Real-world data
Data networks, standardization, and federated analysis

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Harvard Medical School and Harvard Pilgrim Health Care Institute

January 18, 2022
When or why do we need large amount of real-world data?
To study rare exposures
To study rare exposures

To study rare outcomes
To study rare exposures

To study rare outcomes

To study specific patient subgroups
To study specific patient subgroups
To study rare exposures
To study rare outcomes
To study newly approved medical products
How do we get large amount of real-world data?
Wait for the data to accrue over time...
Bring multiple real-world data sources together
How do we bring multiple real-world data sources together?
Ask everyone to send all their data to a centralized location
But is that feasible?
Loss of patient privacy
Loss of patient privacy

Unauthorized uses of transferred data
Loss of patient privacy

Unauthorized uses of transferred data

Inaccurate analysis or interpretation of data
Loss of patient privacy

Unauthorized uses of transferred data

Inaccurate analysis or interpretation of data

Disclosure of sensitive corporate information
Loss of patient privacy
Unauthorized uses of transferred data
Inaccurate analysis or interpretation of data
Disclosure of sensitive corporate information
Regulatory or contractual restrictions
Design of a National Distributed Health Data Network

Judith C. Maro, MS; Richard Platt, MD, MSc; John H. Holmes, PhD; Brian L. Strom, MD, MPH; Sean Hennessy, PharmD, PhD; Ross Lazarus, MBBS, MPH; and Jeffrey S. Brown, PhD

Developing the Sentinel System — A National Resource for Evidence Development

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


The FDA Sentinel Initiative — An Evolving National Resource

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

• How Sentinel gets, standardizes, and checks its data
• How Sentinel performs privacy-protecting analysis
• How Sentinel contributes to FDA’s regulatory mission
• How Sentinel builds trust through transparency
• How Sentinel continues to innovate and expand its capabilities
• Discussion
• How Sentinel gets, standardizes, and checks its data

• How Sentinel performs privacy-protecting analysis

• How Sentinel contributes to FDA’s regulatory mission

• How Sentinel builds trust through transparency

• How Sentinel continues to innovate and expand its capabilities

• Discussion
Male, 55 Years Old, From Boston

Has Appendectomy

Diagnosed with Hypertension

Routine Office Visit

2017

1/1/2017

Encounter

Office Visit Diagnosis: Influenza with pneumonia

Dispensings

Prescription: Antibiotic

2018

3/15/2018

Encounters

Emergency Department Procedure: Appendectomy

3/15/2018 - 3/18/2018

Dispensings

Hospital: Inpatient Stay

2019

12/11/2018

Encounter

Office Visit Diagnosis: Hypertension

Dispensings

Prescription: Anti-hypertensive

2020

10/31/2019

Encounter

Office Visit Diagnosis: Hypertension
### DEMOGRAPHIC

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### DIAGNOSIS

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### DEATH

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### CAUSE OF DEATH

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Hypothetical numbers; for illustrative purposes only
Individual data partners

Site 1
Site 2
Site 3
Site 4

Data standardization

Site 1
Site 2
Site 3
Site 4
**Preparation**

Sentinel Operations Center prepares quality review and characterization package for new dataset.

**Data Quality Review and Characterization Process**

Data quality review and characterization process may refresh quarterly, semi-annually, or annually, depending on the data partner.

**Transformation**

Data Partner transforms source data into the Sentinel Common Data Model.

**Distribution**

Sentinel Operations Center distributes quality review and characterization package for new dataset.

**Quality Assurance Checks & Model Compliance**

Data Partner runs quality review and characterization package completing the following:

- Level 1 checks: single table checks
- Level 2 checks: cross-table checks

Quality reviews and characterization package outputs lists of errors or anomalies (flags) identified during data checks.

Data Partner resolves these flags and sends a detailed response to the Sentinel Operations Center.

**Quality Assurance Review**

Sentinel Operations Center receives output from Data Partner and reviews.

- Level 3 checks: cross-time checks

Sentinel Operations Center runs additional quality assurance checks.

Sentinel Operations Center evaluates any additional flags and creates issue report for Data Partner to address.

**Approval**

Sentinel Operations Center Quality Assurance Manager approves dataset for use in queries.

**Completion**

Data Partner investigates issues identified in report generated by the Sentinel Operations Center and resolves remaining flags.
Guidance for Industry and FDA Staff

Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

SENTINEL DATA QUALITY ASSURANCE PRACTICES

COMPLIANCE WITH “GUIDANCE FOR INDUSTRY AND FDA STAFF: BEST PRACTICES FOR CONDUCTING AND REPORTING PHARMACOEPIDEMIOLOGIC SAFETY STUDIES USING ELECTRONIC HEALTHCARE DATA”
### Administrative Data

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<td>Patient ID</td>
<td>Patient ID</td>
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<td>Enrollment Start &amp; End Dates</td>
<td>Patient ID</td>
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<tr>
<td>Medical Coverage</td>
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<td>Drug Coverage</td>
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<td>Amount Dispensed</td>
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### Clinical Data

#### Lab Result
- Patient ID
- Result & Specimen
- Collection Dates
- Test Type, Immediacy & Location
- Logical Observation Identifiers Names and Codes (LOINC®)
- Etc.

#### Vital Signs
- Patient ID
- Measurement Date & Time
- Height & Weight
- Diastolic & Systolic BP
- Tobacco Use & Type
- Etc.

### Registry Data

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<tr>
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### Inpatient Data

#### Inpatient Pharmacy
- Patient ID
- Encouter ID
- Rx Administration Date & Time
- National Drug Code (NDC)
- Rx ID
- Route
- Dose
- Etc.

#### Inpatient Transfusion
- Patient ID
- Encouter ID
- Transfusion Administration ID
- Administration Start & End Date & Time
- Transfusion Product Code
- Blood Type
- Etc.

### Mother-Infant Linkage Data

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<td>Mother Admission &amp; Discharge Date</td>
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### Auxiliary Data

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What are you investigating?

Medical Products Only

Outcomes Only

Medical Products & Outcomes

- Type 1: Background Rates
- Type 2: Incidence Rates
- Type 2 or 4: Propensity Score Analysis
- Type 2 or 4: Covariate Stratification
- Type 3: Self-Controlled Risk Interval Design
- Type 2: Interrupted Time Series
- Type 2: Multiple Events Tool

Utilization of Individual Drugs
- Type 5: Medical Product Utilization
- Type 2: Medical Product Use Overlap
- Type 6: Medical Product Switching

Utilization Patterns Between Multiple Drugs

Utilization in Pregnancy
- Type 4: Medical Product Use in Pregnancy
788 million person-years of data

15 billion pharmacy dispensing

71 million individuals currently accruing data

14 billion medical encounters
Claims (with Limited EHR Network)

Active Risk Identification and Analysis (ARIA)*

- Sentinel Distributed Database
- IBM® MarketScan® Research Databases
  - Sentinel Common Data Model
  - Sentinel Analytic Tools
  - Access to Medical Records within the Sentinel Distributed Database

EHR Data Aggregators

- TriNetX
- IBM Watson Health
  - Proprietary Common Data Models
  - Web-Based Query Interface & Custom Programming
  - Access to Medical Records varies by Source

EHR Data Warehouse

- HCA Healthcare
- Veradigm
  - Data Warehouse for Multiple Healthcare Organizations in a System
  - Custom Programming
  - Access to Medical Records

EHR Networks

- PCORnet
  - PCORnet Common Data Model
  - PCORnet Analytic Tools
  - Access to Medical Records

*Note: The Active Risk Identification and Analysis (ARIA) System is comprised of the Sentinel Distributed Database, the Sentinel Common Data Model, and Sentinel analytic tools.
A systematic review of validated methods for identifying cerebrovascular accident or transient ischemic attack using administrative data

Susan E. Andrade\(^6\), Leslie R. Harrold, Jennifer Tjia, Sarah L. Cutrona, Jane S. Saczynski, Katherine S. Dodd, Robert J. Goldberg and Jerry H. Gurwitz

Meyers Primary Care Institute (Reliant Medical Group, Fallon Community Health Plan, and University of Massachusetts Medical School), Worcester, MA, USA

A systematic review of validated methods for identifying heart failure using administrative data

Jane S. Saczynski\(^9\), Susan E. Andrade, Leslie R. Harrold, Jennifer Tjia, Sarah L. Cutrona, Katherine S. Dodd, Robert J. Goldberg and Jerry H. Gurwitz

Division of Geriatric Medicine and Meyers Primary Care Institute, University of Massachusetts Medical School, Worcester, MA, USA

A systematic review of validated methods for identifying suicide or suicidal ideation using administrative or claims data

James T. Walkup\(^1\), Lisa Townsend\(^2\), Stephen Crystal\(^3,4\) and Mark Olsson\(^4\)

1 Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, USA
2 School of Social Work, Rutgers University, New Brunswick, NJ, USA
3 Chronic Disease Management and Outcomes, Center for Health Services Research on Pharmacotherapy, New Brunswick, NJ, USA
4 Department of Psychiatry, Columbia University, New York, New York, USA

A systematic review of validated methods for identifying pancreatitis using administrative data

Kevin Moores\(^1,2,5\), Bradley Gilchrist\(^1,2\), Ryan Carnahan\(^1\) and Thad Abrams\(^4,5\)

1 Division of Drug Information Service, The University of Iowa College of Pharmacy, Iowa City, IA, USA
2 Iowa Drug Information Service, The University of Iowa College of Pharmacy, Iowa City, IA, USA
3 Department of Epidemiology, University of Iowa College of Public Health, Iowa City, IA, USA
4 Department of Internal Medicine, Division of General Internal Medicine, University of Iowa Carver College of Medicine, Iowa City, IA, USA
5 Center for Implementation of Innovative Strategies in Practice, Iowa City Veterans Affairs Medical Center, Iowa City, IA, USA
Validation of acute myocardial infarction in the Food and Drug Administration’s Mini-Sentinel program

Sarah L. Cutrona1,2*, Sengwee Toh3, Aarthi Iyer7, Sarah Foy4, Gregory W. Daniel5, Vinit P. Nair6, Daniel Ng7, Melissa G. Butler4, Denise Boudreau8, Susan Forrow2, Robert Goldberg1, Joel Gore6, David McManus8, Judith A. Racoosin7 and Jerry H. Gurwitz7

Validation of anaphylaxis in the Food and Drug Administration’s Mini-Sentinel

Kathleen E. Walsh1,2, Sarah L. Cutrona1,2, Sarah Foy4, Meghan A. Baker3,4, Susan Forrow2, Azadeh Shoaiib2, Pamela A. Pawloski6, Michelle Conroy3, Andrew M. Fine3, Lise E. Nigrovic6, Nandini Selvam9, Mano S. Selvan10, William O. Cooper11 and Susan Andrade1

Validation of acute kidney injury cases in the Mini-Sentinel Distributed Database

Prepared by: Uptal D. Patel, MD,1,2* N. Chantelle Hardy, MPH,2 David H. Smith, RPh, PhD,2 Jerry H. Gurwitz, MD,2 Chi-yuan Hsu, MD, MSC,2 Chirag R. Parikh, MD, PhD,2 Steven M. Brunelli, MD, MSC,7 Meghan Baker, MD, ScD,9 Susan Forrow, BA,9 Carly Comins, BS,9 Denise M. Boudreau, PhD, RPh,7 Chunfu Liu, ScD,10 Pamela A. Pawloski, PharmD,12 Nandini Selvam, PhD, MPH,11 Mano S. Selvan, PhD,11 Shannon Stratton, BS,11 Jeffrey J. VanWormer, PhD,12 George Aggrey, MD, MPH,2 Melanie Blank, MD,13 Patrick Archdeacon, MD,13
Early impact of the ICD-10-CM transition on selected health outcomes in 13 electronic health care databases in the United States

Catherine A. Panozzo | Tiffany S. Woodworth | Emily C. Welch | Ting-Ying Huang | Qoua L. Her | Kevin Haynes | Catherine Rogers | Talia J. Menzin | Max Ehrmann | Katherine E. Freitas | Nicole R. Haug | Sengwee Toh

[Graph showing the impact of the ICD-10-CM transition on health outcomes]
Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM

Mara M. Epstein1,2 | Sarah K. Dutcher3 | Judith C. Maro4 | Cassandra Saphirak1,2 | Sandra DeLuccia4 | Muthalagu Ramanathan5 | Tejaswini Dhawale6 | Sonali Harchandani5 | Christopher Delude2 | Laura Hou4 | Autumn Gertz4 | Nina DiNunzio4 | Cheryl N. McMahill-Walraven7 | Mano S. Selvan8 | Justin Vigeant4 | David V. Cole4 | Kira Leishear3 | Jerry H. Gurwitz1,2 | Susan Andrade1,2 | Noelle M. Cocoros4

Validation of an ICD-10-based algorithm to identify stillbirth in the Sentinel System

Susan E. Andrade1 | Mayura Shinde2 | Tiffany A. Moore Simas3 | Steven T. Bird4 | Justin Bohn2 | Kevin Haynes6 | Lockwood G. Taylor4 | Julianne R. Lauring3 | Erin Longley6 | Cheryl N. McMahill-Walraven7 | Connie M. Trinacty8 | Cassandra Saphirak1 | Christopher Delude1 | Sandra DeLuccia2 | Tancy Zhang2 | David V. Cole2 | Nina DiNunzio2 | Autumn Gertz2 | Elnara Fazio-Eynullayeva2 | Danijela Stojanovic4
Successful Comparison of US Food and Drug Administration Sentinel Analysis Tools to Traditional Approaches in Quantifying a Known Drug-Adverse Event Association

JJ Gagne, X Han, S Hennessy, CE Leonard, EA Chrischilles, RM Carnahan, SV Wang, C Fuller, A Iyer, H Katcoff, TS Woodworth, P Archdeacon, TE Meyer, S Schnecwiss and S Toh

Sentinel Modular Program for Propensity Score-Matched Cohort Analyses

Application to Glyburide, Glipizide, and Serious Hypoglycemia


Epidemiology 2017;28: 838–846

Evaluation of the US Food and Drug Administration sentinel analysis tools in confirming previously observed drug-outcome associations: The case of clindamycin and Clostridium difficile infection


Evaluation of the US Food and Drug Administration Sentinel Analysis Tools Using a Comparator with a Different Indication: Comparing the Rates of Gastrointestinal Bleeding in Warfarin and Statin Users

Ryan M. Carnahan, Joshua J. Gagne, Christian Hampp, Charles E. Leonard, Sengwee Toh, Candace C. Fuller, Sean Hennessy, Laura Hou, Noelle M. Cocoros, Genna Panucci, Tiffany Woodworth, Austin Cosgrove, Aarhi Iyer, Elizabeth A. Chrischilles

https://doi.org/10.1007/s11300-018-00265-w
• How Sentinel gets, standardizes, and checks its data

• **How Sentinel performs privacy-protecting analysis**

• How Sentinel contributes to FDA’s regulatory mission

• How Sentinel builds trust through transparency

• How Sentinel continues to innovate and expand its capabilities

• Discussion
1. FDA data request sent to Data Partners via FISMA-compliant secure network portal
2. Data Partners retrieve query
3. Data Partners review and run query against their local data behind their firewalls
4. Data Partners review results for accuracy and privacy compliance
5. Data Partners return de-identified results to SOC via secure portal

Firewall
Local Data
Privacy Compliance
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Sentinel Secure Network Portal

Data Partner 1

- Retrieve Query
- Review & Run Query
- Review & Return Results
  - Enrollment
  - Demographics
  - Utilization
  - Pharmacy Etc.

Data Partner N

- Retrieve Query
- Review & Run Query
- Review & Return Results
  - Enrollment
  - Demographics
  - Utilization
  - Pharmacy Etc.
Analysis of person-level datasets with individual covariates

Analysis of summary score-based datasets

Meta-analysis of database-specific effect estimates

Distributed regression using intermediate statistics
Identify exposure and comparator cohorts

Extract covariate information

Estimate an exposure propensity score

Match/stratify/weight exposed & comparator patients on PS

Generate effect estimates and create report

Cohort Identification and Descriptive Analysis Tool

Propensity Score Analysis Tool

Other Tools (depending on analysis)
1. Identify exposure and comparator cohorts
2. Extract covariate information
3. Estimate an exposure propensity score
4. Match/stratify/weigh exposed & comparator patients on PS
5. Generate effect estimates and create report

Female
Age 25
Diagnosis
History
Drug History

Propensity Score

Performed at the data partner sites

Performed at the analysis center
Analytic and Data Sharing Options in Real-World Multidatabase Studies of Comparative Effectiveness and Safety of Medical Products

Sengwee Toh\textsuperscript{1,*}
• How Sentinel gets, standardizes, and checks its data
• How Sentinel performs privacy-protecting analysis
• **How Sentinel contributes to FDA’s regulatory mission**
• How Sentinel builds trust through transparency
• How Sentinel continues to innovate and expand its capabilities
• Discussion
Risk of Psychiatric Adverse Events Among Montelukast Users

Veronica Sansing-Foster, PhD\textsuperscript{a}, Nicole Haug, MS\textsuperscript{b}, Andrew Mosholder, MD, MPH\textsuperscript{a}, Noelle M. Cocoros, PhD\textsuperscript{b}, Marie Bradley, PhD\textsuperscript{a}, Yong Ma, PhD\textsuperscript{c}, Dinci Pennap, PhD\textsuperscript{a}, Elizabeth C. Dee, MPH\textsuperscript{b}, Sengwee Toh, ScD\textsuperscript{b}, Ella Pestine, MPH\textsuperscript{b}, Andrew B. Petrone, MPH\textsuperscript{b}, Ivone Kim, MD\textsuperscript{d}, Jennifer G. Lyons, PhD\textsuperscript{b}, and Efe Eworuke, PhD\textsuperscript{a}  \textit{Silver Spring, Md; and Boston, Mass}

\textit{J Allergy Clin Immunol Pract} 2021;9:385-93
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before matching</th>
<th>ICSs</th>
<th>After matching</th>
<th>ICSs</th>
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<tr>
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<td>38.5 ± 18.3</td>
<td>38.5 ± 19.3</td>
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<tr>
<td>Age group (y)</td>
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<td></td>
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<tr>
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<td>92,294</td>
<td>269,772</td>
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<td>96,887</td>
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<td>61,854</td>
<td>152,571</td>
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<td>18+</td>
<td>359,371</td>
<td>910,188</td>
<td>318,009</td>
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<td>Asthma—Emergency</td>
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COPD, Chronic obstructive pulmonary disease; DSC, Drug Safety Communication.
<table>
<thead>
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<th>After matching</th>
</tr>
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<td>(n = 1,332,531) %</td>
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</tr>
<tr>
<td>Mean age (y), mean ± SD</td>
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<td>152,571 13.5</td>
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<tr>
<td>18+</td>
<td>359,371 70.0</td>
<td>910,188 65.4</td>
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<tr>
<td>Female</td>
<td>321,937 62.7</td>
<td>789,900 60.4</td>
</tr>
<tr>
<td>Male</td>
<td>191,582 37.3</td>
<td>542,631 39.6</td>
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<td>53,082 10.3</td>
<td>380,780 46.0</td>
</tr>
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<td>951,751 54.0</td>
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<td>Combined comorbidity score, mean ± SD</td>
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<tr>
<td>Phosphodiesterase inhibitors</td>
<td>3,039 0.6</td>
<td>6,091 0.9</td>
</tr>
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COPD, Chronic obstructive pulmonary disease; DSC, Drug Safety Communication.
FDA NEWS RELEASE

FDA Requires Stronger Warning About Risk of Neuropsychiatric Events Associated with Asthma and Allergy Medication Singulair and Generic Montelukast
The FDA updated the product labeling in 2008 to include information about neuropsychiatric events reported with use of montelukast. In response to continued reports of suicide and other adverse events, the FDA evaluated available data regarding the risk of neuropsychiatric events, including reports submitted through the FDA Adverse Event Reporting System (FAERS) and observational studies in the published literature. The FDA also conducted an observational study using data in the Sentinel Distributed Database and presented the findings at an FDA advisory committee meeting in 2019.

As part of its review, the FDA re-evaluated the benefits and risks of montelukast as the treatment landscape has evolved since the drug was first approved in 1998. Based upon this assessment, the FDA determined the risks of montelukast may outweigh the benefits in some patients, particularly when the symptoms of the disease are mild and can be adequately treated with alternative therapies. For allergic rhinitis in particular, the FDA has determined that montelukast should be reserved for patients who have not responded adequately to other therapies — or who cannot tolerate these therapies.
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Conduct prospective safety surveillance of new medications

Prospective Postmarketing Surveillance of Acute Myocardial Infarction in New Users of Saxagliptin: A Population-Based Study

Sengwee Toh,1 Marsha E. Reichman,2 David J. Graham,2 Christian Hampp,2 Rongmei Zhang,3 Melissa G. Butler,4 Aarthi Iyer,1 Malcolm Rucker,1 Madelyn Pimentel,2 Jack Hamilton,5 Samuel Lendle,3 and Bruce H. Fireman,5 for the Mini-Sentinel Saxagliptin-AMI Surveillance Writing Group

Diabetes Care 2018;41:39-48 | https://doi.org/10.2337/dc17-0476
Data Mining for Adverse Drug Events With a Propensity Score-matched Tree-based Scan Statistic

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

Epidemiology 2018;29: 895–903
Evaluate impact of FDA regulatory actions

The impact of FDA regulatory activities on incident dispensing of LABA-containing medication: 2005–2011

Meghan A. Baker, MD, ScD, b, c, 7, Melissa G. Butler, PharmD, MPH, PhD, c, d, e, Sally Seymour, MD, b, Fang Zhang, PhD, a, Yute Wu, PhD, a, Ann Chen Wu, MD, MPH, a, Mark S. Levenson, PhD, a, Pingsheng Wu, PhD, a, Aarthi Iyer, MPH, a, Sengwee Toh, ScD, a, Solomon Iyassu, MD, MPH, a, e, and Esther H. Zhou, MD, PhD

Figure 2. Percentage of LABA product initiation before, between and after the 2005 and 2010 FDA regulatory activities for LABA-containing agents in children and adults with asthma and no history of a LABA dispensing in 180 days.
Examining medication exposure during pregnancy

Antiemetic use among pregnant women in the United States: the escalating use of ondansetron

Lockwood G. Taylor, Steven T. Bird, Leyla Sahin, Melissa S. Tassinari, Patty Greene, Marsha E. Reichman, Susan E. Andrade, Katherine Haffenreffer and Sengwee Toh

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; 26: 592–596
Published online 21 February 2017 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.4385
Approximately 2% of the 100,000 infants born in the United States each year of the Sentinel Initiative were vaccinated with vaccines within 2 days following the first dose of Rotarix. In the first round of surveillance, vaccines were awarded to infants of all ages and in the second round of surveillance, vaccines were awarded to infants under 3 months of age. In both surveillance programs, a total of 30,000 infants were vaccinated with vaccines within 2 days following the first dose of Rotarix. In the second round of surveillance, vaccines were awarded to infants under 3 months of age. In the first round of surveillance, vaccines were awarded to infants of all ages. In the second round of surveillance, vaccines were awarded to infants under 3 months of age.
Inform label change

Risk of Nonmelanoma Skin Cancer in Association With Use of Hydrochlorothiazide-Containing Products in the United States

Efe Ewuoke, PhD,¹,4 Nicole Haug, MPH,¹ Marie Bradley, PhD,¹ Austin Cosgrove, BS,² Tancy Zhang, MPH,² Elizabeth C. Dee, MPH,² Sreuthi Adimadhyan, PhD² Andrew Petrone, MPH,² Hana Lee, PhD,¹ Tiffany Woodworth, MPH,² Sengwee Toh, ScD³

Postmarketing Experience: Non-melanoma Skin Cancer

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. In a study conducted in the Sentinel System, increased risk was predominantly for squamous cell carcinoma (SCC) and in white patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for white patients taking a cumulative dose of ≥50,000 mg the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.
A COVID-19-ready public health surveillance system: The Food and Drug Administration's Sentinel System

Noelle M. Cocoros1, Candace C. Fuller1, Sruthi Adimadhyan1, Robert BalP, Jeffrey S. Brown1, Gerald J. Dal Pan1, Sheryl A. Kluberg1, Vincent Lo Re 3rd1, Judith C. Maro1, Michael Nguyen1, Robert Orr2, Dianne Paraoan1, Jonathan Perlin1, Russell E. Poland1, Meighan Rogers Driscoll1, Kenneth Sands1, Sengwee Toh1, W. Katherine Yih1, Richard Platt1, and the FDA-Sentinel COVID-19 Working Group

Enable international collaboration during pandemic

COVID-19 Coagulopathy Study
• Assessment of arterial and venous thrombotic events among COVID-19 patients

Natural History of COVID-19 among Pregnant Women
• CONSIGN (Covid-19 infectiON and medicineS In pregnancy) conceptual replication

Outpatient Corticosteroid Use Among a Non-Hospitalized COVID+ Population
• Initial US-based study done with 4 sources (Sentinel, CMS, HealthVerity, VA)
Enable international collaboration to address global issues

Quantitative Assessment of the Impact of Nitrosamine Contamination and Angiotensin Receptor Blockers (ARB) Recall on ARB Utilization: A Multinational Study

<table>
<thead>
<tr>
<th>Details</th>
<th>Additional Information</th>
<th>Contributors</th>
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</table>

**Date Posted:** Tuesday, August 18, 2020

**Status:** IN PROGRESS

**Medical Product:** angiotensin II receptor blocker (ARB), angiotensin receptor blocker, angiotensin-converting enzyme (ACE) inhibitor, calcium channel blockers (CCB)
• How Sentinel gets, standardizes, and checks its data
• How Sentinel performs privacy-protecting analysis
• How Sentinel contributes to FDA’s regulatory mission

**How Sentinel builds trust through transparency**
• How Sentinel continues to innovate and expand its capabilities
• Discussion
The reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE)

Sinéad M Langan,1 Sigrún AJ Schmidt,2 Kevin Wing,1 Vera Ehrenstein,2 Stuart G Nicholls,3,4 Kristian B Filion,2,6 Olaf Klungel,7 Irene Petersen,2,8 Henrik T Sorensen,2 William G Dixon,9 Astrid Guttmann,10,11 Katie Harron,12 Lars G Hemkens,13 David Moher,3 Sebastian Schneeweiss,16 Liam Smeeth,1 Miriam Sturkenboom,15 Erik von Elm,16 Shirley V Wang,16 Eric I Benchimol10,17,18

BMJ 2018;363:k3532

STaRT-RWE: structured template for planning and reporting on the implementation of real world evidence studies

Shirley V Wang,1 Simone Pinheiro,2 Wei Hua,2 Peter Arlett,3,4 Yoshiaki Uyama,5 Jesse A Berlin,6 Dorothee B Bartels,7 Kristijan H Kahler,9 Lily G Bessette,1 Sebastian Schneeweiss1

BMJ 2021;372:m4856
Eliquis (Apixaban), Pradaxa (Dabigatran), and Xarelto (Rivaroxaban) & Severe Uterine Bleed

Details

Status: Complete

Last Updated: Monday, May 24, 2021

Original Posting Date: Thursday, April 18, 2019

Health Outcome(s):
- severe uterine bleed

Purpose: Drug and Outcome Analysis
Regulatory Determination / Use:

Cases of severe uterine bleeding associated with use of novel oral anticoagulants (ACs) have been reported in the FDA Adverse Event Reporting System (FAERS) and the medical literature. FDA conducted a Sentinel study to examine severe uterine bleeding events requiring medical intervention in women treated with oral ACs. Among 1,050,192 new users of oral ACs, the incidence rates of severe uterine bleeding with medical, transfusion, and surgical (e.g., hysterectomy, myomectomy) management were 0.6, 1.7, and 5.0 per 1000 person-years, respectively. These findings contributed to the following class-wide label change for oral ACs in Section 8.3, “The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including [PRODUCT name] should be assessed in females of reproductive potential and those with abnormal uterine bleeding.”
Analytic Code Link(s) (1)

Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Propensity Score Analysis
Specifications for Request cder_mpl2_wp018

The purpose of this request is to execute the Cohort Identification and Descriptive Analysis (CIDA) tool to perform a risk assessment of serious anticoagulants (rivaroxaban vs. dabigatran, rivaroxaban vs. apixaban, dabigatran vs. apixaban, rivaroxaban vs. warfarin). This is an update to custom code for propensity score (PS) stratification analysis.

Query Period: October 19, 2010 to September 30, 2015
Coverage Requirement: Medical and Drug Coverage
Pre-exposure Enrollment: 183 days
Post-Index Enrollment Requirement: 8 days

Enrollment Gap: 45 days
Sex: Female

Stratifications:
- Age (years): 18-50; 51+
- Index-defining novel oral anticoagulant (NOAC) dose: low; high
- Any gynecological disorder (see Appendix C)
- Age*sex: 18-50, low; 18-50, high; 51+, low; 51+, high
- Deep vein thrombosis (DVT)/Pulmonary embolism (PE)
- Age*DVT/PE
- Atrial Fibrillation (AF)
- Age*AF

Return: Aggregated-level, index code distribution, censoring table
Envelope Macro Use: On

Frozen Data: Yes
Notes: Default stockpiling specifications will be used; stockpiling

+Specifications for Request cder_mpl2_wp018
Result(s) (3)

- Incidence of Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Descriptive Analysis
- Severe Uterine Bleed Following Novel Oral Anticoagulants Use: A Propensity Score Analysis
- Incidence Rate of Severe Uterine Bleeding Among New Users of Oral Anticoagulants: A Descriptive Analysis
Table 2a. Effect Estimates for Severe Uterine Bleed (SUB) Defined by Surgical Management in the Sentinel Distributed Database (SDD) between October 19, 2010 to September 30, 2015, by Analysis Type, Rivaroxaban vs. Dabigatran

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<th>Medical Product</th>
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<th>Person-Years at Risk</th>
<th>Average Person-Days at Risk</th>
<th>Average Person-Years at Risk</th>
<th>Number of Events</th>
<th>Incidence Rate per 1,000 Person-Years</th>
<th>Risk per 1,000 New Users</th>
<th>Incidence Rate Difference per 1,000 Person-Years</th>
<th>Difference in Risk per 1,000 New Users</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
<th>P-Value</th>
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<tr>
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<td>196.07</td>
<td>0.54</td>
<td>801</td>
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<td>2.77</td>
<td>1.54</td>
<td>-1.05</td>
<td>1.35 (1.17, 1.54)</td>
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<td>Dabigatran</td>
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<td>85,311.95</td>
<td>385.44</td>
<td>1.06</td>
<td>309</td>
<td>3.62</td>
<td>3.82</td>
<td>1.14</td>
<td>0.20</td>
<td>1.15 (0.89, 1.50)</td>
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<td></td>
</tr>
<tr>
<td>Rivaroxaban</td>
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<td>4.29</td>
<td>1.48</td>
<td>0.57</td>
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<td>Dabigatran</td>
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<td>104</td>
<td>3.72</td>
<td>1.29</td>
<td>0.57</td>
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<td>1.15 (0.89, 1.50)</td>
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<td><strong>1:1 Matched Unconditional Predefined Analysis; Caliper= 0.05</strong></td>
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<td><strong>Predefined Percentile Analysis; Percentile = 10</strong></td>
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<td>1.15 (0.91, 1.40)</td>
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Data are not presented in shaded cells due to their inability to be calculated.
Regulatory Link(s) (3)

- Drug Safety-related Labeling Change (Xarelto)
- Drug Safety-related Labeling Change (Pradaxa)
- Drug Safety-related Labeling Change (Eliquis)
### ELIQUIS (NDA-202155)

**APIXABAN**

Safety-related Labeling Changes Approved by FDA Center for Drug Evaluation and Research (CDER)

<table>
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<tr>
<th>Date</th>
<th>Description</th>
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<tbody>
<tr>
<td>04/20/2021</td>
<td>Approved Drug Label (PDF)</td>
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#### 8 Use in Specific Populations

**8.3 Females and Males of Reproductive Potential**

( Newly Added Subsection)

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

The risk of clinically significant uterine bleeding, potentially requiring gynecological surgical interventions, identified with oral anticoagulants including ELIQUIS should be assessed in females of reproductive potential and those with abnormal uterine bleeding.
Related Publication(s) and/or Presentation(s) (1)

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

Efe Eworuke¹, Laura Hou², Rongmei Zhang³, Hui-Lee Wong⁴, Peter Waldron⁵, Abby Anderson⁶, Audrey Gassman⁶, David Moeny¹, Ting-Ying Huang²
• How Sentinel gets, standardizes, and checks its data
• How Sentinel performs privacy-protecting analysis
• How Sentinel contributes to FDA’s regulatory mission
• How Sentinel builds trust through transparency

• How Sentinel continues to innovate and expand its capabilities
• Discussion
Research and Applications

Electronic phenotyping of health outcomes of interest using a linked claims-electronic health record database: Findings from a machine learning pilot project

Teresa B. Gibson, Michael D. Nguyen, Timothy Burrell, Frank Yoon, Jenna Wong, Sai Dharmarajan, Rita Ouellet-Hellstrom, Wei Hua, Yong Ma, Elande Baro, Sarah Bloemers, Cory Pack, Adee Kennedy, Sengwee Toh, and Robert Ball
Use of The Tree-Based Scan Statistic for Surveillance of Maternal Outcomes Following Medication Use During Gestation

Sentinel Methods

Thuy N Thai, Almut G Winterstein, Elizabeth A Suarez, Michael Nguyen, Danijela Stojanovic, Jane Liedtka, Abby Anderson, Di Zhang, Yueqin Zhao, Monica Munoz, Wei Liu, Steven Bird, Inna Dashevsky, David Cole, Talia Menzin, Sandra DeLuccia, Jennifer Noble, Judith C Maro

Use of the Tree-Based Scan Statistic for Surveillance of Infant Outcomes Following Maternal Perinatal Medication Use

Sentinel Methods

Elizabeth A Suarez, Michael Nguyen, Di Zhang, Yueqin Zhao, Danijela Stojanovic, Monica Munoz, Jane Liedtka, Abby Anderson, Wei Liu, Steven Bird, Inna Dashevsky, David Cole, Sandra DeLuccia, Talia Menzin, Jennifer Noble, Judith C Maro
FDA-Catalyst—Using FDA’s Sentinel Initiative for large-scale pragmatic randomized trials: Approach and lessons learned during the planning phase of the first trial

Noelle M Cocoros1, Sean D Pokorney2, Kevin Haynes3, Crystal Garcia1, Hussein R Al-Khalidi4, Sana M Al-Khatib3, Patrick Archdeacon5, Jennifer C Goldsack6, Thomas Harkins7, Nancy D Lin8, David Martin5, Debbe McCall9, Vinit Nair7, Lauren Parlett3, Robert Temple8, Cheryl McMahill-Walgren10, Christopher B Granger2 and Richard Platt1

*Baseline characteristics of delayed and early intervention cohorts will be taken from the same time point at randomization from a dataset that is archived at randomization, while exclusion criteria for evidence of OAC medication fill or P2Y12 antagonist use was determined at randomization for the early intervention cohort and approximately 12 months post-randomization for the delayed intervention cohort.

**All possible person-time will be used to assess participants’ outcomes (patients will have different duration of follow-up).

For analysis, treatment status is at time of randomization or corresponding early intervention mailing for the delayed intervention mailing if prior to mailing.
Use of a mobile app to capture supplemental health information during pregnancy: Implications for clinical research

Claire W. Rothschild\textsuperscript{1} | Sascha Dublin\textsuperscript{1,2} | Jeffrey S. Brown\textsuperscript{3,4} | Predrag Klasnja\textsuperscript{2} | Chayim Herzig-Marx\textsuperscript{3,4} | Juliane S. Reynolds\textsuperscript{3,4} | Zachary Wyner\textsuperscript{3,4} | Christina Chambers\textsuperscript{5} | David Martin\textsuperscript{6}
Broadening the reach of the FDA Sentinel system: A roadmap for integrating electronic health record data in a causal analysis framework

Rishi J. Desai1✉, Michael E. Matheny1, Kevin Johnson2, Keith Marsolo3, Lesley H. Curtis3, Jennifer C. Nelson4, Patrick J. Heagerty5, Judith Maro6, Jeffery Brown6, Sengwee Toh6, Michael Nguyen7, Robert Ball7, Gerald Dal Pan7, Shirley V. Wang1, Joshua J. Gagne1,8 and Sebastian Schneeweiss1

npj Digital Medicine (2021) 170
### Administrative Data

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<thead>
<tr>
<th>Enrollments</th>
<th>Demographics</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Procedure</th>
<th>Prognosis</th>
<th>Predisposing</th>
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<tbody>
<tr>
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<td>Provider ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
<td>Patient ID</td>
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<td>Enrollment Start &amp; End Dates</td>
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### Clinical Data

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<td>Measurement Date &amp; Time</td>
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<td>Test Type, Immediacy &amp; Location</td>
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<td>Tobacco Use &amp; Type</td>
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<th>State Vaccine</th>
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<td>Cause of Death</td>
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<td>Source</td>
<td>Admission Date</td>
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<td>Confidence</td>
<td>Vaccine Code &amp; Type</td>
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### Inpatient Data

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### Mother-Infant Linkage Data

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<td>Patient ID</td>
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<td>Mother ID</td>
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### Auxiliary Data

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<tr>
<td>Provider</td>
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<td>Specialty &amp; Specialty Code Type</td>
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**Sentinel’s Multi-Modal Response System**

### Claims (with Limited EHR Network)
- **Active Risk Identification and Analysis (ARIA)**
- **Sentinel Distributed Database**
- **IBM® MarketScan® Research Databases**
  - Sentinel Common Data Model
  - Sentinel Analytic Tools
  - Access to Medical Records within the Sentinel Distributed Database

### EHR Data Aggregators
- **TriNetX**
- **IBM Watson Health**
  - Proprietary Common Data Models
  - Web-Based Query Interface & Custom Programming
  - Access to Medical Records varies by Source

### EHR Data Warehouse
- **HCA Healthcare**
- **Veradigm**
  - Data Warehouse for Multiple Healthcare Organizations in a System
  - Custom Programming
  - Access to Medical Records

### EHR Networks
- **PCORnet**
  - PCORnet Common Data Model
  - PCORnet Analytic Tools
  - Access to Medical Records

---

*Note: The Active Risk Identification and Analysis (ARIA) System is comprised of the Sentinel Distributed Database, the Sentinel Common Data Model, and Sentinel analytic tools.*
Fig. 1 Conceptual overview of the integration of claims data and electronic health records in Sentinel. Solid box on the left indicates data elements currently available in the Sentinel common data model, dotted box on the right indicates elements from electronic health records that will be considered for inclusion.
**Fig. 3 The Sentinel Innovation Center initiatives and vision.** Arrow at the bottom indicates timeline for the proposed activities.
• How Sentinel gets, standardizes, and checks its data
• How Sentinel performs privacy-protecting analysis
• How Sentinel contributes to FDA’s regulatory mission
• How Sentinel builds trust through transparency
• How Sentinel continues to innovate and expand its capabilities
• Discussion
Developing the Sentinel System — A National Resource for Evidence Development

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


The FDA Sentinel Initiative — An Evolving National Resource

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

Real-world data
Data networks, standardization, and federated analysis

Darren Toh, ScD

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darren_toh@harvardpilgrim.org
@darrentoh_epi