Enhancing Biologics Adverse Event Surveillance via Scalable, FHIR-based Infrastructure

How Does the FDA Use Real World Data and Real-World Evidence?

October 2023

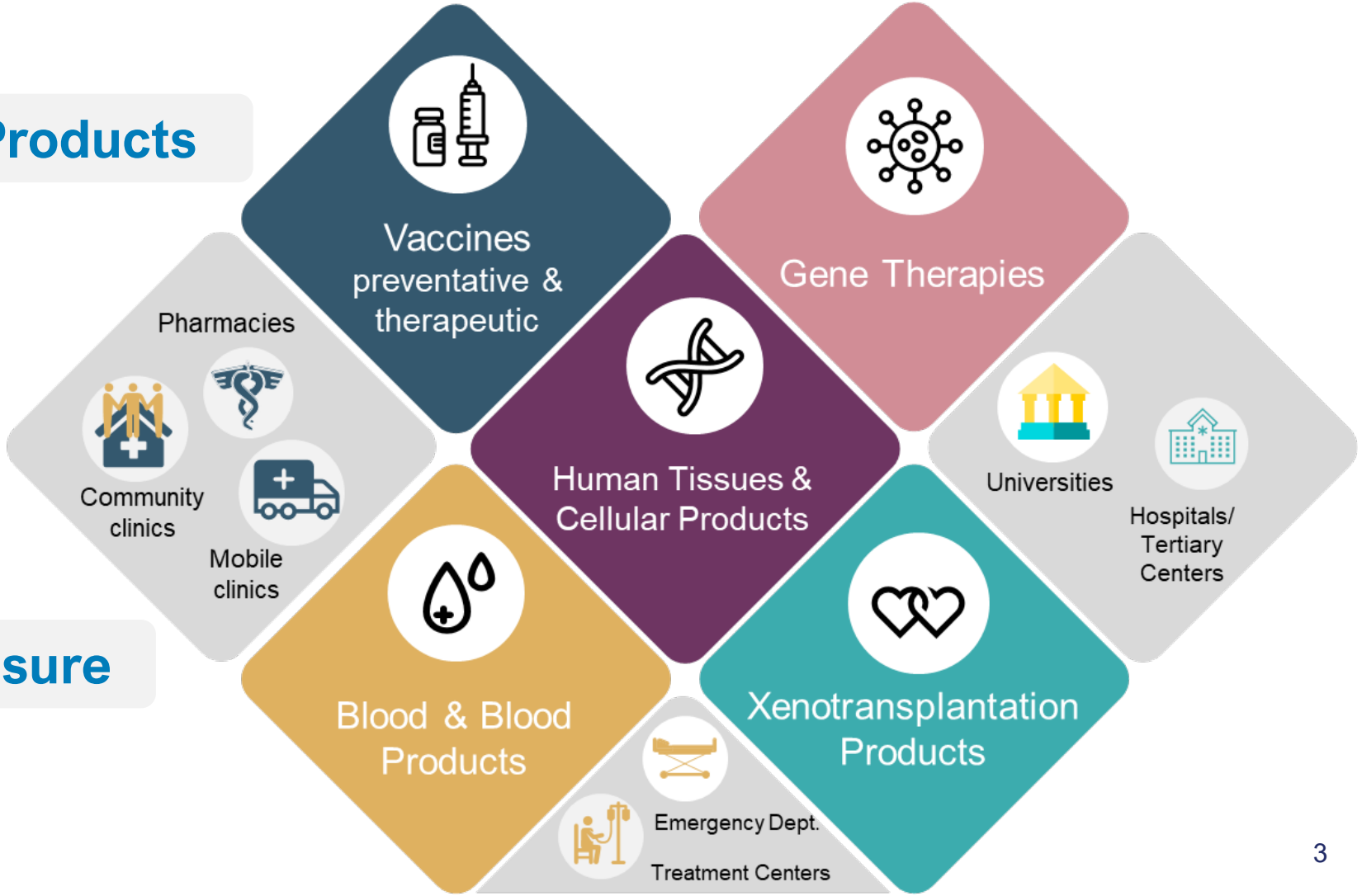
Hussein Ezzeldin, PhD
Analytics and Real-World Evidence Branch (ARWEB)
Division of Analytics and Benefit-Risk Assessment (DABRA)
Office of Biostatistics and Pharmacovigilance (OBPV)
Center for Biologics Evaluation and Research (CBER)
U. S. Food and Drug Administration (FDA)

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



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**

Current

Manual Detection

Individual flagging of potential AEs

Under-recognition of outcomes

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

Automated Detection

Batch detection, more focus on patient care

AI algorithm scores potential cases

Semi-Automated Validation

Evidence integration reduces burden

Flagged and prioritized cases sent for review

Case definition integrated

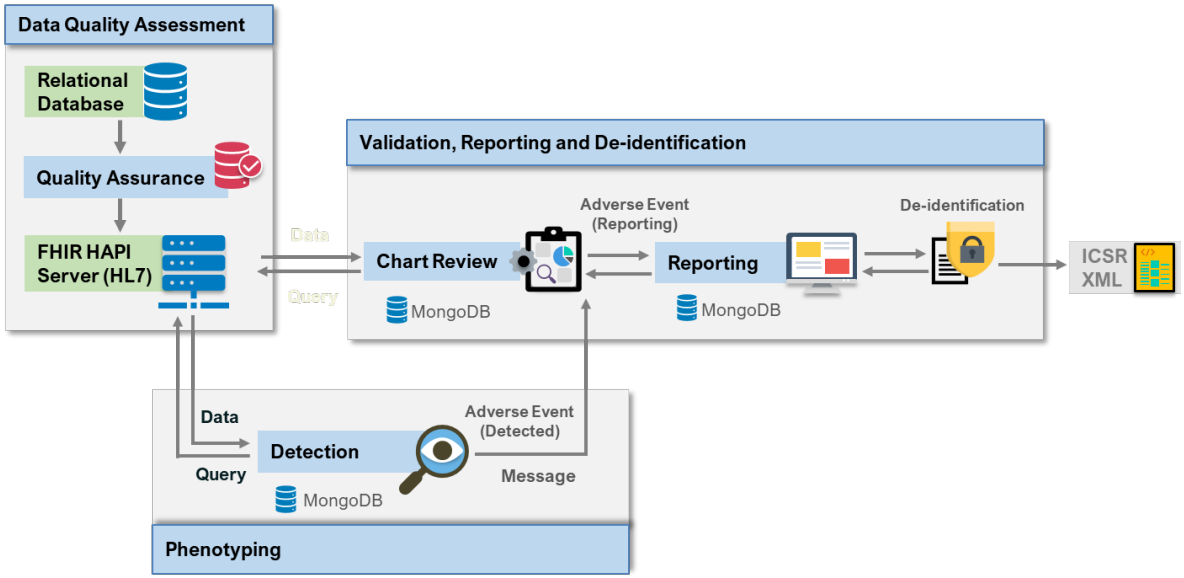
Semi-Automated Reporting

Auto-population of granular ICSR evidence

Generation of evidence-based ICSR narrative

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

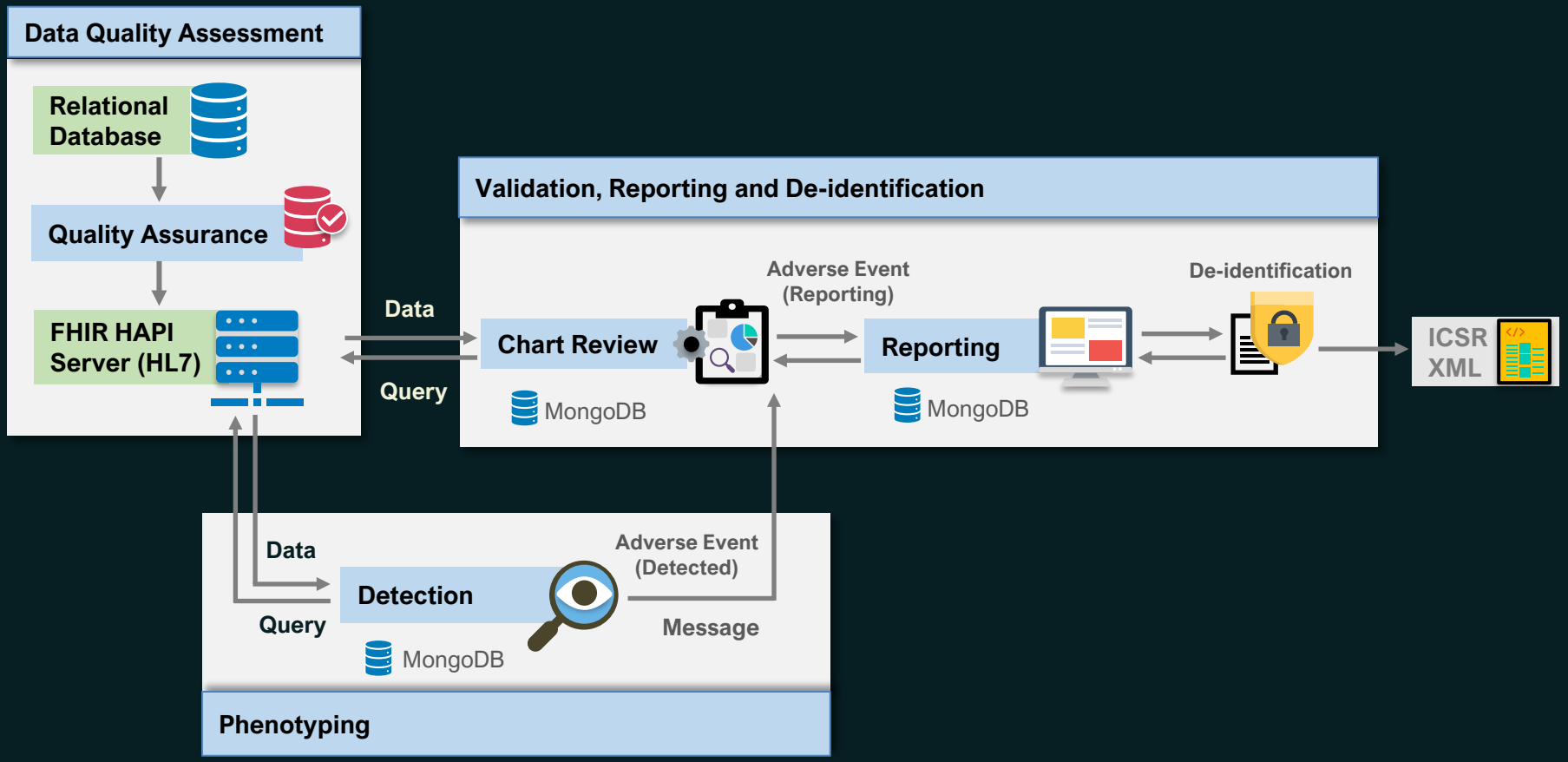
ICSR, individual case safety report



BEST ADVERSE EVENTS REPORTING PIPELINE

BEST 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

Data Quality Assessment

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].

Fit for Purpose & BEST-specific examples

Conformance

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

Are ISBT-128 codes recorded in proper format?

Plausibility

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

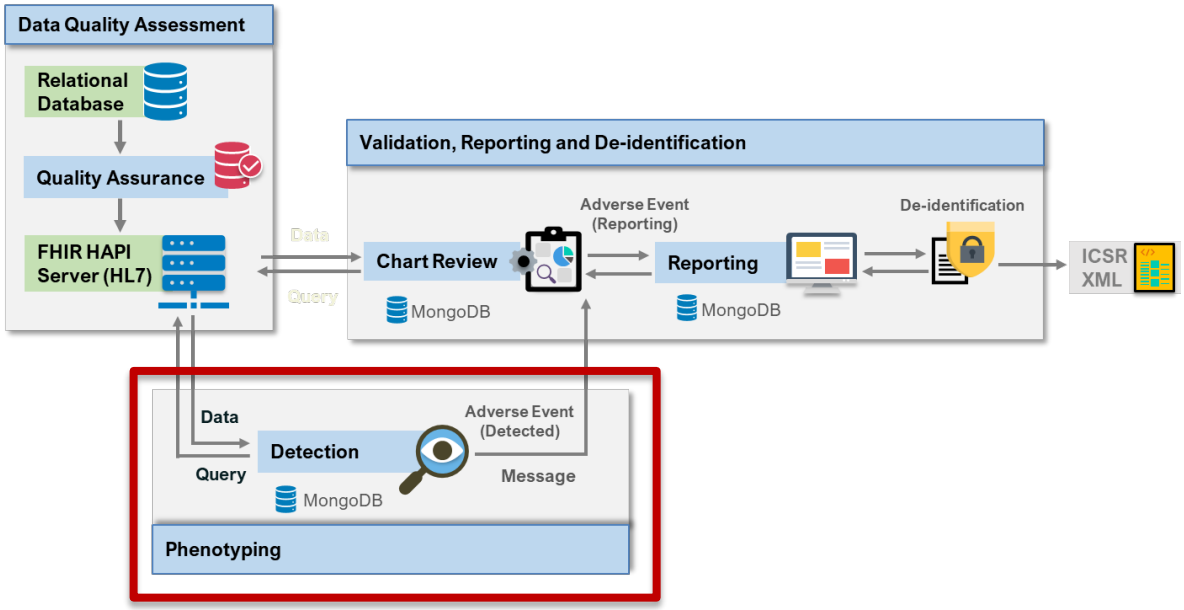
Are transfusion start times realistic or recorded as the discharge datetime?

Completeness

Are variables present? Do they contain all recorded values?

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

[1] Kahn, Michael G., et al. "A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data." *Egems* 4.1 (2016). **[2]** https://ohdsi.github.io/TheBookOfOhdsi/DataQuality.html#DataQuality



BEST PIPELINE: DETECTION

Phenotyping: Overview

1 Simple/Scalable

Dx Codes

DX codes

+ Clean window & Risk window

2 Enhanced

1 Simple/ Scalable + Structured

Vitals Meds Labs

+ Clean window & Risk window

3 Complex

2 Enhanced + Unstructured

Clinical, Discharge, Educational Notes, etc.

+ Clean window & Risk window

Low Complexity, PPV High

High Interoperability Low

Ensure shareability and interoperability (FHIR CQL, OMOP)
PPV, Positive Predicted Value

Phenotyping Library

I. Claims Comparable Algorithms

Detailed logic overview can be found here.

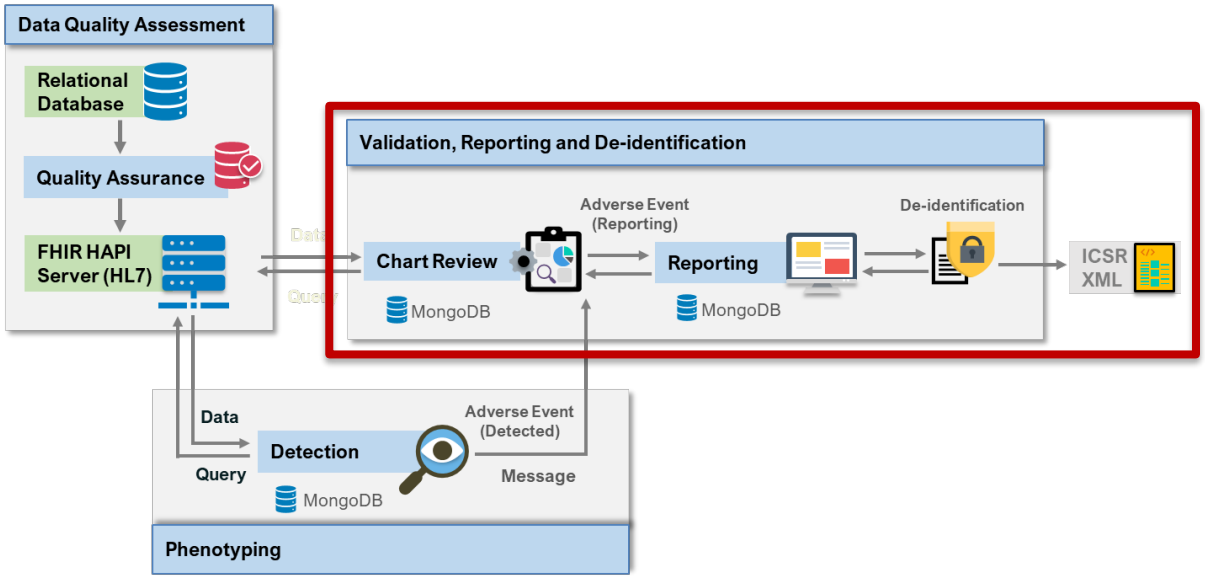
II. Reporting (Structured Data Only) Algorithms

Detailed algorithm logic can be found here.

Available Termsets

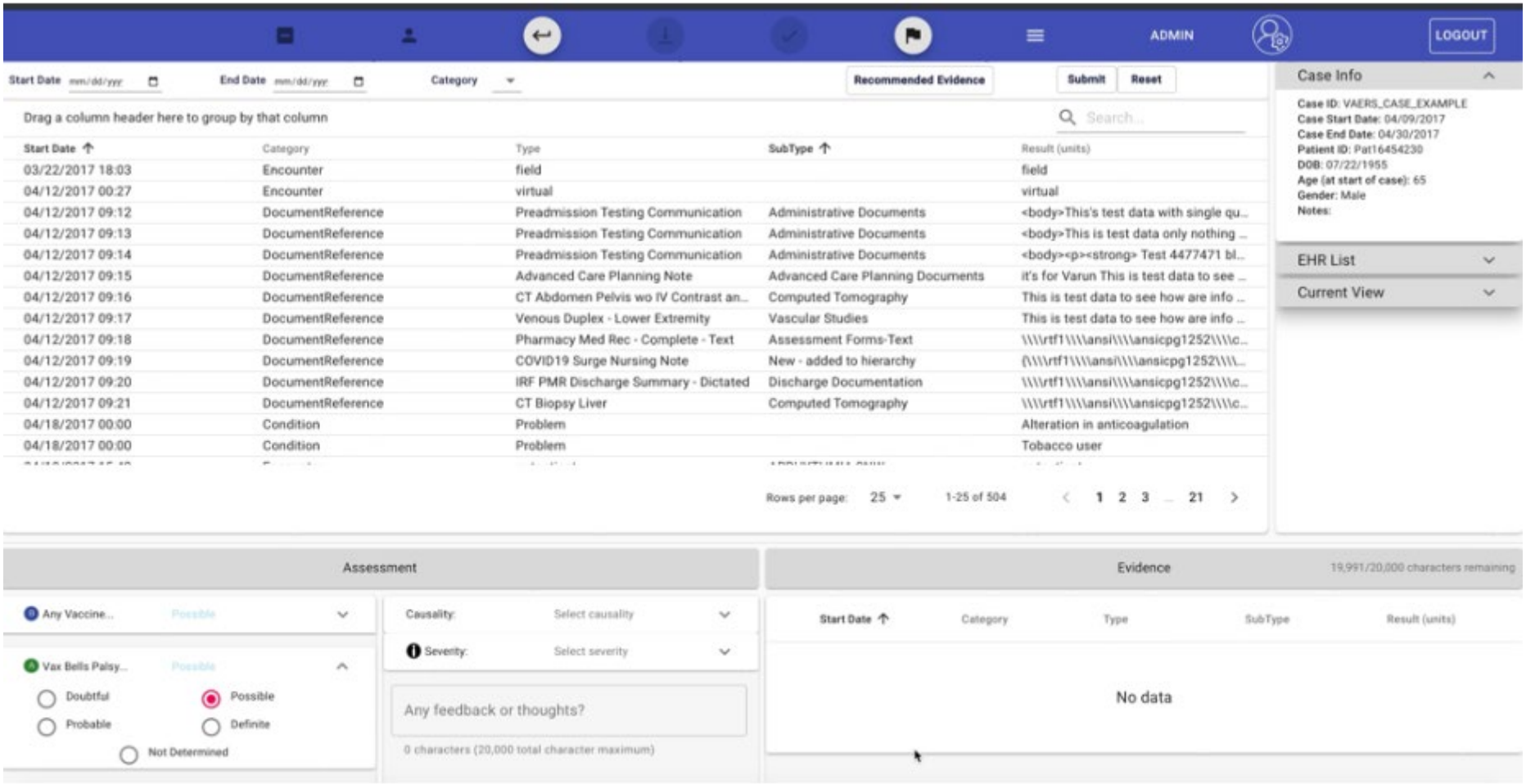
The table below summarizes the termsets available in this repository and the terms included in each phenotype's termset folder. A detailed description of the termsets can be found here.

Phenotype	Terms
Anaphylaxis	Anaphylaxis, Antihistamine H1, Antihistamine H2, Sympathiometic
Bell's Palsy	Facial Palsy, Antivirals, Steroids
Deep Vein Thrombosis	Deep Vein Thrombosis, Vitamin K Antagonists, Radiology, D-Dimer, Anticoagulants, Enzymes, MRA, Direct Factor Xa Inhibitors, Thrombectomy, Vena Cava Filter
Guillain-Barre Syndrome	GBS, Antivirals, CSF Lab Test
Hemorrhagic Stroke	Hemorrhagic Stroke, PCC, Surgeries, MRA, CT Scan, MRI, INR, Platelet Count, PTT
Myocarditis	Myocarditis, Creatine Kinase, Ejection Fraction, Myocardial Band, Troponin, ACE Inhibitors, Anti-Inflammatory, ARBs, Beta-blockers, Vasodilators

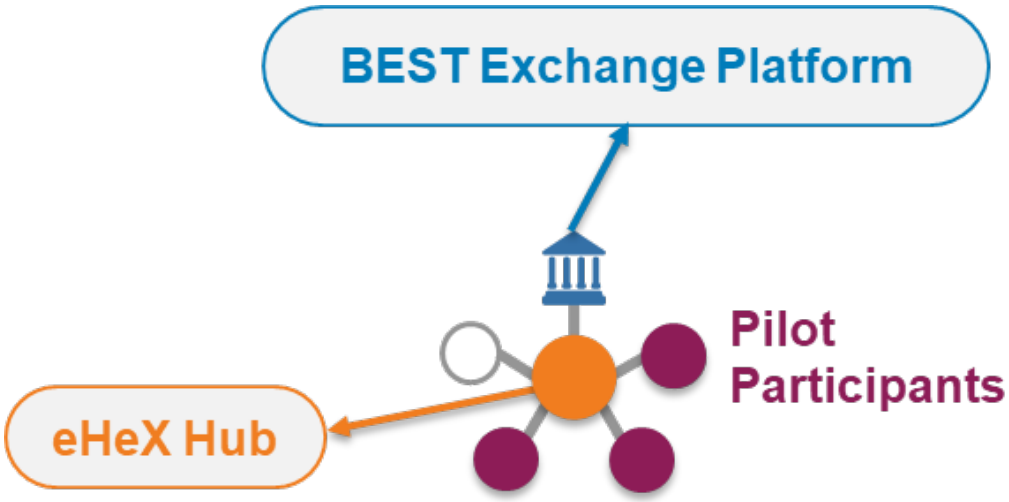


BEST PIPELINE: VALIDATION AND REPORTING

Validation: Chart Review Tool (CRT)

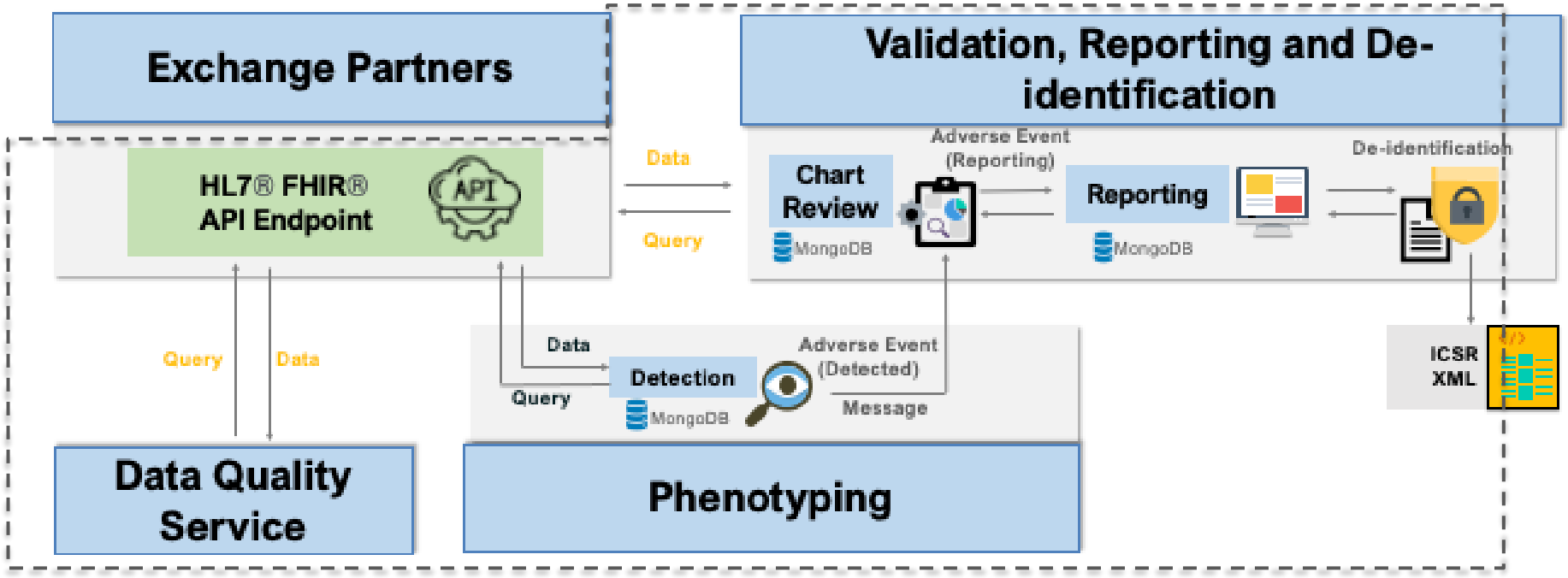


Note: Any images, videos, or other representations of an individual's health record shown on slides is synthetic and does not contain actual patient data.



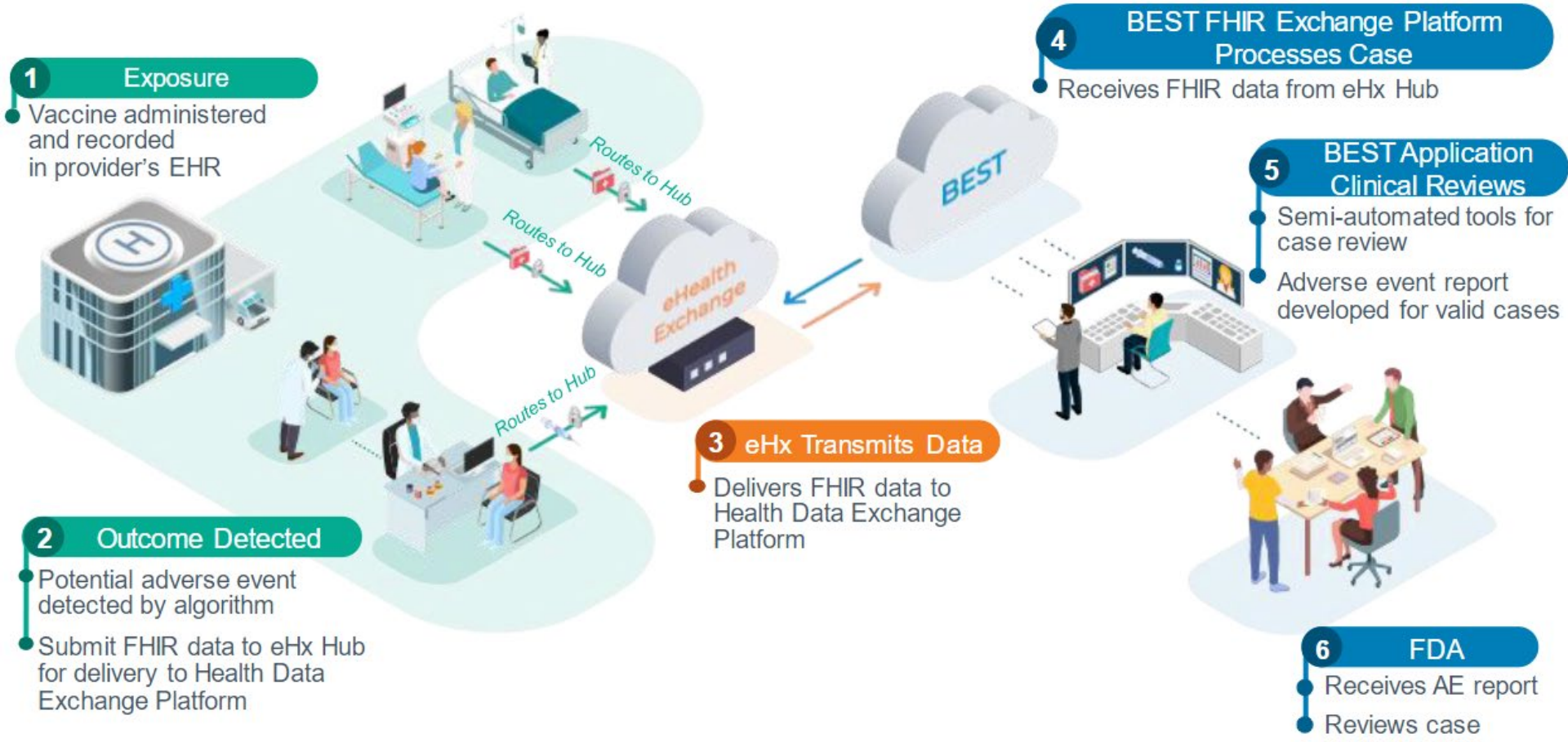
BEST EXCHANGE PLATFORM

BEST Exchange Platform



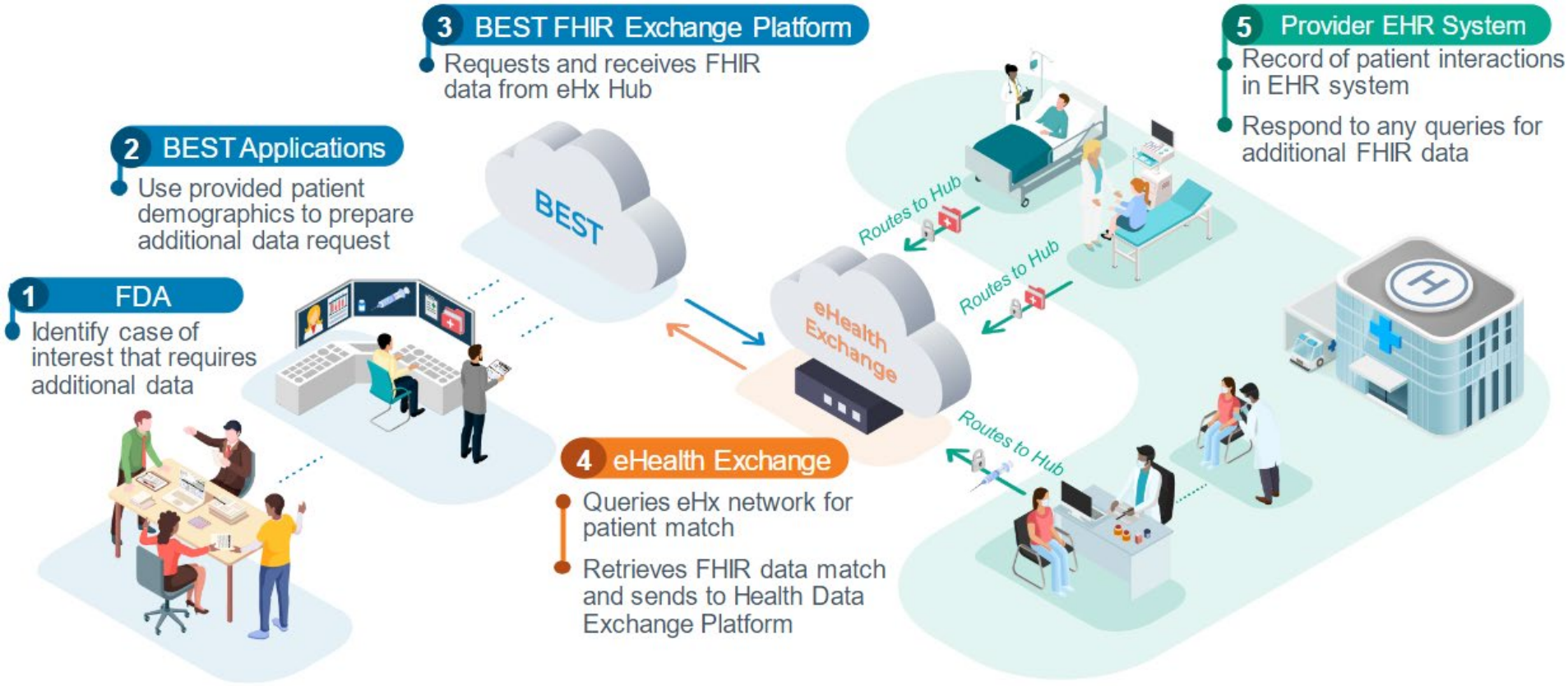
Components of BEST Platform

BEST Exchange Platform, Push Use Case



eHx, eHealth Exchange

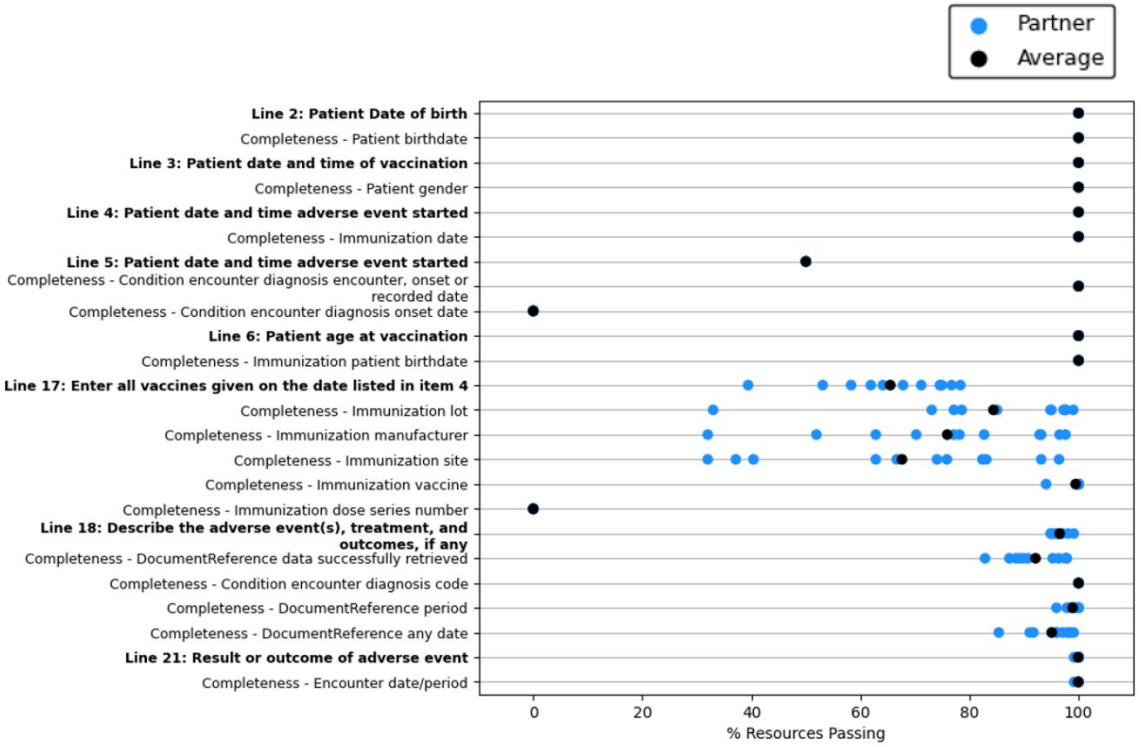
BEST Exchange Platform, *Pull Use Case*



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

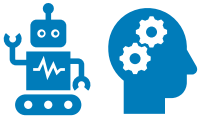


Conclusion and Summary

- 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 trail 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

- *Data Quality Assessment*
- *Detection*
- *Validation and Reporting*

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.

* **F**indability, **A**ccessibility, **I**nteroperability, and **R**euse of digital assets

Acknowledgement

FDA CBER	Barbee Whitaker, Artur Belov, Manette Niu, Jane Mutanga, Brian Hively, Steven Anderson
IBM	Lance Jones, Matthew Deady, Brian Goodman, Haley Huang, Deepa Youssef, Kathryn Matto
eHx	Jay Nakashima, Eric Heflin, Mike Y and Mike M

THANK YOU!
QUESTIONS??

hussein.ezzeldin@fda.hhs.gov