Enhancing Biologics Adverse Event Surveillance via Scalable, FHIR-based Infrastructure
How Does the FDA Use Real World Data and Real-World Evidence?

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Hussein Ezzeldin, PhD
Analytics and Real-World Evidence Branch (ARWEB)
Division of Analytics and Benefit-Risk Assessment (DABRA)
Office of Biostatistics and Pharmacovigilance (OBPV)
Center for Biologics Evaluation and Research (CBER)
U. S. Food and Drug Administration (FDA)
Outline

• Background
  – Objectives
  – Challenges

• BEST Pipeline Prototype
  – Architecture
  – Data Quality (Standards and Assurance)
  – Detection (Phenotyping)
  – Validation (Review)
  – Reporting

• BEST Exchange Pilot
  – Pull and Push Use Cases
  – Preliminary Results

• Conclusions and Summary
Background: CBER Portfolio

CBER-Regulated Products

Products

- Vaccines preventative & therapeutic
- Gene Therapies
- Human Tissues & Cellular Products
- Blood & Blood Products
- Xenotransplantation Products

Exposure

- Pharmacies
- Community clinics
- Mobile clinics
- Universities
- Hospitals/Tertiary Centers
- Emergency Dept.
- Treatment Centers
Background: **Objective**

**CBER Mission Focus**

*Ensure post-market biologic-product safety and effectiveness through active surveillance*

**CBER Need**

*Enhanced post-market adverse event (AE) reporting*

**Action**

*CBER Launched Biologic Effectiveness and Safety (BEST) in 2017*

**Objective**

*Highlight how BEST is fulfilling CBER Need*
### Background: Challenges

Existing Manual Process Creates Burden, How RWD-RWE can help!!

#### Clinical exposure and potential outcome

<table>
<thead>
<tr>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manual Detection</strong></td>
<td><strong>Automated Detection</strong></td>
</tr>
<tr>
<td>Individual flagging of potential AEs</td>
<td>Batch detection, more focus on patient care</td>
</tr>
<tr>
<td>Under-recognition of outcomes</td>
<td>AI algorithm scores potential cases</td>
</tr>
<tr>
<td><strong>Manual Validation</strong></td>
<td><strong>Semi-Automated Validation</strong></td>
</tr>
<tr>
<td>Time-intensive to review dispersed data</td>
<td>Evidence integration reduces burden</td>
</tr>
<tr>
<td>Potential AEs not always communicated</td>
<td>Flagged and prioritized cases sent for review</td>
</tr>
<tr>
<td>Case definitions separate</td>
<td>Case definition integrated</td>
</tr>
<tr>
<td><strong>Manual Reporting</strong></td>
<td><strong>Semi-Automated Reporting</strong></td>
</tr>
<tr>
<td>Data re-entry to report externally</td>
<td>Auto-population of granular ICSR evidence</td>
</tr>
<tr>
<td>Lack of granularity in report evidence</td>
<td>Generation of evidence-based ICSR narrative</td>
</tr>
</tbody>
</table>

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

ICSR, individual case safety report.
BEST ADVERSE EVENTS REPORTING PIPELINE
BEST* Innovative Methods (IM) Initiative developed a Pipeline prototype to address current challenges through AI and automation.

**BEST** Biologics Effectiveness and Safety
BEST PIPELINE: DATA QUALITY ASSURANCE

Are vaccine brand or lot numbers captured for all immunization administrations?
For Regulatory Grade Data

Existing Data Quality Tools

Generating **FHIR-ready** and **OMOP-ready** files from data partners, the team uses the Framework described by Kahn et al.\(^1\) and the Data Quality chapter of The Book of OHDSI \(^2\).

**Conformance**
Adherence to specified standards and formats? Sub-types include Value, Relational, and Computational

- Are ISBT-128 codes recorded in proper format?

**Completeness**
Are variables present? Do they contain all recorded values?

- Are vaccine brand or lot numbers captured for all immunization administrations?

**Plausibility**
Are data values believable? Sub-types include Uniqueness, Atemporal, and Temporal.

- Are transfusion start times realistic or recorded as the discharge datetime?
BEST PIPELINE: DETECTION
Phenotyping: Overview

Ensure shareability and interoperability (FHIR CQL, OMOP)

PPV, Positive Predicted Value
### Phenotyping Library

#### I. Claims Comparable Algorithms

Detailed logic overview can be found [here.](#)

#### II. Reporting (Structured Data Only) Algorithms

Detailed algorithm logic can be found [here.](#)

### Available Termsets

The table below summarizes the termsets available in this repository and the terms included in each phenotype's termset folder. A detailed description of the termsets can be found [here.](#)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Terms</th>
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<tbody>
<tr>
<td>Anaphylaxis</td>
<td>Anaphylaxis, Antihistamine H1, Antihistamine H2, Sympathetic</td>
</tr>
<tr>
<td>Bell's Palsy</td>
<td>Facial Palsy, Antivirals, Steroids</td>
</tr>
<tr>
<td>Deep Vein Thrombosis</td>
<td>Deep Vein Thrombosis, Vitamin K Antagonists, Radiology, D-Dimer, Anticoagulants, Enzymes, MRA, Direct Factor Xa Inhibitors, Thrombectomy, Vena Cava Filter</td>
</tr>
<tr>
<td>Guillain-Barre Syndrome</td>
<td>GBS, Antivirals, CSF Lab Test</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>Hemorrhagic Stroke, PCC, Surgeries, MRA, CT Scan, MRI, INR, Platelet Count, PTT</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Myocarditis, Creatine Kinase, Ejection Fraction, Myocardial Band, Troponin, ACE Inhibitors, Anti-Inflammatory, ARBs, Beta-blockers, Vasodilators</td>
</tr>
</tbody>
</table>
BEST PIPELINE: VALIDATION AND REPORTING
Validation: Chart Review Tool (CRT)

Note: Any images, videos, or other representations of an individual's health record shown on slides is synthetic and does not contain actual patient data.
BEST EXCHANGE PLATFORM

BEST Exchange Platform

eHeX Hub

Pilot Participants
BEST Exchange Platform

Components of BEST Platform
BEST Exchange Platform, Push Use Case

1. **Exposure**
   - Vaccine administered and recorded in provider's EHR

2. **Outcome Detected**
   - Potential adverse event detected by algorithm
   - Submit FHIR data to eHx Hub for delivery to Health Data Exchange Platform

3. **eHx Transmits Data**
   - Delivers FHIR data to Health Data Exchange Platform

4. **BEST FHIR Exchange Platform Processes Case**
   - Receives FHIR data from eHx Hub

5. **BEST Application Clinical Reviews**
   - Semi-automated tools for case review
   - Adverse event report developed for valid cases

6. **FDA**
   - Receives AE report
   - Reviews case

*eHx, eHealth Exchange*
BEST Exchange Platform, **Pull Use Case**

1. **FDA**
   - Identify case of interest that requires additional data

2. **BEST Applications**
   - Use provided patient demographics to prepare additional data request

3. **BEST FHIR Exchange Platform**
   - Requests and receives FHIR data from eHx Hub

4. **eHealth Exchange**
   - Queries eHx network for patient match
   - Retrieves FHIR data match and sends to Health Data Exchange Platform

5. **Provider EHR System**
   - Record of patient interactions in EHR system
   - Respond to any queries for additional FHIR data

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eHx, eHealth Exchange
Pilot Findings/Results

- 271 post-vaccination AE patients EHRs were queried
- Across 11 different health provider data partners
- Epic EHRs
- Generally, the data had the necessary elements, or workarounds for CBER’s use case
- Important gaps were identified due to:
  - Lack of inclusion in USCDI data set
  - Lack of Epic FHIR API support
  - Varying levels of completeness across partners
Conclusion and Summary

• For CBER’s use case, the overall data quality meets general requirements, as partner’s EHR HL7® FHIR® APIs are showing high adherence to USCDI data set.

• Due to variability - even with same EHR vendor - in security authorization settings, these required trial and error with individual partners:
  – The team worked with EHR vendors to create a new policy that standardizes this process across partners to reduce the connection set-up time.

• The BEST team continues to develop the Platform infrastructure to:
  – enhance our querying capabilities
  – efficiently federate AE detection logic
  – conduct evaluation and validation studies to enhance CBER’s passive and active post-market surveillance capabilities.
Conclusion and Summary

CBER BEST Platform is:

- utilizing **RWD, automation and AI**, to address the challenges of the current adverse events (AE) reporting system;

- **driving innovation** across multiple work streams;

- adopting the **FAIR* principles** in the design and implementation of the BEST pipeline prototype;

- **evolving to scale** at production level to fulfill CBER’s active post-marketing surveillance responsibilities.

*Findability, Accessibility, Interoperability, and Reuse of digital assets*
## Acknowledgement

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<thead>
<tr>
<th>FDA CBER</th>
<th>Barbee Whitaker, Artur Belov, Manette Niu, Jane Mutanga, Brian Hively, Steven Anderson</th>
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<tbody>
<tr>
<td>IBM</td>
<td>Lance Jones, Matthew Deady, Brian Goodman, Haley Huang, Deepa Youssef, Kathryn Matto</td>
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<td>eHx</td>
<td>Jay Nakashima, Eric Heflin, Mike Y and Mike M</td>
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THANK YOU!
QUESTIONS??

hussein.ezzeldin@fda.hhs.gov