NIH Collaboratory

Health Care Systems Research Collaboratory

Millions more people. Stronger collaborations: The new and improved NIH Collaboratory Distributed Research Network

Richard Platt, Denise Boudreau, Kevin Haynes, Jerry Gurwitz, Christopher Granger

December 6, 2019

Re-introducing the NIH Collaboratory Distributed Research Network

- FDA Sentinel System, designed to assess medical product safety and effectiveness, has ability to support research topics
- Created to allow investigators supported by NIH and other not-for-profit sponsors to collaborate with Sentinel investigators
- Focus is on multi-center research, especially requiring:
  - Access to full text records
  - Linkage to external sources
  - Contact with clinicians and/or patients
  - Collection of patient generated data
- New research partners wanted!

www.rethinkingclinicaltrials.org/nih-collaboratory-drn

NIH COLLABORATORY
LIVING TEXTBOOK
of Pragmatic Clinical Trials

ABOUT RESOURCES GRAND ROUNDS NEWS Search …

DESIGN CONDUCT DISSEMINATION

NIH Collaboratory Distributed Research Network (DRN)

Drs. Jeffrey Brown and Lesley Curtis explain the NIH Collaboratory DRN

Millions of people. Strong collaborations. Privacy first.

Leadership: Richard Platt and Lesley Curtis
Project Manager: Sarah Malek

Publications and Supplementary Material | Presentations

The NIH Collaboratory Distributed Research Network (DRN) enables investigators funded the NIH and other not-for-profit sponsors to collaborate with investigators based in healt plans that participate in the FDA's Sentinel System. The DRN is especially useful for supporting multisite research programs.

https://rethinkingclinicaltrials.org/nih-collaboratory-drn/

DRN Collaborating Organizations

Coordinating Center:

DEPARTMENT OF POPULATION MEDICINE
HARVARD MEDICAL SCHOOL
Harvard Pilgrim Health Care Institute

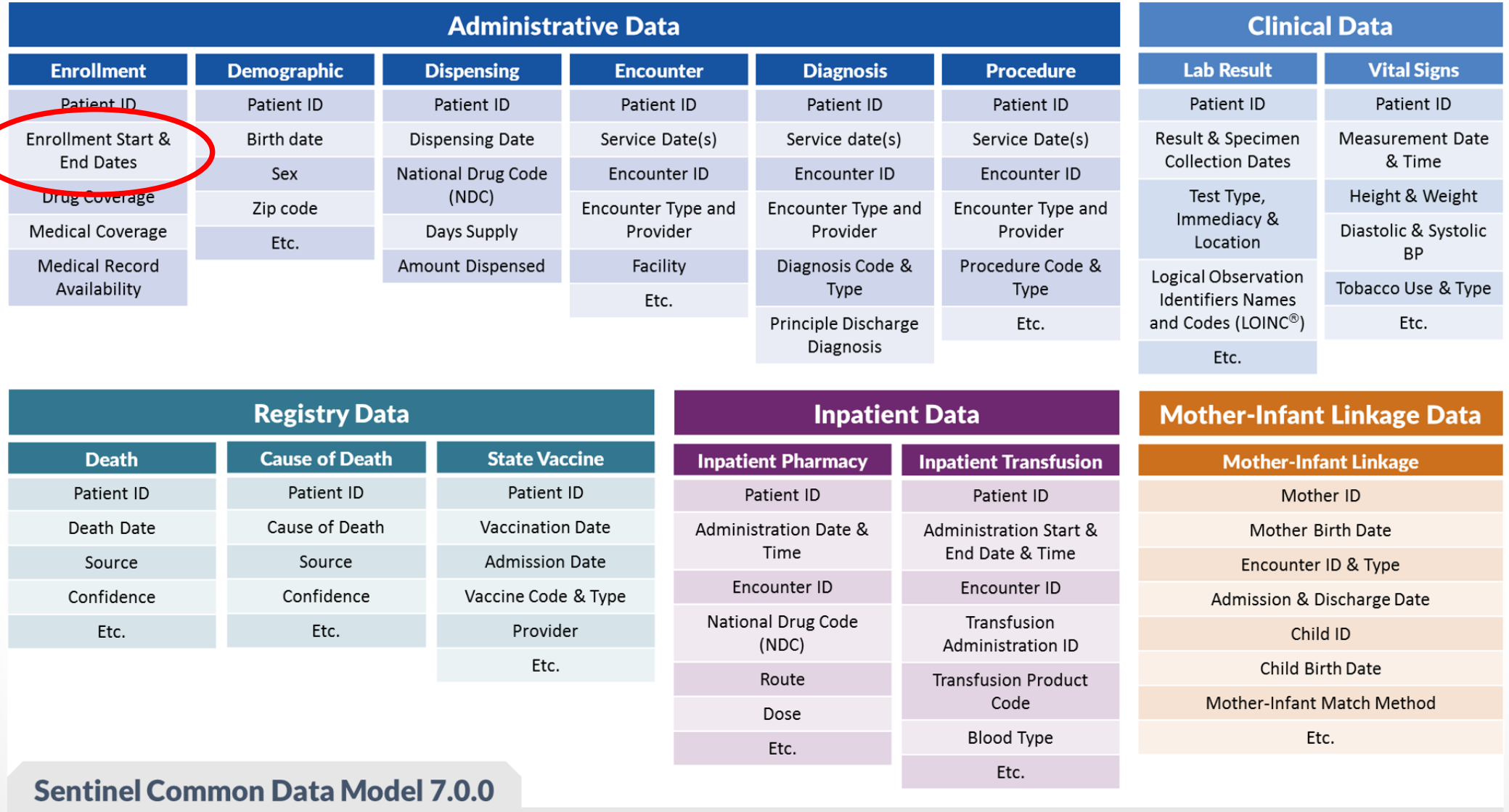
14 Data & Scientific Partners

HealthCore
Anthem
Healthagen
aetna™
OPTUM®
KAISER PERMANENTE®
Hawaii
Mid-Atlantic
Northern California
Northwest
Washington
VANDERBILT UNIVERSITY MEDICAL CENTER
TennCare
Marshfield Clinic Research Institute
Humana
HealthPartners®
MASSACHUSETTS
Harvard Pilgrim HealthCare

NIH Collaboratory DRN's Distributed Database

Database Statistic	Total
Members Currently Accruing New Data	~45 million
Person-years of Data	~450 million
Pharmacy Dispensings	~7 billion
Unique Medical Encounters	~10 billion

Sentinel Common Data Model



Sentinel Common Data Model 7.0.0

Capabilities

- Work with Sentinel's highly curated distributed dataset

Antibiotic use in pediatrics

ORIGINAL ARTICLE

Antibiotic dispensing following pediatric visits in the US emergency departments and outpatient settings from 2006 to 2016

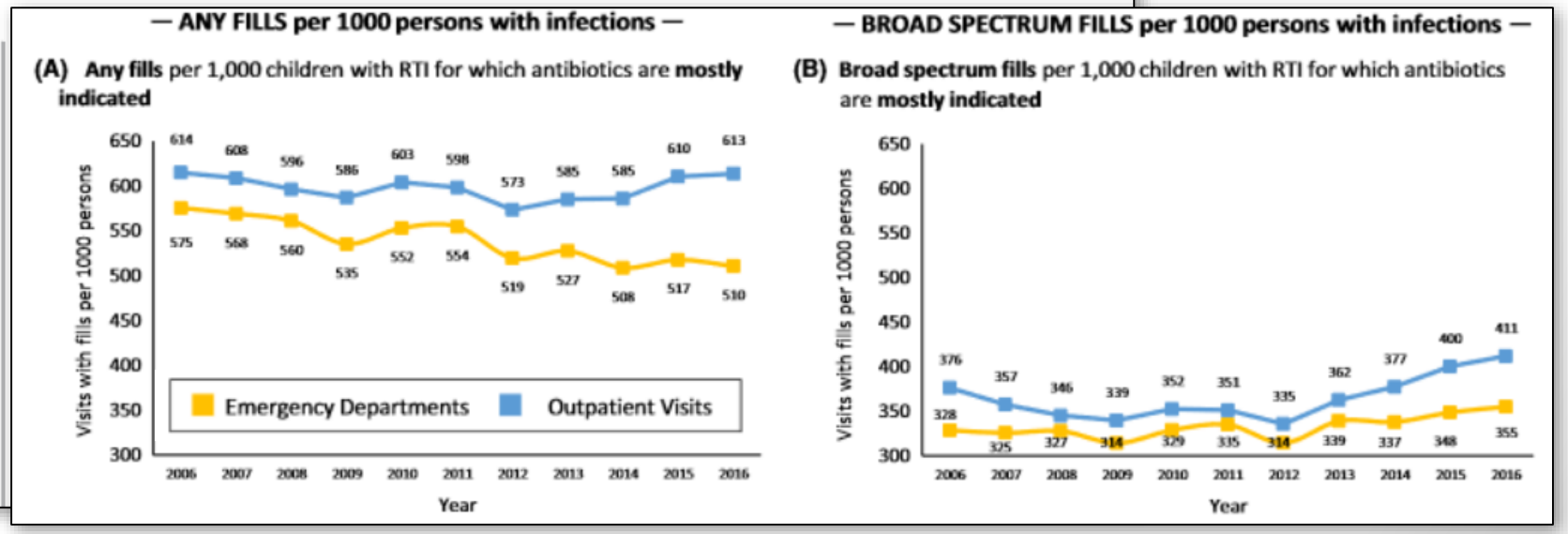
Abiy Agiro[1] | Gayathri Sridhar[1] | Aliza Gordon[1] | Jeffrey Brown[2] | Kevin Haynes[1]

[1]Translational Research for Affordability and Quality, HealthCore, Wilmington, DE

[2]Harvard Medical School, Boston, MA

Correspondence
Abiy Agiro, 123 Justison Street, Suite 200, Wilmington, DE 19801.
Email: aagiro@healthcore.com

Funding information
National Center for Complementary & Integrative Health of the National Institutes of Health, Grant/Award Number: U54AT007748



- 74 million ambulatory and ED visits

Pharmacol Res Perspect. 2019;00:e00512.|doi.org/10.1002/prp2.512

Chemo-induced neuropathy

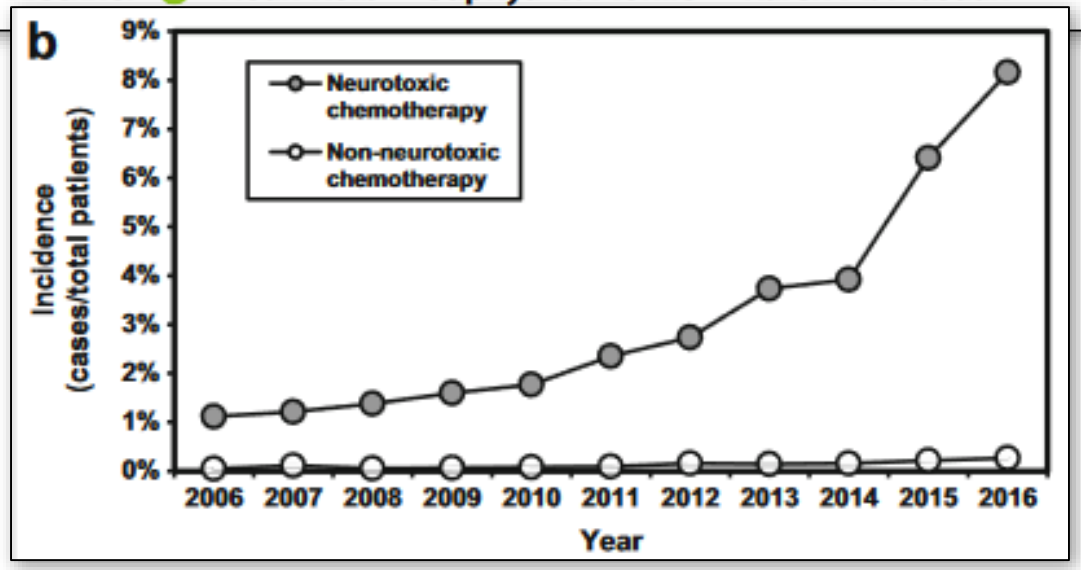
Supportive Care in Cancer
https://doi.org/10.1007/s00520-019-05063-x

ORIGINAL ARTICLE

Check for updates

Chemotherapy-induced peripheral neuropathy (CIPN) and its treatment: an NIH Collaboratory study of claims data

Jennifer S. Gewandter[1] · Amber S. Kleckner[2] · James H. Marshall[3] · Jeffrey S. Brown[3] · Lesley H. Curtis[4] · Javier Bautista[2] · Robert H. Dworkin[1] · Ian R. Kleckner[2] · Noah Kolb[5] · Supriya G. Mohile[6] · Karen M. Mustian[2]



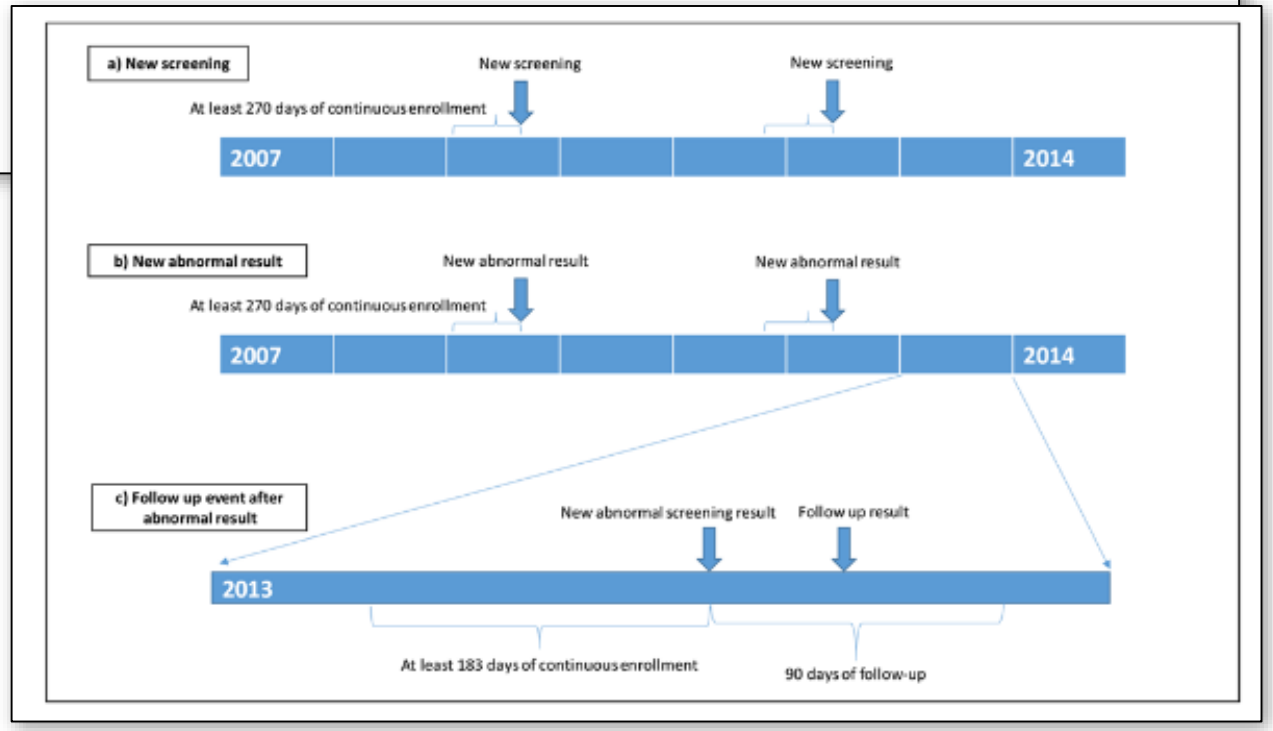
- 187,000 exposed to neurotoxic chemo
- 284,000 exposed to non-neurotoxic chemo

Cancer screening and follow up

Cancer Screening Results and Follow-up Using Routinely Collected Electronic Health Data: Estimates for Breast, Colon, and Cervical Cancer Screenings

Sudha R. Raman, PhD[1], Jeffrey S. Brown, PhD[2], Lesley H. Curtis, PhD[1], Kevin Haynes, MSCE, PharmD[3], James Marshall, MPH[2], Pamala A. Pawloski, PharmD[3], and Richard Platt, MD, MSc[2]

J Gen Intern Med 34(3):341–3
DOI: 10.1007/s11606-018-4697-y



Patients with new abnormal screening results:

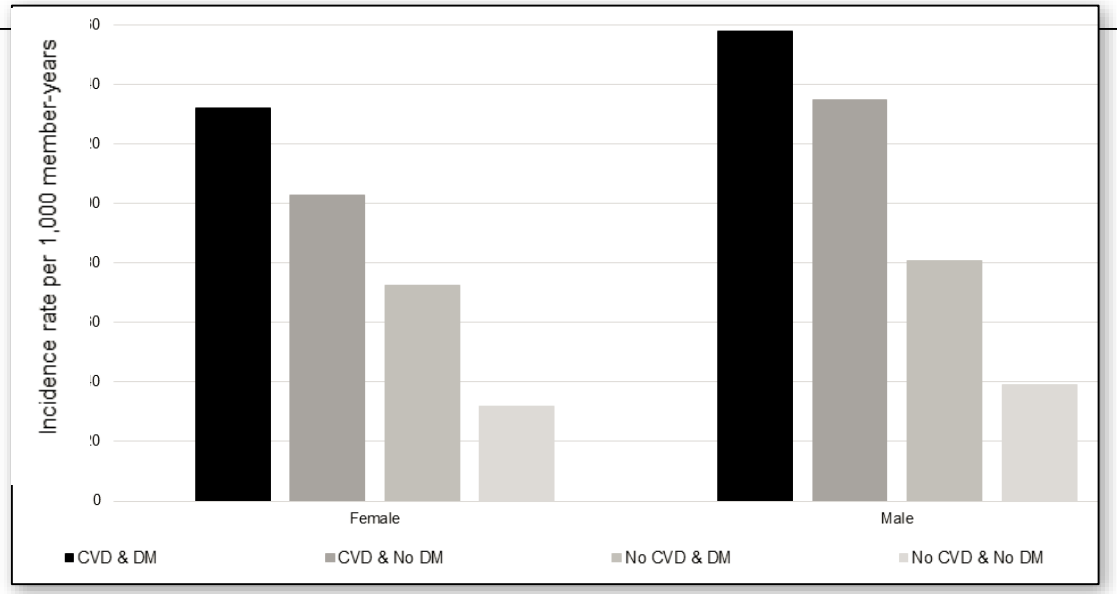
- Colorectal: 70K
- Breast: 1.1M
- Cervical: 781K

- Also addressed % with follow-up and time lag

Statin use in the elderly

Incidence of statin use in older adults with and without cardiovascular disease and diabetes mellitus, January 2008- March 2018

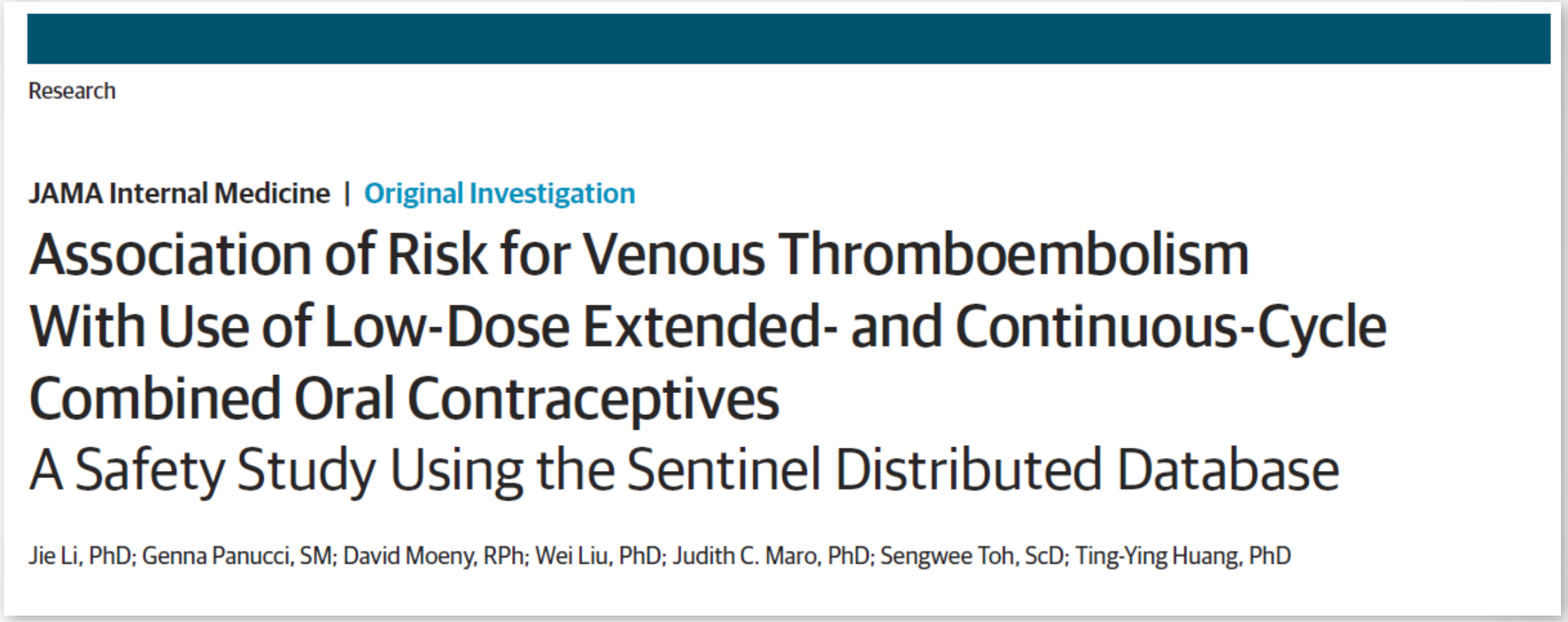
Catherine A. Panozzo, Lesley H. Curtis, James Marshall, Lawrence Fine, Barbara L. Wells, Jeffrey S. Brown, Kevin Haynes, Pamala A. Pawloski, Adrian F. Hernandez, Sarah Malek, Beth Syat, Richard Platt



- 758K people ≥75 years old
- 109K initiated statins
- 55K became long term users

PLOS One. In press

Propensity score matched new user comparisons



Research

JAMA Internal Medicine | Original Investigation

Association of Risk for Venous Thromboembolism With Use of Low-Dose Extended- and Continuous-Cycle Combined Oral Contraceptives

A Safety Study Using the Sentinel Distributed Database

Jie Li, PhD; Genna Panucci, SM; David Moeny, RPh; Wei Liu, PhD; Judith C. Maro, PhD; Sengwee Toh, ScD; Ting-Ying Huang, PhD

Li JAMA Int Med 2018;178:1482

Continuous vs Cyclic Oral Contraceptives and Venous Thromboembolism

- **Question: Is risk of venous thromboembolism (VTE) higher with use of extended/continuous combined oral contraceptives (COCs) than cyclic COCs?**
- **Population: 210,691 continuous initiators and 522,316 cyclic initiators**
- **VTE events: 228 among continuous users and 297 in cyclic users**
- **Selected characteristics: Continuous users more likely to have**

Age >35 years:	**31% vs 23%**
CV/metabolic conditions:	**7% vs 5%**
Gynecologic conditions:	**40% vs 32%**

- **Propensity score matched Hazard Ratio: 1.32 (1.07-1.64)**
- **Adjusted absolute risk difference 0.27/1,000 persons (0.35/1,000 p-yrs)**

Li JAMA Int Med 2018;178:1482

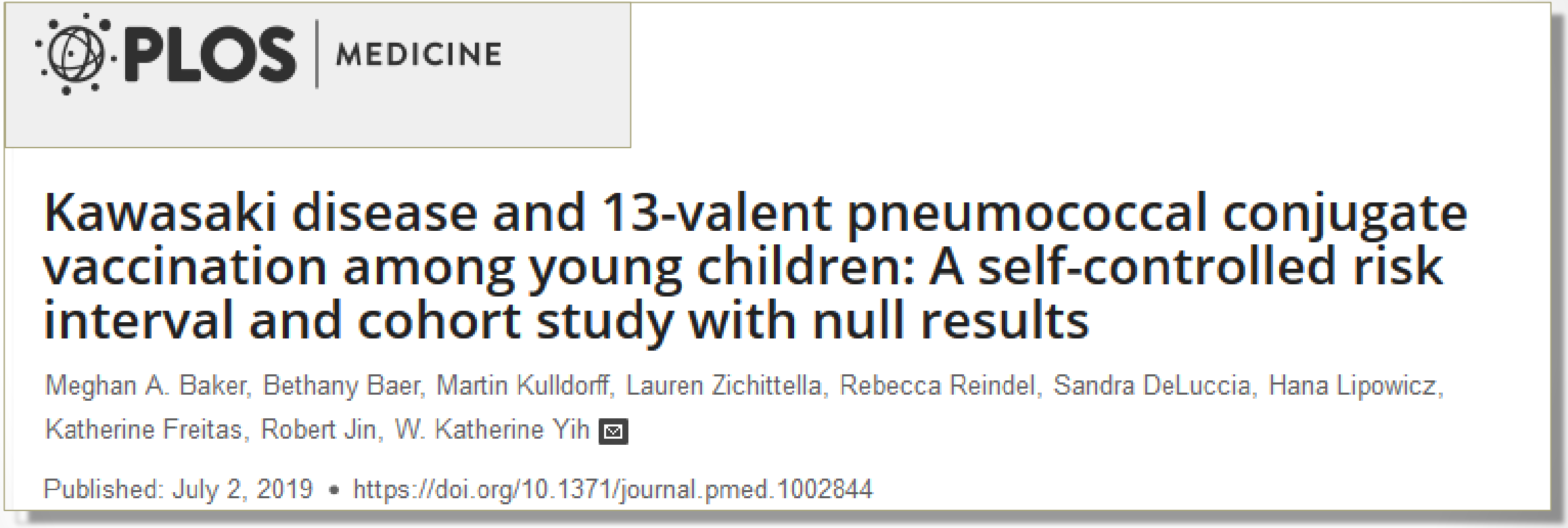
DRN organizations and investigators are part of delivery systems

- Subject to approval of system leadership, and IRBs when appropriate, it is possible to:
  - Identify individuals, providers, sites of care
  - Directly contact individuals and providers

Capabilities

- Work with Sentinel's highly curated distributed dataset
- Obtain full text records

Full text record retrieval



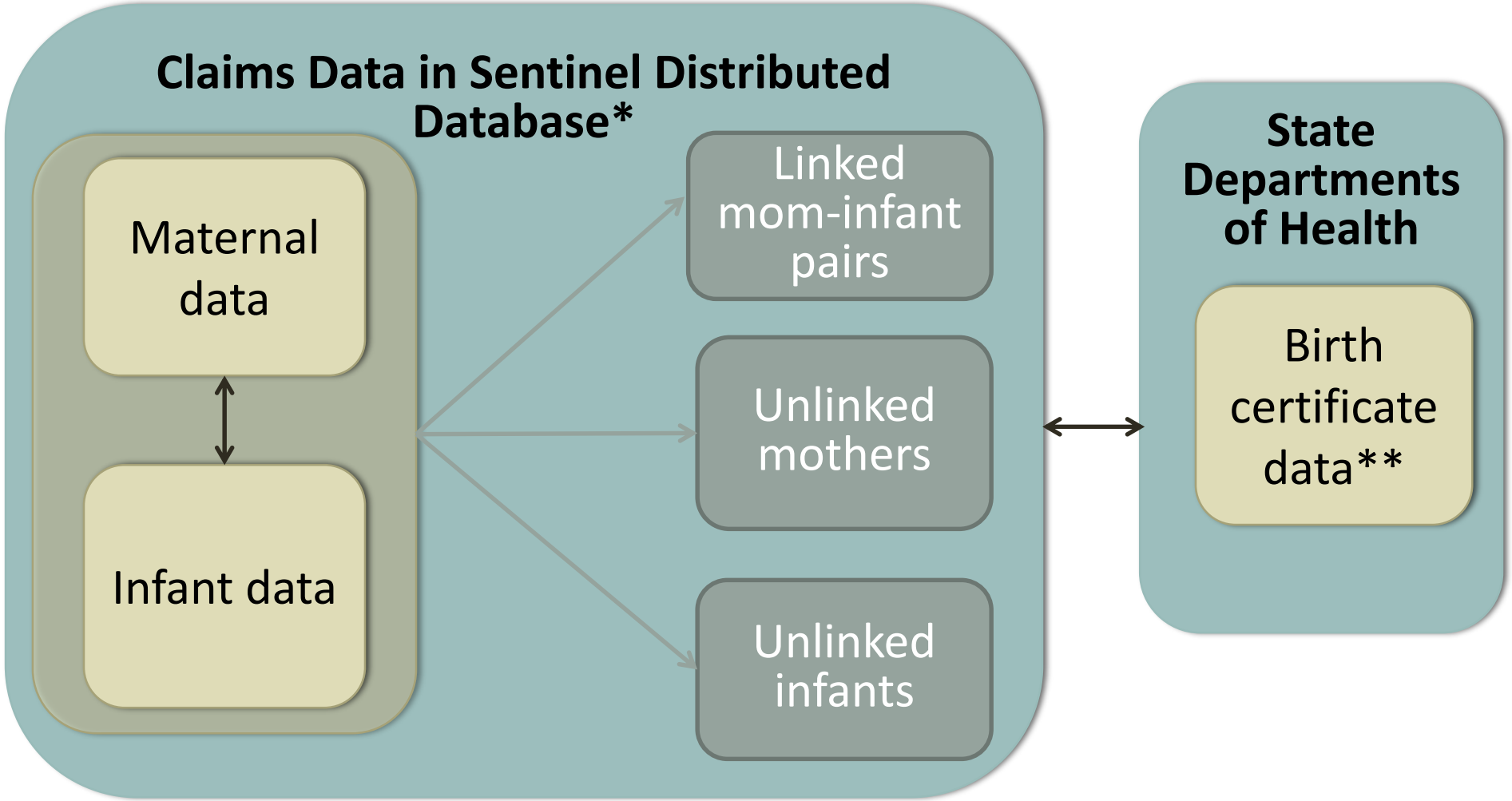
Kawasaki and Pneumococcal Conjugate Vaccine (PCV-13)

- 6,177,795 doses of PCV13 vaccine were identified
- 206 potential cases of Kawasaki disease, ascertained by the presence of ICD-9 code 446.1, identified within 70 days of immunization
- 184 (89%) charts were obtained for expert adjudication
- 125 (68%) confirmed as Kawasaki level 1
- Self-controlled risk interval logistic regression, **age adjusted risk ratio was 1.07** (95% CI 0.70–1.63; *p* = 0.76)

Capabilities

- Work with Sentinel's highly curated distributed dataset
- Obtain full text records
- Link to external registries

Linking Claims to Birth Registries

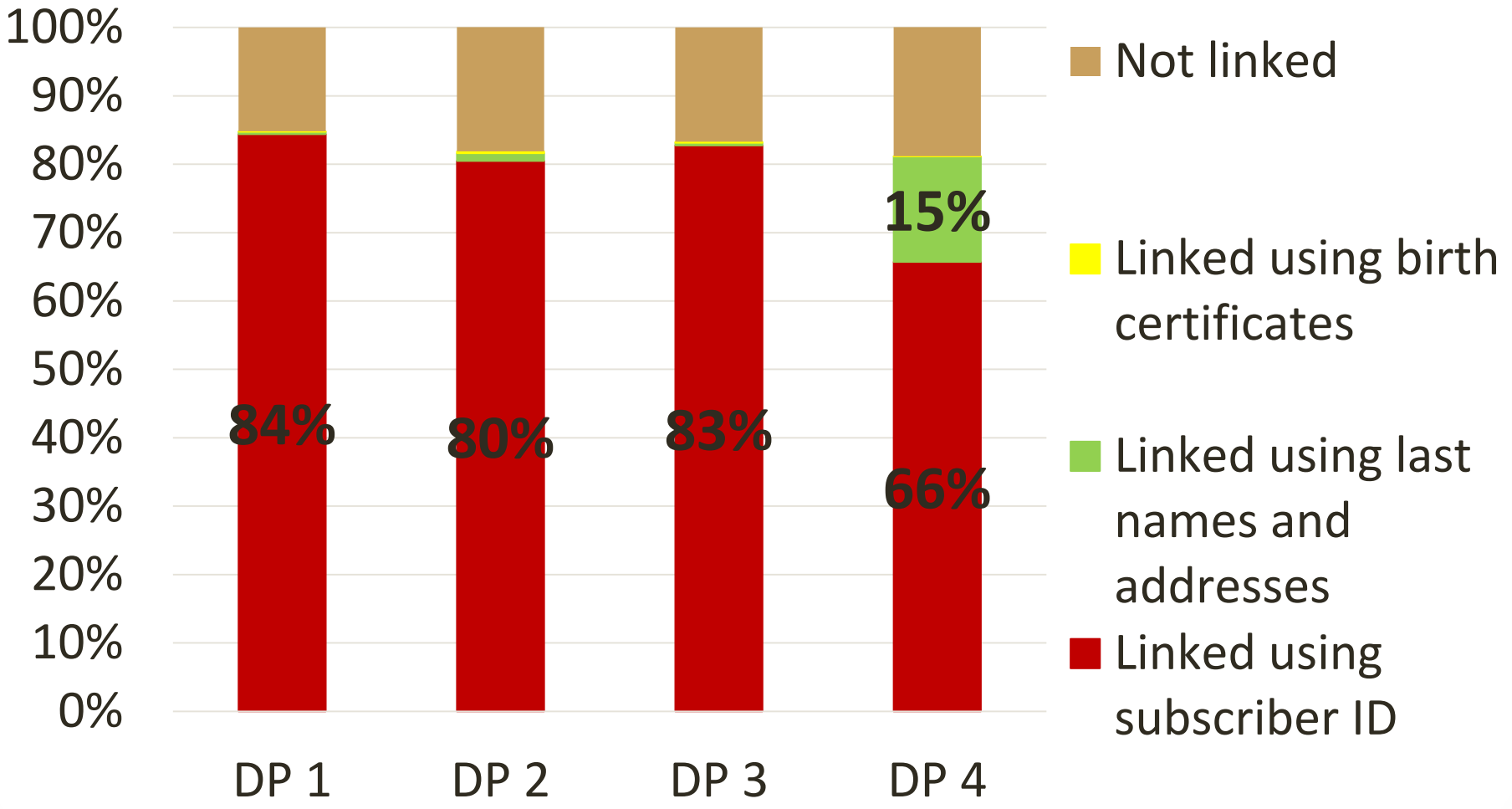


* 4 Data Partners

** Birth certificates available for 9 states

www.sentinelinitiative.org/sites/default/files/Sentinel-ICPE-2017-Presentation-PRISM-Mother-Infant-Cohort.pdf

Percent deliveries linked to infants (N=651,607)

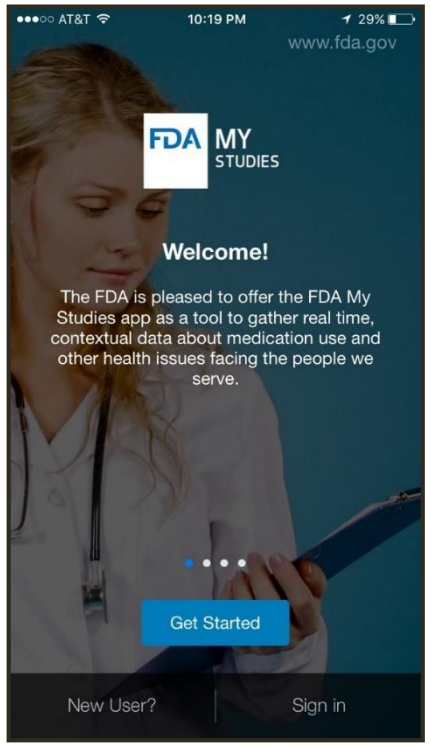


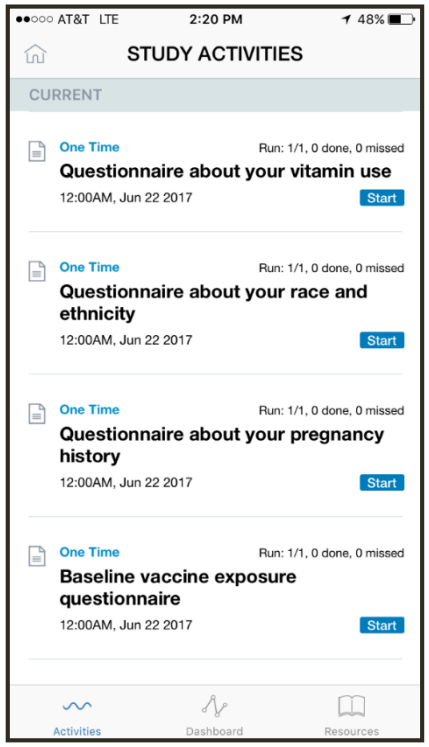
www.sentinelinitiative.org/sites/default/files/Sentinel-ICPE-2017-Presentation-PRISM-Mother-Infant-Cohort.pdf

Capabilities

- Work with Sentinel's highly curated distributed dataset
- Obtain full text records
- Link to external registries
- Collect patient reported data

The MyStudies Smartphone App





- Public domain customizable smartphone app
- Supports secure linkage to individuals' own data in the distributed dataset
- Compliant with 21 CFR part 11, FISMA, and HIPAA

www.fda.gov/drugs/science-and-research-drugs/fdas-mystudies-application-app

Capabilities

- Work with Sentinel's highly curated distributed dataset
- Obtain full text records
- Link to external registries
- Collect patient reported data
- Contact providers
- Conduct randomized trials

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IMPACT-AFib: An 80,000 Person Randomized Trial Using the FDA Sentinel System Platform

IMPACT-AFib randomized trial

IMplementation of a randomized controlled trial to im**P**rove treatment with oral **A**nti**C**oagulan**T**s in patients with **A**trial **Fib**rillation

- Direct mailer to health plan members with AFib, high risk for stroke and no oral anticoagulant treatment, and to their providers, to encourage consideration of treatment
- Use claims data and pharmacy dispensing information to:
  - Identify eligible patients
  - Assess new oral anticoagulant dispensings and refills
  - Identify stroke, transient ischemic attacks, and bleeds

Capabilities

- Work with Sentinel's highly curated distributed dataset
- Obtain full text records
- Link to external registries
- Collect patient reported data
- Contact providers
- Conduct randomized trials

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Mortality after discontinuation of buprenorphine:
Example of linking to an external registry

Denise Boudreau, PhD
Senior Scientific Investigator
Kaiser Permanente Washington Health Research Institute

Duration of medications to treat opioid use disorder and mortality

Background

- Methadone improves survival of opioid use disorder, but mortality increases after treatment ends
- Buprenorphine is increasingly used
- Patients, clinicians, and policymakers need to know if there is some “safe” duration of buprenorphine and other drugs
- Specific questions include:
  - Optimal duration of treatment
  - Whether to taper or discontinue treatment abruptly

Submitted to NIDA CTN concept proposals May 2019 and not funded

Submitting as NIDA R01 TBD

Specific aims

- Aim 1: What is the 1-year overall mortality rate and fatal overdose rate among patients who discontinue buprenorphine, naltrexone, and methadone compared to those who continue, adjusted for differences in demographic, clinical, and system factors?
  - H1: Mortality rates are higher off versus on treatment.

- Aim 2: Estimate the 1-year overall mortality rate and fatal overdose rate and test how mortality rates differ by duration of treatment prior to discontinuation.
  - H2: There is an inverse dose-response association between duration of treatment and post-discontinuation mortality.

Secondary aims

- Replicate Specific Aims for individual treatments (buprenorphine alone, buprenorphine w/ naloxone, injectable naltrexone, methadone) and for other outcomes (suicide attempt and non-fatal OD– separately and as a composite endpoint with mortality)
- Estimate changes in mortality rates during the first year off treatment, e.g., first 4 weeks vs remainder of the year
- Estimate mortality rates and test for differences by:
  - Switched to naltrexone vs switched to methadone vs maintained on buprenorphine;
  - Taper buprenorphine vs stop abruptly
  - Demographic and clinical risk factors, e.g. mental health and other substance use disorders, benzodiazepine use, co-prescribing of naloxone
- Describe patient characteristics associated with post-discontinuation mortality

Study design

- Design and sample:
  Retrospective new user cohort of users 16+ years of age in 2008-2018
- Participating organizations:
  HealthCore, Aetna, Kaiser Washington, Kaiser Northern California, Health Partners, and Harvard Pilgrim Health Care
- Data: 1-year before treatment until death, 12/31/2019, or disenrollment (survivors)
- Main exposures:
  1) Exposure to drugs of interest; 2) duration of treatment.
  Manually review charts sample who discontinue
- Main outcomes:
  Fatal overdose and all deaths determined by linking to the National Death Index
- Secondary outcomes: Attempted suicides, and non-fatal overdose from diagnosis codes
- Analytic plan: Modified Poisson regression to estimate incidence rate ratios, adjusting for duration of treatment along with a parsimonious list of potential confounders

Prep to research data

- Sites provided preliminary data for the submission on a very tight timeline via distributed data model
- ~159,000 buprenorphine users and ~12,000 naltrexone users among ~52 million unique patients during 2008-2017
- 80% power to detect ~45% excess risk following discontinuation

	Buprenorphine users	Naltrexone users
	N=158,660	N=11,786
	%*	
Age first use, yrs		
16-19	5%	4%
20-29	33%	40%
30-39	29%	20%
40-49	18%	18%
50-59	12%	13%
60-69	3%	4%
70-79	<1%	<1%
Sex		
Female	38%	36%
Male	62%	64%
Year first use		
2008	16%	3%
2009	13%	3%
2010	13%	4%
2011	8%	6%
2012	7%	8%
2013	8%	10%
2014	8%	12%
2015	8%	15%
2016	9%	19%
2017	10%	20%

Strengths of the Collaboratory DRN for this study

- Leverage Sentinel's highly curated distributed common data model to build a large cohort with rich data for addiction medicine research
- Build on prior collaborations with data partners and data coordination center
- Link to National Death Index
- Conduct chart review

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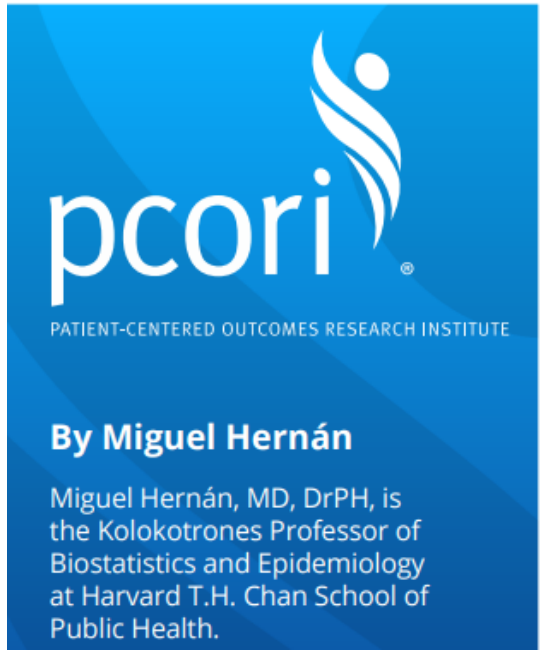
Comparative effectiveness of oral hypoglycemics:
Example of obtaining patient reported data

Kevin Haynes, PharmD, MSCE
Principal Scientist
HealthCore

Comparative effectiveness of 2nd line oral diabetes drugs

- PCORI requested information regarding an ability to emulate a clinical trial of 2nd line oral diabetes drugs
- Respondents were required to address study design issues explicated in this white paper:



Antihyperglycemic Therapy and Cardiovascular Risk: Design and Emulation of a Target Trial Using Healthcare Databases

Published May 24, 2019

Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. American Journal of Epidemiology 2016;183:758-64.

White Paper: Recommended data elements

Eligibility Criteria:

- Type 2 Diabetes
- Age >= 45
- Antihyperglycemic monotherapy with metformin
- Not currently pregnant
- No history of specific conditions in the year before beginning second-line therapy
- Suboptimal glycemic control

Treatment Strategies:

- Assigned to one of the following treatments within 12 months of suboptimal control:

GLP-1 receptor agonist

SGLT2 inhibitor

DPP-4 inhibitor

Sulfonylurea

Outcomes: MACE

- Myocardial infarction
- Stroke
- Hospitalization due to heart failure
- Cardiovascular death
- Severe hypoglycemia
- Microvascular disease
- Renal impairment
- All-cause mortality

Key Covariates:

- Labs: Hba1c, eGFR
- Clinical: BP, Ht/Wt, Smoking

White Paper: Recommended data elements

Eligibility Criteria:

- Type 2 Diabetes
- Age >= 45
- Antihyperglycemic monotherapy with metformin
- Not currently pregnant
- No history of specific conditions in the year before beginning second-line therapy

- Suboptimal glycemic control

Treatment Strategies:

- Initiated one of the following as 2nd line treatment:

  GLP-1 receptor agonist

  SGLT2 inhibitor

  DPP-4 inhibitor

  Sulfonylurea

Available now for everyone

Available now for some;
Add'l Ht/Wt, smoking from pts

Available from Nat'l Death Index

Outcomes: MACE

- Myocardial infarction
- Stroke
- Hospitalization due to heart failure
- Cardiovascular death
- Severe hypoglycemia
- Microvascular disease
- Renal impairment

- All-cause mortality

Key Covariates:

- Labs: Hba1c, eGFR
- Clinical: BP, Ht/Wt, Smoking

Prep to Research Data Part 1:
Cohort Size, Data Completeness, and Longitudinality

	Number	Comments
Total population in 2018	14,228,136	All had medical and pharmacy benefits
Persons with Type 2 diabetes, 18 - 90 yrs	1,972,275	All have one year of medical and pharmacy benefits prior to first diagnosis of DM in 2018
Length of continuous retrospective observation		
At least 1 year	1,972,275	Follow-up time based on look back from first diabetes diagnosis in 2018.
At least 2 years	1,608,936	
At least 5 years	851,847	
At least 10 years	335,261	
For a population with T2DM diagnosed in 2013 with a one year baseline (1,540,948), the length of continuous prospective observation		
<1 year	305,173	Based on patients with a diabetes diagnosis in 2013 followed forward
1-2 yrs	220,085	
2-5 yrs	450,282	
> 5 yrs	565,408	

Prep to Research Data Part 2:
Follow up time After First Dispensings of Antidiabetic Drugs

	Total	0-1 years	1-2 years	2-5 years	5-10 years
Second Generation Sulfonylureas	1,948,113	613,978	383,221	585,776	365,138
Dipeptidyl Peptidase 4 Inhibitors	910,348	299,837	190,205	290,824	129,482
Glucagon-Like Peptide1 Receptor Agonists	424,697	169,430	96,541	118,217	40,509
Sodium Glucose Cotransporter-2 Inhibitors	318,545	132,139	81,905	101,677	2,824

Strengths of the Collaboratory DRN for this study

- Large population with defined person time during which rigorously curated, complete drug exposure and outcomes are available
- Laboratory test results, vital signs, height, weight, smoking available for a substantial fraction
- Patient-engagement through the **FDA MyStudies App** allows collection of:
  - Date of diabetes onset, race/ethnicity, height/weight, and smoking status
  - Seek authorizations to conduct member-level linkages to other data sources for richer clinical detail
- Subject matter experts with a deep understanding of the source data

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Outreach providers and patients/families to reduce prescribing cascades:
Example of an embedded pragmatic trial

Jerry H. Gurwitz, MD
Professor of Medicine, Family Medicine and Community Health, and
Population & Quantitative Health Sciences
University of Massachusetts Medical School
Executive Director, Meyers Primary Care Institute

CASCADES-AD

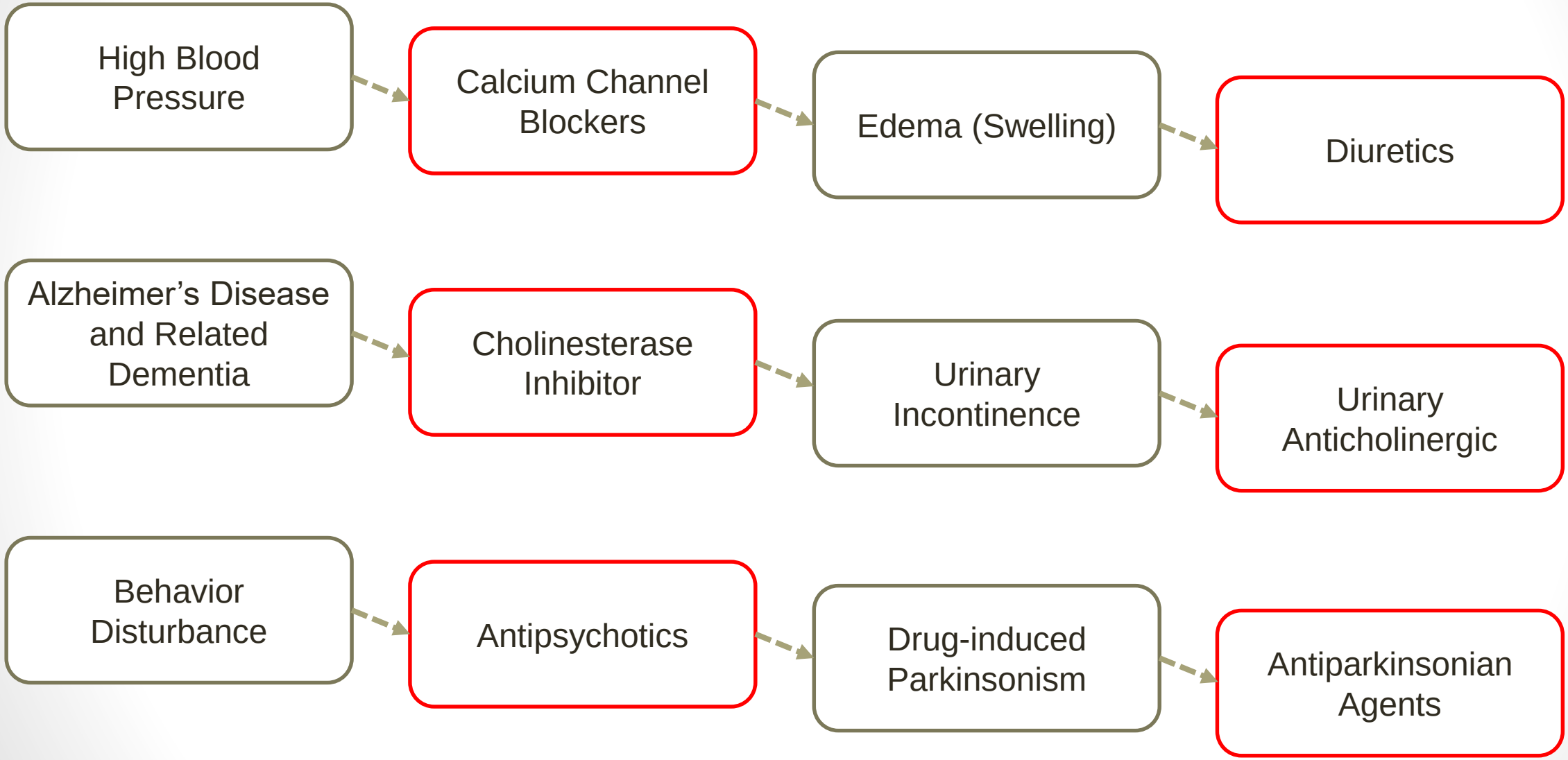
- Controlling And Stopping Cascades leading to Adverse Drug Effects Study in Alzheimer's Disease (CASCADES-AD)

- A collaborative endeavor of the Meyers Primary Care Institute, Harvard Pilgrim Health Care Institute, Women's College Research Institute, Anthem, and Humana

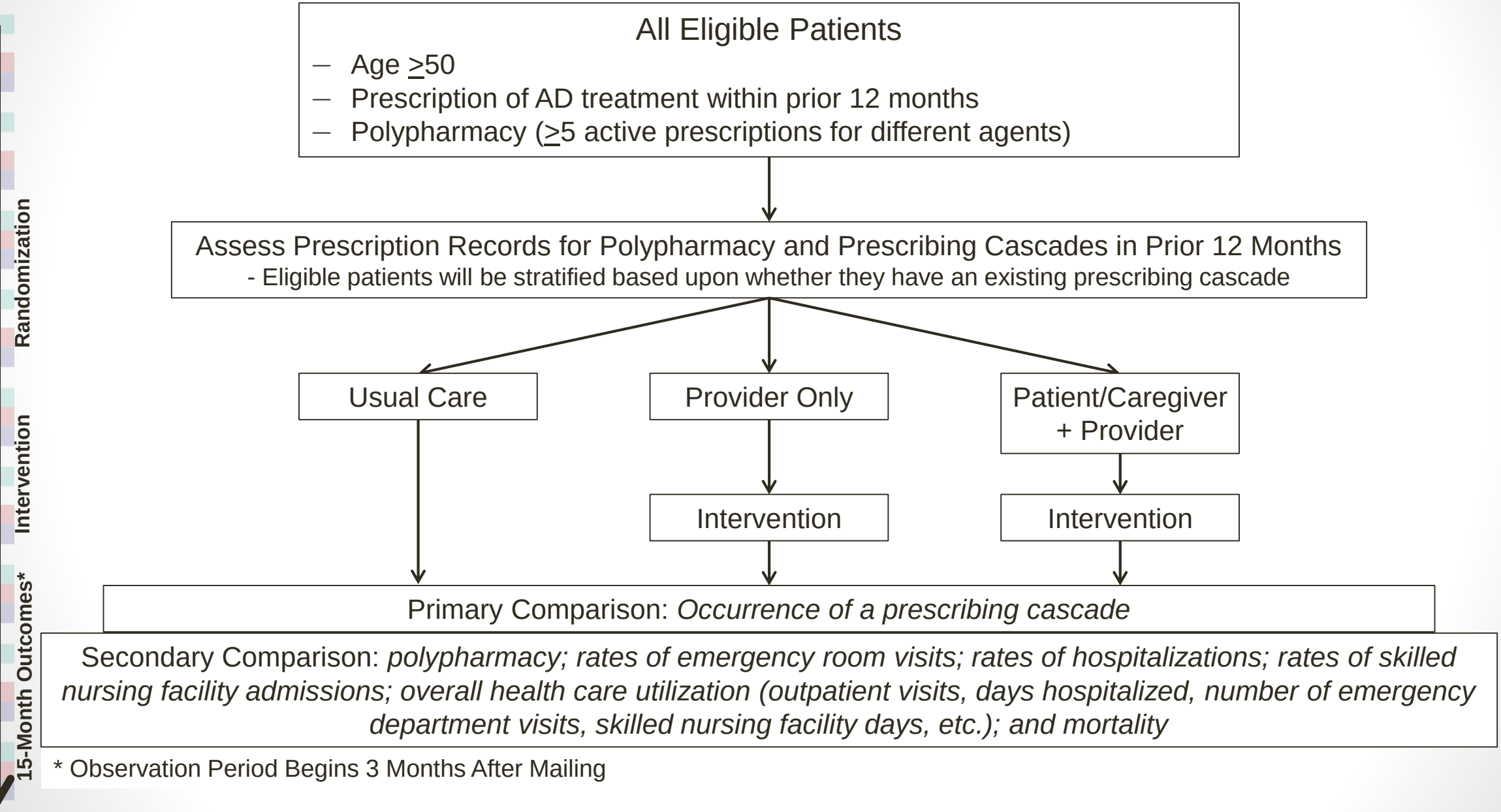
Funder: National Institute on Aging: R56 AG061813

JG

Exemplar Cascades



CASCADES-AD Trial Study Design



* Observation Period Begins 3 Months After Mailing

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Prep to Research Data 1: Prevalence of CCB-Diuretic Prescribing Cascade

- AD identified using NDC codes for a medication specific to AD
- Subjects ≥ 50 years of age and have received an AD drug within year prior to index date 1/1/2017
- With medical and pharmacy coverage for 1 year through cohort entry
- We excluded individuals with an institutional stay encounter 45-days prior to index date

Prep to Research Data 2: Prevalence of CCB-Diuretic Prescribing Cascade

- **CCB-Diuretic Prescribing Cascade is <u>not</u> common**
- Among 121,538 participants with Alzheimer's disease or related dementias, only 0.1% of eligible patients had incident CCB use followed by incident diuretic use
- Another 1.3% had prevalent CCB use, followed by incident diuretic use
- These constitute only 1.4% - which is not enough to provide adequate power for CASCADES-AD

Strengths of the Collaboratory DRN for this study

- Ability to embed a randomized clinical trial in real world clinical settings
  - Direct outreach to providers AND to patients/families
- Ability to determine feasibility with high accuracy allows confidence in planning of ambitious clinical trials

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Working with the Distributed Research Network

Christopher Granger, MD
Professor of Medicine
Duke University

Summary

- The NIH Collaboratory Distributed Research Network is a valuable resource for a wide array of studies
- Specific attributes include:
  - Health plan based scientists with deep expertise in the data and operations of their organizations, as well as subject matter and methodologic expertise
  - Extensively curated longitudinal data with complete capture of all medically attended events during known period of time
  - Ability to supplement these data by linking to external registries or by directly contacting providers and members or their families
  - Ability to embed pragmatic clinical trials in practice settings
  - Ability to develop preliminary data as part of prep-to-research activities

To work with the DRN

- DRN investigators seek partners on a wide range of topics

- Learn more – https://rethinkingclinicaltrials.org/nih-collaboratory-drn
- Contact us – nih-collaboratory@dm.duke.edu