FDA Sentinel Initiative: Active Surveillance of Post-Market Drug Safety

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Outline

- Sentinel Initiative Goals
- Mini-Sentinel (MS) Pilot
- Transition to Sentinel System
- Data Availability/Infrastructure
- Surveillance of NOACs
FDA Sentinel Initiative - Goals

• Develop a national electronic safety monitoring system
  – Leveraging multiple sources of currently available electronic data
  – By partnering with data holders
    • Healthcare systems, insurance companies, etc

• Enhance active post-market monitoring of medical product safety
  – More effectively look at common outcomes (e.g. MI, fractures)
  – Have denominators to easily calculate rates
  – Increase sample size with improved access to population subgroups

• Use validated design and statistical methods

• Near real-time monitoring by using a
  – Common data model & “Library” of tools/resources

• Integrate active surveillance with current post-market safety monitoring systems
Mini-Sentinel Pilot

• Claims and administrative data
  – Assessments depend on **defining exposures and outcomes through codes** (drugs - NDC, diagnoses - ICD-9, procedure codes)

• 18 Data Partners

• Investigators from additional sites

• Approximately 160 million individuals, 2000 - present
  – Different sites have data for different time periods
  – Average length of enrollment (data availability) = 28 months
  – 50 million enrollees currently accumulating data

• Ability to obtain medical records (redacted and de-identified)
Transition from Mini-Sentinel Pilot to Sentinel System

- Current year – transition
Mini-Sentinel to Sentinel: Similarities and Differences

Similarities:
- Lead institution – Harvard Pilgrim Healthcare Institute
- Retain data partners, most other partner institutions
- Build on existing infrastructure

Changes:
- Incorporation of use of Sentinel into standard FDA post-market formal surveillance processes
- Continued enhancement of tools – especially rapid, semi-automated tools with adjustment for confounding and sophisticated epi designs
- Additional data partners being explored
  - HCA beginning to provide some data elements
  - Possible federal partners, international partners
- Assess adding additional data types
Mini-Sentinel Partner Organizations

Lead – HPHC Institute

Data and scientific partners

Scientific partners
Distribution of Age Groups

Demographic Table: Distribution of Age Groups as of November 25, 2014 (Unique Individuals = 197,296,356)

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Unique Individuals (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1 Yrs</td>
<td>1.0%</td>
</tr>
<tr>
<td>2-4 Yrs</td>
<td>2.2%</td>
</tr>
<tr>
<td>5-9 Yrs</td>
<td>5.2%</td>
</tr>
<tr>
<td>10-14 Yrs</td>
<td>5.6%</td>
</tr>
<tr>
<td>15-18 Yrs</td>
<td>4.7%</td>
</tr>
<tr>
<td>19-21 Yrs</td>
<td>3.9%</td>
</tr>
<tr>
<td>22-44 Yrs</td>
<td>35.3%</td>
</tr>
<tr>
<td>45-64 Yrs</td>
<td>26.8%</td>
</tr>
<tr>
<td>65-74 Yrs</td>
<td>8.4%</td>
</tr>
<tr>
<td>75+ Yrs</td>
<td>6.9%</td>
</tr>
<tr>
<td>Missing</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

Source: Dem_I3_ageyrsdist2 dataset from last approved data refresh for each Data Partner as of November 25, 2014. Age is calculated as age at refresh date.
Data Capabilities and Challenges

- **Drugs/Dispensings**
  - Outpatient – complete
  - Inpatient – not available
  - IV, Infusion – depends on care setting and whether this is bundled into a larger treatment code

- **Diagnoses/Outcomes**
  - Many validated in published observational studies; some MS validation
  - Difficult Outcomes – suicide, severe pancreatitis, seizures, rhabdomyolysis (need lab value), etc.

- **Numbers of Data Partners change over time**
  - Denominators must be specific for individual query
  - Rates are needed for trends
Mini-Sentinel Distributed Analysis

1- User creates and submits query to MSOC.

MSOC creates a computer program for data partners

2- Data partners retrieve program

3- Data partners review and run program against their local data

4- Data partners review results

5- Data partners return results via secure network to MSOC

6 MSOC aggregates results into a report for CDER/FDA
What is Needed for Successful Surveillance Using Sentinel?

• Ability to ascertain exposure
• Ability to ascertain outcome of interest
  – Code based algorithm that is reasonably reliable and accurate in claims data
  – Outcome must occur in a medical care setting where it can be reliably ascertained; many assessments use in-patient and ER outcomes
• Active comparator group or population to compare to those exposed to the drug of interest
• Statistical power to see a meaningful hazard ratio – frequency of “events” and level of exposure/uptake
Surveillance of NOACs
November 2012 FDA DSC: Dabigatran and Warfarin - GIH

Rationale for MS MP

- Unexpectedly high rates of reporting of gastrointestinal bleeding with dabigatran compared to warfarin
- Use newly implemented active surveillance capability to provide objective data on hospitalized events in those MS enrollees with new dabigatran and warfarin exposure

Effects of MS MP:

- Provided reassurance that, overall, new users of dabigatran were not experiencing a higher than expected level of hospitalized GIH or ICH events compared to new users of warfarin.
Post-Market Surveillance of Other NOACs

- PROMPT Assessment
  - Allow for adjustment for confounding through propensity score matching
  - Allow for some subgroup and sensitivity analyses
    - Rivaroxaban compared to Warfarin
      - Stroke, ICH, GIH
      - Sequential analysis over time from approval
    - Apixaban compared to Warfarin – initial assessment

- Protocol Based Assessment
  - Complete epidemiologic study
    - Dabigatran compared to Warfarin
Death and Mini-Sentinel

- MS obtains death information only if a medical claim/administrative data is generated
- Standardized information on out of hospital death/cause of death is highly desirable – sudden cardiac death, suicide, etc.
- Potential linkage with National Death Index (NDI+) – National Center for Health Statistics / CDC
  - Centralized database of state-based death record information
  - Retrieval of an NDI death record requires a match on various combinations of data including:
    - SSN, first /last name, month/day/year of birth, sex
NDI+ Linkage Project: Outcomes of Death and SCD

• Rationale - Identify outcomes of death and SCD in four cohorts:
  – Cohort 1: Antiarrhythmic medication users ↑ risk Sudden Cardiac Death (SCD)
  – Cohort 2: General Population ↓ risk SCD
  – Cohort 3: Users of select Antibiotics
  – Cohort 4: Users of select Antidepressants

• Status
  – Protocols are being reviewed and finalized
  – Survey of data partners complete – availability of data needed for linkage
  – Defining the process and the programming specifications
  – Application to NCHS for linkage w NDI+ is under development
Post-Market Surveillance of NOAC Reversal Agents: Possibilities

- Use historic data to set some risk thresholds for adverse outcomes and compare these to actual rates in the MSDD. Provide reassurance that incidence rates of adverse outcomes are below a certain level.
  - Determine number of treatment events that would be needed to provide this assurance at various risk levels. Since this is a rare occurrence the database may or not be able to meet these exposure occurrence levels.

- Compare reversal treatment for NOACs with warfarin.
  - Could look in current data to see how warfarin reversal is coded and how treatment captured; look at incidence of this

- Comparator situations as have been described in recent white paper.
Some Mini-Sentinel Participants

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Thank You,

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