Fourteenth Annual Sentinel Initiative Public Workshop

November 15, 2022 | 1:00 – 5:00 ET

November 16, 2022 | 12:00 – 4:15 ET

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

If you are interested in using or referencing these slides, please contact the appropriate presenter.

Welcome & Overview | Day 1

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Agenda: Day 1

- Keynote Presentation – Patrizia Cavazzoni
- Fireside Chat with Sentinel Initiative Leadership
- Reflections on PDUFA VI Commitments and Looking Ahead to PDUFA VII
- BEST Operations and Coordinating Center Perspectives
- Sentinel System Operations and Coordinating Center Perspectives

Agenda: Day 2

- Sentinel System Innovations in Data Infrastructure and Analytic Methods
- BEST Innovations in Data Infrastructure and Analytic Methods
- Key Collaborations with Stakeholders and Development of New Partnerships in the Sentinel Initiative

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.

Virtual Meeting Reminders

- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
  - Audience questions will be incorporated into panel discussions whenever possible

- Join the discussion on Twitter using the #SentinelInitiative hashtag

Keynote Presentation

Patrizia Cavazzoni

U.S. Food and Drug Administration

Fireside Chat with Sentinel Initiative Leadership

- **Gerald Dal Pan**, U.S. Food and Drug Administration
- **Steven Anderson**, U.S. Food and Drug Administration

Reflections on PDUFA VI Commitments and Looking Ahead to PDUFA VII

- **Patricia Bright,** U.S. Food and Drug Administration

CDER Sentinel System: Reflections on PDUFA VI and Looking Ahead to PDUFA VII

Patricia Bright, PhD, MSPH
Sentinel System Program Lead, CDER

The Prescription Drug User Fee Act (PDUFA) was a law passed by the United States Congress in 1992 which allowed the FDA to collect fees from drug manufacturers to fund the new drug approval process.

The fifth reauthorization of PDUFA (PDUFA VI) in 2017 called for an “expanded set of commitments related to scaling up and expanding the Sentinel System while continuing to embed its use” in FDA post-market surveillance operations for regulatory decisions.

Agenda:

- Reflecting on PDUFA VI
  - Successes
  - Challenges
- Looking ahead to PDUFA VII
  - Maintenance
  - Pregnancy Safety
  - Negative Controls

PDUFA VI

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PDUFA VI Commitment Letter*

August 18, 2017

PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES
FISCAL YEARS 2018 THROUGH 2022

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 and sponsor 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 programs 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 the regulatory purposes, e.g., in the context of labeling changes, PMRs, or PMCs,

Good News!

PDUFA VI 1.a-h requirements have been completed

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PDUFA VI Commitment Letter

August 18, 2017

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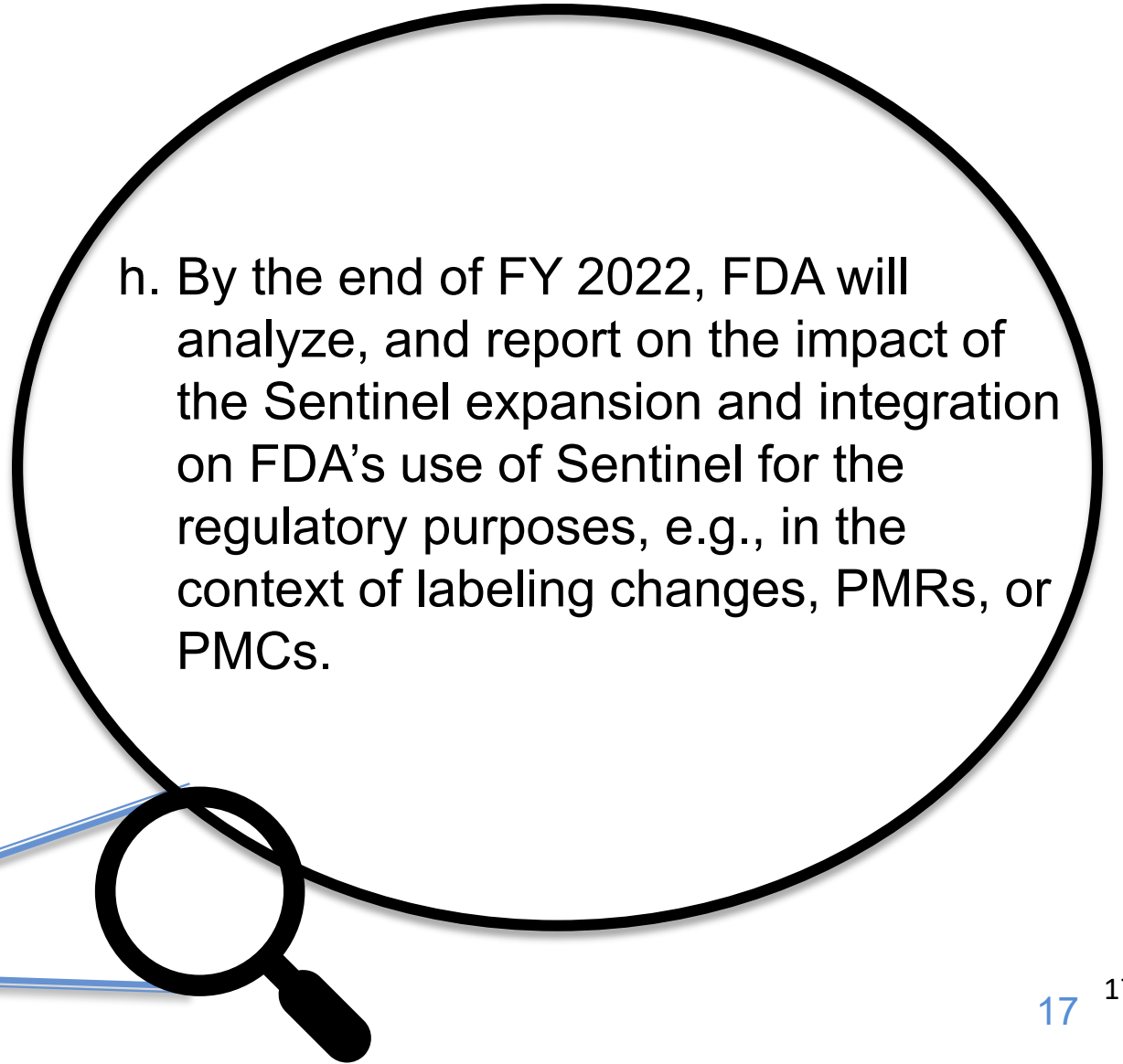

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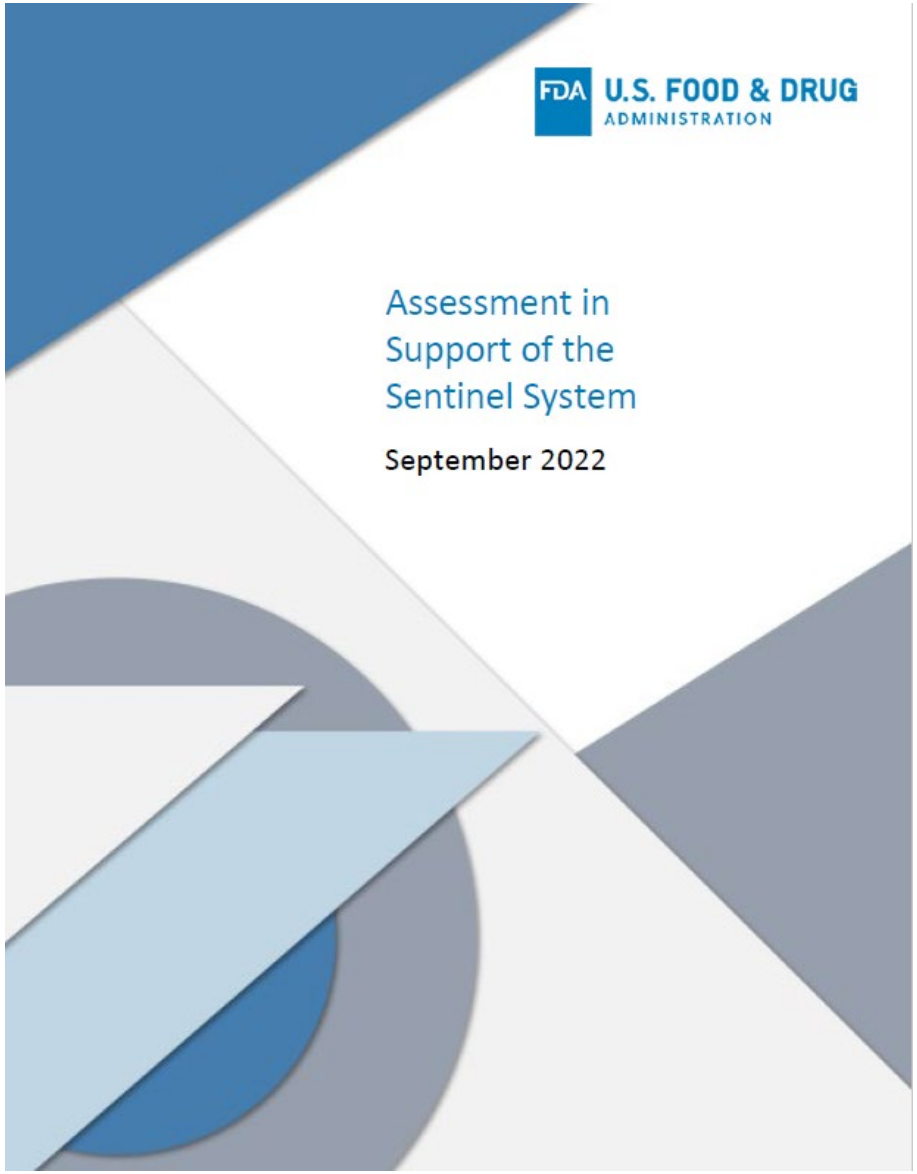
Posted online:
https://www.fda.gov/industry/prescription-drug-user-fee-amendments/pdufa-vi-commitment-assessment-support-sentinel-system



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PDUFA VI

- Successes
  - Met PDUFA VI goals
- Challenges
  - When a post market requirement (PMR) for an observational study is under consideration, CDER determines whether the Active Risk Identification and Analysis (ARIA) tools in the Sentinel System are sufficient to conduct the analysis
  - Found that the ARIA tools are not sufficient to address a majority of the requested observational PMRs

Factors in ARIA Sufficiency Determination

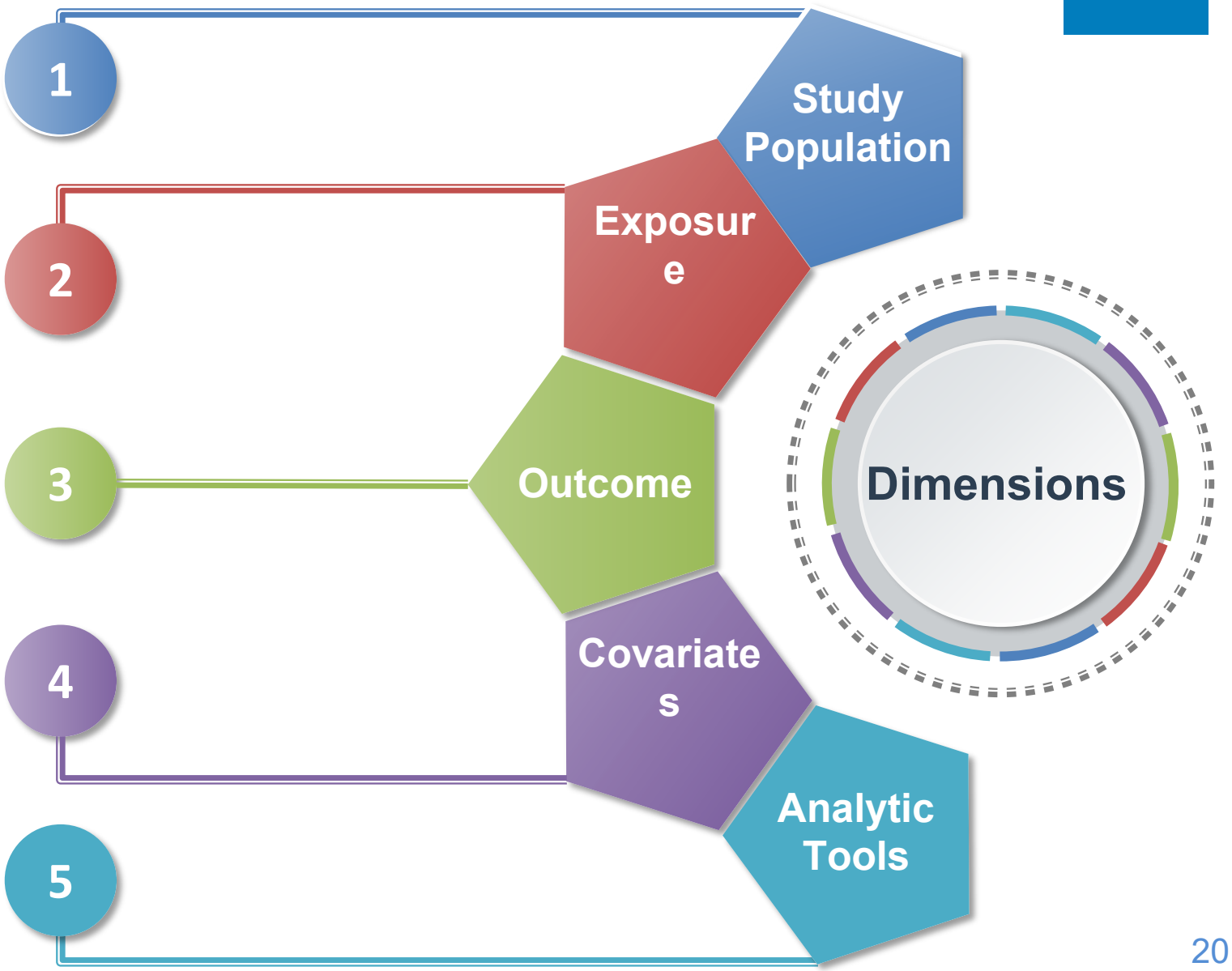
Demographics
- Indication
- Clinical setting

Study drug and comparator
- Pattern and timing of use
- Clinical setting

Case definition or identification algorithm
- Clinical setting
- Need for imaging or lab data?

Confounders
- Effect modifiers

Desired study design
- Analytic method



Distribution of Safety Concerns Insufficient for Assessment in ARIA Attributed to Capture of Health Outcome

A majority of the PMRs where ARIA was determined to be insufficient were related to pregnancy studies, which are a focus of Sentinel's PDUFA VII work

Health Outcome (MedDRA System Organ Class)	Safety Concerns Identified Pre-Approval	Safety Concerns Identified Post-Approval	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	1	3
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
Other[1]	12	2	14
Total	112	18	130

[1] A recording of "Other" indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.

PDUFA VII

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FDA

2. Optimization of the Sentinel Initiative

The user fee funds initially provided in PDUFA VI to expand the Sentinel program will continue to systematically implement and integrate Sentinel and BEST (Biologics Effectiveness and Safety) Systems in FDA drug safety activities by sustaining the high quality and large quantity of data available, allowing continued application of advanced methods for determining when and how those data are utilized, and ensuring comprehensive training of review staff on the use of Sentinel and BEST. These capabilities will support the use of the Sentinel Initiative for regulatory decision making to address questions of product safety and advance our understanding of how real-world evidence can be used for studying effectiveness.

a. Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities

FDA will use user fee funds to maintain the quality and quantity of data available through the Sentinel Initiative (Sentinel and BEST), to m tools for determining when and how those data are utiliz comprehensive training of review staff on the use of Sen

i. FDA will maintain the Sentinel's sources of data and the safety surveillance of drugs and biologics, includi ARIA system.

ii. FDA will continue its communication with sponsors a regarding general methodologies for Sentinel queries, Agency has learned regarding the most appropriate w Sentinel data.

iii. By the end of FY 2025, FDA will publish on its webs facilitation of public and sponsor access to Sentinel's network to conduct safety surveillance.

iv. FDA will continue to post study results, study parame code online and maintain a strong Sentinel web prese information.

v. FDA will continue to maintain a comprehensive FDA program for all relevant staff (e.g., epidemiologists, st managers, medical officers, clinical analysts, and othe members) to ensure that staff have a working knowle identify when Sentinel can inform important regulato decisions, and are able to consistently participate in u evaluate safety issues.

vi. By the end of FY 2025, FDA will analyze, and report Sentinel for regulatory purposes, e.g., in the contexts PMRs, or PMCs.

vii. For FY 2023-2027, FDA will report its obligations fo commitments for PDUFA VII Sentinel Initiative annu Financial Report. This reporting will provide detail fo categories (e.g., data infrastructure, analytical capabil analyses, dissemination of relevant product and safety information, and Sentinel system development).

b. Enhancement of the Analytic Capabilities of the Sentinel Initiative to Address Questions of Product Safety and Advance the Understanding of How Real-World Evidence Can Be Used for Studying Effectiveness

FDA will use user fee funds to advance the analytic capabilities of the Sentinel Initiative by i) developing a consistent approach to post-market requirements and commitments during NDA and BLA review related to assessing the outcomes of pregnancies in women exposed to drugs and biological products and clarifying the optimal use and value of pregnancy registries and electronic healthcare data for assessing pregnancy safety and ii) supporting the use of real-world evidence to address questions of product safety and advancing our understanding of how real-world evidence may be used for studying effectiveness.

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

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.

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.

eal-World Evidence – Negative Controls

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

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.

PDUFA VII: Optimization of the Sentinel Initiative

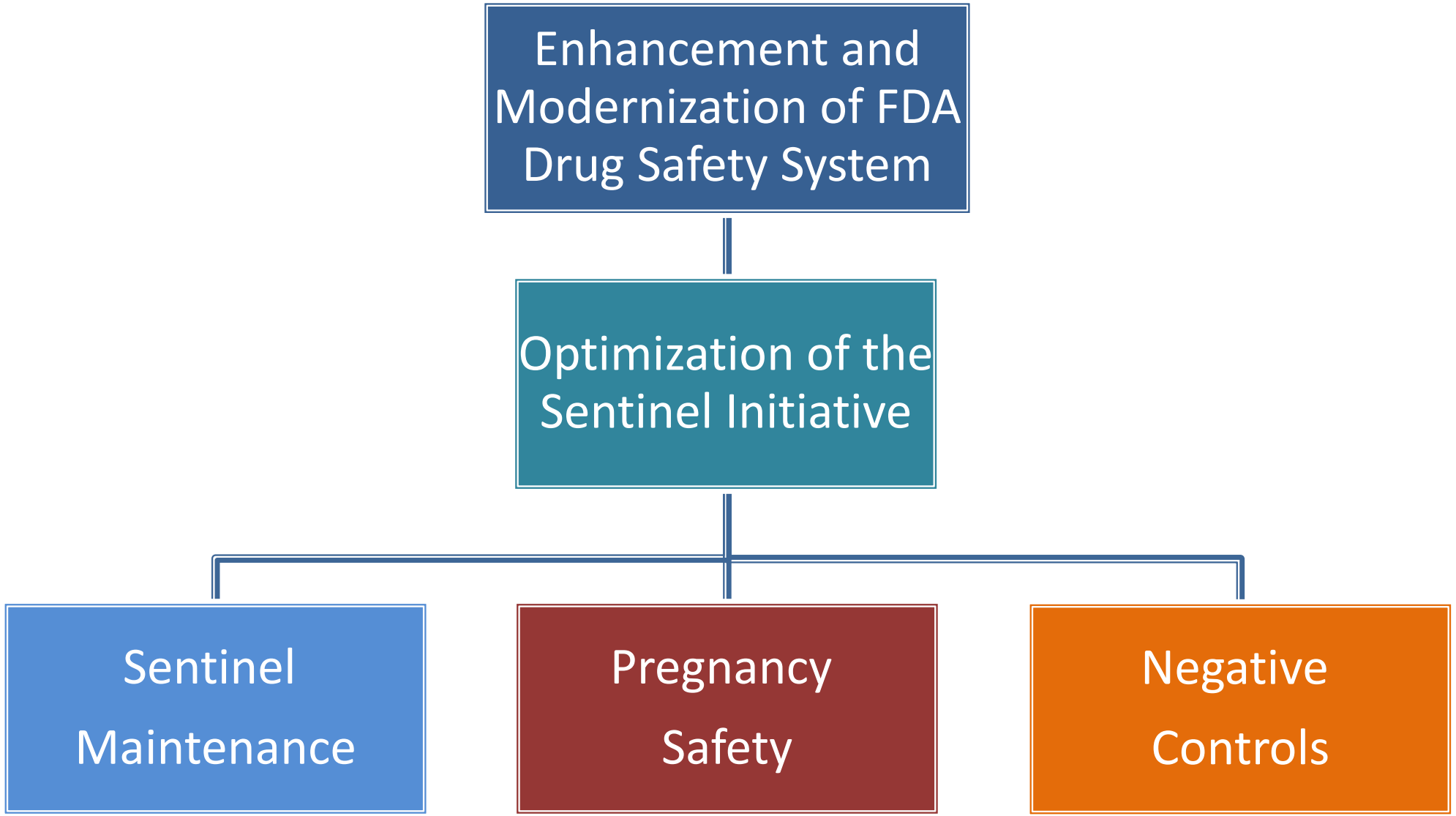
a. Maintenance of the Sentinel Initiative Capabilities and Continued Integration into FDA Drug Safety Activities

i-Vii

b. Enhancement of the Analytic Capabilities

i Pregnancy Safety
ii Use of Real-World Evidence – Negative Controls

Sentinel PDUFA VII Commitments



Optimizing the Sentinel Initiative

- Maintain Sentinel's data sources and core capabilities
- Continue communications with sponsors and public
- Maintain comprehensive training program
- Post study results, parameters and analysis code
  - Report on the use of Sentinel for regulatory purposes, (e.g., in the contexts of labeling changes, PMRs, PMCs)
  - Report on spending for the Sentinel Initiative in important categories (e.g., data infrastructure, analytical capabilities)

M2: Optimizing the Sentinel Initiative

b. Enhancement of the analytic capabilities of the Sentinel Initiative to address questions of product safety and advance the understanding of how real-world evidence can be used for studying effectiveness

i Pregnancy Safety

ii Negative Controls

What to watch for: Public Workshops (to be posted in Federal Register)

- 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.

- 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.


FDA
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ADMINISTRATION

Break

We will be back momentarily.

The next panel will begin at 2:30 p.m. (U.S. Eastern Time)

Session I: BEST Operations and Coordinating Center Perspectives

- **Azadeh Shoaibi,** U.S. Food and Drug Administration, CBER
- **Mao Hu,** Acumen LLC
- **Yoganand Chillarige,** Acumen LLC
- **Hui Lee Wong,** U.S. Food and Drug Administration, CBER

CBER's Biologics Effectiveness and Safety (BEST) Initiative Response to the COVID-19 Pandemic

Azadeh Shoaibi, PhD MHS[1]
Mao Hu, BS[2]
Yoganand Chillarige, MPA[2]
Hui Lee Wong, PhD MSc[1]

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

14th Annual Sentinel Initiative Public Workshop
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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 or Acumen, LLC.

Outline

- BEST Initiative Data Network
- COVID-19 Vaccine Safety Monitoring
  - Descriptive Monitoring
  - Signal Detection
  - Signal Evaluation
  - Regulatory Impact
- Monkeypox Vaccine Monitoring

BEST Initiative Data Network
COVID-19 Vaccine Safety Monitoring

Azadeh Shoaibi, PhD MHS
U.S. FDA CBER

Outline

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CBER Surveillance Program

CBER-Regulated Products

- Vaccines (preventative and therapeutic)
- Blood (components and derived)
- Human Tissues and Cellular Products
- Gene Therapies
- Xenotransplantation Products

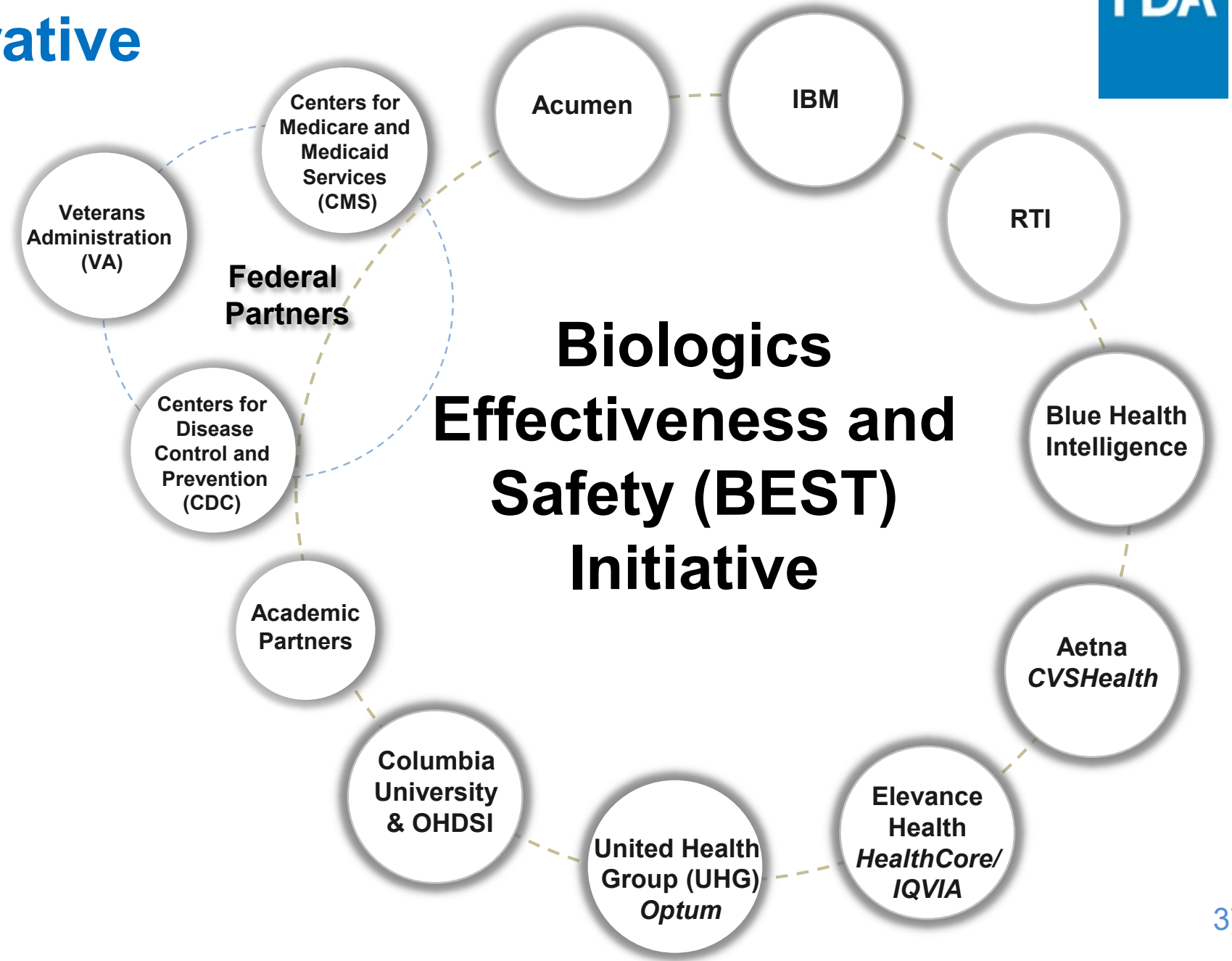
FDA CBER Mission Focus

Evaluate and ensure biologic products safety and effectiveness through active surveillance

CBER Surveillance Program's Vision

Build and utilize a national post-market surveillance system for CBER-regulated products to provide data for evidence-based regulatory decisions

CBER Active Surveillance Program Collaborative



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
MarketScan Commercial (IBM)	Claims	65	2016 - present
Blue Health Intelligence	Claims	93	2016 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	31	2017 - present
HealthCore	Claims	70	2010 - present
CVS Health	Claims	41	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	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

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

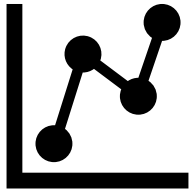
COVID-19 Response
Immunization Information Systems

- Immunization information systems (IIS)
  - Confidential, population-based, computerized databases that record all immunization doses administered by participating providers to persons in U.S. public health jurisdictions
- COVID-19 vaccine administration
  - Outside healthcare system and not captured in claims databases

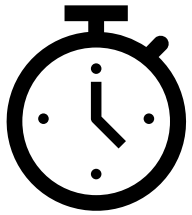
COVID-19 Response
Immunization Information Systems

- Linkage of BEST administrative claims data to IIS data
  - Supplement COVID-19 vaccines exposure data and expand BEST data network and infrastructure
- Total number of IIS local and state jurisdictions: ~60
- BEST linkage with more than half of IIS

Phases of COVID-19 Vaccine Active Surveillance



Descriptive Monitoring provides descriptive statistics of vaccine doses and selected adverse events.



Signal Detection performs sequential testing, while vaccine doses accumulate, to identify potential safety risks early; does not prove causal relationship.

Signal Evaluation uses more robust study designs to evaluate potential safety signals.

Outline

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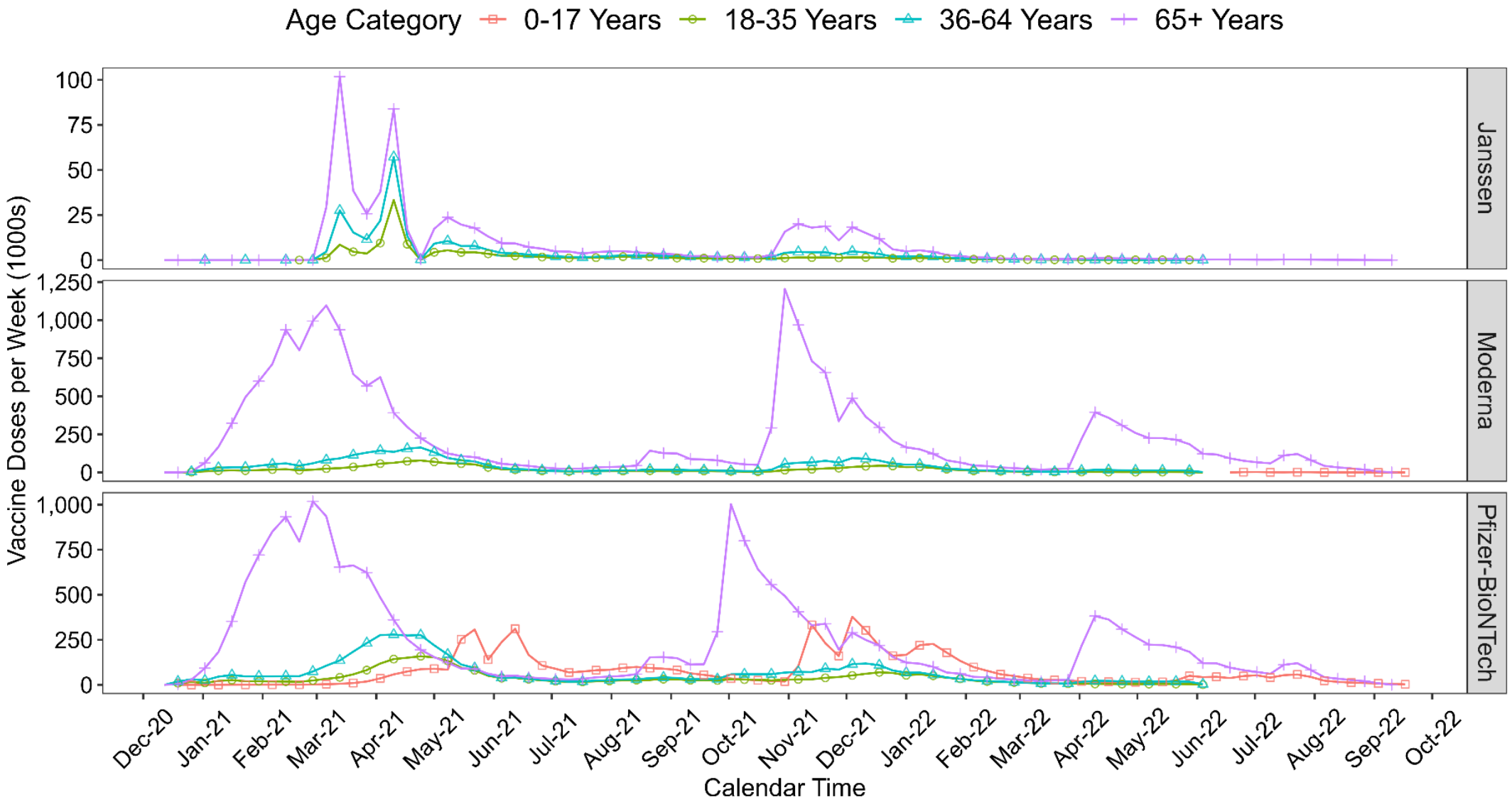
  - Descriptive Monitoring
  - Signal Detection
  - Signal Evaluation
  - Regulatory Impact
- Monkeypox Vaccine Monitoring

BEST Data: COVID-19 Vaccines Administered Doses

Product	Dose	Data Partner (Age Group)				Total Count
		Data Partner 1 (0-64)	Data Partner 2 (0-64)	Data Partner 3 (0-64)	CMS Medicare (65+ only)	
Pfizer-BioNTech	All Doses	10,239,672	12,615,848	9,718,475	20,476,913	53,050,908
	Dose 1	4,393,641	5,841,329	4,361,663	5,811,625	20,408,258
	Dose 2	3,721,921	4,596,380	3,584,693	5,090,259	16,993,253
	Third Dose or Monovalent Booster	2,124,110	2,178,139	1,772,119	8,062,925	14,137,293
	Bivalent Booster	-	-	-	1,512,104	1,512,104
Moderna	All Doses	4,801,751	6,384,105	4,519,857	20,833,096	36,538,809
	Dose 1	1,958,944	2,946,562	1,943,987	5,740,825	12,590,318
	Dose 2	1,589,561	2,232,398	1,562,108	5,127,435	10,511,502
	Third Dose or Monovalent Booster	1,253,246	1,205,145	1,013,762	8,968,423	12,440,576
	Bivalent Booster	-	-	-	996,413	996,413
Janssen	All Doses	441,160	613,297	429,328	616,080	2,099,865
	Dose 1	398,214	560,364	393,631	551,111	1,903,320
	Booster Dose	42,946	52,933	35,697	64,969	196,545
Novavax	All Doses	-	-	229	396	625
	Dose 1	-	-	165	343	508
	Dose 2	-	-	53	53	106
	Booster Dose	-	-	11	-	11

Data cuts: Data Partner 1: 6/22, Data Partner 2: 9/22, Data Partner 3: 9/22, CMS 9/22 (Monovalent) and 10/22 (Bivalent)

COVID-19 Vaccines Administered Doses By Age Group



COVID-19 Vaccine Safety Monitoring: Signal Detection

Mao Hu, BS
Acumen, LLC

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Safety Signal Detection: Adverse Events Monitored

Adverse Events Monitored in Adult and Pediatric Populations	
Acute Myocardial Infarction (AMI)	Hemorrhagic Stroke
Anaphylaxis	Myocarditis/Pericarditis
Appendicitis	Narcolepsy
Disseminated Intravascular Coagulation (DIC)	Non-hemorrhagic Stroke (NHS)
Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)
Bell's Palsy	Transverse Myelitis
Encephalomyelitis/Encephalitis	Immune Thrombocytopenia (ITP)
Guillain-Barré Syndrome (GBS)	Thrombosis with Thrombocytopenia Syndrome (TTS) (unusual, common site)

Adverse Events Monitored in Pediatric Populations Only
Seizure/Febrile Seizure
Kawasaki Disease
Multisystem Inflammatory Syndrome in children (MIS-C)

These AEs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

COVID-19 Vaccine Safety Signal Detection

- **Objective:** Rapid identification of potential safety signals
- **Population:** 6 months and older
- **Exposure:** Pfizer-BioNTech and Moderna (primary series), Janssen COVID-19 vaccines
  - Primary series: original formulation in two doses
- **Statistic**: Unadjusted rate of safety outcomes in risk windows
- **Comparator:** Historical rates
- **Study Design:** Near real-time monitoring (rapid cycle analysis [RCA]); does not provide evidence of causal link between vaccination and outcome

RCA Signals Detected: Primary Vaccine Series – Doses 1 & 2

Safety Outcomes with Statistical Testing	CMS Medicare[1] (65+ years)	Adults[2] (12-64 years)	Pediatrics[3] (6 months – 17 years)
Acute Myocardial Infarction	**Pfizer-BioNTech**	NO	NO
Anaphylaxis	**Pfizer-BioNTech** **Moderna** **Janssen**	**Pfizer-BioNTech** **Moderna**	NO
Appendicitis	NO	NO	NO
Disseminated Intravascular Coagulation	**Pfizer-BioNTech**	NO	NO
Deep Vein Thrombosis	NO	NO	NO
Bell's Palsy	NO	NO	NO
Encephalomyelitis/Encephalitis	NO	NO	NO
Guillain-Barré Syndrome	NO	NO	NO
Hemorrhagic Stroke	NO	NO	NO
Myocarditis/Pericarditis	NO	**Pfizer-BioNTech**	**Pfizer-BioNTech**
Common Site Thrombosis with Thrombocytopenia	NO	NO	NO
Uncommon Site Thrombosis with Thrombocytopenia Syndrome	NO	NO	NO
Narcolepsy	NO	NO	NO
Non-Hemorrhagic Stroke	NO	NO	NO
Pulmonary Embolism	**Pfizer-BioNTech**	NO	NO
Transverse Myelitis	NO	NO	NO
Immune Thrombocytopenia	**Pfizer-BioNTech**	NO	NO

1. Data cuts: CMS 1/22
2. Data cuts: DP1 2/22; DP21/22; DP3 12/21
3. Data cuts: DP1 9/22; DP2 8/22; DP3 7/22

COVID-19 Vaccine Safety Signal Detection: Monovalent Third/Booster Doses

- **Objective:** Identification of potential safety signals
- **Population:** 18-64 years, ≥65 years
- **Exposure:** Pfizer-BioNTech, Moderna COVID-19 vaccines
  - Monovalent third/booster: 3rd dose of original formulation
- **Statistic**: Unadjusted rate of outcomes in risk windows
- **Comparator:** Historical rates
- **Study Design:** Retrospective cohort

COVID-19 Vaccine Safety Signal Detection: Bivalent Booster Monitoring

- **Study Design:** Near real-time surveillance (RCA); no causal association established
- **Population:** 5-17 years, 18-64 years, ≥65 years
- **Exposure:** Pfizer-BioNTech, Moderna COVID-19 vaccines
  - Bivalent booster: original virus and Omicron variants BA.4 and BA.5.
- **Statistic**: Unadjusted rate of safety outcomes in risk windows
- **Comparator:** Historical rates

COVID-19 Vaccine Safety Signal Detection: Summary

- Near real-time surveillance (RCA) detected a number of signals in a timely manner.
- Published manuscripts, pre-prints, or public communications
  - Initial Results of Near Real-Time Safety Monitoring of COVID-19 Vaccines in Persons Aged 65 Years and Older (FDA website and medRXiv)
  - Near real-time surveillance of safety outcomes in US COVID-19 vaccine recipients aged 12 to 64 years (*Vaccine*)
  - Results of safety monitoring of Pfizer-BioNTech COVID-19 vaccine in U.S. children aged 5-17 years (medRXiv)
- **Next step: more robust studies with confounding adjustment to follow up signals (signal evaluation)**

COVID-19 Vaccine Safety Monitoring: Signal Evaluation

Yoganand Chillarige, MPA
Acumen, LLC

Outline

- BEST Initiative Data Network
- COVID-19 Vaccine Safety Monitoring
  - Descriptive Monitoring
  - Signal Detection
  - Signal Evaluation
  - Regulatory Impact
- Monkeypox Vaccine Monitoring

COVID-19 Vaccine Safety Signal Evaluation

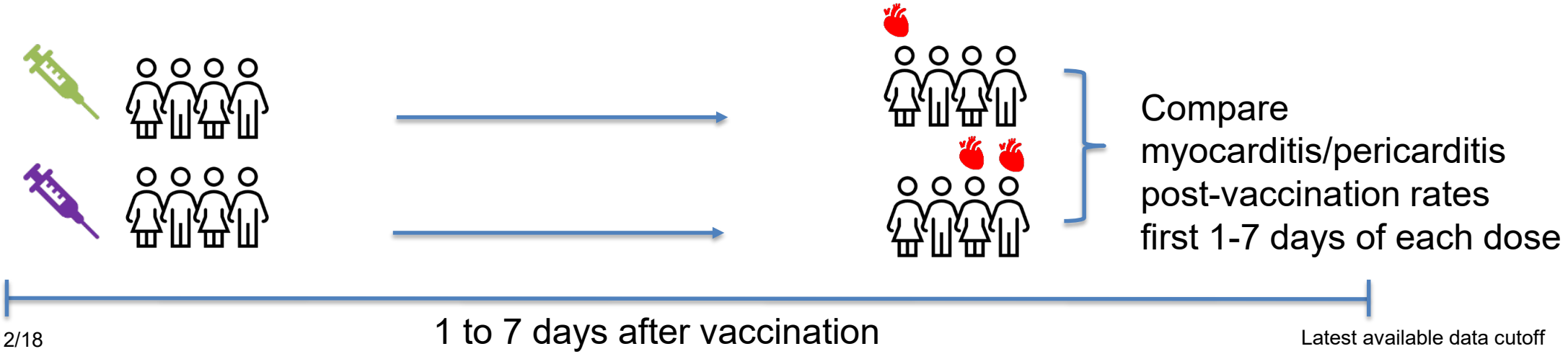
- Myocarditis/Pericarditis risk after exposure to mRNA COVID-19 vaccines in adults
- Self-controlled studies for signal evaluation in older adults

Myocarditis/Pericarditis Study of mRNA Vaccines in Adults

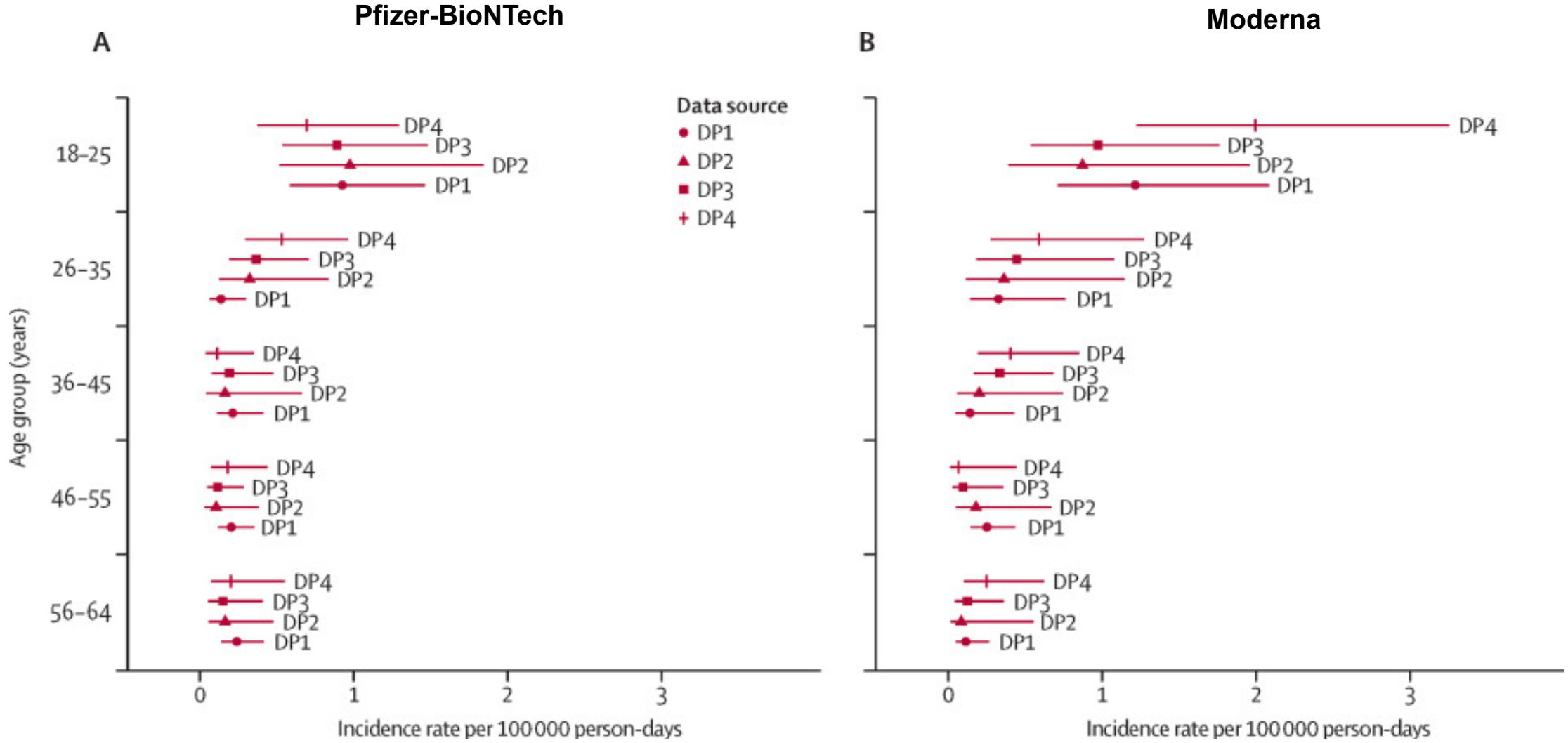
- **Objective:**
  - Estimate incidence rate of myocarditis/pericarditis after exposure to COVID-19 mRNA vaccines
  - Compare incidence rate of myocarditis/pericarditis between Moderna and Pfizer-BioNTech (reference) COVID-19 vaccines
- **Outcomes:** Myocarditis, or pericarditis, or both
  - Myocarditis: inflammation of heart muscle
  - Pericarditis: inflammation of outer lining of heart
- **Risk window:** 1-7 days post-vaccination

Myocarditis/Pericarditis Study of mRNA Vaccines in Adults: Methods

- **Study Design:** retrospective comparative cohort design
- **Data Sources:** Optum, HealthCore, Blue Health Intelligence, CVS Health administrative claims databases
- **Study Population:** 18-64 years; focusing on men aged 18-25 years
- **Exposure and Follow Up:** receipt of at least one dose; followed until end of risk window, disenrollment, administration of subsequent dose, or study end date



Myocarditis/Pericarditis Study of mRNA Vaccines in Adults: Results in BEST



Data cuts: DP1 9/21, DP2 10/21, DP3 11/21, DP4 12/21

Myocarditis/Pericarditis Study of mRNA Vaccines in Adults: Results in BEST

Males 18-25 and 18-35 years by care setting, any dose[1]

	Pfizer-BioNTech		Moderna		Moderna vs. Pfizer-BioNTech (reference)	
Age Group by Care Settings (Males)	**# Cases**	**IR per 100k person-days (95%CI)**	**# Cases**	**IR per 100k person-days (95%CI)**	**IRR (95%CI)**	**Excess Risk[2] (95% CI)**
18-25 All Care Settings	68	0.88 [0.67,1.15]	46	1.27 [0.88,1.84]	1.43 [0.88,2.34]	27.80 [-21.88,77.48]
18-25 Inpatient and Emergency Department	48	0.63 [0.47,0.84]	29	0.79 [0.56,1.13]	1.25 [0.79,1.98]	11.40 [-17.92,40.72]
18-35 All Care Settings	99	0.56 [0.44,0.71]	69	0.75 [0.57,0.99]	1.33 [0.94,1.88]	13.22 [-7.95,34.39]
18-35 Inpatient and Emergency Department	64	0.36 [0.28,0.48]	44	0.47 [0.32,0.68]	1.30 [0.85, 1.98]	7.38 [-6.19, 20.96]

IR=Incidence Rate IRR=Incidence Rate Ratio.

1. Data cuts: DP1 9/21, DP2 10/21, DP3 11/21, DP4 12/21
2. Risk = Difference in incident cases per million doses between Moderna and Pfizer-BioNTech (reference) based on adjusted incidence rates, assuming 7 days at risk.

Myocarditis/Pericarditis Study of mRNA Vaccines in Adults in BEST: Summary

- Incidence rate of myocarditis/pericarditis post-vaccination is highest among males aged 18-25 years
- Head-to-head comparison between Moderna and Pfizer-BioNTech vaccines
  - Results do not support a statistically significant risk difference between two vaccines for males aged 18-25 years
  - IRR attenuated for 18-35 years and when restricted to Inpatient/ED care settings
- Study published
  - Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases. June 2022 (Wong *et al*. Lancet 2022)

Signal Evaluation Studies in Older Adults Vaccines Primary Series

- **Exposure:** Pfizer-BioNTech and Moderna [primary Series (doses 1 and 2)], and Janssen COVID-19 vaccines
- **Population:** ≥65 years
- **Database:** CMS Medicare
- **Study design:** Self-controlled
- **Outcomes:** Acute Myocardial Infarction, Pulmonary Embolism, Disseminated Intravascular Coagulation, and Immune Thrombocytopenia

Signal Evaluation Studies in Older Adults Monovalent Booster Dose

- **Exposure:** Pfizer-BioNTech and Moderna monovalent third/Booster dose COVID-19 vaccines
- **Population:** ≥65 years
- **Database:** CMS Medicare
- **Study design:** Self-controlled
- **Outcomes:** Acute Myocardial Infarction, Pulmonary Embolism, Immune Thrombocytopenia, Myocarditis/Pericarditis, and Bell's Palsy

COVID-19 Vaccine Safety Monitoring: Regulatory Impact Monkeypox Vaccine Monitoring

Hui Lee Wong, PhD MSc
U.S. FDA CBER

Outline

- BEST Initiative Data Network
- COVID-19 Vaccine Safety Monitoring
  - Descriptive Monitoring
  - Signal Detection
  - Signal Evaluation
  - Regulatory Impact
- Monkeypox Vaccine Monitoring

Regulatory Contribution & Impact of BEST to COVID-19 Pandemic Response

- Studies generated a significant level of scientific evidence for the safety profile of vaccines in a timely manner.
- Contribution to vaccines effectiveness profile
- Regulatory and public health contribution
  - Vaccine and Related Biologic Products Advisory Committee (VRBPAC) meetings
  - Emergency Use Authorizations (EUA) and approval
  - CDC Advisory Committee on Immunization Practices (ACIP) recommendations
  - FDA benefit-risk assessments of vaccines
- Contribution to national pandemic response and international regulators

COVID-19 Vaccines Evaluation
Regulatory & Public Health Impact: Example

Communicated safety profile of vaccines

Risk of myocarditis and pericarditis after the COVID-19 mRNA vaccination in the USA: a cohort study in claims databases

Hui-Lee Wong, Mao Hu*, Cindy Ke Zhou, Patricia C Lloyd, Kandace L Amend, Daniel C Beachler, Alex Secora, Cheryl N McMahill-Walraven, Yun Lu, Yue Wu, Rachel P Ogilvie, Christian Reich, Djeneba Audrey Djibo, Zhiruo Wan, John D Seeger, Sandia Akhtar, Yixin Jiao, Yoganand Chillarige, Rose Do, John Hornberger, Joyce Obidi, Richard Forshee, Azadeh Shoaibi, Steven A Anderson*

Summary

Background Several passive surveillance systems reported increased risks of myocarditis or pericarditis, or both, after COVID-19 mRNA vaccination, especially in young men. We used active surveillance from large health-care databases to quantify and enable the direct comparison of the risk of myocarditis or pericarditis, or both, after mRNA-1273 (Moderna) and BNT162b2 (Pfizer–BioNTech) vaccinations.

Methods We conducted a retrospective cohort study, examining the primary outcome of myocarditis or pericarditis, or both, identified using the International Classification of Diseases diagnosis codes, occurring 1–7 days post-vaccination, evaluated in COVID-19 mRNA vaccinees aged 18–64 years using health plan claims databases in the USA. Observed (O) incidence rates were compared with expected (E) incidence rates estimated from historical cohorts by each database. We used multivariate Poisson regression to estimate the adjusted incidence rates, specific to each brand of vaccine, and incidence rate ratios (IRRs) comparing mRNA-1273 and BNT162b2. We used meta-analyses to pool the adjusted incidence rates and IRRs across databases.

Lancet 2022; 399: 2191–99

See Comment page 2168

*Joint first authors

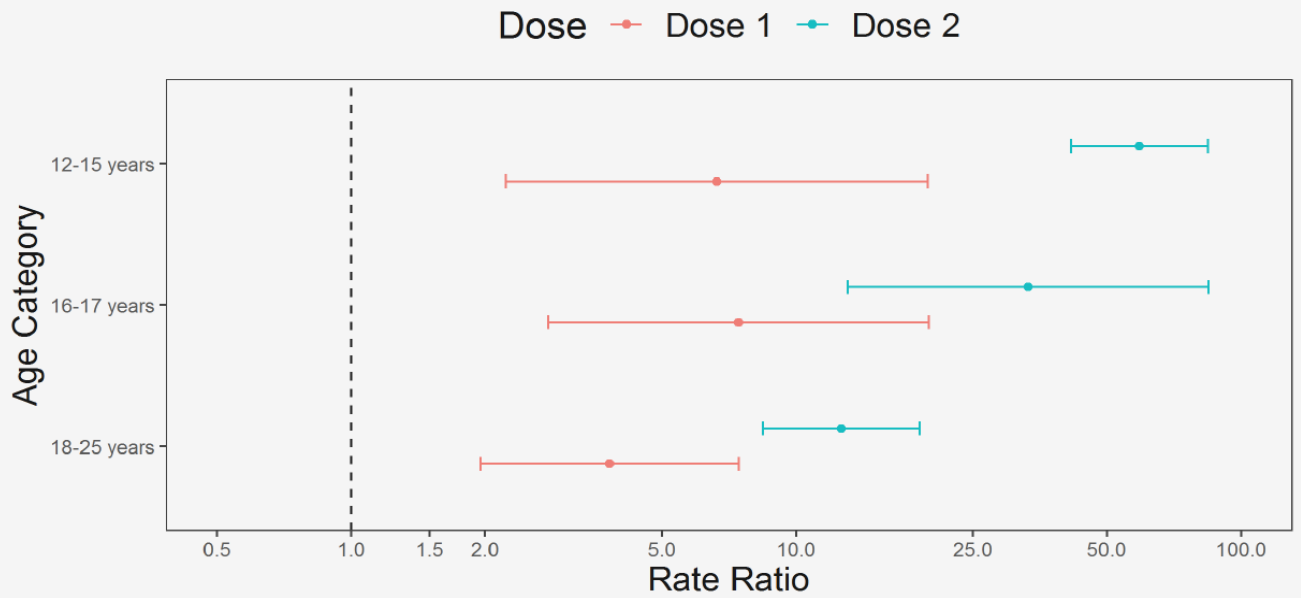
Office of Biostatistics and Pharmacovigilance, Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA (H-L Wong PhD, C K Zhou PhD, P C Lloyd PhD, Y Lu PhD, J Obidi PhD, R Forshee PhD, A Shoaibi PhD, S A Anderson PhD);

COVID-19 Vaccines Evaluation
Regulatory & Public Health Impact: Example

Supported EUA and approval of vaccines

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

Observed/Expected Rate Ratio of Myocarditis/Pericarditis Risk after Receipt of Pfizer-BioNTech COVID-19 vaccine in Males 12-25 years of age, by dose



VRBPAC. Safety Surveillance of COVID-19 Vaccines in Children and Adolescents; June 14, 2022

COVID-19 Vaccines Evaluation
Regulatory & Public Health Impact: Example

Risk estimates of myocarditis/pericarditis as input for benefit-risk assessment of vaccines

Benefit-risk assessment, VRBPAC

Benefits-Risks of Pfizer-BioNTech COVID-19 Vaccine for Ages 5 to 11 Years

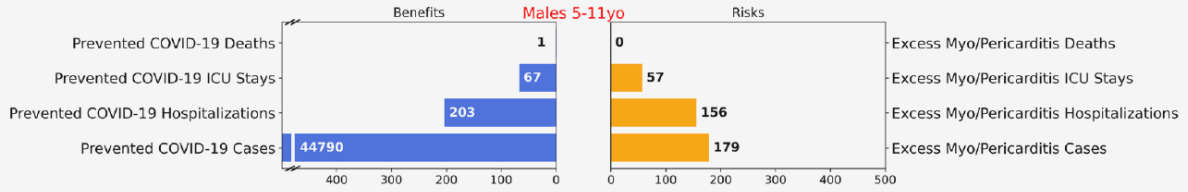
Hong Yang, Ph.D.

FDA VRBPAC, October 26, 2021

Scenario 1 (Base)

- COVID incidences the week of September 11, 2021
- Vaccine efficacy 70% against case and 80% against hospitalization
- Rate of excess myocarditis: OPTUM data for ages 12-15 years

MALES (Cases Per Million)



VRBPAC. Benefits-Risks of Pfizer-BioNTech COVID-19 Vaccine for Ages 5 to 11 Years; October 26, 2021

COVID-19 Vaccines Evaluation
Regulatory & Public Health Impact: Example

Risk estimates of myocarditis/pericarditis following vaccination in pediatric population

Advisory Committee on Immunization Practices (ACIP)

VaST assessment – Review of U.S. monitoring data for consideration of Moderna COVID-19 vaccine in 6–17-year-olds

System	Pfizer-BioNTech vaccine in children & adolescents aged 5–17 years
V-safe	• Patterns of reports for local and systemic reactions similar for all age groups
VAERS	• Reporting rates for myocarditis exceed background for males ages 5–11-, 12–15-, 16–17 (mainly for dose 2 and booster) and for females 12–15-, 16–17 (dose 2 only)
VSD	• Risk for myocarditis/pericarditis is elevated; greatest in age groups 16–17 and 12–15 years, generally higher after dose 2 vs dose 1 primary series and in males vs females • No statistical signals for children ages 5–11 years
BEST	• Risk appears greatest in age groups 16–17 and 12–15 years, generally higher after dose 2 than dose 1 • No statistical signals for children ages 5–11 years • Only statistical signals for 12–15- and 16–17-year-olds: myocarditis/pericarditis

VAERS, Vaccine Adverse Event Reporting System; VSD, Vaccine Safety Datalink; BEST, Biologics Effectiveness and Safety system

11

ACIP. COVID-19 Vaccine Safety Technical (VaST) Work Group; June 23, 2022

Summary

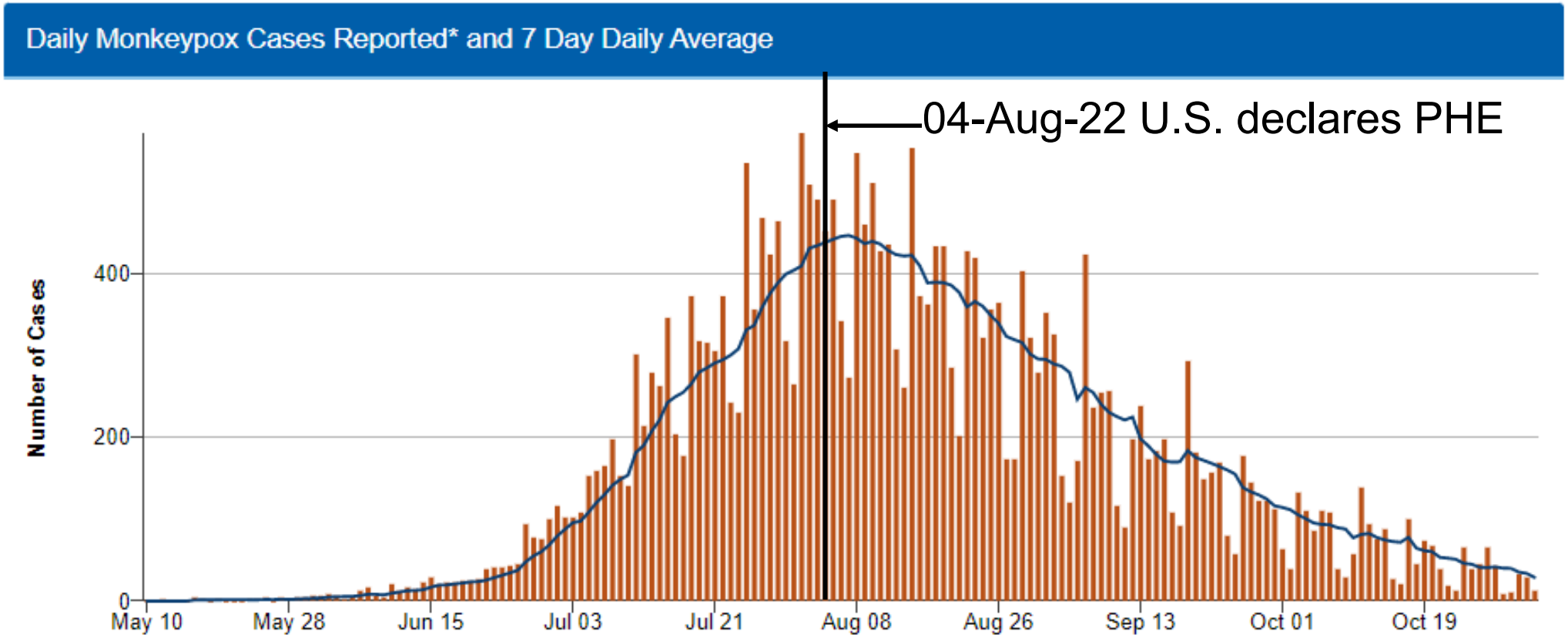
- BEST Initiative facilitates CBER's mission to ensure biologic products safety and effectiveness through active surveillance.
- BEST generates data for evidence-based regulatory decisions in a timely manner.
- CBER enhances and expands BEST infrastructure and capacity to remain agile and efficient.
- Advanced and up-to-date capabilities of BEST generated a rapid and comprehensive response to the COVID-19 pandemic.

Outline

- BEST Initiative Data Network
- COVID-19 Vaccine Safety Monitoring
  - Descriptive Monitoring
  - Signal Detection
  - Signal Evaluation
  - Regulatory Impact
- Monkeypox Vaccine Monitoring

2022 Monkeypox Outbreak: Background

- **Monkeypox infection**: caused by monkeypox virus
- **Primary population**: gay, bisexual, and other men who have sex with men



https://www.cdc.gov/poxvirus/monkeypox/response/2022/mpx-trends.html

Monkeypox Vaccine Monitoring

2 vaccines available for use in US

- **JYNNEOS:**
  - Licensed to prevent monkeypox and smallpox in adults ≥18 years
  - **Primary vaccine used in outbreak**
- **ACAM2000**:
  - Licensed to prevent smallpox
  - Expanded Access IND for use against monkeypox
  - Known serious adverse events

Descriptive monitoring of JYNNEOS underway

- **Study population:** persons aged 12-64 years
- **Data sources**: administrative claims and IIS

Adverse Events
Myocarditis / Pericarditis
Cardiomyopathy
Myelitis/Encephalomyelitis
Deep Vein Thrombosis
Pulmonary Embolism
Bell's Palsy
Anaphylaxis
Transverse Myelitis
Guillain-Barré Syndrome
Non-Hemorrhagic Stroke
Acute Myocardial Infarction

Conclusion

- BEST Initiative leverages its infrastructure and capacity to
  - Generate data for evidence-based regulatory decisions
  - Rapidly respond to emerging public health concerns
  - Expand the scientific evidence base
  - Inform and promote public health

Acknowledgements

- Steven A. Anderson
- Richard Forshee
- CBER Surveillance Team: Tainya C. Clarke, Joyce Obidi, Kristin Sepúlveda, Joann F. Gruber, Patricia C. Lloyd
- CBER OBPV
- Federal Partners: CMS, VA, CDC
- FDA Partners: Acumen, Blue Health Intelligence, CVS Health, HealthCore, IBM, IQVIA, OHDSI, Optum, RTI Health Solutions

www.bestinitiative.org

Session II: Sentinel System Operations and Coordinating Center Perspectives

- **Darren Toh,** Harvard Pilgrim Health Care Institute
- **Judith Maro,** Harvard Pilgrim Health Care Institute
- **Efe Eworuke**, US, Food and Drug Administration, CDER
- **Yandong Qiang**, US, Food and Drug Administration, CDER

Sentinel

Sentinel Operations Center

Darren Toh, Principal Investigator

Judith Maro, Operations Lead

November 15, 2022

Disclaimer

The views expressed in all presentations represent those of the presenters and do not necessarily represent the official views of the U.S. Food and Drug Administration.

Collaborating Institutions

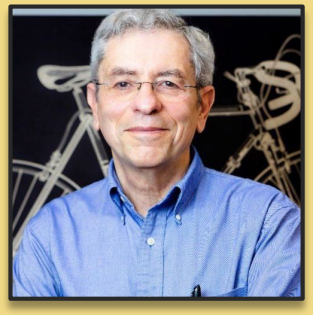
Sentinel Operations Center Leadership Team

Sentinel Operations Center Executive Committee

Judith Maro
Operations Chief

Anjum Khurshid
Lead Data Scientist

Darren Toh
Principal Investigator



Richard Platt
Co-Investigator

Noelle Cocoros
Lead Epidemiologist

Sentinel Operations Center Program Managers

Joy Kolonoski
Data Operations Portfolio

Meighan Rogers Driscoll
Innovation Center Liaison & COVID-19 Portfolio

Christine Halbig
Infrastructure Portfolio

Stephen Keylor
Administrative Portfolio

Sentinel Distributed Database Statistics, 2000-2022

874 million
person-years of data

64 million
individuals currently accruing new data

17 billion
pharmacy dispensings

16 billion
unique medical encounters

6 million
deliveries with a mother-infant linkage

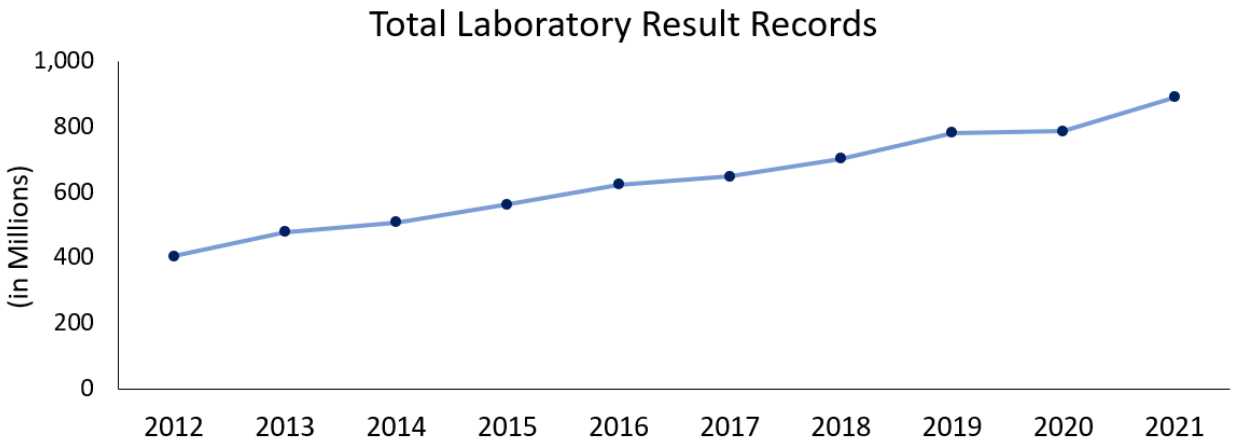
Clinical Data in Sentinel Distributed Database, 2000-2022

Table	DP Count	Member Count	Record Count
Laboratory Results	12	93,673,498	7,385,600,657
Vital Signs	6	7,014,002	215,433,394
Prescribing	2	4,361,680	177,402,763

Members with Medical and Drug Coverage who Have at least One Vital Sign Measurement, by Vital Sign Measure

Vital Sign	Member Count
Diastolic Blood Pressure	4,927,124
Systolic Blood Pressure	4,928,145
Weight	5,065,358
Height	4,726,237

Growth in Laboratory Result Data By Year



Rapid Sentinel Distributed Database Statistics, 2017-2022

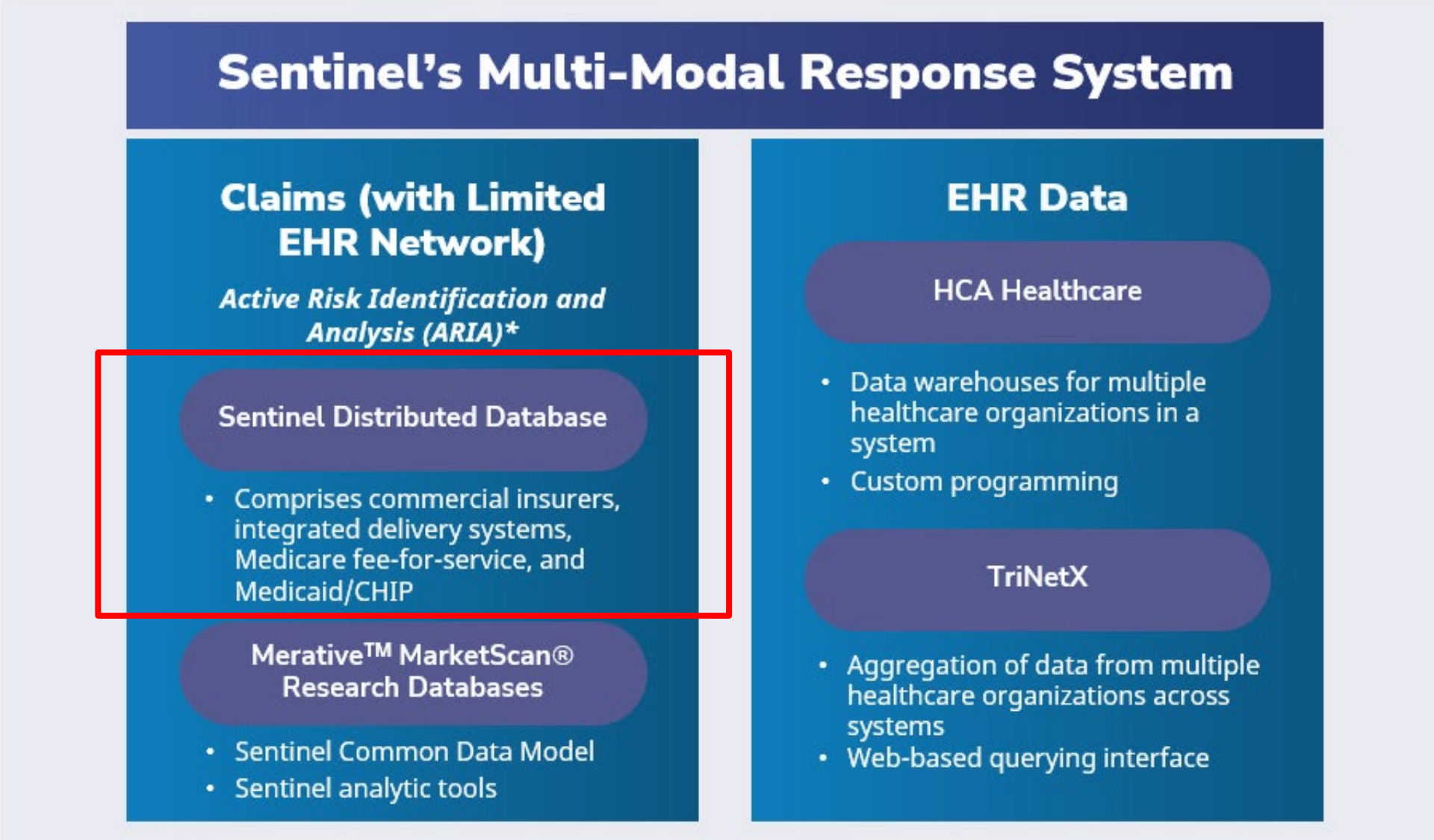
289 million
person-years of data

31 million
individuals currently accruing new data

2 billion
pharmacy dispensings

2 billion
unique medical encounters

1.5 million
deliveries with a mother-infant linkage



**Note: The Active Risk Identification and Analysis (ARIA) System is comprised of the Sentinel Distributed Database, the Sentinel Common Data Model, and Sentinel analytic tools.*

Sentinel

- Active Risk Identification and Analysis (ARIA) queries
- COVID-19 activities
- Expansion of data resources
- Expansion of tools
- Updates on signal identification in the Sentinel System

- **Active Risk Identification and Analysis (ARIA) queries**
- COVID-19 activities
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Summary of ARIA Analyses, Fiscal Year 2022

Distributed Queries in Fiscal Year 2022

Query Type	Total
Descriptive	37
Inferential	6
Patient Episode Profile Retrieval	3
Signal Identification	2
Total	48

Over the course of fiscal year 2022, ARIA supported work on **79 analyses assessing 97 product-outcome pairs**

Public sharing of findings, by the numbers:

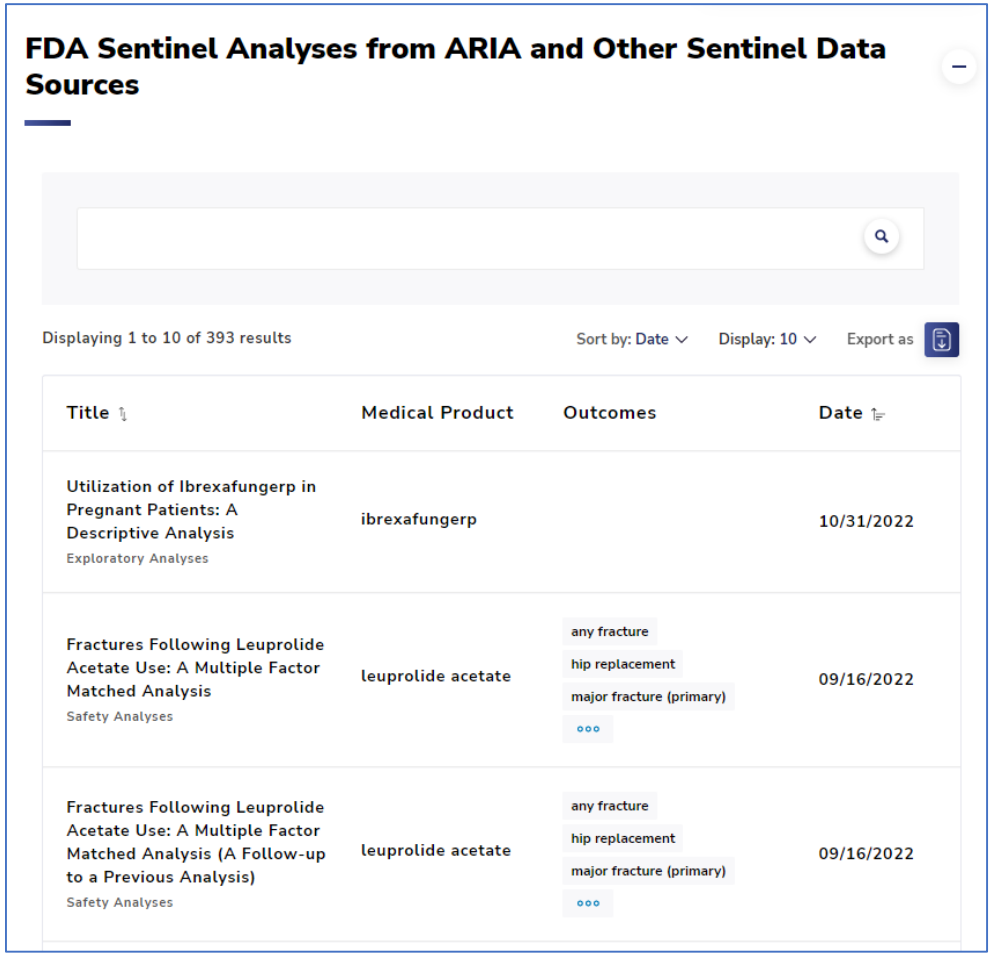
48 reports posted to the Sentinel website

7 analytic packages posted to the Sentinel website

27 public presentations and publications of results

8 regulatory impacts posted to the Sentinel website

Regulatory Decisions Supported by ARIA



FDA Sentinel Analyses from ARIA and Other Sentinel Data Sources

Displaying 1 to 10 of 393 results

Sort by: Date | Display: 10 | Export as

Title	Medical Product	Outcomes	Date
Utilization of Ibrexafungerp in Pregnant Patients: A Descriptive Analysis Exploratory Analyses	ibrexafungerp		10/31/2022
Fractures Following Leuprolide Acetate Use: A Multiple Factor Matched Analysis Safety Analyses	leuprolide acetate	any fracture hip replacement major fracture (primary) ooo	09/16/2022
Fractures Following Leuprolide Acetate Use: A Multiple Factor Matched Analysis (A Follow-up to a Previous Analysis) Safety Analyses	leuprolide acetate	any fracture hip replacement major fracture (primary) ooo	09/16/2022

Lupron Depot/Lupron Depot PED (Leuprolide Acetate) & Major Fracture, Any Fracture, Hip Replacement, and Temporomandibular Joint Replacement

Because results from this study provided no evidence for an increased risk of fracture following leuprolide use during childhood, FDA determined that no regulatory action is needed at this time.

https://www.sentinelinitiative.org/studies/drugs/lupron-depotlupron-depot-ped-leuprolide-acetate

Eliquis (Apixaban), Pradaxa (Dabigatran), and Xarelto (Rivaroxaban) & Severe Uterine Bleed

These findings contributed to the following class-wide label change for oral ACs - "The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including [PRODUCT name] should be assessed in females of reproductive potential and those with abnormal uterine bleeding."

https://www.sentinelinitiative.org/studies/drugs/eliquis-apixaban-pradaxa-dabigatran-and-xarelto-rivaroxaban-2

https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses

Assessment of Heart Failure in Pregnancy to Support Pre-Market Review of Vericiguat

Background

U.S. FOOD & DRUG ADMINISTRATION

Vericiguat–Under Review

Indicated for heart failure (HF)

Embryo-fetal malformations in animal studies

Should a Risk Evaluation and Mitigation Strategy (REMS) program be required for vericiguat?

Analysis and Findings

Sentinel Distributed Database

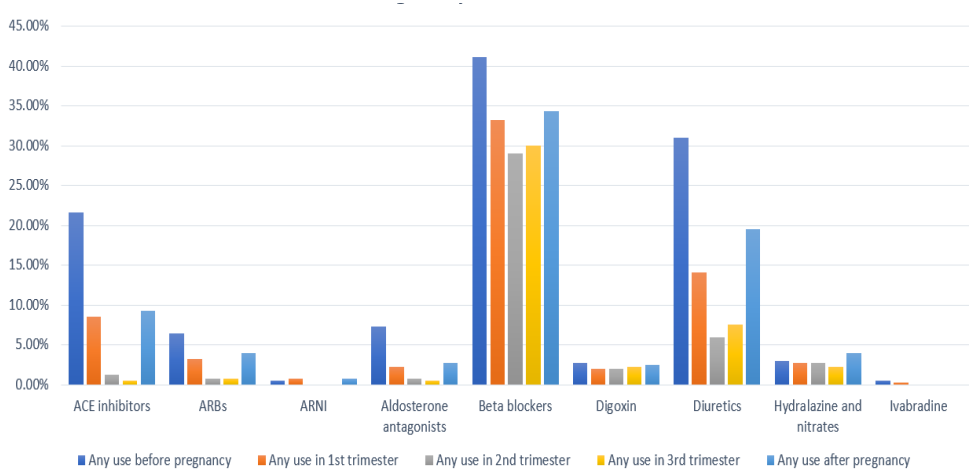
- Estimated prevalence of HF among reproductive age women
- Characterized medication use among pregnancies with HF

Jan. 2010 – Feb. 2020

Jan. 2010 – Mar. 2021

HF rare (0.5%) among women of reproductive age

Potential embryo-toxic HF medication use during pregnancy was rare



Regulatory Recommendation: This information contributed to the FDA's determination that labeling would provide sufficient information to ensure the benefits of vericiguat outweigh its risks.

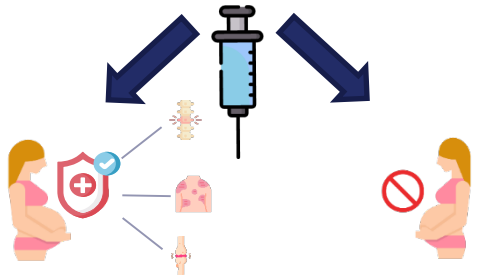
https://www.sentinelinitiative.org/studies/drugs/women-heart-failure

Ixekizumab Utilization among Pregnant Women

RETROSPECTIVE COHORT STUDY AMONG PREGNANCIES ENDING IN LIVE-BIRTH DELIVERY

Sentinel

From March 2016 to June 2021, identify live-birth deliveries and assess ixekizumab (duration ~5x half-life to estimate true biological exposure)



Pregnancies with common indications

Pregnancies regardless of indication

14,823 pregnancies potentially indicated

0.2% exposed during pregnancy:
N = 4, 5, and 15
in 2018, 2019, and 2020

Regulatory Recommendation:

Given the observed increase in the number of pregnancies exposed to ixekizumab over time, continue evaluating potential risks associated with ixekizumab use during pregnancy via the pregnancy safety postmarket requirement (PMR).

- Average age at delivery 33 ± 5 YO
- 2/3^{rds} of pregnancies delivered at term
- Most common indication was plaque psoriasis
- Women similar regardless of whether indicated

Sentinel

- Active Risk Identification and Analysis (ARIA) queries
- **COVID-19 activities**
- Expansion of data resources
- Expansion of tools
- Updates on signal identification in the Sentinel System

COVID-19 Natural History Master Protocol

W. Katherine Yih, PhD, MPH,[1] Wei Hua, MD, PhD, MHS, MS,[2] Christine Draper, BA,[1] Sarah Dutcher, PhD, MS,[2] Candace Fuller, PhD, MPH,[1] Maria Kempner, BA,[1] Brian Kit, MD, MPH,[2] Jennifer Lyons, PhD, MPH,[1] Meighan Rogers Driscoll, MPH,[1] Darren Toh, ScD,[1] Vincent Lo Re III, MD, MSCE[3]

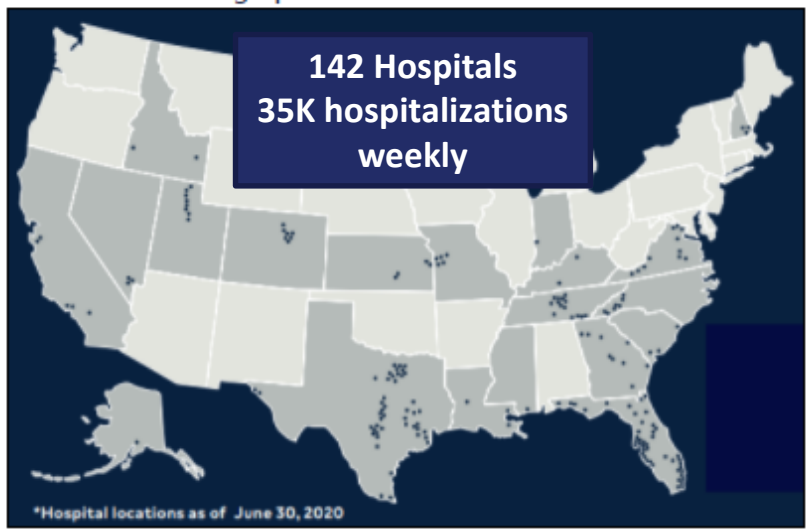
Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 2. Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD; 3. Division of Infectious Diseases, Department of Medicine and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.

Version 3.0

October 9, 2020

Hospitalizations with COVID-19 Diagnosis, Feb 2020 – Jul 2022

Geographic Distribution of Facilities



Among adult hospitalizations from 142 hospitals

45% admitted to ICU

77% ventilated or used oxygen

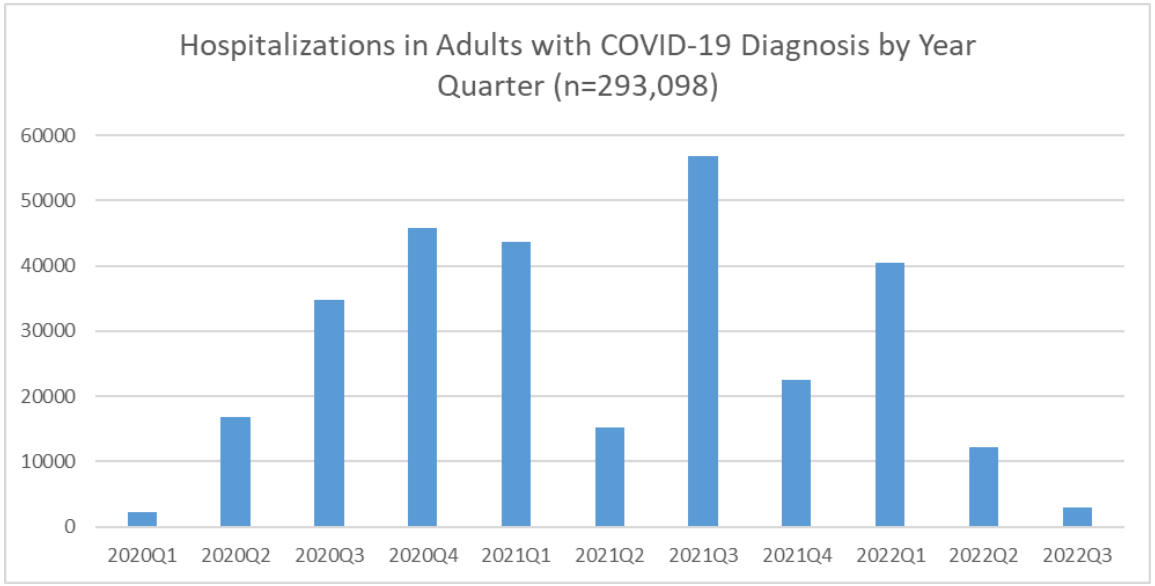
11% death

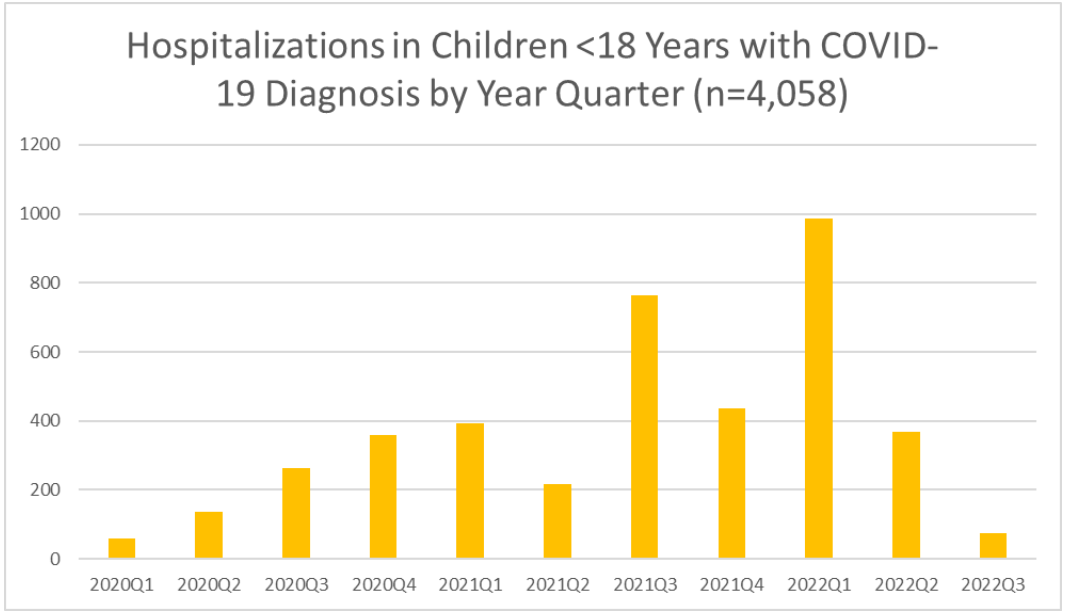
Among pediatric hospitalizations from 128 hospitals

67% in pts <age 12

41% ventilated or used oxygen

<0.5% death





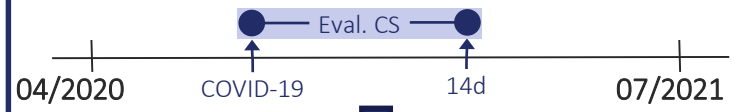
This research was supported (in whole or in part) by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

Systemic Corticosteroid Use for COVID-19 in U.S. Outpatient Setting

RETROSPECTIVE COHORT STUDY

Sentinel

Distributed Database of
Administrative Health Insurance Claims



9.4%

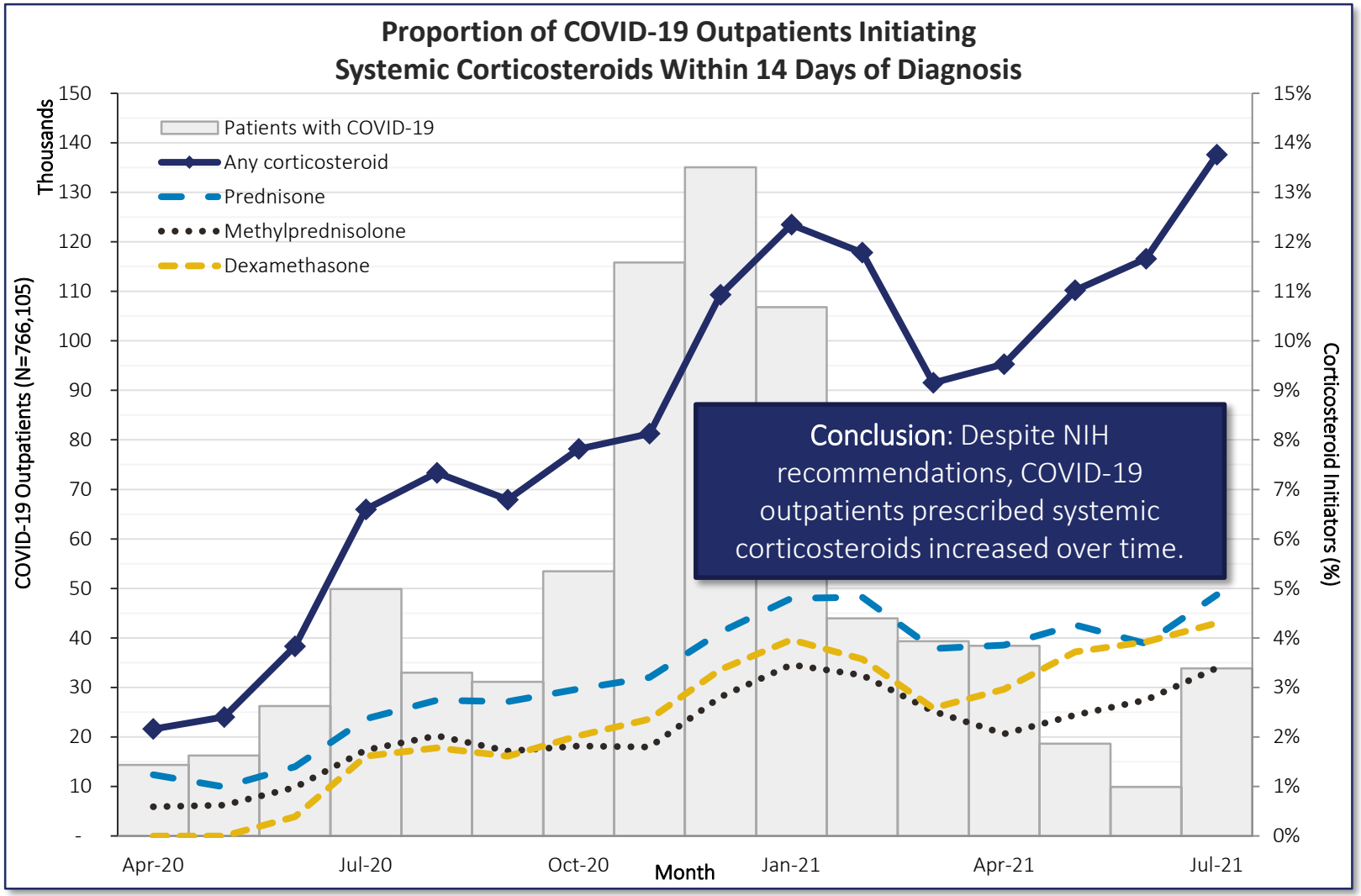
of ~766K COVID-19 outpatients initiated CS within 14 days

At baseline, compared to non-initiators, CS initiators were:

~11 years older (avg. 58 vs. 47 YO)

1.5x more likely to reside in Southern USA

More likely to have chronic conditions



Systemic Corticosteroid Use for COVID-19 in U.S. Outpatient Setting

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

[1]Office of Surveillance and Epidemiology, US Food and Drug Administration, Silver Spring, Maryland

[2]Acumen LLC, Burlingame, California

[3]Department of Veterans Affairs Center for Medication Safety, Hines, Illinois

[4]Department of Population Medicine, Harvard Medical School, Boston, Massachusetts

[5]Aetion Inc, New York, New York

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

COVID-19 Resource Center

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

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

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to update healthcare providers, public health departments, and the public about the availability and use of recommended therapies for COVID-19 and to advise against using unproven treatments that have known or potential harms for outpatients with mild to moderate COVID-19. For patients with mild to moderate COVID-19 who are not hospitalized and who are at increased risk for severe COVID-19 outcomes, several treatment options are now widely available and accessible.

References

1. Geller AI, Lovegrove MC, Lind JN, Datta SD, Budnitz DS. Assessment of outpatient dispensing of products proposed for treatment of prevention of COVID-19 by U.S. retail pharmacies during the pandemic. JAMA Intern Med 2021;181:869-72. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2776456
2. Tsay SV, Bartoces M, Goulin K, Kabbani S, Hicks, LA. Antibiotic prescriptions associated with COVID-19 visits among Medicare beneficiaries, April 2020 to April 2021. JAMA 2022. https://jamanetwork.com/journals/jama/fullarticle/2791077
3. Bradley MC, Perez-Vilar S. Chillarige Y, Dong D. Martinez AI, Weckstein AR, Dal Pan GJ. Systemic corticosteroid use for COVID-19 in U.S. outpatient settings from April 2020 to August 2021. JAMA 2022. https://jamanetwork.com/journals/jama/fullarticle/2791078

NIH COVID-19 Treatment Guidelines

Immunomodulators

For Nonhospitalized Patients With Mild to Moderate COVID-19

The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** to treat outpatients with mild to moderate COVID-19 who do not require hospitalization or supplemental oxygen **(AIIb)**. However, patients who are receiving **dexamethasone** or **another corticosteroid** for other indications should continue therapy for their underlying conditions as directed by their health care providers **(AIII)**.

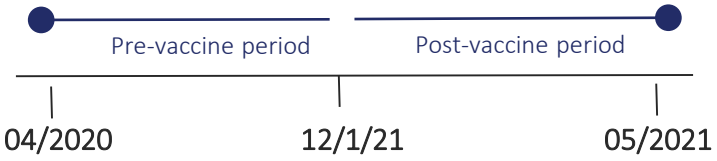
Medicare and FDA data show a significant increase in the number of prescriptions for systemic corticosteroids among nonhospitalized patients with COVID-19[35] despite a lack of safety and efficacy data on the use of systemic corticosteroids in this setting. Systemic glucocorticoids may cause

35. Bradley MC, Perez-Vilar S, Chillarige Y, et al. Systemic corticosteroid use for COVID-19 in US outpatient settings From April 2020 to August 2021. *JAMA*. 2022;327(20):2015-2018. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35394487.

Association of COVID-19 vs. Influenza with Risks of Arterial and Venous Thrombotic Events

RETROSPECTIVE COHORT STUDY

~85K hospitalized with COVID-19, two periods
~8K hospitalized with 2018-19 seasonal influenza



ATE: acute myocardial infarction, ischemic stroke
VTE: deep vein thrombosis, pulmonary embolism

JAMA | Original Investigation

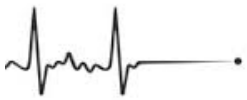
Association of COVID-19 vs Influenza With Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients

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

Hospitalized COVID-19 patients compared to hospitalized influenza patients had:

Increased risk of VTE

Little or no increased risk of ATE

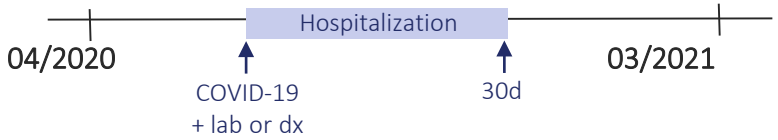


>3X risk of death after an ATE or VTE

Race and COVID-19 outcomes in U.S. (2020-2021)

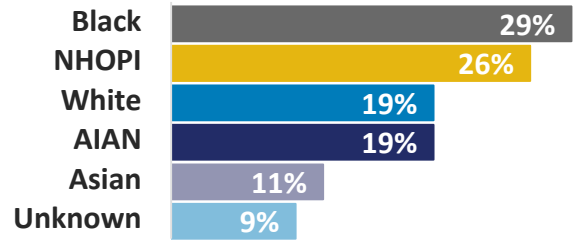
RETROSPECTIVE COHORT STUDY

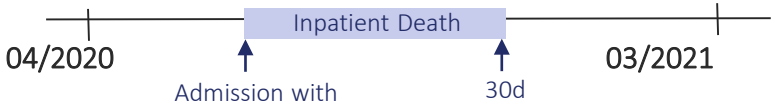
Sentinel



15% of ~841K COVID+ **hospitalized** within 30 days

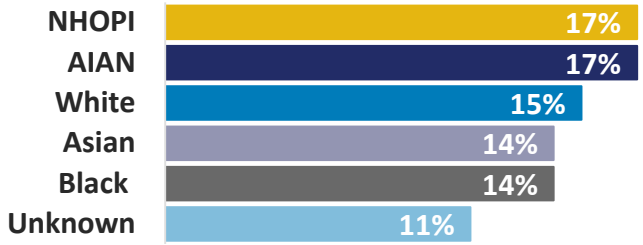
Blacks, Native Hawaiians had highest rates of hosp:





14% of ~133K COVID hospitalized **died** within 30 days

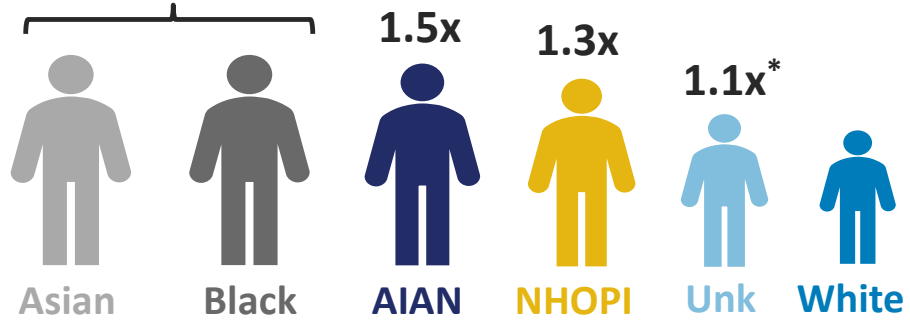
Native Americans, Hawaiians had highest rates of death:



After controlling for demographic, clinical and socioeconomic differences at baseline, **minoritized groups** had **increased odds** for **hospitalization** and **mortality** following COVID-19 relative to their White counterparts in the United States in the first year of the pandemic

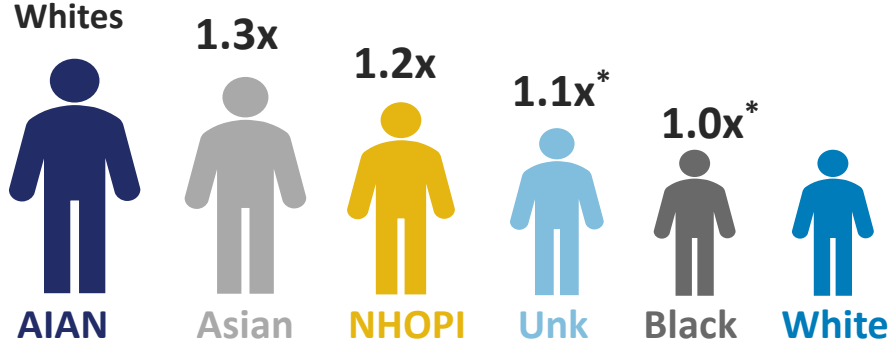
Hospitalization within 30 days of COVID-19 diagnosis or positive lab result

1.6x more likely to be hospitalized compared to Whites



Inpatient mortality within 30 days of COVID-19 hospitalization

1.5x more likely to die compared to Whites

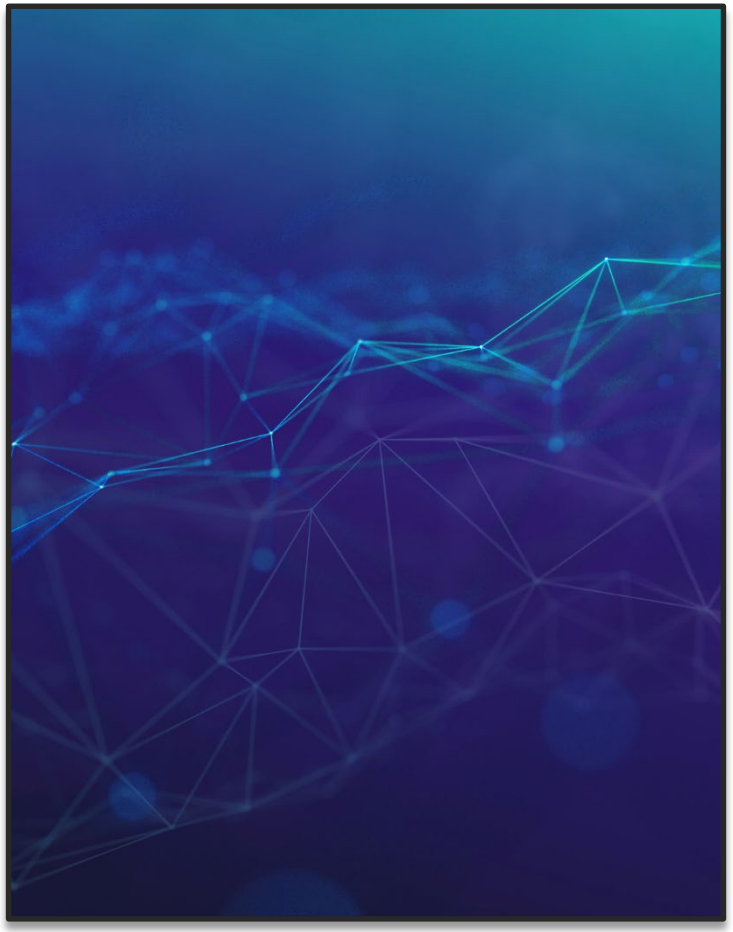


*not statistically significant

AIAN: American Indian or Alaska Native; NHOPI: Native Hawaiian or Other Pacific Islander; Unk: Unknown

Sentinel

- Active Risk Identification and Analysis (ARIA) queries
- COVID-19 activities
- **Expansion of data resources**
- Expansion of tools
- Updates on signal identification in the Sentinel System



New CMS Medicaid Dataset

This is part of a joint agency project supported by the Patient-Centered Outcomes Research Trust Fund (PCORTF) involving the Food and Drug Administration (FDA) and National Institutes of Health/ National Library of Medicine (NIH/NLM) funded by the Office of the Assistant Secretary for Planning and Evaluation

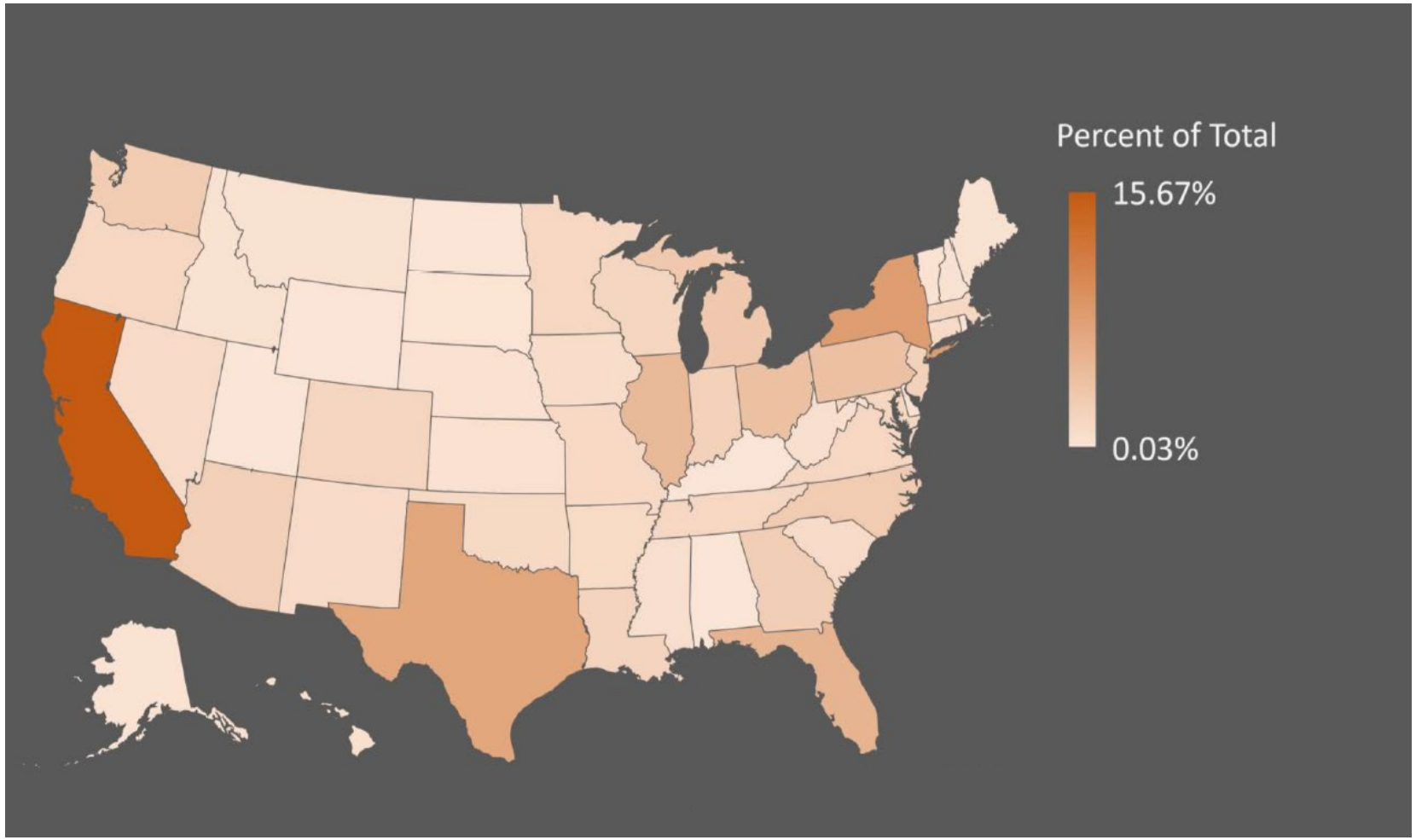
How Adding CMS Medicaid Data will Improve Sentinel

Increases available data on **low-income families**

Increases number of **deliveries**

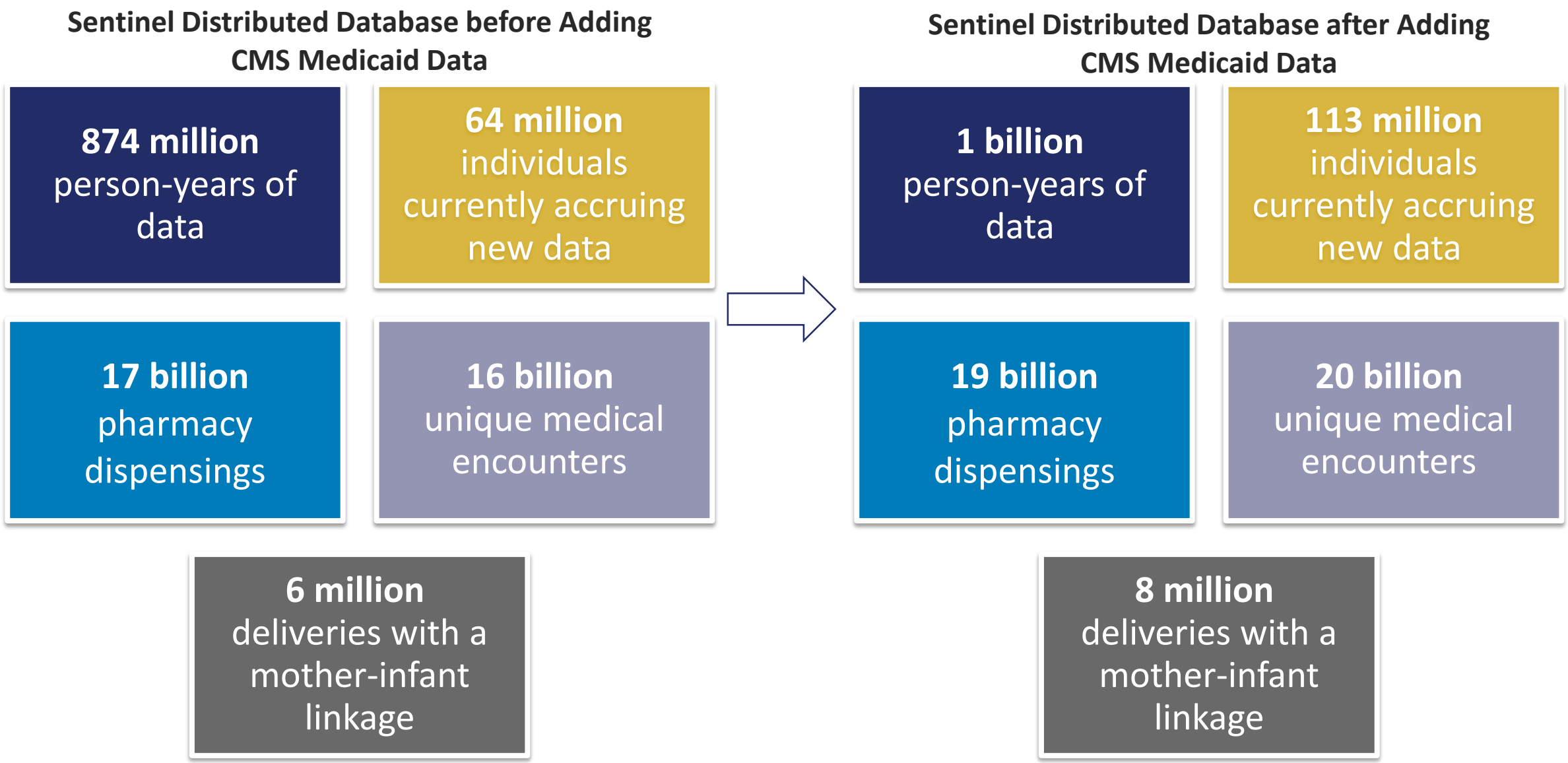
Increases available data on **people with disabilities**

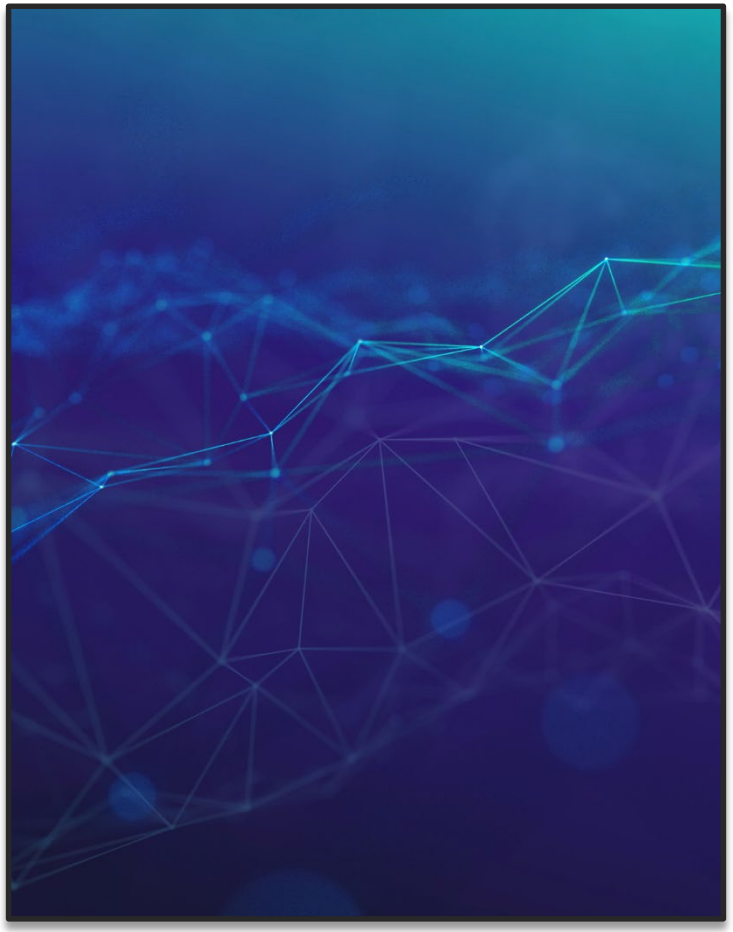
CMS Medicaid Dataset by Jurisdiction



49 jurisdictions wholly or partially included in the Medicaid Dataset

Addition of CMS Medicaid Data to the Sentinel Distributed Database

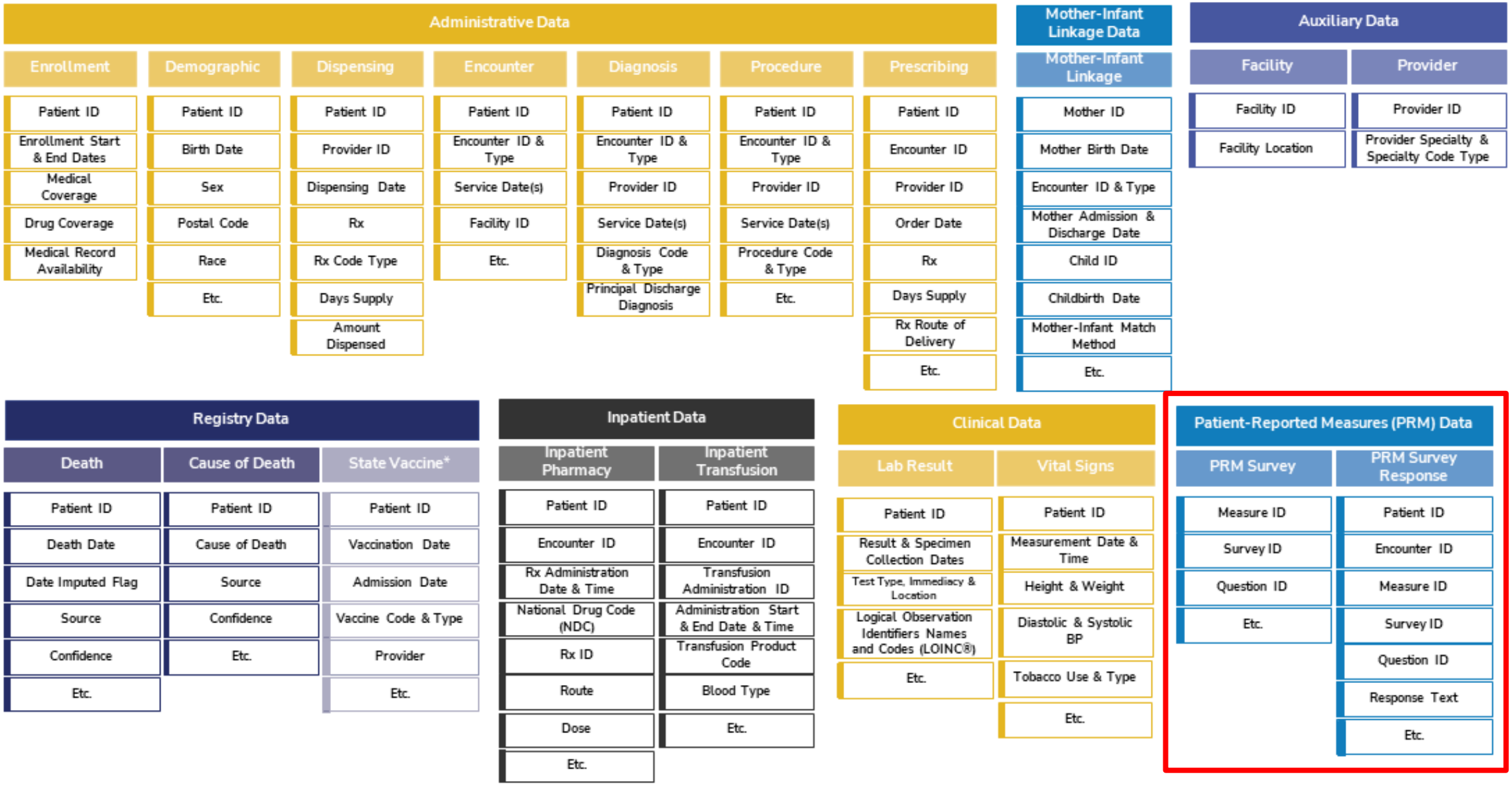




Sentinel Common Data Model Enhancements

Inclusion of Patient-Reported Measures

Sentinel Common Data Model v8.1.0 Enhancements



Inclusion of Patient-Reported Measures

Brief Pain Inventory (BPI)	Brief Pain Inventory – 12 (BPI-12) Brief Pain Inventory – 4 (BPI-4) Brief Pain Inventory 4 (PEGS)
Exercise as a Vital Sign (EVS)	Exercise as a Vital Sign (EVS)
Patient Health Questionnaire (PHQ)	Patient Health Questionnaire - 2 (PHQ-2) Patient Health Questionnaire - 8 (PHQ-8) Patient Health Questionnaire – 9 (PHQ-9) Patient Health Questionnaire Modified for Teens – 2 (PHQ-T2) Patient Health Questionnaire Modified for Teens – 8 (PHQ-T8) Patient Health Questionnaire Modified for Teens – 9 (PHQ-T9)
Medicare Total Health Assessment (MTHA)	Medicare Total Health Assessment – MTHA questions (MTHA) Medicare Total Health Assessment – EVS questions (EVS) Medicare Total Health Assessment – PHQ-2 questions (PHQ-2) Medicare Total Health Assessment – GAD-2 questions (GAD-2)
Alcohol Use Disorders Identification Test (AUDIT)	Alcohol Use Disorders Identification Test (AUDIT-10) Alcohol Use Disorders Identification Test (AUDIT-2) Alcohol Use Disorders Identification Test (AUDIT-C)
Generalized Anxiety Disorder (GAD)	Generalized Anxiety Disorder – 2 (GAD-2) Generalized Anxiety Disorder – 7 (GAD-7)

PROMIS	Patient-Report Outcomes Measurement Information System (Sleep Disturbance) Patient-Report Outcomes Measurement Information System (Upper Extremity) Patient-Report Outcomes Measurement Information System (Ability to Participate) Patient-Report Outcomes Measurement Information System (Anxiety) Patient-Report Outcomes Measurement Information System (Pain Interference) Patient-Report Outcomes Measurement Information System (Depression) Patient-Report Outcomes Measurement Information System (Fatigue) Patient-Report Outcomes Measurement Information System (Anger) Patient-Report Outcomes Measurement Information System (Physical Function)
Your Current Life Situation (YCLS)	Your Current Life Situation (YCLS)
Short Form Health Survey	Short Form Health Survey – 36 Questions (SF-36) Short Form Health Survey – 12 Questions (SF-12)
Columbia Suicide Severity Rating Scale (CSSRS)	Columbia Suicide Severity Rating Scale (CSSRS)
Well Child Visits	Well Child Visits

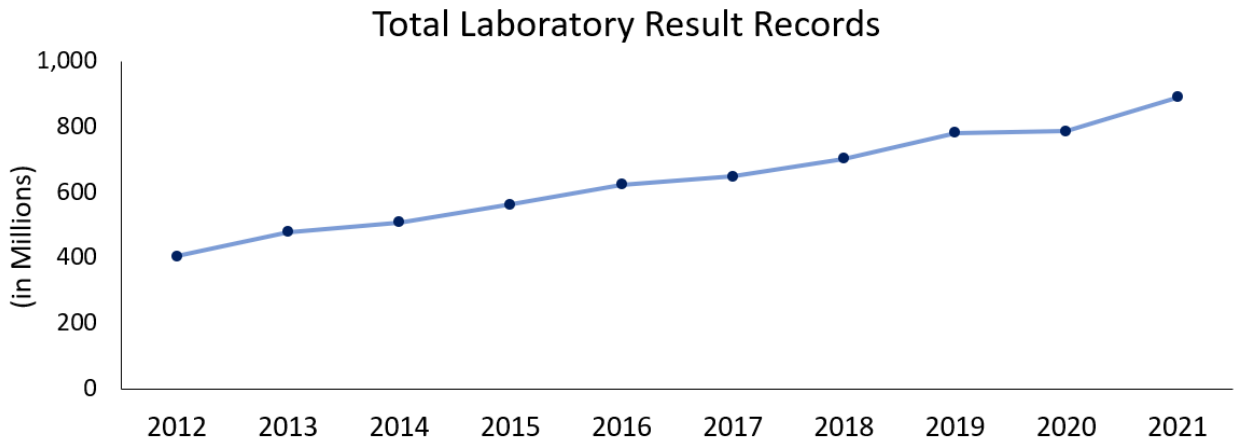
Clinical Data in Sentinel Distributed Database, 2000-2022

Table	DP Count	Member Count	Record Count
Laboratory Results	12	93,673,498	7,385,600,657
Vital Signs	6	7,014,002	215,433,394
Prescribing	2	4,361,680	177,402,763
Patient Reported Measures	3	3,426,375	172,800,409

Members with Medical and Drug Coverage who Have at least One Vital Sign Measurement, by Vital Sign Measure

Vital Sign	Member Count
Diastolic Blood Pressure	4,927,124
Systolic Blood Pressure	4,928,145
Weight	5,065,358
Height	4,726,237

Growth in Laboratory Result Data By Year



Sentinel Innovation Center Roadmap

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

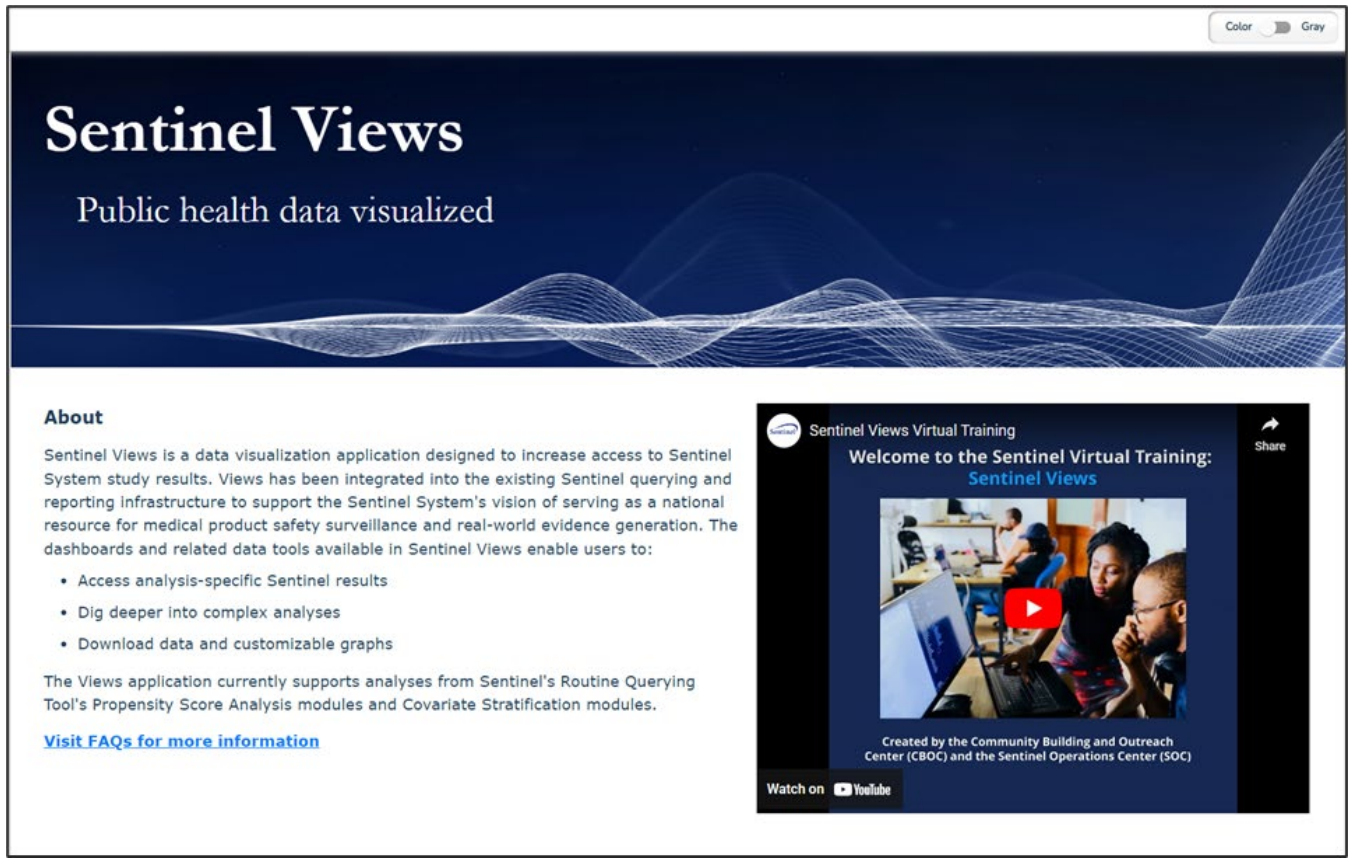
2020 → **2024**

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

Sentinel

- Active Risk Identification and Analysis (ARIA) queries
- COVID-19 activities
- Expansion of data resources
- **Expansion of tools**
- Updates on signal identification in the Sentinel System

Sentinel Views



https://views.sentinelsystem.org/

Sentinel Views

Study List | Study Details

Study Title: Thromboembolic Stroke, Major Extracranial Bleeding, Gastrointestinal Bleeding, and Intracranial Hemorrhage following Direct Oral Anticoagulant Use: An Inverse Probability of Treatment Weighting Analysis

Monitoring Period: 10/19/2010 to 09/30/2015 Source: Aggregate

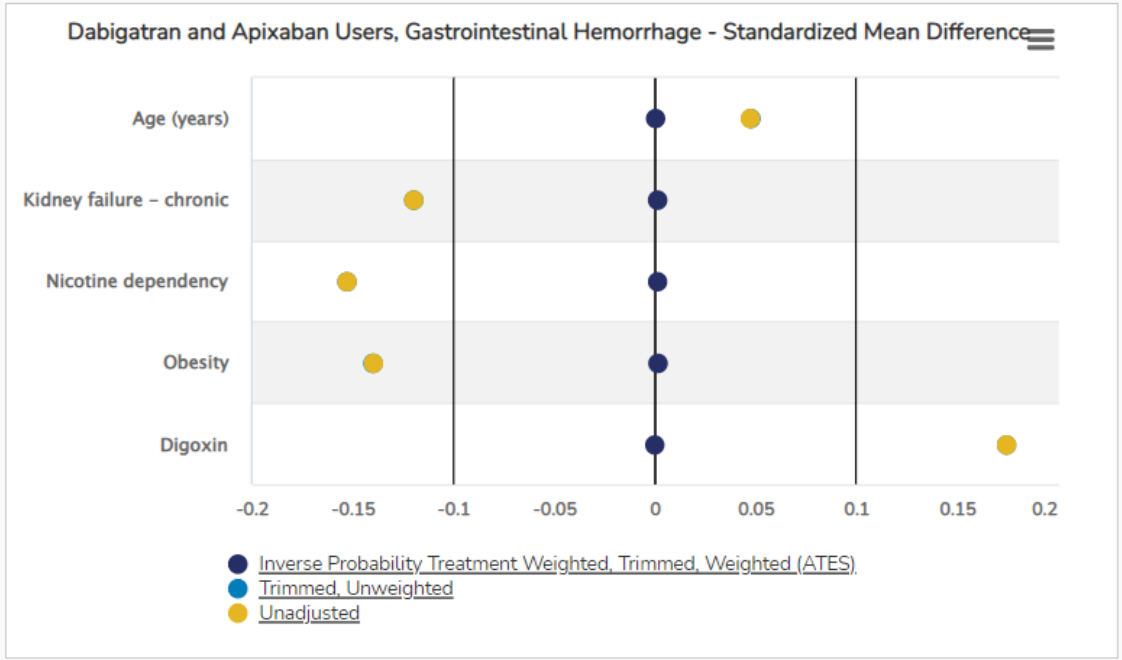
Analysis Group Title: Dabigatran and Apixaban Users, Gastrointestinal Hemorrhage Exposure of Interest: Dabigatran Users Reference Group: Apixaban Users Health Outcome of Interest: Risk of Stroke or Bleeding

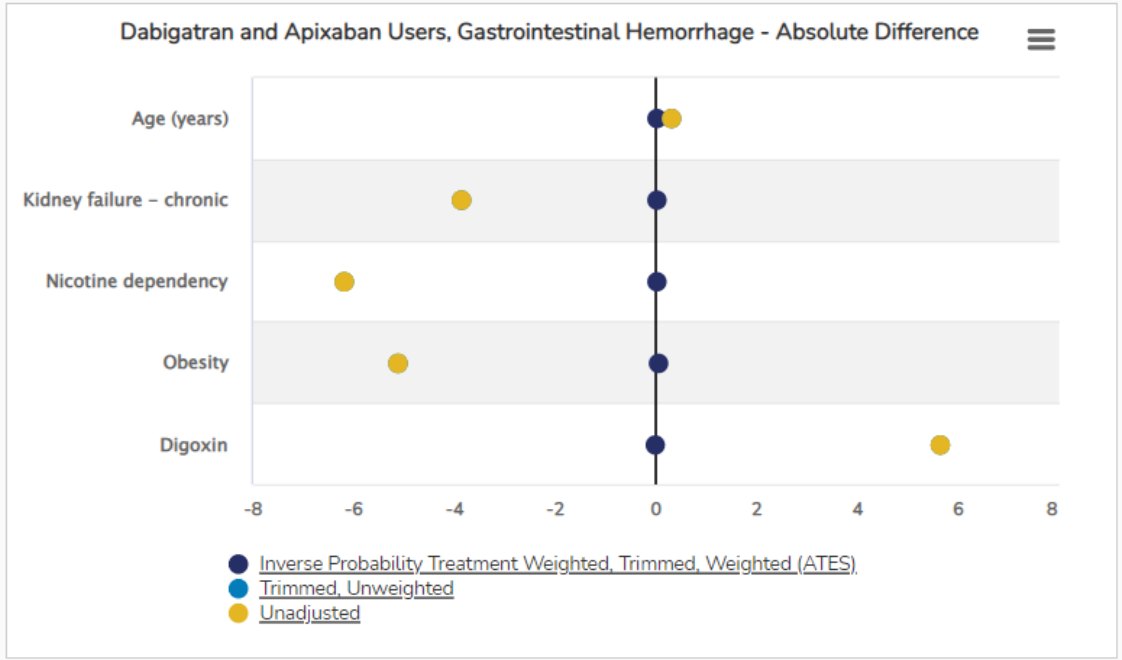
Design Parameters: Enrollment: 183 days; Enrollment Gap: 45 days Adjustment Method: Inverse Probability Treatment Weighted Weighting Method: ATES Model Parameters: Trimmed

Analysis Groups | Summary | Patient Attrition | **Covariate Balance** | Propensity Score Distribution | Results Table | Incidence Rate | Forest Plot | K-M Curve

Show only variables used for PS estimation ☑ Variables : Select Analysis Type : 3 Selected

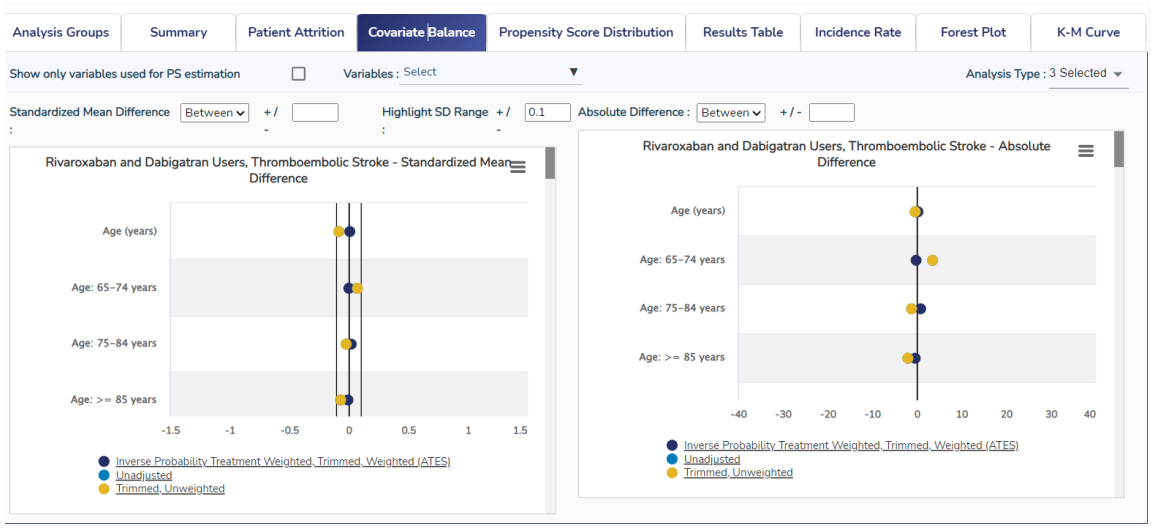
Standardized Mean Difference : Betweer +/- Highlight SD Range : +/- 0.1 Absolute Difference : Betweer +/-



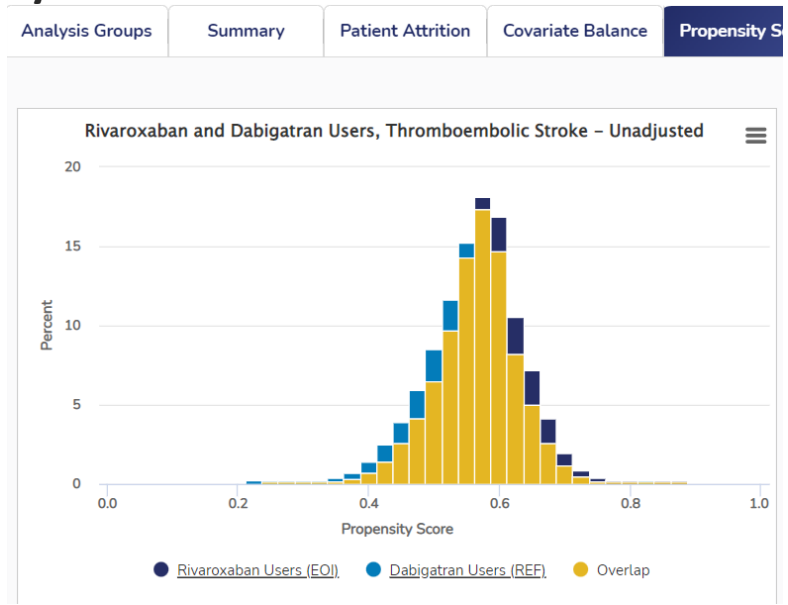


Sentinel Views

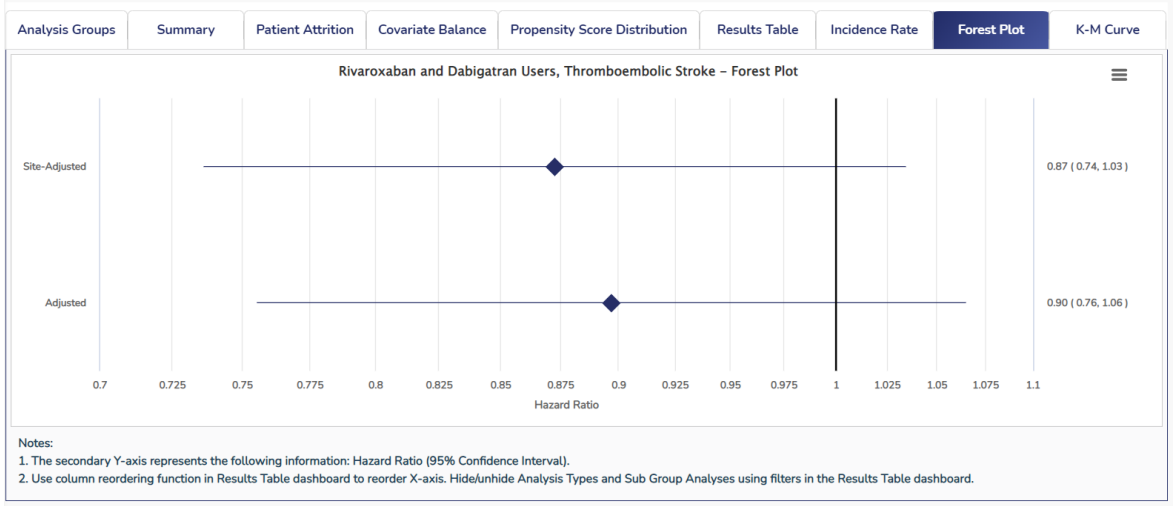
Covariate Balance



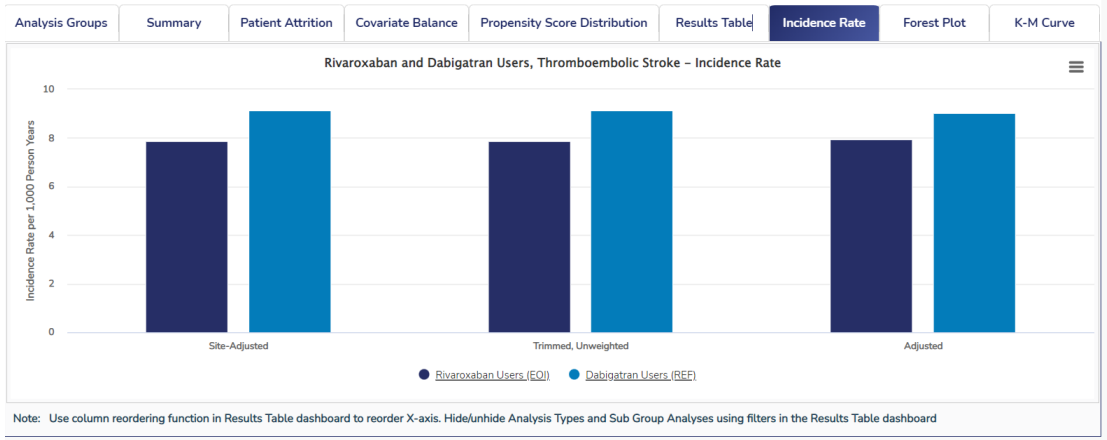
Propensity Score Distribution



Forest Plot



Incidence Rate



Developing the Sentinel System — A National Resource for Evidence Development

Rachel E. Behrman, M.D., M.P.H., Joshua S. Benner, Pharm.D., Sc.D., Jeffrey S. Brown, Ph.D., Mark McClellan, M.D., Ph.D., Janet Woodcock, M.D., and Richard Platt, M.D.

N Engl J Med 2011; 364:498-499

The FDA Sentinel Initiative — An Evolving National Resource

Richard Platt, M.D., Jeffrey S. Brown, Ph.D., Melissa Robb, M.S., Mark McClellan, M.D., Ph.D., Robert Ball, M.D., M.P.H., Michael D. Nguyen, M.D., and Rachel E. Sherman, M.D., M.P.H.

N Engl J Med 2018; 379:2091-2093

The US Food and Drug Administration Sentinel System: a national resource for a learning health system

Jeffrey S. Brown [1], Aaron B. Mendelsohn[1], Young Hee Nam[1], Judith C. Maro [1], Noelle M. Cocoros[1], Carla Rodriguez-Watson[2], Catherine M. Lockhart[3], Richard Platt[1], Robert Ball [4], Gerald J. Dal Pan[4], and Sengwee Toh[1]

Journal of the American Medical Informatics Association, 00(0), 2022, 1–10
https://doi.org/10.1093/jamia/ocac153

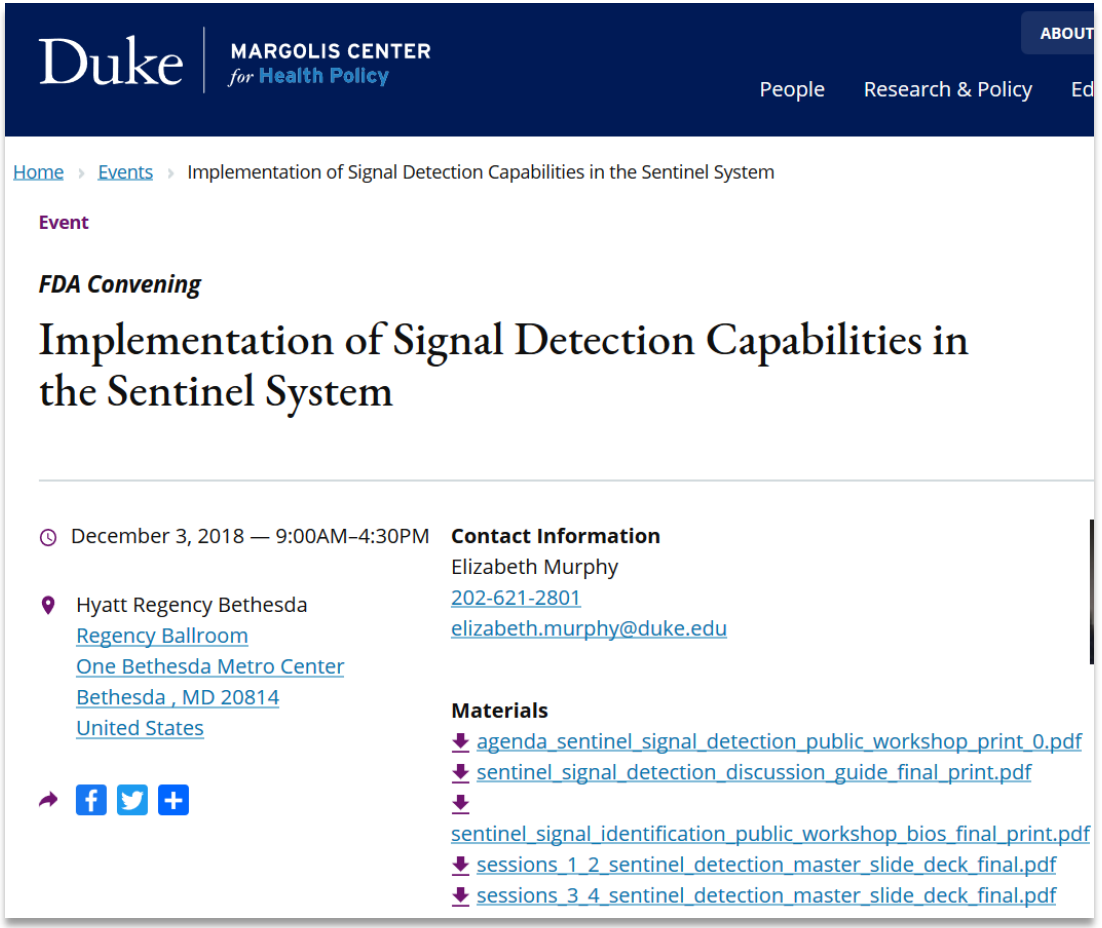
Sentinel

- Active Risk Identification and Analysis (ARIA) queries
- COVID-19 activities
- Expansion of data resources
- Expansion of tools
- **Updates on signal identification in the Sentinel System**

Rewind to 2018 Public Meeting…

- FDA had completed several methods projects exploring the use of TreeScan for Signal Identification in adult populations emphasizing **new user, active comparator cohort designs.**

- FDA was just launching a project on TreeScan in pregnancy.



https://healthpolicy.duke.edu/events/implementation-signal-detection-capabilities-sentinel-system

Proposed Sentinel Signal Identification Process

Integrated Safety Summary

Clinical Trial Data | **Prescribing Information**

Signal identification led by **Divisions of Pharmacovigilance** and Sentinel Program Team

Follow up investigations to be conducted by **Divisions of Epidemiology**

1. Select 1 product
2. Choose study design(s) or tool
3. Conduct analysis
4. Review and classify statistical alerts
5. Integrate results with other sources of information

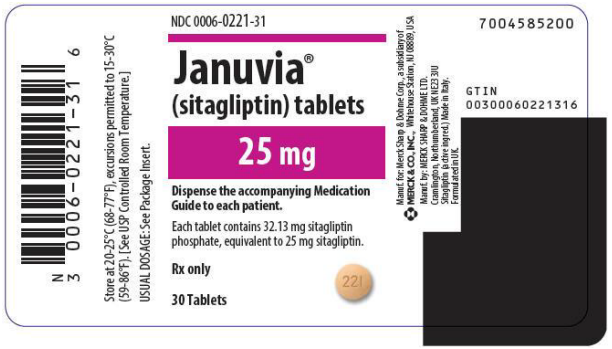
Identify Outcome for Further Evaluation (if any)

20

https://healthpolicy.duke.edu/events/implementation-signal-detection-capabilities-sentinel-system

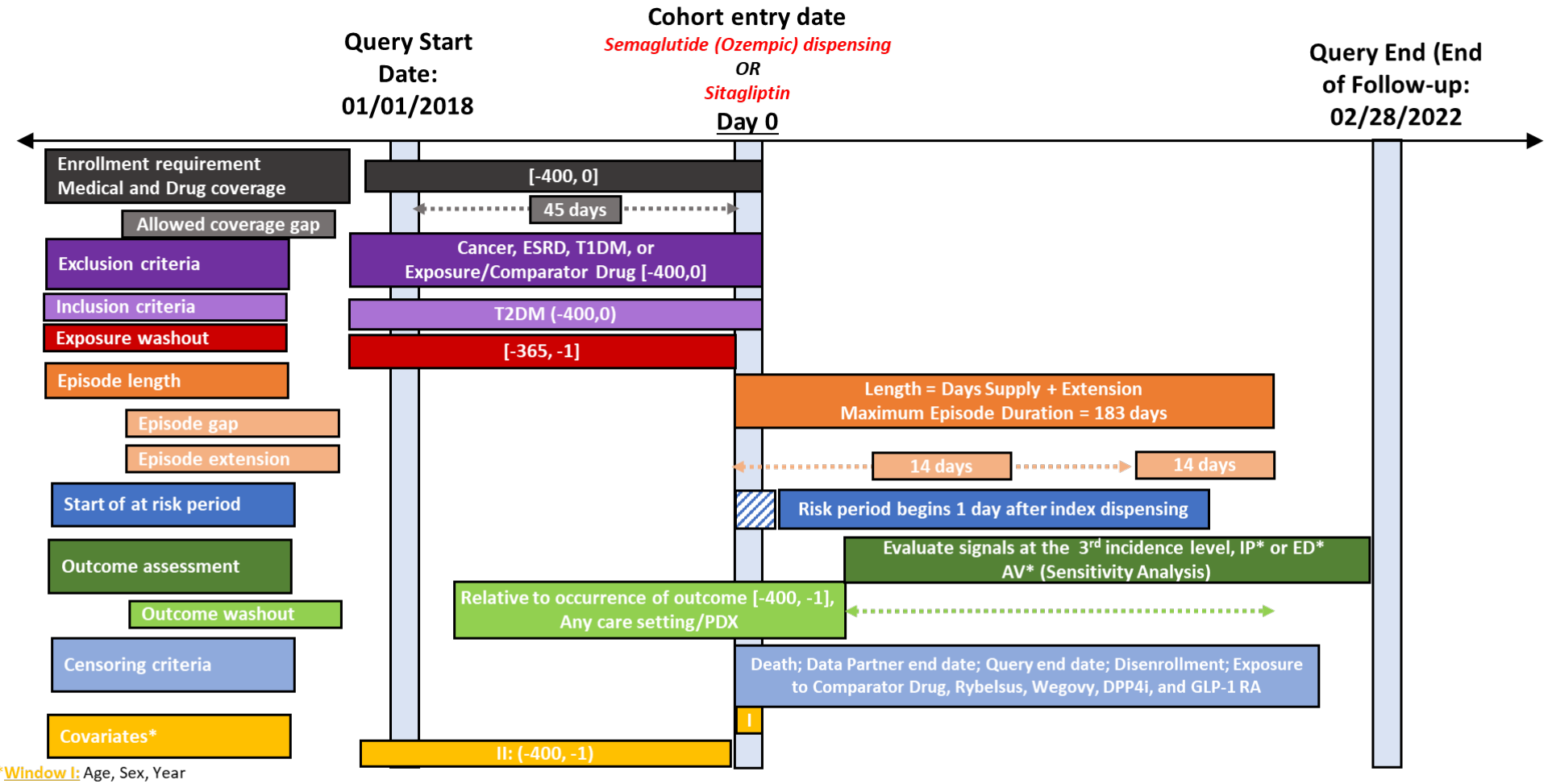
Initial Pilot Projects Selected: Ozempic and Zarxio

1. Anti-diabetic Drugs



2. Biosimilars

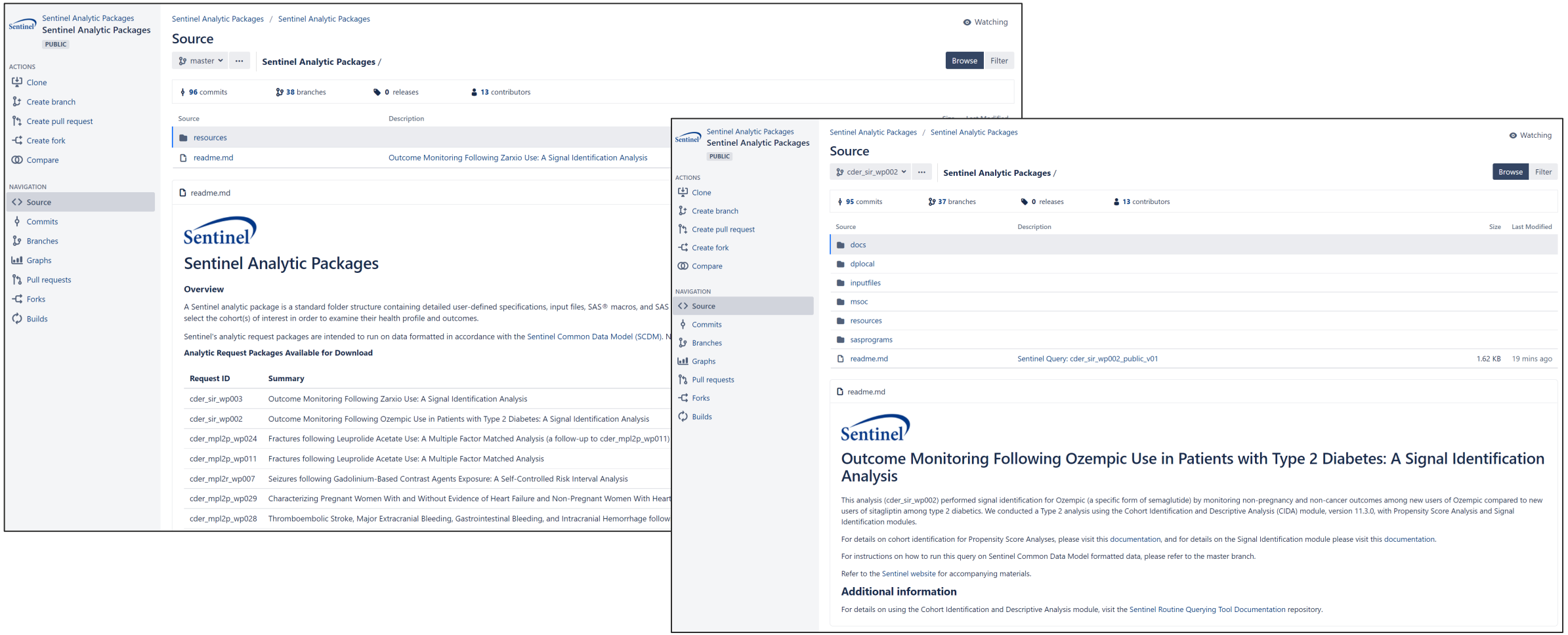
https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2
https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-zarxio-use-signal



*Window I: Age, Sex, Year

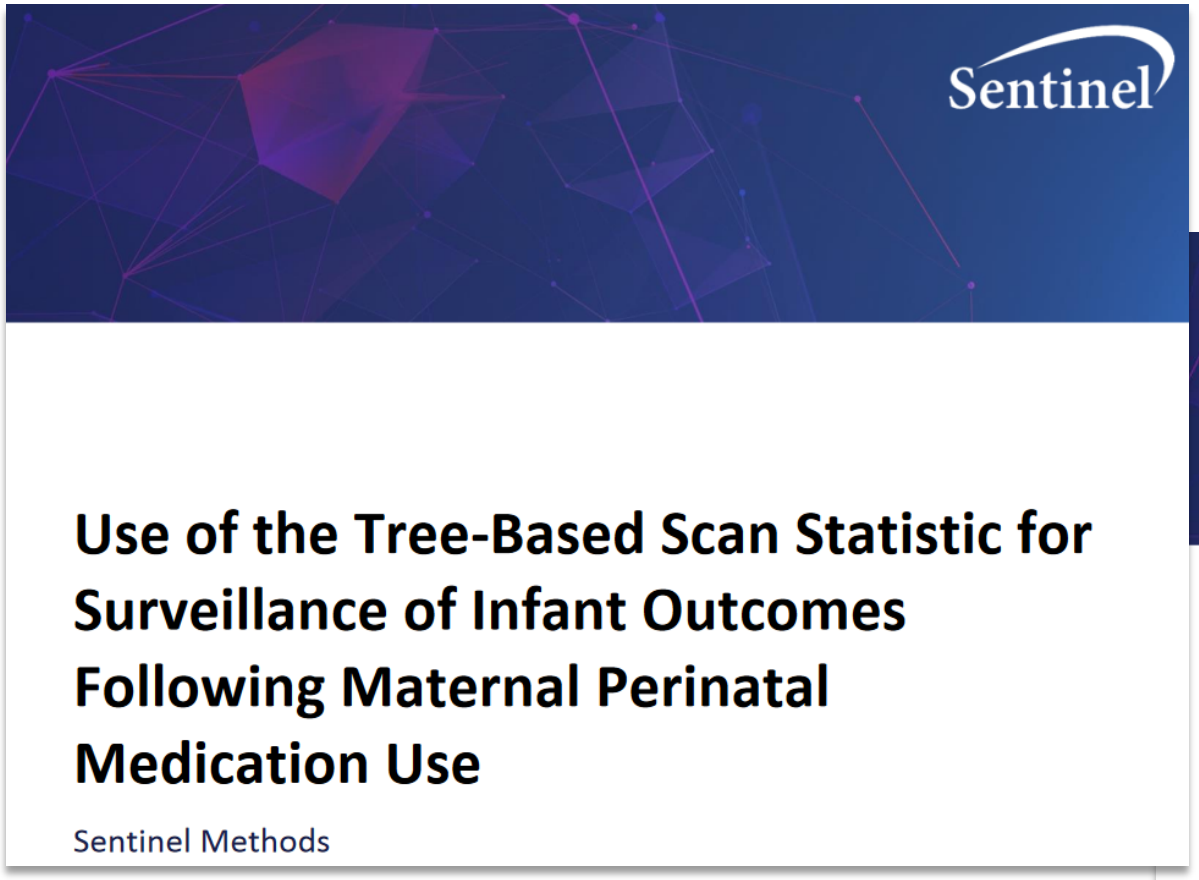
*Window II: CCI, Acquired hypothyroidism, ADHD, Conduct Disorders, Hyperkinetic Syndrome, AMI, Alzheimer's disease, Anemia, Anxiety Disorders, Asthma, Arrhythmia, Autoimmune Disease, Autism Spectrum Disorder, Bacterial infection, Benign prostatic hyperplasia, Cataracts, Chronic kidney disease, COPD, Coagulopathy, Cystic Fibrosis and other metabolic developmental disorders, Cerebral palsy, Degenerative disease of central nervous system; Depression, Bipolar or other Depressive Disorders, Drug Use Disorders, Diabetes, Durable medical equipment, Epilepsy; Fibromyalgia, Chronic Pain and Fatigue, Fluid and Electrolyte Disorder, Gallstones, Glaucoma, Gout medication, Heart failure and non-ischemic heart disease, Hip/Pelvic Fracture, HIV/AIDs, HPV DNA test, Hyperlipidemia, Hyperparathyroidism, Hypertension, Hypothyroidism, Intellectual Disabilities and Related Conditions, Ischemic heart disease, Insulin use, Learning disabilities, Leukemias and lymphomas, Liver Disease, Cirrhosis and Other Liver Conditions, Kawasaki disease, Migraine and chronic headache, Mobility impairments, MS and transvers myelitis, Muscular dystrophy, Non-Alzheimer's Dementia, Obesity, Opioid Use Disorder, Osteoporosis, Organ transplant, Other Developmental Delays, Other infectious Diseases, Oxicam anti-inflammatory drugs, Parkinson's Disease and Secondary Parkinsonism, Pap smear, All-cause Pneumonia, Peripheral Vascular Disease, Personality Disorder, Pressure or Chronic Ulcers, PTSD, Pulmonary Disease, Pulmonary Circulation, PSA test, Psychosis Renal Failure, Reyes syndrome, Rheumatoid arthritis and osteoarthritis, Stroke/Transient ischemic attack; Screenings, examinations and disease management, Sulfa Antibiotics, Sertraline, Sensory - Deafness and Hearing Impairment, Sensory – Blindness and Visual Impairment, Schizophrenia, Schizophrenia, and other psychotic disorders, Spina Bifida and Other Congenital Anomalies of the Nervous System, Spinal cord injury, Thrombotic Thrombocytopenic purpura, Tobacco Use, Traumatic Brain Injury and Nonpsychotic Mental Disorders due to Brain Damage, Viral Hepatitis, Weight Loss, Mean number of ambulatory encounters, Mean number of emergency room encounters, Mean number of inpatient hospital encounters, Mean number of unique drug classes, Mean number of filled prescriptions

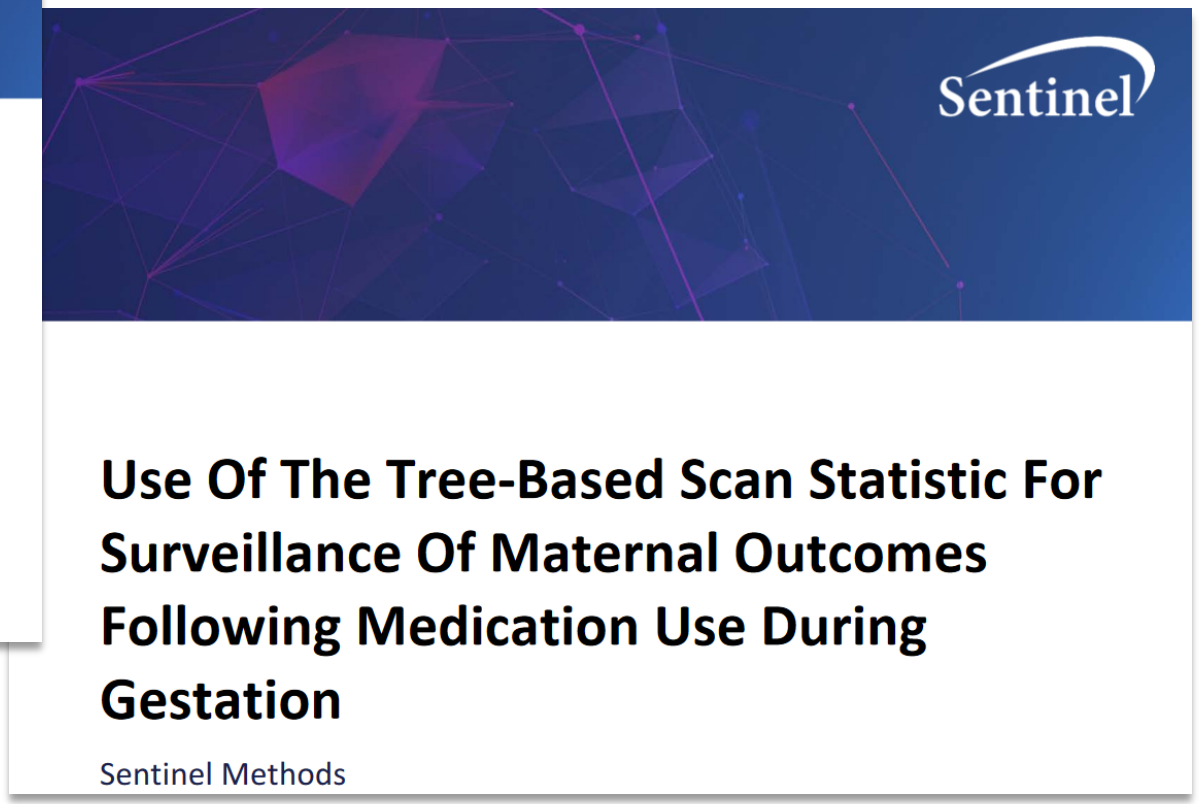
FDA is committed to Transparency and Reproducibility



https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse
https://dev.sentinelsystem.org/projects/AP/repos/sentinel-analytic-packages/browse?at=refs%2Fheads%2Fcder_sir_wp002

TreeScan in Pregnancy: Methods Work





https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf
https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Protocol_TreeScan_Pregnancy_Maternal-Outcomes_v2.1.pdf

TreeScan in Pregnancy Study Aims

Infant Outcome Studies

1. **Simulation study: Assess the performance of TreeScan under known conditions**
   - Can TreeScan identify an increase in risk for a specific malformation in our tree, given a certain sample size?
2. **Case study: Demonstrate the use of TreeScan in real data, in a cohort of pregnant women linked to their live-born infants**
   - How do results look in real data?
   - How do results compare when we use different propensity score methods/TreeScan models?

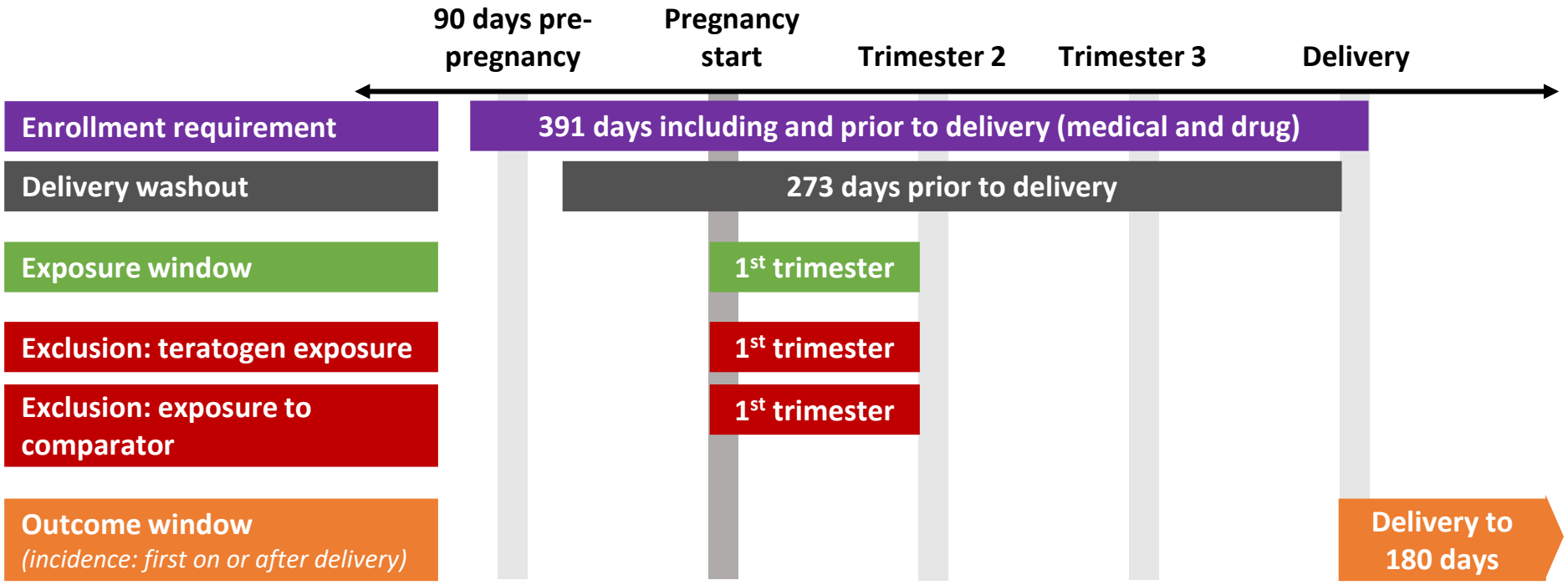
Maternal Outcome Studies

3. **Simulation study: Assess the performance of TreeScan under known conditions**
   - What is the impact of high numbers of strata on bias and power?
4. **Case study: Demonstrate the use of TreeScan in real data, in a cohort of pregnant women with active and unexposed comparators**
   - How do results look in real data?
   - How do results compare when we use different propensity score methods/TreeScan models?

https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf
https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Protocol_TreeScan_Pregnancy_Maternal-Outcomes_v2.1.pdf

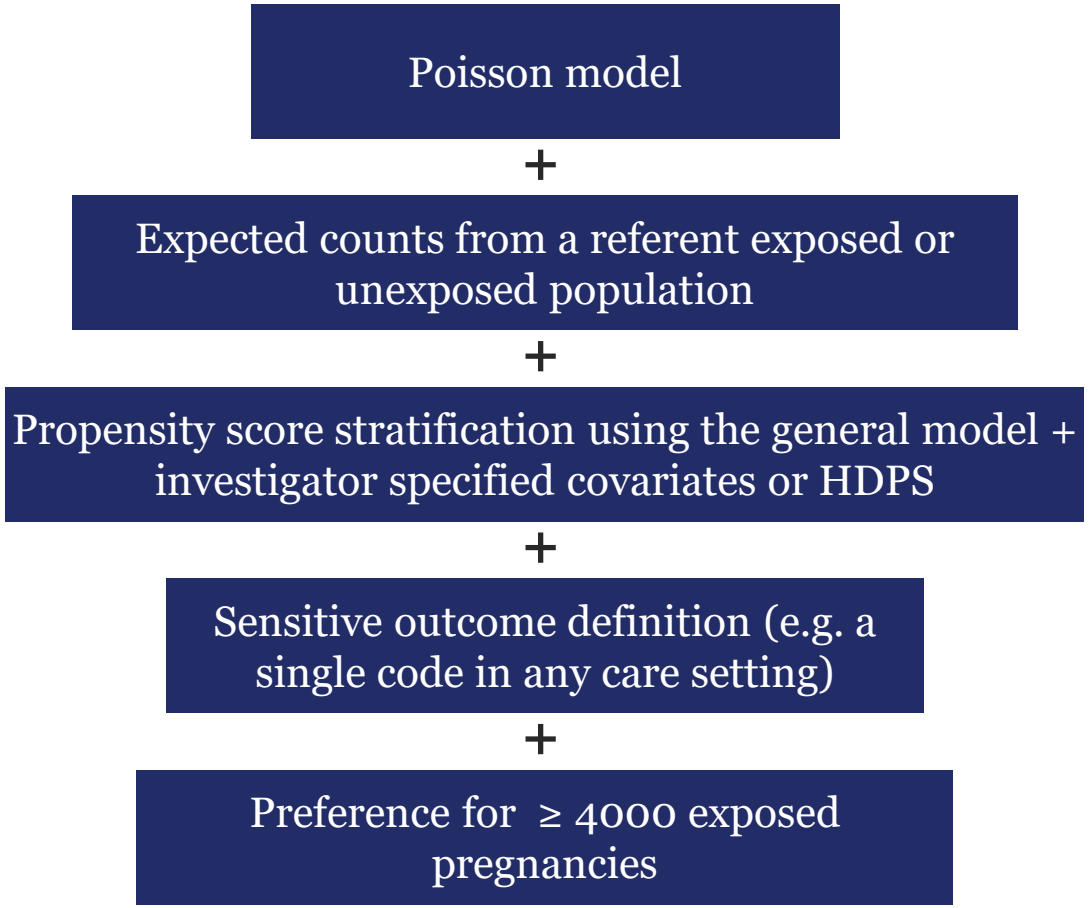
Infant Outcomes Study Design

Data source	Merative MarketScan® Research Database
Eligible population	Women with live birth deliveries between October 1, 2015, and December 31, 2018, aged 10-55 years at delivery



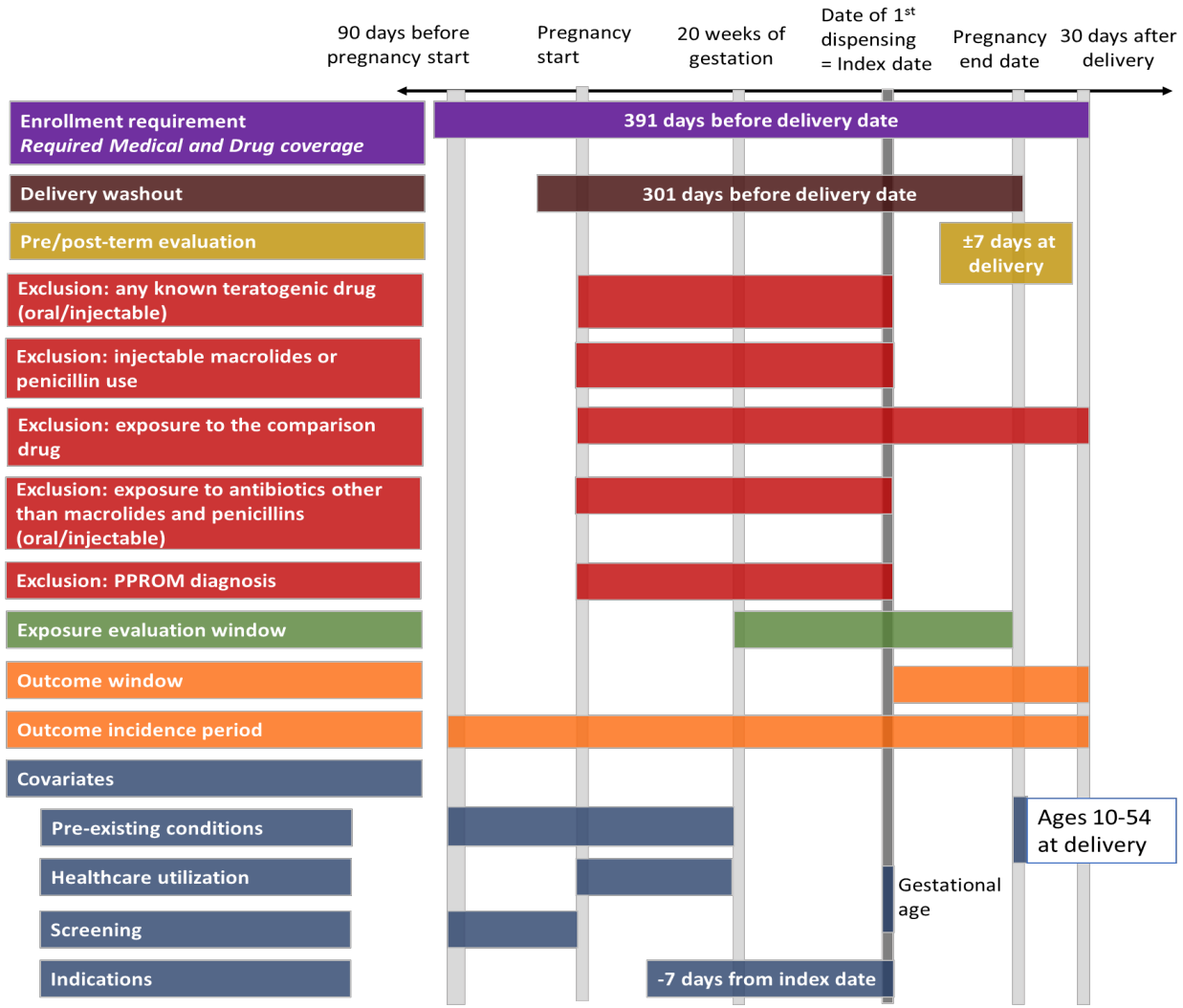
https://www.sentinelinitiative.org/sites/default/files/Methods/Sentinel_Protocol_TreeScan_Pregnancy_V3.pdf

Recommendations for Infant Outcome Studies



Suarez EA, Nguyen M, Zhang D, Zhao Y, Stojanovic D, Munoz M, Liedtka J, Anderson A, Liu W, Dashevsky I, DeLuccia S, Menzin T, Noble J, Maro JC. Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs. Epidemiology. 2022 Oct 18. doi: 10.1097/EDE.0000000000001561. Epub ahead of print. PMID: 36252086.

Maternal Outcomes Study Design



Cohort: Singleton livebirth deliveries
Query period: October 1, 2015 – February 29, 2020
First valid livebirth delivery date: October 26, 2016
Last valid livebirth delivery date: January 30, 2020

https://www.sentinelinitiative.org/sites/default/files/documents/Sentinel_Protocol_TreeScan_Pregnancy_Maternal-Outcomes_v2.1.pdf

Signal Identification Takeaways

- TreeScan is a promising method for identifying unexpected potential adverse infant events and adverse maternal outcomes following maternal medication exposure during pregnancy
- Using TreeScan in administrative data within Sentinel offers notable advantages:
  - Utilize the large sample sizes available in administrative data, and build off previous methods to identify pregnancies and pregnancy exposures
  - Not limited to major congenital malformations as a primary outcome – can scan for all types of outcomes individually and in clinically relevant groupings (e.g., atrial septal defect, any cardiac malformation)
- Alerts that are identified are able to be quickly triaged by reviewing claim profiles among patients with those alerts

Vericiguat Query

FDA	Sentinel Operations Center	Sentinel Data Partners
Corey, Catherine	Carruth, Amanda	CVS Health Clinical Trial Services (Aetna)
Eworuke, Efe	Cosgrove, Austin	HealthCore/Elevance Health
Li, Yan	Kolonoski, Joy	Humana Healthcare Research Inc.
Moeny, David	Martinez, Ashley	Kaiser Permanente Northwest Center for Health Research
	Schoeplein, Ryan	OptumInsight Life Sciences Inc.
	Shinde, Mayura	Vanderbilt University Medical Center, Department of Health Policy
	Smith, Samantha	
	Thompson, Jennifer	
	Zhang, Tancy	

Ixekizumab Query

FDA

Adereti, Modupeola
Booth, Benjamin
Dutcher, Sarah
Ho, Amy
Peprah, Sally
Weissfeld, Joel
Woods, Corinne
Zhang, Mingfeng

Sentinel Operations Center

Beers, Lizzie
Cosgrove, Austin
Her, Meg
Kolonoski, Joy
Martinez, Ashley
Nandyala, Sampada
Payson, Morgaine
Schoeplein, Ryan
Shinde, Mayura

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)
HealthCore/Elevance Health
Humana Healthcare Research Inc.
OptumInsight Life Sciences Inc.
Vanderbilt University Medical Center, Department of Health Policy

HCA Healthcare COVID-19 Queries

FDA

Bright, Patricia
Dutcher, Sarah
Kit, Brian
Pratt, Natasha

Sentinel Operations Center

Brisbane, Gifty
Cocoros, Noelle
Cosgrove, Austin
Fearrington, Julia
Froman, Allison
Fuller, Candace
Gowda, Abinav
Haffenreffer, Katie
Hoffman, Emma
Hague, Christian
Jin, Robert
Nathwani, Neesha
Noble, Jennifer
Ochoa, Aileen
Rai, Ashish
Rosen, Edward
Shinde, Mayura
Varma. Neha
Zichittella, Lauren

Sentinel Data Partners

HCA Healthcare

Systemic Corticosteroid in Outpatient COVID-19 Query

FDA

Bradley, Marie
Corey, Catherine
Eworuke, Efe
Graham, David
Kit, Brian
Lee, Hana
Perez-Vilar, Silvia

Sentinel Operations Center

Cocoros, Noelle
Cosgrove, Austin
Martinez, Ashley I.
Maro, Judith C.

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)
HealthPartners Institute
Humana Healthcare Research Inc.
Kaiser Permanente Northwest Center for Health Research

Acumen & the Centers for Medicare & Medicaid Services

Akhtar, Sandia
Chillarige, Yoganand
Kelman, Jeffrey
Lyu, Hai
Naik, Kushal B.

Department of Veterans Affairs

Cunningham, Fran
Dong, Diane
Zhang, Rongping

Aetion/HealthVerity

Baglivo, Aidan
Garry, Elizabeth
Gatto, Nicolle M.
Leonard, Sandy
Vititoe, Sarah
Weckstein, Andrew

Coagulopathy in COVID-19 Patients

FDA

Dutcher, Sarah K.

Perez-Vilar, Silvia

Sentinel Operations Center

Cocoros, Noelle

Connolly, John G.

Hou, Laura

Kempner, Maria E.

Mosley, Jolene

Petrone, Andrew

Rogers Driscoll, Meighan

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)

HealthPartners Institute

Humana Healthcare Research Inc.

Kaiser Permanente Colorado Institute for Health Research

Kaiser Permanente Northwest Center for Health Research

Kaiser Permanente Washington Health Research Institute

University of Pennsylvania

Carbonari, Dena M

Hennessy, Sean

Hubbard, Rebecca A.

Lo Re, Vincent

Pishko, Allyson M.

Multi-State Medicaid Data

FDA

Bright, Patricia

Cherkaoui, Sanae

Dutcher, Sarah

Eworuke, Efe

Menegussi, Lucia

Moeny, David

Mwidau, Jamila

Sentinel Operations Center

Halbig. Christine

Kiernan, Daniel

Mai, Alexander

Maro, Judith

Rosofsky, Robert

Shapiro, Katie

Shockro, Laura

Vigeant, Justin

Zichittella, Lauren

Department of Population Health Sciences, Duke University School of Medicine

Adhikari, Pratap

Hammill, Brad

Lippmann, Steven J.

Pritchard, Jessica E.

Stagner, Michael

Office of the Assistant Secretary for Planning and Evaluation

Lee, Euny

Race and COVID-19 Outcomes in U.S.

FDA

Ajao, Adebola
Baumblatt, Jane
Eworuke, Efe
Hernandez, Jose
Jjingo, Caroline
Lee, Christine
Lee, Hye Seung
Merenda, Christine
Moeny, David
Stojanovic, Danijela
Zhao, Yueqin

Sentinel Operations Center

Adimadhyam, Sruthi
Chlon, Whitney
Hawrusik , Rebecca
Mosley, Jolene
Petrone, Andrew
Siranosian, Liz
Thompson, Jen
Wiley, Megan

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)
HealthPartners Institute
Humana Healthcare Research Inc.
Kaiser Permanente Colorado Institute for Health Research
Kaiser Permanente Northwest Center for Health Research
Kaiser Permanente Washington Health Research Institute

Sentinel Views

FDA

Bright, Patricia
Dutcher, Sarah
Eworuke, Efe
Ma, Yong
Nguyen, Michael
Stojanovic, Danijela
Woods, Corinne

Sentinel Operations Center

Beers, Lizzie
Connolly, John
Cosgrove, Austin
Czernizer, Eric
Ehrmann, Max
Epperson, Meredith
Guzman, Mike
Huang, Jane
Kempner, Maria
Kolonoski, Joy
Marshall, Jim
Martin, Chris
Nandyala, Sampada
Nolan, Jamie
Patel, Ankit
Petrone, Andrew
Purington, Carolyn
Woodnutt, Regan

Patient-Reported Measures

FDA

Dutcher, Sarah
Bright, Patricia
Hernandez, Jose
Corey, Catherine
Kit, Brian
Mengussi, Lucia
Mwidau, Jamila
Nguyen, Michael
Stojanovic, Danijela

Sentinel Operations Center

Carter, Suzanne
Cho, Yong
Diaz, Tia
Fredette, Mary
Halbig. Christine
Kiernan, Daniel
Ko, Jenice
Mai, Alexander
Maro, Judith
Moisuk, Stacey
Nandyala, Sampada
Nathwani, Neesha
Petrone, Andrew
Ryan, Janine
Rucker, Malcolm
Shapiro, Katie
Vigeant, Justin
Zichittella, Lauren
Rosofsky, Robert

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)
HCA Healthcare
HealthPartners Institute
Humana Healthcare Research Inc.
Kaiser Permanente Colorado Institute for Health Research
Kaiser Permanente Hawai'i, Center for Integrated Health Care Research
Kaiser Permanente Mid-Atlantic States, Mid-Atlantic Permanente Research Institute
Kaiser Permanente Northwest Center for Health Research
Kaiser Permanente Washington Health Research Institute
Marshfield Clinic Research Institute
OptumInsight Life Sciences Inc.

Signal Identification

FDA

Anderson, Abby
Dutcher, Sarah
Eworuke, Efe
Hernandez, Jose
Liedtka, Jane
Liu, Wei
Ma, Yong
Moeny, David
Mundkur, Malika
Munoz, Monica
Nguyen, Michael
Stojanovic, Danijela
Zhang, Di
Zhao, Yueqin

Sentinel Operations Center

Cole, David
Dashevsky, Inna
DeLuccia, Sandra
Epperson, Meredith
Hou, Laura
Maro, Judy
Marshall, Jim
Menzin, Talia
Noble, Jennifer
Peters, Alexander
Siranosian, Liz
Suarez, Elizabeth
Whited, Emma

Sentinel Data Partners

CVS Health Clinical Trial Services (Aetna)
Duke - Center for Medicare and Medicaid Services – Medicare Fee-for-Service data
HealthCore/Elevance Health
Humana Healthcare Research Inc.
OptumInsight Life Sciences Inc.
Sentinel Operations Center MarketScan
Vanderbilt University Medical Center, Department of Health Policy

Thank You

Sentinel

FDA U.S. FOOD & DRUG ADMINISTRATION

Fourteenth Annual Sentinel Initiative Public Workshop, November 15, 2022

Severe Abnormal Uterine Bleeding among Oral Anticoagulant Users

COLLABORATORS

FDA Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology: Efe Eworuke, Hui-lee Wong, David G. Money

Division of Biometrics VII: Rongmei Zhang

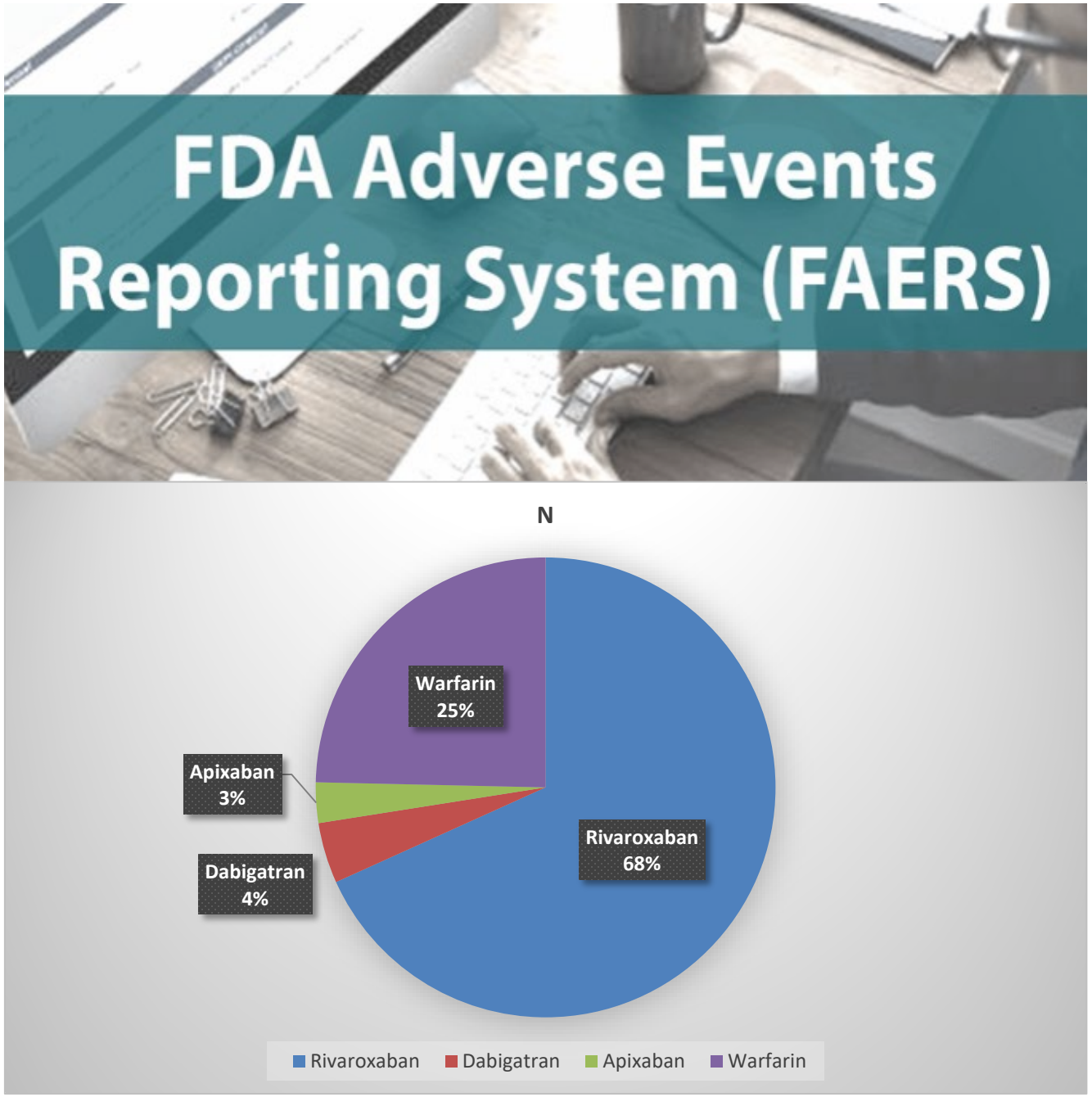
Division of Urologic Obstetrics, and Gynecology (DUOG): Abby Andersen, Audrey Gassman

Harvard Pilgrim Health Care Institute

Laura Hou, Ting-Ying Huang

Menorrhagia cases (n=76) reported with Rivaroxaban

- Mean Age (40 years)
- Time to onset (82% [n=56] occur within one month –first menstrual period
- Surgical intervention (n=20): Endometrial ablation, D&C, Hysterectomy
- Transfusion (n=30)
- Adaptation of treatment: change of anticoagulant (n=34) or dose reduction (n=6)



Martinelli, Ida et al. "Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use." *Blood* vol. 127,11 (2016): 1417-25. doi:10.1182/blood-2015-08-665927

- Re-analysis of EINSTEIN DVT and PE trials (women <60 years; mean: 41.3) Comparative risk estimates:
  - Abnormal Uterine Bleeding:
    - Hazard Ratio (HR) – rivaroxaban (n=122) vs. enoxaparin (n=63): 2.13 (95% CI: 1.57-2.89)
  - Uterine Bleeding leading to transfusion:
    - Rivaroxaban (n=19) compared to enoxaparin (n=3)

Regulatory Gap

- Women of childbearing age were poorly represented in pivotal trials
- Likely menorrhagia risk is underestimated from these data
- Menorrhagia leading to severe outcomes poorly understood (Re-analysis of the EINSTEIN trial)
- No data on uterine bleeding outcomes for the other NOACs

Study Objectives

01

Determine incidence rates of severe uterine bleeding:

Among oral anticoagulant users and the general population

02

Compare rates of severe uterine bleed among NOACs

03

Compare rates of severe uterine bleed associated with rivaroxaban to warfarin

- Undertaken to examine adjustment performance
- Compare with the randomized trial results

Study Design

P

- Retrospective Cohort Study (FDA Sentinel System: October 2010 – September 2015)
- All Females (18+ years| excluded women with recent replacement surgery, study outcomes)

I

- Rivaroxaban

C

- Warfarin
- Dabigatran
- Apixaban

O

- Vaginal Bleeding leading to Surgical Intervention* (within 30 days)
- Vaginal Bleeding leading to same-day transfusion

*Hysteroscopic polypectomy, Hysteroscopic laparoscopic or abdominal myomectomy, Other hysteroscopy procedures, uterine embolization, hysterectomy, endometrial ablation [thermal, cryo or section], dilation and curettage with or without hysteroscopy

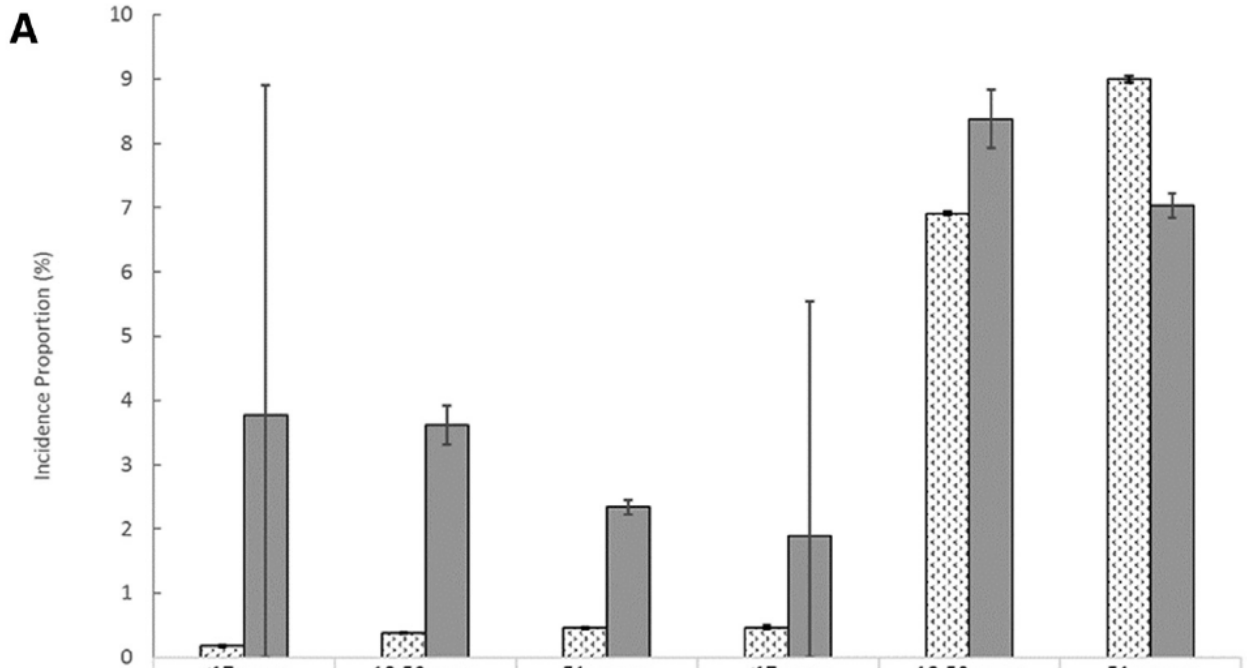
American Journal of Obstetrics and Gynecology
Volume 226, Issue 1, January 2022, Pages 140-143

Research Letter

Incidence of severe uterine bleeding outcomes among oral anticoagulant users and nonusers

Ting-Ying Huang PhD ✉, Laura Hou MS, Abby Anderson MD, Audrey Gassman MD, David Moeny RPh, MPH, Efe Eworuke PhD

A higher incidence of uterine bleeding events leading to same-day transfusion and surgical interventions within 30 days was observed with oral anticoagulant users compared to non-users



	Transfusion (SUB-T)			Surgery* (SUB-S)		
	≤17 years	18-50 years	51+ years	≤17 years	18-50 years	51+ years
OA nonusers	0.2	0.4	0.5	0.5	6.9	9.0
OA users	3.8	3.6	2.3	1.9	8.4	7.0
Std Diff	-0.3	-0.2	-0.2	-0.1	-0.1	0.1

* Gynecological surgeries of interest included polypectomy (hysteroscopic, laparoscopic, abdominal), myomectomy, dilatation and curettage, hysterectomy, endometrial ablation (thermal, cryo, or section), other hysteroscopic procedures, and uterine artery embolization.
OA= oral anticoagulant; Std Diff= standardized difference between OA nonusers and users, for which ±0.1 is the commonly used threshold to indicate statistical difference.

Higher Incidence of Uterine Bleeding Outcomes among Younger women

- Strong effect modification by age
- Younger women at higher risk due to reproductive status
- Highest risk for Surgical management outcome
  - Hysteroscopic polypectomy and Hystectomy contributed the largest number of events

TABLE
Incidence (per 1000 person-years) of UB requiring intervention among Novel Oral Anticoagulants (NOAC)[a] and warfarin users

Management after uterine bleed	Overall	≤50 y	51+ y
Medical management within 24 h	0.6	11.8	0.2
Medical management within 5 d	0.7	12.8	0.2
Same-day transfusion management	1.7	13.7	1.2
Surgical management within 30 d	5.0	33.0	3.9
Surgical management within 60 d	5.3	34.0	4.2

Medical management: insertion of an intrauterine system or vaginal packing or initiation of an oral contraceptive or antifibrinolytic agent after UB diagnosis.

Transfusion management: same-day red blood cell transfusion after UB diagnosis.

Surgical management: surgical intervention, including hysterectomy, polypectomy, myomectomy, dilation and curettage, endometrial ablation, and uterine artery embolization occurring after UB diagnosis. NOAC drugs include rivaroxaban, apixaban, and dabigatran.

[a] NOAC: rivaroxaban, apixaban and dabigatran.

Anderson. Incidence of uterine bleeding following oral anticoagulant use in Food and Drug Administration's Sentinel System. Am J Obstet Gynecol 2021.

Research Letters

Incidence of uterine bleeding following oral anticoagulant use in Food and Drug Administration's Sentinel System

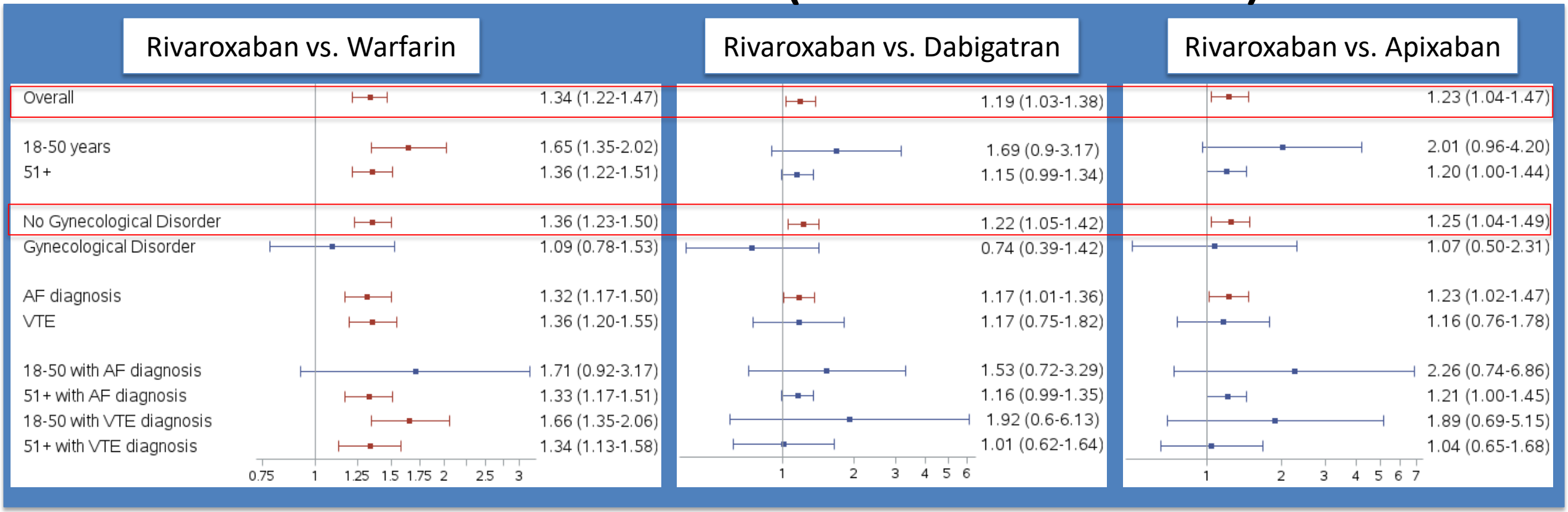
Abby Anderson MD ✉, Audrey Gassman MD, Laura Hou MS, Ting-Ying Huang PhD, Efe Eworuke PhD, David Moeny RPh, Hui-Lee Wong PhD

ORIGINAL RESEARCH ARTICLE

Risk of Severe Abnormal Uterine Bleeding Associated with Rivaroxaban Compared with Apixaban, Dabigatran and Warfarin

Efe Eworuke[1] · Laura Hou[2] · Rongmei Zhang[3] · Hui-Lee Wong[4] · Peter Waldron[5] · Abby Anderson[6] · Audrey Gassman[6] · David Moeny[1] · Ting-Ying Huang[2]

Risk Estimates* (Hazard Ratios)



*demographic and clinical characteristics were adjusted by propensity score stratification

Study Impact

- Labeling Update for all NOACs in **Section 8: Use in Specific Populations**

8.3 Females and Males of Reproductive Potential

Females of reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician.

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including [redacted] should be assessed in females of reproductive potential and those with abnormal uterine bleeding.

Eliquis (apixaban) Pradaxa (dabigatran etexilate mesylate) Savaysa (edoxaban tosylate) Xarelto (ribaroxaban) Generic products containing dabigatran etexilate mesylate Generic products containing ribaroxaban	Menorrhagia	The "Use in Specific Populations" section was updated April 2021 to add language to describe the risk of clinically significant uterine bleeding in females of reproductive potential. Eliquis label Pradaxa label Savaysa label Xarelto label


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Leuprolide and Fracture Risk in Patients With Central Precocious Puberty

Yandong Qiang
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration, Silver Spring, MD

November 15, 2022, Sentinel Annual Meeting

DISCLAIMER

The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

BACKGROUND

- Central Precocious Puberty (CPP) causes early sexual development, rapid bone maturation and early epiphyseal closure, which can result in stunted adult height
- Leuprolide is the most commonly used gonadotropin-releasing hormone (GnRH) analog that helps to delay puberty and epiphyseal closure that ultimately increase adult height
- Fracture signaled in the analysis of post-marketing safety reports from the FDA Adverse Event Reporting System (FAERS) database in pediatric patients previously treated with GnRH agonists for CPP (January - March 2017 | Potential Signals of Serious Risks/New Safety Information Identified by the FDA Adverse Event Reporting System (FAERS) | FDA)

OBJECTIVE

- To study the relationship between leuprolide and fracture
- To provide data from the Sentinel System to support FDA's evaluation of potential signal of serious risk

STUDY POPULATION

- A retrospective cohort study using data from 12 Sentinel data partners during the period between 2000 and 2018
- Eligible patients were classified as the following three cohorts:
  - Leuprolide-exposed cohort with CPP: patients with a CPP diagnosis during 183 days prior to the leuprolide initiation (index date)
  - 1st Leuprolide unexposed cohort with CPP: patients diagnosed with CPP, indexed on median time from the 1st CPP diagnosis to exposure summarized from the leuprolide-exposed cohort
  - 2nd Leuprolide unexposed cohort without CPP: individuals with no baseline CPP diagnosis, indexed on the 1st well visit
- Patients were excluded if meeting any of the following criteria during the 183-day baseline period prior to the index date
  - Age≥ 11 years on the index date; Diagnosis of osteogenesis imperfecta; Use of long-acting GnRH agonist; Exposure to drugs that affect bone density; Any fracture

EXPOSURE, OUTCOME, FOLLOW-UP

- Leuprolide Exposure: identified using National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) codes recorded in medical and outpatient pharmacy claims
- Outcome: Major Fracture (Composite of humerus fracture, radius/ulna fracture, vertebral fracture, hip fracture, femur fractures)
  - ICD-9/10-CM diagnosis code with at least one procedure code for the same fracture site within 7 days
  - Major trauma excluded
- Follow-up: from the index date to the earliest of major fracture, major trauma, disenrollment, recorded death, or data end

STATISTICAL ANALYSIS

- Variable ratio matching (1: ≤10) on continuous age (in days) and calendar month of the index date
- Exploratory data analysis for patient characteristics and outcome events during follow-up
- Time-to-event analysis comparing the risks of the first fracture in the leuprolide-exposed cohort with the unexposed cohort with CPP and unexposed cohort without CPP for males and females separately
- Post-hoc analysis that stratified on age integer (in years) and calendar month of index event to account for the impact of differentially truncated follow-up time due to conditioning on matched sets

Follow-up Time and Age Distribution of Children with and without Leuprolide Exposure

	Exposed with CPP (# Subjects)	Unexposed with CPP (#Matched Sets)		Exposed with CPP (# Subjects)	Unexposed without CPP (#Matched Sets)
Female					
Patients (N)	2,841 (100.0%)	2,841 (100.0%)		2,845 (100.0%)	2,845 (100.0%)
Follow-up time (person-days; mean, SD)	1,043.8 (981.0)	1,079.0 (1018.8)		1,043.0 (981.1)	1,077.7 (1145.6)
Mean age (years)	8.0 (1.7)	8.0 (1.7)		8.0 (1.7)	8.0 (1.7)
Age (years)					
0-2	78 (2.7%)	80 (2.8%)		79 (2.8%)	79 (2.8%)
3-4	100 (3.5%)	98 (3.4%)		101 (3.6%)	101 (3.6%)
5-6	373 (13.1%)	377 (13.3%)		374 (13.1%)	373 (13.1%)
7-8	1,479 (52.1%)	1,471 (51.8%)		1,479 (52.0%)	1,479 (52.0%)
9-10	811 (28.5%)	816 (28.7%)		812 (28.5%)	813 (28.6%)
Male					
Patients (N)	432 (100.0%)	432 (100.0%)		439 (100.0%)	439 (100.0%)
Follow-up time (person-days; mean, SD)	1,014.5 (918.8)	1,021.1 (962.1)		1,020.3 (918.7)	1,018.2 (1050.9)
Mean age (years)	9.1 (1.8)	9.1 (1.7)		9.1 (1.8)	9.1 (1.8)
Age (years)					
0-2	9 (2.1%)	10 (2.2%)		11 (2.5%)	11 (2.5%)
3-4	5 (1.2%)	4 (0.9%)		5 (1.1%)	5 (1.1%)
5-6	25 (5.8%)	26 (6.1%)		26 (5.9%)	26 (5.9%)
7-8	120 (27.8%)	118 (27.2%)		123 (28.0%)	123 (28.0%)
9-10	273 (63.2%)	274 (63.5%)		274 (62.4%)	274 (62.4%)

Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children with CPP

Cohorts	Number of Indexed children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	2,845	8,124.33	2.86	63	7.75	22.14	0.81
Unexposed with CPP	65,313	199,566.94	3.06	1,780	8.92	27.25	(0.63, 1.04)
1:many Matched Conditional Analysis							
Exposed with CPP	2,841	7,478.99	2.63	56	7.49	19.71	0.75
Unexposed with CPP	26,811	39,149.67	1.46	445	11.37	16.60	(0.57, 1.00)
Male							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	439	1,226.34	2.79	19	15.49	43.28	1.35
Unexposed with CPP	10,509	29,996.24	2.85	341	11.37	32.45	(0.85, 2.15)
1:many Matched Conditional Analysis							
Exposed with CPP	432	1,064.22	2.46	18	16.91	41.67	1.28
Unexposed with CPP	3,474	4,880.93	1.40	66	13.52	19.00	(0.75, 2.20)

Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children without CPP

Cohorts	Number of Indexed Children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	2,845	8,124.33	2.86	63	7.75	22.14	0.86
Unexposed without CPP	6,547,116	19,008,132.21	2.90	162,613	8.55	24.84	(0.67, 1.10)
1:many Matched Conditional Analysis							
Exposed with CPP	2,845	7,599.92	2.67	58	7.63	20.39	0.66
Unexposed without CPP	28,450	40,316.85	1.42	510	12.65	17.93	(0.50, 0.87)
Male							
Unmatched Analysis (Site-adjusted only)							
Exposed with CPP	439	1,226.34	2.79	19	15.49	43.28	1.45
Unexposed without CPP	6,739,063	19,523,714.76	2.90	193,777	9.93	28.75	(0.93, 2.28)
1:many Matched Conditional Analysis							
Exposed with CPP	439	1,146.65	2.61	19	16.57	43.28	1.07
Unexposed without CPP	4,390	6,169.19	1.41	98	15.89	22.32	(0.64, 1.77)

Estimated Hazard Ratios of Major Fracture between Leuprolide-Exposed and the Matched Leuprolide-Unexposed Children with or without CPP (Post-hoc Stratified Analysis)

Cohorts	Number of Indexed Children	Person Years at Risk	Average Person Years at Risk	Number of Events	Incidence Rate per 1,000 Person Years	Risk per 1,000 Indexed Children	Hazard Ratio (95% CI)
Female							
Exposed with CPP	2,841	7,957.46	2.80	62	7.79	21.82	0.80 (0.62, 1.05)
Unexposed with CPP	26,811	64,408.29	2.40	679	10.54	25.33	
Exposed with CPP	2,845	8,042.14	2.83	62	7.71	21.79	0.70 (0.54, 0.91)
Unexposed without CPP	28,450	65,972.84	2.32	750	11.37	26.36	
Male							
Exposed with CPP	432	1,109.90	2.57	18	16.22	41.67	1.27 (0.76, 2.12)
Unexposed with CPP	3,474	6,551.65	1.89	91	13.89	26.19	
Exposed with CPP	439	1,185.45	2.70	19	16.03	43.28	1.17 (0.72, 1.91)
Unexposed without CPP	4,390	8,053.54	1.83	124	15.40	28.25	

CONCLUSIONS

- Compared separately to the leuprolide-unexposed children with or without CPP, the study observed a lower risk of fracture in female leuprolide users with CPP, but no statistically significant difference in male leuprolide users with CPP
- There were consistent results from the post hoc analysis, accounting for the impact of differentially truncated follow-up time due to conditioning on matched sets
- Because results from this study provided no evidence for an increased risk of fracture following leuprolide use during childhood, FDA determined that no regulatory action is needed at this time.

ACKNOWLEDGEMENTS

- This project was supported by Task Orders HHSF22301012T and 75F40119F19001 under Master Agreements HHSF223201400030I and 75F40119D10037 from the US Food and Drug Administration (FDA)
- Many thanks are due to the Sentinel Data Partners who provided data used in this analysis
- Sentinel Operations Center
  - Talia J Menzin
  - Ting-Ying Huang
- FDA Team
  - Hye Seung Lee
  - Shannon Sullivan
  - Yueqin Zhao
- Christian Hampp (former FDA investigator, currently with Regeneron Pharmaceutical)


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Closing Remarks | Day 1

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

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Subscribe to our monthly newsletter at
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Fourteenth Annual Sentinel Initiative Public Workshop

November 15th, 2022 | 1:00 – 5:00 ET

November 16th, 2022 | 12:00- 4:15 ET

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

Welcome & Overview | Day 2

Rachele Hendricks-Sturrup, DHSc, MSc, MA

Research Director, Real World Evidence (RWE), Duke-Margolis Center for Health Policy

Summary: Day 1

- Keynote Presentation – Patrizia Cavazzoni
- Fireside Chat with Sentinel Initiative Leadership
- Reflections on PDUFA VI Commitments and Looking Ahead to PDUFA VII
- BEST Operations and Coordinating Center Perspectives
- Sentinel System Operations and Coordinating Center Perspectives

Agenda: Day 2

- Sentinel System Innovations in Data Infrastructure and Analytic Methods
- BEST Innovations in Data Infrastructure and Analytic Methods
- Key Collaborations with Stakeholders and Development of New Partnerships in the Sentinel Initiative

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.

Virtual Meeting Reminders

- Attendees are encouraged to contribute throughout the meeting with questions in the Zoom Q&A function.
  - Audience questions will be incorporated into panel discussions whenever possible

- Join the discussion on Twitter using the #SentinelInitiative hashtag

Session III: Sentinel System Innovations in Data Infrastructure and Analytic Methods

- **Sebastian Schneeweiss**, Brigham and Women's Hospital
- **Rishi Desai,** Brigham and Women's Hospital
- **David Carrell**, Kaiser Permanente Washington
- **Colin Walsh**, Vanderbilt University Medical Center
- **Richie Wyss**, Brigham and Women's Hospital
- **Keith Marsolo,** Duke University
- **Shirley Wang**, Brigham and Women's Hospital

Sentinel

Sentinel Innovation Center

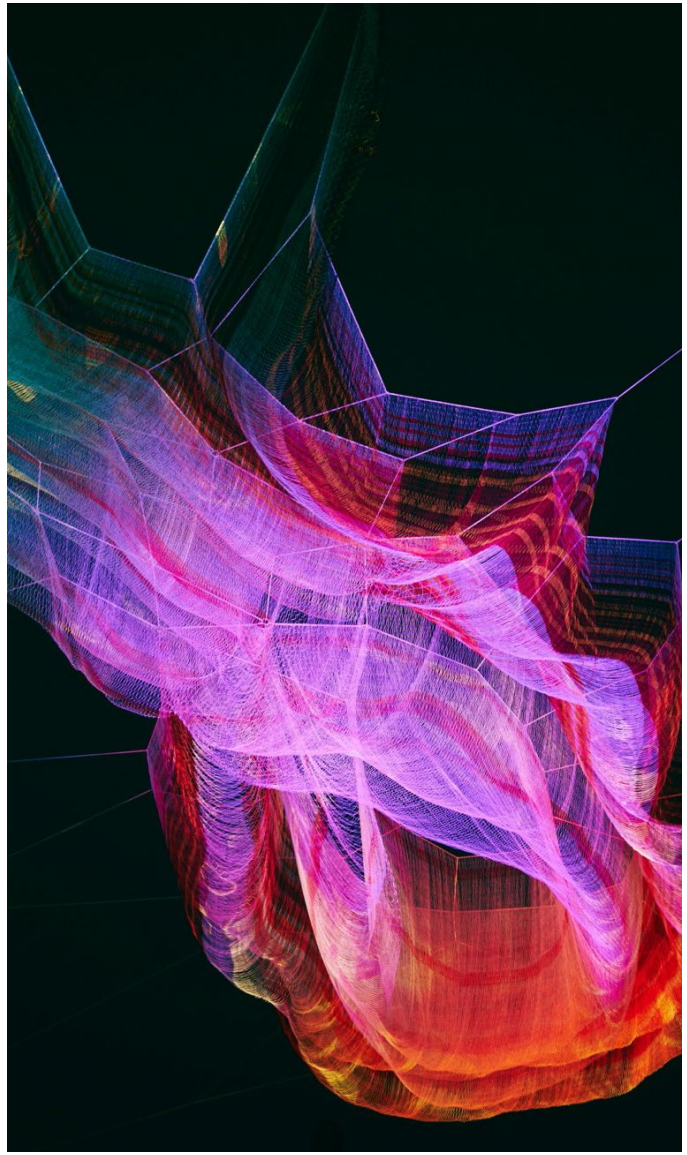
November 16, 2022

Agenda

- Sentinel Innovation Center Vision
- Causal Inference: Advances in Computable Phenotyping using Electronic Health Records (EHRs)
- Feature Engineering: Leveraging Machine Learning for Ultra High Dimensional Confounding Adjustment in Electronic Health Record Data
- Data Infrastructure: Representation of Unstructured Data Across Common Data Models
- Detection Analytics: Advances in Signal Detection Methodology in Sentinel

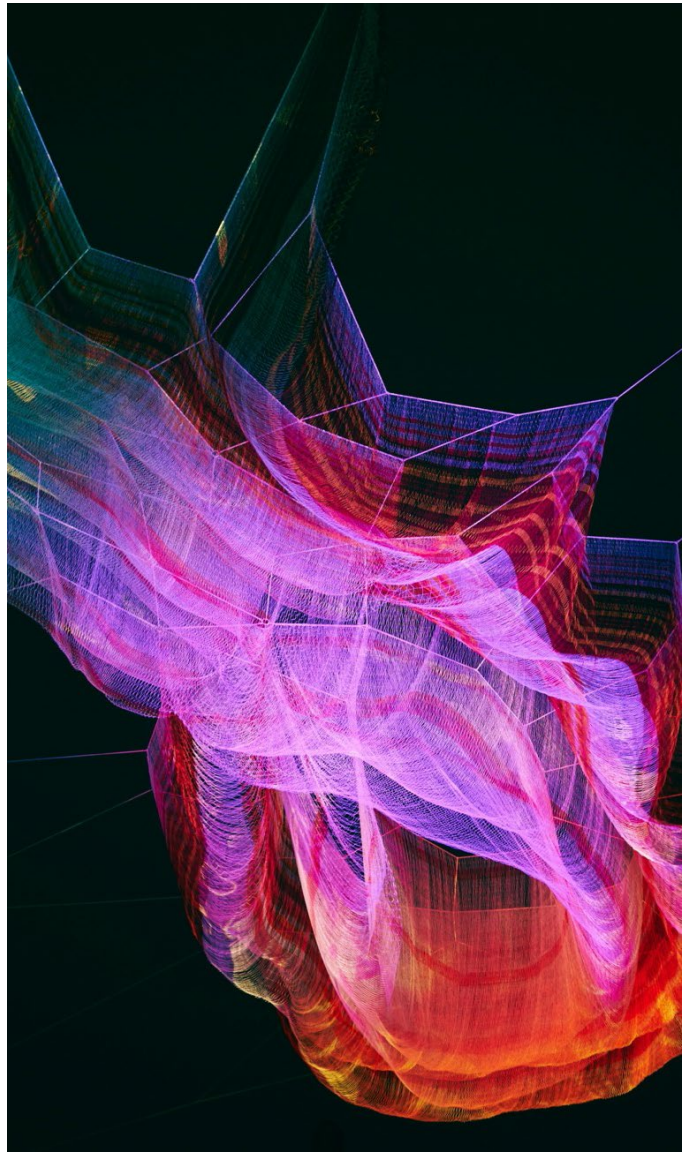
Sentinel Innovation Center Vision

Sebastian Schneeweiss, MD, ScD
Brigham and Women's Hospital (Mass General Brigham)
Harvard Medical School



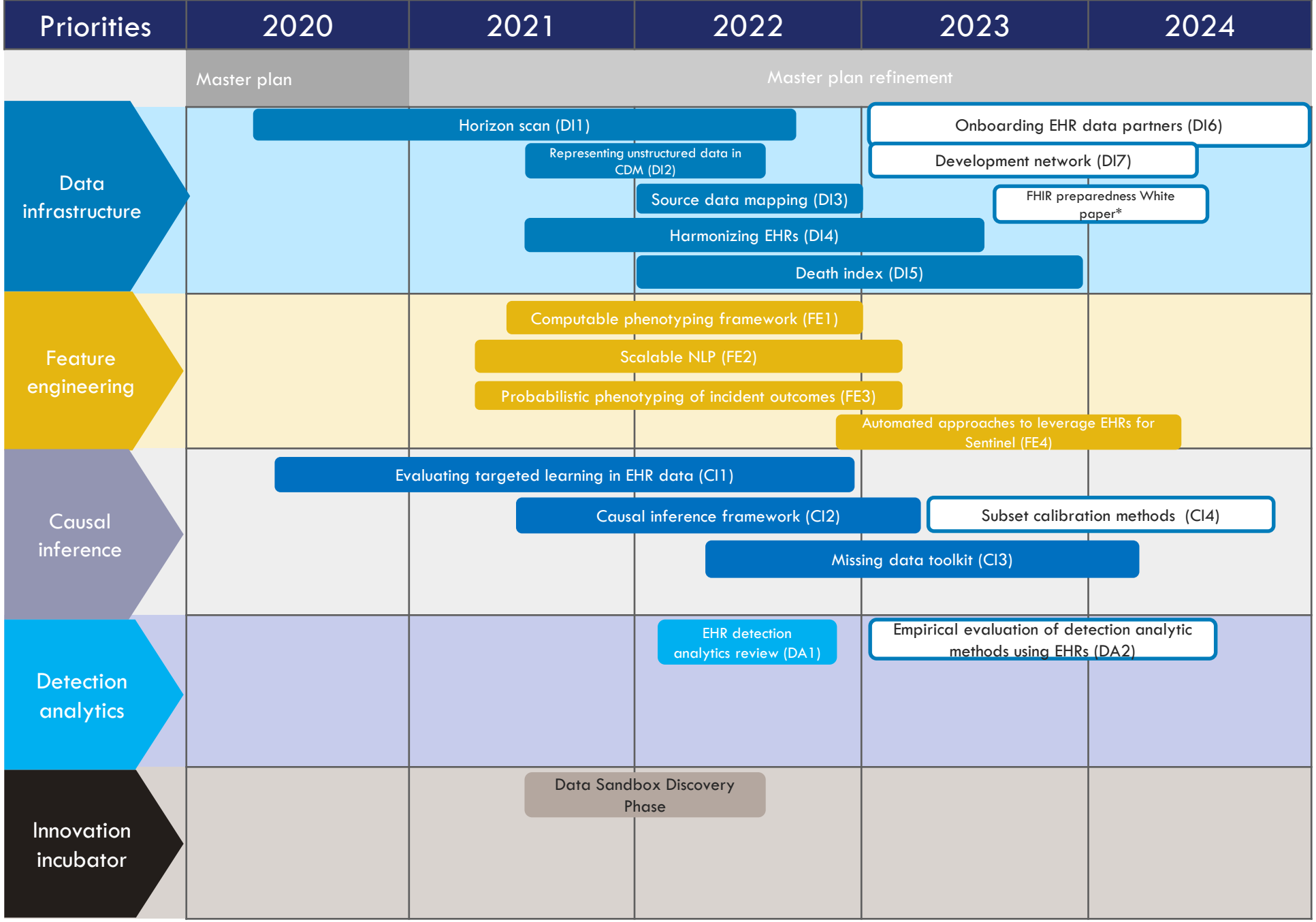
Sentinel Innovation Center VISION

Improve human health by expanding Sentinel's Active Risk Identification and Analysis (ARIA) capabilities to effectively use electronic health care data sources for drug safety surveillance and increase confidence in and use of real-world data for regulatory decision-making.



Sentinel Innovation Center MISSION

Establish a query-ready, quality-checked, distributed data network containing electronic health records with reusable analysis tools.



*ASPE supported project

Sentinel Innovation Center Executive Leadership Team

Sebastian Schneeweiss, MD, ScD
Brigham and Women's Hospital (Mass General Brigham)
Harvard Medical School

Lesley Curtis, PhD
Duke Clinical Research Institute,
Duke University

Jennifer Nelson, PhD
Kaiser Permanente Washington Health Research Institute

Kevin Johnson, MD, MS
University of Pennsylvania

Rishi Desai, MS, PhD
Brigham and Women's Hospital (Mass General Brigham)
Harvard Medical School

Keith Marsolo, PhD
Duke Clinical Research Institute,
Duke University

Patrick Heagerty, PhD
University of Washington

Michael Matheny, MD, MS, MPH
Vanderbilt University Medical Center

Broadening the Reach of the FDA Sentinel System: A Roadmap for Integrating Electronic Health Record Data in a Causal Analysis Framework

Rishi J. Desai, MS, PhD
Assistant Professor of Medicine
Division of Pharmacoepidemiology and Pharmacoeconomics
Department of Medicine
Brigham and Women's Hospital (Mass General Brigham), Harvard Medical School, Boston

Disclaimer

The views expressed in all presentations represent those of the presenters and do not necessarily represent the official views of the U.S. FDA.

Recognizing the Need to Harness Alternative Data Sources and Methods

Call for collaboration

Our Sentinel System experience suggests that improving the ability to define computable phenotypes in distributed networks is a critical next step that has multiple immediate downstream consequences that would benefit from a collaborative effort across disciplines. FDA's use case prioritizes identification of incident outcomes and onset dates rather than general assessments of whether a patient should be considered to have a specific condition or not. To that end, a critical step will be to develop best practices for populating common data models with information from EHRs that allows temporally sequenced analyses or information with specific dates of onset. While focused on HOIs, collaborative efforts (Table 2) will have broad value for other purposes and support the FDA's general mission to use RWD to inform decision-making.[39,40] The FDA recently funded an Innovations Center and a Community Building and Outreach Center that will provide a nexus for collaboration across disciplines and communities with a goal of improving Sentinel System functionality specifically, and real-world data capabilities generally.[41]

Brown et al. JAMIA 2020

FDA Budget Matters: A Cross-Cutting Data Enterprise for Real World Evidence

June 10, 2018

By: Scott Gottlieb, M.D.

Over time, as our experience with new medical products expands, our knowledge about how best to maximize their benefits and minimize any potential risks, sharpens with each data point we gather. Every clinical use of a product produces data that can help better inform us about its safety and efficacy.

FDA Commissioner Scott Gottlieb, MD

The FDA is committed to developing new tools to help us access and use data collected from all sources. This includes ways to expand our methodological repertoire to build on our understanding of medical products throughout their lifecycle, in the post market. We don't limit our knowledge to pre-market information, traditional de novo post-market studies, and passive reporting. Newer methodologies enable us to collect data from routine medical care and develop valid scientific evidence that's appropriate for regulatory decision making to help patients and health care providers prevent, diagnose, or treat diseases.

Sentinel Innovation Center Roadmap

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

10+ million people

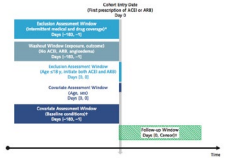
EHR + Claims

Assessing fit-for-purpose and data completeness in EHR-claims data

- Data leakage in EHR and continuity cohorts
- Non-random missingness in EHR data

Causal study design

Provide clarity on temporality and causal effects by using target trial thinking



Red text = Ongoing or new research effort

New user cohort design or variations

Pre-exposure data space

for **confounding** adjustment, subgroup identification

Known and measurable important risk factors

Addressing missing data in some EHR confounders

Individual considerations for analysis, e.g. individual variable matching before additional balancing?

Performance metrics and reporting standards

Automated feature generation algorithms

Feature type pre-processing:
1) Structured: Dx, Px, Rx
2) Semi-structured: Labs
3) Unstructured: Text notes

Automated assessment of likely confounding

Automated, optimized and scalable confounding adjustment, e.g. high-dimensional propensity scores, targeted maximum likelihood

Performance metrics and reporting standards

Complex treatment strategies: Time-varying confounding

Post-exposure data space

for **outcome** identification

Existing algorithm for outcome identification is acceptable

E.g. an acceptable validation shows good measurement characteristics

Outcome validation in a subset of patients is necessary

A new outcome definition needs validation but is thought to be generalizable and transportable to others

Outcome validation in all patients is necessary

Lack of a well-performing generalizable outcome algorithm persists and requires 100% abstraction

Single database study

- Automated feature generation algorithm
- Efficient Silver Standard (SS) definition using priors and unsupervised learning
- Electronic review tool to confirm Gold Standard (GS) in patients
- Supervised ML to optimize outcome identification; test generalizability
- Performance metrics

Multi database study

- Do we really need another database? value of information assessment.
- Assess code transportability to other EHR systems
- Electronic review tool to confirm GS in patients across multiple systems

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

10+ million people

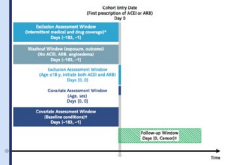
EHR + Claims

Assessing fit-for-purpose and data completeness in EHR-claims data

- Data leakage in EHR and continuity cohorts
- Non-random missingness in EHR data

CI2: Causal inference framework

New user cohort design or variations



Red text = Ongoing or new research effort

ML - augmented causal inference

Known and measurable important risk factors

FE2: NLP-based feature generation

Automated feature generation using claims

Feature type preprocessing:

1) Structured: Dx, Px, Rx
2) Semi-structured: Labs
3) Unstructured: Text notes

CI3: Missing data

Addressing missing data in some EHR confounders

Individual considerations for analysis, e.g. individual variable matching before additional balancing?

Performance metrics and reporting standards

CI1: Targeted learning in EHRs

Automated assessment of likely confounding

Automated, optimized and scalable confounding adjustment, eg high-dimensional propensity scores, targeted maximum likelihood

Performance metrics and reporting standards

Complex treatment strategies: Time-varying confounding

ML - supported endpoint identification

Existing algorithm for outcome identification is acceptable

E.g. an acceptable validation shows good measurement characteristics

Outcome validation in a subset of patients is necessary

A new outcome definition needs validation but is thought to be generalizable and transportable to others

Outcome validation in all patients is necessary

Lack of a well-performing generalizable outcome algorithm persists and requires 100% abstraction

FE1, FE3: NLP-based outcome phenotyping

Single database study

- Automated feature selection for algorithm
- Efficient Silver Standard (SS) definition using priors and unsupervised learning
- Electronic review tool to confirm Gold Standard (GS) in patients
- Supervised ML to optimize outcome identification; test generalizability
- Performance metrics

Multi database study

- Do we really need another database? value of information assessment.
- Assess code transportability to other EHR systems
- Electronic review tool to confirm GS in patients across multiple systems

PRINCIPLED: A PRocess guide for INferential studies using secondary data from routine ClinIcal Practice to evaLuate causal Effects of Drugs

Study planning

STEP 1

Well defined research question in the target trial framework

STEP 2

Determining fit-for-purpose data source

STEP 3

Refining target trial parameters considering measurement characteristics of the key variables in data source

STEP 4

Feasibility assessment including cohort feasibility, outcome feasibility, and diagnostic evaluations

STEP 5

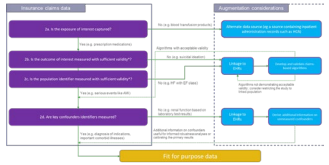
Robustness evaluations including deterministic sensitivity analyses, quantitative bias analyses, and net bias analyses

Inference

STEP 6

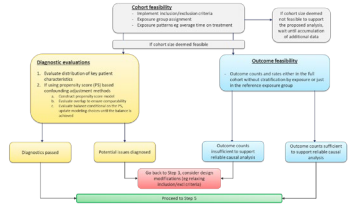
Inferential analysis

See Figure for Step 2

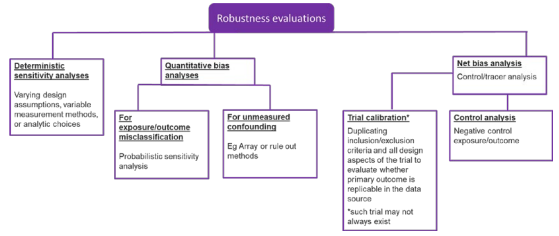


See Table for Step 3

See Figure for Step 4



See Figure for Step 5



Sentinel

Feature Engineering (FE 2): Advancing Scalable Natural Language Processing (NLP) Approaches for Unstructured Electronic Health Record Data

David S. Carrell, PhD

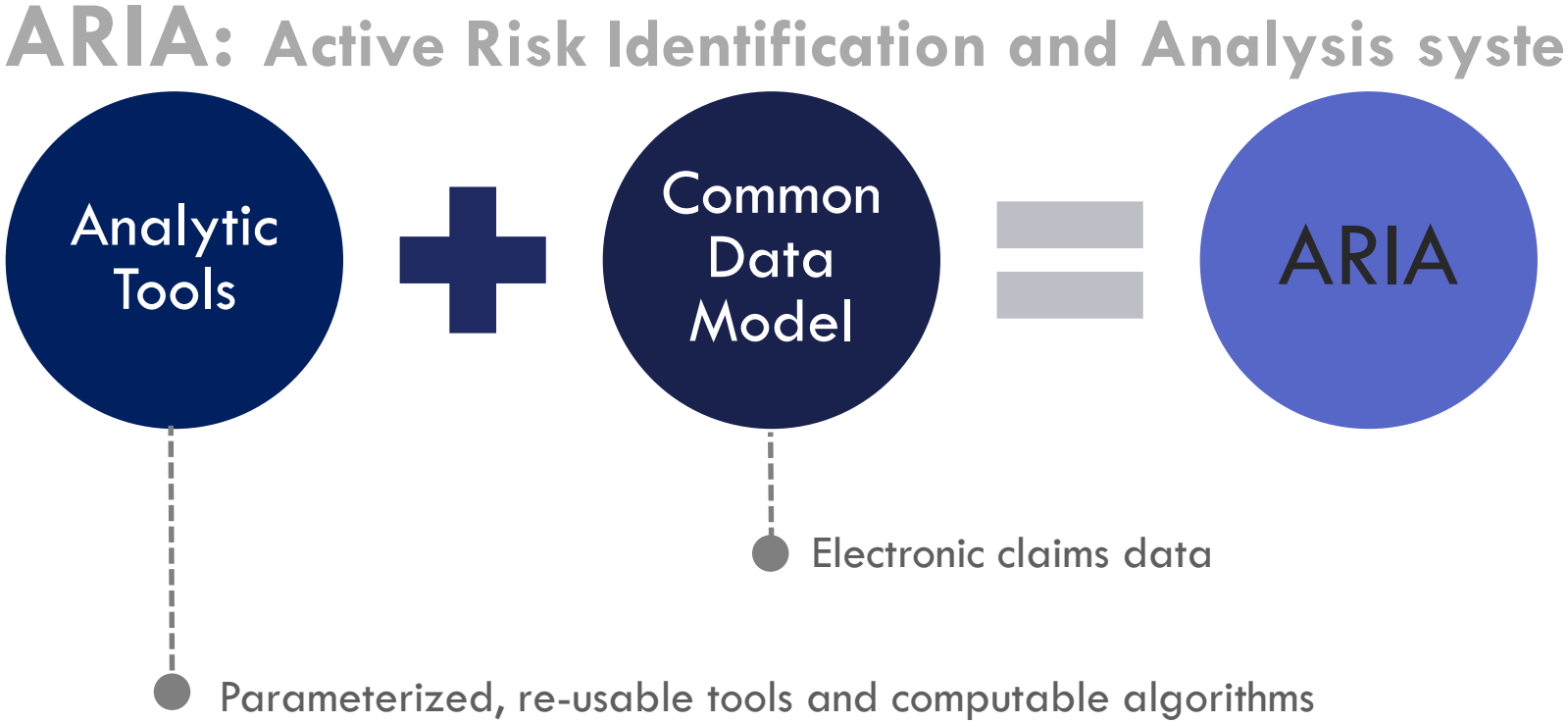
Kaiser Permanente Washington Health Research Institute

Agenda

- **Motivation**
  - Improving the sufficiency of Sentinel's ARIA system for automated identification of health outcomes of interest
    - Existing approaches are sometimes insufficient
  - Reducing algorithm development time and cost burdens
    - Feature engineering burden
    - Gold standard data creation burden
- **Objective**
  - Investigate whether scalable NLP approaches can improve outcome identification *and* reduce development time and cost burdens
- **Automating Algorithm Development**
  - Example: Identifying patients with COVID-19 disease
- **Results: COVID-19 Automated Algorithm**
- **Future Work**

Motivation

Motivation: Improve ARIA Sufficiency



Slide courtesy of Michael Nguyen

Motivation: Improve ARIA Sufficiency

ARIA is sufficient when …

- Data are adequate for identifying:
  - Health outcome of interest (HOI)
  - Exposure & comparator groups
  - Confounders & covariates
- Methods can assess:
  - Exposure-related risk
  - With satisfactory precision

ARIA was insufficient in 2016-2018 …

- For 51% of drug-adverse event pairs (45/89)
- Inadequate identification of HOI: n=38

Motivation: Improve ARIA Sufficiency

ARIA *sufficient* outcomes

- GI bleeding
- Heart failure
- Lymphoma
- MACE (cardiac)
- MI
- MS relapse
- Non-melanoma skin cancer
- Seizure
- Stroke

ARIA *insufficient* outcomes

- Acute pancreatitis
- Adverse fetal outcomes
- Adverse pregnancy outcomes
- Anaphylaxis
- Drug-induced liver injury
- Fatal MACE (cardiac)
- Malignancies (several)
- Nerve injury
- Suicide/ideation

Questions

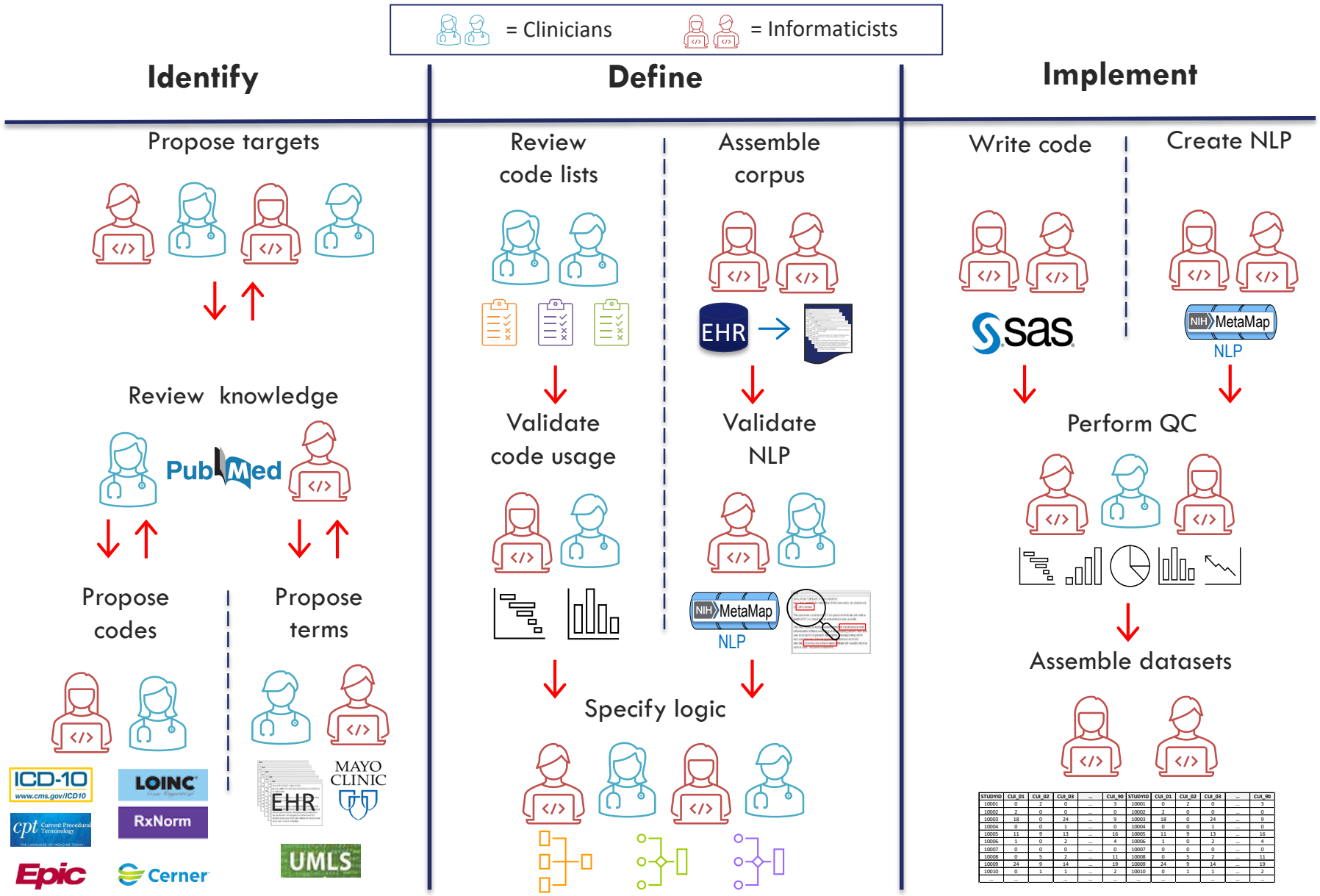
- Can *NLP-extracted data* improve capture of clinically complex outcomes?
- Can *scalable development approaches* yield algorithms with sufficiently good performance?

Motivation: Reducing Time & Cost Burdens of Developing Automated Algorithms

1. **Feature engineering burden (traditional, manual)**
   - Expert-intensive (clinical, EHR, NLP expertise)
     - May not be available in all settings
     - Expensive
     - Potential operator-dependence
   - Time-intensive
     - Pressure to limit the number of features engineered
2. **Gold standard data burden (manual chart review)**
   - Expert-intensive (*same as above*)
   - Time-intensive
     - Limits the amount of labeled data available for model training

} Time/cost burdens constrain the number of outcomes a team can investigate

Motivation: Feature Engineering Burden

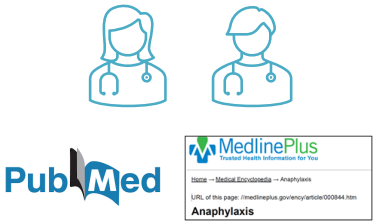


Motivation: Gold Standard Burden

= Clinicians = Informaticists = Chart abstractors

Define Outcome

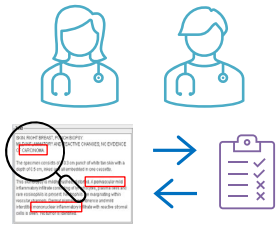
Identify diagnostic criteria



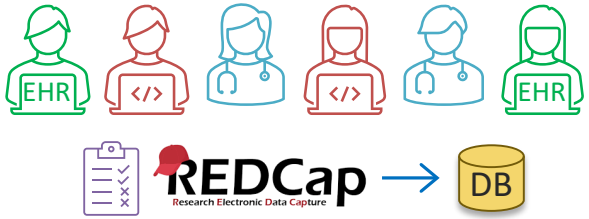
Operationalize diagnostic criteria

Develop Protocol

Develop abstraction guidelines, rules

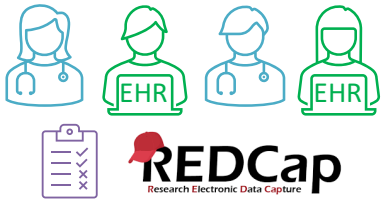


Create/pilot/revise abstraction forms



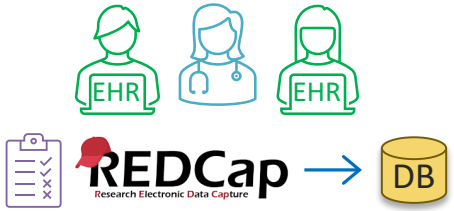
Review Charts

Train chart abstractors



Assess agreement (IRR)

Review charts



Objective

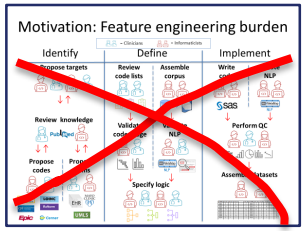
Objective: Scalable NLP in Sentinel

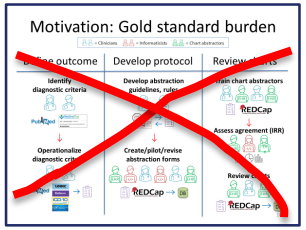
- Can *scalable NLP methods* improve outcome identification in Sentinel?
- *"Scalable"* methods are:
  - Affordable
  - Timeline-friendly
  - Applicable to diverse Sentinel Data Partners with
    - Heterogeneous data sources
    - Varying access to technical experts

Automating Algorithm Development

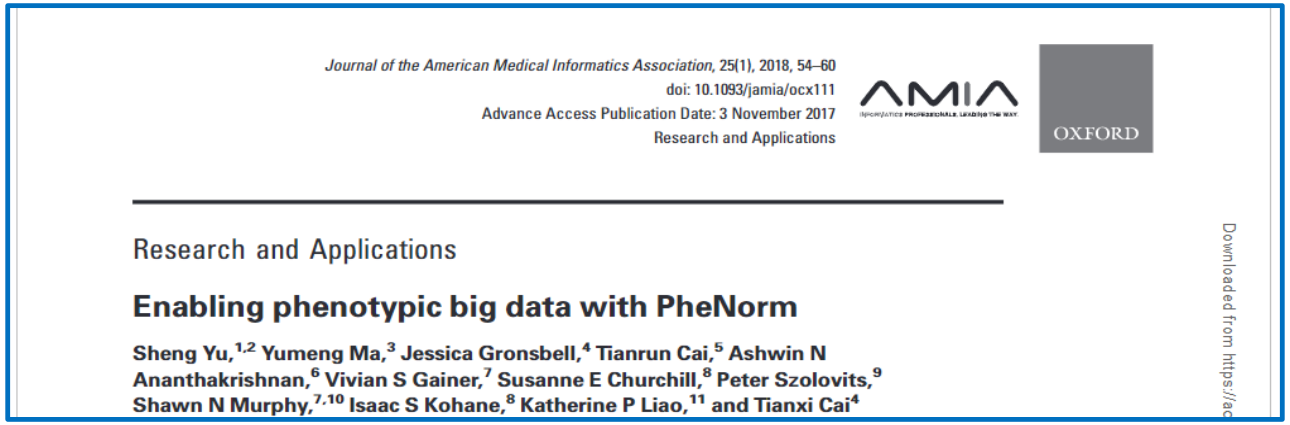
Automating Algorithm Development

- **PheNorm*** -- a general-purpose automated approach to creating computable phenotype algorithms using:
  - *NLP* for feature engineering
  - *Silver-standard* surrogate labels
  - *Machine learning* for model training





* Sheng Yu and colleagues, JAMIA 2018 https://pubmed.ncbi.nlm.nih.gov/29126253/



Journal of the American Medical Informatics Association, 25(1), 2018, 54–60
doi: 10.1093/jamia/ocx111
Advance Access Publication Date: 3 November 2017
Research and Applications

Research and Applications

Enabling phenotypic big data with PheNorm

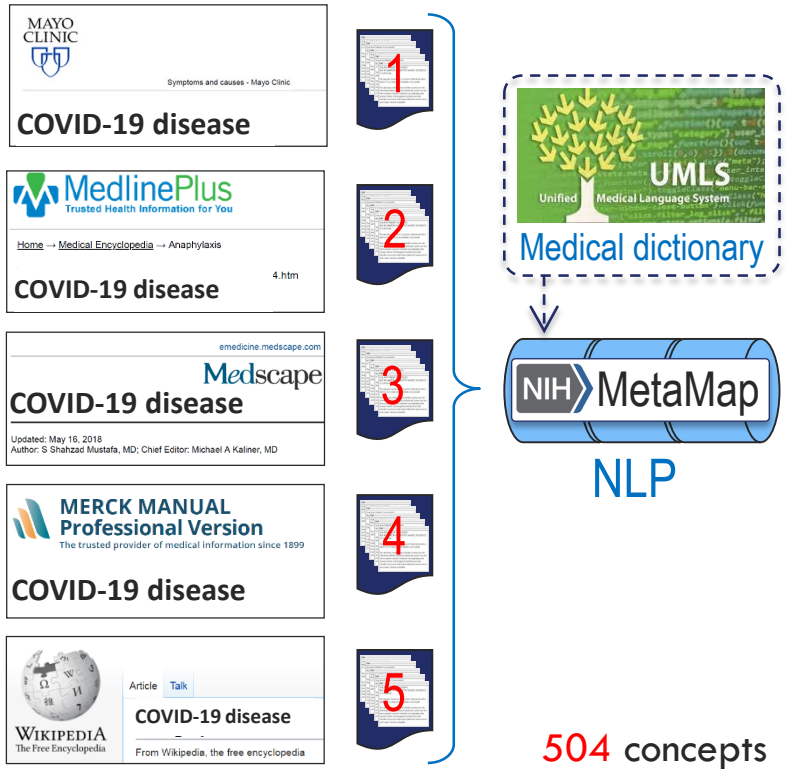
Sheng Yu,[1,2] Yumeng Ma,[3] Jessica Gronsbell,[4] Tianrun Cai,[5] Ashwin N Ananthakrishnan,[6] Vivian S Gainer,[7] Susanne E Churchill,[8] Peter Szolovits,[9] Shawn N Murphy,[7,10] Isaac S Kohane,[8] Katherine P Liao,[11] and Tianxi Cai[4]

Downloaded from https://ac

Automating Algorithm Development

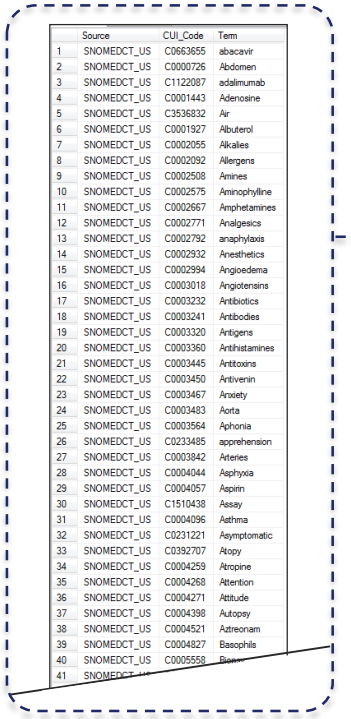
- *NLP* for feature engineering*

1. Mine medical concepts from clinical knowledge articles (COVID-19 disease)



504 concepts

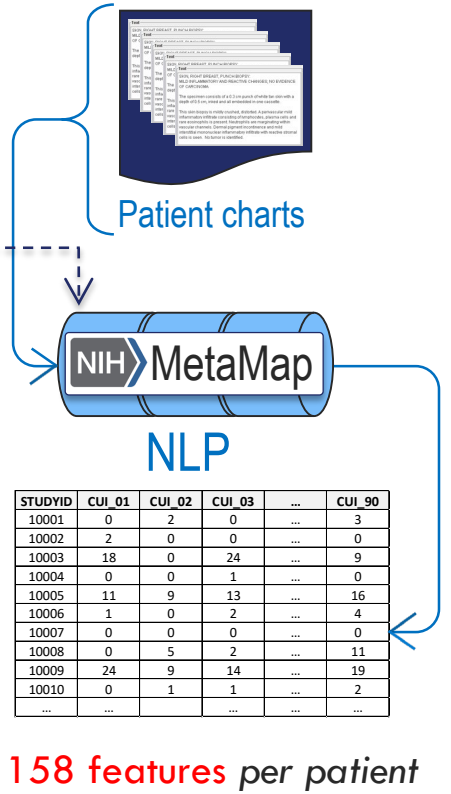
2. Keep concepts in any 3 of 5 articles



	Source	CUI_Code	Term
1	SNOMEDCT_US	C0663655	abacavir
2	SNOMEDCT_US	C0000726	Abdomen
3	SNOMEDCT_US	C1122087	adalimumab
4	SNOMEDCT_US	C0001443	Adenosine
5	SNOMEDCT_US	C3536832	Air
6	SNOMEDCT_US	C0001927	Albuterol
7	SNOMEDCT_US	C0002055	Alkalies
8	SNOMEDCT_US	C0002092	Allergens
9	SNOMEDCT_US	C0002508	Amines
10	SNOMEDCT_US	C0002575	Aminophylline
11	SNOMEDCT_US	C0002667	Amphetamines
12	SNOMEDCT_US	C0002771	Analgesics
13	SNOMEDCT_US	C0002792	anaphylaxis
14	SNOMEDCT_US	C0002932	Anesthetics
15	SNOMEDCT_US	C0002994	Angioedema
16	SNOMEDCT_US	C0003018	Angiotensins
17	SNOMEDCT_US	C0003232	Antibiotics
18	SNOMEDCT_US	C0003241	Antibodies
19	SNOMEDCT_US	C0003320	Antigens
20	SNOMEDCT_US	C0003360	Antihistamines
21	SNOMEDCT_US	C0003445	Antitoxins
22	SNOMEDCT_US	C0003450	Antivenin
23	SNOMEDCT_US	C0003467	Anxiety
24	SNOMEDCT_US	C0003483	Aorta
25	SNOMEDCT_US	C0003564	Aphonia
26	SNOMEDCT_US	C0233485	apprehension
27	SNOMEDCT_US	C0003842	Arteries
28	SNOMEDCT_US	C0004044	Asphyxia
29	SNOMEDCT_US	C0004057	Aspirin
30	SNOMEDCT_US	C1510438	Assay
31	SNOMEDCT_US	C0004096	Asthma
32	SNOMEDCT_US	C0231221	Asymptomatic
33	SNOMEDCT_US	C0392707	Atopy
34	SNOMEDCT_US	C0004259	Atropine
35	SNOMEDCT_US	C0004268	Attention
36	SNOMEDCT_US	C0004271	Attitude
37	SNOMEDCT_US	C0004398	Autopsy
38	SNOMEDCT_US	C0004521	Aztreonam
39	SNOMEDCT_US	C0004827	Basophils
40	SNOMEDCT_US	C0005558	
41	SNOMEDCT_US		

158 of 504 in ≥3

3. Count mentions of each concept in patient chart



STUDYID	CUI_01	CUI_02	CUI_03	...	CUI_90
10001	0	2	0	...	3
10002	2	0	0	...	0
10003	18	0	24	...	9
10004	0	0	1	...	0
10005	11	9	13	...	16
10006	1	0	2	...	4
10007	0	0	0	...	0
10008	0	5	2	...	11
10009	24	9	14	...	19
10010	0	1	1	...	2
...	...		...	...	...

158 features *per patient*

* Yu et al. Toward high-throughput phenotyping: unbiased automated feature extraction and selection from knowledge sources. JAMIA 2015

Automating Algorithm Development

- *Silver-standard surrogate labels* *

What's a good silver label?

- Anything countable for a patient believed to be associated with the phenotype

Our silver labels: *Patient-level counts* of

- N days with a COVID-19 dx (U07.1)
- N days with any COVID-19-related dxs (U07.1, J12.81, J12.82, B34.2, B97.21, B97.29)
- N mentions of "COVID-19" in chart notes

N days w/ a COVID-19 dx	
Count	Percent
0	18%
1	50%
2	15%
3	7%
4	4%
5	2%
6-29	4%
	100%

* Yu et al., Enabling phenotypic big data with PheNorm, JAMIA 2018.

Automating Algorithm Development

Sample demographics by Study Site.					
		VUMC		KPWA	
		Patients	Percent	Patients	Percent
Gender Female					
	no	**10216**	42%	3492	42%
	yes	**14088**	58%	4837	58%
Ethnicity Hispanic					
	no	**23283**	96%	7573	91%
	yes	1021	4%	756	9%
Race White					
	no	7840	32%	2994	36%
	yes	16464	68%	5335	64%
Age Range					
	18-29	5672	23%	1104	13%
	30-49	8196	34%	2503	30%
	50-69	7465	31%	3126	38%
	70+	2971	12%	1596	19%
Total		**24304**	**100%**	**8329**	**100%**

Gold standard reviews for evaluation: 484 437 (~60% true cases)

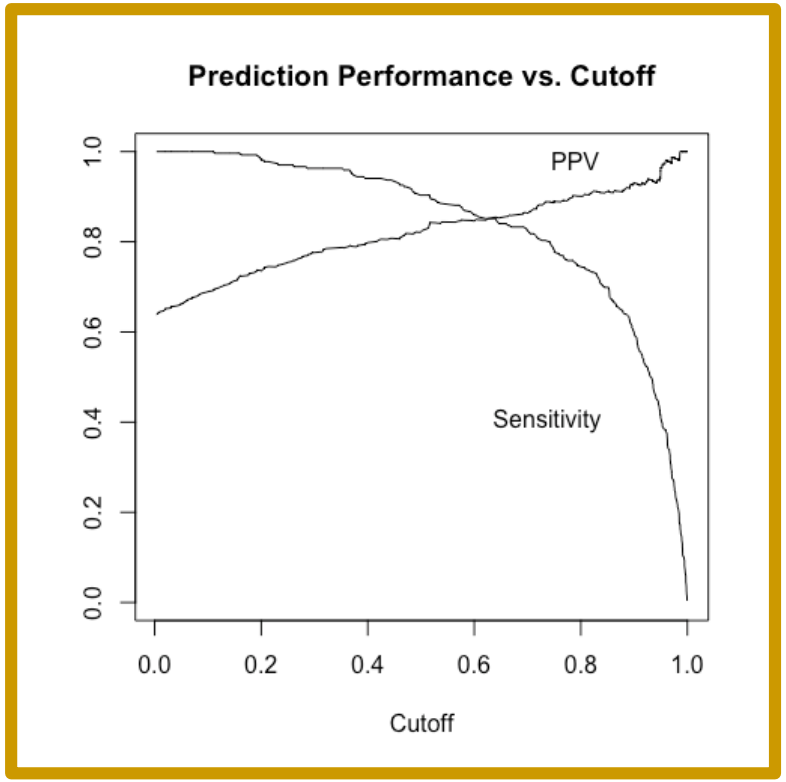
Results

Results: COVID-19 Automated Algorithm

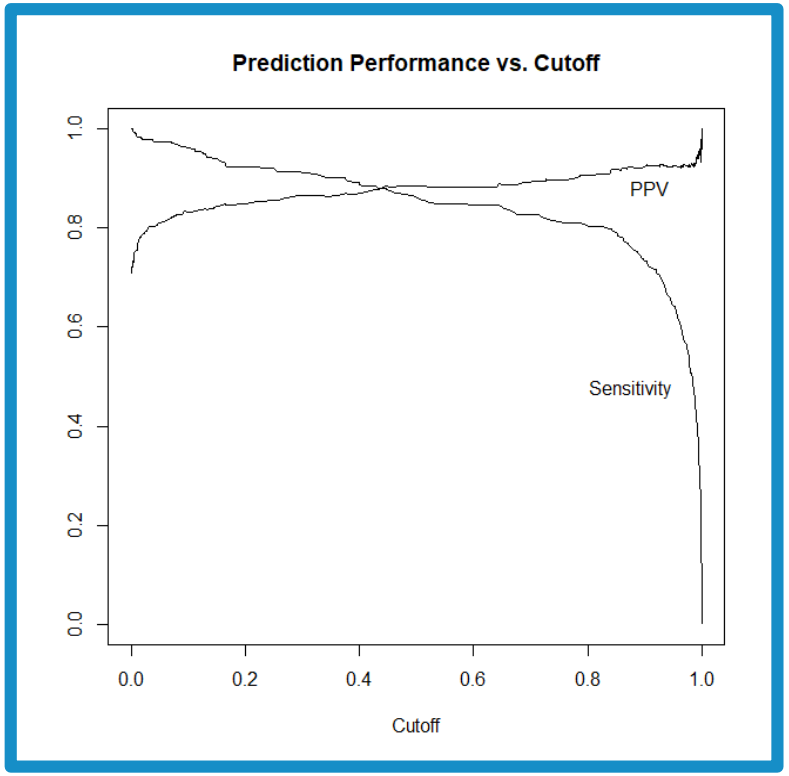
Silver-standard label	Site	AUC	Sensitivity at PPV=0.80
N days w/ COVID-19 dx	KPWA	.773	.89
	VUMC	.901	.99
N days w/ COVID-19-related dxs	KPWA	.766	.88
	VUMC	.899	.95
N mentions of “COVID-19” (NLP)	KPWA	.864	.98
	VUMC	.887	.94

Automating Algorithm Development

VUMC



KPWA



- Achieved strong performance …
- With modest expertise …
- On a reasonable timeline …
- In heterogeneous Sentinel sites (VU, KP)

} *Scalable* NLP

Future Work

Future Work

- Apply automated development methods to more phenotypes (FDA outcomes of interest)
- Apply to *sub*-phenotypes (e.g., "*high-severity* [outcome]")
- Assess relevance of negation for NLP feature engineering
- Propose strategies for defining silver-standard labels relevant to acute health conditions

Acknowledgements: Scalable NLP (COVID-19) Project Team

Food and Drug Administration
- Danijela Stojanovic
- Saranrat Wittayanukorn
- Yueqin Zhao

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- Darren Toh

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- Shamika More
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Kaiser Washington
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- Linda Kiel
- Arvind Ramaprasan
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- Brian Williamson
- Jing Zhou

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Vanderbilt University
- Michael Matheny
- Michael McLemore
- Joshua Osmanski
- Daniel Park
- Joshua Smith
- Dax Westerman
- Jill Whitaker
- Robert Winter

University of Pennsylvania
- Kevin Johnson

** alphabetical by last name*

Related Work: Sentinel Advanced Phenotyping Framework Team

Food and Drug Administration
- Adebola Ajao
- Robert Ball
- Steven Bird
- Sara Karami
- Yong Ma
- Michael Nguyen
- Danijela Stojanovic
- Mingfeng Zhang
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- Mayura Shinde

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- Monica Fujii
- Vina Graham
- Kara Haugen
- Ron Johnson
- Jennifer Nelson
- Mary Shea
- Jing Zhou

University of Washington
- Patrick Hagerty

University of Michigan
- Xu Shi

Kaiser Northwest
- Andrew Felcher
- Brian Hazlehurst
- Denis Nyongesa
- Daniel Sapp
- Matthew Slaughter

Putnam Data Science
- Susan Gruber

Vanderbilt University
- Cosmin (Adi) Bejan

HealthCore
- Kevin Haynes

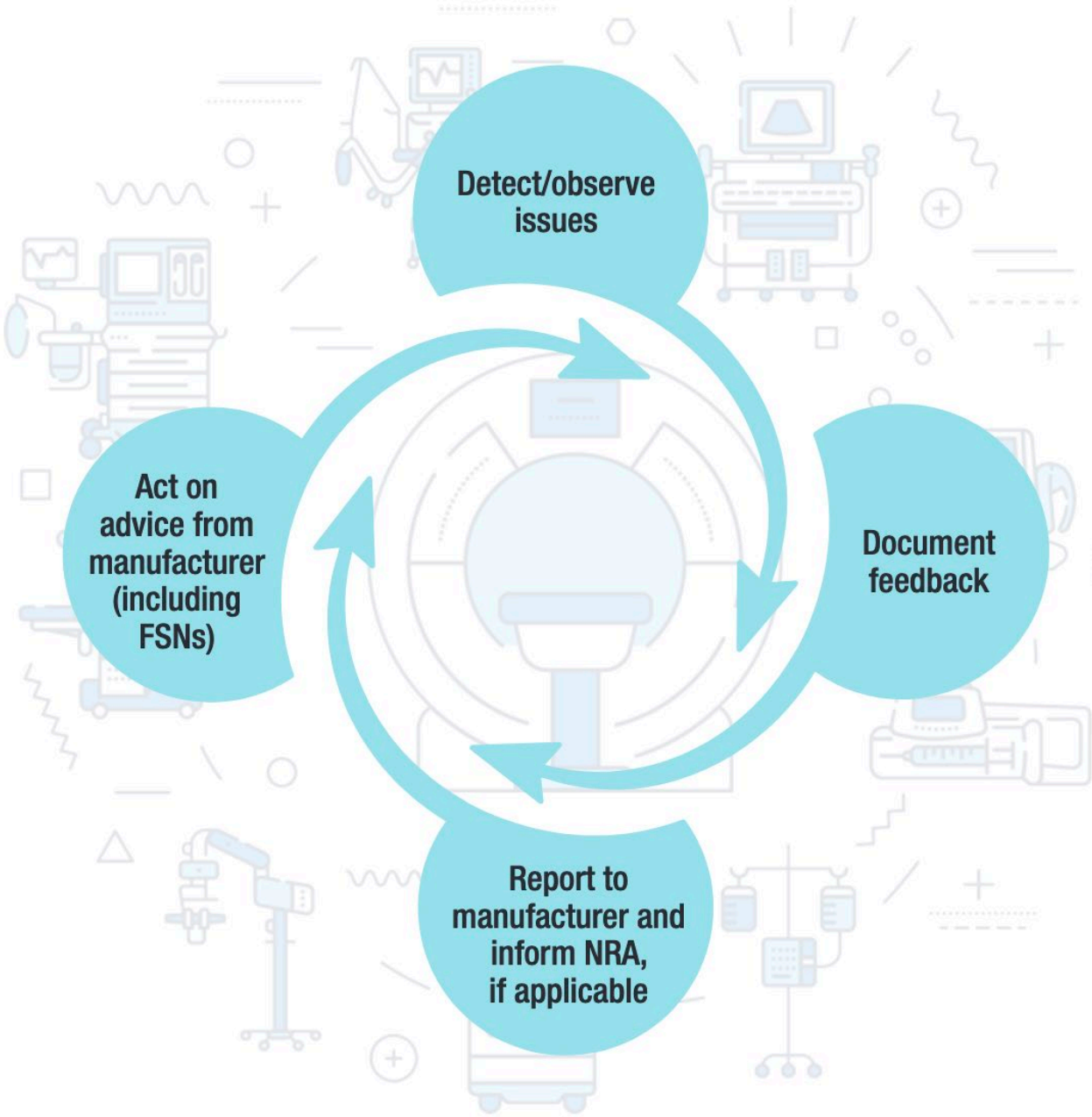
** alphabetical by last name*

Sentinel

Feature Engineering (FE 3): Improving Probabilistic Phenotyping of Incident Outcomes with Natural Language Processing

Colin G. Walsh, MD, MA
Associate Professor of Biomedical Informatics, Medicine & Psychiatry
Vanderbilt University Medical Center

Fig. 2.
Actions of users in relation to manufacturers' post-market surveillance



Guidance for post-market surveillance and market surveillance of medical devices, including in vitro diagnostics

World Health Organization

Imagine a new medication or device enters the market

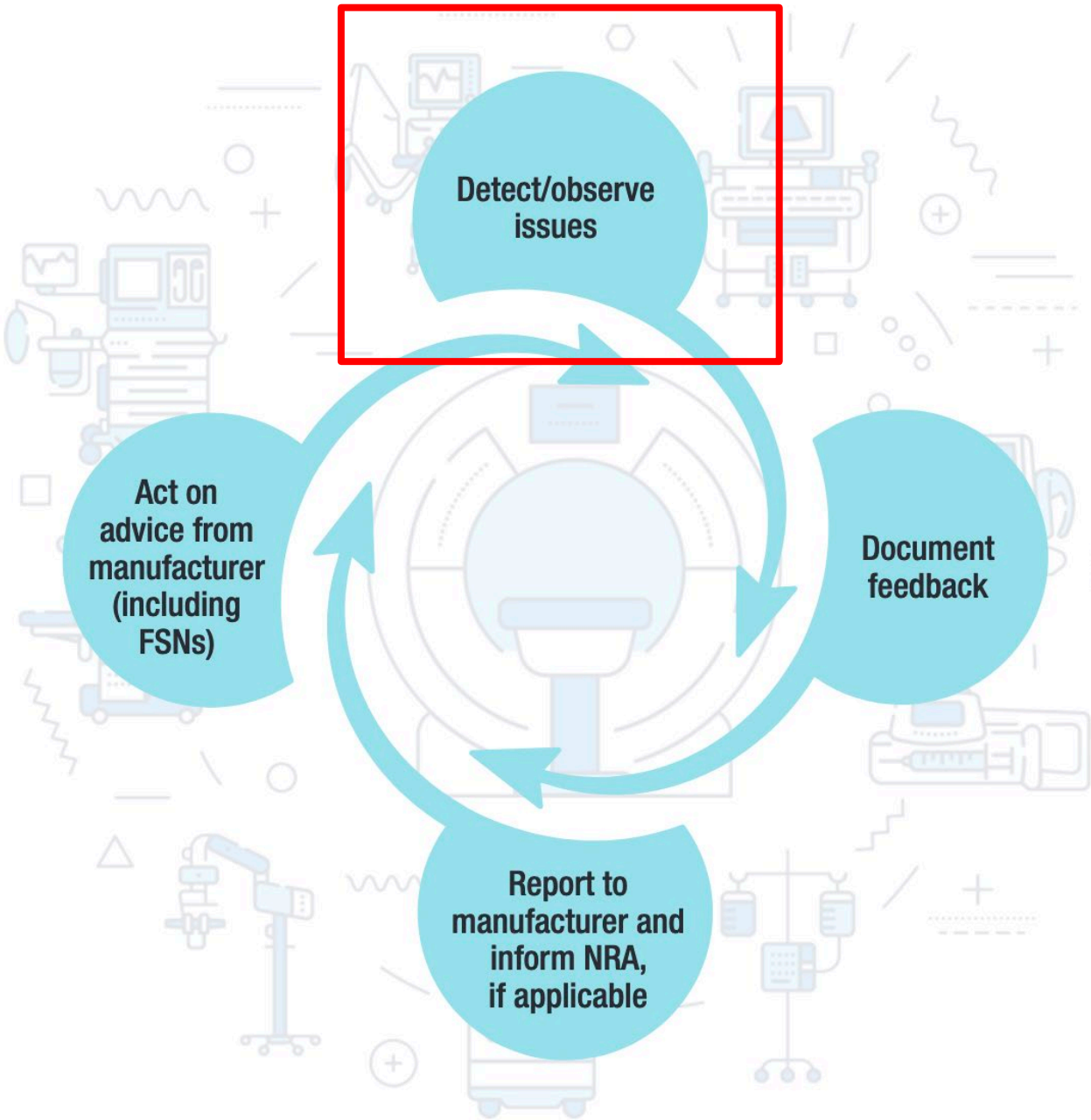
Millions of patients might receive it across thousands of sites

How do we 1) identify **adverse events with 2) messy, noisy data** in **diverse** clinical settings 3) **at-scale?**

Guidance for post-market surveillance and market surveillance of medical devices, including in vitro diagnostics

World Health Organization

Fig. 2.
Actions of users in relation to manufacturers' post-market surveillance



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doi: 10.1093/jamia/ocx059
Advance Access Publication Date: 8 July 2017
Research and Applications

Research and Applications

Mining 100 million notes to find homelessness and adverse childhood experiences: 2 case studies of rare and severe social determinants of health in electronic health records

Cosmin A Bejan,[1] John Angiolillo,[2] Douglas Conway,[3] Robertson Nash,[2] Jana K Shirey-Rice,[3] Loren Lipworth,[2] Robert M Cronin,[1,2,4] Jill Pulley,[3] Sunil Kripalani,[2] Shari Barkin,[4] Kevin B Johnson,[1,4] and Joshua C Denny[1,2]

Finding phenotypes using clinical text -> Natural Language Processing (NLP)

We Have to Deal with Time and States

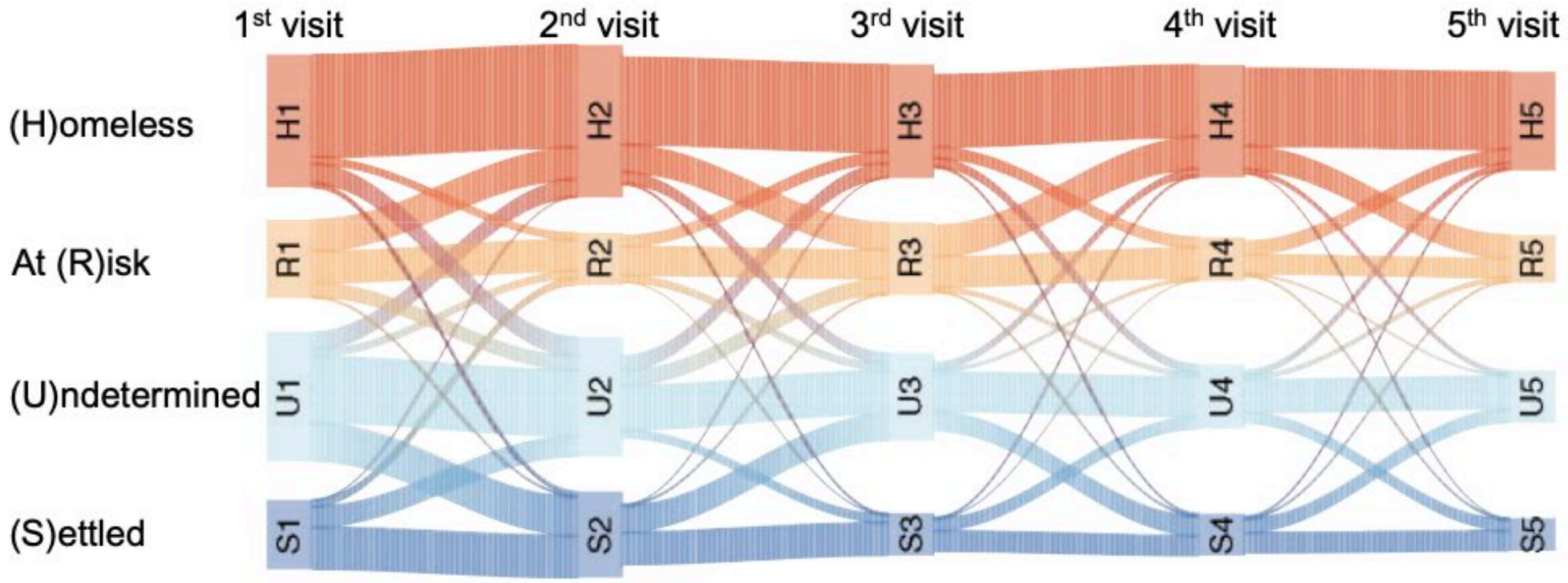


Figure 6. Trends in homelessness status across patient visits

Testing Generalizability of the NLP on a New Phenotype

We showed good precision without differences by coded race. Would performance generalize to a new phenotype?

Secondary descriptive type

John Everett Millais, *The Somnambulist*, 1871

New Phenotype

Sleep-related Behaviors

Priorities in Selection

Of interest to the FDA Sentinel IC, e.g., “would it prompt a black-box warning?”

Feasible for text extraction

Diagnostic codes an imperfect current state solution

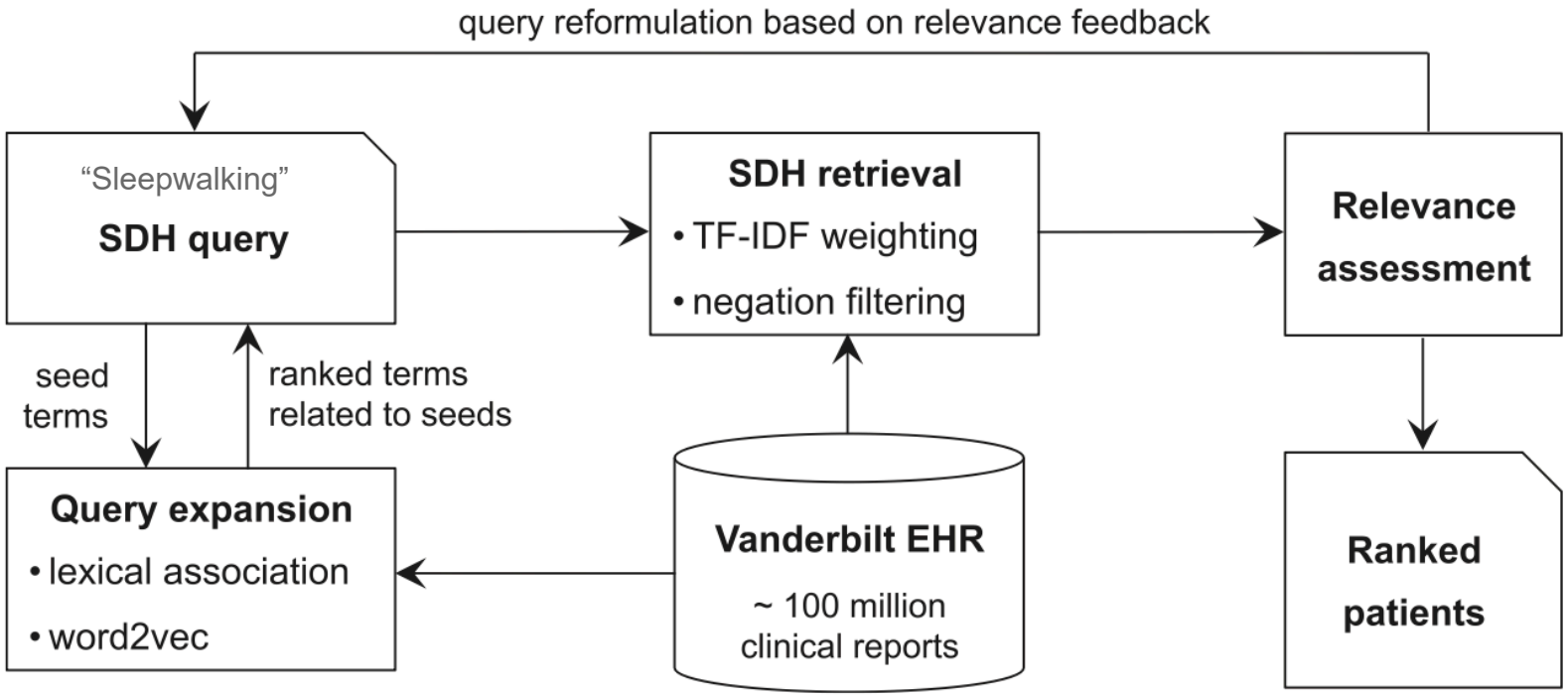
Subtypes of Sleep-related Behaviors

Sleep-walking
Sleep-eating
Sleep-driving

ir.re10
~~parasomnia~~
sleep (-)* walk
sleep (-)* driv(e|ing)
asleep while driving
sleep (-)* eat

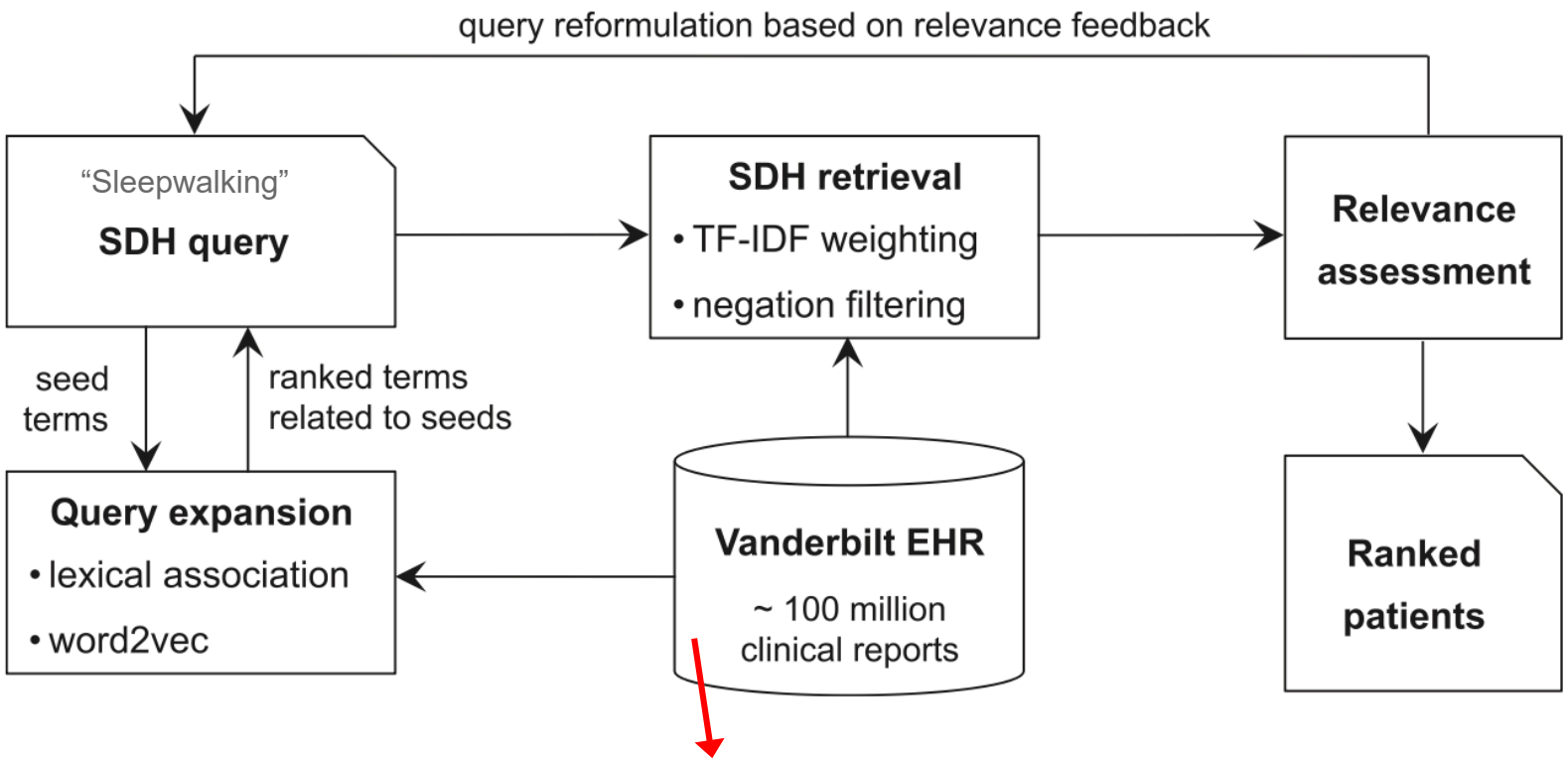
Methods: Natural Language Processing (NLP) Architecture

SDH = Social Determinants of Health



https://doi.org/10.1093/jamia/ocx059

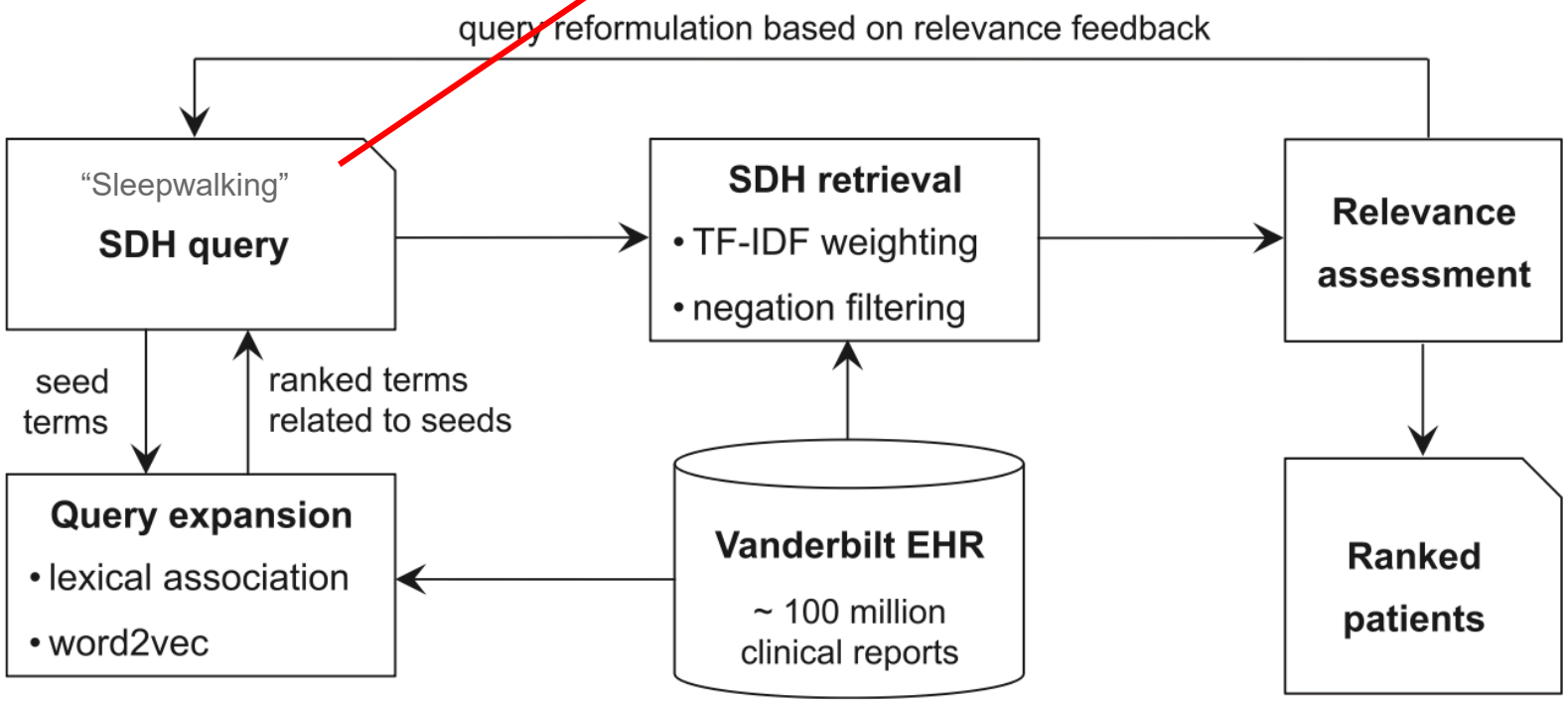
Methods: NLP Architecture



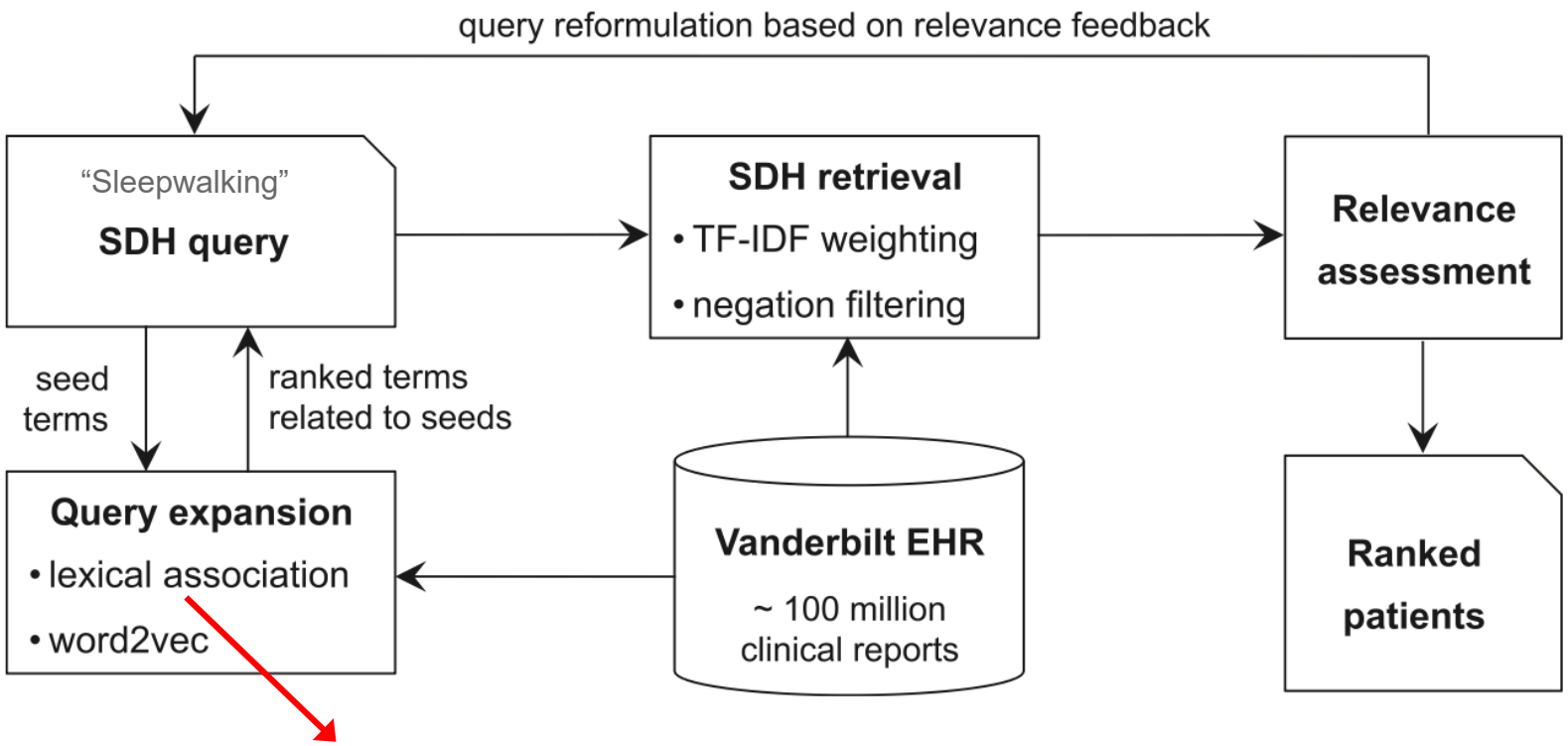
Our data source (could be any source of clinical text – agnostic to setting and formatting)

Methods: NLP Architecture

What are the phrases used to direct the NLP algorithm?



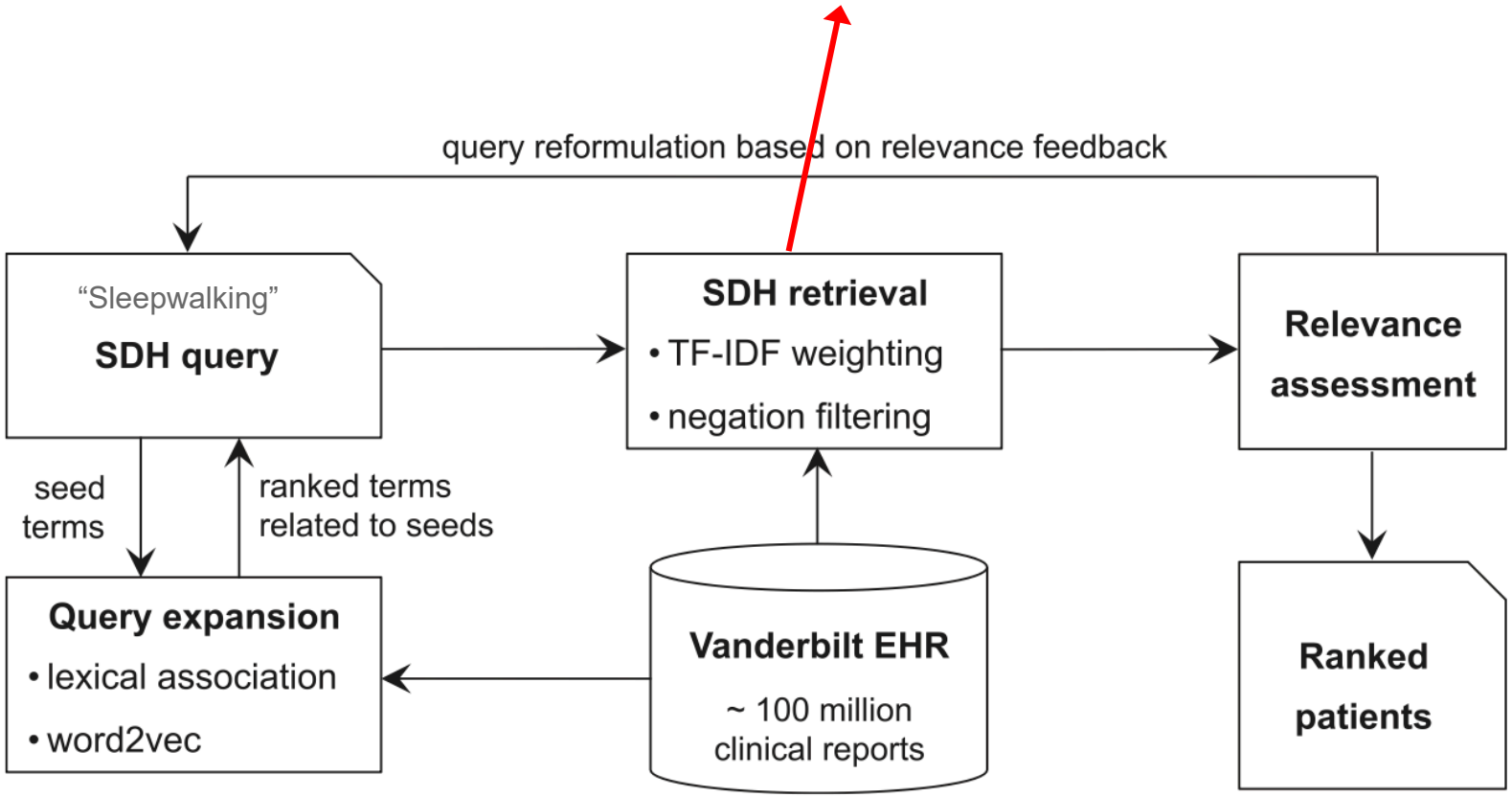
Methods: NLP Architecture



Turn patterns of words into numbers
"King – Man = Queen"

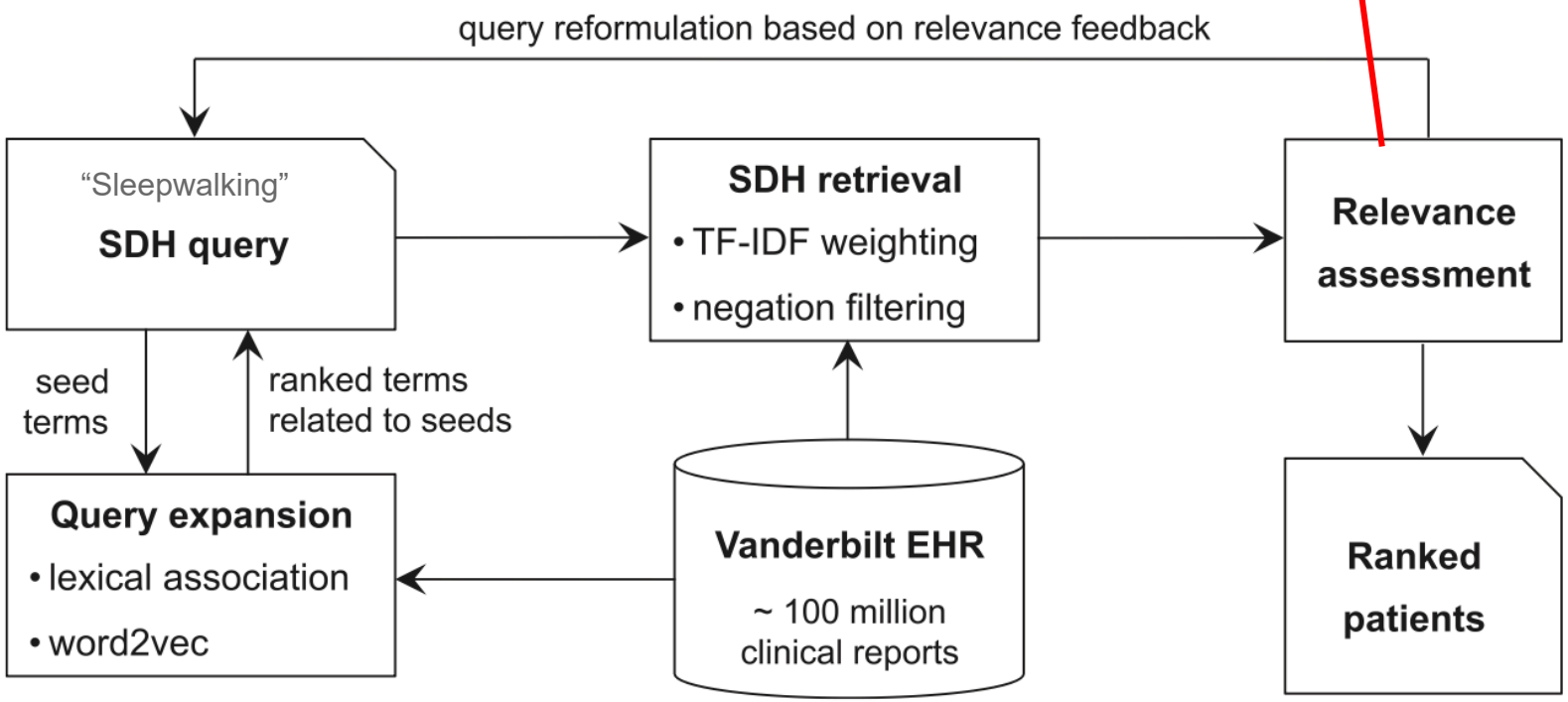
Methods: NLP Architecture

Handle negation "denied symptoms"



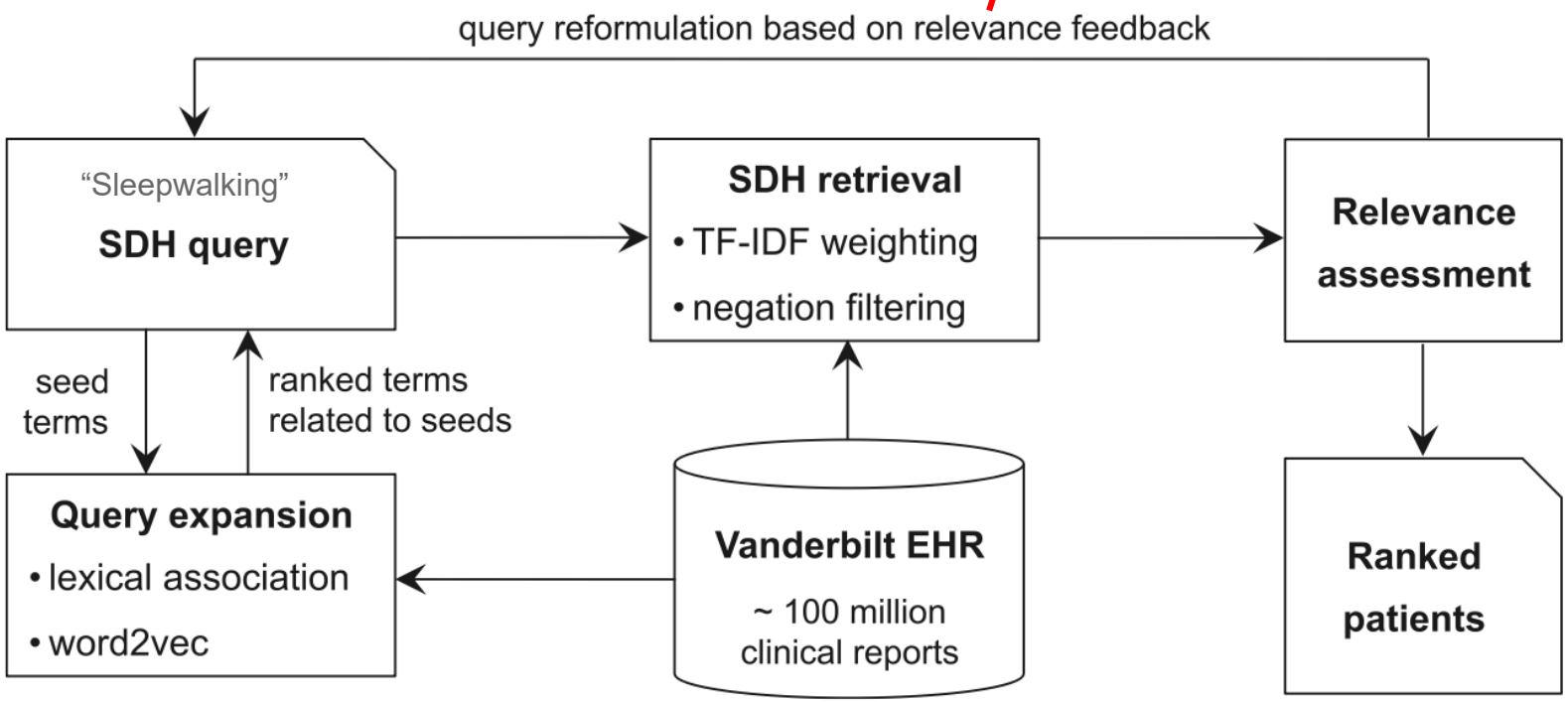
Methods: NLP Architecture

Humans in the loop -> review the results!

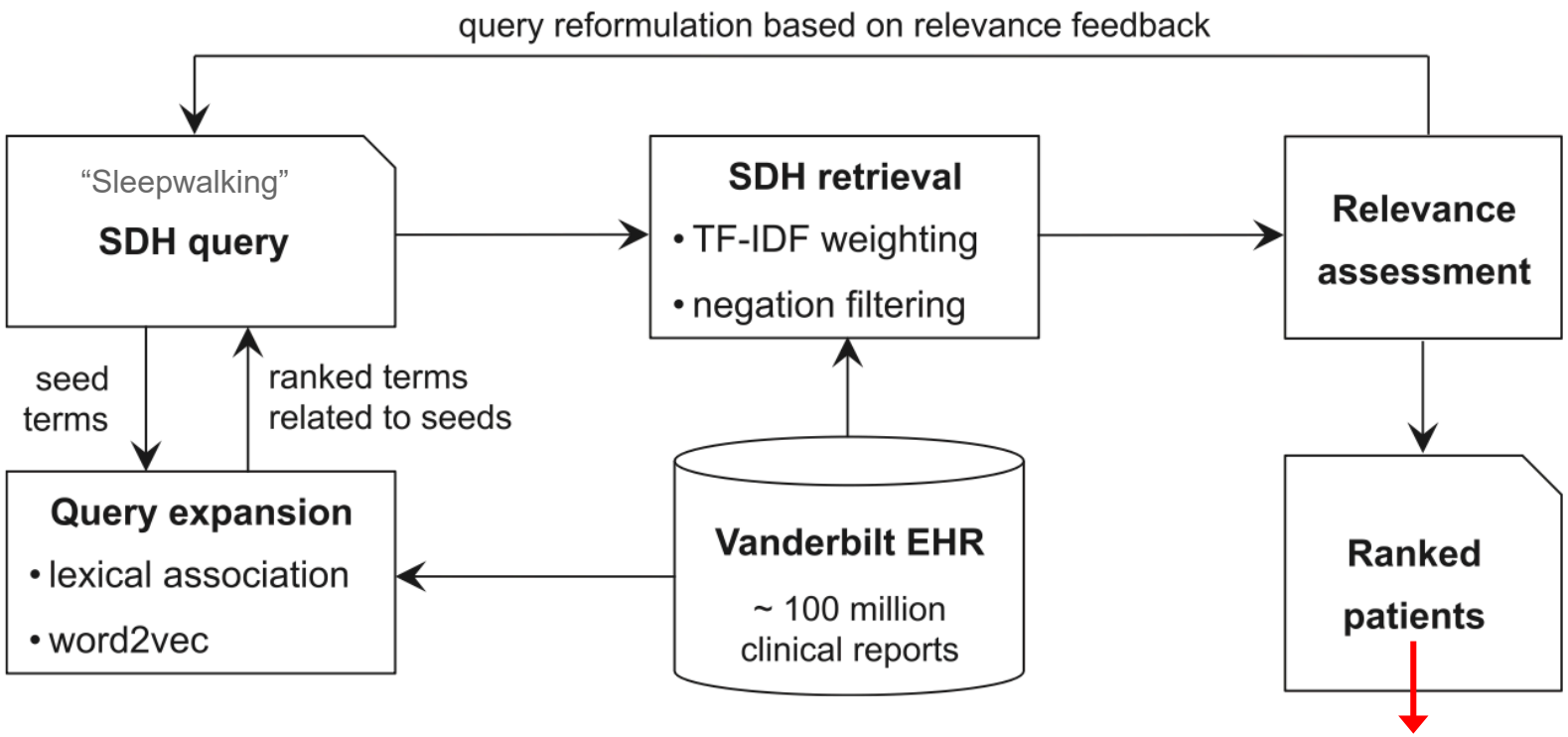


Methods: NLP Architecture

Based on human feedback, go back and refine



Methods: NLP Architecture



Send these results for full manual chart validation, multiple reviewers and formal guidelines

The Current Pipeline

NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

Apply a “silver standard” if possible to obtain preliminary performance estimates

Use prelim performance to determine sample sizes for chart validation across score distribution

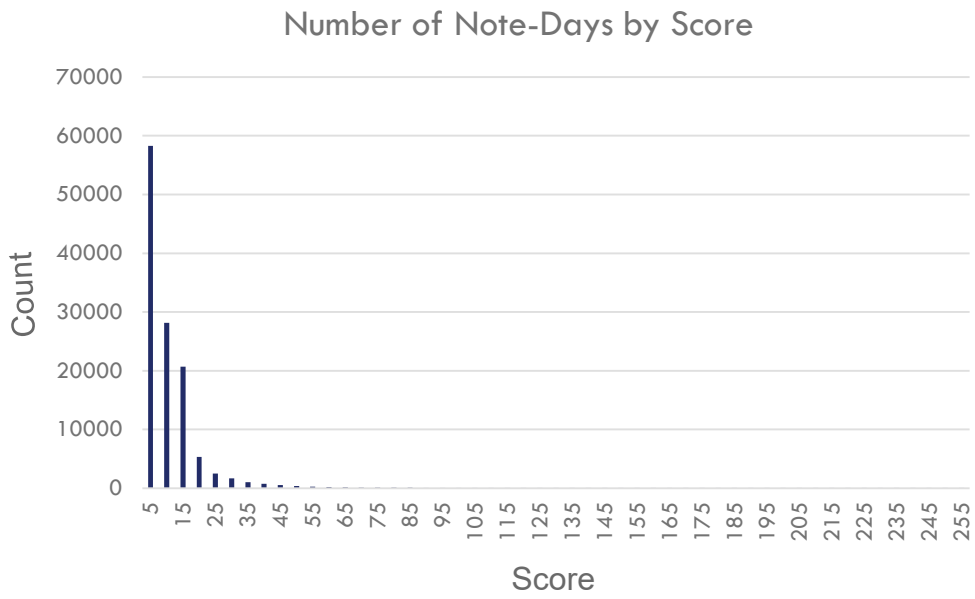
Perform manual chart validation

The Current Pipeline

NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

120K charts with scores



Score = likelihood text describes the phenotype (higher, more likely)

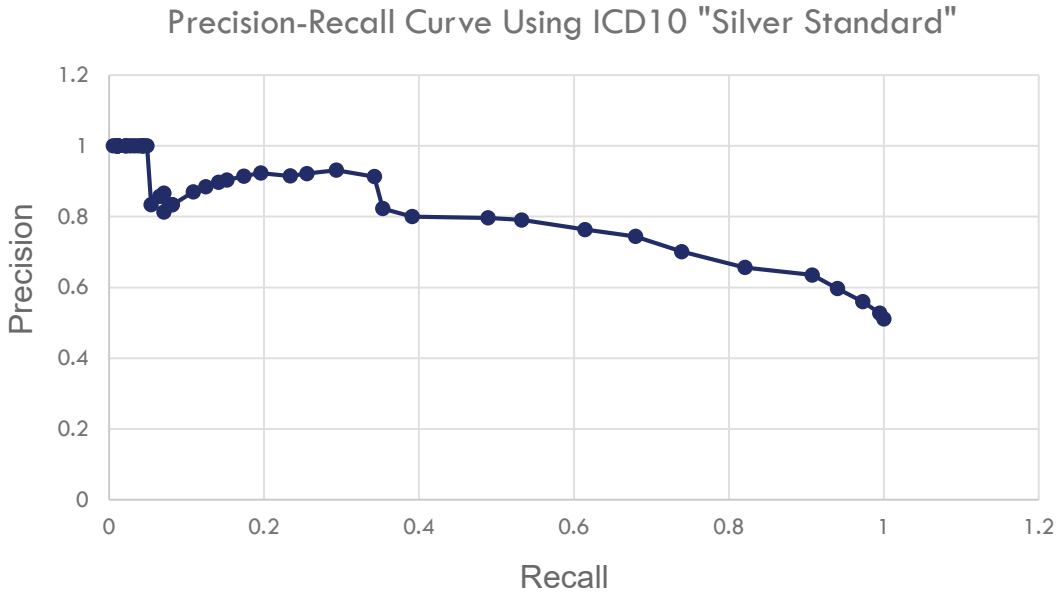
The Current Pipeline

NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

Apply a “silver standard” if possible to obtain preliminary performance estimates

Name	ICD-9-CM	ICD-10-CM
Sleepwalking	307.46	F51.3
Sleepwalking (somnambulism)	307.46	F51.3
Sleepwalking disorder	307.46	F51.3
Night-waking disorder with sleepwalking	307.46, 327.37	F51.3, G47.27
Partial-arousal sleep disorder with sleepwalking	307.46	F51.3
Night-waking disorder, sleepwalking type	307.46, 327.37	F51.3, G47.27
Sleep walking and eating	307.46	F51.3
Sleep related eating disorder	327.49	G47.8
Sleep-related eating disorder	327.49	G47.8
Nocturnal sleep-related eating disorder	307.50, 780.59	G47.8
Somnambulance	307.46	F51.3
Somnambulism	307.46	F51.3
Somnambulism with sleep terror disorder	307.46	F51.3, F51.4



“Silver standard” = reasonable proxy for the outcome but not as rigorous as a gold standard, which is manual chart review here

The Current Pipeline

NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

Apply a “silver standard” if possible to obtain preliminary performance estimates

A note on “silver standards”

We want to estimate how many charts we need to review to be confident

We also want early benchmarks for comparison and to make sure our algorithm isn’t badly biased right at the start

The Current Pipeline

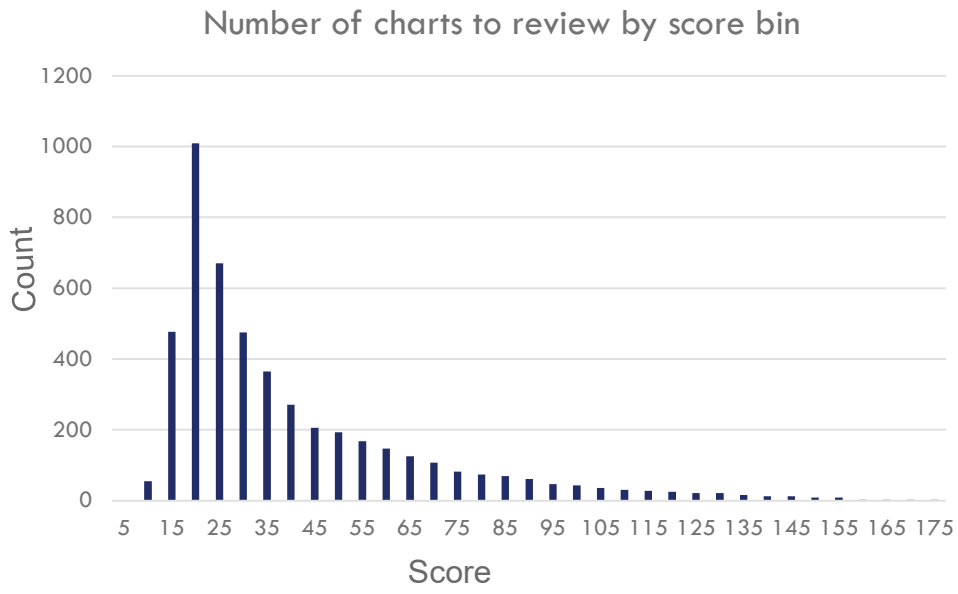
NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

Apply a “silver standard” if possible to obtain preliminary performance estimates

Use prelim performance to determine sample sizes for chart validation across score distribution

Score Bin = a small range of scores, e.g., scores 5 through 10 would be one bin



The Current Pipeline

NLP applied to Clinical Notes

(multiple iterations of term lists attempted)

Apply a “silver standard” if possible to obtain preliminary performance estimates

Use prelim performance to determine sample sizes for chart validation across score distribution

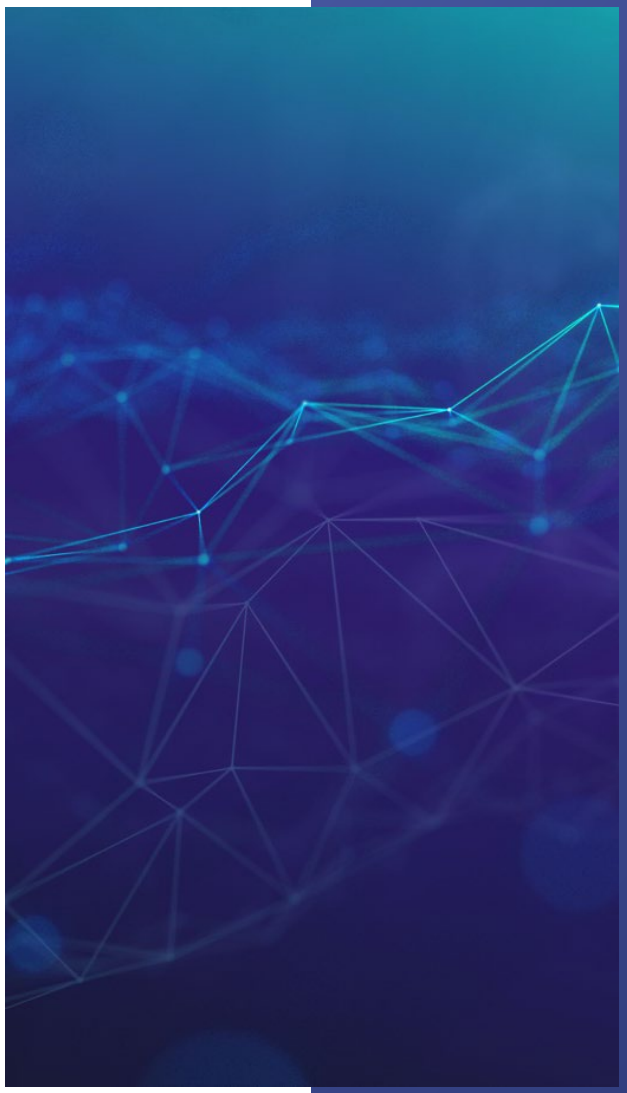
Perform manual chart validation

Underway now N=4,279

Key Steps for Chart Validation

- Annotation Guidelines = Required
- Review a training set (N~50) with all annotators then regroup on guidelines
- Check performance in batches as you proceed (recalculate error estimates based on % of charts done)

Conclusions



01 Feasible

NLP enabled scalable incident detection agnostic to note type or source

02 Accurate

Encouraging precision estimates based on one set of phenotypes

03 Generalizable?

Work underway now to assess if this approach is as accurate in a new phenotype

Future work to scale this system to new sites

Acknowledgements: Project Team

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- Adi Bejan
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- Danijela Stojanovic

Workgroup Leader: Walsh; Timeline: 2/1/2021 – 1/31/2023

Sentinel

Causal Inference (CI 1): Leveraging Machine Learning for Ultra High Dimensional Confounding Adjustment in Electronic Health Record Data

Richard Wyss, PhD, MSc
Brigham and Women's Hospital (Mass General Brigham)
Harvard Medical School

Background

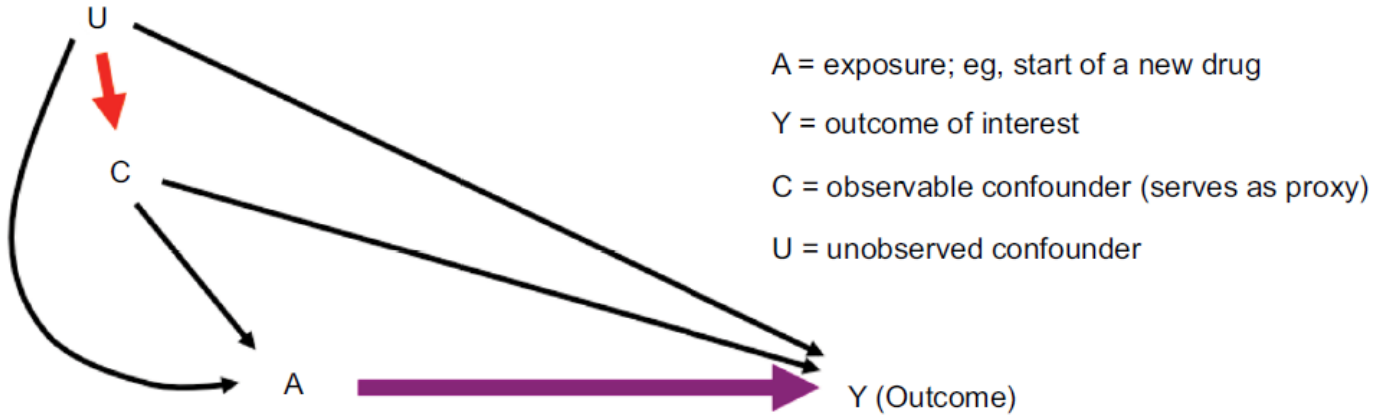
Background: Challenges for Confounding Control in Real Word Evidence (RWE) Studies

- Confounding arising from non-randomized treatment choices remains a fundamental challenge for extracting valid evidence to help guide treatment and regulatory decisions.

- Standard tools for confounding adjustment have typically relied on adjusting for a limited number of investigator specified variables.
  - Adjusting for investigator-specified variables alone is often inadequate
    - Some confounders are unknown at the time of drug approval
    - Many confounders are not directly measured in routine-care databases.

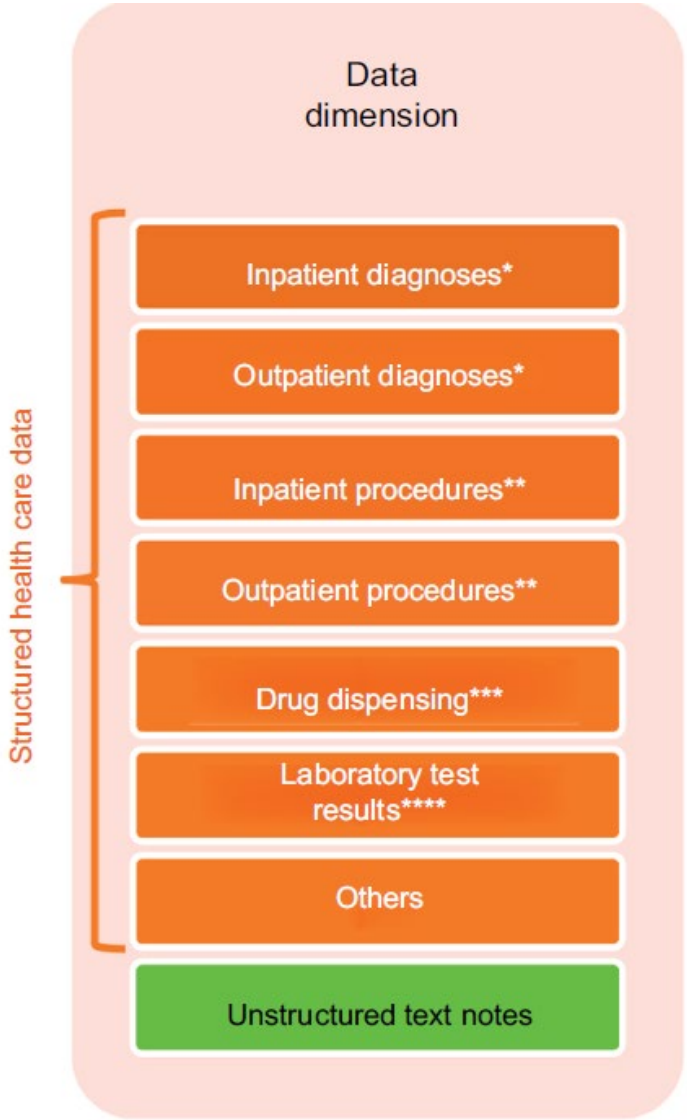
Background: Proxy Confounder Adjustment

- 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

Background: High-dimensional Proxy Confounder Adjustment



- How to identify/generate proxy variables for adjustment?
  - High-dimensional propensity score (Schneeweiss 2009)
    - Does not require data pre-processing
  - Observational Medical Outcomes Partnership (OMOP) approach:
    - Pre-process data into a common data model then use machine learning algorithms for variable selection (e.g., Lasso)
- **Current approaches for generating proxy variables for confounder adjustment do not leverage information from unstructured EHR text notes.**

Background: Leveraging Unstructured Electronic Health Records for Large-scale Proxy Adjustment

- NLP tools turn free-text notes from EHR data into structured features that can supplement confounding adjustment.
  - However, traditional applications are difficult to scale for large-scale proxy adjustment.

- In separately funded, but collaborative work done in parallel with this Sentinel project, our team used scalable applications of NLP to generate structured features from high-dimensional data for large-scale proxy adjustment.
  - Leverages work from RO1 (Josh Lin, PI; Richie Wyss, Co-Investigator; Sebastian Schneeweiss, Co-Investigator)
  - Related to Objective 3 of the Sentinel Initiative (use of NLP-generated information from unstructured data).
  - Unanswered Questions: Once data are in structured format, unclear on how best to identify and adjust for confounder information

- **Aim of this project:** To evaluate the use of Targeted Learning for large-scale covariate adjustment in ultra high-dimensional RWE studies involving linked claims data with EHR records.

Methods

Methods: Data Source for Generating Cohort Studies

- Mass General Brigham (MGB) Research Patient Data Registry (RPDR)
  - EHRs of all the patients aged 65 and above identified in the MGB RPDR were linked to Medicare claims data

- Linked RPDR-Medicare claims were used to generate three cohort studies comparing different classes of medications (details on later slide).
  - Purpose: case studies for evaluating and testing various methods for NLP feature generation for ultra high-dimensional proxy confounder adjustment.

Methods: Study Cohorts

Table 1. Characteristics for Studies 1 and 2

	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 (63.6%)	7,767 (36.4%)	899 (4.2%)	14,937	91	14,846
Study 2:[B]	35,031	12,872 (36.7%)	22,159 (63.3%)	251 (0.7%)	12,464	91	12,373

[A] Study 1: effect of NSAIDs versus Opioids on acute kidney injury; Study 2:

[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**

Methods: How to Best Identify Confounder Information in High-dimensional Real-world Data?

- We focused on the evaluation and comparison of eight Lasso-based propensity score (PS) models for large-scale covariate adjustment. We briefly outline Models 1 through 8 below.
  - **Model 1:** Traditional Lasso
  - **Model 2:** Outcome-adaptive Lasso (OAL)
  - **Model 3:** Collaborative-controlled Lasso
  - **Model 4:** Collaborative-controlled Outcome-adaptive Lasso
  - **Models 5-8:** Equivalent to Models 1 through 4, except that they incorporate cross-fitting when modeling treatment assignment and assigning predicted values for the propensity score.
- Each of the PS models were implemented using Target Maximum Likelihood Estimated (TMLE) with an outcome Lasso model to optimize cross-validated prediction for the outcome, and inverse probability of treatment weight (IPTW) (we only present results here for TMLE).

Fully Synthetic Simulations

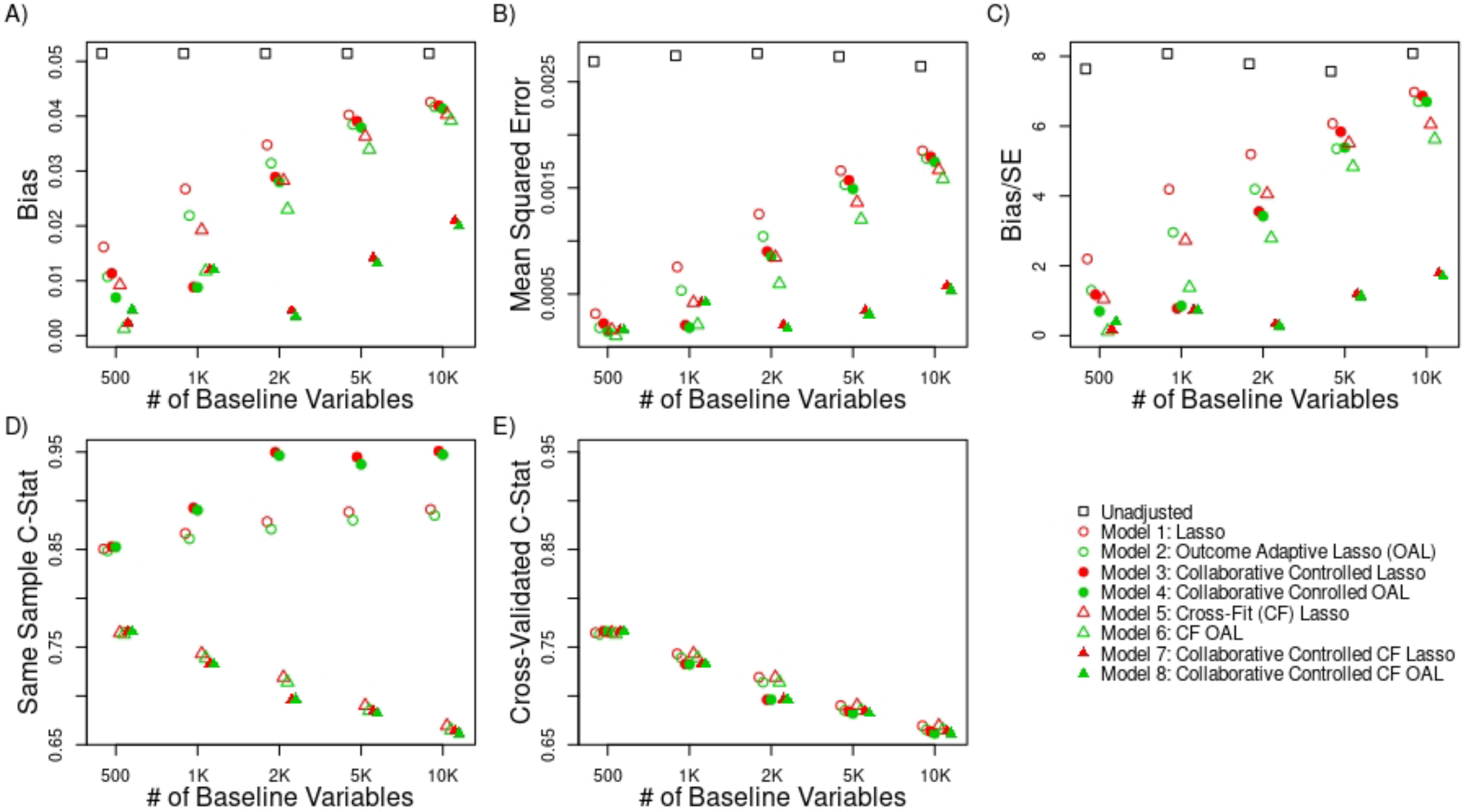
- We constructed a series of synthetic data experiments under tightly controlled settings where all data generating parameters were known.
  - The goal of these experiments was to better understand patterns in the performance of the Lasso-based models in controlling for confounding as the amount of noise (i.e., spurious variables) in the data increased.
  - The simulated data structure included 500 variables that were not spurious (consisting of instrumental variables, confounders with varying strengths, and risk factors with no effect on treatment).
  - We considered 5 scenarios where we varied the number of spurious variables available for adjustment. Scenarios considered ranged from 0 spurious variables for a total of 500 baseline covariates (Scenario 1) to 9,500 spurious variables for a total of 10,000 baseline covariates (Scenario 5).

Plasmode Simulation

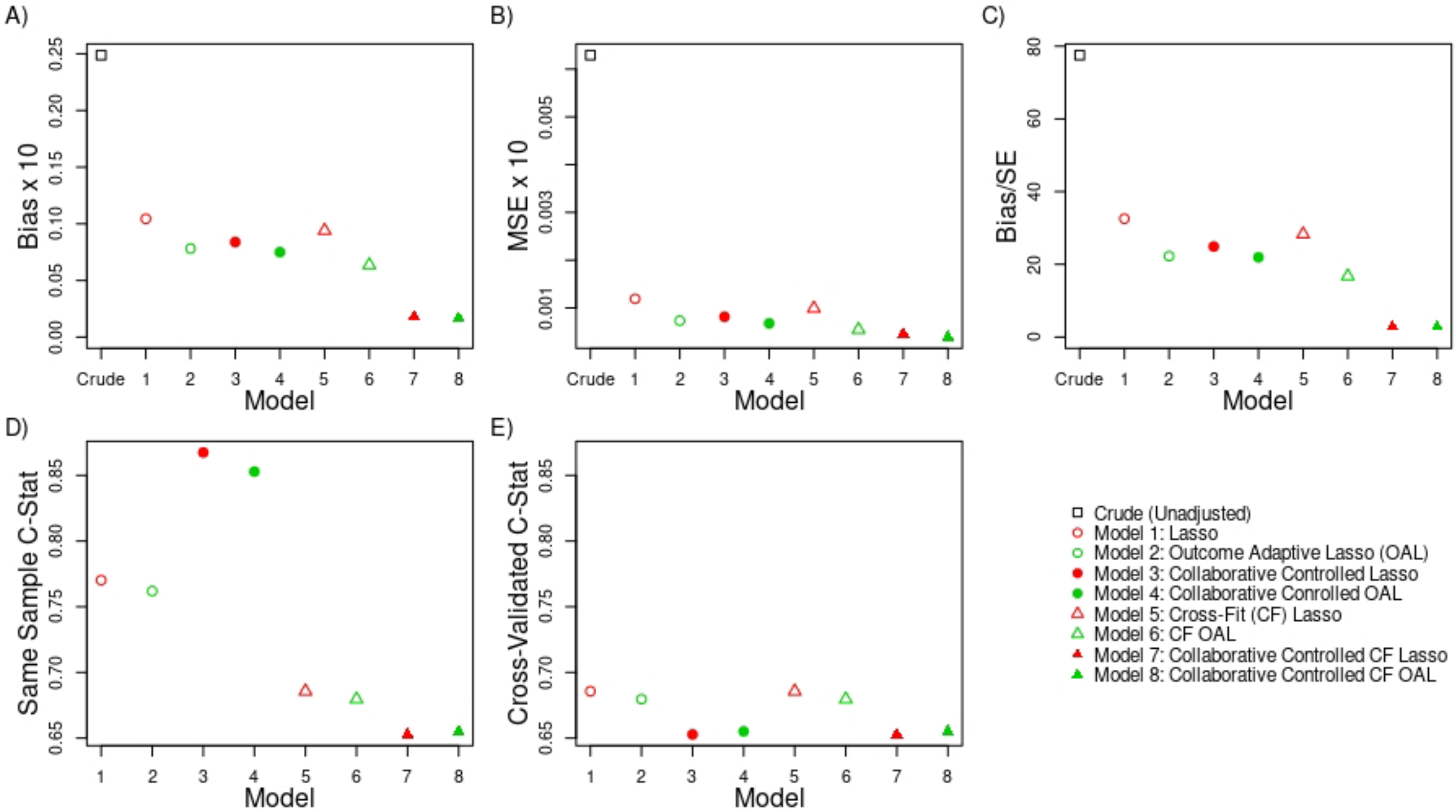
- Conducted a ‘Plasmode Simulation’ (Franklin et al. 2014) to evaluate performance in a more realistic data setting where truth is known.
  - Similar to simulation setup for synthetic simulations
  - However, use the parametric bootstrap from the study cohort (study 1) prior to simulating the treatment and outcome to retain the complex correlation structure of baseline covariates.
  - Prevalence of treatment and outcome were simulated to reflect actual study population

Simulation Results

Selected Results for Synthetic Simulations


A)
Bias
0.00
0.01
0.02
0.03
0.04
0.05
500
1K
2K
5K
10K
# of Baseline Variables
B)
Mean Squared Error
0.0005
0.0015
0.0025
500
1K
2K
5K
10K
# of Baseline Variables
C)
Bias/SE
0
2
4
6
8
500
1K
2K
5K
10K
# of Baseline Variables
D)
Same Sample C-Stat
0.65
0.75
0.85
0.95
500
1K
2K
5K
10K
# of Baseline Variables
E)
Cross-Validated C-Stat
0.65
0.75
0.85
0.95
500
1K
2K
5K
10K
# of Baseline Variables
Unadjusted
Model 1: Lasso
Model 2: Outcome Adaptive Lasso (OAL)
Model 3: Collaborative Controlled Lasso
Model 4: Collaborative Conrolled OAL
Model 5: Cross-Fit (CF) Lasso
Model 6: CF OAL
Model 7: Collaborative Controlled CF Lasso
Model 8: Collaborative Controlled CF OAL

Selected Results for Plasmode Simulations


A)
Bias x 10
0.00
0.05
0.10
0.15
0.20
0.25
Crude
1
2
3
4
5
6
7
8
Model
B)
MSE x 10
0.001
0.003
0.005
Crude
1
2
3
4
5
6
7
8
Model
C)
Bias/SE
0
20
40
60
80
Crude
1
2
3
4
5
6
7
8
Model
D)
Same Sample C-Stat
0.65
0.70
0.75
0.80
0.85
1
2
3
4
5
6
7
8
Model
E)
Cross-Validated C-Stat
0.65
0.70
0.75
0.80
0.85
1
2
3
4
5
6
7
8
Model
Crude (Unadjusted)
Model 1: Lasso
Model 2: Outcome Adaptive Lasso (OAL)
Model 3: Collaborative Controlled Lasso
Model 4: Collaborative Conrolled OAL
Model 5: Cross-Fit (CF) Lasso
Model 6: CF OAL
Model 7: Collaborative Controlled CF Lasso
Model 8: Collaborative Controlled CF OAL

Discussion

General Points for Discussion

- In general, we found that choosing the degree of regularization in the PS model to optimize out-of-sample prediction (e.g., cross-validation) tended to exclude important confounder information in sparse high-dimensional database studies.
  - This finding is consistent with previous work that has shown benefits to undersmoothing nuisance functions for causal inference (Ju et al. 2017).

- Using collaborative learning to select the degree of regularization within the Lasso model resulted in less regularization (undersmoothing) which harmed out-of-sample prediction, but captured more confounder information and often improved confounding control.

General Points for Discussion

- While undersmoothing (overfitting) the Lasso PS model can capture more confounder information, it can also come at a cost of reduced covariate overlap due to modeling spurious associations in the data (overfitting).

- When overfitting was severe, we found that cross-fitting can often help to reduce problems of nonoverlap caused by modeling spurious associations.

- Our findings also suggest that doubly robust estimation (TMLE) is less sensitive to extreme weights than inverse probability of treatment weighting (IPTW) (note: results shown here did not include IPTW).

- Overall, when estimating the average treatment effect (ATE), we found that large-scale covariate adjustment using doubly robust methods (TMLE) with the Collaborative-Controlled Outcome-Adaptive Lasso with cross-fitting of the propensity score was more robust for reducing bias in estimated treatment effects.

Acknowledgements: Project Team

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- Lars van der Laan

University of Michigan
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Putnam Data Sciences
- Susan Gruber, PhD, MS, MPH

Sentinel

Data Infrastructure (DI 2): Representation of Unstructured Data Across Common Data Models

Keith Marsolo, PhD
Associate Professor
Department of Population Health Sciences
Duke Clinical Research Institute
Duke University School of Medicine

Incorporating Unstructured Data into a Common Data Model

As the Sentinel Network expands its access to EHR data, this will include information from both structured (e.g., laboratory results, inpatient administrations) and unstructured domains (e.g., free-text clinical notes). Unstructured sources are of particular interest because they often include information not captured anywhere else. **The goal of this project is to guide the Sentinel Network on how best to incorporate information derived from unstructured data into a CDM framework.**

Objectives:

1) *What information is important?* – Identify the priority elements that should be derived from unstructured data

2) *A: What NLP tools are in use & how are they used?* – Assess the overall availability of the priority elements within the Sentinel ecosystem based on current NLP capabilities

   B: What information is available within a note? - How often do these elements appear in the text?

3) *How to best represent information derived from unstructured text?* – Recommend how those priority elements should be represented in the Sentinel Common Data Model

Objective 1 – What Information is Important?

Methods:

- To bootstrap the prioritization process, generated list of concepts from commonly-used NLP pipelines (commercial & open-source)
  - Focused mainly on broad categories or classes, not specific items, unless called out in documentation (e.g., medications, not aspirin)
  - Looked at the standard functionality provided by each tool, not every research project
  - Generated "good enough" list – stopped when we reached saturation

- FDA reviewed list, identified any missing elements & then assigned priority rankings (high / medium / low) - highest priority given to those concepts not easily obtained from claims that are also important for drug safety studies

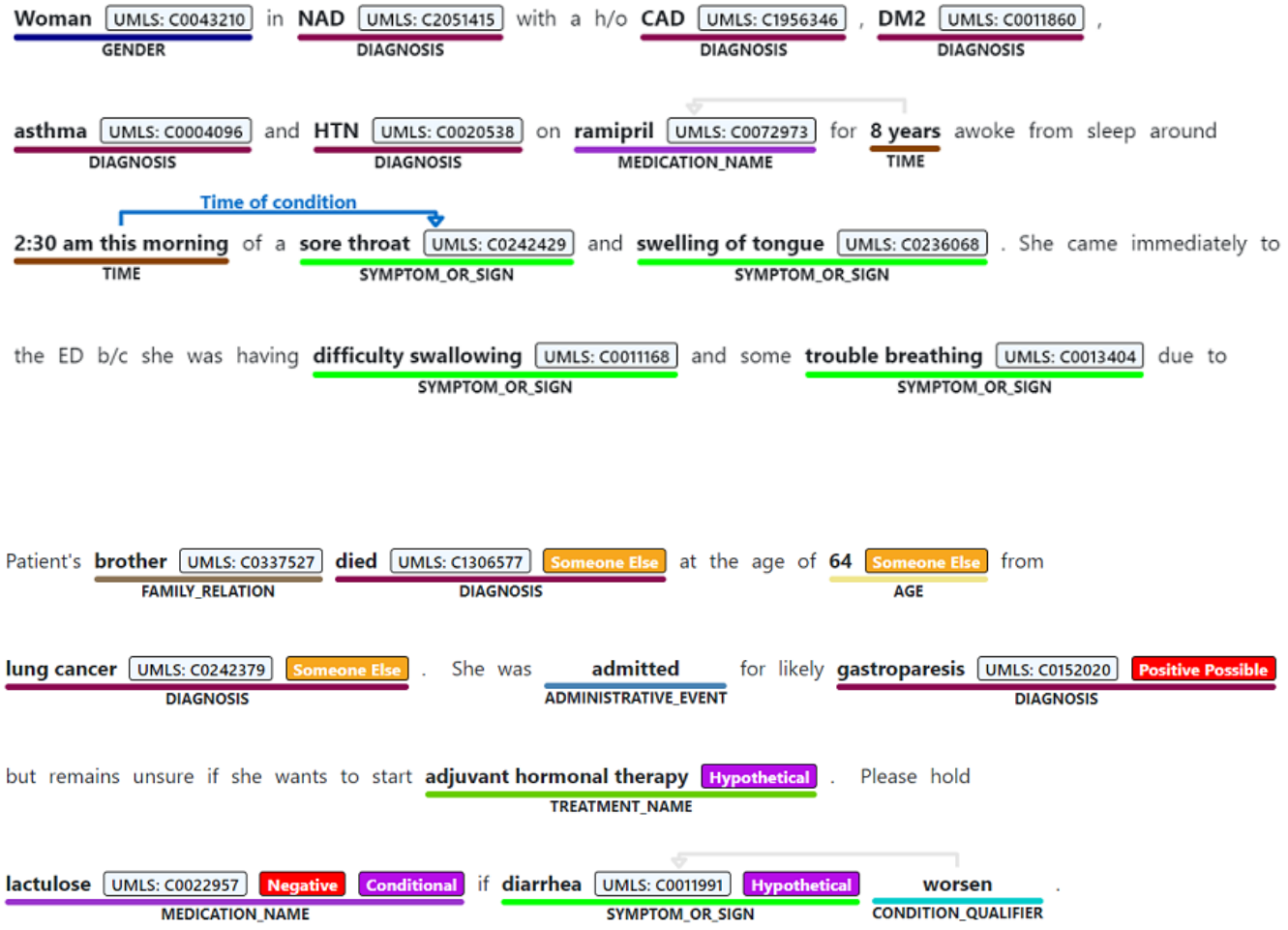


Image source: https://docs.microsoft.com/en-us/azure/cognitive-services/text-analytics/how-tos/text-analytics-for-health

Results: Example Priority Rankings (subset)

Concepts from existing tools

Domain	Concept(s)	Priority	Notes
Cancer	Site	High	Several Active Risk Identification and Analysis (ARIA) System insufficiency rankings due to lack of data on cancer (e.g., staging)
	Histology	High	
	Procedure	High	
Condition	Diagnoses	Medium	Often captured in claims
	Signs / Symptoms	High	Less available in claims, useful in different aspects of studies
	Family History (Type)	Medium	Useful in some studies, but not all
	Medical History (Type)	High	Given gaps in EHR data, medical history important to capture
Medication	Class	Low	Can be inferred from drug name

Missing concepts

Concept(s)	Priority	Notes
Timing & duration of medication	High	Particularly important for inpatient medications
Physical findings (e.g., vital signs)	High	Key covariate for FDA studies, under-captured in claims; may also be in structured fields
Indication for a drug	High	Rationale for why a drug is given, not always available elsewhere
Oxygen support	High	Relevant for many COVID-19 studies
Death (date) & cause	High	Capture of death data varies by Sentinel Data Partner

Objective 2a - What NLP Tools are in Use; What Data are Extracted?

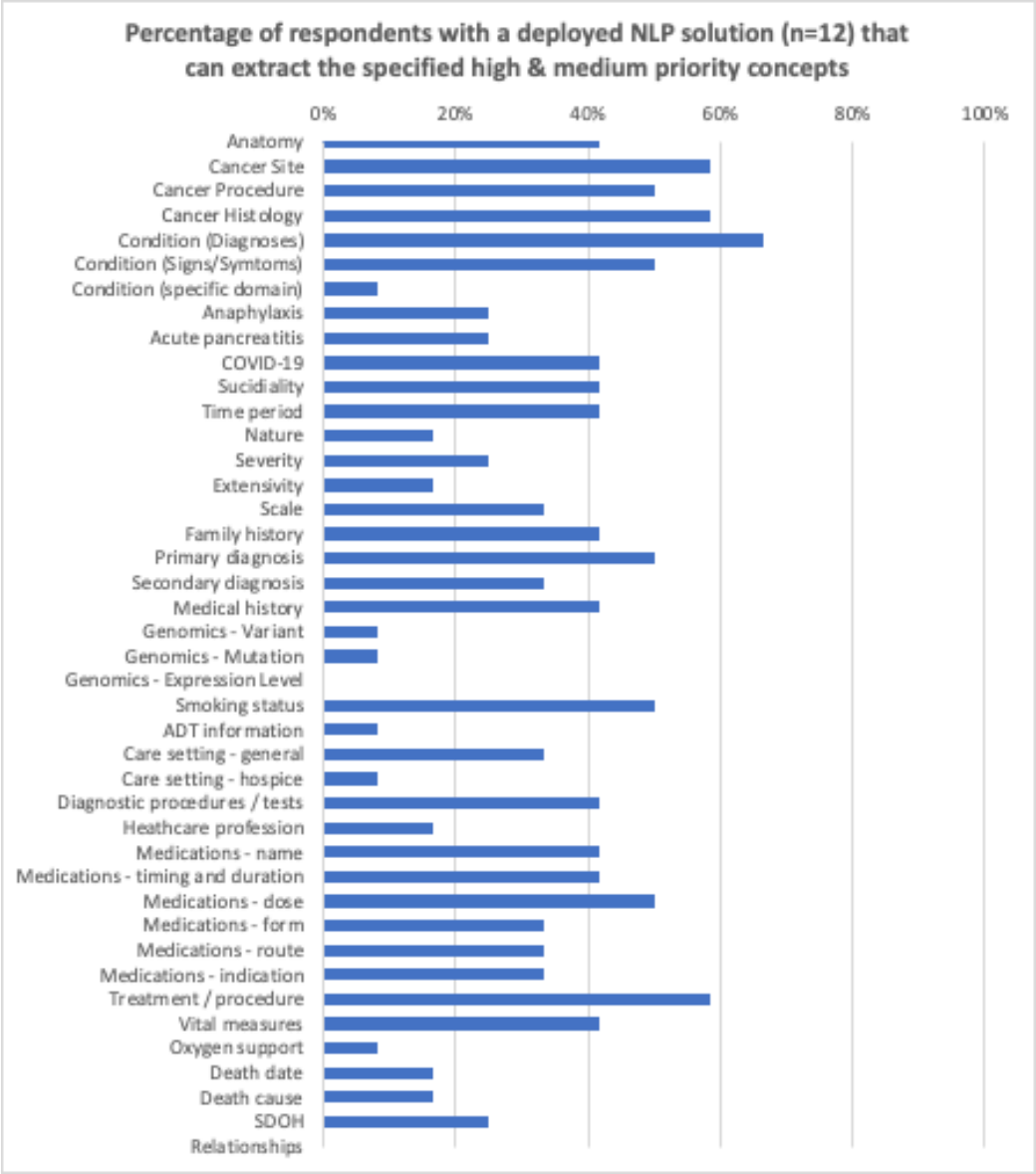
Methods:

- Distributed survey to partners within the Sentinel ecosystem to assess their NLP capabilities (e.g., tool(s) used, notes processed, concepts extracted, etc.)
  - 14 Sentinel Data Partners
  - 8 partners affiliated with the Innovation Center

Results:

- A total of 17 responses received (13 from Sentinel Data Partners)
  - 12 use NLP in some capacity
  - 50% for project-specific research; 50% for research & "operational" purposes

- Wide variety of tools used / notes processed (type, number of years)
- Scope of concepts extracted also varies widely
  - 9 of 12 report being able to extract Diagnoses (highest percentage)
  - Handful of other concepts extracted by >50% of respondents (e.g., cancer site & histology, smoking status, signs & symptoms)



Objective 2b – What Information is Available Within a Note?

Motivation:

- NLP pipelines are increasingly being advertised as commodity software-as-a-service offerings by cloud providers, lowering the barrier to entry
- We can imagine a future state where Sentinel Data Partners with access to EHR data have processed some / all of their clinical notes through one or more NLP pipelines
- If we want to rely on those "stock" NLP outputs, what kind of information can we expect to find within the text?

Use Cases: Identified by FDA through the Objective 1 prioritization process

- Hospitalization patients with COVID-19, with an emphasis on documenting the use of supplemental oxygen
  - Adults >= 18 with inpatient encounter with a COVID-19 admitting diagnosis between April 1, 2020 and December 31, 2021
- Cancer, focusing on patients with a new order/prescription for darzalex (daratumumab)
  - Order/prescription between January 1, 2016 and November 30, 2021 and no prior evidence of an order in prior 3 years
  - Underlying rationale – does the note capture information that would allow us to determine the indication behind prescription?

Annotation Partners:

- Mass General Brigham
- Vanderbilt University Medical Center

Objective 2b - Annotation Process

Methods:

- ***Defined a cohort*** for each use case ***and sampling strategy***
  - COVID-19 – Annotate the discharge summary from the hospitalization
    35 patients with a billing code for supplemental oxygen (select at random)
    35 patients without a billing code for supplemental oxygen (select at random)
  - Cancer – Annotate the note associated with the visit where the patient was prescribed darzalex
    Select 30 patients at random
- ***Created pseudo code*** that could be used to identify patients
  - Each partner could tweak code as necessary given their local source systems
- ***Defined an annotation guide*** that provided instructions to the annotators on what items to mark within the note and how to handle edge cases
  - Included both classes (e.g., Condition), attributes (e.g., positive mention, resolved problem) & relationships (e.g., medication dose or timing associated with a prior mention of a medication)
- Each site ***double-annotated a small set of notes*** (5-6) and then ***proceeded with single annotation*** if >80% performance at the class + attribute level
- Partners ***shared the underlying annotations metadata*** (without the actual text snippets) for analysis [single-annotated notes]

Class Assignment Guidelines

1) **Oxygen Support** PRIMARY CLASS: Mark references to supplemental oxygen device or oxygen delivery method , or refence to oxygen administration
   - ✓ *attribute:* ***Assertion*** [positive, negative, uncertain, hypothetical]
   - ✓ *attribute* (unique to class) ***Change Status:*** [singular (default) if no other O2 device mentioned, change]
   - ✓ *attribute:* ***TimePerspective*** [current (default), history, predicted]

Example Expressions

Nasal Cannula	Oxygenation		ECMO	on oxygen	Non-rebreather mask	Oxygen conserving device
High-flow O2		BIPAP	oxygen delivery		Invasive mechanical ventilation	

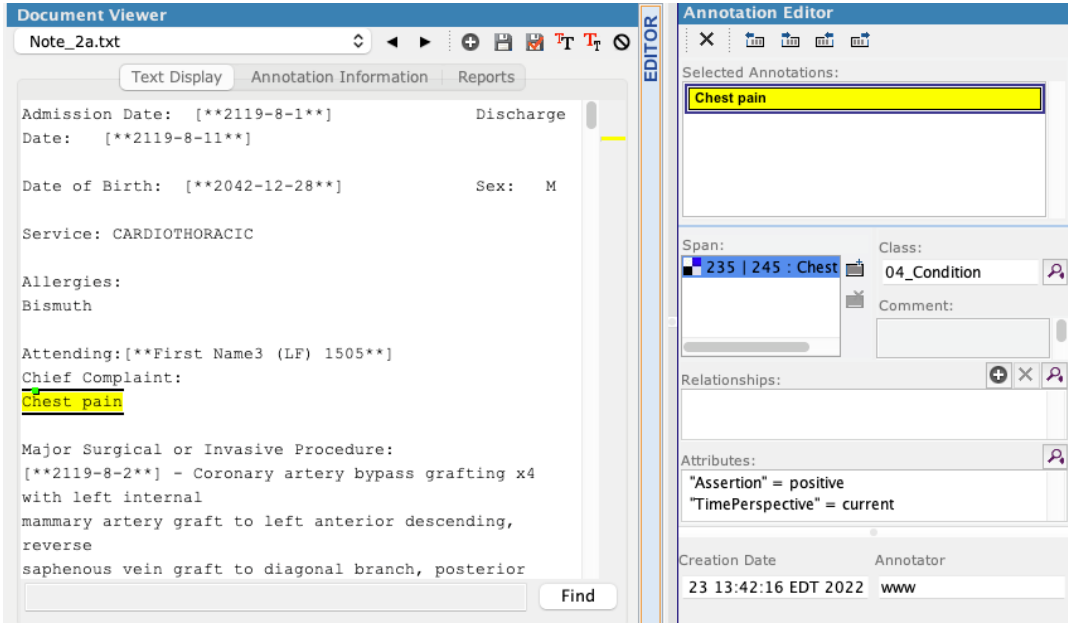
⊗ **Please note**: change status value 'change' should only be used if there are more than one instance of the secondary class Oxygen Support Volume linked to the instance of Oxygen Support

1) **Oxygen Support Volume** Secondary Class: Mark mentions of oxygen volume
Relation: *02* ***VOLUME LINK*** → Link the annotated instance of "Oxygen Support Volume" to the annotated instance of "Oxygen Support" with which it is associated in the document

Example Expressions

3L		2 Liters	

⊗ **Please note**: If oxygen device or oxygen delivery method is not mentioned, annotate any word that let you know the topic was related to oxygen as the oxygen support.



Objective 2b – Selected Results (COVID-19)

Primary Class	MGB: Notes with at least 1 annotation of the class characteristic (N=33) total notes	MGB: Total annotations (N=3,022)	MGB: Number or percent of annotations per note Median (Min, Max)	VUMC: Notes with at least 1 annotation of the class characteristic (N=35) total notes	VUMC: Total annotations (N=2,243)	VUMC: Number or percent of annotations per note Median (Min, Max)
Oxygen Support	27/27 (100.0%)	102/2,719 (3.8%)	3.0 (1.0, 8.0)	31/35 (88.6%)	210/3,120 (6.7%)	5.0 (1.0, 25.0)
Assertion						
Hypothetical	1/27 (3.7%)	1/102 (1.0%)	0.0 (0.0, 14.3)	1/31 (3.2%)	1/210 (0.5%)	0.0 (0.0, 33.3)
Negative	16/27 (59.3%)	27/102 (26.5%)	33.3 (0.0, 100.0)	N/A	N/A	N/A
Positive	23/27 (85.2%)	73/102 (71.6%)	66.7 (0.0, 100.0)	31/31 (100.0%)	209/210 (99.5%)	100.0 (66.7, 100.0)
Unknown	1/27 (3.7%)	1/102 (1.0%)	0.0 (0.0, 14.3)	N/A	N/A	N/A
Time perspective						
Current	27/27 (100.0%)	91/102 (89.2%)	100.0 (33.3, 100.0)	30/31 (96.8%)	190/210 (90.5%)	100.0 (0.0, 100.0)
History	7/27 (25.9%)	9/102 (8.8%)	0.0 (0.0, 66.7)	9/31 (29.0%)	16/210 (7.6%)	0.0 (0.0, 100.0)
Predicted	2/27 (7.4%)	2/102 (2.0%)	0.0 (0.0, 14.3)	4/31 (12.9%)	4/210 (1.9%)	0.0 (0.0, 20.0)

Annotations for the class "Oxygen Support" in patients **with** a billing code for supplemental oxygen

Primary Class	MGB: Notes with at least 1 annotation of the class characteristic (N=33) total notes	MGB: Total annotations (N=3,022)	MGB: Number or percent of annotations per note Median (Min, Max)	VUMC: Notes with at least 1 annotation of the class characteristic (N=35) total notes	VUMC: Total annotations (N=2,243)	VUMC: Number or percent of annotations per note Median (Min, Max)
Oxygen Support	28/33 (84.8%)	90/3,022 (3.0%)	2.0 (1.0, 14.0)	16/35 (45.7%)	54/2,243 (2.4%)	3.0 (1.0, 8.0)
Assertion						
Hypothetical	2/28 (7.1%)	2/90 (2.2%)	0.0 (0.0, 50.0)	3/16 (18.8%)	3/54 (5.6%)	0.0 (0.0, 33.3)
Negative	18/28 (64.3%)	25/90 (27.8%)	45.0 (0.0, 100.0)	7/16 (43.8%)	7/54 (13.0%)	0.0 (0.0, 100.0)
Positive	15/28 (53.6%)	63/90 (70.0%)	46.7 (0.0, 100.0)	11/16 (68.8%)	42/54 (77.8%)	77.5 (0.0, 100.0)
Unknown	0/28 (0.0%)	0/90 (0.0%)	0.0 (0.0, 0.0)	2/16 (12.5%)	2/54 (3.7%)	0.0 (0.0, 100.0)
Time perspective						
Current	27/28 (96.4%)	82/90 (91.1%)	100.0 (0.0, 100.0)	15/16 (93.8%)	46/54 (85.2%)	100.0 (0.0, 100.0)
History	4/28 (14.3%)	6/90 (6.7%)	0.0 (0.0, 100.0)	4/16 (25.0%)	6/54 (11.1%)	0.0 (0.0, 100.0)
Predicted	2/28 (7.1%)	2/90 (2.2%)	0.0 (0.0, 50.0)	2/16 (12.5%)	2/54 (3.7%)	0.0 (0.0, 25.0)

Annotations for the class "Oxygen Support" in patients **without** a billing code for supplemental oxygen

Objective 2b – Selected Results (Cancer)

Substantial differences in many classes depending on the specialty & note type (total number of annotations / class presence)

Mass General Brigham (MGB) notes

Specialty	Note Type	Count
Hematology Oncology	Progress Note	2
Infusion Therapy	Progress Note	15
Medical Oncology	Progress Note	4
Medicine	Progress Note	1
Myeloma	Progress Note	2
Nursing	Plan of Care	2
Nursing	Plan of Care	1
Oncology	Plan of Care	1
Oncology	Progress Note	1
Pharmacy	Progress Note	1

VUMC notes

- Limited to Oncology notes written by physicians, physician assistants and nurse practitioners

	MGB			VUMC		
Primary Class	**Notes with at least 1 annotation of the class characteristic (N=24) total notes**	**Total annotations (N=1,354)**	**Number or percent of annotations per note Median (Min, Max)**	**Notes with at least 1 annotation of the class characteristic (N=28) total notes**	**Total annotations (N=7,379)**	**Number or percent of annotations per note Median (Min, Max)**
Condition	18/24 (75.0%)	350/1,354 (25.8%)	11.0 (1.0, 69.0)	28/28 (100.0%)	1,795/7,379 (24.3%)	58.0 (17.0, 163.0)
Assertion						
Hypothetical	4/18 (22.2%)	21/350 (6.0%)	0.0 (0.0, 30.4)	10/28 (35.7%)	19/1,795 (1.1%)	0.0 (0.0, 8.3)
Negative	8/18 (44.4%)	114/350 (32.6%)	0.0 (0.0, 66.7)	27/28 (96.4%)	739/1,795 (41.2%)	31.8 (0.0, 74.8)
Positive	18/18 (100.0%)	204/350 (58.3%)	91.7 (16.7, 100.0)	28/28 (100.0%)	1,038/1,795 (57.8%)	67.9 (22.8, 100.0)
Unknown	1/18 (5.6%)	12/350 (3.4%)	0.0 (0.0, 80.0)	9/28 (32.1%)	12/1,795 (0.7%)	0.0 (0.0, 4.8)
Time perspective						
Current	18/18 (100.0%)	292/350 (83.4%)	100.0 (67.4, 100.0)	28/28 (100.0%)	1,427/1,795 (79.5%)	89.1 (37.3, 100.0)
History	5/18 (27.8%)	39/350 (11.1%)	0.0 (0.0, 33.3)	24/28 (85.7%)	372/1,795 (20.7%)	10.9 (0.0, 62.7)
Predicted	3/18 (16.7%)	20/350 (5.7%)	0.0 (0.0, 30.4)	1/28 (3.6%)	1/1,795 (0.1%)	0.0 (0.0, 2.0)
Test/Procedure	16/24 (66.7%)	132/1,354 (9.7%)	6.5 (1.0, 36.0)	28/28 (100.0%)	2,820/7,379 (38.2%)	65.5 (2.0, 265.0)
Assertion						
Hypothetical	1/16 (6.3%)	1/132 (0.8%)	0.0 (0.0, 2.8)	13/28 (46.4%)	29/2,820 (1.0%)	0.0 (0.0, 7.9)
Negative	2/16 (12.5%)	2/132 (1.5%)	0.0 (0.0, 9.1)	18/28 (64.3%)	57/2,820 (2.0%)	1.4 (0.0, 7.7)
Positive	16/16 (100.0%)	126/132 (95.5%)	100.0 (81.8, 100.0)	28/28 (100.0%)	2,718/2,820 (96.4%)	96.7 (89.5, 100.0)
Unknown	3/16 (18.8%)	3/132 (2.3%)	0.0 (0.0, 9.1)	9/28 (32.1%)	16/2,820 (0.6%)	0.0 (0.0, 7.7)
Time perspective						
Current	16/16 (100.0%)	98/132 (74.2%)	100.0 (35.7, 100.0)	28/28 (100.0%)	768/2,820 (27.2%)	32.5 (4.0, 100.0)
History	3/16 (18.8%)	8/132 (6.1%)	0.0 (0.0, 40.0)	26/28 (92.9%)	1,968/2,820 (69.8%)	59.3 (0.0, 92.9)
Predicted	6/16 (37.5%)	26/132 (19.7%)	0.0 (0.0, 64.3)	13/28 (46.4%)	84/2,820 (3.0%)	0.0 (0.0, 20.0)
Gene/Protein	6/24 (25.0%)	251/1,354 (18.5%)	11.5 (7.0, 169.0)	27/28 (96.4%)	114/7,379 (1.5%)	4.0 (1.0, 12.0)
Assertion						
Negative	2/6 (33.3%)	18/251 (7.2%)	0.0 (0.0, 39.5)	2/27 (7.4%)	2/114 (1.8%)	0.0 (0.0, 25.0)
Positive	6/6 (100.0%)	233/251 (92.8%)	100.0 (60.5, 100.0)	27/27 (100.0%)	112/114 (98.2%)	100.0 (75.0, 100.0)
Stem Cell Transplant	2/24 (8.3%)	4/1,354 (0.3%)	2.0 (1.0, 3.0)	22/28 (78.6%)	87/7,379 (1.2%)	3.0 (1.0, 11.0)
Assertion						
Hypothetical	N/A	N/A	N/A	5/22 (22.7%)	9/87 (10.3%)	0.0 (0.0, 66.7)
Negative	N/A	N/A	N/A	2/22 (9.1%)	3/87 (3.4%)	0.0 (0.0, 100.0)
Positive	2/2 (100.0%)	4/4 (100.0%)	100.0 (100.0, 100.0)	19/22 (86.4%)	67/87 (77.0%)	90.0 (0.0, 100.0)
Unknown	N/A	N/A	N/A	7/22 (31.8%)	8/87 (9.2%)	0.0 (0.0, 100.0)

Objective 3 – How to Best Represent Information Derived From Unstructured Text?

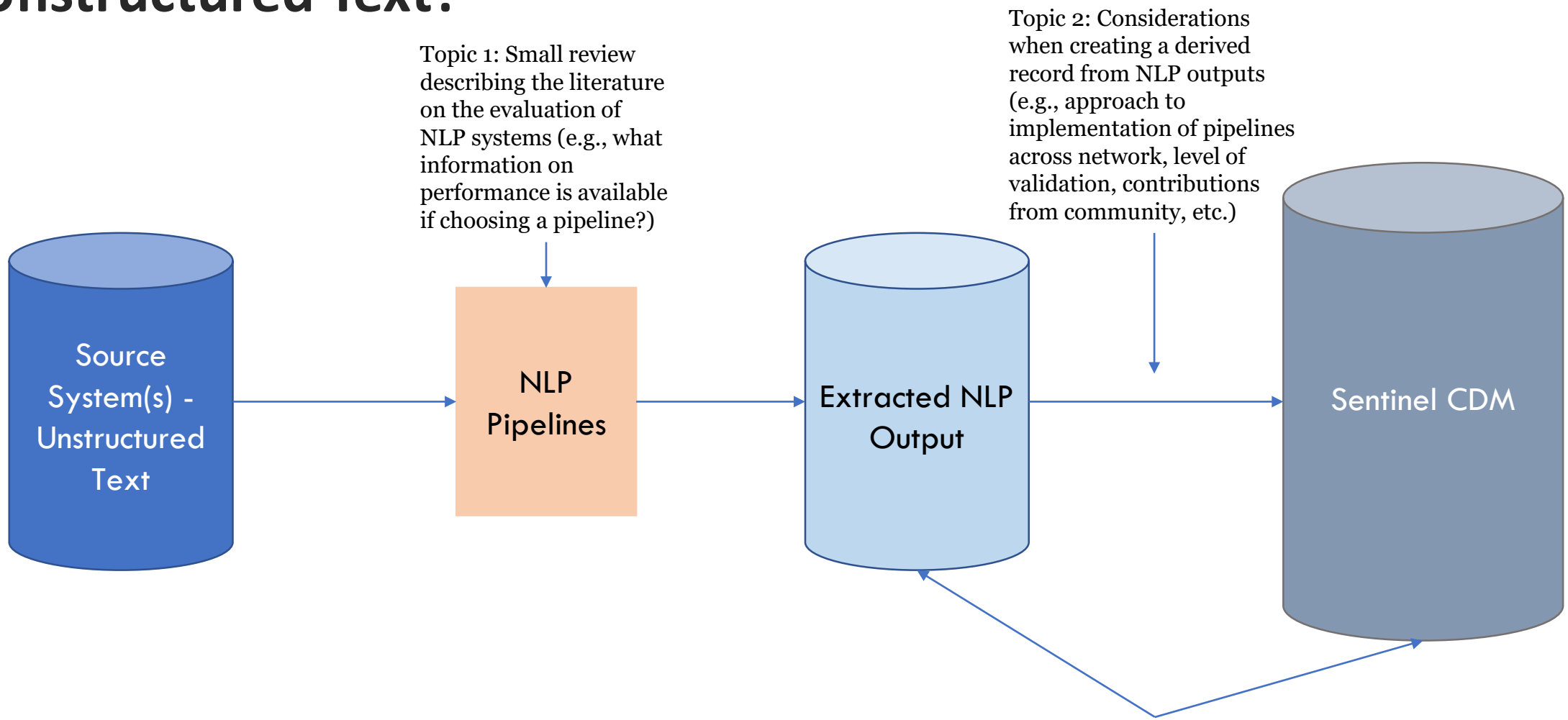


Image adapted from Hua Xu webinar - Representing and Utilizing Clinical Textual Data for Real World Studies: An OHDSI Approach (https://www.sentinelinitiative.org/news-events/meetings-workshops-trainings/representing-and-utilizing-clinical-textual-data-real)

Acknowledgements: Project Team

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- Juan Zhao
- Jill Whitaker
- Tina French
- Liz Hanchrow
- Dax Westerman

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- Li Zhou
- Suzanne Blackley
- John Laurentiev

Food and Drug Administration

- Sara Dutcher
- Efe Eworuke
- Aida Kuzucan

Sentinel

Detection Analytics (DA 1): Advances in Signal Detection Methodology in Sentinel

TreeScan™ Past and Future Directions

Shirley Wang, PhD, ScM
Associate Professor
Brigham and Women's Hospital (Mass General Brigham)
Harvard Medical School

Current State of Signal Detection Approaches Using Electronic Health Records (EHRs)

We identified articles from the published literature to inform the key areas for methodological development in EHR-based safety signal identification for Sentinel

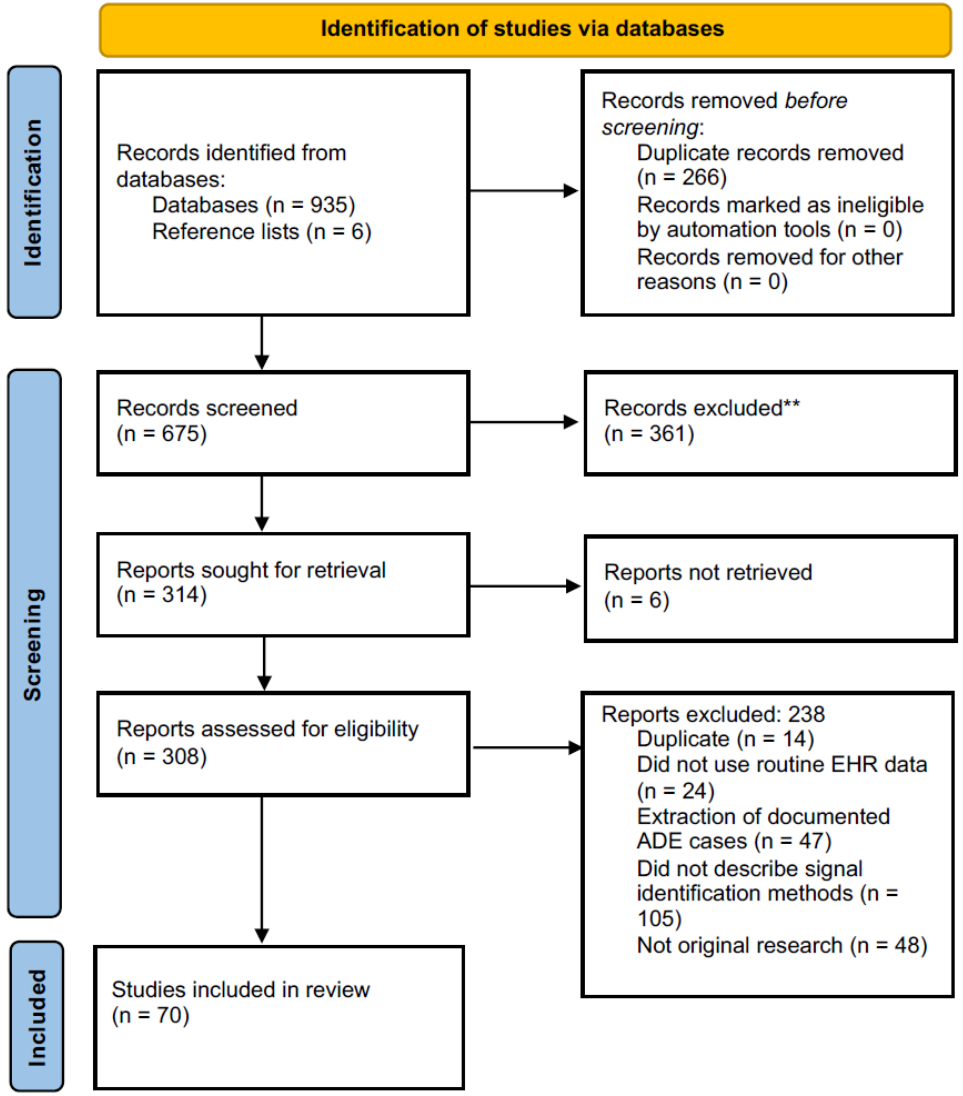
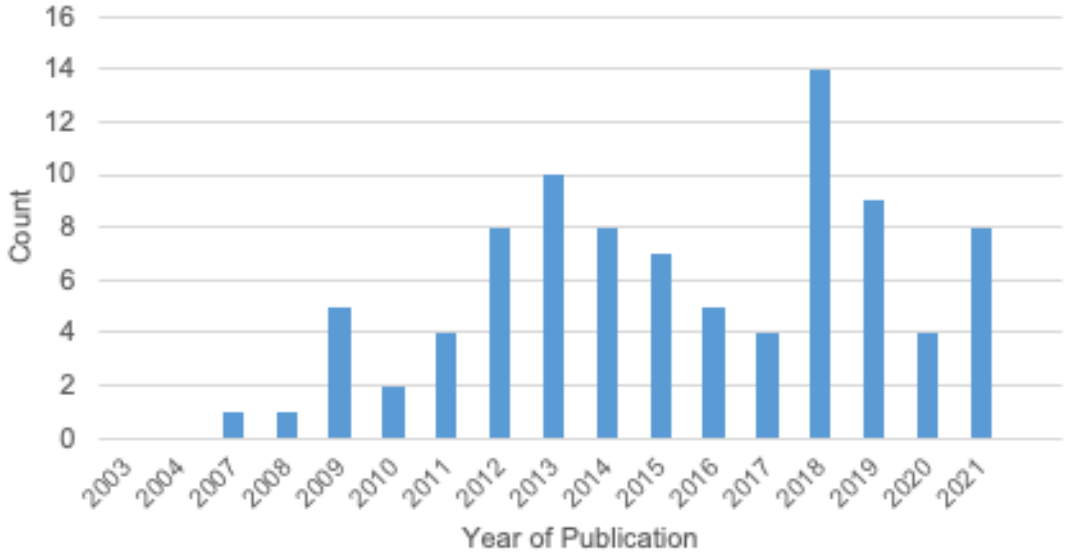


Figure: Included studies of EHR-based signal identification by year



Figures courtesy: Sharon Davis, Joshua Smith

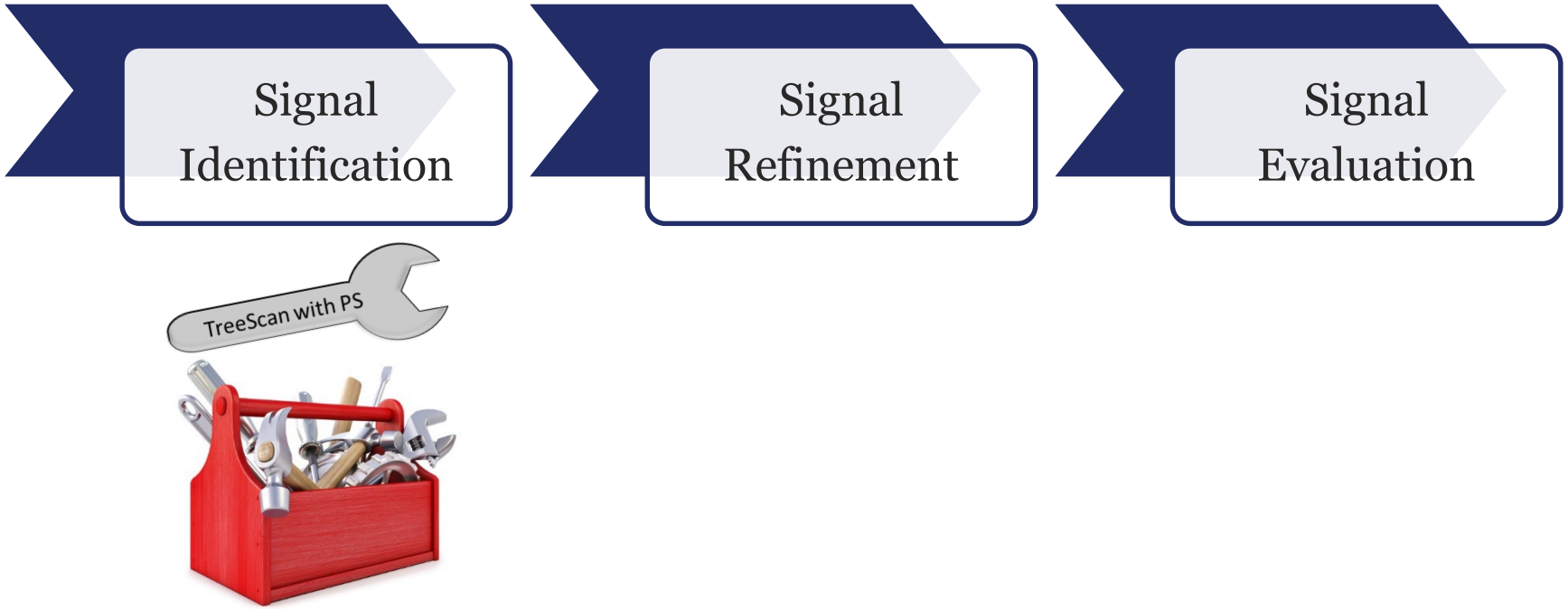
What is TreeScan™?

- A statistical data mining tool for signal detection
  - Utilizes tree-based scan statistics
  - Addresses issues with multiple testing in evaluation of thousands of potential adverse events

Kulldorff, M. Drug safety data mining with a tree-based scan statistic. PDS, 2013

TreeScan is a First Step for Active Drug Safety Surveillance

- Relevant alerts should be *refined* and *evaluated* with pharmacoepidemiologic assessment where confounding control is tailored to the specific outcome(s) under investigation



How Has TreeScan Been Used Before?*

Self-controlled design (vaccine safety)

- Li PDS 2018 (meningococcal)
- Yih 2019 AJE (herpes zoster)
- Wintzell 2020 (TNF-i)
- Lee 2020 Vaccines (pneumococcal)
- Kim 2020 Vaccine (Bacillus Calmette-Guerin)
- Liu 2021 Vaccine (varicella)
- Yih AJE 2021 (vaccine)

Case Control (drug repurposing/risk factor identification)

- Maro 2017 DrugScan
- Wang 2021 Ophthalmology (wet AMD)

Poisson model with non-user cohort (drug safety)

- Kulldorff PDS 2013
- Wintzell 2020 (TNF-i)

Active Comparator New User Propensity Score (ACNU PS) matched cohort (drug safety)

- Wang 2018 Epidemiology (simulation)
- Wang 2021 AJE (general PS)
- Fralick 2021 Endocrinol Diabetes Metab (SGLT2i)
- Huybrechts 2021 AJE (pregnancy/congenital malformations)
- Maro (in progress) TreeScan in pregnancy

* Non-exhaustive list

ORIGINAL ARTICLE

Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

Shirley V. Wang,[a] Judith C. Maro,[b] Elande Baro,[c] Rima Izem,[c] Inna Dashevsky,[b] James R. Rogers,[a] Michael Nguyen,[d] Joshua J. Gagne,[a] Elisabetta Patorno,[a] Krista F. Huybrechts,[a] Jacqueline M. Major,[d] Esther Zhou,[d] Megan Reidy,[b] Austin Cosgrove,[b] Sebastian Schneeweiss,[a] and Martin Kulldorff[a]

Performance of TreeScan with ACNU

- Power and type I error
- Patterns of alerts when there is an effect in at least one node

Practice of Epidemiology

A General Propensity Score for Signal Identification Using Tree-Based Scan Statistics

Shirley V. Wang*, Judith C. Maro, Joshua J. Gagne, Elisabetta Patorno, Sushama Kattinakere, Danijela Stojanovic, Efe Eworuke, Elande Baro, Rita Ouellet-Hellstrom, Michael Nguyen, Yong Ma, Inna Dashevsky, David Cole, Sandra DeLuccia, Aaron Hansbury, Ella Pestine, and Martin Kulldorff

Performance of alternative general PS

- Screening thousands of outcomes, can't pick risk factors for all

Illustration of screening → refinement → patient profile review

ORIGINAL RESEARCH ARTICLE

A novel data mining application to detect safety signals for newly approved medications in routine care of patients with diabetes

Michael Fralick[1,2] | Martin Kulldorff[1] | Donald Redelmeier[3,4] | Shirley V. Wang[1] | Seanna Vine[1] | Sebastian Schneeweiss[1] | Elisabetta Patorno[1]

Case studies with well-characterized safety profiles in diabetes

- International Classification of Diseases, Ninth Revision (ICD-9) digit-based tree with >10,000 outcomes
- Two statistical alerts for outcomes where signal was expected
- No unexpected statistical alerts

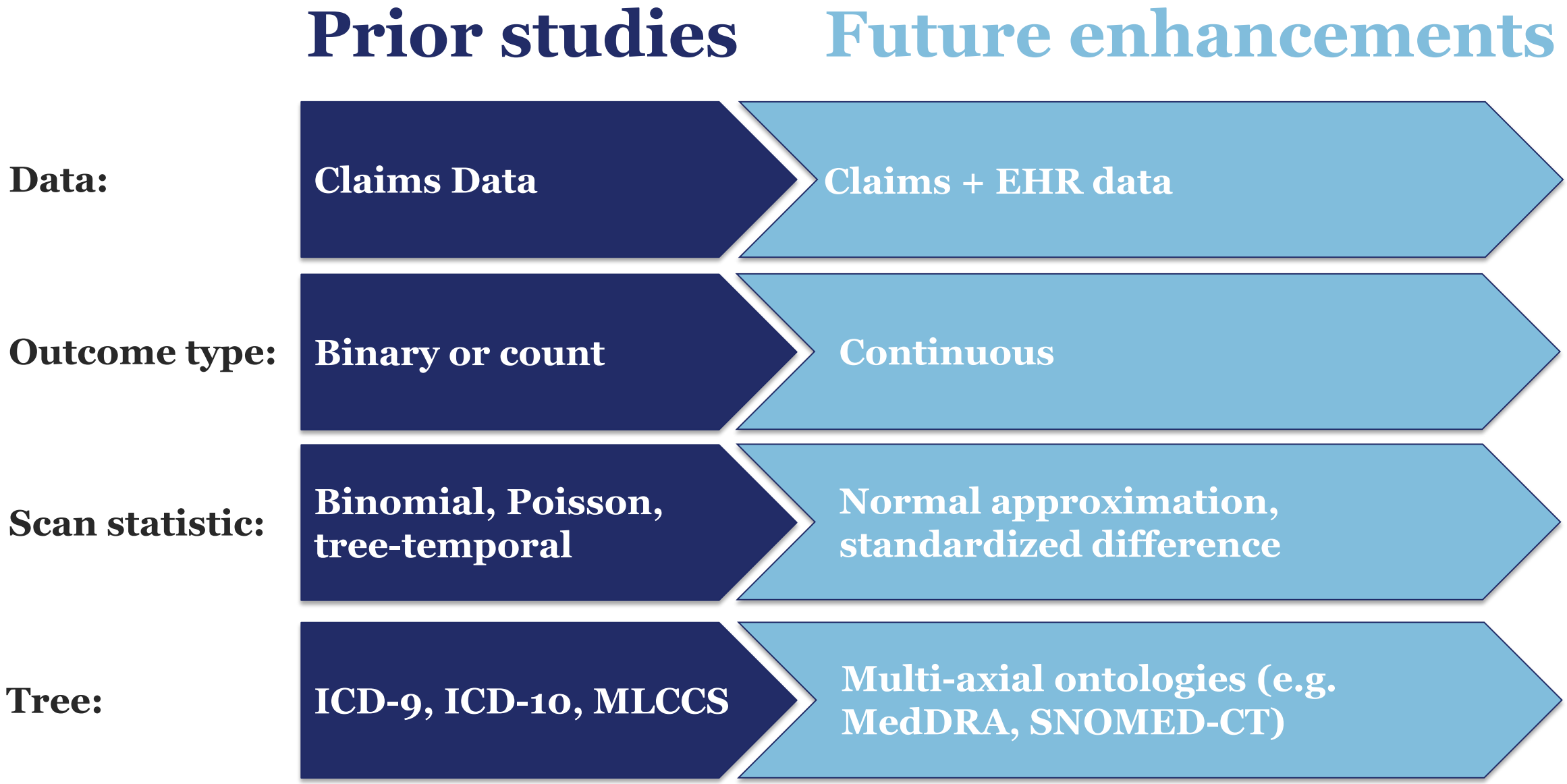
Practice of Epidemiology

Active Surveillance of the Safety of Medications Used During Pregnancy

Krista F. Huybrechts*, Martin Kulldorff, Sonia Hernández-Díaz, Brian T. Bateman, Yanmin Zhu, Helen Mogun, and Shirley V. Wang

Two case studies with well-characterized safety profiles in pregnancy

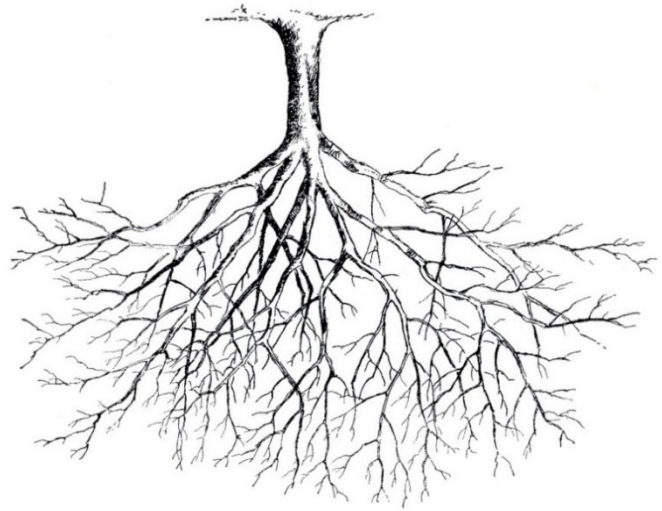
- Congenital malformation tree with >700 outcomes
- Statistical alerts identified expected signals
- Only one statistical alert for outcome not previously reported


Prior studies
Future enhancements
Data:
Claims Data
Claims + EHR data
Outcome type:
Binary or count
Continuous
Scan statistic:
Binomial, Poisson, tree-temporal
Normal approximation, standardized difference
Tree:
ICD-9, ICD-10, MLCCS
Multi-axial ontologies (e.g. MedDRA, SNOMED-CT)

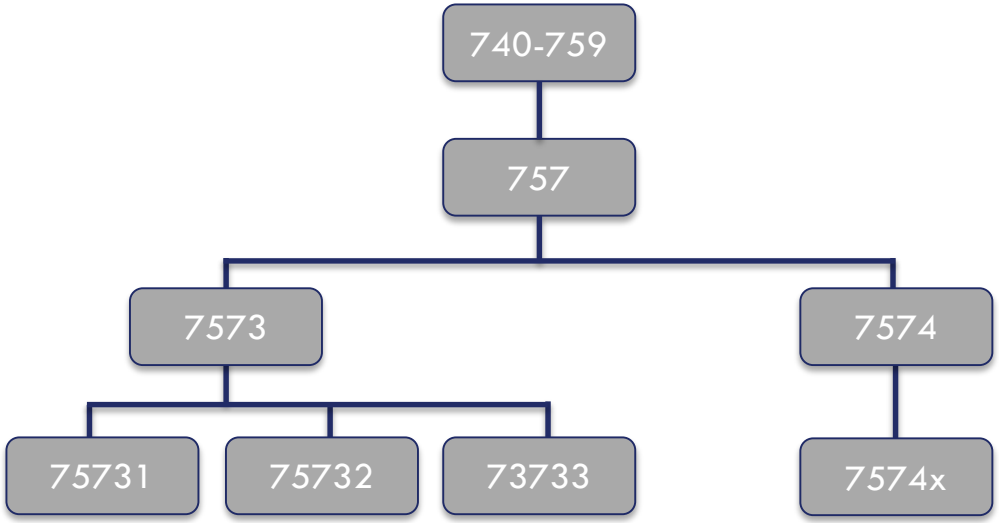
The Tree

Any hierarchical classification system for clinical concepts

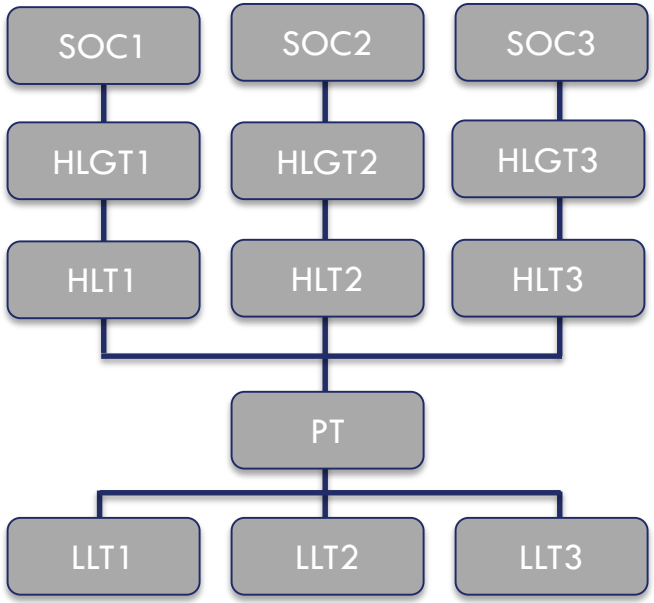
- International Classification of Diseases (ICD) 9th or 10th revision
- Multi-Level Clinical Classification Software (MLCCS)
- Medical Dictionary for Regulatory Activities (MedDRA)
- Systematized Nomenclature of Medicine (SNOMED-CT)



Single pathway for aggregation



Multiple pathways (multi-axial)



LLT = lower level term, PT = preferred term, HLT = higher level term, HLGT = higher level group term, SOC = system organ class

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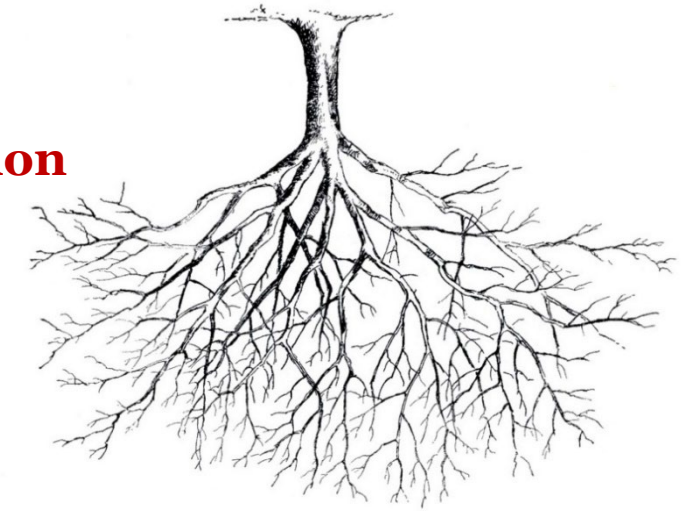
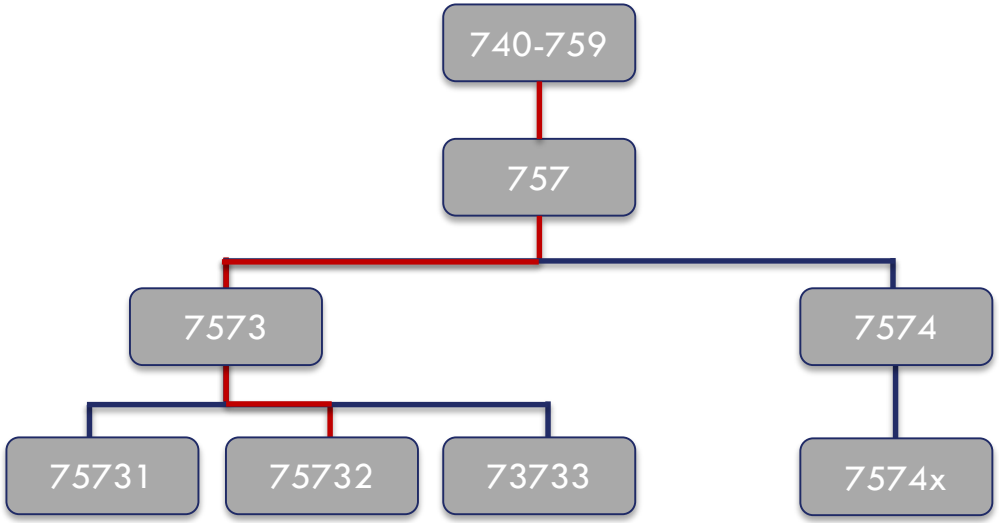
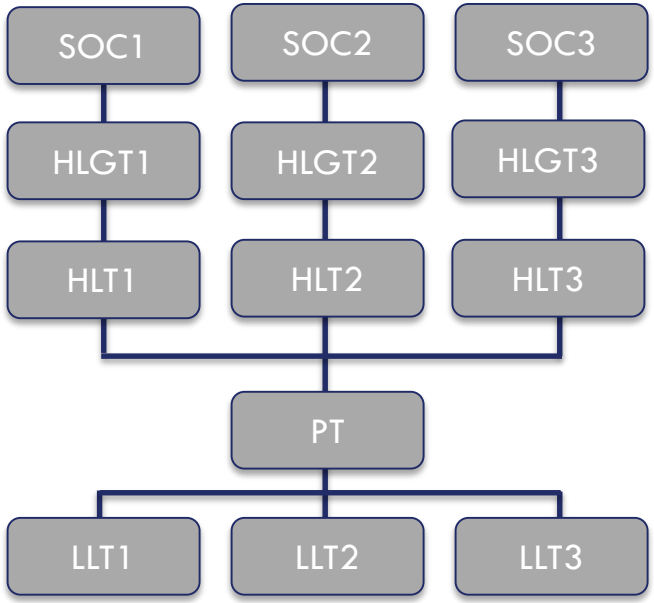


Single pathway for aggregation



Multiple pathways (multi-axial)



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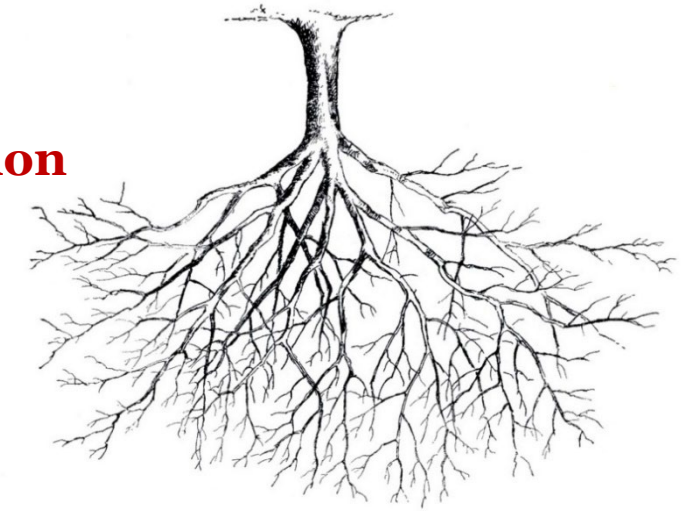
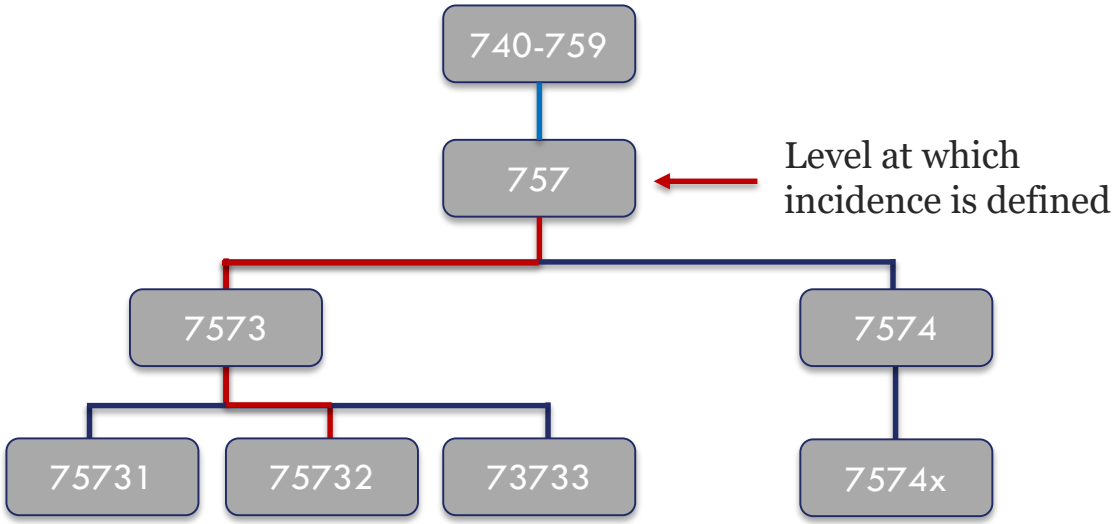
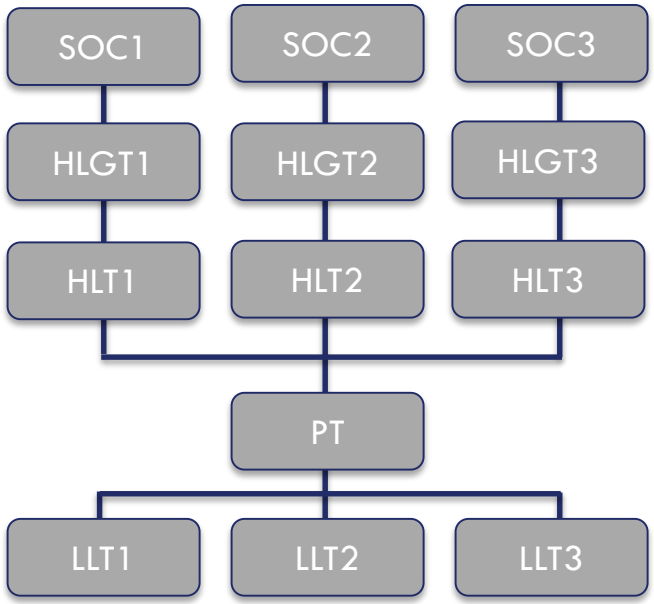


Single pathway for aggregation



Multiple pathways (multi-axial)



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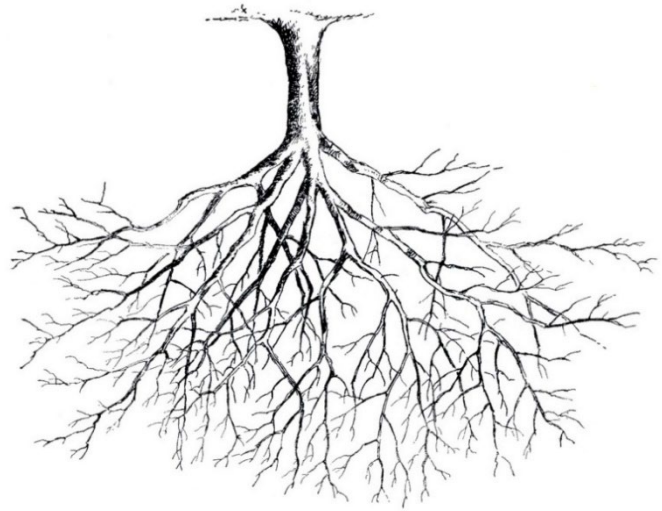
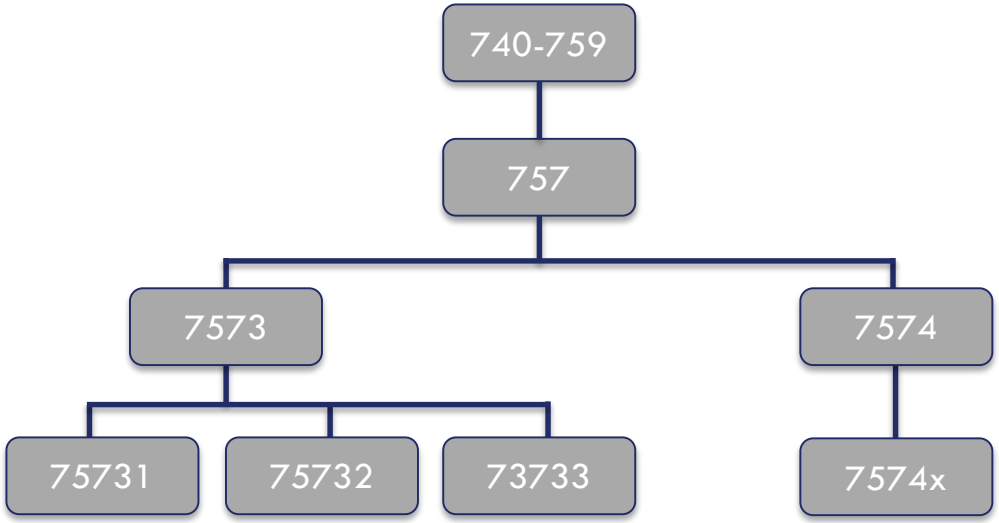
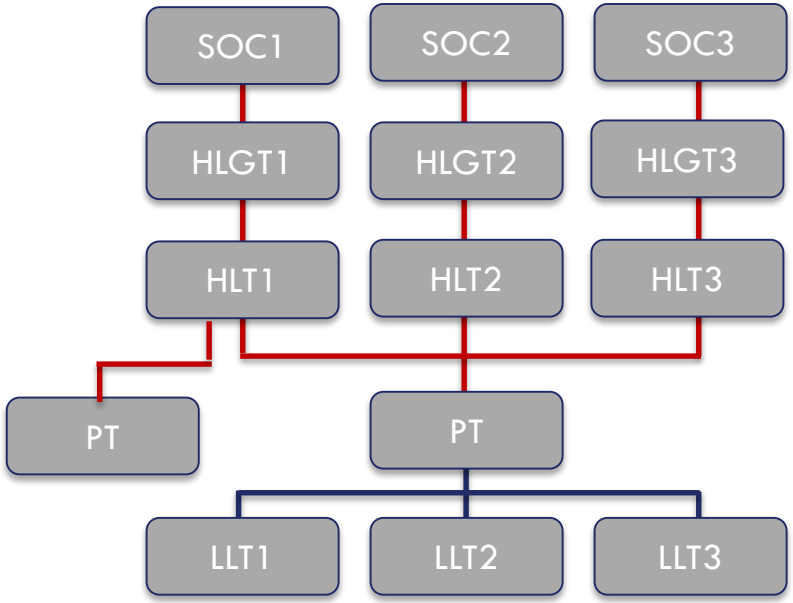


Single pathway for aggregation



Multiple pathways (multi-axial)



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The Scan Statistic

Null hypothesis: there are no outcomes for which there is an effect of exposure

Alternative hypothesis: there is ≥1 outcome(s) for which there is increased risk with exposure

Pick test statistic T

The Scan Statistic

Null hypothesis: there are no outcomes for which there is an effect of exposure

Alternative hypothesis: there is ≥1 outcome(s) for which there is increased risk with exposure

Pick test statistic T

Example: T = unconditional Bernoulli scan statistic

$$LLR(G) = ln\left(\frac{\left(\frac{c_G}{c_G + n_G}\right)^{c_G}\left(\frac{n_G}{c_G + n_G}\right)^{n_G}}{(p)^{c_G}(1-p)^{n_G}}\right) I\left(\frac{c_G}{c_G + n_G} > p\right)$$

G = node of interest

c_G = cases in the treatment group for a given node

n_G = cases in the comparator group for a given node

p = probability of being in the treatment group (for 1:1 matched this is 0.5)

Maro, J et al. Using tree-based scan statistics to evaluate outcomes following incident antibiotic use. Sentinel Methods Protocol.
Kulldorff, M. Drug safety data mining with a tree-based scan statistic. PDS, 2013
Kulldorff, M. TreeScan User Guide, version 1.2

The Scan Statistic

Null hypothesis: there are no outcomes for which there is an effect of exposure

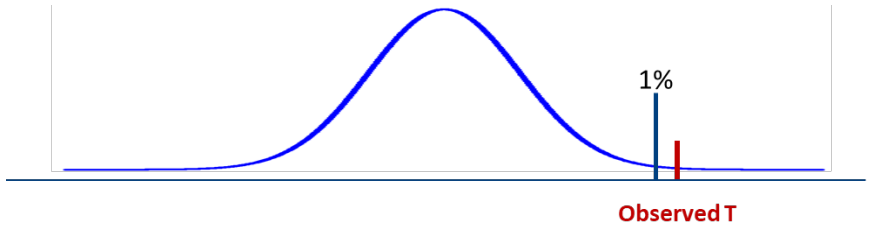
Alternative hypothesis: there is ≥1 outcome(s) for which there is increased risk with exposure

Pick test statistic T

Set threshold for statistical alerts (e.g. p<0.01)

Use Monte Carlo based p-value

1. Generate test statistic T for 9999 random datasets (under the null)
2. Rank T for randomly generated datasets (R = rank)
3. P-value accounting for evaluation of multiple tree nodes= R/(9,999+1)
4. Statistical alert if p ≤ pre-specified threshold



A statistical alert ≠ safety signal and always requires further clinical correlation and evaluation for bias and confounding

The Scan Statistic

- Binomial, Poisson test statistics not appropriate for continuous outcomes
  - Continuous outcome can be scanned with Gaussian likelihood

- Propose alternative test statistics that will allow binary/count and continuous outcomes to be scanned simultaneously on the same scale
  1. Approximate Binomial and Poisson LRT with Gaussian likelihood
  2. Likelihood free test statistics that are naturally on the same scale, e.g., standardized mean differences, “p-values”

Future enhancements

Data: **Claims + EHR data**

Outcome type: **Continuous**

Scan statistic: **Normal approximation, standardized difference**

Tree: **Multi-axial ontologies (e.g. MedDRA, SNOMED-CT)**

1. Develop a **portable pipeline**
   - Produce outcome counts for hierarchical MedDRA tree
   - Include structured EHR data, NLP-extracted data from clinical notes, lab, vital signs data

2. Develop **scan test statistics**
   - Can simultaneously evaluate binary/Poisson and continuous outcomes

3. Develop **software procedures**
   - Can handle multi-axial pathways in hierarchical trees

4. **Proof of concept**
   - Application in 2-3 examples

Sentinel Innovation Center Vision

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

Thank you

Session IV:BEST Innovations in Data Infrastructure and Analytic Methods

- **John Seeger,** Optum
- **Bradley Layton,** RTI Health Solutions
- **Yun Lu,** US, Food and Drug Administration, CBER
- **Richard Forshee,** US, Food and Drug Administration, CBER

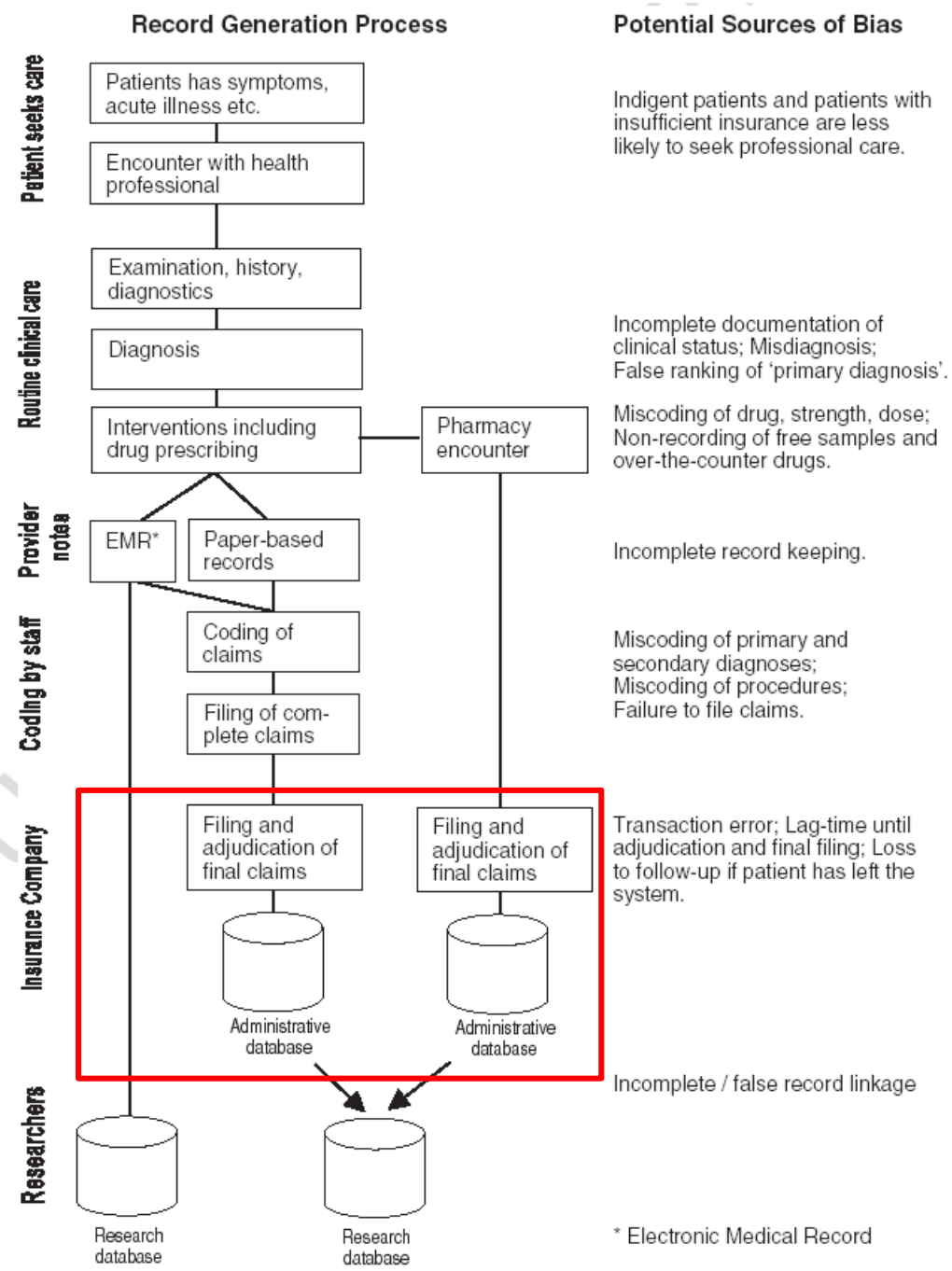
Optum

Data Linkage to Address COVID-19 Vaccine Misclassification

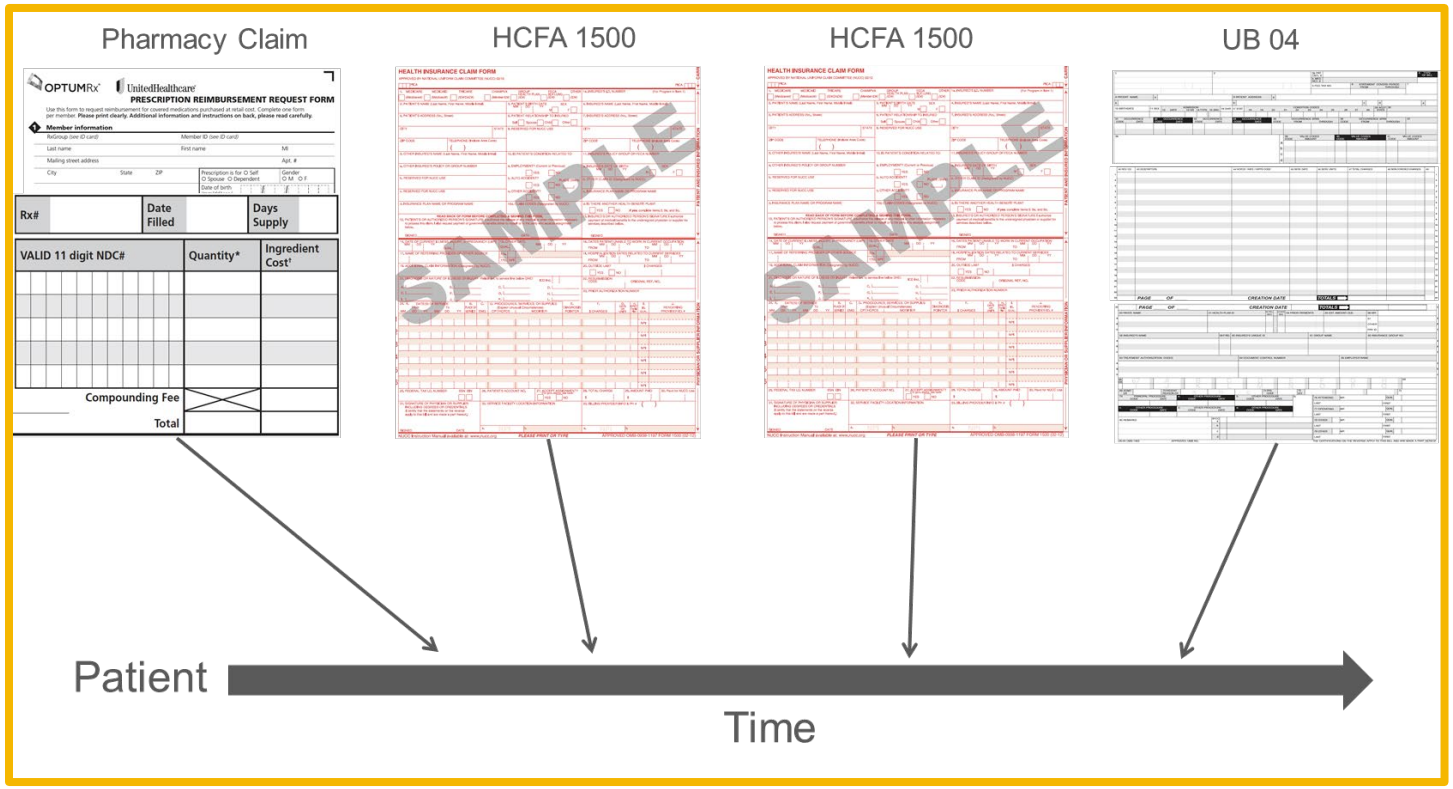
John Seeger, PharmD, DrPH, FISPE
Chief Scientific Officer for Epidemiology, Optum

Fourteenth Annual Sentinel Initiative Public Workshop
November 15-16, 2022

From Health Service to Database



Schneeweiss & Avorn. J Clin Epi 2005



Adult Patient, Vaccination at Mass Immunization Site

Patient
Age: 24, Sex: M
Vaccine Brand: PFIZER
Facility: MASS

Event	Relative Date	Setting	Facility	Type of code	Code	Code Description
	-16	RX	PHARM	RX	8627001601	DEXCOM G6
	-16	RX	PHARM	RX	8627005303	DEXCOM G6
Y	0	PB	MASS	DX	Z23	Encounter For Immunization
Y	0	PB	MASS	PX	0001A	Imm Admn Sarscov2 30mcg/0.3ml Dil Recon 1st Dose
Y	0	RX	PHARM	RX	59267100003	PFIZER COVID-19 VACCINE (EUA)
	2	RX	PHARM	RX	2879959	HUMALOG KWIKPEN U-100
	15	RX	PHARM	RX	24586903	TOUJEO SOLOSTAR
	16	RX	PHARM	RX	24586903	TOUJEO SOLOSTAR
	19	RX	PHARM	RX	2879959	HUMALOG KWIKPEN U-100
Y	23	PB	MASS	DX	Z23	Encounter For Immunization
Y	23	PB	MASS	PX	0002A	Imm Admn Sarscov2 30mcg/0.3ml Dil Recon 2nd Dose
	28	RX	PHARM	RX	24586903	TOUJEO SOLOSTAR

COVID-19 Vaccine Administration Sites

Optum claims data through 16 April 2022

Care Setting	Number	%
Pharmacy	2,808,402	54%
Office	943,113	18%
Mass Immunization Center	550,388	11%
Hospital	534,991	10%
Other	137,024	3%
Multiple	4,794	0.1%
Home Health	917	0%
Skilled Nursing Facility	273	0%

Optum

Vaccine Effectiveness With Exposure Misclassification

Assuming 70% vaccine effectiveness and COVID-19 incidence among unvaccinated of 6%

50% misclassification of vaccinated as unvaccinated: vaccine effectiveness declines from 70% to 49%

Original table

Vaccinated	COVID-19 diagnosis		
		Yes	No
	Yes	52,534	2,866,009
	No	59,938	939,026

Misclassified table

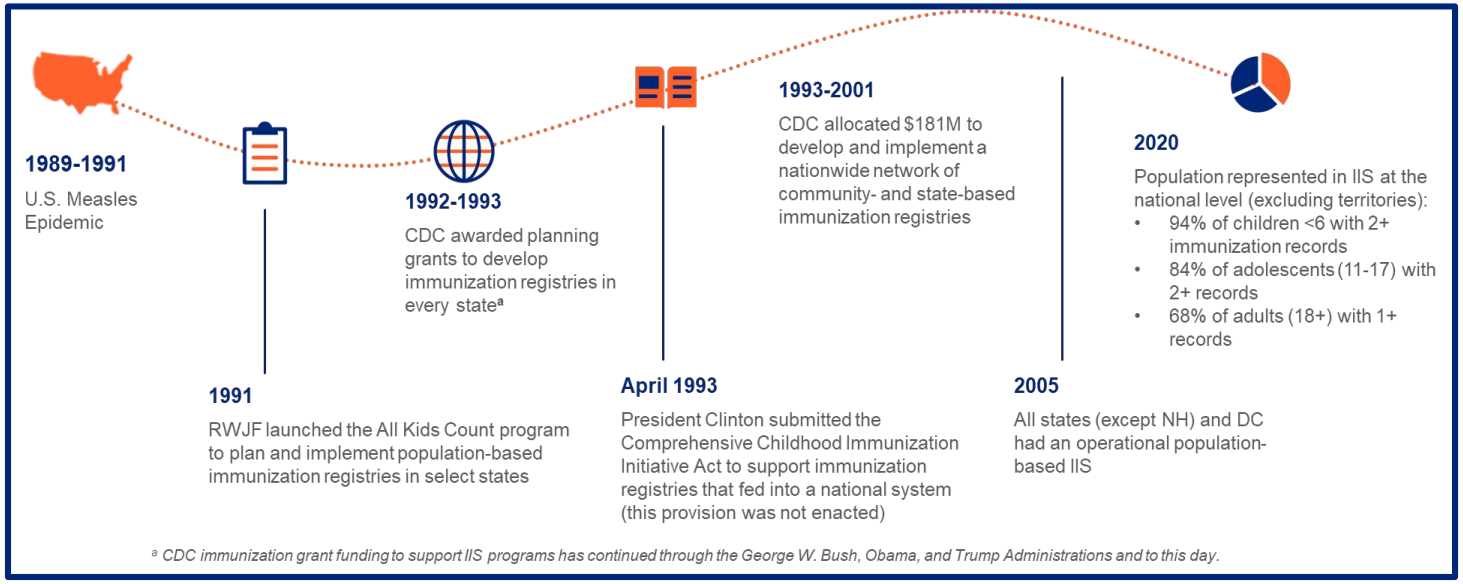
Vaccinated	COVID-19 diagnosis		
		Yes	No
	Yes	26,267	1,433,005
	No	86,205	2,372,030

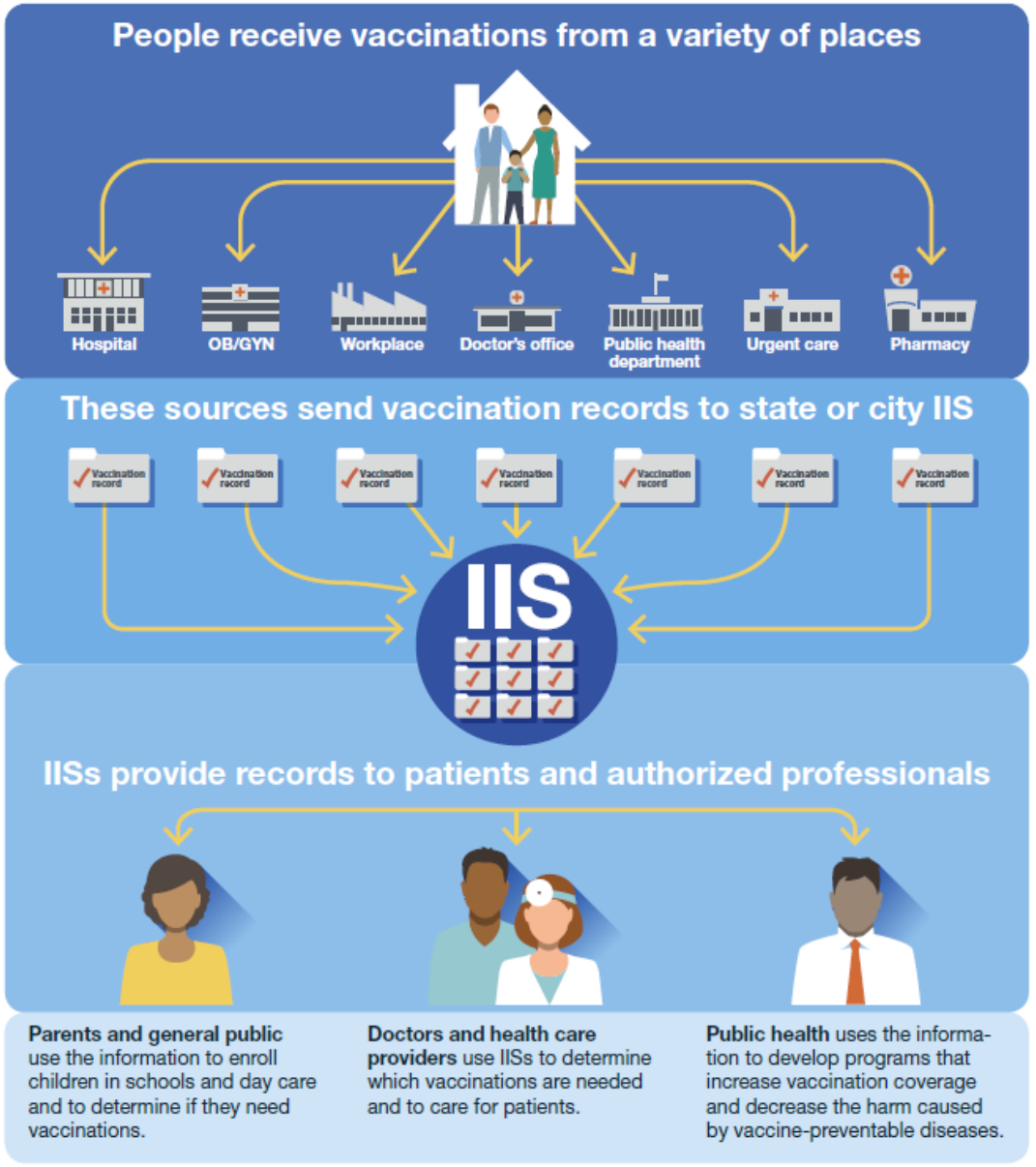
VE = 1 − (26,267/[26,267+1,433,005])/(86,205/[86,205+2,372,030]) = 49%

Optum

Background

Immunization Information Systems (IIS)





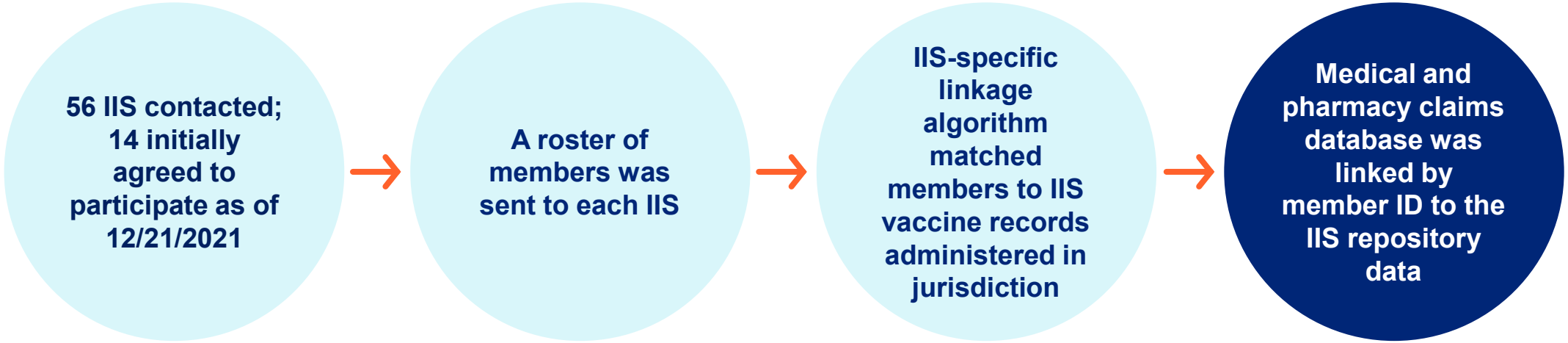
Distributed by:

Optum

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Creation of linked IIS-claims database

When you have engaged with one IIS, you have engaged with one IIS



Challenges engaging IIS

- All jurisdictions required legal reviews of this data request
  - Some needed new data sharing agreements or amendments to existing agreements
  - Some had statutory restrictions for data sharing
  - Others cited state rules regarding sharing of data with insurers
- Limited resources and capacity to collaborate
- High cost for routine data exchange
- Difficulty establishing and maintaining contact

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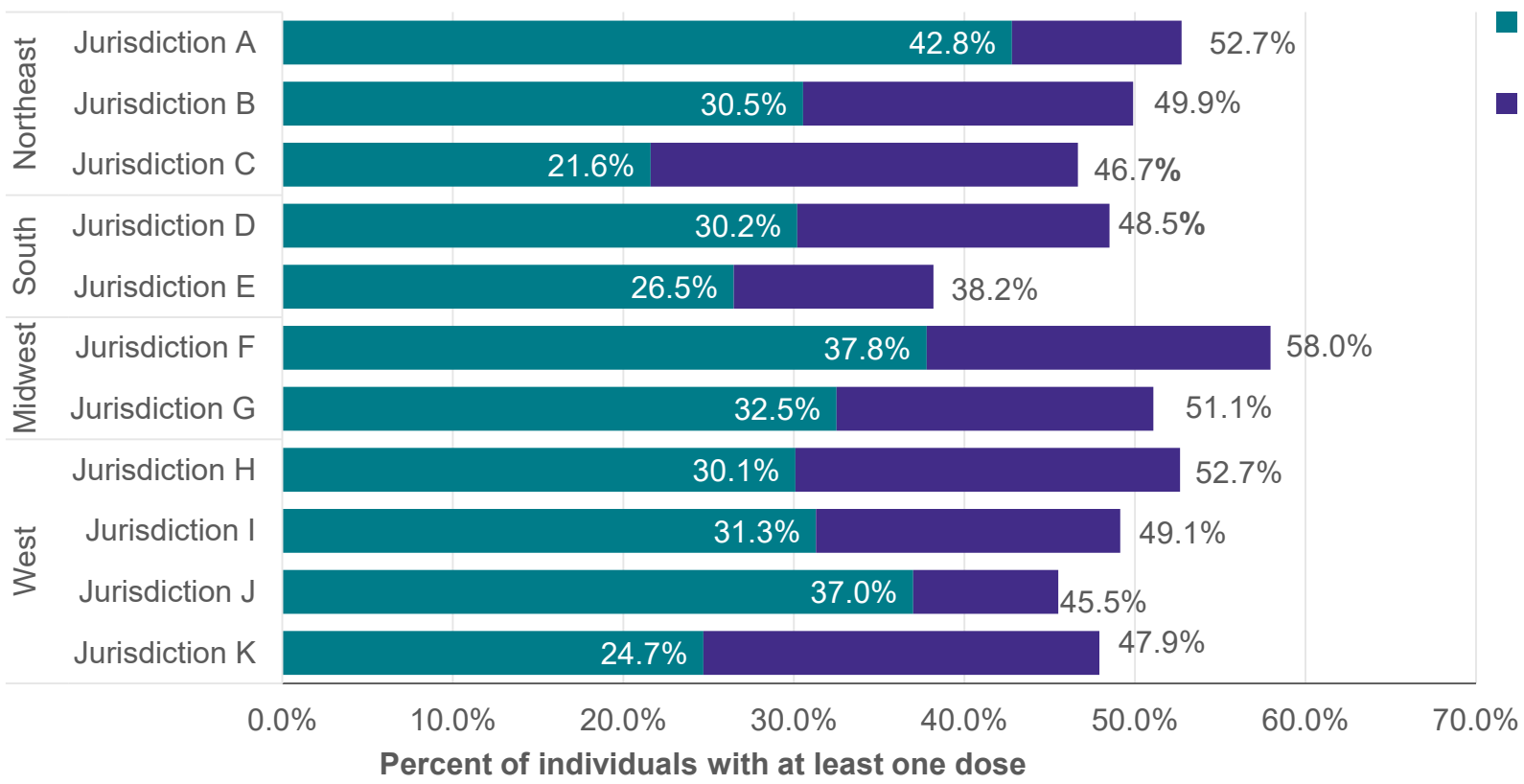
Heterogeneity at the jurisdiction level

Jurisdiction	Optum refresh frequency of IIS data	Last date of IIS vaccine record[1]	Description of Linkage
Jurisdiction A	Weekly	31 Dec 2021	Linkage variables: first, middle and last name; address; date of birth; phone number. Only returns data for patients with 1:1 matches.
Jurisdiction B	Monthly	23 Dec 2021	Linkage variables: first and last name; date of birth. If multiple matches, use WebIZ ID, social security number, middle name, gender, suffix.
Jurisdiction C	Daily	30 Dec 2021	Linkage variables: first and last name; date of birth. Deterministic matching.
Jurisdiction D	Monthly	02 Dec 2021	Linkage variables: first and last name; date of birth. If multiple matches, use WebIZ ID, social security number, middle name, gender, suffix, phone number.
Jurisdiction E	Semi-monthly	03 Dec 2021	Linkage variables: first and last name; date of birth; chart ID.
Jurisdiction F	Weekly	31 Dec 2021	Linkage variables: first and last name; date of birth. Probabilistic matching and returns only 1:1 matches.
Jurisdiction G	Weekly	31 Dec 2021	Linkage variables: first and last name; date of birth. If multiple matches, use address.
Jurisdiction H	Monthly	17 Dec 2021	Linkage variables: first and last name; date of birth; gender; address; phone. Deterministic matching.
Jurisdiction I	Monthly	21 Nov 2021	Linkage variables: first, middle and last name; date of birth; gender; medical record number. If multiple matches, use address, phone number, guardian name.
Jurisdiction J	Monthly	31 Dec 2021	Linkage variables: member ID; first and last name; date of birth.
Jurisdiction K	Monthly	23 Nov 2021	Linkage variables: first, middle, and last name; suffix; date of birth; gender; social security number; mother's first and maiden name; address; phone number. Mix of probabilistic and deterministic matching.

[1]As of data pulled from IIS repositories on 10 January 2022 and restricted to dates of service through 31 December 2021 (i.e. end of study period)

Variation in vaccination estimates by jurisdiction



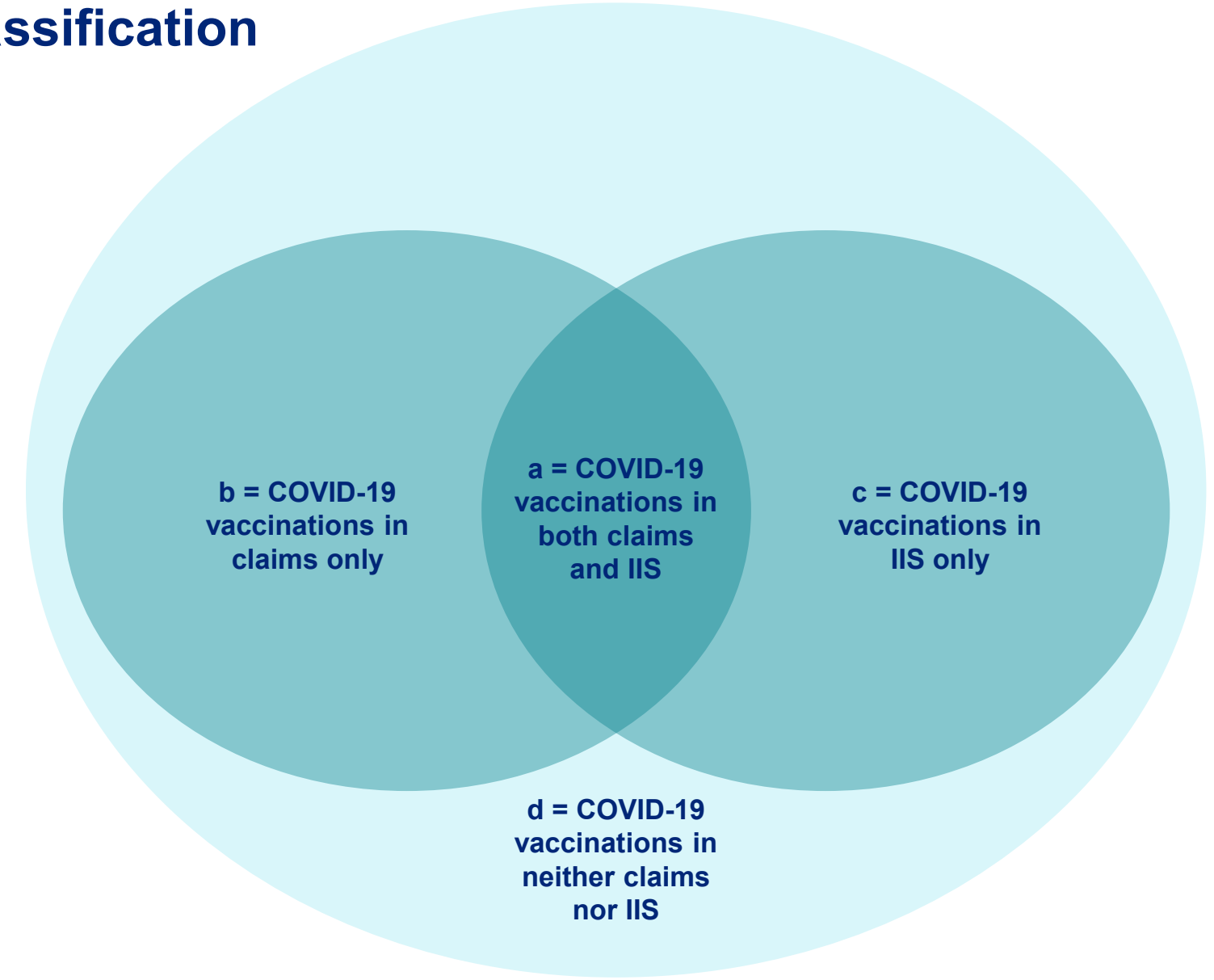
The increase in vaccine exposure ascertainment from IIS linkage over claims alone varied by jurisdiction, ranging from a 23% to 116%.

Vaccine status (all jurisdictions)	**Pre-adj. claims** N=5,112,722	**IIS data** N=5,112,722	**IIS-claims** N=5,112,722	**% Increase**
1+ dose	32.8% (1,676,235)	32.2% (1,643,733)	48.1% (2,458,231)	+46.7%
Complete series	24.4% (1,248,637)	29.2% (1,493,706)	41.9% (2,143,556)	+71.7%

Estimating remaining misclassification

Remaining misclassification assessment by comparison to:

1) age-standardized CDC vaccine administration estimates
2) age-standardized department of health (DOH) vaccine administration estimates
3) capture-recapture estimates



Methods

Heterogeneity of CDC and DOH vaccination estimates

Jurisdiction	Last date of IIS vaccine record[1]	Date of CDC data[2,3]	Date of DOH data[2,4]	DOH groups for age-standardization
Jurisdiction A	31 Dec 2021	13 Jan 2022	11 Jan 2022	0-4, 5-11, 12-15, 16-19, 20-29, 30-39, 40-49, 50-64
Jurisdiction B	23 Dec 2021	13 Jan 2022	14 Jan 2022	5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64
Jurisdiction C	30 Dec 2021	13 Jan 2022	01 Jan 2022	0-4, 5-9, 10-14, 15-18, 19-24, 25-29, 30-39, 40-49, 50-59, 60-69
Jurisdiction D	02 Dec 2021	13 Jan 2022	N/A	N/A
Jurisdiction E	03 Dec 2021	13 Jan 2022	11 Jan 2022	0-4, 5-9, 10-14, 15-19, 20-24, 25-34, 35-44, 45-54, 55-64
Jurisdiction F	31 Dec 2021	13 Jan 2022	17 Jan 2022	5-11, 12-15, 16-17, 18-49, 50-64
Jurisdiction G	31 Dec 2021	13 Jan 2022	11 Jan 2022	5-11, 12-17, 18-64
Jurisdiction H	17 Dec 2021	13 Jan 2022	15 Dec 2021	12-15, 16-17, 18-34, 35-49, 50-64
Jurisdiction I	21 Nov 2021	03 Nov 2021	21 Nov 2021	<20, 20-34, 35-44, 45-54, 55-64
Jurisdiction J	31 Dec 2021	13 Jan 2022	11 Jan 2022	5-11, 12-17, 18-45, 50-64
Jurisdiction K	23 Nov 2021	13 Jan 2022	23 Nov 2021	5-11, 12-18, 19-29, 30-39, 40-49, 50-59, 60-69

Notes: CDC age groups used for age standardization were 0-4 years, 5-11 years, 12-17 years, and 18-64 years. N/A = age-specific vaccination estimates were not available on the DOH website for Jurisdiction D
[1]As of data pulled from IIS repositories on 10 January 2022 and restricted to dates of service through 31 December 2021 (i.e. end of study period)
[2]Dates for the CDC and DOH data were chosen to most closely match the last date of service of the IIS data.
[3]We accessed CDC's data through a Mayo Clinic website (https://www.mayoclinic.org/coronavirus-covid-19/vaccine-tracker), which refreshes the CDC data daily and presents age-stratified vaccination estimates by state.
[4]Accessed through state and jurisdiction Department of Health websites.

Results

Sensitivity estimates of the linked IIS-claims measure of percent with at least one dose

Sensitivity: 100 – percent under-recording

Under-recording: Difference between vaccination estimate from other source and from combined IIS/claims estimate, divided by vaccination estimate from other source

Since no gold standard for vaccine coverage, estimates of sensitivity of the linked IIS-claims measure subject to limitations of the comparison data

Jurisdiction	Region	Sensitivity estimates of linked IIS-claims measure of percent with at least one dose, as derived from comparison with the following source:		
		CDC	DOH	Capture-recapture
Total	**Total**	**68%**	**71%**	**77%**
Jurisdiction A	Northeast	59%	64%	80%
Jurisdiction B		67%	83%	80%
Jurisdiction C		53%	65%	73%
Jurisdiction D	South	79%	N/A	84%
Jurisdiction E		62%	64%	75%
Jurisdiction F	Midwest	85%	90%	91%
Jurisdiction G		72%	78%	83%
Jurisdiction H	West	69%	77%	83%
Jurisdiction I		83%	86%	87%
Jurisdiction J		56%	61%	61%
Jurisdiction K		81%	81%	80%

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Correcting for misclassification

Illustrating with mock numbers how estimates of sensitivity can be used to correct for misclassification of COVID-19 vaccine

Applying the 71% sensitivity of vaccine exposure, we can correct for misclassification

52,534 * 0.71 = 37,299

37,299 were observed in cell a and the other 15,235 (i.e., 52,534 - 37,299) actually vaccinated were misclassified as unvaccinated in cell c

2,866,009 * 0.71 = 2,034,866

2,034,866 were observed in cell b and the other 831,143 (i.e., 2,866,009 - 2,034,866) vaccinated were misclassified as unvaccinated in cell d

Observed table, with misclassification

Vaccinated	COVID-19 diagnosis		
		Yes	No
	Yes	a = 37,299	b = 2,034,866
	No	c = 75,173	d = 1,770,169

Corrected table

Vaccinated	COVID-19 diagnosis		
		Yes	No
	Yes	52,534	2,866,009
	No	59,938	939,026

Thank-You!

Elizabeth Bell
Grace Yang
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Michael Wilkinson
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Optum Tech Team

Steven Anderson
Azadeh Shoaibi
Hui-Lee Wong
Patricia Lloyd
Tainya C. Clarke
Richard Forshee
Cindy Ke Zhou

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RTI (h)(s)
Health Solutions

16 November 2022

Assessment of Effectiveness of COVID-19 Vaccination in the United States

J. Bradley Layton, PhD, FISPE

The power of **knowledge.**
The value of **understanding.**

Disclosures

- Employee of RTI Health Solutions, an independent, nonprofit research institute
- Contributed to studies of COVID-19 vaccine safety and effectiveness funded by regulatory agencies and vaccine manufacturers
- The project being discussed was funded by the US FDA

COVID-19 = coronavirus disease 2019; FDA = Food and Drug Administration.

Background

Background

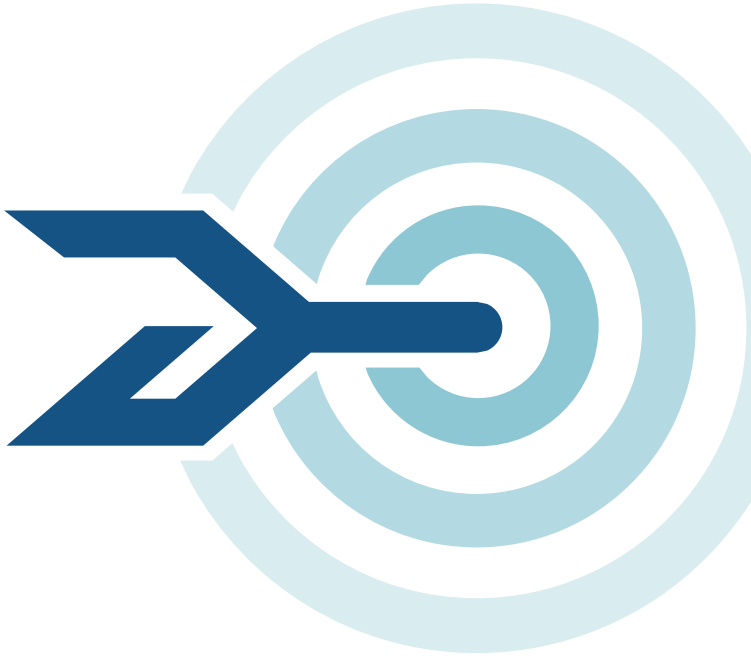
- The real-world effectiveness of COVID-19 vaccines needs to be evaluated
- There are multiple questions of regulatory interest that have evolved over time
  - Potential waning effectiveness over time
  - New variants
  - New authorizations and recommendations

Study Objectives

Primary Objectives

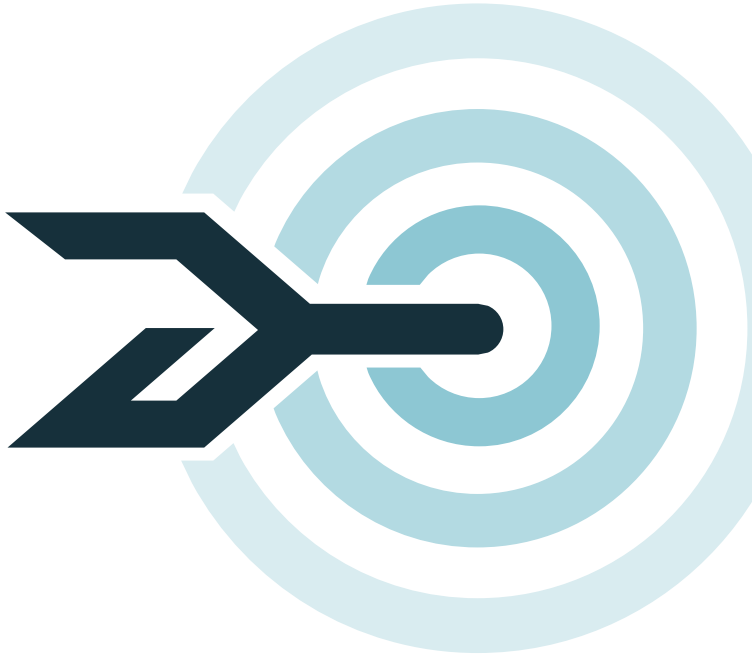
- To assess the effectiveness of receiving a **complete primary series** of COVID-19 vaccination in adults aged 18 to 64 years, by brand, **compared with being unvaccinated**

- To describe/characterize the effectiveness **over time, across eras of different circulating variants, and potential waning effectiveness** of receiving a complete primary series of COVID-19 vaccination in adults aged 18 to 64 years, by vaccine brand, compared with being unvaccinated



Secondary Objectives

- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination in **subgroups of special interest**
- To assess the **comparative effectiveness** of the complete series of each brand of COVID-19 vaccine
- To assess the effectiveness of receiving **a single dose of a 2-dose primary series** of COVID-19 vaccination
- To assess the effectiveness of receiving a complete primary series of COVID-19 vaccination in **individuals aged 5 to 17 years** for vaccines authorized for use in this age group
- To assess the effectiveness of receiving a **booster/additional dose compared with not receiving an additional dose or booster dose** in individuals authorized to receive a booster/additional dose during the study period



Study Approach

Study Setting

- Linked data sources for individual-level information on vaccination, COVID-19 outcomes, demographic and clinical characteristics
  - Optum administrative claims data
  - Immunization Information System (IIS) vaccination records

- Study period
  - Began 11 December 2020
  - End times vary based on the analysis (latest of 31 May 2022)

IIS = immunization information systems.

Three Unique Study Cohorts

RTI (h)(s) Health Solutions

Adult primary series analysis

- Overall primary series VE
- Time-varying VE and variant eras
- Clinical subgroups
- Single-dose
- Comparative effectiveness

Pediatric primary series analysis

- Overall primary series VE
- Age subgroups
- Variant eras

Booster/additional dose analysis

- Overall booster/additional dose VE (ages 12+ years)
- Subgroups
- Variant eras

VE = vaccine effectiveness.

Cohort Entry and Time 0

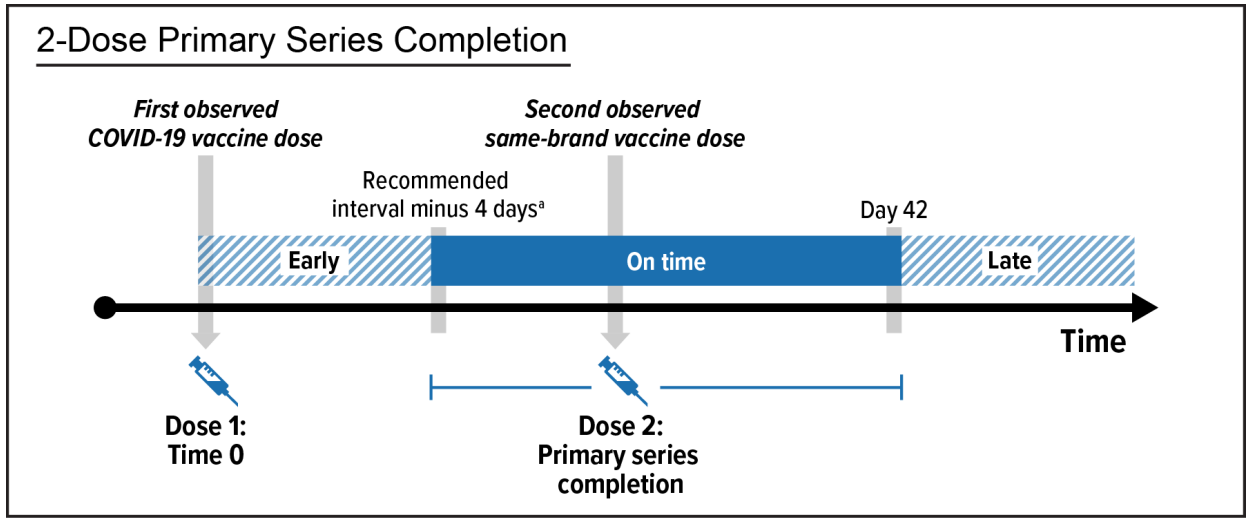
- Identify vaccinated individuals on the day of a vaccine record
- Match unvaccinated individuals on the same day on the following:
  - Age
  - State and county of residence
  - Sex
  - Immunocompromised status
  - Pregnancy status
  - History of COVID-19 diagnosis
  - Presence of at least 1 of the conditions identified by the CDC as increasing individuals' risk of severe COVID-19 infection
- Goal is to balance calendar time, geography, vaccine eligibility, and prioritization

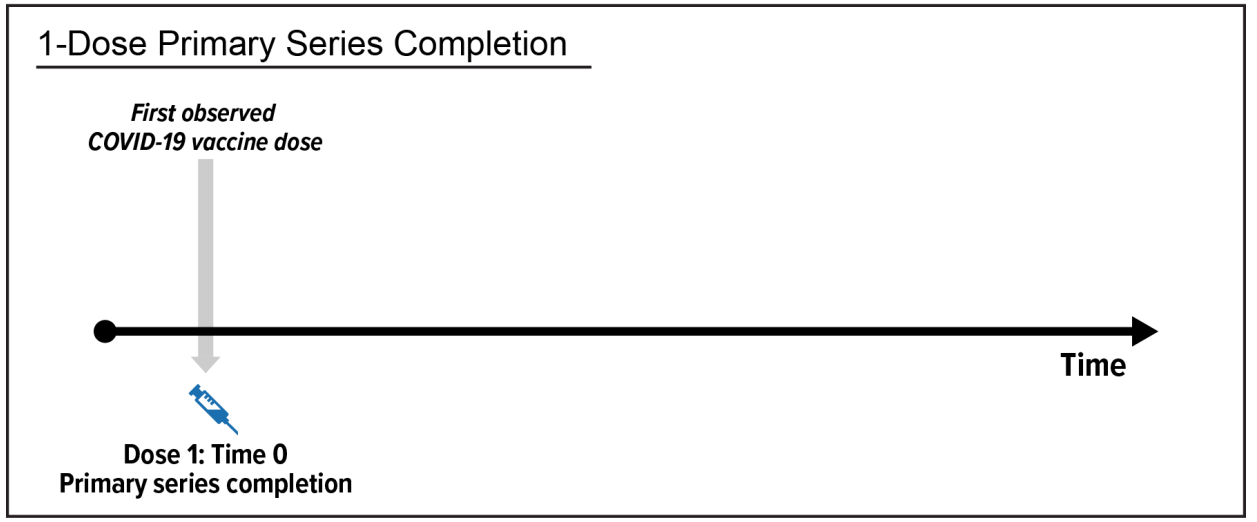
CDC = US Centers for Disease Control and Prevention.

Follow-up

- Start follow-up on day of vaccination (time 0)
  - Avoid looking into the future to assign current exposure
  - Censoring rules to define deviation from exposure initial exposure

- Identify COVID-19 outcomes
  - COVID-19 diagnosis in any medical setting
  - Hospital/ED-diagnosed COVID-19



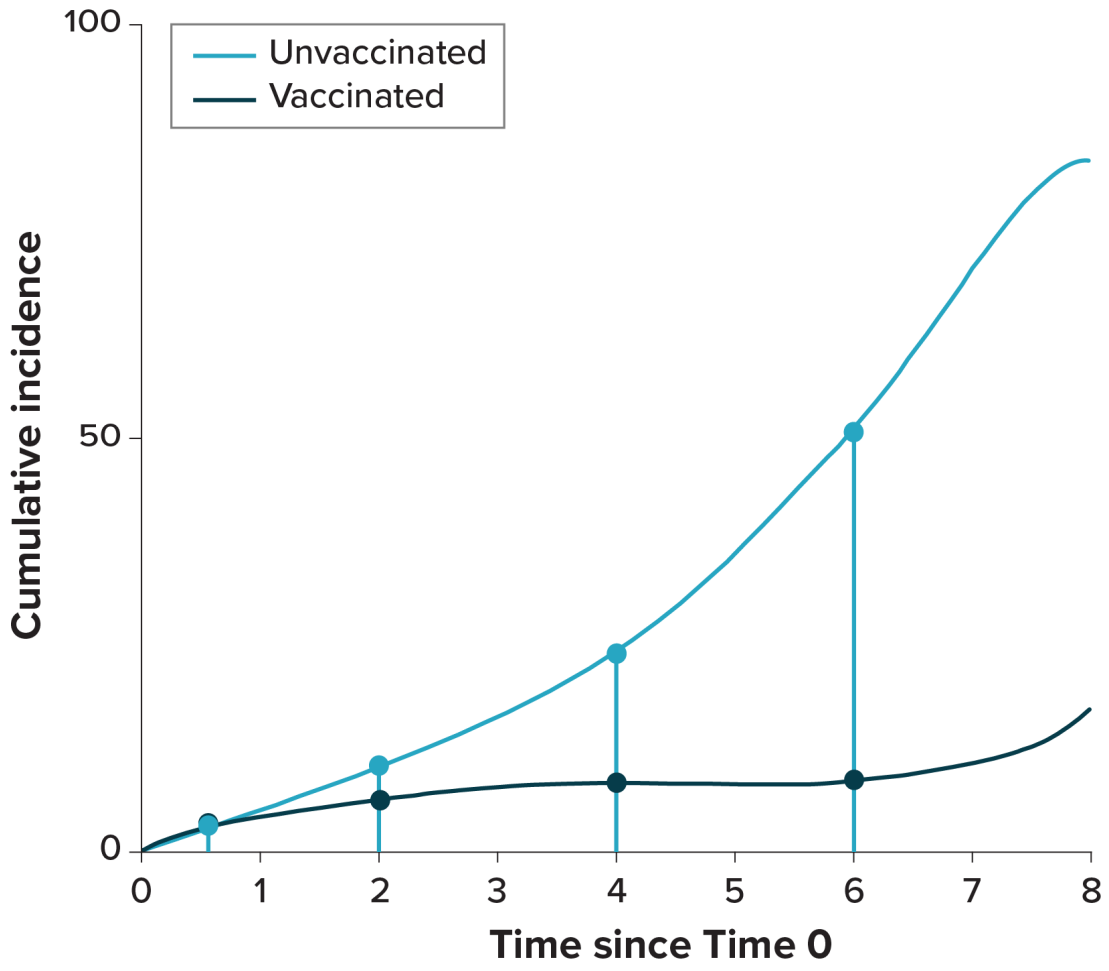


ED = emergency department

[a] Day 17 for BNT162b2, day 24 for mRNA-1273.

Estimating Vaccine Effectiveness

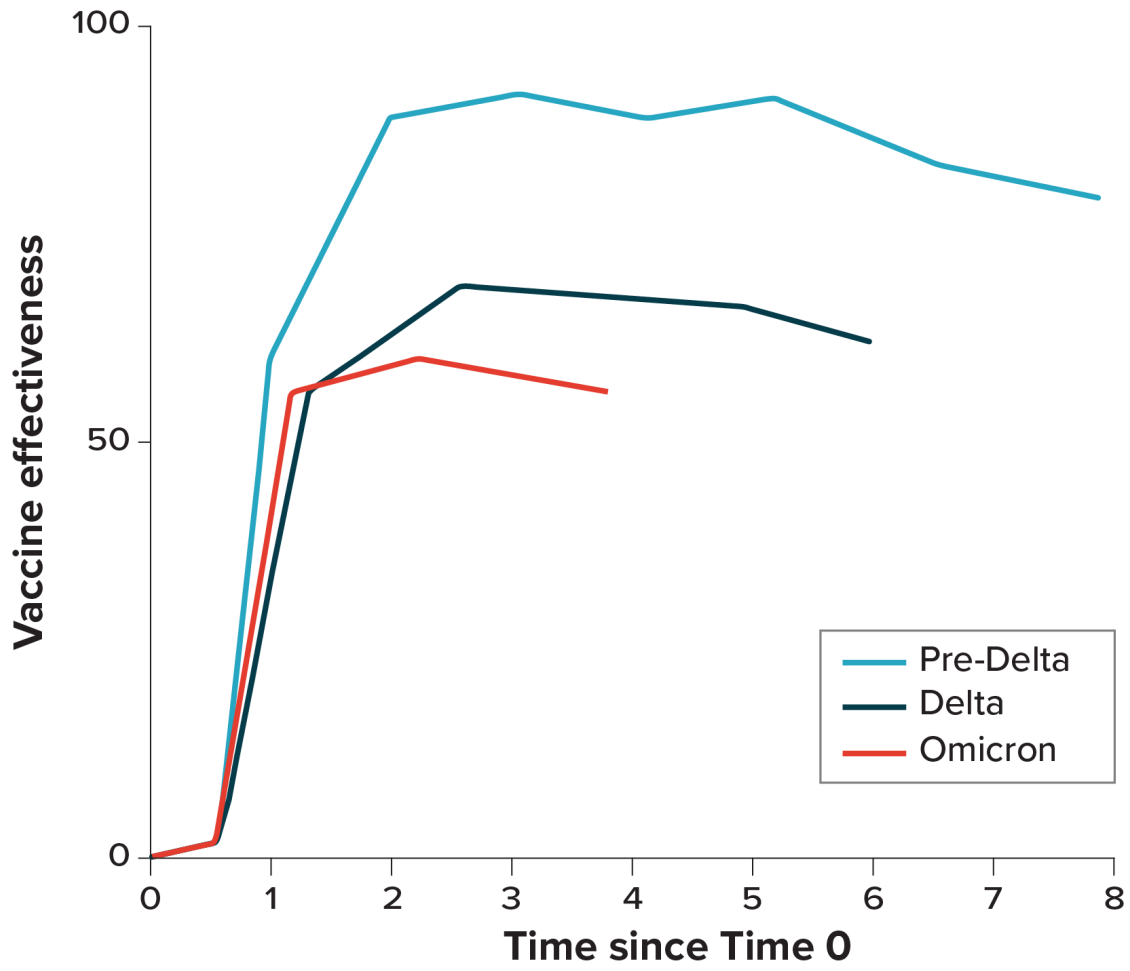
- Overall
  - Estimate summary hazard ratio (HR) across all of follow-up
- Over time (i.e., waning effectiveness)
  - Estimate cumulative incidence of COVID-19 outcomes
    - Plot daily risk estimates in exposure groups
  - Estimate risk ratios (RR) and risk differences (RD) at fixed time points
- VE = 1 – RR (or HR)



HR = hazard ratio. RD = risk difference; RR = risk ratio; VE = vaccine effectiveness.

Evaluate Changing VE Over Time and Variants

- Evaluate changing VE over time
  - Estimate VE at a range of time points
  - Plot VE over time
- Stratify by variant era of time 0 (date of first vaccine dose)
- Censor at the end of variant era



VE = vaccine effectiveness

Conclusions

Conclusions

Accurate assessments of VE require appropriate sources of data and robust methods

Acknowledgement of potential residual sources of bias

- Sensitivity analyses
- Negative control outcome analyses
- Quantitative bias analyses for exposure and outcome misclassification

Analyses are ongoing. Dissemination is planned soon.

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- Melissa McPheeters

BEST

- US FDA/CBER/OBPV
- Optum
- Acumen

Thank You

Questions?

jblayton@rti.org

U.S. FOOD & DRUG ADMINISTRATION

Real-World Effectiveness of mRNA COVID-19 Vaccines Among U.S. Nursing Home Residents Aged ≥65 Years

Yun Lu, Ph.D. on behalf of the FDA, CMS, and Acumen Team

Office of Biostatistics and Pharmacovigilance (OBPV)

FDA/Center for Biologics Evaluation and Research (CBER)

The 14th Annual Sentinel Initiative Public Workshop, November 16, 2022

Disclaimer

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, CMS, Acumen or any other organization

Background

The COVID-19 pandemic caused substantial morbidity and mortality, especially among older adults residing in nursing homes (NH).

Understanding the effectiveness of mRNA COVID-19 vaccines among this population and across time is crucial for effective policy making and vaccine development.

Methods

OBSERVATION PERIOD

December 13, 2020 to November 20, 2021

EXPOSURES

Time-varying mRNA COVID-19 vaccination status

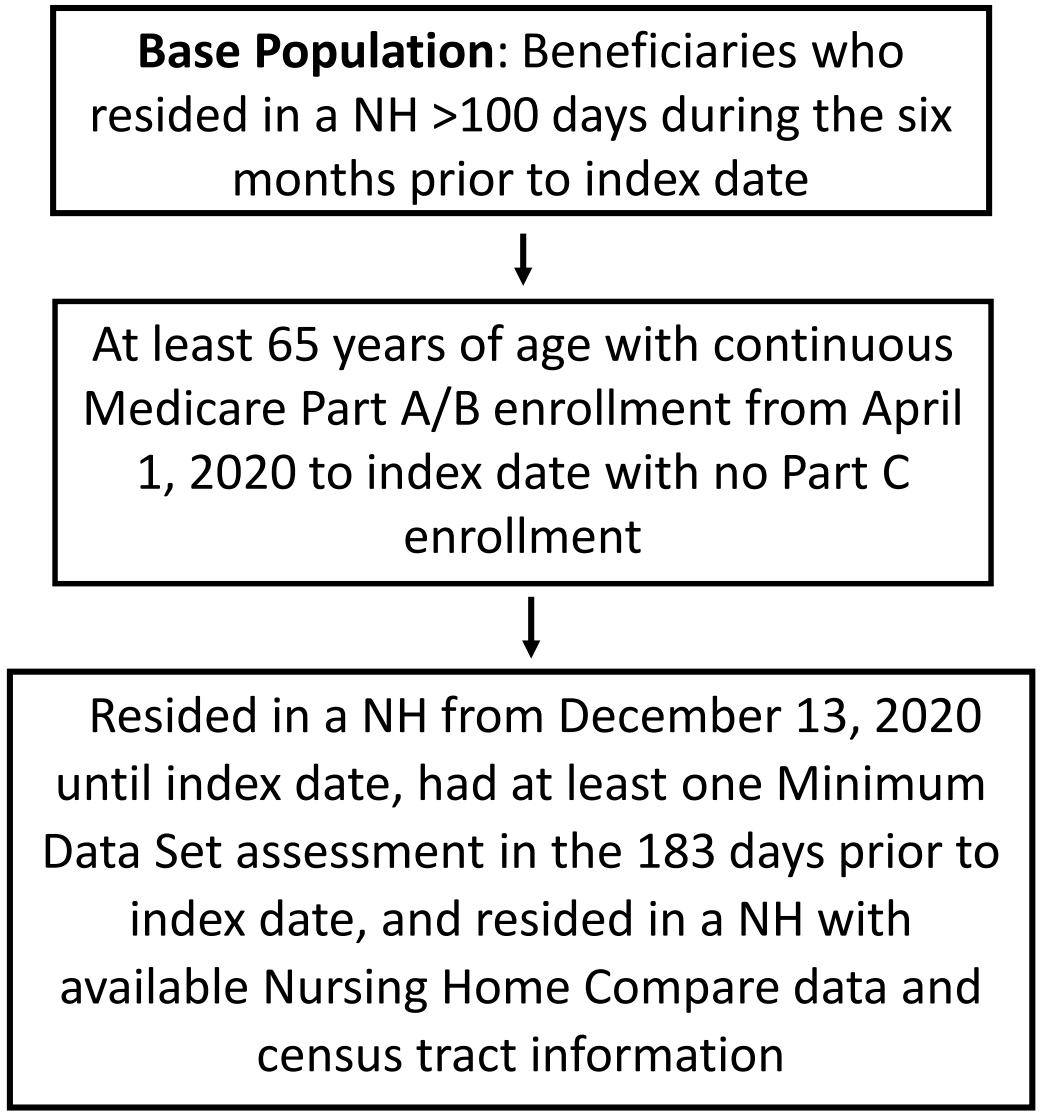
POPULATION

Medicare Fee-for-Service beneficiaries aged ≥65 years residing in U.S. NHs

OUTCOMES

Primary: COVID-19 related deaths, COVID-19 hospitalizations, and combined COVID-19 hospitalization or death

Selection Process for Beneficiaries Included in the Study



Addressing Underreporting of Vaccination

- Quantitative Bias Analysis was conducted to evaluate the impact of potential exposure misclassification
- Beneficiaries were excluded if they:

  (1) resided in a NH with less than 10% of residents vaccinated with one dose on or before March 1st, 2021; or

  (2) if a second or third dose was observed without the preceding dose

Final Study Populations

NH Residents ≥65 years of age:	**N= 348,310**
By the end of the study period November 20, 2021	
Unvaccinated Cohort :	**N= 14%**
One-Dose Cohort:	**N= 4%**
Two-Dose Cohort:	**N= 61%**
Booster Cohort:	**N= 21%**

Measured Covariates

- Individual-level characteristics included demographics, socioeconomic status, health status (including prior COVID status), flu vaccination, and mortality risk score.
- NH-level characteristics included quality measure rating, health inspection rating, nurse staffing hours, number of residents per day, and ownership type.
- Time-varying risk factors included measures of local COVID-19 circulation rates and the Delta variant share.

Covariate Balance

- Standardized mean differences (SMDs) were used to determine cohort balance for covariates
- Imbalances between cohorts were initially observed
- Inverse probability of treatment weighting (IPTW) was used to address imbalance in all measured covariates
- Following IPTW, some residual imbalance remained for influenza vaccination and prior COVID-19 infection status. Additional imbalance were found for the booster cohort.

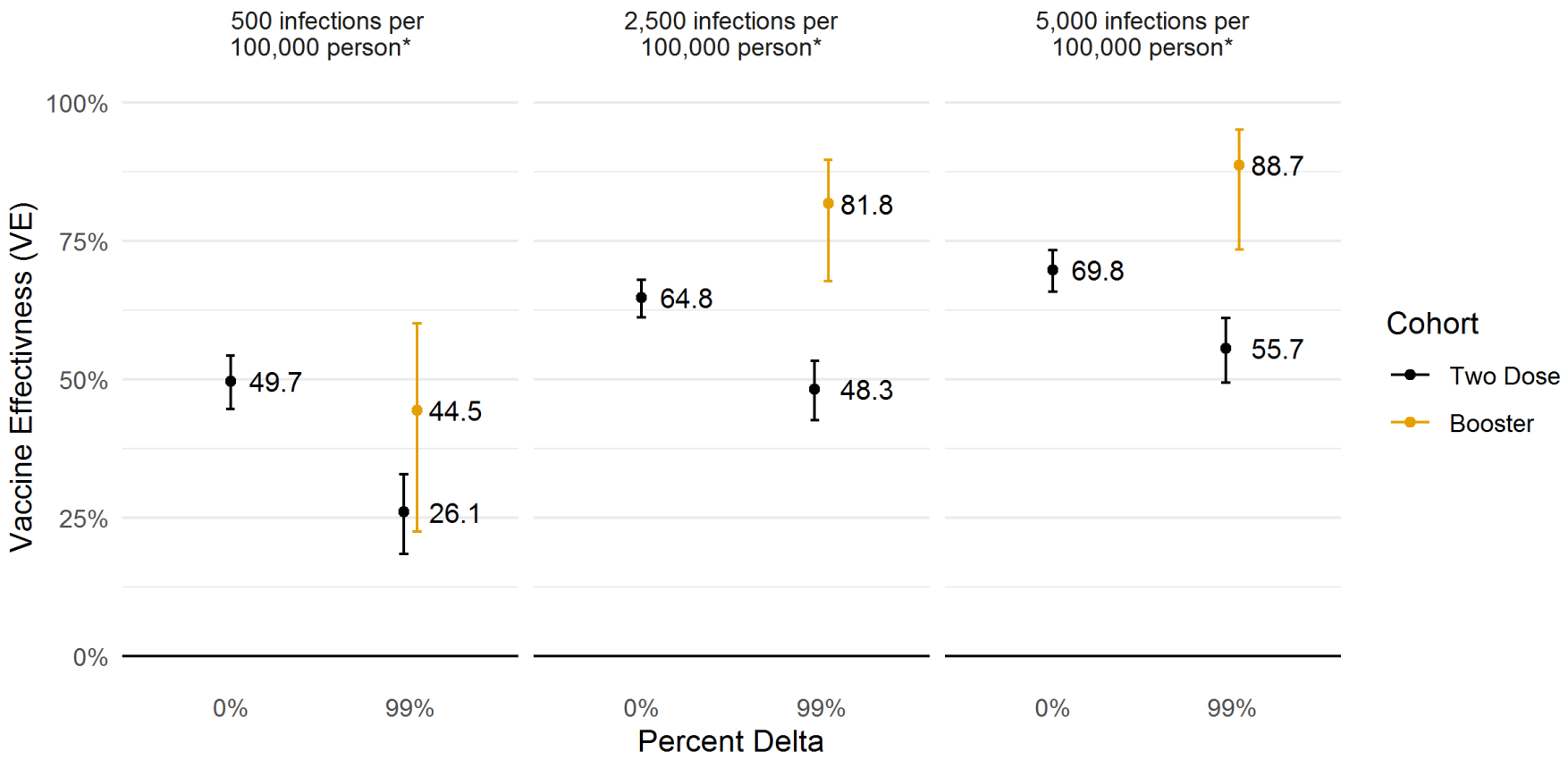
Addressing Potential Sources of Bias

- Used time-varying IPTW to address imbalance in all measured covariates
- IPTW did not necessarily address imbalance for potential unmeasured confounders, an issue often found when real world data are used
- IPTW-adjusted vaccine effectiveness (VEs) were estimated using Marginal Structural Cox regression models, while including all covariates in both the weighting and outcome model.

COVID-19 Related Outcome Rates; Death and Hospitalization; Unweighted

Cohort	Outcome Count	Rate per 100,000 Person Weeks	95% CI
Death			
Unvaccinated	3,483	140.24	(135.58, 144.9)
One Dose	2,388	198.02	(190.00, 206.05)
Two Dose	4,179	50.75	(49.21, 52.28)
Booster Dose	72	47.44	(36.48, 58.4)
Hospitalization			
Unvaccinated	3,360	136.76	(132.14, 141.38)
One Dose	1,355	116.47	(110.27, 122.67)
Two Dose	2,215	27.07	(25.94, 28.19)
Booster Dose	22	14.6	(8.5, 20.71)

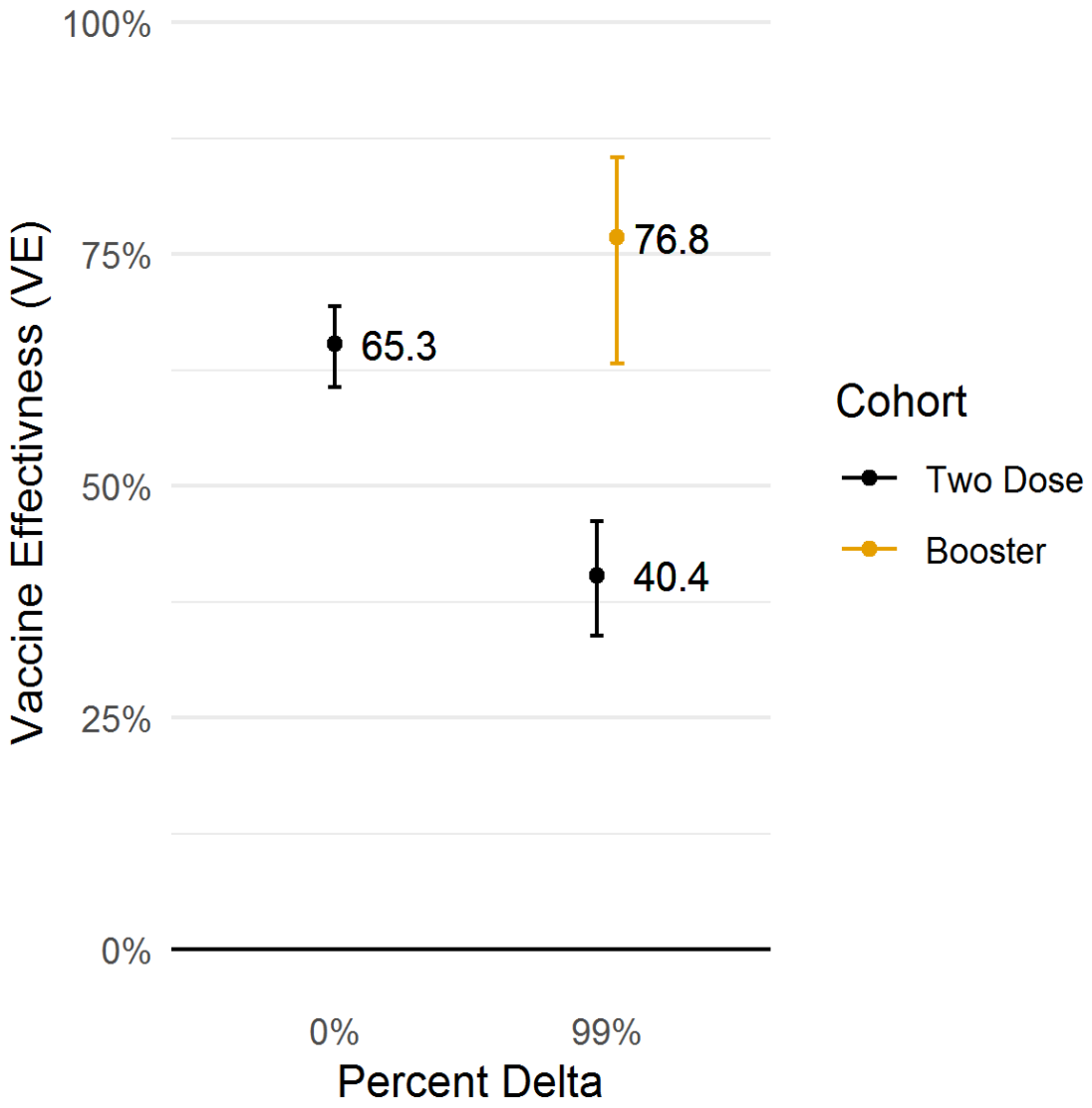
Adjusted VE for Death by Delta Share and COVID-19 Circulation Rate



The 0% Delta share period corresponds to pre-Delta, a period generally closer in time to vaccination date. Reference Group was unvaccinated.

* Infection rate over a 28-day period

Adjusted VE for Hospitalization by Delta Share



The selected model did not include interaction term of COVID-19 circulation rate

Adjusted VE Estimates:

Cohort	Delta Share			
	0%		99%	
	VE	95% CI	VE	95% CI
Death				
Two Dose	69.84%	(65.88%, 73.34%)	55.65%	(49.49%, 61.06%)
Third/Booster Dose			88.74%	(73.54%, 95.21%)
Hospitalization				
Two Dose	65.30%	(60.65%, 69.41%)	40.36%	(33.84%, 46.24%)
Third/Booster Dose			76.83%	(63.20%, 85.41%)

At COVID circulation rate of 5,000 infections per 100,000 persons over a 28-day period

Strengths

- This was a large COVID-19 vaccine effectiveness study conducted among the U.S. nursing home population using real world data.
- We incorporated NH facility characteristics which have the potential to influence resident health outcomes.

Limitations

- The effects of the increase in the Delta share and potential waning immunity from the vaccine over time could not be separated; both likely contributed to the observed decrease in effectiveness in the higher Delta periods.
- The study period does not extend far into the booster dose administration phase. As such, conclusions about effectiveness over time could not be drawn for the boosted population.

Summary

- Booster dose VE was significantly higher than two-dose VE.
- Two-dose VE was lower during the 99% Delta period than the 0% Delta period, waning immunity may have contributed to the finding.
- VE for death was higher and less impacted by the change in Delta variant share/waning immunity than hospitalization.
- Observed real-world VE was potentially more accurate during high COVID-19 circulation than low circulation periods.

FDA, CMS, and Acumen LLC Team

Center for Biologics Evaluation and Research (CBER), FDA

Yun Lu, Hector S Izurieta,
Mikhail Menis, Whitney Steele
Hui Lee Wong, Richard A Forshee

Centers for Medicare & Medicaid Services (CMS)

Jeffrey Kelman

Acumen, LLC

Arnstein Lindaas, Kathryn Matuska,
Xiangyu Shi, Rowan McEvoy,
Carla Gomez-Victor, Jessica Hervol,
Michael Wernecke, Yoganand Chillarige


FDA
U.S. FOOD & DRUG
ADMINISTRATION

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

Richard Forshee and Hong Yang

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

Sentinel Annual Meeting, November 14-15, 2022

Disclaimer

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

FDA Benefit-Risk Framework

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

Therapeutic context

Product profile

Real-World Data (RWD) & Real-World Evidence (RWE)

- The 21st Century Cures Act (Cures Act) places additional focus on the use of RWD/RWE to accelerate drug development and support regulatory decision making to bring innovation faster to the patients

- **RWD** is the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources:
  - Electronic health records, insurance claims, product and disease registries, etc.

- **RWE** is the clinical evidence regarding the usage, potential benefits or risks of a medical product derived from analysis of RWD

- FDA guidance for RWD/RWE: https://www.fda.gov/drugs/news-events-human-drugs/fda-issues-draft-guidances-real-world-evidence-prepares-publish-more-future

Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Pfizer-BioNTech) 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 cases and 4.3 million deaths worldwide by August 2021
- 90% cases among age 16 + years of age

Current Treatment Options

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
- EUAs 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

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 and severe COVID-19 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		

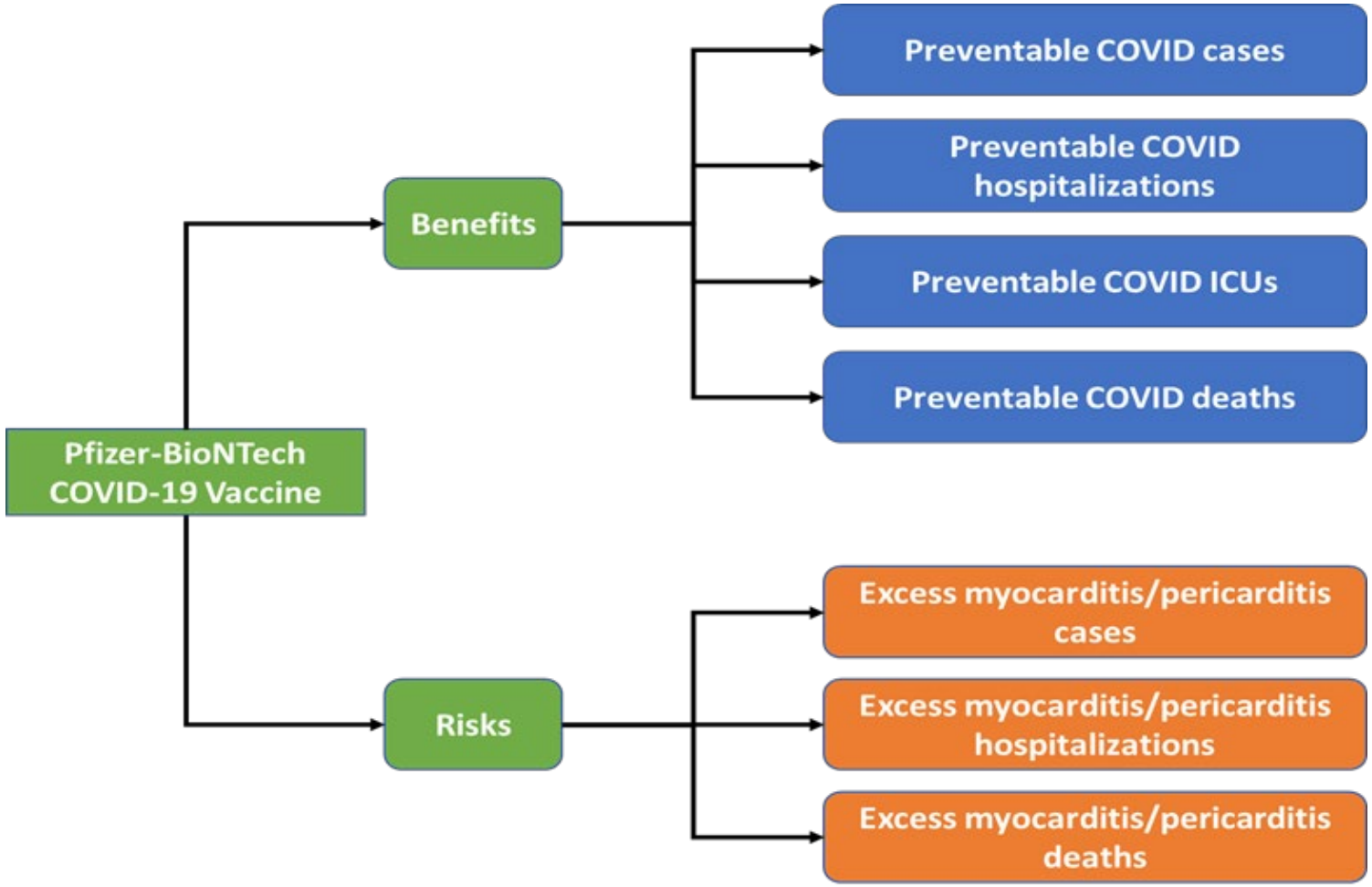
- No notable serious adverse events and deaths related to vaccination reported in clinical trials
- Elevated myocarditis/pericarditis case rate identified by post-EUA safety surveillance
  - Clinically significant risk
  - Higher risk among male adolescents
- Risk management options:
  - Product label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

Whether Benefits of Pfizer-BioNTech Outweigh the Risks?

- 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 (Pfizer-BioNTech) for Age 16-29 years, *Vaccine, March 2022*

Per million individuals with two-doses of vaccine



Why is RWD/RWE Important?

- Vaccine benefit depends on disease incidence among the population
- Vaccine effectiveness in real-world is not identical to the vaccine efficacy demonstrated by well controlled clinical trial
- Vaccine effectiveness changes due to emerging of new variants and waning of immunity
- Rare adverse effects may not be observed in the clinical trial due to small sample size and short follow-up

What RWDs/RWEs Were Used?

Benefits
(Prevented COVID-19 cases)

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

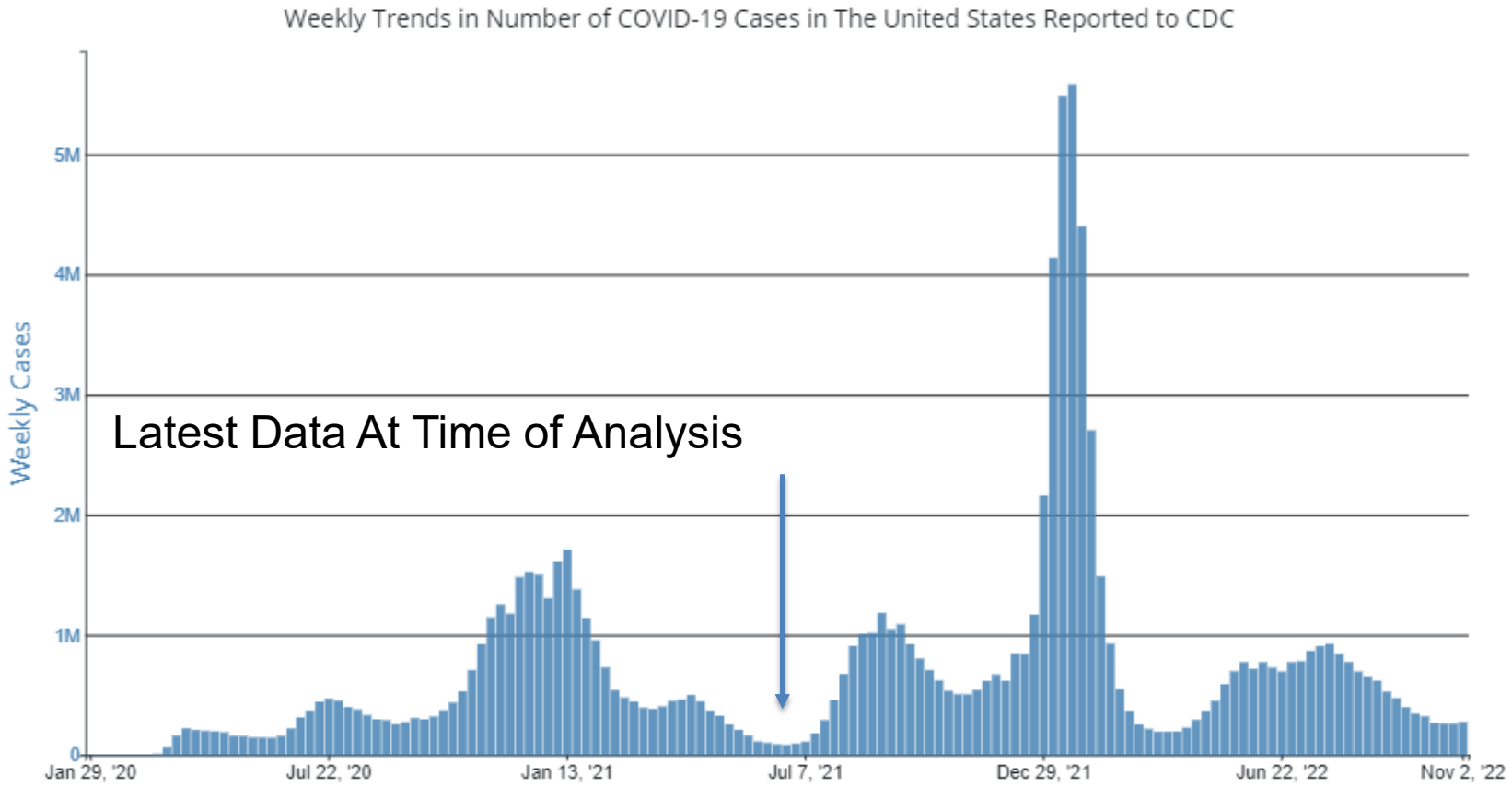
Risks
(Excess myo/pericarditis cases)

Myocarditis/pericarditis rate attributable to vaccine (cases, hospitalization, deaths)	• CBER Biologics Effectiveness and Safety (BEST) System • CDC Vaccine Safety Datalink (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 the purpose?
  - Any way to reduce the bias?
- **Sensitivity analysis to evaluate the uncertainty**
- **Acknowledge limitations**

Weekly Trends in COVID-19 Cases



Source: [CDC https://covid.cdc.gov/covid-data-tracker/#trends_weeklycases_select_00](https://covid.cdc.gov/covid-data-tracker/#trends_weeklycases_select_00)

Model Scenarios

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

Common Model Inputs

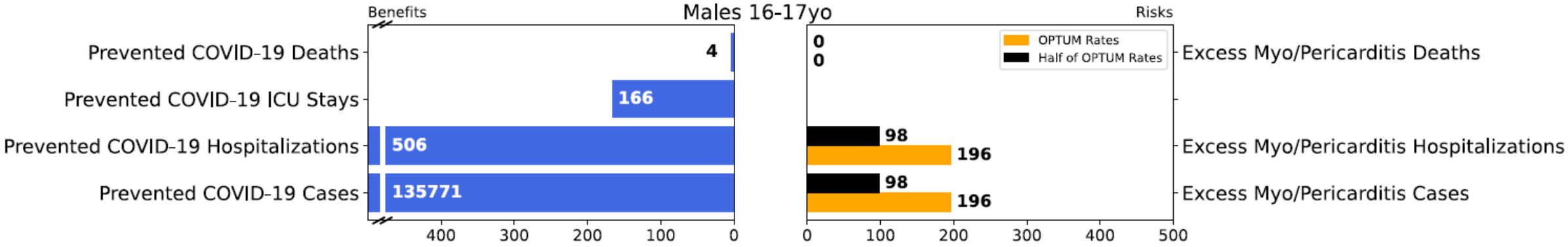
- Protection period[1]: 6 months
- Vaccine effectiveness[2] against
  - Cases: 70%
  - Hospitalization: 80%
- Myocarditis/pericarditis rate: FDA BEST/Optum

Two Major Scenarios

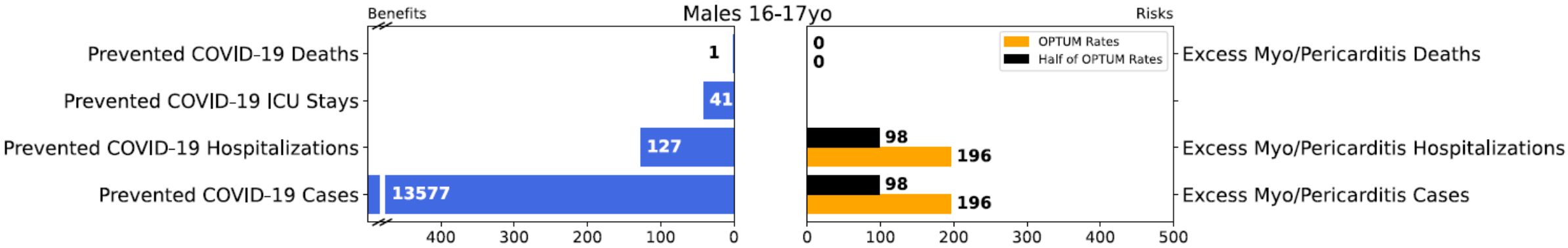
	COVID-19 case incidence[3]	COVID-19 hospitalization incidence[3]	Vaccine attributable myocarditis/ pericarditis death rate[4]
Pessimistic Scenario	July 10, 2021 rate	July 10, 2021 rate	0.002%
Most Likely Scenario	10x July 10, 2021 rate	4x July 10,2021 rate	0%

[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, ICU admissions, and deaths
- Indirect benefits: reduced disease transmission, economic and societal impacts
- Uncertainty in dynamics of pandemic, new virus strain, protection waning, protection for subpopulation with comorbidities

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 Pfizer-BioNTech in Nov. 2021

FDA U.S. FOOD & DRUG ADMINISTRATION

Acknowledgment

- Drs. Patrick Funk and Osman Yogurtcu contributed to benefit-risk modeling
- Pfizer-BioNTech 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

Break

We will be back momentarily.

The next panel will begin at 2:50 p.m. (U.S. Eastern Time)

Session V: Key Collaborations with Stakeholders and the Development of New Partnerships in the Sentinel Initiative

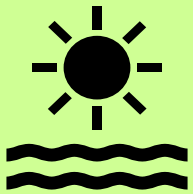
- **Margaret Anderson**, Deloitte
- **Grace Marx**, Centers for Disease Control and Prevention
- **Eric Heflin,** eHealth Exchange
- **Lance Jones**, IBM Consulting

Deloitte.

Sentinel 14th Annual Public Workshop

NOVEMBER 16, 2022

CBOC Agenda



CBOC Overview

CBOC Master Plan

2022 Project Accomplishments

Featured Project: CBOC Webinar

The Community Building & Outreach Center

The Community Building and Outreach Center (CBOC) was created to **broaden and activate a strong scientific community to advance the Sentinel Initiative.** The CBOC supports Food and Drug Administration (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.

The CBOC Master Plan

The CBOC Master Plan identifies stakeholder priorities, **outlines a set of projects**, describes the action plan, and proposes methods to evaluate project impact.

CBOC Projects:

Communications and Training

- Ongoing Website Design and Implementation
- Public facing Newsletters
- Templates, Standardized Presentations, and Informational Videos
- Graphics
- Virtual Training Sessions

Bidirectional Engagement

- Webinar Series
- Bidirectional Engagement Charters and Reports

Projects implemented by the CBOC Master Plan aim to:

Increase awareness of the Sentinel Initiative and the design of the Sentinel System

Increase understanding of Sentinel tools, methods, data, and infrastructure

Increase opportunities for stakeholder contribution to the Sentinel community

CBOC Master Plan Accomplishments

The following projects within the CBOC Master Plan were implemented or are ongoing in order to increase awareness of the Sentinel Initiative and the design of the Sentinel System, increase understanding of Sentinel tools and infrastructure through training and/or increase stakeholder contribution to the Sentinel community.

Sentinel Website Redesign & Implementation

Release 4.0 was deployed in April, with a new 'Featured' tab to showcase Sentinel activities in key topical areas (i.e., COVID-19, Pediatrics, and Pregnancy). CBOC also conducted regular Drupal updates, in addition to other website O&M and specific requests.

IMPACT
Optimized user interface and user experience of the Sentinel website, impacting **1000+ updated webpages**, allowing stakeholders to better locate Sentinel resources and stay informed of Sentinel

Quarterly Public Facing Newsletter

CBOC releases quarterly newsletters that highlight recent developments within the Sentinel System. This year included a redesign of the Newsletter in a new, more modern format in addition to increased marketing efforts.

IMPACT
Three newsletters were released in 2022 thus far, with the Q4 Newsletter upcoming in December. Marketing led to an **increase of 450 subscribers**, for a total of **5,950 subscribers**.

CBOC 2022 Webinar Series

CBOC hosted two (2) Webinars this year: "An Overview of the Sentinel Website for Health Advocates," which provided information on the basics of the Sentinel System for non-technical users, and "An Overview of Sentinel's Publicly Available Tools," which covered the Sentinel Common Data Model (SCDM) and Routine Querying Tools for the more technically-inclined.

IMPACT
Increased visibility of Sentinel to new stakeholder groups, including informaticists, epidemiologists, and health advocates by reaching **300+ live viewers** and additional online audiences.

CBOC Master Plan Accomplishments (continued)

The following projects within the CBOC Master Plan were implemented or are ongoing in order to increase awareness of the Sentinel Initiative and the design of the Sentinel System, increase understanding of Sentinel tools and infrastructure through training and/or increase stakeholder contribution to the Sentinel community.

Virtual Training Series: Sentinel Views

CBOC delivered a virtual training video that instructs audiences on how to use the data visualization platform launched by Sentinel, known as Sentinel Views.

IMPACT
Provided support and increased understanding to stakeholders interested in using **Sentinel's tools and infrastructure** more effectively to **100+ viewers**

Templates, Standardized Presentations & Informational Videos

CBOC has developed/currently developing the following (5) slide sets: Major Moments in the Development of Sentinel, the Sentinel Userbase, Understanding the SCDM, Sentinel for Research and Public Health Purposes, Potential and Limits of EHR Data Sources & Claims

IMPACT
Provided FDA and Sentinel Centers with consistent materials and design elements for **information sharing** about Sentinel and **educated stakeholders** on Sentinel's origins and capabilities for **300+ online viewers**

Data Sandbox Support

CBOC completed two projects for the Data Sandbox: (1) Data Sandbox Technical Discovery, which included development of optimal users and use cases for the Data Sandbox in collaboration with the IC and (2) the CBOC Data Sandbox Engagement Strategy Report, which was a comprehensive report on the user engagement methods aligned with each user/use case identified by the Technical Discovery

IMPACT
Developed a **comprehensive and individualized engagement strategy** for marketing the potential Data Sandbox project to reach the identified target user groups and their corresponding use cases

Graphics

Ongoing CBOC 2-week sprint cycle graphics support.

IMPACT
Created and maintained **50 graphics** for publication on Sentinel Website

Featured Project: CBOC Analytics Tools Webinar

The second webinar of the CBOC Webinar Series, titled, "**An Overview of the Sentinel's Publicly Available Analytics Tools**," was conducted in September. Recording and slides are on the Sentinel Website and YouTube!

256
Individuals Registered

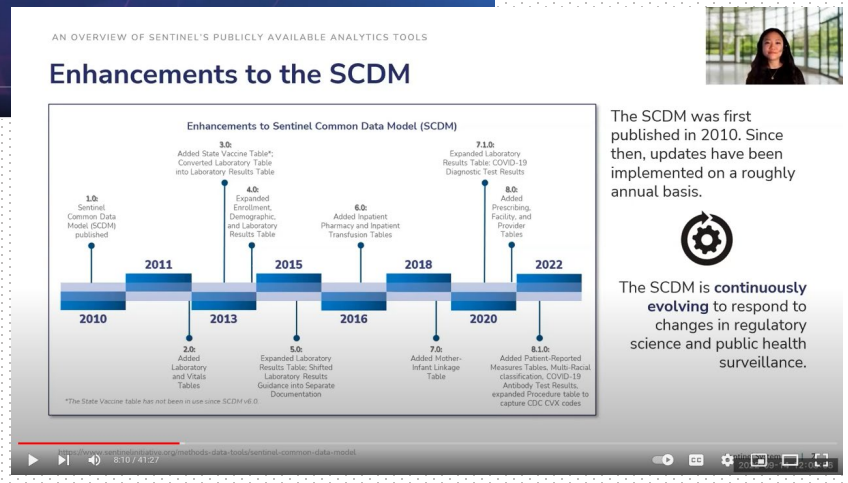
129 Total Attendees

9 Federal Agencies

150+ Private Firms

Objectives

- Learn about the key components in the SCDM
- Learn about the different types of Sentinel's Routine Querying Tools
- Learn how to access Routine Querying Tools and SCDM on the Sentinel Website



APPENDIX

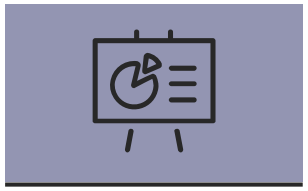
Agenda

CBOC Master Plan

11:00 – 11:05

5 minutes

Outline the overarching strategic aims of the Community Building and Outreach Center (CBOC) as it fits into Sentinel's Five-Year Strategy



Project Accomplishments

11:05 – 11:20

15 minutes

Provide CBOC's accomplishments in 2022 on all projects under the CBOC Master Plan

CBOC 2022 Webinar Series

11:20 – 11:30

10 minutes

Review content and statistics for the webinars held in 2022 for the CBOC 2022 Webinar Series

Sentinel Quarterly Newsletter

11:30 – 11:40

10 minutes

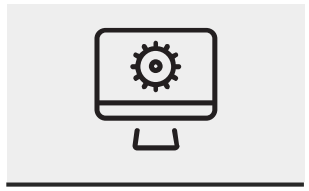
Review public Newsletter statistics across the four quarters in 2022, engagement strategy updates, and what to expect in the last Newsletter of this year

Data Sandbox Engagement Report

11:40 – 11:45

5 minutes

Discuss the accomplishments of the CBOC Data Sandbox Engagement Strategy Report



Website Enhancements

11:45 – 11:55

10 minutes

Review changes made to the Sentinel Website in 2022, including creation of Featured Pages, Drupal updates, and ongoing website O&M

Using FDA's Sentinel System to Surveil Lyme Disease Post-Exposure Prophylaxis

Grace E. Marx, MD, MPH

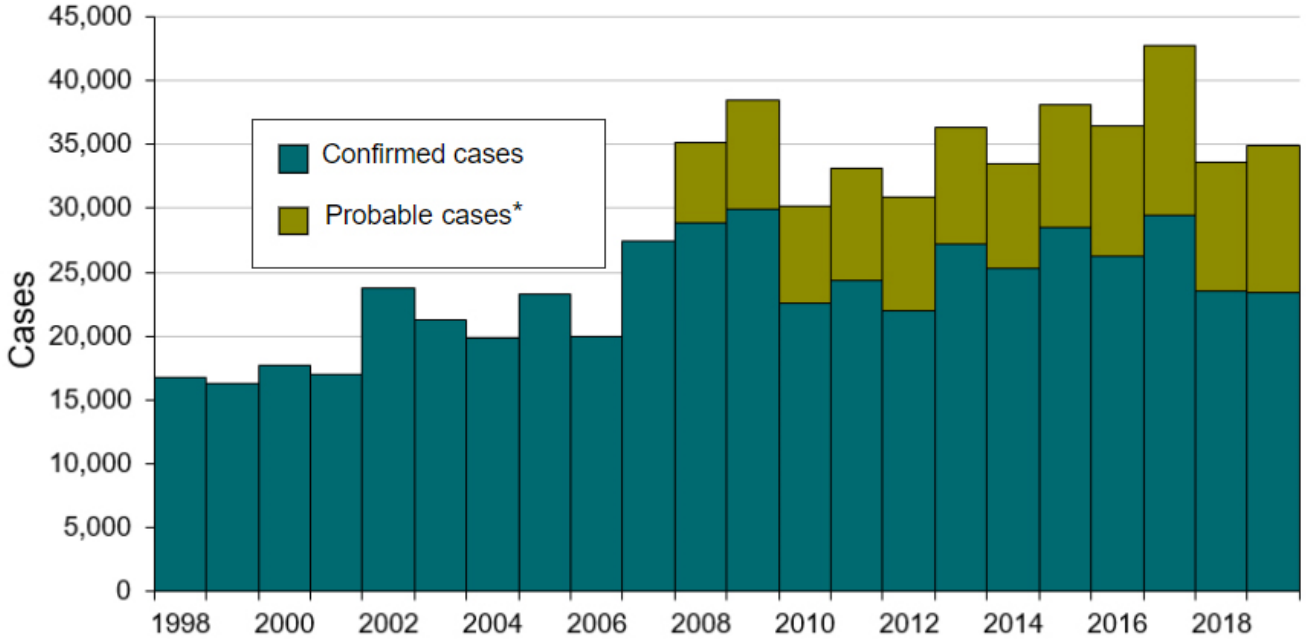
Medical Epidemiologist, BDB/DVBD/NCEZID

Fourteenth Annual Sentinel Initiative Public Workshop
November 16, 2022

Lyme Disease

- **Most common vector-borne disease in the US***
- **Only a fraction of cases are reported**
  - ~476,000 cases diagnosed and treated annually†

Reported Lyme Disease Cases by Year

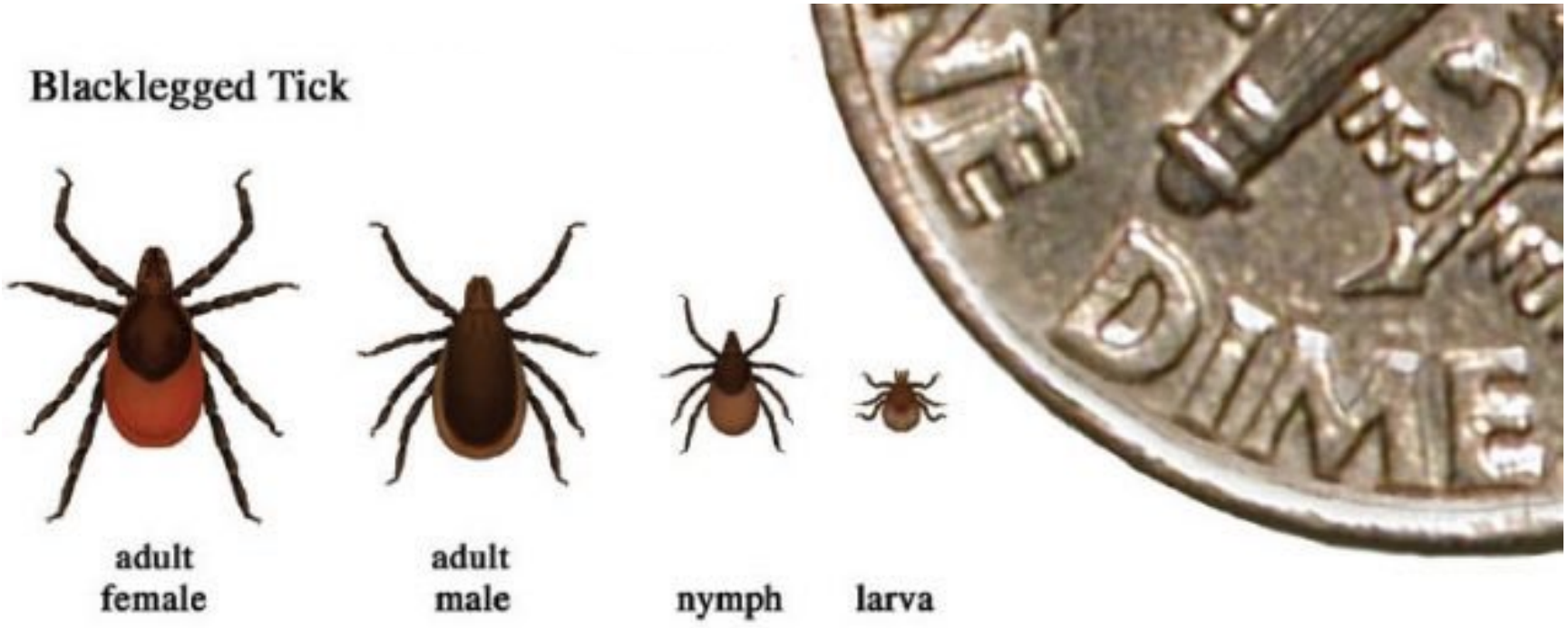


*Rosenberg R *et al.* MMWR 2018; 67(17):496-501

† Kugeler K. *et al.* Emerg Infect Dis 2021; 27(2):616-9

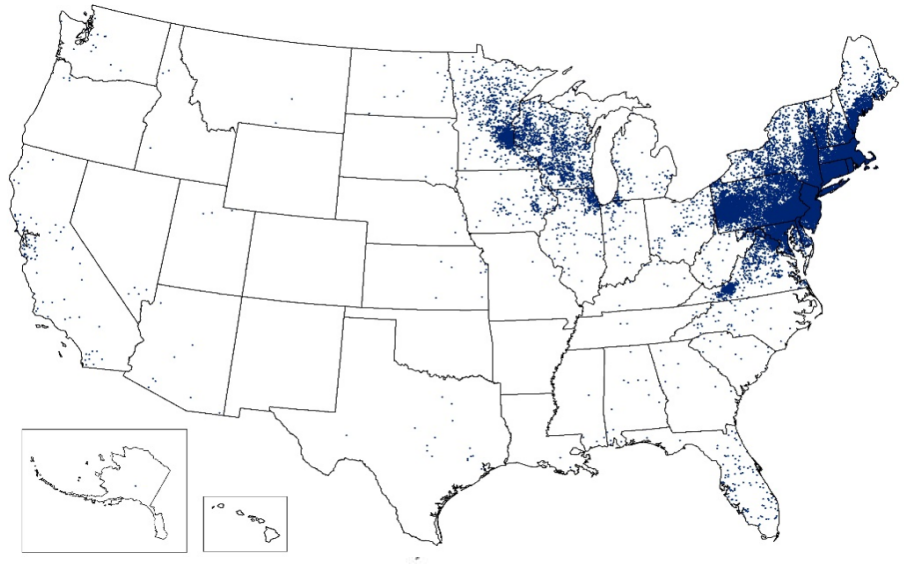
Lyme Disease: Transmission

- **Bacterial disease transmitted by the bite of infected blacklegged ticks (*Ixodes scapularis* and *Ixodes pacificus*)**

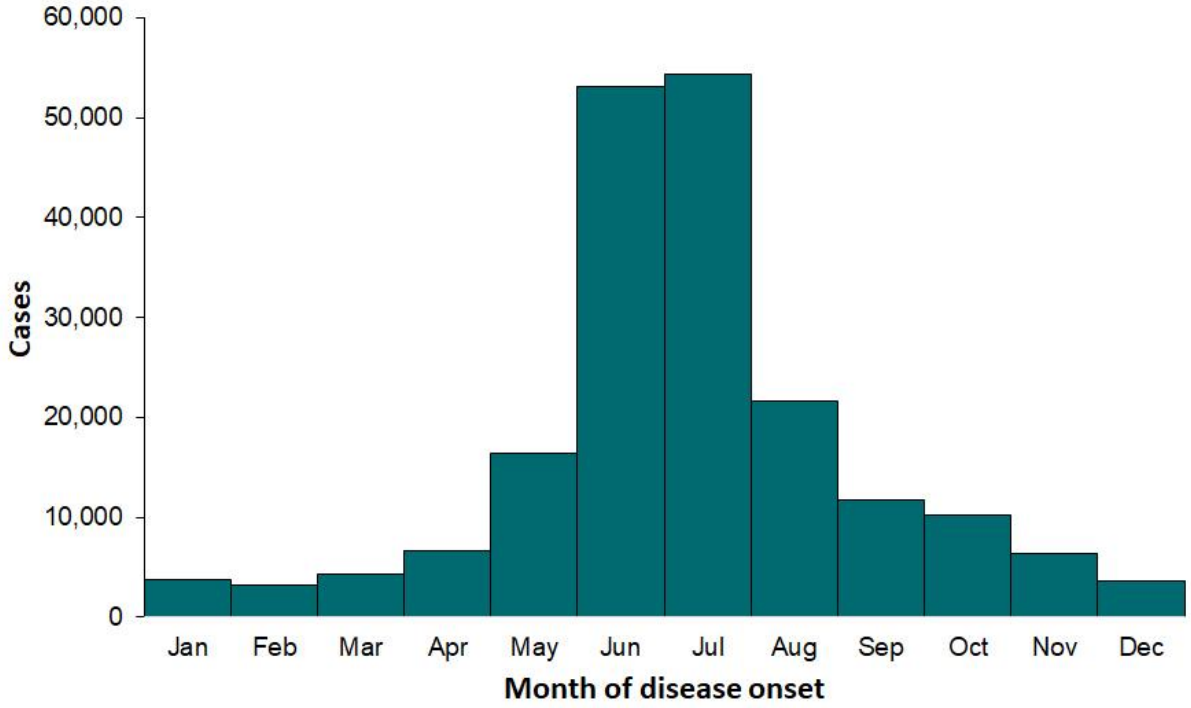


Lyme Disease: Epidemiology

- **Geographic distribution**
  - 15 high incidence states
  - Increasing incidence in neighboring states
  - Some areas on the west coast



- **Seasonality**
  - Most cases occur in mid-summer following peak nymphal tick activity
  - Adult *Ixodes* ticks also active in the fall



- **Lyme disease can be prevented by a single dose of doxycycline when taken within 72 hours of a high-risk tick bite***

- **The only recommended regimen for Lyme disease prevention is single-dose doxycycline†**

*Nadelman R. *et al.* NEJM 2001; 345:79-84
*Harms M. *et al.* J Infect 2021; 82(1): 98-104
†Lantos P. *et al.* Clin Infect Dis 2021; 72(1):e1-e48

Doxycycline

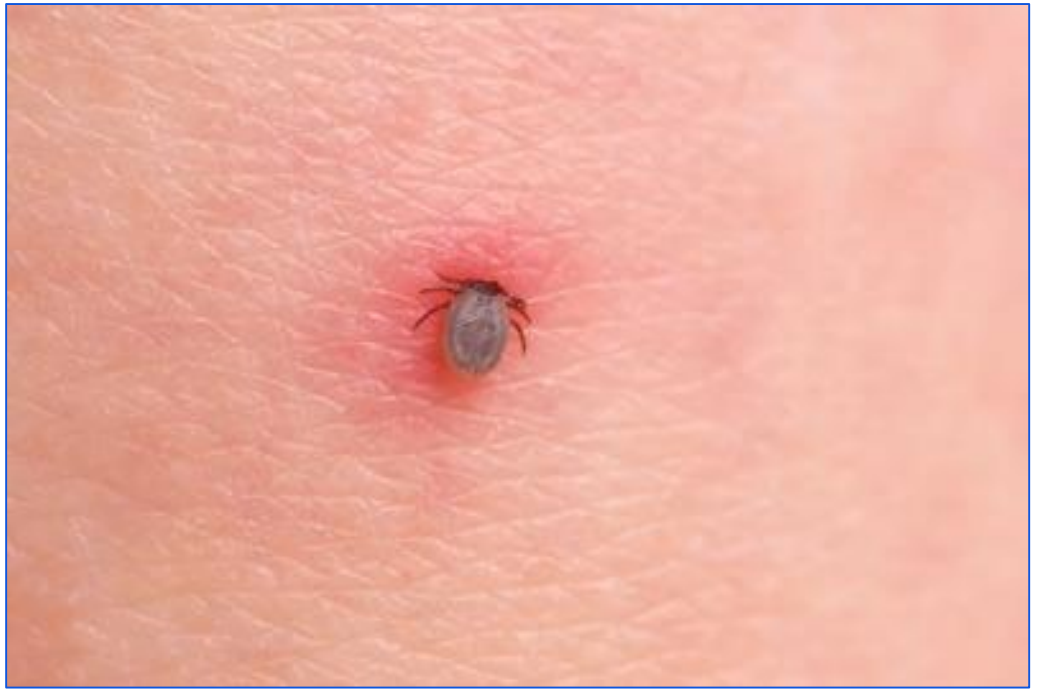
- **Post-exposure prophylaxis (PEP) for Lyme disease**

Age Category	Drug	Dosage	Maximum	Duration
Adults	Doxycycline	200 mg orally	N/A	**Once**
Children weighing less than 45 kg	Doxycycline	4.4 mg/kg orally	200 mg	**Once**

- **Doxycycline for any other indication almost always include multiple consecutive days of twice-daily dosing**

Lyme Disease Post-Exposure Prophylaxis (PEP)

- **Tick bites not nationally notifiable (unlike Lyme disease)**
- **Lyme disease PEP is prescribed to patients who are asymptomatic and when laboratory testing is not appropriate**
  - Laboratory-based surveillance not helpful
  - Diagnostic code-based surveillance not available: no ICD code for “tick bite”



Goals

By describing single-dose doxycycline pharmacy dispensings, we might better understand

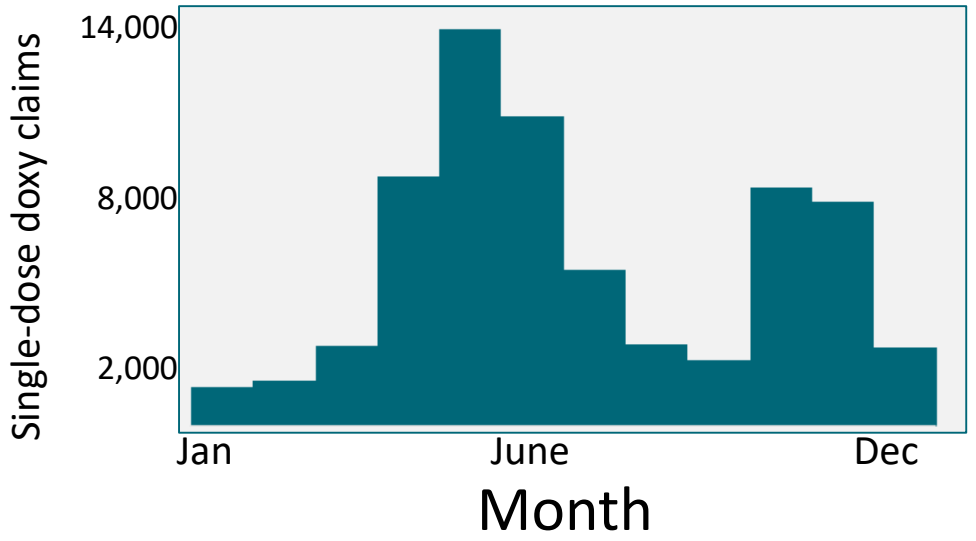
- **Patient-seeking behavior for Lyme disease prevention**
- **Geography and seasonality of highest risk for tick bites**
- **Healthcare burden of patients presenting after tick bite**
- **Health system dispensing patterns for Lyme disease prevention**

Single-dose Doxycycline Claims in MarketScan®

- **In 2019, analysis of single-dose doxycycline claims during 2014-2017 using CDC-licensed MarketScan®***
  - MarketScan®: Distributed database of electronic medical records of primary beneficiaries and their dependents of employer-sponsored health insurance
  - Excludes
    - Patients aged >64 years
    - Recipients of government-sponsored insurance
    - People experiencing unemployment

Claims Characteristics

- Dose
  - » 200 mg: 91%
  - » 100 mg: 6%
- 2% were refills
- Average cost to patient: $2.60



* Marx *et al.* OFID 2019: S589

MarketScan® vs FDA Sentinel Distributed Database

- **Potential advantages of Sentinel Distributed Database***
  - Larger sample size (national health insurance plans, regional integrated delivery systems, state Medicaid plan, and Medicare Fee for Service)
  - Geographic information, which allows for examination of State, or urbanicity in some cases (using zip code)
  - Inclusion of patients with greater diversity (ages >64; diverse employment and insurance status)

* *Sentinel Initiative*. https://www.sentinelinitiative.org/

Sentinel Query Design

- **Retrospective cohort**
  - Period: 1/1/2009 – 2/29/2020
  - **Inclusions**: single-dose doxycycline (≤200 mg) pharmacy dispensings
  - **Exclusions**
    - Doxycycline forms not consistent with Lyme disease PEP (e.g., extended release, powder, topical, intravenous)
    - Consecutive days of doxycycline pharmacy dispensings
    - Enrollment gap >45 days
- **Iterative process of refining query specifications**
- **MarketScan® data used for initial test run**

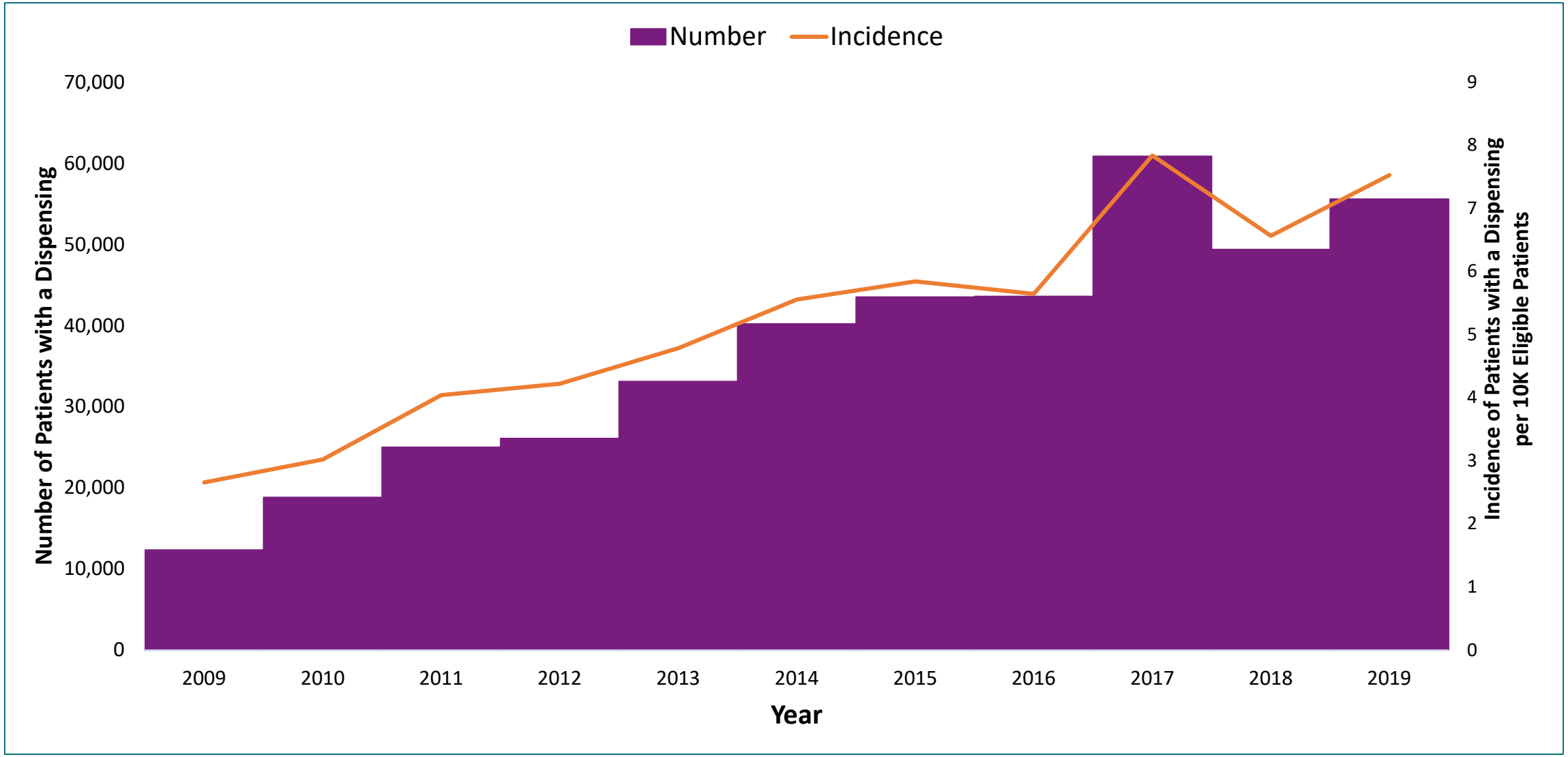
Objective: Describe Single-Dose Doxycycline Dispensing Patterns

- **Dispensing characteristics**
  - State-level annual trends: year of dispensing
  - Seasonality: month of dispensing

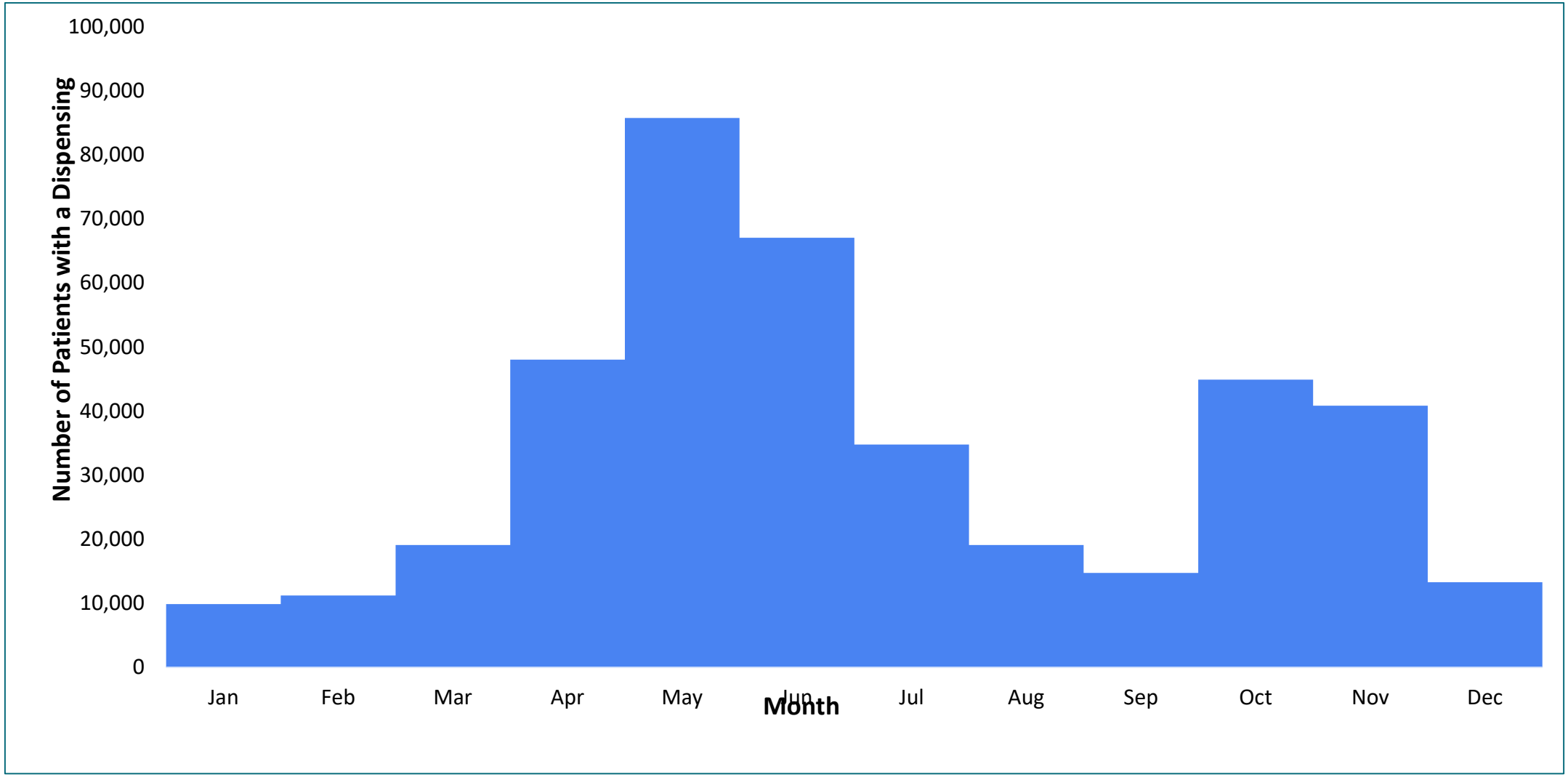
- **Patient characteristics**
  - Demographics: sex; age; race/ethnicity
  - Region: state of residence; residence urbanicity

- **Healthcare utilization**
  - Encounter setting
  - Diagnostic coding patterns

Results: Dispensing Characteristics

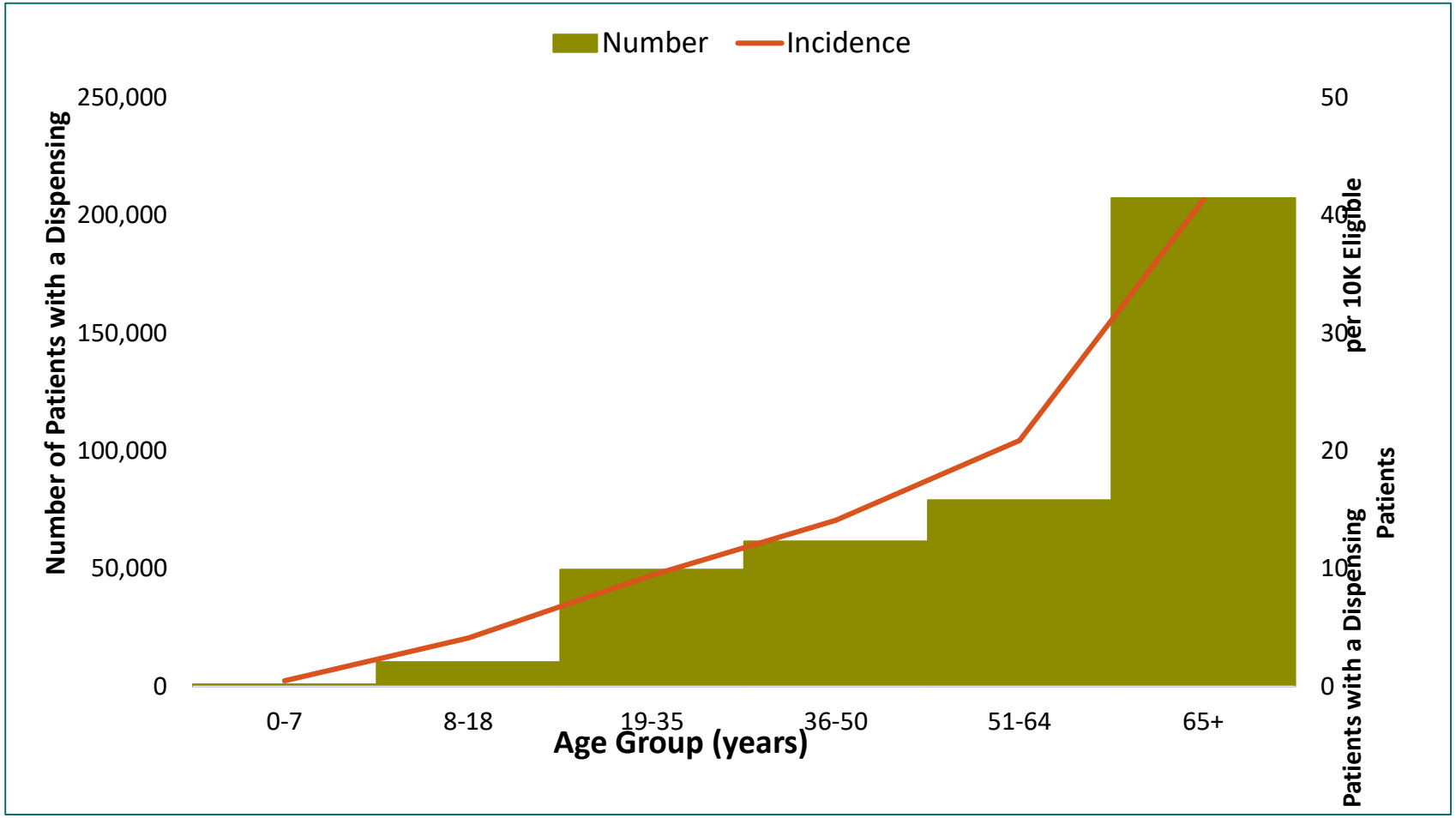


Results: Month of Dispensings



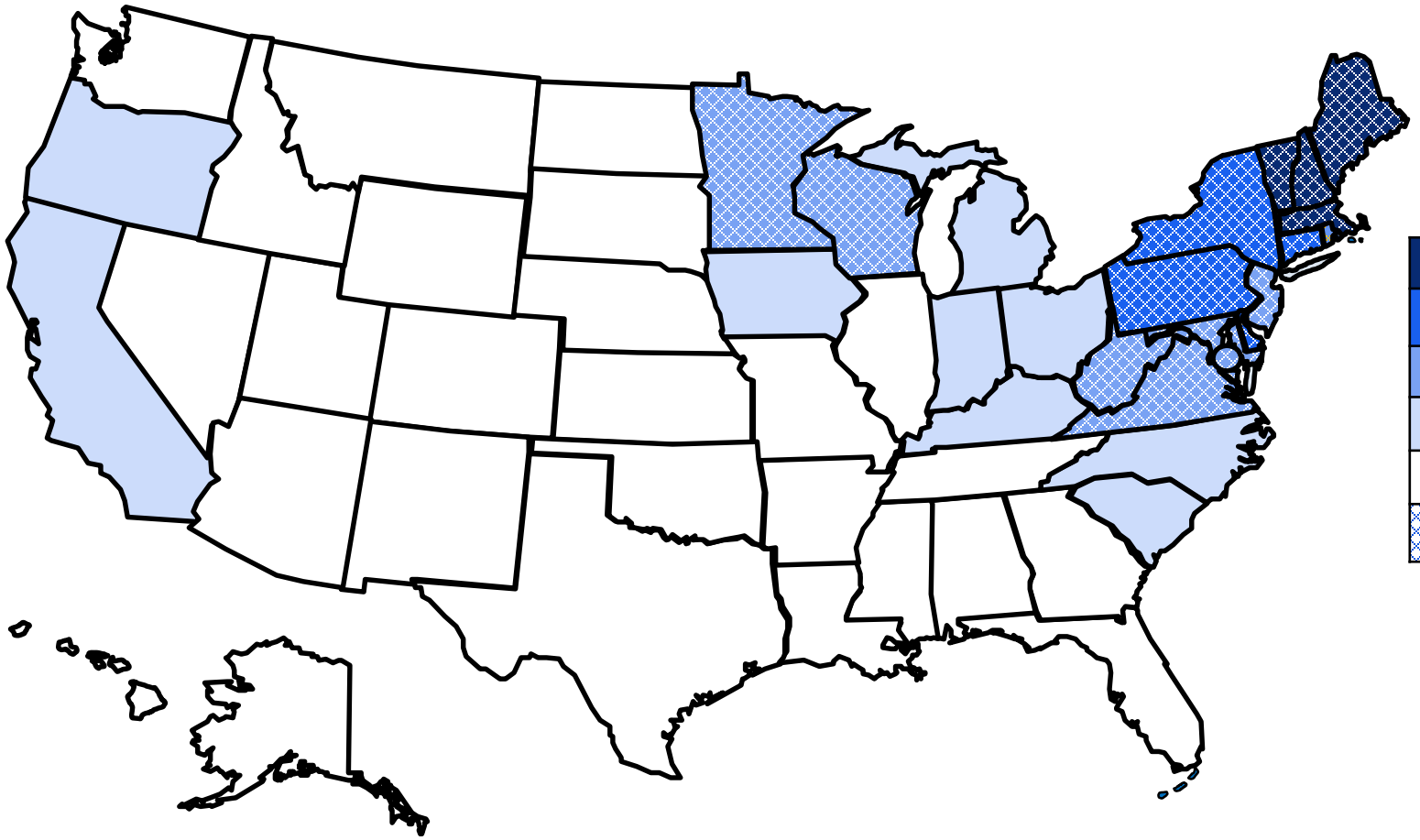
Results: Patient Characteristics

- 56% female
- 96% non-Hispanic White*
- Older (>50% aged 65+yrs)



* Race and ethnicity available for 49% of patients

Results: Geography of Dispensings



>100 Dispensings per 10K Members*

50 – 100 Dispensings per 10K Members*

20 – <50 Dispensings per 10K Members*

10 – <20 Dispensings per 10K Members*

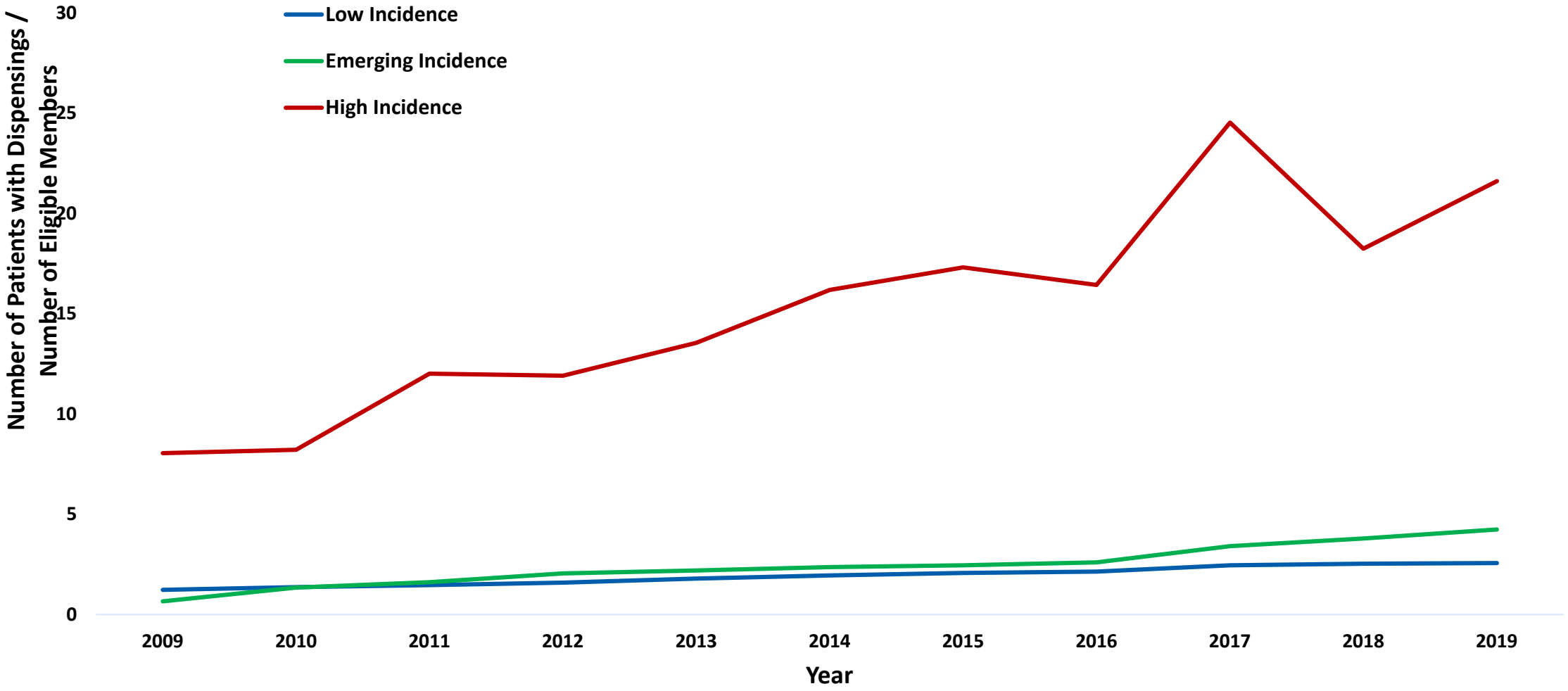
<10 Dispensings per 10K Members*

High Incidence** Lyme Disease

*Members with a dispensing of single-dose doxycycline per 10,000 eligible members

**High incidence = average incidence of ≥10 confirmed cases per 100,000 for three reporting years (https://www.cdc.gov/lyme/datasurveillance)

Dispensings by Lyme Disease Incidence Category



Results: Urbanicity

- **Dispensings per 10K eligible members**
  - Rural (population <2,500): **30**
  - Suburban (population 2,500 – <50,000): **39**
  - Urban (population ≥50,000): **18**

Results: Patient Healthcare Utilization

- **Most patients had an ambulatory medical encounter/visit within 7 days of a dispensing (80%)**
- **Within 7 days of dispensing, 45% of patients had a billing diagnostic code for *arthropod encounter***

Sensitivity Analyses

- **Potential problem**
  - Single-dose doxycycline may be prescribed for surgical prophylaxis for obstetric procedures and/or for dermatologic conditions

- **Solution**
  - Restrict members with no diagnostic codes for obstetric or dermatological conditions in the 30 days surrounding PEP dispensing

Results: Sensitivity Analysis (excluding patients with obstetric/dermatologic diagnoses +/- 30 days)

- **Dispensings**
  - 474,141 → 431,047
- **Female sex**
  - 56% → 53%
- **Age 65+ years**
  - 53%→ 57%

- **Similar dispensing patterns**
  - Season
  - Geography
  - Urbanicity

Conclusions

- Single-dose doxycycline dispensings closely mirror Lyme disease epidemiology and likely represent post-exposure prophylaxis
- Lyme disease post-exposure prophylaxis may be under-prescribed for children, people of color, and men
- Increasing patient awareness of and accessibility to single-dose doxycycline after a high-risk tick bite should be promoted to reduce Lyme disease incidence

Limitations

- **Data generated for insurance claims/reimbursement, not for Lyme disease surveillance**

- **Findings may not be generalizable to general public**
  - Less representation: uninsured patients, cash payers

Next Steps

- **Develop targeted educational campaigns to encourage Lyme disease post-exposure prophylaxis**
  - Vulnerable patient groups, including children
  - Frontline provider types and patient settings
- **Consider Sentinel system for additional surveillance questions related to emerging infectious diseases of public health concern**

Many thanks to data partners who provided data used in the analysis.

THANK YOU

Grace E. Marx, MD, MPH

GMarx@CDC.GOV

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention or the U.S. Food and Drug Administration.

November 2022

eHealth Exchange™

A Single Connection to the Country

To contact the eHealth Exchange:
administrator@ehealthexchange.org

Supporting the FDA

What is the eHealth Exchange?

The 501(c)(3) Non-Profit National Network That Connects:

 All 50 States	70,000 Medical Groups 
 Five Federal Agencies (DoD, VA, Indian Health, FDA, SSA)	5,800 Dialysis Centers 
 75% of U.S. Hospitals	61 State & Regional HIEs 

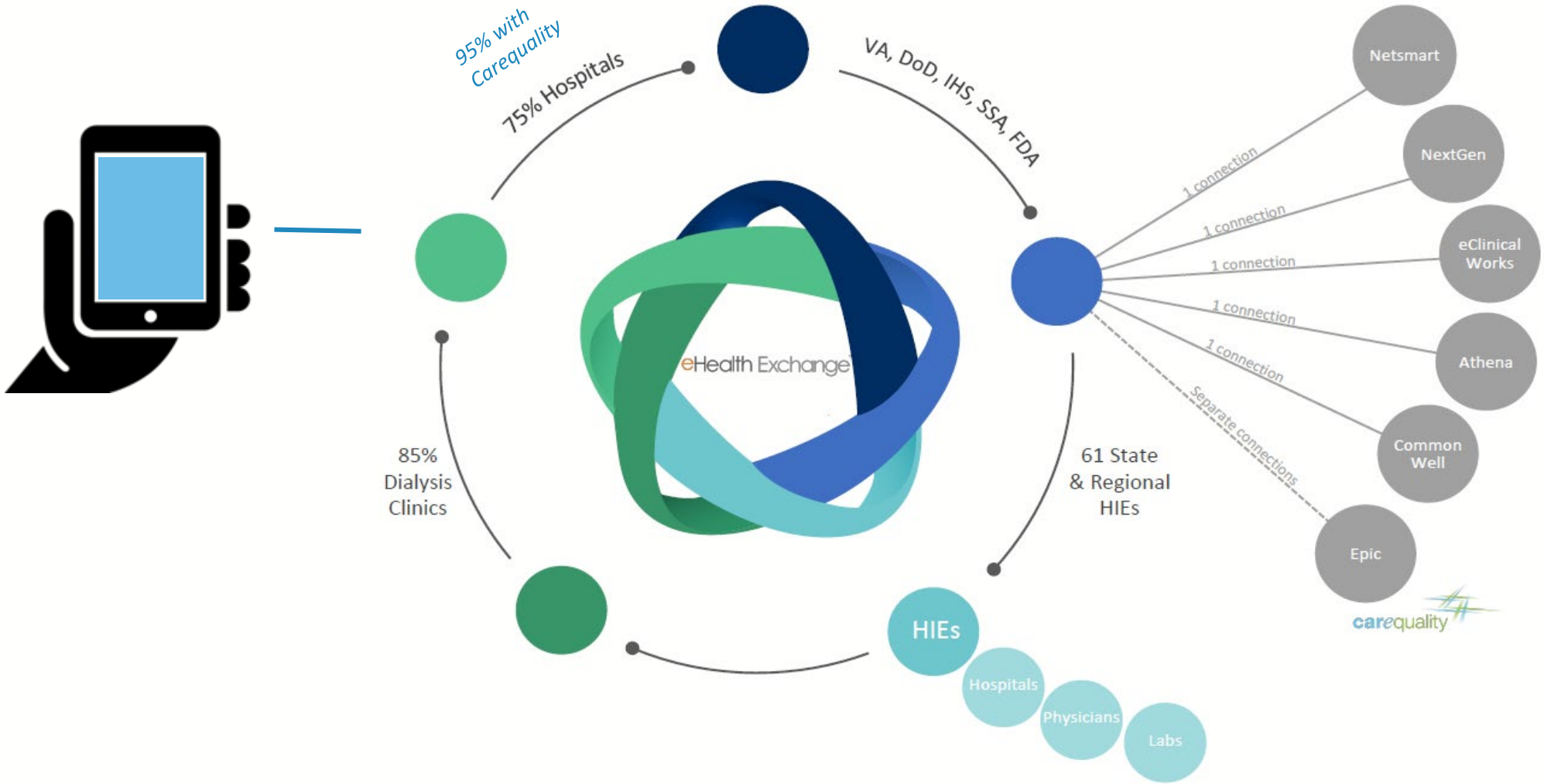
Supporting more than 250 million patients

Exchanging more than 12 billion transactions annually

+ connectivity with carequality-enabled HINs

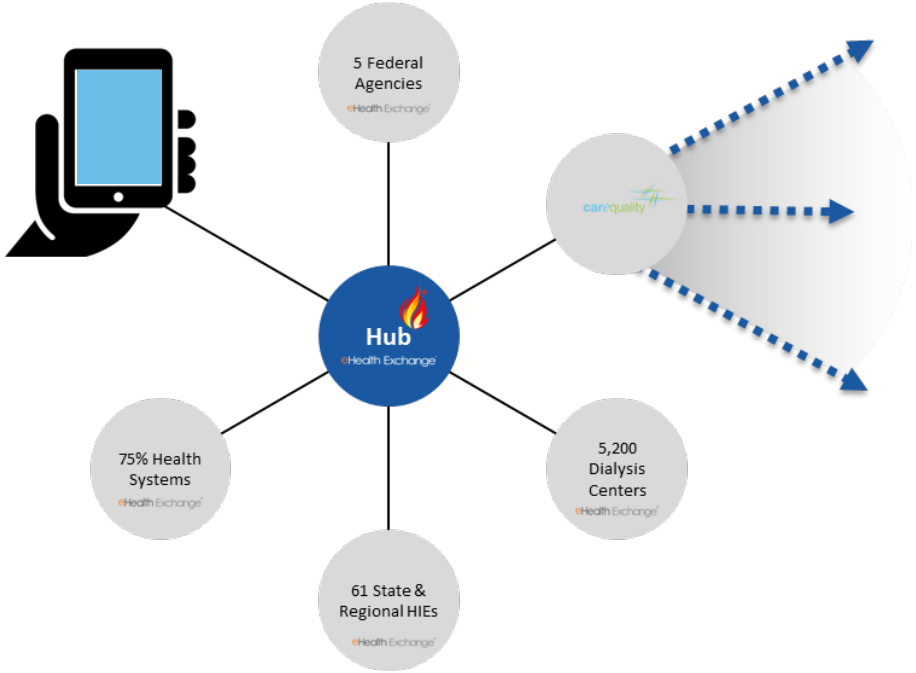
Connecting federal agencies & the private sector in all 50 states

One Connection to the eHealth Exchange Network



Using a hub & spoke architecture, eHealth Exchange participants leverage 1 connection to exchange 12 billion transactions annually within all 50 states

One Connection to 25+ Other Networks



Allscripts · AMBRA · athenahealth · AZUBA · commonwell HEALTH ALLIANCE · CRISP

eClinicalWorks · eHealth Exchange · ELLKAY Healthcare Data Plumbers · eMedicalPractice · Epic · GE Healthcare

Glenwood Systems · HEALTH GORILLA · HealthLX · HIE · inovalon · iPatientCare An AssureCare Product

JCMR · Kno2 · LifeImage · Manifest MEDEX · MatrixCare · MEDENT

Medicity · MiHIN Shared Services · Netsmart · nextgen · onerecord · ORION HEALTH

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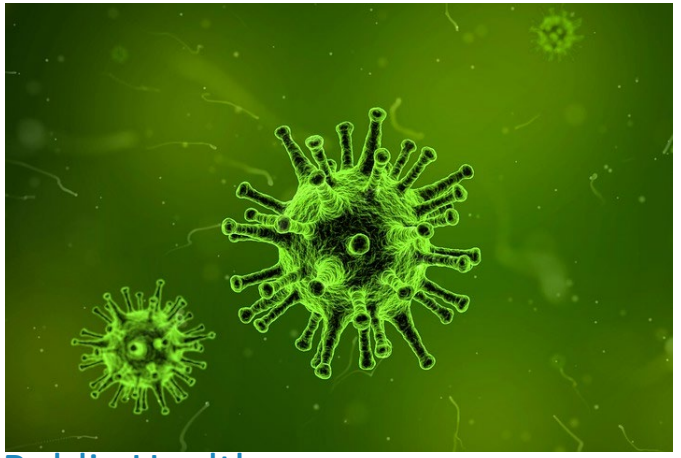
SAFE HEALTH · SAFETY NET CONNECT · Santa Cruz Health Information Exchange · surescripts · swellbox · WOMBA Powered by MeOnly

zen Healthcare IT

What is the eHealth Exchange Used For?

Disaster Response

Treatment



Public Health

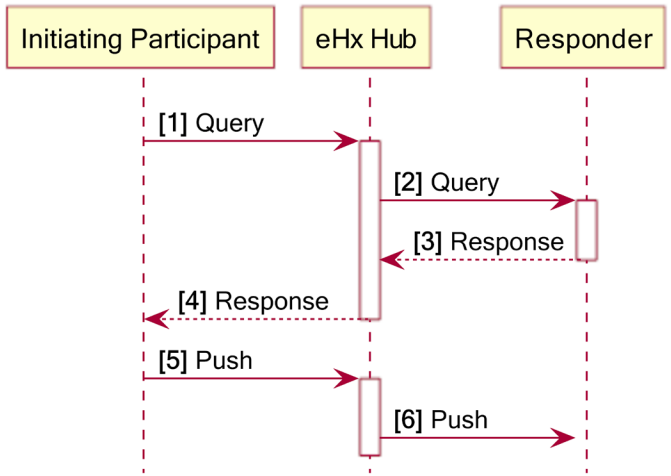
Care Coordination

Private / Public Sector Exchange

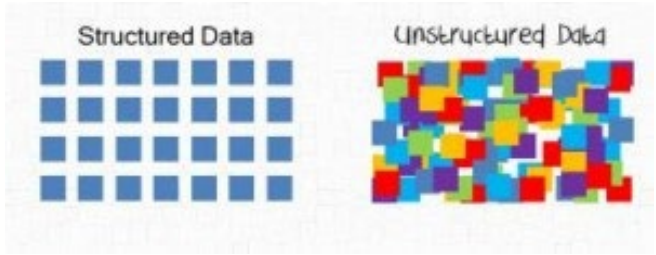
Social Security Benefits Determination

Image credits: pixabay.com, istock.com and tmc.com

eHealth Exchange Data Exchanges



FHIR HL7 CDA



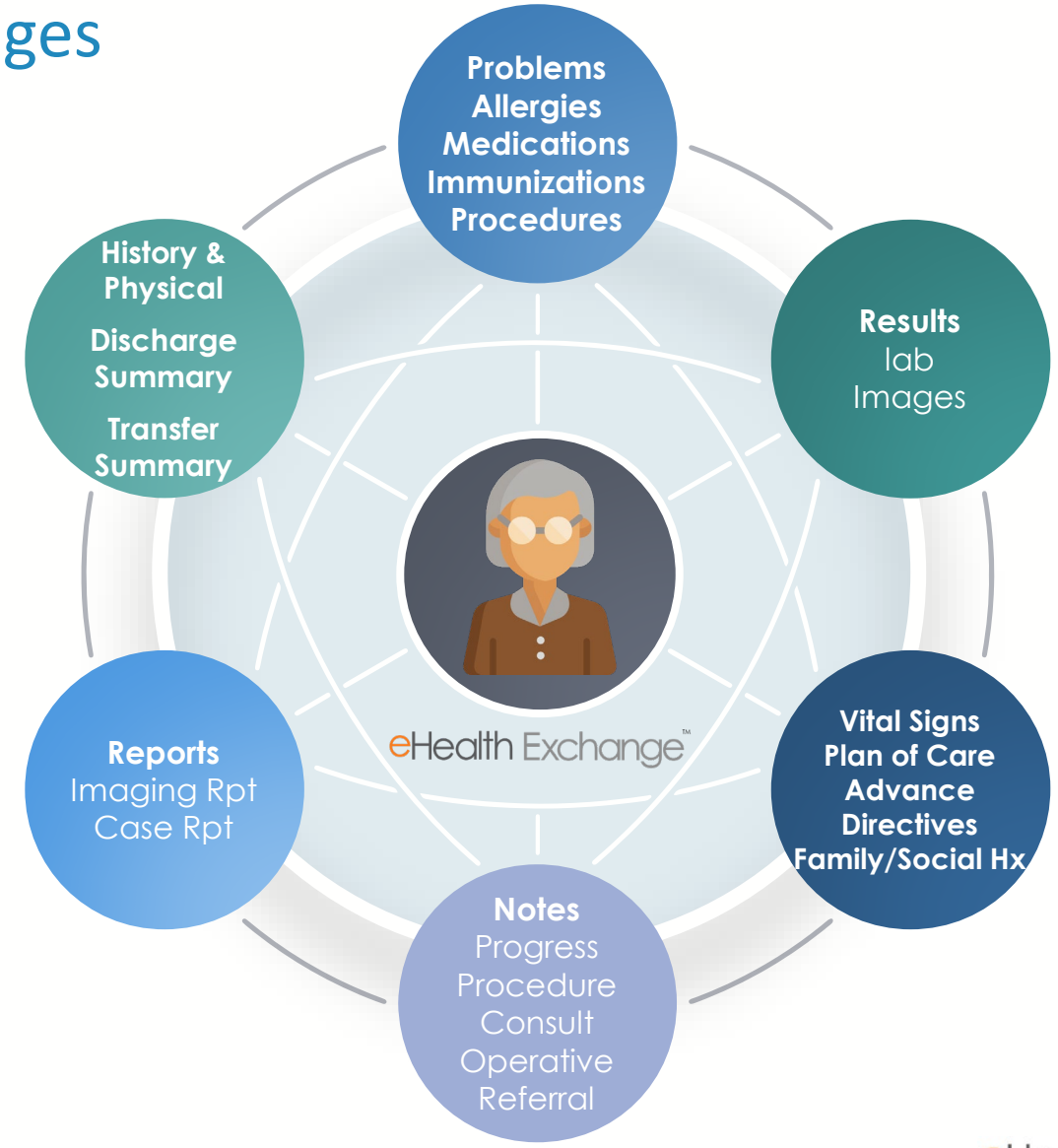
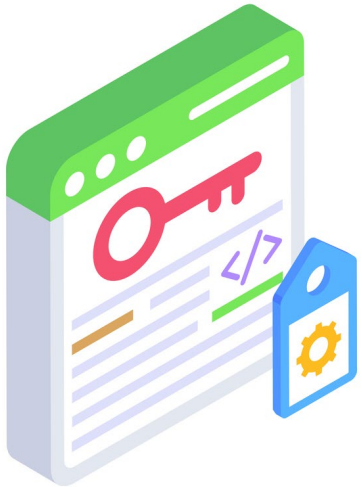


Image credits: https://eclipsesol.com/wp-content/uploads/unstructured-data-pictures.jpg, hl7.org

Quality Assured eHealth Exchange Data Enable Analytics



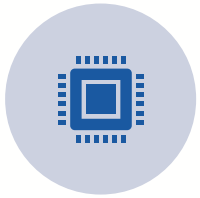
- Mandatory metadata
- Allows for automation
- Privacy by design

- Content is quality assured:
  - Structure
  - Interoperability
  - Conformance
  - Value sets
  - Values
  - Completeness
  - Use case

- Important content types are quality assured
- Enables reporting and analytics
- Consistency is required for ML, AI and Data Science

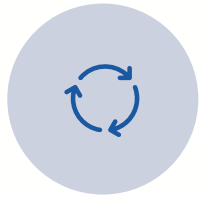
Image credits: iStock.com and Pixabay.com

How the eHealth Exchange Collaborated with the FDA



Requirements: Worked with the FDA and their vendor, IBM to understand requirements

Survey: Survey of, and engagement with eHx, network Participants to gauge interest and capabilities



Development: Added FHIR support to the eHx Hub as a passive (and later active) participant to FHIR transactions

Standards: Standards development & connectathons for FHIR directories, FHIR security, FHIR routing/intermediaries

Advocacy: Promoted the FDA use case to all eHx network Participants (webinars, meetings, EMR vendors, users groups, email blasts, eHx work groups, vendor meetings, Participant meetings, etc.)

Financial incentives program

Lessons Learned

- FHIR Query is easy (½ a day)

- Identification of candidate cases is difficult at the data holder (using standards-based approaches)
- Not all EMRs are ready to respond to FHIR queries…but the number is increasing
- FHIR standards are maturing
- HL7 UDAP for FHIR security is a good fit

- FHIR is the preferred approach, but SOAP/CCDA or a hybrid FHIR/SOAP/CCDA is a fallback

**** THANK YOU ****

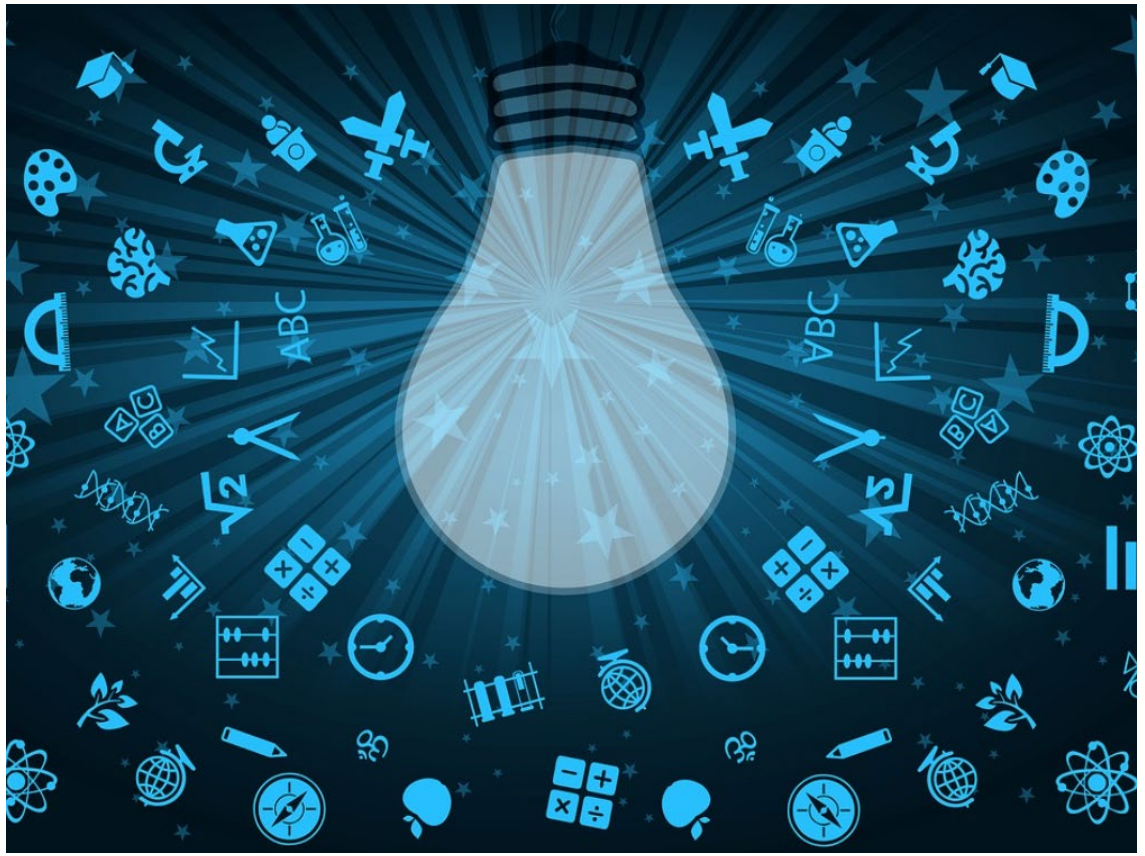


Image credit: pixabay.com

References

For more information about the eHealth Exchange:

Contacts:

administrator [at] ehealthexchange [dot] org

Eric [dot] Heflin [at] ehealthexchange [dot] org

https://www.linkedin.com/in/eric-heflin/

List of Participants and those currently engaged with the FDA:

https://ehealthexchange.org/participants/

https://ehealthexchange.org/participants/?participant_type=fda-pilot

BEST Exchange Platform

Biologics Effectiveness and Safety (BEST) Initiative

Lance Jones
Data Scientist and Technical Project Manager, IBM Consulting
jonesld@us.ibm.com

November 2022

IBM **Consulting**

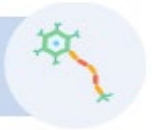
IBM

Introduction

CBER OBPV Mission

Ensure post-market biologic-product safety and effectiveness

Regulated Products

- Vaccines (preventative and therapeutic) 
- Blood (components and derived) 
- Human Tissues and Cellular Products 
- Gene Therapies 
- Xenotransplantation Products 

FDA BEST Initiative Objective

The objective of the Biologics Effectiveness and SafeTy (BEST) Initiative is to ensure post-authorization biologic-product safety and effectiveness through leveraging eHealth Exchange national connectivity.

Exchange Pilot Objective

To enable more robust monitoring of post-authorization adverse events while minimizing the burden on providers through an exchange-based FHIR infrastructure.

CBER = Center for Biologics Evaluation and Research
FDA = U.S. Food and Drug Administration
OBPV = Office of Biostatistics and Pharmacovigilance

Roadmap: Path to Scalability

FY 19-20

Prototype on Foundational Network

- **E2E** EHR to FDA **Pipeline** built
- **20+ Phenotypes** developed and validated
- **100+ ICSR** cases reported for assessment

D.C.
MD
VA
FL

Prototype on Exchange Network

- Leverage pipeline to design a **POC exchange** architecture
- Support with **data agreements** and **standards**

Operationalize BEST IM Pipeline

- Leverage and **enhance** pipeline
- Pilot **scalable phenotypes** for vaccines outcomes of interest

FY21

FY22

Operationalize BEST IM Exchange Platform

- Implement **detection** and **validation** Use cases with early adopter participants
- **Mature** and **scale** nationwide

National Coverage

FY23

Accomplished Ongoing

Data Quality Assessment

For Regulatory Grade Data

Existing Data Quality Tools

Generating **FHIR-ready** and **OMOP-ready** files from data partners, the team uses the Framework described by Kahn et al.[1] and the Data Quality chapter of The Book of OHDSI[2].

Expand Tools

BEST developed 200+ checks for files ingested into the BEST pipeline.

Fit for Purpose & BEST-specific examples

Conformance

Adherence to specified standards and formats?
Sub-types include Value, Relational, and Computational

Are ISBT-128 codes recorded in proper format?

Completeness

Are variables present?
Do they contain all recorded values?

Are vaccine brand or lot numbers captured for all immunization administrations?

Plausibility

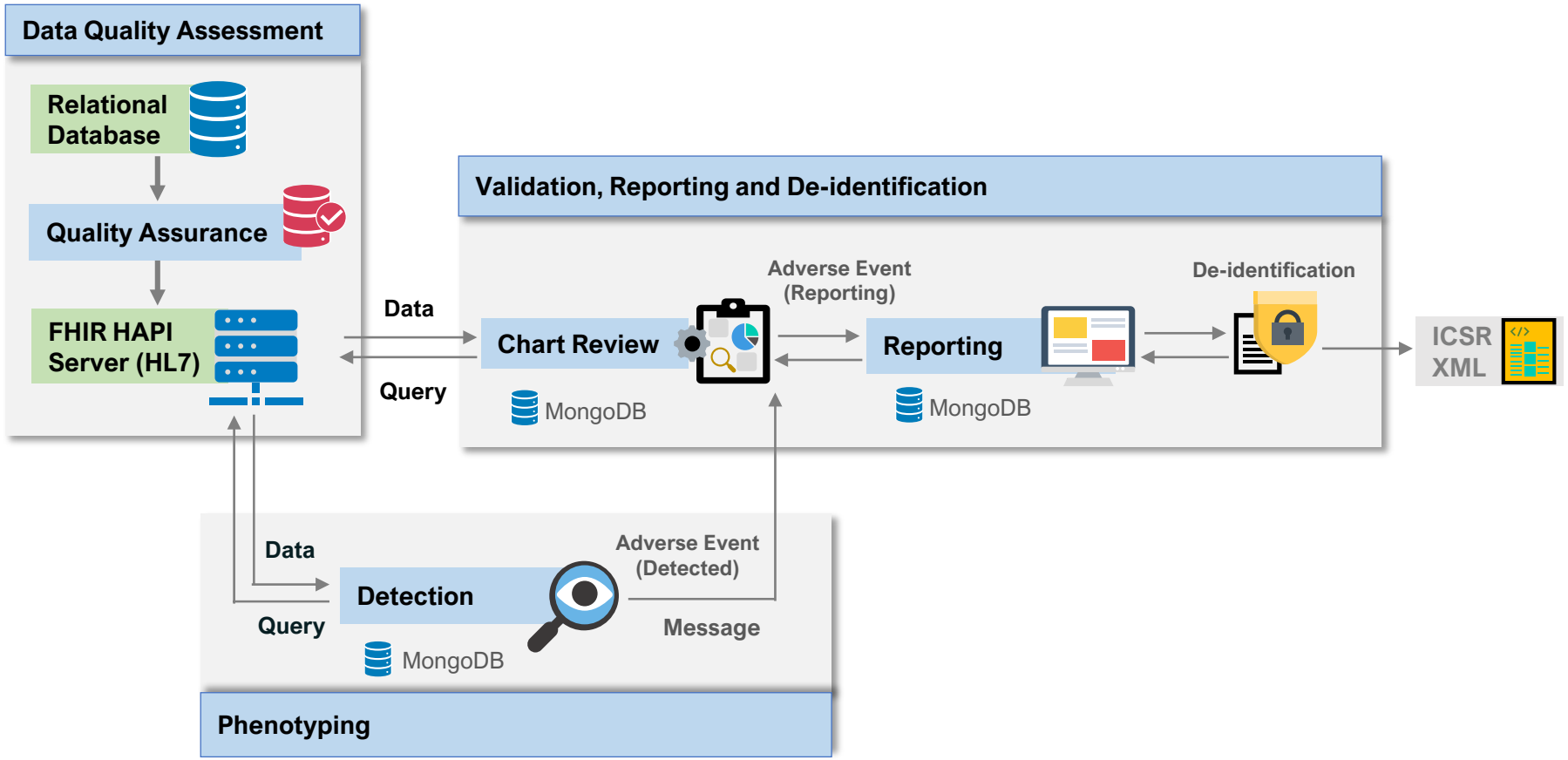
Are data values believable?
Sub-types include Uniqueness, Atemporal, and Temporal.

Are transfusion start times realistic or recorded as the discharge datetime?

[1] Kahn, Michael G., et al. "A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data." *Egems* 4.1 (2016).
[2] https://ohdsi.github.io/TheBookOfOhdsi/DataQuality.html#DataQuality

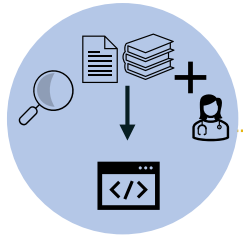
BEST Foundational Work

BEST* Innovative Methods (**IM**) Initiative developed a Pipeline prototype to address current challenges through AI and automation.



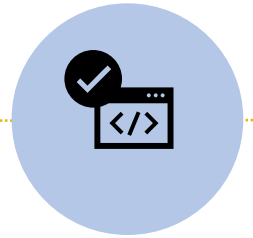
* ***BEST,*** *Biologics Effectiveness and Safety*

Phenotypes Development Framework



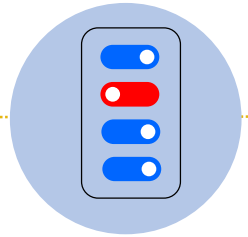
1 Simple Phenotype Development

- Literature review
- Case Definitions (e.g. Brighton Collaboration),
- SME input



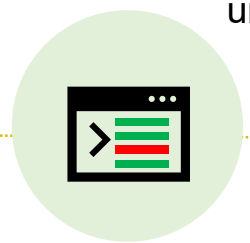
2 Development Validation

- Review select cases
- Recommend changes



3 Enhanced Phenotype Development

- Include input from dev. Validation
- Add features (structured, or unstructured, or both)



4 Development Validation

- Review select cases
- Examine/omit/Add features (usually unstructured)

5 Formal Validation

- Apply phenotype to validation set
- Estimate final performance metrics

FDA BEST Exchange Platform Overview

Among the First Public Health HL7® FHIR® National-scale System

Health Care Providers in eHx Network

eHealth Exchange Data Hub

FDA BEST Exchange Platform (with BEST Applications)

Expected Benefits:

- Uses FHIR R4 endpoints
- Reduced burden for responders
- Reduced latency
- Efficiencies in EHR data requests

Use Case: Requesting Clinical Charts for Reviews of Reported Cases

1 FDA

- Identify AE case of interest that requires additional data

2 BEST Applications

- Use provided patient demographics to prepare additional data request

3 FDA BEST Platform

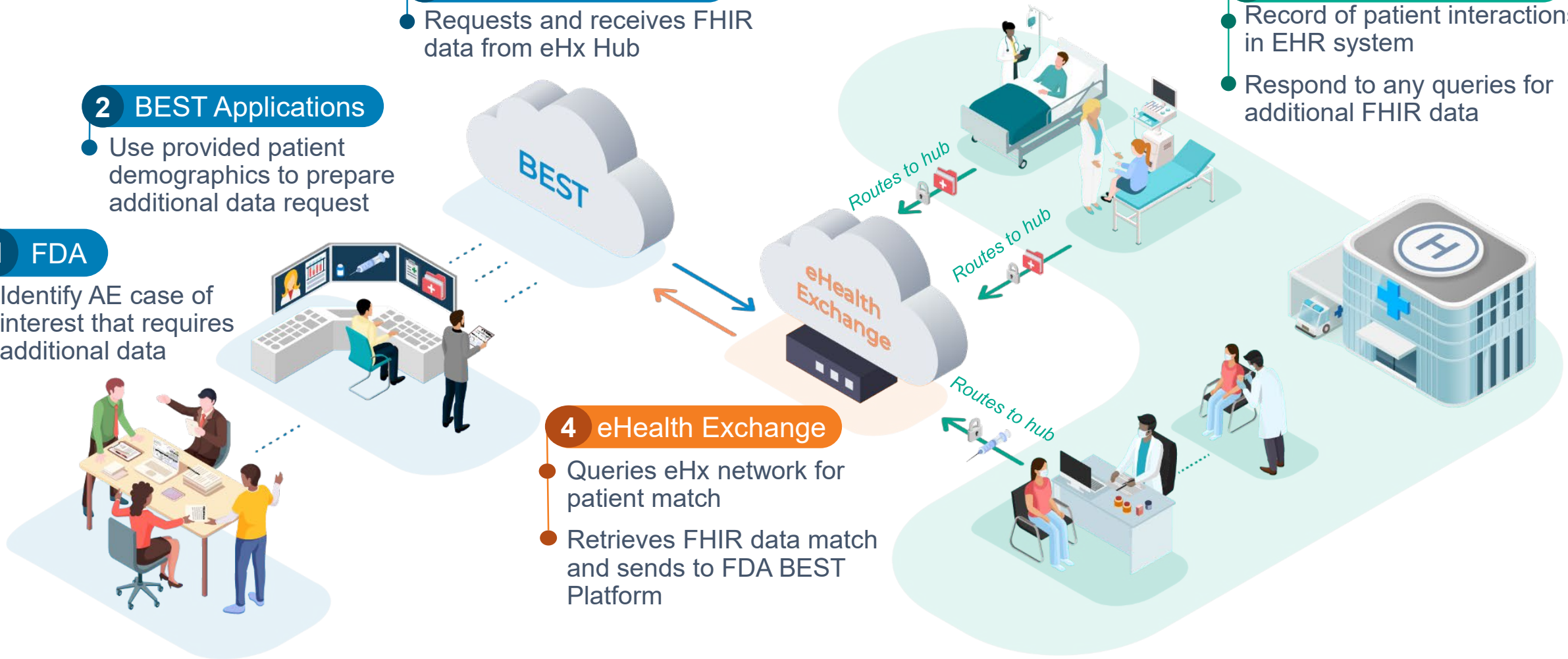
- Requests and receives FHIR data from eHx Hub

4 eHealth Exchange

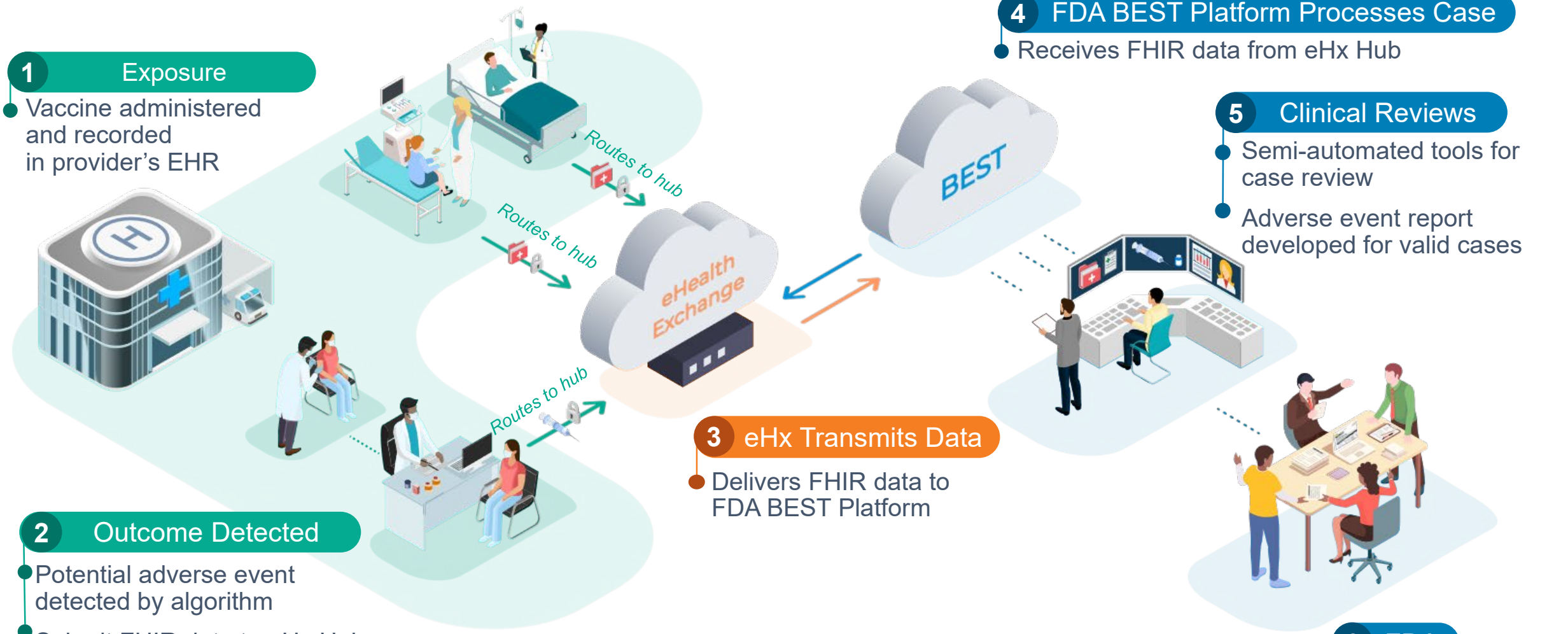
- Queries eHx network for patient match
- Retrieves FHIR data match and sends to FDA BEST Platform

5 Provider EHR System

- Record of patient interactions in EHR system
- Respond to any queries for additional FHIR data



Use Case: Detect, Validate, and Report Adverse Event Cases



1 Exposure

- Vaccine administered and recorded in provider's EHR

2 Outcome Detected

- Potential adverse event detected by algorithm
- Submit FHIR data to eHx Hub for FDA BEST delivery

3 eHx Transmits Data

- Delivers FHIR data to FDA BEST Platform

4 FDA BEST Platform Processes Case

- Receives FHIR data from eHx Hub

5 Clinical Reviews

- Semi-automated tools for case review
- Adverse event report developed for valid cases

6 FDA

- Receives AE report
- Reviews case

References

- Standards
  - BEST FHIR IG
  - BEST FHIR on ISA
  - Biologically Derived Products on USCDI
- Conferences
  - FHIR Dev Days 2020, Development of a SMART-on-FHIR enabled Semi-Automated Adverse Event Validation & Reporting Application / Presentation Recording
  - HL7 Connectathon 2021, BEST FHIR Implementation Guide
  - AABB 2021, Development of an Application that Semi-Automates Clinician Verification and Reporting of Transfusion Allergic Reaction Cases
- Publications
  - The Food and Drug Administration Biologics Effectiveness and Safety Initiative Facilitates Detection of Vaccine Administrations from Unstructured Data in Medical Records through Natural Language Processing
  - Detection of Allergic Transfusion-Related Adverse Events from the Electronic Medical Record
- GitHub Repos
  - Rapid Term Set Generator

Closing Remarks | Day 2

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

Contact Us

healthpolicy.duke.edu

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dukemargolis@duke.edu

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