An FDA-CBER Update on Surveillance, Epidemiology and Risk Management Approaches for Biologics

Steven A. Anderson, Ph.D.
Director of Office of Biostatistics and Epidemiology
FDA Center for Biologics Evaluation and Research

DIA PV and Risk Management Strategies Conference
January 29, 2020
OVERVIEW

Agenda:
- Background
- CBER Postmarket Safety Surveillance Programs
- Pilot case example
- Acknowledgements
Background: CBER-Regulated Products

- Vaccines (preventative and therapeutic)
- Blood (components and derived)
- Human Tissues & Cellular Products
- Gene Therapies
- Xenotransplantation Products
CBER Postmarket Safety Surveillance Programs
CBER Postmarket Safety Surveillance Programs

1. Passive Surveillance
   - FDA Adverse Event Reporting system (FAERS)
   - Vaccine Adverse Event Reporting system (VAERS)

2. Active Surveillance
   - FDA / CBER Postmarket Safety Surveillance Systems
     • BEST with IQVIA, Acumen, IBM Watson Health
     • Centers for Medicare & Medicaid Services Data
     • Sentinel with Harvard Pilgrim HealthCare Institute
1. Passive Surveillance

Adverse Event Reporting Systems

• **VAERS** – Run jointly by FDA and CDC
  - ~50,000 reports/yr

• **FAERS** – Run by FDA
  - ~10,000 reports/yr

• Reports from HC providers, manufacturers, patients
• CBER Medical Officers review all serious AE reports (VAERS) and expedited reports (FAERS)
2. Active Surveillance

FDA Amendments Act (2007) – establish an Active Postmarket Risk Identification and Analysis System

CBER Postmarket Safety Surveillance Systems

1. BEST (Biologics Evaluation and Safety)
2. CMS (Centers for Medicare & Medicaid Services) Data
3. Sentinel with Harvard Pilgrim HealthCare Institute
2. Active Surveillance: CBER BEST

Goals

1. Use new EHR data sources to improve queries
   - Establish query evaluation system for unique challenges of Vaccines, Blood Products and applied to other biologics

2. Employ innovative technologies – Artificial Intelligence, NLP, semi-automated chart review to advance biologic safety
   - Improve efficiencies (e.g., chart review, quicker data access)
2. Active Surveillance: CBER BEST

**BEST Contractors:** IQVIA, Acumen, IBM Watson

**Data Sources** cover:
- ~50-70 million persons with EHR data
- ~160 million persons with Claims data
- ~5 million persons with linked EHR and Claims data

**Tools**
- OMOP Common Data Model (CDM), Others
- On-Demand Analytic Tools
- Contractor-specific or publicly available Artificial Intelligence, NLP tools
CBER Postmarket Surveillance Accomplishments (1)

Infrastructure and Development:

• BEST: Awarded Several Surveillance Contracts and four task orders to IQVIA, Acumen, IBM Watson Health
• Onboarded 4 new BEST data partners
• Build new surveillance infrastructure: New data and On-demand tools and analytics
• Performed several simple, medium and complex queries
• Developed a semi-automated medical chart review tool
• Completed two pilot product/AE pair case examples and prototype to advance automation of AE reporting
CBER Postmarket Surveillance Accomplishments (2)

Specific BEST Product Studies:

• Two product safety studies initiated in lieu of PMRs
• Validation of Gestational Age and Pregnancy Outcomes
• Hemovigilance Study
• Rotavirus Vaccine Adherence Study
• Vaccine Exposure During Pregnancy
• Blood-derived Products and Advanced Therapeutics Epidemiologic Studies
FDA – CMS Vaccine Effectiveness and RWE generation studies:

• Annual Influenza Vaccine Effectiveness Studies 2019-2020 Season using CMS data:
  – Evaluation of overall annual influenza vaccine effectiveness
  – Comparisons High Dose v. Standard dose, Egg-based v. Cell-based, adjuvanted v. non-adjuvanted, and others

• Herpes Zoster (shingles) vaccine effectiveness studies
CBER Postmarket Surveillance Accomplishments (4)

**Sentinel Biologic Product Safety Studies:**

- Conducted several query evaluations to address regulatory questions
- Completed three protocol-based studies
Pilot case example –
Leveraging Artificial Intelligence methods to advance automated adverse event reporting
Transfusion Associated Circulatory Overload: Unreported AEs Can Create Public Health Risks

The BEST prototype is designed for unreported adverse events (where clinical recognition or evidence exists) following biologic product exposure. This demo uses simulated data for a patient with a Transfusion-Associated Circulatory Overload.

**Jane Doe**

- Age: 71
- Gender: Female

**Background History**
- Alcoholic hepatitis
- Alcohol use disorder
- Chronic renal failure
- Splenomegaly

**Healthcare Interaction**
- Symptoms on admission: Dysmenorrhea
- Fatigue
- Melena

**Biologic Exposure**
- 2 units packed RBC transfusions

**Biologic Adverse Event**
- Unreported TACO reaction
- Potentially life-threatening to Jane in future
- Unrecorded and unreported AEs limit the hospital’s ability to monitor

*Simulated data*
### Data Generated: EHR Contains Data to Detect AEs

<table>
<thead>
<tr>
<th>EHR</th>
<th>Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td>2017-02-17 and 2017-02-19 – Transfusion procedures</td>
</tr>
<tr>
<td>2017-02-17 11:20 – Packed RBC transfused (ISBT-128: 1234567890)</td>
<td></td>
</tr>
<tr>
<td>2017-02-19 14:30 – Packed RBC transfused (ISBT-128: 2345678901)</td>
<td></td>
</tr>
<tr>
<td><strong>Labs</strong></td>
<td>Charges for lab tests performed (without results)</td>
</tr>
<tr>
<td>Hemoglobin – 7.2 grams/L</td>
<td></td>
</tr>
<tr>
<td>Hematocrit – 25%</td>
<td></td>
</tr>
<tr>
<td>WBC count – 7,200/mcL</td>
<td></td>
</tr>
<tr>
<td>Brain natriuretic peptide - 110 pg/mL</td>
<td></td>
</tr>
<tr>
<td>AST – 150 IU/L, ALT – 71 IU/L</td>
<td></td>
</tr>
<tr>
<td><strong>Diagnoses</strong></td>
<td>Anemia, Alcoholic Hepatitis, Dysmenorrhea (at discharge date)</td>
</tr>
<tr>
<td>Anemia, Abnormal liver function tests, Dysmenorrhea</td>
<td></td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>No notes</td>
</tr>
<tr>
<td>Physician Progress Note: 3 hours following the second transfusion, developed dyspnea, drop in SPO2, mild edema, increase in blood pressure and tachycardia. CXR showed bilateral pulmonary edema. Patient was then treated with Lasix and O2 and vital signs returned to baseline within two hours.</td>
<td></td>
</tr>
<tr>
<td>Vital Signs:</td>
<td></td>
</tr>
<tr>
<td>Blood pressure increase – 111/72 to 123/95 mmHg</td>
<td></td>
</tr>
<tr>
<td>HR increase from 92 to 119 bpm</td>
<td></td>
</tr>
<tr>
<td>SpO2 decrease – 97% to 88%</td>
<td></td>
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</table>
Evidence Generated: AI and Expert Driven Algorithms

Extract Evidence

**EHR**

**Exposure**
- 2017-02-17 11:20 – Packed RBC transfused (ISBT-128: 1234567890)
- 2017-02-19 14:30 – Packed RBC transfused (ISBT-128: 2345678901)

**Labs**
- Hemoglobin – 7.2 grams/L
- Hematocrit – 25%
- WBC count – 7,200/mcL
- **Brain natriuretic peptide - 110 pg/mL**
- AST – 150 IU/L, ALT – 71 IU/L

**Diagnoses**
- Anemia, Abnormal liver function tests, Dysmenorrhea

**Notes**
Physician Progress Note: 3 hours following the second transfusion, developed dyspnea, drop in SPO2, mild edema, increase in blood pressure and tachycardia. CXR showed bilateral pulmonary edema. Patient was then treated with Lasix and O2 and vital signs returned to baseline within two hours.

Vital Signs:
- Blood pressure increase – 111/72 to 123/95 mmHg
- HR increase from 92 to 119 bpm
- SpO2 decrease – 97% to 88%

**Detection Features**

- Transfusion_Administered = True
- BNP>100 = True
- Relevant_Diagnosis = True
- Dyspnea = True
- Pulmonary_Edema = True
- New_Diuretic = True
- SpO2<90 = True

*Simulated data*
Automated Detection: Algorithms Rank Potential AEs

### Cases in EHR

<table>
<thead>
<tr>
<th>Patient #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion Admin</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Relevant Diagnosis</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td></td>
</tr>
<tr>
<td>Pulmonary Edema</td>
<td>✅</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased BNP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New Diuretic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>[...]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probability Score</td>
<td>0.00</td>
<td>0.68</td>
<td>0.98</td>
<td>0.22</td>
<td>0.00</td>
<td>0.91</td>
</tr>
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### Prioritized Cases

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<th>Patient #</th>
<th>Probability Score</th>
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<tr>
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</tr>
<tr>
<td>5</td>
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</table>

**Functionality:** Detects unreported cases using validated algorithms leveraging innovative methods, such as NLP, ML, and computational phenotyping

**Impact:** Reduces burden of manually identifying and tracking potential AEs and increases number of reported cases

*[Simulated data]*
Cases Aggregated: Probable AEs Sent for Validation

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</table>

>0.75 Threshold

### Features:
Seamlessly links automated detection with semi-automated validation

### Impact:
Increases efficiency through prioritization and communication of cases for review

### Flagged Cases For Validation in Chart Review

<table>
<thead>
<tr>
<th>Case ID</th>
<th>Product Type</th>
<th>Date Created</th>
<th>Date Last Updated</th>
</tr>
</thead>
<tbody>
<tr>
<td>155552642019-01-23T154600-0500</td>
<td>Blood Transfusion</td>
<td>09/09/2019</td>
<td>09/09/2019</td>
</tr>
<tr>
<td>32583682015-04-04T003000-0500</td>
<td>Blood Transfusion</td>
<td>09/09/2019</td>
<td>09/09/2019</td>
</tr>
</tbody>
</table>

*Simulated data*
Semi-Automated Chart Review Tool Increases Efficiency

Chart Review Tool: Enables semi-automated clinical assessment with an intuitive user interface

Abstraction: Allows for simplified visualization of patient EHR information

Classification: Reviewers efficiently document information related to classification, including:

- Assessment of causality
- Evidence for conclusions
- Certainty of exposure
- Certainty of adverse event
- Severity of reaction

*Simulated data*
Reporting: Reviewer Saves Time with ICSR Auto-population

**Features:** Auto-population and generation of ICSR from FHIR to XML format (with future functionality for final review and editing)

**Impact:** Increased efficiency through auto-population of ICSR

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**Step 1**
Reviewer confirms evidence and other information prior to submission

**Step 2**
Reviewer clicks to auto populate ICSR report

**Step 3**
Reviewer completes final check and then submits

*Simulated data*
Impact: Prototype Demonstrates Improved Efficiency and Accuracy

**Current**
- Clinical exposure and outcome
- **Manual Detection**
  - Under-recognition of outcomes
  - Individual flagging of potential AEs
- **Manual Validation**
  - Time-intensive to review dispersed data
  - Potential AEs not always communicated
  - Case definitions separate
- **Manual Reporting**
  - Data re-entry to report externally
  - Lack of granularity in report evidence

**Future**
- Clinical exposure and outcome
- **Automated Detection**
  - AI algorithm scores potential cases
  - Batch detection, more focus on patient care
- **Semi-Automated Validation**
  - Evidence integration reduces burden
  - Flagged and prioritized cases sent for review
  - Case definition integrated
- **Semi-Automated Reporting**
  - Auto-population of granular ICSR evidence
  - Generation of evidence-based ICSR narrative

Prototype demonstrates use of innovative methods to reduce burden, while increasing quantity and quality of AE reports.
Limitations

Initial efforts focused on building the infrastructure and software needed for semi-automated detection and reporting of adverse events due to biologic exposures. The initial analysis has several limitations:

- Electronic Health Records were converted to HL7 FHIR DSTU2 format as a prototype for interoperability between EMR systems. DSTU2 is not the most current standard. Additionally, flexibility in implementations of FHIR standards could lead to variability across sites that limit generalizability of results based on the preliminary results.
- Adverse events due to biologic exposure are rare events which can be challenging to model. Models were built with k-fold cross validation, and final models were compared to a hold-out set to avoid Type I errors (overfitting). However, results should be replicated on additional data.
- Further analyses are required to validate the performance of detection models on case features or events that may not have occurred in the initial training data.
- Data represent multiple care settings, but further work should validate the applicability of findings to different modalities of care.
- Data for the prototype development were not nationally representative.
- Small sample sizes may have limited the power to detect clinically significant features such as product type effects or the impact of specific rare medical conditions. Additional data are required for sufficient statistical power to detect rare edge cases.
- Natural Language processing of clinical notes is an ongoing effort for the BEST initiative. Results presented here do not include more advanced NLP techniques under review at the time of the presentation.
- Iterations for active learning require considerable time and effort to evaluate cases and review complex transfusion cases. In some cases, multiple adverse events may apply, further complicating machine learning efforts.
- Work on computational phenotypes will supplement active learning efforts to improve detection of adverse events for extremely rare conditions.
Acknowledgements

CBER Sentinel Core Team
OBE colleagues
CBER product office colleagues from OBRR, OVRR, and OTAT

Acumen and partners
IBM and partners, Gevity, 1upHealth, and an academic health system.
IQVIA and partners
Thank you!

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