Thirteenth Annual Sentinel Initiative Public Workshop

November 8, 2021 | 10:00 - 2:00 ET

November 9, 2021 | 10:00 - 2:00 ET

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

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

Welcome & Overview | Day 1

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Agenda: Day 1

- Keynote Presentation – Patrizia Cavazzoni
- Fireside Chat with Sentinel Initiative Leadership
- Sentinel Coordinating Center Perspectives
- Improving Causal Inference for RWE Generation
- Fireside Chat with Robert Califf: Building Robust Evidence Generation Systems

Agenda: Day 2

- Sentinel Collaborations for COVID-19 Response
- BEST's COVID-19 Response
- BEST Collaborator Perspectives

Statement of Independence

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

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

Virtual Meeting Reminders

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

- Join the discussion on Twitter using the #SentinelInitiative hashtag

Keynote Presentation

Patrizia Cavazzoni

U.S. Food and Drug Administration

Fireside Chat with Sentinel Initiative Leadership

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

Discussion Questions

- What development opportunities or projects are you most excited about as we move into 2022?
- What steps can these systems take to help us be prepared for future pandemics?

Session I: Sentinel Coordinating Center Perspectives

- **Patricia Bright,** U.S. Food and Drug Administration
- **Richard Platt,** Harvard Pilgrim Health Care Institute
- **Sebastian Schneeweiss**, Harvard Medical School
- **Asif Dhar**, Deloitte

U.S. FOOD & DRUG ADMINISTRATION

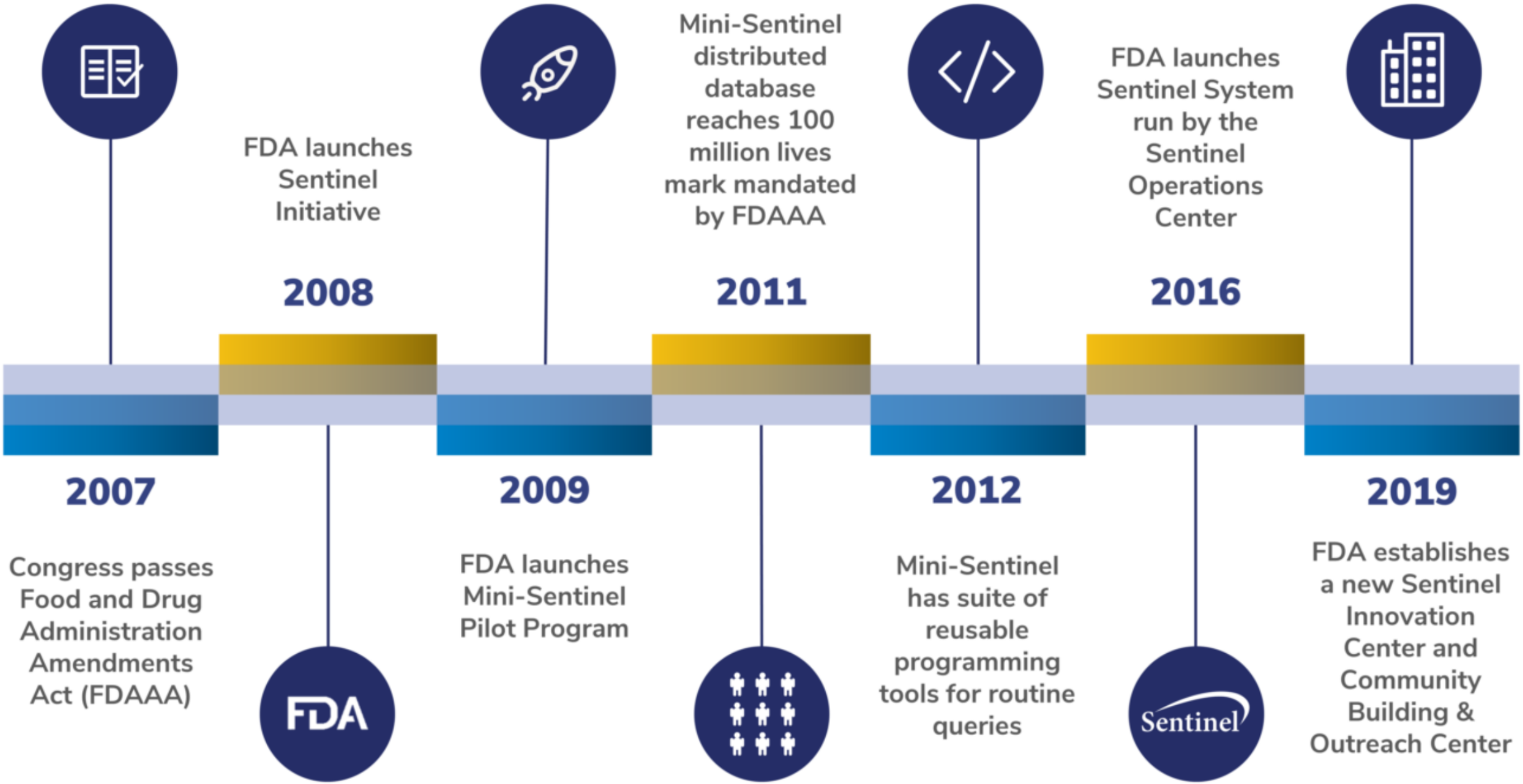
Session I
Sentinel Coordinating Center Perspectives

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

Sentinel Coordinating Center Perspectives

- Brief recap of Sentinel's history
- Sentinel System 5-Year Strategy
- The larger landscape of the Sentinel System
- CDER's Sentinel Coordinating Centers

History of the Sentinel Initiative



Defining ARIA

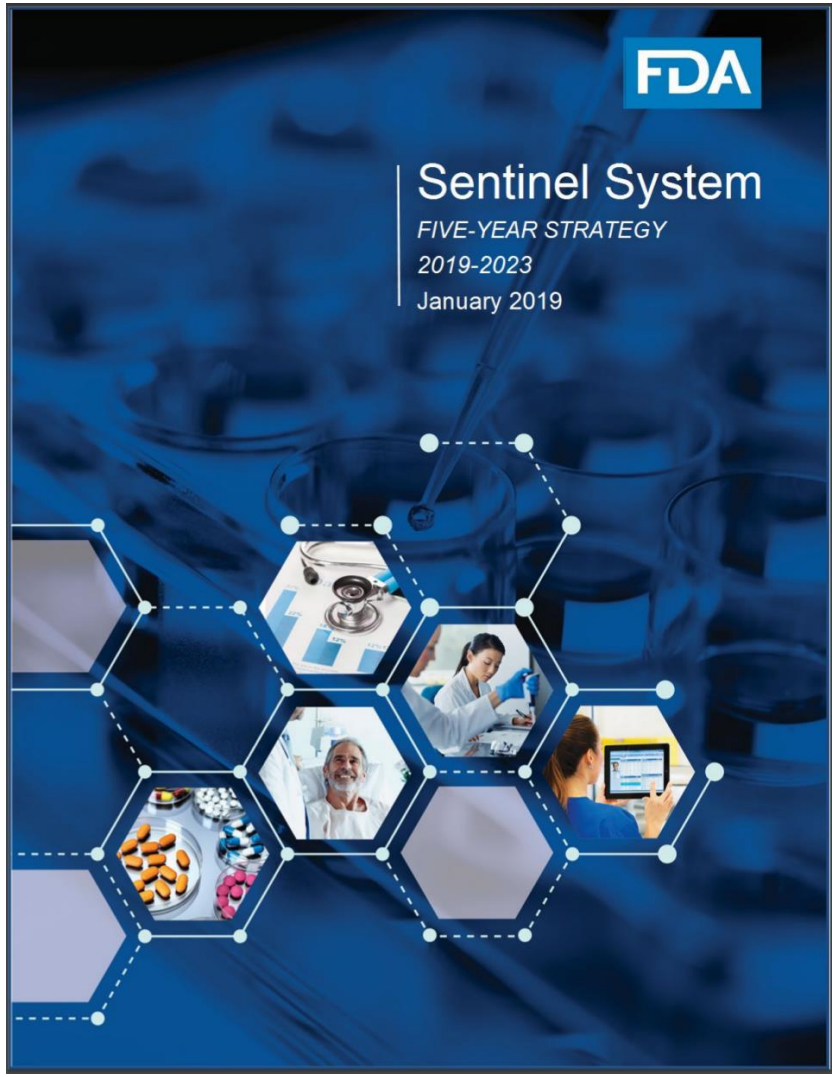
Active Risk Identification and Analysis (ARIA) System

ARIA uses a subset of Sentinel System's full capabilities to fulfill the FDAAA mandate to conduct active safety surveillance

* Pre-defined, parameterized, and re-usable to enable faster safety surveillance in Sentinel (in contrast to protocol-based assessments with customized programming)

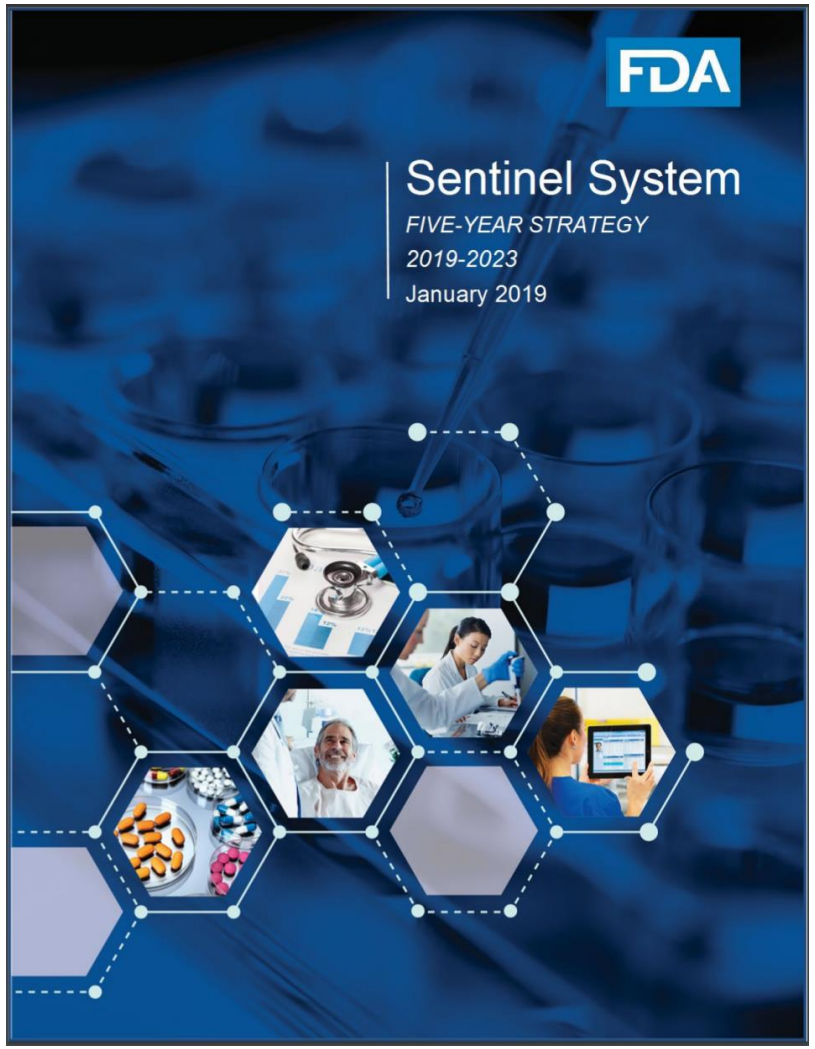
† Electronic claims data, without manual medical record review

Sentinel System 5-Year Strategy



- Maintain and enhance the foundation of the Sentinel System, preserving FDA's long-term investment in Sentinel's analysis tools and data infrastructure
- Diversify data sources, especially EHRs and claims linked to EHR's
- Incorporate advanced analytics
- Broaden touch points for participating in Sentinel's development
- Establish a Sentinel scientific community and disseminate knowledge to improve public health

Sentinel System: Continued Development



A sample of some of the work:

IC
Causal Inference
Harmonizing EHRs
Machine Learning
Computable Phenotyping Framework
Natural Language Programming
Considerations for Adding Unstructured Data

CBOC
Newsletter
Training
Website re-design
Informational Videos

SOC
COVID-19 Work
ARIA Tool Enhancements
Mother-infant Linked Data
Nitrosamine Contamination
Tree-based Scan Statistic for Pregnancy Related Signal Detection

Sentinel: A Range of Regulatory Activities

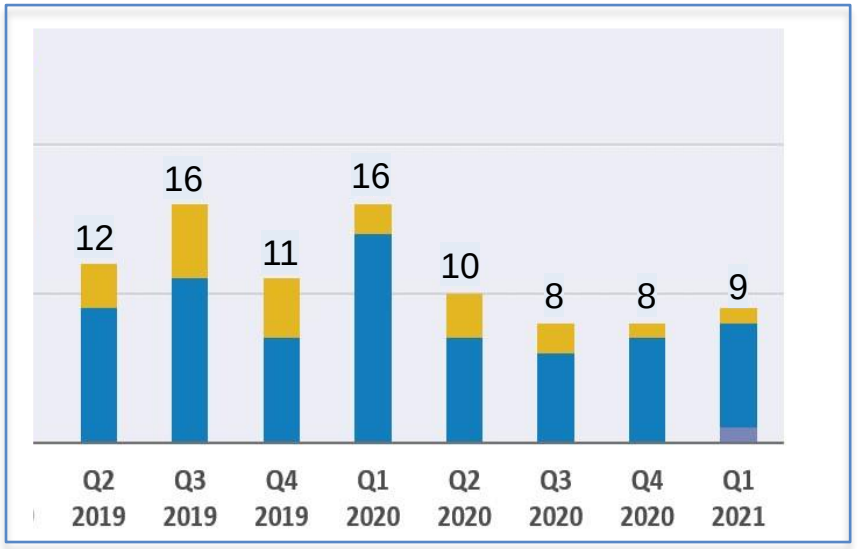
- Signal Identification Work:
  - ➢ Tree-based scan statistics for pregnancy related signal identification
- COVID-19 Work:

  Querying with new data sources and approaches to address the pandemic
  - ➢ Monitoring critical drugs
  - ➢ Natural history of COVID-19 disease in pregnant women

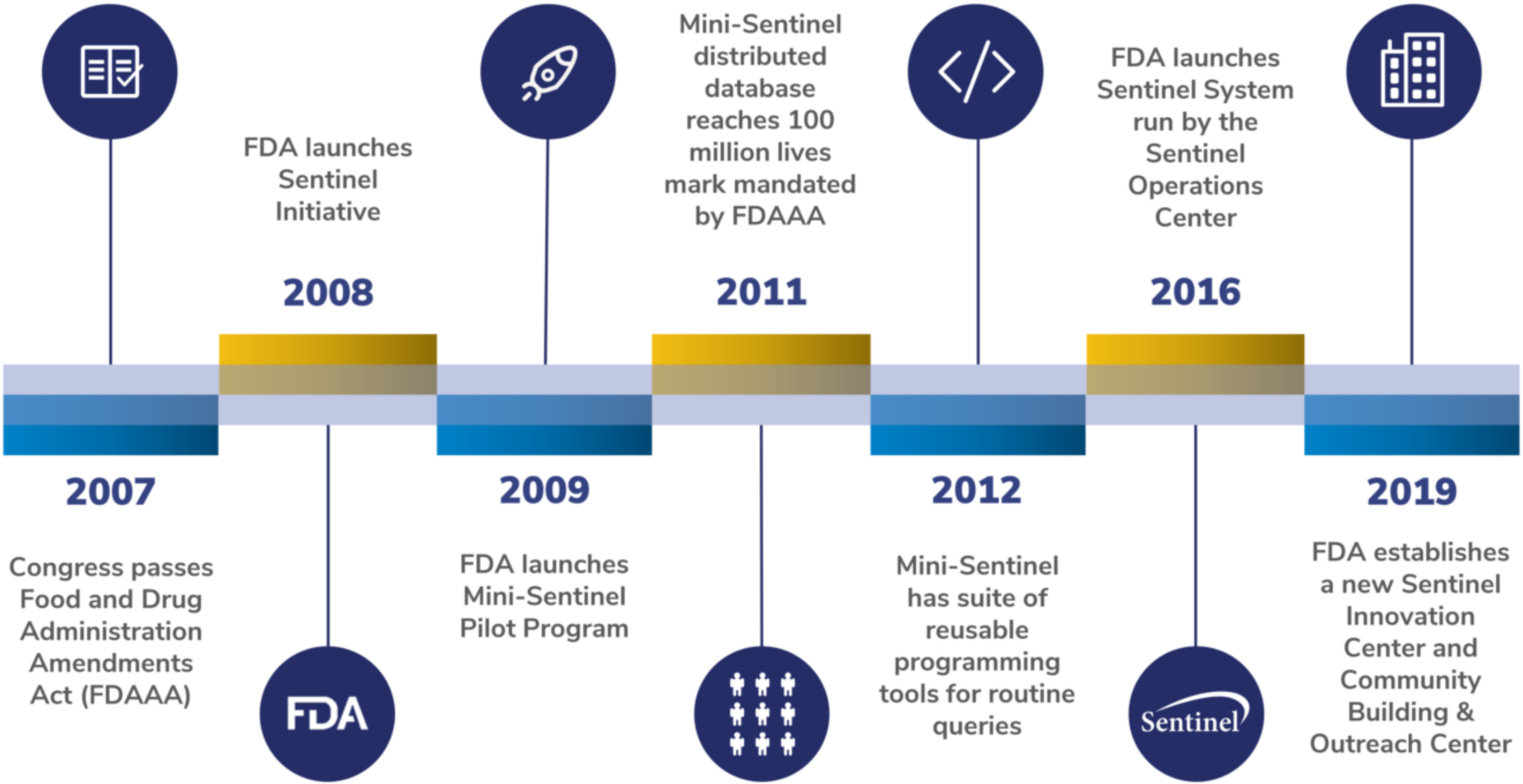
ARIA Analysis by Quarter

= Level 1 analysis

= Level 2 analysis

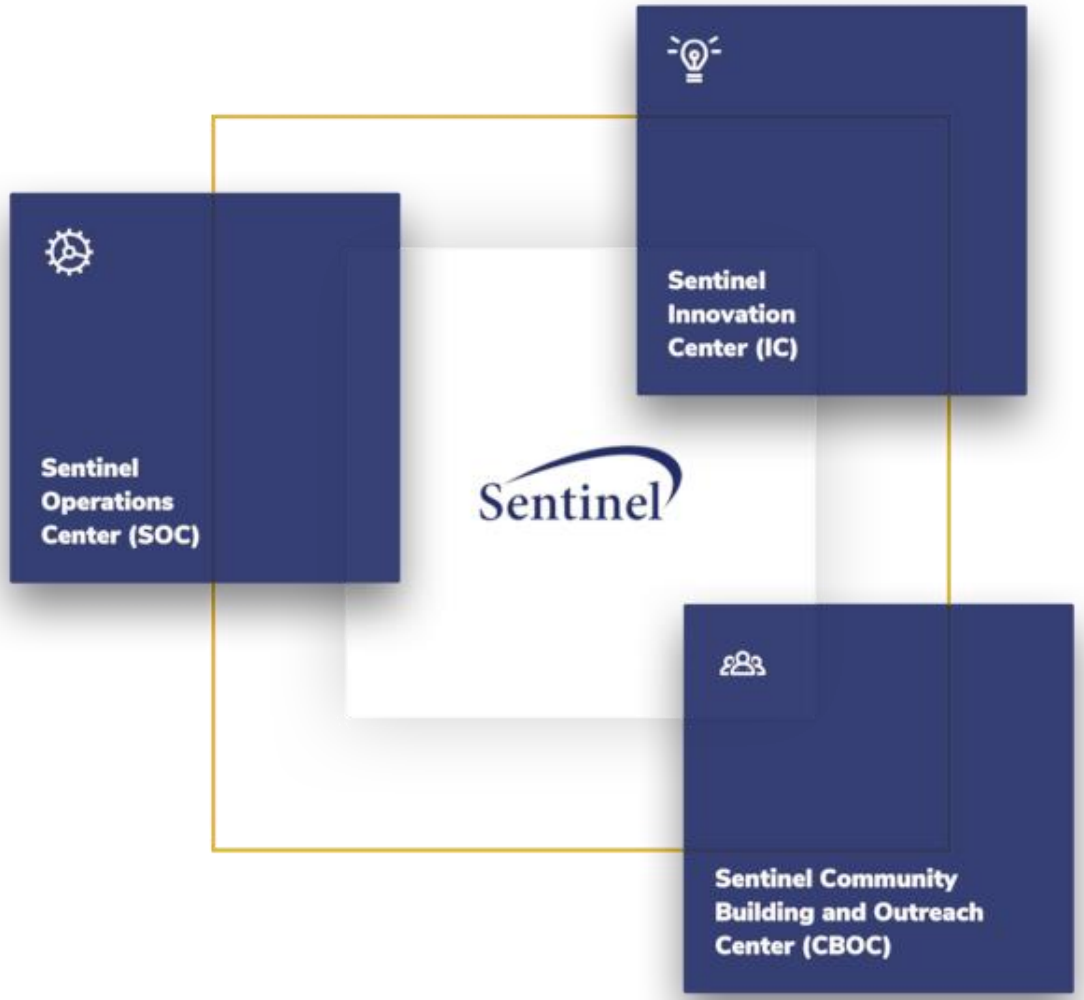


History of the Sentinel Initiative



New Sentinel System Structure

Conduct analyses and Enhance the Infrastructure



Advance the Science

Engage the Community


FDA
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ADMINISTRATION

The FDA Sentinel Initiative – An Evolving National Resource

Richard Platt

For the Sentinel Investigators

November 8, 2021

Operations Center Collaborating Organizations

Sentinel

Lead: Harvard Pilgrim Health Care Institute

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

Data & Scientific Partners

HealthCore
Anthem
Healthagen
aetna
KAISER PERMANENTE
CMS
Humana
OPTUM
TennCare
Marshfield Clinic Research Institute
HealthPartners Institute
pcornet
veradigm
TriNetX
HCA Healthcare
RTI INTERNATIONAL
UF College of Pharmacy UNIVERSITY of FLORIDA
VANDERBILT UNIVERSITY MEDICAL CENTER
The Meyers Primary Care Institute
RUTGERS
Penn Medicine
IBM Watson Health
SCHOOL OF PUBLIC HEALTH UNIVERSITY of WASHINGTON
UAB
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
Brigham and Women's Hospital Founding Member, Mass General Brigham
Duke Clinical Research Institute
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

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The Sentinel Distributed Database: Claims and Administrative Data

- **788 million** person-years of data
- **64 million** people currently accruing new data
- **14 billion** medical encounters
- **16 billion** pharmacy dispensings
- **41 million** with at least one laboratory test result
- **6 million** linked mother-baby pairs

Operations Center Collaborating Organizations

Sentinel

Lead: Harvard Pilgrim Health Care Institute

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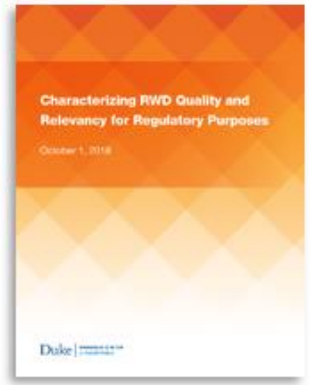
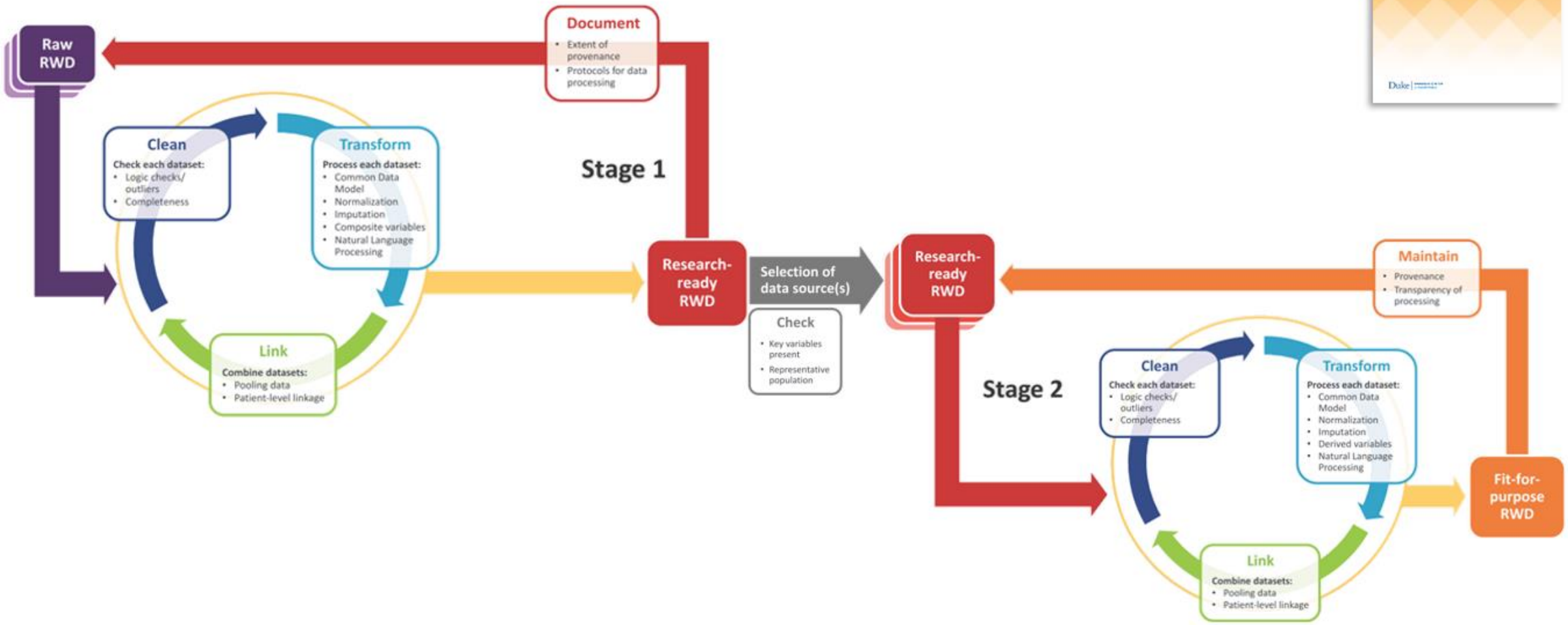
CURATION IS OFTEN COMPLEX AND HARD TO EXPLAIN





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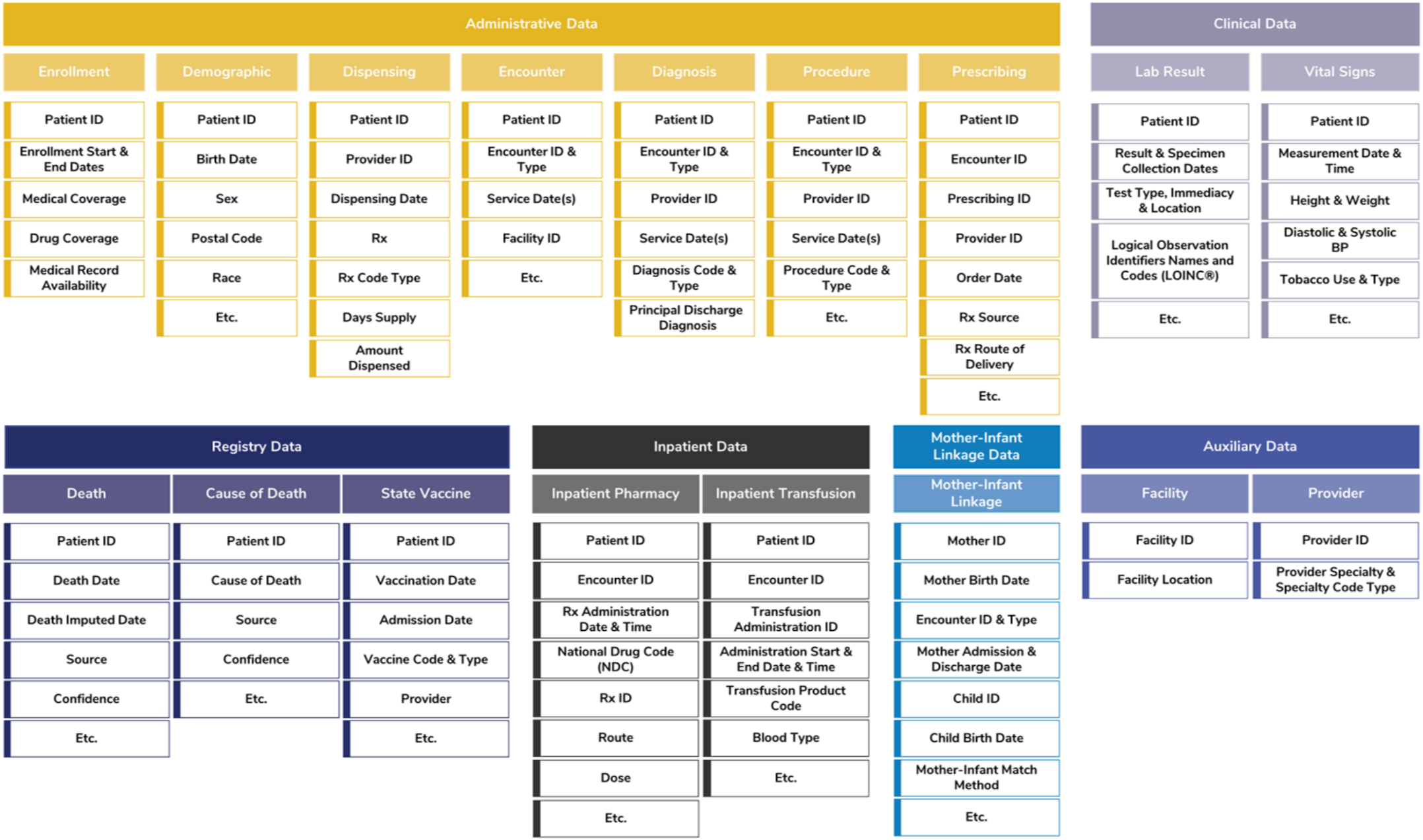
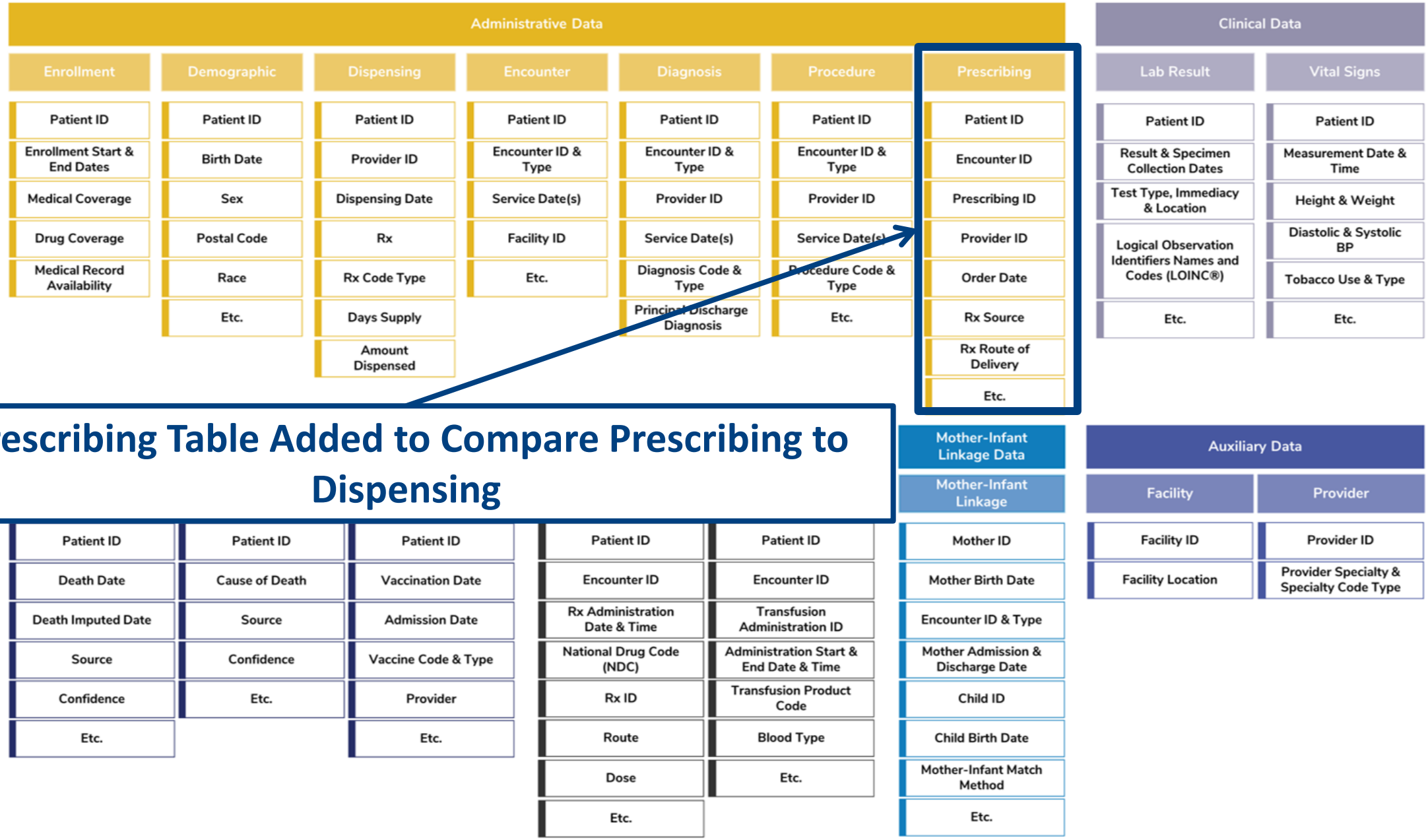
Sentinel Common Data Model



https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

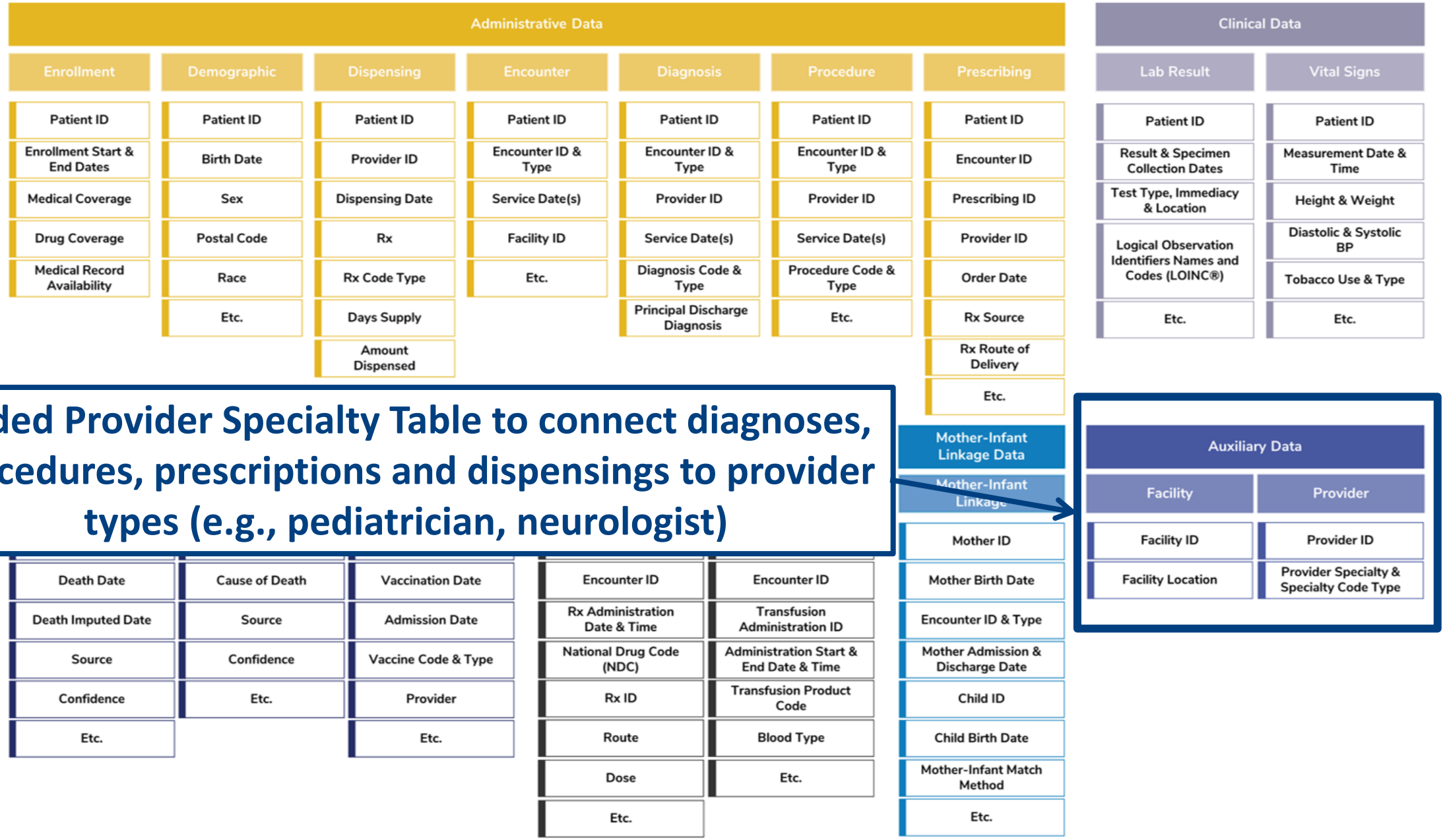
Sentinel Common Data Model



Prescribing Table Added to Compare Prescribing to Dispensing

https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

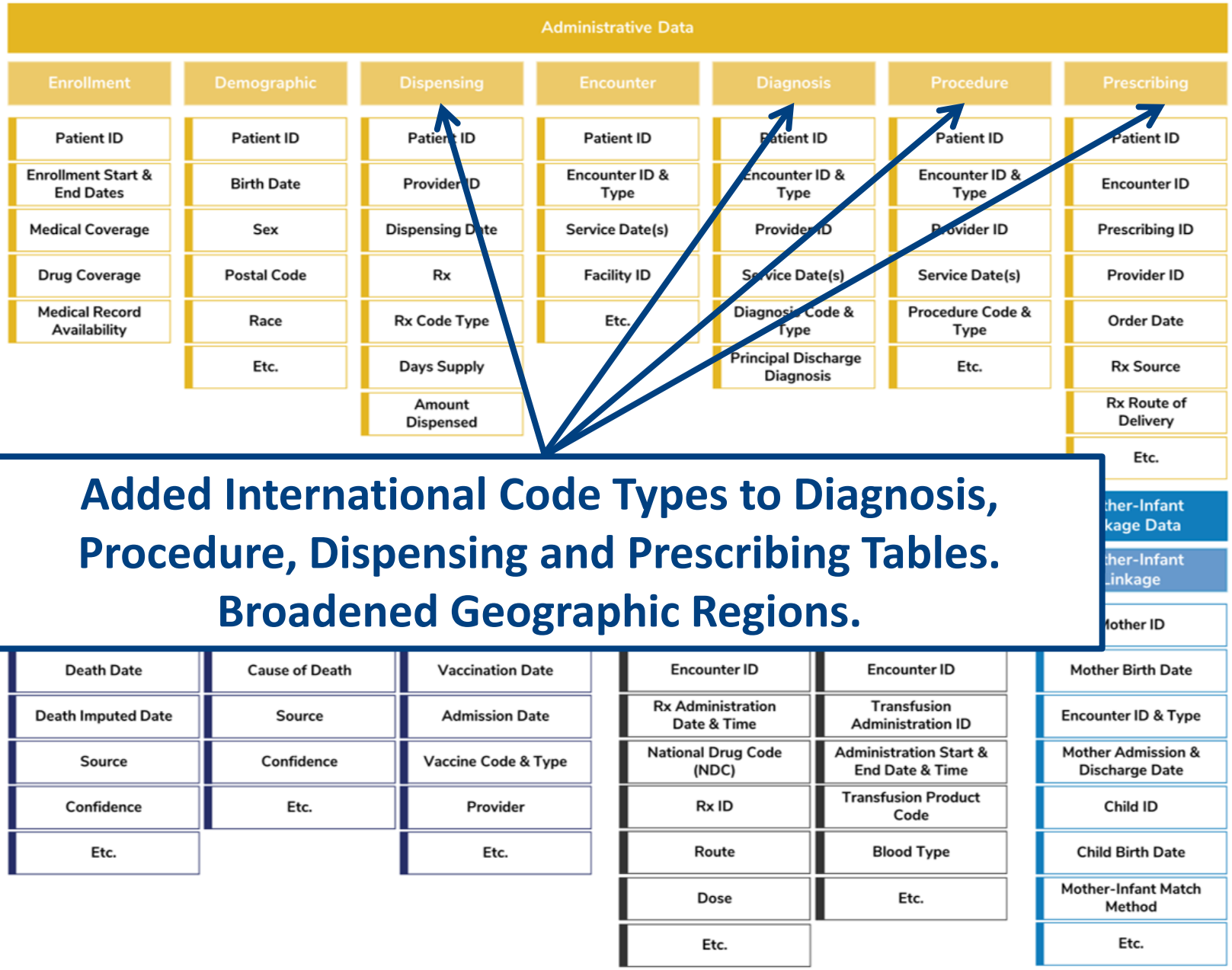
Sentinel Common Data Model



Added Provider Specialty Table to connect diagnoses, procedures, prescriptions and dispensings to provider types (e.g., pediatrician, neurologist)

https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Sentinel Common Data Model



https://sentinelinitiative.org/methods-data-tools/sentinel-common-data-model

Since 2016, Sentinel Studies have Contributed to the following Regulatory Actions (Preliminary Data):

- 9 Labeling Changes
- 13 Other Regulatory Actions
- 5 Inform Other Agency Requests
- 3 Drug Safety Communications
- 7 FDA Advisory Committee Meetings
- 1 Inform NDA/BLA Review
- 12 Provided Safety Information Not Requiring Regulatory Action
- 1 Inform Clinical Trial Development
- 3 Inform Feasibility or Utility of an Ongoing PMR
- 1 Assist an FDA Response to a Public Inquiry

SENTINEL'S SUITE OF REUSABLE TOOLS

https://www.sentinelinitiative.org/assessments/drugs#fda-sentinel-drug-assessments-from-aria-and-other-sentinel-data-sources

Potential Use of Tree-Based Scan Statistic for Pregnancy Related Signal Identification

- Surveillance of maternal outcomes following medication use during gestation
- Surveillance of infant outcomes following maternal medication use

https://www.sentinelinitiative.org/methods-data-tools/methods/treescan-pregnancy

Mother-Infant Linked Data

- **5,533,236** of **6,999,639** deliveries (**79%**) are now linked
- Now converting Medicaid data into Sentinel Common Data Model format:
  - Medicaid covers **nearly half of all U.S. births**
  - Contains an additional >**13 million** deliveries (~50% linked)

Palmsten, K. et al. (2013) 'Harnessing the Medicaid Analytic eXtract (MAX) to Evaluate Medications in Pregnancy: Design Considerations', PloS One, 8(6), p. e67405. doi:10.1371/journal.pone.0067405.

Sentinel Support for Pandemic Preparedness

- Support for FDA's Office of Counter Terrorism and Emerging Threats (OCET)
  - Leverage Sentinel infrastructure to monitoring and assess safety and effectiveness of medical countermeasures
  - Influenza was used as a proxy for other public health emergency events
- Support for FDA's COVID-19 response

Office of Counterterrorism &Emerging Threats Funded Studies

Received: 10 September 2021 | Accepted: 25 September 2021

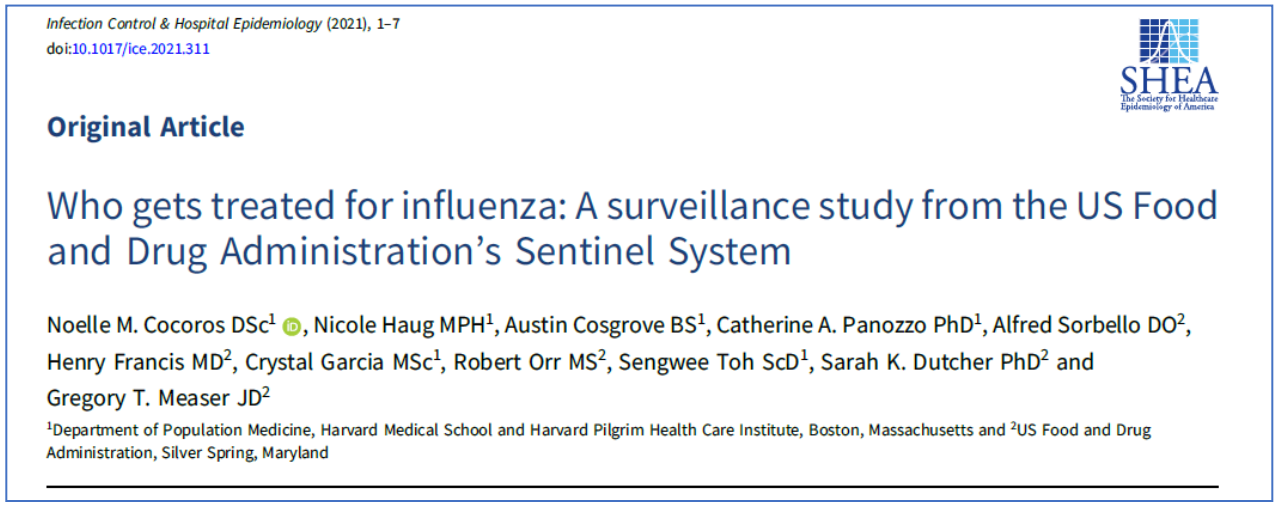
DOI: 10.1111/irv.12921

ORIGINAL ARTICLE

WILEY

Using inpatient electronic medical records to study influenza for pandemic preparedness

Candace C. Fuller[1] | Austin Cosgrove[1] | Kenneth Sands[1,2] | Karla M. Miller[2] | Russell E. Poland[1,2] | Edward Rosen[1] | Alfred Sorbello[3] | Henry Francis[3] | Robert Orr[3] | Sarah K. Dutcher[3] | Gregory T. Measer[4] | Noelle M. Cocoros[1]



Infection Control & Hospital Epidemiology (2021), 1–7

doi:10.1017/ice.2021.311

SHEA The Society for Healthcare Epidemiology of America

Original Article

Who gets treated for influenza: A surveillance study from the US Food and Drug Administration's Sentinel System

Noelle M. Cocoros DSc[1], Nicole Haug MPH[1], Austin Cosgrove BS[1], Catherine A. Panozzo PhD[1], Alfred Sorbello DO[2], Henry Francis MD[2], Crystal Garcia MSc[1], Robert Orr MS[2], Sengwee Toh ScD[1], Sarah K. Dutcher PhD[2] and Gregory T. Measer JD[2]

[1]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts and [2]US Food and Drug Administration, Silver Spring, Maryland

Pandemic preparedness studies positioned Sentinel to be immediately responsive to COVID-19, particularly for identifying hospitalized cases and inpatient medications and care (e.g., oxygen related therapy)

Sentinel

PDS Pharmacoepidemiology & Drug Safety

ispe Official Journal of the International Society for Pharmacoepidemiology

REVIEW | Free Access

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

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

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

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

Cocoros NM, et al. A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System. Pharmacoepidemiol Drug Saf. 2021 Jul;30(7):827-837. doi: 10.1002/pds.5240. Epub 2021 Apr 18. PMID: 33797815.

Oxygen-related therapy in hospitalized adult patients with COVID-19 diagnosis, Feb 2020 – Mar 2021

Sentinel

- Nursing documentation improved both granularity and capture of oxygen-related therapy
- **79% were ventilated or on supplemental oxygen (vs 28% in code-based definition)**

Oxygen-related care, nursing documentation[1]	COVID-19 hospitalizations (N=137,565)
Bilevel Positive Airway Pressure (BiPAP)	15%
High flow nasal cannula	24%
Nasal cannula (routine)	74%
Non-rebreather	20%
Oxygen conserving device	4%
Simple mask	13%
Ventilator	14%
Any oxygen or ventilator	**79%**

[1]Data derived from oxygen-related nursing documentation, leveraging mappings from clinical experts.

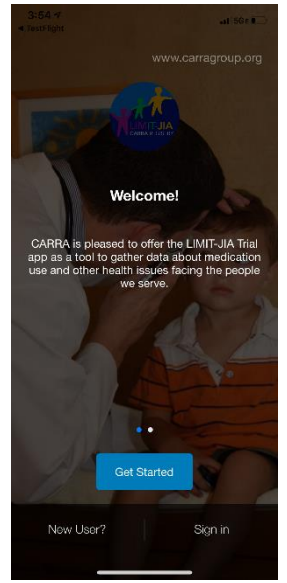
FDA Catalyst Projects

Title	Status	Date
COVID MyStudies Mobile App for E-Consent	IN PROGRESS	06/01/2020
FDA-Catalyst Alignment with the CMS Linkage to the PCORI RELIANCE Trial	IN PROGRESS	05/08/2019
Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib)	IN PROGRESS	05/07/2019
FDA-Catalyst MyStudies App Alignment with Pragmatic Trials and/or Registries	IN PROGRESS	10/15/2018
Collection of Patient-Provided Information Through a Mobile Device Application for Use in Comparative Effectiveness and Drug Safety Research	COMPLETE	01/02/2017

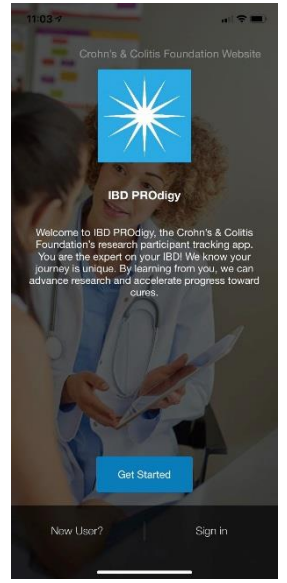
https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects

FDA MyStudies – Non-Sentinel Branded Apps

- Childhood Arthritis and Rheumatology Research Alliance (CARRA) - LimitJIA (PCORI-funded registry)



- Crohn's and Colitis Foundation - SPARC IBD (Study of a Prospective Adult Research Cohort with IBD)



National Collaborations

CDC

Centers for Disease Control and Prevention

BBCIC

Biologics & Biosimilars Collective Intelligence Consortium

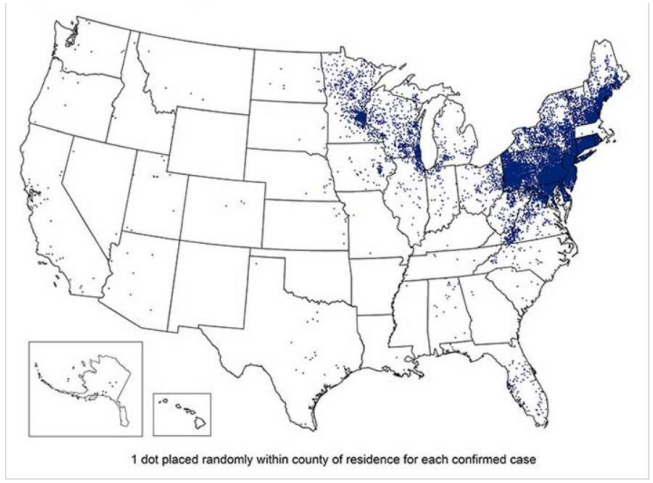
Reagan-Udall Foundation for the Food and Drug Administration

LYME DISEASE POST-EXPOSURE PROPHYLAXIS WITH 1 DOSE DOXYCYCLINE

Sentinel

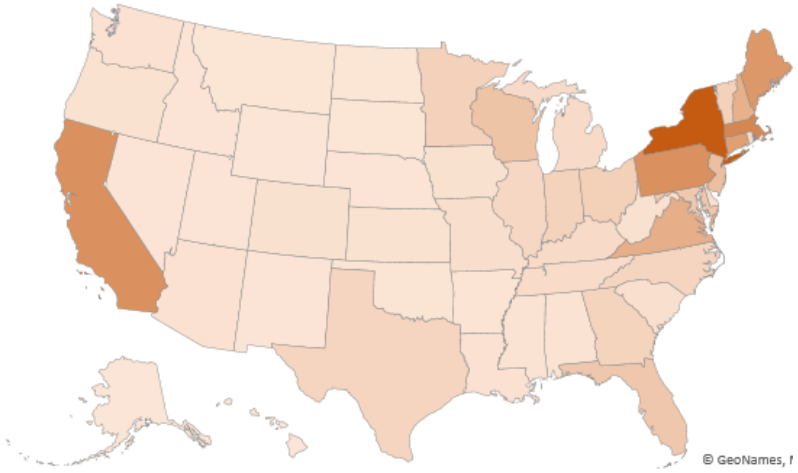
- Over 400,000 patients with post-exposure prophylaxis (PEP) dispensing from 2009-2020, mean age 60 years, few children
- Most PEP dispensings in states with high incidence of Lyme disease

Lyme disease cases, 2018

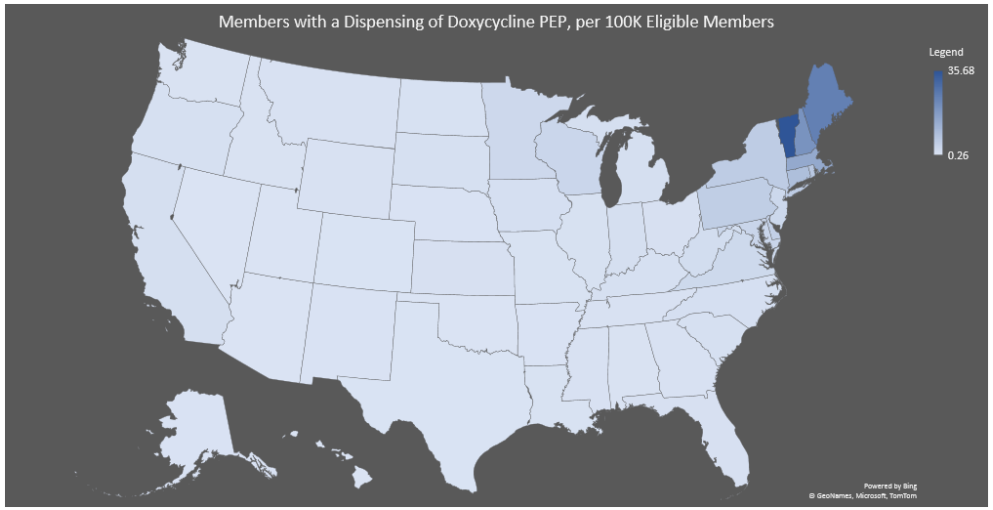


https://www.cdc.gov/lyme/stats/maps.html

Dispensing of Doxycycline PEP



Dispensing of Doxycycline PEP, per 100K Eligible Members



NIH Collaboratory Distributed Research Network

- Facilitates investigator-initiated NIH funded research in collaboration with the Sentinel partners, using their data and tools
- Supports both observational studies and clinical trials
- Most Sentinel distributed data partners participate

https://rethinkingclinicaltrials.org/nih-collaboratory-drn/

National Institute on Aging-Funded Research: Improving Medication Safety in Dementia

- **Controlling And Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)** R56AG061813
  - Quantify prescribing cascades among people with dementia living at home

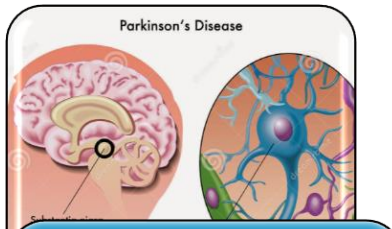
Principal investigator: J. Gurwitz

Prescribing Cascade Concept

Initial drug therapy

Drug A

E.G., Antipsychotics



New medical condition

Parkinsonism

New drug treatment

Drug B

Antiparkinsonian drugs

Further medical condition

Develops in weeks to months

Not well recognized as drug-related

Perhaps confused with age-related changes

Principal investigator: J. Gurwitz

The Controlling And Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)

Prescribing cascades in 121,538 older adults living at home with dementia are less common than expected:

Antidopaminergic-antiparkinsonian medication cascade

- Only **0.8%** of new users of antipsychotic/metoclopramide initiated therapy with anti-Parkinson's drugs

Calcium Channel Blocker Diuretic Cascade

- Only **2.1%** experienced a prevalent CCB-diuretic prescribing cascade

Principal investigator: J. Gurwitz

J Am Geriatr Soc 2021 May;69(5):1328-1333.
Pharmacoepidemiol Drug Saf.2021 Aug;30(8):1066-1073

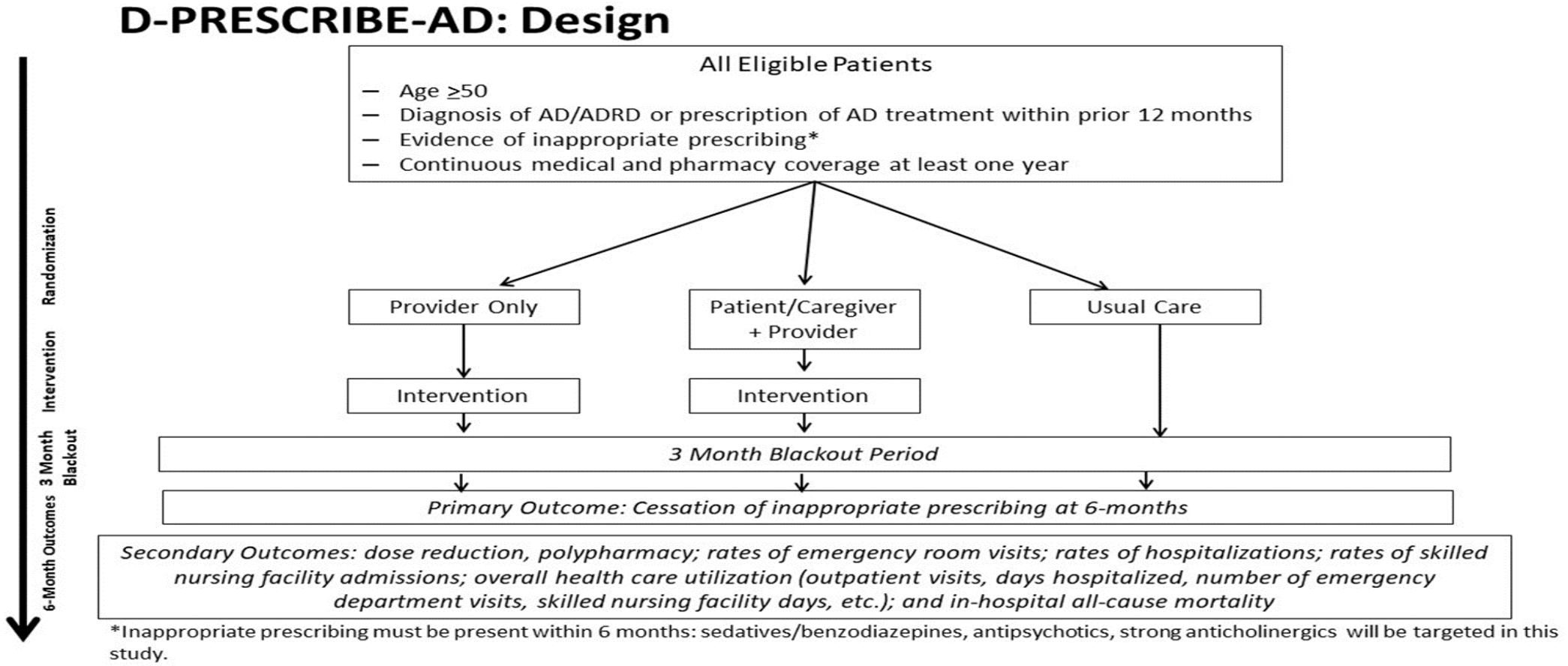
National Institute on Aging-Funded Research: Improving Medication Safety in Dementia

- **Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD)**
  R61AG069794/R33AG069794
  - A large simple pragmatic clinical trial to reduce use of potentially inappropriate medications

Principal investigator: J. Gurwitz

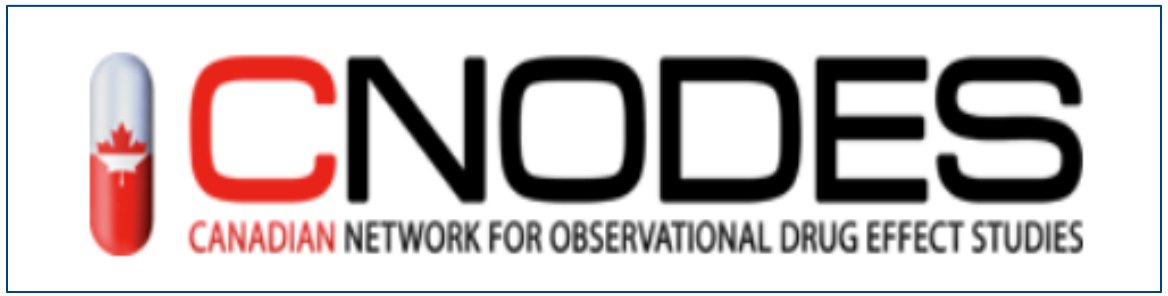
Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD)

Pragmatic open Label RCT in two Sentinel health plans (n ≈11,250 to be randomized)

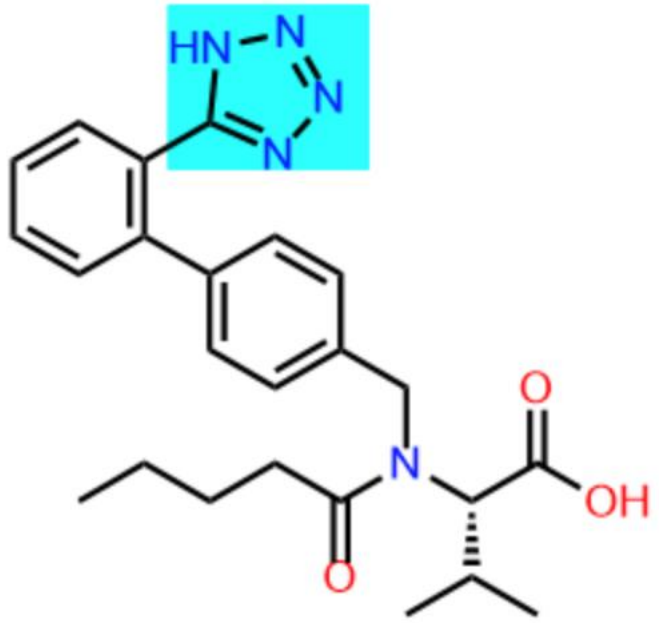


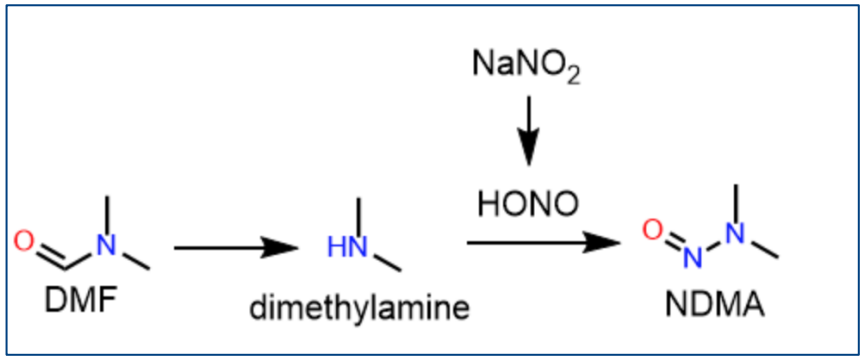
Principal investigator: J. Gurwitz

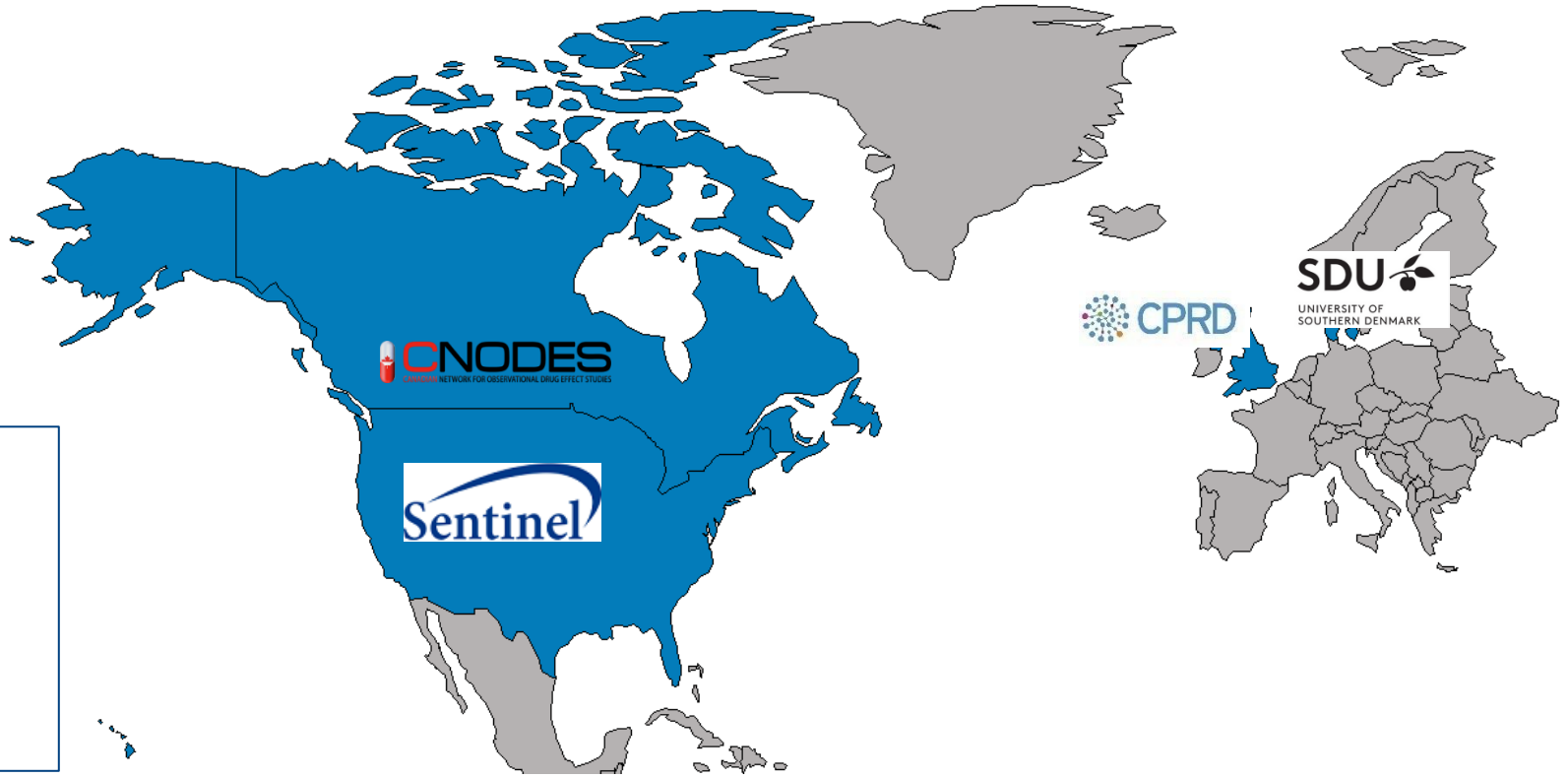
INTERNATIONAL COLLABORATIONS



Impact of Nitrosamine Contamination Effects on Angiotensin Receptor Blocker Utilization







https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-angiotensin-ii-receptor-blocker-arb-recalls-valsartan-losartan

HIGHLIGHTS: INTERNATIONAL COOPERATION

- Queries executed against 20 databases:
  14 US, 4 Canada, 1 UK CPRD, 1 Denmark
- All databases executed identical data characterization and quality assurance programs without failure
- The same analytic package was run at all sites, making aggregation possible across all sites
- Code files included all jurisdictions
  - Used original codes without mapping
  - Maximal investigator control with local insight around key clinical definitions.
- Accommodated each jurisdiction's rules for masking small cell counts

Three International Partnerships for COVID-19 Studies

- **COVID-19 Coagulopathy Study**
  - Assessment of arterial and venous thrombotic events among COVID-19 patients
- **Natural History of COVID-19 among Pregnant Women**
  - CONSIGN (Covid-19 infectiON and medicineS In pregnancy) conceptual replication
- **Outpatient Corticosteroid Use Among a Non-Hospitalized COVID+ Population**
  - Initial US-based study done with 4 sources (Sentinel, CMS, HealthVerity, VA)

ICMRA
International Coalition of Medicines Regulatory Authorities

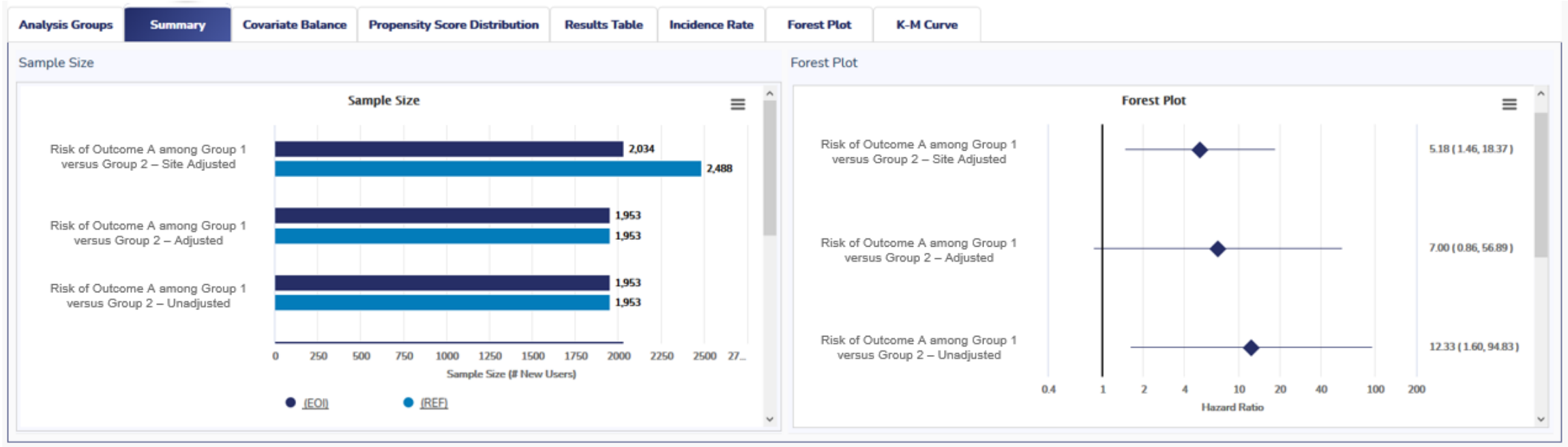
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CNODES
Canadian Network for Observational Drug Effect Studies

http://www.icmra.info/drupal/covid-19/10may2021

TRANSPARENCY - SENTINEL VIEWS

New interactive dashboards for Exposure and Follow-up Time queries



TRANSPARENCY - SENTINEL VIEWS


Jim Marshall
Jack Sternal
Charlaine Washington
Emmanuel Qiao

Thank you

Sentinel

Sentinel Innovation Center

Integrating innovation for a strategic objective

Nov, 2021

Innovation Center: Improving FDA's capabilities for Active Risk Identification and Analysis (ARIA)

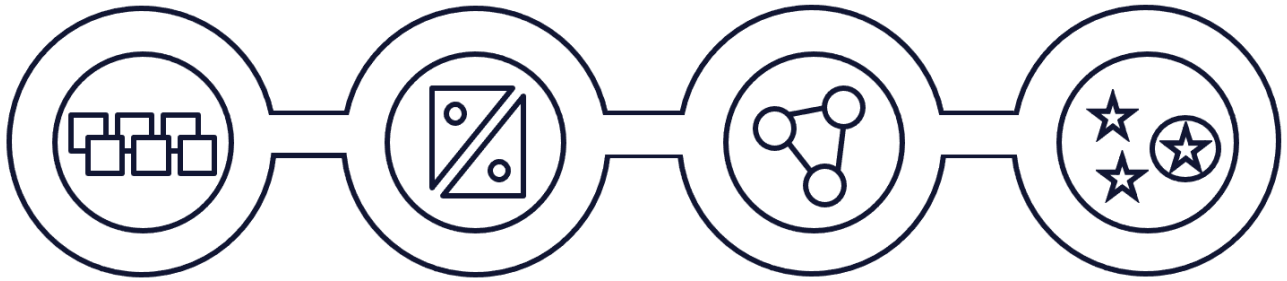
Current challenges

Identify study populations of interest based on biomarkers and clinical symptoms

Identify certain outcomes of interest not coded in insurance claims data

Inadequate duration of follow-up,
Need for additional signal identification tools

IC Initiatives



Data infrastructure

- Data partners
- Data elements
- Governance
- Harmonization
- Data quality assurance

Feature engineering

- Natural language processing
- Automated feature extraction
- Computable phenotyping

Causal inference

- Target trial design
- Advanced, semi-automated analytics
- Subset calibration
- Distributed methods

Detection analytics

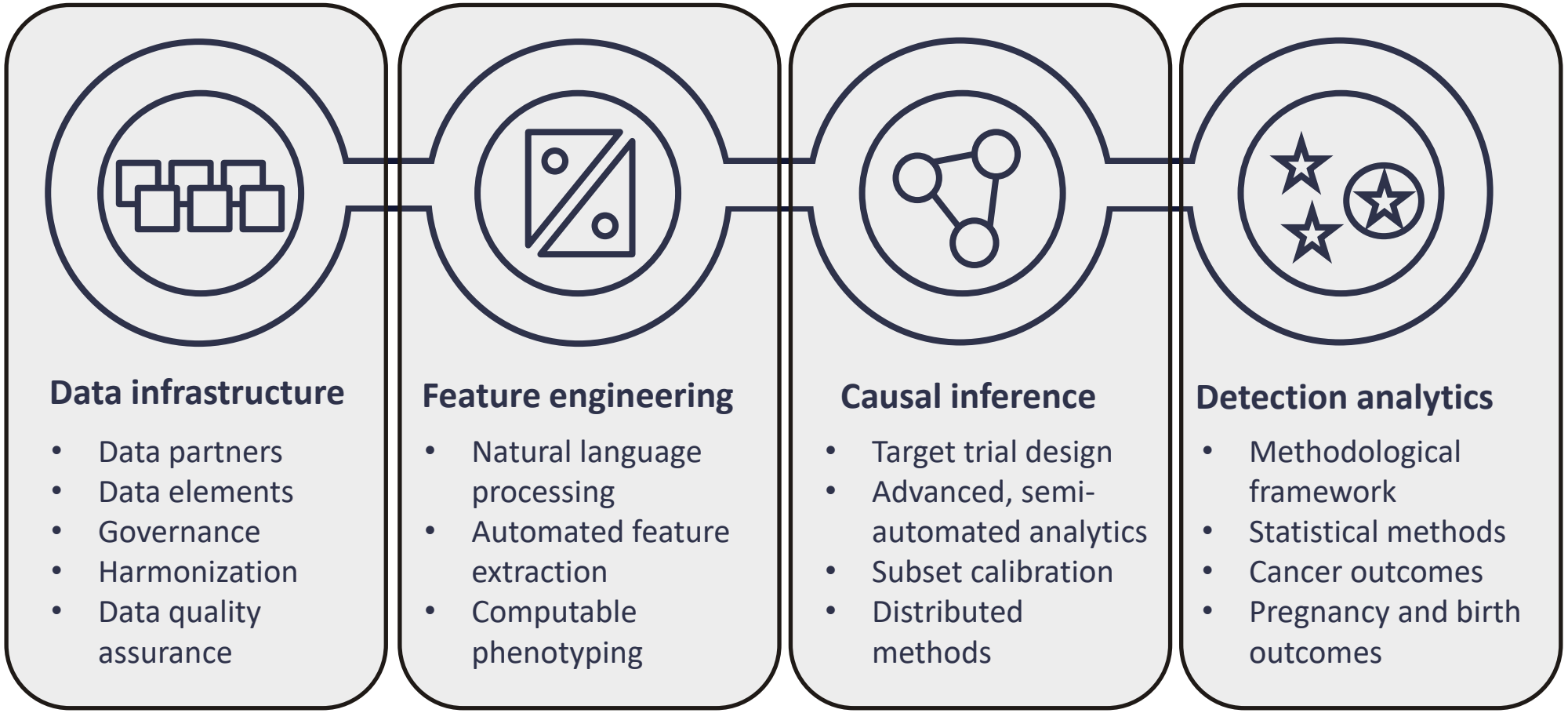
- Methodological framework
- Statistical methods
- Cancer outcomes
- Pregnancy and birth outcomes

IC Vision

A query-ready, quality-checked distributed data network containing EHR-claims linked data from at least 10 million patients with modular analysis tools

Year 1 → **Year 5**

Innovation Center: Improving FDA's capabilities for Active Risk Identification and Analysis (ARIA)



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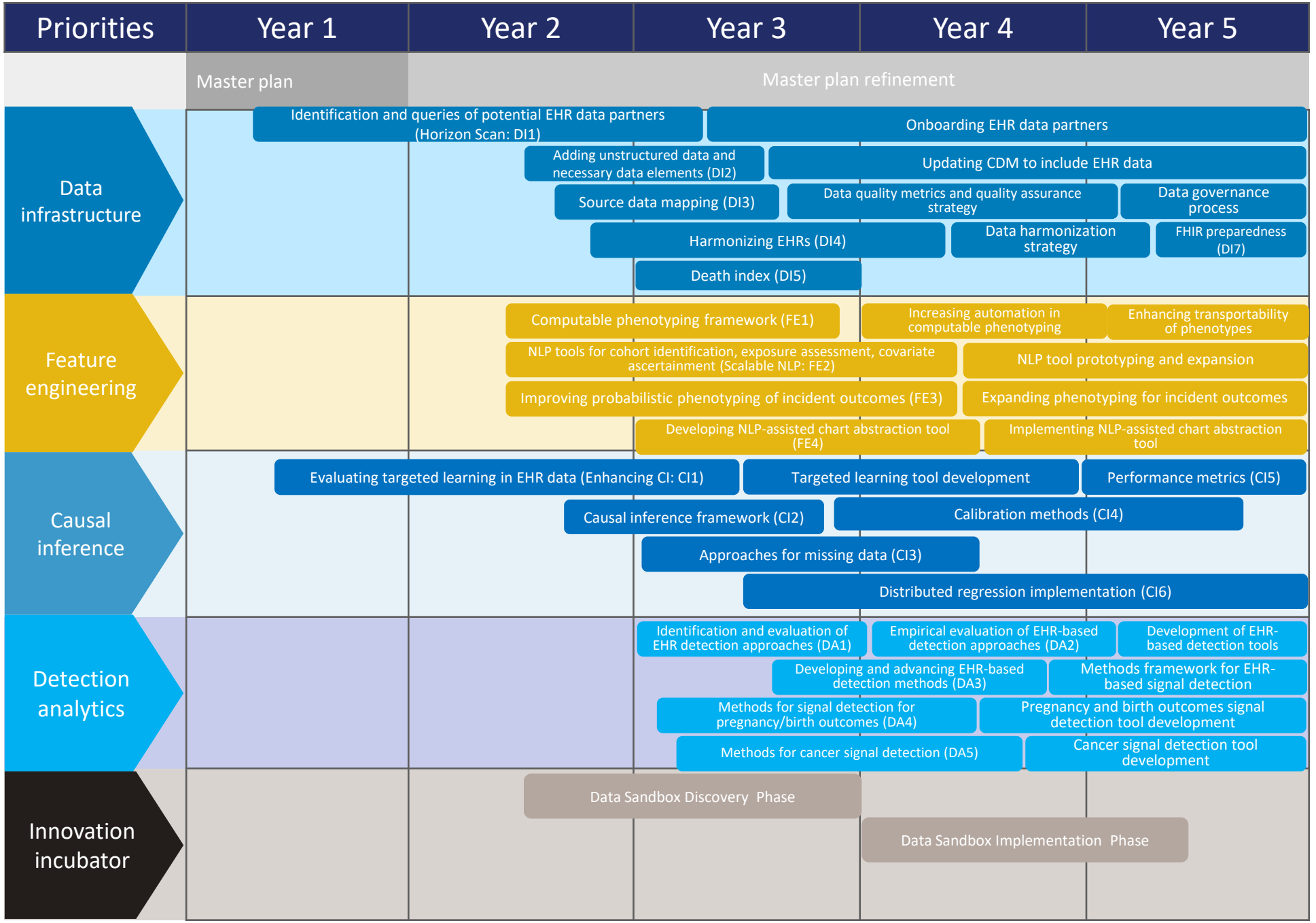
- Pregnancy and birth outcomes

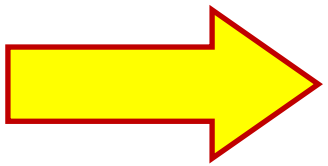
IC Master Plan:

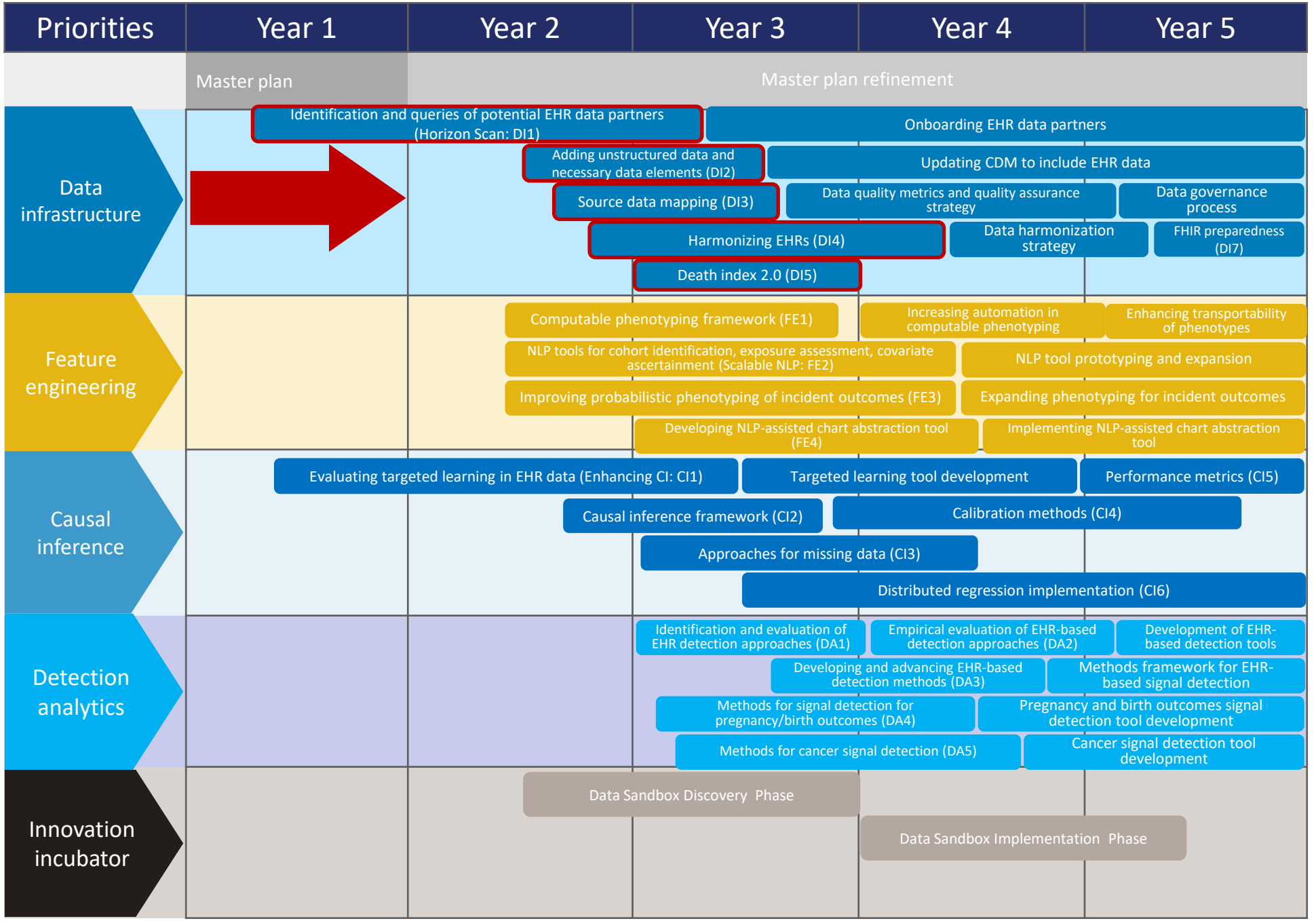
A snapshot of ongoing and future activities



IC Master Plan:

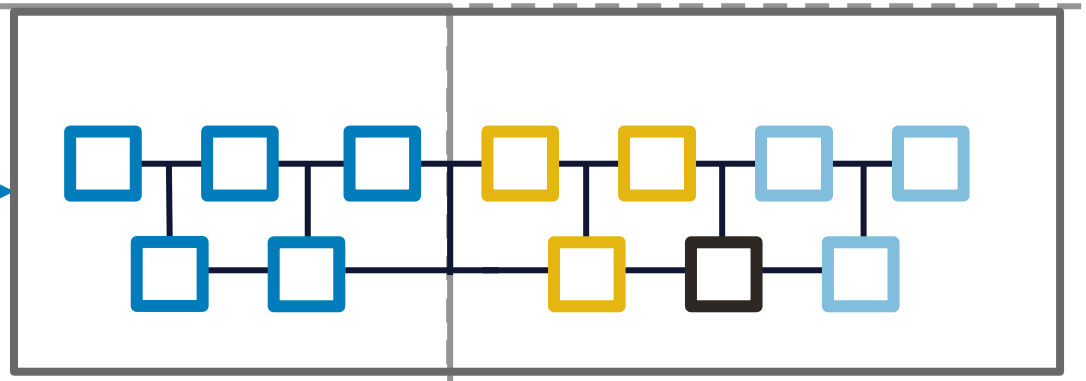
Data infrastructure cluster





Sentinel Common Data Model

Mainstay of the current Sentinel system

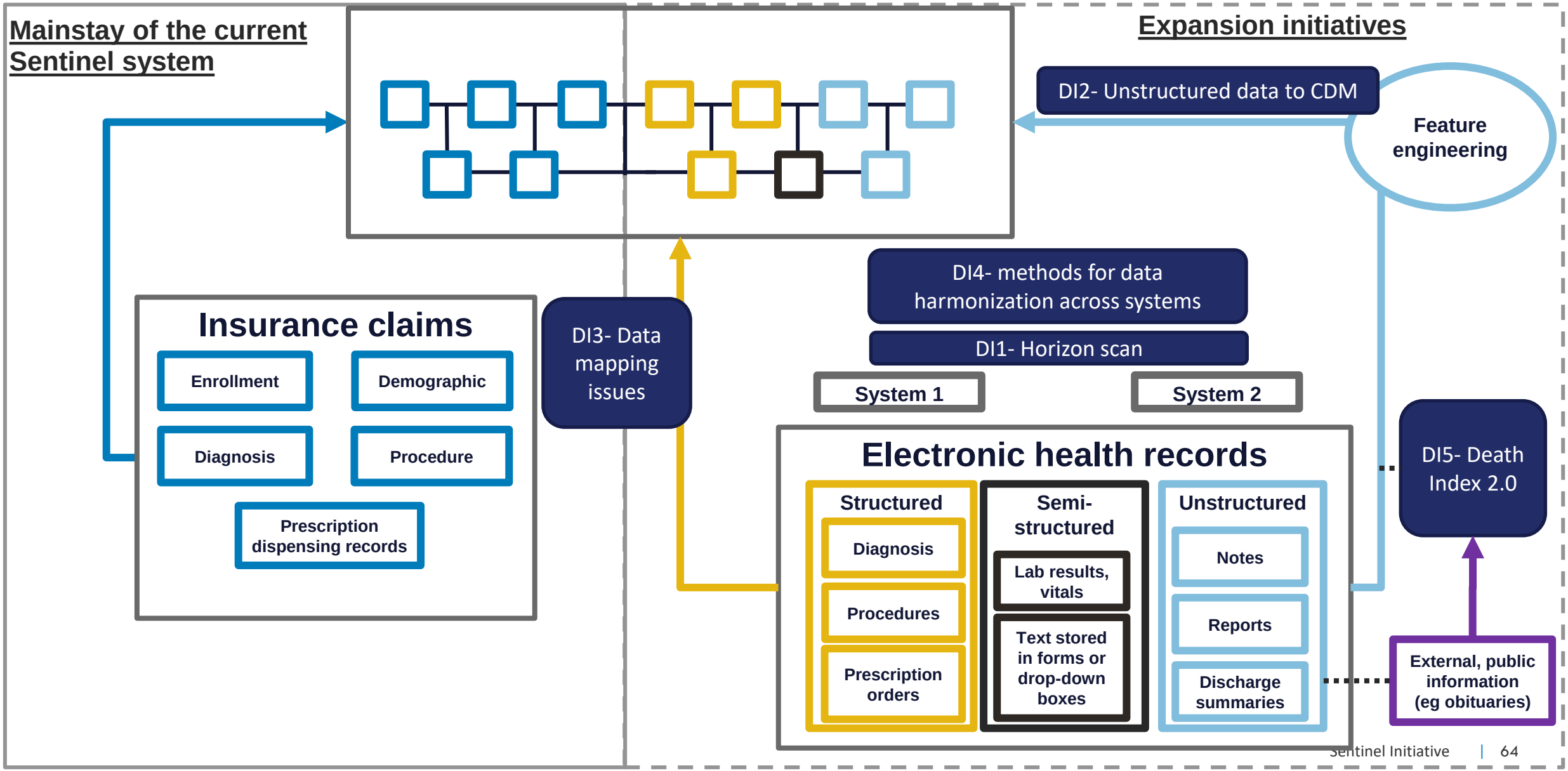


Insurance claims

- Enrollment
- Demographic
- Diagnosis
- Procedure
- Prescription dispensing records

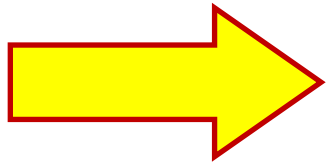
Sentinel data infrastructure development initiatives

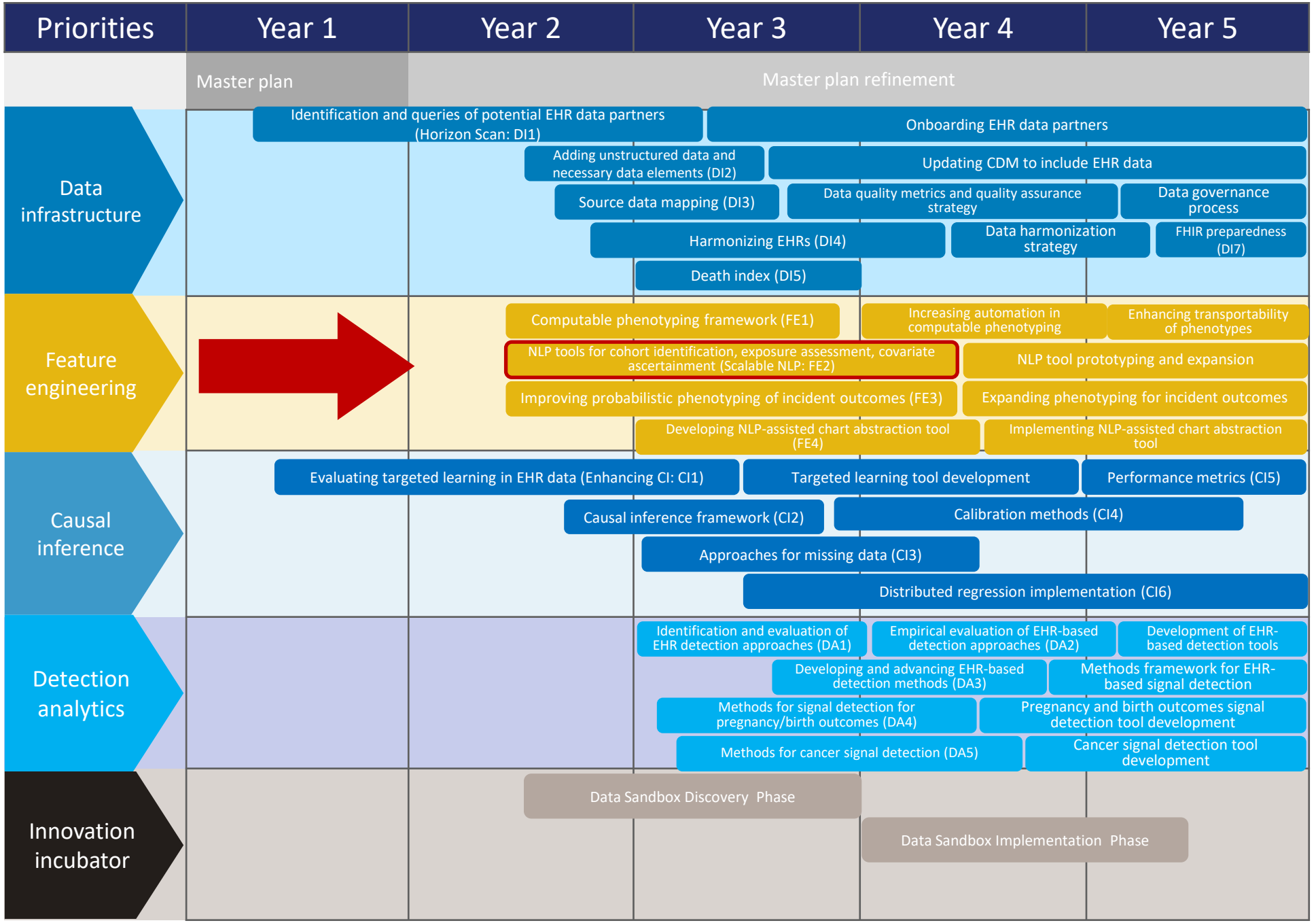
Sentinel Common Data Model



IC Master Plan:

Feature engineering cluster





1) Improving Cohort identification in EHR data: Patients with **COVID**

PIs: Joshua Smith (Vanderbilt), PhD and David Carrell, PhD (KP WA)

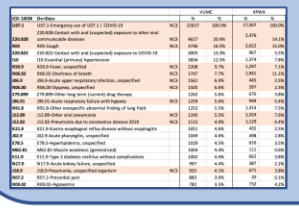
Data-driven approach to specifying filter criteria

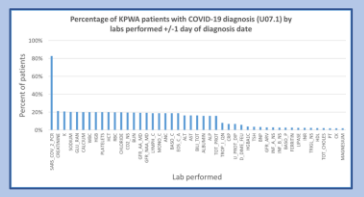
Specify "silver" case definition
Ex: ICD-10 DX code U07.1, "COVID-19"

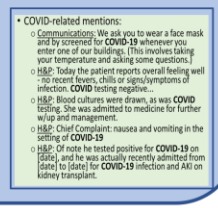
Select qualifying encounters
Ex: 20,000+ VUMC encounters 4/20—3/21

Describe co-occurring EHR data

DXs ... Lab results ... Text mentions

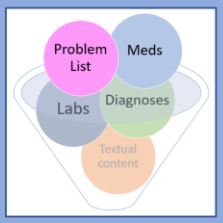






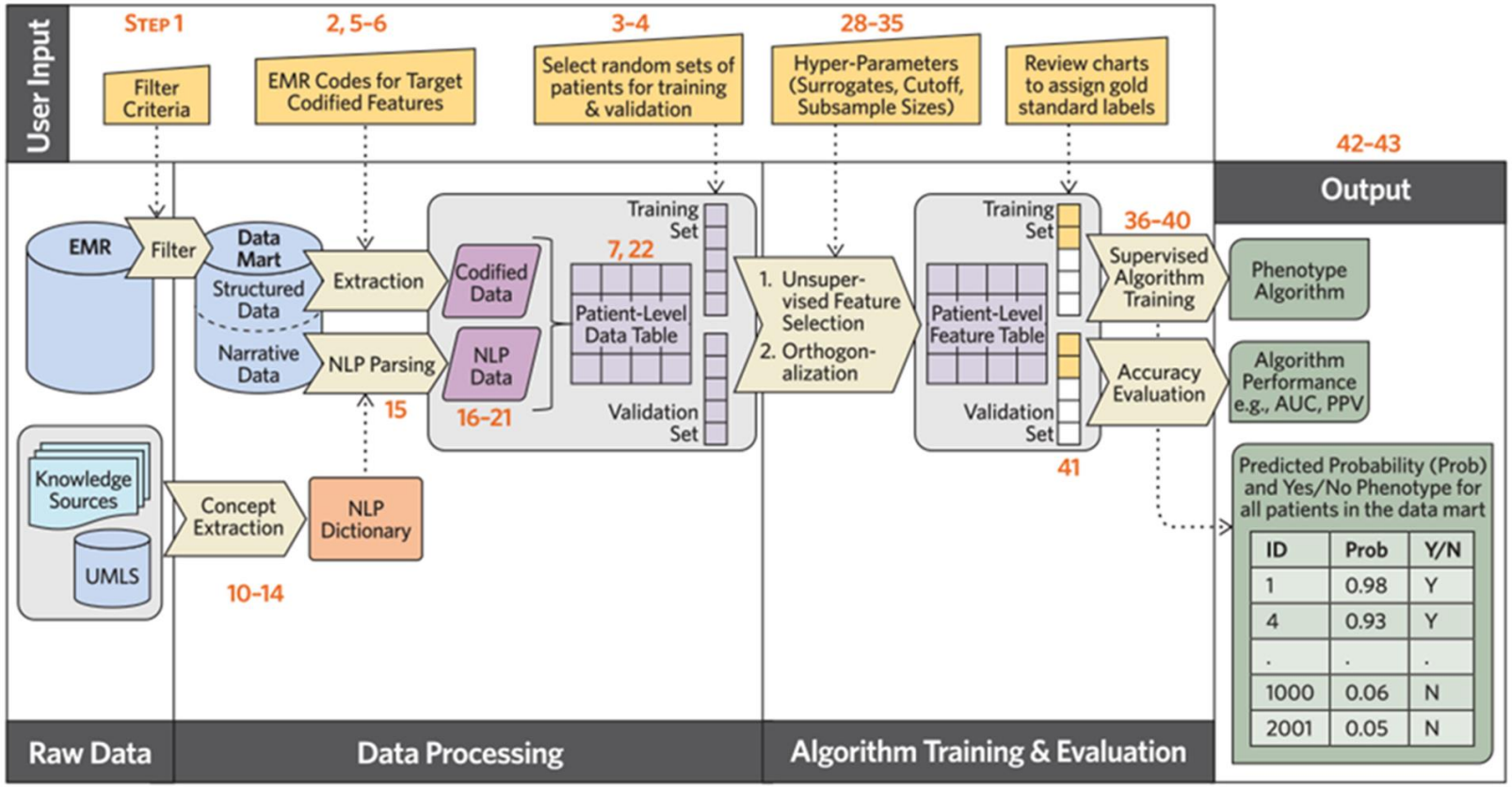
Day	Setting	Clinical text mentions of COVID-19
0	PHONE	"tested positive for COVID-19 *4 days ago*" "sore throat and cough"
0	URGENT CARE	"presents to Urgent Care secondary to a positive COVID test from an outside facility" "exposed approximately *14 weeks ago*"
+2	OUTPATIENT MD VISIT (virtual)	"Tested positive for COVID-19 at outside facility." "I ask her 3 different times if her breathing is worse & she unequivocally answered no." "Seek immediate medical attention for any new or worsening symptoms."
+9	HOSPITAL ADMISSION	"Tested positive on [DATE=DAY -3]... contracted the virus at a party on [DATE=DAY -14] where ... 90% of the participants of that event tested positive for COVID" "Discharge Diagnoses: COVID 19 pneumonia, HTN, DM 2, Obesity BMI >40"
+9	LABS	"CORONAVIRUS NOT DETECTED" *(Note: this is the only SARS-CoV-2 lab in KPWA EHR)*

Manually review, select filter



2) Feature generation for semi-automated confounder and outcome identification in EHR

PIs: Joshua Smith (Vanderbilt), PhD and David Carrell, PhD (KP WA)



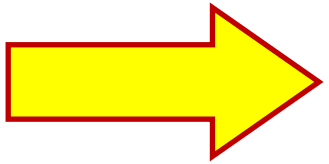
Candidate clinical concepts: ***HOIs – clinical***

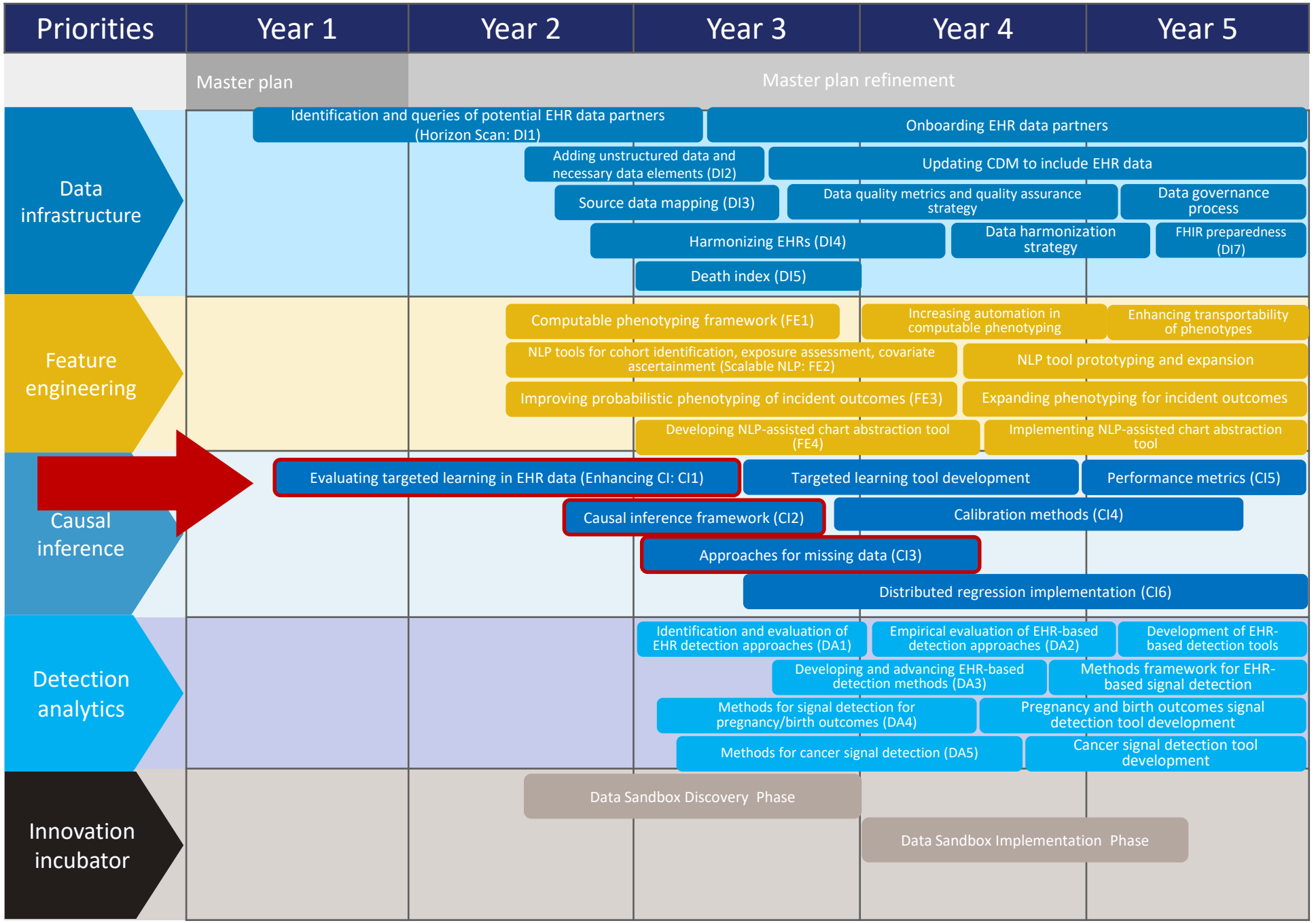
1. COVID-19 PCR test
2. Mortality (led by another IC project)
3. Respiratory symptoms/outcomes
   a) Hypoxia
   b) ARDS
   c) Respiratory failure
   d) Dyspnea
   e) Tachypnea
   f) Cyanosis
4. Heart failure
5. Renal failure
6. Multi-organ failure/dysfunction
7. Pneumonia*
8. Bronchitis*
9. Gastroenteritis*
10. Encephalopathy*
11. Thrombosis (blood clots)
    a) DVT
    b) Pulmonary embolism
12. Oxygen saturation
13. Stroke
14. Sore throat*
15. Cough*
16. Hoarseness*
17. Nausea/vomiting*
18. Diarrhea*
19. Fever*
20. Chills*
21. Fatigue*
22. Muscle pains/body aches*
23. Chest pain*
24. Abdominal pain*
25. Headache*
26. Loss of sense of taste (ageusia)*
27. Loss of sense of smell (anosmia)*
28. Loss of appetite*
29. Shock
30. Confusion*

*potentially well-captured by NLP alone

IC Master Plan:

Causal inference cluster





CI1, CI2, CI3: Causal inference advancement initiatives

10+ million people

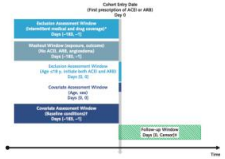
EHR + Claims

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

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

Causal study design

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



Red text = Ongoing or new research effort

New user cohort design or variations

Pre-exposure data space

for **confounding** adjustment, subgroup identification

Known and measurable important risk factors

Addressing missing data in some EHR confounders

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

Performance metrics and reporting standards

Automated feature generation algorithms

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

Automated assessment of likely confounding

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

Performance metrics and reporting standards

Complex treatment strategies: Time-varying confounding

Post-exposure data space

for **outcome** identification

Existing algorithm for outcome identification is acceptable

E.g. an acceptable validation shows good measurement characteristics

Outcome validation in a subset of patients is necessary

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

Outcome validation in all patients is necessary

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

Single database study

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

Multi database study

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

CI1, CI2, CI3: Causal inference advancement initiatives

10+ million people

EHR + **Claims**

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

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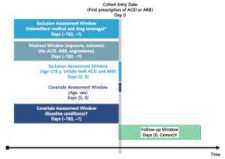
- Non-random missingness in EHR data

Causal study design



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New user cohort design or variations

ML - augmented causal inference

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ML - supported endpoint identification

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CI1, CI2, CI3: Causal inference advancement initiatives

10+ million people

EHR + Claims

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

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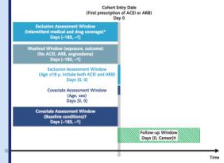
- Non-random missingness in EHR data

CI2: Causal inference framework

New user cohort design or variations



Red text = Ongoing or new research effort

ML - augmented causal inference

Known and measurable important risk factors

FE2: NLP-based feature generation

Feature type pre-processing:

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

CI3: Missing data

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

Performance metrics and reporting standards

CI1: Targeted learning in EHRs

Automated assessment of likely confounding

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

Performance metrics and reporting standards

Complex treatment strategies: Time-varying confounding

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Multi database study

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- Electronic review tool to confirm GS in patients across multiple systems

Innovation Center collaborating organizations

Lead sites:

KAISER PERMANENTE®
Kaiser Permanente Washington Health Research Institute

VANDERBILT UNIVERSITY MEDICAL CENTER

BRIGHAM HEALTH
BWH BRIGHAM AND WOMEN'S HOSPITAL

SCHOOL OF PUBLIC HEALTH
UNIVERSITY of WASHINGTON

Duke Clinical Research Institute

Deloitte.

Sentinel 13th Annual Public Workshop

NOVEMBER 8, 2021

Sentinel Coordinating Center Perspectives: CBOC

1 The Community Building & Outreach Center (CBOC)

2 CBOC Key Findings

3 The CBOC Master Plan

4 CBOC Master Plan Accomplishments

5 Projected CBOC Master Plan Activities

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The Community Building & Outreach Center (CBOC)

The CBOC was created to **broaden and activate a strong scientific community to advance the Sentinel Initiative.** The CBOC supports FDA in accomplishing three of the strategic aims outlined in "The Sentinel System Five Year Strategy 2019-2023." These aims are reflected in the recommendations and projects outlined in the CBOC Master Plan.

SENTINEL'S STRATEGIC AIMS

supported by CBOC

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

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CBOC Key Findings

By combining input from Sentinel stakeholder interviews with epidemiologists, informaticists, and health advocates, the goals of the SOC and IC, and FDA's strategic aims for the Sentinel Initiative, the CBOC identified **three key findings** related to awareness of Sentinel and its capabilities that informed the CBOC Master Plan.

STAKEHOLDERS WOULD LIKE TO:

Understand the design decisions and the specific questions and challenges the Sentinel System can answer

Understand which data, infrastructure, tools, and analytical methods are available that can be used to inform their work

Increase knowledge sharing and training opportunities to foster collaboration with and contribution to the Sentinel community

The CBOC aims to achieve outcomes related to the key findings above through the projects outlined in the **CBOC Master Plan.**

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The CBOC Master Plan

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

CBOC Projects:

Communications & Training

- Communication and Training Goals
- Ongoing Website Design & Implementation
- Public Facing Newsletters
- Templates, Standardized Presentations, & Informational Videos
- Graphics
- Webinar Series
- Virtual Training Sessions

Bidirectional Engagement

- Real-World Data Forum

Projects implemented by the CBOC Master Plan aim to:

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

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

Increase opportunities for stakeholder contribution to the Sentinel community

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CBOC Master Plan Accomplishments

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

Sentinel Website Redesign & Implementation

The redesign included an updated navigation menu, a new standardized table search, sort and filter; a modernized look and feel; improvements to-search engine optimization (SEO), usability, and access to training and webinar materials.

IMPACT

Optimize user interface and user experience of the Sentinel website, with **1000+ redesigned and improved pages**, allowing stakeholders to better locate Sentinel resources and updates and stay informed of Sentinel

Quarterly Public Facing Newsletter

CBOC releases quarterly newsletters that highlight recent developments within the Sentinel System, upcoming events, and new features and content on the Sentinel website.

IMPACT

Increase awareness of Sentinel's activities and promote opportunities for stakeholders to get involved with Sentinel, with 3 newsletters released and **5,500+ subscribers**, helping to create a national and global analytic resource

Templates, Standardized Presentations & Informational Videos

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

IMPACT

Provide FDA and Sentinel Centers with consistent materials and design elements for information sharing about Sentinel and educate stakeholders on Sentinel's development, infrastructure, and capabilities to further engage the Sentinel community

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Projected CBOC Master Plan Activities

The following projects within the CBOC Master Plan are planned to start this year in order to continue increasing awareness of the Sentinel Initiative and the design of the Sentinel System, increase understanding of Sentinel tools and infrastructure through training and/or increase stakeholder contributions to the Sentinel community.

In Progress

CBOC Webinar Series

The CBOC Webinar Series focuses on benefits of the Sentinel System and how stakeholders can use Sentinel resources to inform their work. These webinars will require less technical understanding of Sentinel. It will be led by CBOC with input from SOC and IC

IMPACT
Increase awareness of the Sentinel System, its capabilities, benefits, and how stakeholders such as epidemiologists, informaticists, and health advocates can participate

Planned

Virtual Training Series

The Virtual Training Series will focus on a range of topics, including how to convert data into the SCDM and how to use the analytic tools available on the Sentinel Website

IMPACT
Provide support and increase understanding to stakeholders interested in using the Sentinel tools, methods, and infrastructure more effectively

Scientific Deck

The Scientific Deck will provide background and technical steps on Sentinel's hybrid capabilities for technical audiences

IMPACT
Increase understanding for technical stakeholders on the potential data innovations and hybrid capabilities that could expand Sentinel's capabilities and use

Real-World Data Forum (RWDF)

The RWDF will aim for stakeholders to rapidly explore their own data using the Sentinel infrastructure and tools

IMPACT
Increase understanding of how to use the Sentinel System infrastructure and tools, provide areas of potential improvement and innovation in real time, and determine potential returns on investment

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Discussion Questions

- While we understand that Sentinel is on a trajectory to become more useful to many stakeholders, for whom is engagement with Sentinel most promising right now and in the very near term future?
- How has each Center sustained or scaled their community-level engagement efforts regarding Sentinel over the past year?
- How can the community engage with the Sentinel Initiative and its Coordinating Centers?
- How have the Centers scaled up their work to meet the unique challenges of the Covid-19 pandemic?

Break

We will be back momentarily.

The next panel will begin at 12:20 p.m. (U.S. Eastern Time)

Session II: Improving Causal Inference for RWE Generation

- **Robert Ball,** U.S. Food and Drug Administration
- **John Concato**, U.S. Food and Drug Administration
- **Rich Forshee,** U.S. Food and Drug Administration
- **Gianmario Candore,** European Medicines Agency
- **Josh Gagne,** Johnson & Johnson

How the Sentinel System supports FDA's Understanding of Real-World Evidence to Support Regulatory Decisions for Drugs and Biologics

Sentinel Annual Meeting

8 November 2021

Robert Ball MD, MPH, ScM
Deputy Director, Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Topics for Focus

1) Overview of FDA's Real-World Evidence (RWE) Program

2) Activities in the Sentinel System to support FDA's understanding of RWE generation

21st Century Cures Act (2016)

- **FDA established a program to evaluate the potential use of real-world evidence (RWE) to:**
  - **Support new indication for a drug approved under section 505(c)**
  - **Satisfy post-approval study requirements**
- **Draft framework issued in Dec 2018**
  - **Describes sources of RWE, challenges, pilot opportunities, etc.**
- **Draft guidance for industry issued in Sep & Oct 2021**
  - **EHR/Claims guidance; Data Standards guidance**
- **Standard for *substantial evidence* remains unchanged; commitments are aligned with Prescription Drug User Fee Act (PDUFA)**

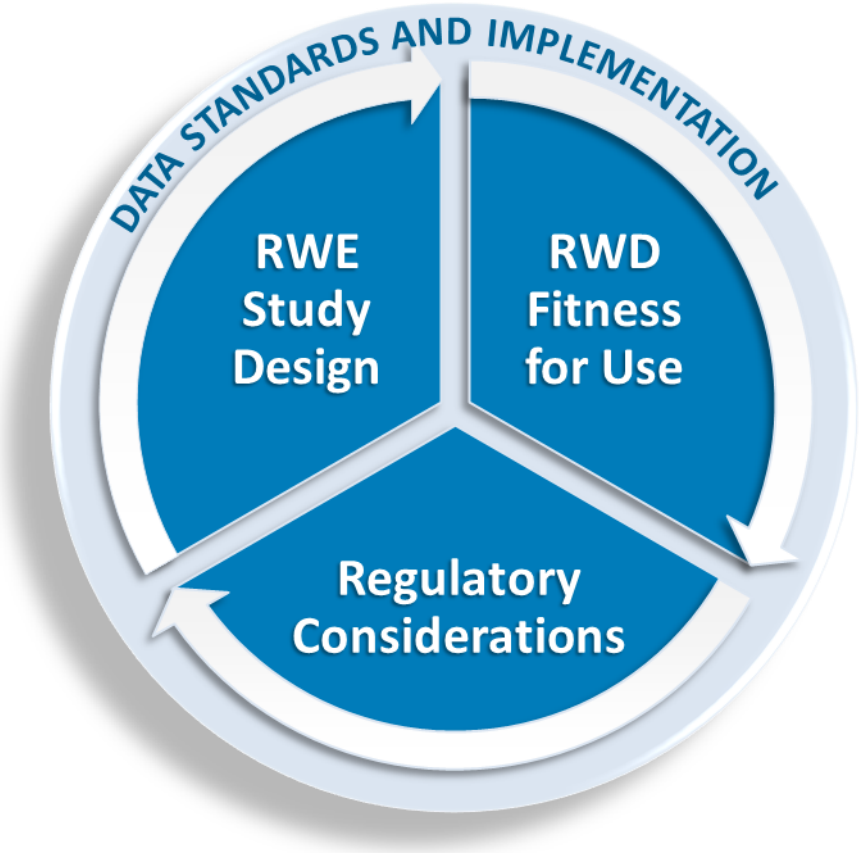
‘Real-World’ Definitions

from FDA’s Framework for Real-World Evidence (2018):

Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources (e.g., *medical claims, electronic health records (EHRs), registries, digital health technologies*)

Real-World Evidence (RWE) is clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD (*involving various study designs, such as randomized or externally controlled trials as well as observational studies)*

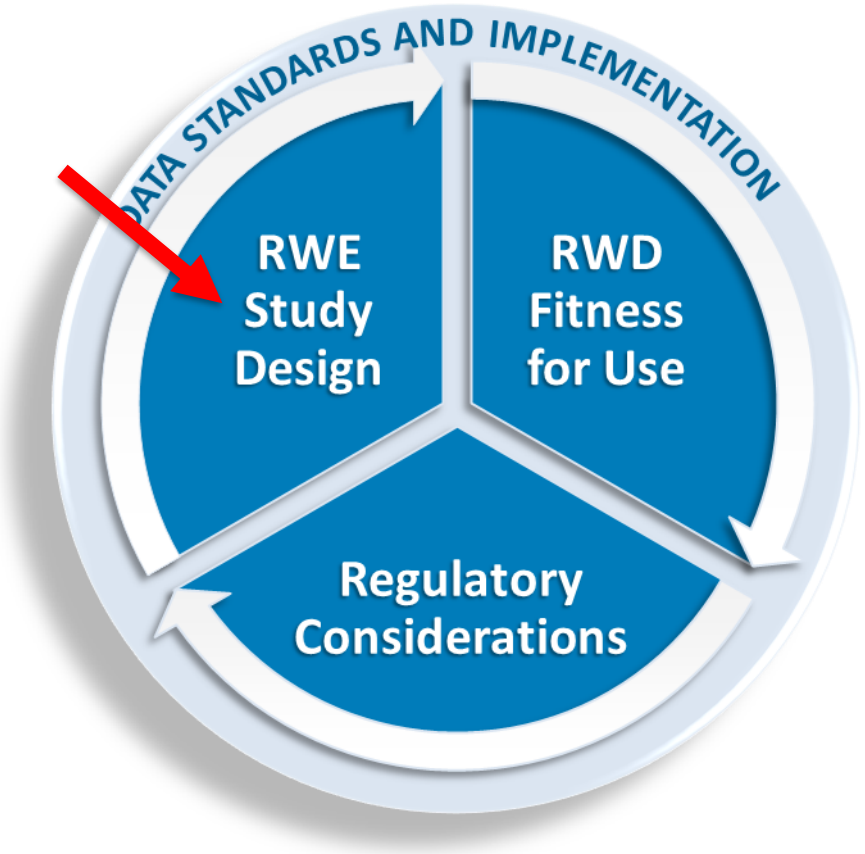
FDA RWE Framework – Key Considerations



Considerations:

- **Whether the RWD are fit for use**
- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**
- **Whether the study conduct meets FDA regulatory requirements**

RWE Framework: Design

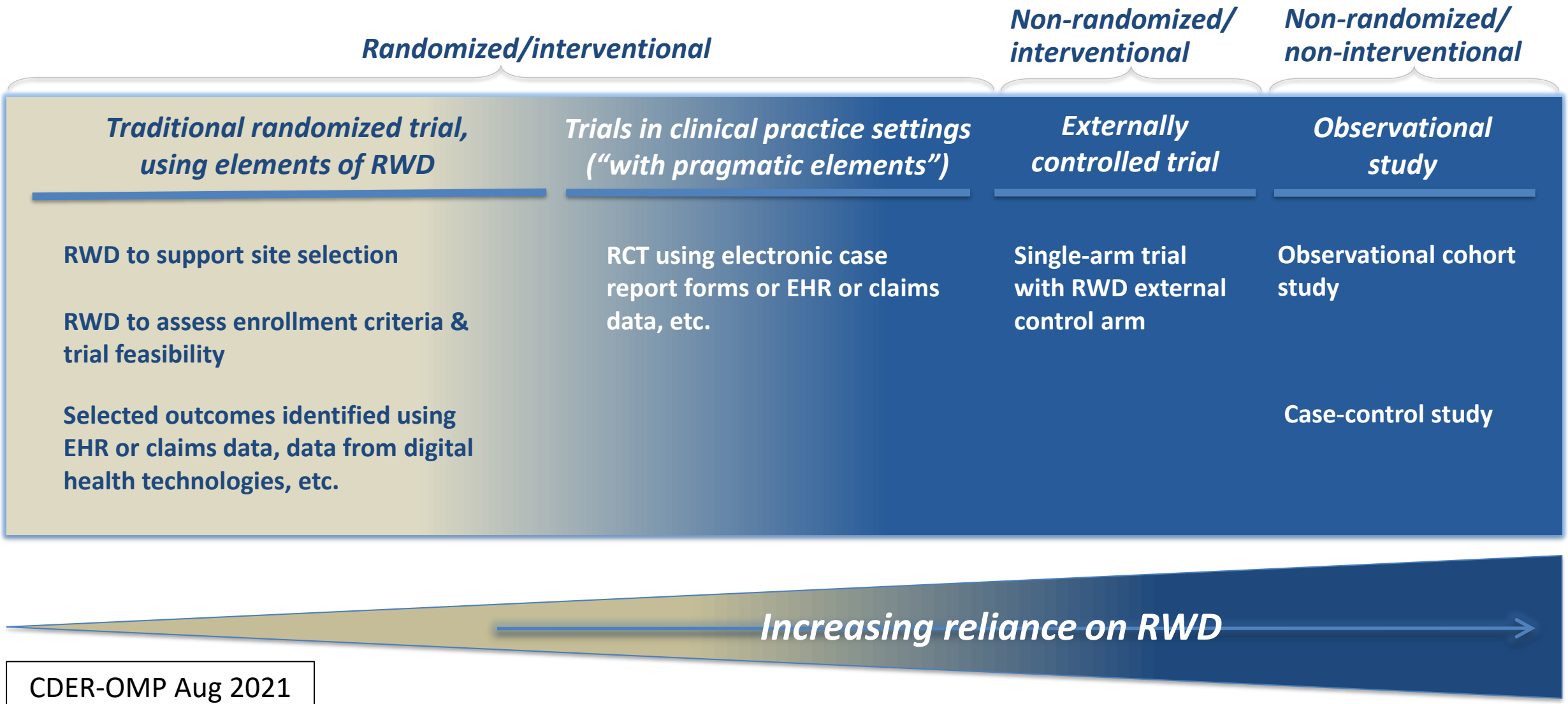


Considerations:

- **Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question**

Randomized, observational, interventional, and real-world — what's in a name? *Pharmacoepidemiology and Drug Safety*. 29:1514–1517, 2020.

Overview of Real-World Data and Study Design

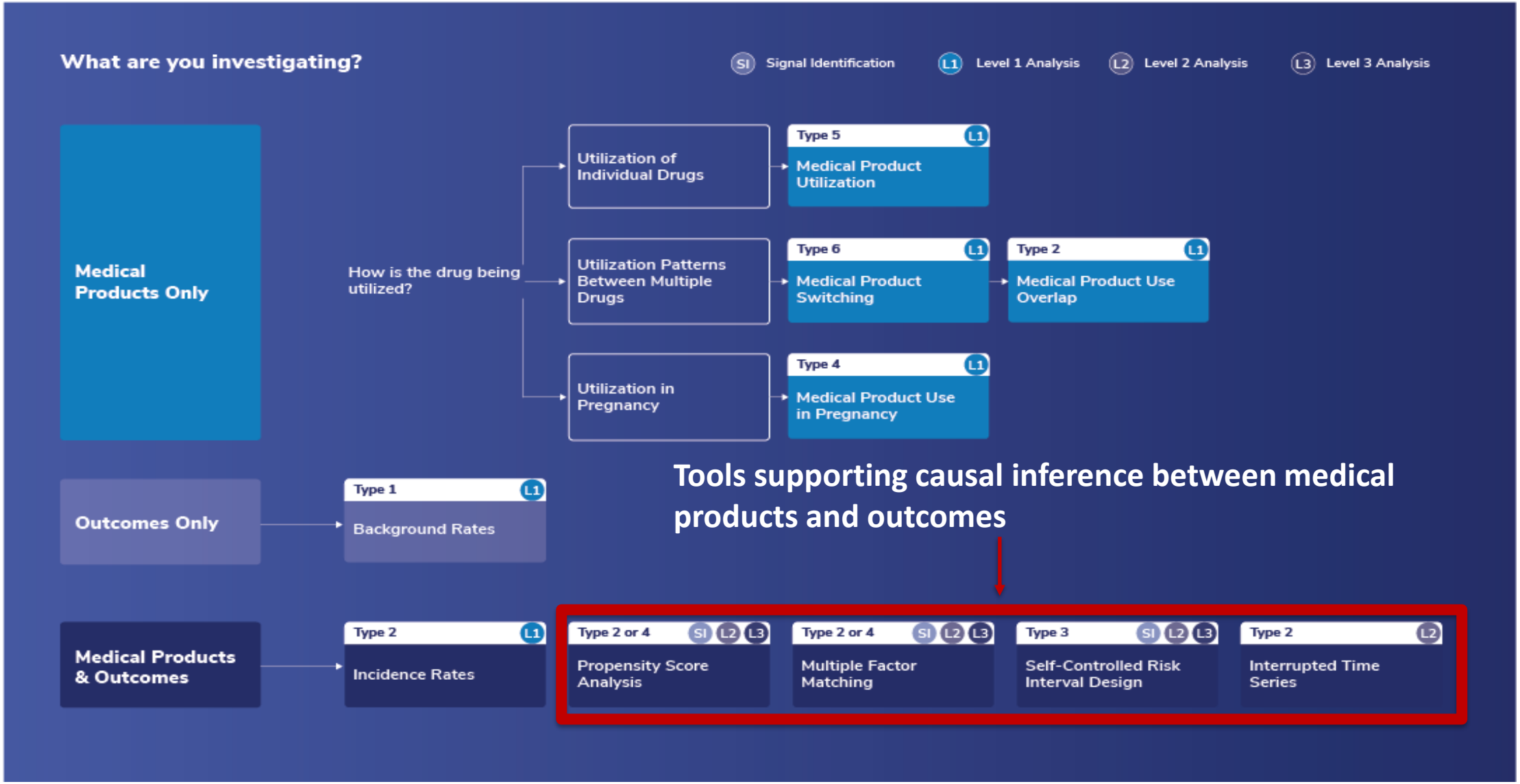


CDER-OMP Aug 2021

Activities in the Sentinel System to support FDA's understanding of RWE generation

- Tools for causal inference in observational studies in the Sentinel System
- Causal Inference Master Plan of the Sentinel Innovation Center
- Projects and capabilities in Sentinel Catalyst System for interactions and interventions with patients

Tools for causal inference in observational studies in the Sentinel System



Causal Inference Research Logic of the Sentinel Innovation Center Master Plan

Design Layer

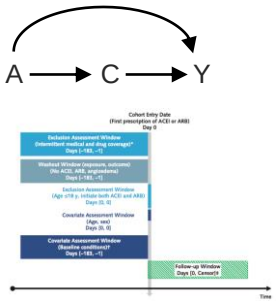
Achieve causal study design

Considering:
- Study question
- Exposure variation
- Measurement quality

DESIGN CHOICE

1) Controlled 2) self-controlled 3) scanning
- Medically-informed target pop^{n}
- Patient-informed outcomes
- Biologically-informed effect window

BIAS REDUCTION
- New users, active comparators
- Causal temporality
  - Exposure before outcome
  - Confounder before exposure



Measures Layer

Achieve fit-for-purpose measurement

Considering:
- sensitivity
- specificity,
- completeness
- mean sqr diff

Filling Rx	**Dx, Px codes**	**Dx, Px, Rx codes**	**Dx, Px, Rx codes**
Prescribing Rx, self-report, infusers, pill caps, UDI from OR notes	Labs, imaging, digital health dev, physician notes, patient reports	Labs, stage, imaging, BMI, genomics, physician notes, services use intensity	Monitors, physician notes, biomarker, omics, behavior, socio-econ

Longitudinal record processing, Machine learning, NLP, bioinformatics

EXPOSURE *OUTCOME* *CONFOUNDERS* *TARGET POP^{N}*

Analytics Layer

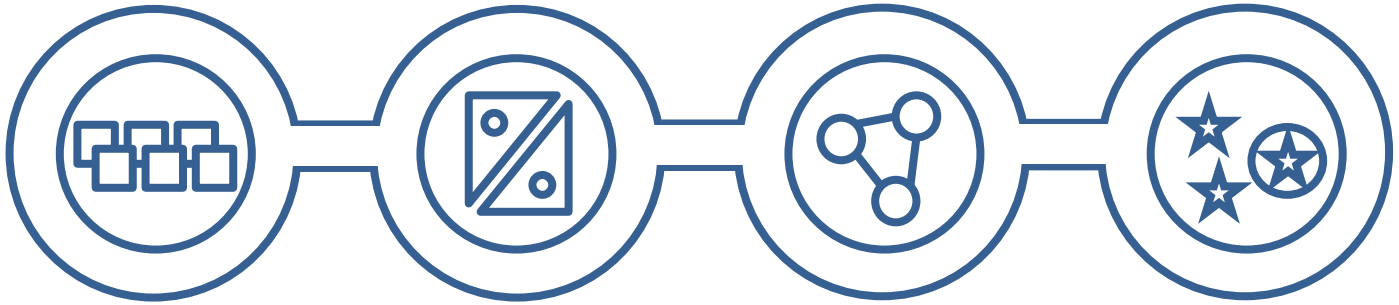
Achieve causal analysis

Considering:
- Confounders
- Follow-up model
- Measurement quality

BALANCE
- Achieve balance:
  - Regression, PS analysis
  - Proxy adjustment: HDPS, CTMLE
  - Time-varying exposure: MSM
- Check balance:
  - SD, residuals, c-stat

ROBUSTNESS
- Sensitivity analyses of design
- Quantitative bias analysis
- Neg./pos. control endpoints
- Balance in unmeasured confounders
- Multiple comparisons

Sentinel Innovation Center Master Plan



Data strategy

- Data partners
- Data elements
- Governance
- Harmonization
- Quality assessment

Feature engineering

- Natural language processing
- Automated feature extraction
- Computable phenotyping

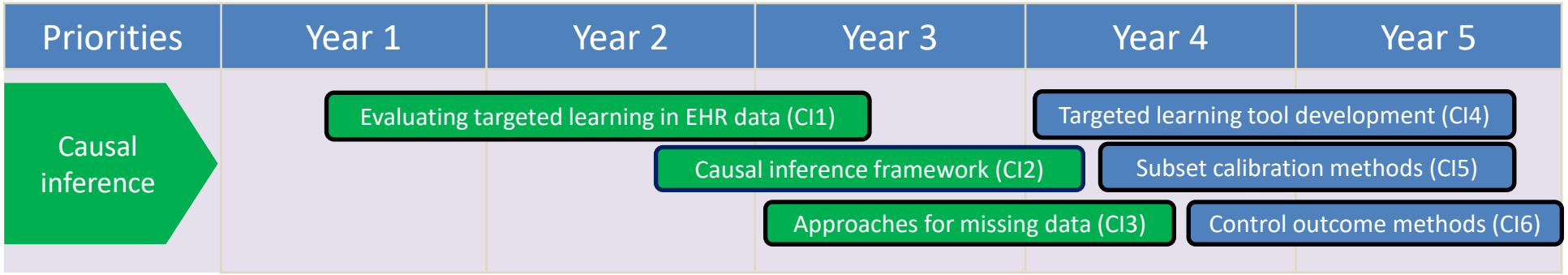
Causal inference

- Target trial design
- Advanced, semi-automated analytics
- Subset calibration
- Distributed methods

Detection analytics

- Detection designs
- Statistical methods
- Signal prioritization
- Cancer outcomes
- Pregnancy and birth outcomes

Sentinel Innovation Center Webinar Series
Open to Public | Recorded and Viewable Online



CI1- Targeted learning

Flexible *data-driven, machine-learning, tools for PS estimation with 'super learner' approach* incorporating empirically identified covariates from EHRs:

- Structured: Dx, Px, Drugs
- Semi-structured: Lab test results
- Unstructured: notes

Treatment effect estimation with targeted maximum likelihood estimation (TMLE):

- doubly robust approach

CI2- Causal inference framework

Framework proposing a stepwise process that systematically considers key choices with respect to *design and analysis* that influence the validity of studies conducted with non-randomized data

A *standardized "industrial" process* that will be outlined in this framework will serve as a valuable tool to inform the conduct and assessment of the quality of non-randomized studies of drug-outcome evaluation

CI3- Missing data

Develop *methods to routinely identify missingness patterns* for EHR-based confounding variables to evaluate compliance with assumptions needed for approaches to handle missingness

Compare approaches to missingness given different underlying missingness mechanisms

FDA Catalyst Projects

Title	Status	Date
COVID MyStudies Mobile App for E-Consent	IN PROGRESS	06/01/2020
FDA-Catalyst Alignment with the CMS Linkage to the PCORI RELIANCE Trial	IN PROGRESS	05/08/2019
Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib)	IN PROGRESS	05/07/2019
FDA-Catalyst MyStudies App Alignment with Pragmatic Trials and/or Registries	IN PROGRESS	10/15/2018
Collection of Patient-Provided Information Through a Mobile Device Application for Use in Comparative Effectiveness and Drug Safety Research	COMPLETE	01/02/2017

https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects

Summary

- FDA's Real-World Evidence Program for drugs and biologics is advancing as outlined in the agency's 2018 'RWE Framework'
- Sentinel System has built capabilities for both observational and randomized studies that support FDA's understanding of RWE
- Sentinel Innovation Center Master Plan provides a roadmap for improving RWE generation capabilities for observational studies by improving methods for causal inference

Acknowledgements

- Gerald Dal Pan, John Concato, Trish Bright, Sarah Dutcher, Rishi Desai, FDA Sentinel Program Team, and Sentinel partners

Thank You

U.S. FOOD & DRUG ADMINISTRATION

Sentinel Annual Public Workshop

FDA Catalyst Projects

8 November 2021

John Concato, MD, MS, MPH

Associate Director for Real-World Evidence Analytics, Office of Medical Policy, Center for Drug Evaluation and Research, U.S. Food and Drug Administration

Disclaimer

- **Views and opinions expressed are those of the presenter and should not be attributed to the Food and Drug Administration**

- **No conflicts of interest exist related to this presentation**

FDA Catalyst: Overview

FDA-Catalyst is an important addition to surveillance and research of marketed medical products. It leverages the Sentinel Infrastructure and other capabilities of the Sentinel System to answer a wider range of questions than can be addressed by the Sentinel System data alone. These activities ultimately complement the existing post-market surveillance system.

From https://www.sentinelinitiative.org/methods-data-tools/fda-catalyst-projects

FDA Catalyst: Projects

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Medicare Data Linked to RELIANCE trial

Roflumilast or Azithromycin to Prevent COPD Exacerbations:

RELIANCE is a parallel, pragmatic, non-inferiority trial designed to evaluate chronic roflumilast versus azithromycin therapy in reducing exacerbations of chronic obstructive pulmonary disease

In collaboration with the Office of Medical Policy at U.S. FDA, the Sentinel Operations Center is working with the Department of Population Health Sciences at Duke University School of Medicine to link patients enrolled in the Patient-Centered Outcomes Research Institute RELIANCE trial to Medicare data

Linkage to RELIANCE trial (cont'd)

<u>Roflumilast or Azithromycin to Prevent COPD Exacerbations</u>:

Linkage of Medicare data to RELIANCE will provide additional information on the primary outcome (all-cause rehospitalization or death) and selected secondary outcomes; it will also provide an opportunity to test distributed regression methods with vertically partitioned data

This activity supports FDA's assessment of real-world evidence to help support the approval of new indications for approved drugs which is mandated by the 21st Century Cures Act; the activity also will build and test infrastructure and methods to conduct pragmatic clinical trials

Related to RELIANCE: 'CARE' Study

<u>COPD, Asthma, and Respiratory Disease Effectiveness (CARE) study</u>:

- **Queries using Sentinel modular programs and Common Data Model**
  - **feasibility assessments**
  - **characterization of study population**
  - **development and preliminary validation of potential endpoints**
  - **[completed in 2021]**
- **"Pre-replication" of results from the RELIANCE trial**
  - **[estimated start spring 2022]**
- **Additional (observational) comparative-effectiveness study**
  - **[estimated start spring 2023]**

IMPACT-AFib Trial

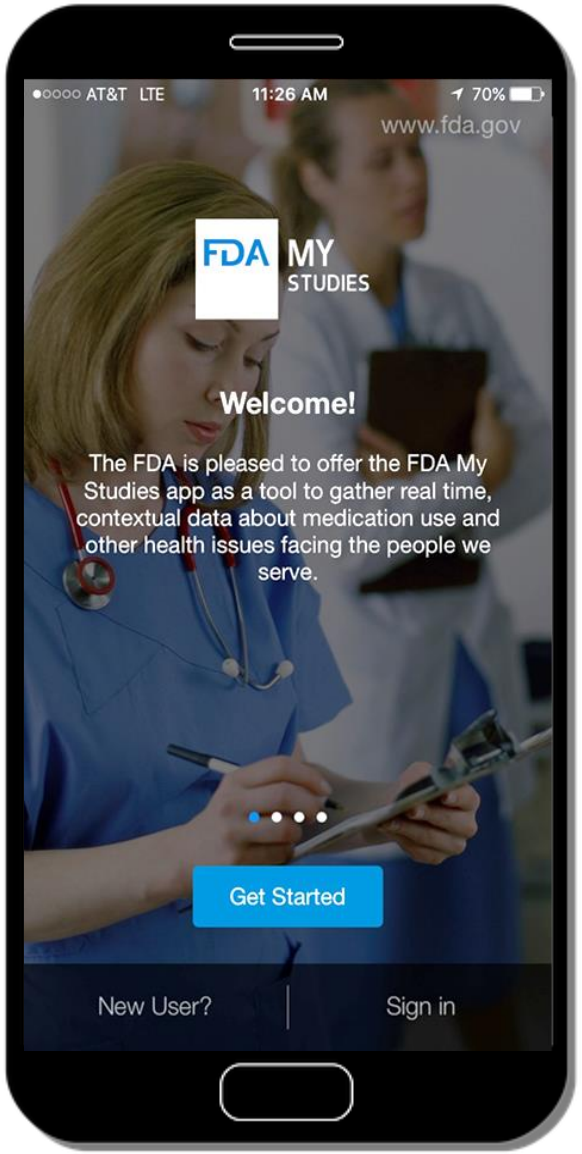
IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation:

IMPACT-AFib is a randomized clinical trial aimed at increasing the use of oral anticoagulants by individuals with atrial fibrillation who were at high risk of stroke and not on treatment; the underlying thesis was that patients could be change agents to initiate prescribing discussions with their providers

Trial sites were linked to additional internal source data to implement the intervention—an educational information mailed to patients and their providers in the "early" intervention arm, and to providers of patients in the "delayed" intervention arm approximately 12 months later

Challenges identified during the planning phase include convening multi-stakeholder investigator teams and advisors, addressing ethical concerns about not intervening in a usual-care comparison group, and identifying & avoiding interference with sites' routine programs that were similar to the intervention

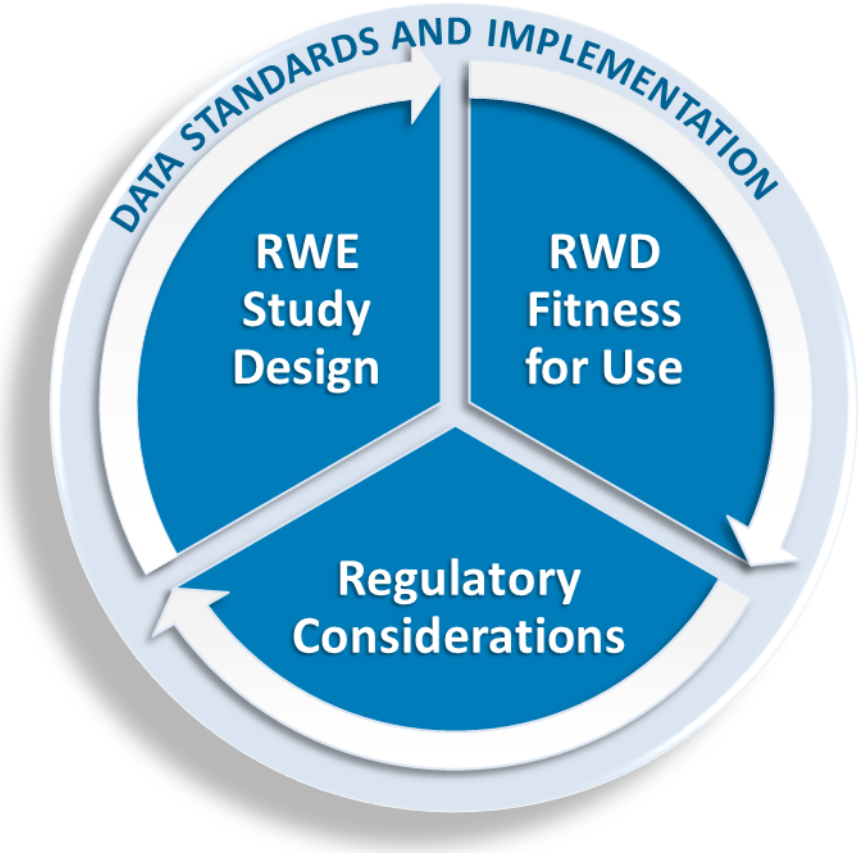
MyStudies and COVID MyStudies App



FDA MyStudies app:

- **Web-based configuration portal**
  - **secure storage environment**
- **Deployed in several demonstration projects**
  - **collect RWD in randomized trial of patients with juvenile idiopathic arthritis**
  - **collect RWD for registry of patients with inflammatory bowel disease**
- **Repurposed as *COVID MyStudies* to facilitate enrollment in clinical trials (https://www.fda.gov/drugs/science-and-research-drugs/covid-mystudies-application-app)**

FDA RWE Framework: Approach to Causality



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Acknowledgements

Robert Ball, Jacqueline Corrigan-Curay, Gerald Dal Pan, Khair ElZarrad,

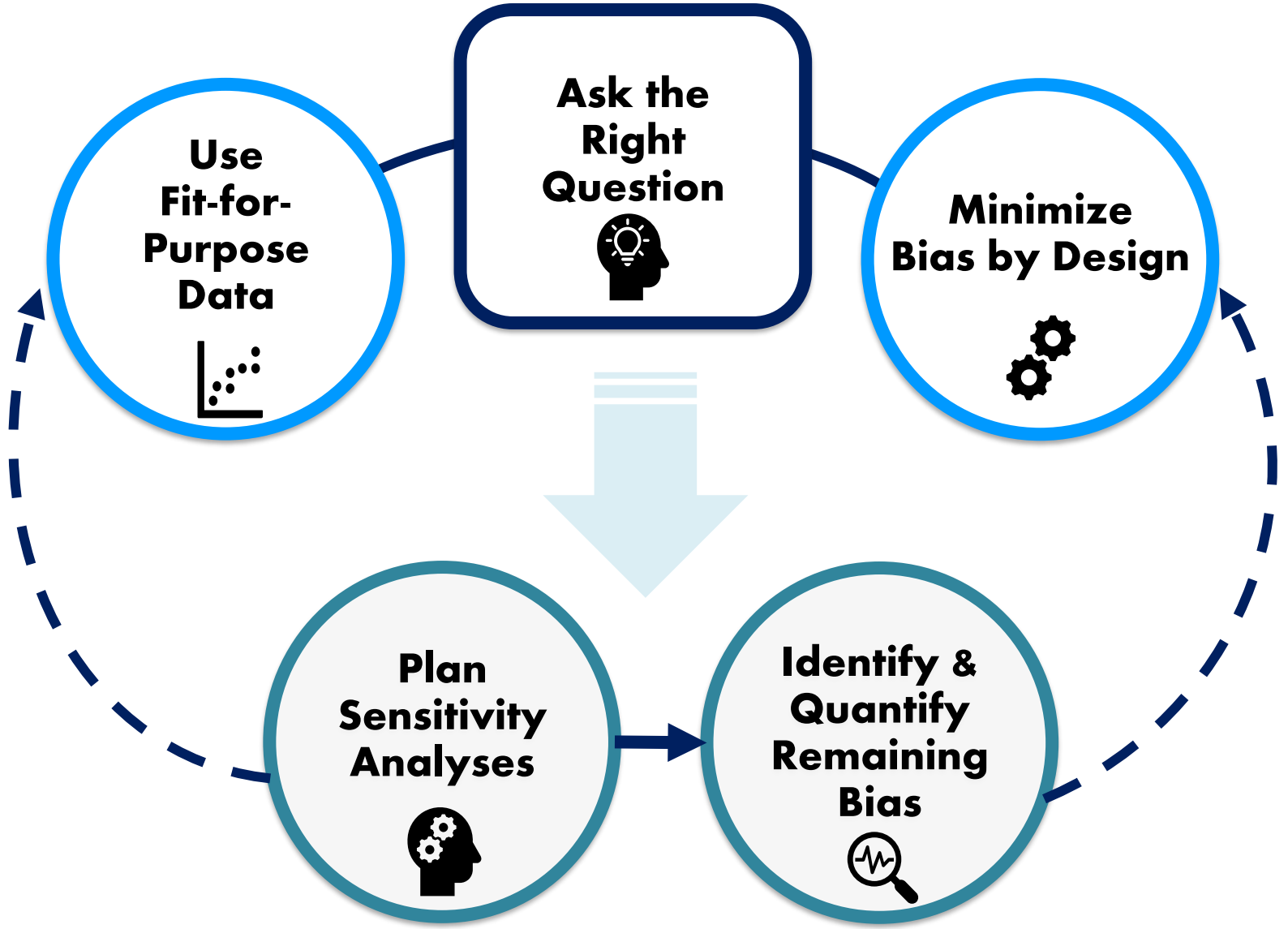
Rich Forshee, Dianne Paraoan, Ken Quinto, and FDA Sentinel team & partners

CDERMedicalPolicy-RealWorldEvidence@fda.hhs.gov

Causal Inference at FDA CBER

Richard Forshee, PhD
Acting Deputy Office Director, OBE
Center for Biologics Evaluation and Research
US Food and Drug Administration

My Team's Approach to RWE

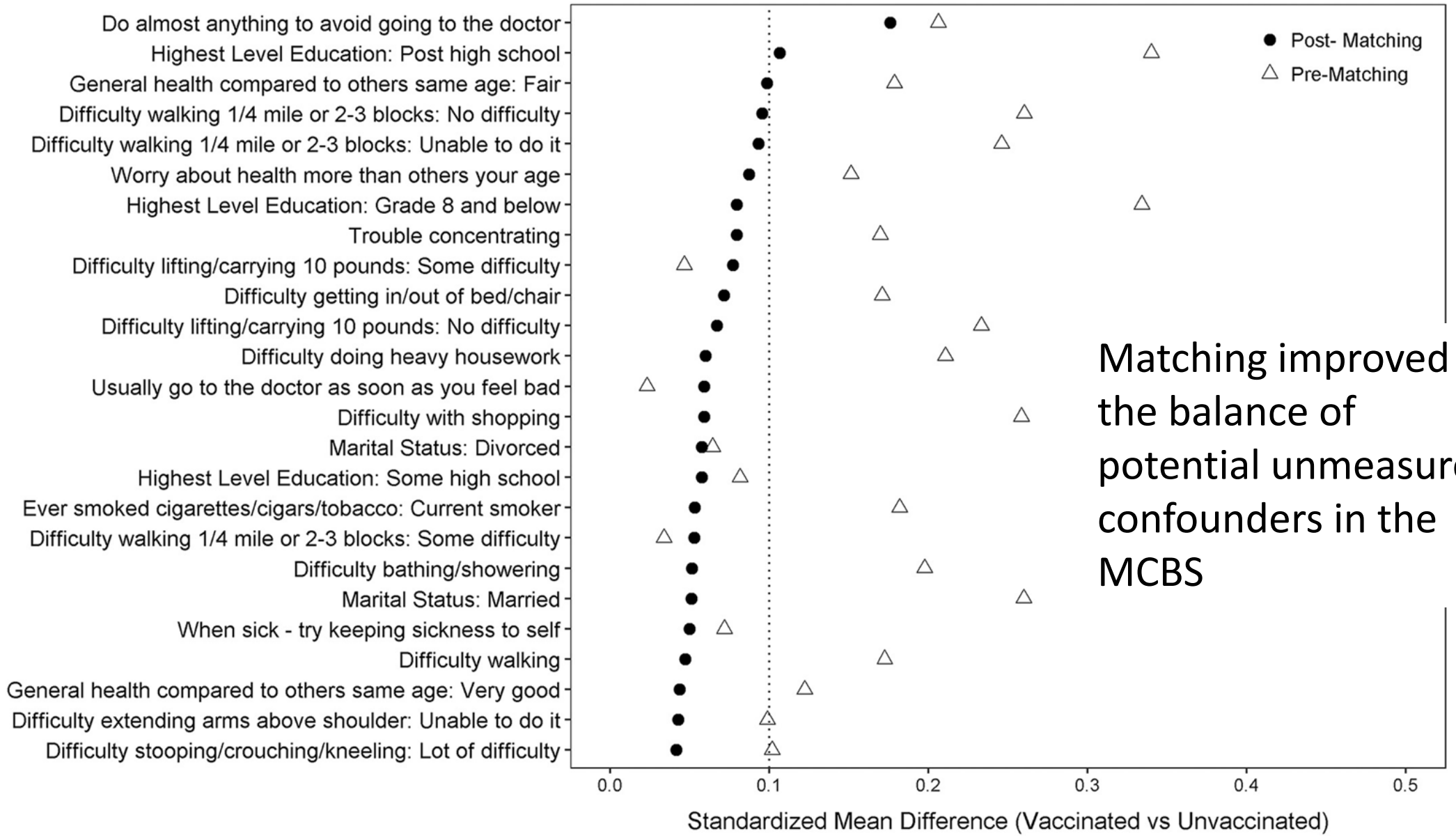


Fit-for-Purpose Data

- Medicare claims and enrollment data
  - Extensive demographic and health data
  - Large database including most people 65y and older in US
  - Exposures and outcomes reliably captured
  - Relevant patients
  - Little missing data

Identify and Quantify Remaining Bias

Using a linked outside source: Medicare Current Beneficiaries Survey



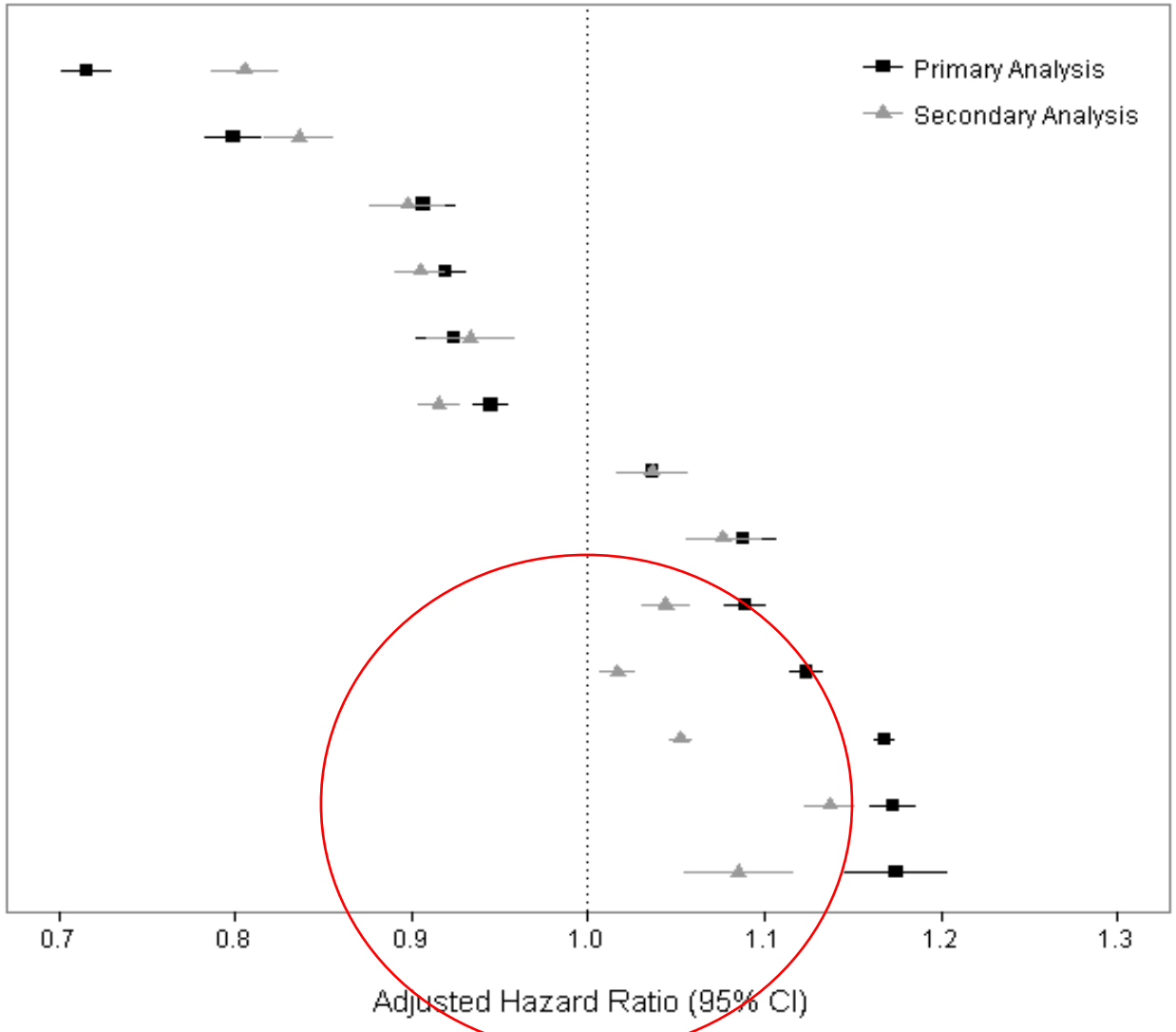
Matching improved the balance of potential unmeasured confounders in the MCBS

Izurieta et al, Pharmacoepidemiol Drug Saf 2019

Falsification outcomes:
Vaccinees compared with: (a) unvaccinated, (b) rec. another vaccine

Comparison of Adjusted Hazard Ratios of 13 Falsification Outcomes in Matched Populations

Falsification Outcome	Primary	Secondary
Hip fracture	0.72	0.80
Thrombosis	0.80	0.84
Cholelithiasis and cholecystitis	0.91	0.90
Renal stone	0.92	0.90
Wrist fracture	0.92	0.93
Gout	0.95	0.92
Epistaxis	1.04	1.04
Wound of hand or finger	1.09	1.08
Ingrown nail	1.09	1.04
Hemorrhoids	1.12	1.02
Cataract	1.17	1.05
Eyelid disorder	1.17	1.14
Lipomas	1.17	1.09



Collaborators, partial list

- FDA: Hector S. Izurieta, Yun Lu, Douglas Pratt, Paula Ehrlich Agger, Yandong Qiang, and Philipp Krause
- CDC: Kathleen Dooling, David Shay, Ruth Link-Gelles, Rafael Harpaz
- CMS: Jeffrey Kelman
- ACUMEN: Yoganand Chillarige, Michael Wernecke, Bradley Lufkin, Heng-Ming Sun, Qin Sun, Sarah Wong, Carmen Dekmezian, Arjun Lyengar, Nicole Thadani, Riley Franks, Aaron Maurer, Jonathan Gibbs, Han Hong, Tom MaCurdy

Thank You!

Richard.Forshee@fda.hhs.gov

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA's initiatives on Real-World Evidence and DARWIN EU

DARWIN EU

13th Annual Sentinel Public Workshop – Improving Causal Inference for RWE Generation
08th November 2021

Gianmario Candore - Data Analytics and Methods Task Force
European Medicines Agency

Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties

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The European Medicines Regulatory Network (EMRN) RWE framework

RWD/RWE provided by	Pharmaceutical companies	National competent authorities or EMA
RWD/RWE used to	Support marketing authorisation submissions	Support committees' decision making
EMRN role	Guidance	Analyses/studies

Guideline on registry-based studies
Standard definitions
Quality assessment criteria

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Vision to raise health and innovation impact of RWE through its increased generation and use in decision-making

Pharmaceutical companies

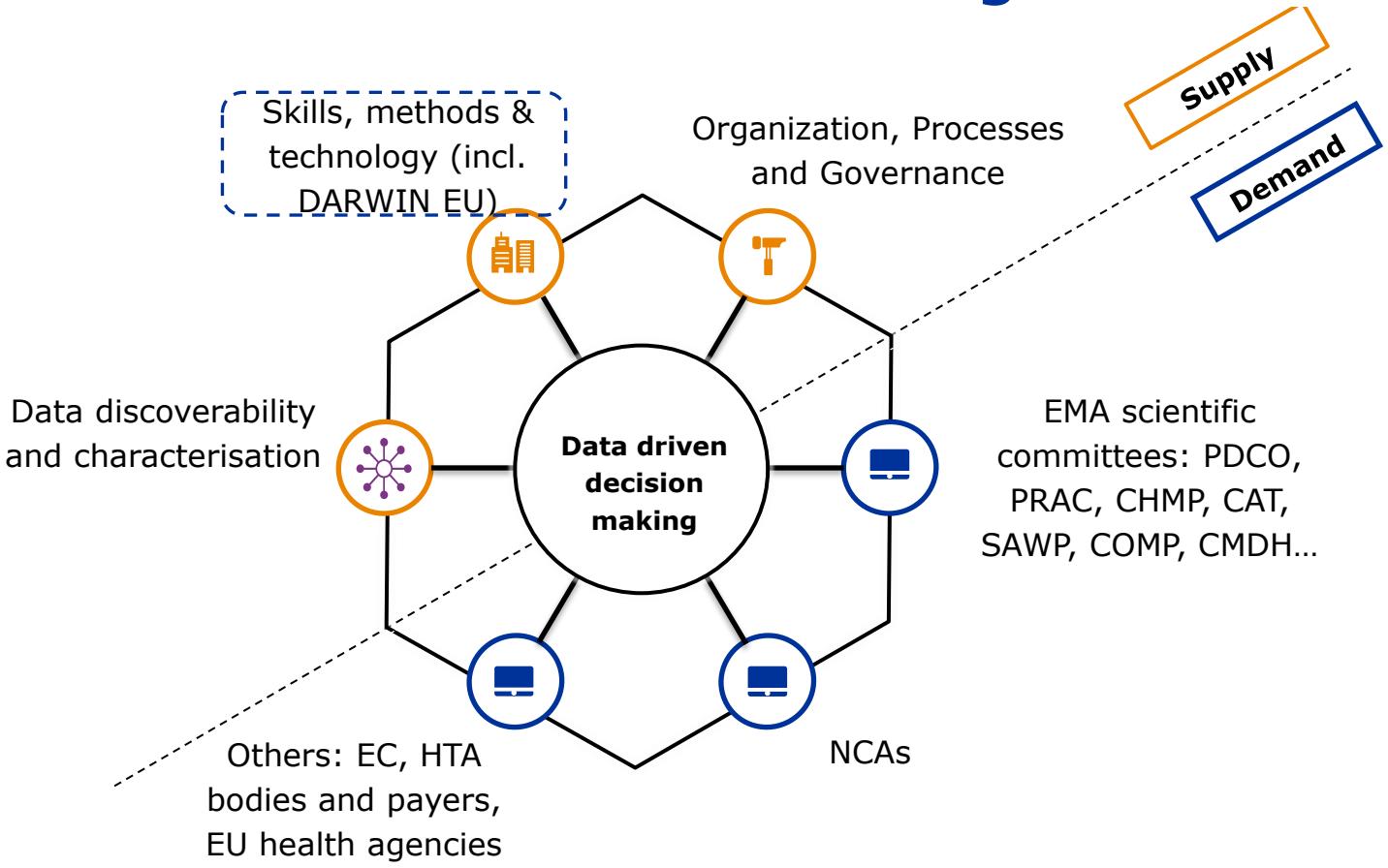
Support marketing authorisation submissions

National competent authorities or EMA

Support committees' decision making

Guidance

Analyses/studies



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Coming in 2022: Data Analysis and Real-World Interrogation Network - DARWIN EU®

DARWIN EU is a federated network of data, expertise and services

EU Medicines Regulatory Network

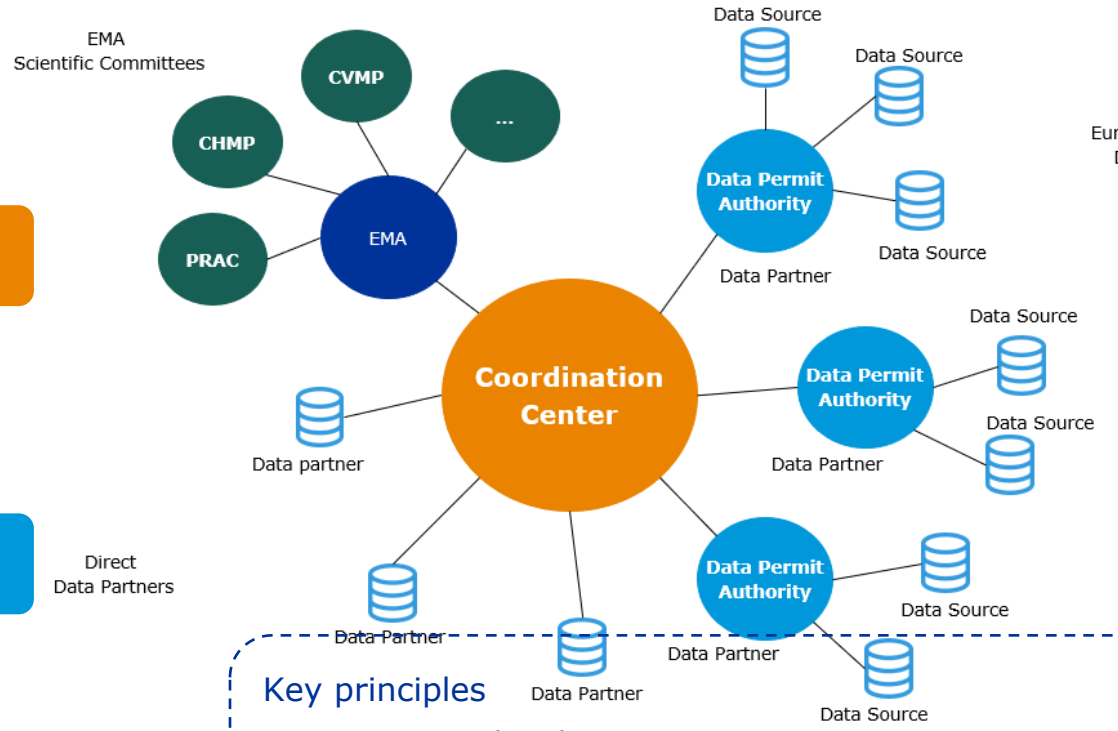
- **EMA** - provides leadership, setting standards, contracting studies, **overseeing**
- **EMRN -** including EMA scientific committees and working parties, national competent authorities (NCAs) and the European Commission: **request studies** via EMA

The Coordination Centre

- **Establishes** and **maintains the network** (including onboard/maintain data sources), manage the **execution of scientific studies**

Data Partners, incl. Data Permit Authorities

- **Partners** who have access to data, or who may request analyses in a data source and provide results to the Coordination Centre
- This includes **Data Permit Authorities** (DPAs), already existing or to be created as part for the European Health Data Space (EHDS)



Key principles

- Data stays local
- A common data model will help performing studies timely and increasing consistency of results

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How to support translating from RWD to RWE

Data

- Developing a catalogue of data sources with metadata describing the main characteristics of each source
- Developing a data quality framework reproducible across different types of RWD sources

Stepwise approach

- Pilot-based approach to iteratively refine processes, use cases and methodologies
  - Start with more traditional use cases: safety, disease epidemiology, informing on design and feasibility of studies

Methodology and capabilities

- Continuous update of the ENCePP guidelines on pharmacoepidemiology
- Creation of a Methodology Working Party with dedicated expertise in RWE
- Refine methodologies for the use of RWE collaborating with DG Research
  - HORIZON-HLTH-2022-TOOL-11-02: New methods for the effective use of real-world data and/or synthetic data in regulatory decision-making and/or in health technology assessment
  - Framework to enhance causal inference from observational studies (e.g. through the target approach)
- Developing training on Data Science, Pharmacoepidemiology and Biostatistics

Transparency

- Each study published in the EU PAS Register for transparency

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Any questions?

Further information

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Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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Discussion Questions

- Where are there parallels between FDA's and EMA's work on generating and using RWE for causal inference? How can Sentinel and DARWIN encourage collaboration to amplify their respective capabilities?
- How can common data models and efforts to standardize terminology help advance causal inference capabilities?
- How have these approaches to causal inference helped to bolster your work on pandemic response?

Session III: Fireside Chat on Building Robust Evidence Generation Systems

- **Mark McClellan**, Duke-Robert J. Margolis, MD, Center for Health Policy
- **Robert Califf,** Verily

Closing Remarks | Day 1

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

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Thirteenth Annual Sentinel Initiative Public Workshop

November 8, 2021 | 10:00 - 2:00 ET

November 9, 2021 | 10:00 - 2:00 ET

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

Welcome & Overview | Day 2

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Summary: Day 1

- Keynote Presentation – Patrizia Cavazzoni
- Fireside Chat with Sentinel Initiative Leadership
- Sentinel Coordinating Center Perspectives
- Improving Causal Inference for RWE Generation
- Fireside Chat with Robert Califf: Building Robust Evidence Generation Systems

Agenda: Day 2

- Sentinel Collaborations for COVID-19 Response
- BEST's COVID-19 Response
- BEST Collaborator Perspectives

Statement of Independence

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

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

Virtual Meeting Reminders

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

- Join the discussion on Twitter using the #SentinelInitiative hashtag

Session IV: Sentinel Collaborations for COVID-19 Response

- **Michael Blum,** U.S. Food and Drug Administration
- **Noelle Cocoros,** Harvard Pilgrim Institute
- **Susan Winckler,** Reagan-Udall Foundation for the FDA
- **Catherine Cohet,** European Medicines Agency

An FDA Perspective on the Value of Sentinel and Collaborative Regulatory Agency COVID-19 Studies

Michael D. Blum, MD, MPH
Deputy Director
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology, CDER, FDA

Why Would a Regulatory Agency Conduct a Post-Approval/Authorization Study Rather Than or In Addition to Industry or Academia?

- Regulatory agency questions may need rapid answers
- Some questions apply to classes of medicines
- In some cases, there is a need to validate industry answers
- Need to develop evaluation methods
- Data sources available to the agency may be superior to those available to industry or academia (e.g., larger databases, more representative of the population of interest)
- Agency may have a legislative mandate to conduct a study

Collaborative Regulatory Agency Studies

- Opportunities
  - Economies of scale
  - Capitalize on each others' strengths
  - Improve sample size and analytic power
  - Standardize methods to optimize comparability
- Challenges
  - Privacy legislation
  - Issues of data "ownership"
  - Trust
  - Lack of standardization
  - Dedicated time and resources


FDA
U.S. FOOD & DRUG
ADMINISTRATION

The Sentinel System's Response to COVID-19

Noelle M. Cocoros, DSc, MPH
Sentinel Operations Center

13th Annual Sentinel Initiative Public Workshop

November 9, 2021

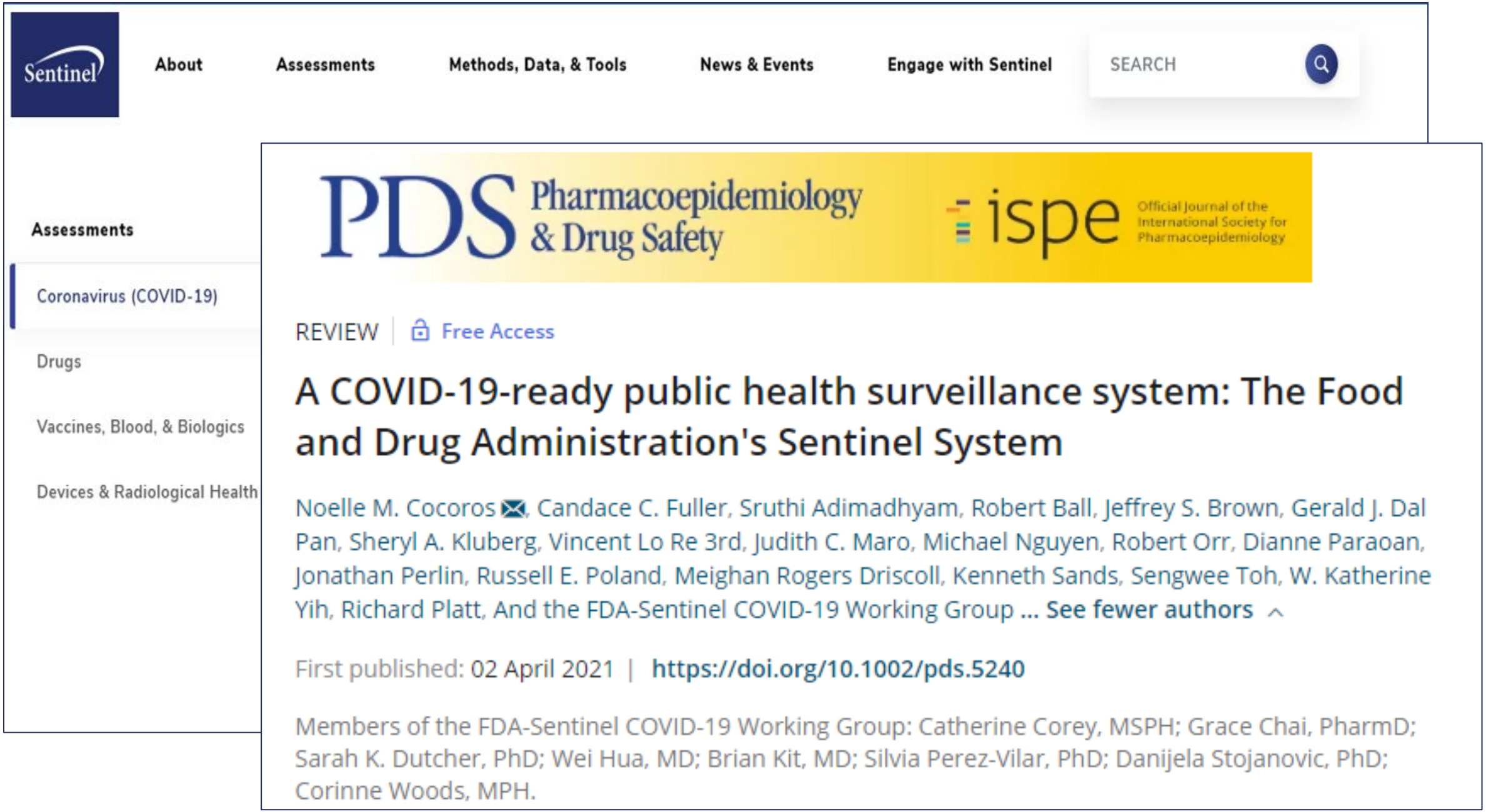
Disclosures, Funding, and Disclaimers

Work discussed was supported in part by HCA Healthcare and/or an HCA Healthcare affiliated entity. The views expressed represent those of the authors and do not necessarily represent the official views of HCA Healthcare or any of its affiliated entities.

FDA's COVID-19 related needs

- Near real time data
  - Well-characterized, quality-checked
  - Enable identification of cohorts, medical history, care received, and outcomes, including severity, across care settings

- Collaboration with deliberate coordination
  - For robust science, transparency, replication, efficiency
  - Built on long-term relationships and collaborations (e.g., within the Sentinel network, across public health agencies)
  - Facilitated by use of master protocols


Sentinel
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Devices & Radiological Health
PDS Pharmacoepidemiology & Drug Safety
ispe Official Journal of the International Society for Pharmacoepidemiology
REVIEW
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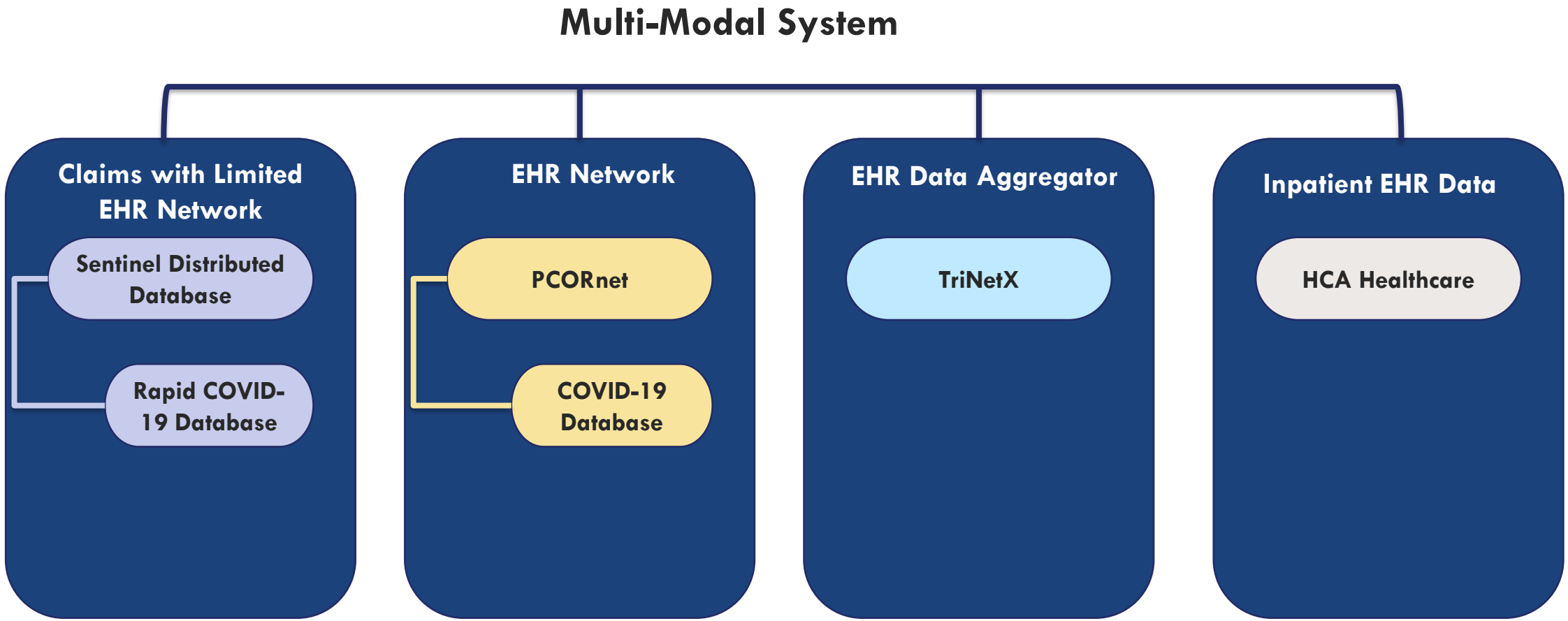
A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System
Noelle M. Cocoros, Candace C. Fuller, Sruthi Adimadhyam, Robert Ball, Jeffrey S. Brown, Gerald J. Dal Pan, Sheryl A. Kluberg, Vincent Lo Re 3rd, Judith C. Maro, Michael Nguyen, Robert Orr, Dianne Paraoan, Jonathan Perlin, Russell E. Poland, Meighan Rogers Driscoll, Kenneth Sands, Sengwee Toh, W. Katherine Yih, Richard Platt, And the FDA-Sentinel COVID-19 Working Group ... See fewer authors
First published: 02 April 2021 | https://doi.org/10.1002/pds.5240
Members of the FDA-Sentinel COVID-19 Working Group: Catherine Corey, MSPH; Grace Chai, PharmD; Sarah K. Dutcher, PhD; Wei Hua, MD; Brian Kit, MD; Silvia Perez-Vilar, PhD; Danijela Stojanovic, PhD; Corinne Woods, MPH.

Currently Available Data Sources for Sentinel



Rapid COVID-19 Sentinel Distributed Database

- Over 77 **million** patient IDs, **8.6 million** SARS-COV-2 laboratory records
- All patients with records in 2020 contribute data, regardless of COVID-19 status

Humana Healthcare Research

aetna®

HealthPartners Institute

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Center for Health Research

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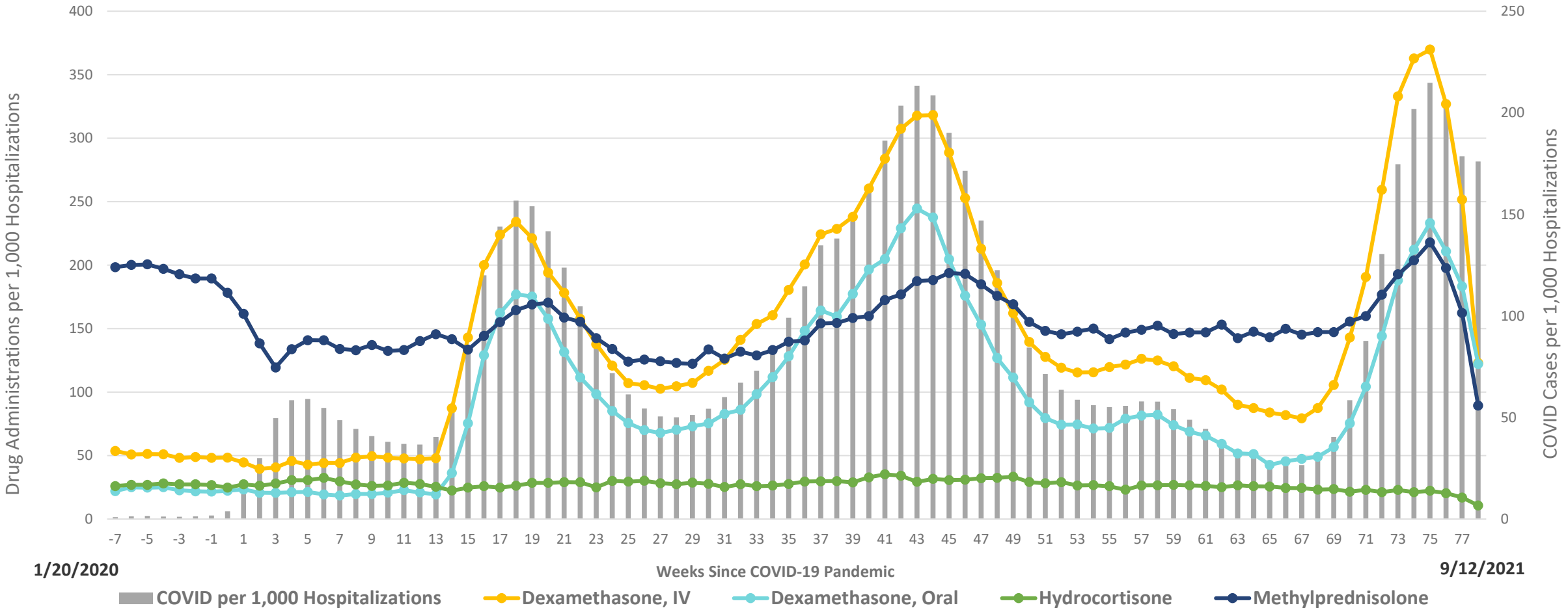
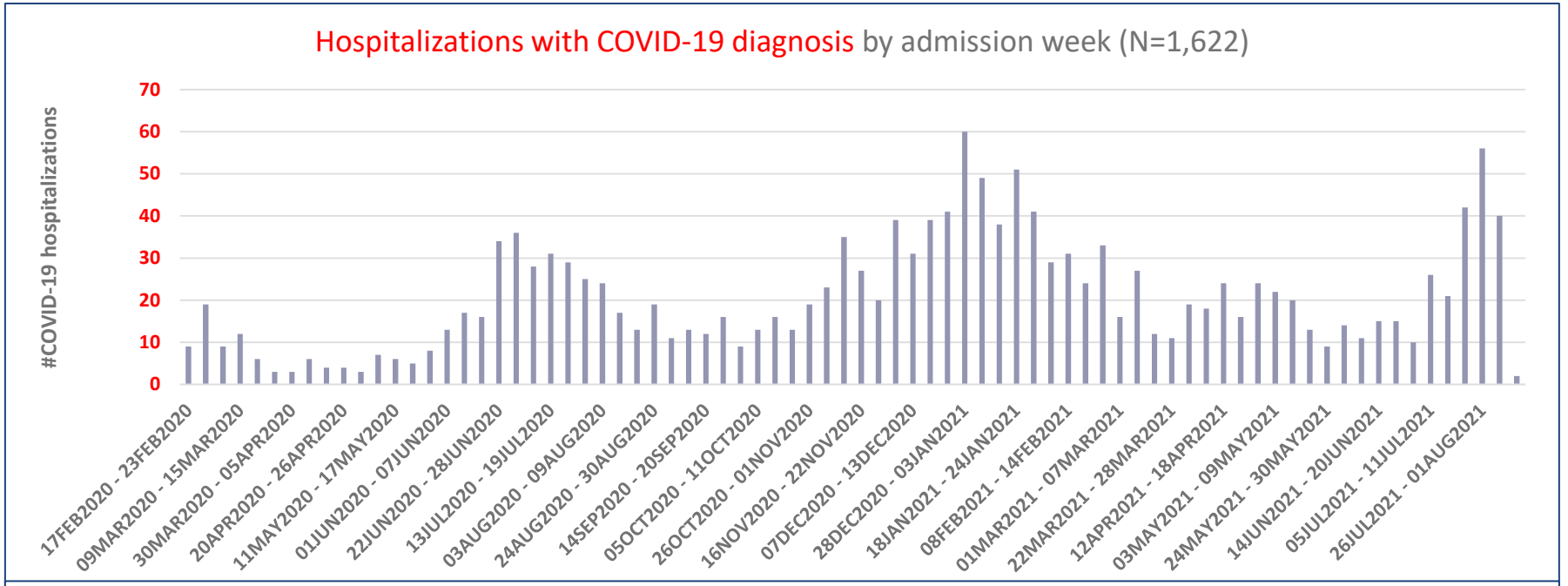
Washington

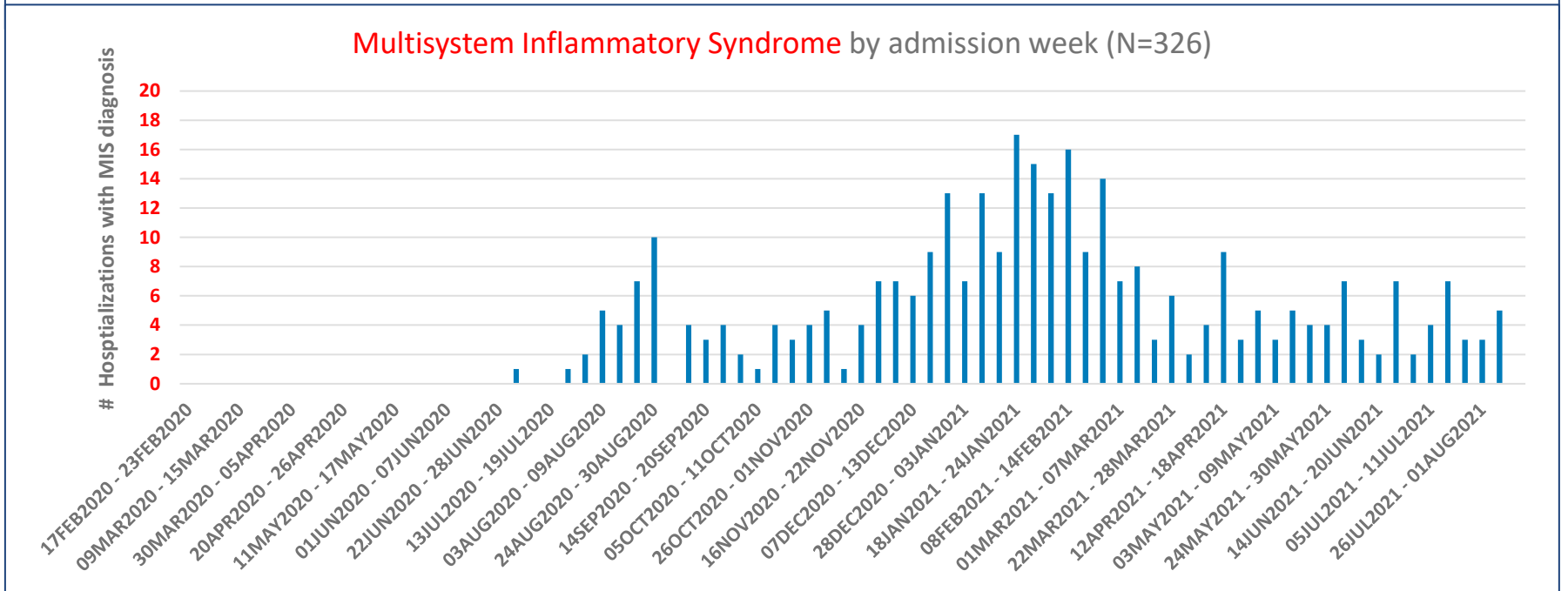
Monitoring Critical Drugs – Steroids, HCA Healthcare



Drug administrations are de-duplicated by patient-day during a hospital stay

Pediatric Hospitalizations, HCA Healthcare, Feb. 20, 2020 – Aug. 10, 2021





Oxygen-Related Therapy in Hospitalized Adult Patients with COVID-19 Diagnosis, Feb. 2020 – March 2021

Oxygen-related care, nursing documentation	Hospitalizations with COVID-19 diagnosis (N=137,565)
Bilevel Positive Airway Pressure (BiPAP)	15%
High flow nasal cannula	24%
Nasal cannula (routine)	74%
Non-rebreather	20%
Oxygen conserving device	4%
Simple mask	13%
Ventilator	14%
Any oxygen	78%
Any oxygen or ventilator	79%

Nursing documentation improved both granularity and capture of oxygen-related therapy

- **79% were ventilated or on supplemental O2 (compared to 28% using codes only)**
- Capture of invasive mechanical ventilation did not significantly change with nursing documentation

Natural History of Coagulopathy in COVID-19

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Health Canada

IMPORTANCE: There are major knowledge gaps on the incidence, determinants, and consequences of arterial and venous thrombotic complications with COVID-19

AIMS:

1. Determine the 90-day incidence of arterial and venous thrombotic complications with COVID-19 and subsequent risk of death within 30 days of the event
2. Evaluate patient characteristics present prior to COVID-19 diagnosis as risk factors for arterial and venous thrombotic events
3. Compare the 90-day risk of arterial and venous thrombotic events between health plan members diagnosed with COVID-19 and those diagnosed with 2018-19 influenza

https://www.sentinelinitiative.org/methods-data-tools/methods/assessment-natural-history-coagulopathy-covid-19

COVID-19 Pregnancy - CONSIGN

IMPORTANCE: Little information is available to support understanding the natural history of COVID-19 disease in pregnant women, or the impact of COVID-19 treatment upon pregnant women or the developing fetus

OBJECTIVES:

(1) To estimate the prevalence of medicines used and compare this among pregnant women with COVID-19, pregnant women without COVID-19, and non-pregnant women with COVID-19

(2) To describe severity and clinical outcomes of COVID-19 disease in pregnant women with COVID-19, according to treatments received during pregnancy, and compare these data with those of nonpregnant women of reproductive age with COVID-19

https://www.sentinelinitiative.org/methods-data-tools/methods/covid-19-pregnancy-study-implementation

Sentinel

Thank you

COVID-19 Evidence Accelerator

Susan Winckler, RPh, Esq.

CEO, Reagan-Udall Foundation for the FDA

swinckler@reaganudall.org

Thirteenth Annual Sentinel Initiative Public Workshop

11.09.2021

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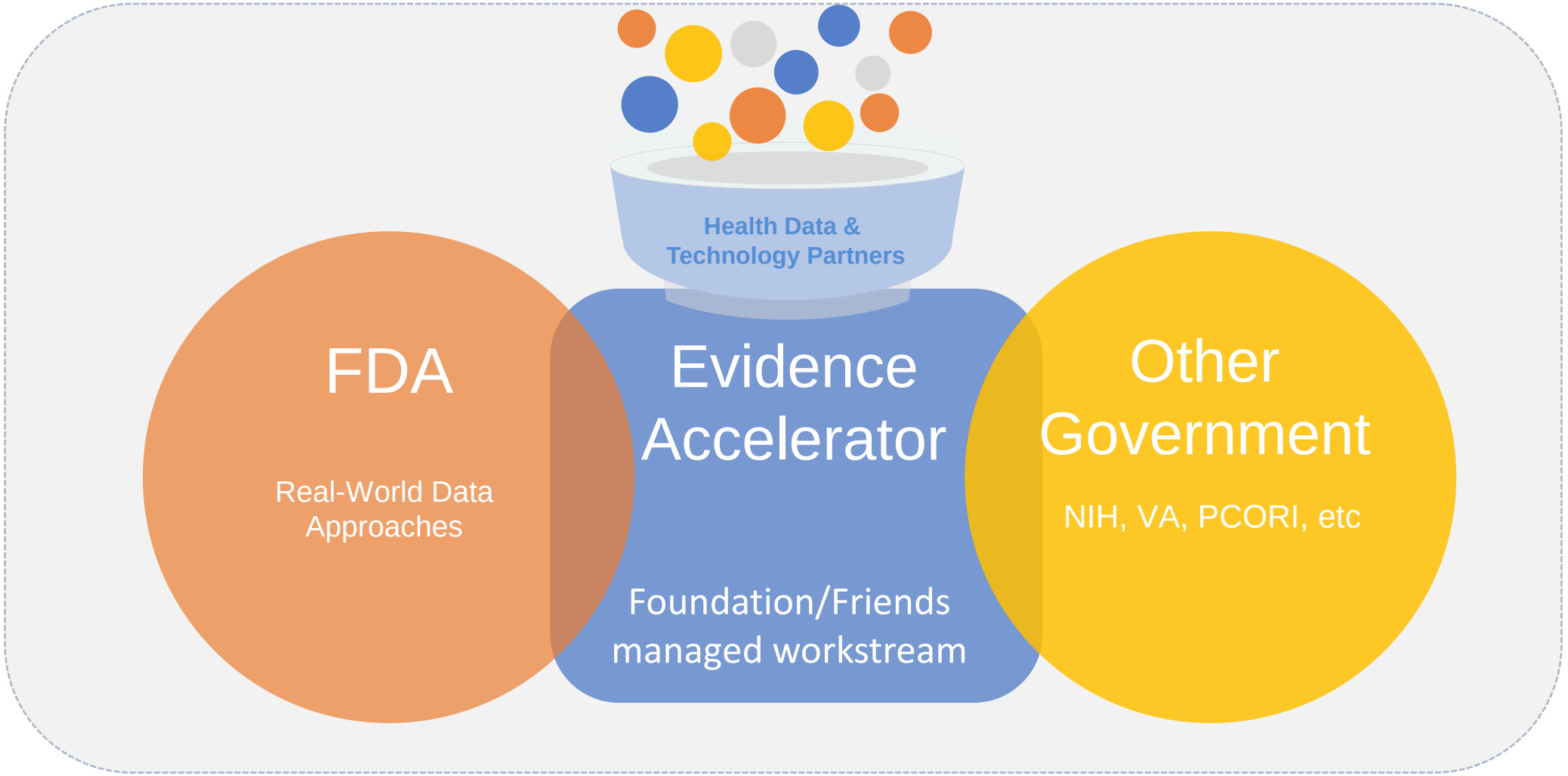
COVID-19 Evidence Accelerator evidenceaccelerator.org



A community of data and analytic partners ready to urgently address questions about COVID-19

REAGAN-UDALL FOUNDATION FOR THE FDA

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Foundation & Friends Experience with RWD/RWE

Reagan-Udall Foundation for the FDA

- We are FDA's Foundation, created to support FDA
- Operate Innovation in Medical Evidence Development and Surveillance (IMEDS) Program
- IMEDS is a public-private partnership that provides a framework and entry point for regulated industry into Sentinel
- Through our IMEDS Network, we conduct sponsor-initiated post-market safety evaluations of products using distributed real-world data sets (claims codes and EHRs) with >117 million patient lives
- Collaboration with several Sentinel and non-Sentinel data partners and Harvard Pilgrim HealthCare Institute who serves as our analytic partner

Friends of Cancer Research

- Friends is an advocacy organization based in Washington, DC that drives collaboration among partners to power advances in science, policy, and regulation
- Friends recently convened six organizations with oncology-focused health care data to conduct a pilot RWD project
- The primary collective goals of the study were to agree on and execute a common protocol using diverse RWD and to explore how real-world end points could be used to rapidly address clinically relevant questions about treatment effectiveness
- This parallel analysis method has served as a model for the work of the Evidence Accelerator

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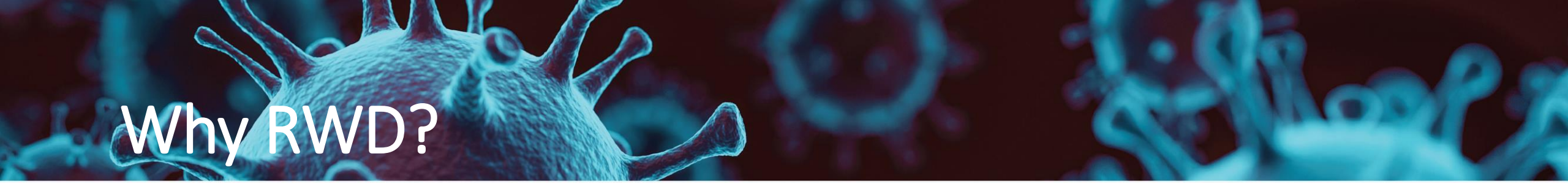

Why RWD?

- Urgent need to rapidly understand the natural history of COVID-19
- Many critical clinical evidence needs but limited clinical trial resources (patients, time, competing tasks)
  - RWD evaluation of treatment patterns and impact improves understanding of 'real-life' environment
  - RWD can help prioritize research questions to be answered with clinical trials
  - RWD can improve study design and support participant enrollment
  - Pragmatic and platform/adaptive study designs can improve efficiency and generalizability
- Near real-time performance of diagnostics authorized under EUA
- Near real-time vaccine performance authorized under EUA

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COVID-19 RWD Learning Snapshots

Original Research | August 2021

Optimizing SARS-CoV-2 Surveillance in the United States: Insights From the National Football League Occupational Health Program

FREE

Christina DeFilippo Mack, PhD, MSPH, Michael Osterholm, PhD, ... View all authors +

Author, Article and Disclosure Information

https://doi.org/10.7326/M21-0319

Veterans Health Administration

Impact of Delta on Vaccine Effectiveness
VA COVID Vaccine Surveillance

9/23/21

Slides by Yinong Young-Xu, ScD, MA, MS
Clinical Epidemiology Program
White River Junction VA Medical Center

Evidence Accelerator Tools

Prioritized research questions

Common data elements and translation tables between common data models

Common protocol for repeated analysis of priority research questions across multiple data partners (the “parallel analysis”)

Meetings and forum for rapid cycle feedback and learning

Individual Accelerator communities focused on specific topics (e.g., therapeutics and vaccines, diagnostics)

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FRIENDS of CANCER RESEARCH

COVID-19 Evidence Accelerator Work Streams (as of 11/21)

Online Community

THERAPEUTICS EA

Twice-Monthly Lab Meeting (1st and 3rd Thursdays)

Planning for next steps underway…

DIAGNOSTICS EA

Twice-Monthly Lab Meeting (1st and 3rd Thursdays)

Data interoperability work underway…

VACCINES EA

Twice-Monthly Lab Meeting (1st and 3rd Thursdays)

Planning for next steps underway…

Oncology work group

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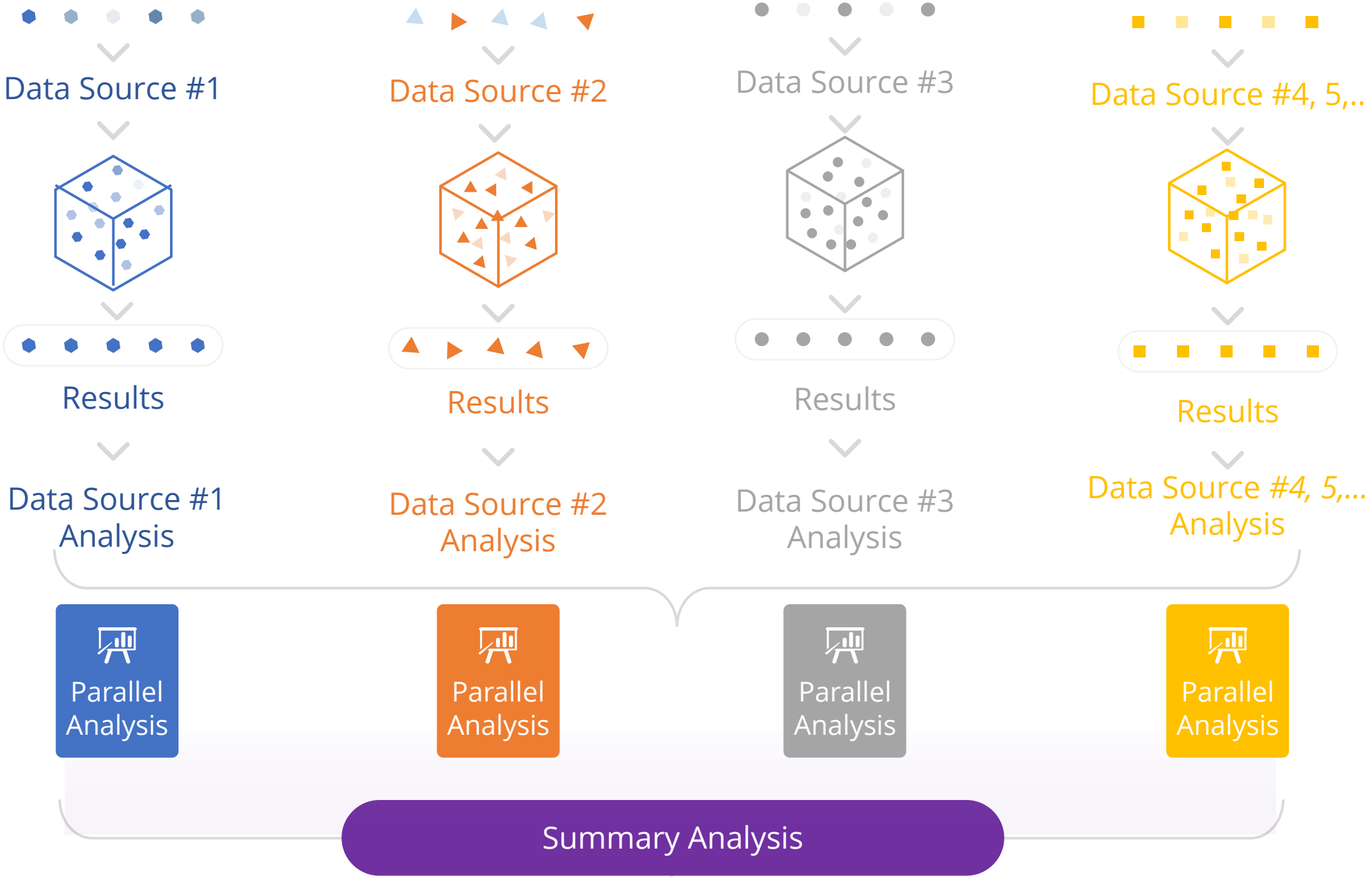
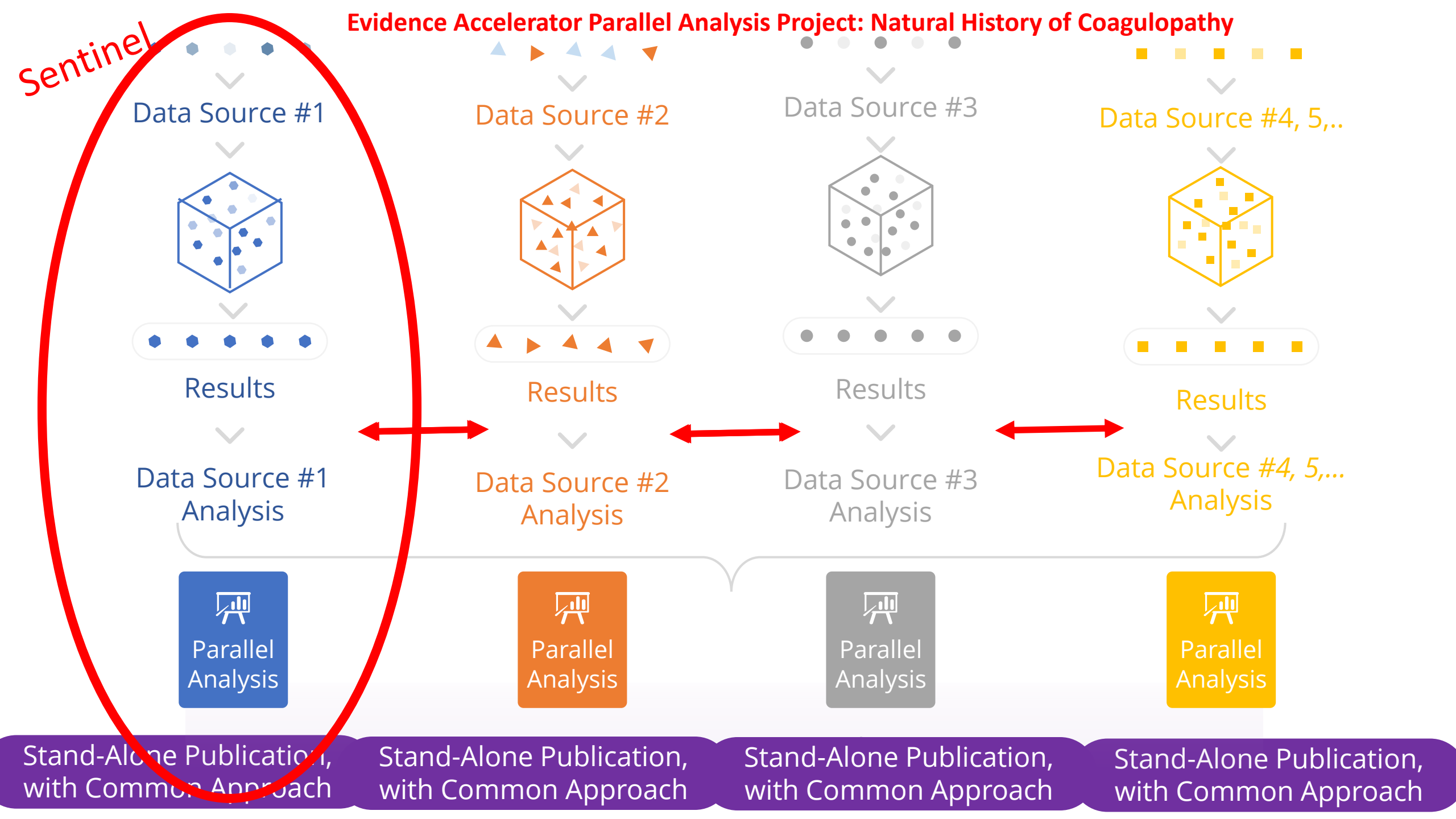

Data Source #1
Data Source #2
Data Source #3
Data Source #4, 5,..
Results
Results
Results
Results
Data Source #1 Analysis
Data Source #2 Analysis
Data Source #3 Analysis
Data Source #4, 5,... Analysis
Parallel Analysis
Parallel Analysis
Parallel Analysis
Parallel Analysis
Summary Analysis

Evidence Accelerator Parallel Analysis Project: Natural History of Coagulopathy

Sentinel



COVID-19 and RWD: Timing Matters

Data Parameters Evolved

- ICD codes for COVID-19 became available April 1, 2020; until then miscellaneous codes were used to document a COVID-19 diagnosis
- Early in the pandemic, products made available under Emergency Use Authorization (EUA) lacked National Drug Codes (NDC)
- Severity of COVID-19 was (and is) classified in varying ways, often using objective data such as labs, biomarkers, vitals, or imaging
- Challenging to identify the level of ventilation or oxygen support provided

Product Status Evolved

- Devices, diagnostics, therapeutics and vaccines were made available under emergency use authorization (EUA)—over time, some moved to full FDA approval/clearance, others had their authorization revoked, some remain available under EUA.

Standard of Care Evolved

- Important to understand the dynamics of the "windows of time" both for baseline and index periods

COVID-19 and RWD… Data Set Limitations:

Understanding data completeness and data lag in underlying data sources is essential.
How much do we have?
When do we have ‘enough’?
How quickly can data be accessed?

- Claims data often lacked detail on inpatient medications and tests conducted
- Availability and quality of testing data varied over time.
- We don't have a common patient-centric repository of health data (vaccines, labs, diagnostics, etc.). Absence of vaccine administration *data* does not mean absence of vaccine *administration*.
- EHR data may yield under-estimation of pre-existing medical conditions as compared to claims data
- Difficult to determine which phase of infection was treated with what therapy
- When doing string-based searches for medications, e.g., steroids, filter out topical/ophthalmic/otic medicines.
- Data use agreements may limit ability to characterize geographic distribution of health systems

COVID-19 EVIDENCE ACCELERATOR PRINCIPLES

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

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

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

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

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

T **TRANSPARENCY** — ruthless transparency.

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

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

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

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

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

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EUROPEAN MEDICINES AGENCY
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COVID-19 real-world evidence generation: the EU perspective

13th Sentinel Annual Public Workshop - Sentinel Collaborations for COVID-19 Response

9 November 2021

Catherine Cohet, Data Analytics and Methods Task Force, EMA

An agency of the European Union

Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of, or reflecting the position of the European Medicines Agency or one of its committees or working parties

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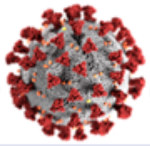
COVID-19 response: from early times to expanding vaccine safety monitoring

ACCESS
vACCine covid-19 monitoring readinESS



2020 ACCESS project

Preparedness
- Data sources
- AESI background rates
- templates, feasibility

2021 'Early' safety study
- AESI incidence rates (primary data collection)
- Monitoring in EU healthcare databases
- **Feb-Nov 2021**

Ongoing

2021-23 Ongoing + future studies
- Extended active surveillance and signal strengthening
- Framework for signal evaluation

★ **Background incidence rates**
★ **Signal evaluation**

- Large EU consortia with access to networks of data sources mapped to CDMs
- 5 to 10 EU databases in each study

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International collaborations for COVID-19 observational studies

- European COVID-19 Observational Research Exchange (E-CORE)
  - Multinational collaboration for observational studies of COVID-19 medicines (drug use, safety, effectiveness): set of cohorts, common protocol and/or established CDM
  - Feasibility: pilot study of systemic glucocorticoids in hospital/ambulatory care using the OMOP CDM → identified challenges (sample size for rare outcomes, heterogeneity) and opportunities (network can be used for studying COVID-19 therapies in international setting)
- COVID-19 infectiOn aNd medicineS In pregnancy (CONSIGN)
  - Impact of COVID-19 treatments in pregnancy (ConcePTION, COVI-PREG, INOSS)
  - Meta-analysis: FDA adaptation of WP1 protocol (EHR/ConcePTION) within Sentinel, + non-EU regulators
- Natural history of coagulopathy and use of anti-thrombotic agents (COVID-19 patient cohort + vaccinated cohort)
  - Initiated by FDA as part of ICMRA WG on RWE: feasibility of joint protocol
  - EU study procured through EMA frameworks contracts with protocol adapted to OHDSI and EHDEN environments using the OMOP CDM

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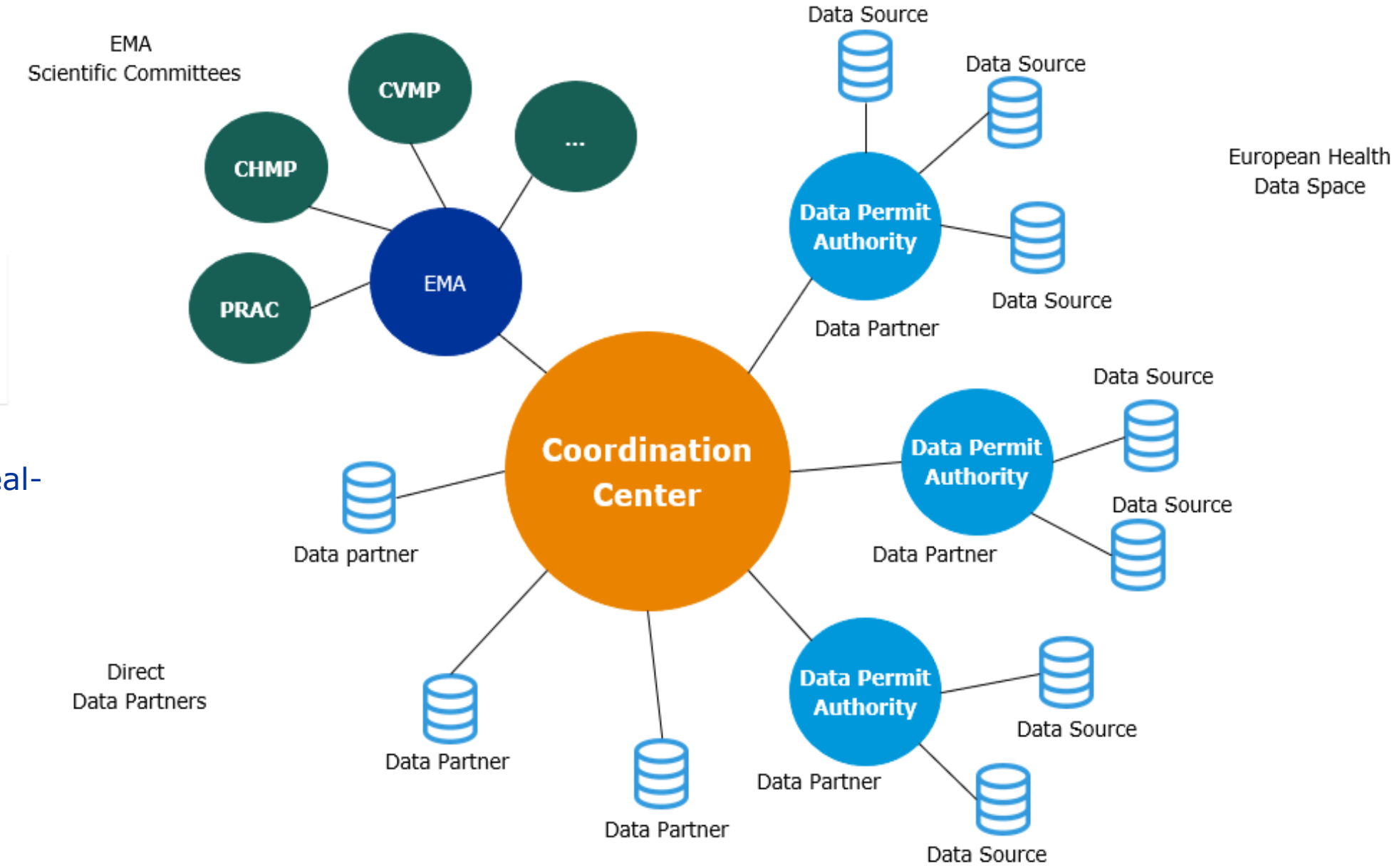
DARWIN EU

Data Analysis and Real-World Interrogation Network



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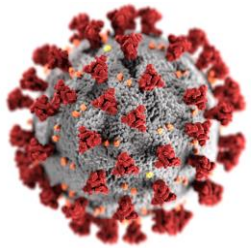
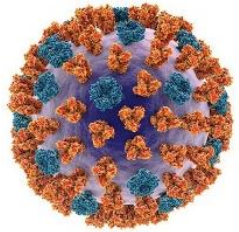
Central pillar for health crisis planning and response





- DARWIN EU will support future crisis responses with an operational infrastructure for conducting rapid studies (change to EMA's mandate)
- Use cases include:
  - ✓ Monitoring the use of medicines to predict demand and shortages
  - ✓ Understanding the disease natural history to support development of vaccines and therapeutics
  - ✓ Provide evidence for repurposing existing medicines
  - ✓ Monitor the post-authorisation safety and effectiveness of vaccines and therapeutics

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What have we learned from COVID-19 multi-database studies in Europe?

- Need for timely, high-quality, fit-for-purpose RWE, with focus on strengthening all steps of evidence generation and appraisal
- Unprecedented collaborative efforts
- Preparedness is key
- Large healthcare databases from several MS can be used and rapid analyses are possible, but challenges still exist
- International collaboration is key to share information, data, experience, and leverage this knowledge to develop a global public health strategy
- Joint EMA and ECDC coordination of vaccine safety and effectiveness monitoring in the context of the European Health Union

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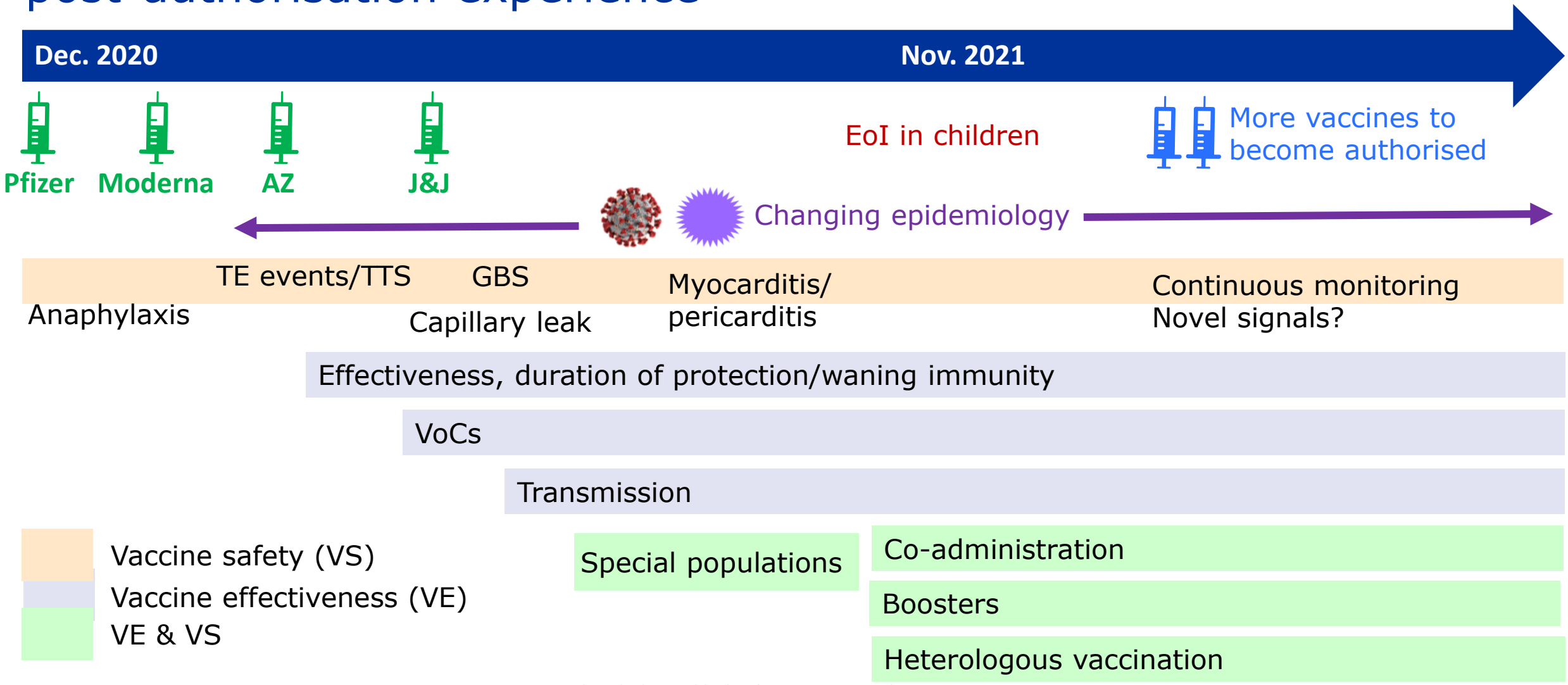
COVID-19 evidence needs mirror vaccination campaigns and the post-authorisation experience



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Further information

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DARWIN EU - Benefits

- National and EU regulation of medicines
  - Drug development – disease epidemiology, unmet need, historical controls, planning
  - Authorisation – contribution to B/R, comparators, extrapolation to general and/or special populations
  - Post-authorisation – benefit-risk monitoring, extension of indication, risk minimisation measures

DARWIN EU will significantly **increase the capacity** of the Network to undertake high-quality observational studies based on RWD

- Additional benefits
  - **International collaborations -** Sentinel, CNODES, OHDSI, VAC4EU, etc.
  - European Commission – key use cases for the European Health Data Space
  - National governments - to support health policy and delivery of healthcare systems
  - HTA bodies and payers - to support better quality decisions on cost-effectiveness
  - EU health agencies - use cases specific for EFSA, ECDC, ECHA, JRC
  - EU patients - faster access to innovative medicines and safe and effective use

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Discussion Questions

- What capabilities have we built or leveraged during COVID-19 that can prepare us for implementing more accelerated responses to public health emergencies?

- It has become clear that COVID-19 either required or inspired Sentinel to adapt and/or incorporate new focus areas beyond its initial mission of safety and surveillance. What are top lessons learned to inform Sentinel's future work?

- Building on lessons learned during COVID-19, how can FDA and EMA collaborate with other national agency counterparts today and into the foreseeable future to support and enhance their safety and surveillance capabilities?

- How has the Sentinel common data model helped throughout the pandemic?

Session V: BEST's COVID-19 Response

- **Hui-Lee Wong,** U.S. Food and Drug Administration
- **Eric Weintraub,** Centers for Disease Control and Prevention
- **Fran Cunningham,** Department of Veterans Affairs

FDA Biologics and Effectiveness Safety System: COVID-19 Response

Thirteenth Annual Sentinel Initiative Public Workshop
November 9, 2021

Hui-Lee Wong, PhD, MSc
Associate Director for Innovation and Development
Office of Biostatistics and Epidemiology
Center for Biologics Evaluation and Research
US Food and Drug Administration

Outline

- Background: FDA Biologics and Effectiveness Safety (BEST) System
- COVID-19 Response
  - Vaccine Safety
    - Federal Inter-Agency Coordination
  - Vaccine Effectiveness
  - Expansion of BEST Infrastructure
- Summary

Back at 12th Sentinel Meeting (October 2020) – Preparation for COVID-19 Response

Preparation for COVID-19 Response Shared at 12th Sentinel Meeting (October 2020)

Current Status – Nov 2021: Studies Completed

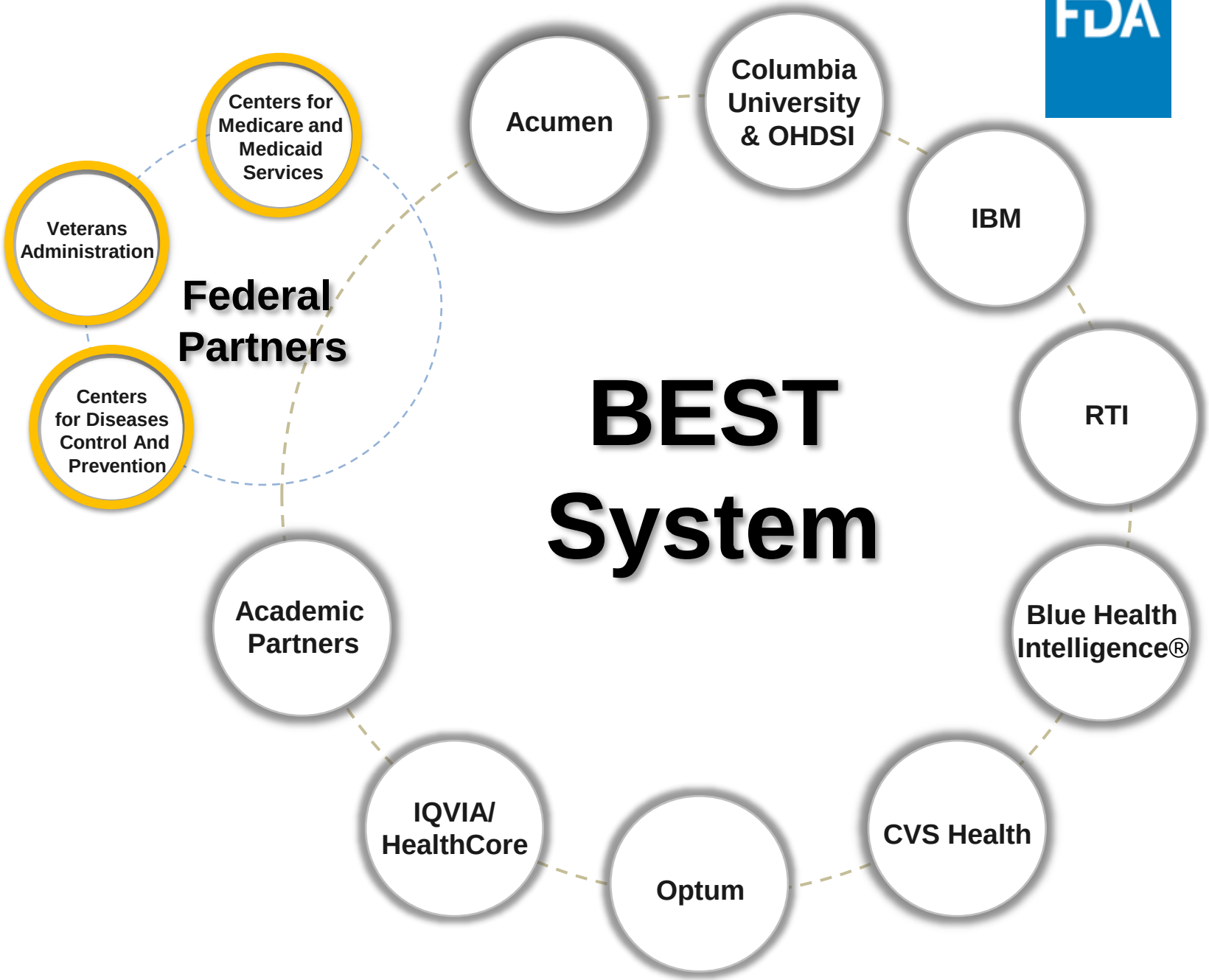
- Linked claims-EHRs
  - Validation of claims-based COVID-19 ICD-10CM diagnoses codes
- EHRs
  - Characterization of hospitalized patients with COVID-19
  - COVID-19 test positivity trends
  - Impact of convalescent plasma on mortality in hospitalized COVID-19 patients
- Claims: FDA-CMS study
  - Risk factors of COVID-19 mortality

Note: EHRs = electronic health records

FDA BEST COVID-19 Response (Nov 2020 – Present)

- Vaccine Safety
- Vaccine Effectiveness
- Expansion of FDA BEST infrastructure

FDA CBER Active Surveillance Program



CBER: Center for Biologics Evaluation and Research
BEST: Biologics Effectiveness and Safety

BEST System Data Sources

Data Source*	Database Type	Number of Patients Covered (Millions)	Time Period Covered
CMS- Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
Blue Health Intelligence	Claims	33.6	2012 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	22	2017 - present
HealthCore	Claims	76	2006 - 2020
CVS Health	Claims	26	2014 - 2020
OneFlorida Clinical Research Consortium - Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium - EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 - 2020
OneFlorida Clinical Research Consortium – Linked EHR Claims	Linked EHR Claims	1.5	2012 - present

*Data lag varies for different databases, and it is approximately 3 months.

COVID-19 Response:

Vaccine Safety

- Signal Detection
  - Near Realtime Surveillance/Rapid Cycle Analyses

- Signal Characterization - including
  - Additional Analysis
  - Cross-check with other federal surveillance systems

- Signal Verification – including
  - Fully adjusted epidemiology studies

Federal Inter-Agency Coordination of COVID-19 Response

Vaccine Safety

- Weekly and biweekly meetings, including,
  - ACIP COVID-19 VaST Work Group Meeting
  - USG Vaccine Safety Meeting
  - FDA/VA leadership meeting
  - FDA/CDC leadership meeting
  - FDA/CMS leadership meeting

- Direct Interactions
  - Rapid communication where needed

Signal Detection:

Near Real-Time Surveillance of COVID-19 Vaccines

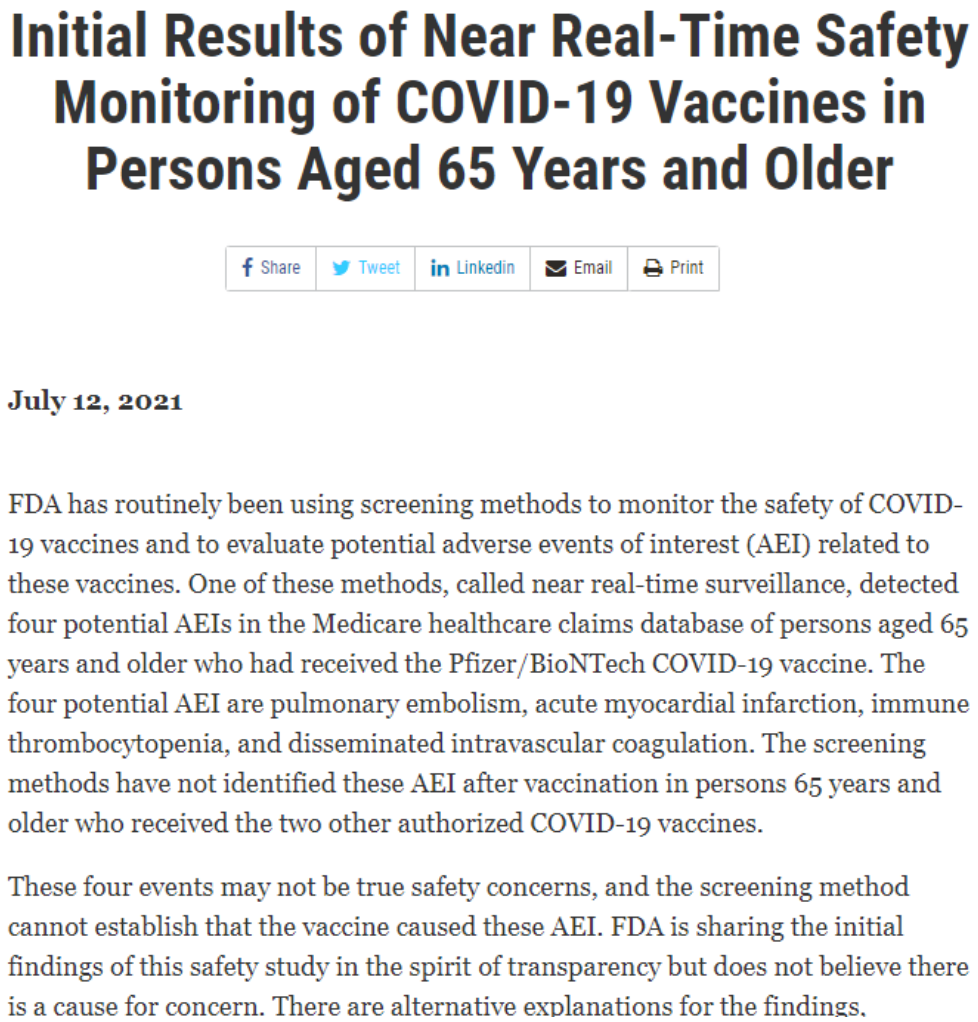
- Sequential testing
  - Post-vaccination rates versus background rates
  - 12-64 years – biweekly, monthly
  - 65+ years – weekly
- Safety signals will be evaluated in robust epidemiological studies

These potential adverse events of special interest have not been associated with COVID-19 vaccines based on pre-authorization evidence

Acute myocardial infarction	Bell's Palsy	Narcolepsy
Anaphylaxis	Encephalomyelitis	Non-hemorrhagic Stroke
Appendicitis	Guillain-Barré syndrome	Pulmonary Embolism
Disseminated intravascular coagulation	Hemorrhagic Stroke	Transverse Myelitis
Deep Vein Thrombosis	Myocarditis/Pericarditis	Immune thrombocytopenia
	Thrombosis with Thrombocytopenia	

Signal Detection:

FDA Communication of FDA-CMS Results



Initial Results of Near Real-Time Safety Monitoring of COVID-19 Vaccines in Persons Aged 65 Years and Older

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July 12, 2021

FDA has routinely been using screening methods to monitor the safety of COVID-19 vaccines and to evaluate potential adverse events of interest (AEI) related to these vaccines. One of these methods, called near real-time surveillance, detected four potential AEIs in the Medicare healthcare claims database of persons aged 65 years and older who had received the Pfizer/BioNTech COVID-19 vaccine. The four potential AEI are pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation. The screening methods have not identified these AEI after vaccination in persons 65 years and older who received the two other authorized COVID-19 vaccines.

These four events may not be true safety concerns, and the screening method cannot establish that the vaccine caused these AEI. FDA is sharing the initial findings of this safety study in the spirit of transparency but does not believe there is a cause for concern. There are alternative explanations for the findings.

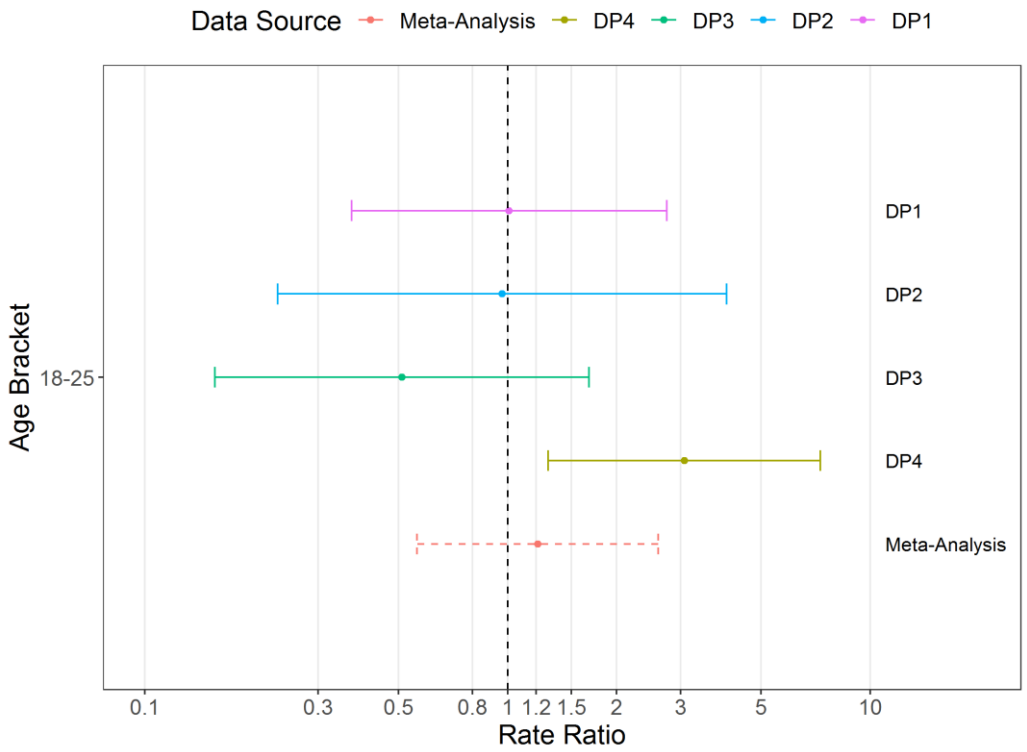
Informing Regulatory Decision-Making

- Transparent communication of safety signals
- Fully adjusted analyses in near completion

Signal Characterization:

Ad-hoc Analyses

Incident Rate Ratios of Myocarditis/Pericarditis (Moderna vs. Pfizer-BioNTech (ref)), males 18-25 years, any dose - Risk window 1-7 days



Supporting Regulatory Decision-Making

- Excess Risks: Input for Benefit-Risk Assessment for mRNA vaccines; VRBPAC* Oct 26, 2021
- Comparative Analyses; VRBPAC* Oct 14 2021

*VRPBAC: Vaccines and Related Biological Products Advisory Committee

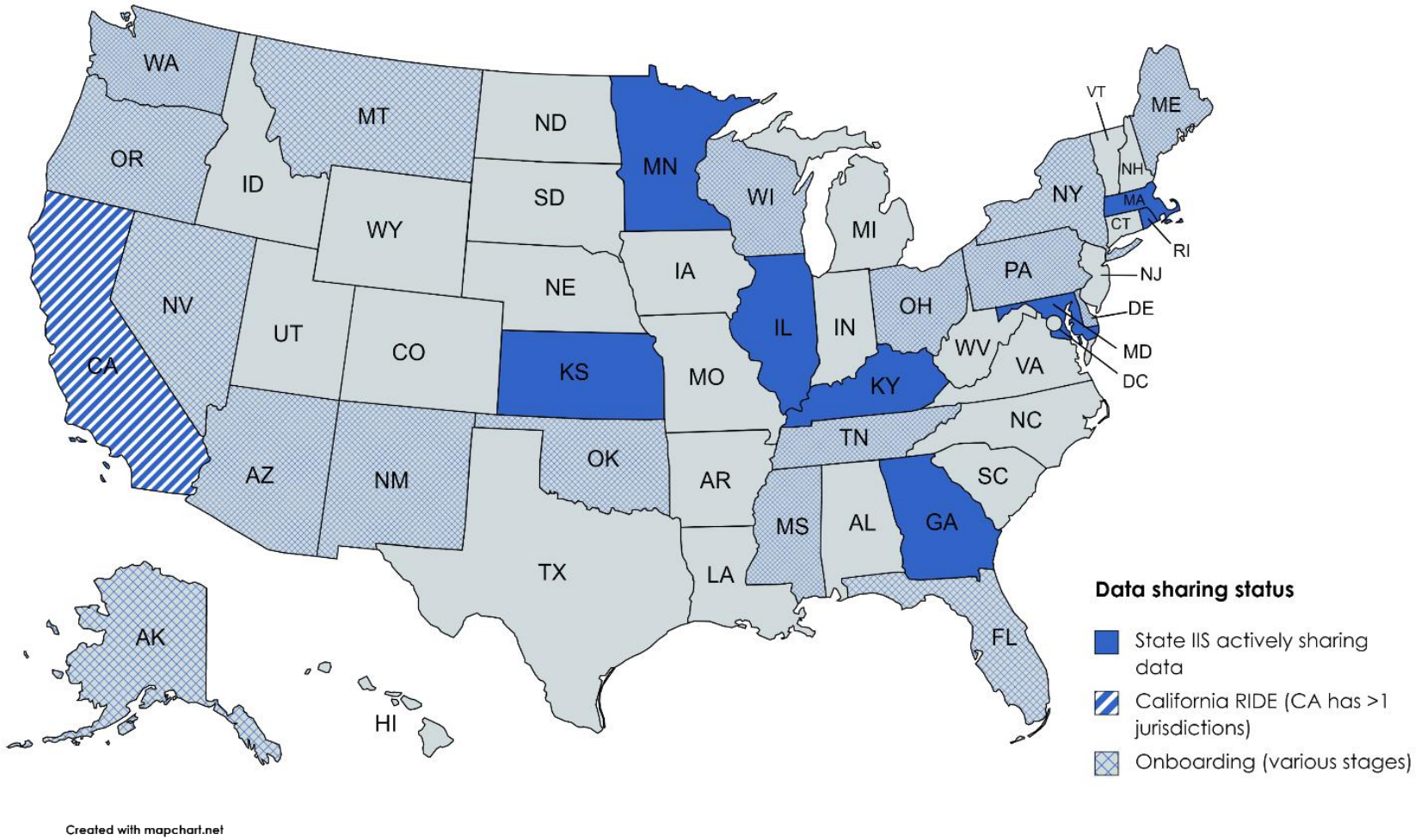
COVID-19 Response:

Expansion of BEST Infrastructure

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

- Infrastructure
  - Augmenting vaccination capture in claims data bases with external data sources

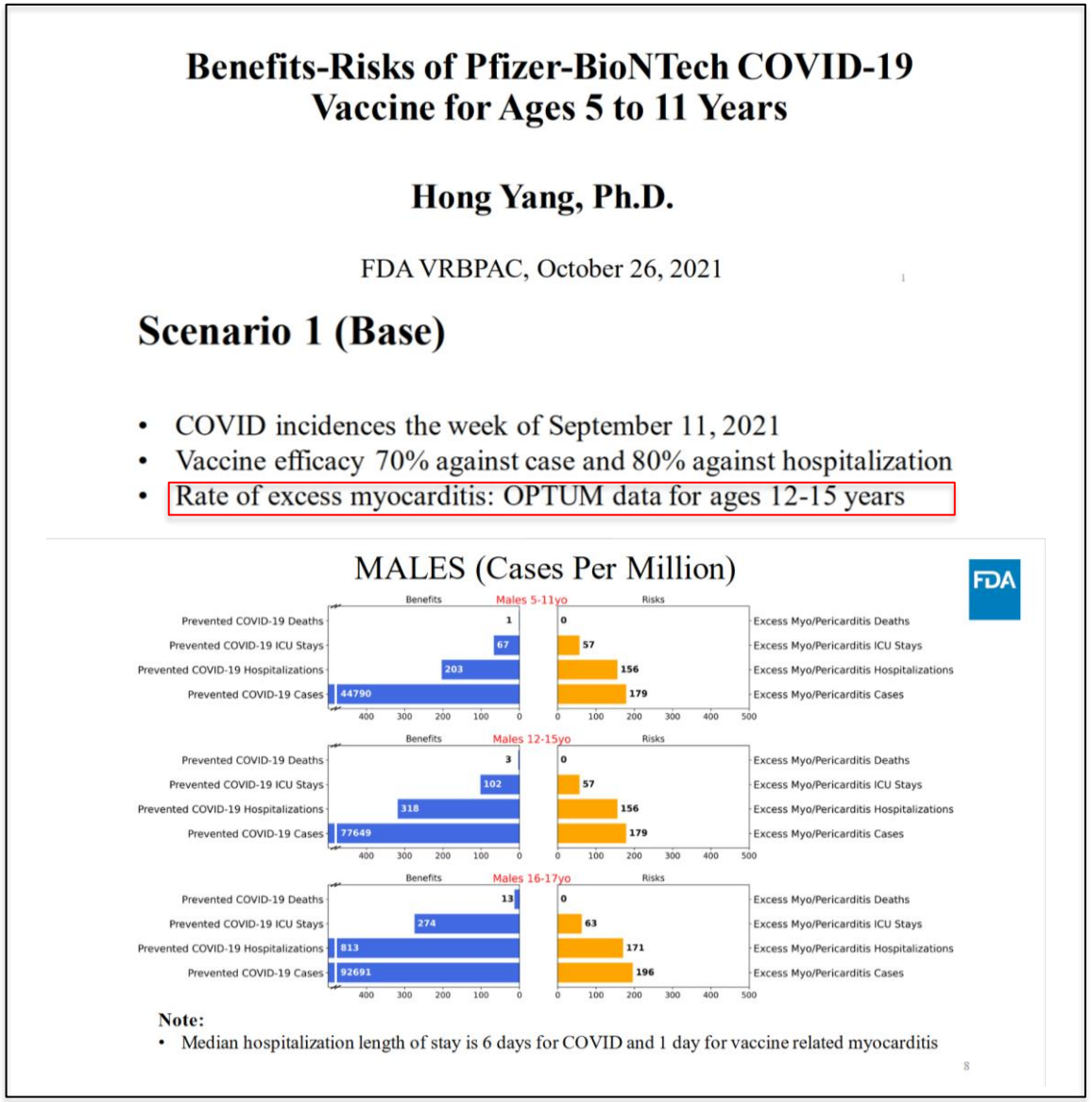
Expansion of BEST Infrastructure for COVID-19 Response



Summary: FDA BEST COVID-19 Response

- Actively monitoring the safety of COVID-19 vaccines
  - Federal Inter-Agency Pandemic Response
- COVID-19 vaccine effectiveness studies
- Expanding infrastructure for COVID-19 pandemic response

Summary: FDA BEST COVID-19 Response



IMPACT

Public Health Communication, e.g.,

- National Vaccine Advisory Committee
- VRPBAC*
- WHO R&D Blueprint Meeting

Supporting Regulatory Decision-Making

- FDA communication of FDA-CMS near real-time surveillance findings
- Informs benefit-risk assessment; VRBPAC October 26, 2021*

*VRPBAC: Vaccines and Related Biological Products Advisory Committee

Acknowledgements

FDA BEST Partners

Acumen

CVS Health

Optum

IQVIA/HealthCore

Blue Health Intelligence®

IBM

PEDSnet, OneFlorida, Explorys, Medstar

RTI

Columbia University/OHDSI

Federal Partners

CDC, CMS, VA

FDA

Steven Anderson

Richard Forshee

Azadeh Shoaibi

CBER Surveillance Program

- Cindy Zhou, Patricia Lloyd, Joyce Obidi, Kristin Sepúlveda, Tainya Clarke

Narayan Nair and CBER/OBE/DE

CBER OBE Colleagues

www.bestinitiative.org

U.S. Department of Veterans Affairs

VA Vaccine Safety Surveillance

13th Annual Sentinel Initiative Public Workshop
November 9, 2021

FRAN CUNNINGHAM, PHARM.D.

DIRECTOR, CENTER FOR MEDICATION SAFETY

ASSOCIATE CHIEF CONSULTANT, PBM

DEPARTMENT OF VETERANS AFFAIRS

VA Healthcare System and Population

- Healthcare system
  - VA Medical Centers: > 150
  - VA Outpatient Clinics: ~1200
  - Frontline employees/volunteers - ~ 400,000
- VA Veteran Population
  - Size - ~6.5M (treated), Enrollees > 9M
  - Longitudinal Care
  - Complex healthcare needs
  - Multiple comorbidities
- Data Sources
  - Data Warehouse
  - Electronic Health Record

VA Vaccine Safety Surveillance System

VA tracks and monitors vaccine adverse events (AEs) to ensure safety and promote continued safe use in Veteran patient population.

VA Uses Two Systems to Track and Monitor AEs

- Passive Surveillance
- Active Surveillance

- Active Surveillance System
  - Identify pre-defined AESIs
  - AESIs – identified and defined in collaboration with federal partners
  - Validate and assess pertinent AEs in near real time utilizing EHR and chart review

Covid-19 Vaccine - Rapid Cycle Analysis (RCA)

- Compare observed to expected number of AESIs
  - Weekly analysis adjusting for sequential tests
- Conduct near-real time chart reviews for assessment of specific events
  - Initial review
    - Rule-out cases
  - Robust chart review
    - Assess outcomes
    - SME review for confirmation
- Dissemination of Results
  - Summary reports
  - Newsletter
  - RCA Presentations
- Full studies conducted

Collaboration with Federal Partners

- Interagency Meetings
  - Weekly
  - Bi-weekly
- AESI definitions
- Outcome definitions and validation tools
- Utilize systems to compare and evaluate potential signals
- Enhance evaluations based on collaboration (e.g. myocarditis/myopericarditis)
- Collaboration enhances response for VA population

Acknowledgements

VAMedSAFE Analytic Team
VA Validation Team
VA COVID-19 Vaccine Safety Committee
VA Subject Matter Experts
Federal Partners – FDA, CDC, DoD

Discussion Questions

- What were some key successes from your inter-agency collaborations for COVID response?
- What are some areas where inter-agency collaborations could be improved for future pandemic response?
- How might inter-agency collaboration enhance BEST's work post-pandemic?
- What can we do to increase coordination between regulatory agencies on study goals and methods? On communicating in a clear and timely fashion on adverse events?
- How might your agencies work to better integrate with public health systems at the state and local levels? What kinds of resources do you need to support that integration?

Break

We will be back momentarily.

The next panel will begin at 12:40 p.m. (U.S. Eastern Time)

Session VI: BEST Collaborator Perspectives

- **Rich Forshee,** U.S. Food and Drug Administration
- **George Hripcsak,** Columbia University
- **John Seeger,** Optum
- **Tom MaCurdy,** Acumen
- **Bradley Layton,** RTI Health Solutions

FDA BEST CONVENER

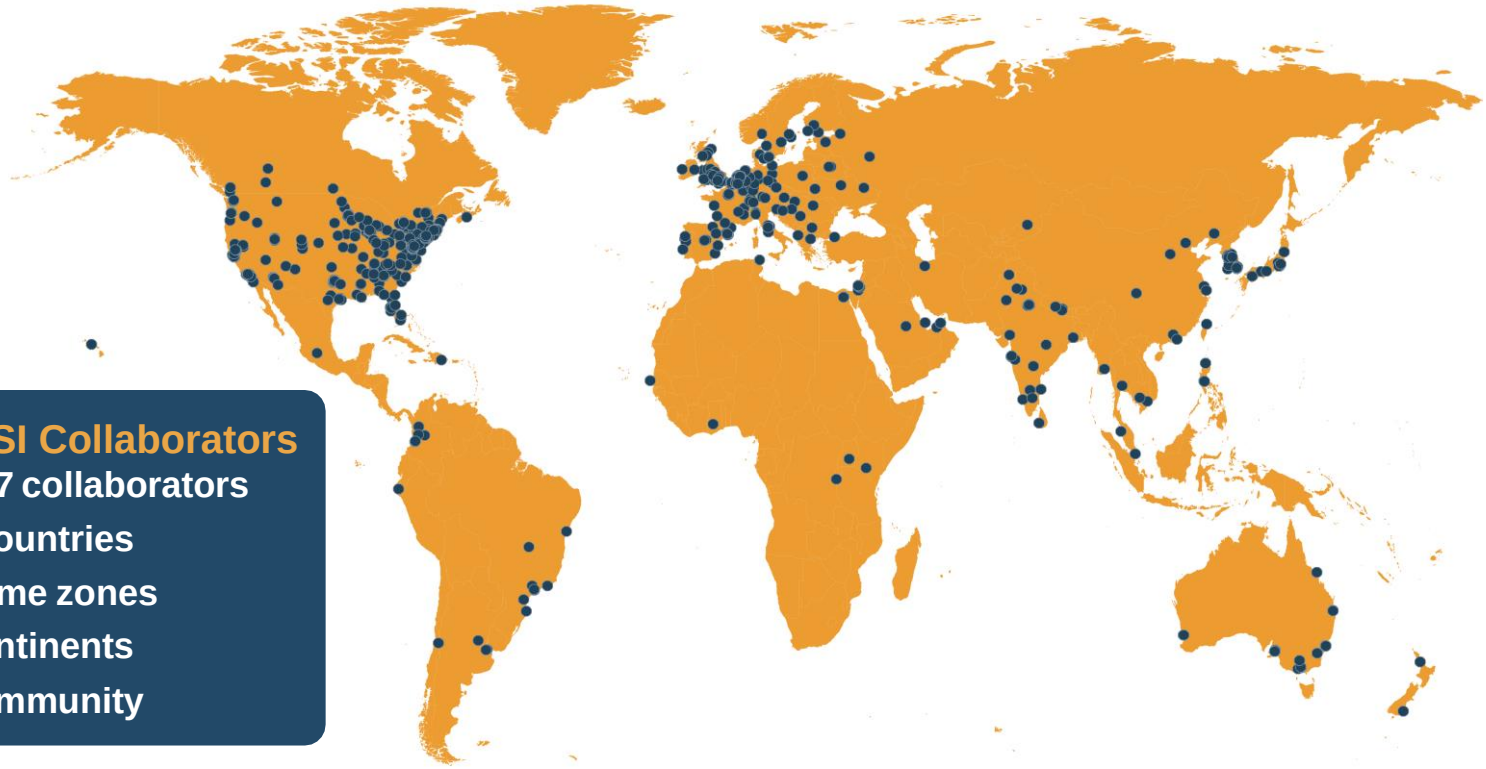
presented by George Hripcsak

Objective: Work collaboratively with the FDA and provide support to the CBER BEST initiative through a convener organization to

1. Host and convene meetings
2. Methods development
3. Conduct training and outreach on BEST
4. Sharing and dissemination of findings and outcomes

Observational Health Data Sciences and Informatics (OHDSI)

Mission: To improve health by empowering a community to collaboratively generate the evidence that promotes better health decisions and better care



OHDSI Collaborators
- 2,367 collaborators
- 74 countries
- 21 time zones
- 6 continents
- 1 community

OHDSI BEST Convener
- Columbia University
- Northeastern U
- UCLA
- Hopkins University

- Experts in informatics, statistics, epidemiology, clinical sciences
- Active participation from academia, government, industry, providers
- Currently records on about **800 million unique patients** in >300 databases
- 344 papers, specific influence on EMA and FDA for COVID-19

Seminars and speakers: vaccine safety

- Viewers from US, France, Canada, Belgium, Singapore, Spain, Switzerland, Taiwan, Uganda, United Kingdom, Norway, Australia

Date	Speaker	Affiliation	Title	Recording Link	Number of participants
03/24/2021	Dr. Daniel Salmon	Johns Hopkins University	Vaccine safety surveillance systems for routine and pandemic immunization programs	https://vimeo.com/528468920/0527eab12a	122
05/05/2021	Dr. Ben Goldstein	Duke	Understanding Informed Presence Bias in EHR Data	https://vimeo.com/545597782/a1d5123678	147
06/16/2021	Bruce Fireman	Kaiser Permanente	Methods for Monitoring the Safety and Effectiveness of COVID-19 vaccines	NA (No permission to record)	131
07/28/2021	Dr. Jessica Gronsbell	University of Toronto	Statistical learning with electronic health records data	https://vimeo.com/580522878	108
09/08/2021	Dr. Robert Platt	McGill University	COVID-19 pharmacoepidemiology in Canada	https://vimeo.com/601207962	122
10/20/2021	Dr. Nicola Klein	Kaiser Permanente	Exploring Vaccine Safety Datalink COVID vaccine rapid cycle analysis (RCA) methods	https://vimeo.com/637546714	206
12/01/2021	Dr. Heather Whitaker	Open University	Vaccine safety evaluation using the self-controlled case series method	NA	NA

Research

BEST: Methods research for FDA BEST initiative

OHDSI: OHDSI methods and clinical research informed by public BEST progress and reported to BEST

BEST: Comment on FDA protocols

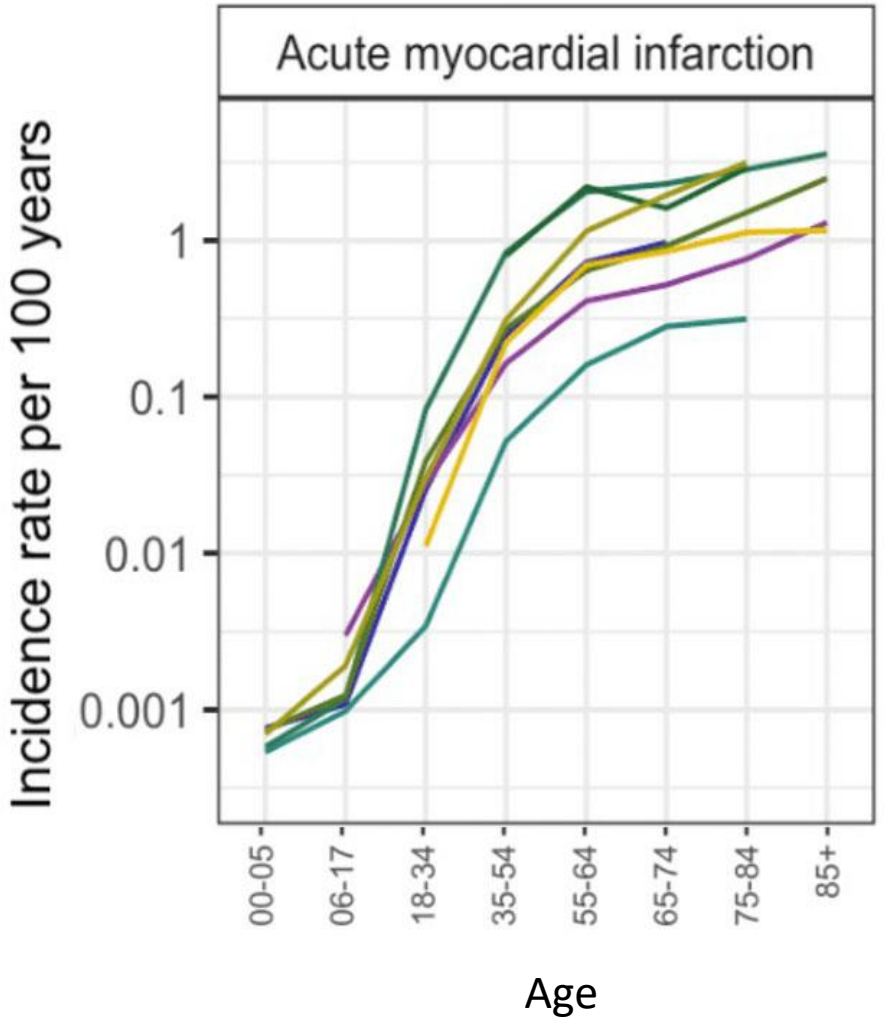
- Background Rates of Adverse Events of Special Interest for COVID-19 Vaccine Safety Monitoring
- Assessment of Risk of Safety Outcomes Following COVID-19 Vaccination

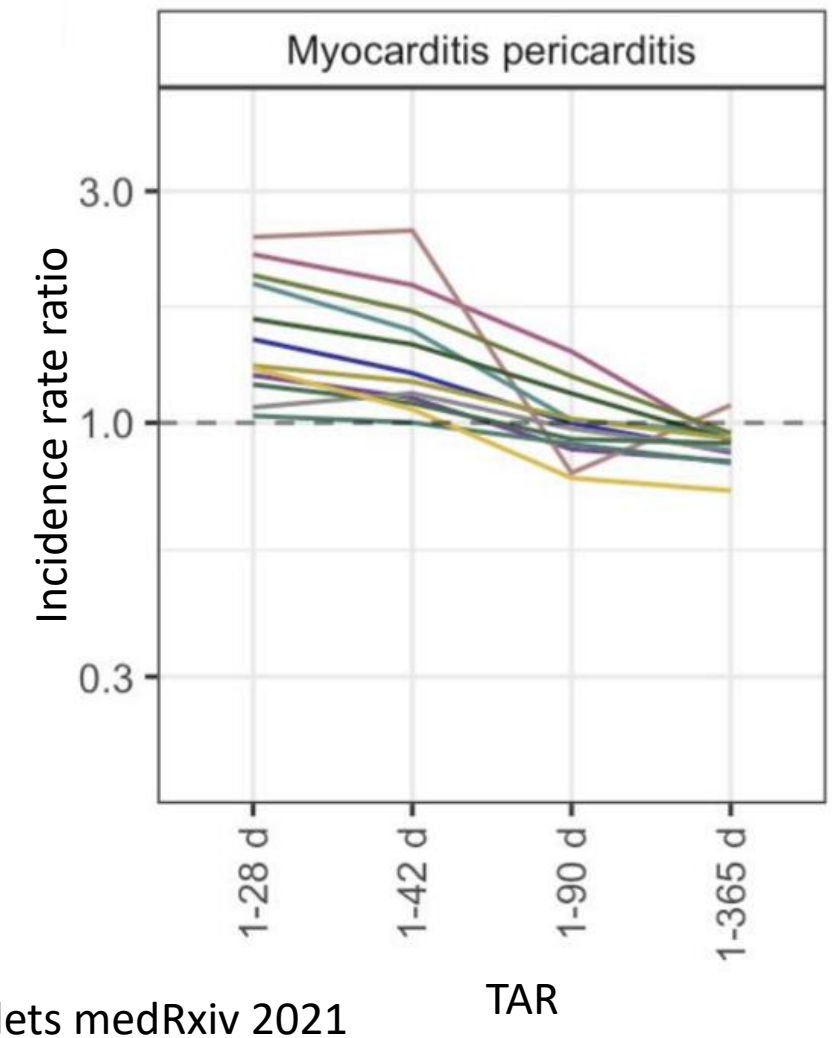
BEST: Sensitivity of background rates to design

- Background rates of vaccine AESI vary by study design
  - Formal pre-specified protocol to quantify bias
  - Based on historical comparison, but biases apply broadly to cohort, SCCS, etc.
- Population
  - age, sex, race
  - heath state (pregnant, chronic disease)
  - health behavior (seeking vaccination)
- Time at risk
  - **anchoring**: in control group, what index date corresponds to vaccination
  - include index date in TAR?
  - duration (2 days to 365+)
  - year and season
  - new cases versus recurrence of AESI

BEST: Sensitivity of background rates to design

- Some biases so large that correction is complicated
- **Anchoring** largely unreported but critical in short TAR
  - random date, visit, healthy visit





Ostropolets medRxiv 2021

OHDSI: Background rates of AESI

Incidence rate (per 100,000 person-years) by age group

Outcome	Sex	1 - 5	6 - 17	18 - 34	35 - 54	55 - 64	65 - 74	75 - 84	85+
Non-hemorrhagic stroke	Female	4 (2-9)	4 (1-12)	18 (4-86)	83 (11-617)	217 (25-1882)	413 (77-2198)	874 (197-3884)	1523 (320-7239)
	Male	6 (2-20)	5 (2-10)	17 (4-75)	119 (21-664)	370 (67-2046)	612 (145-2578)	1063 (242-4662)	1495 (260-8607)
Acute myocardial infarction	Female	<1 (<1-1)	<1 (<1-1)	6 (1-49)	54 (7-430)	171 (24-1235)	312 (76-1280)	617 (184-2069)	1144 (313-4184)
	Male	<1 (<1-1)	1 (1-1)	16 (4-72)	172 (40-740)	467 (135-1611)	653 (214-1994)	934 (290-3013)	1514 (356-6432)
Deep vein thrombosis	Female	12 (3-50)	18 (8-40)	140 (66-298)	306 (117-797)	428 (150-1224)	683 (257-1820)	975 (360-2642)	1206 (407-3572)
	Male	14 (4-55)	14 (6-32)	80 (28-228)	272 (88-836)	499 (194-1289)	695 (250-1931)	831 (254-2720)	1003 (278-3616)
Hemorrhagic stroke	Female	7 (2-28)	5 (2-16)	13 (4-47)	36 (7-175)	77 (15-389)	124 (29-527)	249 (56-1108)	412 (85-1986)
	Male	8 (2-43)	8 (3-24)	19 (5-76)	51 (10-268)	115 (23-562)	178 (49-650)	312 (73-1340)	506 (86-2961)
Pulmonary embolism	Female	1 (<1-36)	3 (1-13)	38 (11-124)	81 (21-309)	125 (33-470)	217 (77-611)	358 (135-951)	427 (154-1184)
	Male	1 (<1-24)	2 (<1-12)	20 (5-80)	80 (20-318)	171 (59-497)	256 (96-683)	349 (119-1030)	398 (124-1277)
Appendicitis	Female	32 (12-84)	154 (55-430)	134 (69-260)	85 (42-172)	66 (28-156)	53 (20-143)	40 (13-124)	35 (12-98)
	Male	38 (17-85)	194 (101-372)	146 (81-266)	88 (49-159)	65 (32-132)	57 (23-144)	47 (15-152)	45 (14-143)
Bells palsy	Female	15 (9-27)	25 (12-51)	44 (23-84)	61 (26-140)	76 (31-184)	86 (29-256)	101 (31-330)	92 (31-274)
	Male	15 (10-24)	21 (13-34)	43 (29-64)	68 (37-125)	86 (43-172)	94 (35-252)	92 (29-291)	100 (34-292)
Anaphylaxis	Female	49 (16-150)	50 (16-154)	39 (16-95)	34 (13-91)	35 (14-85)	29 (11-76)	23 (7-73)	12 (4-36)
	Male	74 (26-209)	56 (18-175)	29 (14-63)	24 (11-53)	25 (11-53)	24 (9-68)	18 (7-49)	10 (2-50)
Immune thrombocytopenia	Female	12 (8-19)	9 (4-21)	14 (6-36)	15 (5-43)	18 (6-53)	25 (8-82)	30 (8-110)	36 (11-118)
	Male	17 (12-23)	8 (3-19)	8 (2-23)	10 (3-35)	19 (6-57)	30 (9-105)	41 (10-170)	56 (15-210)
Myocarditis pericarditis	Female	6 (1-25)	7 (2-21)	16 (8-32)	22 (9-53)	31 (13-72)	35 (12-97)	39 (11-138)	34 (8-143)
	Male	7 (1-32)	11 (5-24)	37 (16-88)	37 (16-87)	45 (20-102)	49 (17-139)	54 (15-193)	41 (9-193)
Disseminated intravascular coagulation	Female	2 (<1-104)	2 (<1-48)	4 (<1-99)	5 (<1-75)	10 (1-89)	14 (2-97)	19 (4-94)	16 (3-82)
	Male	3 (<1-137)	2 (<1-44)	4 (<1-31)	5 (1-56)	12 (1-120)	17 (2-154)	23 (4-152)	24 (5-126)
Encephalomyelitis	Female	5 (2-15)	5 (2-16)	5 (2-19)	6 (1-44)	9 (1-61)	11 (2-62)	12 (2-77)	14 (2-100)
	Male	5 (2-12)	5 (2-14)	5 (2-17)	7 (1-55)	12 (3-58)	16 (3-73)	18 (3-101)	16 (1-180)
Narcolepsy	Female	1 (<1-5)	7 (3-17)	15 (4-52)	11 (2-55)	9 (2-42)	10 (2-46)	8 (1-49)	9 (2-42)
	Male	1 (<1-5)	6 (2-18)	13 (4-40)	10 (2-47)	11 (3-44)	10 (2-50)	10 (2-68)	10 (2-60)
Guillain-Barre syndrome	Female	1 (<1-8)	1 (<1-2)	3 (1-5)	3 (1-11)	5 (1-18)	6 (2-19)	6 (3-16)	7 (2-22)
	Male	2 (<1-18)	1 (<1-3)	2 (1-4)	4 (2-7)	7 (4-14)	8 (3-25)	11 (3-40)	12 (2-68)
Transverse myelitis	Female	1 (<1-3)	1 (<1-3)	3 (1-8)	4 (1-12)	4 (2-13)	4 (2-13)	4 (1-11)	2 (1-9)
	Male	1 (<1-2)	1 (<1-3)	2 (1-6)	3 (1-10)	4 (1-10)	4 (1-11)	4 (1-13)	4 (1-11)

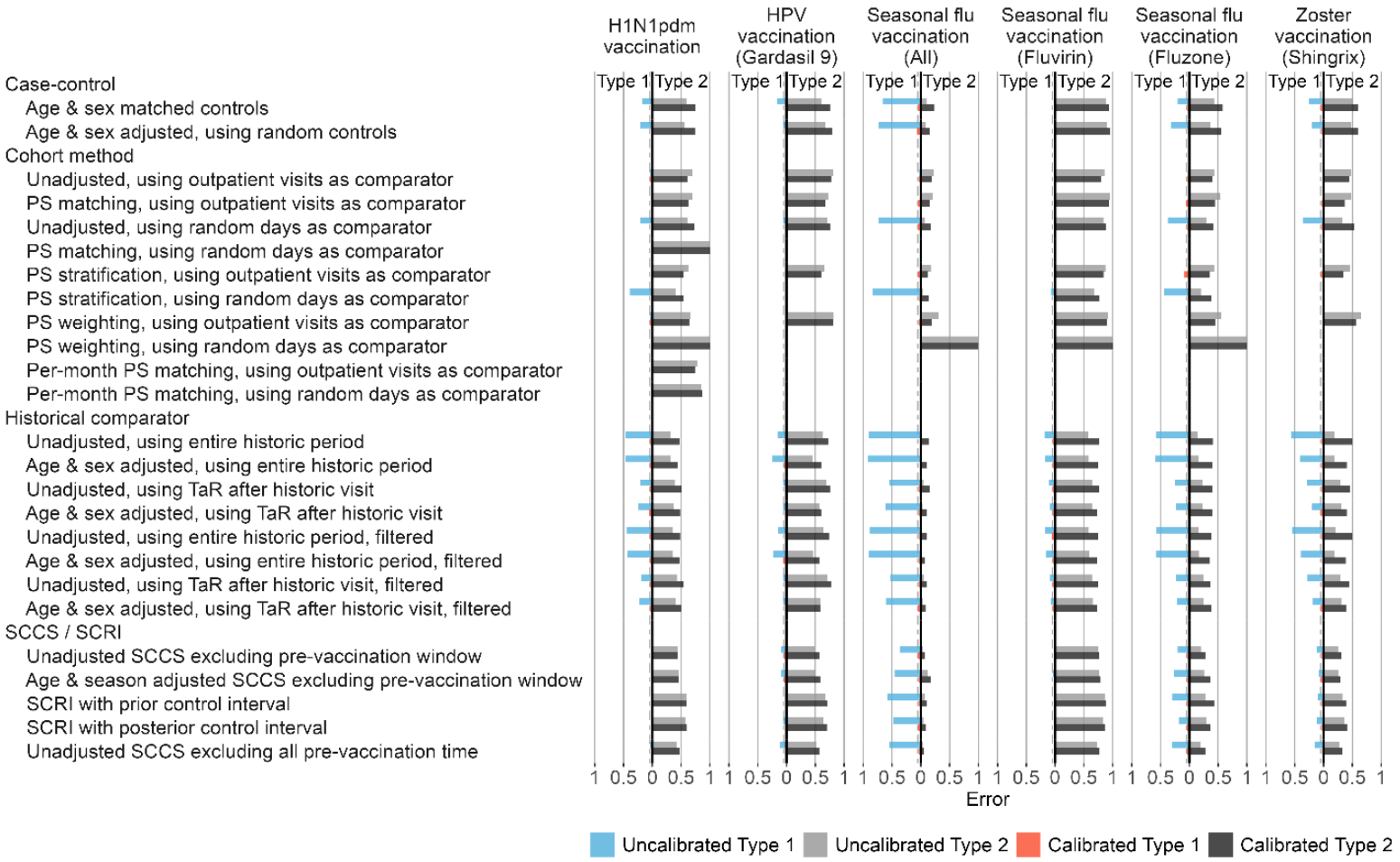
CIOMS Frequency classification

Very rare: <1/10,000
Rare: >1/10,000 AND <1/1,000
Uncommon: >1/1,000 AND <1/100
Common: >1/100 AND <1/10
Very common: >1/10

Li BMJ 2021

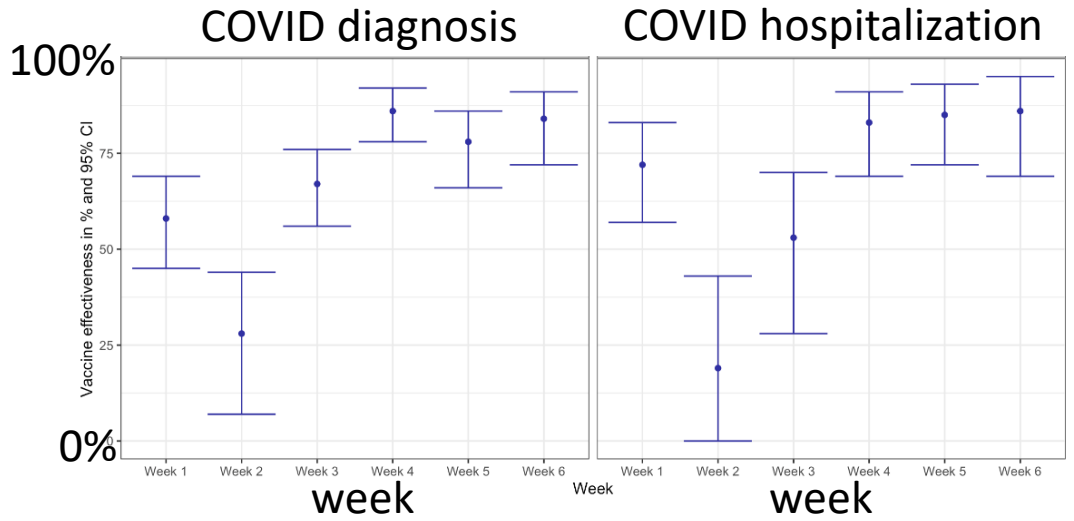
OHDSI: Comparison of vaccine safety methods

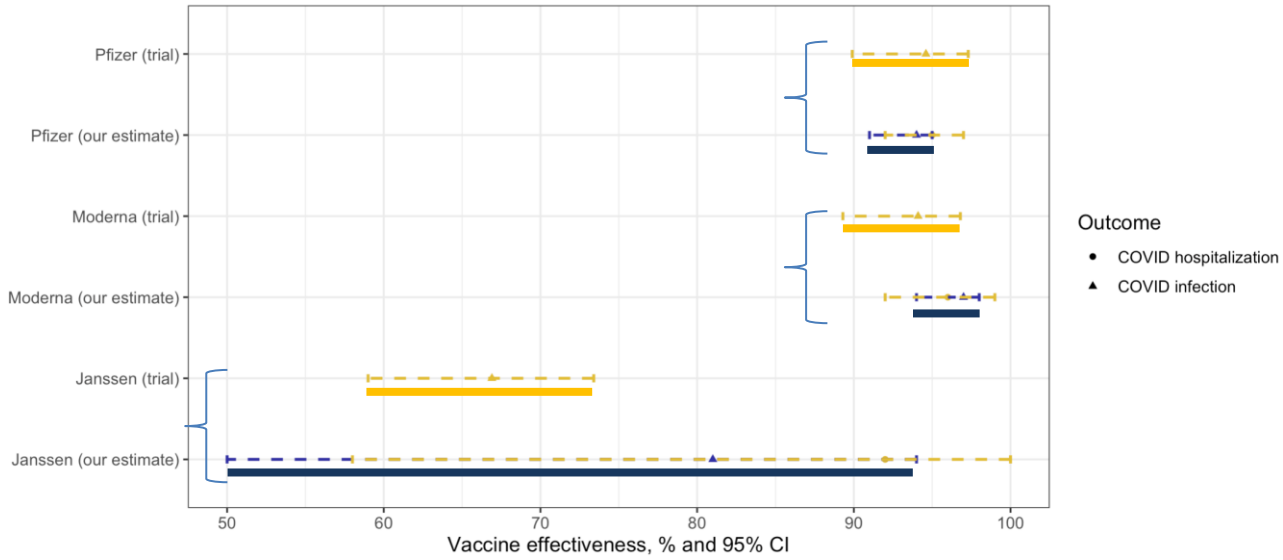
- Methods
  - Case-control
  - Cohort
  - Historical comparator
  - **SCCS**, SCRI
- Large type 1 error
  - **Outweighs other**
  - Calibration



OHDSI: Vaccine effectiveness

- First Columbia, then other OHDSI network members
  - City- and state-wide vaccination records
  - Cohort study to complement other studies
  - Looking at biases and week-by-week
    - Proof of concept
  - Includes chart review
- Anchoring matters, COVID-19 best matches random date
- COVID diagnosis can have high false positive
- Week 1 biases
  - Mild COVID ascribed to vaccination, etc.
- Otherwise accurate match to RCT results for fully vaccinated





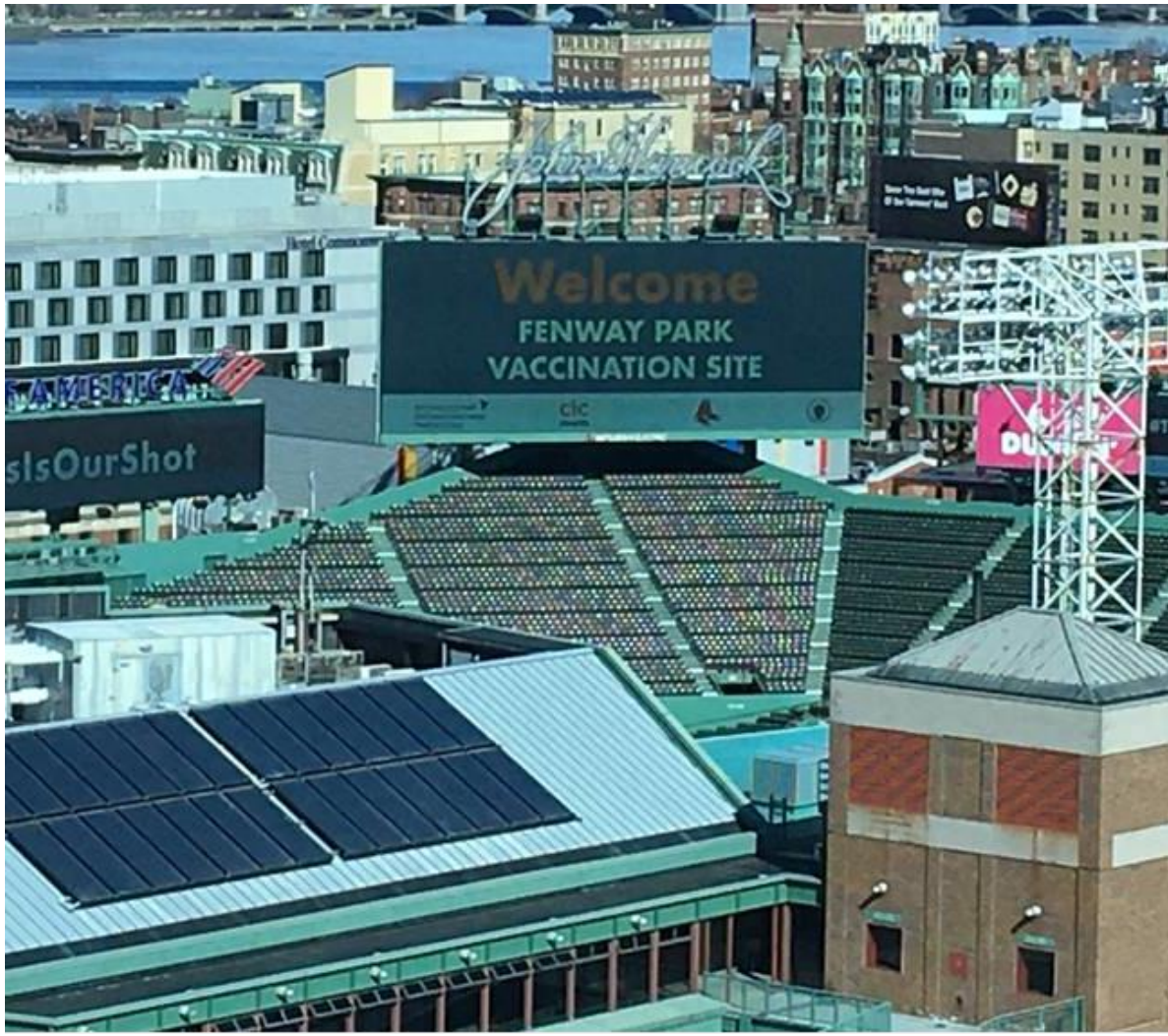
BEST: Bayesian approach to sequential testing

- Landscape analysis and survey of existing Bayesian signal detection methods.
- Develop Bayesian signal detection methods
  - Bayesian decision rule as a signal detection alternative
  - Bayesian sensitivity analysis of causal estimates to weigh evidence from multiple design choices through developing appropriate priors on designs
  - Small-count Bayesian meta-analysis to combine effect estimates across a distributed research network when event outcomes are rare
  - Bayesian treatment effect heterogeneity to establish which subgroups of patients experience differential effects without prespecifying subgroups
- Disseminate results

COVID-19 Vaccine Surveillance Within the FDA BEST Initiative

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

November 09, 2021



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SCHOOL OF PUBLIC HEALTH

Optum Background

UNITEDHEALTH GROUP®

$257.1B
FY 2020 revenue

Ranked **7th**
on the Fortune 500

330,000 Employees

OPTUM Labs
(UHG R&D)

UnitedHealthcare®
Health Benefits

OPTUM®
Health Services

OptumInsight
Life Sciences
Research and consulting, technology and managed services

OptumHealth
Providing effective and lower-cost local care delivery

OptumRx
Empowering better medication choices through synchronized care

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Claims Generation/Lag

- Claims lag arises from multiple stages
  - Provider submission
  - Payer adjudication
  - Database incorporation
- Varies by claim source

Standard Claims Lag	Pre-Adjudicated Claims Lag
1-2 months for Rx	1-2 months for Rx
1-2 months for lab	1-2 months for lab
2-4 months for OP	1-2 months for OP
4-6 months for IP	2-4 months for IP

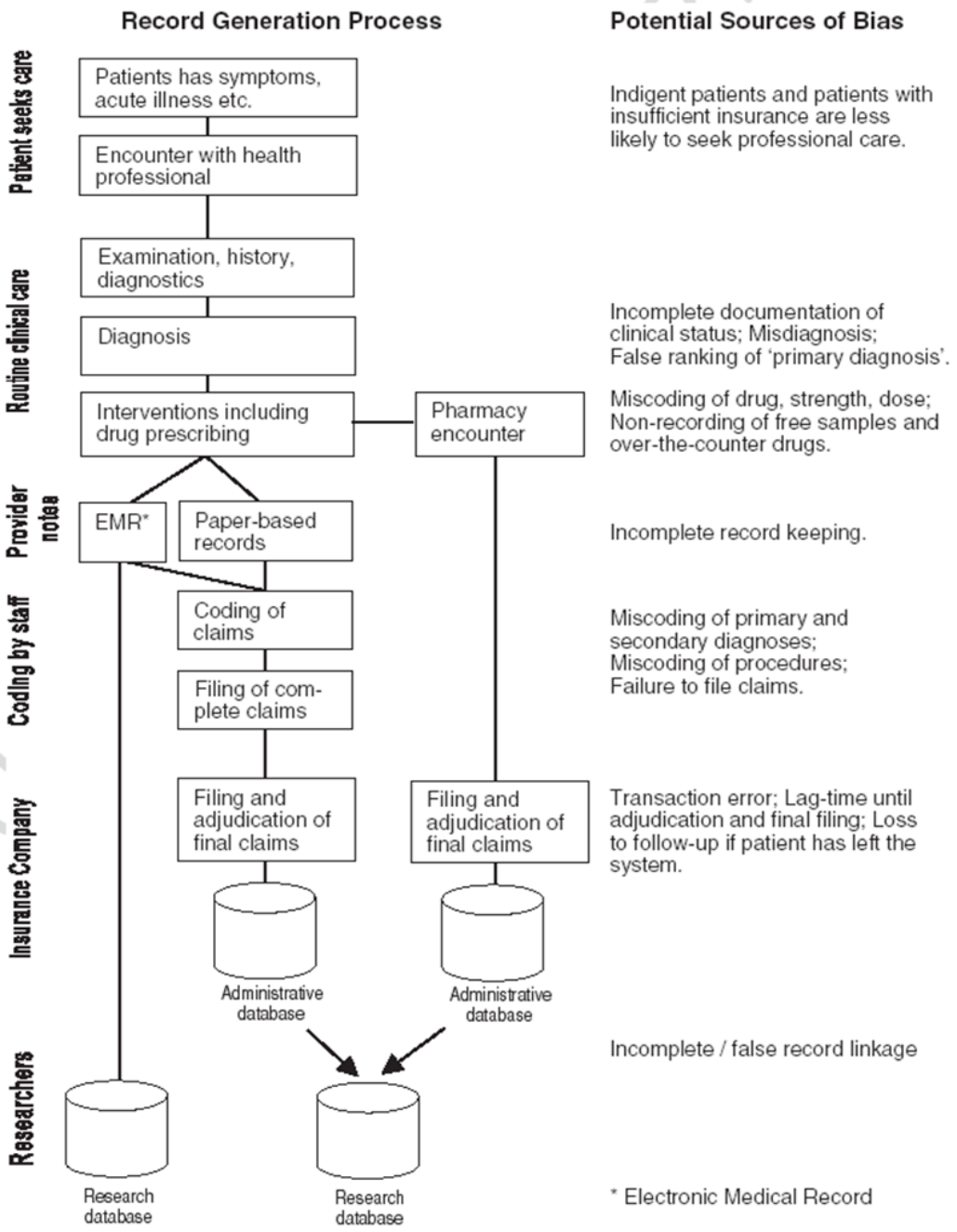

Figure from: Schneeweiss & Avorn. J Clin Epi 2005

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Rapid-Cycle Analysis Concept

- Observe what happens after COVID-19 vaccine
  - Claims for services (diagnosis or procedure codes)
  - Which outcomes to track?
  - Count occurrence of adverse effects (by codes/logic)
- Comparison
  - Are the observed outcomes after vaccination expected?
    - Above or below?
  - "Background" rates – what would have happened
    - Among unvaccinated
    - Concurrently
    - Previously (last year/two years ago)
  - What needs to be accounted for?
    - Person-time, age, sex, seasonality, anomalies (pandemics)

Table 2. Potential AESIs, age groups, settings, clean windows, and risk windows. These AESIs have not been associated with COVID-19 vaccines based on available pre-licensure evidence.

AESI	Age Group of Interest	Setting	Clean Window	Risk Window
Primary Outcomes				
General Population Outcomes				
Guillain-Barré syndrome	All	IP- primary position only	365 days*	1-42 days [14, 15]
Bell's Palsy	All	IP, OP, PB	183 days*	1-42 days [16]
Anaphylaxis	All	IP, OP, PB	30 days*	0-2 days [17, 18]
Encephalomyelitis	All	IP	183 days*	1-42 days [19]
Narcolepsy	All	IP, OP, PB	365 days*	1-42 days† [20-22]
Appendicitis	All	IP,	365 days*	1-42 days [23, 24]
Non-hemorrhagic Stroke	All	IP	365 days*	1-28 days [25, 26]
Hemorrhagic Stroke	All	IP	365 days*	1-28 days [25, 26]
Acute myocardial infarction	All	IP	365 days*	1-28 days [25, 26]
Myocarditis/Pericarditis	All	IP, OP, PB	365 days*	1-42 days [27]
Deep Vein Thrombosis (DVT)	All	IP, OP, PB	365 days*	1-28 days [28-30]
Pulmonary Embolism# (PE)	All	IP, OP, PB	365 days*	1-28 days [28-30]
Disseminated intravascular coagulation (DIC)	All	IP	365 days*	1-28 days [31]
Immune thrombocytopenia (ITP)	All	IP, OP	365 days*	1-42 days [32, 33]
Transverse Myelitis	All	IP	365 days*	1-90 days [34]
Multisystem Inflammatory Syndrome	All	IP	365 days*	1-42 days [35]

Definitions: Clean Window is defined as an interval used to define incident outcomes where an individual enters the study cohort only if the AESI of interest did not occur during that interval. Risk Window is defined as an interval during which occurrence of the AESI of interest will be included in the analyses.

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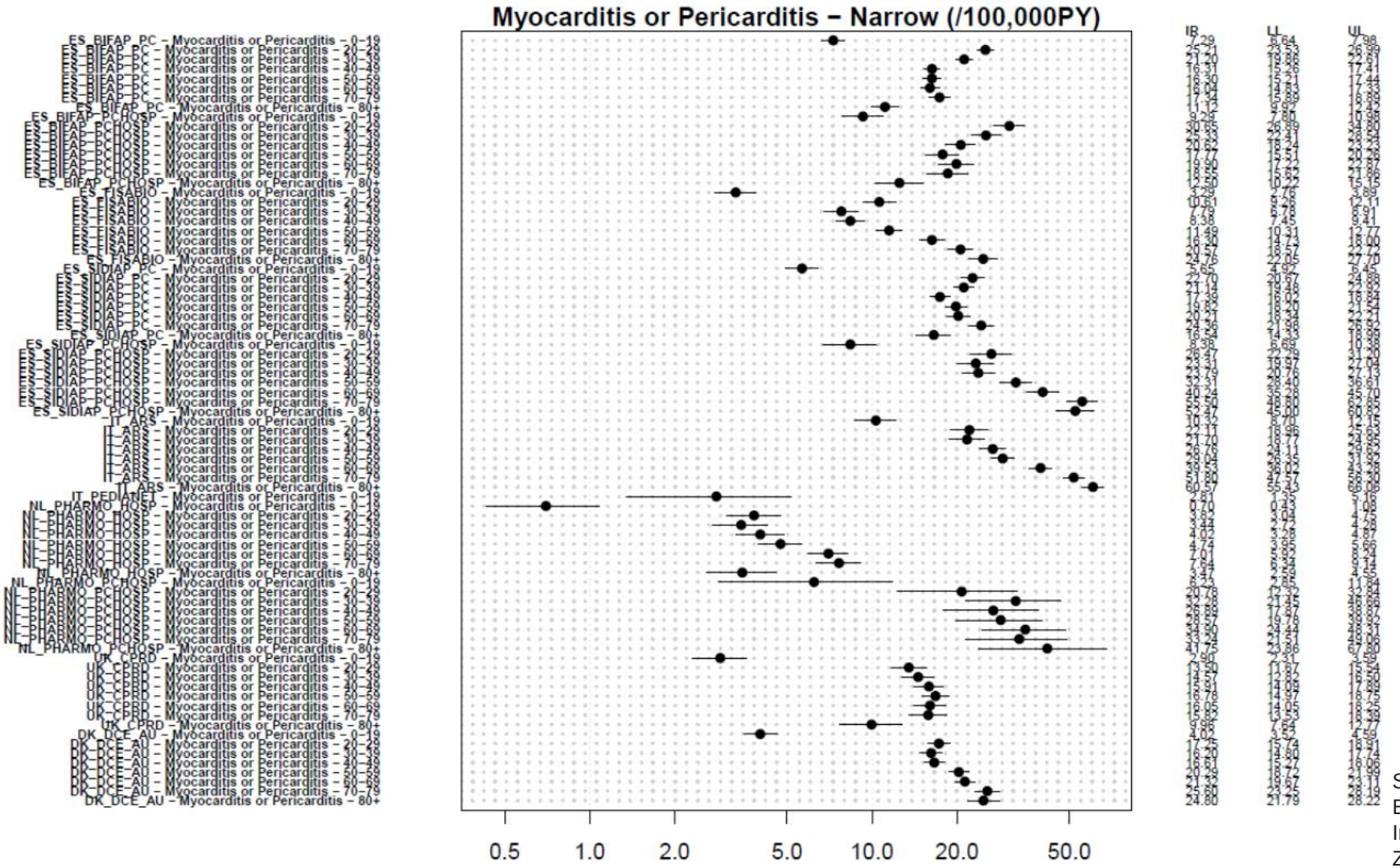
Background Rates



Source: Willame, C; Dodd, C; Gini, R, et al. (2021). Background rates of Adverse Events of Special Interest for monitoring COVID-19 vaccines (2.0). Zenodo. https://doi.org/10.5281/zenodo.5255870

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Pediatric Population, Estimated Percent Coverage, and Pfizer-BioNTech COVID-19 Vaccine Doses by Age in Optum Administrative Claims

	0-4 Years	5-11 Years	12-15 Years	16-17 Years
Pediatric Population in Administrative Claims[1]	1,020,020	1,362,267	891,228	461,513
Census Estimate of US Population (2020)	19,301,292	28,384,878	16,783,176	8,352,767
Optum Estimated Percent Coverage of US Population	5.3%	4.8%	5.1%	5.5%
Pfizer-BioNTech COVID-19 Vaccine Doses[2]	-	-	405,534	209,091

[1]Number of enrollees ever enrolled in the Optum Research Database from 12/22/2020 to 9/18/2021
[2]First, second, and third or unknown/unspecified doses through 9/18/2021

Source: Wong HL. 2021. Vaccines and Related Biologic Products Advisory Committee meeting. October 26, 2021

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Adverse Events of Special Interest	Risk Window (days)	Safety Signal During Testing
Acute Myocardial Infarction	1-28	No
Anaphylaxis	0-1	Yes
Appendicitis	1-42	No
Bell's Palsy	1-42	No
Common Thromboses* with Thrombocytopenia	1-28	No
Unusual Site Thromboses** with Thrombocytopenia Syndrome	1-28	No
Deep Vein Thrombosis	1-28	No
Disseminated Intravascular Coagulation	1-28	No
Encephalomyelitis	1-42	No
Guillain-Barré Syndrome	1-42	No
Hemorrhagic Stroke	1-28	No
Immune Thrombocytopenia	1-42	No
Multisystem Inflammatory Syndrome	1-42	No
Myocarditis/Pericarditis	1-42	No
Narcolepsy	1-42	No
Non-Hemorrhagic Stroke	1-28	No
Pulmonary Embolism	1-28	No
Transverse Myelitis	1-42	No

Data through 9/18/2021

*acute myocardial infarction, deep vein thrombosis, pulmonary embolism, hemorrhagic stroke, non-hemorrhagic stroke

** cerebral and abdominal

Source: Wong HL. 2021. Vaccines and Related Biologic Products Advisory Committee meeting. October 26, 2021

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Extensions and Enhancements

- Move beyond surveillance
- Contextualize
- Address competing hypotheses
- Address exposure misclassification

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Thank You!

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SCHOOL OF PUBLIC HEALTH

Leveraging BEST Data Network to Support Pandemic Response

Acumen, LLC

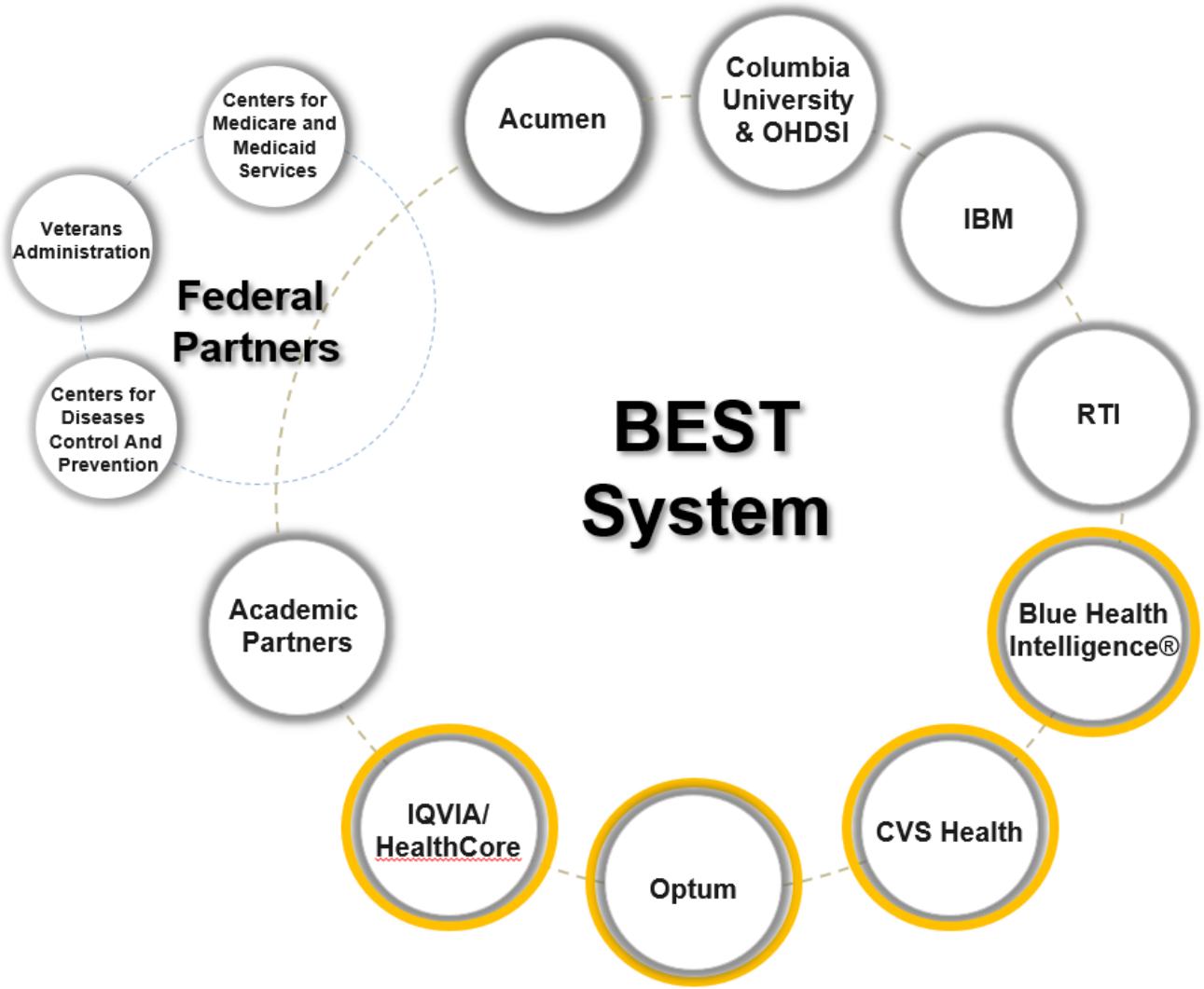
November 9, 2021

Presentation Outline

1. **Overview of BEST data network**
2. **Real-time monitoring of COVID-related measures during the pandemic**
3. **Near real-time surveillance of COVID-19 vaccines**

BEST Data Network

FDA CBER Active Surveillance Program



CBER: Center for Biologics Evaluation and Research
BEST: Biologics Effectiveness and Safety

BEST Distributed Data Network

- Flexible system designed specifically for CBER surveillance of biologic products
- Commercial claims data sources and partners:

Data Partner	Blue Health Intelligence	CVS Health	HealthCore/ IQVIA	IBM	Optum
Data Source	BCBS Health Plans	Aetna	Anthem	MarketScan	United

- Protocol development (e.g., background rates for historical comparators, active monitoring master protocol)
- Implementation:
  - Distribute standardized coding packages
  - Conduct rapid cycle analysis (RCA) sequential testing to identify elevated risks
- Conduct medical record reviews to validate cases identified in claims

Acumen Serves Two Roles in BEST

- Acumen manages the BEST Data Coordination Center on behalf of CBER
  - Coordination Center is a distributed data network for commercial claims databases
  - Coordinates BEST data partners by facilitating and validating their transition into a common data framework (OMOP CDM or standard analytic file)
  - Coordinates BEST research activities (protocol development, code development, results review, and deliverable production)

- Acumen maintains large bodies of claims databases and analytical capacities directly supporting CBER in its post-market surveillance activities

CBER's Near Real-Time Surveillance Capacities

- Acumen maintains a unified data center and analytical capacities to work closely with CBER to monitor disease incidence and safety of biologics
- Data sources include
  - **Medicare:** 100% claims updated daily for FFS and weekly for Medicare Advantage and drug claims
  - **Medicaid:** 100% claims updated monthly
  - **CMS assessment data:** 100% of clinical and functional attribute records for all patients in nursing homes and HHAs, updated weekly
- Medicare claims data sufficiently informative to conduct analysis about 10 days after service
- Analytical tools developed to use Medicare data to conduct near real-time monitoring of any form of health event measurable through claims

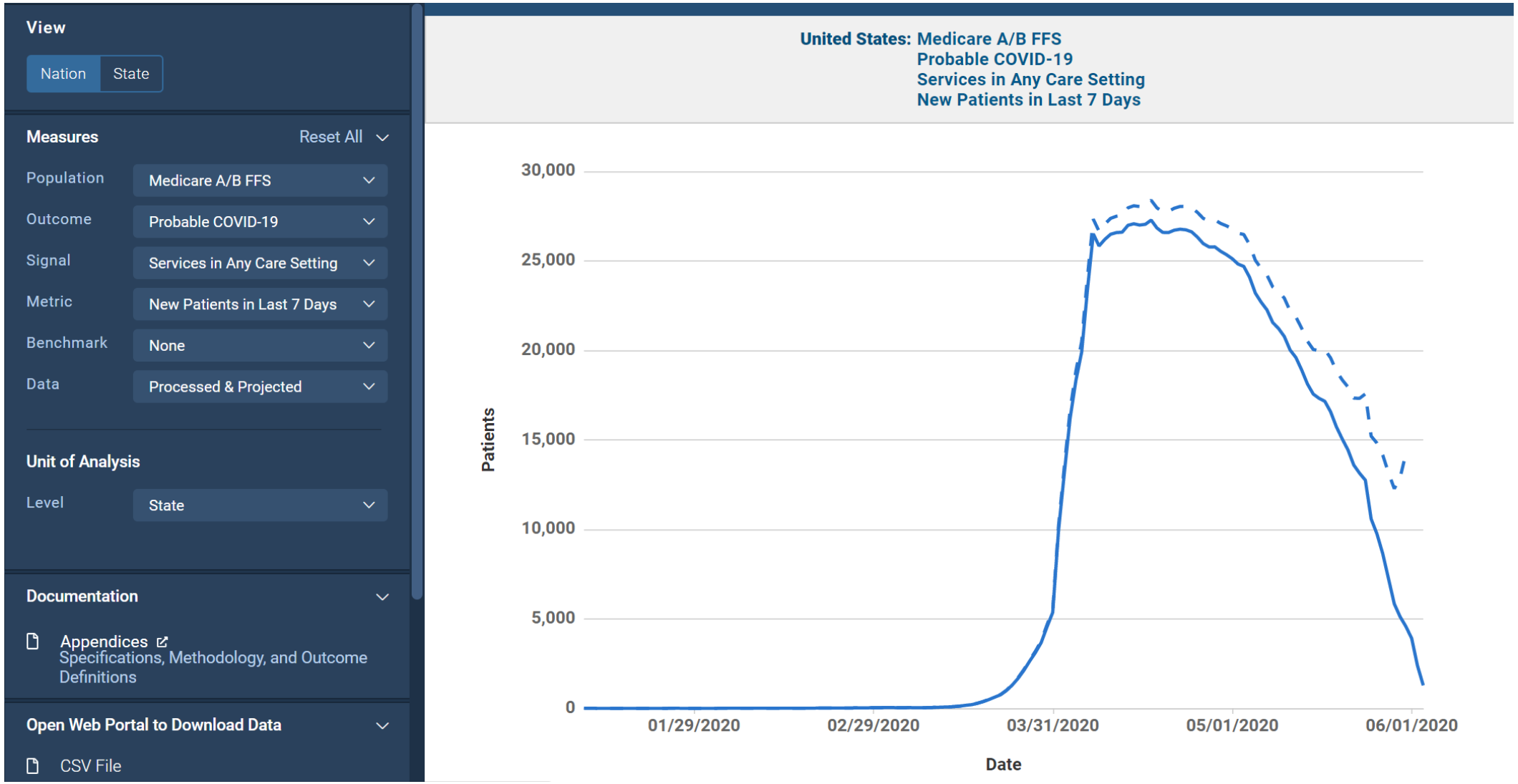
Presentation Outline

1. BEST distributed data network
2. **Real-time monitoring of COVID-related measures during the pandemic**
3. Near real-time surveillance of COVID-19 vaccines

CBER's Surveillance Activities During the COVID Pandemic

- CBER has supported development of near real-time monitoring frameworks for more than a decade, principally in area of influenza vaccines
- CBER immediately implemented this framework at the onset of the COVID-19 pandemic to track disease intensity and progression
  - Mapping temporal and spatial trends at census track, county, state and national level
  - Measured COVID-related events stratified by population, care setting, and evaluated using different metrics

Probable COVID-19 Cases Among Elderly in Nation
(Medical Services in Any Care Setting)



Probable COVID Cases Among Elderly in County
(Medical Services in Any Care Setting)

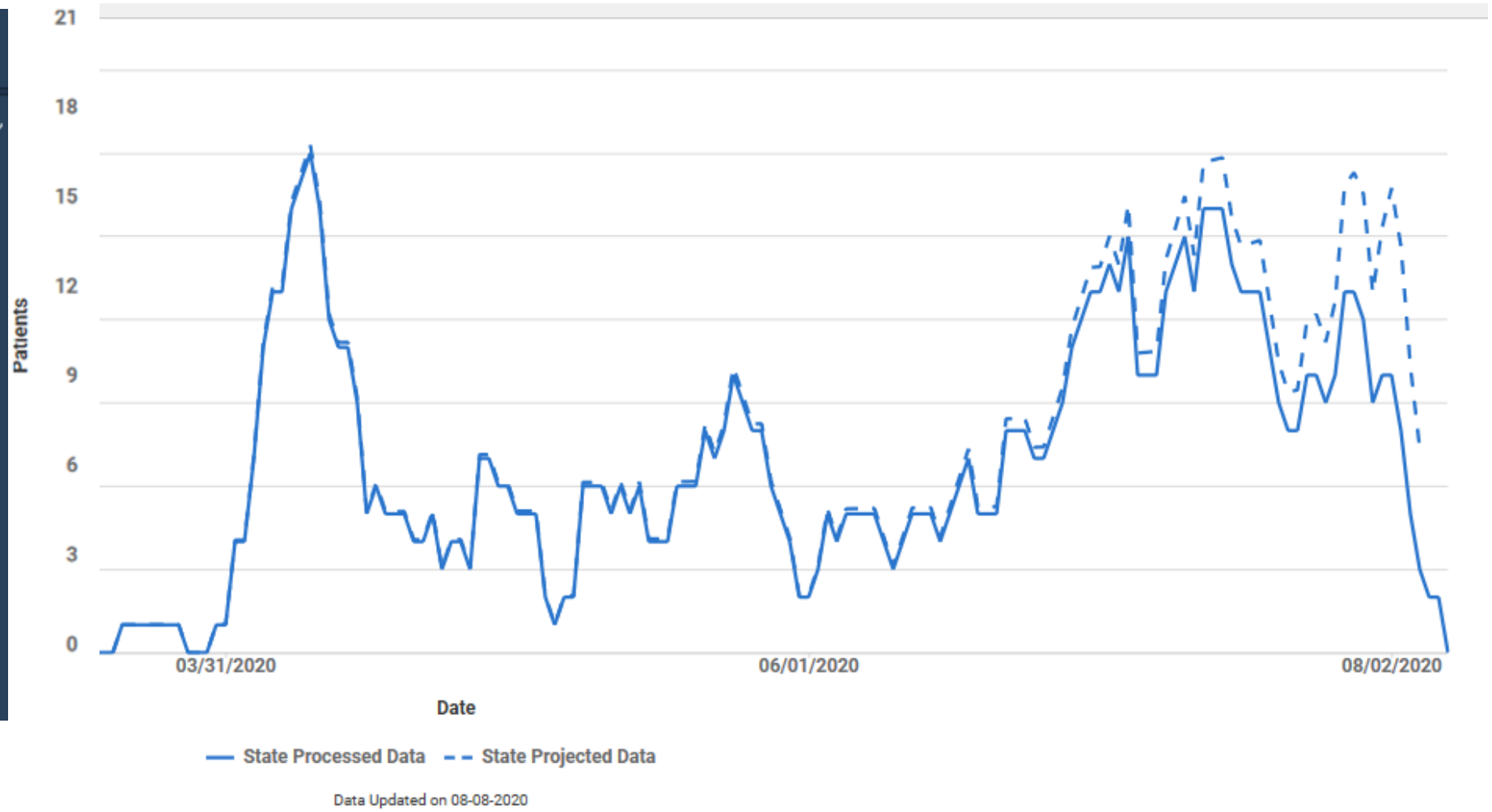
Wyoming

Measures

Population	Medicare A/B FFS
Outcome	Probable COVID-19
Signal	Services in Any Care Setting
Metric	New Patients in Last 7 Days
Benchmark	None
Data	Processed & Projected

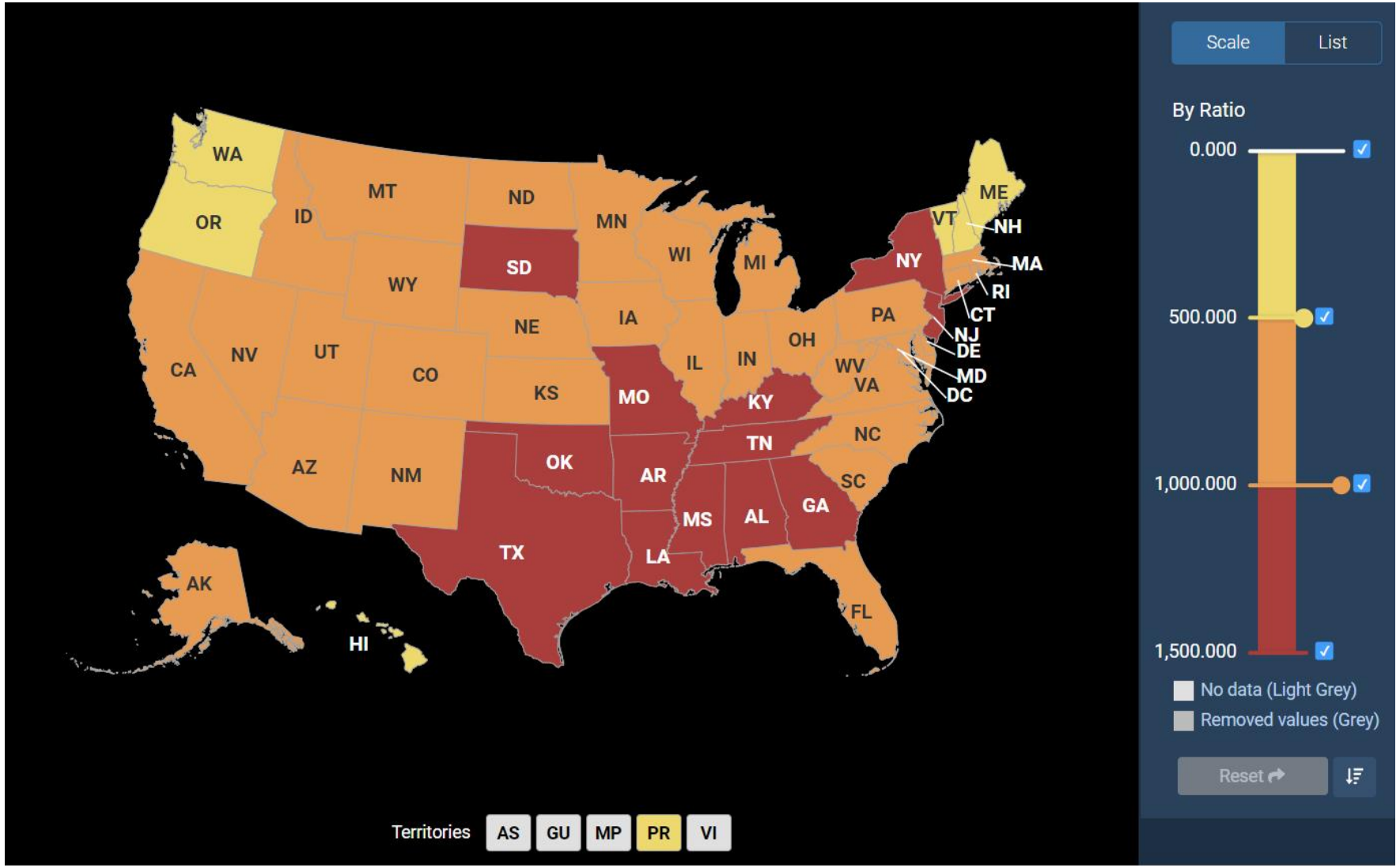
Unit of Analysis

Level	County

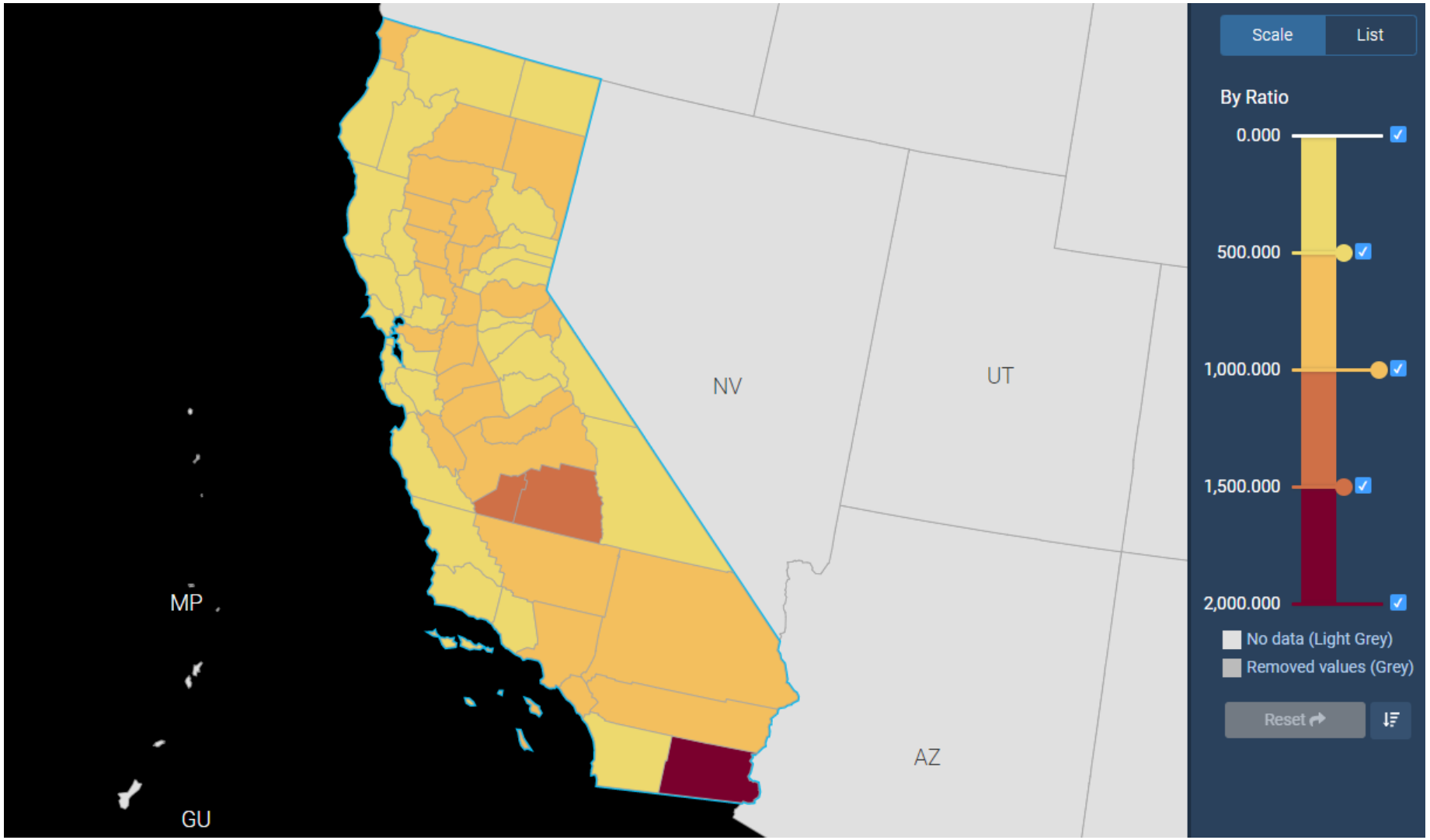


ACUMEN

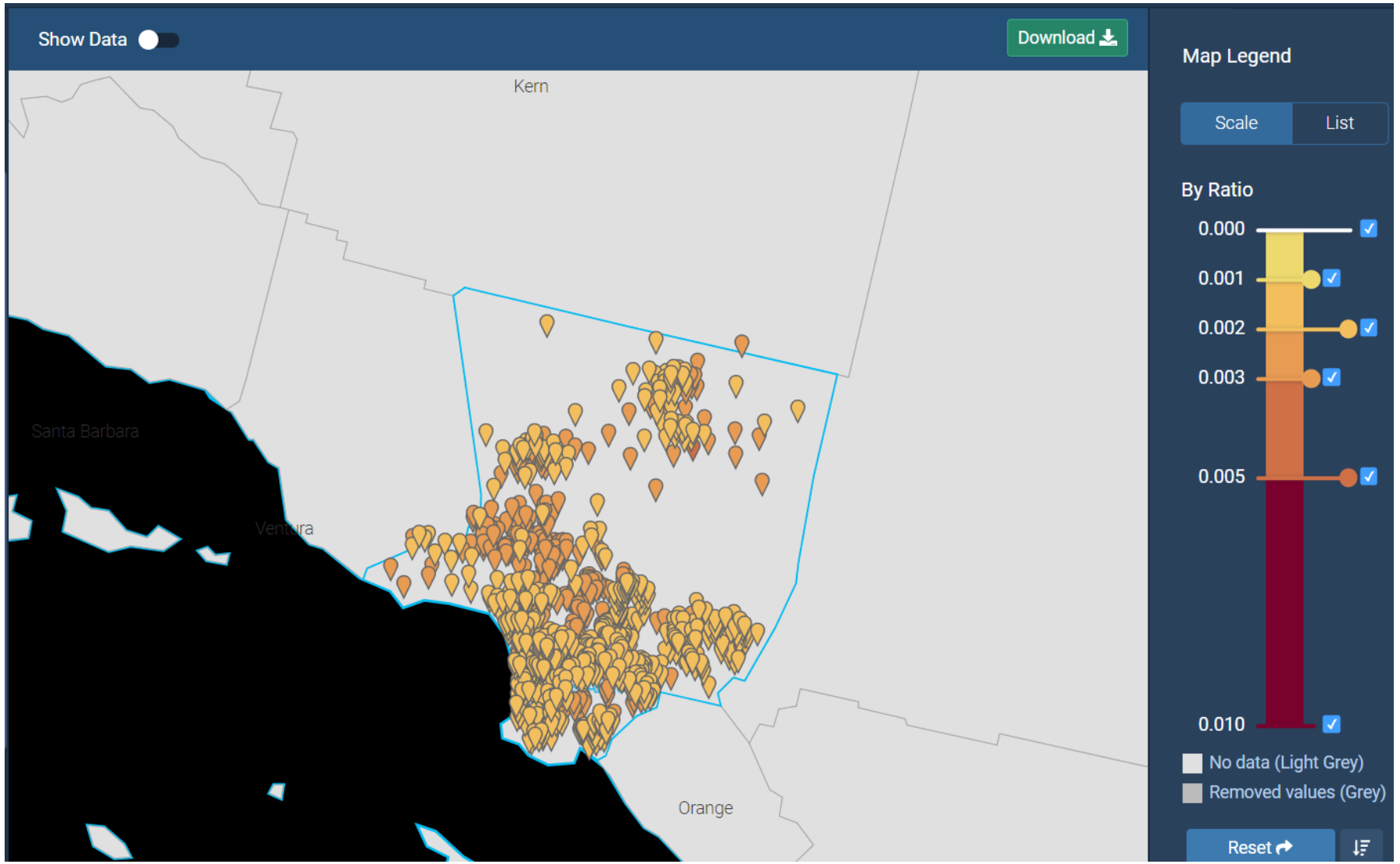
National Map of Probable COVID-19 Case
(Rates per 10,000)



California Map of Probable COVID-19 Cases
(Rates per 10,000)

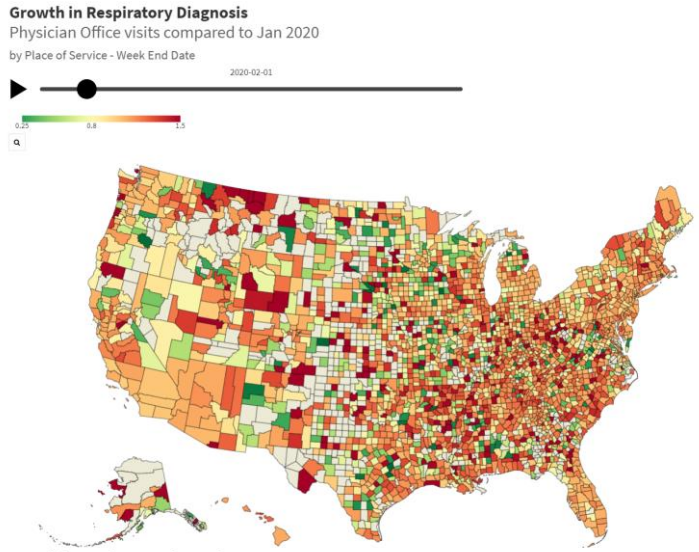


COVID-Like Illness in Los Angeles County, CA
(Rates per 10,000)

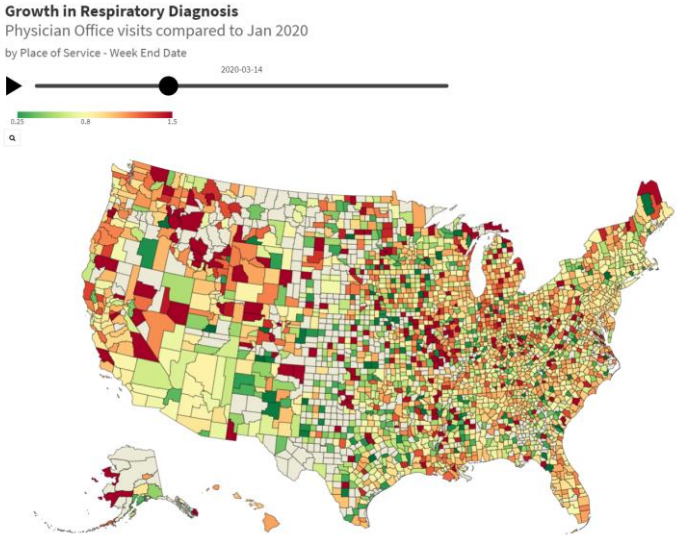


Daily Tracking of Medical Service Utilization: Growth in Respiratory Diagnoses

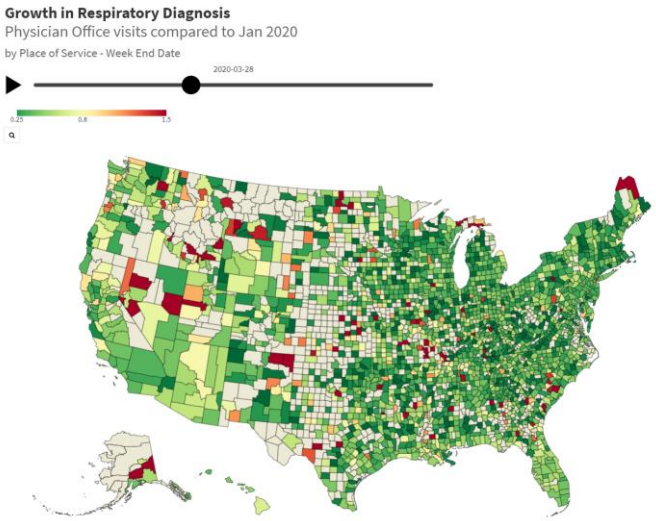
Feb. 1



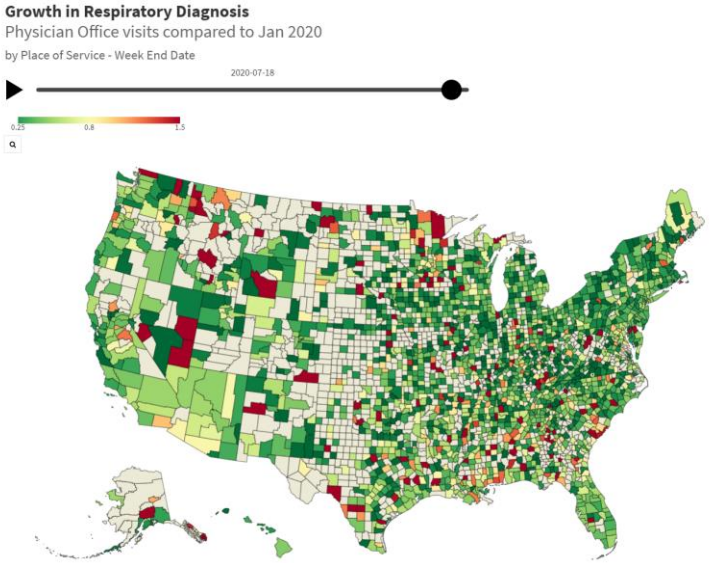
Mar. 14



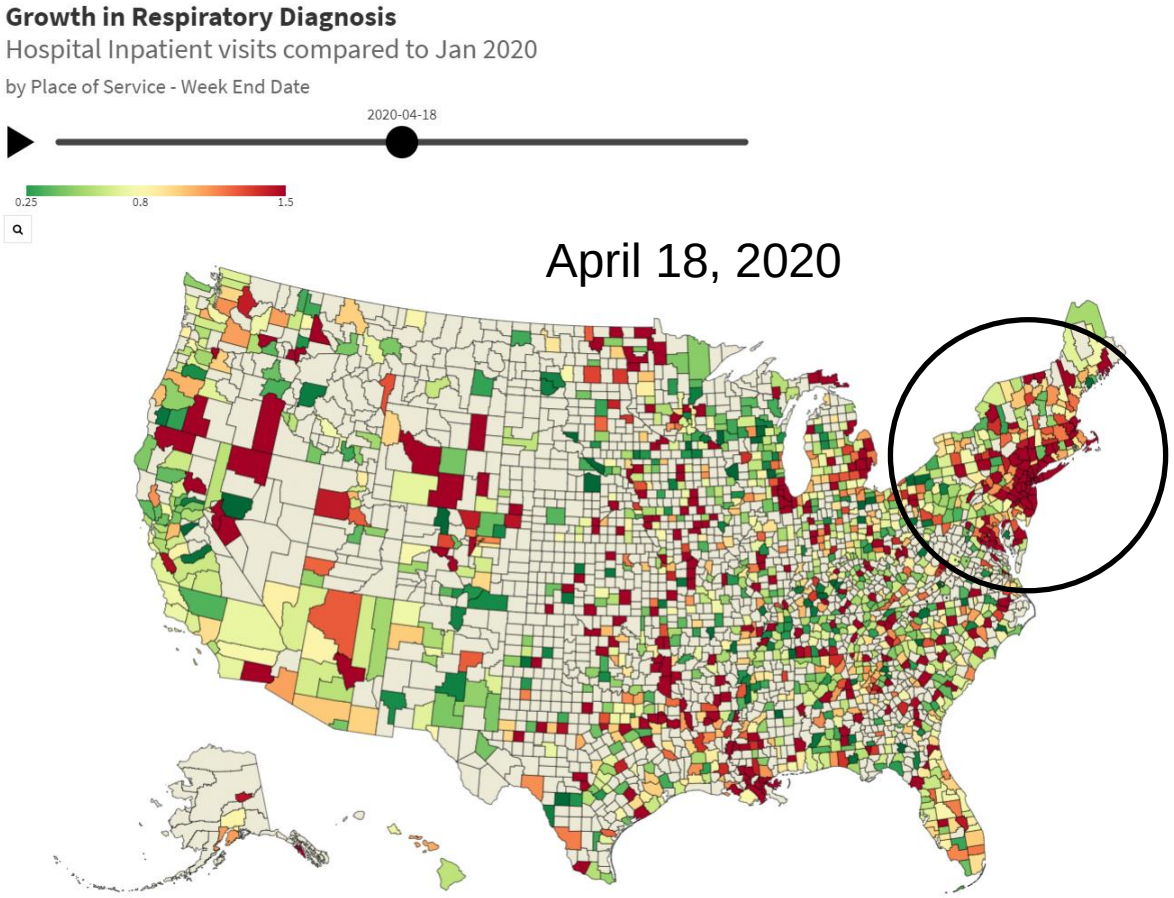
Mar. 28

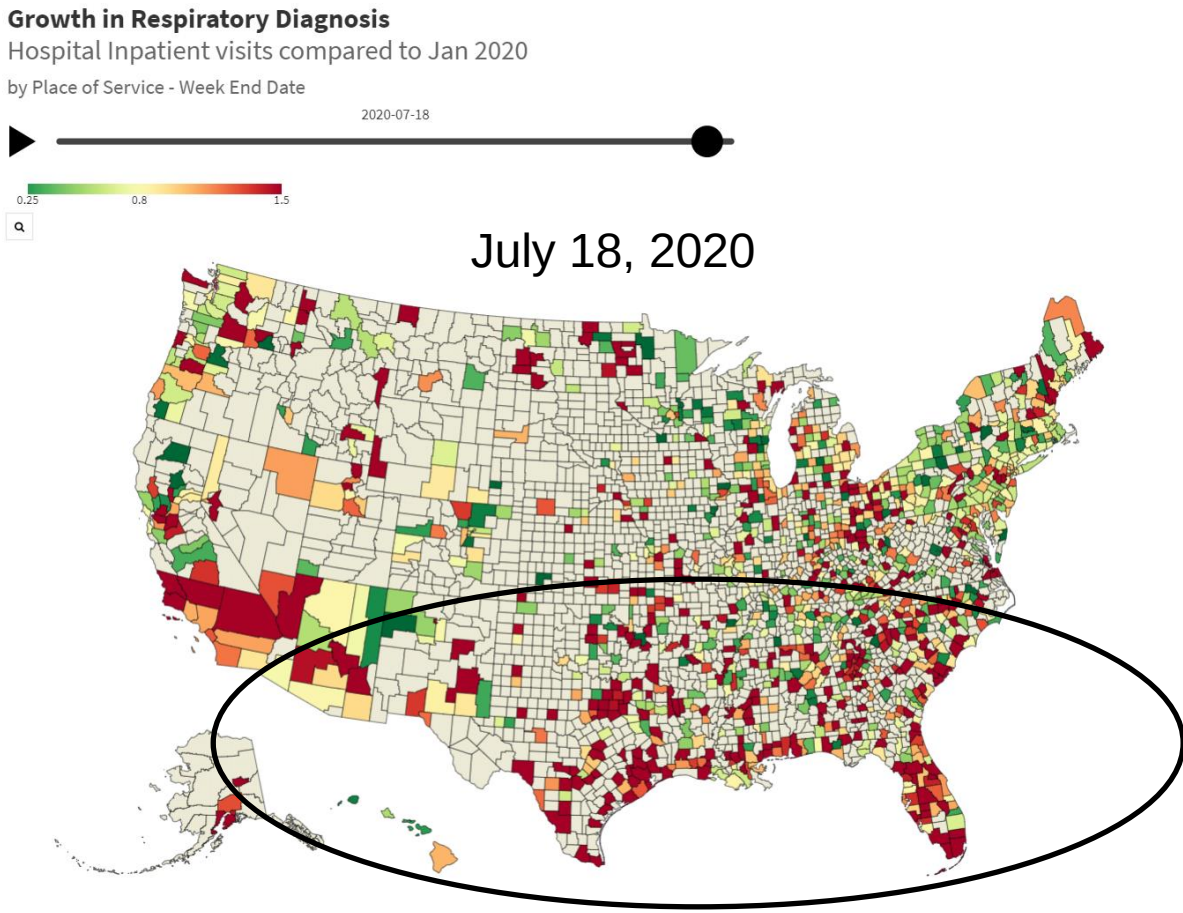


July 18

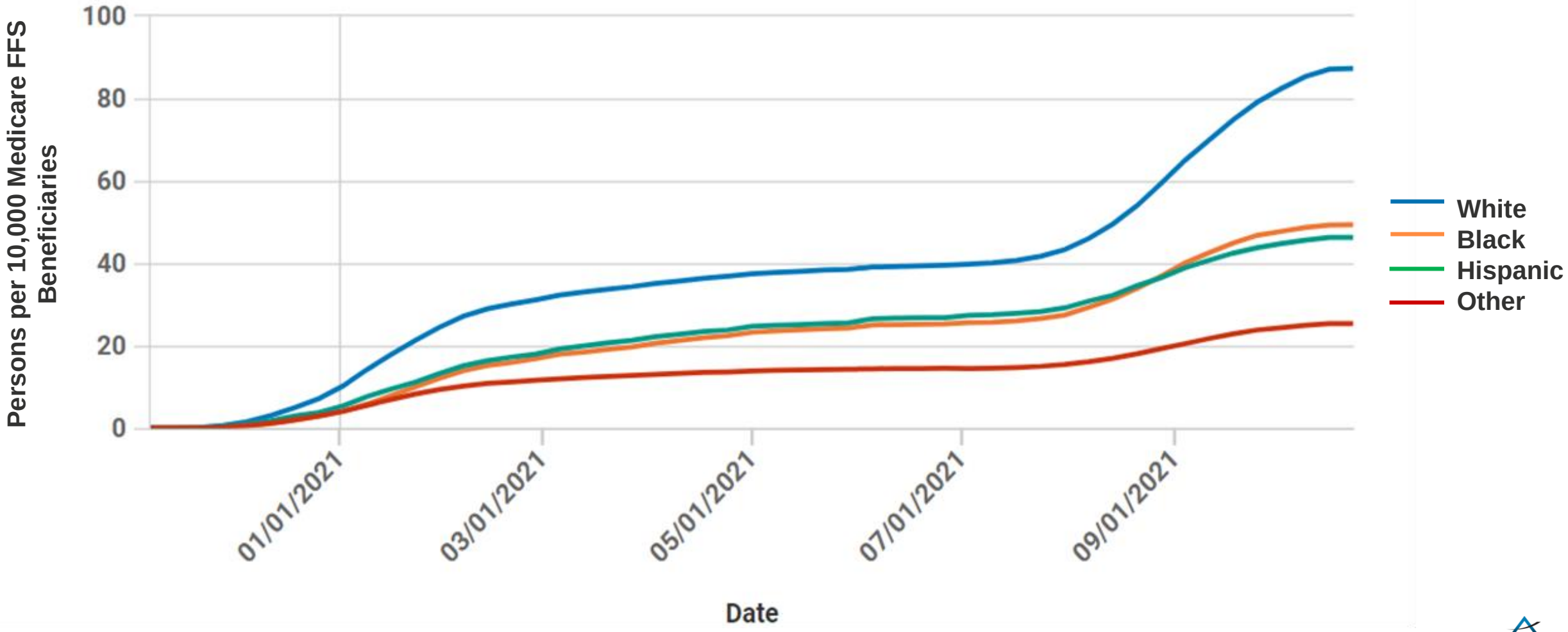


Daily Tracking of Hospital Utilization: Growth in Respiratory Diagnoses





Monoclonal Antibody Treatment for Mild-to-Moderate COVID-19 among Elderly by Race/Ethnicity over Time



Presentation Outline

1. BEST distributed data network
2. Real-time monitoring of COVID-related measures during the pandemic
3. **Near real-time surveillance of COVID-19 vaccines**

CBER's Activities Monitoring Safety and Effectiveness of COVID-19 Vaccines

- Leveraging capacities of the BEST distributed data network, CBER instituted protocols for tracking potential safety events—adverse event of special interest (AESI)—associated with the different COVID-19 vaccines
- Surveillance consists of two phases:

Rapid Cycle Initial Exploratory Investigations	Rapid Cycle Analysis Sequential Testing of Signals
• Background rates for AESI (historical comparator) • Statistical monitoring of elevated rates	• Use of PMaxSPRT to identify statistical importance of elevated risks • Rapid cycle analysis frequency varies by data source

- Surveillance also includes analyses assessing COVID-19 vaccine effectiveness, including profiles of effectiveness over time and across various population segments

Overview of Status of Inferential Analyses and Impacts

- Rapid turnaround safety inferential analyses
  - Comparative risk of myocarditis or pericarditis following COVID-19 mRNA vaccination
  - Observation of higher myocarditis/pericarditis rates post-mRNA vaccination in VAERS and other data sources (not motivated through RCA signal)
  - Impact:
    - VRBPAC decision to expand the Pfizer EUA for younger populations
    - VRBPAC meeting for Moderna booster vaccination authorization
- Epidemiologic safety/effectiveness inferential analyses
  - Assessment of vascular outcomes (AMI, PE, DIC, and ITP) following COVID-19 vaccination
  - Detection of statistical association between vaccination and AESI in Medicare

Questions?

RTI (h)(s)
Health Solutions

9 November 2021

Evaluating COVID-19 Vaccine Effectiveness within the BEST Initiative

13th Annual Sentinel Initiative Public Workshop

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

COVID-19 Vaccine Effectiveness

Objective: to evaluate the real-world effectiveness of COVID-19 vaccines in the BEST Initiative data network

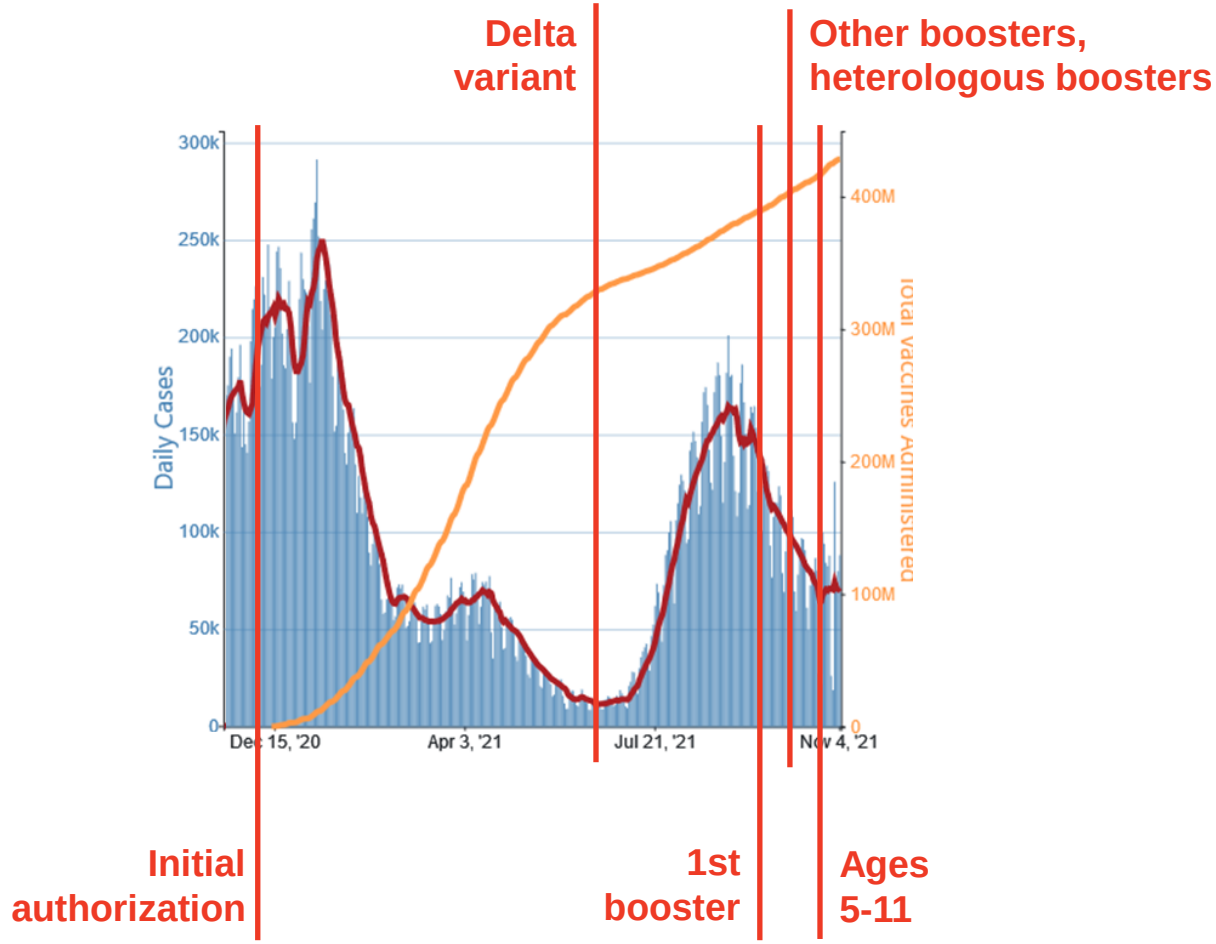
- Lead development of a vaccine effectiveness protocol for implementation
- Organizing scientific working group meetings with CBER and other BEST Initiative collaborators
- Support BEST Initiative data partners and collaborators during implementation

The power of knowledge.
The value of understanding.

Changing Pandemic and Vaccination Dynamics

- Waning effectiveness over time
- Delta variant, pandemic waves, calendar time

- Priority vaccination groups
- Booster doses
- Heterologous boosters
- Pediatrics



The power of knowledge.
The value of understanding.

Defining the Relevant and Possible Questions

- Evaluate feasibility of addressing various effectiveness-related research questions
  - Are they of regulatory and scientific interest?
  - What are the real-world decisions individuals and providers are making?
  - Can they be validly addressed using available data?

The power of knowledge.
The value of understanding.

Working Through Challenges

- Methods
  - Confounding between vaccinated and unvaccinated
  - Study designs to avoid selection bias and other time-related biases
  - Defining and aligning relevant vaccination strategies and appropriate comparisons
  - Methods for evaluating changing vaccine effectiveness over time
  - Interpreting absolute and relative effect measure estimates during an evolving pandemic

- Data issues
  - Vaccine capture
  - COVID-19 outcomes

The power of knowledge.
The value of understanding.

Flexibility Required

- Regulatory priorities and scientific questions of interest have evolved
- Populations of interest have expanded
- Data availability has increased

The power of knowledge.
The value of understanding.

Thank You

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The power of knowledge.
The value of understanding.

Discussion Questions

- What have you learned from this pandemic that will help us respond faster to the next one - particularly as it relates to accelerating the development of vaccines?
- To what extent can BEST serve a centralized coordinating function to help understand the totality of evidence on rapidly developing vaccine safety information?
- What infrastructure do we still need to build now to be ready to respond quickly in the future?
- How has the context of the COVID pandemic changed your approach to safety and surveillance work? What adaptations have you made to ensure your work is nimble and adaptable to this ever-evolving landscape?
- How can the new research methods and capabilities developed for pandemic response, particularly those related to near-real-time data analysis, enhance BEST's work in the future?

Closing Remarks | Day 2

Mark McClellan, MD, PhD

Director, Duke-Margolis Center for Health Policy

Thank You!

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