Using Sentinel to Evaluate Effectiveness or Efficacy

Richard Platt MD, MS
Harvard Pilgrim Health Care Institute and Harvard Medical School
for the Sentinel Investigators
September 19, 2017
Disclosures

- None related to this presentation
Sentinel’s charge

Assess the use, safety, and effectiveness of regulated medical products by using electronic healthcare data plus other resources.

Create data, informatics, and methodologic capabilities to support these activities.
Curated Distributed Data Using a Common Data Model

Medical Product Safety Surveillance

Quality of Care Public Health Surveillance

Clinical Research

Randomized trials

Comparative Effectiveness Research
Sentinel partner organizations

Lead – HPHC Institute

DEPARTMENT OF POPULATION MEDICINE

HARVARD MEDICAL SCHOOL

Harvard Pilgrim Health Care Institute

Data and scientific partners

HealthCore

Anthem

VANDERBILT SCHOOL OF MEDICINE

HCA

Hospital Corporation of America

health care systems research network

CMS.gov

OPTUM

KAISER PERMANENTE

aetna

QUINTILES

Scientific partners

Penn Medicine

UAB

DEPARTMENT OF MEDICINE
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL

AHIP

America's Health Insurance Plans

UNC

GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH

HARVARD T.H. CHAN

SCHOOL OF PUBLIC HEALTH

UF

College of Pharmacy
UNIVERSITY of FLORIDA

UIC

The University of Iowa

COLLEGE OF PUBLIC HEALTH
Numerous data elements are available

**Administrative**

<table>
<thead>
<tr>
<th>Enrollment</th>
<th>Demographic</th>
<th>Dispensing</th>
<th>Encounter</th>
<th>Diagnosis</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Enrollment start &amp; end dates</td>
<td>Birth date</td>
<td>Dispensing date</td>
<td>Service date(s)</td>
<td>Service date(s)</td>
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<tr>
<td>Drug coverage</td>
<td>Sex</td>
<td>National drug code (NDC)</td>
<td>Encounter ID</td>
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<tr>
<td>Medical coverage</td>
<td>ZIP code</td>
<td>Days supply</td>
<td>Encounter type &amp; provider</td>
<td>Encounter type &amp; provider</td>
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<tr>
<td>Medical record availability</td>
<td>Etc.</td>
<td>Amount dispensed</td>
<td>Facility</td>
<td>Diagnosis code &amp; type</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical**

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
<th>Death</th>
<th>Cause of Death</th>
<th>State Vaccine</th>
<th>Inpatient Pharmacy</th>
<th>Inpatient Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Result and specimen collection dates</td>
<td>Measurement date and time</td>
<td>Death date</td>
<td>Cause of death</td>
<td>Vaccination date</td>
<td>Administration date and time</td>
<td>Blood Type</td>
</tr>
<tr>
<td>Test type, immediacy &amp; location</td>
<td>Height and weight</td>
<td>Source</td>
<td>Source</td>
<td>Administration Type</td>
<td>Encounter ID</td>
<td>Etc.</td>
</tr>
<tr>
<td>Logical Observation Identifiers Names and Codes (LOINC ©)</td>
<td>Diastolic &amp; systolic BP</td>
<td>Confidence</td>
<td>Confidence</td>
<td>Vaccine code &amp; type</td>
<td>National Drug Code (NDC)</td>
<td>Etc.</td>
</tr>
<tr>
<td>Test result &amp; unit</td>
<td>Tobacco use &amp; type</td>
<td>Etc.</td>
<td>Etc.</td>
<td>Provider</td>
<td>Route</td>
<td>Etc.</td>
</tr>
</tbody>
</table>

**Registry**

<table>
<thead>
<tr>
<th>Inpatient Pharmacy</th>
<th>Inpatient Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person ID</td>
<td>Person ID</td>
</tr>
<tr>
<td>Administration date and time</td>
<td>Administration start and end date and time</td>
</tr>
<tr>
<td>Encounter ID</td>
<td>Encounter ID</td>
</tr>
<tr>
<td>National Drug Code (NDC)</td>
<td>Transfusion administration ID</td>
</tr>
<tr>
<td>Route</td>
<td>Blood Type</td>
</tr>
<tr>
<td>Dose</td>
<td>Etc.</td>
</tr>
</tbody>
</table>
The quality assurance process

Send a standard QA program to check DP’s data in waiting

Compliance Checks
Level 1: Completeness, validity, accuracy
Level 2: Cross-variable and cross-table integrity

Judgment Call Checks
Level 3: Trends: consistency
Level 4: Logical: plausibility, convergence

Data Partner
Sentinel distributed analysis

1- User creates and submits query
2- Data Partners retrieve query
3- Data Partners review and run query against their local data
4- Data Partners review results
5- Data Partners return results via secure network
6 Results are aggregated and returned

https://www.sentinelinitiative.org/privacy-and-security
Sentinel distributed database*

Population with well-defined person-time for which most medically-attended events are known

- 425 million person-years of observation time
- 43 million people currently accruing new data
- 5.9 billion dispensings
- 7.2 billion unique encounters
- 42 million people with ≥1 laboratory test result

* As of January 2017
Sentinel and effectiveness/efficacy

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials
Sentinel distributed data alone
Prospective Surveillance Pilot of Rivaroxaban Safety

Elizabeth Chrischilles
College of Public Health, University of Iowa
Workgroup

- Leads: Elizabeth Chrischilles, Ryan Carnahan
- Co-investigators: Joshua J. Gagne, Bruce Fireman, Jennifer Nelson, Sengwee Toh, Azadeh Shoaibi, Marsha E. Reichman, Shirley Wang, Michael Nguyen, Rongmei Zhang, Rima Izem, Margie R. Goulding, Mary Ross Southworth, David J. Graham, Candace Fuller, Hannah Katcoff, Tiffany S. Woodworth, Catherine Rogers, Ryan Saliga, Nancy D. Lin, Cheryl N McMahill-Walraven, Vinit P. Nair, Nandini Selvam
- Many thanks are due to Data Partners who provided data used in the analysis
Propensity Score Matching (1/2)

- Variable ratio propensity score (PS) matching (each new rivaroxaban user matched to up to 10 new warfarin users)
- Using nearest neighbor algorithm, matching caliper 0.05
- PS estimation and matching within Data Partner
Propensity Score Matching (2/2)

- 70+ confounders:
  - Age, sex, year of index date
  - Combined comorbidity score
  - Health service utilization
    - Counts of encounters by setting
    - Number of drugs
  - Procedures and diagnoses:
    - Risk factors for bleeding and atherosclerotic stroke
  - Medications:
    - Oral cardiovascular agents,
    - Medications that increase bleeding risk,
    - Interacting medications
Statistical Analysis

- Cox regression stratified by Data Partner and matched set to estimate hazard ratio

- Sequential testing
  - Group sequential design, multiple looks, flat boundary
  - Initial threshold for signal (5 looks): Wald z-score > 2.37 (P<0.018)
  - Revised signaling threshold (2 looks): Wald z-score >2.06 (P<0.039)
    - To reflect change of number of looks and amount of information at each look
    - Delay due to tool refinements

- End-of-surveillance analysis (one-time estimation)
  - Included only diagnosis codes in primary position
Histograms of Propensity Scores, Unmatched Cohort, 4 Data Partners, Gastrointestinal Bleeding Analysis Cohort

Data Partner 1

Data Partner 2

Data Partner 3

Data Partner 4
Histograms of Propensity Scores, Propensity Score-Matched Cohort, 4 Data Partners, Gastrointestinal Bleeding Analysis Cohort

Data Partner 1

Data Partner 2

Data Partner 3

Data Partner 4
# Rivaroxaban vs Warfarin: Comparing Sentinel to ROCKET-AF

<table>
<thead>
<tr>
<th></th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ROCKET-AF(^1)</td>
</tr>
<tr>
<td>GI Bleed</td>
<td>1.61 (1.30-1.99)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.67 (0.47-0.93)</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.94 (0.75-1.17)</td>
</tr>
</tbody>
</table>

\(^1\)ROCKET-AF compared rivaroxaban with warfarin for stroke prevention in non-valvular atrial fibrillation 
Patel NEJM 2011;364:883
Rivaroxaban compared with warfarin in risk of stroke/TE in AF patients.

<table>
<thead>
<tr>
<th>Study, year (Dose)</th>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bouillon, 2015</td>
<td></td>
<td>0.75 (0.39, 1.45)</td>
<td>3.62</td>
</tr>
<tr>
<td>Maura, 2015</td>
<td></td>
<td>0.93 (0.47, 1.85)</td>
<td>2.27</td>
</tr>
<tr>
<td>Chan, 2016</td>
<td></td>
<td>0.51 (0.35, 0.74)</td>
<td>13.68</td>
</tr>
<tr>
<td>Larsen, 2016</td>
<td></td>
<td>0.83 (0.69, 0.99)</td>
<td>16.64</td>
</tr>
<tr>
<td>Yao, 2016</td>
<td></td>
<td>0.93 (0.72, 1.19)</td>
<td>11.43</td>
</tr>
<tr>
<td>Laliberte, 2014</td>
<td></td>
<td>0.77 (0.55, 1.09)</td>
<td>9.77</td>
</tr>
<tr>
<td>Gorst-Rasmussen, 2016 (LD)</td>
<td></td>
<td>0.46 (0.26, 0.82)</td>
<td>9.35</td>
</tr>
<tr>
<td>Gorst-Rasmussen, 2016 (HD)</td>
<td></td>
<td>0.72 (0.51, 1.01)</td>
<td>10.68</td>
</tr>
<tr>
<td>Staerk, 2016</td>
<td></td>
<td>0.91 (0.74, 1.12)</td>
<td>13.99</td>
</tr>
<tr>
<td>Coleman, 2016 -IS</td>
<td></td>
<td>0.71 (0.47, 1.07)</td>
<td>8.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.75 (0.64, 0.85)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.0128, \chi^2 = 16.40, df = 9, (p = 0.059); I^2 = 45.1\%$

Test for overall effect: $z = 13.38 (p < 0.0001)$

Ying Bai et al. Stroke. 2017;48:970-976
Sentinel with chart review
Risk of Intussusception after Rotavirus Vaccination: Results of the Mini-Sentinel/PRISM* Study

W. Katherine Yih, PhD, MPH
Sentinel Initiative Public Workshop 2014

* Post-licensure Rapid Immunization Safety Monitoring
Background

- RotaShield, first vaccine for prevention of rotavirus infection in infants, licensed in 1998
  - Withdrawn in 1999 due to risk of intussusception, a form of bowel obstruction
- For RotaTeq and Rotarix, no increased risk in clinical trials of >60,000 children each
  - But post-licensure studies in other countries later suggested increased risk of intussusception after both
- In 2010, FDA’s Center for Biologics Evaluation and Research (CBER) initiated this study to quantify the possible risk among U.S. infants
Source data and chart review

- Data partners: Aetna, HealthCore, Humana
- Date range: 2004 - mid-2011
- CPT-4 codes for immunization:
  - CPT-4 codes 90680 (RotaTeq) and 90681 (Rotarix)
- CPT-4 and ICD-9 codes for outcomes:
  - ICD-9 codes 560.0 (intussusception), 543.9; CPT-4 code 74283 (therapeutic enema...)
- Chart review to validate both outcome and exposure
  - Pediatrician adjudicators classified cases using Brighton Collaboration criteria
Intussusception confirmation

Algorithm-identified potential cases = 343

Potential cases are from whole population aged 5-36 weeks and include unexposed
Intussusception confirmation

Algorithm-identified potential cases = 343

Those for whom chart obtained = 267 (78%)

Potential cases are from whole population aged 5-36 weeks and include unexposed
Intussusception confirmation

Algorithm-identified potential cases = 343

Those for whom chart obtained = 267 (78%)

Confirmed as intussusception, Brighton Level 1 = 124 (46%)

Classified as Brighton Level 2 = 20 (7%)

Potential cases are from whole population aged 5-36 weeks and include unexposed
Sentinel linked to registries
Claims Data in Sentinel Distributed Database

Maternal data

Infant data

Linked mom-infant pairs

Unlinked mothers

Unlinked infants

State Departments of Health

Birth certificate data*

*Birth certificates available for 9 states
Percent deliveries linked to infants (N=651,607)

- DP 1: 84%
- DP 2: 80%
- DP 3: 83%
- DP 4: 66%

- Not linked
- Linked using birth certificates
- Linked using last names and addresses
- Linked using subscriber ID
Sentinel linked to EHRs
ADAPTABLE Trial
ADAPTABLE Study Design

Patients with known ASCVD + ≥ 1 “enrichment factor”*

Identified through EHR (computable phenotype)

ASA 81 mg QD
ASA 325 mg QD

Electronic follow-up: Every 3–6 months
Supplemented with EHR/CDM/claims data

Primary endpoint:
Composite of all-cause mortality, hospitalization for MI or stroke

Primary safety endpoint:
Hospitalization for major bleeding

† Participants without internet access may be consented and followed via a parallel system.
ADAPTABLE Computable phenotype

History of CAD
- Prior MI
  OR
- Prior angiogram showing significant CAD
  OR
- Prior revascularization (PCI/CABG)

At least one:
- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Current cerebrovascular disease and/or peripheral artery disease
- Known ejection fraction <50%
- Current smoker
Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

DCRI FOLLOW-UP
- Patient Reported Outcomes
- Medication use
- Health outcomes

Portal FOLLOW-UP
- Patient Reported Outcomes
- Medication use
- Health outcomes

PCORNNet Coordinating Center FOLLOW-UP
- Via Common Data Model
- Longitudinal health outcomes

CMS & Payer Virtual Data Warehouse FOLLOW-UP
- Longitudinal health outcomes

ADAPTABLE Enrollee

Baseline Data
Sentinel linked with patient reported data
Developing a Mobile App for Studies of Medication Safety

Sascha Dublin, MD, PhD, Kaiser Permanente Washington
August 2017
Screenshots from App

Welcome!

The FDA is pleased to offer the FDA My Studies app as a tool to gather real-time, contextual data about medication use and other health issues facing the people we serve.

Get Started

STUDY ACTIVITIES

CURRENT

- **One Time**
  - **Questionnaire about your vitamin use**
  - Run: 1/1, 0 done, 0 missed
  - Start

- **One Time**
  - **Questionnaire about your race and ethnicity**
  - Run: 1/1, 0 done, 0 missed
  - 12:00AM, Jun 22 2017
  - Start

- **One Time**
  - **Questionnaire about your pregnancy history**
  - Run: 1/1, 0 done, 0 missed
  - 12:00AM, Jun 22 2017
  - Start

- **One Time**
  - **Baseline vaccine exposure questionnaire**
  - Run: 1/1, 0 done, 0 missed
  - 12:00AM, Jun 22 2017
  - Start

Congratulations! What is your due date?

<table>
<thead>
<tr>
<th>Month</th>
<th>Day</th>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>April</td>
<td>2</td>
<td>2014</td>
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<tr>
<td>May</td>
<td>3</td>
<td>2015</td>
</tr>
<tr>
<td>June</td>
<td>4</td>
<td>2016</td>
</tr>
<tr>
<td>July</td>
<td>5</td>
<td>2017</td>
</tr>
<tr>
<td>August</td>
<td>6</td>
<td>2018</td>
</tr>
<tr>
<td>September</td>
<td>7</td>
<td>2019</td>
</tr>
<tr>
<td>October</td>
<td>8</td>
<td>2020</td>
</tr>
</tbody>
</table>

Next

Skip this question
Link Primary and Secondary Data
Sentinel and randomized trials
Sentinel IMPACT-AFib: Transforming Pragmatic Clinical Trials Using a Nationwide Distributed Claims Database
IMPACT-Afib Participating Sites
FDA-Catalyst: IMPACT-AFib randomized trial

**IM**plementation of a randomized controlled trial to **imP**rove treatment with oral **AntiCoagulantTs** in patients with **Atrial Fibrillation**

- Direct mailer to 40,000 health plan members with AFib, high risk for stroke, and no oral anticoagulant (OAC) treatment, and their providers to encourage consideration of OACs
IMPACT-AFib Outcomes

- **Primary outcome:** Proportion who fill ≥1 OAC prescription within 12 months

- **Secondary outcomes:**
  - Rates of stroke hospitalizations
  - Time to first OAC dispensing
  - Proportion of days with OAC days supplied
  - Proportion of patients on OAC at end of follow up
  - Rates of bleeding hospitalizations
  - Health care utilization
  - Hospital mortality

- Outcomes will be assessed 12 and 24 months
12-Months

Comparison of Early versus Delayed Intervention
~40,000 enrolled patients

Delayed Intervention
Patients

Early Intervention
Patients

Delayed Intervention

No OAC fill during the first 12 months of the trial

Provider Intervention Mailed

1+ OAC fill during the first 12 months of the trial

Secondary outcomes: proportion of days covered with OAC prescription, number of patients on OAC at end of two years; admissions for stroke or bleeding; deaths (subset)
Trial cohort eligibility

- Adult ≥30 years old
  - Medical & pharmacy coverage for ≥365 days
- ≥2 AFib diagnosis codes
- No OAC dispensing (or ≥4 INR measurements) within the last year
- High risk for stroke (CHA2DS2-VASc score ≥2)
- Exclusions:
  - History of mechanical prosthetic valve, deep vein thrombosis, pulmonary embolism, intracranial bleed
  - Hospitalized bleed in last 6 months
  - Current pregnancy
  - Current P2Y12 inhibitor treatment, e.g., clopidogrel
Estimating CHA$_2$DS$_2$-VASc in feasibility query

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>If patient has risk factor, add points</th>
</tr>
</thead>
<tbody>
<tr>
<td>C Congestive Heart Failure</td>
<td>+1</td>
</tr>
<tr>
<td>H High Blood Pressure (hypertension, including normal blood pressure on blood pressure medications)</td>
<td>+1</td>
</tr>
<tr>
<td>A$_2$ Age 75 years old or older</td>
<td>+2</td>
</tr>
<tr>
<td>D Diabetes</td>
<td>+1</td>
</tr>
<tr>
<td>S$_2$ Stroke or TIA (mini-stroke)</td>
<td>+2</td>
</tr>
<tr>
<td>V Vascular Disease (prior bypass surgery, heart attack peripheral artery disease, or aortic plaque)</td>
<td>+1</td>
</tr>
<tr>
<td>A Age 65-74 years</td>
<td>+1</td>
</tr>
<tr>
<td>Sc Sex Category: Female sex</td>
<td>+1</td>
</tr>
</tbody>
</table>

TOTAL
Follow-up period: 365 days after 2013 diagnosis or until an event or disenrollment

Event definitions:

• Anticoagulant treatment (≥1 NDC or ≥2 INR CPT codes)
• Stroke or TIA (≥1 ICD-9-CM code in any care setting)
• Bleeding (≥1 ICD-9-CM code in any care setting)
Preliminary Data from Five Data Partners

- **44,786** individuals identified with AF with no evidence of current or recent OAC use
- **38,759 (87%)** eligible for anticoagulant treatment

Among those, by end of follow up:
- 12,867 (33%) had evidence of anticoagulant dispensing
- 5,917 (15%) had a documented TIA or stroke
- 3,469 (9%) had a documented bleeding event
Proportion of AFib members at five Data Partners with an event at end of follow up

- **OAC initiation**
  - CHA2DS2-VASc score ≥2 (N=38,759) - 33%
  - CHA2DS2-VASc score <2 (N=6,027) - 24%

- **TIA or stroke**
  - CHA2DS2-VASc score ≥2 - 15%
  - CHA2DS2-VASc score <2 - 2%

- **Bleeding event**
  - CHA2DS2-VASc score ≥2 - 9%
  - CHA2DS2-VASc score <2 - 3%
Conclusions

- Identified a large number of health plans members potentially eligible for IMPACT-AFib
- Confirmed public health importance
- Sentinel infrastructure able to support
  - Assessment of trial feasibility
  - Implementation
  - Followup
Acknowledgements

- **Aetna**: Cheryl Walraven, Daniel Knecht
- **Clinical Trials Transformation Initiative**: Jennifer Goldsack
- **Duke Clinical Research Institute**: Christopher Granger, Sean Pokorney, Hussein Al-Khalidi, Emily O’Brien, Jennifer Rymer, Sana Al-Khatib
- **Harvard Pilgrim Health Care Institute**: Crystal Garcia, Richard Platt, Ryan Saliga, Robert Jin, Jeff Brown, Hannah Katcoff
- **HealthCore**: Kevin Haynes, Lauren Parlett
- **Humana**: Vinit Nair, Thomas Harkins, Daniel Lane, Yunping Zhou
- **Optum**: Nancy Lin
- **Patient Representative**: Debbe McCall
- **U.S Food & Drug Administration**: Melissa Robb, Patrick Archdeacon
ADAPTABLE Computable phenotype

History of CAD
- Prior MI
  OR
- Prior angiogram showing significant CAD
  OR
- Prior revascularization (PCI/CABG)

At least one:
- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Current cerebrovascular disease and/or peripheral artery disease
- Known ejection fraction <50%
- Current smoker
HealthCore Anthem Research Network (HCARN)

- **Identified 150,000 eligible members** from 30,000 providers with PCORnet Computable Phenotype Common Data Model code

- Provider letters will go out informing providers of ADAPTABLE

- Two weeks after provider letters three batches of member mailers
  - Initial email or mailing
  - Reminder mailing
  - Telephone call

- Eligible patients will be instructed to the ADAPTABLE web recruitment portal

- For enrolled patients Duke will conduct reminders and further outreach

ClinicalTrials.gov: NCT02697916
Sentinel and effectiveness/efficacy

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials
Thank you!