The FDA BEST System: Leveraging EHR data and Innovative Approaches for Surveillance of Biologic Products

Steve Anderson, PhD, MPP

Director

Office of Biostatistics & Epidemiology

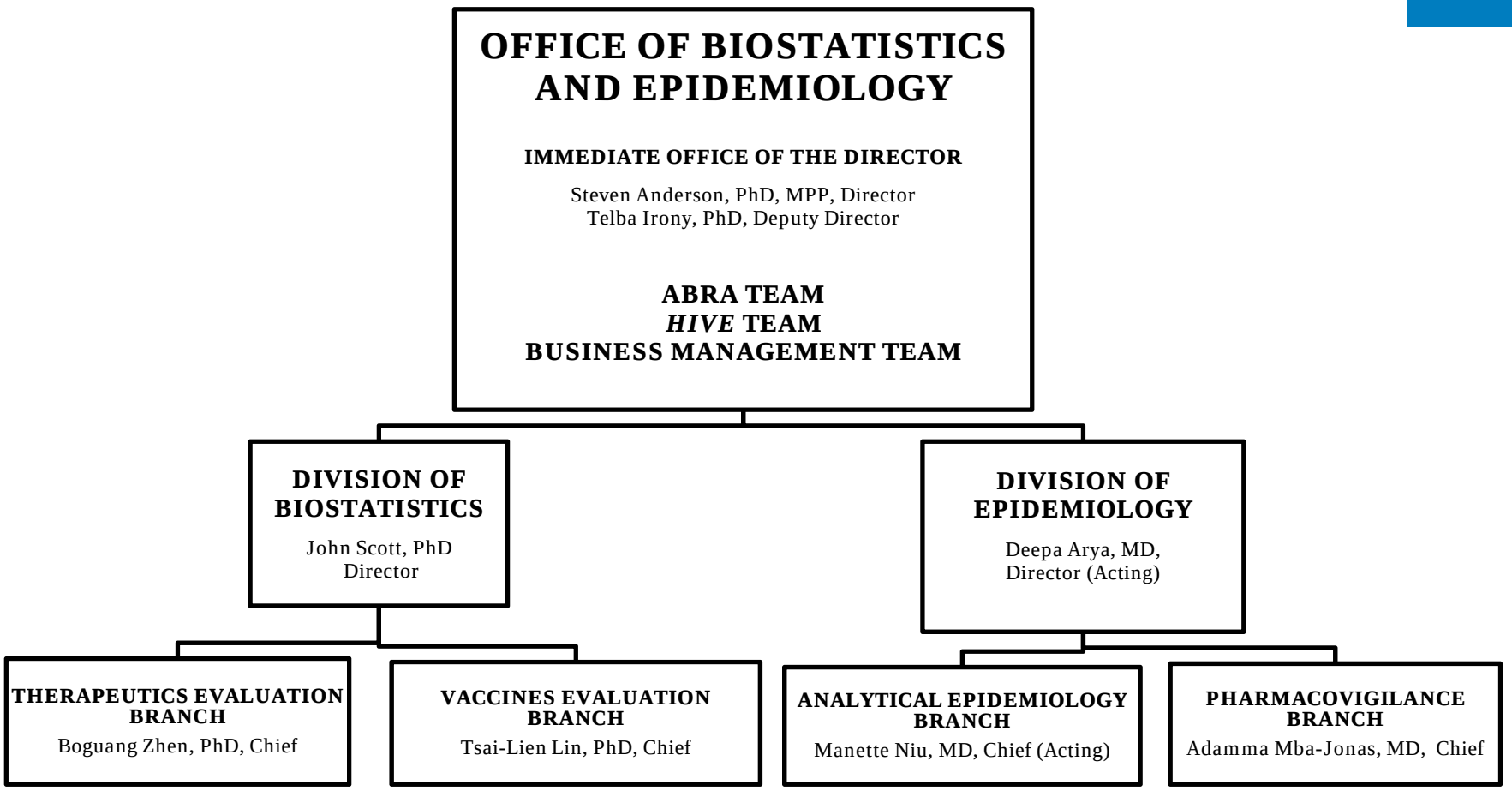
Center for Biologics Evaluation and Research, FDA

FDA Center for Biologics Evaluation & Research (CBER)

Regulatory responsibility for:

- Allergenics
- Vaccines
- Blood and blood products
- Tissues
- Cellular Therapies
- Gene Therapies
- Advanced therapeutics

OBE Organization Chart



OBE Staff & Responsibilities

Areas of Expertise

- Biostatistics
- Computer modeling
- Epidemiology
- Pharmacovigilance
- Clinical expertise
- High performance computing - HIVE

Regulatory & Research Activities

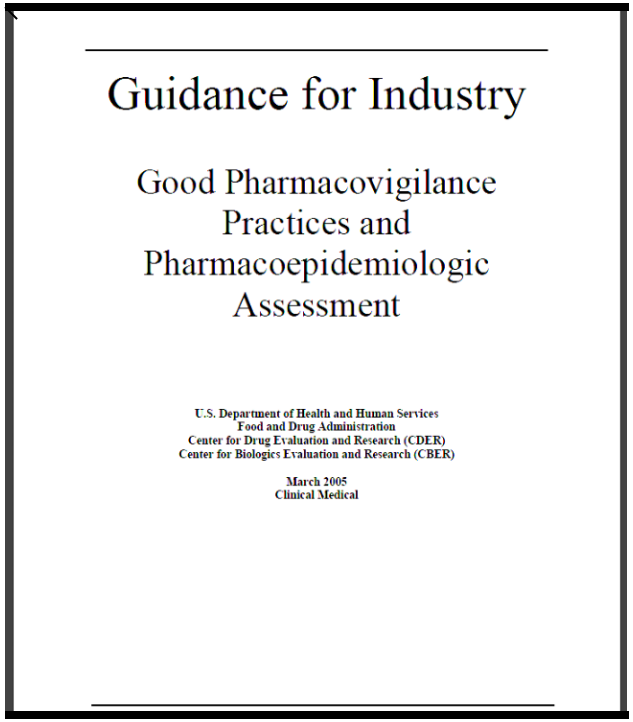
- Covers all CBER-regulated products
- Statistical review efficacy and safety data submitted by sponsors
- Prelicensure review of safety monitoring plans (PVP)
- Routine pharmacovigilance
- Passive surveillance –FAERS, VAERS
- Active surveillance-Sentinel, BEST, CMS
- High performance computing and next generation sequencing
- Benefit-Risk Modeling

Legislative mandates drive CBER regulatory activities

- FDA Amendments Act (FDAAA) of 2007
  - Sentinel, government data, Clinical Trials.gov, PMC, PMR, REMs, safety reporting, pediatric safety
- Prescription Drug User Fee Act (PDUFA) VI
  - Sentinel, Real-world evidence (RWE), innovative clinical trials, patient input, benefit-risk assessment, guidance development, public meetings, others
- 21st Century Cures (2016)
  - RWE, vaccine innovation, patient-informed drug development, and others

Guidance: Good Pharmacovigilance Practices

- Identifying and describing safety signals
- Investigating a signal through observational studies
- Interpreting safety signals
- Developing a pharmacovigilance plan


Guidance for Industry

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

March 2005
Clinical Medical

http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126834.pdf

CBER Active Postmarket Surveillance Systems

- FDA Sentinel Initiative
  - Sentinel PRISM – Harvard Pilgrim system (Claims)
  - CBER BEST (Largely EHR data and some claims data)
- Center for Medicare & Medicaid data
- Veterans Administration Data
- VSD

Sentinel PRISM – Harvard Pilgrim system

- Workhorse for many years for CBER regulatory/safety studies
  - >80 queries, >20 comprehensive studies
- Largely claims data
- PRISM for vaccines – covers 170 million persons
- BloodSCAN –covers ~200 million person

Limitations of Claims Data for Regulatory Studies

- >6 months to retrieve analyze medical charts
- Long study times
- Long data lags ~9-12 mos
- Transfusions not always captured

- **Need for another EHR-based system to better address CBER regulatory surveillance needs**

Biologics Effectiveness and Safety (BEST) Initiative

- New CBER Active Post-market Surveillance Program
  - Largely EHR-based
- Started in 2017 with pilot program
- Awarded two five-year IDIQ contracts in FY2019
  - IQVIA
  - IBM Watson Health
  - Acumen
  - Dovell
- BEST continues as a pilot program into 2020

Why BEST?

- Expanded EHR data sources
- Claims data
- New linked EHR-Claims data
- Reduced data lag ~3-4 mos
- On-demand analytic capabilities
- Improved operational speed & more rapid study turnaround

- Better addresses unique characteristics of biologics
  - o Incorporates unique coding such as ISBT-128 for blood
  - o Rapid access to medical charts

BEST Goals

1. Fully Operational Query, study and production enterprise system

2. Leverage innovations such as AI, NLP, and semi-automation of medical chart review and automated AE reporting

CBER Surveillance Priorities

- Routine Surveillance: Conduct evaluations of safety and effectiveness of biologic products (including vaccines)
- Evaluating safety of vaccination during pregnancy
- Signal Detection – use of NLP and Artificial Intelligence
- Pandemic Preparedness – near real-time surveillance
- Emerging Infectious Disease Surveillance & Monitoring

BEST Initiative

IBM	IQVIA/OHDSI	Acumen
Collaborators	**Collaborators**	
MedStar Health Foundation	Regenstrief Institute	
	Columbia University	
	University of Colorado	
	Cerner	
	University of California, Los Angeles	

Add New Data Sources for Millions of Patients (2)

IBM

Data Sources	# Patient Records (millions)
MarketScan	60
CED (linked EHR and claims data)	4.9
MedStar (EHR)	5

IQVIA

Data Sources	# Patient Records (millions)
LRxDx (Claims)	160
Regenstrief Inst. (claims, EHR)	19
Columbia Univ (EHR)	6.5
Univ of Colorado (EHR)	17
Cerner (EHR)	23

Acumen

Data Sources	# Patient Records (millions)
Blue Health Intelligence (Claims)	23

BEST Initiative GOAL 1: Data, Tools and Infrastructure for Surveillance of Biologics

ACCOMPLISHMENTS: DESCRIPTIVE STUDIES

Current Activities

IBM | IQVIA | Acumen

Descriptive Epidemiologic Studies:

Vaccines

- HEPLISAV-B
- SHINGRIX
- ZOSTAVAX
- FluMist
- All influenza vaccines
- TRUMENBA and BEXSERO
- GARDASIL9

Blood-derived products

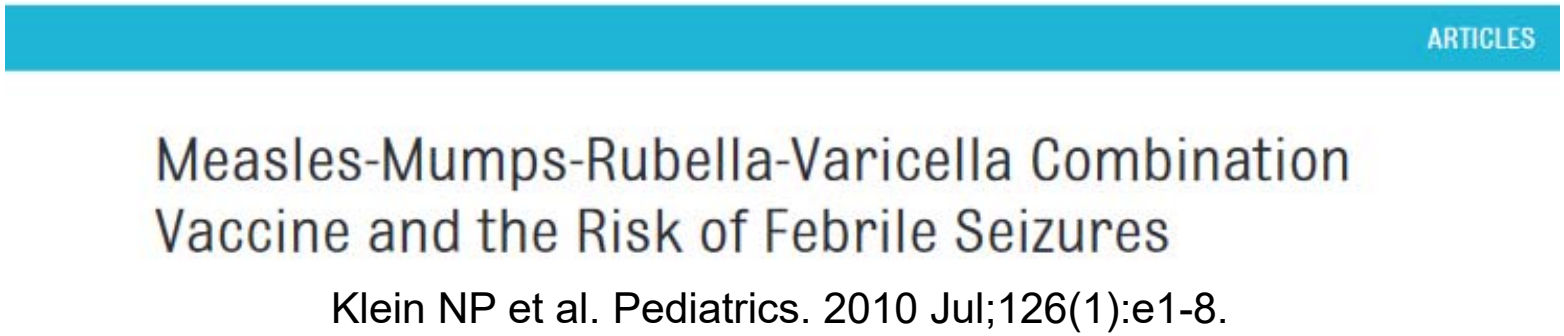
- Intravenous immunoglobulin (IVIG)
- Factor VIIa
- Factor VIII
- von Willebrand factor
- FEIBA
- KCENTRA
- Fibrin sealant
- Fibrinogen concentrate

Outcomes

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

Replication of Vaccine Study (Test Case)

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



Klein NP et al. Pediatrics. 2010 Jul;126(1):e1-8.

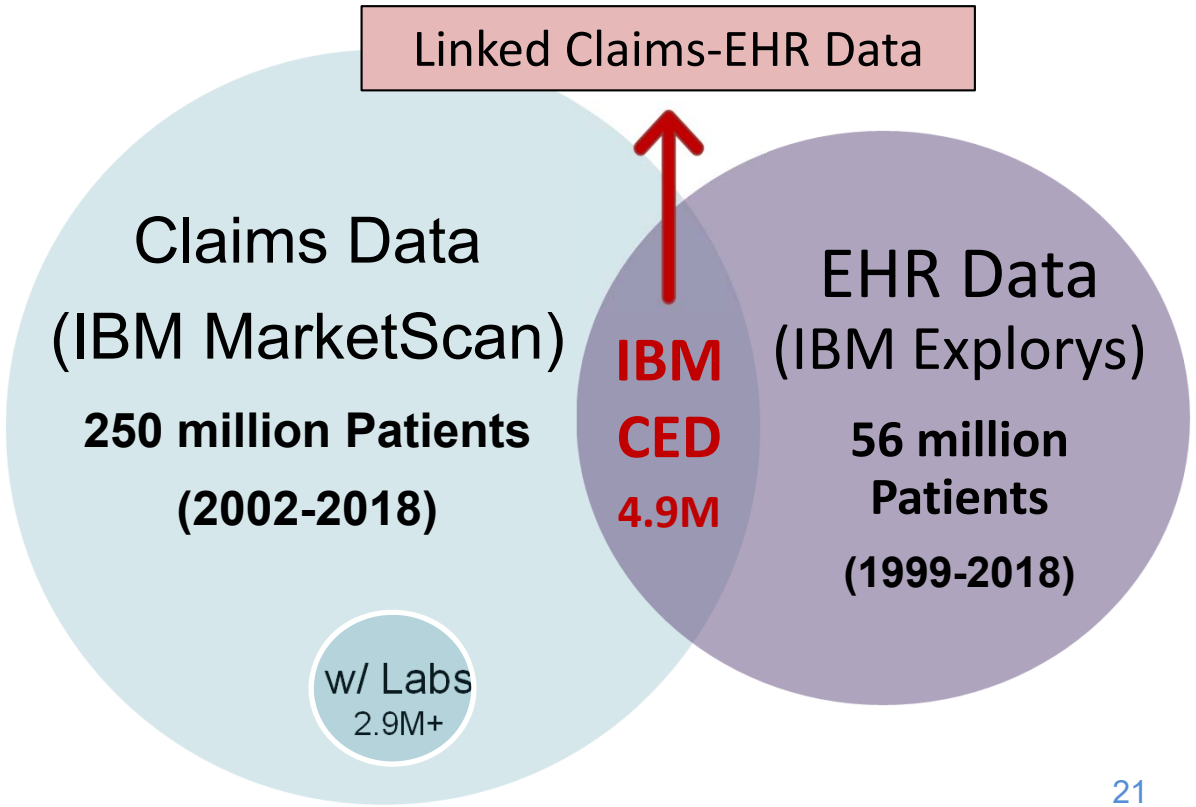
- **Study Objective:** To assess the risk of febrile seizures in children receiving first dose of Measles, Mumps, Rubella, & Varicella (MMRV) compared to that of MMR and Varicella administered separately on the same day

LINKED EHR-CLAIMS DATABASE

Study Population

Use of deterministically linked Claims-EHR Data (IBM CED) enables:

- **Algorithms** to be applied to claims data elements
- **Validations** to be performed using structured EHR data elements



Source: IBM, 2018

CED DATABASE: PREGNANCY OUTCOMES & GESTATIONAL AGE VALIDATION

Study Objectives

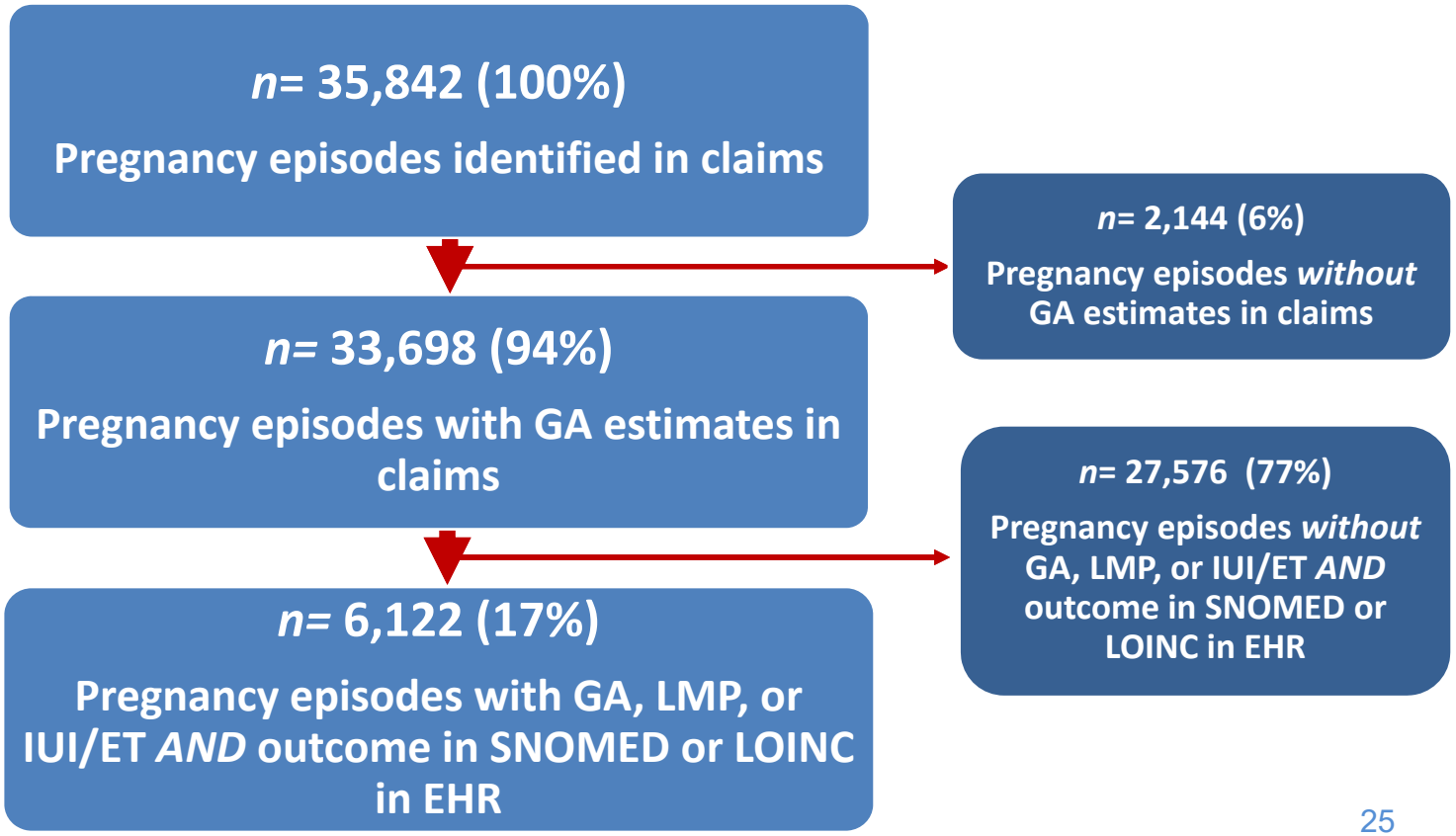
1. Develop algorithms using ICD10 diagnosis codes and CPT/HCPCS procedure codes to
   a) Determine gestational age
   b) Classify pregnancy episodes as one of 4 outcomes:
      i. Full-term birth
      ii. Pre-term birth
      iii. Stillbirth
      iv. Spontaneous abortion

Study Objectives

2. Using GAIA* case definitions as a reference method
   - To validate estimated gestational age and outcomes classifications
   - Stratification of outcome certainty by strength of evidence
   - By comparing to clinician-adjudicated results based on review of structured CED (EHR) data elements
   - Example outcomes of interest: stillbirth, spontaneous abortion, live birth, low birth weight, etc.

*GAIA = Global Alignment of Immunization Safety Assessment in pregnancy

Study Population



Source: IBM Watson Health, 2018

Note: Preliminary results and subject to change

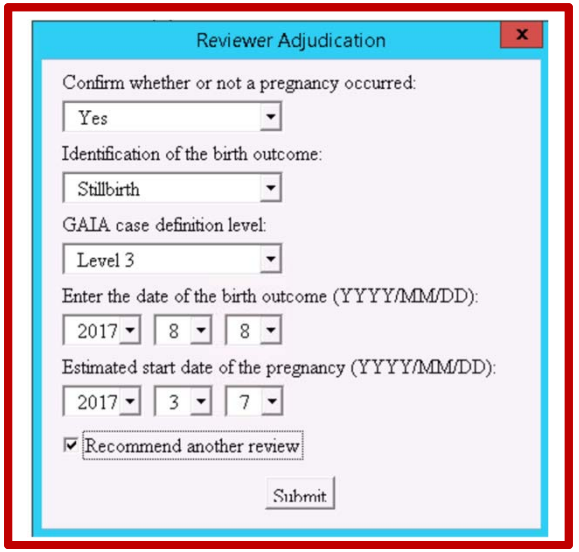
Clinician Adjudication Using Semi-Automated Chart Review

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

BEST Goal 2: Progress

- Semi-automated data extraction from EHR of:
  - CBER Product exposures
  - Product-related adverse events that meet defined criteria
- Development and validation of descriptive case reports
- Electronic submission of reports via FDA electronic gateway (e.g., FAERS and VAERS)

BEST GOAL 2: Approach Overview

Innovative approaches are needed to achieve BEST's aim of biologic product active surveillance

Phase	Traditional Approaches	Innovative Methods
Data	**Claims-Based**: Insufficient for determining biologic exposure and outcomes	**EHR-Based**: Access critical data including clinical notes, product codes, vital signs, and time stamps
Infrastructure	**Claims-Focused Common Data Models**: Reduced granularly, data loss, and data lag	**EHR-Oriented Standards:** Interoperability and granularly enabled through use of HL7 FHIR and OHDSI OMOP
Detection	**Rules-Based and Expert-Curated Algorithms**: Built for curated claims queries	**Artificial Intelligence**: High-dimensional EHR requires natural language processing, machine learning, deep learning, and computational phenotyping
Validation	**Manual:** Costly and slow	**Semi-Automated:** Efficient application-based tool
Reporting	**Manual:** Voluntary and underreported	**Automated:** Automated population and submission

BEST Aim 2: Contracts

I. Pilot Year (FY2018):

IQVIA, including: Georgia Tech Research Institute (GTRI), Columbia University, Stanford University, and Regenstrief Institute

II. Five-Year Vehicle (FY2019-FY2023):

IBM (awarded FY2019 task order), IQVIA, Acumen, and Dovel

Accomplishments for Goal 2: Pilot year

1. **Improved sensitivity and granularity of transfusion exposures compared to claims data alone**
   - Results: Applied NLP to transfusion nursing notes, component identification for 34,000 transfusions.
   - Chart review validation of 100 cases demonstrated 100% accuracy.

2. **Development of computable phenotypes (CP) for Transfusion-Associated Circulatory Overload (TACO)**
   - NLP-based queries = ~10% improvement in PPV for identified TACO cases.

Accomplishments for Goal 2: Pilot year (2)

3. NLP-based development of computable phenotypes (CP) for Post-Transfusion Sepsis (PTS)

- Identified two definitive and several candidate PTS cases.

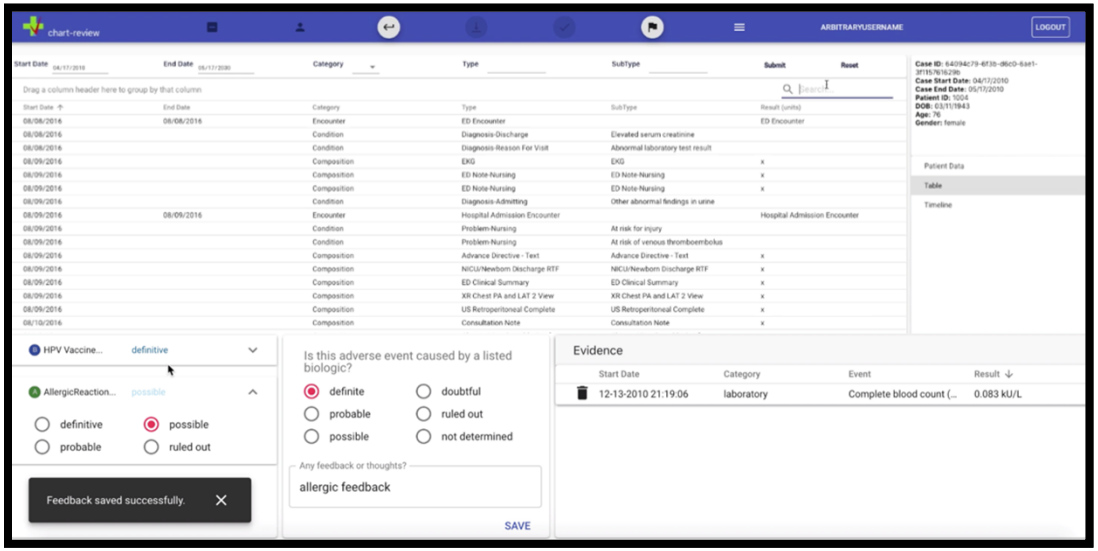
4. Infrastructure to support interoperability within BEST through CLARITY NLP platform

5. Building infrastructure for scale-up of CP-based case identification and automated report generation

– *Demonstrated with MIMIC test database using case characteristics from a published TACO case.*

FY2019: Semi-Automated Validation Tool

- **Chart Review Tool**: Enables semi-automated clinical assessment with an intuitive UI
- **Abstraction**: Allows for simplified visualization of patient EHR information
- **Classification**: Reviewers efficiently document information related to, including:
  - Certainty of **biologic exposure**
  - Certainty of **adverse event** (or health outcome of interest)
  - Assessment of **causality** (or imputability)
  - **Evidence** for conclusions (used for both ICSR reporting and algorithm training)



REAL WORLD DATA GENERATION AND REAL WORLD EVIDENCE (RWE)

21st Century Cures Act Framework for the RWE Program

- The 21st Century Cures Act (Public Law 114-255), signed into law on December 13, 2016 (Cures Act)

"Food and Drug Administration (FDA) is required to develop a framework for a program that **will evaluate the use of real-world evidence (RWE)** to help support the approval of a new indication for an approved drug or to satisfy post approval study requirements (RWE Program)".

CBER RWD/RWE Generation Systems

CBER uses a number of population-based data systems to conduct RWE safety and effectiveness studies including:

1. **CBER BEST** - Covers >20 million (EHRs)
2. **Sentinel – Harvard Pilgrim (HP)** - ~200 million persons (claims)
3. **Center for Medicare & Medicaid Services** ~50 million persons (claims) ≥65yrs

***Goal is to build RWE generation systems for use by FDA and stakeholders**

U.S. FOOD & DRUG ADMINISTRATION

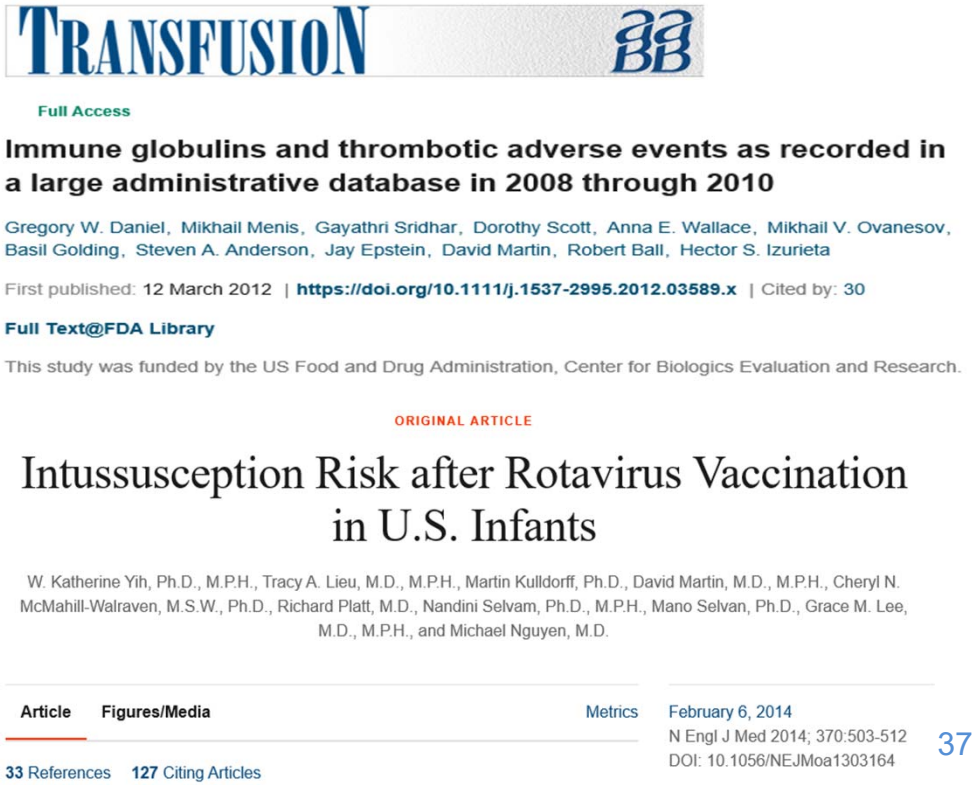
CBER RWD/RWE Studies

CBER RWE Safety Studies:
CMS and Sentinel HP

Two examples of published studies leading to label changes, regulatory actions:

1. Immune globulins and Thrombotic events (Transfusion 2012) –CMS

2. Rotavirus vaccines and Intussusception (NEJM 2014) – Sentinel HP



TRANSFUSION

Full Access

Immune globulins and thrombotic adverse events as recorded in a large administrative database in 2008 through 2010

Gregory W. Daniel, Mikhail Menis, Gayathri Sridhar, Dorothy Scott, Anna E. Wallace, Mikhail V. Ovanesov, Basil Golding, Steven A. Anderson, Jay Epstein, David Martin, Robert Ball, Hector S. Izurieta

First published: 12 March 2012 | https://doi.org/10.1111/j.1537-2995.2012.03589.x | Cited by: 30

Full Text@FDA Library

This study was funded by the US Food and Drug Administration, Center for Biologics Evaluation and Research.

ORIGINAL ARTICLE

Intussusception Risk after Rotavirus Vaccination in U.S. Infants

W. Katherine Yih, Ph.D., M.P.H., Tracy A. Lieu, M.D., M.P.H., Martin Kulldorff, Ph.D., David Martin, M.D., M.P.H., Cheryl N. McMahill-Walraven, M.S.W., Ph.D., Richard Platt, M.D., Nandini Selvam, Ph.D., M.P.H., Mano Selvan, Ph.D., Grace M. Lee, M.D., M.P.H., and Michael Nguyen, M.D.

Article Figures/Media Metrics

33 References 127 Citing Articles

February 6, 2014
N Engl J Med 2014; 370:503-512
DOI: 10.1056/NEJMoa1303164

CBER RWE Effectiveness Studies:

CBER-CMS collaboration to study vaccine effectiveness in Medicare population (>65 years)

Two examples of published studies:

1. High dose vs. Standard dose influenza vaccine effectiveness (Lancet Infect Dis 2015; JID 2017)
2. Herpes zoster vaccine effectiveness and duration of effectiveness (CID 2017)

One very recent study:

3. Rapid response effectiveness study of cell versus egg-based influenza vaccines, 2017-18 season

Project Leads: Rich Forshee, Hector Izurieta

1. High dose vs. Standard dose influenza vaccine effectiveness study, 2012-2013 season

- **FDA-CMS Retrospective cohort study**
  >2.6 million beneficiaries ≥ 65 yrs
- High-dose vaccine = 22% (95% CI 15–29) more effective than the standard-dose vaccine for:
  - prevention of probable influenza infections and
  - influenza hospital admissions

- **Sponsor required confirmatory trial** (n> 30,000) showed clinical benefit of HD vaccine
- Relative efficacy HD vs Standard = 24.2% (95%CI, 9.7-36.5)

- **Conclusion:** Good agreement between the two studies – FDA-CMS RWE study much greater study size and power

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee, Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Methods In this retrospective cohort study, we identified Medicare beneficiaries aged 65 years and older who received high-dose or standard-dose inactivated influenza vaccines from community pharmacies that offered both vaccines during the 2012–13 influenza season. Outcomes were defined with billing codes on Medicare claims. The primary outcome was probable influenza infection, defined by receipt of a rapid influenza test followed by dispensing of the neuraminidase inhibitor oseltamivir. The secondary outcome was a hospital or emergency department visit, listing a Medicare billing code for influenza. We estimated relative vaccine effectiveness by comparing outcome rates in Medicare beneficiaries during periods of high influenza circulation. Univariate and multivariate Poisson regression models were used for analyses.

Findings Between Aug 1, 2012 and Jan 31, 2013, we studied 929 730 recipients of high-dose vaccine and 1 615 545 recipients of standard-dose vaccine. Participants enrolled in each cohort were well balanced with respect to age and presence of underlying medical disorders. The high-dose vaccine (1·01 outcomes per 10 000 person-weeks) was 22% (95% CI 15–29) more effective than the standard-dose vaccine (1·30 outcomes per 10 000 person-weeks) for prevention of probable influenza infections (rapid influenza test followed by oseltamivir treatment) and 22% (95% CI 16–27%) more effective for prevention of influenza hospital admissions (0·86 outcomes per 10 000 person-weeks in the high-dose cohort *vs* 1·10 outcomes per 10 000 person-weeks in the standard-dose cohort).

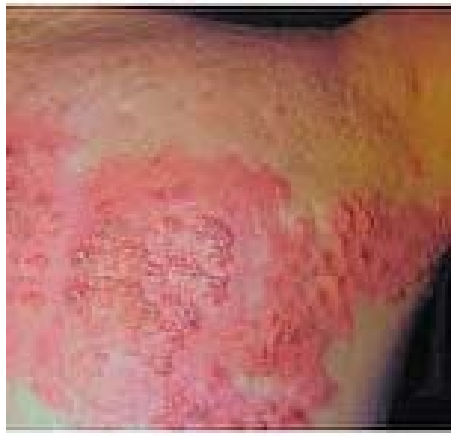
Interpretation Our retrospective cohort study in US Medicare beneficiaries shows that, in people 65 years of age and older, high-dose inactivated influenza vaccine was significantly more effective than standard-dose vaccine in prevention of influenza-related medical encounters. Additionally, the large population in our study enabled us to show, for the first time, a significant reduction in influenza-related hospital admissions in high-dose compared to standard-dose vaccine recipients, an outcome not shown in randomised studies. These results provide important new information to be considered by policy makers recommending influenza vaccinations for elderly people

MERCK Zostavax for Herpes Zoster (HZ)

Pre-approval efficacy trials:

- **Shingle Prevention Study (SPS)**
  - Double-blind, placebo-controlled (DBPC) RCT 38,000 individuals > 60
  - Median follow-up 3.1 years - reduction in HZ incidence 51%

- **ZOSTAVAX Efficacy and Safety Trial (ZEST)**
  - DBPC RCT of 22,200 individuals 50-59 years of age
  - Median follow-up 1.3 years - reduction in HZ incidence 70%



MERCK Zostavax for Herpes Zoster (HZ) *(cont.)*

Post Marketing Commitment to study long-term efficacy in ages 50-59

- Prospective observational study run by Kaiser Permanente Northern California
- Data on 1.3 million members, with over 350,000 individuals who received Zostavax and 100,000 individuals with more than 5 years follow up post vaccination
- Study is ongoing and will continue through 2023

Clinical studies section of labeling updated:

- In assessing effectiveness adjustments made for calendar time, age, sex, race/ethnicity, healthcare resource utilization, comorbid conditions, and immunocompromise status
- Vaccine effectiveness (VE) against HZ for 50-59 over first 3 years following vaccination was 60%
- For individuals 60-69, 70-79 and 80 or older average VE against 49%, 46% and 44% respectively.

Summary

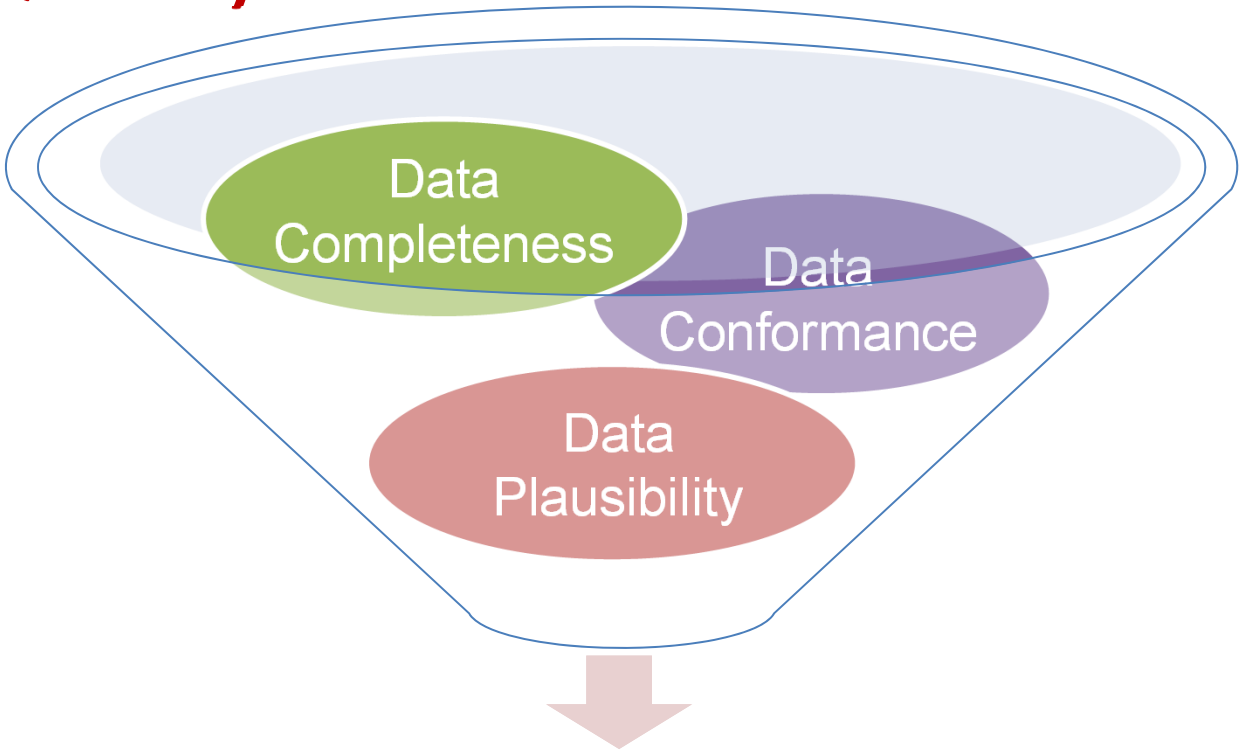
- CBER uses a number of active surveillance systems to evaluate biologic product safety and effectiveness
- Launched BEST in 2017: a new active surveillance system for biologic products
  - Incorporates multiple large sources of EHR
  - Improved access to EHR provides
  - Reduced data lag
- BEST and other active surveillance systems can be successfully used for RWE generation

Acknowledgements

- CBER Sentinel Central Team
- Office of Biostatistics and Epidemiology
- CBER product offices: OVRR, OBRR, OTAT
- CMS Colleagues
- CDC and VSD Colleagues
- IBM Global Business Services, IBM Watson Health Team
- Acumen Team
- IQVIA Team
- OHDSI Collaborators
  - Columbia University
  - Regenstrief Institute
  - University of Colorado
  - Cerner
  - University of California Los Angeles
  - Georgia Tech Research Institute
  - Stanford University

Thank You

Data Quality Assessment



Data Quality Assessment Checks