Ninth Annual Sentinel Initiative Public Workshop

Barbara Jordan Conference Center at the Kaiser Family Foundation
February 2, 2017

Join the conversation with #sentinelinitiative
Welcome & Overview

Join the conversation with #sentinelinitiative
Keynote Address

Join the conversation with #sentinelinitiative
The Sentinel Initiative: Perspectives from FDA’s Leadership
Questions & Answers
Updates from the Sentinel Coordinating Center

Join the conversation with #sentinelinitiative
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
OPTUM
KAISER PERMANENTE
Aetna

Scientific partners

Quintiles
Penn Medicine
UAB
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
College of Pharmacy
UNIVERSITY OF FLORIDA
UIC
The University of Iowa
COLLEGE OF PUBLIC HEALTH

AHIP
America's Health Insurance Plans

BWH
BRIGHAM AND WOMEN'S HOSPITAL
HARVARD MEDICAL SCHOOL

DEPARTMENT OF MEDICINE

Duke Medicine
Sentinel Common Data Model and Distributed Database

<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>
<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>
<td>Encounter ID</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>
<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>Procedure code &amp; type</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Result</th>
<th>Vital Signs</th>
<th>Inpatient Pharmacy</th>
<th>Inpatient Transfusion</th>
<th>Death</th>
<th>Cause of Death</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>Result and specimen collection dates</td>
<td>Measurement date and time</td>
<td>Administration date and time</td>
<td>Blood product code and type</td>
<td>Death date</td>
<td>Cause of death</td>
</tr>
<tr>
<td>Test type, immediacy &amp; location</td>
<td>Height and weight</td>
<td>Encounter ID</td>
<td>Encounter ID</td>
<td>Source</td>
<td>Cause of death</td>
</tr>
<tr>
<td>Logical Observation Identifiers Names and Codes (LOINC®)</td>
<td>Diastolic &amp; systolic BP</td>
<td>National Drug Code (NDC)</td>
<td>Blood type</td>
<td>Confidence</td>
<td>Source</td>
</tr>
<tr>
<td>Test result &amp; unit</td>
<td>Tobacco use &amp; type</td>
<td>Route</td>
<td>Administration start and end dates and times</td>
<td>Etc.</td>
<td>Confidence</td>
</tr>
</tbody>
</table>
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.sentinelnitiativ.org/privacy-and-security
Sentinel distributed database*

- Populations with well-defined person-time for which most medically-attended events are known
  - 223 million unique member IDs
  - 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 Initiative

Sentinel Infrastructure

Sentinel System
- ARIA
- PRISM (vaccines)
- BloodSCAN (blood products)

FDA-Catalyst
Sentinel in 2016

- Janet Woodcock, Director of Center for Drug Evaluation and Research (CDER) at 8th Annual Sentinel Initiative Public Workshop:
  - Sentinel is now an "integral part of routine safety surveillance"

- Two classes of activity
  - Production
    - New FDA requesters
    - Requests for new routine capabilities
  - Development
Protocol based analyses – Custom programs

- New programs to answer questions not addressable with existing tools
- Requires extensive planning, implementation, and testing
Production

- Routine Analytic Framework reusable programs that support ARIA: Active Risk Identification and Analysis
Sentinel’s Tools

Summary Table Tool

Cohort ID and Descriptive Analysis (CIDA) Tool
Options:
- Propensity Score Matching or Stratification
- Self-controlled Risk Interval Design
- Drug Use in Pregnancy
- Drug Utilization
- Concomitant Drug Utilization
- Pre/Post Index Tool
Rapid querying via reusable programs

Three ways to address questions

Routine Analytic Framework (RAF)  RADaR: Rapid Analytic Development and Response: RAF + custom code  Custom Programs

• Off-the-shelf query “templates”
• Standard inputs, standard output
• Quick execution

• Hybrid approach: custom code leveraging RAF
• Standard inputs, custom output

• Analysis as specified
• Custom inputs, custom output
• Longer execution
Querying Sequence

1. Simple counts
2. Complex counts
3. Compare event rates
4. Follow-up

- Determine use and frequency
- Identify/describe population
- Comparative assessment
- New queries; Line Lists; Chart Review
Querying Sequence

1. Simple counts
2. Complex counts
3. Compare event rates
4. Follow-up

- Determine use and frequency
- Identify/describe population
- Comparative assessment
- New queries; Line Lists; Chart Review
Simple counts (summary table queries)

- Counts of individuals with exposure or condition
- 49 queries / 291 scenarios in 2016
Querying Sequence

Simple counts → Complex counts → Compare event rates → Follow-up

Determine use and frequency → Identify/describe population → Comparative assessment → New queries; Line Lists; Chart Review
Complex count queries (Level 1 / 1+)

- Counts and rates of events within user specified times, among populations identified using complex “and/or/not” relationships.
  - Example: Rates of first diagnosis of heart failure or cardiomyopathy among new users of different drugs used to treat ADHD, by age and duration of exposure

- 53 queries, 800+ scenarios in 2016
You can observe a lot by just watching

Yogi Berra

www.brainyquote.com/quotes/quotes/y/yogiberra125285.html
Background

• Ondansetron is ... approved for prevention of nausea and vomiting (NV) with chemotherapy, radiotherapy, and post-operatively
  – Not approved for NV in pregnancy (NVP) but prescribed off-label
  – Only doxylamine/pyridoxine(Diclegis™, approved 2013) approved for NVP

• Several recent studies suggest an increase in congenital malformations with ondansetron use in early pregnancy; however evidence is inconclusive

• Needed to better understand antiemetic use in a cohort of pregnant women

Lockwood G. Taylor, PhD, MPH, ICPE Aug 26, 2016
Use of antiemetic drugs among live birth pregnancies in the Sentinel Distributed Database, 2001-2014\textsuperscript{a,b}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chart.png}
\caption{Graph showing the percentage of total antiemetic use from 2001 to 2014.}
\end{figure}

\begin{itemize}
\item \textsuperscript{a} Dashed lines for oral and injection ondansetron form represent a portion of all total ondansetron use as shown by the solid purple line. Summation of oral and injection utilization sums to greater than total ondansetron use since some women received both products.
\item \textsuperscript{b} Not all Mini-Sentinel data partners contributed data for the entire study period.
\end{itemize}

Lockwood G. Taylor, PhD, MPH, ICPE Aug 26, 2016
Conclusion

• Given the widespread use of ondansetron in pregnancy, a great need exists for data establishing its efficacy as well as methodologically rigorous post-marketing assessments to evaluate its safety in pregnant women.

Lockwood G. Taylor, PhD, MPH, ICPE Aug 26, 2016
Blood transfusion during pregnancy

- Need for rapid assessment of frequency of transfusion during pregnancy
- Sentinel Distributed Dataset identified 1,946,032 deliveries with coverage during entire pregnancy from 2008-2015 (~8% of U.S. deliveries)
- 21,048 (1.1%) pregnancies had blood transfusion
- Report with integrated data from 15 data partners returned to FDA within 3 working days of final specification
Querying Sequence

- Simple counts
- Complex counts
- Compare event rates
- Follow-up

Determine use and frequency
Identify/describe population
Comparative assessment
New queries; Line Lists; Chart Review
Comparison of rates (Level 2 / 2+)

- Adjusted relative rates or hazard ratios comparing outcomes among two cohorts identified by complex count program
  
  or

- Adjusted self-controlled risk interval analysis
  - Example: Risk of seizures associated with new use of ranolazine

- 11 queries / 100+ scenarios in 2016
Querying Sequence

Simple counts → Complex counts → Compare event rates → Follow-up

- Determine use and frequency
- Identify/describe population
- Comparative assessment
- New queries; Line Lists; Chart Review
### Patient Episode Profile Retrieval (PEPR)

**Episode Detail**

<table>
<thead>
<tr>
<th>Days from expos</th>
<th>Enc type</th>
<th>LOS Cat</th>
<th>Clinical code</th>
<th>Code description</th>
<th>Incidence^</th>
<th>P Dx#</th>
<th>Node (Y/N)</th>
<th>Main expos (Y/N)</th>
<th>Any vacc (Y/N)</th>
<th>Rx days supp</th>
<th>Rx amt</th>
<th>Cov start~</th>
<th>Cov end~</th>
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<tbody>
<tr>
<td>0 AV</td>
<td>DX</td>
<td>09</td>
<td>V0382</td>
<td>Need Proph Vacc Agnst Strep Pne</td>
<td>F</td>
<td>1</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
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<tr>
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<td>DX</td>
<td>09</td>
<td>V068</td>
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<td>DX</td>
<td>09</td>
<td>V202</td>
<td>Routine Infant/Child Health Check</td>
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<td>PX</td>
<td>C4</td>
<td>90471</td>
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<td>4 AV</td>
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<td>Inf Colitis Enterit &amp; Gastroenterit</td>
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<td>C4</td>
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</tr>
</tbody>
</table>

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Day 0, office visit
Routine health check
Immunization

Day 4, office visit
Gastroenteritis

Day 7, hospitalized
Vomiting / cough
Dehydration
Gastroenteritis

---

^ Incidence: F = first observed; I = incident; blank = prevalent
# Primary Dx: P = primary; S = secondary; X = N/A
~ Med enroll segment containing the admission date of the encounter
or the drug enroll segment containing the dispensing date

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[Link to document](www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_PRISM_Data-Mining-Infrastructure_Report_0.pdf)
New Types of Queries for Other Uses

- Medications errors
  - Name confusion medication errors
  - Dosing errors
- Geographic location stratification
Development Projects in 2016

**Methods Development**
- Review Literature/Develop Method: 14
- Evaluate Method: 13
- Develop Prototype: 4

**Tool Development**
- Tool Development: 2
- Tool Beta-Testing: 0
- Tool Complete: 12

**Data Expansion**
- Discovery: 2
- Implementation: 1
- Integration: 2
- Planning: 0
## Data expansion projects

<table>
<thead>
<tr>
<th>Project name</th>
<th>Description</th>
<th>Status and timeline</th>
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</thead>
<tbody>
<tr>
<td>Centers for Medicare and Medicaid Services (CMS) fee for service beneficiary on-boarding</td>
<td>• Initial extract, 2010-2015, covers ~35 million with prescription drug coverage</td>
<td>2nd quarter 2017 for quality-checked, queryable data</td>
</tr>
<tr>
<td>Inpatient data expansion</td>
<td>• Three sites exploring populating inpatient pharmacy + inpatient transfusion tables</td>
<td>Go / no-go decision expected 2(^{nd}) quarter 2017.</td>
</tr>
<tr>
<td>Rapid surveillance / refresh-on-demand</td>
<td>• Plan and build a ‘refresh on-demand’ system using freshest-feasible data extracts</td>
<td>Go / no-go decision expected 1st quarter 2017</td>
</tr>
<tr>
<td>Diagnosis date and procedure date/time expansion</td>
<td>• Inpatient records will add actual diagnosis date and procedure date and time</td>
<td>Approx. 12 months</td>
</tr>
<tr>
<td>Methods development active in 2016 (selected)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td></td>
<td></td>
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<tr>
<td>ICD10 preparedness</td>
<td></td>
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<tr>
<td>Disease risk score exploratory methods</td>
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<tr>
<td>Optimal propensity score matching strategies for subgroup analyses</td>
<td></td>
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<tr>
<td>Analyzing Laboratory data for routine surveillance</td>
<td></td>
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<tr>
<td>Evaluating performance of analytic modules using simulation (Big Sim)</td>
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<td></td>
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<tr>
<td>Quantitative Bias Analysis (QBA)</td>
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<td></td>
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<tr>
<td>TreeScan Bias / Power Calculation / Evaluation / Propensity scores</td>
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<td></td>
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<tr>
<td>Outcome-based TreeScan (aka DrugScan)</td>
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</tr>
</tbody>
</table>
Medically Product Safety Surveillance

- FDA

- Sentinel Coordinating Center

- Coordinating Center(s)

- Sponsor(s)

Clinical Research

Randomized Clinical Trials

Comparative Effectiveness Research

- Providers
  - Hospitals
  - Physicians
  - Integrated Systems

- Registries
  - Disease-specific
  - Product-specific

- Payers
  - Public
  - Private

Pooled Data

Common Data Model

- Data Standards

Quality of Care

- Sponsor(s)

- Coordinating Center(s)

Public Health Surveillance

- Sponsor(s)

- Coordinating Center(s)

Medical Product Safety Surveillance

- Sentinel Coordinating Center

- Coordinating Center(s)

- Sponsor(s)
National Medical Evidence Generation Collaborative (EvGen Collaborative)
Coordinating Center(s)
Quality of Care Sponsor(s)
Public Health Surveillance Coordinating Center(s)

Medical Product Safety Surveillance
FDA

Sentinel Center

Innovation in Medical Evidence Development and Surveillance
Biologics & Biosimilars Collective Intelligence Consortium

Clinical Research

Comparative Effectiveness Research

Common Data Model Data Standards

Providers
- Hospitals
- Physicians
- Integrated Systems

Registries
- Disease-specific
- Product-specific

Payers
- Public
- Private

Queries
Results

CDC

NIH

NIH Collaboratory
Health Care Systems Research Collaboratory
NIH Collaboratory: Rethinking Clinical Trials
NIH Collaboratory Distributed Research Network

pcornet: The National Patient-Centered Clinical Research Network

Clinical Trials Transformation Initiative

IMPACT-AFib
The Reagan-Udall Foundation for the FDA is a not-for-profit organization established by the United States Congress to advance regulatory science.

The Innovation in Medical Evidence Development and Surveillance (IMEDS) program provides an entry point for private and public sector stakeholders that would like to use Sentinel data, tools, and methods.
Introducing IMEDS, a Public-Private Resource for Evidence Generation

Posted on January 17, 2017 by FDA Voice

By: Robert M. Califf, M.D.

FDA has been working to establish a national resource for FDA-approved medical products that can be used by public and private-sector entities, including regulated industry, to conduct large scale evaluations of safety issues in an environment that is secure and protects patient privacy. These evaluations include epidemiologic studies of medical products in collaboration with multiple healthcare data partners and the analytic center utilized by FDA through the agency’s Sentinel System. This new resource is called the Innovation in Medical Evidence Development and Surveillance System, or IMEDS.

One of the unique aspects and advantages of IMEDS is that it was launched on January 1, 2017 as a public-private partnership by the Reagan-Udall Foundation for the Food and Drug Administration, a not-for-profit organization created by Congress in 2007 to advance regulatory science. The IMEDS framework specifically provides governance that allows private-sector entities to gain access to the system with appropriate oversight. As a result, the FDA Sentinel System’s distributed data as well as scientific methods and tools will now be available for
Insights from Phase II of the IMEDS Evaluation Pilot – Lessons Learned and Future Needs

_PPIs Usage Patterns before/after 2010 Label Change_

Rachel Sobel

January 4, 2017
Results – PPI Use Patterns and Incident Fractures

Days Supplied/User - All Users

Days Supplied/User - Users >1 yr

Proportion Users w/Fractures

Proportion LT Users (>1 yr)

Results similar for prevalent users (data not shown)
NIH Collaboratory Distributed Research Network

Millions of people. Strong collaborations. Privacy first.

The NIH Collaboratory Distributed Research Network enables investigators to collaborate with each other in the use of electronic health data in multisite research programs.

The Network’s querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send queries (queries) to data partners. In some cases, queries can take the form of computer programs that a data partner can execute on a preexisting dataset. The data are aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and technical research.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people.

What does the NIH Collaboratory Distributed Research Network do?

- Provides infrastructure and mechanisms to facilitate multicenter studies using electronic clinical, administrative, and research data
- Allows searchable discovery of available data resources, health systems, researchers, and re-usable analytic tools
- Enables authorized investigators to identify clinical, administrative, and research datasets of interest
- Facilitates multisite distributed querying of data resources, while allowing the data to remain in the control of the data owners
- Serves as a repository of tools to leverage EHRs to support clinical research across multiple health systems

www.nihcollaboratory.org/Pages/distributed-research-network.aspx
NIH Collaboratory is soliciting users

NIH Collaboratory Invites Requests to Query the Distributed Research Network

Do you have a question about the rates of medical conditions or the frequency of use of medical and surgical treatments? data that can answer these questions. The Collaboratory invites prep-to-research questions.

Download the guidance document (Word) for full details on the application process.
PCORnet: The National Patient-Centered Clinical Research Network

The Patient-Centered Outcomes Research Institute (PCORI) is supporting the development of PCORnet, the National Patient-Centered Clinical Research Network, to create a large, highly representative, national network for conducting clinical outcomes research.

PCORnet will transform clinical research by engaging patients, care providers, and health systems in collaborative partnerships to improve healthcare and advance medical knowledge. By bringing research and patient care together, this innovative health data network will be able to explore the questions that matter most to patients and their families. Read more ....
PCORnet-Sentinel Collaborations (Genesis) with CDC

- Surveillance methods for congenital Zika syndrome
- Inpatient antibiotic utilization
Oseltamivir dispensing: Influenza proxy

New Users / 1,000 members

Month

www.sentinelinitiative.org/sites/default/files/Drugs/Assessments/Sentinel_Modular-Program-Report_cder mpl1r_wp030_nsdv_v01.1.pdf, p. 30-31
Sentinel Initiative

Sentinel Infrastructure

Sentinel System
- ARIA
- PRISM (vaccines)
- BloodSCAN (blood products)

FDA-Catalyst
**FDA-Catalyst: IMPACT-AFib Randomized Trial**

**Implementation** of a randomized controlled trial to *imProve* treatment with oral *AntiCoagulanTs* in patients with *Atrial Fibrillation*

- Randomized controlled trial of **direct mail to health plan members with AFib and to their providers** to encourage consideration of oral anticoagulation
- Proof of concept multicenter randomized trial using Sentinel Initiative infrastructure
IMPACT-AFib Workgroup
According to our records, you may have been diagnosed with AFib. We know that managing your health can be a challenge, and hope this information about how to lower your risk for stroke will help.

**People who have the heart condition known as "atrial fibrillation" are at an increased risk of having a stroke.**

Please visit [www.Impact-AFib.org](http://www.Impact-AFib.org) to learn more about atrial fibrillation, stroke risk, and anticoagulant medications. More information about the IMPACT-AFib initiative is available by calling [XXX-XXX-XXXX] or emailing [afib@sentinelsystem.org].

If you have questions about your benefits, call the number on the back of your health plan ID card.

**Talk to your doctor about anticoagulant medications.**

This packet contains information about the benefits of taking anticoagulant medications, also called blood thinners, to lower your risk of having a stroke. We recommend that you bring this information packet to your next doctor’s appointment. We sent similar information to your doctor. Anticoagulant medications may not be right for all patients, but they might be right for you. Even if you have talked about this with your doctor in the past, we encourage you to have another conversation about these medications. New anticoagulant medications are safe and effective options for many patients.

**Protecting your health information**

We take protecting your health information seriously. None of your health information has been shared with other health organizations. Only you and your doctor were sent this information.

Sincerely,

Chief Medical Officer

Enclosures

If you have any questions, please contact [name] at [phone #] or [email]
**IMPACT-AFib**

**Patient Information**

You may have atrial fibrillation and may be at risk of a stroke.

**Taking an anticoagulant medication may prevent a stroke.**

Atrial fibrillation (AFib) is a heartbeat irregularity. If you have AFib, your blood can pool, which increases the risk of a blood clot forming in your heart. The blood clot can travel to your brain, causing a stroke.

Anticoagulant medications, also called blood thinners, can prevent most strokes in patients with AFib. If you are not taking an anticoagulant medication, you may suffer a stroke that could have been prevented.

Please review this information and talk with your doctor to find out if you should be on an anticoagulant medication to prevent a stroke.

---

**How do I know if I’m at a high risk for stroke?**

If you have AFib, you are at a higher risk of stroke. You are at additional risk if you:

- Have high blood pressure
- Have high blood sugar
- Have weak heart function
- Have had a stroke or mini-stroke
- Have had a heart attack or blocked blood vessel in your leg
- Are over 64 years old
- Are a woman

**I have AFib only sometimes. Am I still at risk for a stroke?**

Yes, the risk is similar whether your AFib is all the time, often, or only occasionally.

**What is an anticoagulant?**

Anticoagulants are medications that:

- Prevent blood clots
- Keep existing clots from moving

Examples include: Coumadin, Eliquis, Pradaxa, Savaysa, warfarin, and Xarelto.*

*The information in this mailing is NOT sponsored by any drug company.

**For more information, please visit impact-afib.org**

---

**If my doctor prescribes an anticoagulant, how should I take it?**

- Take your medication exactly as directed by your doctor
- Take it at the same time each day
- If you forget to take your medication one day, take a dose as soon as possible on the same day
- Do not take a double dose the following day to “catch up”

Tell your doctor if you are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed, if you have liver or kidney problems, or are planning to have surgery.

**Will anticoagulant medications prevent strokes?**

- Anticoagulant medications reduce the risk of stroke by 70% in patients with atrial fibrillation.

**What about aspirin?**

- Aspirin is not an effective medication for decreasing the risk of stroke caused by atrial fibrillation.
Intervention Materials for Providers

- Provider letter – sent from health plan Chief Medical Officer, describes call to action
- Provider enclosure – myths and facts on use of OACs
- Response mailer – way for providers to share feedback
Welcome to Mini-Sentinel

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products. Mini-Sentinel uses pre-existing electronic healthcare data from multiple sources. Collaborating Institutions provide access to data as well as scientific and organizational expertise. Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues.

Most Mini-Sentinel activities focus on assessments, methods, or data. Visit the following links to learn more about each type of activity:

- Assessments - Medical product exposures, health outcomes, and links between them
- Methods - Techniques for identifying, validating, and linking medical product exposures and health outcomes
- Data - Mini-Sentinel Distributed Dataset and tools used to access the data

The information contained on this website is provided as part of FDA's commitment to place knowledge acquired from the Mini-Sentinel Pilot in the public domain as soon as possible. FDA will continue to communicate information about the safe use of medical products using existing channels, such as FDA's press announcements, MedWatch Alerts, Drug Safety Communications, and Safety Communications.
MiniSentinel.com is for sale (Mini Sentinel)

Click here to buy MiniSentinel.com for $1,995

Create a blog, promote your business, or build a site for your personal use.
Your web address is memorable and uniquely your own.

Buy Now

Only $1,995
Call us for more information: 1-303-893-0552

Shop with confidence - return any domain within 30 days
30 Day Satisfaction Guarantee! Learn More
SentinelInitiative.com is for sale

Buy Now: $3695
- Take immediate ownership
- Transfer the domain to the Registrar of your choosing

Financing This Domain: $3695
12 monthly payments of $308

- 12 monthly payments, only $307.92 per month
- Start using the domain today

Talk to a domain expert: 1-303-893-0552

Hurry - once it's sold this opportunity will be gone!
Updates from the Sentinel Coordinating Center

Join the conversation with #sentinelinitiative
State of Sentinel Safety Surveillance Activities
FDA’s Active Risk Identification and Analysis (ARIA) System

Robert Ball, MD, MPH, ScM
Deputy Director
Office of Surveillance and Epidemiology
Center of Drug Evaluation and Research
February 2, 2017
2007 FDA Amendments Act (FDAAA)

- Post Marketing Requirements
- Safety Labeling Changes
- Risk Evaluation and Mitigation Strategies (REMS)
- Required Safety Reviews ("915" and "921")
- **Active post-market Risk Identification and Analysis system**
  - FDA Sentinel Initiative
Active Risk Identification and Analysis (ARIA) System

• Mandated creation in Section 905 of FDAAA 2007
• Linked to PMR in Section 901(3)(D)(i):
  – “The Secretary may not require the responsible person to conduct a study under this paragraph, unless the Secretary makes a determination that the reports under subsection (k)(1) and the active postmarket risk identification and analysis system as available under subsection (k)(3) will not be sufficient to meet the purposes set forth in subparagraph (B).”

Defining ARIA

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

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

† Electronic claims data, without manual medical record review
ARIA is Comprised of Distributed Querying Approach using Modular Programs

**Level 1**
Descriptive Analyses, Unadjusted Rates

**Level 2**
Adjusted Analyses with Sophisticated Confounding Control

**Level 3**
Sequential Adjusted Analyses with Sophisticated Confounding Control

Modular Programs Currently in ARIA

Future ARIA Capabilities
What is Sufficiency?

• Adequate data
  – Drug
  – Health Outcomes of Interest
  – Confounders

• Appropriate method

• To answer the question of interest*

• To a satisfactory level of precision

*FDAAA study purpose is one of the following:

  • assess a known serious risk related to the use of the drug
  • assess signals of serious risk related to the use of the drug
  • identify an unexpected serious risk when available data indicate the potential for a serious risk
Sufficiency: A Regulatory Decision Point

Safety Concern

ARIA Sufficient?

No

PMR

Yes

Epidemiologic Assessment Desired

Capability Development or Related Study

ARIA
Post-Market Safety Assessment

Signal Identification: Potential safety concern identified
Signal Refinement: Initial evaluation of safety concerns
Signal Evaluation: Detailed assessment

Case Reports
Registries
Observational Studies
Clinical Trials

Data Mining (e.g. TreeScan)
Modular Programs
>Level 2 Modular Programs/ Protocol-based Assessments
Thank you
State of Sentinel Safety Surveillance Activities
Integrating Sentinel Activities into the Drug Review Process: A CDER Perspective

Ninth Annual Sentinel Initiative Public Workshop
February 2, 2017

Mwango Kashoki, MD MPH
Associate Director for Safety
Office of New Drugs (OND)
FDA/Center for Drug Evaluation and Research (CDER)
Highlights from CDER Activities

Widespread Adoption & Integration ARIA

- Implementation of new processes for routine integration of ARIA into CDER review activities
- Routine use of ARIA in majority of therapeutic areas regulated by CDER

New Tools

- Evaluating confounding control tools and methods and developing new tools for generic drug switching, REMS evaluation, and medication errors

New Data Sources, Tough Outcomes

- Continuing to add new data partners
  - Expanding the CDM to capture Hospital Corporation of America’s EMR data elements
  - Add Medicare Virtual Research Data Center
- Assess new approaches for detecting health outcomes of interest
Opportunities for Integration of Sentinel Analyses into Drug Review

• Review of new and supplemental marketing applications (NDAs/BLAs)
  – Determination of whether ARIA is sufficient for the purposes under section 505(o)(3) of the FDCA, or if a PMR is necessary
  – To supplement information about drug use and/or drug effects

• Postmarket surveillance
  – Signal identification

• Assessment of known or potential safety signals
  – Signal refinement
  – Signal evaluation
Integrating Sentinel Into NDA/BLA Review

ARIA sufficiency and PMR determinations
Integrating Sentinel Into NDA/BLA Review Processes (contd.)

• Scientific considerations
  – What characteristics indicate sufficiency of ARIA for assessment of a particular safety signal

• Defining roles and responsibilities in Sentinel analyses
  – Office of Surveillance and Epidemiology (OSE)
  – Office of New Drugs (OND)
  – Office of Biostatistics (OB)
  – Other CDER offices

• Establishing processes for internal communication and documentation
  – Timeframes for assessment of ARIA sufficiency
  – Review team discussions about purpose of the signal evaluation and sufficiency of ARIA for this purpose
  – Documenting ARIA sufficiency determination
Results of Sentinel Analyses and Regulatory Decision Making

Works in progress...

• Process for communicating results of Sentinel analyses with review teams

• Interpretation of Sentinel analysis output

• Consideration of Sentinel analysis results in context of other available information
  – Strengths, limitations of Sentinel as a data source
  – Strengths, limitations of Sentinel analytic method(s)
Communicating about Sentinel

• Public communication about sentinel analyses and related work products
  – Completed Sentinel analyses
    www.sentinelinitiative.org
  – Posters, abstracts, manuscripts

• In progress - Policies and procedures for informing sponsors about:
  – Planned use of Sentinel to evaluate a safety signal involving their respective products
  – Results from completed Sentinel analyses
PDUFA VI Commitment Letter:
“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.”

Other existing (or new) MAPP or guidance?
State of Sentinel Safety Surveillance Activities
Integrating Sentinel Activities into the Regulatory Process: A CBER Perspective

Scott Proestel, M.D.
Director, Division of Epidemiology
FDA Center for Biologics Evaluation and Research
Ninth Annual Sentinel Initiative Public Workshop
February 2, 2017
CBER Safety Surveillance Data Sources

- Premarket safety data
- Postmarket spontaneous AE surveillance (FAERS/VAERS)
- Medical literature
- Other national regulatory authorities
- Signal detection in claims data (Sentinel/TreeScan)
- Pharmacoepidemiologic studies
  - Centers for Medicare and Medicaid Services data
  - Vaccine Safety Datalink (VSD)
  - Sentinel
CBER Use of Sentinel

- Historically, CBER has used PBAs in all 3 product offices
- ARIA tools have become more sophisticated
- Transitioned to more use of ARIA
- Continue with some PBAs and methods development
CBER Sentinel Case Study -
Blood Safety Continuous
Active Surveillance Network (BloodScan)

- Safety surveillance for blood/blood products
- Uses all 18 data partners
- Claims data and electronic health records
- Inpatient blood transfusion data has improved surveillance
- Immune globulin (IVIG) and thromboembolic events (TEE) case study
CBER Sentinel Case Study

IVIG

- Purified plasma fraction of polyclonal immunoglobulin G
- Derived from pooled donor plasma
- Used for immune deficiency diseases, autoimmune disorders, and inflammatory disorders
CBER Sentinel Case Study

IVIG and TEE

- Case series first reported in 1986
- Spontaneous case reports
- Laboratory evaluations – thrombogenicity
- Warning labeling in 2002
- Pharmacoepi study of IVIG-associated same day TEE (HealthCore claims data)
- Box warning in 2013
- Magnitude of risk and risk factors?
CBER Sentinel Case Study

“Evaluation of the Risk of Thromboembolic Events After Immunoglobulin Administration”

- Protocol-based assessment
- Retrospective, self-controlled risk-interval design
- Initiated IVIG use between 2006-2012
- 14 data partners, medical record confirmation
- Physician-adjudicators confirm exposures, outcomes, and timing
- Goal: estimate RR of IVIG for TEE, identify potential risk factors
- Results: to be posted on Sentinel Website soon!
Regulatory Decisions

• Continued monitoring
• Further study
• Public communication
• Label/PV plan revisions
• PMC/PMR/REMS
• Market withdrawal
Acknowledgments

IVIG and TEE Sentinel Assessment Workgroup:

- Eric M. Ammann, MS, PhD, Elizabeth A. Chrischilles, MS, PhD, Ryan M. Carnahan, PharmD, MS, BCPP, Bruce Fireman, MA, Candace C. Fuller, PhD, MPH, Marin L. Schweizer, PhD, Crystal Garcia, MPH, Madelyn Pimentel, BA, Charles E. Leonard, PharmD, MSCE, Meghan A. Baker, MD, ScD, Adam Cuker, MD, MS, Enrique C. Leira, MD, MS, Jennifer G. Robinson, MD, MPH, Scott K. Winiecki, MD, Sudeepta Dandapat, MD, Jayasheel Eshcol, MD, Saket Girotra, MD, MS, Sherry Grund, RN, Cole Haskins, BS, Rami Kafa, MD, David Martin, MD, MPH, Nandakumar Nagaraja, MD, MS, Michael Nguyen, MD, Adela Niedermann, RN, Angela M. Overton MSN, RN, CNRN, SCRN, Lois Pedelty, RN, Usha Perepu, MBBS, MRCP, Victoria Polich, RN, Kim Price, RN, CCM, Erin Rindels, MSN, RN, CNRN, SCRN, NVRN-BC, Nicholas Rudzianski, BS, Darren Toh, ScD, James C. Torner, PhD

Slide reviewers:

- Azadeh Shoaibi
- Richard Forshee
State of Sentinel Safety Surveillance Activities

Join the conversation with #sentinelinitiative
Questions & Answers
Break

Join the conversation with #sentinelinitiative
Overview of CBER’s Current Sentinel System Activities
CBER Sentinel Program

Azadeh Shoaibi, PhD, MHS
CBER Sentinel Lead
On behalf of CBER Sentinel Team

Office of Biostatistics and Epidemiology
FDA Center for Biologics Evaluation and Research

February 2, 2017
Outline

1. Current priority areas
2. Update on recent activities
3. Major accomplishments
4. Future direction
CBER Sentinel

Regulated Products

- Vaccines
- Blood & Blood-Derived Products
- Cellular, Tissue, Gene Therapies

Sentinel Components

- Post-licensure Rapid Immunization Safety Monitoring (PRISM)
- Blood Safety Continuous Active-surveillance Network (BloodSCAN)
- General Sentinel
CBER Sentinel Program
Current Priority Areas

1. Expansion of hemovigilance capabilities
2. Signal refinement/evaluation of vaccines & blood through use of claims data, EHR such as HCA
3. Safety of vaccines in pregnancy
4. Signal identification of vaccines using TreeScan
5. Vaccine effectiveness activities
Current Instruments

Rapid Query Tools (ARIA)

- Summary Tables
- Level 1: Cohort identification
- Level 2: Adjusted analysis
- Level 3: Sequential analysis

Protocol-Based Activities

- Infrastructure building
- Methods development
- Product assessments
Update on recent activities
Rapid Queries (ARIA) 2016

<table>
<thead>
<tr>
<th>Query Type</th>
<th>Frequency</th>
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<tr>
<td>Summary Tables</td>
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<tr>
<td>Level 1</td>
<td>10</td>
</tr>
<tr>
<td>Level 2</td>
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<tr>
<td>Level 3</td>
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<tr>
<td>Total</td>
<td>16</td>
</tr>
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</table>
## Protocol-Based Activities (Completed)

### Methods Development Infrastructure Building
- Data mining infrastructure
- Birth certificate linkage
- Scan statistics
- Self-controlled risk interval tool pilot
- Vaccine effectiveness pilot

### Product Assessments
- Influenza vaccine and birth outcomes
- Intravenous immunoglobulins and thromboembolic events
## Protocol-Based Activities (Ongoing)

<table>
<thead>
<tr>
<th>Methods Development Infrastructure Building</th>
<th>Product Assessments</th>
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<tbody>
<tr>
<td>Quantitative bias analysis</td>
<td>Pneumococcal conjugated 13-valent (PCV13) vaccine and Kawasaki Disease</td>
</tr>
<tr>
<td>TreeScan power calculation</td>
<td>Influenza vaccine 2 seasons and febrile seizure in children</td>
</tr>
<tr>
<td>TreeScan bias</td>
<td>Human papilloma virus 9-valent (HPV9) vaccine TreeScan analysis</td>
</tr>
<tr>
<td>Influenza vaccine and birth defects</td>
<td></td>
</tr>
<tr>
<td>Transfusion-Related Acute Lung Injury in HCA database</td>
<td></td>
</tr>
</tbody>
</table>
Vaccine Safety in Pregnancy

• Protocol-based activity with medical chart review

• Test case
  – Exposure: inactivated influenza vaccine
  – Outcome: spontaneous abortion vs. live birth, oral cleft in newborns
Objectives

• Build infrastructure and develop methods to examine pregnancy outcomes (PRISM priority area) and birth defects following vaccination

• Examine positive predictive value of claims-based algorithms for spontaneous abortion (SAB), gestational age, and oral cleft
Current Status

• Pregnancy outcomes: SAB and gestational age
  – Project almost completed

• Birth defects: oral cleft in newborns
  – Medical chart review close to completion
Signal Identification: TreeScan

- Human papilloma virus 4-valent (HPV4) vaccine analysis as a pilot completed
- HPV9 vaccine analysis underway
- Expanding TreeScan capabilities
  - Longer term and variable follow-up period
  - Power calculation
BloodSCAN

• Data sources:
  – Claims and administrative data
  – Inpatient electronic health records (EHR): Hospital Corporation of America (HCA) database

• Access to inpatient blood transfusion data broadens capabilities for blood safety surveillance
BloodSCAN

- Intravenous immunoglobulins (IVIg) and thromboembolic events (TEE)
- Transfusion-Related Acute Lung Injury (TRALI)
Intravenous Immunoglobulins and Thromboembolic Events

- Data source
  - Claims and administrative data

- Objective
  - Evaluate risk of TEE following IVIg exposure

- Study design
  - Self-controlled risk-interval

- Current status
  - Project almost completed
Transfusion-Related Acute Lung Injury (TRALI)

- Data source: HCA inpatient EHR
- Infrastructure building: become familiar with HCA database
- Test case: TRALI assessment
- Objective: to evaluate incidence rate of TRALI after plasma, platelet, packed RBC administration
- Current status:
  - TRALI cases identified electronically
  - Medical chart retrieval and adjudication underway
Vaccine Effectiveness

• Assessing use of Sentinel capabilities for effectiveness evaluation in a limited capacity for specific situations
  – Pilot project almost completed
CBER Sentinel Program
Major Accomplishments

1. Use of rapid query tools (ARIA)
2. Integration of Sentinel into regulatory process and participation of product offices
3. Transition from development to production mode
4. Initiation of vaccine effectiveness activities
Future

• Less focus on protocol-based activities, more focus on rapid query tools (ARIA) for product safety assessments

• Continue to expand infrastructure and capacity

• In collaboration with the Sentinel Operations Center and CBER product offices
  – Work toward making Sentinel more efficient
  – Areas of improvement:
    • Reduce data lag
    • Explore alternative data sources, such as EHR, due to limitations in claims-administrative data
Summary

1. Significant accomplishments for CBER Sentinel Program over the past year
2. Availability and utilization of more sophisticated rapid query tools (ARIA) to interrogate database
3. Incorporation of biologics effectiveness activities
4. Integration of Sentinel into regulatory process
5. Transition from development to production mode
6. Contribution of Sentinel to medical product safety and to public health
Acknowledgements

- Sentinel Operations Center at Harvard Pilgrim
- Data Partners
- CBER Sentinel Central Team, OBE and other CBER investigators
- Sentinel investigators and collaborators across many institutions
Thank you!

azadeh.shoaibi@fda.hhs.gov
Overview of CBER’s Current Sentinel System Activities
Conducting Vaccine Effectiveness Surveillance in Sentinel’s PRISM Program

Maria Said, MD, MHS
FDA/CBER/OBE
Sentinel Annual Meeting
February 2, 2017
Project Rationale

• PRISM, which is part of Sentinel and uses a subset of Sentinel data partners, is a valuable and rich resource.
  – Large number of members from geographically diverse areas
  – Multiple potentially useful data elements (e.g. demographics, outpatient pharmacy dispensing, outcome data etc.)

• PRISM had been used for successful vaccine safety studies; why not also for vaccine effectiveness?

• PRISM’s observational data might be able to supplement data from randomized clinical trials (RCTs) under certain circumstances.
What Gaps Could PRISM Fill?

• In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
  • Evaluation of effectiveness in specific populations
  • Evaluation of effectiveness to prevent rare conditions
  • Situations in which an RCT is not ethical and/or feasible
  • Supplement/confirm what has already been learned in an RCT
Biologics Licensure Pathways: Some Key Aspects

• “Traditional” Approval
  – Provides direct pre-licensure evidence of effectiveness by demonstrating protection against disease or, in some cases, through use of a scientifically well-established correlate that predicts protection against disease

• Accelerated Approval
  – Demonstrates effectiveness using a surrogate endpoint that is reasonably likely to predict clinical benefit

• “Animal Rule” Approval
  – Demonstrates effectiveness in animal model(s) and applies to products that would ameliorate or prevent serious or life-threatening conditions
What Gaps Could PRISM Fill?

• In certain situations, for confirmation of effectiveness for vaccines approved under accelerated approval or the animal rule
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• Evaluation of effectiveness to prevent rare conditions or a more specific endpoint
• Situations in which an RCT is not ethical and/or feasible
• Supplement/confirm what has already been learned in an RCT
Project Overview

• Objective: To address the suitability of using PRISM to estimate vaccine effectiveness

• Project Components
  – Overview of study designs and methods used in vaccine effectiveness studies, particularly observational studies using administrative databases
  – Exploration of the PRISM database through a use case
Project Approach

• **Data Elements** (Study Population, Exposures, Outcomes, Covariates)

• **Methods** (Study Designs and Statistical Adjustment)

• **Assessments**: Existing Sentinel/PRISM Tools and Protocol Based Assessments

• **A Descriptive Use Case** (would not link the exposure to the outcome)
Use Case

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta*, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas Macurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.
Use Case

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Could we do the same study, but using the PRISM Database?
# Use Case

**Table 1: Baseline characteristics of high-dose and standard-dose cohorts from 24,501 matched pharmacies**

<table>
<thead>
<tr>
<th></th>
<th>High-dose cohort (n=929730)</th>
<th>Standard-dose cohort (n=1615545)</th>
<th>Standardised mean difference</th>
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<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Female</td>
<td>538380 (57.91%)</td>
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<tr>
<td>Male</td>
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<td>656473 (40.63%)</td>
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<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
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<td>1512633 (93.63%)</td>
<td>0.01</td>
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<tr>
<td>Black</td>
<td>25463 (2.74%)</td>
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<td>21178 (1.31%)</td>
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<td>6112 (0.66%)</td>
<td>10328 (0.64%)</td>
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<tr>
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<td>2121 (0.13%)</td>
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<tr>
<td><strong>Dual enrolled</strong></td>
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<td>79750 (4.94%)</td>
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<tr>
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<td>841789 (52.11%)</td>
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</tr>
<tr>
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<td>340728 (36.65%)</td>
<td>561385 (34.75%)</td>
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</tr>
<tr>
<td>85 and older</td>
<td>127742 (13.74%)</td>
<td>212371 (13.15%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

(1) Data Elements

• Data Elements - Study Population
  – Size
  – Geographic coverage
  – Age distribution
  – Representativeness
## (2) Methods (Study Designs)

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Description</th>
<th>Applicability to Sentinel</th>
<th>Recommended /Viable for Sentinel?</th>
<th>Example(s) from Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Control Study etc...</td>
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</table>
(3) Assessments/Tools

Summary Table Tool

Pre-/Post Exposure Evaluation Tool

Drug Utilization Tool

Concomitant Utilization Tool

Cohort ID and Descriptive Analysis (CIDA) Tool
(4) Use Case Output

- Numbers of patients receiving high-dose vs. standard-dose influenza vaccination
- Numbers of episodes and patients with influenza diagnosis or pneumonia diagnosis
- Patient characteristics including age, sex, and medical history
Project Status

- Draft White Paper completed and revisions ongoing
- White Paper to be posted on the website
Acknowledgments

Harvard SOC
- Meghan Baker
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- Cathy Panozzo

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- Douglas Pratt
- Azadeh Shoaibi

Work Group Members
- Roger Baxter
- Kevin Fahey
- Bruce Fireman
- Lisa Jackson
- Nicola Klein
- James Nordin
- Carla V. Rodriguez
- Nandini Selvam
Overview of CBER’s Current Sentinel System Activities
Using Sentinel Data for Benefit-Risk Assessments

Richard Forshee, Ph.D.
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology

Sentinel Annual Meeting
Washington, DC
February 2, 2017
CBER is responsible for regulating vaccines, blood and blood products, and cellular, tissue, and gene therapies with diverse benefits and risks.

Consider three examples...
Zika infections increasing rapidly in Puerto Rico

Widespread Zika infections warrant urgent action to protect pregnant women

**Figure 2.** Municipality of residence of persons with Zika virus disease*,† — Puerto Rico, November 23, 2015 – January 28, 2016

**Range of Microcephaly Severity**

- Baby with Typical Head Size
- Baby with Microcephaly
- Baby with Severe Microcephaly

**Whitman-Walker Health**

MSM who have ever engaged in sex with a male partner since 1977...

Can't Donate

MSM who have engaged in sex with a male partner within one year...

Can't Donate

Based on science. Doesn't discriminate.

**FDA 1985**

Draft Proposal

**FDA 2015**

Proposal

**Flu vaccination and GBS**
Sentinel Data Can Help CBER Accomplish Our Public Health Mission

- Timely Data to support benefit-risk assessment
- Assessments support decision-making by FDA and stakeholders

- Will discuss two transfusion B-R assessments
  - Transfusion-transmission of Zika
  - Testing strategies of US blood supply for Babesia
Blood donation is common and provides multiple life-saving products


Public Domain: https://commons.wikimedia.org/wiki/File:Bagram_blood_donation_-a.jpg
Blood and Blood Products

• Blood Donations and Transfusions
  – About 14.2 M RBC Units collected
  – About 13.2 M RBC Units were transfused

• Blood donations are the source for other blood products
  – Clotting Factor Products
  – Immune Globulin Products
  – Others
Sentinel can provide timely data to support benefit-risk assessment:

Zika Virus in Puerto Rico Example
Background: Zika Virus

- Local transmission of Zika virus (ZIKV) in more than 59 countries and territories
- Microcephaly associated with infection during pregnancy
- Known risk of transmission through blood
- FDA recommended travel-based donor deferral and testing of blood collected in areas with active local transmission in Feb. 2016
Background: Zika Virus Outbreak in Puerto Rico

- Blood collection in Puerto Rico was temporarily suspended
- Nucleic acid test (NAT) under IND for testing of whole blood and components became available in March 30, 2016
- Local blood collection has been resumed and tested with NAT since April 3, 2016
Objectives of CBER TTZIKV Risk Assessment

- To develop a tool for rapid assessment of risk of transfusion-transmission of ZIKA Virus (TTZIKV)

- To estimate risk after blood screening using individual nucleic acid testing (ID NAT) for blood units collected in Puerto Rico

- To estimate the risk for pregnant women
Some of the Major Model Inputs

Input Parameters

Window period (days)
- Triangular (0, 0.5, 3)

References

AABB Zika Virus Symposium
O’Connor et al. 2016

Sentinel Database (Not Puerto Rico specific)

Transfused units for pregnant women

Normal (0.48%, 6.6x10⁻⁵)

Transfusion transmission rate

Triangular (37.5%, 37.5%, 100%)

Minimum and most likely values- Sabino et al. 2016
Maximum value- assumption
### Some of the Major Model Inputs

<table>
<thead>
<tr>
<th>Input Parameters</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Transfused units for pregnant women</td>
<td>Sentinel Database (Not Puerto Rico specific)</td>
</tr>
<tr>
<td>Normal (0.48%, 6.6x10^-5)</td>
<td></td>
</tr>
<tr>
<td>Transfusion transmission rate</td>
<td>Minimum and most likely values- Sabino et al. 2016</td>
</tr>
<tr>
<td>Triangular (37.5%, 37.5%,100%)</td>
<td>Maximum value- assumption</td>
</tr>
</tbody>
</table>

Sentinel was able to quickly provide a key input for a risk assessment with important public health implications.
Partial Results- Model predicted cumulative risk, period April 3rd - November 17th, 2016
(33,227 total reported clinical cases)

<table>
<thead>
<tr>
<th></th>
<th>Mean Cumulative Risk (2.5-97.5\textsuperscript{th}%ile)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without blood testing</td>
</tr>
<tr>
<td>Infectious RBC units</td>
<td>1936</td>
</tr>
<tr>
<td>TTZIKV</td>
<td>1128</td>
</tr>
<tr>
<td></td>
<td>(159-3751)</td>
</tr>
<tr>
<td>TTZIKV in pregnant women</td>
<td>5.4</td>
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<tr>
<td></td>
<td>(0.8-18)</td>
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<tr>
<td>TTZIKV in immunocompromised</td>
<td>393</td>
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<tr>
<td></td>
<td>(56-1309)</td>
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</table>

ID NAT reduces TTZIKV risk by ~86%
Geographic data to support benefit-risk assessment: Transfusion-Transmitted Babesiosis
Babesia microti and Blood Safety

- Tick-borne disease
- Chronically infected asymptomatic individuals cause Transfusion Transmitted Babesiosis (TTB)
- Discussed at 2015 Blood Products Advisory Committee Meeting

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER
Why this Issue is Important

• No licensed donor testing is available
• *B. microti* is among the most frequently transfusion-transmitted infections
• Cases of Babesia in the U.S. are regionally located but risk of transfusion-transmitted infection is nationwide
• Recent investigational testing of blood donations for *Babesia microti* infections provides data on the potential utility of testing

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER
Clinical Symptoms and Pathogenesis

- Ranges from asymptomatic to mild to life-threatening severe disease
- Neonates, immuno-compromised, asplenic, and elderly are at the highest risk of severe disease
- Fatality rates of 6 - 9% in the hospitalized cases and 21% in immuno-compromised cases

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER
Geographic Distribution of Babesiosis (CMS)

- 2006-2013
  - 10,301 unique diagnoses of babesiosis
- Cases reported from all states and Washington D.C., except Wyoming

Slide courtesy of Dr. Sanjai Kumar, FDA/CBER
Summary of TTB Benefit-Risk Assessment

- TTB B-R Assessment presented at and used to inform discussion/decisions at FDA Blood Products Advisory Committee Meeting in 2015
- Used Center for Medicare & Medicaid Services (CMS) data to evaluate possible Testing Scenarios
Scenarios overview

<table>
<thead>
<tr>
<th>No Testing</th>
<th>Serology Only</th>
<th>Serology + NAT</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Scenarios Overview**

- **S**: 5 States*
- **S+N**: 5
- **S**: 9
- **S+N**: 9
- **S**: 15 + DC
- **S+N**: 15 + DC
- **S**: 5 States*
- **S+N**: 5
- **S**: 50 + DC
- **S+N**: 50 + DC

*Number of States Using Testing
Summary of Benefits and Risks under Selected TTB Testing Scenarios

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>TTB Risk Reduction (%)</td>
<td>70</td>
<td>74</td>
<td>73</td>
<td>77</td>
<td>84</td>
<td>87</td>
<td>88</td>
<td>91</td>
<td>95</td>
<td>96</td>
</tr>
<tr>
<td>Positive Units Interdicted</td>
<td>716</td>
<td>752</td>
<td>748</td>
<td>787</td>
<td>858</td>
<td>894</td>
<td>902</td>
<td>939</td>
<td>975</td>
<td>978</td>
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<tr>
<td>Positive Predictive Value</td>
<td>57</td>
<td>58</td>
<td>51</td>
<td>52</td>
<td>39</td>
<td>39</td>
<td>40</td>
<td>19</td>
<td>19</td>
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<tr>
<td>Donors with False Positive Results</td>
<td>315</td>
<td>315</td>
<td>424</td>
<td>424</td>
<td>804</td>
<td>804</td>
<td>804</td>
<td>2,422</td>
<td>2,422</td>
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</tr>
</tbody>
</table>

Blood Products Advisory Committee Meeting, May 13, 2015
Geographic Distribution

• Data on the geographic distribution of emerging infectious diseases (and other conditions) can inform important regulatory decisions
• We have successful examples using CMS data
• Most CMS participants are 65+ years old
• For certain projects, Sentinel data with geographic data would be very helpful
• CBER recognizes the need to aggregate to appropriate geographic levels, such as 3-digit ZIP code
Conclusion

• Sentinel data has already been used as inputs in CBER benefit-risk assessments
• CBER continues to explore other ways that Sentinel data can help us accomplish our public health mission
Acknowledgments

• Zika
  – Hong Yang
  – Kinnera Chada
  – Yin Huang
  – Steve Anderson
  – Office of Blood Research and Review

• Babesiosis
  – Arianna Simonetti
  – Mikhail Menis
  – Sanjai Kumar
  – Office of Blood Research and Review

• Previously presented at Society for Risk Analysis 2016
• Previously presented at Blood Products Advisory Committee 2015
Thank you!
Overview of CBER’s Current Sentinel System Activities
Questions & Answers
Lunch Break
Overview of CDER’s Current Sentinel System Activities

Join the conversation with #sentinelinitiative
Incidence of heart failure and cardiomyopathy following initiation of medications for attention deficit hyperactivity disorder

COLLABORATORS

FDA Center for Drug Evaluation and Research
Division of Epidemiology 1: Andrew D. Mosholder, Lockwood Taylor
Division of Psychiatry Products: Glenn Mannheim

Harvard Pilgrim Health Care Institute
Lisa Ortendahl, Tiffany Woodworth, Darren Toh
Background

- Stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) may be administered for long durations, often well into adulthood.
- Illicit stimulant use is associated with cardiomyopathy (Diercks et al., Am J Cardiol 2008; Jafari Giv, Cardiovasc Toxicol 2016).
- Case reports of cardiomyopathy with therapeutic stimulant use exist (Marks et al., Am J Ther 2008; Nymark et al., Vasc Health Risk Manag 2008), but few available population-based data evaluate the risk.
• Hypothesis: If cardiomyopathy is a long-term adverse effect of stimulant treatment, may observe an increase in the incidence with longer duration of use

• Purpose: To assess the incidence of heart failure & cardiomyopathy, among adult and pediatric ADHD medication users with no history of heart failure, by duration of ADHD medication use.
Methods

• Modified L1 descriptive analysis
• 15 Sentinel Data Partners contributed data
• Time period: January 1, 2000-March 3, 2016
• Patients: Users of amphetamine products (including lisdexamfetamine), methylphenidate, or atomoxetine
• No ADHD medication or outcome within the preceding 183 days
• Age groups: <22, 22-44, 45-64, and 65+ years
• Exposure episodes allowed gaps in days supply up to 90 days (to allow for variability in patterns of use).
• Only each patient’s first treatment episode analyzed
Methods (2)

• Outcome (modified from Allen et al., 2014):
  • Heart failure or cardiomyopathy ICD-9-CM diagnosis codes (398.91, 402.x1, 402.x3, 404.x1, 404.x3, 422.90, 425.4, 425.9, 428.xx)
  • Principal diagnosis if inpatient/institutional
• Durations of use analyzed, in days
  • 0-90
  • 91-180
  • 181-270
  • 271-365
  • 366-730
  • 731-1,095 (=3 yrs)
Figure 1. Rate of heart failure events (per 10,000 person years) by age group, medication, and duration of use
Limitations

• Did not assess risk relative to non use
• Could not account for potential confounding
• Combining heart failure with cardiomyopathy might have obscured a trend for cardiomyopathy alone
Conclusions

- No consistent increases in heart failure/cardiomyopathy over 3 years of ADHD medication use, in any age category.
- Hypothesis of a higher incidence emerging with longer duration of treatment not supported
- In older age groups, trend for higher incidence of heart failure earlier in the course of treatment
- 1.7% of patients 65+ years initiating ADHD medication developed heart failure/cardiomyopathy within 90 days
Conclusions

- Trend suggests depletion of susceptibles, to the extent that patients at risk of developing heart failure while receiving the medication tend to do so earlier in the course of treatment.

- Biological plausibility?
  - Older literature suggests adrenergic agonists harmful in heart failure (Carbonin and Zuccala, 1996).
  - Beta blockers are used therapeutically in heart failure.
Sentinel’s Role in Safety Assessment

• Hypothesis that cardiomyopathy could be associated with long term stimulant use based on
  – Case reports
  – Known association with stimulant abuse

• Sentinel analysis
  – Did not support hypothesis
  – Identified a new signal for heart failure with short term use in patients 65+

• Possible next steps to address this new signal
  – Explore risk factors among older patients who develop heart failure/cardiomyopathy with ADHD medication
  – Conduct meta-analysis of heart failure & cardiovascular outcomes in randomized, controlled trials of ADHD medications in adults
Overview of CDER’s Current Sentinel System Activities

Join the conversation with #sentinelinitiative
Prospective Surveillance of AMI Events in New Users of Saxagliptin

Ninth Annual Sentinel Initiative Public Workshop
Washington, D.C.
February 2, 2017

Christian Hampp, Ph.D., B.S. Pharm
Senior Epidemiologist, Division of Epidemiology I
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research
Food and Drug Administration
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**Mini-Sentinel**
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- Neesha Nathwani
- Amanda McNeill

**FDA**
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- David Graham
- Christian Hampp
- Rongmei Zhang
- Mary Ross Southworth
- Jennifer Pippins
- Mark Levenson
- Amy Egan

### Data Partners

<table>
<thead>
<tr>
<th>Aetna</th>
<th>Humana</th>
<th>KP Southeast</th>
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<td>Group Health</td>
<td>KP Colorado</td>
<td>Lovelace</td>
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<td>Harvard Pilgrim</td>
<td>KP Hawaii</td>
<td>Marshfield</td>
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<td>HealthCore</td>
<td>KP Mid-Atlantic</td>
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<td>HealthPartners</td>
<td>KP N California</td>
<td>Optum</td>
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<tr>
<td>Henry Ford</td>
<td>KP Northwest</td>
<td>Vanderbilt</td>
</tr>
</tbody>
</table>
Motivation

- Need for infrastructure to prospectively monitor the safety of new drugs
- Saxagliptin, a DPP-4 inhibitor, is an oral anti-hyperglycemic agent approved in 2009
- Saxagliptin was chosen by FDA as the first NME to be prospectively monitored in the Mini-Sentinel pilot
  - Results from Mini-Sentinel would complement results from a post-market CV outcomes trial (SAVOR-TIMI 53)
  - Mini-Sentinel could provide interim safety info about saxagliptin while FDA awaited final results from the trial
  - Prospective surveillance could help identify safety issues more quickly than conventional observational studies
Surveillance design

• Protocol-based analysis: Protocol was published, subsequent revisions publicly posted

• New-user cohort design

• Four head-to-head comparisons
  • Saxagliptin
    • vs. sitagliptin
    • vs. pioglitazone
    • vs. second-generation sulfonylureas
    • vs. long-acting insulin products
Surveillance design

- Application of inclusion/exclusion criteria
- Assessment of covariates

Start of follow up (dispensing date)

365-day baseline period

- **Outcome: AMI**
- Death
- Health plan disenrollment
- Discontinuation of initial treatment
- Initiation of another drug in the pair
- End of surveillance period

Contributing person-times
Statistical analysis

• Covariate adjustment:
  – Propensity score matching (1:1)
  – Disease risk score stratification (by decile)

• Covariates:
  – Patient demographics
  – Medical history
  – Medication use
  – Cardiovascular risk factors
  – Other antihyperglycemic treatments
  – Health services utilization measures
Statistical analysis

• Cox regression model to estimate hazard ratios and 95% confidence intervals

• Three patient groups
  – All patients
  – Patients with prior CVD history
  – Patients without prior CVD history
What prospective surveillance looks like

* Data are not from Mini-Sentinel and are shown for illustrative purposes only

Courtesy:
Joshua J. Gagne, ScD
What prospective surveillance looks like

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What prospective surveillance looks like

<table>
<thead>
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<th>Rate difference (per 1,000 person-years)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<th>17</th>
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<th>20</th>
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<tbody>
<tr>
<td><strong>Cumulative rate difference</strong></td>
<td>6.67</td>
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<td><strong>Cumulative events: monitoring drug</strong></td>
<td>3</td>
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<tr>
<td><strong>Cumulative events: comparator drug</strong></td>
<td>2</td>
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<tr>
<td><strong>Cumulative person-years: monitoring drug</strong></td>
<td>150</td>
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<tr>
<td><strong>Cumulative person-years: comparator drug</strong></td>
<td>150</td>
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What prospective surveillance looks like

Rate difference (per 1,000 person-years)

- Lower 95% confidence interval: -22.50
- Cumulative rate difference: 6.67
- Upper 95% confidence interval: 35.88

Cumulative events: monitoring drug: 3
Cumulative events: comparator drug: 2
Cumulative person-years: monitoring drug: 150
Cumulative person-years: comparator drug: 150

* Data are not from Mini-Sentinel and are shown for illustrative purposes only.
What prospective surveillance looks like

- Lower 95% confidence interval: -22.50
- Cumulative rate difference: 6.67
- Upper 95% confidence interval: 35.88

Cumulative events: monitoring drug: 3
Cumulative events: comparator drug: 2
Cumulative person-years: monitoring drug: 150
Cumulative person-years: comparator drug: 150

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What prospective surveillance looks like

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Sequential surveillance

- Prospective surveillance: 7 sequential analyses
- Overall chance of false positive signal kept below 0.05 (one-sided)
- At each sequential analysis step: 2 methods of covariate adjustment x 4 comparisons x 3 CVD strata = 24 analyses
## Selected baseline characteristics

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Saxagliptin*</th>
<th>Sitagliptin</th>
<th>Pioglitazone</th>
<th>2nd-generation sulfonylureas</th>
<th>Long-acting insulin</th>
</tr>
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<tr>
<td><strong>Total N</strong></td>
<td>82,264</td>
<td>220,912</td>
<td>146,045</td>
<td>452,969</td>
<td>262,117</td>
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<td><strong>Patient demographic</strong></td>
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<tr>
<td>Mean age</td>
<td>57.3</td>
<td>59.1</td>
<td>58.4</td>
<td>59.0</td>
<td>59.5</td>
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<tr>
<td>Male sex</td>
<td>56.1%</td>
<td>54.9%</td>
<td>58.1%</td>
<td>55.2%</td>
<td>54.0%</td>
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<tr>
<td><strong>Comorbid condition</strong></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
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<td>Asthma</td>
<td>6.6</td>
<td>7.2</td>
<td>6.6</td>
<td>8.0</td>
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<td>Cancer</td>
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<td>7.4</td>
<td>6.2</td>
<td>7.3</td>
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<td>COPD</td>
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<td>7.7</td>
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<td>7.6</td>
<td>7.6</td>
<td>9.1</td>
<td>13.8</td>
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<td>Dementia</td>
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<td>1.9</td>
<td>2.7</td>
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<td>10.1</td>
<td>9.2</td>
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<td>ESRD</td>
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<td>0.9</td>
<td>0.8</td>
<td>1.1</td>
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<tr>
<td>Fracture</td>
<td>2.8</td>
<td>3.4</td>
<td>3.1</td>
<td>3.3</td>
<td>4.3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5.3</td>
<td>7.5</td>
<td>4.5</td>
<td>7.8</td>
<td>11.8</td>
</tr>
<tr>
<td>HIV / AIDS</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>79.2</td>
<td>77.5</td>
<td>76.7</td>
<td>71.5</td>
<td>76.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78.0</td>
<td>78.0</td>
<td>76.0</td>
<td>74.2</td>
<td>79.4</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>4.2</td>
<td>5.2</td>
<td>5.4</td>
<td>6.4</td>
<td>10.6</td>
</tr>
<tr>
<td>Obesity or weight gain</td>
<td>18.8</td>
<td>19.3</td>
<td>16.9</td>
<td>20.1</td>
<td>24.0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>4.3</td>
<td>4.8</td>
<td>4.2</td>
<td>4.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>14.4</td>
<td>15.9</td>
<td>15.6</td>
<td>15.0</td>
<td>22.9</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>7.2</td>
<td>7.6</td>
<td>7.1</td>
<td>10.4</td>
<td>12.4</td>
</tr>
</tbody>
</table>

* Included saxagliptin users who contributed to one or more pairwise comparisons
# AMI: Saxagliptin vs. Sitagliptin

<table>
<thead>
<tr>
<th>Look 1</th>
<th>Look 2</th>
<th>Look 3*</th>
<th>Look 4</th>
<th>Look 5</th>
<th>Look 6</th>
<th>Look 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data from 8/1/09 through 6/30/11</td>
<td>12/31/11</td>
<td>12/31/11</td>
<td>6/30/12</td>
<td>3/31/13</td>
<td>12/31/13</td>
<td>8/31/14</td>
</tr>
</tbody>
</table>

Each estimate is based on the cumulative data on all AMIs in users since August 1, 2009.

Method: 
- Disease risk score stratification
- Propensity score matching
AMI: Saxagliptin vs. pioglitazone

Signal: HR=1.63 (1.12-2.37)

Each estimate is based on the cumulative data on all AMIs in users since August 1, 2009
AMI: Saxagliptin vs. sulfonylureas

Method: Disease risk score stratification ▲ Propensity score matching

Each estimate is based on the cumulative data on all AMIs in users since August 1, 2009.
AMI: Saxagliptin vs. long-acting insulin

Method: • Disease risk score stratification ▲ Propensity score matching

Each estimate is based on the cumulative data on all AMIs in users since August 1, 2009
For the one analysis that signaled

• PS-matched analysis
  • Fifth look:  HR 1.63 (1.12, 2.37)
  • Sixth look:  HR 1.19 (0.86, 1.66)
  • Seventh look: HR 1.17 (0.86, 1.57)

• Corresponding DRS-stratified analysis
  • Fifth look:  HR 1.18 (0.90, 1.55)
  • Sixth look:  HR 1.17 (0.90, 1.52)
  • Seventh look: HR 1.11 (0.87, 1.42)
Possible reasons for the signal

- Risk of AMI was higher with saxagliptin vs. pioglitazone
- Residual or unmeasured confounding
- Errors in data or analytic code
- Chance finding
Study Conclusion

We found no strong evidence to suggest a higher risk of AMI in saxagliptin users compared to users of sitagliptin, pioglitazone, second-generation sulfonylureas, or long-acting insulin.
SAVOR-TIMI 53 trial

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus


## Comparisons with SAVOR-TIMI 53 trial

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SAVOR-TIMI 53 Trial</th>
<th>Mini-Sentinel surveillance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>Placebo</td>
<td>Select anti-hyperglycemics</td>
</tr>
<tr>
<td>No. saxagliptin users</td>
<td>8,280</td>
<td>82,264</td>
</tr>
<tr>
<td>No. comparator users</td>
<td>8,212</td>
<td>146,045 to 452,969</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>2.1 years (median)</td>
<td>4 to 8 months (mean)</td>
</tr>
<tr>
<td>No. AMI in saxagliptin</td>
<td>265</td>
<td>94 to 171</td>
</tr>
<tr>
<td>No. AMI in comparator</td>
<td>278</td>
<td>75 to 1,085</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>Intention-to-treat</td>
<td>As-treated</td>
</tr>
<tr>
<td>Hazard ratio for AMI</td>
<td>0.95 (95% CI: 0.80, 1.12)</td>
<td>0.54 to 1.17</td>
</tr>
</tbody>
</table>

* From end-of-surveillance analysis that included all patients
Regulatory Importance

• Results from first “looks” were available before SAVOR-TIMI 53
• Real-life, head-to-head comparisons
• First prospective surveillance in (Mini-) Sentinel: established infrastructure for future studies
Thank you

Christian Hampp, PhD
christian.hampp@fda.hhs.gov
Overview of CDER’s Current Sentinel System Activities
Risk of seizures associated with Ranolazine (Ranexa)

COLLABORATORS
FDA Center for Drug Evaluation and Research
Division of Epidemiology 1: Efe Eworuke, Margie Goulding, David Moeny, Michael Nguyen
Division of Cardio-Renal Products: MaryRoss Southworth
Harvard Pilgrim Health Care Institute
Emily Welch, Judith Maro
Background

• Ranexa is an oral drug given twice daily for angina

• Angina is chest pain caused by insufficient blood flow to the heart (myocardial ischemia)
  – Possible pharmacological activity:
    • Demonstrated effects on sodium channels which are present in the cardiac, central and peripheral nervous systems
Safety Issue Timeline

Labeling at approval was based on clinical events (syncope, tremor, paresthesia, hypoesthesia)

Safety Labeling change (2013): Onset of neurologic AEs associated with increased dose

**Convulsions, Sedation, Neurologic AE**

**Case Report: Neurologic events**

**PM Surveillance (FAERS review)**

**Continued PM Surveillance: Signal: Seizures (FAERS review)**

**Signal Assessment initiated**

Pre-clinical studies

Prior to 2006

Jan. 2013

Jul. 2013

Feb. 2016

Apr. 2016
Description of FAERS Case Reports

Median Age: 78 years
Outcome: Hospitalization (63.6%);
Dechallenge: Positive (72.7%)
Renal status: Chronic renal failure (36.3%); not reported (63.6%)

Temporality/Dechallenge: indicators for possible causality
Sentinel Objective

- To investigate whether Ranexa use is associated with an increased risk of seizures
Study Design Considerations

• Absence of an appropriate comparator
  – AHA* recommends Ranexa in circumstances in which beta blockers, calcium channel blockers, and nitrates are not adequately effective or are not tolerated.

• Self-controlled risk interval design (SCRI)-Level 2 Sentinel modular program
  – FAERS data reveal onset of seizures within a short period after exposure (7 out of 9 cases* occurred within 10 days)
  – SCRI design best suited for acute outcome, time-invariant confounders are controlled

*AHA: American Heart Association
* Cases for which onset of seizure was reported
Methods

• Data: 01/01/2006 – 09/30/2015 from 12 health plans
• Cohort Definition: Patients ≥18 years old with at least 183 days medical and drug coverage
• Eligibility Criteria:
  – New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis and/or no anti-epileptic drug (AED) during baseline period – Ranexa cohort
  – New use of Ranexa (no Ranexa during 183 day period (baseline) before use) and No epilepsy or seizure diagnosis but use of AED during baseline period – Ranexa with AED cohort
• First valid 30-day prescription plus a 2-day extension period (observation window)
Self-Controlled Risk Interval Design

- Prescription start
- End date + 2day extension

Observation Window

Risk Interval
Control Interval

- Day 0
- Day 10
- Day 32

# of seizure events*

*Seizure event: ICD-9 codes for Epilepsy (345.X), convulsions (780.3X) or myoclonus (333.2) in Inpatient or Emergency Department discharge (PPV: 84% - Kee et al. 2012)
### Populations of Interest

<table>
<thead>
<tr>
<th>Population of Interest</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranexa Users</td>
<td>Ranexa users with no epilepsy and no use of AED at baseline</td>
</tr>
<tr>
<td>Ranexa Users with AED</td>
<td>Ranexa Users with no epilepsy at baseline but used AED at baseline</td>
</tr>
<tr>
<td>Age categories</td>
<td>55-64 years, 65-74 years, 75+</td>
</tr>
<tr>
<td>Pre-existing renal disease</td>
<td>Presence of a diagnosis code for renal conditions including dialysis at baseline</td>
</tr>
<tr>
<td>Pre-existing liver disease</td>
<td>Presence of diagnosis code for liver conditions at baseline</td>
</tr>
</tbody>
</table>
Cases Characteristics Summary

<table>
<thead>
<tr>
<th>Variables</th>
<th>FAERS cases</th>
<th>Sentinel Cases&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ranexa users</td>
</tr>
<tr>
<td>Number of patients</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Age, 55-64</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Age, 65-74</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Age, 75+</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Gender, Female</td>
<td>50%</td>
<td>42.9%</td>
</tr>
<tr>
<td>Renal Condition</td>
<td>36.3%</td>
<td>64.3%</td>
</tr>
<tr>
<td>Liver Condition</td>
<td>NR</td>
<td>17.9%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Among 58,285 Ranexa users included in the study

<sup>b</sup>AED: Anti-epileptic Drug

NR: Not Reported
Seizure risk in risk window compared to control window

<table>
<thead>
<tr>
<th></th>
<th># Events in risk window</th>
<th># Events in control window</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranexa Users</td>
<td>10</td>
<td>18</td>
</tr>
<tr>
<td>Ranexa users with Anti-epileptic Drug</td>
<td>6</td>
<td>5</td>
</tr>
</tbody>
</table>

Relative Risk: 1.1 (CI: 0.5-2.6)  
Relative Risk: 2.4 (CI: 0.7-7.9)
Seizure risk stratified by population of interest

<table>
<thead>
<tr>
<th>Population of interest</th>
<th>Number of Events in Risk Window</th>
<th>Number of Events in Control Window</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: 55-64</td>
<td>2</td>
<td>3</td>
<td>1.3</td>
<td>0.2, 8.5</td>
</tr>
<tr>
<td>Age: 65-74</td>
<td>3</td>
<td>2</td>
<td>3.0</td>
<td>0.5, 24.1</td>
</tr>
<tr>
<td>Age: 75+</td>
<td>5</td>
<td>11</td>
<td>1.0</td>
<td>0.3, 3.0</td>
</tr>
<tr>
<td>Pre-existing renal disease</td>
<td>7</td>
<td>11</td>
<td>1.3</td>
<td>0.5, 3.7</td>
</tr>
<tr>
<td>Pre-existing liver impairment</td>
<td>1</td>
<td>4</td>
<td>0.5</td>
<td>0.1, 3.8</td>
</tr>
</tbody>
</table>
Result Summary

• Seizure rate within 10 days of Ranexa initiation is rare, and does not appear to be higher than in days 11-30

• For Ranexa users with history of AED, there is a non-significant 2.5 fold increase in seizure risk
  – AED population is a mix of epilepsy patients and those who use AED for other conditions such as pain
    • Role of epilepsy
    • Role of polypharmacy

• Slight increased risk (not significant) for renal impairment patients as well as older patients
Sentinel’s Role in Safety Assessment

• **FAERS data**: Identified seizure signal among Ranexa users
  – Severity of signal, temporality, dechallenge heightened need for further investigation

• **Sentinel**: Signal refinement
  – Quantify seizure risk among Ranexa users
  – Identified populations for future evaluation—older patients, renal disease condition and use of anti-epilepsy drugs

• Further signal refinement in Medicare underway
  – Better representation of cases in an older population
Overview of CDER’s Current Sentinel System Activities

Join the conversation with #sentinelinitiative
Questions & Answers

Join the conversation with #sentinelinitiative
Engagement in the Sentinel System
SENTINEL ENGAGEMENT PARTNERS
WORKGROUP

J. Stephen Mikita
Sentinel Planning Board Member
Patient Advocate

February 2, 2017
SENTINEL ENGAGEMENT PARTNERS WORKGROUP

**Issue:** Critical Stakeholders are largely unaware of the Sentinel System, its commitment to health, safety, and protection of patient privacy.

- Public
- Health Advocacy Groups
- Providers
- Health Plan Members
WORKGROUP CHARTER

“Create a Plan of Action to Increase Awareness and Tell the Sentinel System’s Story, Successes, and Value”

“Develop Messages and Tools to Increase Awareness of the Sentinel System’s Public Health Value and Commitment to Privacy”
WORKGROUP

Patient Representatives
• Stephen Mikita
• Bray Patrick-Lake
• Sharon Terry

FDA
• Carlos Bell
• David Martin
• Anna Staton

Health Plan Members
• Jamie Brocki
• Nancy Falk

Providers
• Barry Dickinson
• Consuelo Wilkins

Sentinel System
• Barbara Evans
• Susan Forrow
• Richard Platt
The Engagement Partners Workgroup

- FDA
- Health Advocacy Groups
- Health Plan Members
- Providers

Public
WORKGROUP OBJECTIVES

Foundational Principles

- Transparency
- Relevance
- Effective Communication
STRATEGIES FOR ENGAGEMENT

• **Coordinated Communication Strategy**—Key Elements of the Sentinel System.

• **Targeted Messages**—Tailored to Each Engagement Partner’s Critical Role.
WHAT IS SENTINEL SYSTEM’S STORY?

- FDA’s Safety Mission/Another Tool
- Critical Components
- Operation
- Sentinel System in Action
- Privacy
Sentinel is a National Medical Product Monitoring System

- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story

- Active Risk Identification and Analysis System
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics

Latest Postings

- **SPOTLIGHT**
  - Public Workshop: The Sentinel Post-Licensure Rapid Immunization Safety Monitoring (PRISM) System
    - Tue, 11/15/2016
  - Sentinel Initiative Public Workshop - Ninth Annual
    - Tue, 11/08/2016

- **MODULAR PROGRAMS**
• Background
• Coordinating Center
• Privacy and Security
• The Sentinel System Story
HOW IT WORKS?

For the Public

Sentinel System's Story

How does the Sentinel System work?

The Sentinel System answers questions like these: How many people are taking the same drug or getting the same vaccine? How many are having bad side-effects? How many are men and women? How many are young, old, pregnant, or take other drugs?

For Providers

Sentinel System's Story

Sentinel System's Current Capabilities

The Sentinel System’s data infrastructure involves a distributed data network that can ask questions of data held by participating health plans, insurers, and hospital networks. These organizations maintain physical and operational control over their respective electronic data in their existing environments. To facilitate analysis, they each transform a copy of their data into a common data model that contains standardized administrative and clinical information.
HOW DOES FDA USE IT?

For the Public

Sentinel System's Story

What does the FDA do with all the information?
The FDA gets important answers from the Sentinel System about bad side effects in certain drugs or vaccines. The FDA studies this new information along with other information it gets from doctors and drug companies. The FDA decides the best way to make doctors and patients aware of side effects. The FDA can send out a warning to doctors and patients. Or the FDA can issue a safety communication to warn the public about taking a medicine or getting a vaccine.

For Providers

Sentinel System's Story

Sentinel System's Current Capabilities
Currently, the Sentinel System can analyze over 300 million person-years of high quality, unduplicated, curated data, working with a broad group of scientific collaborators who regularly provide technical support in evaluating this information for FDA review. When data from Sentinel System queries are evaluated and a potential problem is identified, FDA may require additional study, or initiate specific actions, such as revised labeling requirements, restricted use, issuance of a MedWatch alert, or even removal of a product from the market.
SENTINEL IN ACTION

For the Public

Sentinel System's Story

Sentinel in action

Example 1

In 2012, the FDA got reports from doctors about patients taking a new medicine to help prevent blood clots. The reports were about patients bleeding too much when they took the new medicine. The Sentinel System looked at a big group of patients on the new medicine. Then, it looked at a big group of patients on an older medicine. This information did not suggest the new medicine was less safe than the older medicine. Patients could continue taking the new medicine while additional studies were performed.

For Providers

Sentinel System's Story

Sentinel System's Outcome Assessments

The Sentinel System has been used to ascertain valuable information about new prescription medications and vaccines. As an example, the bleeding rates of two anticoagulants. The Sentinel System’s preliminary analysis did not identify excess risk associated with a certain anticoagulant; a more detailed follow up study is nearing completion. In another instance, the Sentinel System found that the administration of a first dose of a rotavirus vaccine led to an increased risk of intussusception, which was not detected during clinical trials before FDA approved the new vaccine. A final illustration of the Sentinel System’s usefulness involved demonstrating that children vaccinated with a particular influenza vaccine were not at an increased risk of seizures.
PRIVACY

For the Public

Sentinel System's Story

Protecting your privacy
No one at the FDA looks at your personal information. They do not look at your Name, Address, Phone Number, etc. The Sentinel System learns about big groups of patients taking the same medicine or getting the same vaccine.

For Providers

Sentinel System's Story

The Sentinel System Protects Patient Privacy
The Sentinel System aggregates data and produces summary information from large patient cohorts treated with the same drug or vaccine, whenever possible. When individual level data are needed, patients’ identifiers are removed.
NEXT STEPS

Dissemination/Roll Out

• **Public** → Going Live!

• **Health Advocacy Groups** → Organizations & Presentations

• **Providers** → AMA Collaboration

• **Health Plan Members** → Data Partners
THANK YOU!

Special Thanks:
  • Susan Forrow, Senior Project Manager
  • Katherine Freitas, Research Assistant
Engagement in the Sentinel System

Join the conversation with #sentinelinitiative
Questions & Answers

Join the conversation with #sentinelnitiative
Break
Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with #sentinelinitiative
FDA Catalyst Mobile App and IMEDS

David Martin, MD, MPH
Captain, US Public Health Service
Center for Drug Evaluation and Research
FDA Catalyst Mobile App

Wireframes are samples only and are subject to change as development continues.
Linking Primary and Secondary Data

![Diagram showing the process of linking primary and secondary data through a mobile app, unique identifiers, and a storage environment.]

- **Mobile App**
  - Patients
    - Patient enrollment
      - Token supplied to patient by Data Partner

- **Storage Environment**
  - Patient Token
  - Unique Identifier (per study)
  - Registration
  - Study Designer
    - Questionnaire / Active Task Responses - Data Partner 1
      - Study 1
        - Questionnaire 1
        - Questionnaire 2
      - Study 2
        - Questionnaire 1
        - Questionnaire 2

- **Data Partner 1**
  - Descriptive Analysis
    - Matched Data
  - Sentinel CDM Data
  - Sentinel Distributed Database
    - Sentinel Data
  - Sentinel Patient ID
  - Patient Data
  - Data Partner Claims Data Warehouse
  - Patient Token
  - Sentinel Patient ID Crosswalk

www.fda.gov
IMEDS

• Enables sponsors to use modular programs, customized studies, or a blended approach that complements the FDA Active Risk Identification and Analysis system

• Organizations interested in partnering with IMEDS should email IMEDS@reaganudall.org
Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with #sentinelsurveillance
From Vision to Reality
PCORnet Opens for Business

Rachael Fleurence, PhD, Program Director PCORnet
Patient-Centered Outcomes Research Institute (PCORI)
February, 2017
PCORnet: the National Patient-Centered Clinical Research Network

PCORnet is a large, highly representative, national patient-centered clinical research network.

Our **vision** is to support a learning U.S. healthcare system and to enable **large-scale clinical research** conducted with **enhanced quality and efficiency**.

Our **mission** is to enable people to make informed healthcare decisions by efficiently conducting clinical research relevant to their needs.
With PCORnet, we have developed a nationwide functional research network that...

- **Engages** people, clinicians, and health system leaders throughout

- **Creates** infrastructure, tools, and policies to support rapid, efficient clinical research

- **Utilizes** multiple data sources including electronic health records, insurance claims data, data reported directly by people, and other data sources
PCORnet embodies a “community of research” by uniting people, clinicians & systems

20 Patient-Powered Research Networks (PPRNs) + 13 Clinical Data Research Networks (CDRNs) = PCORnet
A national infrastructure for people-centered clinical research
PPRNs

American BRCA Outcomes and Utilization of Testing Patient-Powered Research Network (ABOUT Network)
University of South Florida

ARthritis patient Partnership with comparative Effectiveness Researchers (AR-PoWER PPRN)
Global Healthy Living Foundation

CCFA Partners Patient Powered Research Network
Crohn’s and Colitis Foundation of America

Collaborative Patient-Centered Rare Epilepsy Network (REN)
Epilepsy Foundation

Community and Patient-Partnered Centers of Excellence for Behavioral Health
University of California Los Angeles

Community-Engaged Network for All (CENA)
Genetic Alliance, Inc.

COPD Patient Powered Research Network
COPD Foundation

DuchenneConnect Registry Network
Parent Project Muscular Dystrophy

Health eHeart Alliance
University of California, San Francisco (UCSF)

ImproveCareNow: A Learning Health System for Children with Crohn’s Disease and Ulcerative Colitis
Cincinnati Children’s Hospital Medical Center

Interactive Autism Network
Kennedy Krieger Institute

Mood Patient-Powered Research Network
Massachusetts General Hospital

Multiple Sclerosis Patient-Powered Research Network
Accelerated Cure Project for Multiple Sclerosis

National Alzheimer’s and Dementia Patient and Caregiver-Powered Research Network
Mayo Clinic

NephCure Kidney International
Arbor Research Collaborative for Health

Patients, Advocates and Rheumatology Teams Network for Research and Service (PARTNERS) Consortium
Duke University

Phelan-McDermid Syndrome Data Network
Phelan-McDermid Syndrome Foundation

PI Patient Research Connection: PI-CONNECT
Immune Deficiency Foundation

Population Research in Identity and Disparities for Equality Patient-Powered Research Network (PRIDEnet)
University of California San Francisco

Vasculitis Patient Powered Research Network
University of Pennsylvania
CDRNs

Accelerating Data Value Across a National Community Health Center Network (ADVANCE)
Oregon Community Health Information Network (OCHIN)

Chicago Area Patient Centered Outcomes Research Network (CAPriCORN)
The Chicago Community Trust

Greater Plains Collaborative (GPC)
University of Kansas Medical Center

Kaiser Permanente & Strategic Partners Patient Outcomes Research To Advance Learning (PORTAL) Network
Kaiser Foundation Research Institute

Research Action for Health Network (REACHnet)
Louisiana Public Health Institute (LPHI)

Mid-South CDRN
Vanderbilt University

National Pedsnet: A Pediatric Learning Health System
The Children's Hospital of Philadelphia

New York City Clinical Data Research Network (NYC-CDRN)
Weill Medical College of Cornell University

OneFlorida Clinical Data Research Network
University of Florida

Patient-Centered Network of Learning Health Systems (LHSNet)
Mayo Clinic

Patient-oriented SCAlable National Network for Effectiveness Research (pSCANNER)
University of California, San Diego (UCSD)

PaTH: Towards a Learning Health System
University of Pittsburgh

Scalable Collaborative Infrastructure for a Learning Healthcare System (SCILHS)
Harvard University
PCORnet – Based on Common Data Model

In order to be able to trust results of an analysis, we need to have consistent representations.
Common Data Model

Data domains in the CDM

Data domains that can be added

- Condition
- Vital Status
- Demographic
- Biospecimen & Genomic Data
- Socio-economic Status
- Prescribing
- Encounters
- Claims
- Procedcases
- Patient-reported Outcomes
- Lab Results
- Sexual Orientation and Gender Identity
Data Characterization: Cycle 1

- 82 DataMarts across 13 CDRNs

Cycle 1 of Data Characterization

Characterized 7 tables

- Demographic
- Enrollment
- Encounter
- Diagnosis
- Procedures
- Vital
- Harvest

Run on CDM v3.0
Approximately…

- 90 million patients with a medical encounter in past 5 years
- 42 million records to support clinical trials
- 83 million records to support observational studies

Demographics*: Age
(N=41,216,568)

- 0–20 years: 11,361,889
- 21–44 years: 11,589,633
- 45–64 years: 10,951,968
- 65–74 years: 4,156,901
- 75+ years: 3,156,017

*Number of patients with a given characteristic with an encounter in any care setting divided by the total number of patients with an encounter in any care setting (2014). Individuals who received care at more than one Network Partner during the period would be counted once per Network Partner visit, leading to the potential for double-counting.
## Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>PCORnet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory conditions</td>
<td>2,837,803</td>
</tr>
<tr>
<td>Selected malignancies</td>
<td>1,294,158</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>354,929</td>
</tr>
<tr>
<td>Stroke</td>
<td>420,802</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>254,803</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>88,029</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5,902,641</td>
</tr>
<tr>
<td>Renal disease</td>
<td>1,018,729</td>
</tr>
<tr>
<td>Influenza/pneumonia</td>
<td>869,306</td>
</tr>
</tbody>
</table>
Data Characterization: Cycle 2

- Added 4 tables
  - Prescribing
  - Dispensing
  - Laboratory Results
  - Death

- Ended January 6th 2017
Early Results

Number of patients
- ~94 million patients available for observational studies (with AV, IP or ED visit in the past 5 years)
- ~46 million patients available for clinical trials (with AV, IP or ED visit in the past year)

Query run times
- 57% took < 3 hours
- 18% took > 10 hours
- Strongly correlated with size of the DataMart but not correlated with use of SAS views (25% of DataMarts)
## Lab Results

<table>
<thead>
<tr>
<th>Lab</th>
<th>Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>2.3 billion</td>
</tr>
<tr>
<td>A1C</td>
<td>72 million</td>
</tr>
<tr>
<td>CK</td>
<td>17 million</td>
</tr>
<tr>
<td>CK_MB</td>
<td>8 million</td>
</tr>
<tr>
<td>CK_MBI</td>
<td>3 million</td>
</tr>
<tr>
<td>Creatinine</td>
<td>288 million</td>
</tr>
<tr>
<td>HGB</td>
<td>298 million</td>
</tr>
<tr>
<td>INR</td>
<td>78 million</td>
</tr>
<tr>
<td>LDL</td>
<td>89 million</td>
</tr>
<tr>
<td>TROP_I</td>
<td>21 million</td>
</tr>
<tr>
<td>TROP_T_QL</td>
<td>273K</td>
</tr>
<tr>
<td>TROP_T_QN</td>
<td>4 million</td>
</tr>
<tr>
<td>Other</td>
<td>1.4 billion (~12 DataMarts)</td>
</tr>
</tbody>
</table>
## Medications

<table>
<thead>
<tr>
<th></th>
<th>Dispensings (39 DataMarts)</th>
<th>Orders (72 DataMarts)</th>
<th>Dispensings/Orders in DataMarts with both tables (30 DataMarts)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>1.9 billion</td>
<td>4.0 billion</td>
<td></td>
</tr>
<tr>
<td><strong>10 concepts of interest</strong></td>
<td>744 million</td>
<td>1 billion</td>
<td>439 million/586 million</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>63 million</td>
<td>47 million</td>
<td>38 million/24 million</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>99 million</td>
<td>78 million</td>
<td>53 million/41 million</td>
</tr>
<tr>
<td>Antidiabetics</td>
<td>60 million</td>
<td>64 million</td>
<td>29 million/32 million</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>52 million</td>
<td>55 million</td>
<td>56 million/120 million</td>
</tr>
<tr>
<td>Antirheumatics</td>
<td>94 million</td>
<td>205 million</td>
<td>41 million/36 million</td>
</tr>
<tr>
<td>Antiulcerants</td>
<td>70 million</td>
<td>75 million</td>
<td>25 million/30 million</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>41 million</td>
<td>61 million</td>
<td>55 million/111 million</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>88 million</td>
<td>183 million</td>
<td>60 million /145 million</td>
</tr>
<tr>
<td>Respiratory agents</td>
<td>93 million</td>
<td>283 million</td>
<td>51 million /31 million</td>
</tr>
<tr>
<td>Statins</td>
<td>84 million</td>
<td>57 million</td>
<td></td>
</tr>
</tbody>
</table>

*Required identifying the drug names in each class and the RXCUI (orders) and NDCs (dispensings) for each drug.
PCORnet supports many kinds of research

Pre-research
- Feasibility queries
- Engagement
- Match-making

Interventional studies
- Clinical trials
- Pragmatic randomized clinical trials
  - e-Identification
  - e-Consent
  - e-Randomization
  - e-Data Collection
  - e-Follow-up
- Cluster randomization

Observational studies
- Cross-sectional
- Epidemiology
- Health services
- Comparative effectiveness or safety
Pragmatic Clinical Trials: Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

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

OR

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

ADAPTABLE Enrollee

Baseline Data

4 8 12 16 20 .... 30

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

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

http://adaptablepatient.com
<table>
<thead>
<tr>
<th>CDRN</th>
<th>Site</th>
<th>Site Activated</th>
<th>Started Enrollment</th>
<th>Total Enrolled</th>
<th>Enrollment Rate/Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>MidSouth</td>
<td>Vanderbilt</td>
<td>4/18/2016</td>
<td>April</td>
<td>307</td>
<td>30.7</td>
</tr>
<tr>
<td>OneFlorida</td>
<td>U of Florida</td>
<td>11/1/2016</td>
<td>November</td>
<td>62</td>
<td>20.66</td>
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<tr>
<td>REACHnet</td>
<td>Ochsner</td>
<td>4/18/2016</td>
<td>April</td>
<td>132</td>
<td>13.2</td>
</tr>
<tr>
<td>Path</td>
<td>UPMC</td>
<td>7/18/2016</td>
<td>August</td>
<td>68</td>
<td>11.33</td>
</tr>
<tr>
<td>Path</td>
<td>Penn State</td>
<td>9/23/2016</td>
<td>October</td>
<td>45</td>
<td>11.25</td>
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<tr>
<td>pScanner</td>
<td>UCLA</td>
<td>11/7/2016</td>
<td>November</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Path</td>
<td>Utah</td>
<td>9/23/2016</td>
<td>October</td>
<td>38</td>
<td>9.5</td>
</tr>
<tr>
<td>GPC</td>
<td>KUMC</td>
<td>11/1/2016</td>
<td>November</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td>NYC_CDRN</td>
<td>Montefiore</td>
<td>11/9/2016</td>
<td>November</td>
<td>17</td>
<td>5.66</td>
</tr>
<tr>
<td>GPC</td>
<td>Iowa</td>
<td>7/18/2016</td>
<td>August</td>
<td>32</td>
<td>5.33</td>
</tr>
<tr>
<td>Capricorn</td>
<td>Northwestern</td>
<td>8/30/2016</td>
<td>September</td>
<td>26</td>
<td>5.2</td>
</tr>
<tr>
<td>Mid-South</td>
<td>Duke</td>
<td>11/9/2016</td>
<td>November</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>REACHnet</td>
<td>BSW</td>
<td>9/19/2016</td>
<td>October</td>
<td>10</td>
<td>2.5</td>
</tr>
<tr>
<td>NYC_CDRN</td>
<td>NYU</td>
<td>11/1/2016</td>
<td>November</td>
<td>5</td>
<td>1.66</td>
</tr>
<tr>
<td>Path</td>
<td>Temple</td>
<td>9/23/2016</td>
<td>October</td>
<td>5</td>
<td>1.25</td>
</tr>
<tr>
<td>REACHnet</td>
<td>Tulane</td>
<td>8/30/2016</td>
<td>October</td>
<td>2</td>
<td>0.5</td>
</tr>
</tbody>
</table>
Front Door now open to the PCORnet community, and will be open in April to the outside

Through PCORnet Front Door, we invite PCORnet researchers and other investigators, patient groups, healthcare organizations, clinicians or clinician groups, government and industry scientists, and sponsors to collaborate on important patient-centered clinical research studies.

Faster answers to pre-research queries

Valuable expertise via network collaboration

Enhanced credibility via PCORnet study designation

SUBMIT Data Network Request

SUBMIT Request for Network Collaboration

SUBMIT Request for PCORnet Study Designation
Data Linkage/Collaboration Projects: Data Sources

- PCORnet (EHR, claims, PROs)
- CMS (Medicare/Medicaid)
- Other Administrative Claims (APCD)
- Sentinel (EHR, claims, registries)
- PCORnet (EHR, claims, PROs)
- Registry
- Private Health Plans
- PGD/PROs (mHealth)
- PGD/PROs (mHealth)

- Collaborative FDA, RUF, PCORI Genesis Projects (October 2017)
- CMS Pilot Project (December 2016)
- CDRN Phase II Projects (variable)
- Health Plan Initiative (demos August 2017, October 2019)
- Health Plan/PPRN Methods (TBD)
- PPRN mHealth (September 2017)
- PPRN EHR Extraction (August 2017)
- Collaborative FDA, RUF, PCORI TVTR Projects (July 2017)
# Genesis Pilot Projects

<table>
<thead>
<tr>
<th>Public Health Focus Area</th>
<th>Genesis Project Title</th>
<th>Institute/Affiliation</th>
<th>Principal Investigator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital Zika syndrome surveillance</td>
<td>Planning for Congenital Zika Syndrome Surveillance in PCORnet and Sentinel</td>
<td>University of Florida</td>
<td>Dr. William Hogan</td>
</tr>
<tr>
<td>Monitoring and reporting antimicrobial utilization</td>
<td>Data Model for Initiatives to Monitor Exposure to Antimicrobials in PCORNet and Sentinel (DataMIME)</td>
<td>Medical Research Analytics and Informatics Alliance (MRAIA)</td>
<td>Dr. William Trick</td>
</tr>
</tbody>
</table>
Planning for Congenital Zika Syndrome Surveillance in PCORnet and Sentinel

- **Purpose**: Begin understanding and utilizing the surveillance potential using the EHR and administrative data infrastructure of PCORnet and the Food and Drug Administration’s (FDA’s) Sentinel Initiative

- **Study Goals**:
  - Identify and characterize subpopulations of infants of interest and test within the OneFlorida CDRN data infrastructure
  - Leverage PCORnet and Sentinel capabilities to enhance Zika syndrome detection and reporting
  - Contribute to knowledge of the natural history and outcomes of infants with congenital Zika syndrome
Initiatives to Monitor Exposure to Antimicrobials in PCORnet and Sentinel (DataMIME)

- **Purpose:** Develop and pilot a PCORnet technical infrastructure for the generation of unit-level Antimicrobials (AU) measures critical to antimicrobial utilization and monitoring national public health priorities.

- **Study Goals:**
  - Plan, develop and pilot an open source methodology using the PCORnet CDM as a model.
  - Generate AU reports that can be submitted to CDC’s Natural Healthcare Safety Network (NHSN) and enable surveillance requirements for FDA’s Sentinel CDM.
  - Develop ancillary tables to augment the existing PCORnet and Sentinel data models that will allow hospitals to generate comparable AU reports for hospital inpatients.
Patient-Powered Research Networks

- 20 Patient-Powered Research Networks, 220,000 patients across diseases and conditions consented to participate in research

Future areas to watch:
- First large pragmatic clinical trial in mindfulness
- Use of mHealth data for research
- Patient owned EHR share-able with researchers
- Learning Network Pilots starting in Spring 2017
ICN PPRN is changing patients’ health outcomes

Percent of patients in clinical remission
Crohn’s Disease and Ulcerative Colitis

90 GI Care Centers
>25,000 patients
> 780 physicians
>40% of all patients with Centers >75% registered
Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with #sentinelinitiative
Perspectives from the
NIH Healthcare Systems Research Collaboratory

Sentinel Initiative Public Workshop - February 2, 2017
Moving Beyond Surveillance

Catherine M. Meyers, MD
NIH/NCCIH
Director, Office of Clinical & Regulatory Affairs
NIH Health Care Systems Research Collaboratory

- **Goal**: To strengthen the national capacity to implement cost-effective large-scale research studies that engage health care delivery organizations as research partners.

- **Aim**: To provide a framework of implementation methods and best practices that will enable the participation of many health care systems in clinical research. Research conducted in partnership with health care systems is essential to strengthen the relevance of research results to health practice.
NIH Health Care Systems Research Collaboratory

- Collaboratory Coordinating Center
- Suicide Prevention Outreach Trial (SPOT)
- Time to Reduce Mortality in End-Stage Renal Disease (TIME) (sites in dialysis units across the US)
- Trauma Survivors Outcomes & Support (TSOS)
- Lumbar Image Reporting and Epidemiology
- Strategies and Opportunities to Stop Colorectal Cancer (STOP CRC)
- Collaborative Care for Chronic Pain in Primary Care (PPACT)
- Active Bathing to Eliminate Infections (ABATE)
- Improving Chronic Disease Management with Pieces (ICD-Pieces)
- Pragmatic Trial of Video Education in Nursing Homes (PROVEN) (sites in nursing homes across the US)

National Center for Complementary and Integrative Health
NIH Collaboratory
Pragmatic Trial HCS Partners

- Group Health Cooperative
- Kaiser Permanente
- Mayo Clinic
- Henry Ford Health System
- HealthPartners Institute
- Parkland Health System
- Texas Health Resources
- ProHealth CT
- Fresenius and DaVita
- Dialysis Corporations
- Hospital Corporation of America
- US Level 1 Trauma Care Centers
- Genesis Healthcare
- UHS Pruitt Corporation
- Oregon Community Health Information Network (FQHCs)
- North Texas VA
The NIH Collaboratory Distributed Research Network (DRN) enables investigators to collaborate with each other in the use of electronic health data, while also safeguarding protected health information and proprietary data. It supports both single- and multisite research programs.

The Network’s querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send queries to collaborators holding data (i.e., data partners). In some cases, queries can take the form of computer programs that a data partner can execute on a pre-existing dataset. The data partner can return the query result, typically aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and technical barriers associated with data sharing for research.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people around the world.

**On this page**

- What does the NIH Collaboratory Distributed Research Network do?
- How does the network operate?
- Who can submit a query/data request?
- How do I submit a query/data request?
- What datasets are available in the NIH Collaboratory Distributed Research Network?
- How can my organization/network become a data partner?
- What software platform does the network use?
- What are the confidentiality and nondisclosure rules for data partners and DRN Coordinating Center staff?

**Recent Presentations**

- 6/5/2015: Grand Rounds Presentation: NIH Collaboratory Distributed Research Network (Video; Slides)
- 11/14/2014: Grand Rounds Presentation: Using the NIH
Sharing of Infrastructure

- Each organization can participate in multiple networks
- Each network controls its governance and coordination
- Networks share infrastructure, data curation, analytics, lessons, security, software development
NIH Collaboratory DRN Data Partners

- Aetna
- Group Health Research Institutes
- Harvard Pilgrim Health Care Institute
- HealthCore, Inc.
- HealthPartners Institute for Education and Research
- Humana: Comprehensive Health Insights, Inc.
- Meyers Primary Care Institute
- The MURDOCK Study
- OptumInsight, Inc.
- Ochsner Health Systems
NIH Collaboratory DRN

2014-2016  Pilot project of 3 Queries from NIH
2017     Broader outreach to the research community

NIH Collaboratory Invites Requests to Query the Distributed Research Network

Do you have a question about the rates of medical conditions or the frequency of use of medical and surgical treatments? The NIH Collaboratory’s Distributed Research Network works with large health plans with electronic health data that can answer these questions. The Collaboratory invites prep-to-research questions.

Download the guidance document (Word) for full details on the application process.
Moving Beyond Surveillance: Sentinel as a Component of the National System for Evidence Generation

Join the conversation with #sentinelinitiative
Questions & Answers

Join the conversation with #sentinelinitiative
Closing Remarks

Join the conversation with #sentinelinitiative