Sixteenth Annual Sentinel Initiative Public Workshop

November 7, 2024

9:00 a.m. – 4:15 p.m. ET

Duke | MARGOLIS INSTITUTE *for* Health Policy

Welcome and Opening Remarks

Mark McClellan

Director, Duke-Margolis Institute for Health Policy

Duke | MARGOLIS INSTITUTE *for* Health Policy

Workshop Agenda

9:00 a.m.	**Welcome and Opening Remarks**
9:10 a.m.	**Keynote Address**
9:25 a.m.	**Fireside Chat with Sentinel Initiative Leadership**
9:45 a.m.	**Regulatory Applications of RWD: Highlights from the Sentinel System**
11:00 a.m.	**Break**
11:15 a.m.	**Vaccine Monitoring: Regulatory Impact of the BEST System**
12:30 p.m.	**Break for Lunch**
1:40 p.m.	**Insights into the Future: Sentinel System 3.0**
2:15 p.m.	**BEST System Innovations to Anticipate**
3:00 p.m.	**Break**
3:15 p.m.	**Perspectives on Future Opportunities for the Sentinel Initiative**
4:00 p.m.	**Closing Remarks**
4:15 p.m.	**Adjourn**

Statement of Independence

The Robert J. Margolis, MD, Institute 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.

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Keynote Address

Patrizia Cavazzoni

Director, Center for Drug Evaluation and Research

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Fireside Chat with Sentinel Initiative Leadership

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

Speakers: **Gerald J. Dal Pan**, U.S. Food and Drug Administration

Steve Anderson, U.S. Food and Drug Administration

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

Moderated Discussion and Q&A

Moderator: Mark McClellan

Duke-Margolis Institute for Health Policy

Regulatory Applications of RWD: Highlights from the Sentinel System

Moderator: **Victoria Gemme**, Duke-Margolis Institute for Health Policy

Panelists: **Jamal T. Jones**, U.S. Food and Drug Administration

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

Rishi J. Desai, Harvard Medical School and Brigham and Women's Hospital

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

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Sentinel

Sentinel Innovation Center

Year 5 Demonstrations of New Sentinel Capabilities Using the Real-World Evidence Data Enterprise (RWE-DE)

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

16th Annual Sentinel Initiative Public Workshop

November 07, 2024

Disclaimers

- The views expressed in this presentation represent those of the presenters and do not necessarily represent the official views of the U.S. Food and Drug Administration (FDA).
- The Sentinel Innovation Center is funded by the U.S. FDA through the Department of Health and Human Services (HHS) contract number **75F40119D10037.**

Innovation Center Collaborating Organizations: Data & Scientific Partners

Agenda

1 Real World Evidence Data Enterprise (RWE-DE)

2 Framework for leveraging RWE-DE to address use cases

3 Results from Year 5 demonstration projects

4 Summary

Real World Evidence Data Enterprise (RWE-DE)

Reducing ARIA Insufficiencies

- A recent review by Maro et al.[1] reviewed 197/330 (59.6%) instances of safety concerns brought forward by the FDA between 2016-2021 where the Active Risk Identification and Analysis (ARIA) system was deemed insufficient.
- A root cause analysis identified lack of granular clinical data as a key reason for many ARIA insufficiency determinations.
- The Sentinel Innovation Center (IC), with the Sentinel Operations Center (SOC), has built the Real-World Evidence Data Enterprise (RWE-DE) linking 20+ million lives with information-rich electronic health records (EHR)+claims data.
- The IC has developed methods and processes to make optimal use of these data aiming to reduce the proportion of ARIA requests that are deemed insufficient.

Today, we showcase Sentinel's new capabilities using the RWE-DE.

[1] Maro et al. *CPT. 2023*

The Sentinel RWE-DE based on EHR+claims data today

Commercial *EHR+claims* Network
21 million linked lives

healthverity | TriNetX

Deidentified patient-level data in Sentinel common data model (SCDM)

Derived variables

Phenotyping Algorithms

FDA

Queries

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

Development Network
EHR-based algorithm development
EHR-based toolkit development

Mass General Brigham	1.3M
Duke Clinical Research Institute	0.06M
Vanderbilt University Medical Center	0.7M
Kaiser Permanente Washington Health Research Institute	2.5M

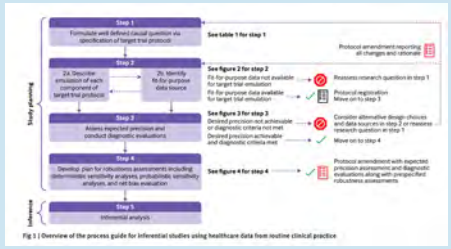
4.5 million EHR+claims linked lives*

Phenotyping Algorithms

Analytic toolkits

Innovation Center analytic hub

Query execution PBAs ** following PRINCIPLED framework

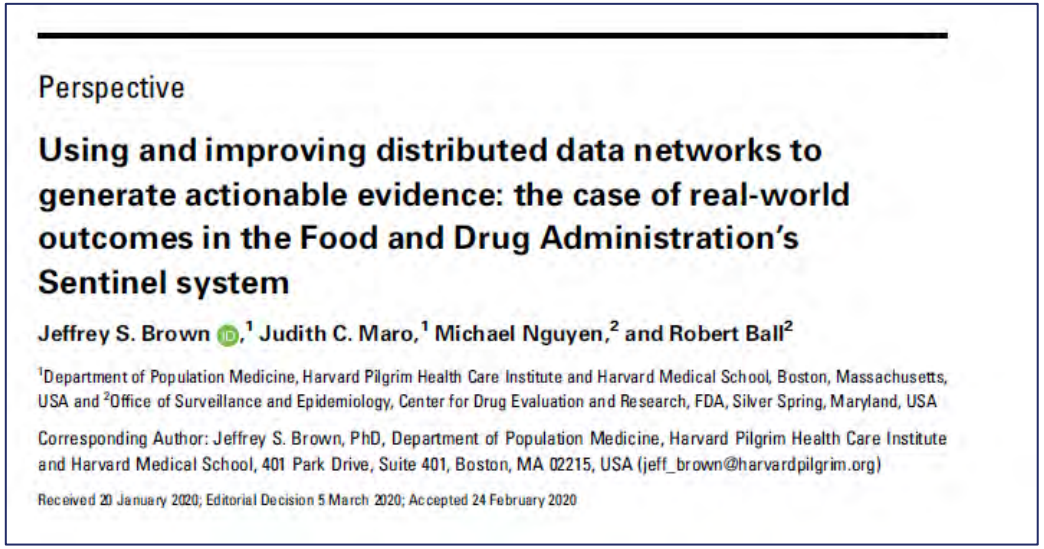


Analyses augmenting claims data analyses in Sentinel Distributed data network

- Rapid balance evaluation
- Expedited endpoint validation
- Subset calibration

* Including metadata on free text notes for rapid queries
** PBA = protocol-based analyses

Papers motivating and describing the new RWE-DE



Perspective

Using and improving distributed data networks to generate actionable evidence: the case of real-world outcomes in the Food and Drug Administration's Sentinel system

Jeffrey S. Brown,[1] Judith C. Maro,[1] Michael Nguyen,[2] and Robert Ball[2]

[1]Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, Massachusetts, USA and [2]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, FDA, Silver Spring, Maryland, USA

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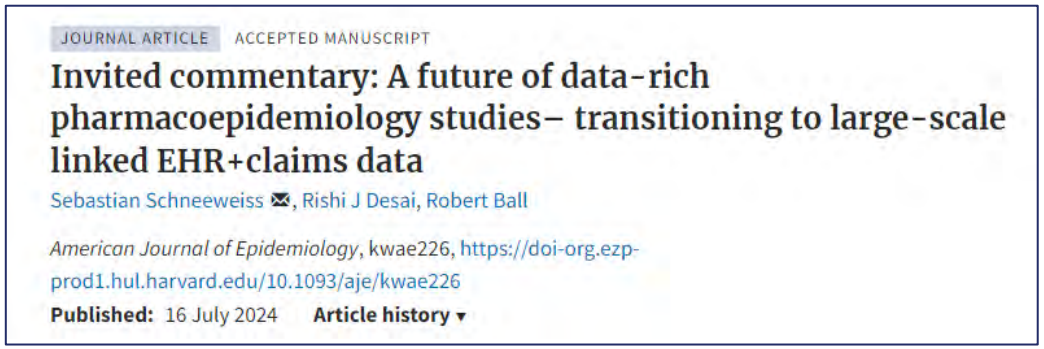

JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Invited commentary: A future of data-rich pharmacoepidemiology studies– transitioning to large-scale linked EHR+claims data

Sebastian Schneeweiss ✉, Rishi J Desai, Robert Ball

American Journal of Epidemiology, kwae226, https://doi-org.ezp-prod1.hul.harvard.edu/10.1093/aje/kwae226

Published: 16 July 2024 **Article history** ▾

npj | Digital Medicine www.nature.com/npjdigitalmed

PERSPECTIVE OPEN

Broadening the reach of the FDA Sentinel system: A roadmap for integrating electronic health record data in a causal analysis framework

Rishi J. Desai ✉, Michael E. Matheny, Kevin Johnson, Keith Marsolo, Lesley H. Curtis, Jennifer C. Nelson, Patrick J. Heagerty, Judith Maro, Jeffery Brown, Sengwee Toh, Michael Nguyen, Robert Ball, Gerald Dal Pan, Shirley V. Wang, Joshua J. Gagne and Sebastian Schneeweiss

The FDA Sentinel Real World Evidence Data Enterprise (RWE-DE)

Rishi J. Desai | Keith Marsolo | Joshua Smith | David Carrell | Robert Penfold | Haritha S. Pillai | Joyce Lii | Kerry Ngan | Robert Winter | Margaret Adgent | Arvind Ramaprasan | Meighan Rogers Driscoll | Daniel Scarnecchia | Daniel Kiernan | Christine Draper | Jennifer G. Lyons | Anjum Khurshid | Judith C. Maro | Ruth Zimmerman | Jeffrey Brown | Patricia Bright | José J. Hernández-Muñoz | Michael E. Matheny | Sebastian Schneeweiss

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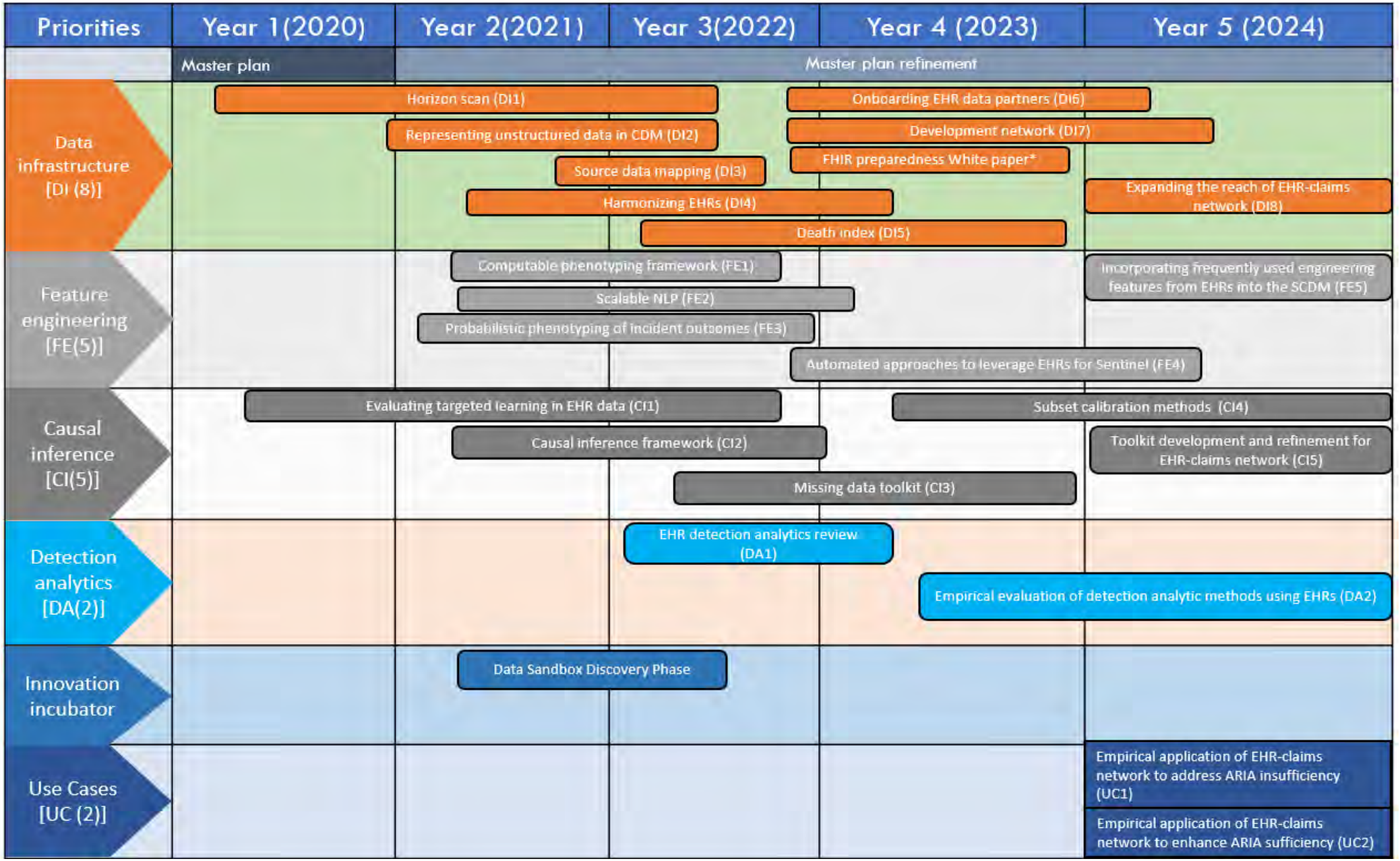
Brown et al. JAMIA 2020
Desai et al. npj Digital Medicine 2021
Schneeweiss et al. AJE 2024
Desai et al. PDS 2024

Purpose

The IC with SOC has built an EHR+claims data network for enhanced causal inference of drug effects on clinical endpoints. The objective is to

- Provide results of the Year 5 demonstration projects:
  - Demonstrate how the new EHR+claims network aims to improve ARIA sufficiency
  - Focus on 1+5 use cases
  - Focus on implementation flexibility, practical issues, and efficiency
  - These are considered methods projects
- Summarize how the 1+5 use cases will enhance ARIA sufficiency for FDA queries to assess the safety of prescription medications

Innovation Road Map translated into projects through 2024

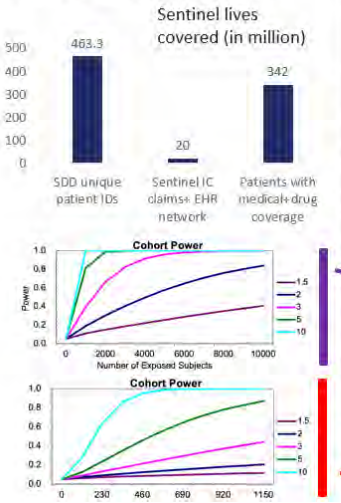


Framework for leveraging RWE-DE to address use cases

The 1+5 standard Use Cases of the Sentinel EHR+claims Network

1 Use Case: ARIA analyses determined to be insufficient will be conducted in the Sentinel EHR+claims network

Safety/RWE Studies Completed Within the Sentinel EHR+claims Network: What is achievable with the expected ~ 20 million lives?



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

* Based on prevalence reported in Horizon scan queries

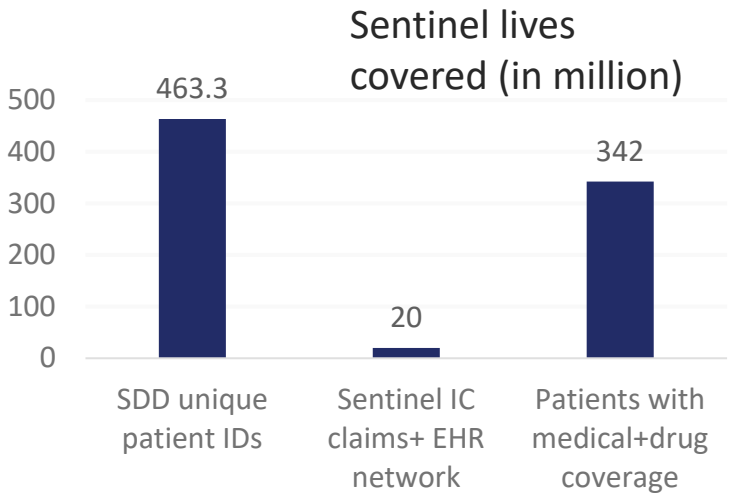
Sentinel System | 13

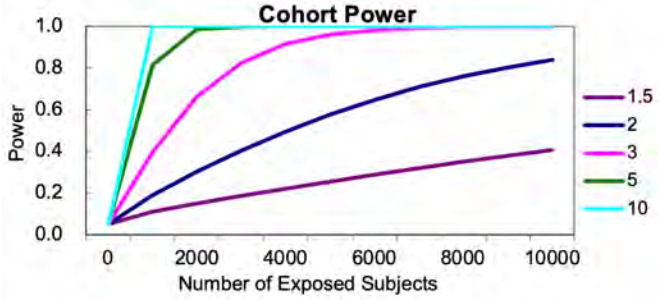
5 Use Cases: Strengthening ARIA sufficient claims analyses with the Sentinel EHR+claims network

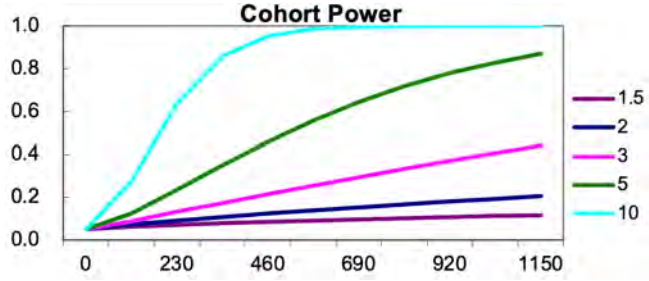
Further Strengthening ARIA Sufficient Analyses via the Sentinel *EHR+claims* Network: 5 Key Use Cases

1. Rapid balance evaluation of patient characteristics in EHRs and not measured in claims data
2. Routinely apply corrections for unmeasured confounding through a subset calibration toolkit
3. Natural Language Processing (NLP)-assisted validation of claims-based outcome algorithms for improved inference in claims data
4. Expand claims-based analyses with deep clinical information on outcomes, exposures, confounders
5. Expanding signal detection capabilities by incorporating EHR data elements

Safety/RWE Studies Completed Within the Sentinel EHR+claims Network: What is achievable with the expected ~ 20 million lives?







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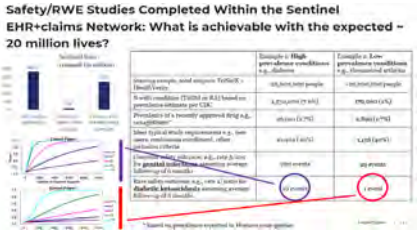
* Based on prevalence reported in Horizon scan queries

Results from Year 5 demonstration projects

Demonstration project (PI Rishi Desai)

UC 1/ Aim 2



Using the **Commercial Network** of 20 million lives linked EHR+claims data we studied the risk of **acute pancreatitis** in patients with T2DM using **SGLT-2 inhibitor vs DPP4 inhibitors.** This was deemed ARIA insufficient in claims data.

ARIA need: Etiologic analyses that can identify clinical endpoints using information beyond administrative claims: acute pancreatitis; the analysis adjusts for risk factors not observable in claims: alcohol, smoking, and BMI.

Methods: A cohort study using propensity score (PS) weighting based on claims and EHR-measured pre-treatment patient characteristics

The outcome, acute pancreatitis, is assessed via a computable phenotyping algorithm, developed in a prior IC project, using structured data, lab results, and unstructured free text notes

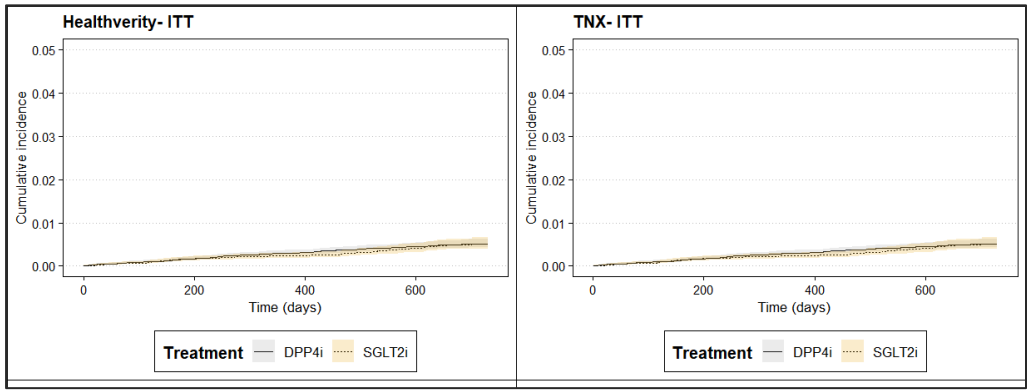
Results:

Incidence of acute pancreatitis

Data	Exposure	Measure	Intent to treat follow-up	Per protocol follow-up
HealthVerity (Jan 2018-Dec 2020)	SGLT-2i initiators (n=30,174)	Number of events/py	88/33,889	40/16,374
		IR/1000 py	2.6 (2.1-3.2)	2.4 (1.7-3.3)
	DPP-4i initiators (n=42,255)	Number of events/py	148/51,561	67/24,608
		IR/1000 py	2.9 (2.4-3.4)	2.7 (2.1-3.5)
TriNetX (Jan 2013-Feb 2024)	SGLT-2i initiators (n=11,943)	Number of events/py	44/22,756	15/7,891
		IR/1000 py	1.9 (1.4-2.6)	1.9 (1.1-3.1)
	DPP-4i initiators (n=12,747)	Number of events/py	94/36,783	26/10,499
		IR/1000 py	2.6 (2.1-3.1)	2.5 (1.6-3.6)

*IR: Incidence Rate; PY: Person-Years; SGLT-2i : Sodium Glucose co-Transporter 2 inhibitors; DPP-4i: Dipeptyl Peptidase 4 inhibitors

Cumulative incidence acute pancreatitis is extremely low



Fully adjusted HRs

Data	Intent to treat	Per protocol
Health Verity	0.92 (0.69-1.22)	0.88 (0.58-1.34)
TriNetX	0.71 (0.47-1.07)	0.73 (0.34-1.56)
Pooled	**0.85 (0.67-1.07)**	**0.84 (0.58-1.22)**

An increase in risk is unlikely

Conclusion

The IC demonstrated a proof-of-concept for future protocol-based assessments (PBAs) in Sentinel that require EHR+claims data. Analytic pipelines and packages from earlier methods projects are key to achieve scalable and timely execution of complex analyses

ARIA impact:

- It is now technically feasible for FDA to execute entire ARIA queries in EHR+Claims data
- Its current size still limits queries to frequent exposures or frequent events

Table: Time to complete each step and opportunities to expedite

Process Step	Time in days (d)	Additional opportunities to expedite/Comments	Days expected in routine use
Data refresh	~60-90 d	Required step only once per refresh cycle, data can be leveraged by multiple queries	Same
Protocol development, refinement, clearance	~90-120 d	Close collaboration with FDA required; possible to expedite for more pressing queries	Variable
Analysis	~30 d	Fast turnaround with Sentinel tools	Same
Reporting	~30 d	NA	Same
TOTAL	150-180 d	(Excluding data refresh time) (Assumed computable phenotyping algorithm is available and previously validated)	-

Further Strengthening ARIA Sufficient Analyses via the Sentinel *EHR+claims* Network: 5 Key Use Cases

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

2. Routinely apply corrections for unmeasured confounding through a subset calibration toolkit

3. Natural Language Processing (NLP)-assisted validation of claims-based outcome algorithms for improved inference in claims data

4. Expand claims-based analyses with deep clinical information on outcomes, exposures, confounders

5. Expanding signal detection capabilities by incorporating EHR data elements

Demonstration Project: UC 2/Aim 1 (PI Shirley Wang)

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

ARIA need: Rapid confirmation that balance in unobserved patient characteristics was achieved in the claims data analysis.

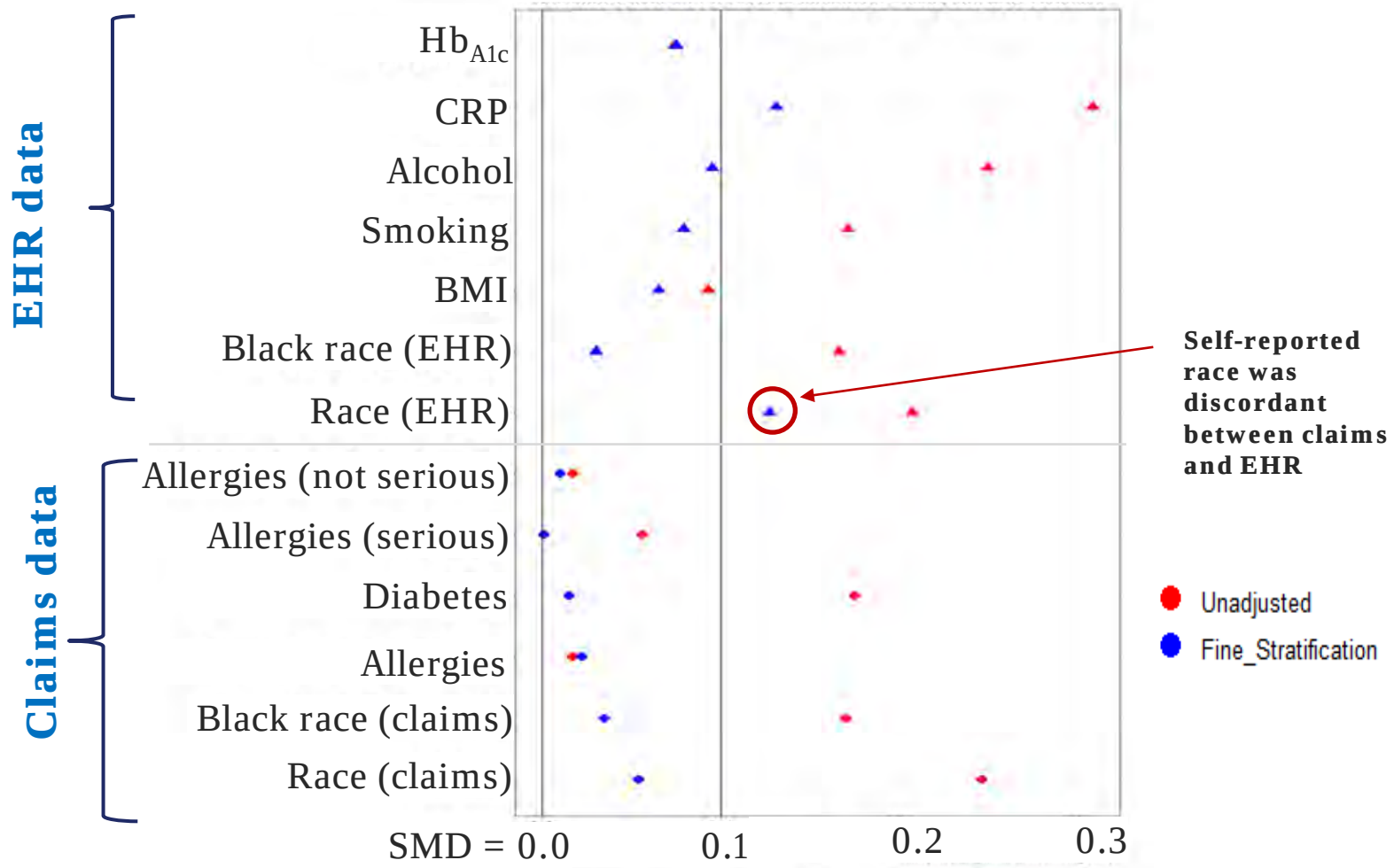
Using the **Development Network (MGB site)** we applied rapid confounder balance evaluation to the following drug safety questions.

Selected use case: ACEI/ARB vs. ARNI (Entresto) in patients with HF for the outcome of angioedema; unmeasured confounders in claims included smoking, BMI, history of allergic reactions etc.

Methods: Using claims data, patient cohorts were identified, and confounders were measured and balanced through propensity scores.
In this claims-balanced cohort additional select variables were identified in the corresponding EHR data and their balance was assessed.

Interpretation: Balance had been achieved in multiple unobserved confounders in claims data adjustment

Results: ACEI/ARB vs. ARNI*



* ACEI = angiotensin converting enzyme inhibitors ; ARB = angiotensin receptor blocker ; ARNI = angiotensin receptor/neprilysin inhibitor.

Demonstration Project: UC 2/Aim 5(PI Rishi Desai)

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

ARIA need: Rapid confirmation that balance in unobserved patient characteristics was achieved in the claims data analysis.

Using the **Development Network (MGB site)** we applied rapid confounder balance evaluation using simulation methods to the following drug safety question:

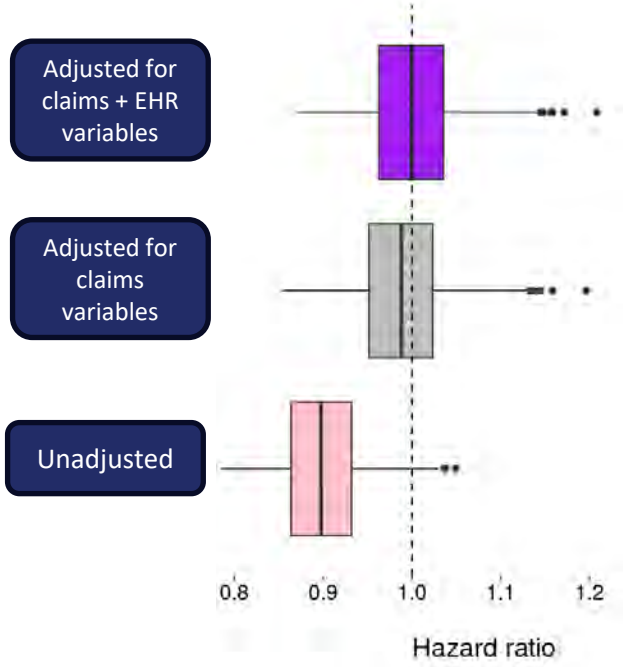
- Selected use case: varenicline vs bupropion for smoking cessation and risk of adverse neuropsychiatric events. The unmeasured confounder of interest is history of suicidal ideation and action as a marker for severe depression extracted through NLP of clinical notes

Methods:
Patient cohorts were identified using claims data. Confounders unmeasured in claims but available in EHR were identified and extracted.

In the second step, a subset with information on the unmeasured confounder is used as the basis for a Plasmode simulation study to describe bias distribution when adjusting for versus not adjusting for the unmeasured confounder of interest

	BUPROPION	VARENICLINE
Total	15,100	6,864
N with ≥1 free text note	12,747 (84.4%)	5,849 (86.7%)
Suicidal ideation identified	1,338 (10.5%)	389 (6.6%)

Distribution of HRs in simulations (simulated true HR = 1.0)



Interpretation:
1) Minor imbalance in suicidal ideation remained after adjusting for claims only variables
2) Likely a small impact on improved confounding control

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

Conclusion

The IC demonstrated the feasibility of expedited, routine evaluation of balance in confounders not measured in claims but measurable in EHR.

In the two examples, such evaluation provided reassurance that potential confounding factors were likely balanced by proxy via claims-based variables.

ARIA Impact:

- FDA now can expeditiously assess the balance in unmeasured confounders achieved by claims data analyses
- Methods for rapid balance evaluation will be important for timely ARIA sufficiency assessment

Table: Time to complete each step and opportunities to expedite (based on Varenicline example)

Process Step	Time in days (d)	Additional opportunities to expedite	Days expected in routine use
Protocol development & QRP implementation	30-45 d	Can be avoided if implementing in parallel with an ARIA query being conducted in SDD	0-45 d
Extraction of EHR variables structured data	7 d	NA	7 d
Extraction of EHR variables with NLP	30 d	Can be more or less depending on complexity	Variable
Simulations	7-14 d	NA	7-14 d
Interpretation and reporting	15-30 d	Dependent on the complexities and refinement needed	15-30 days
TOTAL	~90 d	-	-

Demonstration Project: UC 2/Aim 2 (PI Susan Shortreed)

2. Routinely apply corrections for unmeasured confounding through a subset calibration toolkit

Using the **Development Network (KPWA site)** we implemented methods for unmeasured confounder correction in claims data analyses using KPWA EHR data.

ARIA need: Unmeasured confounding needs to be addressed with additional insight from EHR data

Selected use case: Thromboembolic events in patients with COVID-19 vs. influenza. The key concern for robust conclusions is that BMI is an unmeasured *potential* confounder and may be found to be imbalanced between treatment groups

Methods: Using claims data, patient cohorts were identified, and confounders were measured and balanced using propensity scores. Based on results of CI4 (PI Pam Shaw) *Generalized raking* was implemented, as it performed the best in terms of bias and statistical efficiency in scenarios similar to our scientific study.

Results: After claims adjustment we observed a residual imbalance in EHR-measured BMI (SMD = 0.37).
The claims-only analysis of the risk of arterial thrombotic events showed an HR of 1.35 and after correction for unmeasured BMI status with generalized raking the HR numerically increased to 1.45

Results:

EHR-measured BMI	**COVID-19 N = 139**	**Influenza N = 220**	SMD
BMI in 90 days prior			0.371
< 17.9	3 (2.2%)	11 (5.0%)	
18 – 24.9	22 (16%)	61 (28%)	
25 – 29.9	42 (30%)	63 (29%)	
30 – 34.9	33 (24%)	44 (20%)	
35 +	39 (28%)	41 (19%)	

Risk of arterial thrombotic events among patients hospitalized with COVID-19 compared to influenza.

	N	# events	HR (95%CI)
Generalized raking, BMI measure in prior 90 days from EHR data	**With BMI measured**		
Covid-19 patients	139	21	**1.45** (0.93, 2.25)
Influenza patients	220	28	(ref)
Adjusted for claims-measured covariates	**Claims only**		
Covid-19 patients	449	62	**1.35** (0.91, 2.02)
Influenza patients	463	58	(ref)

Interpretation:
Using linked EHR data, imbalance observed in BMI measurements could be corrected with raking methods, which did not meaningfully change the observed association

*Breslow NE, Lumley T, Ballantyne CM, Chambless LE, Kulich M. Improved Horvitz-Thompson Estimation of Model Parameters from Two-phase Stratified Samples: Applications in Epidemiology. Stat Biosci 2009;1:32.

Conclusion

2. Routinely apply corrections for unmeasured confounding through a subset calibration toolkit

The IC demonstrated the ability to rapidly implement generalized raking, a 2-stage approach to leverage EHR data to address residual confounding.

In this example, correcting for unmeasured BMI imbalances among those hospitalized with COVID-19 vs. influenza had little impact on the relative risk of arterial thrombotic events

ARIA impact:

- Sentinel now has a proven approach for rapidly correcting confounder imbalances.
- This method can be used in conjunction with the rapid balance assessment tool

Table: Time to complete each step and opportunities to expedite

Process Step	Time in days (d)	Additional opportunities to expedite	Days expected in routine use
Protocol development & QRP implementation	30-45 d	Can be avoided if implementing in parallel with an ARIA query being conducted in SDD	0-45 d
Extraction of standard EHR variables	7 d	NA	7 d
Describe missing data pattern with SDMI package	5d	Additional vignette extending to survival models with longer follow-up time and more censoring.	
Applying the calibration package	5-20 d	Additional vignette on 2-phase sampling, efficient influence functions, other efficiency tools	
Interpretation and reporting	20-35 d	Dependent on the complexities and refinement needed	15-30 days
TOTAL	~90 days	-	-

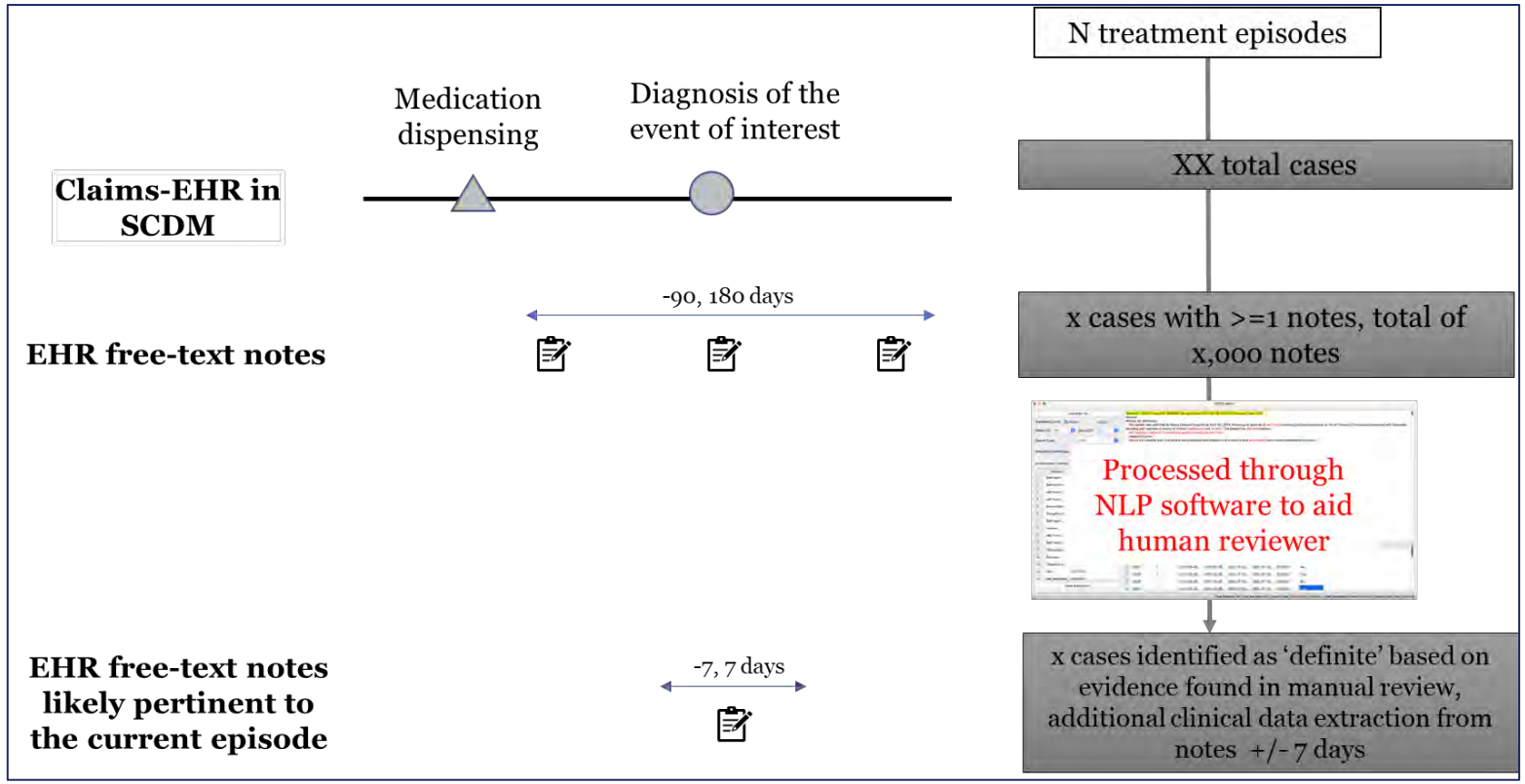
NLP-assisted Chart Review of EHR Data from Development Network (Emerging Needs, PI: Rishi Desai)

Using the **Development Network (MGB site)** we implemented and expedited, NLP-assisted chart review using free-text notes to provide more granular clinical information about cases

ARIA need: Detailed medical notes review in a timely manner

Methods: Using claims data, potential cases of interest were identified among treatment initiators. In this sample, extracted additional clinical data from EHRs including lab results and free-text notes to describe the clinical course and outcomes.

Results:



Conclusion

The IC demonstrated the feasibility of expedited NLP assisted chart review within the EHR+claims development network.

ARIA Impact:

- FDA Sentinel has successfully tested an efficient NLP-supported abstraction tool that works across the EHR+claims data development network

Table: Time to complete each step and opportunities to expedite

Process Step	Time in days (d)	Additional opportunities to expedite	Days expected in routine use
Protocol development & PEPR query	15 days	NA	30 days
Note retrieval and NLP processing	15 days	NA	Volume dependent
Manual review and data extraction	15 days	NA	Volume dependent
Reporting	15 days	NA	NA
TOTAL	60 days		30-90 days

Demonstration Project: UC 2/Aim 4 (PI Josh Smith)

4. Expand claims-based analyses with deep clinical information on outcomes, exposures, confounders

Using the **Development Network (VUMC site)** we are identifying exposures to cannabis and non-FDA approved cannabinoid product (CCP) extracted from EHR data:

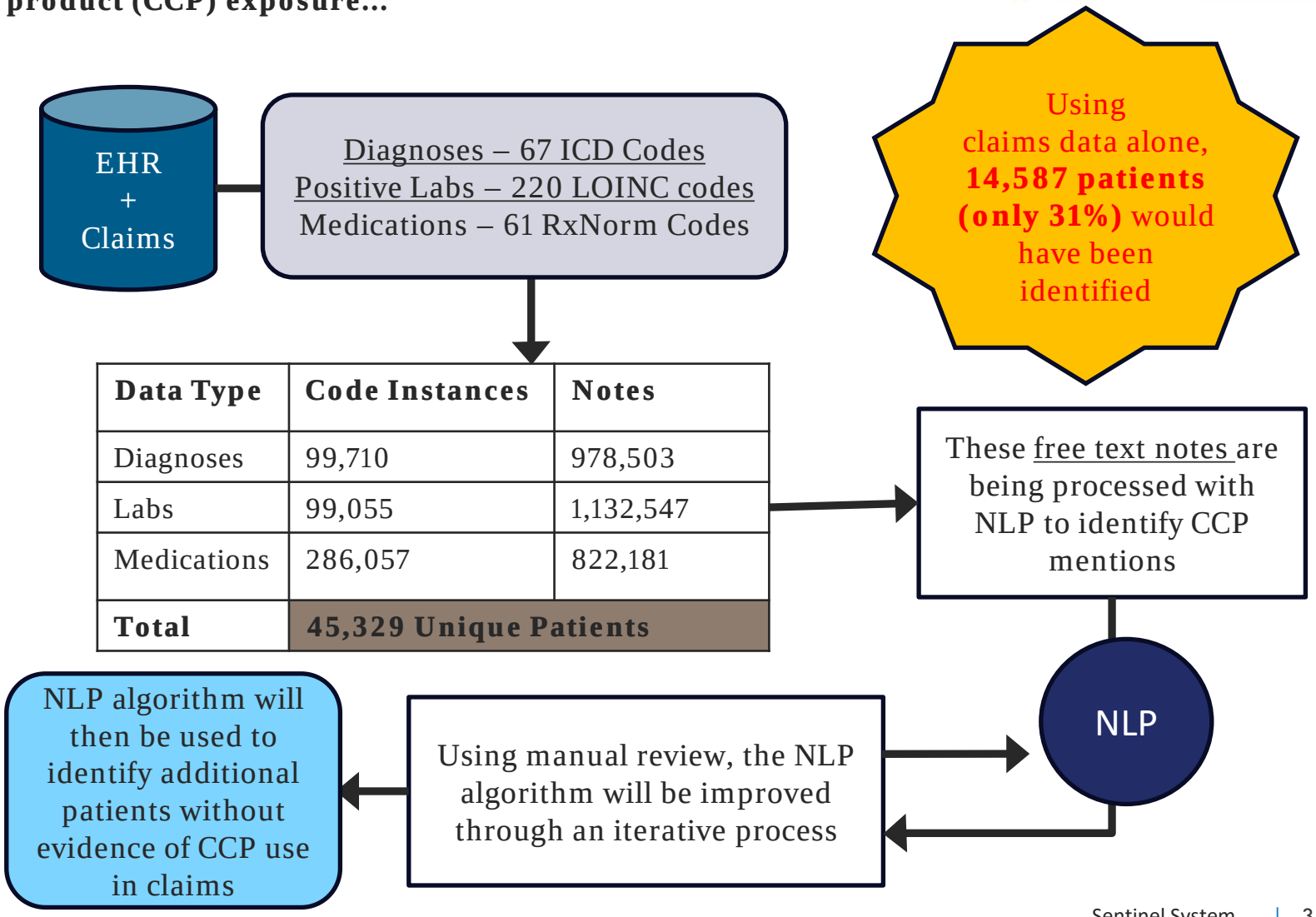
Selected use case: Identifying subjects with past use of CCP describing demographics, co-medications, and other clinical characteristics

Need: The inability to identify exposure to CCP limits the ability to conduct safety analyses and may be overcome with EHR data.

Methods: Using EHR+claims linked data from the development network (VUMC site) we used a transportable, semi-automated NLP pipeline to identify CCP as study exposure, covariate, or subgroup identifier.

Results:
Project ongoing, results expected Spring 2025

Beginning with structured EHR data, we identified individuals with suspected cannabis and cannabinoid product (CCP) exposure…



Data Type	Code Instances	Notes
Diagnoses	99,710	978,503
Labs	99,055	1,132,547
Medications	286,057	822,181
Total	**45,329 Unique Patients**	

Demonstration Project: UC 1/Aim 1 (PI Sascha Dublin)

4. Expand claims-based analyses with deep clinical information on outcomes, exposures, confounders

ARIA Motivation: some health outcomes of interest (HOIs) cannot be accurately identified using administrative claims data alone.

Overview: demonstration project aims to develop and apply a framework for determining whether a given HOI is, or is not, well-suited for **EHR-based computational phenotyping.**

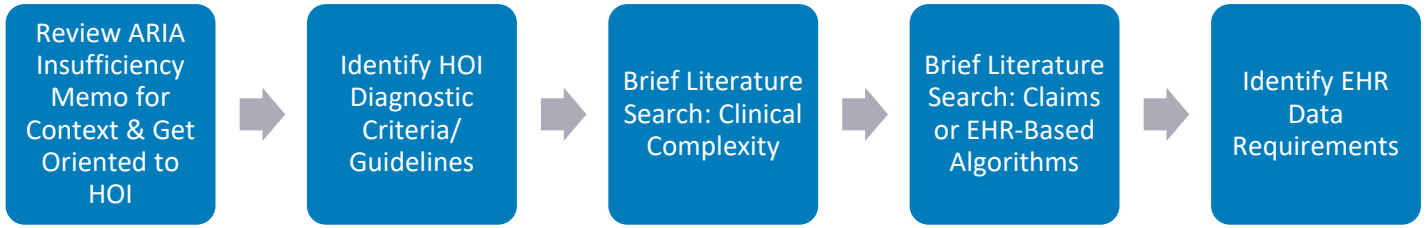
Approach:

- We have developed guidance and processes for assessing whether HOIs are well-suited for EHR-based computational phenotyping (fit-for-purpose).
- We are applying the process to several HOIs previously deemed insufficient for assessment in ARIA claims-based data and are iteratively refining the process as lessons are learned.
- We are developing materials to support the process.

Outputs:

- 7 HOI FFP assessments conducted; 2 in progress
- Detailed report per HOI with considerations and recommendations
- Guidance and worksheets will support future rigorous, efficient assessments of HOIs' suitability for EHR-based computational phenotyping

HOI Fit-for-Purpose Assessment Process



Assessments To-Date

Health Outcome of Interest	Overall Difficulty	Clinical Complexity	Data Complexity
Pericardial Effusion	Moderate	Low	Medium
Drug Induced Liver Injury	Hard	High	High
Outpatient Neutropenia	Easy	Low	Low
Hepatitis B Reactivation	Moderate	Medium	Medium
Encapsulated Bacterial Infections	Hard	High	Medium
Serious Infections	*Determined not amenable to the FFP process without first resolving ambiguity in the HOI definition*		
Venous Thromboembolism	Moderate	Low	Medium
Major Bleeding	*In progress*		
Hematologic Adverse Events	*In progress*		

Conclusion

4. Expand claims-based analyses with deep clinical information on outcomes, exposures, confounders

We conducted fit-for-purpose assessments for common and important HOI and relevant product information for which ARIA is deemed not sufficient.

We developed transportable algorithms to identify c0-medications from free text notes, e.g., non-FDA approved cannabis and cannabinoid products.

ARIA Impact:

- A fit-for-purpose assessed phenotyping pipeline using free-text notes with claims is being established.
- It develops transportable algorithms to identify HOIs and exposures from free text notes in the RWE-DE.
- A catalog of HOI allows expedited determination whether new EHR data resources can be leveraged to assess critical HOIs

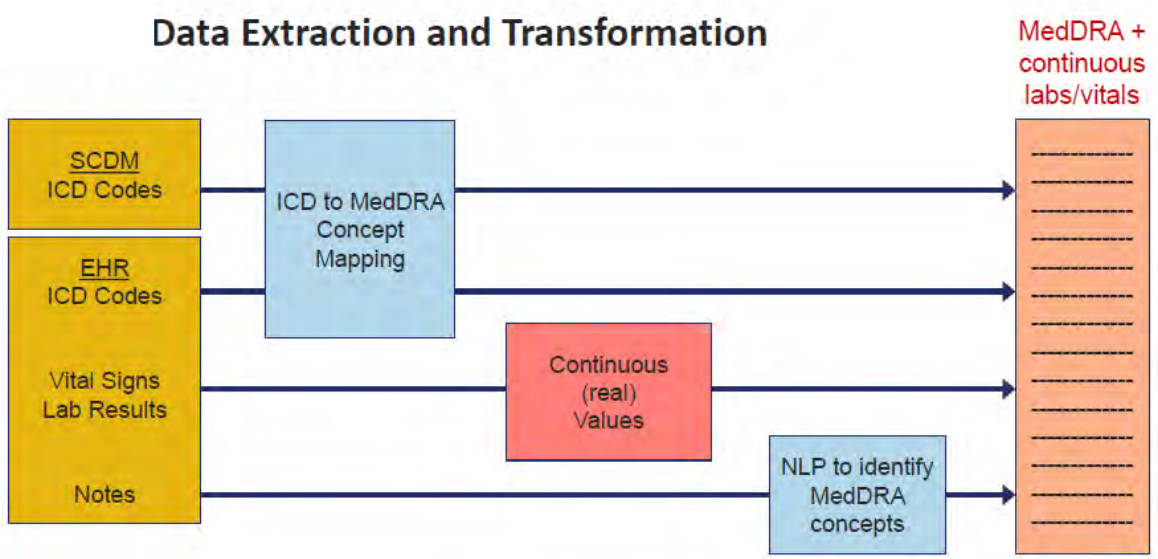
Expand Signal Detection Capabilities Incorporating EHR Data Elements (DA2, PIs: J. Smith, S. Wang)

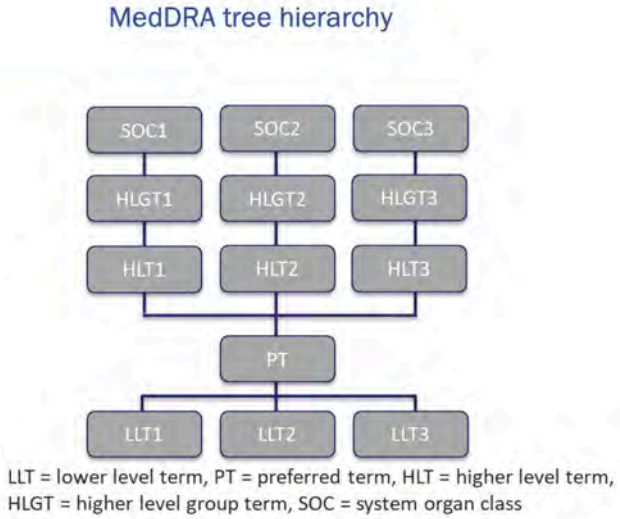
5. Expanding signal detection capabilities by incorporating EHR data elements

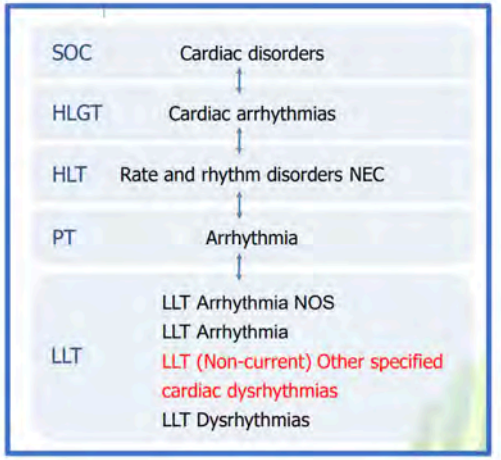
Empirical evaluation of detection analytic methods using structured and unstructured EHR data

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

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







Unstructured, Semi-structured

Structured in MedDRA hierarchy

Demonstration Project: DA2 (PI J. Smith, S. Wang)

5. Expanding signal detection capabilities by incorporating EHR data elements

Using the **Development Network (MGB site)** we expanded the **TreeScan** approach that identifies drug safety signals **to clinically rich yet non-hierarchical EHR data**.

ARIA need: The widely-accepted TreeScan approach to identify drug safety signals cannot be applied to unstructured data that have no hierarchical data structure.

Methods: In a PS-stratified cohort comparing sulfonylurea and DPP4i, outcomes were measured using diagnoses, lab results, and NLP extracted concepts that were mapped to hierarchical MedDRA terminology. Statistical alerting patterns with different specifications of the outcome tree (with and without EHR data) and tree-based scan statistic analysis (binomial, Poisson, Gaussian) were compared using newly developed software packages.

Results:

- The population size from one Development Network site was too small to detect expected signals in claims.
- Adding EHR notes and labs, the top alert was headache, a non-specific symptoms related to hypoglycemia.
- The analysis was underpowered in a single development network site.

Results:

Statistical alerts for sulfonylurea vs DPP4i using claims, claims + notes

		Billing-code data						NLP					
Node description	Node type	Rank	Obs	Exp	RR	LRT	p	Rank	Obs	Exp	RR	LRT	p
Headaches	HLGT	611	7	16.99	0.41			1	66	10.19	6.48	16.45	0.05
Headache	PT	118	7	16.99	0.41			2	66	13.35	4.94	8.64	0.60
Ancillary infectious topics	HLGT							3	17	6.90	2.46	8.52	0.61
Headaches NEC	HLT	385	7	16.99	0.41			4	65	13.35	4.87	8.35	0.64
Tremor	PT							5	29	13.26	2.19	8.21	0.66
Tremor (excl congenital)	HLT							6	29	13.26	2.19	8.08	0.68
Gastrointestinal signs and symptoms	HLGT	606	13	0.00				7	63	24.72	2.55	7.99	0.69
Clostridia infections	HLT	334	1	0.00				8	7	5.58	1.25	6.88	0.86
Hepatomegaly	PT							9	3	1.90	1.58	6.64	0.90
Anaemia	PT	8	3	0.75	4.00	0.67	1.00	10	31	7.06	4.39	5.12	0.99
Cardiovascular disorder	PT							11	7	4.98	1.41	5.04	0.99
Anaemias NEC	HLT	9	3	0.75	4.00	0.67	1.00	12	32	8.95	3.57	4.95	0.99
Appetite and general nutritional disorders	HLGT	1	5	2.04	2.45	6.51	0.49	308	43	33.92	1.27	0.38	1.00
Cardiac disorders	SOC	2	22	5.00	4.40	3.83	0.82	29	47	24.15	1.95	3.56	1.00
Acute kidney injury	PT	3	2	0.75	2.67	2.30	0.96	336	36	21.64	1.66	0.31	1.00
Skin injury	PT	4	4	1.90	2.11	2.27	0.97	116	7	4.29	1.63	1.53	1.00
Vascular disorders	SOC	5	17	7.29	2.33	1.99	0.98	321	31	22.15	1.40	0.36	1.00
Cardiac disorders, signs and symptoms NEC	HLGT	6	16	14.23	1.12	1.89	0.98	30	56	30.13	1.86	3.50	1.00
Back pain	PT	7	2	0.75	2.67	0.75	1.00	212	49	24.04	2.04	0.76	1.00
Skin and subcutaneous tissue infections and infestations N	HLGT	10	3	1.41	2.13	0.63	1.00	516	19	12.16	1.56	0.09	1.00
Bacterial infections NEC	HLT	11	5	1.41	3.55	0.48	1.00	442	27	15.03	1.80	0.16	1.00
Non-site specific injuries NEC	HLT	12	6	5.88	1.02	0.45	1.00	211	39	20.04	1.95	0.78	1.00
Hypoglycaemia	PT							111	23	7.43	3.10	1.56	1.00

Obs = observed; Exp = expected; RR = relative risk; LRT = likelihood ratio test; NLP =natural language processing

Conclusion

5. Expanding signal detection capabilities by incorporating EHR data elements

We demonstrated how Sentinel now, can use free text notes and lab test results to generate hypotheses about unsuspected adverse effects of medical products using Tree Scan.

Impact:

- FDA Sentinel now has a method available to include free text notes to scan for adverse events

Project: Data characterization using health information exchanges (DI8, PIs Rishi Desai & Anjum Khurshid)

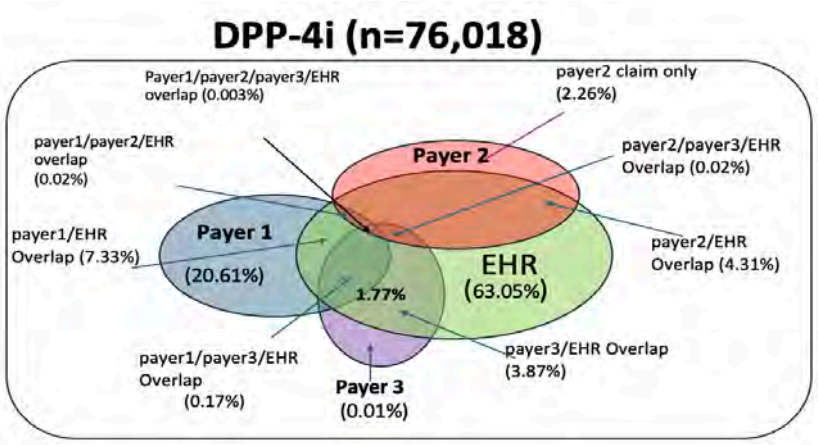
Most EHR or claims data sources are either provider-centric or insurer-centric. **Health Information Exchanges (HIEs)** may provide an opportunity to assemble a large-scale patient-centric data asset for Sentinel.

ARIA need: ARIA queries will benefit from patient-centric data sources to provide comprehensive health status information.

Methods: Working closely with the MyHealth Access Network HIE of Oklahoma, we illustrated how a query could be implemented in a patient-centric EHR+claims data environment.

Results: We were able to identify a cohort of patients with Type-2 diabetes who started either an DDP-4 or SGLT-2 inhibitor. EHR data completeness in HIEs was superior to typical provider-centric data.

MyHealth ACCESS NETWORK



Selected Patient Characteristics	MyHealth Access Network	
OK total population = 4 million	**DPP-4i users with T2DM**	**SGLT-2i users with T2DM**
Total count	**76,018**	**101,599**
Female	49.4%	44.9%
Black or African American	5.4%	6.7%
White	47.2%	57.2%
Hispanic/Latino ethnicity (N, %)	8.5%	7.5%
HbA1c recorded , % N (%)	50%	57.2%
HbA1c (mean, SD)	7.9 ± 1.7	8.2 ± 1.9
Serum creatinine recorded, mg/dL N(%)	61.9%	67.2%
Serum creatinine (mean, SD)	1.3 ± 1.0	1.1 ± 0.6
eGFR recorded, ml/min N(%)	26.6%	28.4%
eGFR (mean, SD)	59.1 ± 27.4	66.7 ± 26.2
Ejection Fraction recorded, % N(%)	4.3%	5.1%
Ejection Fraction (mean, SD)	54.1 ± 14.2	51.9 ± 15.7
Total cholesterol recorded, mg/dL N(%)	44.4%	51.4%
Total cholesterol (mean, SD)	168.6 ± 46	169.4 ± 48.3
LDL recorded, mg/dL N(%)	49.8%	54.2%
LDL (mean, SD)	89.5 + 36	91.1 + 38.8
Triglycerides recorded, mg/dL N(%)	45.1 %	51.4%
Triglycerides (mean, SD)	182.4 + 93.2	184.5 + 95.2
BMI recorded, kg/m2 N(%)	28.4%	45.9%
BMI (mean, SD)	33.4 + 8.0	34.1 + 8.1
Systolic BP, mmHg N(%)	32.4%	50.6%
Systolic BP (mean, SD)	134.1 + 19.5	132.7 + 18.8

Conclusion

- By proactively partnering with the state HIE from Oklahoma, we demonstrated initial feasibility of leveraging this patient-centric and rich EHR data resource
- We were able to conduct descriptive analysis of medication use mimicking Sentinel queries.
- HIEs are promising resources for a potential partnership with Sentinel in the future to bring in timely EHR data that are population-based and patient-centric.

Summary

Overall Impact of the RWE-DE on Future ARIA Requests

- The large-scale data infrastructure of the RWE-DE where EHRs are linked to claims data is now established :
  - It offers visibility into additional clinical information not available in claims.
  - It can improve the validity of studies of medical products in clinical practice.
  - It addressed some ARIA insufficiencies related to availability and measurement of certain study variables.
- Rapid free text queries are enabled by a metadata table supporting all use cases
- The RWE-DE is ready for use and further growth
- Integration of the RWE-DE into FDA ARIA sufficiency determinations is under development

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Thank You!

Sentinel

Sentinel Operations Center

16th Annual Sentinel Initiative Public Workshop

November 7, 2024

Disclaimers

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

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

CCEB | Perelman School of Medicine University of Pennsylvania

Agenda

1 Regulatory Highlights

2 Signal Identification in the Sentinel System

3 Evaluating Risks of Cannabis Use and Evidence for Medical Cannabis Benefits

4 Expansion of Sentinel Tools

Regulatory Highlights

1. Sentinel and ARIA Year-in-Review

2. Serious Infection Following Ustekinumab Use in Patients with Crohn's Disease
   FDA Lead: Joel Weissfeld, MD, MPH

3. Incidence of Interstitial Lung Disease among users of Vedolizumab or Natalizumab
   FDA Lead: Sally Peprah, PhD

4. Use of Armodafinil or Modafinil During Pregnancy and Risk of Non-cardiac Congenital Malformations in the Infant
   FDA Lead: Catherine Callahan, MA, PhD

5. Pediatric and Adult Utilization of Methotrexate Injectable Products – Rapid SDD and TriNetX
   FDA Lead: Grace Chai, PharmD, MPH

6. Utilization of Schedule II Stimulant Medications
   FDA Lead: Rose Radin, MPH, PhD

7. Prenatal and Congenital Syphilis in the US: Characterizing Screening and Treatment
   FDA Leads: Sarah Dutcher, PhD & Dave Moeny, RPh, MPH

FY2024 Sentinel Analyses

Analysis Type	Total
Sentinel Distributed Database	
Descriptive	49
Inferential	12
Signal Identification	6
Additional EHR Data Sources	
Descriptive	15
Total	82

82 reports posted to the Sentinel website

20 analytic packages shared with the public on the Sentinel website

19 manuscripts published

41 posters/podium presentations at scientific meetings

Analyses are assigned to years based on analytic package distribution date

FY2020-FY2024 Sentinel Analyses

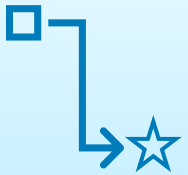
Analysis Type	Total
Sentinel Distributed Database	
Descriptive	228
Inferential	51
Signal Identification	13
Additional EHR Data Sources	
Descriptive	96
Total	**388**

Over the past 5 years, Sentinel monitored **346 new safety concerns**, increasing the program's total from 243 to **589 (142% increase)**

57 analytic packages shared with the public

24 sponsor notification letters supported

297 work products posted, including **96 manuscripts**



67 statements of study impact shared with the public

284 reports posted

Analyses are assigned to years based on analytic package distribution date

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

Product	Approval Date	# Ongoing/Completed ARIA Analyses	Status
Ablysinol (dehydrated alcohol)	06/21/2018	3	☑
Stelara (ustekinumab)	10/18/2019	4	☑
Sinuva (mometasone sinus implant)	12/08/2017	8	☑
Invokana (canagliflozin)	10/29/2018	2	📊
Annovera (segesterone estradiol)	09/10/2018	3	🔍
Gimoti (metoclopramide nasal spray)	06/19/2020	2	🔍
Tremfya (guselkumab)	07/13/2017	3	🔍
Ilumya (tildrakizumab)	03/20/2018	3	🔍
Skyrizi (risankizumab)	04/23/2019	3	🔍
Siliq (brodalumab)	02/15/2017	3	🔍
Ibsrela (tenapanor)	09/12/2019	2	🔍

Status Key

☑ = Complete

📊 = Inferential Analysis Phase

🔍 = Monitoring Ongoing

FDCA = Federal Food, Drug, and Cosmetic Act
ARIA = Active Risk Identification and Analysis System

Additional Sentinel Analyses Assessing Safety Concerns Identified Prior to Product Approval

Product	Approval Date	# Ongoing/Completed ARIA Analyses	Status
Brexafemme (ibrexafungerp)	06/01/2021	4	
Mounjaro (tirzepatide)	05/13/2022	1	
Olumiant (baricitinib)	06/13/2022	1	
Rinvoq (upadacitinib)	03/12/2022	1	
Litfulo (ritlecitinib)	06/23/2023	1	

Status Key

= Complete

= Inferential Analysis Phase

= Monitoring Ongoing

ARIA = Active Risk Identification and Analysis System

Serious Infection Following Ustekinumab Use in Patients with Crohn's Disease

- Human IL-12/IL-23 monoclonal antibody
- Sept 2016 - Approved for Crohn's Disease (CD)
- ARIA considered sufficient to assess risk of serious infection with ustekinumab treatment

Risk Of Serious Infection With Use Of Ustekinumab vs. Comparator (Adalimumab, Infliximab Or Vedolizumab) In Patients With Crohn's Disease

6 Data Partners in the Sentinel Distributed Database (SDD), including CMS Medicare and Medicaid

October 2016 - June 2023

New users of ustekinumab or comparator

No prior use of ustekinumab among comparators

Evidence of CD without other indications[1]

No HIV/AIDS or organ transplantation

Outcomes

Hospitalization for serious infection[2] or COVID-19 infection

Serious infection: composite of seven individual infections

Acute meningitis, acute osteomyelitis, bacteremia, gastrointestinal infection, pneumonia, pyelonephritis, and skin and soft tissue infection

Outpatient infection that leads to hospitalization

COVID-19 infection: code in principal diagnosis position of inpatient stay

Individual infections also assessed separately

Follow-up until earliest of outcome, death, end of exposure episode, switch to other study drugs or biologics/small molecule drugs, disenrollment, or Data Partner data end date

Confounding adjustment

Inverse probability of treatment weighting (IPTW) estimating average treatment effect among the treated (ATT), 1% weight truncation

Sensitivity: Propensity score matching (1:1 fixed ratio, caliper 0.05)

Statistical analysis

Estimate hazard ratios and 95% confidence interval (CIs)

Subgroups: Treatment experienced (yes/no)

Before / after start of COVID-19 pandemic (Apr 1, 2020)

[1]Other indications include ulcerative colitis, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile rheumatoid arthritis, hidradenitis suppurativa and uveitis

[2]Lo Re V, 3rd, Carbonari DM, Jacob J, et al. Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. Pharmacoepidemiol Drug Saf. 2021;30(7):899-909. DOI: 10.1002/pds.5253

Serious Infection Following Ustekinumab Use in Patients with Crohn's Disease

~330 million patients →

Age ≥ 18 years with pre-index enrollment
71,601 potential new ustekinumab (U) users
367,751 potential new comparator (C) users

↓

Comparative analysis cohort: After implementation of all selection criteria & inclusion of earliest eligible exposure episode

Overall	U: 15,565 patients, C: 52,109 patients
Before 1 April 2020	U: 8,545 patients, C: 34,445 patients
On and after 1 April 2020	U: 9,057 patients, C: 20,498 patients

Baseline Demographic and Clinical Characteristics

Overall comparators (52,109):

Adalimumab (20,665), infliximab (17,739) and vedolizumab (13,705) users

U > C
more likely older and female, with more new users over time

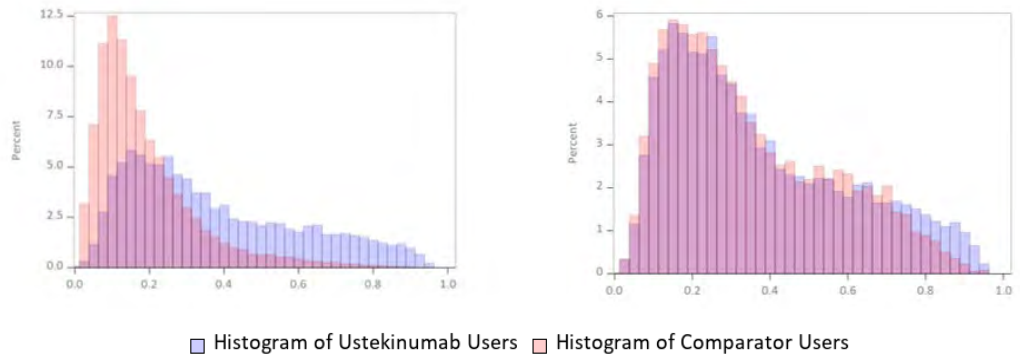
U > C
more markers of CD severity (anemia, colitis, intestinal obstruction and fistula)

Pre-index biologic or small molecule drug i.e., treatment experienced:	U – 6,478 users (41.6%) C – 6,467 users (12.4%)

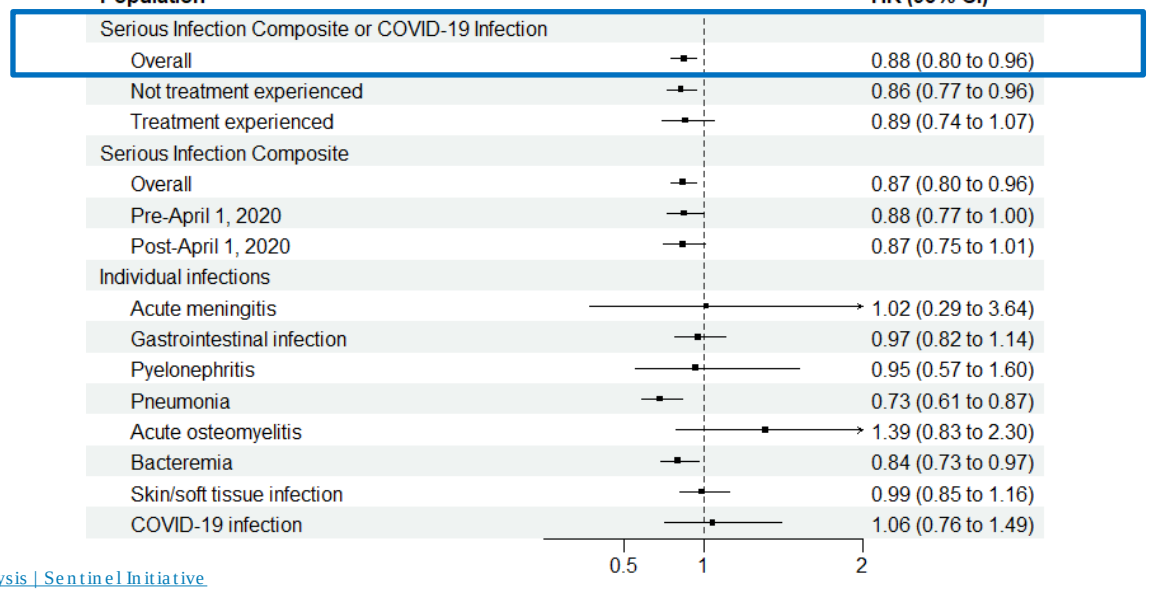
Propensity score distribution – Overall population

(A) Before IPTW weighting

(B) After IPTW weighting



Risk of outcomes among new users of ustekinumab vs comparators



Serious Infection Following Ustekinumab Use in Patients with Crohn's Disease: An Inverse Probability of Treatment Weighting Analysis | Sentinel Initiative
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/ustekinumab-dispensing-patterns-descriptive-analysis;
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/serious-infection-following-ustekinumab-use-patients-crohn-s;
https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/ustekinumab-and-comparator-treatment-utilization-and

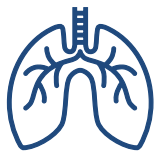
Incidence of Interstitial Lung Disease Among Users of Vedolizumab or Natalizumab

Concerns regarding interstitial lung disease (ILD) and vedolizumab – identified through Periodic Safety Reports from reporting period 05/20/21 to 05/19/22

- The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended updating the summary of product characteristics (SmPC) for vedolizumab based on its evaluation of ILD cases identified from the Sponsor's internal database

June 29, 2021 → SmPC update included ILD under Undesirable Effects (section 4.8) based on PRAC recommendation

January 3, 2023 → FDA opened a Newly Identified Safety Signal (NISS; SSID# 1004988)



August 2023 – March 2024 → Division of Epidemiology I conducted descriptive study using Sentinel Distributed Database (SDD)

Objectives

1. Assess incidence rate of ILD among patients with inflammatory bowel disease (IBD) and treated with vedolizumab or natalizumab
2. Assess background incidence rate of ILD among:
   a) All patients with IBD
   b) All patients with IBD excluding those with a history of vedolizumab or natalizumab exposure
   c) All patients with IBD with a history of advanced therapies other than integrin receptor antagonists.

https://www.sentinelinitiative.org/studies/drugs/entyvio-vedolizumab-and-tysabri-natalizumab

Incidence of Interstitial Lung Disease Among Users of Vedolizumab or Natalizumab

Retrospective Cohort Study

Data from six SDD Data Partners

01/06/2006 – 04/30/2023

Two descriptive queries to assess ILD incidence rates

1. Vedolizumab or natalizumab users – required to have no history of vedolizumab or natalizumab use in previous six months (i.e., 183 days) prior to index exposure
2. Patients with a history of using other advanced therapies* – required to have no history of using therapies in previous six months (i.e., 183 days) prior to index exposure

IBD Patient Type	Number of Patients	Mean Age (Standard Deviation), Years	Percent Female	Number of ILD Events	Patient-Years (PYs)	Incidence Rate per 10,000 PYs (95% CI)
All	2,460,987	57.3 (14.6)	58.9%	124,385	7,854,231	158.37 (157.49, 159.25)
All except patients with any history of vedolizumab/natalizumab	2,439,541	57.4 (14.6)	59.0%	122,636	7,708,427	159.09 (158.21, 159.99)
All with history of other advanced therapies*	296,808	45.1(14.4)	54.5%	8,673	766,661	113.13 (110.77, 115.53)
Initiated and actively used vedolizumab	42,364	51.7 (14.2)	54.8%	630	57,532	**109.51** (101.28, 118.40)
Initiated and actively used natalizumab	754	45.4 (12.8)	71.5%	**	**	**73.94** (30.78, 177.65)
Initiated and actively used other advanced therapies*	134,061	45.9 (14.4)	55.9%	2,819	277,453	**101.60** (97.92, 105.42)

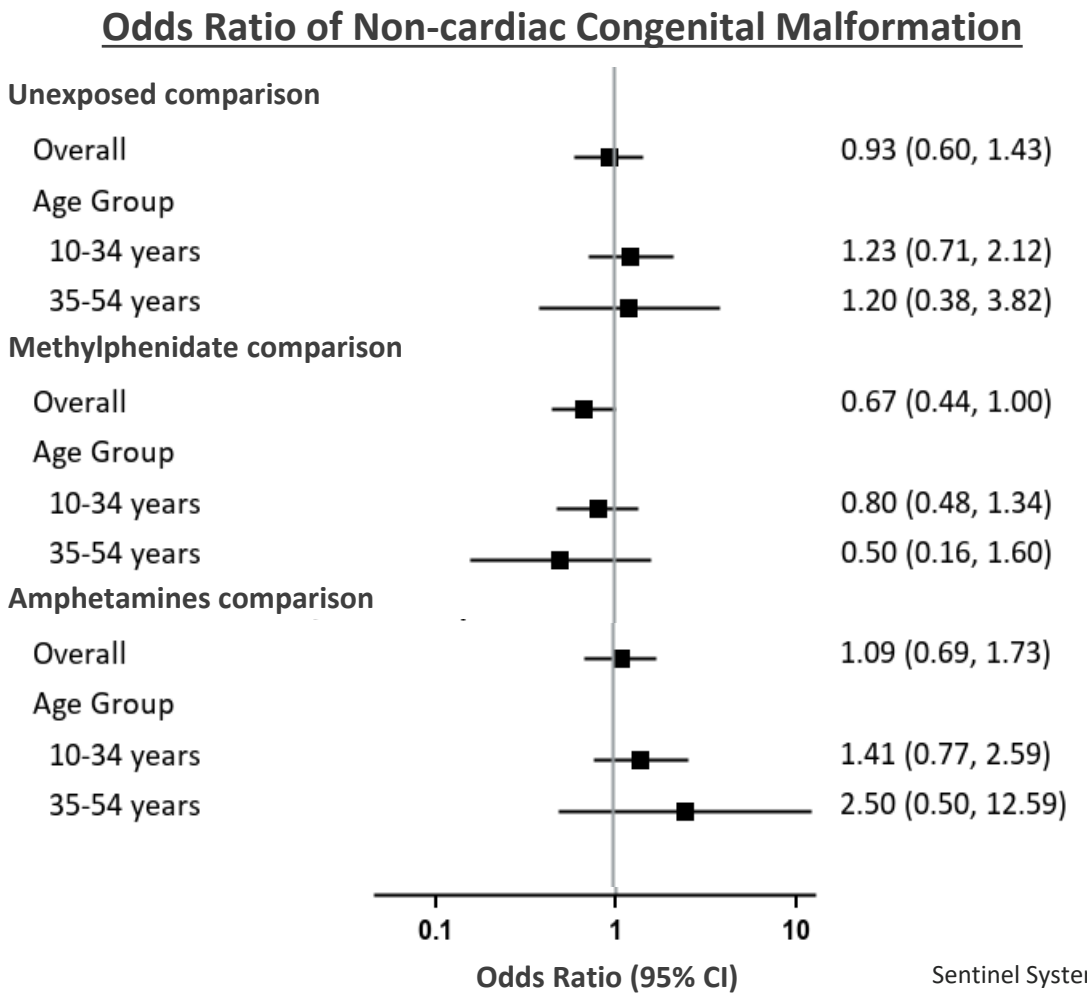
April 18, 2024 → **FDA-approved labeling update to add 'interstitial lung disease, pneumonitis' into the Postmarketing Experience subsection of the Prescribing Information, based largely on FDA Adverse Event Reporting System case data**

*Other advanced therapies comprised infliximab, adalimumab, certolizumab, golimumab, ustekinumab, risankizumab, mirikizumab, ozanimod, etrasimod, tofacitinib, or upadacitinib
** Data not presented due to a small sample size or to prevent recalculation through the cells presented.

Use of Armodafinil or Modafinil During Pregnancy and Risk of Non-cardiac Congenital Malformations in the Infant

Previous studies of in utero exposure to armodafinil/modafinil and prevalence of major congenital malformation (MCMs) have been inconsistent and limited by small sample size. Prior Sentinel work found no association between armodafinil/modafinil and cardiac MCMs.

- Mothers with at least one live-birth delivery linked to infants.
- Exposed to **armodafinil or modafinil** or **methylphenidate, amphetamines** or none of these products in the first trimester.
- 1:1 matched on propensity score.



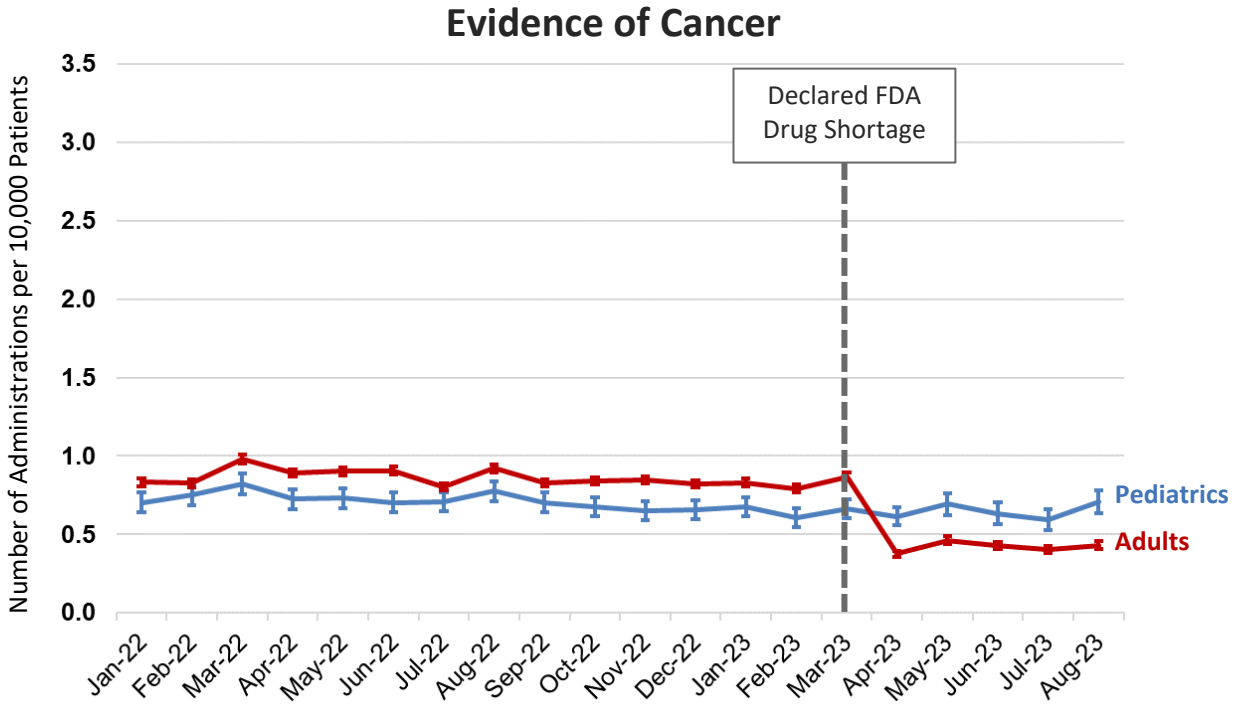
Pediatric and Adult Utilization of Methotrexate Injectable Products Rapid SDD Analysis

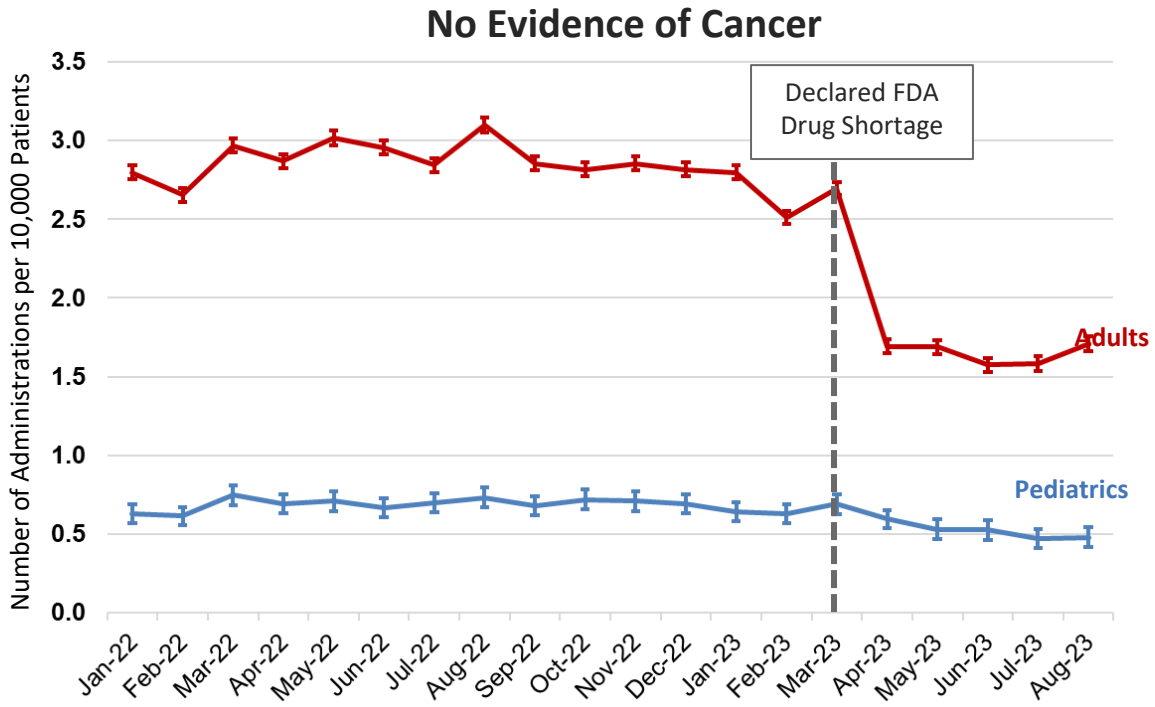
Background: In March 2023, FDA declared a shortage of methotrexate injectable products. FDA was asked to investigate the potential effects of the shortage in response to a public inquiry.

Study Question: How often was injectable methotrexate used in hospitals or outpatient clinics from January 2022 through August 2023, by age and cancer indication?

Results: Among adults in the rapid SDD, injectable methotrexate use appears relatively steady before a sharp and sustained decline in April 2023 (a greater decline was observed among patients without evidence of cancer).

Among pediatric patients in the rapid SDD, injectable methotrexate use appears relatively steady through August 2023 (except for a slight steady decline after April 2023 among patients without evidence of cancer).



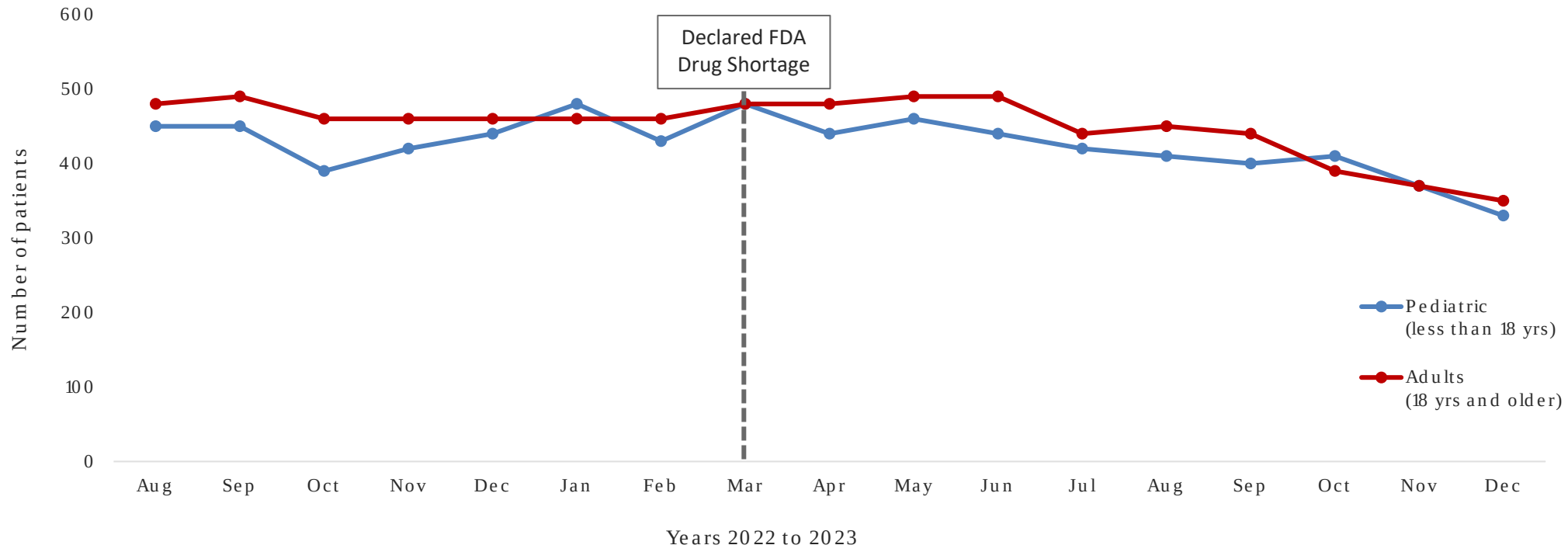


https://www.sentinelinitiative.org/studies/drugs/individual-drug-analyses/utilization-methotrexate-descriptive-analysis

Pediatric and Adult Utilization of Methotrexate Injectable Products TriNetX Analysis

Study Question: What are the trends in injectable methotrexate usage over time, by age group?

Results: Trends in procedures for injected methotrexate follow similar patterns in the TriNetX EHR data as the rapid SDD, however the decline over time in 2023 is less distinct in EHR.



Utilization of Schedule II Stimulant Medications

Background: Dispensing of schedule II (C-II) stimulant medications to adults has increased since 2000 and accelerated during the COVID-19 pandemic. FDA seeks to increase its understanding of changes in utilization of C-II stimulants and potential implications for safety.

Study purpose: Provide foundational data to inform potential, future inferential studies of safety.

1. What are the baseline characteristics and utilization patterns of adult patients starting C-II stimulant medications?
2. How do the baseline characteristics and utilization patterns of patients differ between the pre-pandemic and pandemic eras?

Data Source

7 commercial health plans and Medicare Fee-for-Service

Study Periods

Overall: Jan 2017 - March 2023

Pre-pandemic: April 2018 - March 2020

Pandemic: April 2020 - March 2022

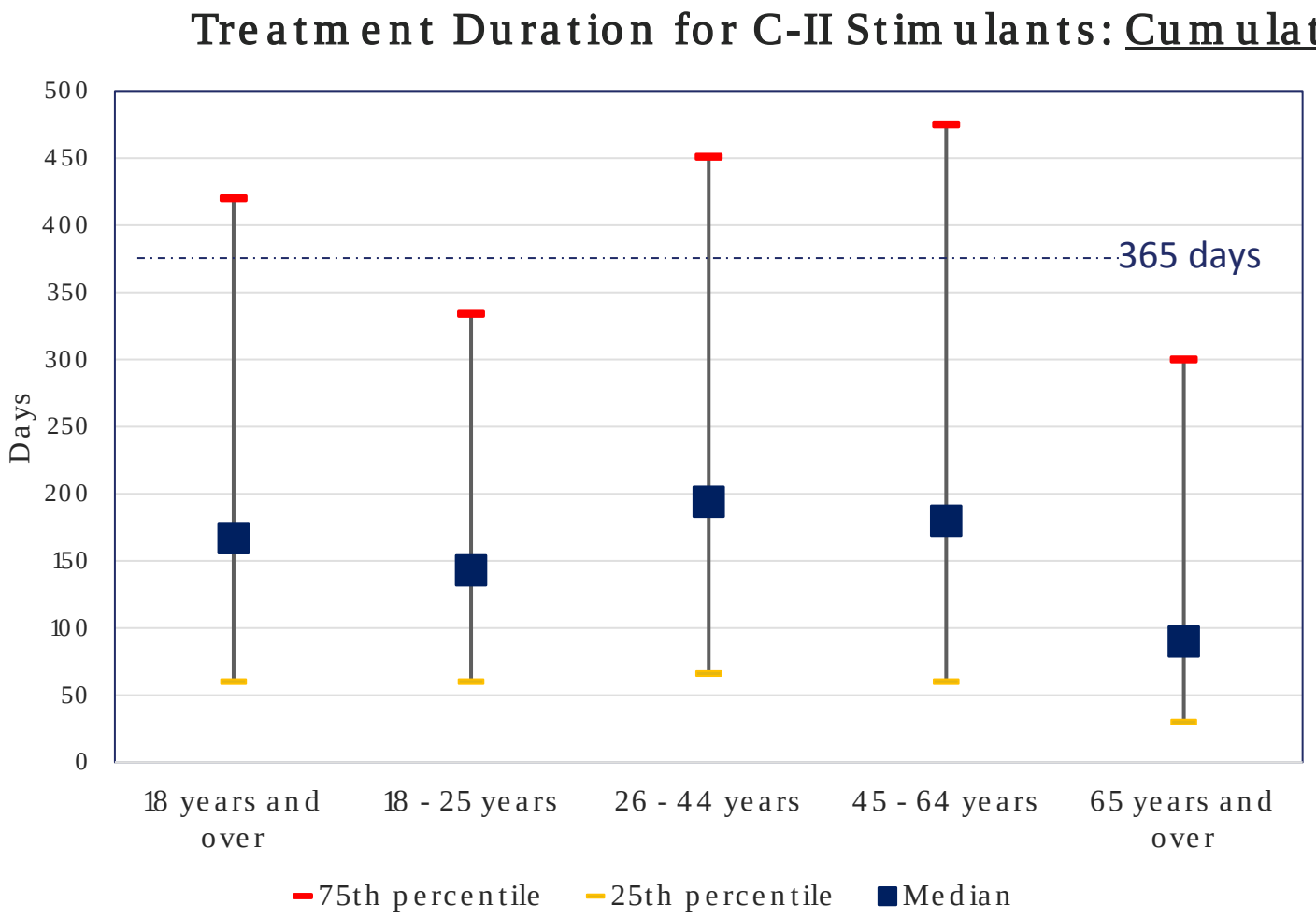
Recent time: April 2022 - March 2023

Exposure

New dispensing for C-II stimulant, including **amphetamine/dextroamphetamine, lisdexamfetamine, methylphenidate, and others.**

These medications are approved for attention deficit hyperactivity disorder (ADHD); some are also approved for narcolepsy or binge-eating disorder.

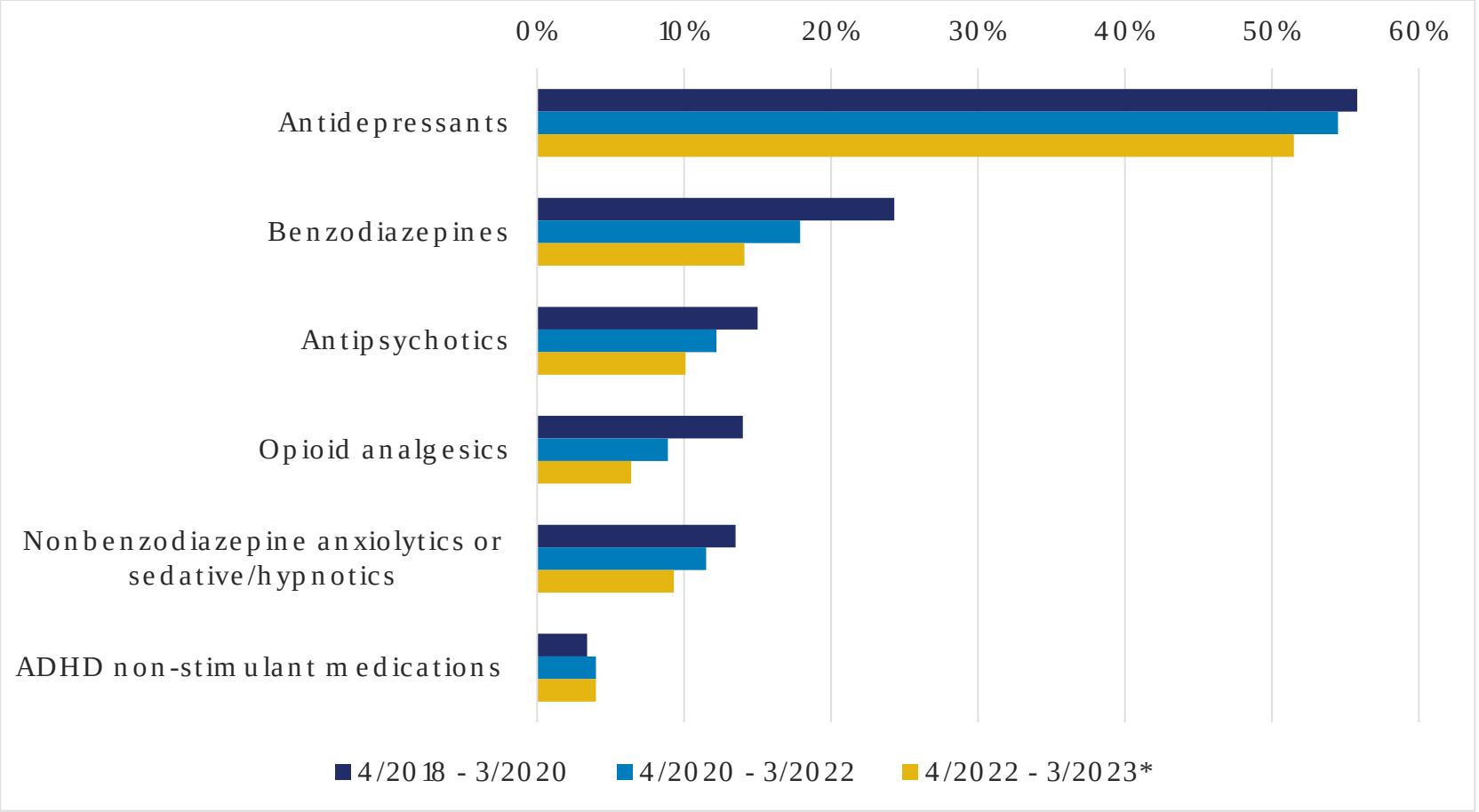
Utilization of Schedule II Stimulant Medications



Adult patients with new use of C-II stimulant medications, Sentinel Distributed Database, 1/1/2017-3/31/2023

Utilization of Schedule II Stimulant Medications

Concomitant Psychoactive Medications & C-II Stimulants in Adults, April 2018 - March 2023



Cautious interpretation of the observed numerical decreases is warranted

- The cohorts differed in their demographic composition (later cohorts had more female patients, younger average age)
- The last period allowed less time for patient follow-up (i.e., 12 months vs 24 months) due to data availability

Pharmacy claims from date of first dispensing of C-II stimulant medications to end of C-II stimulant medication days' supply among 897,333 adults with commercial insurance or Medicare Fee-For-Service in Sentinel Distributed Database.
Concomitant medications defined as at least seven days' supply overlapping with C-II stimulant days' supply. ADHD = attention deficit hyperactivity disorder.
*12-month period, due to data availability, allowed less time for assessing concomitant use.

Prenatal and Congenital Syphilis in the US: Characterizing Screening and Treatment

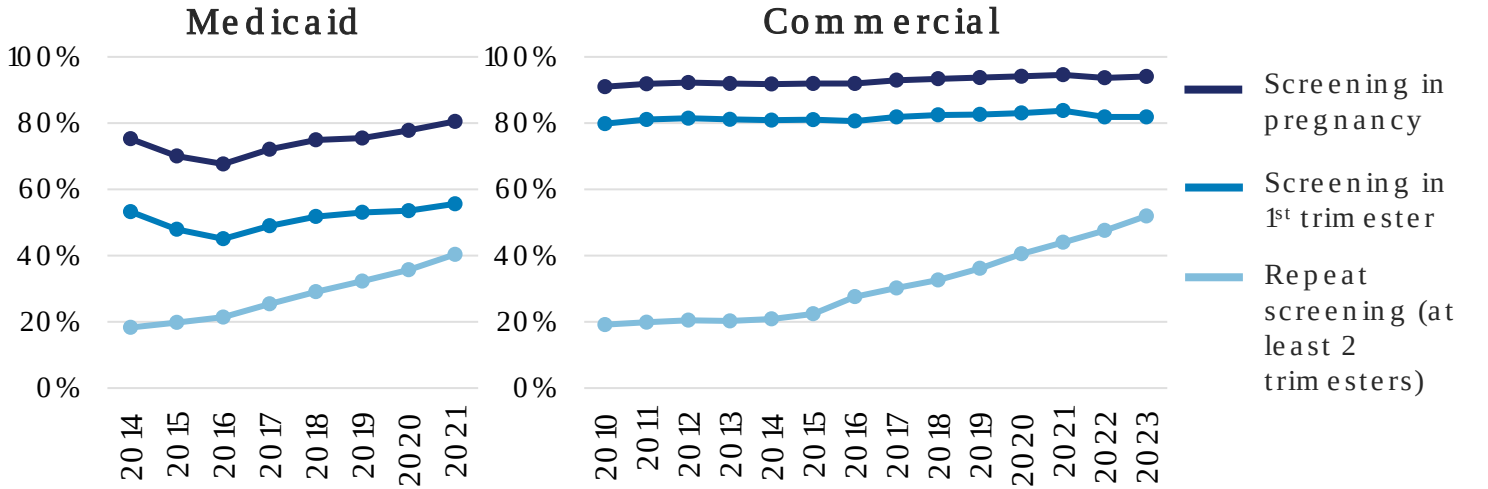
Objective: To assess syphilis screening and treatment during pregnancy among publicly and commercially insured pregnant individuals and their infants in the US

Problem: Incidence of congenital syphilis has risen nearly 1000% in the U.S. since 2011. Congenital syphilis is preventable with timely screening and treatment in pregnancy.

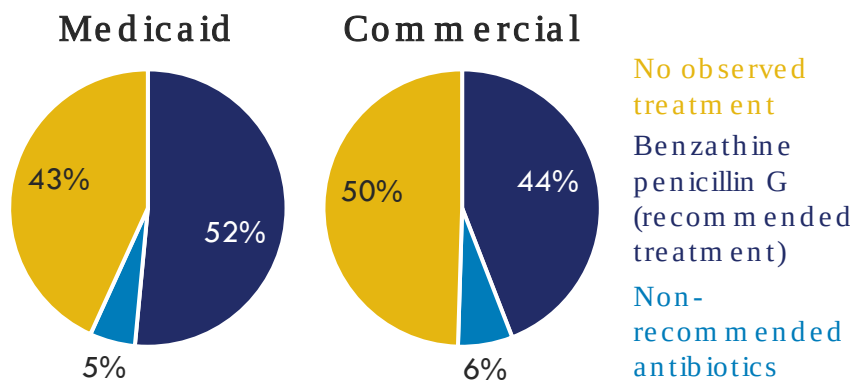
Findings: Syphilis screening in pregnancy is not meeting recommendations and substantial differences are evident by insurance status. Recommended repeat screening during pregnancy is increasing over time. Additional data are necessary to better understand treatment gaps observed in insurance claims.

	Medicaid 2014-2021	Commercial 2010-2023
N live birth deliveries	2,691,021	3,479,840
First screening in pregnancy		
In 1st trimester	51.8%	81.7%
In 2nd trimester	17.1%	9.1%
In 3rd trimester	6.3%	1.6%
At delivery or within 1 week	0.3%	0.4%
No screening in pregnancy	24.8%	7.2%

Syphilis Screening in Pregnancy



Syphilis Treatment in Pregnancy



Signal Identification in the Sentinel System

Sentinel's Growing Contributions to Signal Identification for Broad Screening

Signal identification is the detection of new and unsuspected potential safety concerns. Sentinel's TreeScan® software facilitates:

1. Screening of numerous health outcomes that occur after exposure to a medical product
2. Clinical review and/or epidemiology safety study following identification of an alert
3. The four queries in the table represent signal identification analyses where self-controlled or active-comparator designs were used to monitor alerts

Product Assessed	Product Approval Date	Study Design	Actionable Alerts Detected?
Tremfya (guselkumab)	July 13, 2017	Self-Controlled Risk Interval	• Pending
Tremfya (guselkumab)	July 13, 2017	Active Comparator	• None
Skyrizi (risankizumab-rzaa)	April 23, 2019	Self-Controlled Risk Interval	• **Calculus of gallbladder without cholecystitis**
Skyrizi (risankizumab-rzaa)	April 23, 2019	Active Comparator	• None

Next Steps After Detecting a Statistically Significant Alert for Risankizumab-rzaa

Signal Identification Alert case study: Risankizumab-rzaa

- Human IL-23A monoclonal antibody
- Apr 2019 - Approved for moderate-to-severe plaque psoriasis
- Assessed in Sentinel using a Self-Controlled Risk Interval Design
- Detected statistically significant alert for calculus of gallbladder without cholecystitis

Risankizumab Signal Identification – Patient Episode Profile Retrieval (PEPR)

Medicare Data Partner in the Sentinel Distributed Database (SDD)

April 2019 - March 2023

New users of risankizumab

No evidence of ongoing pregnancy or live-birth delivery in the [-183, 28] and [-56, 28] days around index, respectively

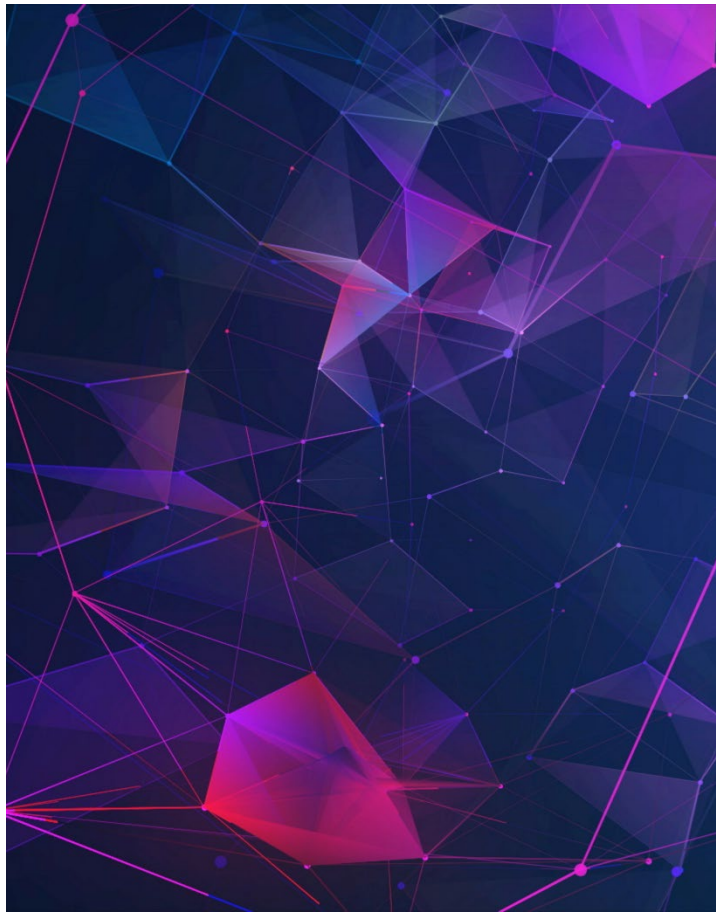
Cases of gallstones in risk window (9-11 days)

PEPR

De-identified, chronological line list of all Sentinel Common Data Model (SCDM) records (medical and pharmacy claims, clinical information) associated with a particular patient

Results

Calculus of gallbladder without cholecystitis was followed up with a Patient Episode Profile Retrieval and was ***determined to be incidental to orders for radiology in support of hospitalization for more serious events.***



Evaluating Risks of Cannabis Use and Evidence for Medical Cannabis Benefits

1. **Medical Literature and Data on Cannabis Use**

   FDA Leads: David Moeny, RPh, MPH & Trish Bright, PhD, MSPH

2. **Trends in Encounters for Substance Poisonings in the US, 2016-2022**

   FDA Lead: Silvia Perez-Vilar, PhD, Pharm D

3. **Trends in Cannabis-Related Encounters in the US, 2017-2022**

   FDA Lead: Silvia Perez-Vilar, PhD, Pharm D

Medical Literature and Data on Marijuana Use

Collaboration

FDA U.S. FOOD & DRUG ADMINISTRATION

Sentinel

Consortium for Medical Marijuana Clinical Outcomes Research

Motivation

Foundational to a **review of marijuana classification as a Schedule I substance** under the United States Controlled Substances Act (CSA) **via eight-factor analysis**

Objectives

1. Critically evaluate and interpret the controlled observational and controlled interventional study literature evaluating the effectiveness and safety of marijuana for several therapeutic indications.

2. Critically evaluate harms, or adverse events, associated with non-medical use and use of uncertain intent of marijuana relative to comparator substances or to no marijuana use within controlled observational studies.

Key Conclusions

- Marijuana exposure measurement strategies in observational studies do not necessarily capture actual marijuana use, dosage, nor cumulative exposures
- "Lifetime use" marijuana exposure definition is problematic for assessing causality
- Marijuana effectiveness varied by therapeutic indication
- Generally, evidence quality was not sufficient to support causal conclusions about the effect of marijuana on harm outcomes relative to comparators

https://www.whitehouse.gov/briefing-room/statements-releases/2022/10/06/statement-from-president-biden-on-marijuana-reform/
https://www.dea.gov/sites/default/files/2024-05/2016-17954-HHS.pdf
https://www.sentinelinitiative.org/methods-data-tools/methods/medical-literature-and-data-cannabis-use

Trends in Encounters for Substance Poisonings in the US, 2016-2022

Background

Several states and territories enacted laws allowing medical or both medical and adult (recreational) use of cannabis[†]

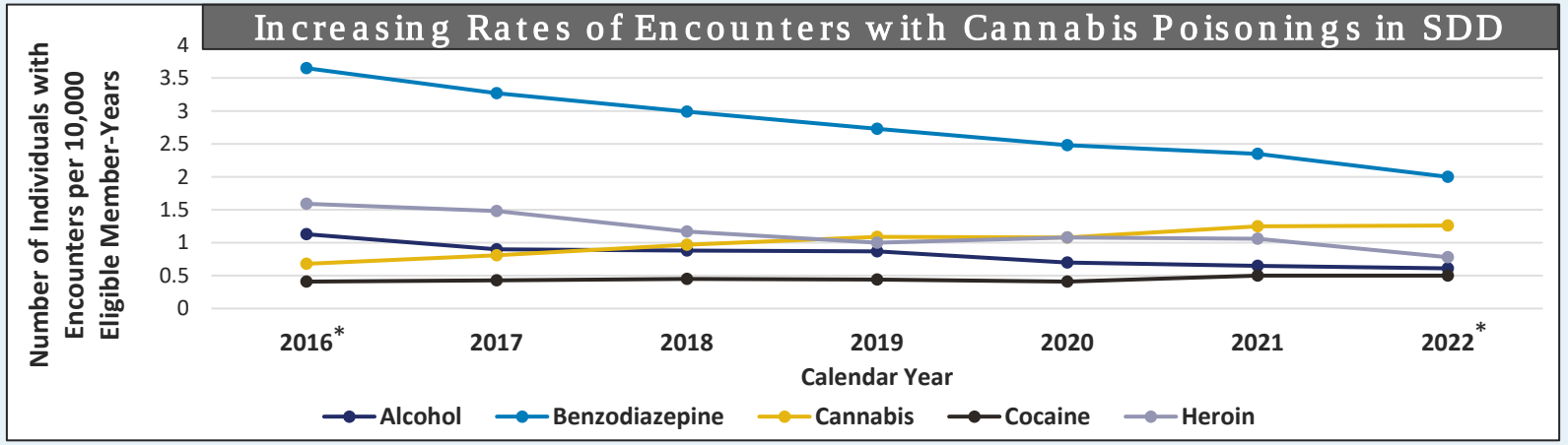
Goal: Describe healthcare encounters for poisonings related to use of cannabis and other select substances among commercially insured individuals aged 18-64 years, 2016-2022

Methods

- Descriptive study in Sentinel Distributed Database (SDD)
- 9 Sentinel Data Partners
- Substances included:
  - cannabis, cocaine, alcohol, heroin, and benzodiazepines

Key Results

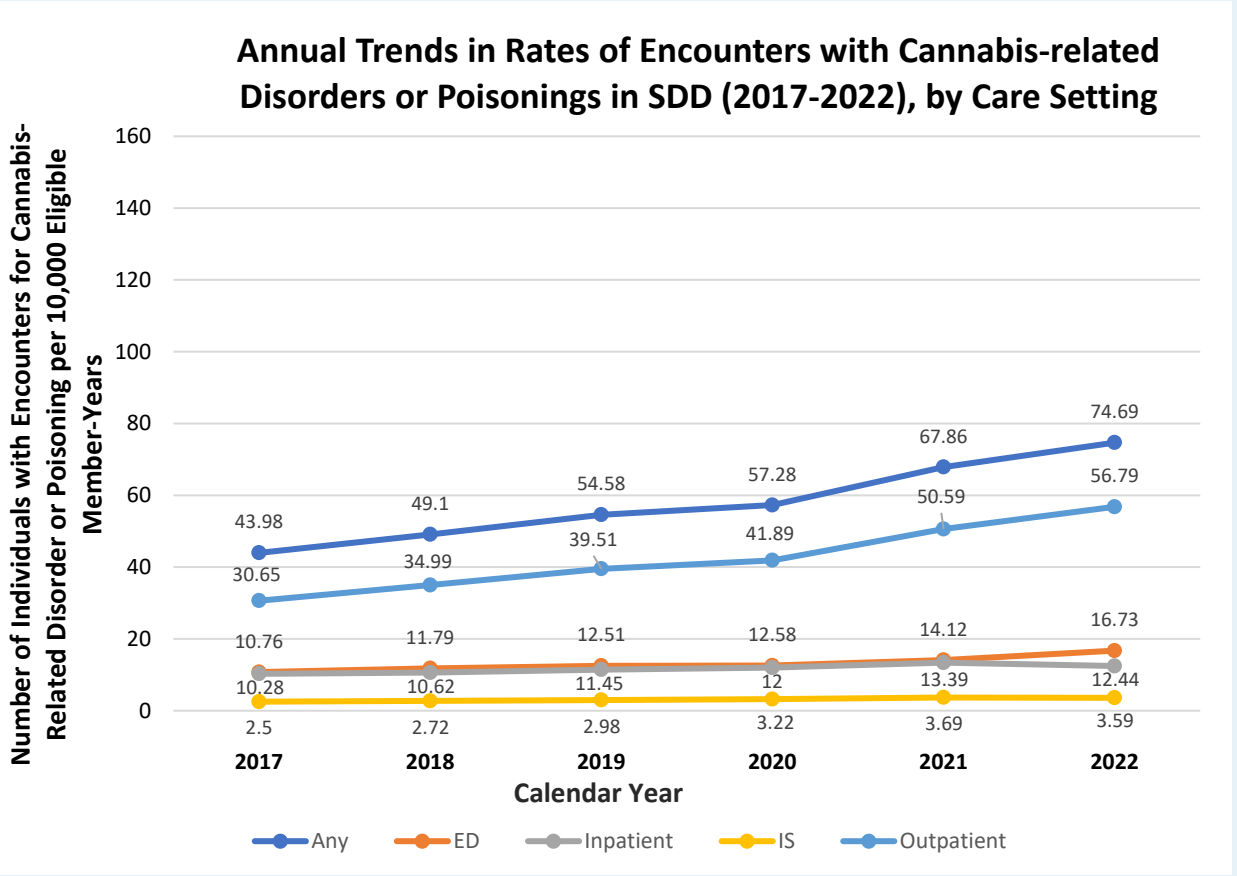
	Alcohol	Benzodiazepines	Cannabis	Cocaine	Heroin
Individuals with Poisoning Encounters	11,891	39,864	14,668	6,382	15,707
Avg. age, years	41	43	35	41	34
% female	48%	62%	47%	30%	32%
Poisoning Encounters	15,599	63,074	17,961	9,062	25,272



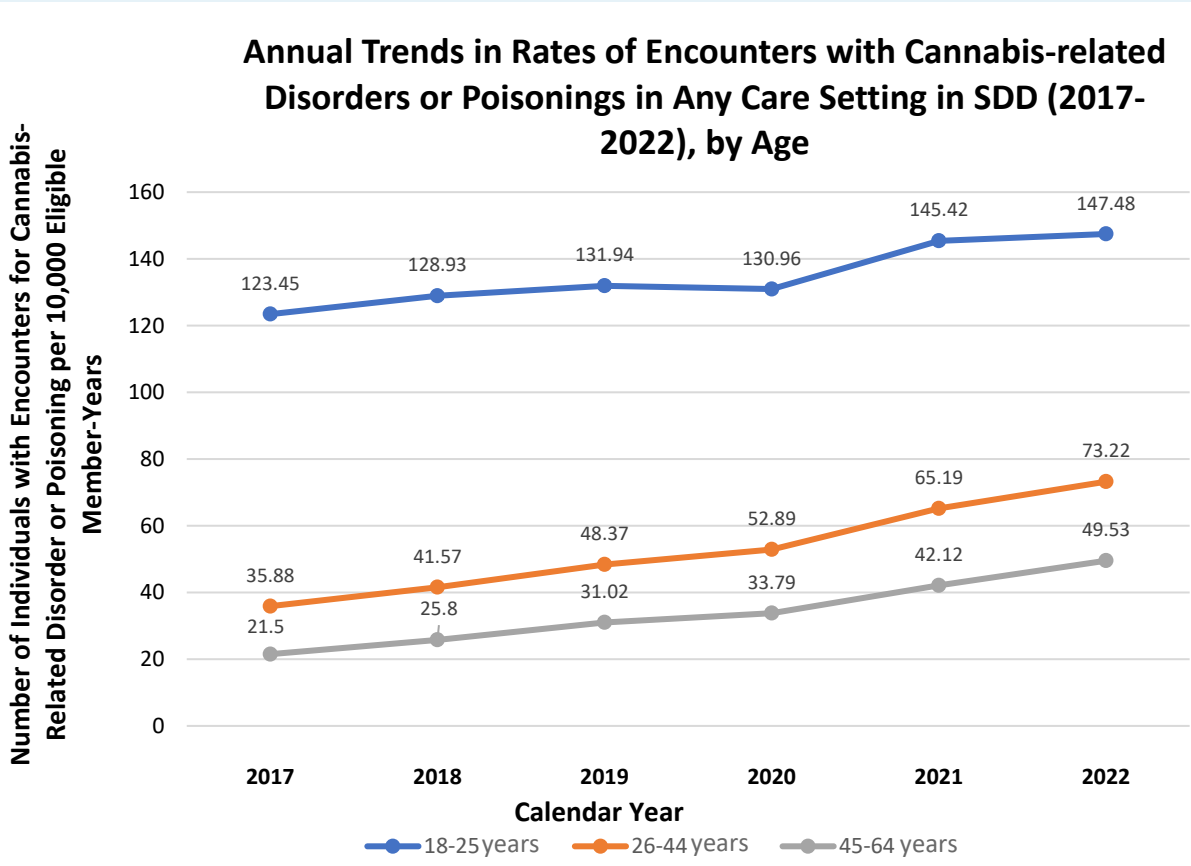
[†]https://www.ncsl.org/health/state-medical-cannabis-laws
*Partial data year
https://www.federalregister.gov/documents/2024/05/21/2024-11137/schedules-of-controlled-substances-rescheduling-of-marijuana
https://www.dea.gov/sites/default/files/2024-05/2016-17954-HHS.pdf

Trends in Cannabis-Related Encounters in the US, by Setting & Age

Increasing rates of cannabis-related encounters; Outpatient and ED encounters contribute to the upward trend



Rates of cannabis-related encounters were higher in 18–25-yr-olds; increasing trends observed across all age groups



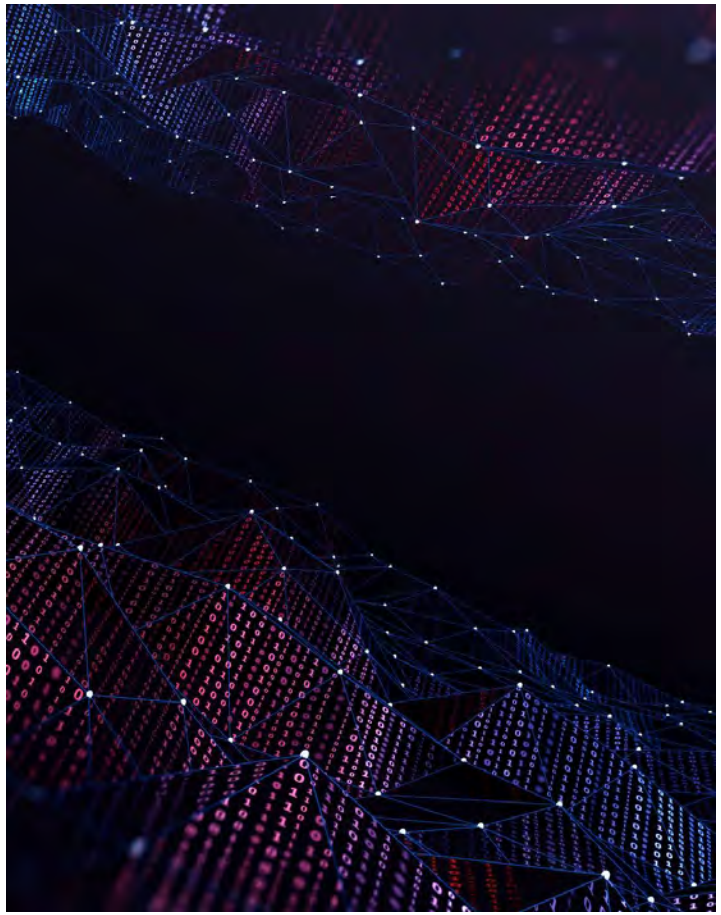
ED = Emergency Department
IS = Non-Acute Institutional Stay

Contributed to U.S. Department of Health and Human Services Evaluation of Eight Factors Determinative of Control Under the Controlled Substance Act (CSA)

Sentinel results are cited in the scientific and medical evaluation of "marijuana" conducted by FDA on behalf of the Department of Health and Human Services (HHS) and transmitted to the Drug Enforcement Administration (DEA). The HHS evaluation provides a basis for DEA's recent proposed rule [Federal Register (89 FR 44597, May 21, 2024)] to reschedule "marijuana" from Schedule I to Schedule III of the Controlled Substances Act.

Upon consideration of the eight factors determinative of control of a substance under 21 U.S.C. 811(c), **HHS recommended that marijuana be placed in Schedule III of the CSA.**

Sentinel's findings were contributing sources of information to this evaluation.



Expansion of Sentinel Tools & Data Sources

1. Query Request Package (QRP) Enhancements for Pregnancy and Signal Identification Studies

2. National Death Index (NDI) Linkage to CMS Medicare and Medicaid Data

Expanded Pregnancy Algorithm to Capture Pregnancies Ending in Either Live and Non-Live Births

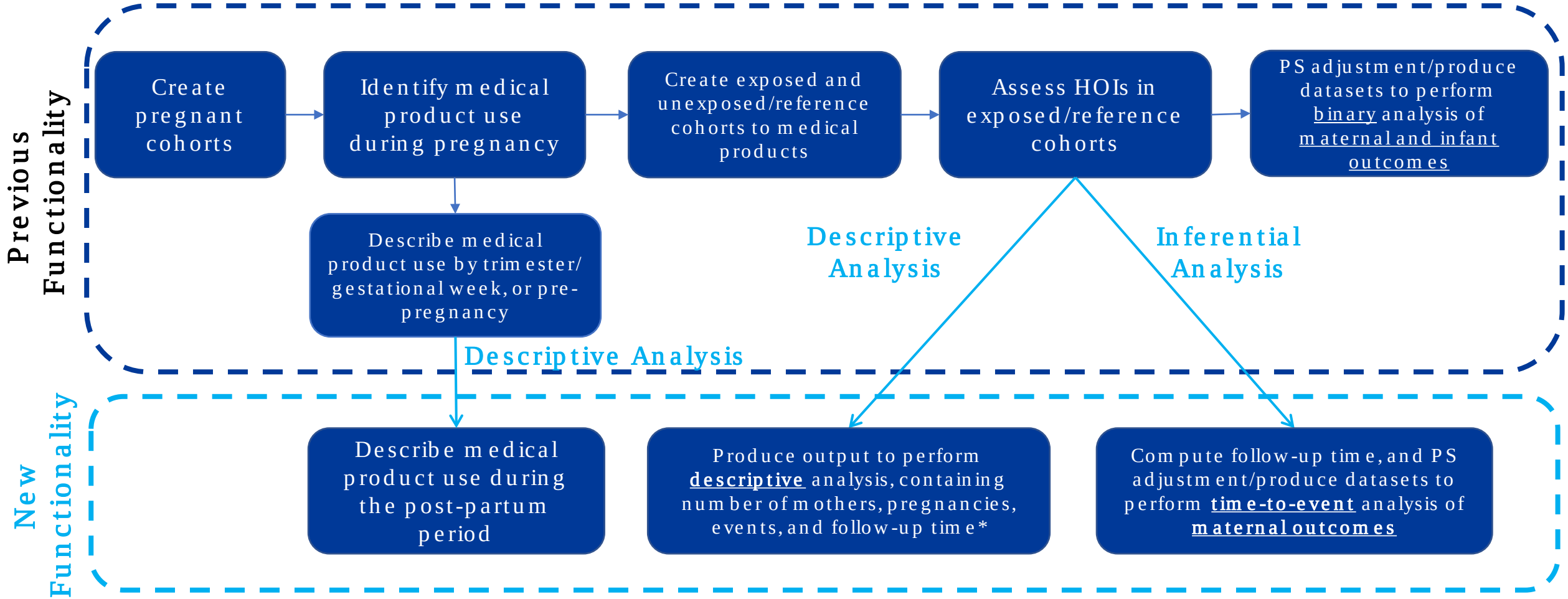
- Previously, the algorithm published by Li et al. was used to identify pregnancies ending in live-birth and estimate gestational age
- Pregnancies ending in other non-live birth outcomes could not be assessed
- **Enhancement:** Updated the algorithm to identify pregnancies ending in live births (via pre-defined codes or Mother-Infant linked table), non-live birth outcomes, or mixed births
- **Enhancement:** Expanded the number of pregnancy markers observed during pregnancy for estimating pregnancy duration

Pregnancy outcomes in Merativeâ MarketScan® Data – 01/01/2010-03/31/2023

Outcome Category	Pregnancy Outcome[1]	Total N (%)
Live birth outcomes	Live births	3,994,476 (69.9%)
	Unclassified deliveries[2]	289,192 (5.1%)
Non-live birth outcomes	Induced abortion	307,708 (5.4%)
	Ectopic pregnancy	129,719 (2.3%)
	Spontaneous abortion	900,888 (15.8%)
	Stillbirth	25,655 (0.4%)
	Trophoblastic disease	34,883 (0.6%)
Mixed births (co-occurring live and non-live birth outcomes)	Mixed births	36,083 (0.6%)

[1]Pregnancy outcomes defined using pre-defined codes
[2]Unclassified Delivery is a delivery without a clear pregnancy outcome type. If the users want to have a high sensitivity to capture live births, unclassified delivery could be considered as live births.
Li Q, Andrade SE, Cooper WO, Davis RL, et al. Validation of an algorithm to estimate gestational age in electronic health plan databases. Pharmacoepidemiol Drug Saf. 2013;22(5):524–32.

Other Pregnancy-Related Enhancements



HOI = Health Outcome of Interest
PS = Propensity Score
*Follow-up time is only provided when evaluating maternal outcomes

Enhancing Death Data in the SDD

CMS Medicare and Medicaid data linked to the National Death Index (NDI) and incorporated into the SDD in Spring 2024.

- The SDD contains NDI data from 2014 through 2021 for Medicare, 2020 for Medicaid
- This linkage improved certainty of **fact of death** for Medicaid data
- It substantially improved capture of **cause of death** for Medicare and Medicaid

Overall increase in **cause of death** records due to NDI linkage at Medicare & Medicaid

- **Medicare** → 0 to 72.4 million records
- **Medicaid** → 0 to 4.6 million records
- **Overall SDD** → 4.9 million records to 81.9 million records

Incorporation of this data improves ability to conduct medical product safety surveillance when mortality is a potential safety concern.

Increase in Capture of Fact and Cause of Death

Fact of Death Source

	Medicare		Medicaid		Overall SDD*	
	Pre-NDI data	Post-NDI data	Pre-NDI data	Post-NDI data	Pre-NDI data	Post-NDI data
Other	100%	16.2%	100%	27.3%	93.0%	35.9%
State Records	--	--	--	--	3.5%	4.0%
Tumor Registry	--	--	--	--	<0.1%	<0.1%
NDI	--	**83.8%**	--	**72.7%**	3.4%	**60.1%**

Cause of Death Source

	Medicare		Medicaid		Overall SDD*	
	Pre-NDI data	Post-NDI data	Pre-NDI data	Post-NDI data	Pre-NDI data	Post-NDI data
Underlying	100%	30.6%	100%	28.6%	31.5%	30.5%
Immediate/Primary	--	18.8%	--	23.1%	3.4%	**18.1%**
Contributory	--	29.5%	--	28.5%	64.4%	31.2%
Other	--	21.1%	--	19.7%	0.7%	20.2%

*13 Data Partners populate the Death table
NDI = National Death Index
SDD = Sentinel Distributed Database

Acknowledgements (1 of 5)

Serious Infection Following Ustekinumab Use in Patients with Crohn's Disease

- FDA
  - Joel Weissfeld
  - Sandhya Apparaju
  - Benjamin Booth
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  - Emma Hoffman
  - Laura Hou
  - Jane Huang
  - Geetha Iyer
  - Sheryl Kluberg
  - Joy Kolonoski
  - Sam McGown
  - Melody Mai
  - Judy Maro
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  - Andrew Petrone
  - Andrew Simon
  - Emma Whited
  - Megan Wiley
- Sentinel Data Partners
  - CVS Health/Aetna
  - Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data
  - Carelon Research/Elevance Health
  - Humana Healthcare Research Inc.
  - Optum Insight Life Sciences Inc.

Vedolizumab and Natalizumab & Interstitial Lung Disease

- FDA
- Sally Peprah
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- Jamal Jones
- Kira Leishear
- Joel Weissfeld
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- Elizabeth Beers
- Joy Kolonoski
- Maria Lewis
- Sophie Mayer
- Ashish Rai
- Andrew Simon
- Samantha Smith
- Amelia Thyen
- Megan Wiley
- Sentinel Data Partners
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- Carelon Research/Elevance Health
- Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data
- Humana Healthcare Research Inc.
- Optum Insight Life Sciences Inc.

Acknowledgements (2 of 5)

Use of Armodafinil or Modafinil During Pregnancy and Risk of Non-cardiac Congenital Malformations in the Infant

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  - Catherine Callahan
  - Sarah Dutcher
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  - Sukhminder Sandhu
  - Yandong Qiang
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  - Kimberely Barrett
  - Elizabeth Beers
  - Derek Campbell
  - Austin Cosgrove
  - Celeste Ewig
  - Joy Kolonoski
  - Jennifer Lyons
  - Kshema Nagavedu
  - Morgaine Payson
  - Ashish Rai
  - Samantha Smith
  - Emma Whited
  - Megan Wiley
- Sentinel Data Partners
  - CVS Health/Aetna
  - Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data
  - Carelon Research/Elevance Health
  - Optum Insight Life Sciences Inc.

Pediatric and Adult Utilization of Methotrexate Injectable Products – Rapid SDD and TriNetX

- FDA
- Grace Chai
- Patricia Bright
- Sarah Dutcher
- Sonal Goyal
- Amy Ho
- Terrence Lee
- Jing Xu
- Yuze Yang
- Sentinel Operations Center
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- Meredith Epperson
- Eric Fung
- Geetha Iyer
- Nathan Kim
- Jenice Ko
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- Thuy Thai
- Emma Whited
- Sentinel Data Partners
- CVS/Aetna Health
- Carelon Research/Elevance Health
- Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data
- Humana Healthcare Research Inc.
- Optum Insight Life Sciences Inc.
- HealthPartners Institute
- Kaiser Permanente Colorado
- Kaiser Permanente Northwest
- Kaiser Permanente Washington Health Research Institute3
- TriNetX

Acknowledgements (3 of 5)

Utilization of Schedule II Stimulant Medications

- FDA
  - Rose Radin
  - Grace Chai
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  - Terrence Lee
  - Celeste Mallama
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  - Jillian Burk
  - Meg Her
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  - Nathan Kim
  - Joy Kolonoski
  - Sam McGown
  - Ashish Rai
  - Bahareh Rasouli
  - Kathleen Shattuck
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- Sentinel Data Partners
  - CVS Health/Aetna
  - Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data
  - Carelon Research/Elevance Health
  - Marshfield Clinic Research Foundation
  - Optum Insight Life Sciences Inc.
  - Humana Healthcare Research Inc
  - Kaiser Permanente Northwest
  - Kaiser Permanente Washington Health Research Institute

Prenatal and Congenital Syphilis in the US: Characterizing Screening and Treatment

- FDA
- Sarah Dutcher
- David Moeny
- Jamal Jones
- Terrence Lee
- Lucia Menegussi
- Rose Radin

- Sentinel Operations Center
- David Cole
- Christian Hague
- Joy Kolonoski
- Judy Maro
- Sam McGown
- June Husn O'Neill
- Katherine Round
- Liz Suarez

- Study Workgroup
- Rachel Abbey, Office of National Coordinator for Health IT, HHS
- Nahida Chaktoura, National Institute for Child Health and Human Development, NIH
- Juanita Chinn, National Institute of Child Health and Human Development, NIH
- Alexander Ewing, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC
- Elizabeth Gray, National Center on Birth Defects and Development Disabilities, CDC
- Phoebe Thorpe, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, CDC
- Catherine Vladutiu, Maternal and Child Health Bureau, HRSA

Acknowledgements (4 of 5)

Medical Literature and Data on Cannabis Use

- Department of Pharmaceutical Outcomes & Policy, Department of Epidemiology, College of Pharmacy, University of Florida / Consortium for Medical Marijuana Clinical Outcomes Research
  - Amie Goodin
  - Lauren Adkins
  - Jungjun (June) Bae
  - Serena Guo
  - Yan Wang
  - Almut Winterstein
  - Tianxiao Zhang
  - And numerous Literature Screeners and Data Extractors
- FDA
  - Dave Moeny
  - Patricia Bright
  - Catherine Callahan
  - Dominic Chiapperino
  - Steven Galati
  - Christina Greene
  - Sara Karami
  - Joshua Lloyd
  - Kira Leishear
  - Tamra Meyer
  - Silvia Perez-Vilar
  - Rose Radin
  - Sukhminder Sandhu
- Sentinel Operations Center
  - Judy Maro
  - Ryan Schoeplein
  - And numerous Literature Screeners and Data Extractors

Trends in Encounters for Substance Poisonings in the US, 2016-2022

- FDA
  - Silvia Perez-Vilar
  - Patricia Bright
  - Catherine Callahan
  - Sarah Dutcher
  - David Graham
  - Christina Greene
  - Kira Leishear
  - Tamra Meyer
  - Rose Radin
  - Sukhminder Sandhu
- Sentinel Operations Center
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  - Jillian Burk
  - Meredith Epperson
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  - Liz Siranosian
  - Megan Wiley
- Sentinel Data Partners
  - CVS Health/Aetna
  - HealthPartners Institute
  - Marshfield Clinic Research 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 Washington Health Research Institute
  - Optum Insight Life Sciences Inc.

Trends in Cannabis-Related Encounters in the US

- FDA
  - Silvia Perez-Vilar
  - Patricia Bright
  - Sarah Dutcher
  - David Graham
  - Christina Greene
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  - Meredith Epperson
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  - Mayura Shinde
  - Viola Spahiu
  - Emma Whited
- Sentinel Data Partners
  - Carelon Research/Elevance Health
  - CVS Health/Aetna
  - Humana Healthcare Research Inc.
  - Optum Insight Life Sciences Inc.

Acknowledgements (5 of 5)

Query Request Package (QRP) Enhancements for Pregnancy and Signal Identification Studies

- Sentinel Operations Center
  - Eric Czernizer
  - Fred Fabila
  - Maria Kempner
  - Jenice Ko
  - Judy Maro
  - Jolene Mosley
  - Ankit Patel
  - Alex Peters
  - Andrew Petrone
  - Daniel Scarnecchia
  - Katie Shapiro
  - Mayura Shinde
  - Andrew Simon
  - Thuy Thai
  - Amelia Thyen
  - Justin Vigeant
  - Megan Wiley
- Statlog Econometrics

National Death Index Linkage to CMS Medicare and Medicaid Data

- FDA
  - Sarah Dutcher
  - Rhoda Eniafe
  - Jamal Jones
- Sentinel Operations Center
  - Sampada Nandyala
  - Morgaine Payson
  - Alex Mai
  - Daniel Kiernan
  - Meg Her
  - Janine Ryan
  - Laura Shockro
  - Lauren Zichittella
  - Daniel Scarnecchia
  - Joy Kolonoski
  - Meredith Epperson
  - Christine Halbig
- Sentinel Data Partners
  - Duke University School of Medicine, Department of Population Health Sciences, through the Centers for Medicare and Medicaid Services which provided data

Sentinel

Thank You

Moderated Discussion and Q&A

Moderator: Victoria Gemme

Duke-Margolis Institute for Health Policy

Break

The workshop will resume at **11:15 a.m. ET**

Vaccine Monitoring: Regulatory Impact of the BEST System

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

Panelists: **Joann F. Gruber**, U.S. Food and Drug Administration

Patricia C. Lloyd, U.S. Food and Drug Administration

Yun Lu, U.S. Food and Drug Administration

Mao Hu, Acumen LLC

Vaccine Monitoring:
Regulatory Impact of the BEST System

Joann F. Gruber, PhD[1]
Patricia C. Lloyd, PhD[1]
Yun Lu, PhD[1]
Mao Hu, BS[2]

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

16th Annual Sentinel Initiative Public Workshop
November 7, 2024

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

- Overview of BEST Initiative, Recent Advancements, and Regulatory Impacts in 2024
- RSV Vaccine Safety Surveillance Among Older Adults
- RSV Vaccine Effectiveness Among Older Adults
- 2025 Vaccine Safety Surveillance Activities

Overview & Advancements in BEST

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

Center for Biologics Evaluation and Research

CBER-Regulated Products

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

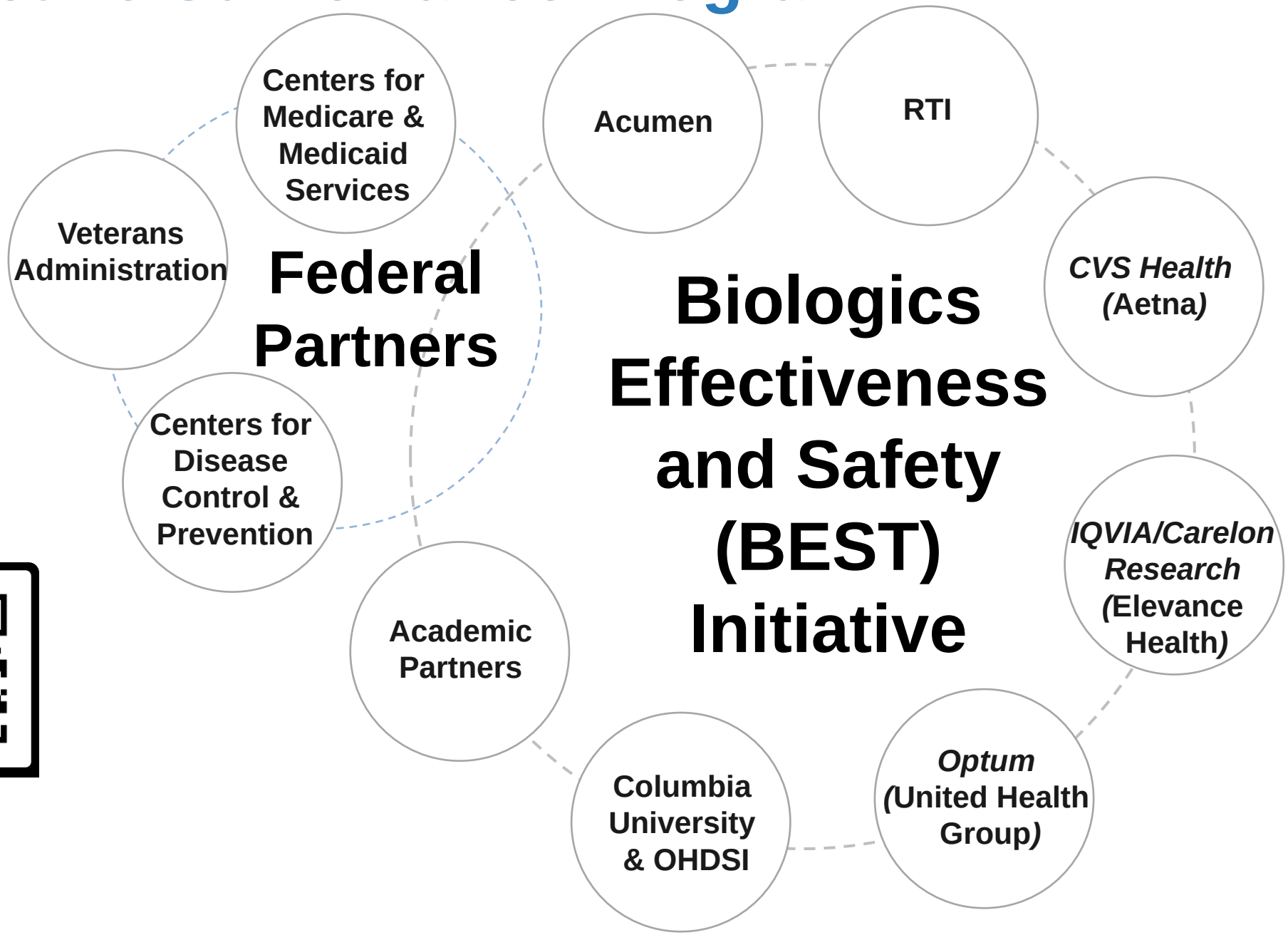
CBER Mission

Evaluate and ensure biologic products safety and effectiveness through active surveillance

CBER Surveillance Program Vision

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

CBER Active Surveillance Program



BEST Initiative Data Sources

Data Source*	Database Type	No. Patients Covered (Millions)	Time Period Covered
CMS: Medicare†	Claims	107	2005 – present
Optum: Adjudicated	Claims	>65	1993 – present
Optum: Pre-adjudicated	Claims	37	2018 – present
Carelon Research	Claims	77	2010 – present
CVS Health	Claims	53	2018 – present
Optum EHR	EHR	>115	2007 – present
Market Clarity	Linked EHR Claims	>85	2007 – present

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

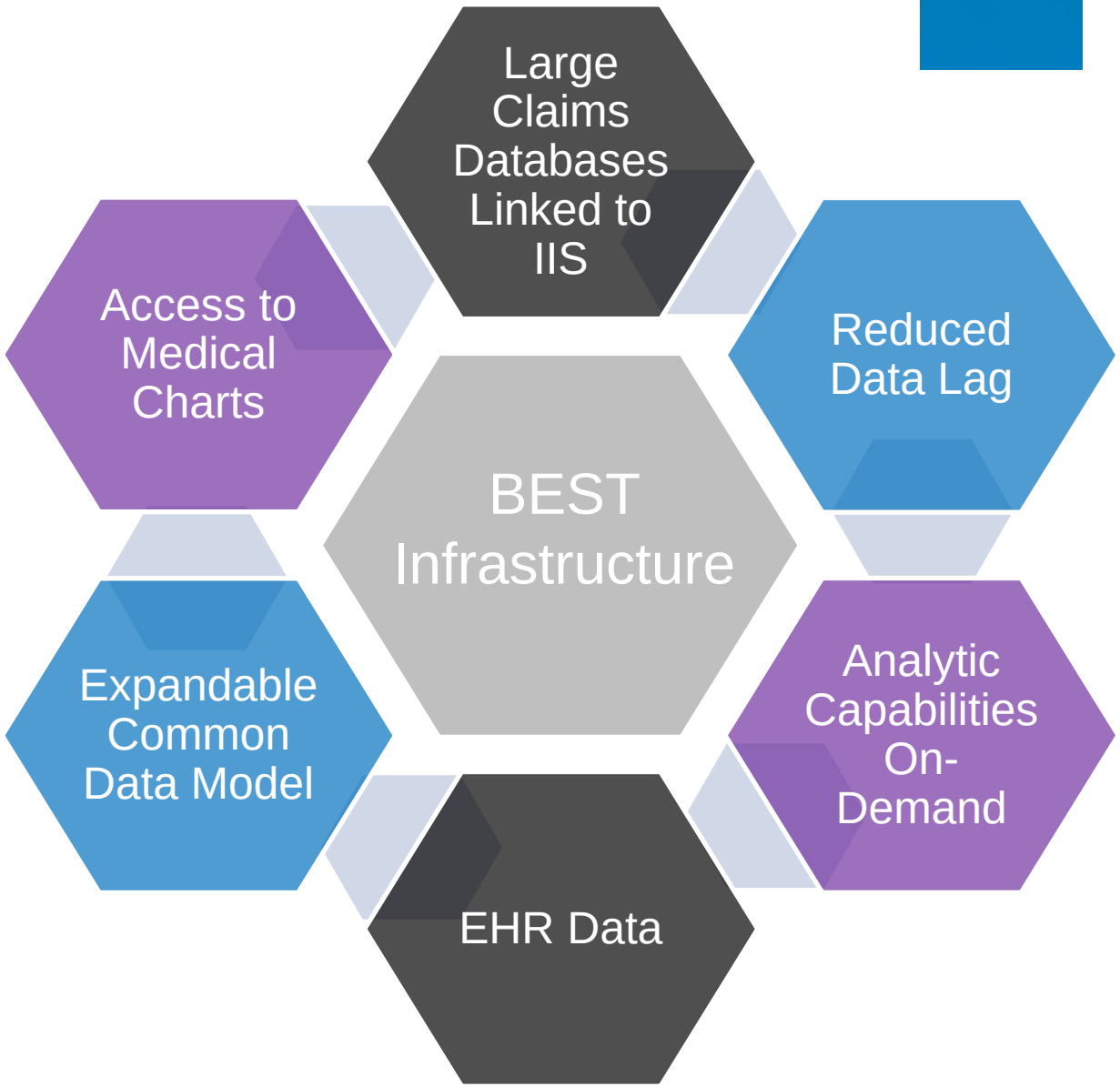
Data Network

Distributed data network

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

Data are standardized

- Transformed into a common data model (CDM)



Advancement to the BEST Infrastructure

- **Data Sources**
  - Shorten data lag for large claims databases to provide more rapid access to information
- **Infrastructure**
  - Expansion of Immunization Information Systems data
  - Successful linkage of mothers and infants in claims databases
- **Methods**
  - Large-scale self-controlled case series studies with multiple exposures and outcomes
  - Execution of novel signal detection techniques

Regulatory Impacts of BEST during 2024

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

Regulatory Contribution of BEST

- Studies generate 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 contributions
  - CDC Advisory Committee on Immunization Practices (ACIP) recommendations
  - Drug labeling
  - Emergency Use Authorizations (EUA) and approval
- Contribution to international regulators

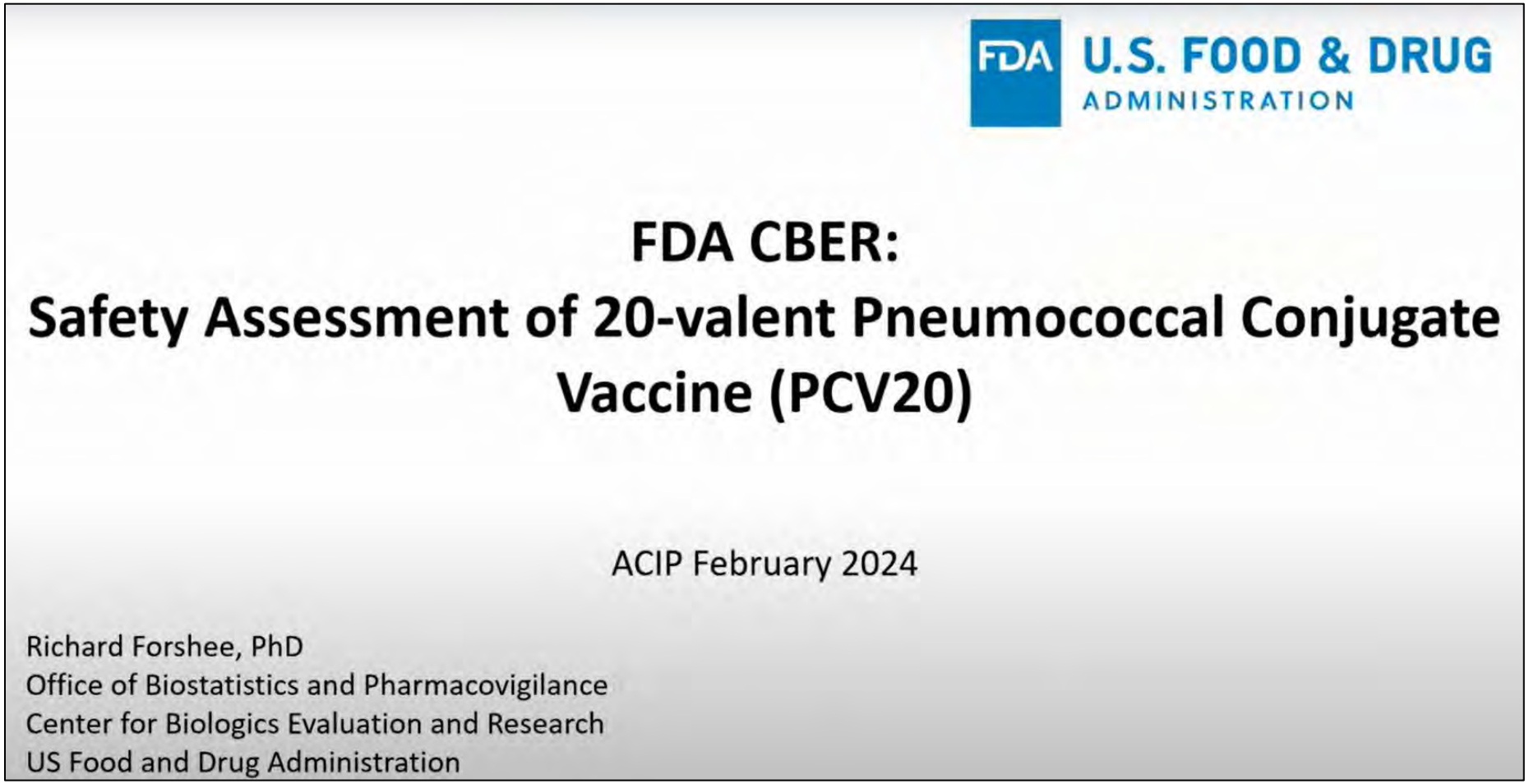
Regulatory & Public Health Impact Example: RSV Vaccines Safety

ACIP Meeting Presentations

February 2024	**Preliminary Analysis of Guillain-Barré Syndrome (GBS) following RSV Vaccination among adults 65 years and older** **Dr. Patricia Lloyd, ScM PhD** Health Statistician Office of Biostatistics and Pharmacovigilance Center for Biologics Evaluation and Research U. S. Food & Drug Administration
June 2024	**Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older** **Dr. Patricia Lloyd, ScM PhD** Health Statistician Office of Biostatistics and Pharmacovigilance Center for Biologics Evaluation and Research U. S. Food & Drug Administration
October 2024	**Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older** **Dr. Patricia Lloyd, ScM PhD** Health Statistician Office of Biostatistics and Pharmacovigilance Center for Biologics Evaluation and Research U. S. Food & Drug Administration

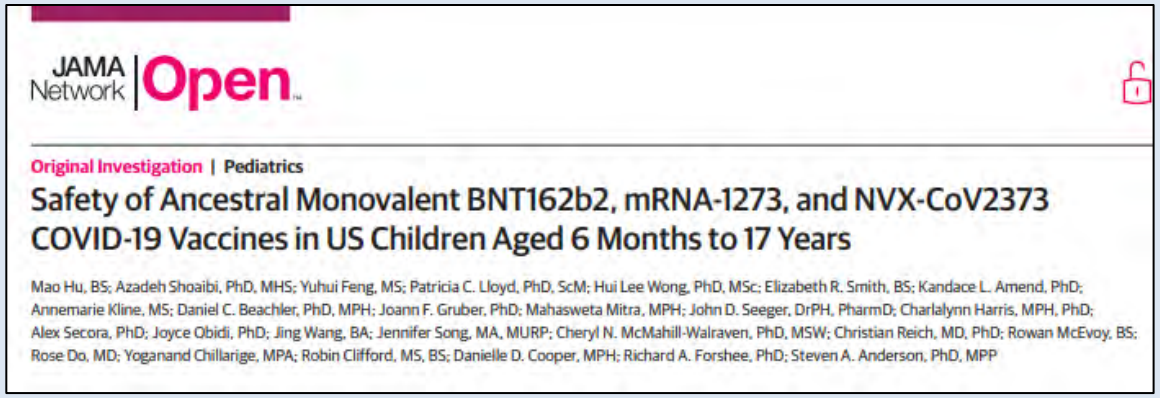
Regulatory & Public Health Impact Example: PCV20 Vaccines Safety

ACIP Meeting Presentations: February 2024



Regulatory & Public Health Impact
Example: COVID-19 Vaccine Safety

Data to inform updating mRNA COVID-19 Vaccine Labeling



JAMA Network | Open

Original Investigation | Pediatrics

Safety of Ancestral Monovalent BNT162b2, mRNA-1273, and NVX-CoV2373 COVID-19 Vaccines in US Children Aged 6 Months to 17 Years

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

medRxiv

Evaluation of Febrile Seizure Risk Following Ancestral Monovalent COVID-19 mRNA Vaccination Among U.S. Children Aged 2-5 Years

Richard A, Forshee, PhD,[1] Elizabeth R Smith, BS,[2] Zhiruo Wan, MS[2], Kandace L Amend, PhD, MPH,[3] Alex Secora, PhD[4], Djeneba Audrey Djibo, PhD, MSBME,[5] Kamran Kazemi, BS,[2] Jennifer Song, MA, MURP[3], Lauren E Parlett, PhD[6], John D Seeger, DrPH, PharmD[3], Nandini Selvam, PhD, MPH[4], Cheryl N McMahill-Walraven, PhD, MSW,[5] Mao Hu, BS,[2] Yoganand Chillarige, MPA[2], Steven A Anderson, PhD, MPP[1]

Example: Healthcare Provider Fact Sheet

Side effects that have been reported during post-authorization use include:

- Severe allergic reactions
- Urticaria (itchy rash/hives)
- Myocarditis (inflammation of the heart muscle)
- Pericarditis (inflammation of the lining outside the heart)
- Fainting in association with injection of the vaccine
- Febrile seizures (convulsions during a fever)

Regulatory & Public Health Impact
Example: COVID-19 Vaccine Safety

Supported EUA for 2024–2025 mRNA COVID-19 Vaccines

Additional doses may be associated with transient local and systemic symptoms similar to those seen previously with Moderna COVID-19 vaccines. The most notable uncommon side effect of the mRNA COVID-19 vaccines has been myocarditis. Based on data from the FDA Biologics Effectiveness and Safety (BEST) System (available only for individuals > 12 years of age), within a week after the first dose of mRNA-based COVID-19 vaccine (2023-2024 Formula), the crude observed rate (without adjustment for delay of reporting and other factors) of myocarditis or pericarditis events in the inpatient or emergency department setting was [redacted] cases per one million doses for persons aged 12 through 45 years (unpublished data, based on fewer than 10 cases).

Emergency Use Authorization (EUA) for an Unapproved Product
Review Memorandum

Application Type	EUA Amendment
Application Number	EUA 27073, Amendments 701-716
Sponsor	ModernaTX, Inc
Submission Date	June 19, 2024
Receipt Date	June 20, 2024
Signatory Authority	David C. Kaslow, MD

Emergency Use Authorization (EUA) for an Unapproved Product
Review Memorandum

Application Type	EUA Amendment
Application Number	EUA 27034, Amendments 797-813
Sponsor	Pfizer, Inc., on behalf of Pfizer and BioNTech
Submission Date	June 26, 2024
Receipt Date	June 26, 2024
Signatory Authority	David C. Kaslow, MD

Summary

- BEST Initiative facilitates CBER’s mission to ensure biologic products safety and effectiveness through active surveillance.
- BEST continues to generate data for evidence-based regulatory decisions in a timely manner.
- CBER enhances and expands BEST infrastructure and capacity to remain agile and efficient.

Post-Market Evaluation of Guillain-Barré Syndrome (GBS) following Respiratory Syncytial Virus (RSV) Vaccination Among Adults 65 Years and Older

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

Outline

- Introduction
- End-of-Season SCCS Analysis Results and Comparison to Early-Season Results
- Discussion
- Conclusions

Introduction

- RSV can cause lower respiratory tract disease and lead to pneumonia and bronchiolitis
- Annually, 60,000-160,000 RSV hospitalizations and 6,000-10,000 deaths among adults 60 years of age and older.
    - Compared to estimated 140,000 - 710,000 flu hospitalizations and 12,000 - 51,000 flu deaths, annually
- Three RSV vaccines were approved for use in the U.S. in adults 60 years and older
    - RSVPreF3+AS01 (GSK – AREXVY®) – May 3, 2023
    - RSVPreF (Pfizer – ABRYSVO®) – May 31, 2023
    - mRNA-1345 (Moderna – mRESVIA®) – May 31, 2024*
- Pre-licensure clinical trials identified a small number of GBS cases in RSVPreF3+AS01 and RSVPreF vaccines
- Reports submitted to Vaccine Adverse Events Reporting System identified higher GBS rates post-RSVPreF3+AS01 and RSVPreF vaccination than expected background rates

** The analyses described in this presentation included vaccinations through Jan 2024, which was prior to the approval of mRNA-1345 vaccine*

RSV Vaccine Post-Market Analyses

- Post-market analyses* to assess the safety of RSV vaccines among Medicare Fee-for-Service (FFS) beneficiaries ages 65 and older

Analyses	Includes Vaccines Administered Through	Data Through Date	Number of Doses		Number GBS Cases
			RSV PreF3+AS01	RSVPreF	
Observed vs Expected	December 2, 2023	December 2, 2023	1,379,335	682,267	<24
Early-Season SCCS	October 22, 2023	April 6, 2024	872,068	456,107	28
End-of-Season SCCS	January 28, 2024	July 13, 2024	2,202,247	1,024,442	95

** The analyses described in this presentation included vaccinations through Jan 2024, which was prior to the approval of mRNA-1345 vaccine.*

Observed vs. Expected Analysis

Methods

- Estimated the observed incidence rates (IRs) and compared to historical comparator (expected) rates, to obtain incidence rate ratios (IRRs) with 95% confidence intervals (CIs)
- This crude analysis allows for a rapid safety signal detection but uses aggregate historical comparator rates, increases the potential for confounding, and does not establish a causal association between RSV vaccines and GBS
- Evaluated risk of GBS following one dose of either RSVPreF3+AS01 or RSVPreF vaccines using a retrospective cohort design with the 2022 historical comparator
- Estimation of GBS positive-predictive value (PPV)-adjusted rates is based on multiple imputed datasets
    - Chart review, PPV for GBS: 71% (95% CI: 63%, 79%)

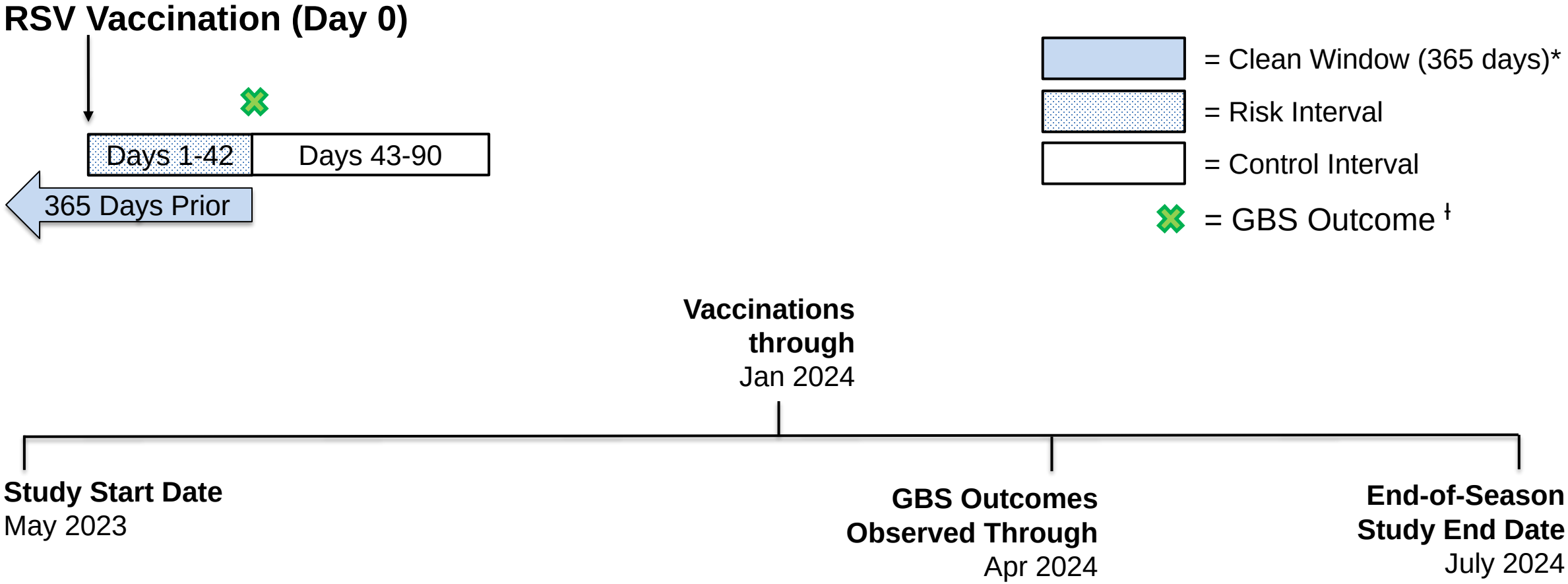
Observed vs. Expected Analysis

Results

	RSVPreF3+AS01	RSVPreF
Inferential Analysis Results		
Observed vs. Expected Analysis	**2.76 (95% CI: 1.32, 5.07)**	**6.94 (95% CI: 3.70, 11.87)**
PPV-Adjusted Analysis	2.75 (95% CI: 0.46, 5.04)	**6.91 (95% CI: 1.85, 11.97)**
GBS Cases per 1 million Doses	10.0	25.1
Descriptive Analysis Results		
Total RSV Vaccine Doses	**2,061,602**	
RSV Vaccine Doses	1,379,335	682,267
Observed GBS cases	<11	13

- **An elevated IRR was observed for GBS following RSV vaccination**
- **Only RSVPreF association was statistically significantly elevated in PPV-adjusted analysis**

Self-Controlled Case Series (SCCS) Design



** The clean window is relative to the outcome date; risk and control intervals are relative to the vaccination date*

ǂ Incident GBS identified in inpatient – primary position only; ICD-10-CM DGN G61.0

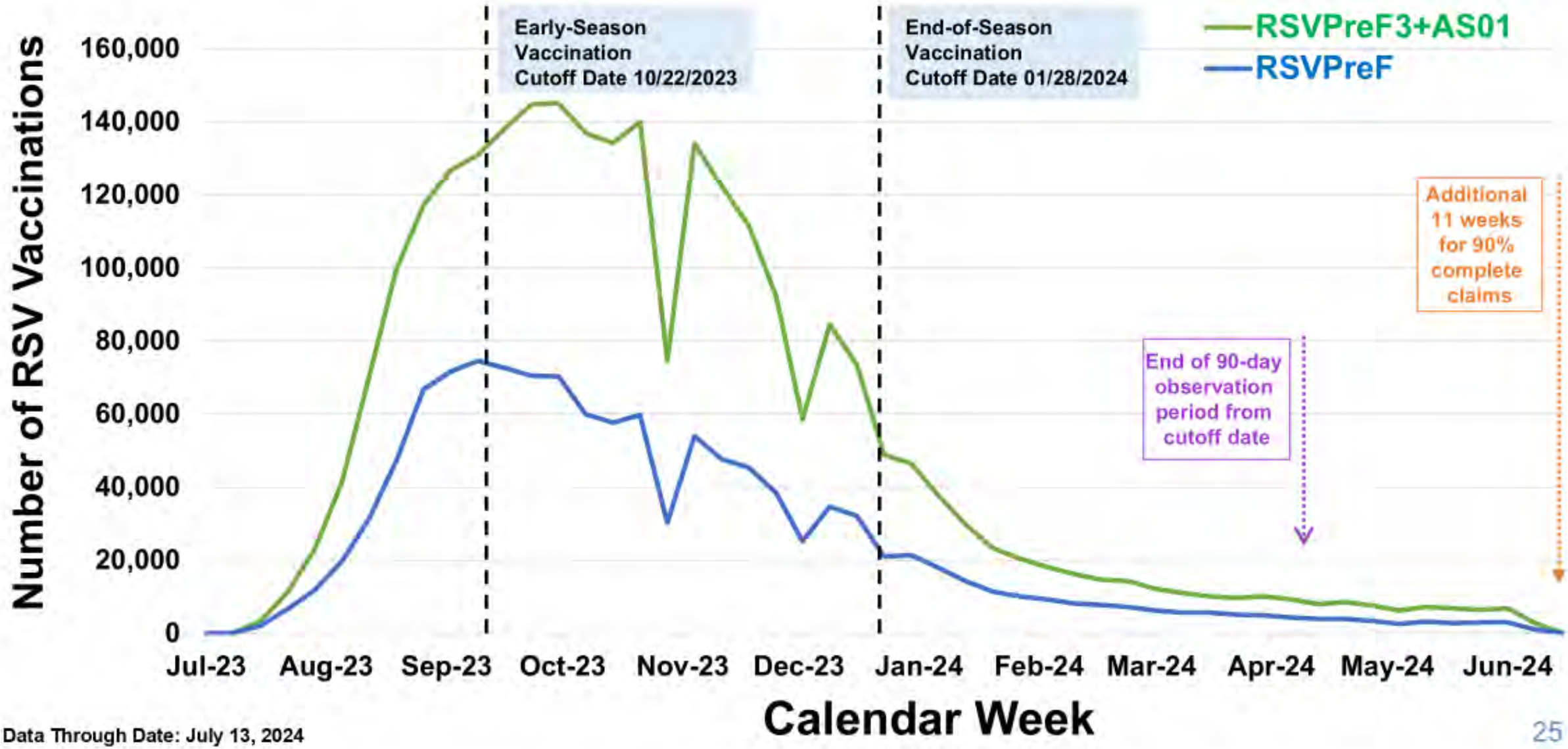
SCCS Analysis: Study Methods

Study Design	Self-Controlled Case Series (SCCS)
Data Sources /Study Population	• Medicare Fee-for-Service (FFS) (Parts A, B and D) beneficiaries aged 65 years and older • Enrolled on date of first observed RSV vaccination and during 1-year prior to vaccination • Incident GBS case during the observation period (i.e., no GBS event in the clean window) • Vaccinated with either RSVPreF3+AS01 or RSVPreF prior to Jan 28, 2024
Study Period	May 2023 – Jul 2024
GBS Outcome Definition	• Risk Interval: 1 - 42 days • Control Interval: 43 - 90 days • Care Setting: inpatient – primary position only; ICD-10-CM DGN G61.0
Statistical Analyses	• Incidence Rate Ratios (IRR) • Absolute Risk: Attributable Risk (AR) per 100,000 doses and 100,000 person-years (PY) • Adjustment for outcome-dependent observation time (Farrington), seasonality, PPV • Chart-confirmed analysis with Farrington and seasonality adjustments • Secondary analyses: IRR, AR stratified by same day concomitant vaccination with 2023-2024 COVID-19, 2023-2024 influenza, pneumococcal, and shingles vaccines

Study end date for End of Season SCCS analysis was July 13, 2024
Note: RSV vaccinations observed prior to Jan 28, 2024 were needed for 90% complete observation in 90 days post vaccination

End-of-Season SCCS Analysis

Weekly Uptake Trends in for RSVPreF3+AS01 and RSVPreF Vaccines



Data Through Date: July 13, 2024

SCCS Analysis: Descriptive Results

Case Counts for GBS following RSV vaccination by Vaccine Type

Case Population Eligibility Criteria	Early-Season SCCS Analysis		End-of-Season SCCS Analysis	
	RSV Vaccinations (n = 1.3 M doses)*		RSV Vaccinations (n = 3.2 M doses)*	
	RSVPreF3+AS01 (n = ~872k doses)*	RSVPreF (n = ~456k doses)*	RSVPreF3+AS01 (n = 2.2 M doses)*	RSVPreF (n = 1.0 M doses)*
Total GBS cases [total number of days in study period]	160 [339 days]	92 [311 days]	236 [437 days]	130 [409 days]
GBS cases during 90-day observation period	105	74	119	89
Incident GBS cases after applying clean window restriction	55	36	<70	<50
GBS cases qualifying for SCCS analyses	**11**	**17**	**56**	**39**

**n = Medicare beneficiaries that received one RSV vaccination and eligible for early- and end-of-season SCCS analysis are presented. Product-specific and total dose counts may not equal due to rounding*

ǂ Cell suppressed to protect patient confidentiality

Early-Season Data Through Date: April 6, 2024
End-of-Season Data Through Date: July 13, 2024

GBS Medical Record Review (MRR) Results

Case Classification of GBS Medical Records

GBS MRR	Overall
Total GBS Cases and Records Requested	95
Records Received and Adjudicated	75
Chart-Confirmed GBS Cases* (Level 1, Level 2, Level 3)	51
Insufficient Evidence or Not a Case* (Level 4, Level 5)	24
Records Not Returned	20

** Medical records were adjudicated per the Brighton Collaboration clinical case definition for GBS*

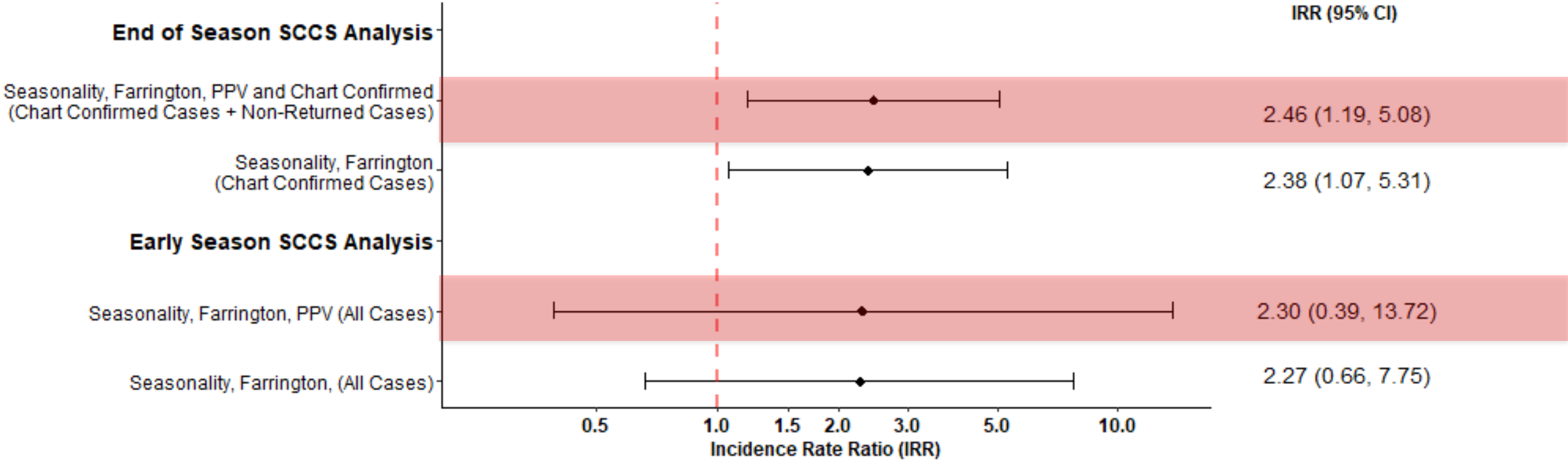
Positive Predictive Value (PPV) of GBS

Category	PPV** with 95% Confidence Interval (CI)
Overall	**68.0% (56.8%, 77.5%)**
Risk Interval	62.3% (48.8%, 74.1%)
Control Interval	81.8% (61.5%, 92.7%)

*** PPV calculations include all GBS case records assigned a case classification based on the MRR in the denominator*

Comparison of Early vs. End of Season Results GBS and RSVPreF3+AS01

Incidence Rate Ratio (IRR) with 95% Confidence Intervals (95% CI)



A statistically significant elevation in GBS risk was observed with seasonality, Farrington, PPV adjusted analysis that included chart-confirmed and non-returned cases:

RSVPreF3+AS01

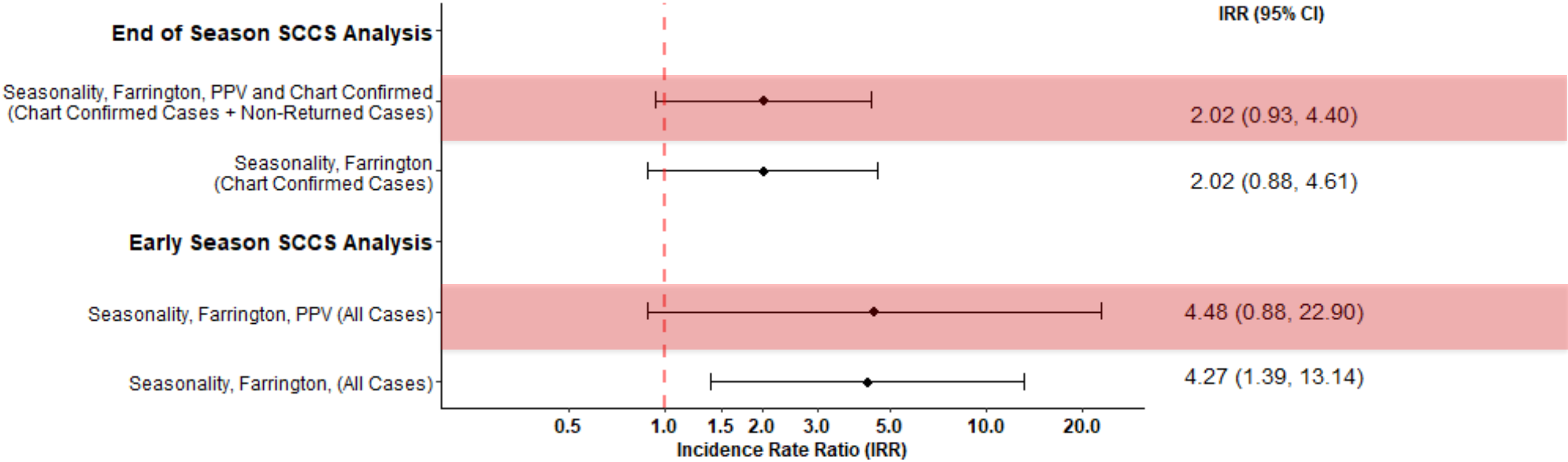
2.46 (95% CI: 1.19, 5.08)

SCCS analyses including most adjustments are highlighted in red

Farrington-Adjusted Analysis = Outcome-Dependent Observation Time Adjustment

Comparison of Early vs. End of Season Results GBS and RSVPreF

IRR with 95% CI



An elevated but non-statistically significant IRR was observed for GBS with seasonality, Farrington, PPV adjusted analysis that included chart-confirmed and non-returned cases:

RSVPreF

2.02 (95% CI: 0.93, 4.40)

SCCS analyses including most adjustments are highlighted in red

Farrington-Adjusted Analysis = Outcome-Dependent Observation Time Adjustment

End-of-Season SCCS Results: GBS and RSV Vaccination

IRR and Attributable Risk (AR)

Seasonality, Farrington Analysis, and PPV-Based Multiple Imputation – Chart Confirmed + Not Returned Cases

Inferential Analysis Results	RSVPreF3+AS01	RSVPreF
Eligible Vaccines	2,202,247	1,024,442
*Cases in the Risk Interval	24	18
*Cases in the Control Interval	11	<11
IRR (95% CI)	2.46 (1.19, 5.08)	2.02 (0.93, 4.40)
AR per 100,000 Doses (95% CI)	0.65 (0.18, 1.12)	0.90 (-0.02, 1.81)
AR Per 100,000 PY (95% CI)	5.71 (1.61, 9.80)	7.82 (-0.17, 15.81)

**Cases in risk and control intervals are the average number of true cases in the multiple imputation process*
Small cell sizes <11; suppressed to protect patient confidentiality

PY = Person-Years

End-of-Season Descriptive Results: Concomitant Vaccination among GBS Cases

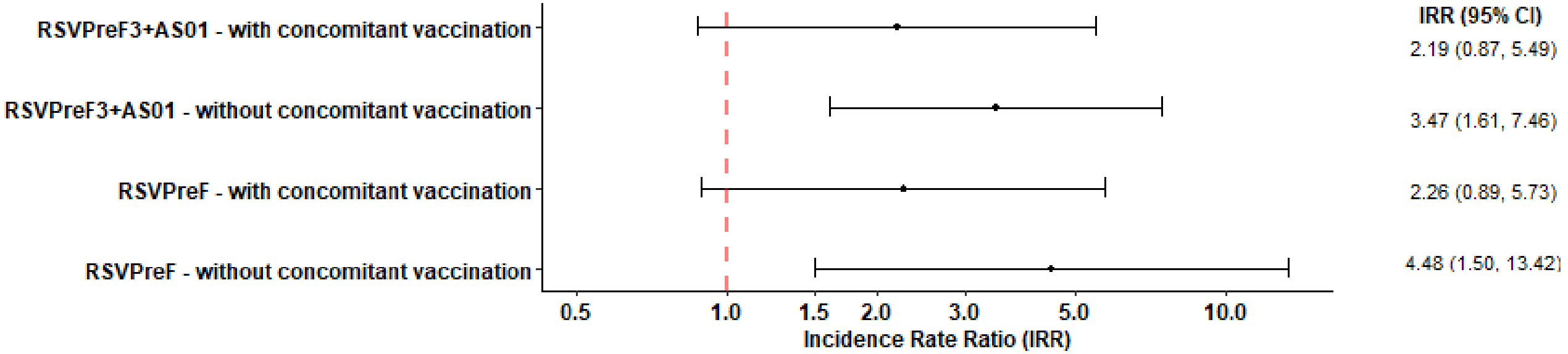
	RSVPreF3+AS01	RSVPreF
Eligible Vaccines	2,202,247	1,024,442
Total GBS Cases	56	39
Number (%) with any concomitant vaccination	20 (35.7%)	19 (48.7%)

Concomitant vaccination is defined as vaccination on the same day as RSV vaccination with at least one of 2023-2024 COVID-19, 2023-2024 influenza, pneumococcal, and shingles vaccines.

Secondary End-of-Season SCCS Results: GBS risk by vaccine type and concomitant vaccination

IRR and 95% CI

Seasonality and Farrington Adjusted Analysis, All Cases



No evidence of difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines

Secondary End-of-Season SCCS Results:

Concomitant Vaccination among GBS cases vaccinated with **RSVPreF3+AS01** – IRR and AR

Seasonality and Farrington Adjusted Analysis

Inferential Analysis Results	With Concomitant Vaccination	Without Concomitant Vaccination
Eligible Vaccines	833,067	1,369,180
Cases in the Risk Interval	<15	<30
Cases in the Control Interval	<11	<11
IRR (95% CI)	2.19 (0.87, 5.49)	3.47 (1.61, 7.46)
AR per 100,000 Doses (95% CI)	0.85 (-0.09, 1.79)	1.40 (0.72, 2.09)
AR Per 100,000 PY* (95% CI)	7.40 (-0.79, 15.59)	12.27 (6.26, 18.28)

Small cell sizes <11; suppressed to protect patient confidentiality

**PY = Person-Years*

Secondary End-of-Season SCCS Results:

Concomitant Vaccination among GBS cases vaccinated with **RSVPreF** – IRR and AR

Seasonality and Farrington Adjusted Analysis

Inferential Analysis Results	With Concomitant Vaccination	Without Concomitant Vaccination
Eligible Vaccines	420,764	603,678
Cases in the Risk Interval	<15	<20
Cases in the Control Interval	<11	<11
IRR (95% CI)	2.26 (0.89, 5.73)	4.48 (1.50, 13.42)
AR per 100,000 Doses (95% CI)	1.59 (-0.18, 3.35)	2.06 (0.99, 3.12)
AR Per 100,000 PY* (95% CI)	13.85 (-1.55, 29.25)	18.01 (8.70, 27.31)

Small cell sizes <11; suppressed to protect patient confidentiality

**PY = Person-Years*

SCCS Design: Strengths and Limitations

Strengths

- SCCS study design provides robust adjustment for potential time-invariant confounding
- Large database facilitates more precise evaluation of GBS
- Study findings are generalizable to U.S. population 65 years and older
- Medical Record Review improved classification of GBS

Limitations

- Potential misclassification of GBS in administrative claims data
- The study is not intended to compare GBS risk between the two vaccine products
- IRR estimates may be sensitive to the number of records returned and adjudicated through MRR
- Potential misspecification of post-RSV vaccination risk and control intervals for GBS
- Potential for residual confounding
- Attributable risk based on small number of cases may be difficult to interpret

Discussion

- **Observed vs. Expected Analysis**
  - Elevated risk of GBS observed following both RSV vaccines
  - Results not statistically significant for RSVPreF3+AS01 when adjusting for PPV
- **Early-Season SCCS**
  - Statistically significant elevation in GBS risk observed following RSVPreF vaccine
  - Results did not remain statistically significant for RSVPreF vaccine when adjusting for PPV-based multiple imputations
- **End-of-Season SCCS**
  - A statistically significant elevated IRR observed for GBS following vaccination with RSVPreF3+AS01; GBS risk elevated yet not statistically significant following RSVPreF vaccination
  - Results remained the same when restricting to confirmed GBS cases through MRR
  - No evidence of difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines

Conclusions

- Findings suggest an increased GBS risk following RSVPreF3+AS01 and RSVPreF among adults aged 65 years and older
- Results are consistent with pre-licensure clinical trials and surveillance systems such as VAERS
- End-of-season SCCS analyses results are largely chart-confirmed from MRR and include ~3x more vaccine doses and GBS cases compared to the early season SCCS results
- GBS risk following vaccination with RSVPreF3+AS01 and RSVPreF is rare (<10 cases per 1 million vaccinations)
- No difference in GBS risk among persons with and without same day concomitant vaccination with RSV vaccines

References

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Centers for Medicare & Medicaid Services

U.S. FOOD & DRUG ADMINISTRATION

Real-World Vaccine Effectiveness of Respiratory Syncytial Virus (RSV) Vaccines Among Community-Dwelling Medicare Beneficiaries Aged ≥65 years

Yun Lu, Ph.D

Division of Analytics and Benefit-Risk Assessment (DABRA)

Office of Biostatistics and Pharmacovigilance (OBPV)

Center for Biologics Evaluation and Research (CBER)

US Food and Drug Administration (FDA)

Disclaimer

- This presentation reflects the views of the author and should not be construed to represent the views or policies of the FDA, Centers for Medicare and Medicaid Services (CMS), or any other organizations.

- No conflicts of interest exist related to this presentation.

- Mention of a commercial product should not be construed as actual or implied endorsement.

Background & Objective

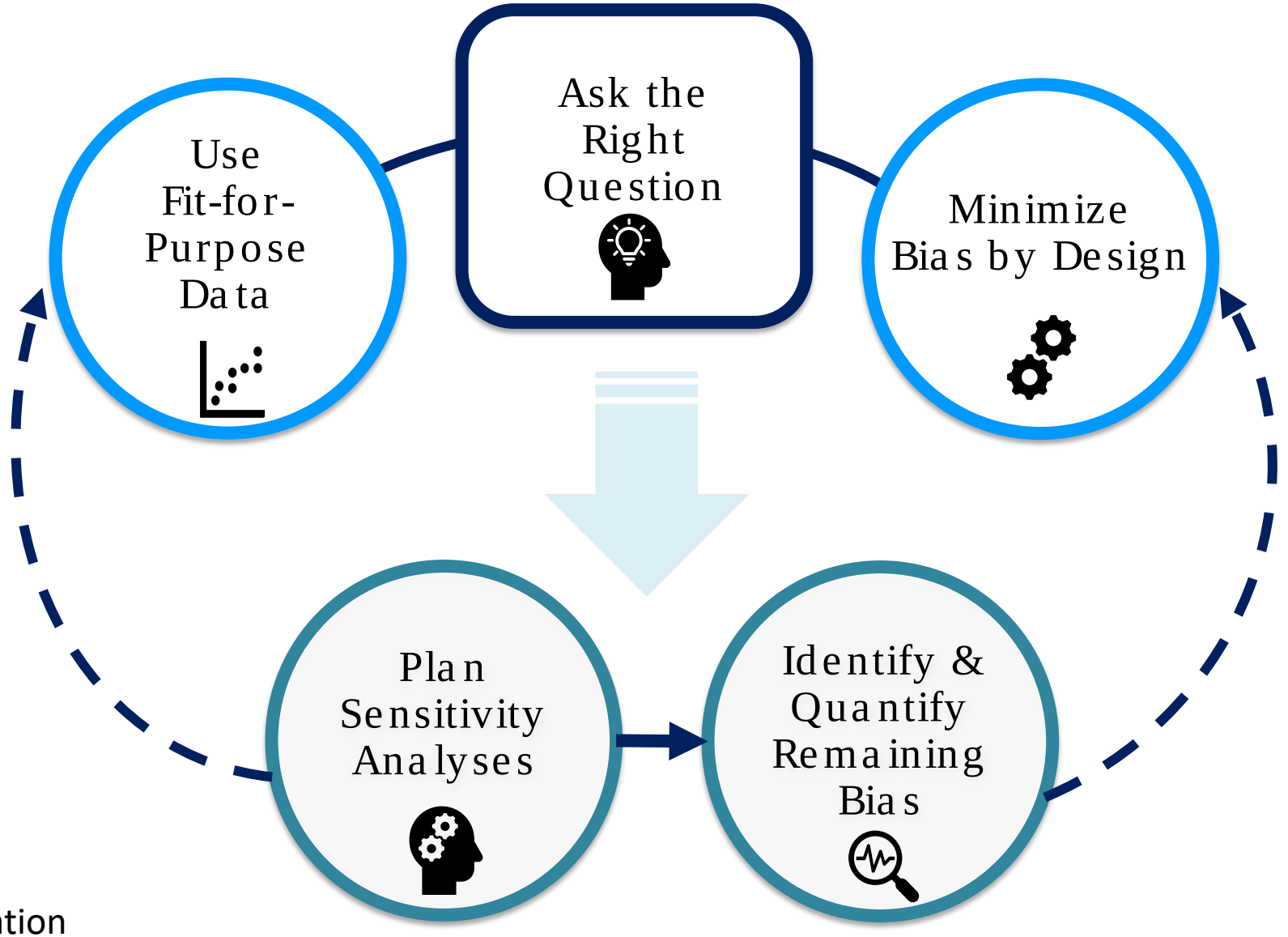
- **Background**: Respiratory syncytial virus (RSV) infection causes significant number of hospitalizations and deaths in older adults.

- Two vaccines approved in May 2023 for prevention of Lower Respiratory Tract Disease (LRTD) caused by RSV for individuals aged 60 years of age and older:[1,2]
  - RSVPreF3+AS01 (AREXVY) - GSK
  - RSVPreF (ABRYSVO) - Pfizer

- **Objective**: Evaluate the effectiveness of RSVPreF3+AS01 and RSVpreF vaccines for preventing RSV-related hospitalization and death among community-dwelling Medicare beneficiaries aged 65 years and older

1. US FDA. FDA Approves First Respiratory Syncytial Virus (RSV) Vaccine: Arexvy Approved for Individuals 60 Years of Age and Older. 2023; https://www.fda.gov/news-events/press-announcements/fda-approves-first-respiratory-syncytial-virus-rsv-vaccine, 2024.
2. US FDA. ABRYSVO. 2024; https://www.fda.gov/vaccines-blood-biologics/abrysvo, 2024.

Our Approach to Generating RWE



Forshee 2021 Presentation

Methods

- **Data Sources**: Medicare enrollment records and claims data from Medicare Parts A (hospital insurance), B (medical insurance), and D (prescription drug coverage)

- **Study Population:** Community-dwelling (not in nursing home) Medicare Fee-For-Service (FFS) beneficiaries aged 65 years and older
  - Required continuous enrollment in the year prior to study start
  - Excluded beneficiaries on dialysis or in nursing home at study start
  - Excluded beneficiaries with prior RSV vaccination

Retrospective cohort study

OBSERVATION PERIOD

August 6, 2023 to March 2, 2024

EXPOSURES

Time-varying RSV vaccination status RSVPreF3+AS01 (GSK) or RSVPreF (Pfizer)

POPULATION

Medicare Fee-for-Service community-dwelling beneficiaries aged ≥65 years

OUTCOMES

RSV-related hospitalization,

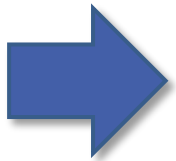
RSV-related death

Methods: Addressing Bias and Challenges

1. **Under-Capture of RSV Diagnosis in Claims Data**
2. **False Positive RSV Diagnoses in Claims Data**
3. **Differential Health Seeking Behavior**

PROBLEM

- Under-capture of RSV diagnosis in claims data



SOLUTION

- Restrict outcomes to severe ones such as RSV-related hospitalization and death

Methods: Addressing Bias and Challenges

1. Under-Capture of RSV Diagnosis in Claims Data
2. **False Positive RSV Diagnoses in Claims Data**
3. Differential Health Seeking Behavior

PROBLEM

- False positive RSV diagnosis in claims data could bias results towards the null

SOLUTION

- Restrict follow-up to after Oct 1, 2023 where beneficiaries live in census tract with RSV circulation ≥8 cases per 100k beneficiaries
- Restrict analyses to severe cases
- Conduct sensitivity analyses for alternative high RSV circulation definition

Methods: Addressing Bias and Challenges

1. Under-Capture of RSV Diagnosis in Claims Data
2. False Positive RSV Diagnoses in Claims Data
3. **Differential Health Seeking Behavior**

PROBLEM

- Vaccinated individuals tend to seek healthcare more than unvaccinated individuals

SOLUTION

- Conduct subgroup analysis to only include people with prior influenza vaccination
- Restrict analyses to severe cases, less likely to be affected by health seeking behaviors

Statistical Analysis: Marginal Structural Model

Covariates: Demographic, socio-economic, clinical characteristics at the time of the index date

Inverse Probability Weighting (IPW): Addressed imbalance in all measured covariates

Model: Poisson model with time-interval (week) intercepts

Adjustments: Doubly robust approach controlled for residual confounding; sensitivity analyses

Population Size and Descriptive Statistics

- **In the last week of the study, before weighting:**
  - 10,843,461 beneficiaries (79.0%) present in unvaccinated cohort
  - 1,970,682 beneficiaries (14.4%) present in GSK vaccinated cohort
  - 909,188 beneficiaries (6.6%) present in Pfizer vaccinated cohort
- **Further descriptive statistics:**
  - Largest age category across all cohorts: ages 70-74 years (~30-31%)
  - A majority of all cohorts: Females: (~58%)
  - Largest race category: Whites (~86-90%)
  - Vast majority of beneficiaries: aged into Medicare without end-stage renal disease (ESRD): (~91-94%)

Propensity Scores

- **In general, covariates were well-balanced (SMD < 0.1)**
  - **Covariates that remained imbalanced after weighting include:**
    - Census-tract level RSV circulation
    - Census-tract level population density
    - Prior influenza vaccination*
    - Prior COVID-19 vaccination*

*Prior vaccination variables were not included in the propensity score model, but were included in the outcome model

RSV-related Hospitalization: Primary Analysis

Table 1. Vaccine Effectiveness Estimates (95% CI), Primary Model

RSV-related Hospitalization	Primary Analysis*
Overall Vaccine Effectiveness (VE)	
RSV Vaccinated vs. Unvaccinated	81.8% (80.0%, 83.4%)
Brand-Specific VE	
Pfizer vs. Unvaccinated	84.9% (82.1%, 87.3%)
GSK vs. Unvaccinated	80.0% (77.8%, 82.1%)

- **Both Pfizer and GSK RSV vaccines are highly effective against RSV-related hospitalization**
- *** Preliminary results**

RSV-related Hospitalization: Subgroup Analysis

Table 2. Vaccine Effectiveness Estimates (95% CI), Subgroup Analysis on Prior Influenza Vaccine

RSV-related Hospitalization	Primary Analysis*	Prior Influenza Vaccination*
Overall VE		
RSV Vaccinated vs. Unvaccinated	81.8% (80.0%, 83.4%)	83.1% (81.3%, 84.7%)
Brand-Specific VE		
Pfizer vs. Unvaccinated	84.9% (82.1%, 87.3%)	86.1% (83.3%, 88.5%)
GSK vs. Unvaccinated	80.0% (77.8%, 82.1%)	81.4% (79.1%, 83.4%)

- **Differential health seeking behavior has limited impact on RSV-related hospitalization VE results**
- *** Preliminary results**

RSV-related Hospitalization: Sensitivity Analyses

Table 3. Vaccine Effectiveness Estimates (95% CI), Alternate Circulation Rate Sensitivity Analyses

RSV-related Hospitalization	Primary Analysis*	Low Circulation Threshold*	High Circulation Threshold*	All Study Time*
Overall VE				
RSV Vaccinated vs. Unvaccinated	81.8% (80.0%, 83.4%)	80.6% (78.7%, 82.3%)	81.4% (79.6%, 83.1%)	81.8% (80.0%, 83.4%)
Brand-Specific VE				
Pfizer vs. Unvaccinated	84.9% (82.1%, 87.3%)	84.2% (81.2%, 86.8%)	84.2% (81.3%, 86.7%)	84.9% (82.1%, 87.3%)
GSK vs. Unvaccinated	80.0% (77.8%, 82.1%)	78.5% (76.1%, 80.7%)	79.8% (77.5%, 81.9%)	80.0% (77.8%, 82.1%)

Primary Analysis: include study time after October 1, 2023 where beneficiaries live in census tracts with ≥8 cases per 100k beneficiaries in follow up

Low Circulation Rate Threshold: include all study time after October 1, 2023 in follow up

High Circulation Rate Threshold: include study time after October 1, 2023 where beneficiaries live in high RSV circulation census tract (≥16 cases per 100k beneficiaries) in follow up

All Study Time: include all study time where beneficiaries live in census tracts with RSV circulation ≥8 cases per 100k beneficiaries in follow up

*** Preliminary results**

RSV-Related Death

Table 4. Vaccine Effectiveness Estimates (95% CI), RSV-Related Death

RSV-related Death	RSV Vaccinated vs. Unvaccinated*
Overall VE	
Death within 14 days of RSV hospitalization	84.4% (74.3%, 90.5%)
Death within 7 days of RSV hospitalization	85.6% (75.5%, 91.6%)
Death during inpatient hospitalization	87.7% (77.4%, 93.3%)

- **Both Pfizer and GSK RSV vaccines are highly effective against RSV-related death**
- *** Preliminary results**

Strengths and Limitations

- Strengths:
  - Largest population-based assessment of RSV vaccine effectiveness
  - Results generalizable to the 65+ years of age population
  - Able to evaluate rare outcomes including death
- Limitations:
  - Remaining imbalances in RSV circulation post-weighting
  - Potential for residual confounding
  - Not able to evaluate waning effectiveness

Conclusion

- Preliminary results found high vaccine effectiveness for Pfizer and GSK RSV vaccines again RSV-related hospitalization and death
- Preliminary results similar across different high RSV circulation definitions and healthcare utilization subgroups
- Next Steps:
  - Waning Immunity
  - Additional sensitivity and subgroup analyses, and secondary outcomes
  - Evaluating new RSV vaccine (mRESVIA by Moderna, approved in May 2024)

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Methods Development and Future Directions of Vaccine Safety Surveillance

Mao Hu, BS
Acumen, LLC

Outline

- 2024 Vaccine Safety Surveillance Methods
- Example: RSV Vaccine Safety Surveillance
- Example: PCV 20 Vaccine Safety Surveillance
- Planned 2025 Vaccine Safety Surveillance Methods

2024 Vaccine Safety Surveillance Methods

- **Descriptive monitoring:** Continuous monitoring of vaccination and outcome counts to assess feasibility of inferential studies
- **Inferential analysis:** Analyses comparing post-vaccination risk versus comparators such as historical background rates, concurrent vaccinated persons in control period, or self-controlled control periods

2024 Vaccine Safety Surveillance Methods

- **Observed Versus Expected:** Compare vaccinated persons in risk period versus historical background rates
- **Concurrent Comparator Design:** Compare vaccinated persons in risk period versus other vaccinated persons in their control period
- **Self-Controlled Case Series:** Compare vaccinated persons in risk period versus self-matched control periods
  - Analyses were conducted early and late season data depending on regulatory need or availability of cases

2024 Vaccine Safety Surveillance Methods

Study Design	Strengths	Limitations
Observed Versus Expected	Rapid identification of elevated risk	Limited adjustment for confounding
Concurrent Comparator Design	Reduced bias due to comparison of vaccinated persons	Less robust adjustment compared to self-controlled case series
Self-Controlled Case Series	Adjustment for time-fixed confounding and other sources of bias	Less rapid identification of elevated risk due to long observation period

RSV Vaccine Safety Surveillance

Observed vs. Expected Analysis (Data Through Dec 2023)

RSV Vaccine Exposure	Eligible Vaccines	IRR	IRR* 95% Confidence Interval (CI)
RSVPreF	682,267	6.9	(1.9, 12.0)
RSVPreF3+AS01	1,379,335	2.8	(0.5, 5.0)

End-of-Season SCCS Analysis (Data Through July 2024)

Seasonality, Farrington Analysis, and PPV-Based Multiple Imputation – Chart Confirmed + Not Returned Cases

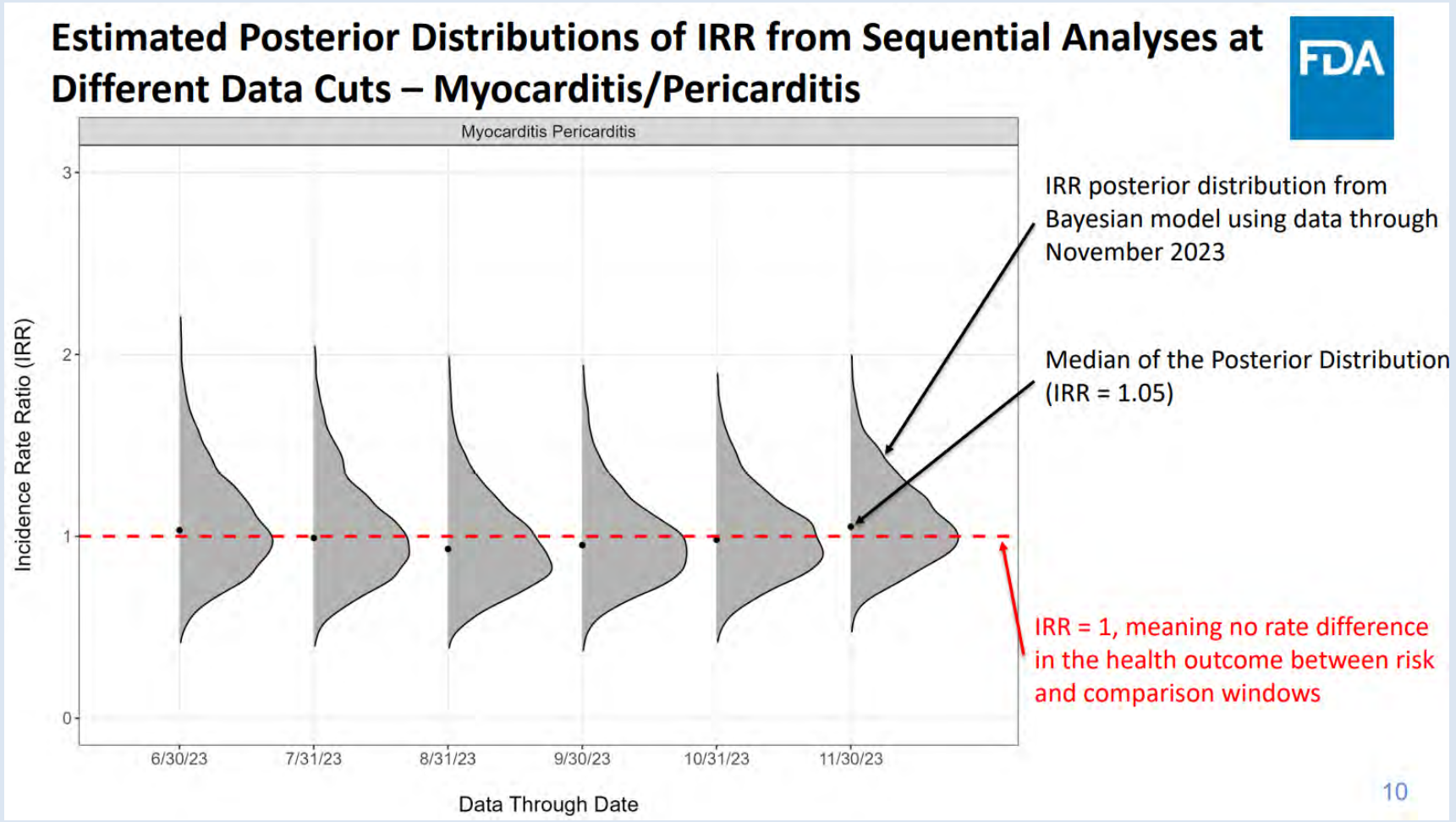
Inferential Analysis Results	RSVPreF3+AS01	RSVPreF
Eligible Vaccines	2,202,247	1,024,442
*Cases in the Risk Interval	24	18
*Cases in the Control Interval	11	<11
IRR (95% CI)	2.46 (1.19, 5.08)	2.02 (0.93, 4.40)

Observed vs. Expected design using historical background rates for early risk assessment

End-of-Season SCCS with chart-confirmed cases for less biased risk assessment

Presented at February 2024 and October 2024 Advisory Committee on Immunization Practices meetings

Concurrent Comparator Design for PCV 20 Safety Surveillance



Concurrent comparator design for near real-time sequential analysis

Bayesian Poisson regression used to update incidence rate ratio estimates

Presented at February 2024 Advisory Committee on Immunization Practices meeting

Planned 2025 Vaccine Safety Surveillance Methods

- **Descriptive Monitoring:** Continuous monitoring of vaccination and outcome counts to assess feasibility of inferential studies
- **Observed vs. Expected (Commercial Data Partners):** Early-season signal detection analyses using historical comparator
- **Concurrent Comparator (Medicare):** Sequential signal detection analyses using vaccinated concurrent comparator
- **Self-Controlled Studies:** Evaluate selected outcomes using fully adjusted inferential analyses

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- CBER OBPV
- Federal Partners: CMS, VA, CDC
- FDA Partners: Acumen, CVS Health, Carelon, IQVIA, OHDSI, Optum

Moderated Discussion and Q&A

Moderator: Christina Silcox

Duke-Margolis Institute for Health Policy

Break for Lunch

The workshop will resume at **1:40 p.m. ET**

Insights into the Future: Sentinel System 3.0

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

Panelists: **Patricia Bright**, U.S. Food and Drug Administration

Amarilys Vega, U.S. Food and Drug Administration

Insights and Innovations Informing our Future

Patricia (Trish) Bright, PhD, MSPH, RN
Sentinel System Program Lead
Office of Surveillance and Epidemiology,
Regulatory Science Staff

November 7, 2024

Disclaimer

- The views expressed in this presentation are those of the presenter and not necessarily those of the US Food and Drug Administration.

Agenda

- Background
- Five years of work
- Extension year
- Informing the direction forward

Background

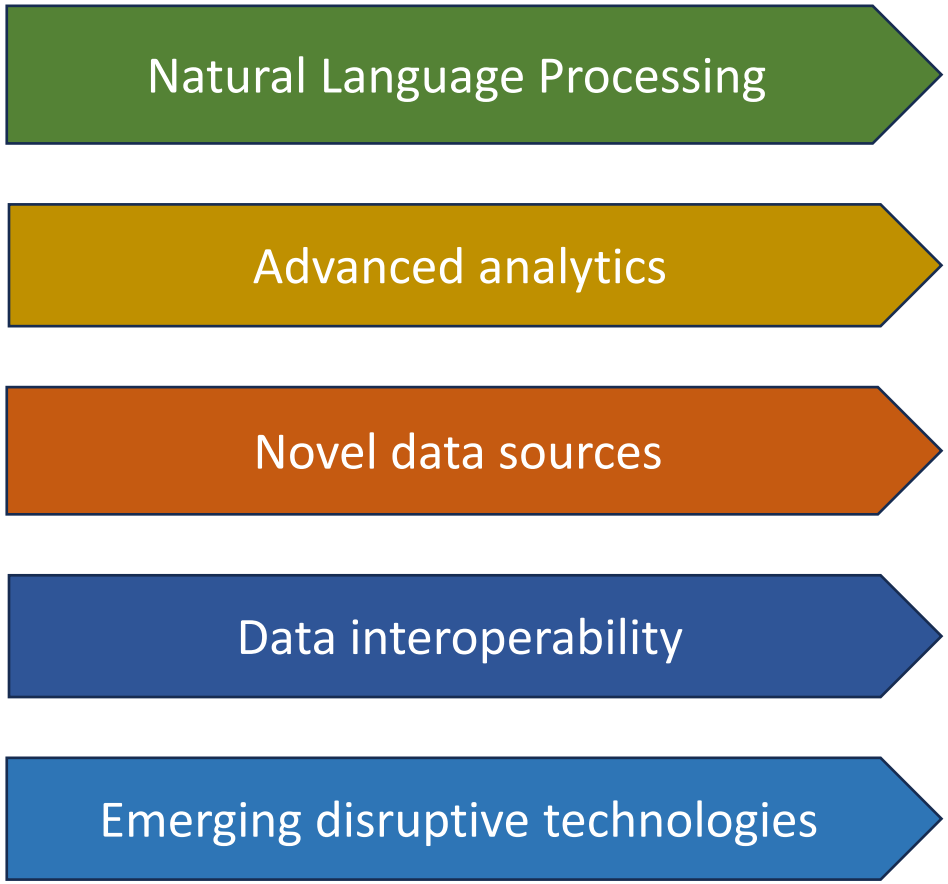
Sentinel System Five- Year Strategy - - January 2019

- An independent assessment of CDER's Sentinel System was completed around 2017 to fulfill the Prescription Drug User Fee Act (PDUFA) V
- In response to the assessment, CDER developed a Strategic Plan that informed the contract (Sentinel 2.0) with a focus on improving Sentinel System capabilities to meet CDER's needs

Sentinel System Five- Year Strategy, January 2019

- The Innovation Center (IC) will prioritize, develop, and incorporate innovative technologies and new data sources into the Sentinel System to help FDA achieve key legislative mandates/strategic priorities

Sentinel System Five- Year Strategy - - January 2019



- Focus investment on innovations emerging from new data science disciplines, such as natural language processing and machine learning, and seek to expand its access to and use of Electronic Health Record (EHR) data
- A more robust Sentinel System: a transformative, multi-purpose national data and scientific resource center for evidence-generation

Five Years of Work

Sentinel Innovation Center Vision

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

Feature Engineering

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

Causal Inference

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

Detection Analytics

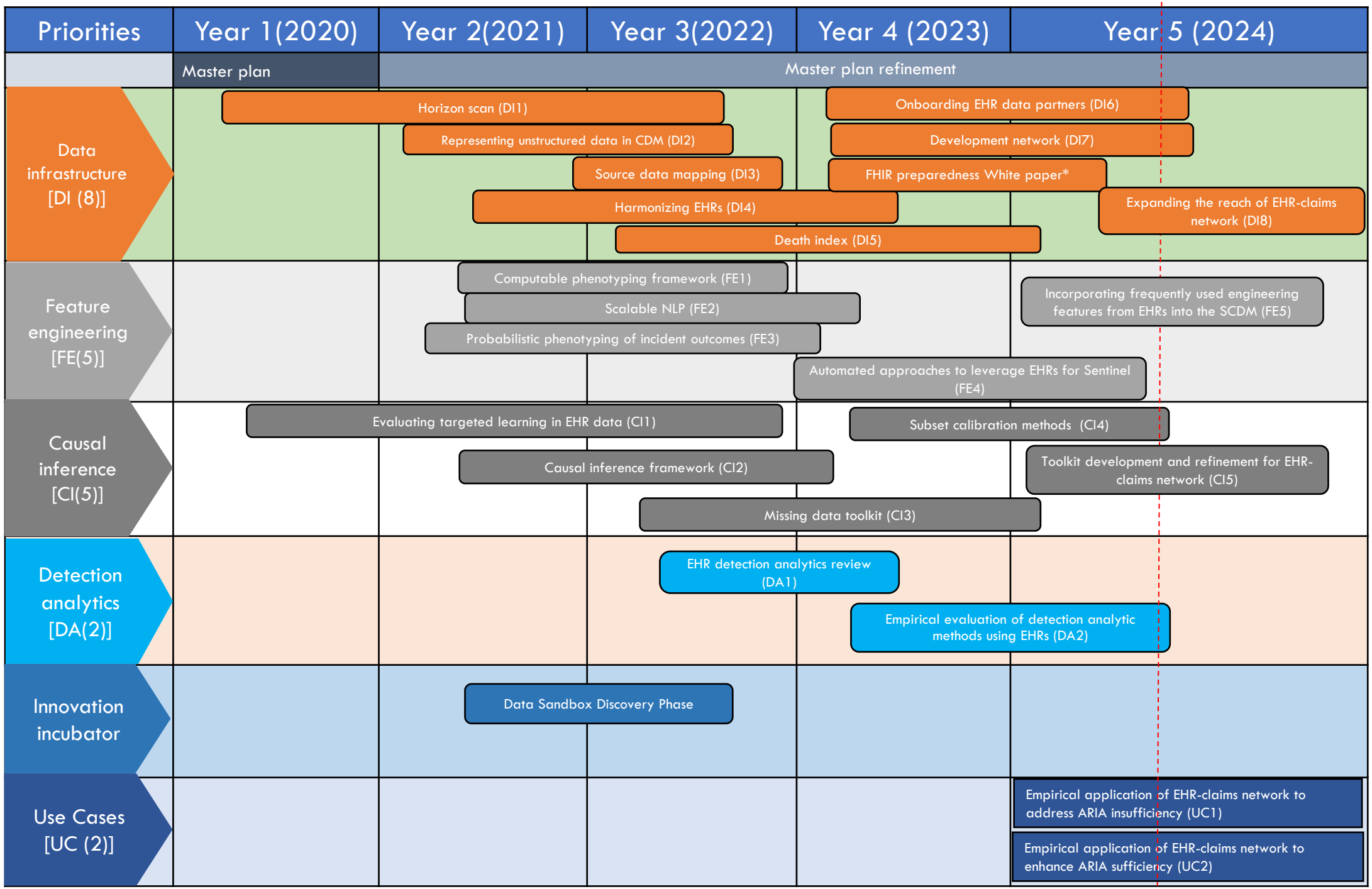
- Development of signal detection approaches to account for and leverage differences in data content and structure of EHRs

Sentinel Innovation Center Vision

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

2020 → 2024

Desai RJ, Matheny ME, Johnson K, et al. Broadening the reach of the FDA Sentinel system: A roadmap for integrating electronic health record data in a causal analysis framework. NPJ Digit Med. 2021;4(1):170.



- Five Years of Work!
- Plus an extra contract extension year allows for folding the learnings from the development projects into an operational system

*ASPE supported project

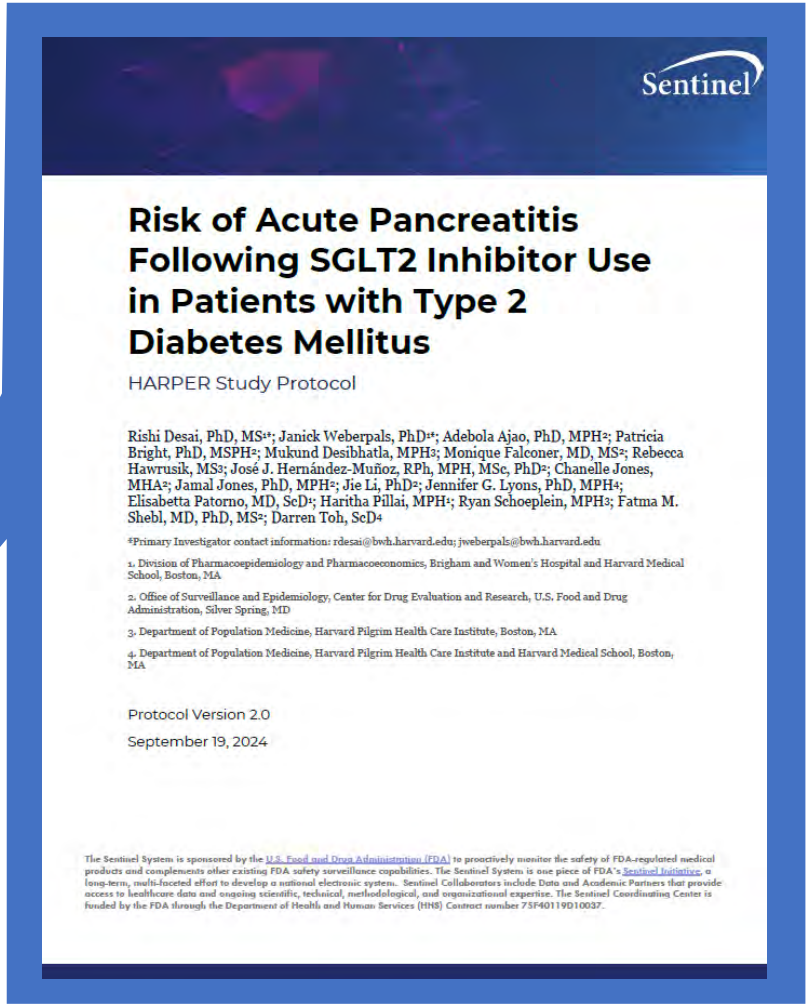
Extension Year

Use Case 1: Improving ARIA Sufficiency

- Due to limitations inherent to claims data, Sentinel's Active Risk Identification and Analysis (ARIA) system is sometimes deemed insufficient to address a regulatory question of interest
- Linking EHRs and claims data and incorporating advanced methods can overcome some of ARIA's current limitations

  Aim 1: For health outcomes of interest for which ARIA analyses were previously determined to be insufficient, conduct fitness-for-purpose analyses and assess the likelihood of successful development of computable phenotypes by incorporating rich EHR data and data-driven modeling methods

  Aim 2: Conduct a protocol-based pharmacoepidemiologic analysis to evaluate the complexities encountered and propose solutions for typical claims-based ARIA analyses that will be handled by linked EHR-claims data


Sentinel

Risk of Acute Pancreatitis Following SGLT2 Inhibitor Use in Patients with Type 2 Diabetes Mellitus

HARPER Study Protocol

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Protocol Version 2.0

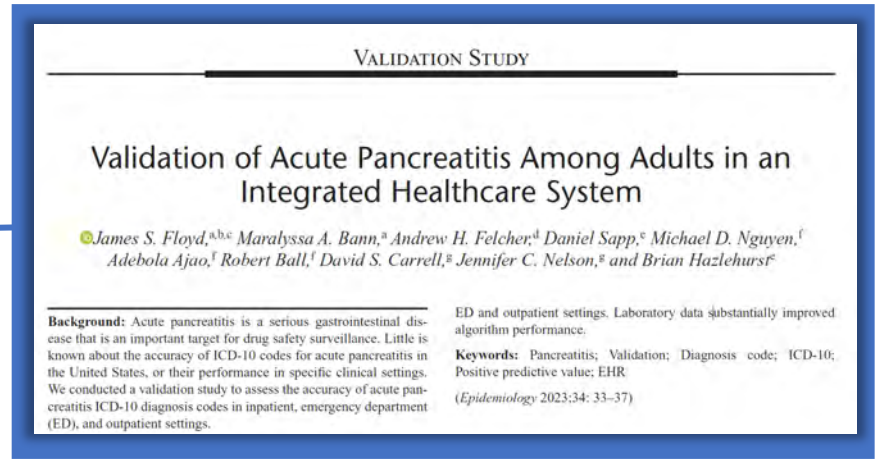
September 19, 2024

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number 75F40119D10037.

https://www.sentinelinitiative.org/methods-data-tools/methods/empirical-application-sentinel-electronic-health-record-ehr-and-claims

Pharmacoepidemiology study in **linked EHR-claims data**

- **Context**: In 2017, ARIA was determined to be insufficient to assess the risk of acute pancreatitis with use of SGLT-2 inhibitors
  - No longer an active safety concern, but data challenges (e.g., outcome identification) are still relevant
  - Diagnosis codes are known to have limited ability to identify acute pancreatitis (PPV: 55-66%), which raises concerns regarding the validity of prior studies due to outcome misclassification
- **Data Source**: Sentinel RWE Data Enterprise commercial network
- **Approach**: A cohort study using propensity-score fine stratification for confounding adjustment
  - Outcome: acute pancreatitis, defined using a probabilistic phenotyping algorithm
  - Applying multiple imputation methods to analytically address missingness in key confounding variables (e.g., HbA1c and BMI)
- **Status**: Results anticipated by the end of the 2024



VALIDATION STUDY

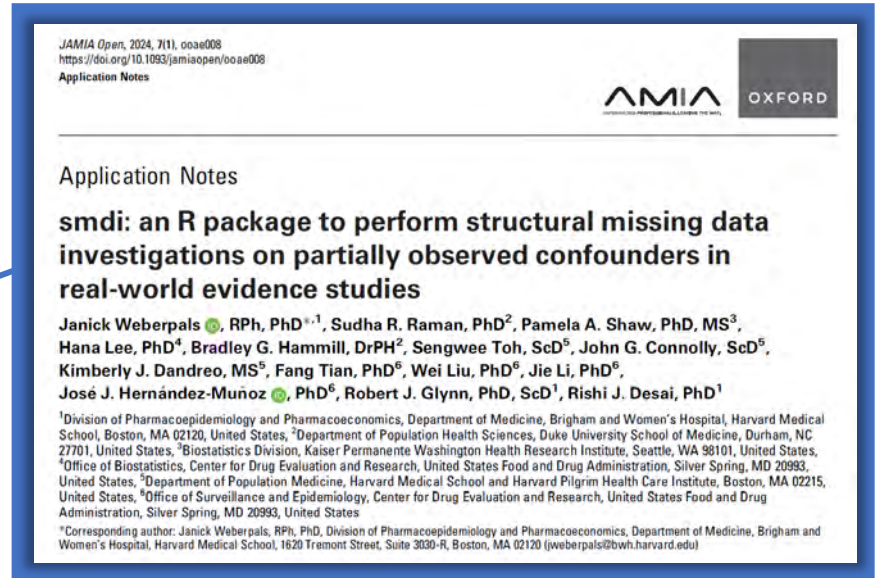
Validation of Acute Pancreatitis Among Adults in an Integrated Healthcare System

James S. Floyd,[a,b,c] Maralyssa A. Bann,[a] Andrew H. Felcher,[d] Daniel Sapp,[e] Michael D. Nguyen,[f] Adebola Ajao,[f] Robert Ball,[f] David S. Carrell,[g] Jennifer C. Nelson,[g] and Brian Hazlehurst[e]

Background: Acute pancreatitis is a serious gastrointestinal disease that is an important target for drug safety surveillance. Little is known about the accuracy of ICD-10 codes for acute pancreatitis in the United States, or their performance in specific clinical settings. We conducted a validation study to assess the accuracy of acute pancreatitis ICD-10 diagnosis codes in inpatient, emergency department (ED), and outpatient settings. ED and outpatient settings. Laboratory data substantially improved algorithm performance.

Keywords: Pancreatitis; Validation; Diagnosis code; ICD-10; Positive predictive value; EHR

(*Epidemiology* 2023;34: 33–37)



JAMIA Open, 2024, 7(1), ooae008
https://doi.org/10.1093/jamiaopen/ooae008
Application Notes

AMIA OXFORD

Application Notes

smdi: an R package to perform structural missing data investigations on partially observed confounders in real-world evidence studies

Janick Weberpals, RPh, PhD*,[1], Sudha R. Raman, PhD[2], Pamela A. Shaw, PhD, MS[3], Hana Lee, PhD[4], Bradley G. Hammill, DrPH[2], Sengwee Toh, ScD[5], John G. Connolly, ScD[5], Kimberly J. Dandreo, MS[5], Fang Tian, PhD[6], Wei Liu, PhD[6], Jie Li, PhD[6], José J. Hernández-Muñoz, PhD[6], Robert J. Glynn, PhD, ScD[1], Rishi J. Desai, PhD[1]

[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02120, United States, [2]Department of Population Health Sciences, Duke University School of Medicine, Durham, NC 27701, United States, [3]Biostatistics Division, Kaiser Permanente Washington Health Research Institute, Seattle, WA 98101, United States, [4]Office of Biostatistics, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD 20993, United States, [5]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA 02215, United States, [6]Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, United States Food and Drug Administration, Silver Spring, MD 20993, United States

*Corresponding author: Janick Weberpals, RPh, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Suite 3030-R, Boston, MA 02120 (jweberpals@bwh.harvard.edu)

Floyd JS, Bann MA, Felcher AH, et al. Validation of Acute Pancreatitis Among Adults in an Integrated Healthcare System. *Epidemiology*. Jan 1 2023;34(1):33-37.
Bann MA, Carrell DS, Gruber S, et al. A comparison of manual and automated approaches to developing computable algorithms for identifying acute pancreatitis. Under review.
Weberpals J, Raman SR, Shaw PA, et al. smdi: an R package to perform structural missing data investigations on partially observed confounders in real-world evidence studies. *JAMIA Open*. Apr 2024;7(1):ooae008.

Use Case 2: Strengthening ARIA Sufficient Analyses

- Although ARIA analyses provide vital information to the FDA to aid in regulatory decision making, often uncertainties remain due to lack of data availability in insurance claims for critical variables pertaining to the research question (e.g., residual confounding, lack of validated outcome algorithms)

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

  Aim 2: Correcting claims analyses for unmeasured confounding using subset calibration tools

  Aim 3: Real-time validation of code-based algorithms

  Aim 4: Identifying use of cannabis-derived products (CDP) from free-text notes

  Aim 5: Expand on a principled quantitative bias analysis (QBA) at the design stage that could allow for better understanding of the uncertainties associated with potential unmeasured confounding

https://www.sentinelinitiative.org/methods-data-tools/methods/empirical-application-sentinel-ehr-and-claims-data-partner-network

Identifying use of cannabis-derived products (CDP) from free-text notes

- **Context**: There is increasing interest in the potential utility of cannabis for a variety of medical conditions, as well as research on the potential adverse health effects from use of cannabis.
  - FDA has not approved cannabis for the treatment of any disease/condition, but has approved Epidiolex®, a cannabis-derived product (CDP) in the form of a cannabidiol (CBD)
  - We selected this as a use case: From a regulatory perspective, we haven't been asked to assess whether Sentinel's ARIA system is sufficient to address CBD-related regulatory questions; however, there is important public health value in better understanding use of these products
  - Despite increased patient usage of unapproved cannabis-derived products in recent years, CDP is not currently captured in structured claims data
  - Usage of cannabis-derived products, however, may be recorded in unstructured patient-reported data EHRs
- **Data Source**: Sentinel RWE Data Enterprise development network (Vanderbilt University Medical Center)
- **Approach**: Develop a method for capturing patient usage of CDP from linked EHR-claims data and perform exploratory analyses to characterize patients using CDP
  - Identify individuals with suspected CDP exposure in structured EHR data
  - Use NLP tools and algorithms to find CDP exposure in text from clinical notes (iterative process)
  - Analyze patient cohorts identified based on exposure to Epidiolex, CBD, and other CDP to understand demographics, clinical characteristics, and comedications
- **Status**: results anticipated in Spring 2025

U.S. Food and Drug Administration. "FDA and Cannabis Research and Drug Approval Process." https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process
Carrell DS, Cronkite DJ, Shea M, et al. Clinical documentation of patient-reported medical cannabis use in primary care: Towards scalable extraction using natural language processing methods. Subst Abus. 2022;43(1): 917-924.

Sentinel System PDUFA VII Commitments

Extension year: Project underway to extend, test, and adapt an algorithm for disconnected negative controls to large-scale healthcare data

M. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

FDA will contin
scientific approa
prevention, and
regulatory activ
system will imp
access to needed

User fees will p
2) optimization
capabilities and
analytic capabil
the understandi

2. Optimization of the Sentinel Initiative

The us
continu
Effecti
quality
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i. Pregnancy Safety

The goal of pregnancy safety
studies is to inform labeling o
or evaluate safety signals in a

(1) FDA will develop a fr
types of post-market p
used, incorporating kn
market studies have be
identifying gaps in kn
demonstration projects
such as, but not limite
studies, anticipated ex
(FRP) and pregnant w
proposed risk mitigati
type of risk to be detec
address the use of preg
data sources including
efficient means of obta

ii. Use of Real-World Evidence – Negative Controls

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

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

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

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

Extension year: developing protocols for pregnancy safety demonstration projects to identify best study approach to fill knowledge gaps

Informing the Direction Forward

FDA- Sentinel System Innovation Center Publications - - 2024

Publications available at SentinelInitiative.org
(under "News & Events" then "Documents, Presentations, & Publications")

The FDA Sentinel Real World Evidence Data Enterprise (RWE-DE), Pharmacoepidemiol Drug Saf. 2024 Oct;33(10):e70028. doi: 10.1002/pds.70028.

Invited commentary: A future of data-rich pharmacoepidemiology studies– transitioning to large-scale linked EHR + claims data, Am. J. Epidemiol. 2024 July 16. doi.org/10.1093/aje/kwae226

A Principled Approach to Characterize and Analyze Partially Observed Confounder Data from Electronic Health Records, J. Clin. Epidemiol. 2024 May 21. doi.org/10.2147/CLEP.S436131

Finding Uncoded Anaphylaxis in Electronic Health Records to Estimate the Sensitivity of ICD10 Codes, Am. J. Epidemiol. 2024 May 16. doi.org/10.1093/aje/kwae063

A General Framework for Developing Computable Clinical Phenotype Algorithms, J Am Med Inform Assoc. 2024 May 15:ocae121. doi: 10.1093/jamia/ocae121

Targeted Learning with an Undersmoothed Lasso Propensity Score Model for Large-Scale Covariate Adjustment in Healthcare Database Studies, AJE. 2024 Mar 21. doi.org/10.1093/aje/kwae023

smdi: An R Package to Perform Structural Missing Data Investigations on Partially Observed Confounders in Real-world Evidence Studies, JAMIA Open. 2024 Jan 31. doi.org/10.1093/ooae008

Scalable incident detection via natural language processing and probabilistic language models. Sci Rep 14, 23429 (2024). Https://doi.org/10.1038/s41598-024-72756-7

Enhancing Postmarketing Surveillance of Medical Products With Large Language Models. JAMA Netw Open. 2024;7(8):e2428276. doi:10.1001/jamanetworkopen.2024.28276

Process guide for inferential studies using healthcare data from routine clinical practice to evaluate causal effects of drugs (PRINCIPLED): considerations from the FDA Sentinel Innovation Center BMJ 2024; 384 :e076460 doi:10.1136/bmj-2023-076460

A simulation-based bias analysis to assess the impact of unmeasured confounding when designing non-randomized database studies. Am. J. Epidemiol. Epub ahead of print. https://doi.org/10.1093/aje/kwae102, 2024.

FDA- Sentinel System Innovation Center Webinars - - 2024

Recorded Webinars available at SentinelInitiative.org
(under "News & Events" then "Meetings, Workshops, & Trainings")
Look for: "2024 Sentinel Innovation and Methods Seminar Series," posted January 1, 2024

September 25, 2024:	Regional Health Information Exchanges as Critical National Infrastructure: Supporting Federal Agency Missions
September 10, 2024:	Assessing Treatment Effects in Observational Data with Missing Confounders: A Comparative Study of Practical Doubly-Robust and Traditional Missing Data Methods
August 5, 2024:	Overview of CDER's Real-World Evidence Demonstration Projects
April 22, 2024:	Opportunities and Challenges in the use of Large Language Models for Post-Marketing Surveillance of Medical Products
March 25th, 2024:	Data-driven Phenotyping Algorithms for Acute Health Conditions: Applying PheNorm to COVID-19
February 29, 2024	A PRocess guide for INferential studies using healthcare data from routine ClinIcal Practice to evaLuate causal Effects of Drugs (PRINCIPLED)

The next presentation will provide an overview of CDER's new Sentinel contract recompete

Thank you

Sentinel System 3.0: An Overview

Amarilys (Lisy) Vega, MD, MPH

Director, Regulatory Science Staff

Office of Surveillance and Epidemiology

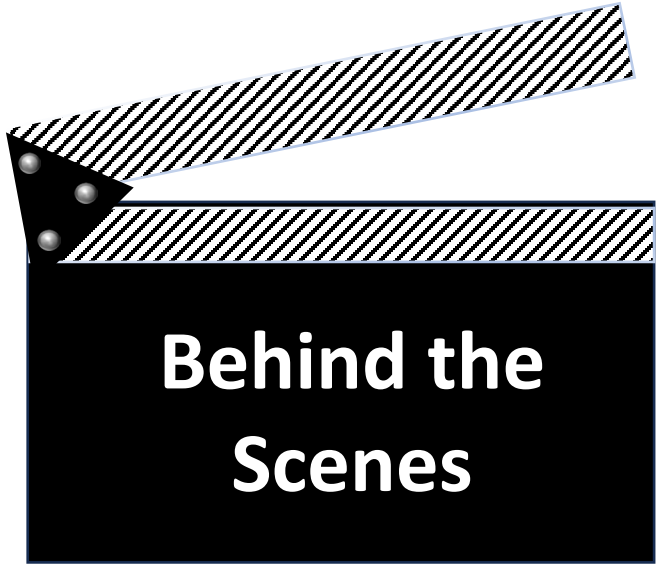
November 7, 2024

Disclaimer

- The views expressed in this presentation are those of the presenter and not necessarily those of the US Food and Drug Administration.

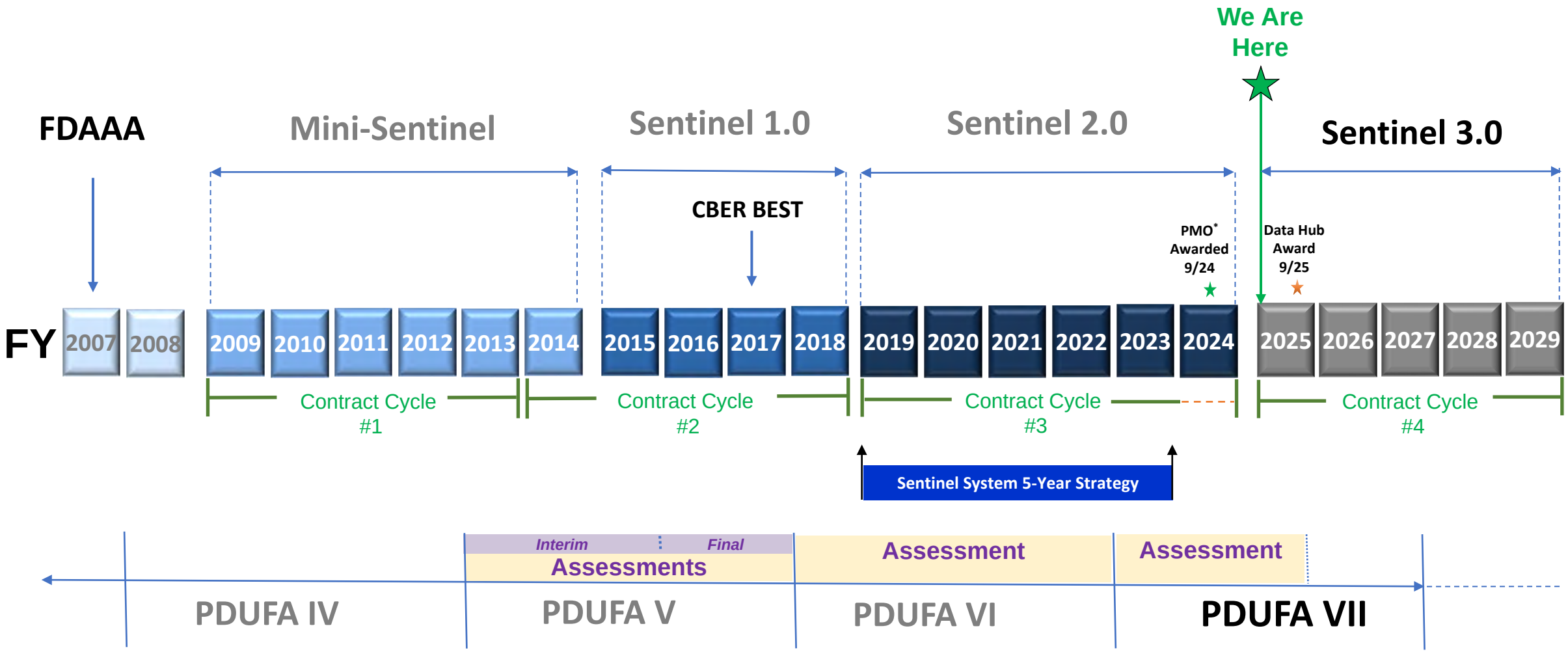
Agenda

- Sentinel System Contract Cycles
- Sentinel 3.0 Update
- Next Steps



Sentinel System Contract Cycles

Sentinel System Contract Cycles

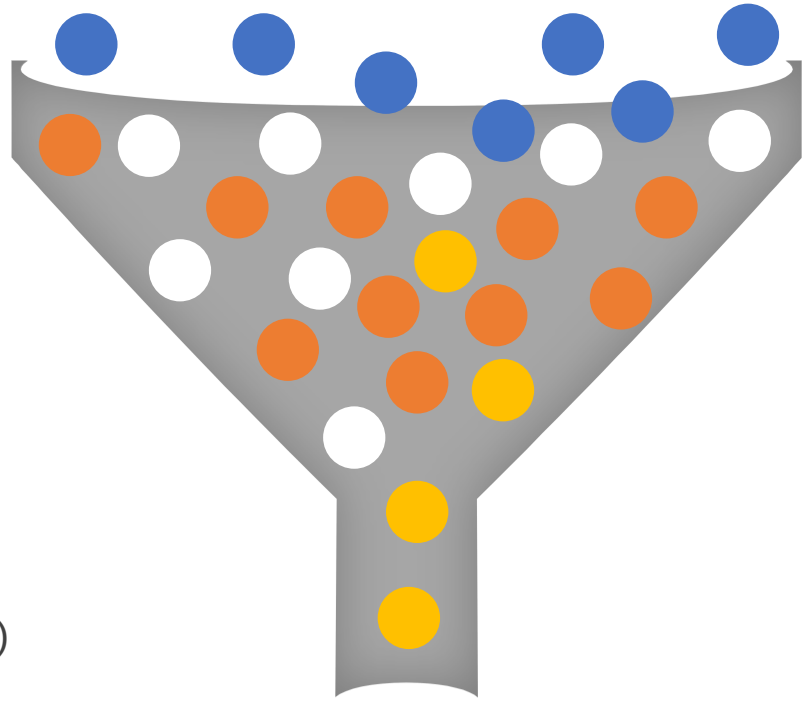


*PMO: Program Management Organization contract

Sentinel 3.0 Update

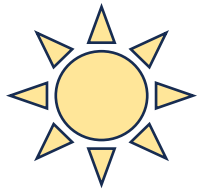
Recompete Process

- Input from CDER Senior Leadership, CDER Sentinel users, Office of Acquisitions and Grant Services (OAGS)
- Sentinel 2.0 scientific work
- Market research
  - Requests for information (RFI)
    - RFI Nov 2022: market capabilities to address requirements (SAM.GOV)
    - RFI Dec 2023: public input on the proposed new contracting approach (i.e., tier approach) (SAM.GOV)
    - RFI March 2024: public comments regarding capabilities to address Sentinel System 3.0 Program Management & Informatics support requirements (SAM.GOV)



Data Collection

Goals of Sentinel System 3.0



- Narrowing the focus
  - Shifting emphasis from building of capabilities in Sentinel 2.0 to the generation of scientific evidence required to fulfill congressional requirements, user fee commitments and CDER priorities
- Broadening access to data resources
  - Expand access to multiple data sources and data types to improve ARIA sufficiency and readiness to address public health emergencies
  - Implement a more flexible, multifaceted approach to access:
    - More granular data
    - Advanced analytics methods to abstract data from medical records
    - Advanced statistical methods to conduct inferential studies
- Scalable capabilities to accommodate funding variability

Key Program Operation Elements

Funding $$$

- Access to data and associated services are expensive
- ARIA is an unfunded mandate
- Funding variability by fiscal year

Staff

- Executive Sponsor: Dr. Gerald Dal Pan
- CDER Lead: Dr. Robert Ball
- Sentinel Program Lead: Dr. Patricia Bright
  - Epidemiologists (7)
  - Program Management (4)
  - Acquisitions (1)

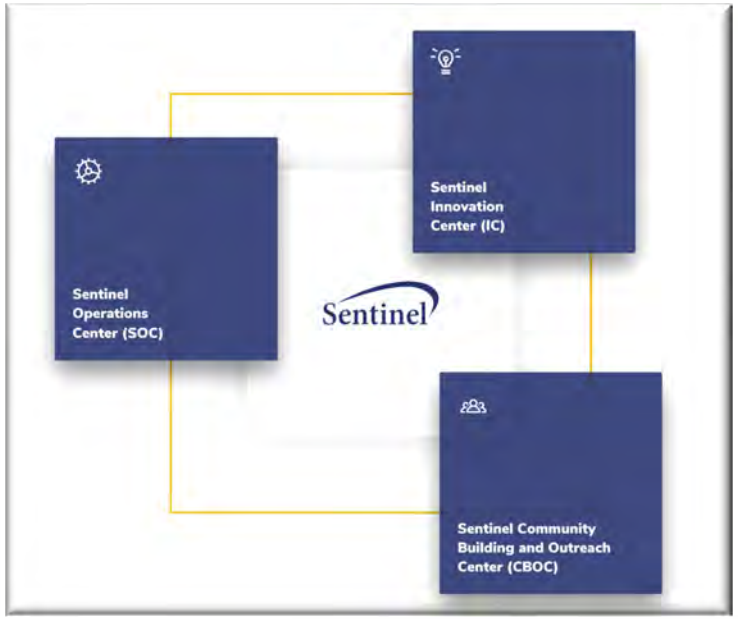
Contract

- CDER/OSE* manages the Sentinel System contract
- Contracting runs in 5-year cycles
- Current contract vehicle is an Indefinite Delivery/Indefinite Quantity (IDIQ) contract

*OSE=Office of Surveillance & Epidemiology

Sentinel System 2.0 to 3.0

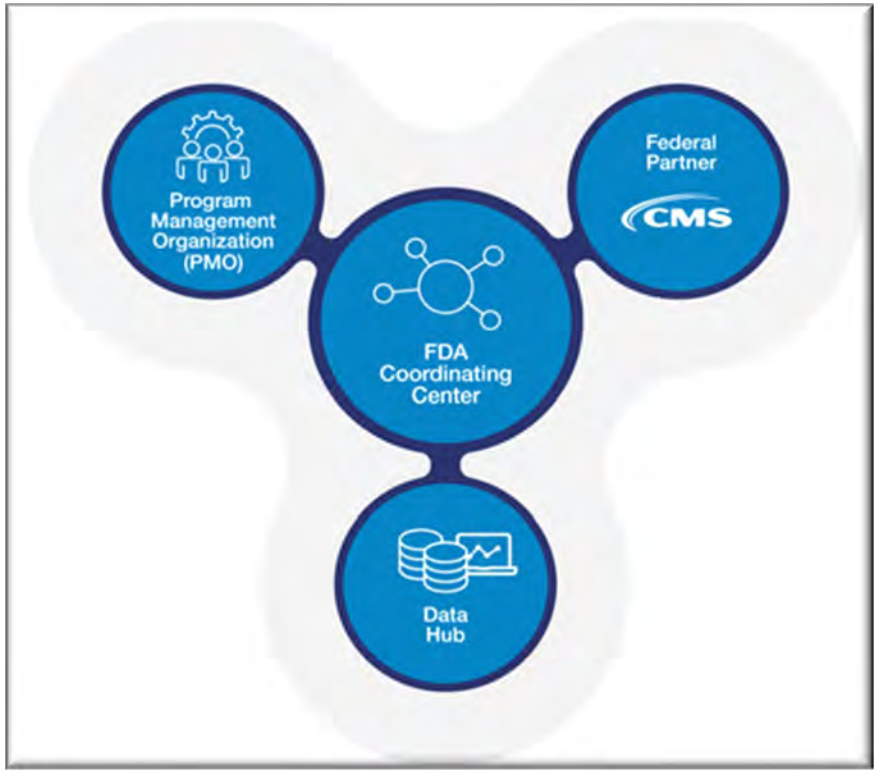
Sentinel System 2.0



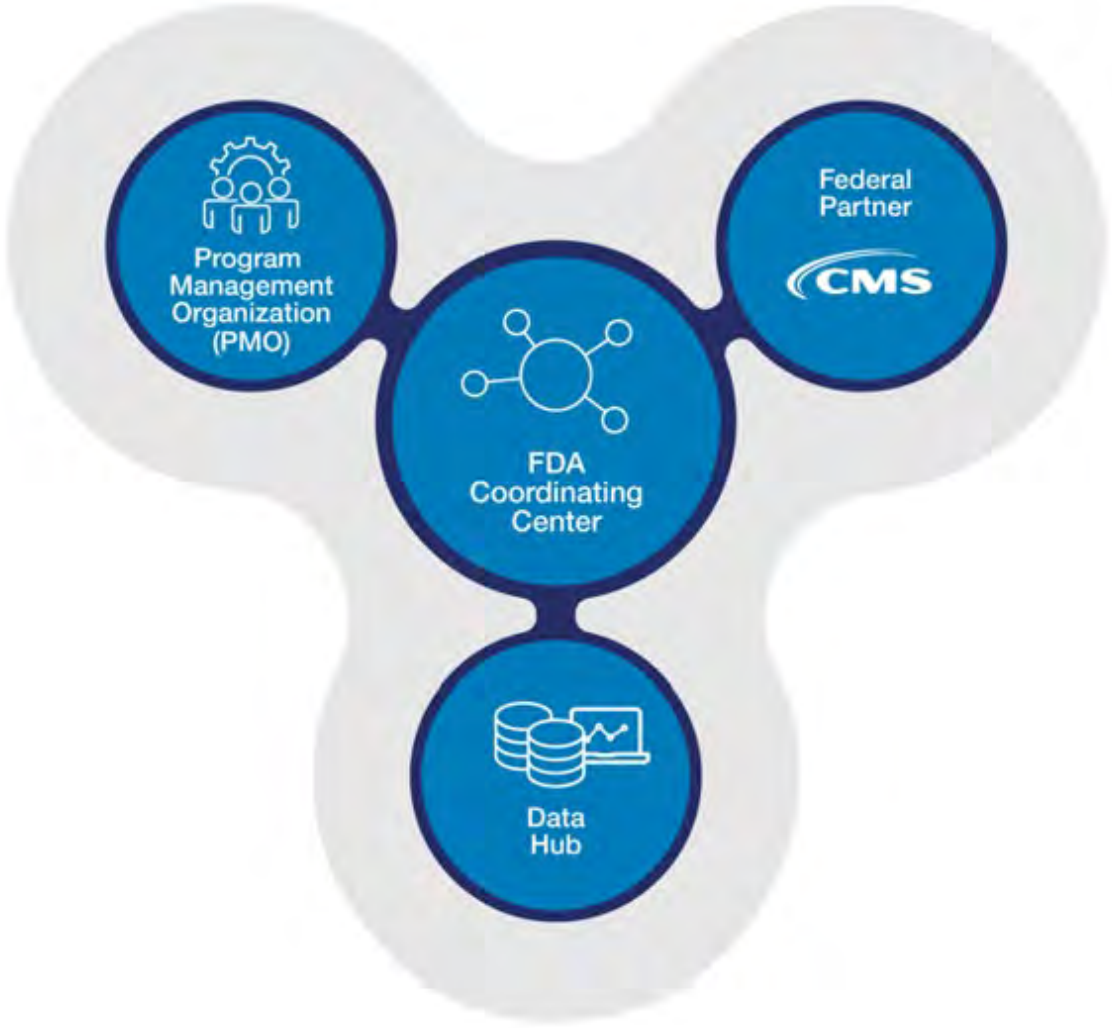
Sentinel Operations Center
Harvard Pilgrim Health Care, Inc.

Year 6 Extension 9/24 to 9/25

Sentinel System 3.0



Sentinel System 3.0



FDA Sentinel System Coordination Center (SCC)

- Managed by Sentinel Program staff in OSE
- Coordinate all scientific and program operations

CMS Inter-Agency Agreement (IAA)

- Expanded current access to CMS data and analytic support services

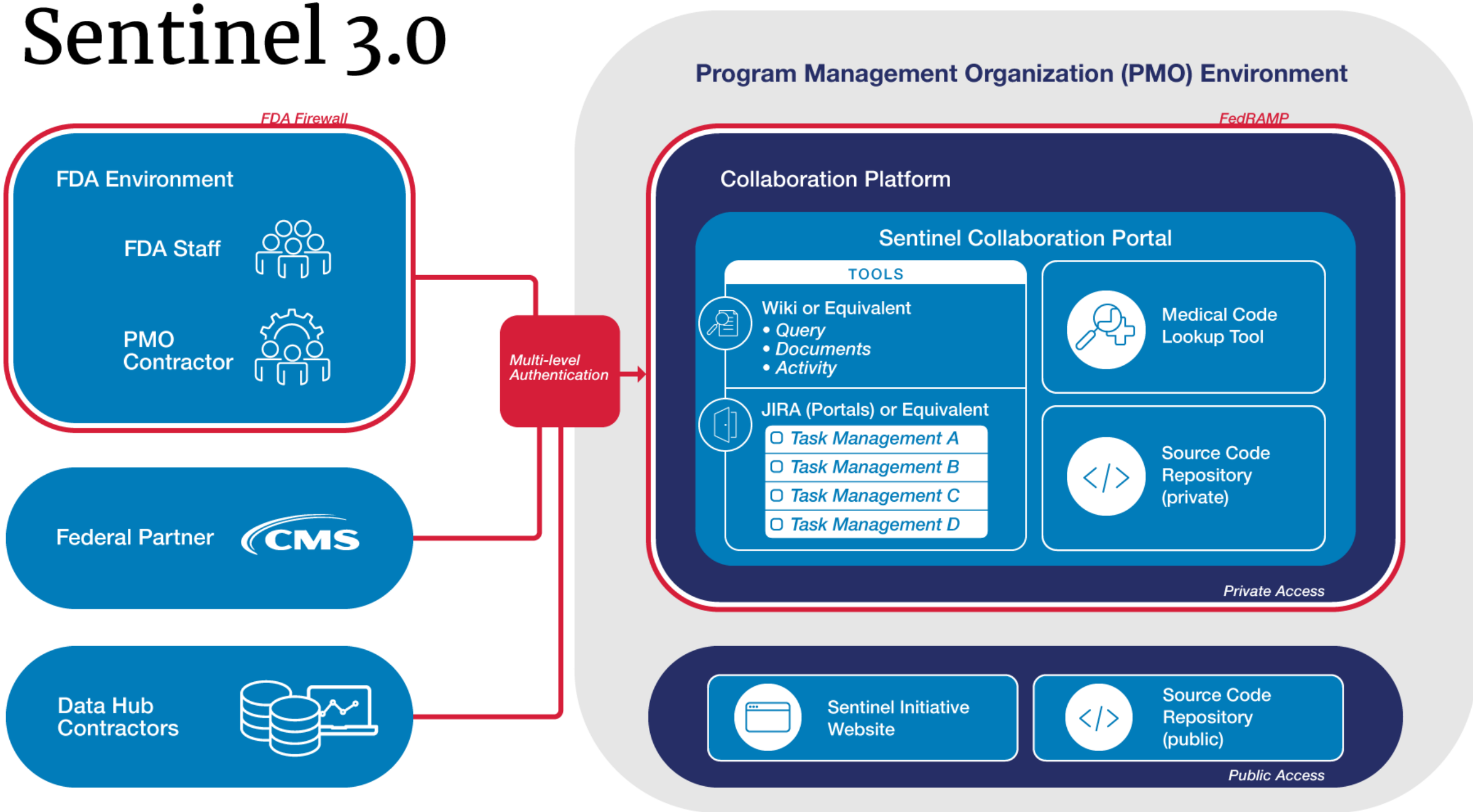
Data Hub Contract

- Access to multiple types of data and data analysis services

Program Management Organization (PMO) Contract

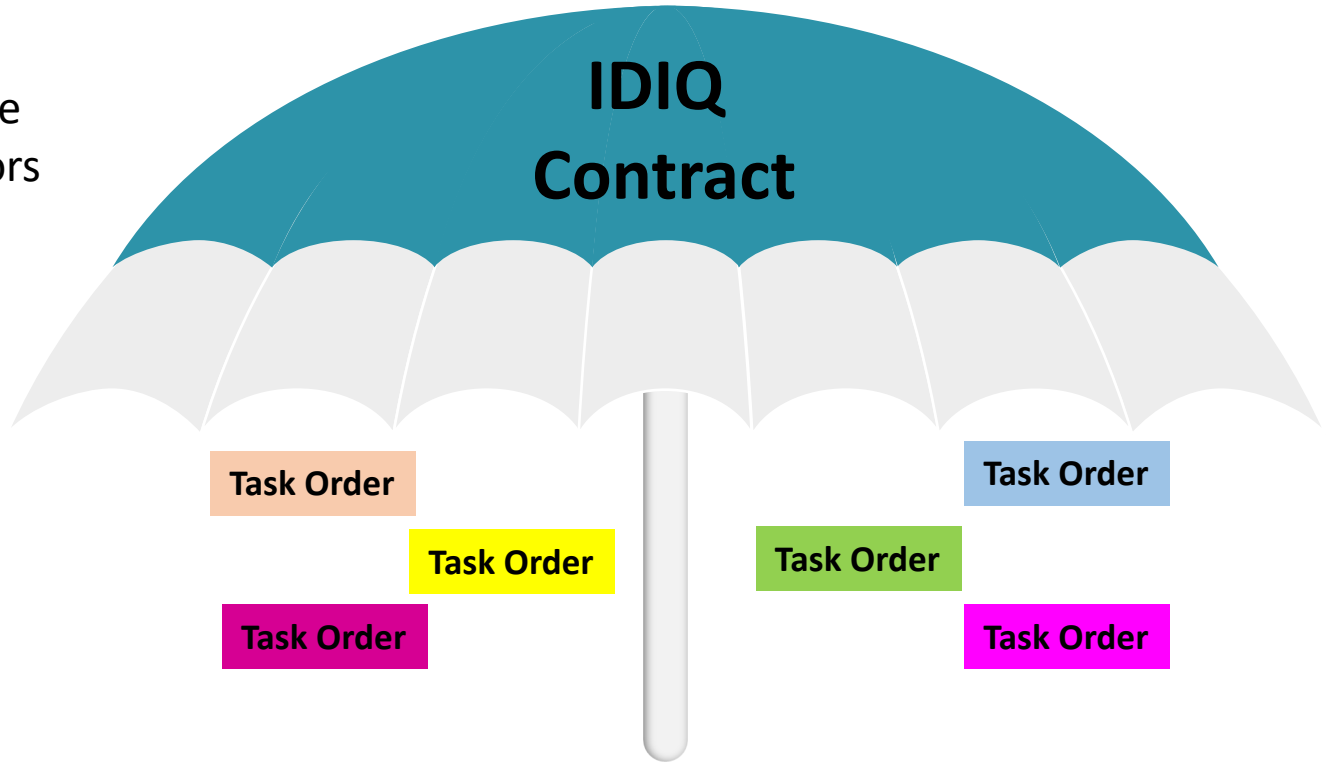
- Small business, Women Owned, awardee: Biswas IT Solutions
  - Awarded in FY24: SAM.gov
- Program/Project Management support
- Manage Sentinel Initiative Website
- Create and maintain a Secure Portal (**Collaboration Platform**) for collaborating with FDA staff, Data Hub contractors, and CMS

Sentinel 3.0


Program Management Organization (PMO) Environment
FDA Firewall
FedRAMP
FDA Environment
FDA Staff
PMO Contractor
Federal Partner
CMS
Data Hub Contractors
Multi-level Authentication
Collaboration Platform
Sentinel Collaboration Portal
TOOLS
Wiki or Equivalent
• Query
• Documents
• Activity
JIRA (Portals) or Equivalent
Task Management A
Task Management B
Task Management C
Task Management D
Medical Code Lookup Tool
Source Code Repository (private)
Private Access
Sentinel Initiative Website
Source Code Repository (public)
Public Access

IDIQ 101: Indefinite Delivery/Indefinite Quantity

IDIQ Awarded to One or Multiple Contractors



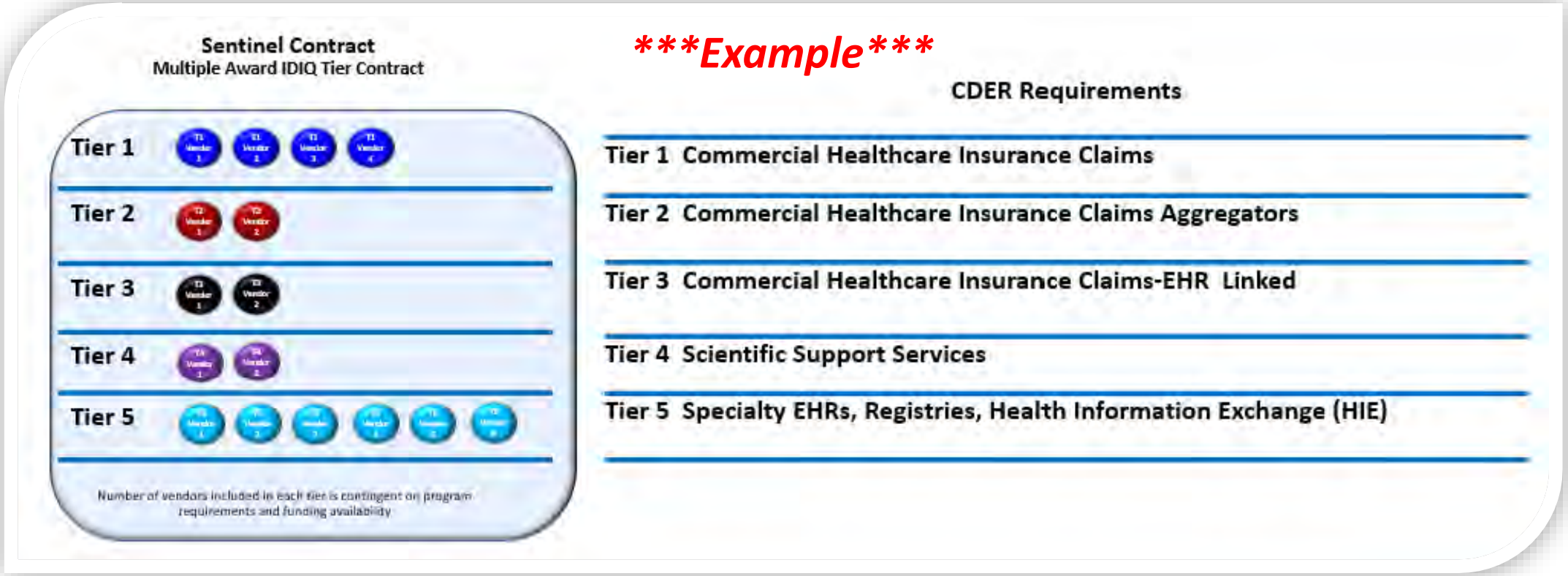
Task Order Contracts: awarded to those Contractors who have been awarded the IDIQ

Task Orders = Projects, $$$

An indefinite-quantity contract provides for an indefinite quantity, within stated limits, of supplies or services during a fixed period, and therefore are often referred to as task order contracts.

Subpart 16.5 - Indefinite-Delivery Contracts | Acquisition.GOV

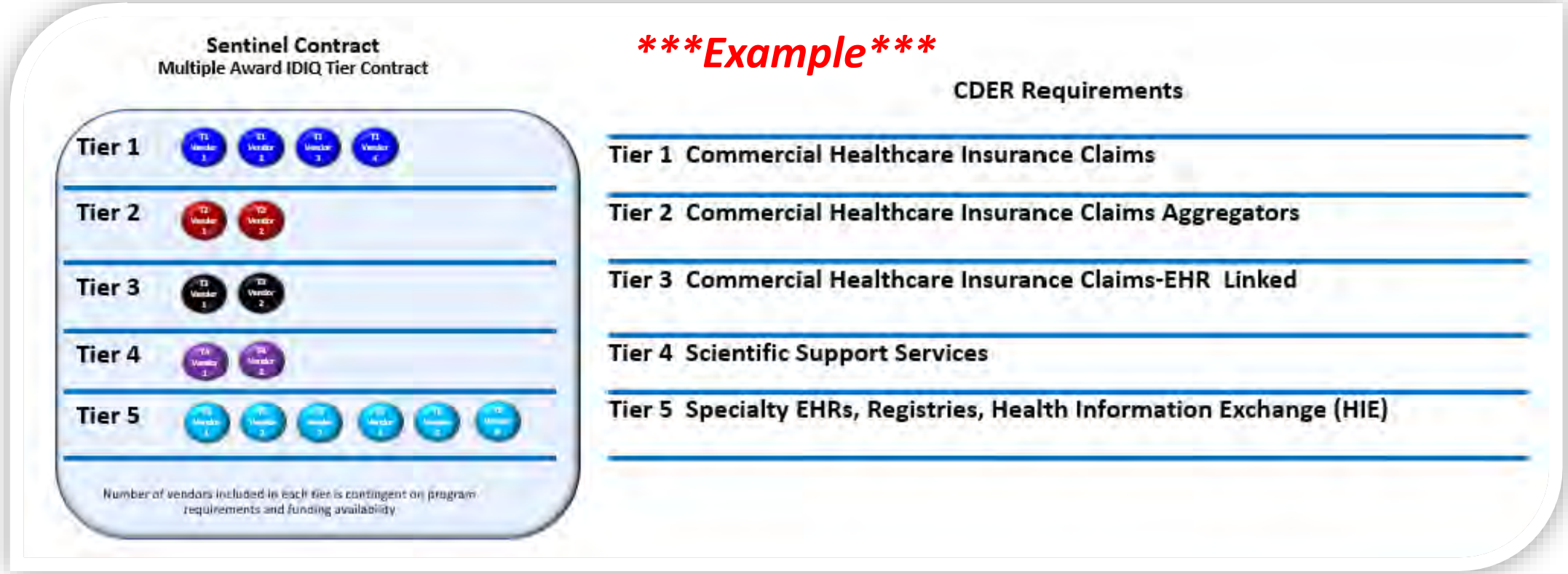
Sentinel 3.0 Data Hub Contract Structure



Multiple Award IDIQ, Tier Contract

- Multiple vendors compete for and may be awarded the IDIQ and task orders in one or more tiers
- An individual vendor does not have to meet requirements for all tiers
- Contract structure will allow for the award of optional tasks, providing flexibility for future program enhancements and responsiveness to public health emergencies

Sentinel 3.0 Data Hub Contract Structure



The Sentinel System 3.0 will not be limited to the use of the Sentinel Common Data Model. Instead, Sentinel System 3.0 will leverage multiple technical approaches, including the use of other common data models.

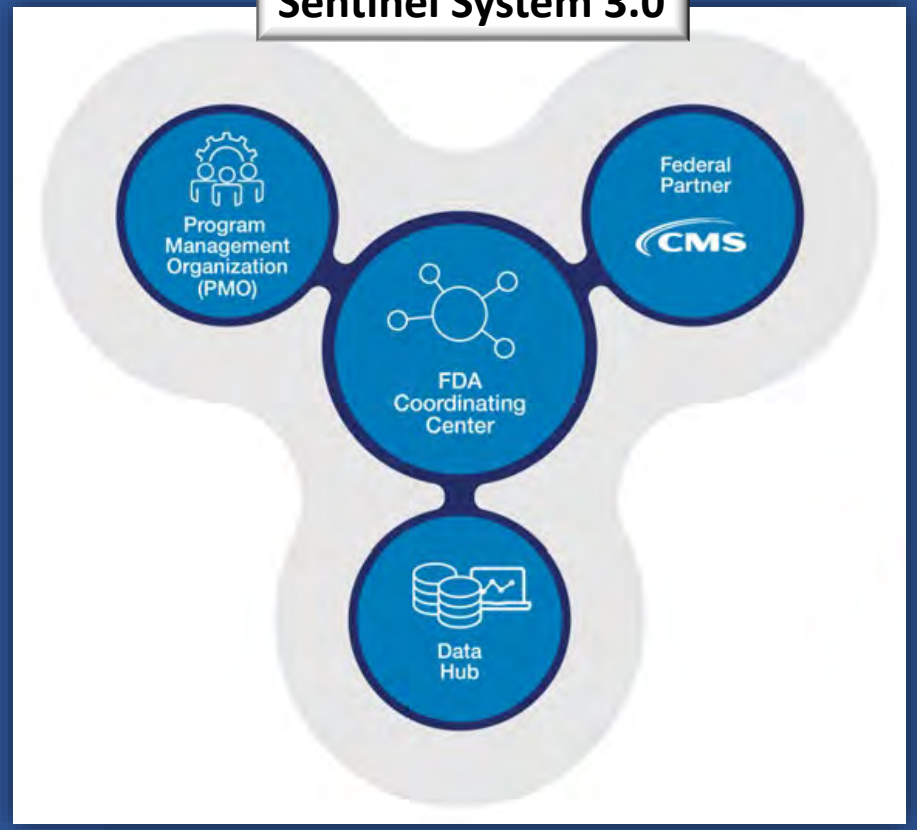
Sentinel 3.0: Safety Question Evaluation Process

Safety Question

Review Team Or DEPI*

Other Sources

Sentinel System 3.0



- Question triaged and tracked
- Scientific discussions about suitable data sources and analytic methods
- Protocol development

Safety Study

Study X

Study Oversight: FDA Sentinel Coordinating Center

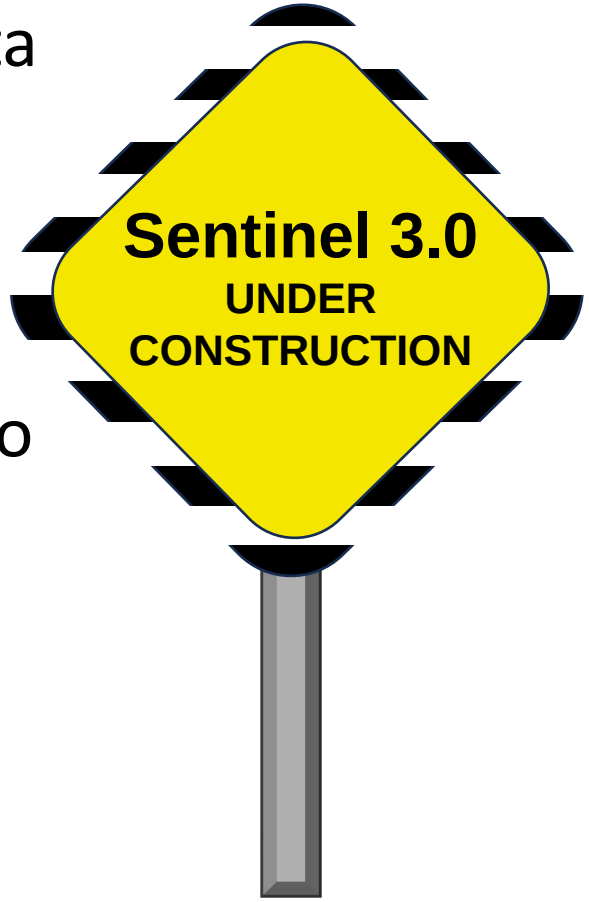
Scientific Contributors: FDA staff, Data Hub contractors and CMS IAA staff

Project Management: PMO contractor

*DEPI = Divisions of Epidemiology

Sentinel 3.0…

- Leverages Sentinel 2.0 scientific work and advances in data science
- Designed to address FDA legal requirements and CDER scientific program needs
- Provide a scalable, more flexible, multifaceted approach to improve ARIA sufficiency
- On track to launch by end of FY25
  - Complex procurement process
  - Implementation requires integration of its 4 main components
  - Potential decreased production during transition



Next Steps

PMO

Stand up infrastructure and develop program management processes in FY 25.

Data Hub

Request for Proposals (RFP) ~Spring 2025.
Award ~Sept 2025.

CDER Utilization of Sentinel 3.0

OSE will continue working with all CDER relevant groups to refine the Center's approach for utilizing the new capabilities of Sentinel 3.0.

Questions About the Future Sentinel 3.0?

Please send your questions or comments to the Office Of Acquisitions & Grant Services (OAGS) by November 14, 2024, 12:00 noon Eastern Standard Time.

- **Contract Specialist: Howard Yablon howard.yablon@fda.hhs.gov**
- **Contracting Officer: Ian Weiss ian.weiss@fda.hhs.gov**

The responses to your questions will be included in a ‘Special Notice’ in SAM.gov

Thanks!

Moderated Discussion and Q&A

Moderator: Rachele Hendricks-Sturrup

Duke-Margolis Institute for Health Policy

Duke | MARGOLIS INSTITUTE for Health Policy

BEST System Innovations to Anticipate

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

Panelists: **Merianne R. Spencer**, U.S. Food and Drug Administration

Hussein Ezzeldin, U.S. Food and Drug Administration

Carla Zelaya, U.S. Food and Drug Administration

Joann F. Gruber, U.S. Food and Drug Administration

BEST System Innovations to Anticipate

Merianne R. Spencer, PhD, MPH[1]
Hussein Ezzeldin, PhD[1]
Carla Zelaya, PhD[1]
Joann F. Gruber, PhD[1]

[1]U.S. FDA CBER

16th Annual Sentinel Initiative Public Workshop
November 7, 2024

CBER Surveillance Program: BEST System Innovations to Anticipate

Merianne R. Spencer, PhD, MPH
U.S. FDA CBER

Disclaimer

- BEST Initiative and its studies are funded by the U.S. Food and Drug Administration (FDA).

- No potentially conflicting relationships to disclose.

- Presentation reflects the views of the author and should not be construed to represent the views or policies of the FDA.

CBER & Biologics Effectiveness and Safety (BEST)

CBER's Vision

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

BEST Initiative

- Part of the Sentinel Initiative fulfilling 2007 FDA Amendments Act of requirements
- Pre-eminent resource for evaluating biologic product safety and effectiveness
- Leverage high-quality data, analytics and innovation to enhance **surveillance** and **real-world evidence generation**

CBER-Regulated Products


Vaccines (preventative and therapeutic)


Blood (components and derived)


Human Tissues and Cellular Products


Cell and Gene Therapies


Xenotransplantation Products

Highlights and Challenges of the BEST Initiative

Highlights: Innovative approaches to advance biologics surveillance for informed regulatory decision-making

- Rare diseases including cell and gene therapies
- Vaccines for the American public including special populations
- Artificial intelligence and data mining

Challenges: Evidence-based real-world data generation is messy

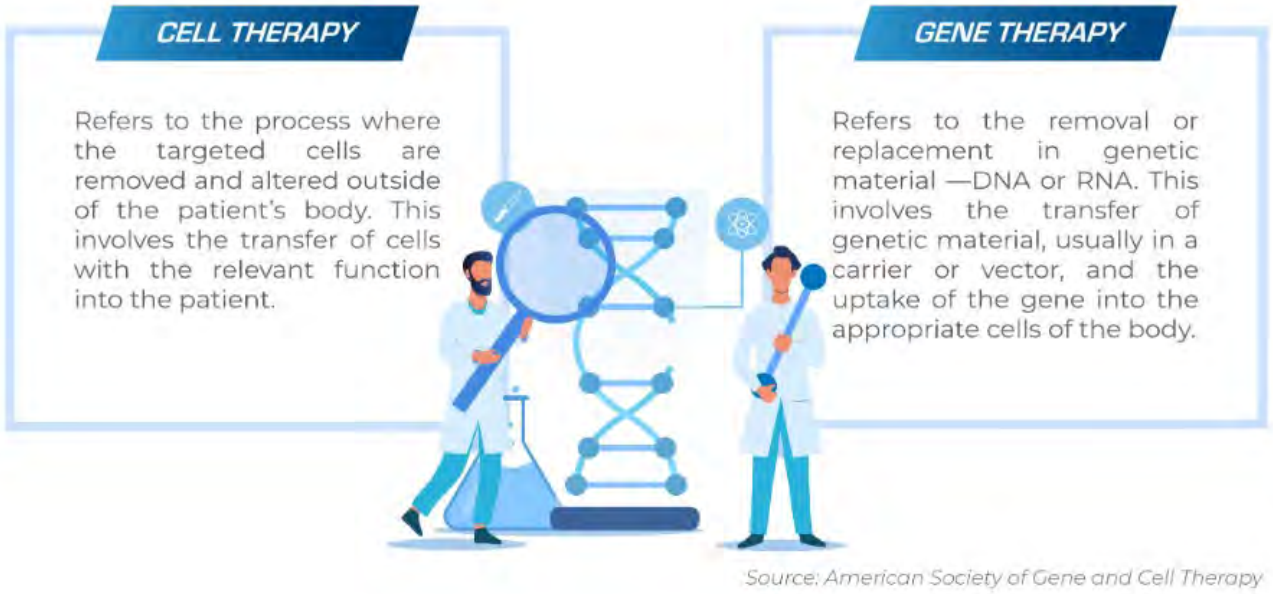
- Small populations and limited detection of adverse events for rare diseases and many advance therapies
- Unique needs and special considerations for subpopulations and groups at-risk
- Data quality concerns (can be incomplete, inconsistent, lack standards)
- Data integration and interoperability considerations
- Subject to bias (selection, information, recall)

Cell and Gene Therapies

- Cell and gene therapies are rapidly growing fields holding promise for treating some cancers and rare diseases

- Especially applicable for conditions that are severe, life-threatening, and pose unique challenges in healthcare

- E.g., Low disease prevalence can result in a limited number of promising therapies and investments for treating rare diseases



Special Populations: Pregnant Individuals

- ~5.5 million pregnancies each year in the United States

- Half of pregnant individuals use at least one drug or biological product to treat acute, chronic, or serious medical conditions

- There are unique challenges to obtaining real-world evidence to determine optimal post-approval study designs to ensure safe use of products among pregnant individuals

Artificial Intelligence and Data Interoperability

- Real-world data from a distributed data network poses unique challenges in data quality and reporting:
  - Inefficient reporting processes (manual reporting and data redundancies)
  - Data integration and interoperability (can have different standards impeding data sharing and flow of information)
- Adverse event detection allows for timely intervention to improve patient safety, monitor efficacy of biologic products, and helps minimize future risk in a timely manner
- BEST is using FHIR-based methods to improve automation and validation of available data

BEST Innovations

Pharmacovigilance in the Age of Interoperability and Artificial Intelligence

Hussein Ezzeldin, PhD
U.S. FDA CBER

Challenges and Opportunities

Assuming a clinical **exposure** and potential **outcome**

Existing manual process **creates burden, under/over reporting**, and **unstandardized quality**

Current

Manual Detection

- Individual flagging of potential AEs
- Under-recognition/under-counting of outcomes

Manual Validation

- Time-intensive to review dispersed data
- Potential AEs not always communicated
- Separate and unstandardized case definitions

Manual Reporting

- Data re-entry to report externally
- Lack of granularity in report evidence

vs.

BEST uses **innovative methods** to **reduce burden**, while **increasing quantity** and **quality** of AE reports

Future

Automated Detection

- Batch detection, more focus on patient care
- AI algorithm scores potential cases

Semi-Automated Validation

- Evidence integration reduces burden
- Flagged and prioritized cases sent for review
- Standardized and integrated case definition

Semi-Automated Reporting

- Auto-population of granular ICSR evidence
- Generation of evidence-based ICSR narrative

ICSR, individual case safety report

CBER BEST Roadmap

2019-2020

Prototype on Foundational Network
- Built healthcare provider's EHR to FDA pipeline
- Developed and validated phenotypes
- Reported ICSR cases

D.C.
MD
VA
FL

Prototype on Exchange Network
- Leveraged pipeline to design a POC exchange architecture
- Supported with data agreements and standards

Operationalize on Foundational Network
- Leveraged and enhanced pipeline
- Piloted scalable phenotypes for vaccines outcomes of interest

2021

2022

Pilot Studies on Exchange Network
- Piloted AE validation use case on 'First-of-a-kind' networked FHIR (Pull)
- Piloted AE detected use case with early adopter (Push)

Operationalize on Exchange Network
- Expand pilot
  - Mature and expand AE validation nationally
  - Leverage interoperable for semi-automated detection

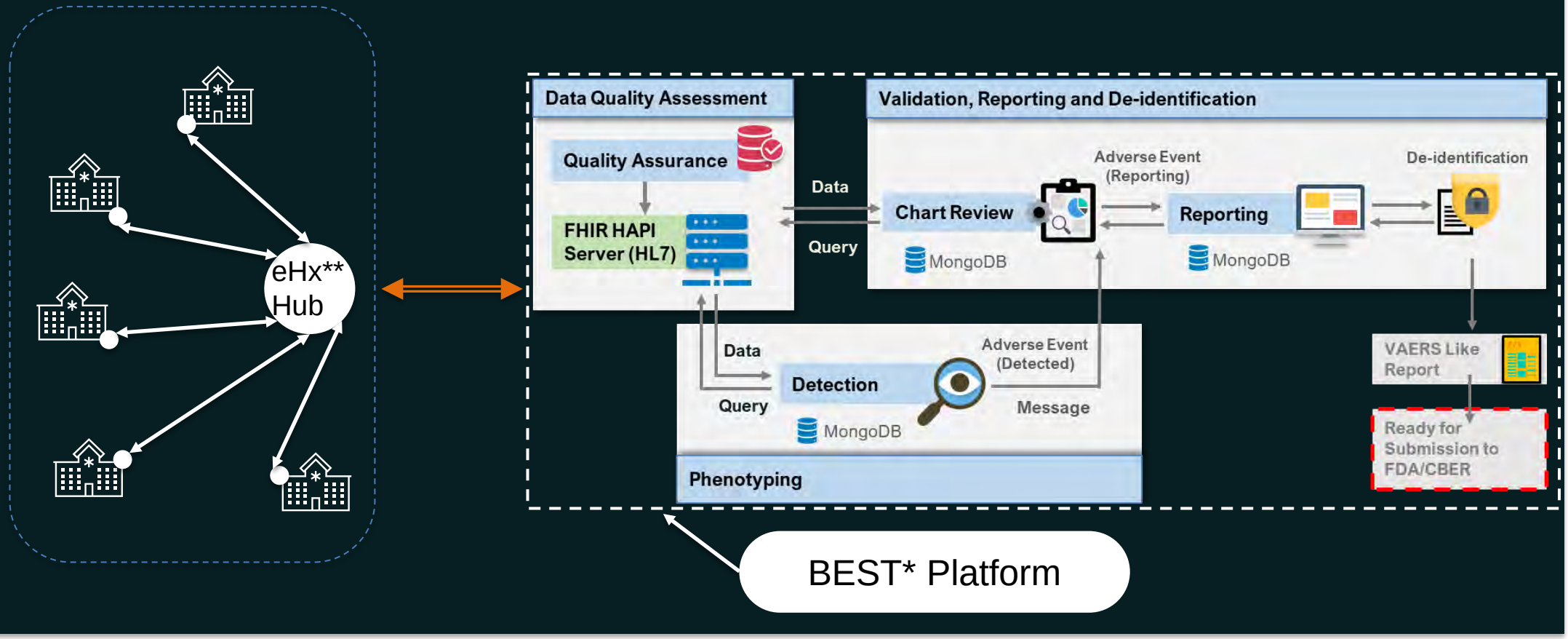
National Coverage

2023+

Accomplished Ongoing

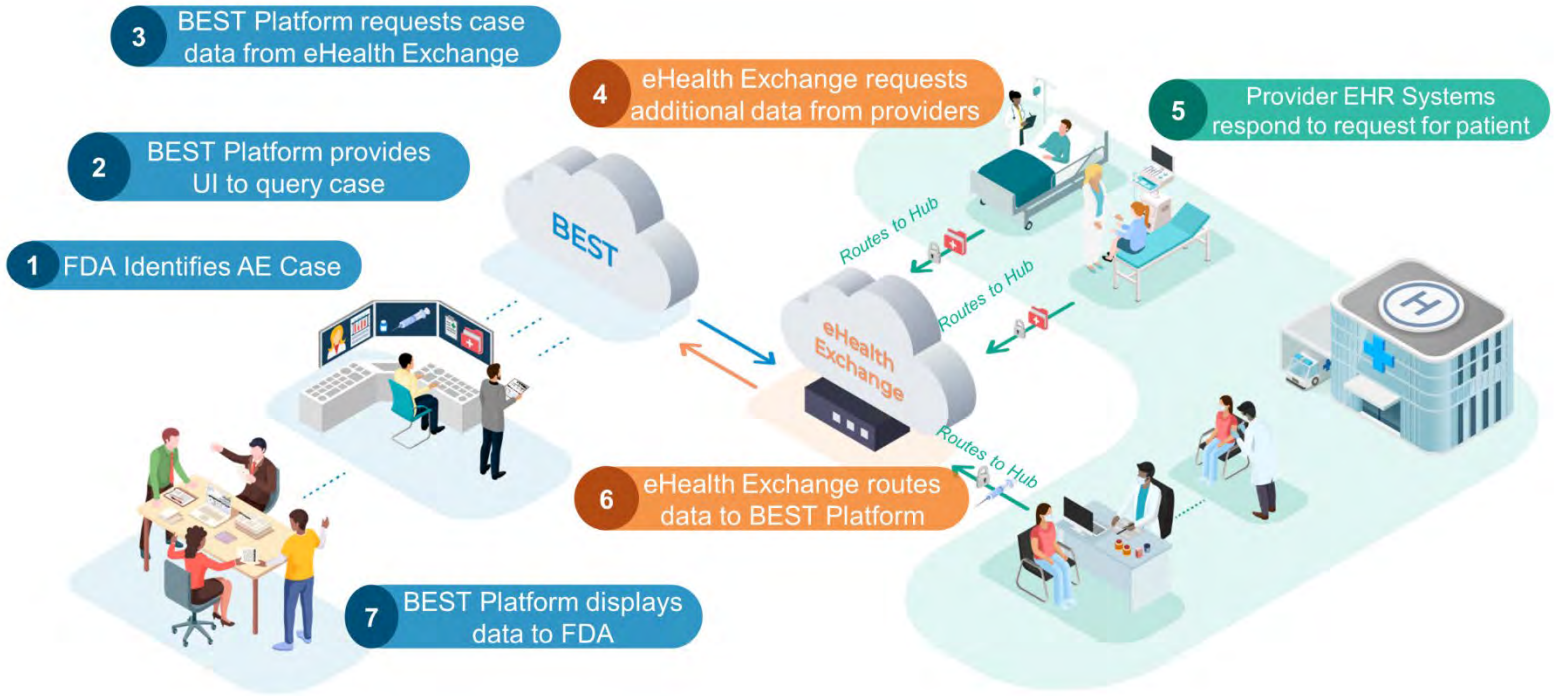
BEST Pilot Platform

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



* ***BEST, Biologics Effectiveness and Safety*** ; ** eHx, eHealth Exchange

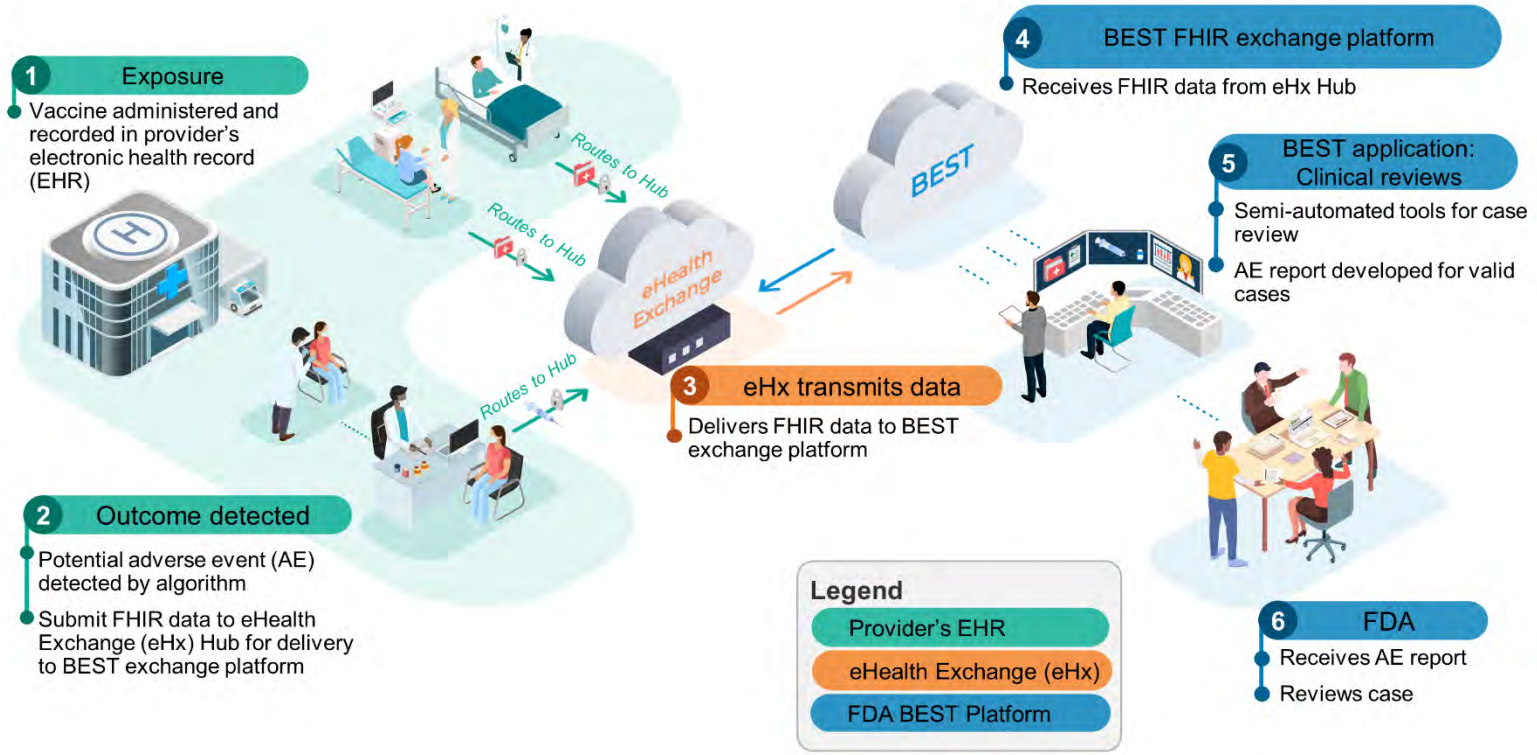
BEST Pilots



Pull Use Case

- First use of networked-FHIR to query health information exchanges for Public Health use case
- Assess data quality
- Inform regulators, industry and the public to improve FHIR-based exchange

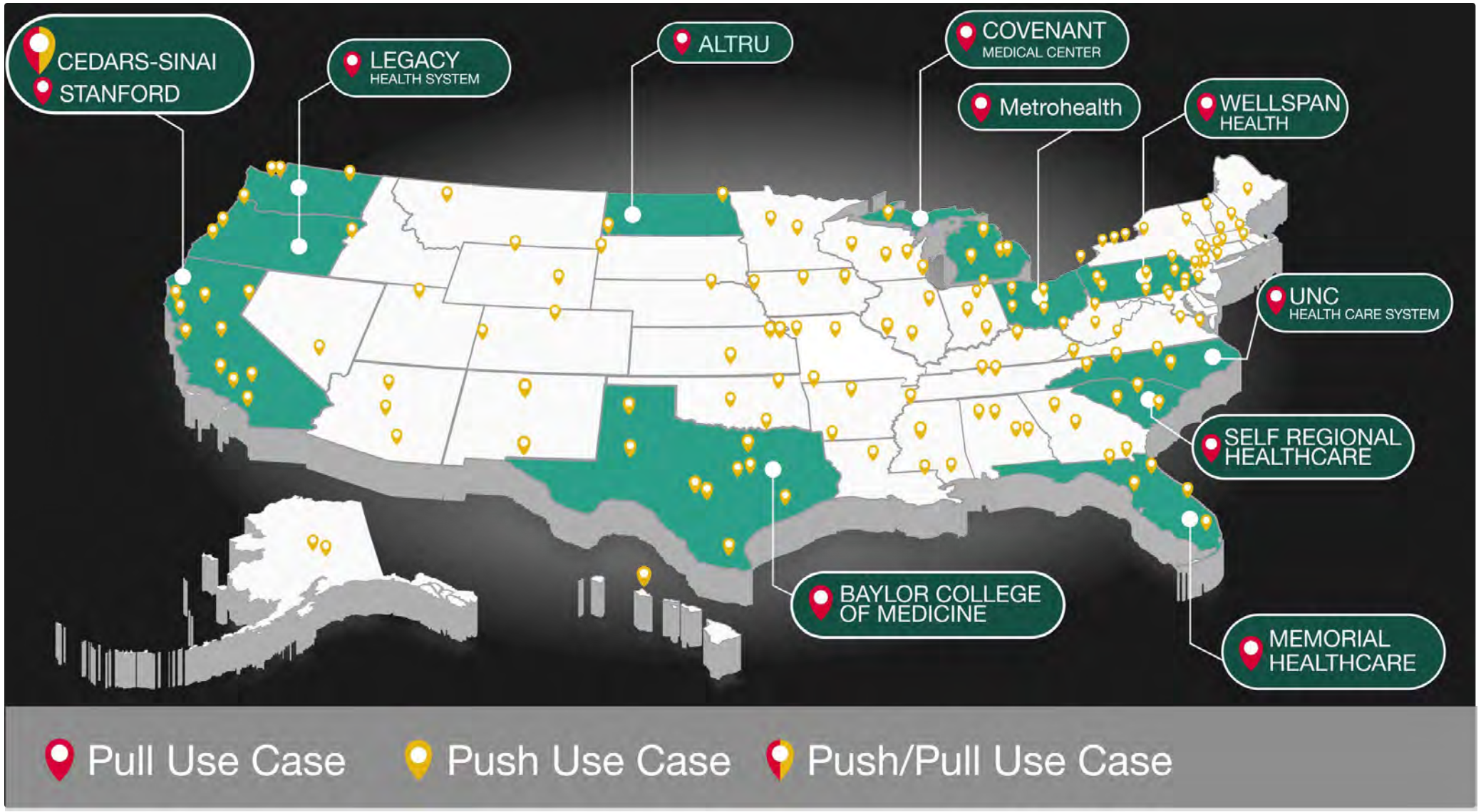
BEST Pilots



Push Use Case

- Explored semi-automated detection using health information exchanges for Public Health
- Assessing computable phenotypes performance
- Inform regulators, industry and the public of

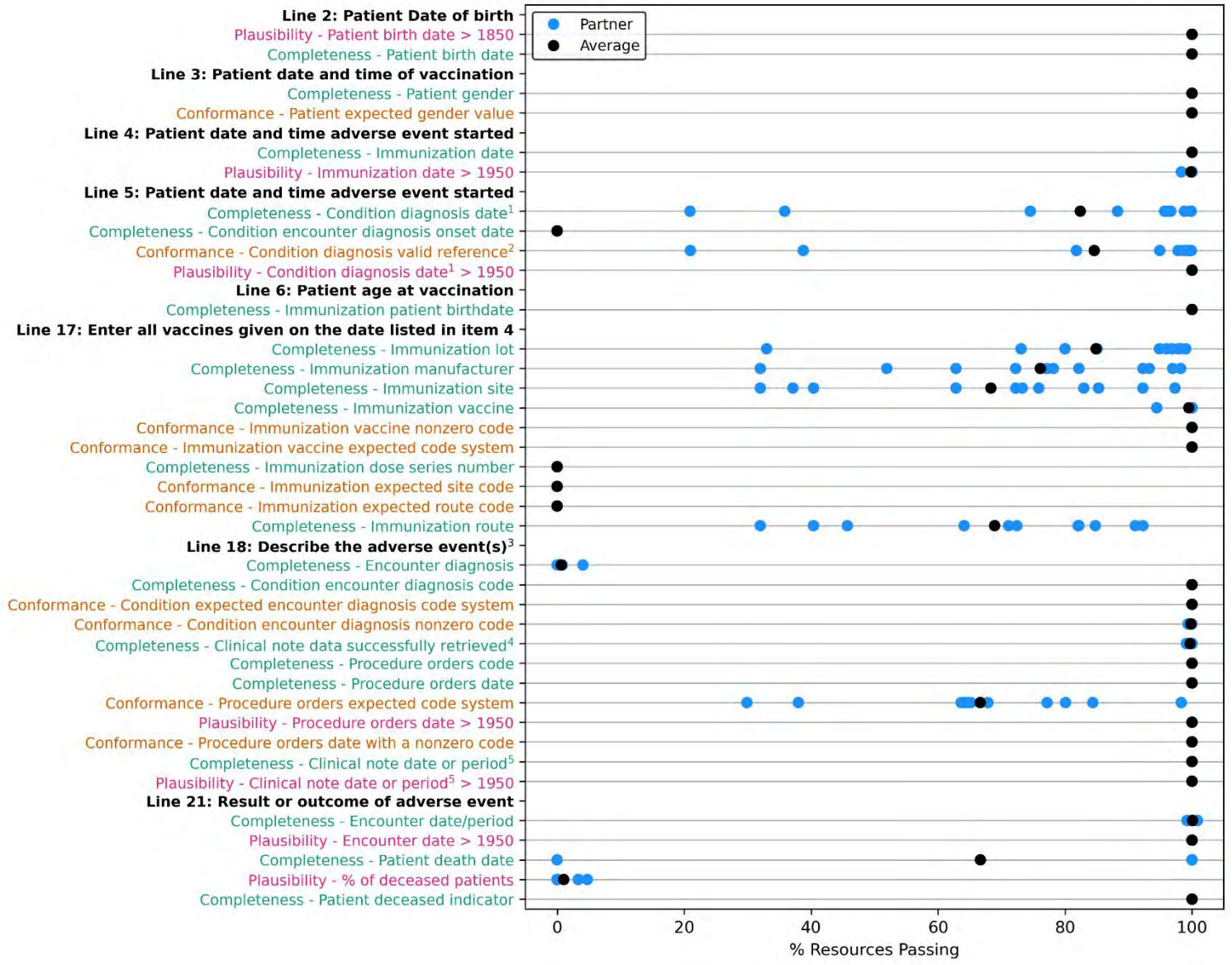
Pilot Participants



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

Pull Use Case Pilot Results

- **271** post-vaccination adverse events were received via BEST Platform
- Across **11** different health provider data partners (Epic EHRs)



Completeness

Conformance

Plausibility

Semi-automated Detection

BEST Developed multi-tiered computable phenotypes for semi-automated detection

1 Simple/Scalable

Dx Codes

DX codes

+ Clean window & Risk window

2 Enhanced

1 Simple/Scalable

+ Structured

Vitals Meds Labs

+ Clean window & Risk window

3 Complex

2 Enhanced

+ Unstructured

Clinical, Discharge, Educational Notes, etc.

+ Clean window & Risk window

Ensure shareability and interoperability (FHIR CQL, OMOP), PPV, Positive Predictive Value

Next Steps: Interoperable Computable Phenotypes Development and Dissemination

5 eHealth Exchange sends back patient clinical data

3 eHealth Exchange Distributes CQL to Network

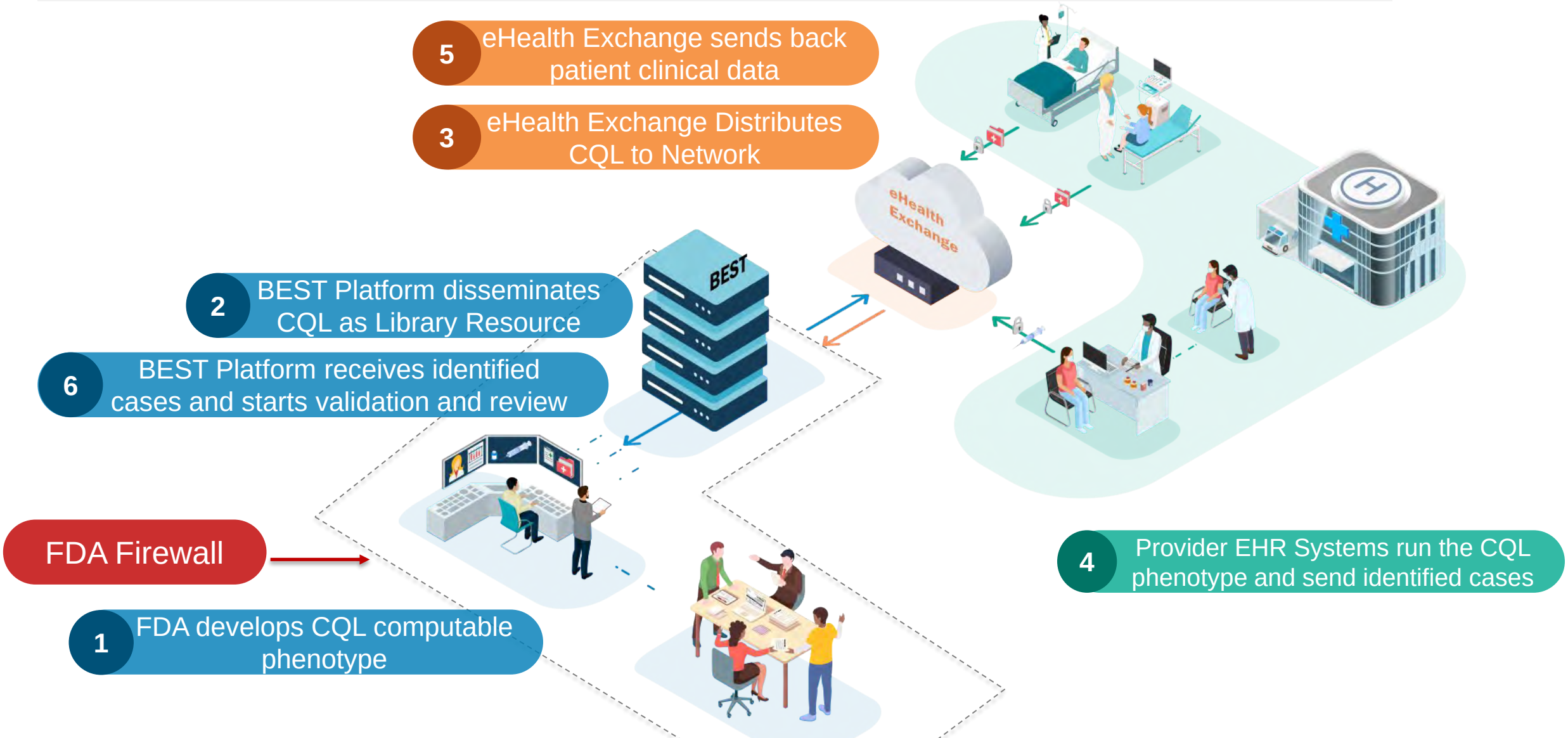
2 BEST Platform disseminates CQL as Library Resource

6 BEST Platform receives identified cases and starts validation and review

FDA Firewall

1 FDA develops CQL computable phenotype

4 Provider EHR Systems run the CQL phenotype and send identified cases

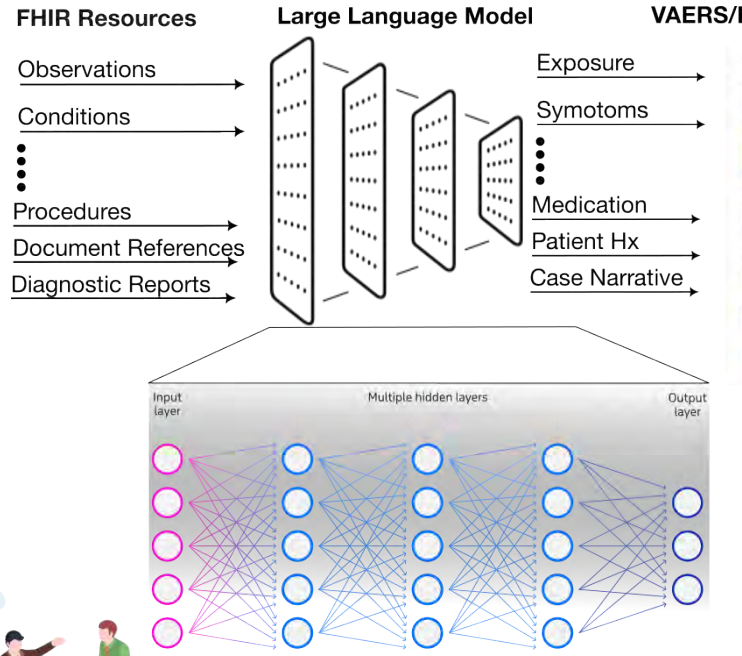


Next Steps: Use of LLMs for Case Processing

5 eHealth Exchange routes case clinical data to BEST Platform

3 eHealth requests additional case clinical data from Providers

6 FHIR data extracted, mapped



FDA Firewall

2 BEST Platform used to query case

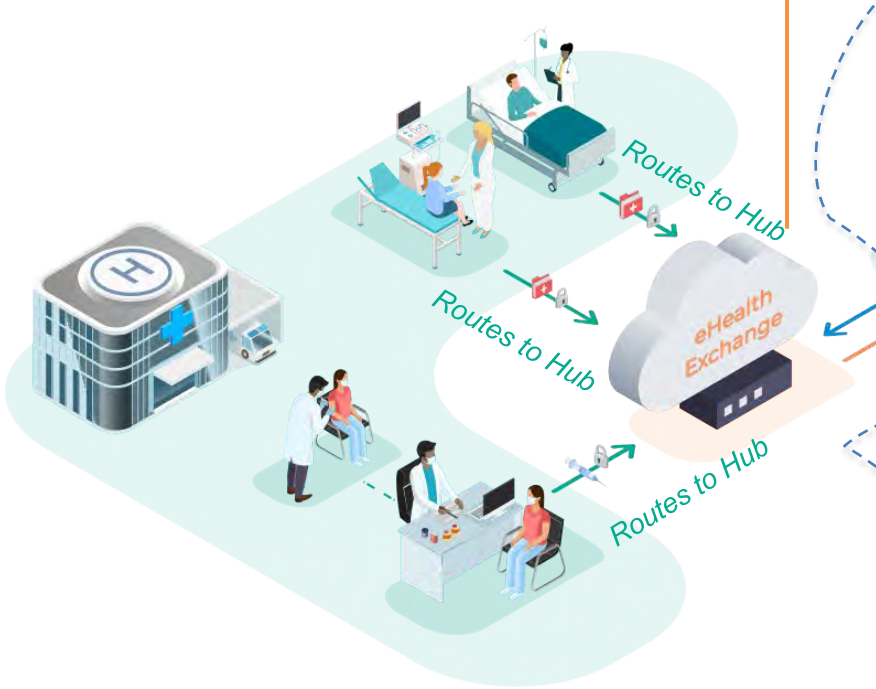
4 Provider EHRs respond when a match is found

1 FDA identifies AE Case

Next Steps: Use of LLMs for Case Adjudication

FDA Firewall

2 eHealth Exchange routes case clinical data to BEST Platform



3 FHIR data + Case definition

FHIR Resources

Observations

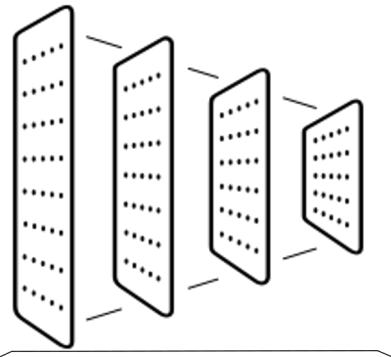
Conditions

Procedures

Document References

Diagnostic Reports

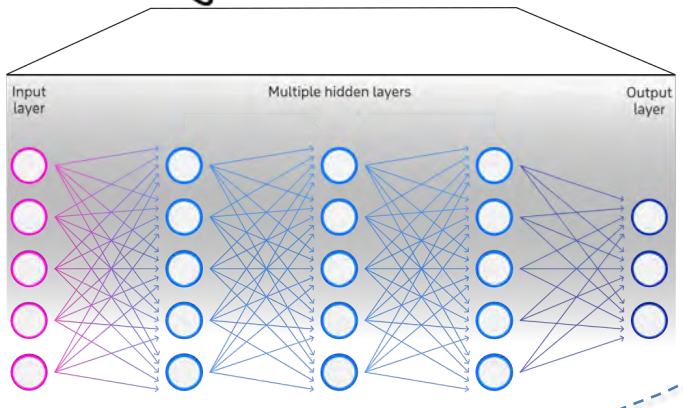
Large Language Model



Case Summary

Outcome

Evidence



1 AE detected in Provider EHR

4 FDA safety officers review AE Case

Summary

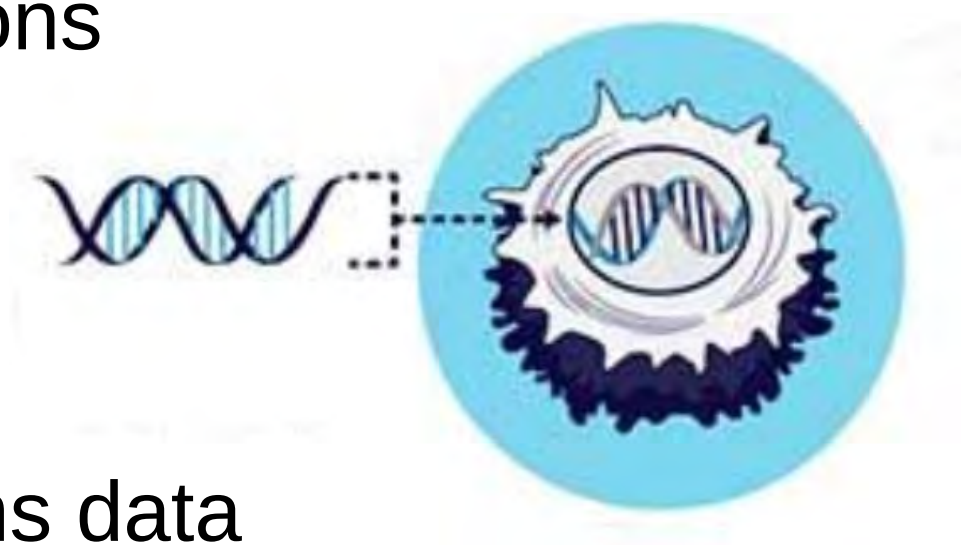
- BEST Platform demonstrates great potential for FHIR-based case validation and detection through health information exchanges
- Future work leverages CQL to scaling semi-automated AE detection
- Use of LLMs may facilitate case processing and adjudication

CAR T-Cell Therapy: Safety Study Planning

Carla E. Zelaya, PhD
U.S. FDA CBER

Outline

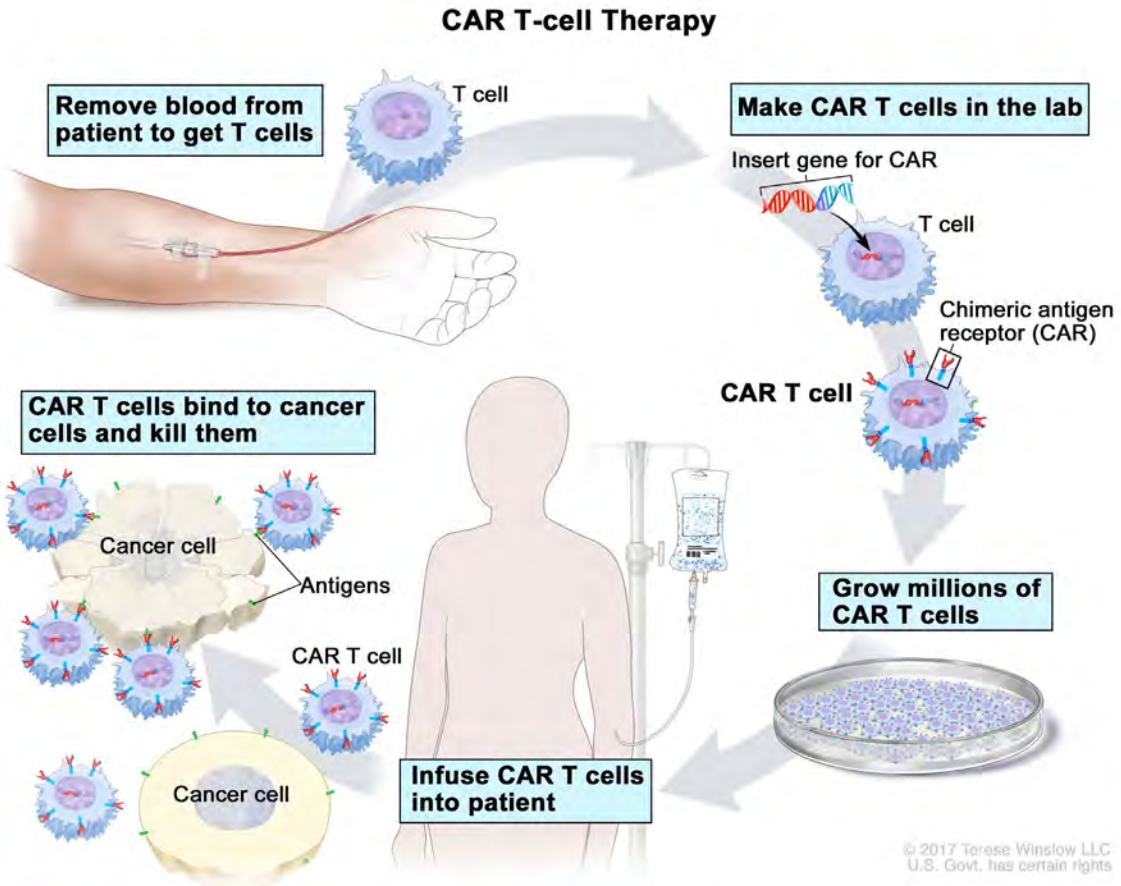
- CAR T-cell therapy and indications
- Approved therapies
- Safety concerns
- Plans for safety study
- Assessing exposure using claims data
- Assessing outcomes of interest using claims data



Overview of CAR T-Cell therapy

Chimeric antigen receptor (CAR) T-cell products are human gene therapy products

Patient's own (autologous) T-cells are genetically modified to enable recognition of a desired target antigen for therapeutic purposes.



Approved CAR T-Cell Therapies

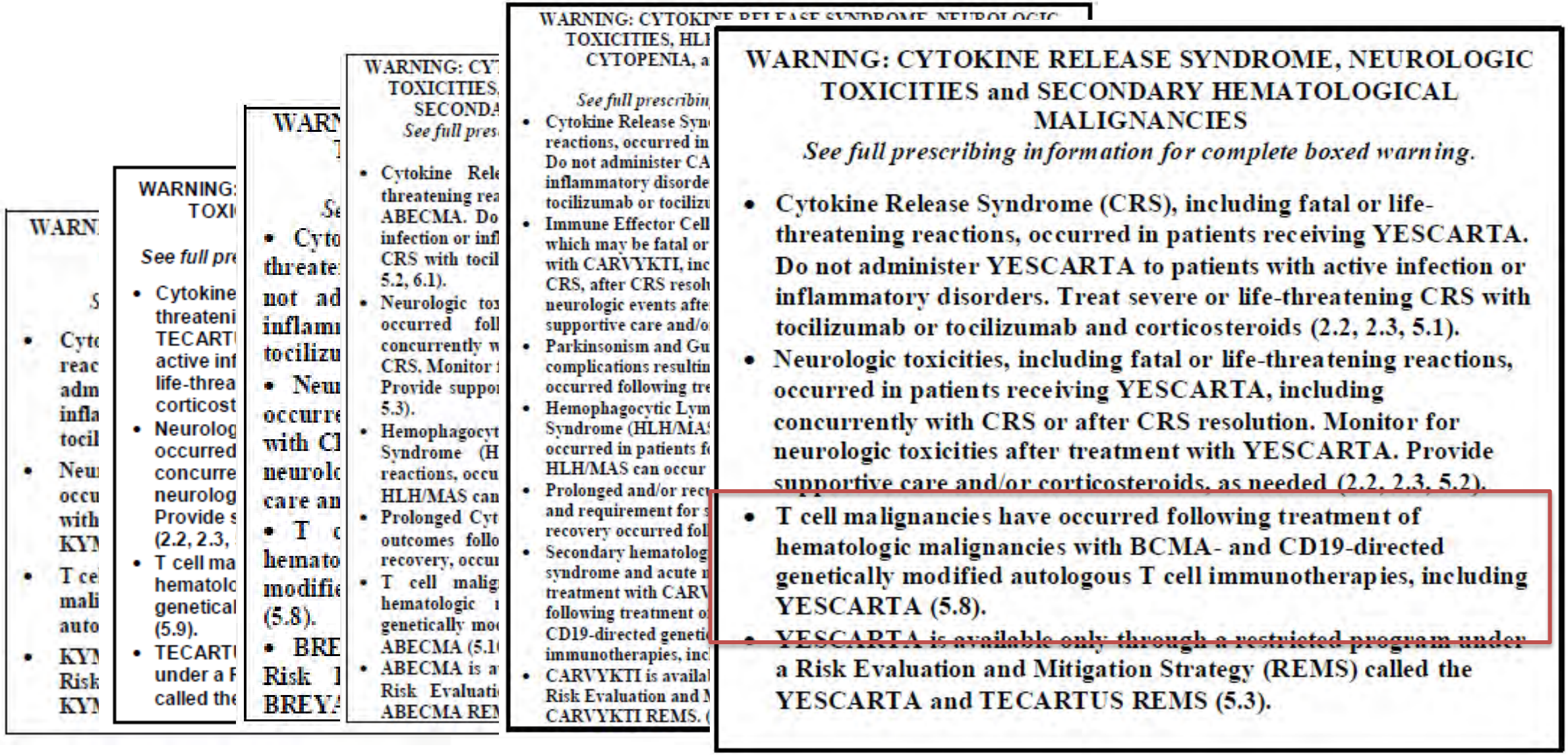
Brand Name	Generic Name	Initial Approval Date	Indication(s)
Kymriah (Novartis)	Tisagenlecleucel	08/30/2017	Children and young adults (<=25 years) with refractory or relapsed (r/r) B-cell acute lymphoblastic leukemia (ALL) Adult patients with r/r large B-cell lymphoma or r/r follicular lymphoma (FL)
Yescarta (Kite)	Axicabtagene Ciloleucel	10/18/2017	Adult patients with relapsed r/r large B-cell lymphoma or r/r FL
Tecartus (Kite)	Brexucabtagene Autoleucel	07/23/2020	Adult patients with r/r mantle cell lymphoma (MCL); or with r/r B-cell ALL
Breyanzi (Juno/BMS)	Lisocabtagene maraleucel	02/05/2021	Adult patients with r/r B-cell lymphoma or r/r FL
Abecma (Celgene/ BMS)	Idecabtagene vicleucel	03/26/2021	Adult patients with r/r multiple myeloma (MM)
Carvykti (Janssen)	Ciltacabtagene autoleucel	02/28/2022	Adult patients with r/r multiple myeloma (MM)

Safety Concerns

- T-cell malignancies, including CAR-positive lymphoma, in patients who received treatment with BCMA- or CD19-directed autologous CAR T-cell immunotherapies reported to the U.S. Food and Drug Administration (FDA)[1]
- FDA reviewed the reports and updated prescribing information for the class of CAR T-cell products
- Overall benefits of these products continue to outweigh potential risks for approved uses

[1] FDA, November 28, 2023. FDA Investigating Serious Risk of T-cell Malignancy Following BCMA-Directed or CD19-Directed Autologous Chimeric Antigen Receptor (CAR) T cell Immunotherapies

Labeling for Secondary Malignancies in CAR T-Cell Therapies



WARNING: CYTOKINE RELEASE SYNDROME, NEUROLOGIC TOXICITIES and SECONDARY HEMATOLOGICAL MALIGNANCIES

See full prescribing information for complete boxed warning.

- Cytokine Release Syndrome (CRS), including fatal or life-threatening reactions, occurred in patients receiving YESCARTA. Do not administer YESCARTA to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab or tocilizumab and corticosteroids (2.2, 2.3, 5.1).
- Neurologic toxicities, including fatal or life-threatening reactions, occurred in patients receiving YESCARTA, including concurrently with CRS or after CRS resolution. Monitor for neurologic toxicities after treatment with YESCARTA. Provide supportive care and/or corticosteroids, as needed (2.2, 2.3, 5.2).
- T cell malignancies have occurred following treatment of hematologic malignancies with BCMA- and CD19-directed genetically modified autologous T cell immunotherapies, including YESCARTA (5.8).
- YESCARTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the YESCARTA and TECARTUS REMS (5.3).

Plans for Safety Study

To conduct a safety study of CAR T-cell therapy in CMS and commercial claims data of BEST to determine if we can:

a) Detect CAR T-cell product use (identification of exposure in cohort)

b) Identify and evaluate adverse events (AEs) of interest (secondary malignancies) following CAR T-cell therapy

BEST Data Sources Selected

- Centers for Medicare and Medicaid Services (CMS)
  - Medicare Fee-For-Service (FFS)
  - Medicare Advantage

- Commercial claims databases
  - Optum Pre-adjudicated Claims Database
  - Carelon/IQVIA
  - CVS Health

Detection of CAR T-Cell Therapy Use in CMS Medicare Databases

- Study cohort: Persons aged 65 years and over, continuously enrolled in health insurance plan for at least 365 days prior to exposure (CAR T-cell therapy)

- Exposures to CAR T-cell treatment identified by CPT code 0540T or product-specific HCPCS/ICD-10 PCS codes on administrative claims from inpatient (IP) facility, outpatient (OP) facility, or professional billing (PB) settings

- Only the first procedure observed for an individual during the study period will be counted as an exposure

CMS Medicare: exposure cohort

Inclusion Criteria	Overall Population	
	n	% of Total
Received a CAR T-cell treatment during study period	10,760	
Enrolled in the corresponding insurance plan on the day of treatment	10,455	97.17%
Aged 65 years or older	8,902	82.73%
Continuously enrolled in their health insurance plan for 365 days prior to the receipt of a CAR T-cell treatment	**8,236**	76.54%

CMS Medicare: Characteristics of exposure cohort

(Aged 65 years and older, and received CAR T-Cell treatment, 365 days continuous enrollment prior to exposure)

	#	% of Total
Total	**8,236**	
Age (years)		
65-69	2,604	31.62%
70-74	2,951	35.83%
75-79	1,997	24.25%
80 and older	684	8.31%
Sex		
Female	3,297	40.03%
Male	4,939	59.97%
Race/Ethnicity		
Asian	177	2.15%
Black	524	6.36%
Hispanic	156	1.89%
White	6,883	83.57%
Other	203	2.46%
Missing/Unknown	293	3.56%
Urban/Rural		
Urban	7,052	85.62%
Rural	1,181	14.34%
Missing/Unknown	3	0.04%

Identify and evaluate adverse events (AEs) of interest in BEST initiative claims databases

- The following adverse events of interest are identified in this study, using HCPCS, CPT, ICD-10-PCS, and NDC codes:
  - Secondary Primary T-Cell Cancer,
  - Myelodysplastic Syndrome (MDS), and
  - Acute Myeloid Leukemia (AML)
- Only incident outcomes will be counted. An incident outcome is defined as a diagnosis without another identical diagnosis in the 365 days prior.
- A patient will be censored from a specific outcome cohort at the occurrence of that outcome. Occurrence of each outcome of interest will be assessed separately; a patient can contribute to multiple outcome cohorts.

Note on abbreviations: HCPCS, Healthcare Common Procedure Coding System; CPT, Current Procedural Terminology; ICD-10-PCS, International Classification of Diseases, 10th Revision, Procedure Coding System; NDC, National Drug Code

Development of algorithms for identifying AEs of interest through procedure codes in CMS and commercial claims data

Algorithms developed, assessed and ranked by:

1. **Clinical plausibility based on a panel of experts**
2. **Provider specialty plausibility:** assessing percentage of outcomes diagnosed by each provider specialty.
3. **Procedure Report Rate:** assessing the percentage diagnosed with an outcome who have accompanying pathology and biopsy procedure codes within a window of 90 days prior to and 90 days after the outcome diagnosis date.
4. **Treatment Report Rate:** assessing the percentage diagnosed with an outcome who have accompanying treatment codes within 90 days after the outcome diagnosis date.
5. **Time from Exposure to Outcome:** assess the percentage diagnosed with an outcome within the expected time between exposure to each outcome (unique for each outcome)

Some Next Steps

- Ascertainment of exposure cohort in commercial claims databases
- Finalizing algorithm to identify AEs of interest
- Calculating rates of AEs of interest in exposure cohort
- Identification of control group

Capabilities of BEST to Study Biologics Safety in Pregnancy and Planned Studies

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

Outline

- Background
- Capabilities of BEST to Study Safety of Biologics in Pregnancy
  - Validating Claims-based Algorithms to Identify Pregnancy Outcomes
  - Linkage of Mothers and Infants in Claims Databases
- Planned Studies

Safety of Medical Products in Pregnancy

- Pregnant persons have historically been excluded from clinical trials of medical products, including biologics

- Post-approval studies are critical for generating human safety data in pregnancy and can inform drug labeling and patient care.

FDA's Current Efforts to Improve Post-approval Pregnancy Safety Data Collection

Prescription Drug User Fee Amendment VII (PDUFA VII) Commitments include pregnancy safety:

"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."

Capabilities of BEST to Study Safety of Biologics in Pregnancy

BEST Capabilities: Claims-based Algorithms to Identify Pregnancy Episodes and Gestational Age

To conduct safety surveillance of biologics in pregnancy, BEST needs the capability to:

- Identify pregnancy outcomes using standard coding systems (ICD-10 era)
- Determine gestational age

Methods

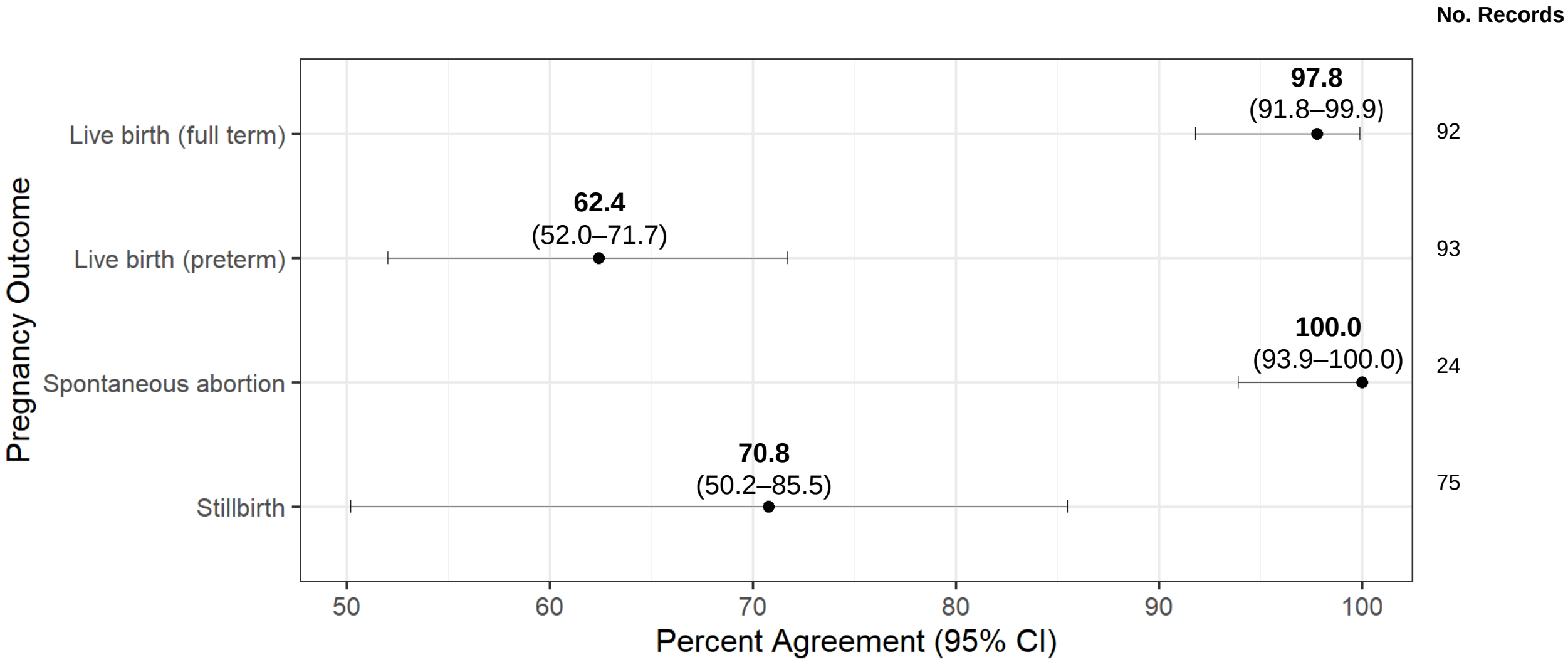
Algorithms: Pregnancy Outcomes of Interest

- Pregnancy Outcomes
  - Live births
    - Full term (≥37 weeks)
    - Preterm (<37 weeks)
  - Stillbirth
  - Spontaneous abortion
- Gestational age

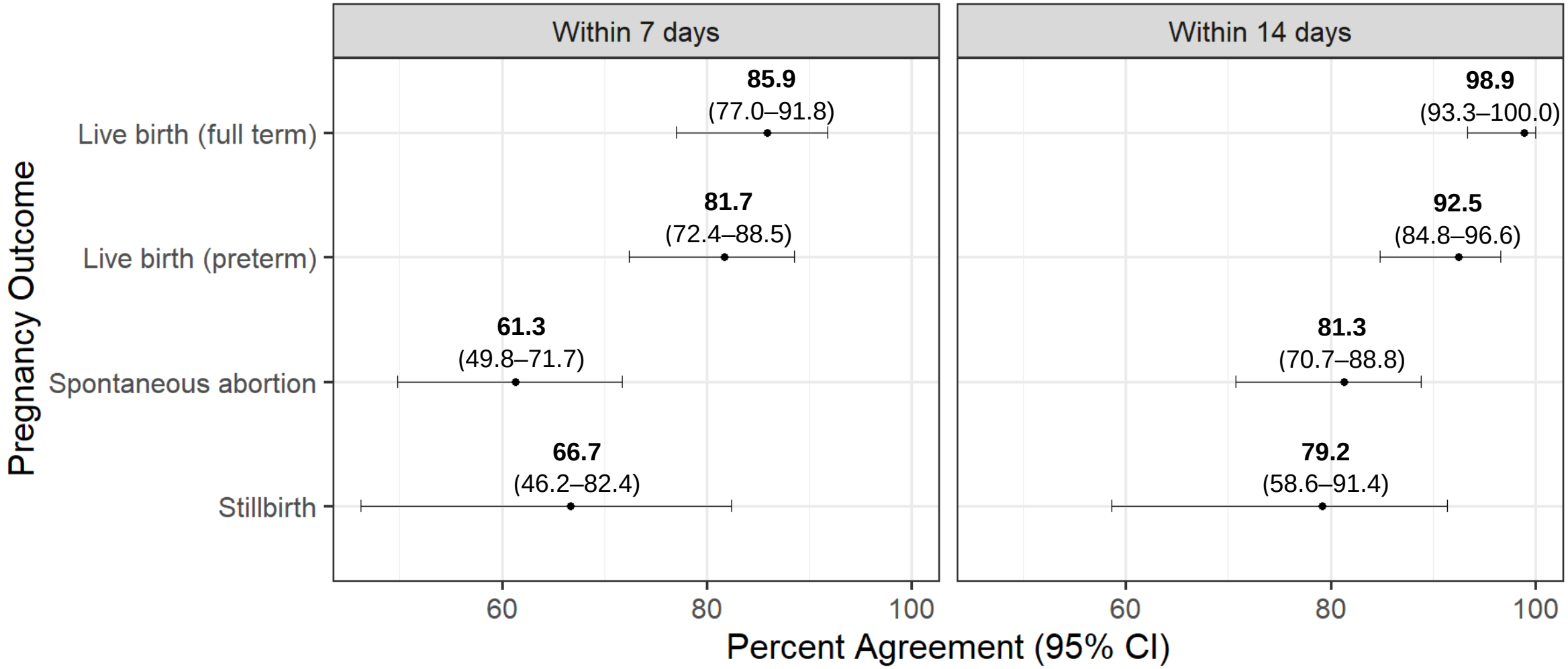
Validation: Use of Structured EHR to Evaluate Algorithms

- Sample identified pregnancy outcomes
- Use structured EHR data and the Global Alignment of Immunization safety Assessment (GAIA) in pregnancy case definitions to evaluate the performance of claim-based algorithms
- Estimate Percent Agreement and 95% Confidence Intervals

Algorithm Performance: Pregnancy Outcomes



Algorithm Performance: Gestational Age by Pregnancy Outcome

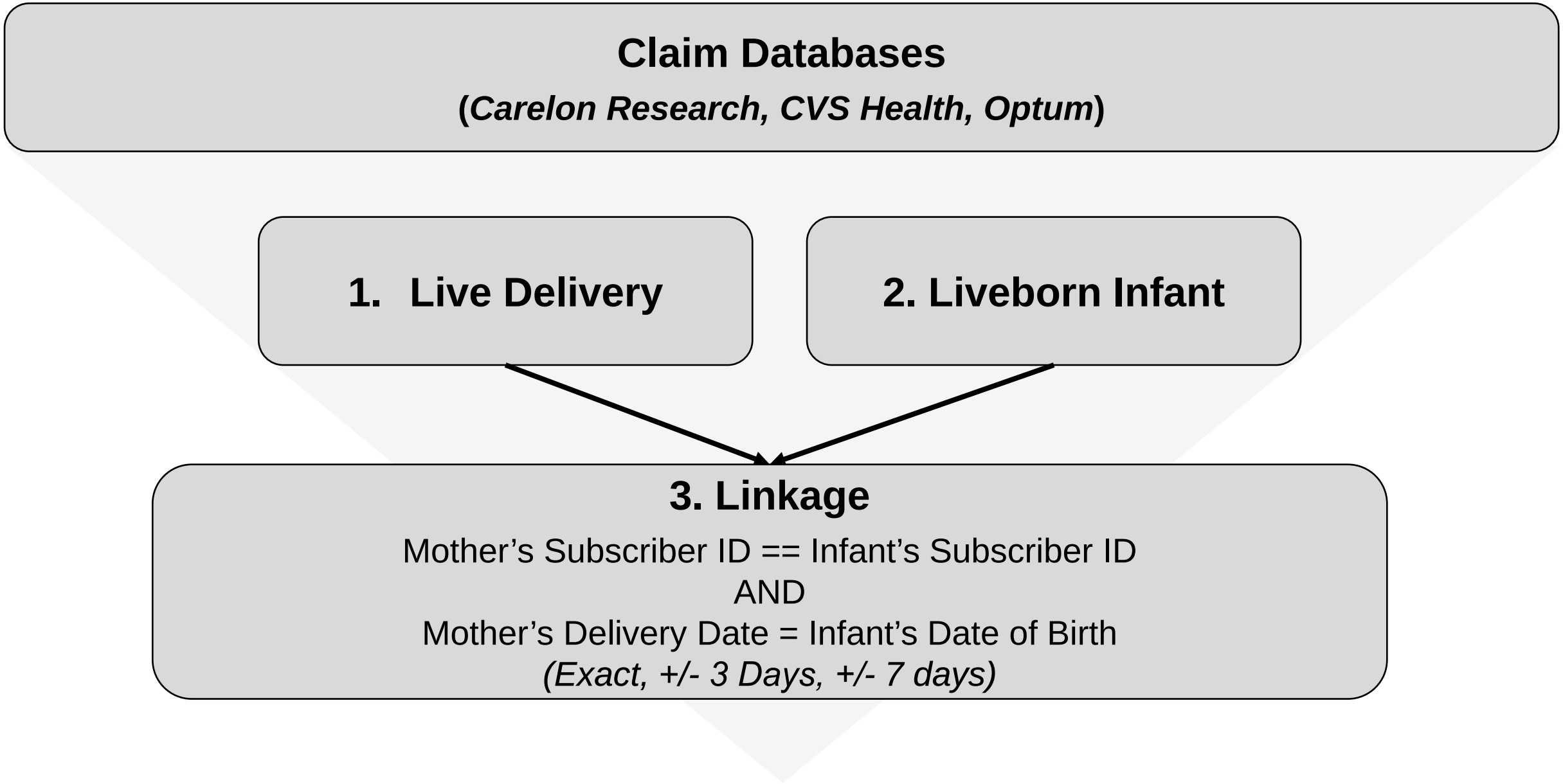


BEST Capabilities:
Linkage of Mothers and Infants in Claims Databases

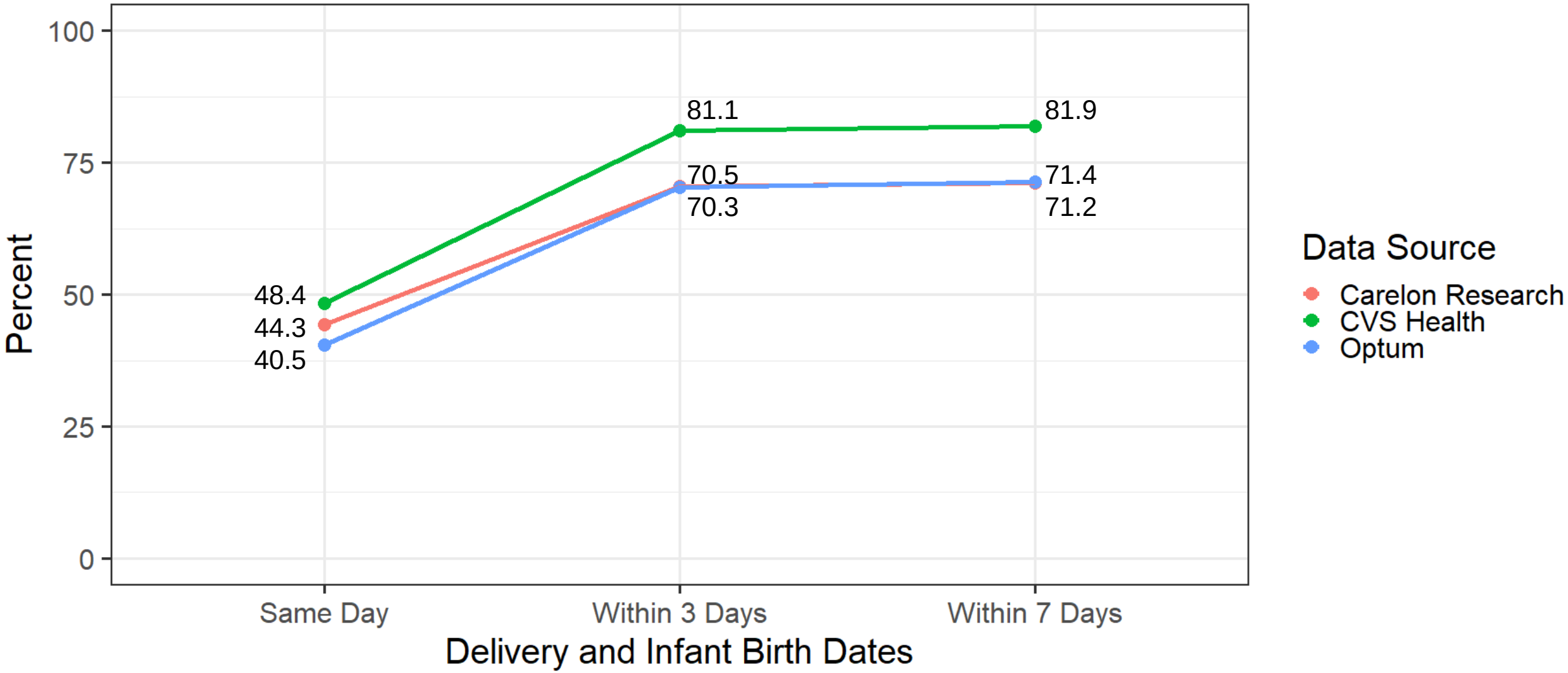
To conduct safety surveillance of biologics in pregnancy and on the health of infants, BEST needs the capability to:

- Link pregnant individuals to infants

Methods


Claim Databases
(Carelon Research, CVS Health, Optum)
1. Live Delivery
2. Liveborn Infant
3. Linkage
Mother's Subscriber ID == Infant's Subscriber ID
AND
Mother's Delivery Date = Infant's Date of Birth
(Exact, +/- 3 Days, +/- 7 days)

Mother-Infant Linkage Rates



Planned Studies

PDUFA Demonstration Project: Improving Algorithms for Identifying Preterm Birth in Claims Databases

- In prior work, gestational age was underestimated
  - Prevalence of Preterm birth
    - Study: 12.3%
    - Vital Statistics (2016): 9.9%

- Small differences in gestational age could result in large amounts of misclassification of preterm birth
  - 35 of the 93 preterm births were full-term
  - 23 of the 35 full-term births had a difference of 1 week GA (36 vs 37 weeks).

RSV Vaccination in Pregnancy

- One respiratory syncytial virus (RSV) vaccine is approved for use in pregnant people in the U.S. to prevent RSV-associated lower respiratory tract infection in infants aged <6 months.
  - RSVPreF (Pfizer – ABRYSVO®): Approved August 21, 2023
- CDC recommends RSV vaccine for pregnant persons at 32–36 weeks gestation from September–January in most of the United States.

RSV Vaccination in Pregnancy

- Pre-licensure clinical trials identified imbalances in rates of preterm births following vaccination compared to placebo.

- FDA BEST
  - Currently planning a study to evaluate safety outcomes including preterm birth following RSV vaccination in pregnancy.

Summary

- BEST has developed capabilities to study the safety of biologics in pregnancy

- BEST continues to develop capabilities and will expand work to improve our understanding of the safety and effectiveness of biologics used in pregnancy

Moderated Discussion and Q&A

Moderator: Christina Silcox

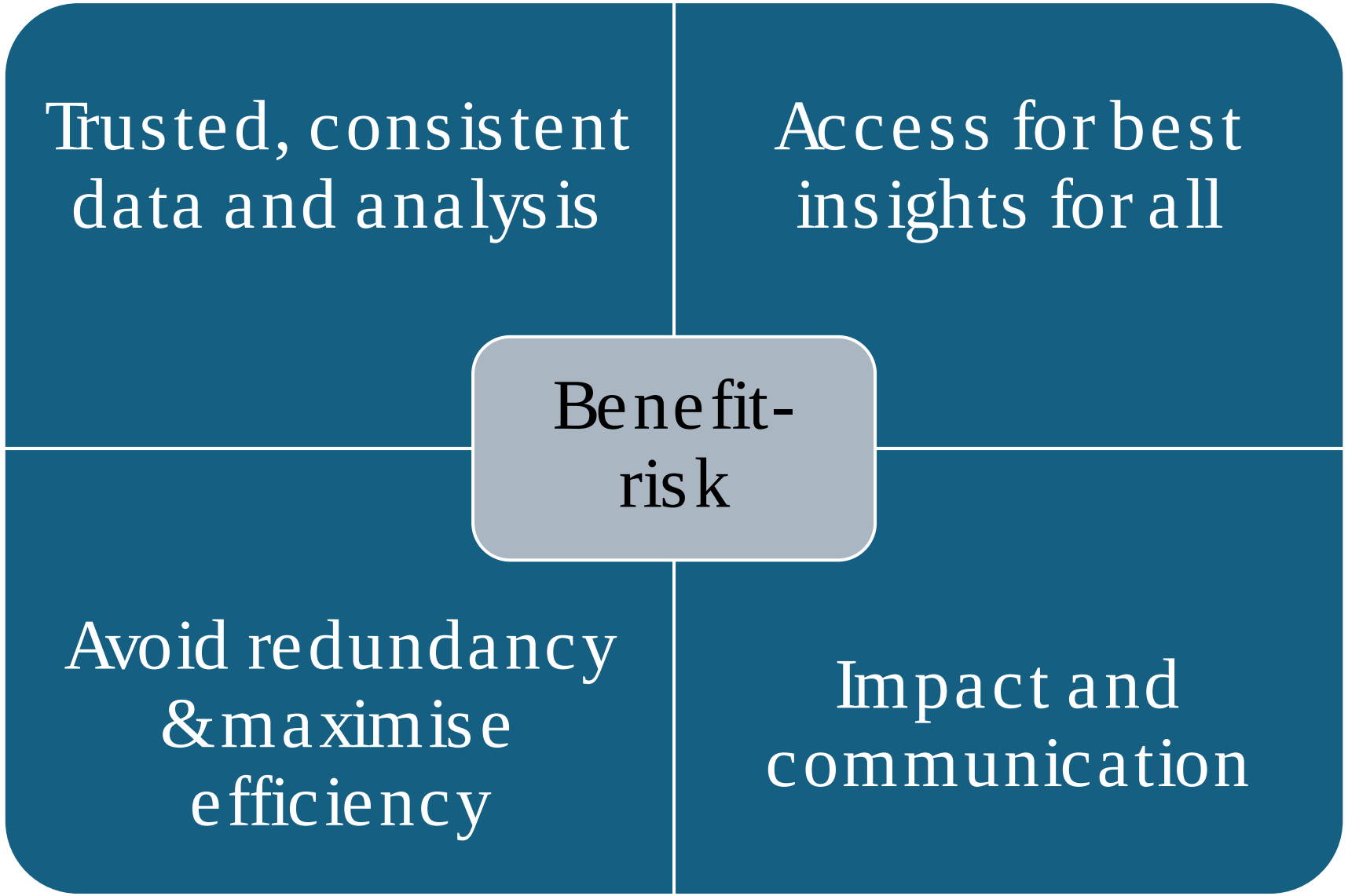
Duke-Margolis Institute for Health Policy

Break

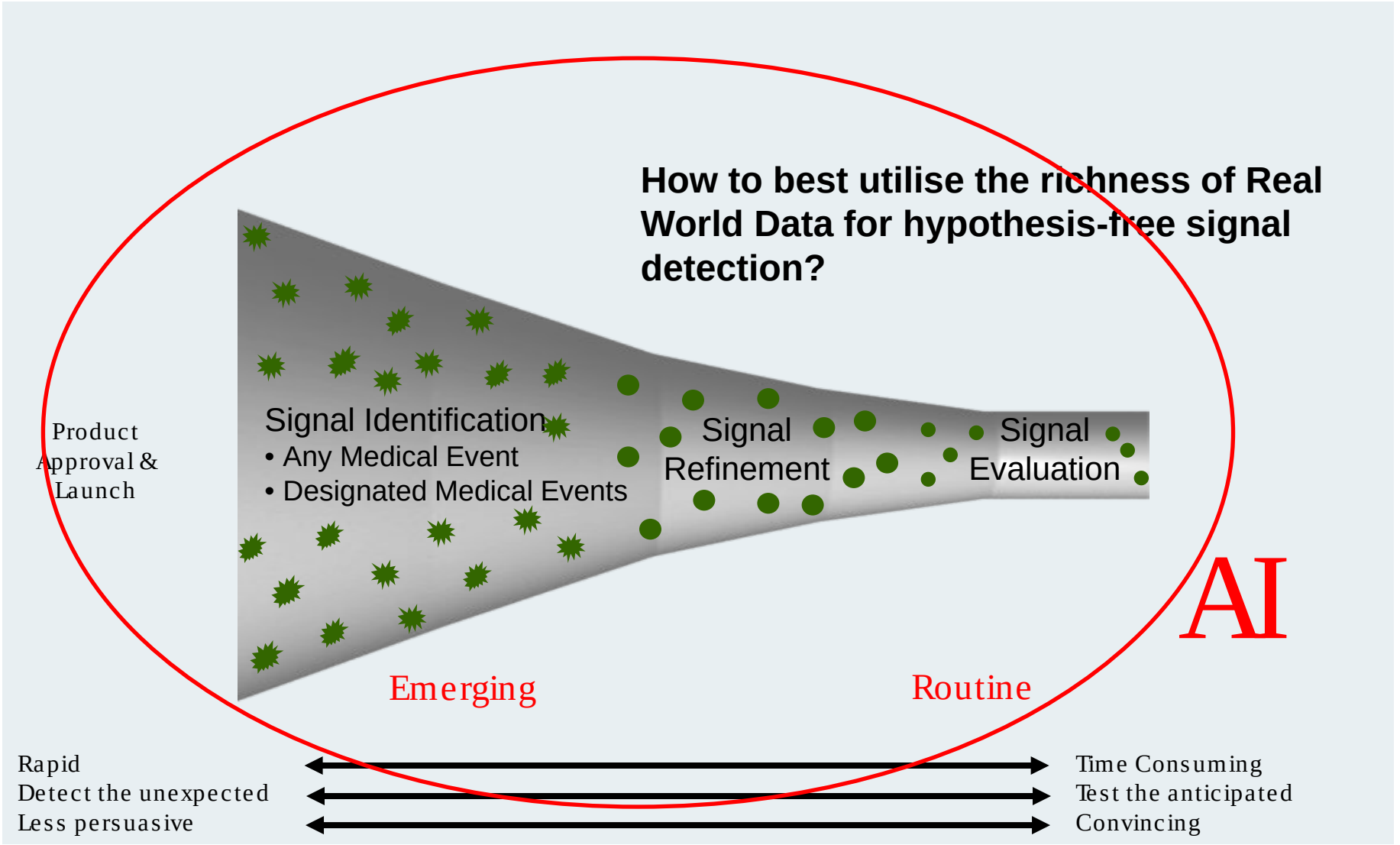
The workshop will resume at **3:15 p.m. ET**

Perspective on Future Opportunities for the Sentinel Initiative

Moderator:	**Trevan Locke**, Duke-Margolis Institute for Health Policy
Panelists:	**Patrice Verpillat**, European Medicines Agency
	Mary Beth Ritchey, CERobs Consulting LLC and Rutgers University
	Fredric S. Resnic, Lahey Health and UMass Chan School of Medicine
	Andrew Bate, GSK plc.
FDA Participants:	**Robert Ball**, U.S. Food and Drug Administration
	Richard Forshee, U.S. Food and Drug Administration


Trusted, consistent data and analysis
Access for best insights for all
Benefit-risk
Avoid redundancy &maximise efficiency
Impact and communication

Signal identification is a potentially important application in RWD- with specific challenges



Ref Bate 2010 Invited Presentation for panel B on "Emerging Data Sources and Methods for Pharmacovigilance" at 3rd meeting of the IOM Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs on Postmarket Surveillance and Drug Safety.

Moderated Discussion and Q&A

Moderator: Trevan Locke

Duke-Margolis Institute for Health Policy

Closing Remarks

Gerrit Hamre

Research Director, Duke-Margolis Institute for Health Policy

Duke | MARGOLIS INSTITUTE *for* Health Policy

Thank You!

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