Biologics Effectiveness and Safety (BEST) Initiative

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FDA Center for Biologics Evaluation and Research (CBER)
On behalf of CBER Sentinel Central Team
CBER-Regulated Products: Biologics

- Vaccines (preventative and therapeutic)
- Blood (components and derived)
- Human Tissues and Cellular Products
- Gene Therapies
- Xenotransplantation Products
CBER Surveillance Priorities

• Evaluating safety of vaccination during pregnancy
• Signal detection – use of natural language processing and artificial intelligence
• Pandemic preparedness – near real-time surveillance
• Emerging infectious disease surveillance & monitoring
Biologics Effectiveness and Safety (BEST) Initiative

- CBER Active Post-market Surveillance Program
- A component of Sentinel Initiative
- Commenced in October 2017
Why the BEST Initiative?

• Biologic products’ special characteristics
  – Require special components in an active surveillance system

• Upgrading infrastructure
  – Access to EHR data sources
  – Reduce data lag
  – Easier, faster, affordable access to medical charts
  – On-demand analytic capabilities (no tools)
  – Large-scale capacity
BEST Initiative Objectives

**Aim 1:** Build data, analytics, infrastructure for an active, large-scale, efficient surveillance system for biologic products

**Aim 2:** Develop innovative methods to utilize electronic health records (EHR) effectively and establish automated adverse events reporting
BEST Initiative

Collaborators

- Regenstrief Institute
- Columbia University
- University of Colorado
- Cerner
- University of California, Los Angeles
# Data Infrastructure

## IBM

<table>
<thead>
<tr>
<th>Data Sources</th>
<th>Patients (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MarketScan (Claims)</td>
<td>60</td>
</tr>
<tr>
<td>CED (Linked EHR-Claims)</td>
<td>4.9</td>
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</tbody>
</table>

## IQVIA/OHDSI

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<th>Data Sources</th>
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<tr>
<td>LRxDx (Claims)</td>
<td>160</td>
</tr>
<tr>
<td>Regenstrief Institute (Claims and EHR)</td>
<td>19</td>
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<tr>
<td>Columbia University (EHR)</td>
<td>6.5</td>
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<tr>
<td>University of Colorado (EHR)</td>
<td>17</td>
</tr>
<tr>
<td>Cerner (EHR)</td>
<td>23</td>
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## Acumen

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<td>Blue Health Intelligence (Claims)</td>
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Data Quality Assessment

- Data Completeness
- Data Conformance
- Data Plausibility

Data Quality Assessment Checks
BEST Initiative: Data, Tools and Infrastructure for Surveillance of Biologics

ACCOMPLISHMENTS
IBM
IQVIA/OHDSI
Acumen

EHR Network
Reduced data lag to 3-4 months
Analytic capabilities on demand
Access to medical charts
Portal for CBER staff to access data for feasibility analyses
Improved operational efficiency and shorter turnaround time
BEST Initiative: Data, Tools and Infrastructure for Surveillance of Biologics

DESCRIPTIVE STUDIES
Vaccines

- Seasonal Influenza
- Hepatitis B
- Herpes Zoster
- Meningococcal
- Human Papillomavirus
Blood-Derived Products

• Intravenous Immunoglobulins (IVIGs)
• Antihemophilic Factor (Factor VIII)
• Anti-inhibitor Coagulant Complex
• Fibrin Sealant
• Fibrinogen Concentrate
• Alpha-1 Proteinase Inhibitors
• C1 Esterase Inhibitors
Outcomes

- Syncope
- Thromboembolic events
- Coagulation product inhibitors (Factor VIII inhibitory antibodies)
- Hemolysis
- Anaphylaxis
Special Populations

- Diabetics
- Hemophilia A
- Immunocompromised patients
Vaccine Study (Test Case)

• To test the new system, reproduced components of a published study


• **Study Objective:** To assess the risk of febrile seizures in children receiving first dose of Measles, Mumps, Rubella, & Varicella (MMRV) compared to that of MMR and Varicella administered separately on the same day
# MMRV vs. MMR+V & Febrile Seizures in Children

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<thead>
<tr>
<th>Study Period</th>
<th>Vaccine Safety Datalink (VSD) Study*</th>
<th>BEST: LRxDx claims database</th>
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<tbody>
<tr>
<td>Age</td>
<td>12-23 months</td>
<td>1-2 years</td>
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<td>Number of MMRV Patients (n)</td>
<td>83,107</td>
<td>920,948</td>
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<td>Number of MMR+V Patients (n)</td>
<td>376,354</td>
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## Risk Windows

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<th>Week 1-2</th>
<th>Vaccine Safety Datalink (VSD) Study*</th>
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<tr>
<td>7-10 days</td>
<td>RR: 2.0 (95% CI=1.4-2.9) OR: 1.86 (95% CI=1.38-2.04)</td>
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<tr>
<th>Week 1-6</th>
<th>Vaccine Safety Datalink (VSD) Study*</th>
<th>BEST: LRxDx claims database</th>
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<tbody>
<tr>
<td>0-42 days</td>
<td>RR: 1.5 (95% CI=1.1-1.9) OR: 1.26 (95% CI=1.22-1.42)</td>
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*Klein NP et al., Pediatrics, 2010*
# MMRV vs. MMR+V & Febrile Seizures in Children

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*Klein NP et al., Pediatrics, 2010*
HEMOVIGILANCE STUDY

EHR Data Sources and ISBT128 Coding System
No. of Transfused Patients Identified by Billing Codes vs. ISBT128 codes

Red Blood Cells

Plasma

Platelets

ISBT128  Billing Codes
**MarketScan (Claims):**
- Includes more than 25% of all employer-sponsored U.S. healthcare beneficiaries
- 150 contributing employers with 200 unique carriers + 20 health plans
- Medicare supplemental plan enrollees
- Medicaid enrollees for 12 states

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**IBM Claims Data (MarketScan)**
250 million Patients (2002-2018)

Source: IBM Watson Health, 2018
EHR Data (Explorys):

- 56 million Patients (1999-2018)
- 39+ Health Systems spanning academic centers and community practices
- ~344,000 Unique Providers
- Inpatient and outpatient encounters
- Clinical events and procedures
- Lab results
- Vital signs and other biometrics
- Medical and surgical history
- Patient-reported outcomes
- Inpatient drugs and ambulatory prescriptions

Source: IBM Watson Health, 2018
EHR Data (Explorys)
56 million Patients
(1999-2018)

IBM Claims Data (MarketScan)
250 million Patients
(2002-2018)

Source: IBM Watson Health, 2018
CED (Linked EHR-Claims Database)  
Deterministically linked patients

EHR Data (Explorys)  
56 million Patients  
(1999-2018)

IBM Claims Data (MarketScan)  
250 million Patients  
(2002-2018)

Source: IBM Watson Health, 2018
CED – Gender and Age Distribution

Gender distribution (%)

- **Male**
  - CED: 45.8%
  - ACS: 49.2%

- **Female**
  - CED: 54.3%
  - ACS: 50.8%

Age distribution (%)

- **0-17**
  - CED: 12%
  - ACS: 23%

- **18-34**
  - CED: 23%
  - ACS: 23%

- **35-44**
  - CED: 15%
  - ACS: 13%

- **45-54**
  - CED: 15%
  - ACS: 16%

- **55-64**
  - CED: 18%
  - ACS: 13%

- **65+**
  - CED: 16%
  - ACS: 15%

CED: CLAIMS-EHR LINKED DATABASE
ACS: AMERICAN COMMUNITY SURVEY, AN ONGOING SURVEY BY US CENSUS BUREAU

Source: IBM Watson Health, 2018 and *ACS or American Community Survey is an ongoing survey by the U.S. Census Bureau
IBM Linked Claims-EHR Database (CED)

EHR Data (Explorys)
- 56 million Patients (1999-2018)

IBM Claims Data (MarketScan)
- 250 million Patients (2002-2018)

CED
- 4.9M

w/ Labs
- 2.9M+

Source: IBM Watson Health, 2018
CED DATABASE: PREGNANCY OUTCOMES & GESTATIONAL AGE VALIDATION
Study Objectives

1. Develop algorithms using ICD10 diagnosis codes and CPT/HCPCS procedure codes to
   a) Determine gestational age
   b) Classify pregnancy episodes as one of 4 outcomes:
      i. Full-term birth
      ii. Pre-term birth
      iii. Stillbirth
      iv. Spontaneous abortion
Study Objectives

2. Using GAIA case definitions as a reference method
   – To validate estimated gestational age and outcomes classifications
   – By comparing to clinician-adjudicated results based on review of structured CED (EHR) data elements
   – GAIA: Global Alignment of Immunization Safety Assessment in pregnancy
Study Population

- $n = 35,842 \ (100\%)$
  Pregnancy episodes identified in claims

- $n = 33,698 \ (94\%)$
  Pregnancy episodes with GA estimates in claims

- $n = 6,122 \ (17\%)$
  Pregnancy episodes with GA, LMP, or IUI/ET AND outcome in SNOMED or LOINC in EHR

- $n = 2,144 \ (6\%)$
  Pregnancy episodes without GA estimates in claims

- $n = 27,576 \ (77\%)$
  Pregnancy episodes without GA, LMP, or IUI/ET AND outcome in SNOMED or LOINC in EHR

Source: IBM Watson Health, 2018

Note: Preliminary results and subject to change
Clinician Adjudication Using Semi-Automated Chart Review

Data Abstraction
- Built-in questionnaire
- Structured components of EHR

Clinician Review
- Display GAIA-related structured EHR elements

Outcome Adjudication
- Full chart of structured EHR pregnancy episode available to clinician in detailed view

Source: IBM Watson Health, 2018
Summary

• Built a new active surveillance system for biologic products

• Incorporated multiple large sources of EHR
  – Claims & administrative databases
  – Linked EHR-claims database

• Access to EHR provides
  – Data elements for clinical data, blood coding system
  – Medical charts
Summary

• Reduced data lag to 3-4 months
• On-demand analytic capabilities
• CBER staff has access to data and tools for feasibility analyses
• Improved operational efficiency and shorter turnaround time
Acknowledgements

• CBER Sentinel Central Team
  – Kinnera Chada, PhD
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  – Kristin A. Sepúlveda
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• CBER product offices: OVRR, OBRR, OTAT

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• Acumen Team
• IQVIA Team
• OHDSI Collaborators
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  – Regenstrief Institute
  – University of Colorado
  – Cerner
  – University of California Los Angeles
Thank You