Statistical methods for improving post-licensure vaccine safety surveillance

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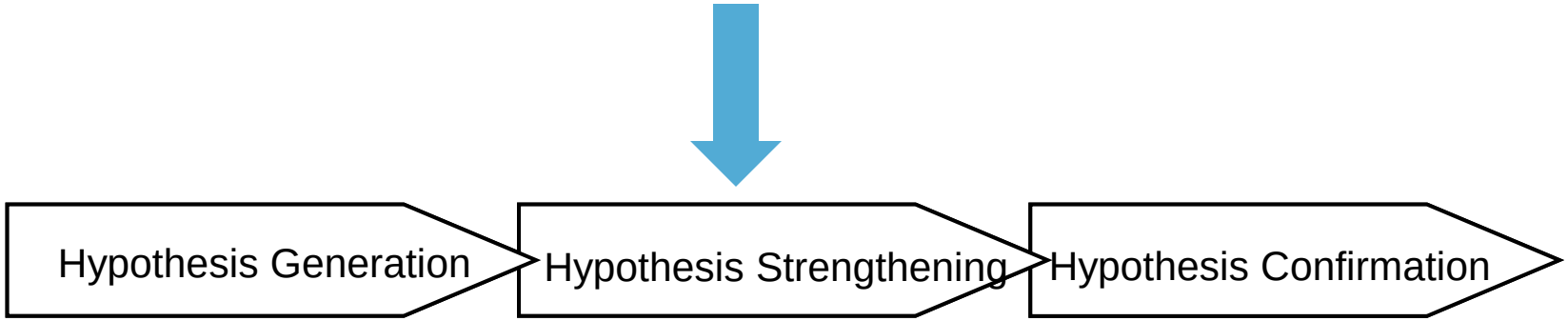
FDA-CBER Biologics Effectiveness & Safety Seminar Series
November 20, 2024

My work's aim is to fill the gap in traditional post-licensure systems



Hypothesis Generation	Hypothesis Strengthening	Hypothesis Confirmation
Data mining of passive spontaneous reports (VAERS) to identify possible associations between *many* vaccine & adverse event pairs (100's, 1000's)	Proactive sequential surveillance to *rapidly* assess the magnitude of suspected associations between several target vaccine-event pairs.	Phase IV trial or rigorous epidemiological cohort study to establish or refute causality between a specific product & adverse event.
Fast, but lower quality data & not targeted	Rapid assessment of targeted high-quality outcomes ("just right")	Higher quality data, but slower & more narrow

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More specifically…

Problem

To rapidly & accurately identifying safety concerns after a new vaccine is licensed or authorized for emergency use

Setting

Large, multi-site claims & electronic health record (EHR) data (i.e., observational data not collected for research)

Statistical challenges

- Misclassification of safety outcomes (using ICD codes)
- Adapting sequential methods (from trials) to this context
  - Identifying an appropriate sequential design
  - Minimizing impacts of an uncontrolled setting

Who are we at KPWHRI?

- **Kaiser Permanente Washington Health Research Institute**
  - Established in 1983 (as Group Health Research Institute)
  - Became KPWHRI via acquisition in 2015
  - Public-interest research center in downtown Seattle
  - Improves health, well-being & health equity for all communities through collaborative research & evaluation
  - Funded primarily (78%) by federal external grants and contracts from NIH, PCORI, FDA, CDC, … (~$67M in 2023)
  - ~85 physician and public health scientists
  - ~275 research support staff
  - Areas of study include biostatistics, epidemiology, mental and behavioral health, preventive medicine, health care delivery, and community health and evaluation
  - Academic group embedded within KPWA
- **Kaiser Permanente Washington (KPWA)**: non-profit health system in Washington State providing health care & insurance coverage for >700,000 people (1 of KP's 8 regions in the U.S.)

Biostatistics Division at KPWHRI

- 10 PhD-level Investigators, all Univ of WA affiliates
- 10 Collaborative Biostatisticians (PhD/MS-level)
- Our role: develop, evaluate & apply methods that…
  - are inspired by scientific collaboration
  - generate actionable evidence from complex health data to address pressing scientific questions
- Proud home to many ASA…
  - Fellows: Pam Shaw, Susan Shortreed, Jen Nelson
  - Committee of Presidents of Statistical Societies Emerging Leaders: Jennifer Bobb, Yates Coley

Biostatistics investigators

Collaborative biostatisticians

Examples of the work we do: Statistical & Clinical Areas

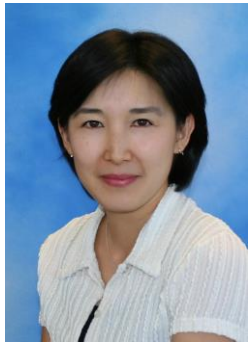
Using clinical data generated during routine health care:
-medical charts & notes
-electronic health records
-health surveys
-administrative claims
-imaging reports
-laboratory values

- Pragmatic trial design
- Longitudinal / clustered data analysis
- Machine and statistical learning
- Survival analysis
- Causal inference
- Risk modeling
- Measurement error
- Missing data

- Substance use disorder
- Cancer prevention
- Mental health
- Drug & vaccine safety
- Aging, dementia, and Alzheimer's
- Equity in health care
- Other diseases and health conditions

UW Biostatistics Students & Alums involved in vaccine safety at KPWHRI

Jennifer Nelson
1999



Onchee Yu
1999

Melissa Anderson
1996

Rob Wellman
2008

Eric Johnson
2008

Shanshan Zhao
2012

Kelly Stratton
2013

Yates Coley
2014

Clara Dominguez
2015

Xu Shi
2017

Tracy Marsh
2017

Brian Williamson
2019

Kendrick Li
2021

Chloe Krakauer
2021

Iris Emerman
2022

Ernesto Ulloa
2022

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Outline

- Introduce the data setting: national multi-site post-licensure medical product safety surveillance systems
  - Vaccine Safety Datalink (CDC)
  - Sentinel Initiative (FDA)
- Provide some vaccine safety examples
- Discuss methodological challenges (& some solutions)
- Where do we go from here?

Big (Health Care) Data 101

- **What is it?**
  - Data collected by public and private organizations for registration, transaction and record keeping during the delivery of health care
  - Also called administrative, clinical, or electronic health care data
- **How does it get generated?**
  - Health care system encounters (outpatient, inpatient, pharmacy) create electronic claims to the payer for reimbursement
  - Paper or electronic health record (EHR) captures standard medical and clinical data gathered in one provider's office
- **What kind of information is collected**?
  - Diagnosis codes (ICD-10), procedure codes (CPT/HCPCS), dates
  - Pharmacy dispensings (drug name, dates), immunization records
  - Patient demographics, care setting, type of provider, vitals…
  - Test results from laboratory, radiology, other specialty visits
  - Unstructured clinical notes & text

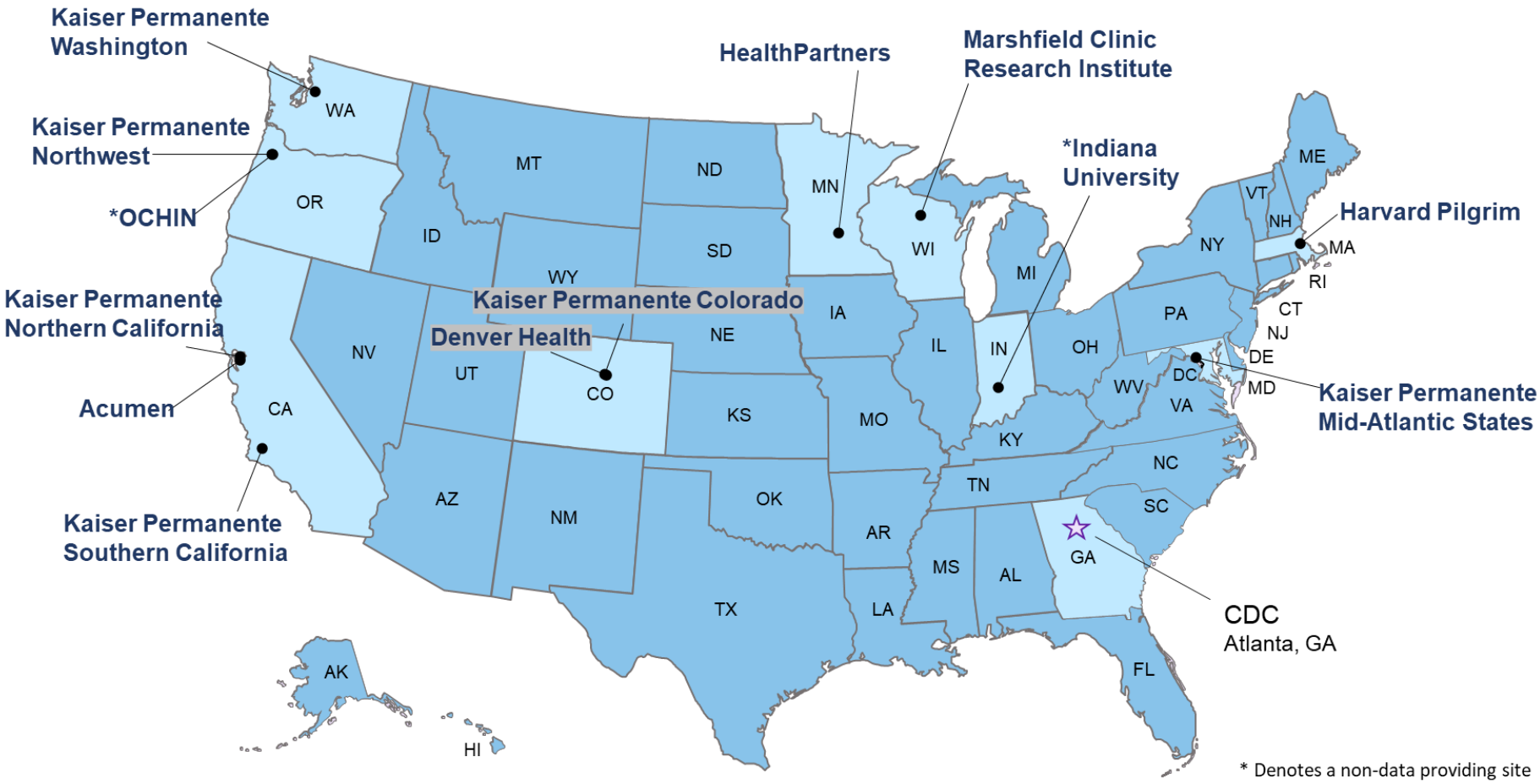
Content courtesy of Denise Boudreau PhD, KPWHRI

Big (Health Care) Data 101

- **How can it be re-purposed for research?**
  - Link data across various sources within a person
  - Commonly define these data elements (common data model)
  - Link them across data partners for multi-site research
  - An integrated picture of health/healthcare emerges for large cohorts
- **Is this a new idea?**
  - No (Health Care Systems Research Network has been used for decades for research) but…
  - Their use has been rapidly expanding with development of new national multi-purpose big data networks (PCORnet, NIH Collab)
- **Is this a good idea?**
  - Yes, we need efficient and cost-effective ways to fill evidence gaps left by traditional RCTs and observational studies
  - But one should proceed with caution & deep knowledge of the data

Content courtesy of Denise Boudreau PhD, KPWHRI

Vaccine Safety Datalink (VSD)



12 participating integrated healthcare organizations + CDC

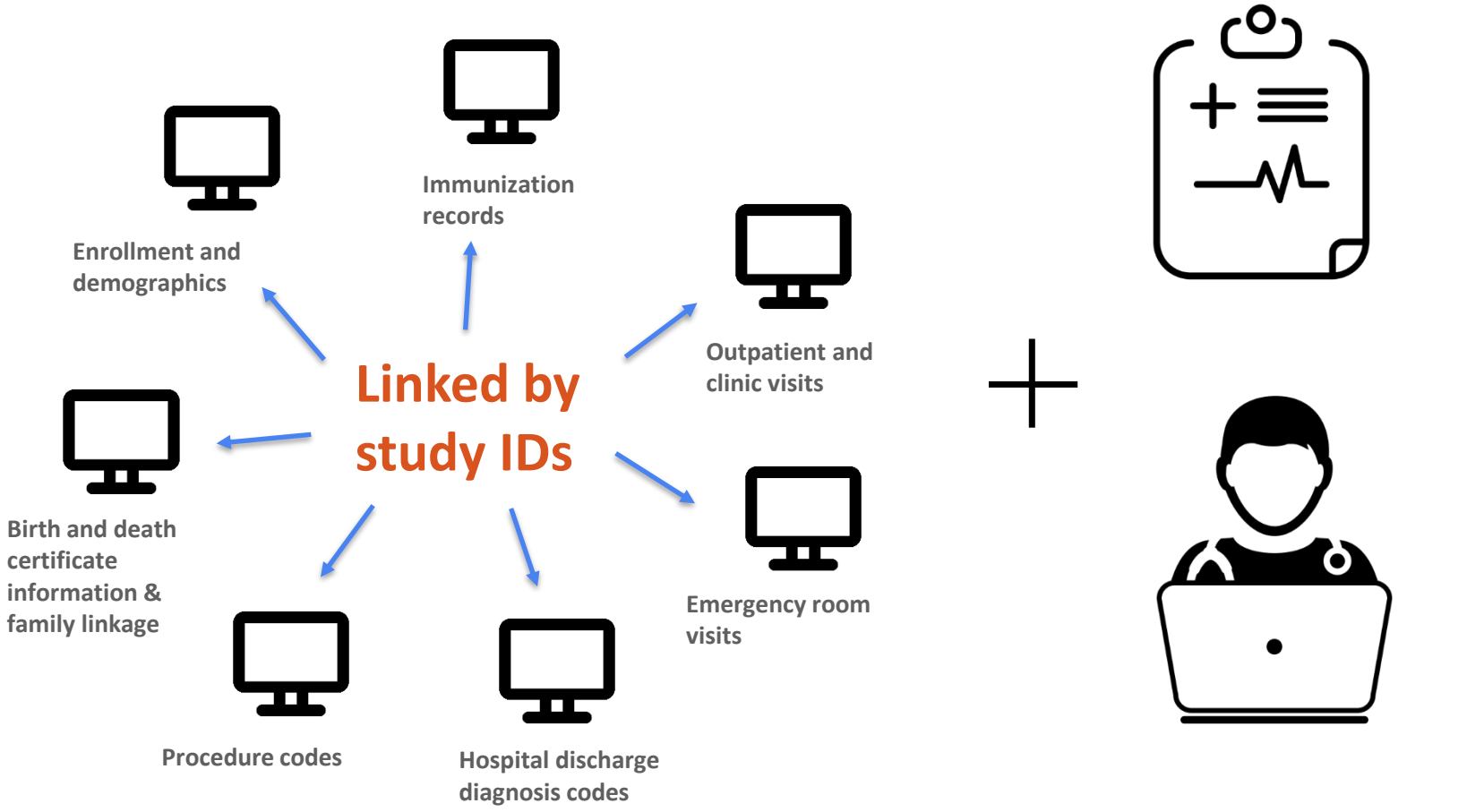
https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vsd/index.html

Vaccine Safety Datalink (VSD)

- Established in 1990
- A collaboration between CDC & numerous integrated healthcare organizations
- Captures administrative & clinical data and uses it for research
- Have assembled vaccine, medical care & demographic data on over 12.1 million persons per year (~3.7% of U.S.)
- Prior to 2005, mostly studied links between vaccines & health outcomes using traditional retrospective observational studies
- In 2005, weekly data updating facilitated active surveillance

Slide courtesy of Dr. Tom Shimabukuro at the Centers for Disease Control and Prevention

VSD electronic information + chart review



Images created by Wilson Joseph, Megan Mitchell, Ananth, and Iga from the noun project

Slide courtesy of Dr. Tom Shimabukuro at the Centers for Disease Control and Prevention

Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,‡ Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,* Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team*

Background: Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect in prelicensure studies and require monitoring after introduction of the agent in large populations. Sequential testing procedures are needed to detect vaccine or drug safety problems as soon as possible after introduction.

Objective: To develop and evaluate a new real-time surveillance system that uses dynamic data files and sequential analysis for early detection of adverse events after the introduction of new vaccines.

Research Design: The Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink Project developed a real-time surveillance system and initiated its use in an ongoing study of a new meningococcal vaccine for adolescents. Dynamic data files from 8 health plans were updated and aggregated for analysis every week. The analysis used maximized sequential probability ratio testing (maxSPRT), a new signal detection method that supports continuous or time-period analysis of data as they are

Conclusions: Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

Key Words: vaccine safety, active surveillance, sequential analysis, meningococcal vaccine, drug safety

(*Med Care* 2007;45: S89–S95)

Concerns about the safety of vaccines and drugs introduced in recent years have highlighted the need to enhance systems for early detection of potential adverse events. Uncommon but serious adverse events have led to the withdrawal of both biologic and pharmacologic agents from the market. Examples include the discontinuation of

FDA's Sentinel Initiative built on this success

"…a national electronic system that will transform FDA's ability to track the safety of drugs, biologics, and medical devices once they reach the market."

"…aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events."

"…enables FDA to actively query diverse automated healthcare data holders—like EHR systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely."

http://www.fda.gov/Safety/FDAsSentinelInitiative

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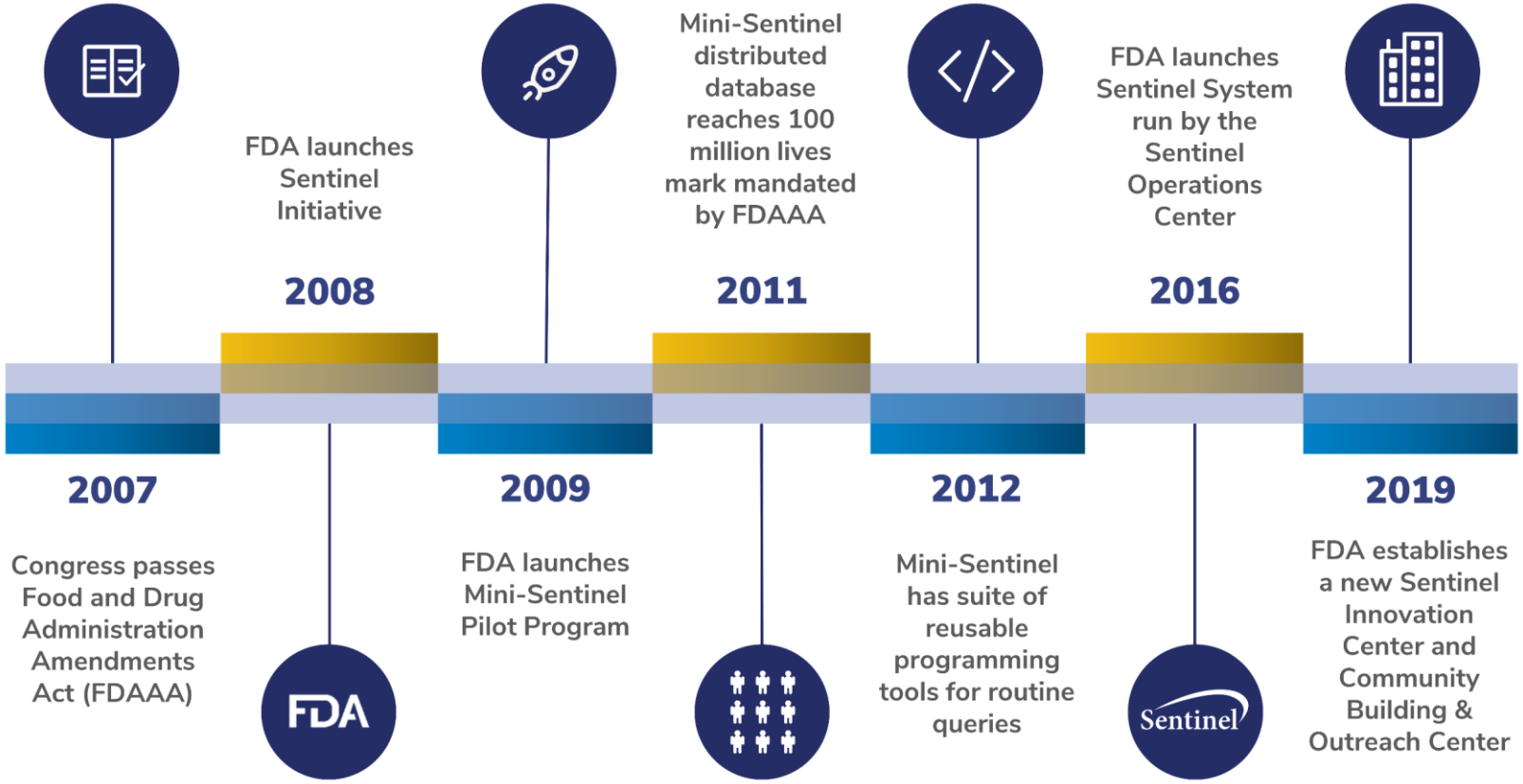
Sentinel timeline



https://www.sentinelinitiative.org/about

Slide courtesy of Dr. Darren Toh at Harvard Medical School

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Sentinel collaboration

Slide courtesy of Dr. Darren Toh at Harvard Medical School

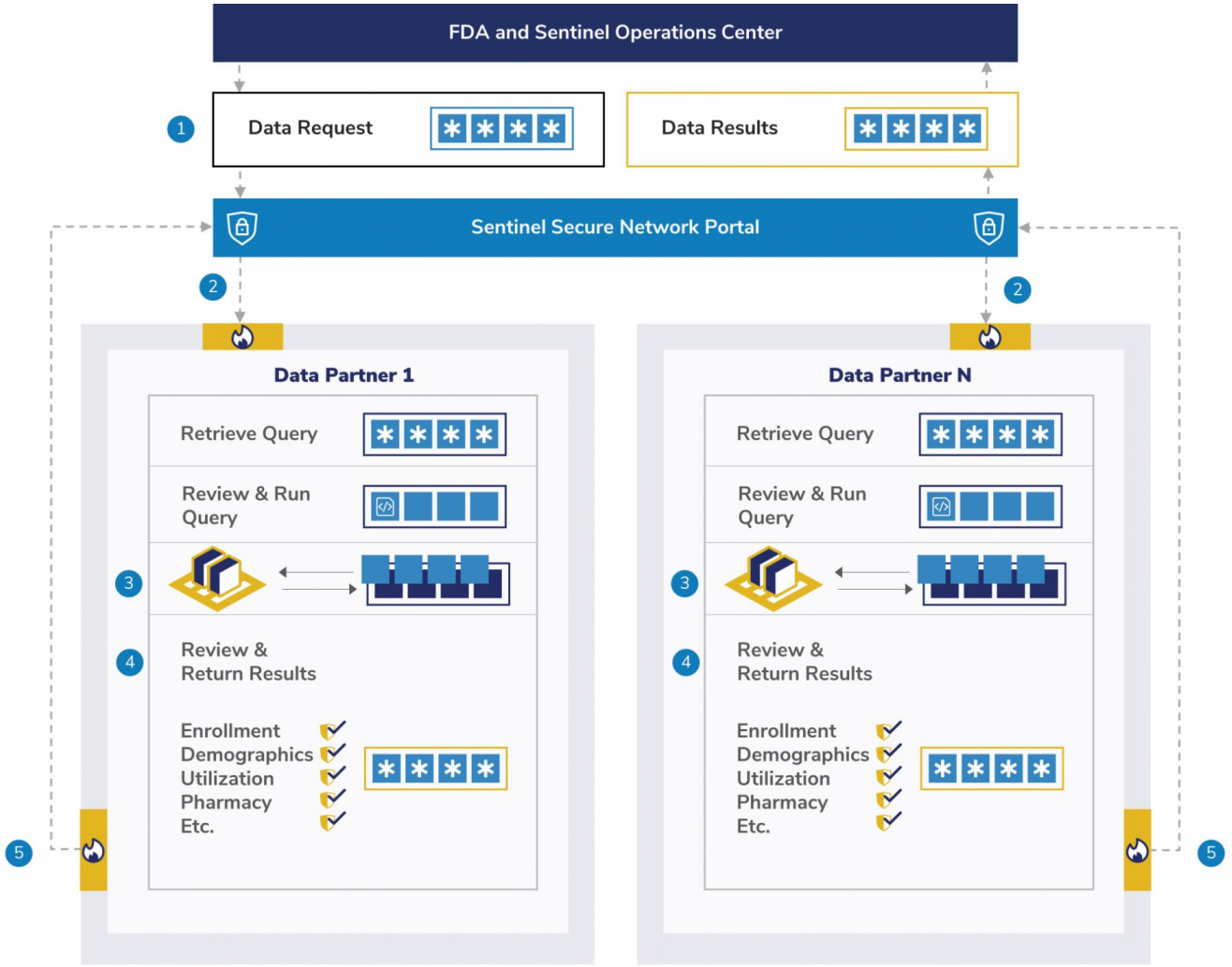
Sentinel distributed data environment

1. FDA data request sent to Data Partners via FISMA-compliant secure network portal
2. Data Partners retrieve query
3. Data Partners review and run query against their local data behind their firewalls
4. Data Partners review results for accuracy and privacy compliance
5. Data Partners return de-identified results to SOC via secure portal

Firewall

Local Data

Privacy Compliance



Slide courtesy of Dr. Darren Toh at Harvard Medical School

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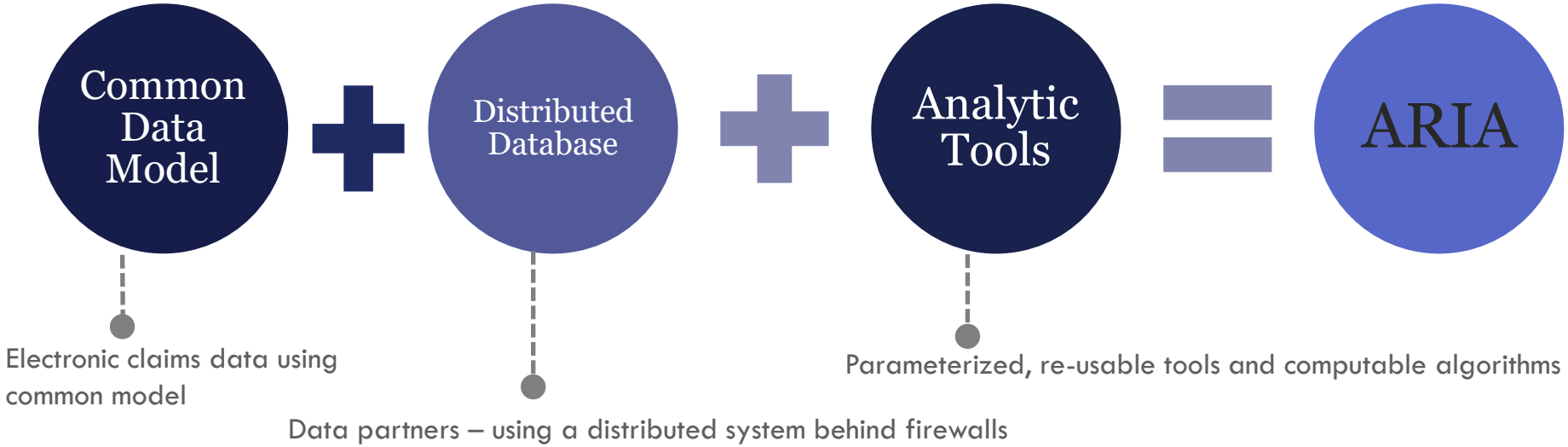
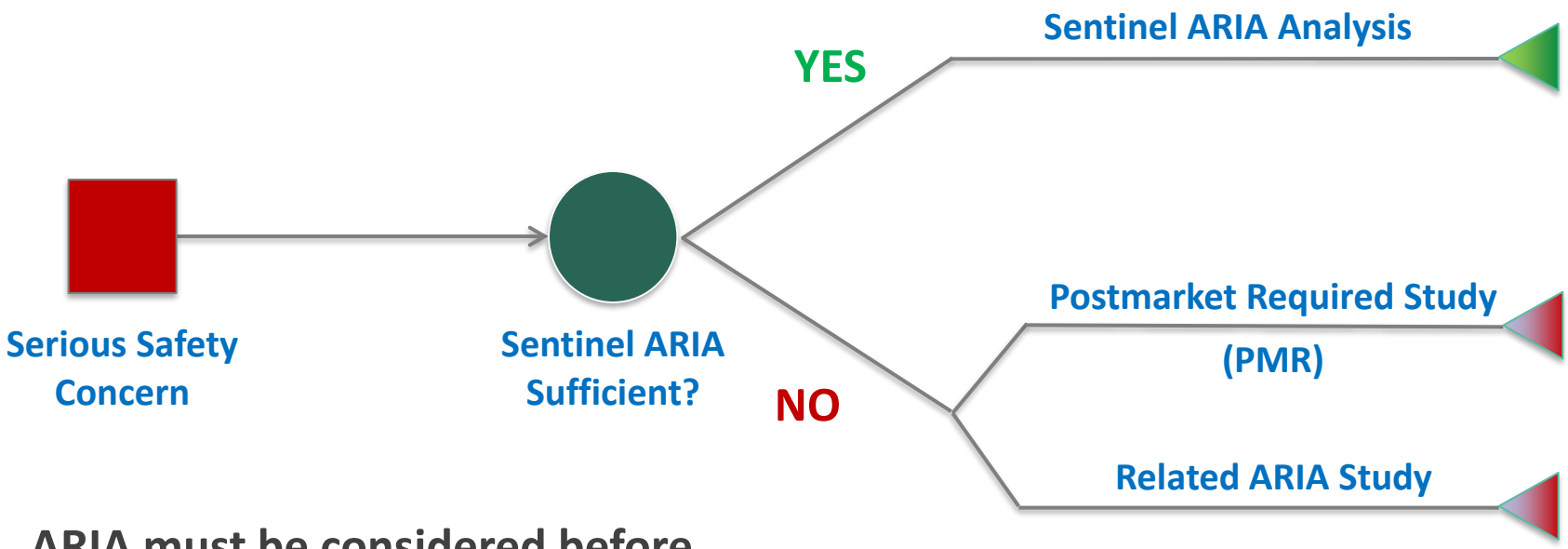
Sentinel's process is known as ARIA

ARIA: Active Risk Identification and Analysis system



Slide courtesy of Michael Nguyen at the FDA

When is the ARIA Process Needed?



ARIA must be considered before a sponsor PMR can be issued

Slide courtesy of Michael D. Nguyen, M.D., former FDA Sentinel Program Lead

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Selected examples of prospective surveillance within VSD since 2005

Meningococcal (Menactra®) – Guillain-Barre Syndrome (GBS), others (Harvard)

Rotavirus (Rotateq®, Rotarix®) – intussusception, others (Marshfield)

MMRV – seizures, fever, others (N California Kaiser)

Tdap -- seizures, other outcomes (Health Partners)

HPV4 & 9 (Gardasil®)– seizures, syncope, stroke, VTE (Kaiser NW, CDC, Marshfield)

Seasonal & H1N1 Influenza – conducted annually (Harvard, CDC)

DTaP-IPV (Kinrix®) – seizures, stroke, GBS, others (Kaiser Colorado)

DTaP-IPV/Hib (Pentacel®) – fever, seizure, allergic reactions (Kaiser Washington)

PCV13 – seizures, Kawasaki disease, others (S California Kaiser)

Herpes Zoster (Shingrix®) – stroke, MI, GBS, others (Kaiser Washington)

COVID-19 – anaphylaxis, myocarditis, MI, many others (N California Kaiser)

CDC Home | Search | Health Topics A-Z

MMWR
Weekly
March 14, 2008 / 57(10);258-260

Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine

On February 27, 2008, new information was presented to the Advisory Committee on Immunization Practices (ACIP) regarding the risk for febrile seizures among children aged 12--23 months after administration of the combination measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®, Merck & Co., Inc., Whitehouse Station, New Jersey). This report summarizes current knowledge regarding the risk for febrile seizures after MMRV vaccination and presents updated ACIP recommendations that were issued after presentation of the new information. These updated recommendations remove ACIP's previous preference for administering combination MMRV vaccine over separate injections of equivalent component vaccines (i.e., measles, mumps, and rubella [MMR] vaccine and varicella vaccine).

The combination tetravalent MMRV vaccine was licensed by the Food and Drug Administration (FDA) on September 6, 2005, for use in children aged 12 months--12 years (*1*). MMRV vaccine can be used in place of trivalent MMR vaccine and monovalent varicella vaccine to implement the recommended 2-dose vaccine policies for prevention of measles, mumps, rubella, and varicella (*1*, *2*). The first vaccine dose is recommended at age 12--15 months and the second at age 4--6 years.

In MMRV vaccine prelicensure studies, an increased rate of fever was observed 5--12 and 0--42 days after the first vaccine dose, compared with administration of MMR vaccine and varicella vacci
visit (*3,4*). Because of the known association between fever and febrile se
Merck initiated postlicensure studies to better understand the risk for febrile seizure
with MMRV vaccination.

The Vaccine Safety Datalink (VSD),* which routinely monitors vaccine safety by nea
using computerized patient data, detected a signal of increased risk for seizures of a
children aged 12--23 months after administration of MMRV vaccine compared with a
vaccine (many children also received varicella vaccine). When children who received

COVID-19 Vaccination
Product Info by U.S. Vaccine +
Interim Clinical Considerations –
Use of COVID-19 Vaccines in the U.S.
Use of COVID-19 Vaccines in the U.S.: Appendices
Myocarditis and Pericarditis Considerations
Provider Requirements and Support
Vaccine Recipient Education +
Health Departments
6 Things to Know
Vaccinate with Confidence +

Clinical Considerations: Myocarditis and Pericarditis after Receipt of COVID-19 Vaccines Among Adolescents and Young Adults

Print

Background

Cases of myocarditis and pericarditis have rarely been observed after COVID-19 vaccination in the United States and evidence from multiple vaccine safety monitoring systems in the United States and around the globe supports a causal association between mRNA COVID-19 vaccines (i.e., Moderna or Pfizer-BioNTech) and myocarditis and pericarditis.

Myocarditis is inflammation of the heart muscle and pericarditis is inflammation of the lining outside the heart; myopericarditis is when both myocarditis and pericarditis occur at the same time. In these conditions, inflammation occurs in response to an infection or some other trigger. CDC has published case definitions for myocarditis and pericarditis.

Though cases of myocarditis and pericarditis are rare, when cases have occurred, they have most frequently been seen in adolescent and young adult males within 7 days after receiving the second dose of an mRNA COVID-19 vaccine; however, cases have also been observed in females, in other age groups, and after other doses.

The severity of myocarditis and pericarditis cases can vary; most patients with myocarditis after mRNA COVID-19 vaccination have experienced resolution of symptoms by hospital discharge. CDC has published studies with clinical

American Journal of Epidemiology

Vol. 177, No. 2
DOI: 10.1093/aje/kws317
Advance Access publication:
January 4, 2013

Practice of Epidemiology

Adapting Group Sequential Methods to Observational Postlicensure Vaccine Safety Surveillance: Results of a Pentavalent Combination DTaP-IPV-Hib Vaccine Safety Study

Jennifer C. Nelson*, Onchee Yu, Clara P. Dominguez-Islas, Andrea J. Cook, Do Peterson, Sharon K. Greene, W. Katherine Yih, Matthew F. Daley, Steven J. Jacobsen, Nicola P. Klein, Eric S. Weintraub, Karen R. Broder, and Lisa A. Jackson

* Correspondence to Dr. Jennifer C. Nelson, Biostatistics Unit, Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101 (e-mail: nelson.jl@ghc.org).

Initially submitted September 7, 2011; accepted for publication March 29, 2012.

To address gaps in traditional postlicensure vaccine safety surveillance and to promote rapid signal identification, new prospective monitoring systems using large health-care database cohorts have been developed. We newly adapted clinical trial group sequential methods to this observational setting in an original safety study of a combination diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), inactivated poliovirus (IPV), and *Haemophilus influenzae* type b (Hib) conjugate vaccine (DTaP-IPV-Hib) among children within the Vaccine Safety Datalink population. For each prespecified outcome, we conducted 11 sequential Poisson-based

VSD Example 1 (Pentacel® vaccine)

- **A combination DTaP-IPV-Hib vaccine** (diphtheria & tetanus toxoids & acellular pertussis adsorbed, inactivated poliovirus, & Haemophilus influenza b)
- **Licensed in 2008** for ages 2, 4, 6 & 15-18 months, to replace separate injections
- **Aim**: To sequentially monitor safety in children aged 6 wks to 2 yrs
- **Historical control design**: Recipients of Pentacel® vs DTaP 2-4 years prior
- **Pre-specified adverse events (AEs)**

AE	ICD-9 Codes	Interval (days)	Visit type
Seizure	345 780.3	0-7	Inpatient ED
Fever	780.6	1-5	All
Serious non-anaphylactic allergic reaction	995.1-2 708.0-1 708.9	1-2	Inpatient ED

- **Potential confounders**: age, gender, VSD site

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American Journal of Epidemiology

Vol. 192, No. 2
https://doi.org/10.1093/aje/kwac170
Advance Access publication:
October 4, 2022

Original Contribution

Active Postlicensure Safety Surveillance for Recombinant Zoster Vaccine Using Electronic Health Record Data

Jennifer C. Nelson*, Ernesto Ulloa-Pérez, Onchee Yu, Andrea J. Cook, Michael L. Jackson, Edward A. Belongia, Matthew F. Daley, Rafael Harpaz, Elyse O. Kharbanda, Nicola P. Klein, Allison L. Naleway, Hung-Fu Tseng, Eric S. Weintraub, Jonathan Duffy, W. Katherine Yih, and Lisa A. Jackson

* Correspondence to Dr. Jennifer C. Nelson, Biostatistics Division, Kaiser Permanente Washington Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101 (e-mail: Jen.Nelson@kp.org).

Initially submitted December 10, 2021; accepted for publication September 30, 2022.

Recombinant zoster vaccine (RZV) (Shingrix; GlaxoSmithKline, Brentford, United Kingdom) is an adjuvanted glycoprotein vaccine that was licensed in 2017 to prevent herpes zoster (shingles) and its complications in older adults. In this prospective, postlicensure Vaccine Safety Datalink study using electronic health records, we sequentially monitored a real-world population of adults aged ≥50 years who received care in multiple US Vaccine Safety Datalink health systems to identify potentially increased risks of 10 prespecified health outcomes, including stroke, anaphylaxis, and Guillain-Barré syndrome (GBS). Among 647,833 RZV doses administered from January 2018 through December 2019, we did not detect a sustained increased risk of any monitored outcome for RZV recipients relative to either historical (2013–2017) recipients of zoster vaccine live, a live attenuated virus vaccine (Zostavax; Merck & Co., Inc., Kenilworth, New Jersey), or contemporary non-RZV vaccine recipients who had an annual well-person visit during the 2018–2019 study period. We confirmed prelicensure trial findings of increased risks of systemic and local reactions following RZV. Our study provides additional reassurance about the overall safety of RZV. Despite a large sample, uncertainty remains regarding potential associations with GBS due to the limited number of confirmed GBS cases that were observed.

VSD Example 2 (Shingrix® vaccine)

- **A recombinant zoster vaccine** to prevent herpes zoster (i.e., shingles)
- **Licensed in 2017**, a 2-dose series 2+ months apart for adults 50 years and older, to replace (live attenuated virus vaccine) Zostavax
- **Aim**: To sequentially monitor safety following Shingrix
- **Historical control design**: Recipients of Shingrix vs Zostavax in 5 years prior
- **Pre-specified 10 primary and 11 secondary adverse events (AEs)**
  - Primary: MI, stroke, Bell's palsy, anaphylaxis, GBS
  - Secondary: systemic and local reactions, eye-related diseases
  - Defined by ICD-9/10 dx codes
- **Potential confounders**: age, gender, VSD site, comorbidities, health care utilization (healthy users)

Sequential design and analysis

Pentacel® Study	Shingrix® Study
Frequency of testing (data accruing weekly)	
1st test at 1 year (~33,000 doses as of Sep 2009) 11 subsequent tests, equally-spaced based on dose	1st test at 6 months (~56,000 doses as of Jun 2018) 18 subsequent monthly tests
Statistical target / Test statistic / confounder control	
LRT (H_0: RR=1 vs H_A: RR>1) Used site, gender, & age-based historical AE rates to compute expected counts	LRT (H_0: RR=1 vs H_A: RR>1) Used site, gender, age and comorbidity-based historical AE rates to compute expected counts
Signaling threshold	
Flat over time (Pocock)	Flat over time (Pocock)

Results

Pentacel® Study	Shingrix® Study
Total vaccine doses at the end of surveillance	
72,651 doses (Sep 2008 - Feb 2010)	647,833 doses (Jan 2018 – Dec 2019)
Sequential testing results	
No increase in risk detected for any pre-specified study outcome	No *sustained* increase in risk detected for any primary pre-specified outcome Test #2: GBS, 3 observed vs 0.6 expected, RR=5.25, p=0.02 Test #5: Bell's palsy, 36 observed vs 24 expected, RR=1.51, p=0.03
End of surveillance results	
Suggestion of increase in risk of fever among booster (12-35mo) group	Confirmed trial results of increase in risk of local and systemic reactions More data needed to assess GBS

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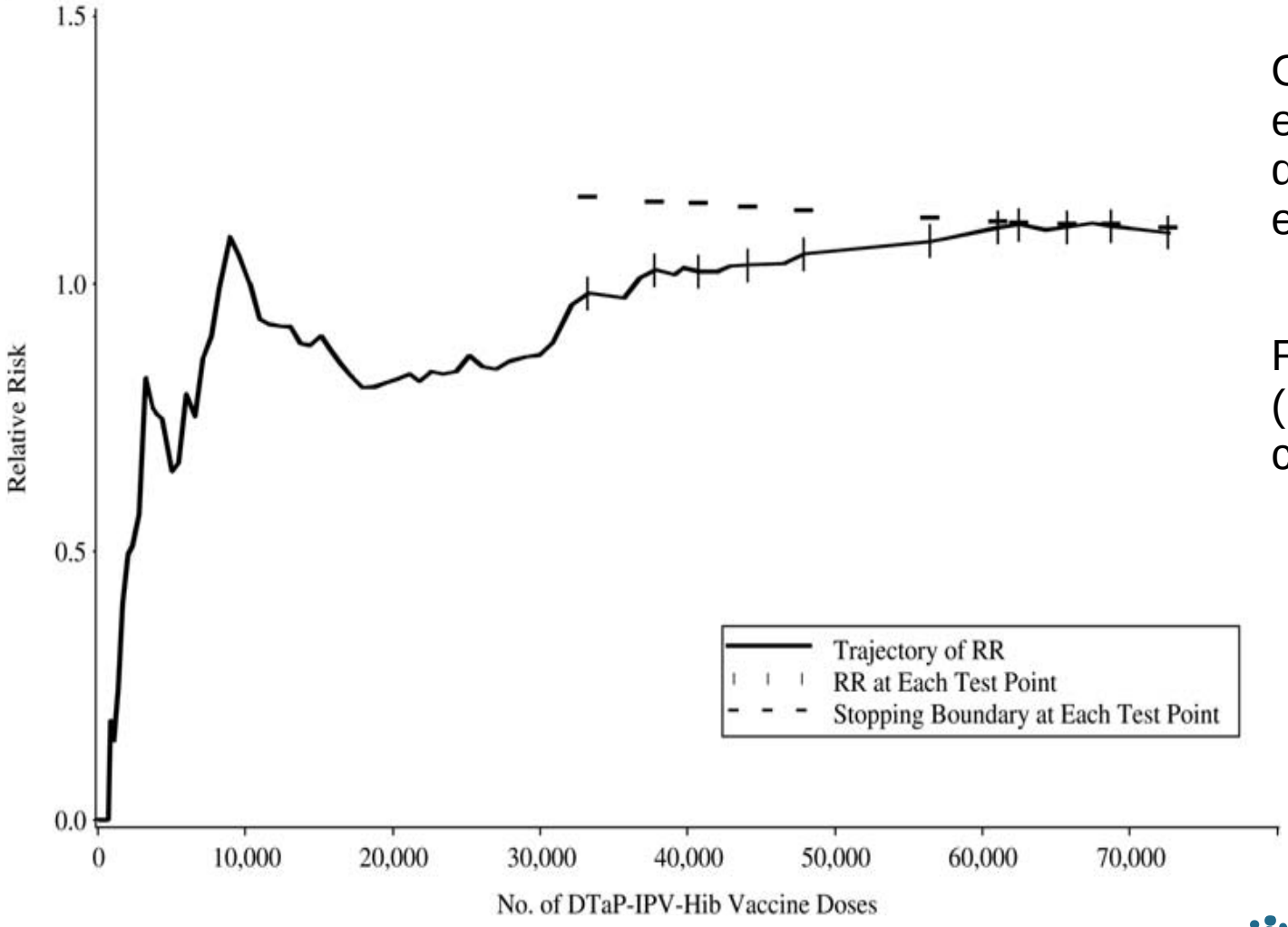
Medically attended fever following Pentacel



Observed 348 events (48/10K doses) versus 310 events expected

RR=1.09, p=0.06 (LLR=1.40 vs. 1.79 critical threshold)

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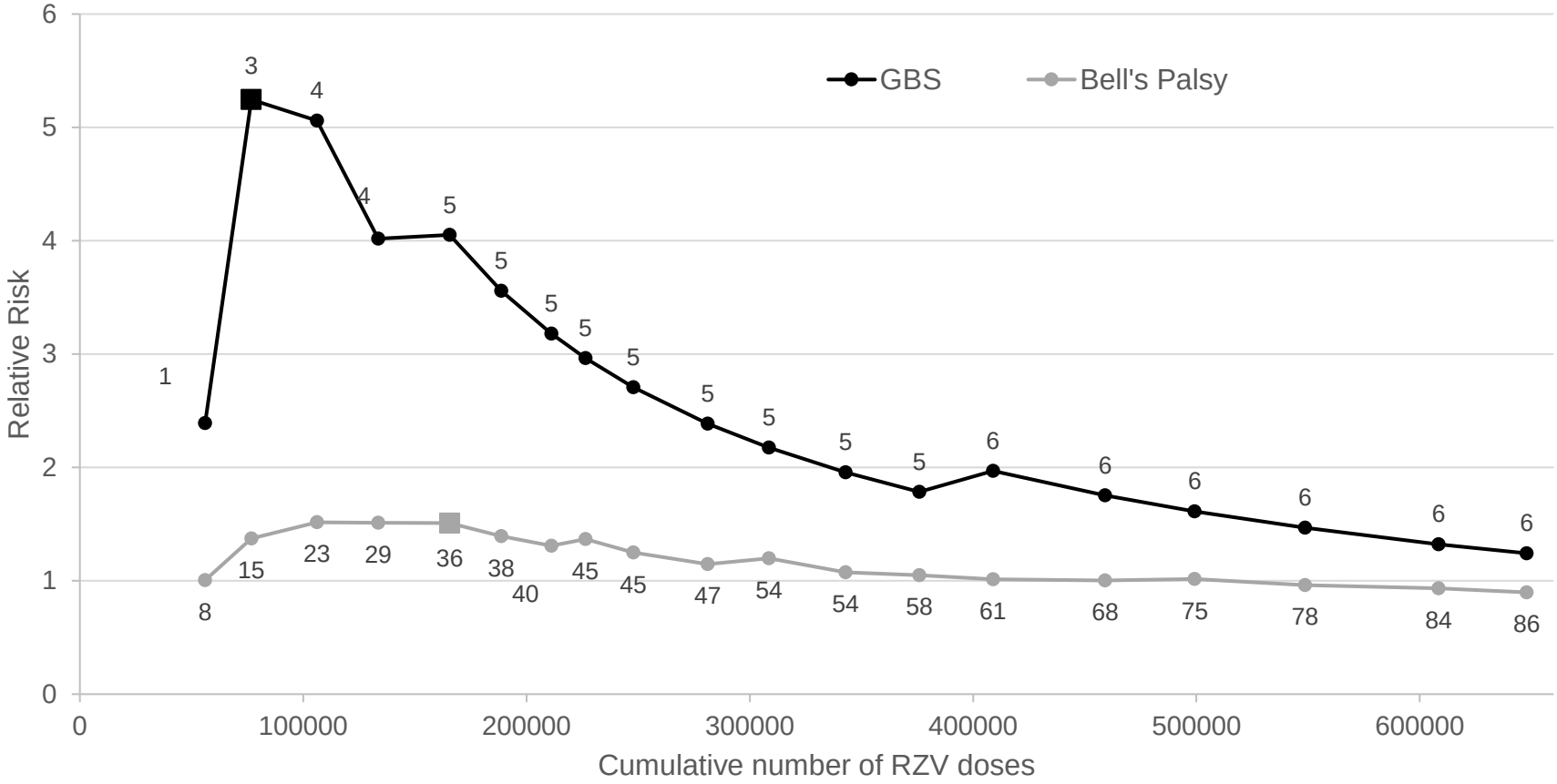
GBS & Bell's palsy following Shingrix



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GBS signal – further follow-up

- 11 total potential cases identified by ICD dx codes
  - 6 following Shingrix
  - 5 following historical Zostavax
- (Gold standard) medical record review by a physician was done to confirm true incident case
- 3 out of 6 following Shingrix were confirmed
- 2 out of 5 following Zostavax were confirmed

# Doses	GBS (ICD)	GBS (Chart)	IR (95% CI) Per million doses	RR (95% CI)
Jan 2018 – Dec 2019				
647,307	6	3	4.63 (0.96-13.54)	**1.56** (0.18-18.62)
Jan 2018 – Apr 2023				
3,526,599	45	21	5.95 (3.69-9.10)	**2.00** (0.49-17.58)

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Research

JAMA Internal Medicine | Original Investigation

Risk of Guillain-Barré Syndrome Following Recombinant Zoster Vaccine in Medicare Beneficiaries

Ravi Goud, MD, MPH; Bradley Lufkin, MPA, MSES; Jonathan Duffy, MD, MPH; Barbee Whitaker, PhD; Hui-Lee Wong, PhD; Jiemin Liao, MS; An-Chi Lo, MS, MPH; Shruti Parulekar, MPH; Paula Agger, MD, MPH; Steven A. Anderson, MPP, PhD; Michael Wernecke, BS; Thomas E. MaCurdy, PhD; Eric Weintraub, MPH; Jeffrey A. Kelman, MD, MMS; Richard A. Forshee, PhD

IMPORTANCE Guillain-Barré syndrome can be reported after vaccination. This study assesses the risk of Guillain-Barré syndrome after administration of recombinant zoster vaccine (RZV or Shingrix), which is administered in 2 doses 2 to 6 months apart.

OBJECTIVE Use Medicare claims data to evaluate risk of developing Guillain-Barré syndrome following vaccination with zoster vaccine.

DESIGN, SETTING, AND PARTICIPANTS This case
RZV-vaccinated and 1 817 099 zoster vaccine
aged 65 years or older. Self-controlled analyse
eligible RZV-vaccinated beneficiaries 65 years
of Guillain-Barré syndrome after RZV vs ZVL,
record-based self-controlled case series analy
during a postvaccination risk window (days 1-
43-183). In self-controlled analyses, RZV vacci
to February 29, 2020. Patients were identifie
(including emergency department), and offic

EXPOSURES Vaccination with RZV or ZVL vacc

MAIN OUTCOMES AND MEASURES Guillain-Bar
administrative claims data, and cases were as
the Brighton Collaboration case definition.

RESULTS Amongst those who received RZV va
dose, and 58% were women, whereas among

Supplemental content

CME Quiz at jamacmelookup.com

FDA U.S. FOOD & DRUG ADMINISTRATION

FDA Requires a Warning about Guillain-Barré Syndrome (GBS) be Included in the Prescribing Information for Shingrix

Safety & Availability (Biologics)

Biologic Product Security

Blood Safety & Availability

CBER-Regulated Products: Shortages and

FDA Safety Communication - March 24, 2021

Purpose: To inform the public and healthcare providers that FDA has required and approved safety labeling changes to the Prescribing Information for Shingrix (Zoster Vaccine Recombinant, Adjuvanted) to include a new warning about the risk for Guillain-Barré Syndrome (GBS) following administration of Shingrix. FDA required GlaxoSmithKline (GSK), the manufacturer of Shingrix, to revise the Prescribing Information to include the following language in the Warnings and Precautions section:

In a postmarketing observational study, an increased risk of GBS was observed during

Outline

- Introduce the data setting: national multi-site post-licensure medical product safety surveillance systems
  - Vaccine Safety Datalink (CDC)
  - Sentinel Initiative (FDA)
- Provide some vaccine safety examples
- Discuss methodological challenges (& some solutions)
- Where do we go from here?

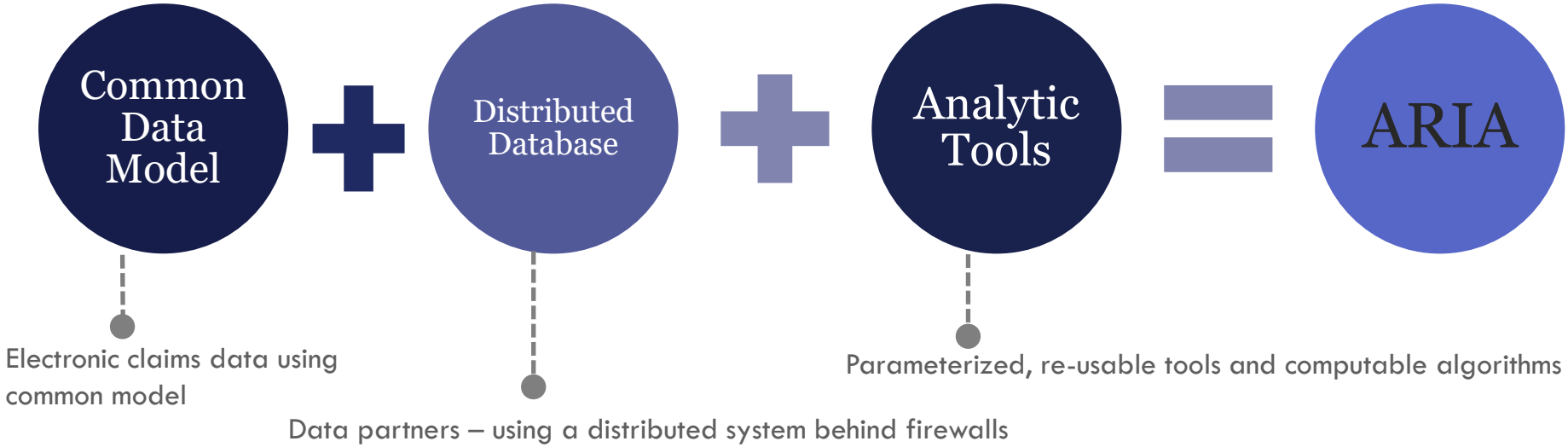
Challenges in data, design, & analysis

1. Creating data infrastructure (common data model, linking, sharing)
2. Establishing data sharing practices & dealing with resulting constraints
3. Ensuring data quality (completeness, accuracy) over time
4. Identifying an appropriate sequential design
   - How often to do analyses? What target of inference? What signal threshold?
5. Minimizing impacts of uncontrolled research setting
   - Confounding, unpredictable vaccine uptake & population composition
6. Managing site heterogeneity
   - Impacts EVERY step (from data linking to analyses to interpretation)
7. Addressing fact that events are rare (limits power, increases variability)
   - Requires large cohort, robust & small sample statistical methods
8. Handling distributed data constraints (no individual level data pooling)

#3 Ensuring data quality

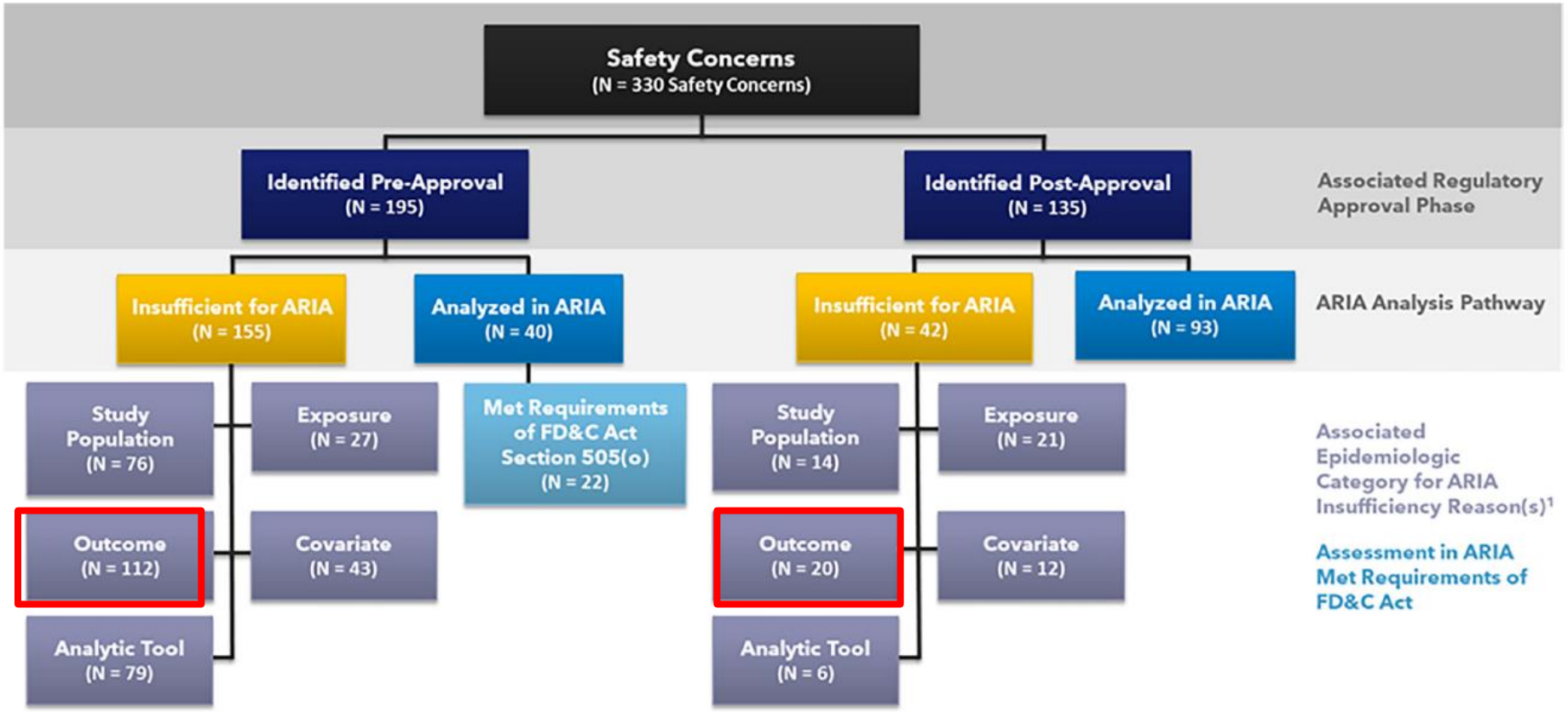
At FDA, this translates to improving ARIA Sufficiency…

ARIA: Active Risk Identification and Analysis system



Slide courtesy of Michael Nguyen at the FDA

ARIA Sufficiency Assessments: 2016-2021



[1]*A single safety concern may be insufficient for analysis in ARIA for several reasons; thus, a single safety concern may be counted in multiple epidemiologic categories.*
***ARIA:** Active Risk Identification & Analysis. **FD&C Act:** Federal Food, Drug, and Cosmetic Act.*

Major goal in Sentinel: Improve ARIA Sufficiency

ARIA *sufficient* outcomes

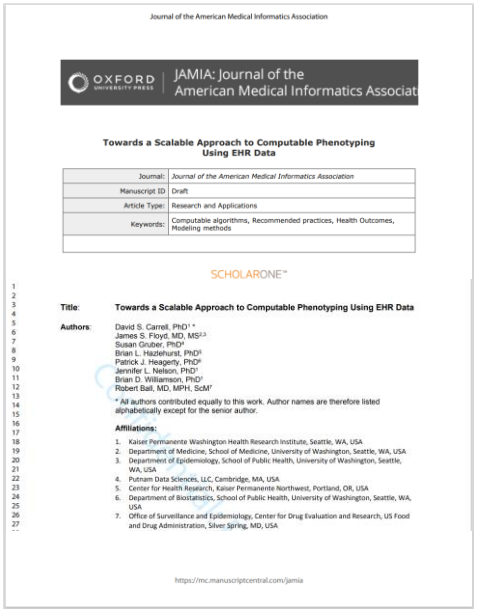
- GI bleeding
- Heart failure
- Lymphoma
- MACE (major adverse cardiac event)
- MI
- MS relapse
- Non-melanoma skin cancer
- Seizure
- Stroke

ARIA *insufficient* outcomes

- Acute pancreatitis
- Adverse fetal outcomes
- Adverse pregnancy outcomes
- Anaphylaxis
- Drug-induced liver injury
- Fatal MACE (cardiac)
- Malignancies (several)
- Nerve injury

- Can *NLP-extracted data (from clinical notes)* improve capture of clinically complex outcomes (i.e., improve **phenotyping** accuracy)?
- Can we identify *scalable development methods* to create these algorithms while retaining good performance (i.e., more readily **computable**)?

Using these examples: we proposed a scalable 5-step approach to EHR-base “computable phenotyping”



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Towards a Scalable Approach to Computable Phenotyping Using EHR Data

Journal:	*Journal of the American Medical Informatics Association*
Manuscript ID	Draft
Article Type:	Research and Applications
Keywords:	Computable algorithms, Recommended practices, Health Outcomes, Modeling methods

SCHOLARONE™

Title: **Towards a Scalable Approach to Computable Phenotyping Using EHR Data**

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Susan Gruber, PhD[4]
Brian L. Hazlehurst, PhD[5]
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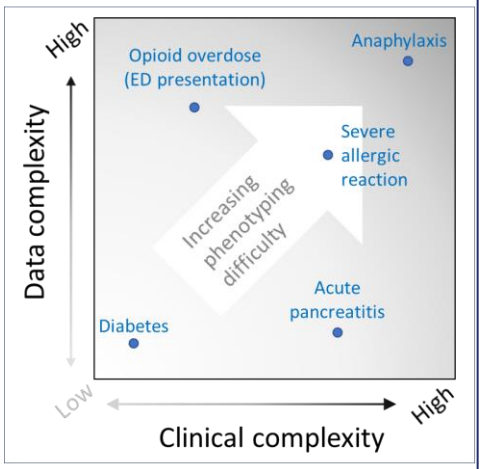
https://mc.manuscriptcentral.com/jamia

Premise (to more accurately/rapidly create algorithms)

- Leverage richer data beyond claims
- Use more automated methods
- Design for reusability/transportability

5 stages of development

- Fitness-for-purpose assessment
- Creating gold standard data (COSTLY)
- Feature engineering (COSTLY)
- Model development
- Model Evaluation

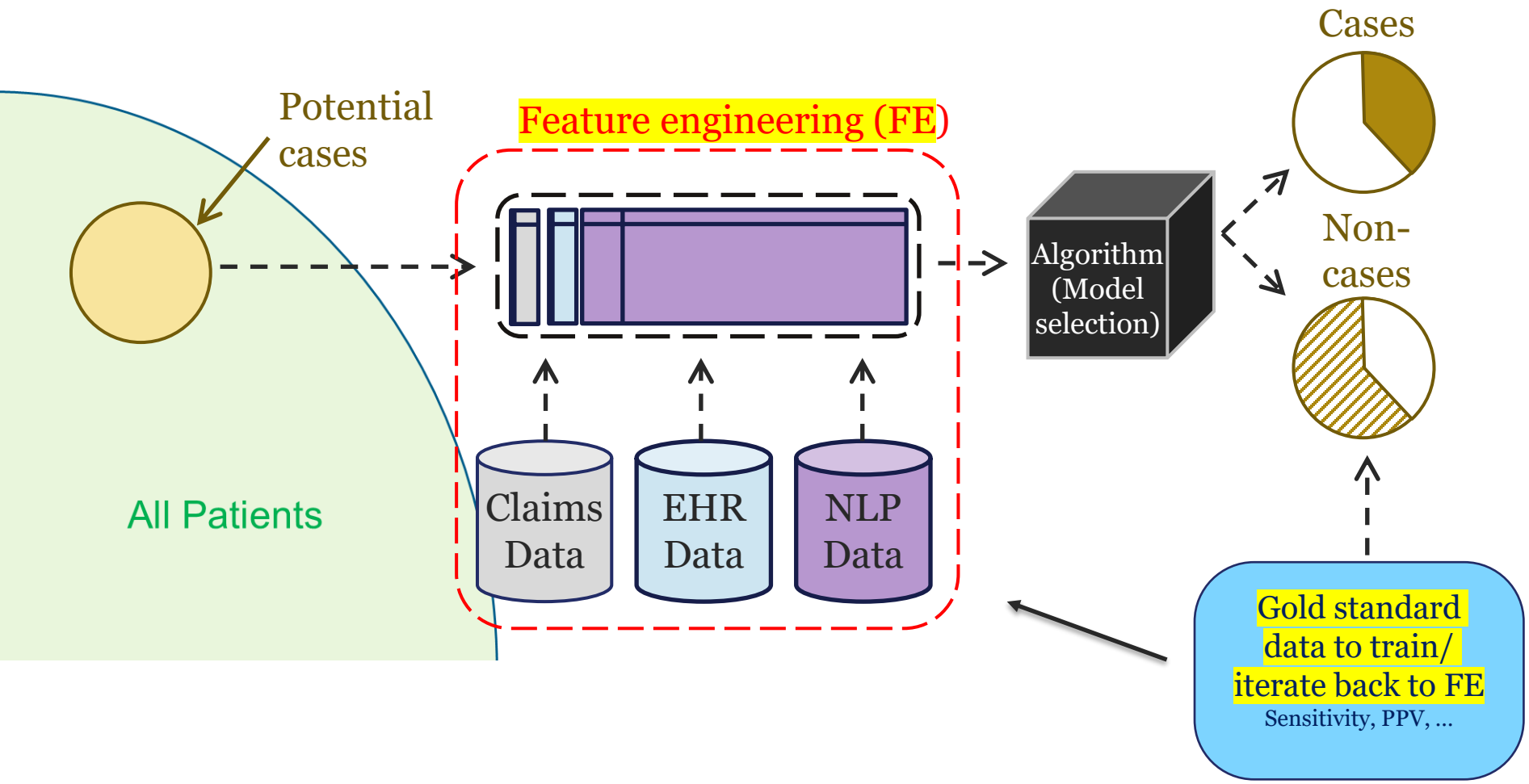


End goal: NOT a one-off outcome-specific solution but a general framework for use/re-use by FDA/others

David S. Carrell, James S. Floyd, Susan Gruber, Brian L. Hazlehurst, Patrick J. Heagerty, Jennifer L. Nelson, Brian D. Williamson, Robert Ball, Towards a Scalable Approach to Computable Phenotyping Using EHR Data, in press at Journal of the American Medical Informatics Association

Traditional phenotype development process

- Algorithms (or models) to determine which patients have a particular clinical condition (AKA phenotype, health outcome of interest, “is a case”)

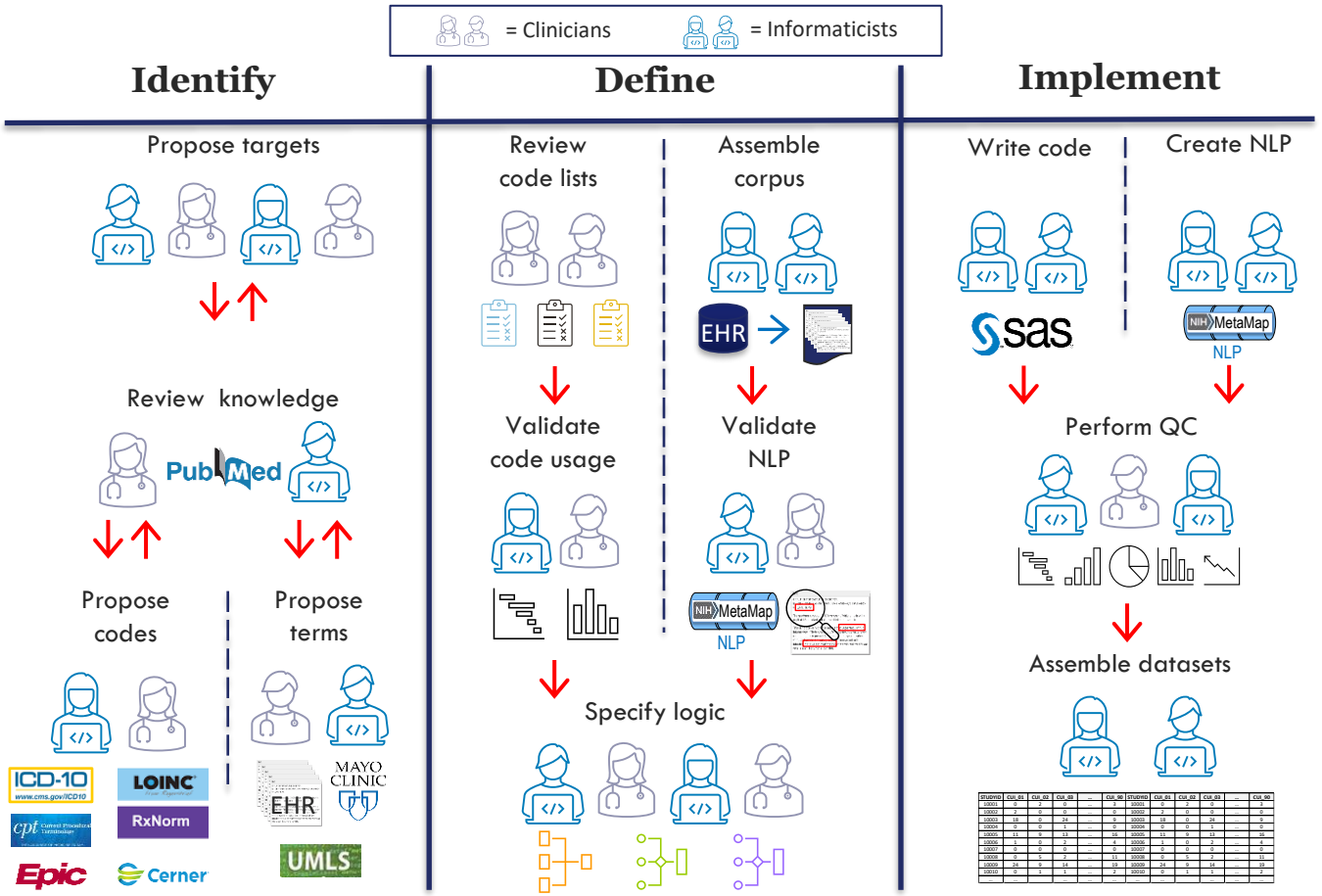


Bottlenecks in traditional phenotyping processes for developing outcome-identifying algorithms

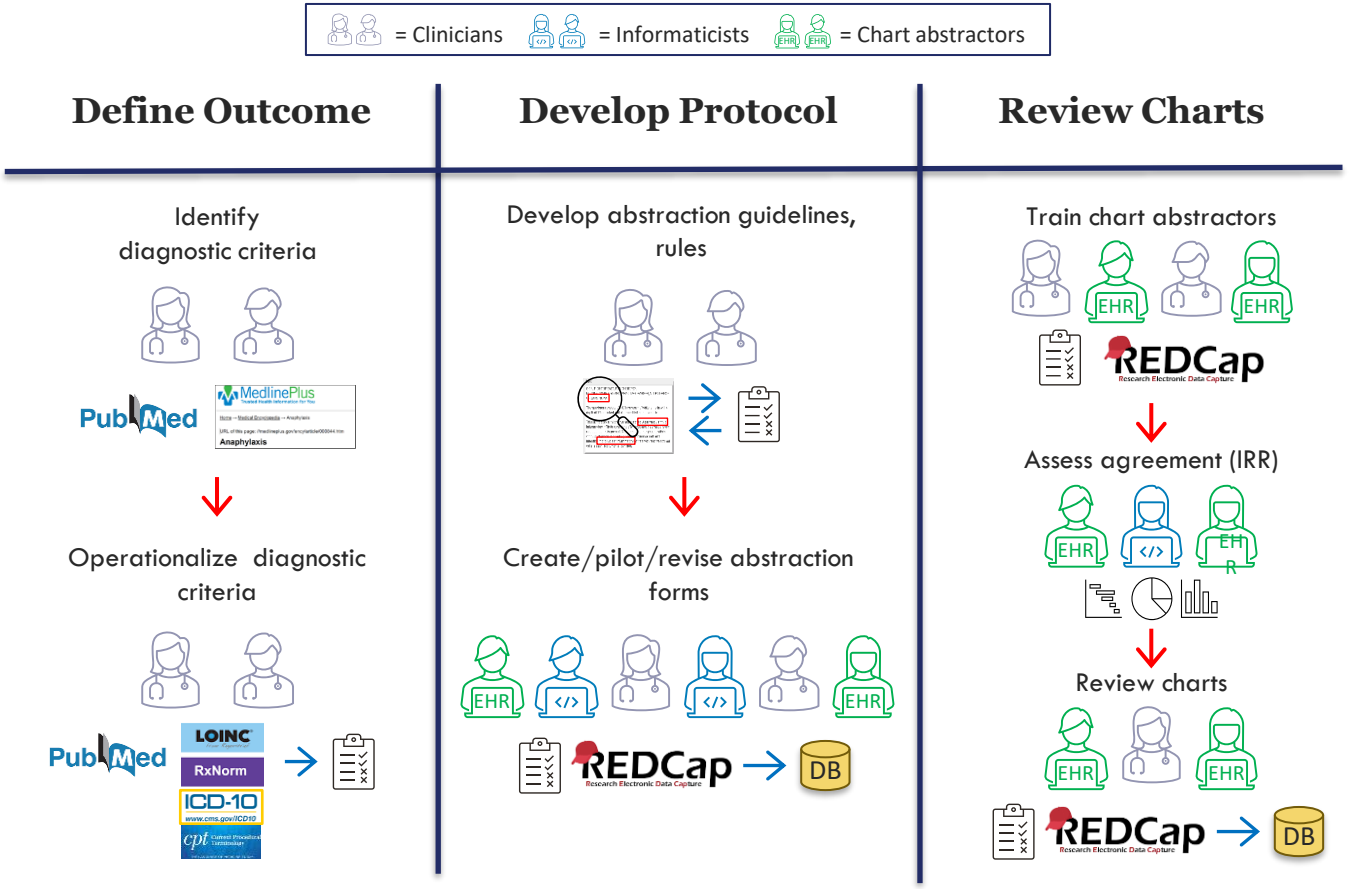
1. **Feature engineering burden (manual)**
   - Expert-intensive (clinical, EHR, NLP expertise)
     - May not be available in all settings
     - Expensive
     - Potential operator-dependence
   - Time-intensive
     - Pressure to limit the # of features engineered
2. **Gold standard data burden (manual review)**
   - Expert-intensive (*same as above*)
   - Time-intensive
     - Limits the amount of labeled data available for model training

Time/cost burdens constrain the number of outcomes a team can investigate

Feature Engineering Burden (traditional/manual)



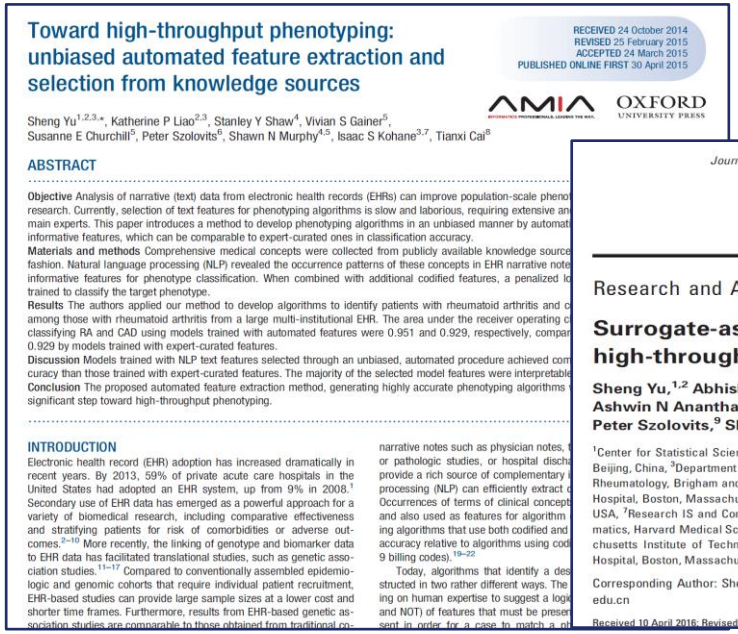
Gold Standard Outcome Data Burden (manual review)



Automated feature engineering – the AFEP approach

Yu and colleagues, 2015, 2017, 2018

AFEP



Toward high-throughput phenotyping: unbiased automated feature extraction and selection from knowledge sources

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REVISED 25 February 2015
ACCEPTED 24 March 2015
PUBLISHED ONLINE FIRST 30 April 2015

AMIA OXFORD UNIVERSITY PRESS

Sheng Yu[1,2,3,*], Katherine P Liao[2,3], Stanley Y Shaw[4], Vivian S Gainer[5], Susanne E Churchill[5], Peter Szolovits[6], Shawn N Murphy[4,5], Isaac S Kohane[3,7], Tianxi Cai[8]

ABSTRACT

Objective Analysis of narrative (text) data from electronic health records (EHRs) can improve population-scale phenot research. Currently, selection of text features for phenotyping algorithms is slow and laborious, requiring extensive an main experts. This paper introduces a method to develop phenotyping algorithms in an unbiased manner by automat informative features, which can be comparable to expert-curated ones in classification accuracy.

Materials and methods Comprehensive medical concepts were collected from publicly available knowledge source fashion. Natural language processing (NLP) revealed the occurrence patterns of these concepts in EHR narrative note informative features for phenotype classification. When combined with additional codified features, a penalized lo trained to classify the target phenotype.

Results The authors applied our method to develop algorithms to identify patients with rheumatoid arthritis and c among those with rheumatoid arthritis from a large multi-institutional EHR. The area under the receiver operating c classifying RA and CAD using models trained with automated features were 0.951 and 0.929, respectively, compar 0.929 by models trained with expert-curated features.

Discussion Models trained with NLP text features selected through an unbiased, automated procedure achieved com curacy than those trained with expert-curated features. The majority of the selected model features were interpretable

Conclusion The proposed automated feature extraction method, generating highly accurate phenotyping algorithms significant step toward high-throughput phenotyping.

INTRODUCTION

Electronic health record (EHR) adoption has increased dramatically in recent years. By 2013, 59% of private acute care hospitals in the United States had adopted an EHR system, up from 9% in 2008.[1] Secondary use of EHR data has emerged as a powerful approach for a variety of biomedical research, including comparative effectiveness and stratifying patients for risk of comorbidities or adverse outcomes.[2–10] More recently, the linking of genotype and biomarker data to EHR data has facilitated translational studies, such as genetic association studies.[11–17] Compared to conventionally assembled epidemiologic and genomic cohorts that require individual patient recruitment, EHR-based studies can provide large sample sizes at a lower cost and shorter time frames. Furthermore, results from EHR-based genetic as-

narrative notes such as physician notes, or pathologic studies, or hospital discha provide a rich source of complementary processing (NLP) can efficiently extract Occurrences of terms of clinical concept and also used as features for algorithm ing algorithms that use both codified and accuracy relative to algorithms using cod 9 billing codes).[19–22]

Today, algorithms that identify a des structed in two rather different ways. The ing on human expertise to suggest a logi and NOT) of features that must be preser sent in order for a case to match a ph

SAFE

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doi: 10.1093/jamia/ocw135
Advance Access Publication Date: 15 September 2016
Research and Applications

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Research and Applications

Surrogate-assisted feature extraction for high-throughput phenotyping

Sheng Yu,[1,2] Abhishek Chakrabortty,[3] Katherine P Liao,[4] Tianrun Cai,[5] Ashwin N Ananthakrishnan,[6] Vivian S Gainer,[7] Susanne E Churchill,[8] Peter Szolovits,[9] Shawn N Murphy,[7,10] Isaac S Kohane,[8] and Tianxi Cai[5]

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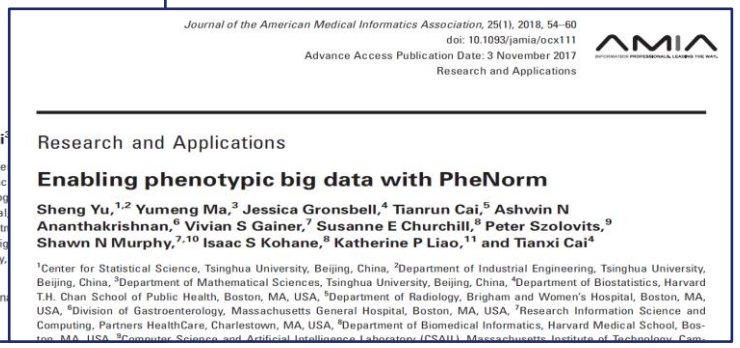
Received 10 April 2016; Revised 8 August 2016; Accepted 17 August 2016

PheNorm



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Advance Access Publication Date: 3 November 2017
Research and Applications

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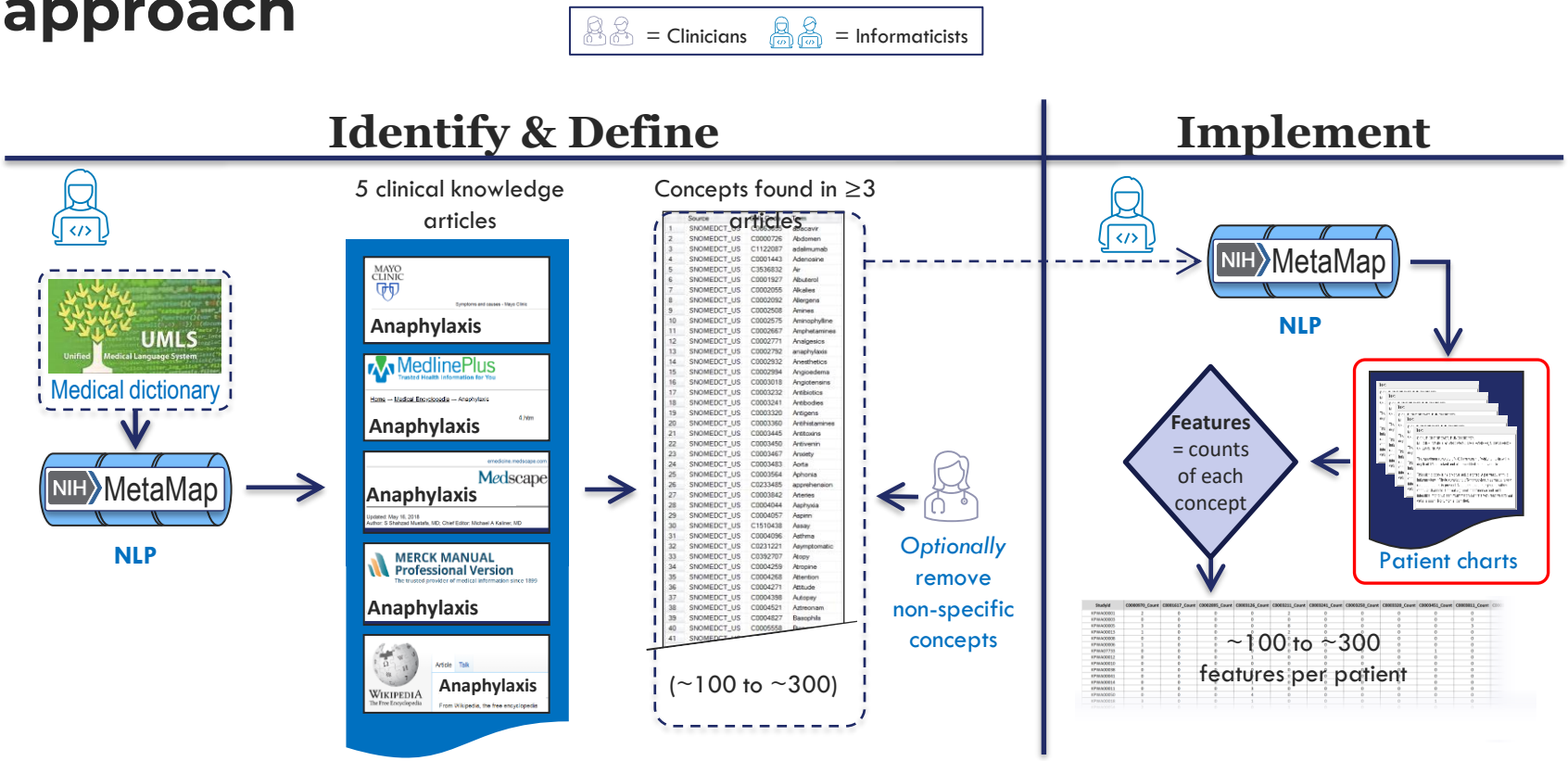
Research and Applications

Enabling phenotypic big data with PheNorm

Sheng Yu,[1,2] Yumeng Ma,[3] Jessica Gronsbell,[4] Tianrun Cai,[5] Ashwin N Ananthakrishnan,[6] Vivian S Gainer,[7] Susanne E Churchill,[8] Peter Szolovits,[9] Shawn N Murphy,[7,10] Isaac S Kohane,[8] Katherine P Liao,[11] and Tianxi Cai[4]

[1]Center for Statistical Science, Tsinghua University, Beijing, China, [2]Department of Industrial Engineering, Tsinghua University, Beijing, China, [3]Department of Mathematical Sciences, Tsinghua University, Beijing, China, [4]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA, [5]Department of Radiology, Brigham and Women's Hospital, Boston, MA, USA, [6]Division of Gastroenterology, Massachusetts General Hospital, Boston, MA, USA, [7]Research Information Science and Computing, Partners HealthCare, Charlestown, MA, USA, [8]Department of Biomedical Informatics, Harvard Medical School, Bos-

Automated feature engineering – the AFEP approach



* Yu S, Liao KP, Shaw SY, Gainer VS, Churchill SE, Szolovits P, Murphy SN, Kohane IS, Cai T. Toward high-throughput phenotyping: unbiased automated feature extraction and selection from knowledge sources. J Am Med Inform Assoc. 2015 Sep;22(5):993-1000. doi: 10.1093/jamia/ocv034. Epub 2015 Apr 29. PMID: 25929596; PMCID: PMC4986664.

Traditional phenotype development process

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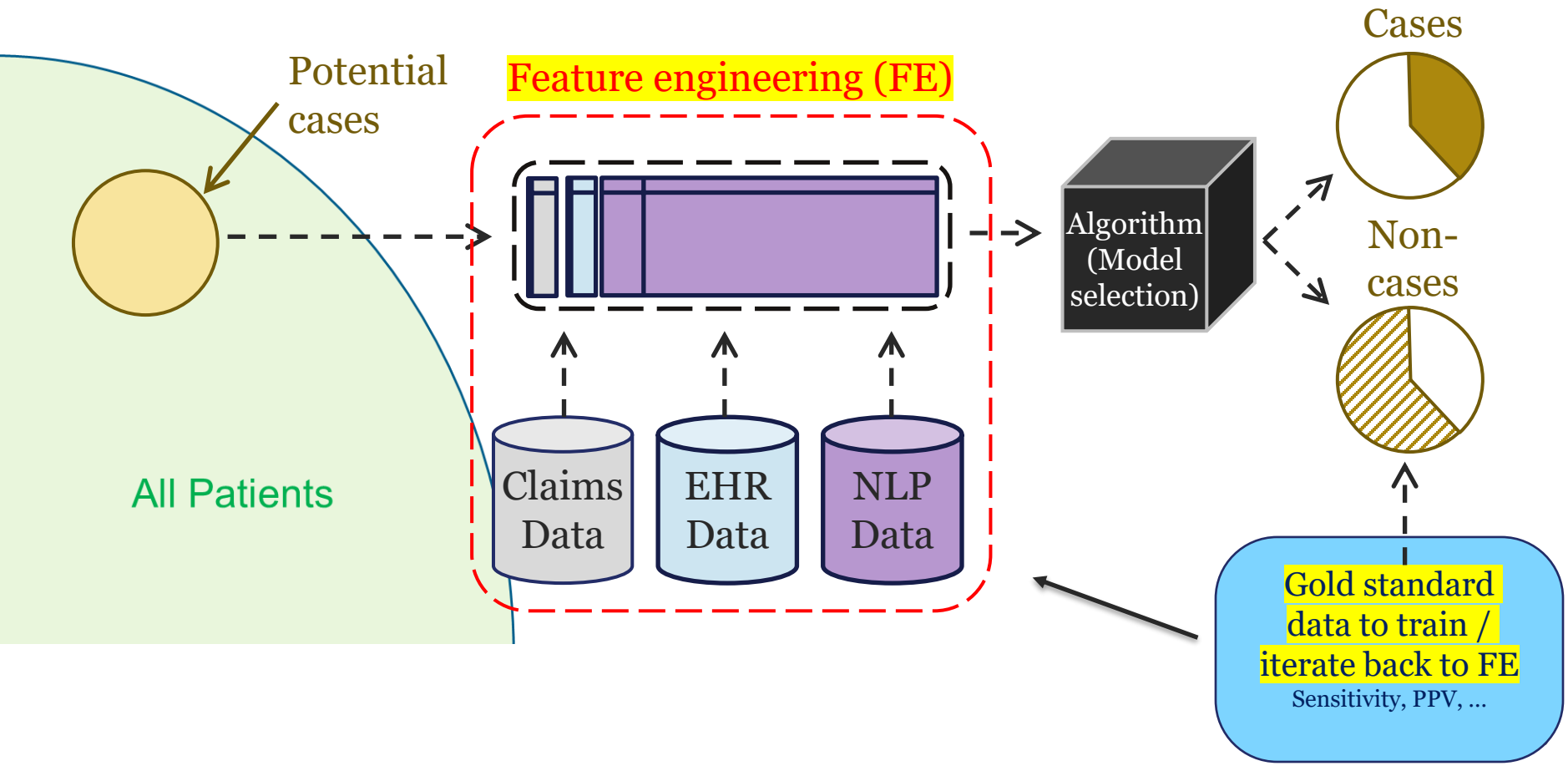
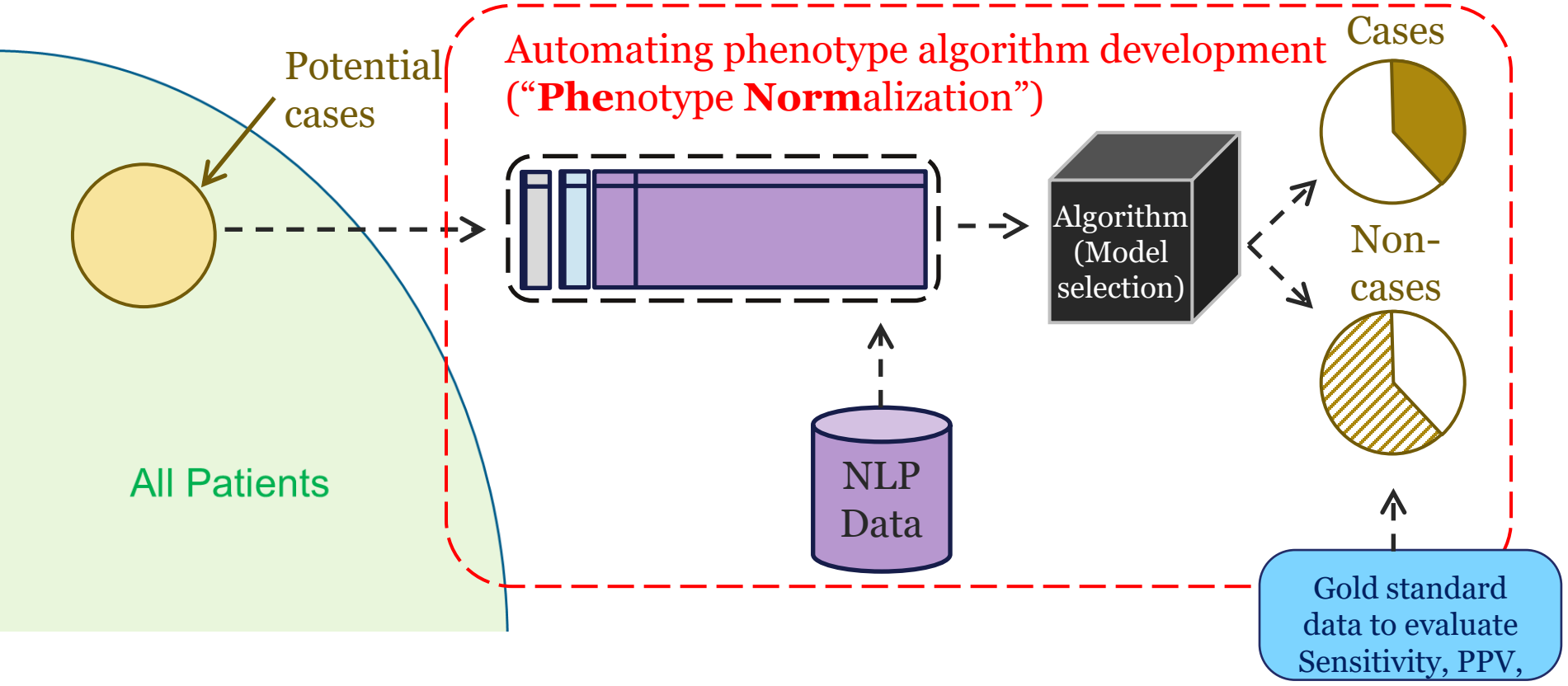


Computable phenotype development *process*

- Fully-automated algorithms (or models) to determine which patients have a particular clinical condition (AKA phenotype, health outcome of interest, “is a case”)



Journal of the American Medical Informatics Association, 2023, 1–9
https://doi.org/10.1093/jamia/ocad241
Research and Applications

Research and Applications

Data-driven automated classification algorithms for acute health conditions: applying PheNorm to COVID-19 disease

Joshua C. Smith, PhD[1,*], Brian D. Williamson, PhD[2], David J. Cronkite, MS[2], Daniel Park, BS[1], Jill M. Whitaker, MSN[1], Michael F. McLemore, BSN[1], Joshua T. Osmanski, MS[1], Robert Winter, BA[1], Arvind Ramaprasan, MS[2], Ann Kelley, MHA[2], Mary Shea, MA[2], Saranrat Wittayanukorn, PhD[3], Danijela Stojanovic, PharmD, PhD[3], Yueqin Zhao, PhD[3], Sengwee Toh, ScD[4], Kevin B. Johnson, MD, MS[5], David M. Aronoff, MD[6], David S. Carrell, PhD[2]

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Challenges in data, design, & analysis

1. Creating data infrastructure (common data model, linking, sharing)
2. Establishing data sharing practices & dealing with resulting constraints
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4. Identifying an appropriate sequential design
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7. Addressing fact that events are rare (limits power, increases variability)
   - Requires large cohort, robust & small sample statistical methods
8. Handling distributed data constraints (no individual level data pooling)

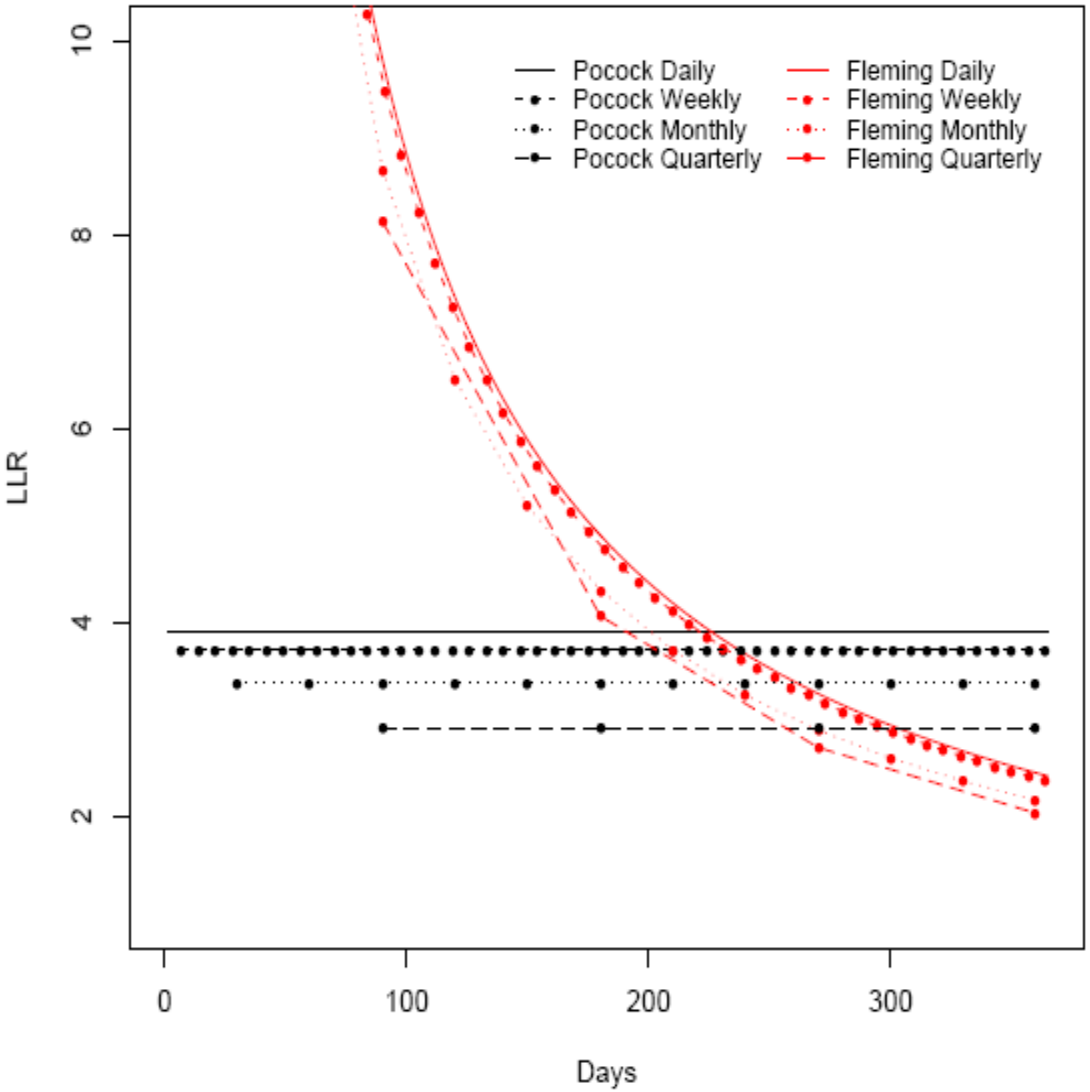
#4 Identifying an appropriate sequential design (literature is vast, trial-oriented)

- Initial work in industrial quality control settings
  - ✓ Sequential probability ratio test (SPRT): Wald 1943, Barnard 1944
  - ✓ Cumulative sum and Shewart charts: Shewart 1931, Page 1954
- Extensive development in RCTs (1950's to present)
  - ✓ Idea introduced for RCTs: Armitage 1958, 1969
  - ✓ Group sequential boundaries: Pocock 1977, O'Brien-Fleming 1979
  - ✓ Alpha-spending: Lan-DeMets 1983, Pampallona 1995
  - ✓ Extensions to failure-time data: Gu & Lai 1995, Tsiatis 1985
  - ✓ Adaptive designs: Cui 1999, Posch & Bauer 1999
  - ✓ Bayesian designs: Berry 1993, Spiegelhalter 1994, Fayers 1997
- Recent use in observational safety studies using EHR data
  - ✓ Generalized likelihood ratio tests: Shih & Lai 2010, Kulldorff 2011
  - ✓ Group sequential methods: Li 2009, Cook 2012, Nelson 2012, Zhao 2012, Stratton 2015, Cook 2015, Nelson 2016, Cook 2019, Nelson 2019

Sequential design specifications

- **What target of inference**? (relative risk--RR or risk difference-RD)
  - ✓ H_o: RR=1 vs H_A: RR>1
  - ✓ Large value implies increased risk among exposed
- **What monitoring frequency**? (daily, weekly, monthly, quarterly)
- **What statistical threshold/shape over time to indicate a signal**? (flat-Pocock, decreasing- (O'Brien-Fleming)
- Once specified, after each new observation or group accrues…
  - ✓ Count up AE among exposed & unexposed
  - ✓ Compute test statistic, Z, to compare risk between groups
  - ✓ If Z > B: stop, signal H_A; else continue
  - ✓ If end of study and no signal, fail to reject H_o
  - ✓ B chosen to maintain a preset false positive (FP) error

Sequential boundary examples



Typical efficacy trial:

- Frequency: quarterly
- Boundary: decreasing
- Test statistic: LRT, RR, RD

Vaccine Safety Datalink:

- Frequency: weekly
- Boundary: flat
- Test statistic: LRT

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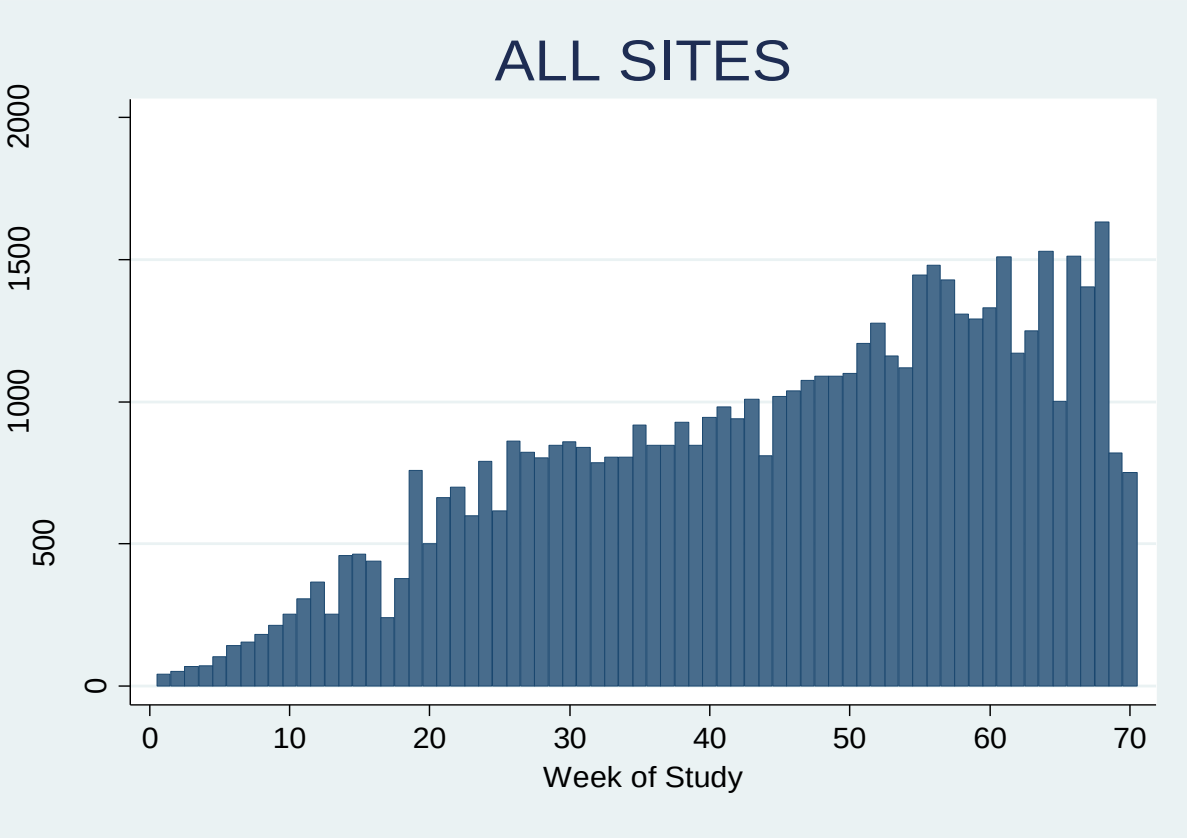
#5 Minimize impact of uncontrolled setting: a) Unpredictable uptake



- Slow uptake implies less stability at early test points
- Harder to plan (align information time statistical planning with calendar time operational constraints)
  - ✓ Statistically: want 80% power to detect RR=2
  - ✓ Need N=73,000 doses
  - ✓ Operationally: Stakeholders want to know--how long it will take to accrue this N?

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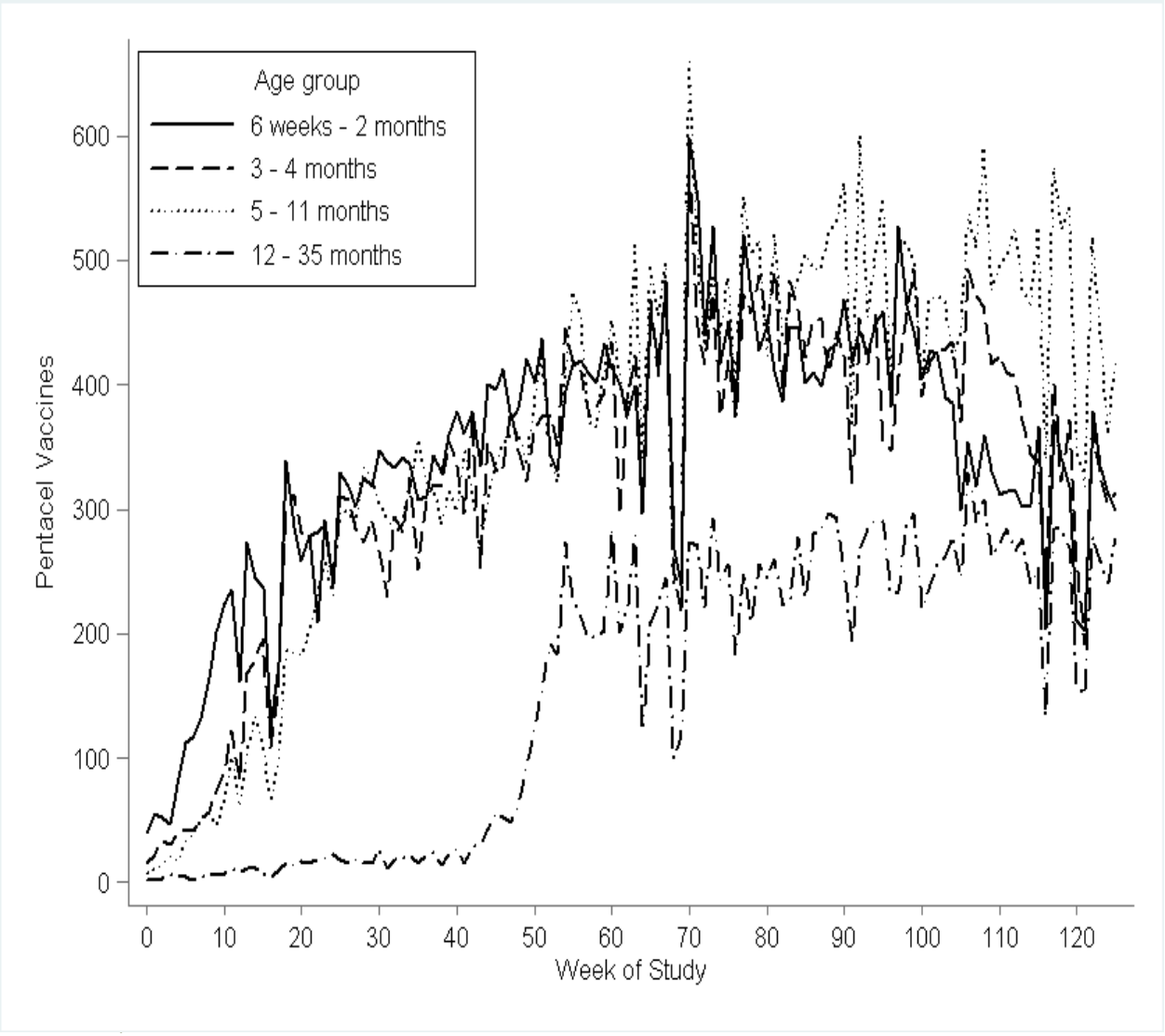
#5 Minimize impact of uncontrolled setting: b) Unpredictable cohort



Population (confounders) may change over time

Impacts ability to adjust for confounding (lack of overlap in exposed/unexposed)

Some standard methods (propensity scores) harder to estimate at early time points when exposure is rare

Impacts sequential boundary plans and formulation

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#5 Minimize impact of uncontrolled setting: c) Unpredictable data

- **Electronic data accessed in real-time are dynamic**
  - ✓ Data can 'arrive late' & people (exposures/events) can disappear
- **Results can vary depending on how you deal with these issues**
  - ✓ Analysis approach #1 (o+n): freeze old and add new data
  - ✓ Analysis approach #2 (cum): cumulatively refresh all data

Adverse event (AE) outcome	Total # of doses	# of AEs	Expected # of AEs	AE rate per 10K	RR	LLR	LLR Critical value
Fever: o+n	66,400	343	303.5	51.7	1.13	**2.47**	**1.93**
Fever: cum	68,826	335	302.5	48.7	1.11	1.69	1.85
Seizure: o+n	66,400	8	7.9	1.2	1.01	<0.01	1.91
Seizure: cum	68,826	9	8.1	1.3	1.11	0.04	1.46

#5 Minimize impact of uncontrolled setting: d) Unmeasured confounding

Published in final edited form as:
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Multiply robust causal inference with double-negative control adjustment for categorical unmeasured confounding

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Kaiser Permanente Washington Health Research Ins

Eric J. Tchetgen Tchetgen
University of Pennsylvania, Philadelphia, USA

Summary.

Unmeasured confounding is a threat to causal inferen
the use of negative controls to mitigate unmeasured c
and popularity. Negative controls have a long-standin
epidemiology to rule out non-causal explanations, alt
detection. Recently, Miao and colleagues have descrit
of negative control exposure and outcome variables c
average treatment effect (ATE) from observational da
establish non-parametric identification of the ATE un
categorical unmeasured confounding and negative cor
semiparametric framework for obtaining inferences a

Xu Shi
2017

Published by Oxford University Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology 2006;**35**:337–344
doi:10.1093/ije/dyi274

Evidence of bias in estimates of influenza vaccine effectiveness in seniors

Lisa A Jackson,[1,2]* Michael L Jackson,[1,2] Jennifer C Nelson,[1,3] Kathleen M Neuzil[4] and Noel S Weiss[2]

Accepted 3 November 2005

Background Numerous observational studies have reported that seniors who receive influenza vaccine are at substantially lower risk of death and hospitalization during the influenza season than unvaccinated seniors. These estimates could be influenced by differences in underlying health status between the vaccinated and unvaccinated groups. Since a protective effect of vaccination should be specific to influenza season, evaluation of non-influenza periods could indicate the possible contribution of bias to the estimates observed during influenza season.

Methods We evaluated a cohort of 72 527 persons 65 years of age and older followed during an 8 year period and assessed the risk of death from any cause, or

Outline

- Introduce the data setting: national multi-site post-licensure medical product safety surveillance systems
  - Vaccine Safety Datalink (CDC)
  - Sentinel Initiative (FDA)
- Provide some vaccine safety examples
- Discuss methodological challenges (& some solutions)
- Where do we go from here?

What we've learned

- Traditional post-licensure safety surveillance methods have gaps
- Rapid surveillance using claims/EHR systems is now established
  - ✓ Data and results are routinely used to guide U.S. policy (by the ACIP)
- Many challenges exist for sequential use of real-world EHR data
  - ✓ Improving the accuracy of outcome identification
  - ✓ Identifying an appropriate sequential design
  - ✓ Minimizing impacts of uncontrolled research setting
- A general framework for **scalable computable phenotyping** and a **new class of sequential methods** have emerged to address these issues
- Continued success needs engaged epidemiological/biostatistical leaders
  - To promote use of pre-defined, principled methods that are question-driven, interpretable, reproducible, & can yield accurate & actionable evidence
- There are many emerging (data) & methods strategies that should be considered to improve the accuracy of inferences

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What we're doing now

- Continued work with CDC & FDA on data infrastructure & applications
  - Sentinel data expansion from claims to more (richer) EHR data sources (Innovation Center development network: KPWA, Duke, Vanderbilt, Harvard)
  - Translation of new methods into practice to learn more (VSD & RSV vaccine)
- Problems we're tackling now
  - Heterogeneity in ICD coding practices across sites & over time
  - Heterogeneity across sites for EHR-based outcome phenotype algorithms
  - Unmeasured confounding bias in causal inference of drug/vaccine effects
  - Missing data (by design) when combining claims with EHR data sources
- Methods we're working on
  - Harmonizing data across sites (& time) before doing inference/prediction
  - Assessing feasibility & transportability of computable phenotyping algorithms (based on machine learned models that use richer EHR data + NLP features)
  - Using negative controls to improve causal inference & reduce unmeasured confounding bias
  - Evaluating/adapting missing data methods for use in distributed data settings

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