U.S. FOOD & DRUG ADMINISTRATION

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

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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

CBER Postmarket Surveillance Accomplishments (3)

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

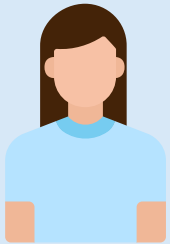
Biologic Exposure

- 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**

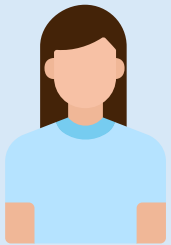
Data Generated: EHR Contains Data to Detect AEs



	EHR	Claims
Exposure	• 2017-02-17 11:20 – Packed RBC transfused (ISBT-128: 1234567890) • 2017-02-19 14:30 – Packed RBC transfused (ISBT-128: 2345678901)	• 2017-02-17 and 2017-02-19 – Transfusion procedures
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	• Charges for lab tests performed (without results)
Diagnoses	• Anemia, Abnormal liver function tests, Dysmenorrhea	• Anemia, Alcoholic Hepatitis, Dysmenorrhea (at discharge date)
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%	• No notes

*Simulated data

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
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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
- Sp02<90 = True

*Simulated data

Automated Detection: Algorithms Rank Potential AEs

Cases in EHR

Features	Patient #	1	2	3	4	5	6
	Transfusion Admin	✓	✓	✓	✓	✓	✓
	Relevant Diagnosis						
	Dyspnea		✓	✓	✓		✓
	Pulmonary Edema			✓			✓
	Increased BNP			✓			
	New Diuretic			✓			
	[…]		✓	✓			✓
	Probability Score	**0.00**	**0.68**	**0.98**	**0.22**	**0.00**	**0.91**

Prioritized Cases

Patient #	Probability Score
3	**0.98**
6	**0.91**
2	**0.68**
4	**0.22**
1	**0.00**
5	**0.00**

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

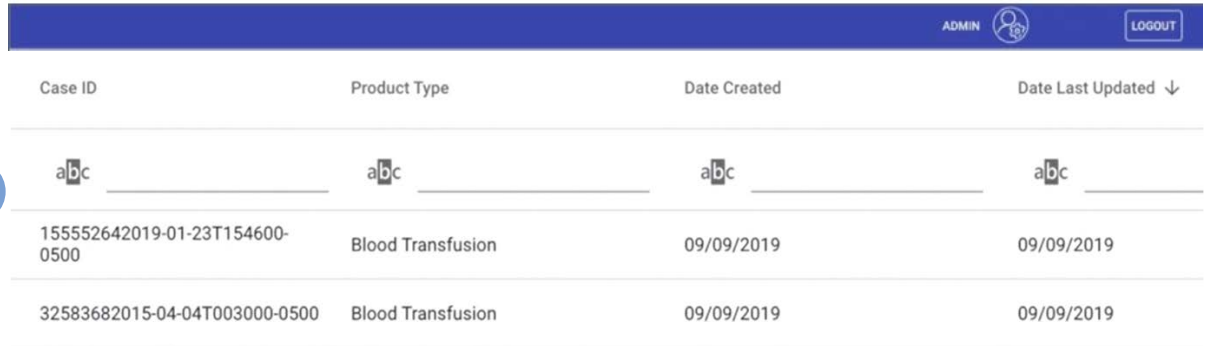
Cases Aggregated: Probable AEs Sent for Validation

Prioritized Cases

Patient #	Probability Score
3	0.98
6	0.91
2	0.68
4	0.22
1	0.00
5	0.00

>0.75 Threshold

Flagged Cases For Validation in Chart Review



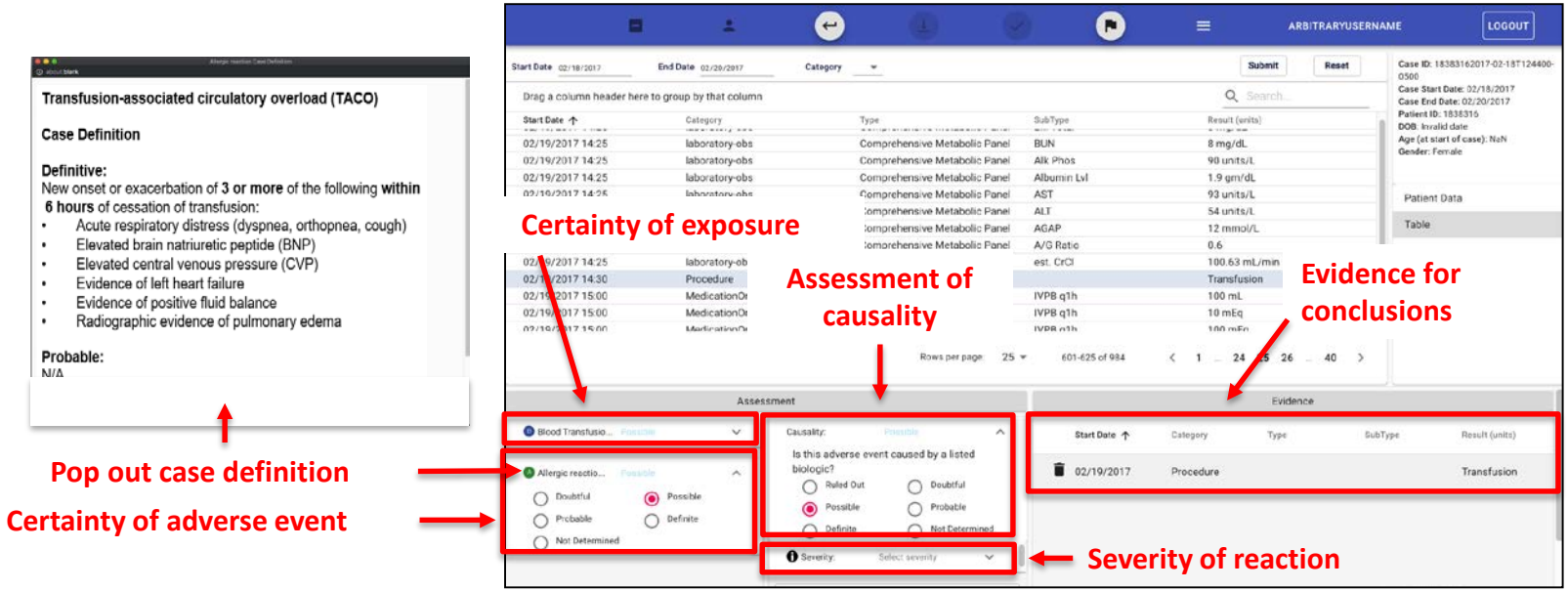
Features: Seamlessly links automated detection with semi-automated validation
Impact: Increases efficiency through prioritization and communication of cases for review

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:



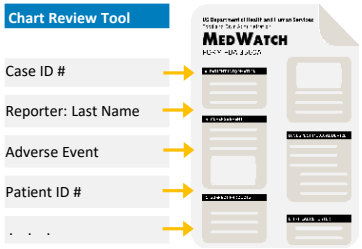
*Simulated data

Reporting: Reviewer Saves Time with ICSR Auto-population

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

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

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

vs.

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.

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IQVIA and partners

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