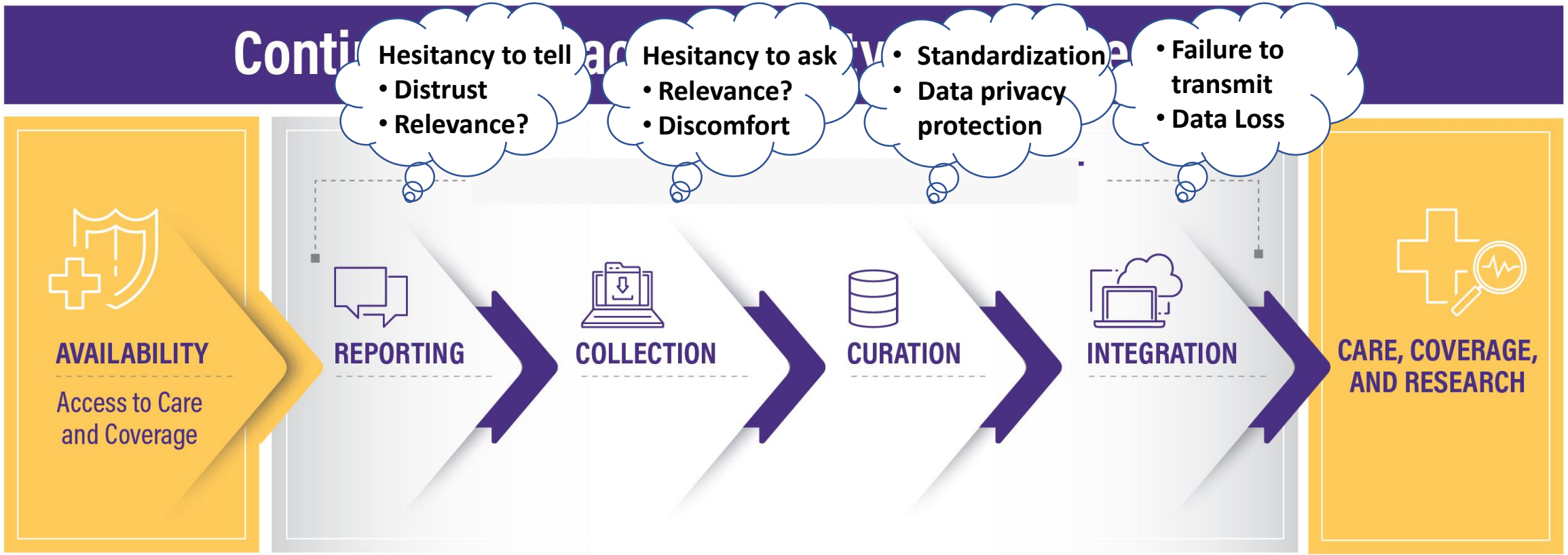
REAL-WORLD ACCELERATOR TO IMPROVE THE STANDARD OF COLLECTION AND CURATION OF RACE AND ETHNICITY DATA IN HEALTHCARE

This project is supported by the Food and Drug Administration (FDA) Office of Minority Health and Health Equity of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award (FAIN) totaling $499,514 (100% funded by FDA OMHHE/HHS). The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS, or the U.S. Government.

RAISE

REAL-WORLD ACCELERATOR TO IMPROVE THE STANDARD OF COLLECTION AND CURATION OF RACE AND ETHNICITY DATA IN HEALTHCARE

Why is Race & Ethnicity Data Missing in Health Care?



RAISE

REAL-WORLD ACCELERATOR TO IMPROVE THE STANDARD OF COLLECTION AND CURATION OF RACE AND ETHNICITY DATA IN HEALTHCARE

RAISE Specific Aims

- **Gather** to create opportunities for Collective Learning and Community Capacity Building
- **Create a Tool** to prioritize solutions
- **Evaluate** the impact of the project to initiate a change in practice

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Thank You/Questions

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Moderated Discussion and Q&A

Moderator: Christina Silcox

Duke-Margolis Center for Health Policy

Stakeholder Reflections on Sentinel

Moderator: **Trevan Locke,** Duke-Margolis Center for Health Policy

Speakers:

Heather Rubino, Pfizer, Inc.

Philip Goodney, Dartmouth College

Jeffrey Brown, TriNetX

Anna McCollister, Patient Advocate, Patient Engagement and Data Use, Access and Governance

Patricia Bright, U.S. Food and Drug Administration

Steve Anderson, U.S. Food and Drug Administration

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Moderated Discussion and Q&A

Moderator: Trevan Locke

Duke-Margolis Center for Health Policy

Closing Remarks

Gerrit Hamre

Research Director, Duke-Margolis Center for Health Policy

Thank You!

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