Fifteenth Annual Sentinel Initiative Public Workshop

November 08, 2023
9:00 a.m. – 5:00 p.m. ET
Welcome and Opening Remarks

Mark McClellan
Director, Duke-Margolis Center for Health Policy
## Workshop Agenda

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

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

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

Janet Woodcock
Principal Deputy Commissioner, U.S. Food and Drug Administration
Fireside Chat with Sentinel Initiative Leadership

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

Speakers:

Steve Anderson, U.S. Food and Drug Administration
Gerald Dal Pan, U.S. Food and Drug Administration
Danica Marinac-Dabic, U.S. Food and Drug Administration
Moderated Discussion and Q&A

Moderator: Mark McClellan
Duke-Margolis Center for Health Policy
Break

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

December 14, 2023
12:30 PM – 5:00 PM

A Virtual Public Workshop

Visit healthpolicy.duke.edu/events
International Approaches to the Distributed Networks Data System

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

Speakers:
- Daniel Morales, European Medicines Agency (EMA)
- Melissa Kampman, Health Canada
- David Moeny, U.S. Food and Drug Administration
Scaling-up Real-World Evidence Generation for Regulators in Europe: DARWIN EU

15th Annual Sentinel Initiative Public Workshop 8th November 2023

Presented by Dr Daniel Morales
European Medicines Agency, Data Analytics and Methods Taskforce – Real World Evidence
DARWIN EU® is a federated network of data, expertise and services that supports better decision-making throughout the product lifecycle by generating reliable evidence from real world healthcare data.

**FEDERATED NETWORK PRINCIPLES**
- Data stays local
- Use of OMOP Common Data Model (where applicable) to perform studies in a timely manner and increase consistency of results
Currently **selecting Phase II DPs** via open call of interest, then Phase III to follow

~26 million active patients
Main areas where RWE will support regulatory decision-making

1. Support the planning and validity of applicant studies
   - Design and feasibility of planned studies
   - Representativeness and validity of completed studies

2. Understand the clinical context
   - Disease epidemiology
   - Clinical management
   - Drug utilisation

3. Investigate associations and impact
   - Safety and effectiveness studies
   - Impact of regulatory actions
Ongoing studies

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

- **EC/EHDS Complex**
  - EHDS coagulopathy of COVID-19
  - Drug utilisation study of medicines with prokinetic properties in children and adults diagnosed with gastroparesis

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

- **CHMP OTS**
  - Naloxone use in treatment of opioid overdose. [EUPAS105644]

- **HTA/Payers OTS**
  - Multiple myeloma: patient characterisation, treatments and survival in the period 2012-2022 [EUPAS105033]

- **NCA OTS**
  - Drug utilisation study of prescription opioids. [EUPAS105641]

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

**OTS** = off-the-shelf study
Challenges of DARWIN EU network

Related to the databases content

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

Related to the organisation of a network

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

Importance of feasibility assessment & an iterative approach to learning
Future perspectives

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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Option I</th>
<th>Option II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off the shelf</td>
<td>2</td>
<td>6</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Routine repeated</td>
<td>1</td>
<td>6</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Complex study</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Very complex</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Data Partners (total)</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>
European Health Data Space

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

**CORE Services**
- provided by EC

**GENERIC Services**
- provided by authorized participants

**Secure Processing Environments**

**LOCAL Services**
- provided by/to local partners

**Data Sharing Infrastructures**

**Health Data Access Bodies**

**Data Sharing Infrastructures**

**Core Services**

**Health Data Access Body**

- **Electronics Health Records**
- Health Data Registries
- Administrative Data
- Claims Data
- Genomics

- **Data Users**
  - Researcher
  - Health Professional
  - Public Health Authority
  - Regulator
  - Innovator
Further information

Official address  Domenico Scarlattilaan 6  •  1083 HS Amsterdam  •  The Netherlands
Telephone  +31 (0)88 781 6000
Send us a question  Go to  www.ema.europa.eu/contact

Follow us on  @EMA_News
International Approaches to the Distributed Networks Data System

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

Speakers:

- Daniel Morales, European Medicines Agency (EMA)
- Melissa Kampman, Health Canada
- David Moeny, U.S. Food and Drug Administration
Moderated Discussion and Q&A

Moderator: Rachele Hendricks-Sturrup
Duke-Margolis Center for Health Policy
Sentinel System and BEST Operations and Coordinating Center Perspectives

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

Speakers:

Margaret Anderson, Deloitte

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

Yoganand Chillarige, Acumen LLC

John Seeger, Optum Epidemiology
15th ANNUAL SENTINEL INITIATIVE PUBLIC WORKSHOP

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

NATIONAL PRESS CLUB | WASHINGTON, DC

November 8, 2023
Introducing Our Speaker

Margaret Anderson

Margaret is a Managing Director at Deloitte and serves as a Principal Investigator for the Sentinel Program. She is a leader in Deloitte's Strategy and Analytics Diversity, Equity, and Inclusion efforts and the Chief Marketing Officer of the firm's Federal Health Sector.
CBOC engages and educates a community of health professionals to advance objectives related to Sentinel
What is the Sentinel CBOC?

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

SENTINEL’S STRATEGIC AIMS supported by CBOC

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

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

2009
FDA launched mini-Sentinel System

2016
FDA advanced the Sentinel Initiative as post-market safety and surveillance system

2019
• FDA announces Community Building and Outreach Center
• Sentinel user research conducted and website launched

2020
• Designed quarterly newsletter to directly communicate updates to the Sentinel community

2021
• Built webinars to educate target audiences
• Designed graphics to visually represent data

2022
• Facilitated and managed an Analytic Tools Webinar to educate the target audience on Sentinel resources
• Created over 45+ Sentinel Graphics to adequately communicate complex data to audiences

2023
• Made Sentinel website updates to enhance and improve the user experience
• Produced videos to educate audiences on EHR v. Claims, with more than 150 views
• Developed an approach for collaboration with other federal health agencies
Spotlight: Quarterly Newsletter

1. Clear calls to action
2. Visual organization
3. Consolidation of content

11 Newsletters sent
9% Subscriber growth
5,750 Subscribers to date
CBOC is building and growing the Sentinel community

COMMUNITY-BUILDING OUTREACH

- Focusing on the tools and services that audiences need and want
- Expanding Sentinel outreach to academia and other government officials
- Keeping audiences engaged with interactive content and experiences

ENGAGEMENT AND IMPACT

- Managed 5+ Sentinel webinars, providing audiences with information to better serve their people and patients
- Created a multi-channel resource for audiences to understand EHR and claims data sources, such as slides and an informational video
- Cultivated a subscriber network, with 14% of quarterly newsletter readers or receivers being academia and 7% being from government agencies
- Increased government and academia subscriber newsletter opens by 86% and 113% respectively, from 2021 to 2023
- Designed over 45 downloadable key database graphics to enhance the user experience on the website
- Provided enhancements to Sentinel website functionality, to include designing and maintaining the site
We created a network of channels to engage stakeholders

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

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

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

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

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

- **Website**
  - Update and improve website design while continuing to perform routine maintenance
  - Improve user experience and access to all resources on the Sentinel site
We are cultivating collaborations to earn trust from the people we strive to serve.

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

WHY PUBLIC HEALTH PARTNERSHIPS?

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

POTENTIAL OUTCOMES FOR SENTINEL

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

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

Trends in Public Health Communications

Spur action in communities using digital channels
• Embrace social marketing campaigns through content
• Create a marketing mix to reach your audience
• Engage your audience through multiple touchpoints

Push the needle on effective communication
• Develop creative partnerships and collaboration channels – partnerships vary from co-creation to innovation labs
• Create room for risk-taking

Use technological progress to optimize communications
• Take advantage of the unprecedented opportunities, like new technology that helps reach and connect with audiences
• Establish meaningful connections through content that fits into audience needs and wants
• Proceed with (some) caution
Disclaimers

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

• This Sentinel Operations Center is funded by the U.S. FDA through the Department of Health and Human Services (HHS) contract number 75F40119D10037
### FY2023 Sentinel Analyses

<table>
<thead>
<tr>
<th>Analysis Type</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sentinel Distributed Database</td>
<td></td>
</tr>
<tr>
<td>Descriptive</td>
<td>34</td>
</tr>
<tr>
<td>Inferential</td>
<td>15</td>
</tr>
<tr>
<td>Signal Identification</td>
<td>3</td>
</tr>
<tr>
<td>Additional EHR Data Sources</td>
<td></td>
</tr>
<tr>
<td>Descriptive</td>
<td>12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>64</strong></td>
</tr>
</tbody>
</table>

- **51 reports** posted to the Sentinel website
- **14 analytic packages** shared with the public on the Sentinel website
- **15 manuscripts** published
- **33 posters / presentations** presented

Analyses are assigned to years based on analytic package distribution date.
## Sentinel Analyses Meeting Requirements of FDCA Section 505(o) Prior to Requiring a Sponsor Postmarket Requirement (PMR)

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

### Status Key
- ✔️ = Complete
- ❓ = Inferential Analysis Phase
- ❗️ = Monitoring Ongoing

FDCA = Federal Food, Drug, and Cosmetic Act
Planned Sentinel Analyses Identified During Approval (1 of 3)

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

**SENTINEL/ARIA NOTIFICATION**

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

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

SENTINEL/ARIA NOTIFICATION

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

FDA plans to evaluate Rinvoq (upadacitinib) in the Sentinel System. We have determined that Sentinel’s Active Postmarket Risk Identification and Analysis System, established under section 505(k)(3) of the FDCA, is sufficient to identify unexpected serious risks (myocardial infarction, stroke, and thrombosis) possibly related to upadacitinib dose during long-term use for ulcerative colitis.
Planned Sentinel Analyses Identified During Approval (3 of 3)

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

SENTINEL/ARIA NOTIFICATION

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

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

FDCA = Federal Food, Drug, and Cosmetic Act

https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/207924Orig1s007ltr.pdf
**Sentinel’s Support of FDA’s Signal Identification Efforts (1 of 3)**

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

[https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide](https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide)
Signal Identification for Ozempic (semaglutide)

Background

Ozempic users are younger, have more visits & fills, history of obesity, and recent insulin.

Analysis and Findings

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


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

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

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

Methods

1:1 PS Match & hdPS match

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

https://sentinelinitiative.org/studies/drugs/individual-drug-analyses/outcome-monitoring-following-ozempic-use-patients-type-2
### Sentinel’s Support of FDA’s Signal Identification Efforts (2 of 3)

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

[https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide](https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide)

[https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz](https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz)
## Sentinel’s Support of FDA’s Signal Identification Efforts (3 of 3)

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

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

[https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide](https://www.sentinelinitiative.org/studies/drugs/ozempic-semaglutide)
[https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz](https://www.sentinelinitiative.org/studies/drugs/zarxio-filgrastim-sndz)
[https://www.sentinelinitiative.org/studies/drugs/aimovig-erenumab-0](https://www.sentinelinitiative.org/studies/drugs/aimovig-erenumab-0)
Support for Eliminating REMS for Lotronex and Alosetron

Lotronex (alosetron hydrochloride) Information

Evidence to support eliminating the Lotronex and Alosetron REMS

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

- Since 2016, when the Lotronex REMS and Alosetron REMS were modified to make prescriber training programs voluntary and to remove the prescription sticker requirement, FDA has not identified any new data suggesting a change in the frequency or severity of ischemic colitis and serious complications of constipation. Reporting of these adverse events associated with alosetron to the FDA Adverse Event Reporting System (FAERS) has been stable since 2002 and an increase in severe outcomes has not been observed. Additionally, an analysis of new female users of alosetron hydrochloride in FDA’s Sentinel Distributed Database from 2016 to 2020 found the rate of ischemic colitis consistent with that listed in the Prescribing Information.

- FDA did not observe increases in drug utilization trends since the approval of the generic version of alosetron hydrochloride. Overall, there has been an ongoing downward trend in the estimated total number of patients receiving prescriptions for all alosetron hydrochloride products. Due to the availability of approved therapeutic alternatives, we do not expect drug usage to increase with removal of the REMS.

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

Judith C. Maro¹*, Michael D. Nguyen², Joy Kolonoski¹, Ryan Schoeplein¹, Ting-Ying Huang¹, Sarah K. Dutcher¹, Gerald J. Dal Pan² and Robert Ball²

CLINICAL PHARMACOLOGY & THERAPEUTICS doi:10.1002/cpt.2979
### Table 4 Reasons for determinations of ARIA insufficiency

<table>
<thead>
<tr>
<th>Reasons for insufficiency</th>
<th>Number of determinations</th>
<th>Example</th>
<th>Direction of future development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient supplemental structured clinical data</td>
<td>89</td>
<td>Lack of laboratory, imaging, or vital signs data</td>
<td>Addressable with the addition of EHR data elements into ARIA</td>
</tr>
<tr>
<td>Inability of ARIA tools to perform required analysis</td>
<td>82</td>
<td>Insufficient signal identification tool</td>
<td>ARIA has integrated signal identification abilities (Figure 1)</td>
</tr>
<tr>
<td>Study requires data elements captured in unstructured clinical data, such as clinical notes.</td>
<td>73</td>
<td>Lack of radiology or pathology findings in notes</td>
<td>Addressable with development of feature engineering capabilities to extract and structure these data</td>
</tr>
<tr>
<td>Absence of validated code algorithm</td>
<td>72</td>
<td>No gold-standard chart review was performed for outcome of interest.</td>
<td>Sentinel has performed several gold standard chart validations but these require substantial resources. Efforts underway to investigate rapid silver standard reviews.</td>
</tr>
<tr>
<td>Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate</td>
<td>60</td>
<td>Codes do not exist for concept or validated performance characteristics are inadequate</td>
<td>Potentially addressable with added EHR elements but if outcome is not well-defined or new (e.g., long COVID), there may be substantial hurdles to identification</td>
</tr>
<tr>
<td>Inadequate sample size</td>
<td>57</td>
<td>Low uptake of drug</td>
<td>Non-actionable as ARIA is the largest system of its kind</td>
</tr>
<tr>
<td>Requires linkage to additional data source that is unavailable</td>
<td>52</td>
<td>Inability to ascertain cause of death</td>
<td>Additional linkages are possible with significant financial resources</td>
</tr>
<tr>
<td>Insufficient observation time available</td>
<td>44</td>
<td>Inability to follow patients across healthcare plans or systems</td>
<td>Actionable with substantial further research and development and resolution of data governance issues</td>
</tr>
<tr>
<td>Insufficient mother-infant linkage</td>
<td>24</td>
<td>Lack of ability to connect mothers and infants</td>
<td>Resolved with 2018 integration of Mother-Infant Linkage</td>
</tr>
<tr>
<td>Insufficient inpatient data</td>
<td>18</td>
<td>Inability to access granular inpatient pharmacy information</td>
<td>Resolved with partnerships with inpatient healthcare systems</td>
</tr>
<tr>
<td>Inability to identify over-the-counter medication use</td>
<td>8</td>
<td>Over-the-counter medication use not captured</td>
<td>Inherent limitation of both claims and EHR data</td>
</tr>
<tr>
<td>Insufficient race capture of information on race</td>
<td>3</td>
<td>Race is not well-captured</td>
<td>FDA is working with Data Partners to understand approaches for better capture of this data</td>
</tr>
<tr>
<td>Insufficient representation of the population of interest</td>
<td>1</td>
<td>Limited generalizability based on commercial claims data</td>
<td>Sentinel added Medicare data in 2018 and Medicaid in 2022</td>
</tr>
</tbody>
</table>

ARIA, Active Risk Identification and Analysis; COVID, coronavirus disease; EHR, electronic health record; FDA, US Food and Drug Administration.
Table 4 Reasons for determinations of ARIA insufficiency

<table>
<thead>
<tr>
<th>Reasons for insufficiency</th>
<th>Number of determinations</th>
<th>Example</th>
<th>Direction of future development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient supplemental structured clinical data</td>
<td>89</td>
<td>Lack of laboratory, imaging, or vital signs data</td>
<td>Addressable with the addition of EHR data elements into ARIA[25,36]</td>
</tr>
<tr>
<td>Insufficiency of ARIA tools to perform required analysis</td>
<td>82</td>
<td>Insufficient signal identification tool</td>
<td>ARIA has integrated signal identification abilities[Figure 1][15-18]</td>
</tr>
<tr>
<td>Study requires data elements captured in unstructured clinical data, such as clinical notes.</td>
<td>73</td>
<td>Lack of radiology or pathology findings in notes</td>
<td>Addressable with development of feature engineering capabilities to extract and structure these data[27]</td>
</tr>
<tr>
<td>Absence of validated code algorithm</td>
<td>72</td>
<td>No gold-standard chart review was performed for outcome of interest</td>
<td>Sentinel has performed several gold standard chart validations[99-102] but these require substantial resources. Efforts underway to investigate rapid silver standard reviews.</td>
</tr>
<tr>
<td>Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate</td>
<td>60</td>
<td>Codes do not exist for concept or validated performance characteristics are inadequate</td>
<td>Potentially addressable with added EHR elements but if outcome is not well-defined or new (e.g., long COVID), there may be substantial hurdles to identification</td>
</tr>
<tr>
<td>Inadequate sample size</td>
<td>57</td>
<td>Low uptake of drug</td>
<td>Non-actionable as ARIA is the largest system of its kind</td>
</tr>
<tr>
<td>Requires linkage to additional data source that is unavailable</td>
<td>52</td>
<td>Inability to ascertain cause of death</td>
<td>Additional linkages are possible with significant financial resources</td>
</tr>
<tr>
<td>Insufficient observation time available</td>
<td>44</td>
<td>Inability to follow patients across healthcare plans or systems</td>
<td>Actionable with substantial further research and development and resolution of data governance issues[43]</td>
</tr>
<tr>
<td>Insufficient mother-infant linkage</td>
<td>24</td>
<td>Lack of ability to connect mothers and infants</td>
<td>Resolved with 2018 integration of Mother-Infant Linkage table[9]</td>
</tr>
<tr>
<td>Insufficient inpatient data</td>
<td>18</td>
<td>Inability to access granular inpatient pharmacy information</td>
<td>Resolved with partnerships with inpatient healthcare systems[10]</td>
</tr>
<tr>
<td>Inability to identify over-the-counter medication use</td>
<td>8</td>
<td>Over-the-counter medication use not captured</td>
<td>Inherent limitation of both claims and EHR data</td>
</tr>
<tr>
<td>Insufficient race capture of information on race</td>
<td>3</td>
<td>Race is not well-captured</td>
<td>FDA is working with Data Partners to understand approaches for better capture of this data</td>
</tr>
<tr>
<td>Insufficient representation of the population of interest</td>
<td>1</td>
<td>Limited generalizability based on commercial claims data</td>
<td>Sentinel added Medicare data in 2018 and Medicaid in 2022</td>
</tr>
</tbody>
</table>

ARIA, Active Risk Identification and Analysis; COVID, coronavirus disease; EHR, electronic health record; FDA, US Food and Drug Administration.
Inability to identify certain study populations of interest from insurance claims

Inability to identify certain outcomes of interest from insurance claims

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

Data infrastructure (DI)

10+ million people
EHR + Claims

Feature engineering (FE)

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

Causal inference (CI)

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

Detection analytics (DA)

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

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

Sentinel Initiative Center Vision

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

Master Plan of the Sentinel Innovation Center
### Table 3 Distribution of safety concerns insufficient for assessment in ARIA attributed to capture of health outcome, by regulatory approval stage *(N=132 safety concerns)*

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

<sup>a</sup>A recording of “Other” indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.

ARIA, Active Risk Identification and Analysis; MedDRA, Medical Dictionary for Regulatory Activities.
Table 3 Distribution of safety concerns Insufficient for assessment in ARIA attributed to capture of health outcome, by regulatory approval stage (N=132 safety concerns)

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

$^a$A recording of “Other” indicates that an appropriate MedDRA code was not identified for a given health outcome of interest.

ARIA, Active Risk Identification and Analysis; MedDRA, Medical Dictionary for Regulatory Activities.
**Table 4 Reasons for determinations of ARIA insufficiency**

<table>
<thead>
<tr>
<th>Reasons for insufficiency</th>
<th>Number of determinations</th>
<th>Example</th>
<th>Direction of future development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient supplemental structured clinical data</td>
<td>89</td>
<td>Lack of laboratory, imaging, or vital signs data</td>
<td>Addressable with the addition of EHR data elements into ARIA[25,36]</td>
</tr>
<tr>
<td>Inability of ARIA tools to perform required analysis</td>
<td>82</td>
<td>Insufficient signal identification tool</td>
<td>ARIA has integrated signal identification abilities (Figure 1)[20,22]</td>
</tr>
<tr>
<td>Study requires data elements captured in unstructured clinical data, such as clinical notes</td>
<td>73</td>
<td>Lack of radiology or pathology findings in notes</td>
<td>Addressable with development of feature engineering capabilities to extract and structure these data[27]</td>
</tr>
<tr>
<td>Absence of validated code algorithm</td>
<td>72</td>
<td>No gold-standard chart review was performed for outcome of interest</td>
<td>Sentinel has performed several gold standard chart validations[28,29] but these require substantial resources. Efforts underway to investigate rapid silver standard reviews.</td>
</tr>
<tr>
<td>Identification of clinical concepts with available code algorithms/terminologies is not possible or inadequate</td>
<td>60</td>
<td>Codes do not exist for concept or validated performance characteristics are inadequate</td>
<td>Potentially addressable with added EHR elements but if outcome is not well-defined or new (e.g., long COVID), there may be substantial hurdles to identification</td>
</tr>
<tr>
<td>Inadequate sample size</td>
<td>57</td>
<td>Low uptake of drug</td>
<td>Non-actionable as ARIA is the largest system of its kind</td>
</tr>
<tr>
<td>Requires linkage to additional data source that is unavailable</td>
<td>52</td>
<td>Inability to ascertain cause of death</td>
<td>Additional linkages are possible with significant financial resources</td>
</tr>
<tr>
<td>Insufficient observation time available</td>
<td>44</td>
<td>Inability to follow patients across healthcare plans or systems</td>
<td>Actionable with substantial further research and development and resolution of data governance issues[43]</td>
</tr>
<tr>
<td><strong>Insufficient mother-infant linkage</strong></td>
<td>24</td>
<td>Lack of ability to connect mothers and infants</td>
<td>Resolved with 2018 integration of Mother-Infant Linkage table[18]</td>
</tr>
<tr>
<td>Insufficient inpatient data</td>
<td>18</td>
<td>Inability to access granular inpatient pharmacy information</td>
<td>Resolved with partnerships with inpatient healthcare systems[10]</td>
</tr>
<tr>
<td>Inability to identify over-the-counter medication use</td>
<td>8</td>
<td>Over-the-counter medication use not captured</td>
<td>Inherent limitation of both claims and EHR data</td>
</tr>
<tr>
<td>Insufficient race capture of information on race</td>
<td>3</td>
<td>Race is not well-captured</td>
<td>FDA is working with Data Partners to understand approaches for better capture of this data</td>
</tr>
<tr>
<td>Insufficient representation of the population of interest</td>
<td>1</td>
<td>Limited generalizability based on commercial claims data</td>
<td>Sentinel added Medicare data in 2018 and Medicaid in 2022</td>
</tr>
</tbody>
</table>

ARIA, Active Risk Identification and Analysis; COVID, coronavirus disease; EHR, electronic health record; FDA, US Food and Drug Administration.
463 million unique patient identifiers (2000-2023)

1.1 billion person-years of data*

113 million members currently accruing data*

20 billion pharmacy dispensing*

20 billion medical encounters*

11 million deliveries with mom-baby linkage

* Among individuals with both medical and drug coverage

https://www.sentinelinitiative.org/about/key-database-statistics
K. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

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

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

   a. FDA will work toward expanding the Sentinel System’s sources of data and enhancing the system’s core capabilities.
   b. FDA will enhance its communication with sponsors and the public regarding general methodologies for Sentinel queries, including what the Agency has learned regarding the most appropriate ways to query and use Sentinel data. This can be done through enhancement of existing mechanisms and/or greater frequency of such mechanisms.
   c. FDA will evaluate additional ways to facilitate public and sponsor access to Sentinel’s distributed data network to conduct safety surveillance.
   d. By the end of FY 2019, FDA will hold or support a public meeting engaging stakeholders to discuss current and emerging Sentinel projects and seek stakeholder feedback and input regarding gaps in the current system to facilitate the further development of Sentinel and its system of Active Risk Identification and Analysis (ARIA).
   e. By the end of FY 2020, FDA will establish policies and procedures (MAPPS and SOPPs) to facilitate informing sponsors about the planned use of Sentinel to evaluate a safety signal involving their respective products. These MAPPS and SOPPs will address what types of evaluations and what information about the evaluations will be shared with sponsors, and the timing of such communications.
   f. By the end of FY 2020, FDA will facilitate integration of Sentinel into the human drug review program in a systematic, efficient, and consistent way through staff development and by updating existing SOPPs and MAPPS, as needed.
   g. By the end of FY 2020, FDA will develop a comprehensive training program for review staff (e.g., epidemiologists, statisticians, medical officers, clinical analysts, project managers, and other review team members) to ensure that staff have a working knowledge of Sentinel, can identify when Sentinel can inform important regulatory questions, and are able to consistenly participate in use of Sentinel to evaluate safety issues.
   h. By the end of FY 2022, FDA will analyze, and report on the impact of the Sentinel expansion and integration on FDA’s use of Sentinel for regulatory purposes, e.g., in the contexts of labeling changes, PMRs, or PMCs.
Looking Ahead: PDUFA VII
October 1, 2022 – September 30, 2027 (Fiscal Years 2023 – 2027)

Focus on Pregnancy Safety

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

“FDA will develop a framework describing how data from different types of post-market pregnancy safety studies might optimally be used, incorporating knowledge of how different types of postmarket studies have been used by FDA and industry and identifying gaps in knowledge needed to be filled by demonstration projects.”

Prescription Drug User Fee Act VII: Fiscal Years 2023-2027
Commitment Letter (I)(M)(2)(b)(i)
PDUFA VII: Focus on Pregnancy Safety

i. Pregnancy Safety

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Characterization of Live Birth Deliveries in the Sentinel Distributed Database: January 1, 2008 – January 31, 2023

<table>
<thead>
<tr>
<th>Year</th>
<th>Live Birth Deliveries</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>7,299,350</td>
</tr>
<tr>
<td>2009</td>
<td>7,193,972</td>
</tr>
<tr>
<td>2010</td>
<td>7,098,643</td>
</tr>
<tr>
<td>2011</td>
<td>7,038,354</td>
</tr>
<tr>
<td>2012</td>
<td>6,988,165</td>
</tr>
<tr>
<td>2013</td>
<td>6,938,674</td>
</tr>
<tr>
<td>2014</td>
<td>6,888,185</td>
</tr>
<tr>
<td>2015</td>
<td>6,838,796</td>
</tr>
<tr>
<td>2016</td>
<td>6,789,407</td>
</tr>
<tr>
<td>2017</td>
<td>6,740,018</td>
</tr>
<tr>
<td>2018</td>
<td>6,690,629</td>
</tr>
<tr>
<td>2019</td>
<td>6,641,240</td>
</tr>
</tbody>
</table>

Steps for an observational single outcome study in EHR data:
1. Identify a cohort
2. Classify exposure based on records of medication dispensings
3. Identify the outcome using a validated algorithm
4. Control for confounding using propensity score methods
5. Calculate a point estimate for the exposure-outcome association

Steps for an observational multiple outcome study in EHR data:
1. Identify a cohort
2. Classify exposure based on records of medication dispensings
3. Create an outcome tree with multiple outcomes of interest
4. Control for confounding using propensity score methods
5. Calculate test statistics for each outcome using TreeScan

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

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

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

ii. Use of Real-World Evidence – Negative Controls

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

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

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

(3) By September 30, 2027, FDA will publish a report on the results of the development projects.
Automated Negative Control Identification in the Sentinel Setting

Xu Shi, PhD
Richard Wyss, PhD
Shirley Wang, PhD
Rishi Desai, PhD

Summary

Phase 1: Empirical methods evaluation
Source data: EHRs, Mass General Brigham, Deterministic linkage, Claims, CMS
Methodology evaluation:
- Phase model
- Parameter estimation with learned graphs
- Application of the EMBER algorithm to evaluate clinical outcomes in identifying potential negative controls and refining study\textsuperscript{a}

Products:
- Early demonstration of methodology and prototype
- Feedback from stakeholders to improve EMBER in sentinel trials at Sentinel

Phase 2: Prototype evaluation
- R package and corresponding SAS codes
- Quality checked codes with documentation

Phase 3: ARIA tool development
- Evaluated and refined implementation
- Use of prototypes ready for deployment in future Sentinel studies

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

Presenter: Richard Wyss, Brigham and Women’s Hospital

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

March 8, 2023
A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

Noelle M. Cocoros¹ | Candace C. Fuller¹ | Sruthi Adimadhyam¹ | Robert Ball² | Jeffrey S. Brown¹ | Gerald J. Dal Pan² | Sheryl A. Kluberg¹ | Vincent Lo Re 3rd³ | Judith C. Maro¹ | Michael Nguyen² | Robert Orr² | Dianne Paraoan² | Jonathan Perlin⁴ | Russell E. Poland¹,⁴ | Meighan Rogers Driscoll¹ | Kenneth Sands¹,⁴ | Sengwee Toh¹ | W. Katherine Yih¹ | Richard Platt¹ | And the FDA-Sentinel COVID-19 Working Group
Utilization of Potential Paxlovid Interactors among Paxlovid-eligible COVID-19 Patients or Patients with a Paxlovid Exposure

**Objective:** Estimate the magnitude of the “at-risk” population using drugs that interact with Paxlovid to inform the Division of Antiviral’s labeling decision

**Rapid Sentinel Distributed Database**

**December 2021 – December 2022**

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

2. Individuals with use of Paxlovid

**Query results were included in Paxlovid NDA review.**

* Health insurance claims data do not capture if concurrent medications were withheld or had their dose adjusted due to Paxlovid
CONSIGN (COVID-19 Infection and Medicines in Pregnancy) Study

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

Key Takeaways: No increased risk of infant outcomes was observed comparing pregnant individuals with COVID-19 to those without COVID-19 but a slightly higher number of infants with congenital malformations and low birth weight was observed among severe COVID-19 pregnant individuals.
Acknowledgements (1 of 2)

**Aimovig**
U.S. Food and Drug Administration
Blum, Michael
Herity, Leah
Hernandez, Jose
Kidd, James
Ma, Yong
Mundkur, Mallika
Munoz, Monica

**Sentinel Operations Center**
Beers, Lizzie
Epperson, Meredith
Kanani, Xhulia
Mai, Xiaodan Melody
Maro, Judy
Marshall, Jim
Peters, Alexander
Siranosian, Liz

**Sentinel Data Partners**
• CVS Health (Aetna), Blue Bell, PA
• Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
• Carelon Research/Elevance Health, Wilmington, DE
• Humana Healthcare Research Inc., Louisville, KY
• OptumInsight Life Sciences Inc., Boston, MA
• Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN

**Ozempic**
U.S. Food and Drug Administration
Blum, Michael
Eworuke, Efe
Herity, Leah
Hernandez, Jose
Kidd, James
Ma, Yong
Mundkur, Mallika
Munoz, Monica
Stojanovic, Danijela

**Sentinel Operations Center**
Epperson, Meredith
Kanani, Xhulia
Maro, Judy
Peters, Alexander
Siranosian, Liz
Whited, Emma

**Sentinel Data Partners**
• CVS Health (Aetna), Blue Bell, PA
• Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
• Carelon Research/Elevance Health, Wilmington, DE
• Humana Healthcare Research Inc., Louisville, KY
• OptumInsight Life Sciences Inc., Boston, MA
• Vanderbilt University Medical Center, Department of Health Policy, Nashville, TN

**Zarxio**
U.S. Food and Drug Administration
Dutcher, Sarah
Eworuke, Efe
Herity, Leah
Hernandez, Jose
Kidd, James
Moeny, David
Mundkur, Mallika
Munoz, Monica
Ryan, Qin
Setse, Rosanna

**Sentinel Operations Center**
Epperson, Meredith
Hou, Laura
Maro, Judy
Marshall, Jim
Siranosian, Liz
Whited, Emma

**Sentinel Data Partners**
• CVS Health (Aetna), Blue Bell, PA
• Duke University School of Medicine, Department of Population Health Sciences, Durham, NC
• Carelon Research/Elevance Health, Wilmington, DE
• Humana Healthcare Research Inc., Louisville, KY
• OptumInsight Life Sciences Inc., Boston, MA
CONSIGN Study
U.S. Food and Drug Administration
Hernandez, Jose
Hua, Wei
Sahin, Leyla
Zhao, Yueqin

Sentinel Operations Center
Anderson, Josie
Chlon, Whitney
Cole, David
Cosgrove, Austin
Hoffman, Emma
Kempner, Maria
Lyons, Jennifer
Messenger-Jones, Elizabeth
Mosley, Jolene
Shinde, Mayura
Toh, Darren

Sentinel Data Partners
• CVS Health (Aetna), Blue Bell, PA
• Carelon Research/Elevance Health, Wilmington, DE
• Humana Healthcare Research Inc., Louisville, KY
• Kaiser Permanente Colorado Institute for Health Research, Aurora, CO
• Kaiser Permanente Northwest Center for Health Research, Portland, OR
• Kaiser Permanente Washington Health Research Institute, Seattle, WA
• OptumInsight Life Sciences Inc., Boston, MA

Paxlovid Utilization Among COVID-19 Patients
U.S. Food and Drug Administration
Greene, Patty
Hernandez, Jose
Hua, Wei
Mistry, Kusum
Perez-Vilar, Silvia
Pratt, Natasha

Sentinel Operations Center
Agan, Anna
Epperson, Meredith
Kanani, Xhulia
Kim, Nathan
Rai, Ashish
Shinde, Mayura
Smith, Samantha
Wiley, Megan

Sentinel Data Partners
• CVS Health (Aetna), Blue Bell, PA
• Carelon Research/Elevance Health, Wilmington, DE
• HealthPartners Institute, Minneapolis, Minnesota
• Humana Healthcare Research Inc., Louisville, KY
• Kaiser Permanente Colorado Institute for Health Research, Aurora, CO
• Kaiser Permanente Northwest Center for Health Research, Portland, OR
Thank you!
FDA Biologics Effectiveness and Safety (BEST) Coordinating Center Perspectives

Yoganand Chillaige
Acumen LLC
November 2023
Outline

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

• **Introduction to CBER BEST**
  – CBER Active Surveillance Program
  – BEST Claims-Based Distributed Data Network

• Expansion of Network Capacities in FY23

• Surveillance Activities in FY23

• Planned Activities for FY24
CBER Active Surveillance Program

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

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

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

• Databases are updated monthly, or more frequently
Outline

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

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

• Improved processes for expedited retrieval of medical records
  – Modified outreach process to increase response rate and time
  – Received over 50% of records within two weeks of request
Improving Capacity for Analysis Implementation

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

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

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

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

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

• Disseminated findings through publications, pre-prints, and presentations at scientific conferences and advisory committees
COVID-19 Related Surveillance Activities

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

• Vaccine Effectiveness (VE):
  – Evaluated effectiveness in preventing severe outcomes in the elderly Nursing Home-dwelling Medicare population
  – Evaluated effectiveness of the primary series and monovalent boosters in preventing severe outcomes and infection in the community-dwelling population, ages 5-64
COVID-19 Related Surveillance Activities

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

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

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

• Introduction to CBER BEST
• Expansion of Network Capacities in FY23
• Surveillance Activities in FY23
• **Planned Activities for FY24**
Looking Ahead: FY24

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

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

- Continue to advance methods for safety surveillance in a distributed data network
Thank You
Perspectives on FDA BEST from the Ground Up

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

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

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

Affiliated Enrollment (1993-2022) - 152M

Optum Clinical Patient 2007-2022 (107M)

Pharmacy Only: 16M
Medical & Pharmacy: 83M
Medical Only: 40M
EMR/EHR: 94M

Gender
- Male: 40.05M
- Female: 38.93M
- Unknown: 0.04M

Age
- 0-9: 3.28M
- 10-17: 5.33M
- 18-24: 6.78M
- 25-34: 13.20M
- 35-44: 14.12M
- 45-54: 2.68M
- 55-64: 12.01M
- 65-74: 8.04M
- 75+: 3.63M
- UNK: 0.00M

State
Unknown State Count: 820540
Growth and Evolution

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

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

Thank You!

John D. Seeger, PharmD, MPH, DrPH, FISPE
Chief Scientific Officer, Optum Epidemiology
Adjunct Assistant Professor of Epidemiology, Harvard T.H. Chan School of Public Health
john.seeger@optum.com
Moderated Discussion and Q&A

*Moderator: Gerrit Hamre*

Duke-Margolis Center for Health Policy
Break for Lunch

Workshop will resume at 1:05 p.m. EST
BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

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

Speakers:

Joann Gruber, U.S. Food and Drug Administration
Mao Hu, Acumen LLC
Patricia Lloyd, U.S. Food and Drug Administration
Lauren Peetluk, Optum Epidemiology
BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

Patricia C. Lloyd, PhD¹
Joann F. Gruber, PhD¹
Mao Hu, BS²
Lauren Peetluk, PhD³

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

15th Annual Sentinel Initiative Public Workshop
November 8, 2023
The BEST Initiative and its studies are funded by the U.S. Food and Drug Administration (FDA)

There are no potentially conflicting relationships to disclose

The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of FDA, Acumen, LLC, or Optum Epidemiology
Outline

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

Patricia C. Lloyd, PhD
U.S. FDA CBER
Through multiple contracts and partnerships, CBER works with a diverse group of epidemiologists, data scientists and clinical experts to conduct active surveillance studies.
Data Network

Distributed data network

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

Data are standardized

- Transformed into a common data model (CDM)
## BEST Initiative Data Sources

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

*Data lag varies for different databases from a few days to a few months.
Enhancements to the BEST Infrastructure

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

• Infrastructure
  ▪ Augmenting vaccination capture in claims databases with external data sources, such as Immunization Information Systems (IIS)
  ▪ Developing algorithms for linking mothers to infants in claims data
Immunization Information System (IIS)

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

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

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

- COVID-19 vaccine safety surveillance studies
- COVID-19 vaccine effectiveness work
- Mpox safety surveillance
Linkage of pregnant individuals and infants within BEST databases

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

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

Next Steps

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

Linkage rates by mother’s age, BEST databases

![Linkage Rate by Mother's Age](image-url)
Session Roadmap

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

• COVID-19
  – Pediatric Population
  – Bivalent Booster

• Other Vaccine Safety Studies
  – Vaccines to Prevent Mpox
  – Influenza Vaccines
Safety of COVID-19 Vaccines in Pediatric Populations

Near-real time monitoring with monthly sequential testing

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

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pfizer-BioNTech (BNT162b2)</td>
<td>6 months–17 years</td>
</tr>
<tr>
<td>Moderna (mRNA-1273)</td>
<td>6 months–17 years</td>
</tr>
<tr>
<td>Novavax (NVX-CoV2373)</td>
<td>12–17 years</td>
</tr>
</tbody>
</table>
Near Real-Time Monitoring: Pediatric Populations

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

~8.4 million doses
Of the 15 AEs sequentially tested:

13 did not meet threshold for statistical signal
2 met the threshold for statistical signal

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Common site TTS</td>
</tr>
<tr>
<td></td>
<td>Encephalitis or encephalomyelitis</td>
</tr>
<tr>
<td></td>
<td>Immune thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Non-hemorrhagic stroke</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td></td>
<td>Myocarditis/pericarditis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Bell’s palsy</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td>Hemorrhagic stroke</td>
</tr>
<tr>
<td></td>
<td>Narcolepsy</td>
</tr>
<tr>
<td></td>
<td>Seizures or convulsions</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Interim Results</th>
<th>Safety of the BNT162b2 COVID-19 Vaccine in Children Aged 5 to 17 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final Results</td>
<td>Safety of Monovalent BNT162b2 (Pfizer–BioNTech), mRNA–1273 (Moderna), and NVX–CoV2373 (Novavax) COVID–19 Vaccines in US Children Aged 6 months to 17 years</td>
</tr>
<tr>
<td>Follow-up Study</td>
<td>FDA Evaluation of a Preliminary Seizure Safety Signal from Rapid Surveillance of Children Ages 2 – 4/5 yrs. following COVID-19 mRNA Vaccination</td>
</tr>
</tbody>
</table>
## Near Real-Time Monitoring: Bivalent Booster

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

~13.9 million doses

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

16 did not meet threshold for statistical signal

2 met the threshold for statistical signal

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

Conclusion: The identified signals are consistent with existing literature. This study supports the safety profile of bivalent COVID-19 mRNA vaccines.
Dissemination & Follow-Up

VRBPAC Meeting: January 26, 2023

- Reported interim results of the bivalent booster monitoring with a particular focus on the population ≥65 years for the outcome non-hemorrhagic stroke
Other Completed/Ongoing COVID-19 Studies

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

Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the U.S.

Evaluating the Risk of Adverse Events After COVID-19 Diagnosis

BEST Post COVID-19 AE Protocol 2023 (pdf)

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

BEST MIS-C Validation Protocol 2023 (pdf)
Other Vaccine Studies

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

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

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

Assessment of Potential Adverse Events Following the 2022–2023 Seasonal Influenza Vaccines Among U.S. Adults Aged 65 Years and Older
Self-Controlled Studies for Fiscal Year 2024 Safety Surveillance Activities

Mao Hu
Acumen, LLC
Self-Controlled Studies for Future Safety Surveillance

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

---

Self-Controlled Studies

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

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

---

Implementation of Self-Controlled Studies in Safety Surveillance

• **Descriptive monitoring:** Continuous monitoring of vaccination and outcome counts to assess feasibility of self-controlled studies

• **Inferential analysis:** Self-controlled analysis conducted with all appropriate adjustments to provide comprehensive assessment of outcome risk following exposure

• Early-period analyses may be conducted based on regulatory need or availability of cases for analysis
Examples of Self-Controlled Studies

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

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

Examples of Self-Controlled Studies

Evaluation of potential adverse events following COVID-19 mRNA vaccination among adults aged 65 years and older: Two self-controlled studies in the U.S.

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

Upcoming Safety Studies

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

BEST Innovations in Data Infrastructure to Support Safety and Effectiveness Activities

Presented by: Lauren Peetluk, PhD, MPH
Optum Epidemiology

November 8, 2023
Disclosures

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

I am an employee at Optum and own stock in UnitedHealth Group.
FDA BEST: Vaccine Effectiveness (VE) Studies

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

- Pediatric VE: 5 to 17 years
- Adult VE: 18 to 64 years
- Booster VE: 12 to 64 years

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

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

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

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

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

Pediatric VE
5 to 17 years

Adult VE
18 to 64 years

Booster VE
12 to 64 years
Objectives

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

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

---

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

**Secondary objectives**
- VE in subgroups of interest
- VE in variant eras
- VE by homologous/heterologous status
**Study Design**

**Data Sources, Study Population, Study Period**

### Data Sources

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

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

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

### Study Design

Matched, retrospective cohort design

### Study Population

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

### Study Period

- **Adult/Pediatric VE:** 11 December 2020
- **Booster VE:** 12 August 2021
Study Design
Data Sources, Study Population, Study Period

Data Sources

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

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

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

Study Design

Matched, retrospective cohort design

Study Population

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

Study Period

- **Adult/Pediatric VE:** 11 December 2020
- **Booster VE:** 12 August 2021
### Study Methods and Analysis

<table>
<thead>
<tr>
<th>Matching</th>
<th>Adult/Pediatric VE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Calendar date</td>
<td>• Pregnancy status</td>
</tr>
<tr>
<td>• Age group</td>
<td>• Previous COVID-19 diagnosis</td>
</tr>
<tr>
<td>• Sex</td>
<td></td>
</tr>
<tr>
<td>• County of residence</td>
<td></td>
</tr>
<tr>
<td>• Immunocompromised status</td>
<td></td>
</tr>
<tr>
<td>• Influenza vaccine receipt</td>
<td></td>
</tr>
<tr>
<td>• Comorbidity increasing risk of COVID-19</td>
<td></td>
</tr>
</tbody>
</table>

| Propensity Score Weighting | Standardized Inverse Probability Weights (siPTW) from propensity score model with all matching characteristics + pre-specified baseline covariates |

<table>
<thead>
<tr>
<th>Study Follow-up</th>
<th>Adult/Pediatric VE:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 0 (cohort entry) until earliest of:</td>
<td>• Deviation from vaccine pattern at Time 0</td>
</tr>
<tr>
<td>• COVID-19 diagnosis</td>
<td></td>
</tr>
<tr>
<td>• End of study period</td>
<td></td>
</tr>
<tr>
<td>• Disenrollment from health plan</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Booster VE:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Any additional COVID-19 vaccine</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Analysis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cox proportional hazards regression to estimate Hazard Ratio (HR)</td>
<td>• Quantitative bias analysis</td>
</tr>
<tr>
<td>• VE = 1-HR * 100%</td>
<td>• Subgroup and sensitivity analyses</td>
</tr>
</tbody>
</table>
## Study Methods and Analysis

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

### Propensity Score Weighting
Standardized Inverse Probability Weights (siPTW) from propensity score model with all matching characteristics + pre-specified baseline covariates

### Study Follow-up
- Time 0 (cohort entry) until earliest of:
  - COVID-19 diagnosis
  - End of study period
  - Disenrollment from health plan
- **Adult/Pediatric VE:**
  - Deviation from vaccine pattern at Time 0
- **Booster VE:**
  - Any additional COVID-19 vaccine

### Analysis
- Cox proportional hazards regression to estimate Hazard Ratio (HR)
- VE = 1-HR * 100%
- **Adult/Pediatric VE:**
  - Pregnancy status
  - Previous COVID-19 diagnosis
- **Booster VE:**
  - Brand of primary series
  - Time since primary series completion

- Quantitative bias analysis
- Subgroup and sensitivity analyses
## Study Methods and Analysis

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

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

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

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

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

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

Matching

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

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

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

Propensity Score Weighting

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

Study Follow-up

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

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

Booster VE:
- Any additional COVID-19 vaccine

Analysis

Cox proportional hazards regression to estimate Hazard Ratio (HR)

VE = 1 - HR * 100%

Quantitative bias analysis

Subgroup and sensitivity analyses
Study Methods and Analysis

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

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

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

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

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

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

Booster VE:
- Any additional COVID-19 vaccine

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


Pediatric VE Results

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

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

<table>
<thead>
<tr>
<th>Variant Era</th>
<th>Data</th>
<th>VE% (95% CI)</th>
<th>Medically Diagnosed COVID-19</th>
<th>VE% (95% CI)</th>
<th>Hospital/ED-Diagnosed COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>Optum</td>
<td>35% (31%, 39%)</td>
<td>55% (41%, 65%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVS Health</td>
<td>39% (37%, 41%)</td>
<td>62% (57%, 67%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Meta-analyzed</strong></td>
<td><strong>38% (36%, 40%)</strong></td>
<td><strong>61% (56%, 65%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Delta</td>
<td>Optum</td>
<td>54% (29%, 70%)</td>
<td>76% (-68%, 96%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVS Health</td>
<td>63% (53%, 71%)</td>
<td>59% (-36%, 86%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Meta-analyzed</strong></td>
<td><strong>61% (52%, 68%)</strong></td>
<td><strong>65% (4%, 87%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delta</td>
<td>Optum</td>
<td>59% (53%, 63%)</td>
<td>81% (62%, 90%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVS Health</td>
<td>62% (60%, 65%)</td>
<td>77% (69%, 83%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Meta-analyzed</strong></td>
<td><strong>61% (59%, 64%)</strong></td>
<td><strong>78% (71%, 83%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omicron</td>
<td>Optum</td>
<td>8% (-17%, 28%)</td>
<td>60% (-54%, 90%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CVS Health</td>
<td>10% (-2%, 21%)</td>
<td>4% (59%, 42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Meta-analyzed</strong></td>
<td><strong>9% (-1%, 19%)</strong></td>
<td><strong>13% (-39%, 46%)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Booster VE Results

Presented by Bradley Layton at ICPE 2023

<table>
<thead>
<tr>
<th>Medically diagnosed</th>
<th>N</th>
<th>Events</th>
<th>VE (95% CI)</th>
<th>Hospital/ED-diagnosed</th>
<th>N</th>
<th>Events</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2</td>
<td>118,326</td>
<td>2,415</td>
<td>52% (49%, 55%)</td>
<td>BNT162b2</td>
<td>118,326</td>
<td>113</td>
<td>73% (65%, 78%)</td>
</tr>
<tr>
<td>None</td>
<td>118,326</td>
<td>3,001</td>
<td></td>
<td>None</td>
<td>118,326</td>
<td>247</td>
<td></td>
</tr>
<tr>
<td>mRNA-1273</td>
<td>68,117</td>
<td>1,297</td>
<td>55% (52%, 59%)</td>
<td>mRNA-1273</td>
<td>68,117</td>
<td>59</td>
<td>73% (63%, 81%)</td>
</tr>
<tr>
<td>None</td>
<td>68,117</td>
<td>1,710</td>
<td></td>
<td>None</td>
<td>68,117</td>
<td>133</td>
<td></td>
</tr>
<tr>
<td>JNJ-7836735</td>
<td>1,615</td>
<td>58</td>
<td>22% (-17%, 47%)</td>
<td>JNJ-7836735</td>
<td>1,615</td>
<td>&lt;11</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>1,615</td>
<td>49</td>
<td></td>
<td>None</td>
<td>1,615</td>
<td>&lt;11</td>
<td></td>
</tr>
</tbody>
</table>

- **Observed**
- **Assuming exposure sensitivity of 84%**
- **Assuming exposure sensitivity of 69%**

58% (-35%, 87%)
Booster VE Results

Presented by Bradley Layton at ICPE 2023
Conclusions

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

Stay tuned for more VE results coming soon!
## Acknowledgements

<table>
<thead>
<tr>
<th>FDA/CBER/OPBV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patricia C. Lloyd, PhD, ScM</td>
<td>Richard A. Forshee, PhD</td>
</tr>
<tr>
<td>Taiyra C. Clarke, PhD, MPH, MSc</td>
<td>Steven A. Anderson, PhD, MPP</td>
</tr>
<tr>
<td>Joann F. Gruber, PhD</td>
<td>Azadeh Shoaibi, PhD, MHS</td>
</tr>
<tr>
<td>Hui-Lee Wong, PhD</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RTI International</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>J. Bradley Layton, PhD</td>
<td>Xabier Garcia de Albeniz Martinez, MD, PhD</td>
</tr>
<tr>
<td>Dora Illei, MSc</td>
<td>Sarah Harris, MA</td>
</tr>
<tr>
<td>Christine Bui, MPH</td>
<td>Melissa McPheeeters, PhD</td>
</tr>
<tr>
<td>Alison Kawai, ScD, ScM</td>
<td>Mary S. Anthony, PhD</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Optum</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Rachel P. Ogilvie, PhD, MPH</td>
<td>Lauren Peetluk, PhD, MPH</td>
</tr>
<tr>
<td>Ron Parambi, MBBS, MPH</td>
<td>Elizabeth J. Bell, PhD, MPH</td>
</tr>
<tr>
<td>Jie Deng, MS</td>
<td>Grace Yang, MPA, MA</td>
</tr>
<tr>
<td>Michael Miller, MS</td>
<td>Kandace Amend, PhD, MPH</td>
</tr>
<tr>
<td>Jennifer Song, MA, MURP</td>
<td>John D. Seeger, DrPH, PharmD</td>
</tr>
<tr>
<td>Lisa Weatherby, MS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Acumen, LLC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yixin Jiao, MPP</td>
<td>Blair Cha, BA</td>
</tr>
<tr>
<td>An-Chi Lo, MS, MPH</td>
<td>Wenxuan Zhou, BS</td>
</tr>
<tr>
<td>Kathryn Matuska, BA</td>
<td>Jessica Hervol, MPH</td>
</tr>
<tr>
<td>Yogarand Chillarige, MPA</td>
<td>Nirabh Koirala, BA</td>
</tr>
<tr>
<td>Michael Wennecke, BS</td>
<td>John Hornberger, MD, MS</td>
</tr>
<tr>
<td>Shanlai Shangguan, MPH</td>
<td>Thomas MaCurdy, PhD</td>
</tr>
<tr>
<td>Zoe Wu, MS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CVS Health</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cheryl N McMahill-Walraven, MSW, PhD</td>
<td>Yi Liu, MDA, MS</td>
</tr>
<tr>
<td>Djenaba Audrey Djibo, PhD</td>
<td>Xun Zhang, MMS</td>
</tr>
<tr>
<td>Anne Marie Kline, MS CHES</td>
<td>Ralph Webber, BS</td>
</tr>
<tr>
<td>Nancy B Shaik</td>
<td>Arka Pal, MCA</td>
</tr>
<tr>
<td>Eugenio Abente, PhD</td>
<td>Raman Kumar, BP</td>
</tr>
<tr>
<td>Jonathan DeShazo, PhD MPH</td>
<td>Anuj Saini , MBA-IT</td>
</tr>
<tr>
<td>Smita Bhatia, MCA</td>
<td>Gaurav Bohra, BT</td>
</tr>
<tr>
<td>Ana M Martinez-Baquero, MA</td>
<td></td>
</tr>
<tr>
<td>Vaibhav Sharma, MS</td>
<td>Steve Magill, BS</td>
</tr>
<tr>
<td>Aparna Srikanth, MSc</td>
<td>Harpreet Kaur Dhillon, MCA</td>
</tr>
<tr>
<td>Carla Brannan, BA</td>
<td>Wuan M Head, BA</td>
</tr>
<tr>
<td></td>
<td>Charalynn Harris, PhD, MPH</td>
</tr>
</tbody>
</table>
Acknowledgements

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

www.bestinitiative.org
Moderated Discussion and Q&A

Moderator: Christina Silcox
Duke-Margolis Center for Health Policy
Linked-Claims EHR Data: Sentinel System’s Efforts at Improving Causal Inference & Broadening Queries

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

Speakers:

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

Jennifer Nelson, Kaiser Permanente Washington Health Research Institute

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

Robert Ball, U.S. Food and Drug Administration
Sentinel Innovation Center
Integrating innovation for a strategic objective

November 8, 2023

Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine
Brigham and Women's Hospital, Harvard Medical School, Boston
Sentinel **EHR+claims** network development

**Commercial EHR+claims Network**
- 20 million linked lives

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

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

  **Active participation by SOC staff**

**Development Network**
- ~3 million EHR+claims linked lives

**DI6: Onboarding of commercial DP—Year 4 project**

**DI7: Development network Year 4 project**
<table>
<thead>
<tr>
<th>Priorities</th>
<th>Year 1 (2020)</th>
<th>Year 2 (2021)</th>
<th>Year 3 (2022)</th>
<th>Year 4 (2023)</th>
<th>Year 5 (2024)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data infrastructure</td>
<td>Master plan</td>
<td>Master plan refinement</td>
<td>Master plan refinement</td>
<td>Master plan refinement</td>
<td>Master plan refinement</td>
</tr>
<tr>
<td>Data infrastructure</td>
<td>Horizon scan (DI1)</td>
<td>Representing unstructured data in CDM (DI2)</td>
<td>Source data mapping (DI3)</td>
<td>Harmonizing EHRs (DI4)</td>
<td>Death index (DI5)</td>
</tr>
<tr>
<td>[DI (8)]</td>
<td>Onboarding EHR data partners (DI6)</td>
<td>Development network (DI7)</td>
<td>FHIR preparedness White paper*</td>
<td>Expanding the reach of EHR-claims network (DI8)</td>
<td></td>
</tr>
<tr>
<td>Feature engineering</td>
<td>Computable phenotyping framework (FE1)</td>
<td>Scalable NLP (FE2)</td>
<td>Probabilistic phenotyping of incident outcomes (FE3)</td>
<td>Automated approaches to leverage EHRs for Sentinel (FE4)</td>
<td></td>
</tr>
<tr>
<td>[FE (5)]</td>
<td>Subset calibration methods (CI4)</td>
<td>Causal inference framework (CI2)</td>
<td>Toolkit development and refinement for EHR-claims network (CI5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal inference</td>
<td>Evaluating targeted learning in EHR data (CI1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[CI (5)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection analytics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[DA (2)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innovation incubator</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use Cases [UC (2)]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- *ASPE supported project

- EHR detection analytics review (DA1)
- Empirical evaluation of detection analytic methods using EHRs (DA2)
- Empirical application of EHR-claims network to address ARIA insufficiency (UC1)
- Empirical application of EHR-claims network to enhance ARIA sufficiency (UC2)
The Sentinel

*EHR+claims network:*

Value Add Part 1:

**Reducing ARIA insufficiencies**

If sample size allows, analyses can be performed using data from the network containing 20 million lives to leverage additional EHR based data on outcomes or confounders not available in claims.
Safety/RWE studies in the Sentinel EHR + claims network: What is achievable with the expected 20 million lives?

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

* Based on prevalence reported in Horizon scan queries
The Sentinel
EHR+Claims
Network:

Value Add Part 2:

Strengthening ARIA sufficient analyses
Further strengthening ARIA sufficient analyses via the Sentinel EHR+claims network: 5 key use cases

1. Rapid balance evaluation of patient characteristics in EHRs and not measured in claims data (Di6)

2. Routinely apply corrections for unmeasured confounding through subset calibration toolkit (Ci4)

3. NLP assisted validation of claims-based algorithms for outcomes to inform quantitative bias analysis (Di7)

4. Routinely expand claims-based analyses with deep clinical information on outcomes, confounders and inclusion criteria (Ci1, Fe2, Fe4)

5. Expanding signal detection capabilities by incorporating EHR data elements (Da1, Da2)

Identifiers in the bracket indicate upcoming or ongoing IC projects that aim to demonstrate proof of concept for these enhancements.
1. Rapid confounder balance evaluation of factors unmeasured in Sentinel claims data

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

<table>
<thead>
<tr>
<th></th>
<th>Before PS-matching</th>
<th>Other DPP-4 inhibitors</th>
<th>After PS-matching</th>
<th>Other DPP-4 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linagliptin (N = 243)</td>
<td>(N = 3041)</td>
<td>Linagliptin (N = 240)</td>
<td>(N = 271)</td>
</tr>
<tr>
<td><strong>Median (IQR) laboratory test results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>7.8 (7.0-9.0)</td>
<td>8.1 (7.1-9.5)</td>
<td>7.8 (7.0-9.0)</td>
<td>7.9 (7.1-9.1)</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.9 (0.8-1.1)</td>
<td>0.9 (0.7-1.0)</td>
<td>0.9 (0.8-1.1)</td>
<td>0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73 m²</td>
<td>98 (84-108)</td>
<td>102 (92-115)</td>
<td>101 (92-115)</td>
<td>103 (92-116)</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>168 (146-197)</td>
<td>171 (147-201)</td>
<td>168 (146-196)</td>
<td>171 (152-200)</td>
</tr>
<tr>
<td>HDL, mg/dL</td>
<td>40 (34-49)</td>
<td>42 (35-50)</td>
<td>40 (34-49)</td>
<td>42 (36-49)</td>
</tr>
<tr>
<td>LDL, mg/dL</td>
<td>100 (76-122)</td>
<td>95 (73-120)</td>
<td>100 (76-121)</td>
<td>97 (70-120)</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>171 (110-233)</td>
<td>156 (105-226)</td>
<td>171 (109-233)</td>
<td>156 (103-216)</td>
</tr>
</tbody>
</table>

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

Year 5 plan: To be applied throughout the Development Network
2. Correcting claims analyses for unmeasured confounding using subset calibration tools

PS calibration

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

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

Steps:

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

Year 5 plan: To be applied throughout the Development Network
3. NLP-assisted chart validation using EHR data from Development Network for efficient gold standard development (free text and structured)

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

- Most important keyword ('topic word')
  - E.g., Crohn for Crohn's disease

- Reviewer sees similar terms highlighted in the text notes
  - E.g., CD, IBD, Crohn's disease

- Reviewer highlights additional keywords that s/he deems related
  - E.g., evidence of treatment with immunosuppressives

Trained model applied to future notes to help highlight context specific terms and lessen reviewer burden as the task proceeds

Highlighted terms used as inputs to iteratively train supervised ML model to predict similar terms

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

Ye et al. BMC Medical Informatics and Decision Making. 2021
4. Expand claims-based analyses with deep clinical information on outcomes, confounders and inclusion criteria using scalable phenotyping

Aim is to identify the most informative features of the Phenotype based on ‘surrogates’/‘silver’ labels e.g. frequency of the ICD codes for the condition of interest.

Aim is to identify the most predictive features of interest, trained using gold standard labels (manually curated from chart review).

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

Year 5 plan: Implementation at KP, VUMC, MGB
5. Expand signal detection capabilities incorporating EHR data elements

Empirical evaluation of detection analytic methods using EHRs (DA2)

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

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

**Aim 1 – Data Extraction and Transformation**

- SCDM ICD Codes
- EHR ICD Codes
- Vital Signs Lab Results
- Notes

IC lead: Josh Smith; Shirley Wang (project kicked off Jan 2023)
A series of use cases emulating ARIA requests

The expansion of ARIA sufficiency will be tested by applying the 5 use cases discussed above to potential ARIA questions
Improving Confounding Control in RWE Studies

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

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

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

![Diagram showing the relationship between exposure (A), observable confounder (C), unobserved confounder (U), and outcome (Y).]

- **A**: exposure; e.g., start of a new drug
- **Y**: outcome of interest
- **C**: observable confounder (serves as proxy)
- **U**: unobserved confounder

<table>
<thead>
<tr>
<th>Unobserved confounder</th>
<th>Observable proxy measurement</th>
<th>Coding examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very frail health</td>
<td>Use of oxygen canister</td>
<td>CPT-4</td>
</tr>
<tr>
<td>Sick but not critical</td>
<td>Code for hypertension during a hospital stay</td>
<td>ICD-9, ICD-10</td>
</tr>
<tr>
<td>Health-seeking behavior</td>
<td>Regular check-up visit; regular screening examinations</td>
<td>ICD-9, CPT-4, #PCP visits</td>
</tr>
</tbody>
</table>
Leveraging Unstructured EHRs for Large-Scale Proxy Adjustment

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

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Sample Size</th>
<th>Outcome</th>
<th>Baseline Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N&lt;sub&gt;Total&lt;/sub&gt;</td>
<td>N&lt;sub&gt;Treated&lt;/sub&gt;</td>
<td>N&lt;sub&gt;Comparator&lt;/sub&gt;</td>
</tr>
<tr>
<td>Study 1:&lt;sup&gt;A&lt;/sup&gt;</td>
<td>21,343</td>
<td>13,576</td>
<td>7,767</td>
</tr>
<tr>
<td>Study 2:&lt;sup&gt;B&lt;/sup&gt;</td>
<td>35,031</td>
<td>12,872</td>
<td>22,159</td>
</tr>
</tbody>
</table>

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

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

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

** N<sub>total</sub> = total sample size, total number of outcomes, and total number of baseline covariates, respectively.

** N<sub>predefined</sub> = Number of prespecified variables
Results for Plasmode Simulations

General Findings:

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

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

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

• Can principles of targeted learning improve large-scale covariate adjustment in ultra high-dimensional RWE studies involving linked claims data with EHR records?
2. Correcting claims analyses for unmeasured confounding using subset calibration tools

- **Key challenge for Active Risk Identification and Analysis (ARIA) system**
  - Incomplete confounder capture in claims data → BIAS
  - **Example**: Confounding by frailty for influenza vaccine effectiveness estimation

- **Promising solution** to both reduce ARIA insufficiency & strengthen ARIA sufficient analyses
  - Obtain more detailed confounder data on a subset using Innovation Center (IC) EHR data
  - Use EHR confounders (on a subset) to reduce bias in (calibration of) claims estimates
  - Can also think of this as a “missing data” problem (EHR data are not available on everyone)

- **Ongoing aims for Subset Calibration (Causal Inference project 4 or CI4)**
  - Build on Sentinel’s Missing Data Toolkit (CI3) framework to assess “why” data are missing
  - By studying a wider range of subset calibration methods
    - ✓ Common methods in practice: complete case, inverse weighting, multiple imputation
    - ✓ Newer methods w/robustness & precision gains: survey calibration, targeting learning
  - Focus is on simulation evaluations to compare methods under known conditions

- **Subset Calibration (CI4) deliverables**
  - Evidence-based guidance on selecting suitable method(s) for Sentinel applications
  - Reusable analyses tools for Sentinel to implement the novel methods that are tested

*Year 5 plan: To be applied throughout the Commercial Data Partner network*
4. Expand claims-based analyses with deep clinical information on outcomes, confounders & inclusion criteria

- **Key challenge for Active Risk Identification & Analysis (ARIA)**
  - Some outcomes are inaccurately captured in claims → BIAS
  - Examples: Anaphylaxis, acute pancreatitis

- **Promising solution** to reduce ARIA insufficiencies is to use NLP
  - Extract structured features from rich unstructured clinical text in EHR
  - Build more accurate outcome-identifying machine-learned models using these NLP features
  - Simple, automated, and reusable

- **Completed aims & deliverables for Feature Engineering project 1 (FE1)**
  - Scalable Phenotyping Framework
    - 2 validation studies using IC EHR data
    - 2 NLP model development studies to ↑ claims-based positive predictive value (PPV)
    - 1 NLP study to find missing cases (↑sensitivity)
    - 1 general framework guidance
      - To facilitate future effective & scalable use of these methods in Sentinel
### Clinical complexity:
- Lack of agreement about diagnostic criteria
- Lack of definitive diagnostic tests
- Presence of competing diagnoses
- Diagnostic resource constraints (time, tech.)

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

---

**Assessing Fitness for Purpose - Complexities**

![Complexity Diagram](image)

- **Opioid overdose** (ED presentation)
- **Severe allergic reaction**
- **Anaphylaxis**
- **Acute pancreatitis**
- **Diabetes**

---

**Slide courtesy of David Carrell, Kaiser Permanente Washington**
Thank you
Linked-Claims EHR Data: Sentinel System’s Efforts at Improving Causal Inference & Broadening Queries

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

Speakers:

Robert Ball, U.S. Food and Drug Administration

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

Jennifer Nelson, Kaiser Permanente Washington Health Research Institute

Richard Wyss, Harvard Medical School and Brigham and Women’s Hospital
Moderated Discussion and Q&A

*Moderator: Rachele Hendricks-Sturrup*
Duke-Margolis Center for Health Policy
Break
Workshop will resume at 2:50 p.m. EST

November 14, 2023
12:30 – 4:30 PM
National Press Club
or
Virtually Via Zoom

Visit healthpolicy.duke.edu/events
Leveraging Lessons Learned to Move Beyond COVID-19

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

Speakers:

Richard Forshee, U.S. Food and Drug Administration
Silvia Perez-Vilar, U.S. Food and Drug Administration
Susan Winckler, Reagan-Udall Foundation for the FDA
FDA Benefit-Risk Assessment of COVID-19 Vaccines and Use of Real-World Data & Evidence

Richard Forshee

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

15th Sentinel Annual Meeting
November 8, 2023
Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent FDA’s views or policies.
Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Comirnaty) for Age 16-29 years

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

Vaccine, March 2022
Analysis of Condition

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

- No licensed vaccines or anti-viral drugs for COVID-19
- Emergency Use Authorizations of three vaccines:
  - Pfizer-BioNTech Vaccine for 16+ years of age
  - Moderna Vaccine for 18+ years of age
  - Janssen for age 18+ years of age
Considerations for Benefits

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

- No notable serious adverse events and deaths related to vaccination reported in clinical trials
- Elevated myocarditis/pericarditis case rate identified by post-EUA safety surveillance
  - Clinically significant risk
  - Higher risk among male adolescents
- Risk management options:
  - Product label
  - Post-market safety surveillance
  - Post-market requirement/commitment
Whether Benefits of COMIRNATY Outweigh the Risks for Age 16-29 years?

• Uncertainty in Benefits
  – Uncertain dynamic of pandemic (greater vaccination benefit when the disease incidence is higher)
  – Emerging Delta variant (unknown vaccine effectiveness)
  – Waning of vaccine protection

• Clinically significant risk of myocarditis/pericarditis
  – Higher risk among male adolescents
Benefit-Risk Assessment of COVID-19 Vaccine, mRNA (Comirnaty) for Age 16-29 years, *Vaccine, March 2022*

Per million individuals with two-doses of vaccine
What RWDs/RWEs Were Used?

Benefits
(Prevented COVID-19 cases)

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

Risks
(Excess myo/pericarditis cases)

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

• **Most RWD/RWE not generated for a specific study**
  – Varied data collection protocols
  – Inconsistent data definitions
  – Bias in data reporting
  – Missing data/information

• **Evaluate the strength of RWD/RWE**
  – Fit for use?
  – Any way to reduce the bias?

• **Use sensitivity analysis to evaluate the uncertainty**

• **Acknowledge limitations**
Model Scenarios for Age 16-29 years

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

Common Model Inputs

- Protection period\(^1\): 6 months
- Vaccine effectiveness\(^2\) against
  - Cases: 70%
  - Hospitalization: 80%
- Myo/pericarditis rate: FDA BEST/OPTUM

Two Major Scenarios

<table>
<thead>
<tr>
<th>Pessimistic Scenario</th>
<th>COVID-19 case incidence(^3)</th>
<th>COVID-19 hospitalization incidence(^3)</th>
<th>Vaccine attributable myo/pericarditis death rate(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>July 10, 2021 rate</td>
<td>July 10, 2021 rate</td>
<td>0.002%</td>
<td></td>
</tr>
</tbody>
</table>

| Most Likely Scenario | 10x July 10, 2021 rate     | 4x July 10, 2021 rate           | 0%                               |

\(^1\)Assumption, \(^2\)Real-world evidence, \(^3\)CDC COVID NET & DataTracker, \(^4\)VAERS data & assumption
Result - Most Likely Scenario (per Million)

Prevented COVID-19 Deaths: 506
Prevented COVID-19 ICU Stays: 135771
Prevented COVID-19 Hospitalizations: 166
Prevented COVID-19 Cases: 4

Excess Myo/Pericarditis Deaths: 98, 196
Excess Myo/Pericarditis Hospitalizations: 0, 0
Excess Myo/Pericarditis Cases: 0, 0
Result - Pessimistic Scenario (per Million)

Benefits
- Prevented COVID-19 Deaths: 1
- Prevented COVID-19 ICU Stays: 41
- Prevented COVID-19 Hospitalizations: 127
- Prevented COVID-19 Cases: 13577

Males 16-17yo
- 0

Risks
- Excess Myo/Pericarditis Deaths
- Excess Myo/Pericarditis Hospitalizations
- Excess Myo/Pericarditis Cases
Conclusion Regarding Benefit-Risk

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

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

Trade-off conclusion & decision
- Known and potential benefits outweigh the known and potential risks
- FDA approved licensure of COMIRNATY for individuals 12y+ in Nov. 2021
Acknowledgment

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

Richard Forshee, Ph.D.
FDA/CBER

Richard.Forshee@fda.hhs.gov
FDA INSISTS REALITY MATTERS.
Leveraging Lessons Learned to Move Beyond COVID-19

15th Annual Sentinel Initiative Public Workshop
November 8, 2023

Silvia Perez-Vilar, PhD, PharmD
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)
The views expressed represent those of the presenter and do not necessarily represent the official views of the U.S. Food and Drug Administration
## Leveraging Lessons Learned to Move Beyond COVID-19

### Agenda

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>COVID-19 Sentinel Surveillance System</td>
</tr>
<tr>
<td>2</td>
<td>Contributions</td>
</tr>
<tr>
<td>3</td>
<td>Strengths</td>
</tr>
<tr>
<td>4</td>
<td>Weaknesses</td>
</tr>
<tr>
<td>5</td>
<td>Opportunities</td>
</tr>
<tr>
<td>6</td>
<td>Challenges</td>
</tr>
<tr>
<td>7</td>
<td>Closing Remarks</td>
</tr>
</tbody>
</table>
COVID-19 Surveillance System

Leveraging Lessons Learned to Move Beyond COVID-19

Common Data Model Enhanced

• SARS-CoV-2 laboratory test results

New Data Sources Incorporated

• Outpatient and inpatient Electronic Health Record (EHR) data

Rapidly refreshed distributed database (RAPID COVID)

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

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

Noelle M. Cocoros, Candace C. Fuller, Sruthi Adimadhyan, Robert Ball, Jeffrey S. Brown, Gerald J. Dal Pan, Sheryl A. Klutberg, Vincent Lo Re III, Judith C. Maro, Michael Nguyen, Robert Orr, Dianne Parris, Jonathan Perlis, Russell T. Poland, Meghan Rogers Driscoll, Kenneth Sands, Serpjeew 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 Ke, MD; Sima Perez-Villar, PhD; Daniela Siljanovic, PhD; Corinne Woods, MPH.

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

Methods development

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

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

Validation of diagnosis codes to identify hospitalized COVID-19 patients in health care claims data

Sheryl A. Kluberg, Laura Hou, Sarah K. Dutcher, Monisha Billings, Brian Kit, Sengwee Toh, Sascha Dublin, Kevin Haynes, Annemarie Kline, Mahesh Malyani, Pamela A. Pawloski, Eric S. Watson, Noelle M. Cocoros, ... See fewer authors

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

Natural history of COVID-19

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

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

JAMA Original Investigation

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

Emergency Response

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

Research Letter

April 8, 2022

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

Marie C. Bradley, PhD, MPH, MScPH¹; Silvia Perez-Vilar, PhD, PharmD¹; Yoganand Chilarrige, MPA²; Diane Dong, RN, MPH³; Ashley I. Martinez, PharmD, PhD²; Andrew R. Weckstein, BA³; Gerald J. Dal Pan, MD, MHS¹

Author Affiliations | Article Information

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

Therapeutic Management of Nonhospitalized Adults With COVID-19

Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021 | Critical Care Medicine | JAMA | JAMA Network
HAN Archive - 00463 | Health Alert Network (HAN) (cdc.gov)
National Institutes of Health (NIH)’s COVID-19 Treatment Guidelines updated on August 8, 2022, Nonhospitalized Adults: Therapeutic Management | COVID-19 Treatment Guidelines (nih.gov)
Sentinel Contributions

Regulatory Decision-Making

- Estimate Magnitude of the “At-risk” Population Using Drugs that Interact with Paxlovid to Inform Labeling Decisions

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

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

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

Support Other Federal Agencies

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

Study Design Based on ACTIV-4a RCT

- Outpatient-identified COVID-19 and subsequent hospitalized thrombotic events. Perez-Vilar S., Martinez A.I., Shinde M., Kempner M.E., Kolonoski J., Dutcher S.K., Kit B.
Sentinel Contributions

Collaboration with other U.S. Stakeholders

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

Study Synopsis: Natural History of Coagulopathy in COVID-19

Vincenzo Lo Re III, MD, MSCE,§ Sarah K. Danteher, PhD,§ Silvia Perez-Viliar, PharmD, PhD,§ Dena M. Carbonari, MS,§ Sean Hennessy, PharmD, PhD,§ Maria E. Kempner, BA,§ Brian Kit, MD,§ Jenice Ko, BS,§ Allyson M. Piskiko, MD, MSCE,§ Meighan Rogers Driscoll, MPH,§ Jeffrey Brown, PhD,§ Noelle Cocoros, DSc, MPH,§
Sentinel Contributions

Collaboration with other Regulatory Agencies

• International Coalition of Medicines Regulatory Authorities (ICMRA)

International Meta-Analyses

Under review

Natural history of coagulopathy (led by FDA)

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

Ongoing

Pregnancy Observational Studies (led by EMA)

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

Search Covid-19 infectiON and medicineS in preGNancy (zenodo.org)
COVID-19 Pregnancy Study Implementation | Sentinel Initiative
FDA Sentinel System's Coronavirus (COVID-19) Activities

FDA's Sentinel System is engaged in numerous activities to protect and promote public health during the COVID-19 pandemic, ranging from monitoring the use of drugs, describing the course of illness among hospitalized patients, and evaluating the treatment impact of therapies actively being used under real-world conditions. Descriptions of efforts led by the Center for Drug Evaluation and Research are shown below. Please visit the links to learn more about each area of activity and also visit:

FDA's Official COVID-19 Drugs Page
Leveraging Lessons Learned to Move Beyond COVID-19

Strengths: What Did We Do Well?

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

Critical data elements
- Infected variant, COVID-19 vaccination status, capture of supplemental oxygen, disease onset date identification, disease severity, race

Timeliness
- Data lag, query turnaround, approval and clearance processes

Nationally representative data sources with EHR inpatient data

Limited experience with newly incorporated EHR databases
- HCA, TriNetX

Research availability not always in step with rapidly evolving pandemic
- Questions no longer relevant, shifting priorities
Opportunities: What Could Give us an Advantage to Prepare For a Future Pandemic?

- Fresher data
- Nationally-representative EHR databases with inpatient data
- Further enhancement of the Common Data Model
- EHR-claims linked databases
- Artificial intelligence
Opportunities: What Could Give us an Advantage to Prepare for a Future Pandemic?

- Streamlined and more affordable access to medical records for validation of case definitions for outcomes, exposures, and covariates
- Data standards/integration
- Foster and maintain internal, national, and international collaborations
- Streamlined processes for approval, query turnaround, and clearance
### Challenges: What Are Potential Barriers to Prepare for a Future Pandemic?

- Data completeness, reliability, relevance
- Inconsistent access to validated and sufficiently large databases
- Privacy/security standards
- Slow development and incorporation of expanded capabilities
- Competing interests/priorities
- Unpredictability of future pandemics
- Maintaining consistent funding
Leveraging Lessons Learned to Move Beyond COVID-19

Closing Remarks

**Strengths**
- Master protocols
- Emergency response
- Regulatory-decision making

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

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

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

CDER OSE, OND, DB7
Sentinel Operations Center
Sentinel Data Partners
Centers for Medicare & Medicaid
International Coalition of Medicines Regulatory Authorities (ICMRA)
Reagan Udall Foundation
Thanks
Leveraging Lessons Learned to Move Beyond COVID-19

Susan C. Winckler, RPh, Esq
CEO

Fifteenth Annual Sentinel Initiative Public Workshop
Nov. 8, 2023
Washington, DC
Together, we will **create** and **lead**.

**CREATE**
- **CONTEXT** — tie data to the question, address bias, explain validation strategies.
- **RESPECT** — for patient privacy and the patient voice is paramount.
- **EARN TRUST** — show processes, analytic approaches, and comparisons. Be open to input. Challenge with productive intent.
- **ACT FAST AND DO GOOD WORK** — act with a sense of urgency, but not at the expense of quality or credibility.
- **TRANSPARENCY** — ruthless transparency.
- **EMBRACE AND EXPLORE** — convergence and discordance to facilitate understanding and generate knowledge.

**LEAD**
- **LEARN** — continually integrate best practices from sharing process, limitations, pitfalls, and successes.
- **EXERCISE PATIENCE** — state when a question can’t be answered right away and institute action to answer it.
- **ACCESSIBILITY AND TRACEABILITY** — document data generation, processing, curation, and analytics.
- **DISSEMINATE WORK** — to show what good looks like. **Teach, Don’t Preach**.
Lesson Learned: We can (and must) improve the collection of real-world data to power the generation of real-world evidence
One Individual’s Clinical Journey:
Diagnostic Testing Data

Credit to then-FDA team members R.J. Andrews and Gina Valo
Data collection in health care delivery and payment inconsistently captures sufficient data about the diagnostic test used.

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

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

- **65%** of confirmed cases reported to the CDC had complete race and ethnicity reported\(^1\)

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

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

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

- Hesitancy to tell
  - Distrust
  - Relevance?
- Hesitancy to ask
  - Relevance?
  - Discomfort
- Standardization
- Data privacy protection
- Failure to transmit
- Data Loss

Continuum of Care

- Availability
  - Access to Care and Coverage
- Reporting
- Collection
- Curation
- Integration

Care, Coverage, and Research
RAISE Specific Aims

- **Gather** to create opportunities for Collective Learning and Community Capacity Building
- **Create a Tool** to prioritize solutions
- **Evaluate** the impact of the project to initiate a change in practice
Thank You/Questions
Moderated Discussion and Q&A

Moderator: Christina Silcox
Duke-Margolis Center for Health Policy
Stakeholder Reflections on Sentinel

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

Speakers:

Heather Rubino, Pfizer, Inc.

Philip Goodney, Dartmouth College

Jeffrey Brown, TriNetX

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

Patricia Bright, U.S. Food and Drug Administration

Steve Anderson, U.S. Food and Drug Administration
Moderated Discussion and Q&A

Moderator: Trevan Locke
Duke-Margolis Center for Health Policy
Closing Remarks

Gerrit Hamre
Research Director, Duke-Margolis Center for Health Policy
Thank You!

Contact Us

healthpolicy.duke.edu

Subscribe to our monthly newsletter at dukemargolis@duke.edu

1201 Pennsylvania Avenue, NW, Suite 500
Washington, DC 20004

DC office: 202-621-2800
Durham office: 919-419-2504

Follow Us

DukeMargolis

@DukeMargolis

@DukeMargolis

Duke Margolis