Using Sentinel to Evaluate Effectiveness or Efficacy

Richard Platt MD, MS
Harvard Pilgrim Health Care Institute and
Harvard Medical School
for the Sentinel Investigators

September 19, 2017

Sentinel | Drugs | Vaccines, Blood & Biologics | Communications | FDA-Catalyst | Report Finder

www.sentinelinitiative.org

Sentinel is a National Medical Product Monitoring System

LEARN MORE

ABOUT

- Background
- Coordinating Center
- Privacy and Security
- The Sentinel System Story

SAFETY ASSESSMENTS

- Active Risk Identification and Analysis System
- Assessments of Drugs
- Assessments of Vaccines, Blood, & Biologics

DATA & SURVEILLANCE TOOLS

- Distributed Database and Common Data Model
- Complementary Data Sources
- Routine Querying Tools
- Validations and Literature Reviews

COMMUNICATIONS

- FDA Safety Communications
- Publications and Presentations
- Sentinel Initiative Events
- Report Finder

Latest Postings

SPOTLIGHT

- Sentinel Initiative Public Workshop - Ninth Annual
  Tue, 11/08/2016

STUDY PROTOCOLS & SURVEILLANCE PLANS

- Influenza Vaccines and Birth Outcomes Protocol (PRISM)
  Fri, 01/20/2017
- Identify and Evaluate Manufacturer-Level Drug Utilization and Switching Patterns in Sentinel
  Mon, 12/12/2016

MODULAR PROGRAMS

- Querying Tools: Overview of Functionality and Technical Documentation
  Tue, 12/27/2016
- Influenza antiviral drug use 2010-2015
  Mon, 10/31/2016

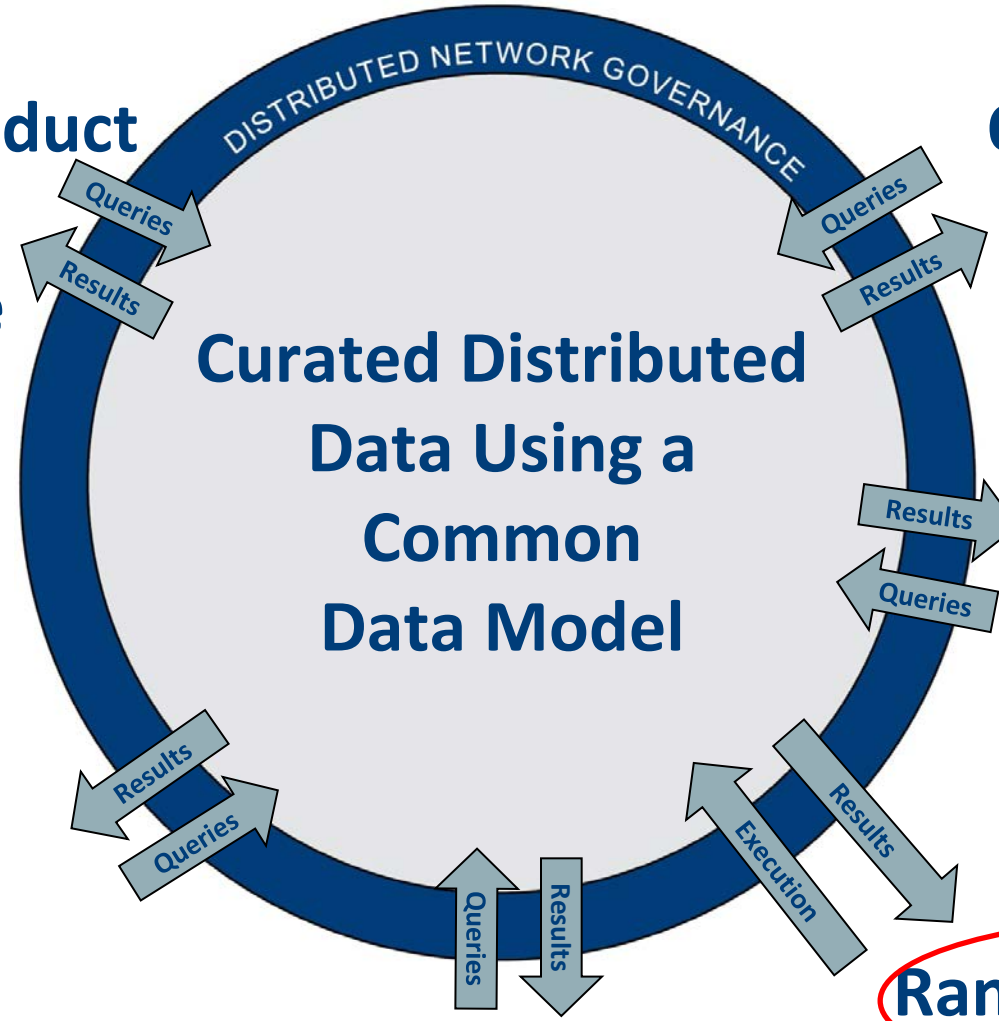
Disclosures

- None related to this presentation

Sentinel's charge

Assess the use, safety, and effectiveness of regulated medical products by using electronic healthcare data plus other resources

Create data, informatics, and methodologic capabilities to support these activities



Medical Product Safety Surveillance

Quality of Care

Public Health Surveillance

Clinical Research

Randomized trials

Comparative Effectiveness Research

Sentinel partner organizations

Lead – HPHC Institute

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

Data and scientific partners

HealthCore Anthem
VANDERBILT SCHOOL OF MEDICINE
health care systems research network
MASSACHUSETTS
HUMANA
HCA Hospital Corporation of America
CMS.gov
OPTUM
KAISER PERMANENTE
aetna

Scientific partners

QUINTILES
DukeMedicine
Penn Medicine
UAB
DEPARTMENT OF MEDICINE BRIGHAM AND WOMEN'S HOSPITAL HARVARD MEDICAL SCHOOL
AHIP America's Health Insurance Plans
UNC GILLINGS SCHOOL OF GLOBAL PUBLIC HEALTH
HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH
UF College of Pharmacy UNIVERSITY of FLORIDA
UIC
THE UNIVERSITY OF IOWA COLLEGE OF PUBLIC HEALTH
RUTGERS

Numerous data elements are available

Administrative

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Person ID	**Person ID**	**Person ID**	**Person ID**	**Person ID**	**Person ID**
Enrollment start & end dates	Birth date	Dispensing date	Service date(s)	Service date(s)	Service date(s)
Drug coverage	Sex	National drug code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical coverage	ZIP code	Days supply	Encounter type & provider	Encounter type & provider	Encounter type & provider
Medical record availability	Etc.	Amount dispensed	Facility	Diagnosis code & type	Procedure code & type
			Etc.	Principal discharge diagnosis	Etc.

Clinical

Lab Result	Vital Signs
Person ID	**Person ID**
Result and specimen collection dates	Measurement date and time
Test type, immediacy & location	Height and weight
Logical Observation Identifiers Names and Codes (LOINC ®)	Diastolic & systolic BP
Test result & unit	Tobacco use & type
Etc.	Etc.

Registry

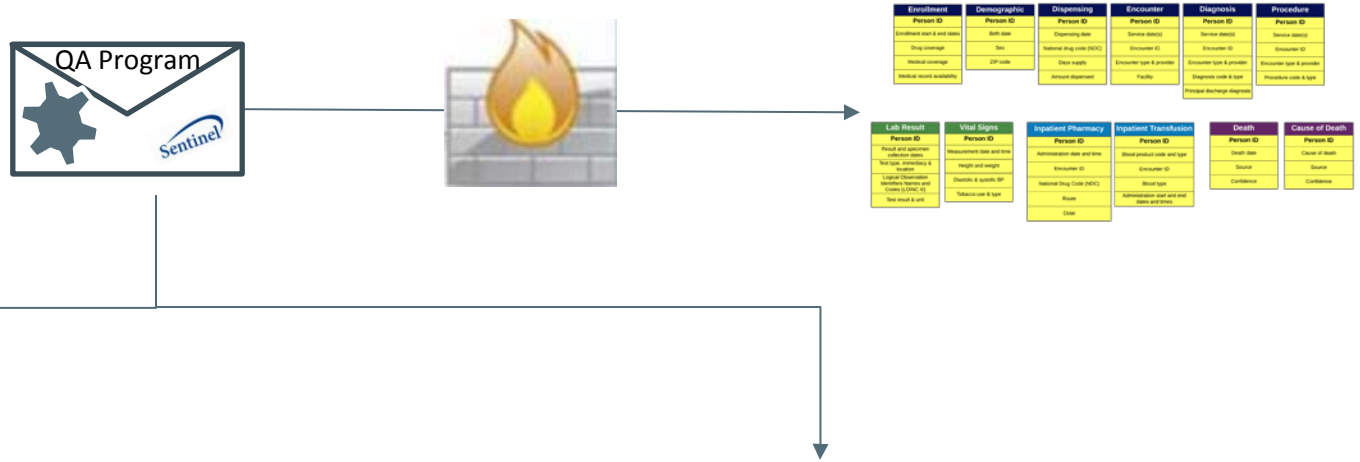
Death	Cause of Death	State Vaccine
Person ID	**Person ID**	**Person ID**
Death date	Cause of death	Vaccination date
Source	Source	Admission Type
Confidence	Confidence	Vaccine code & type
Etc.	Etc.	Provider
		Etc.

Inpatient

Inpatient Pharmacy	Inpatient Transfusion
Person ID	**Person ID**
Administration date and time	Administration start and end date and time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion administration ID
Route	Transfusion product code
Dose	Blood Type
Etc.	Etc.

The quality assurance process

Send a standard QA program to check DP's data in waiting



Compliance Checks

Level 1: Completeness, validity, accuracy

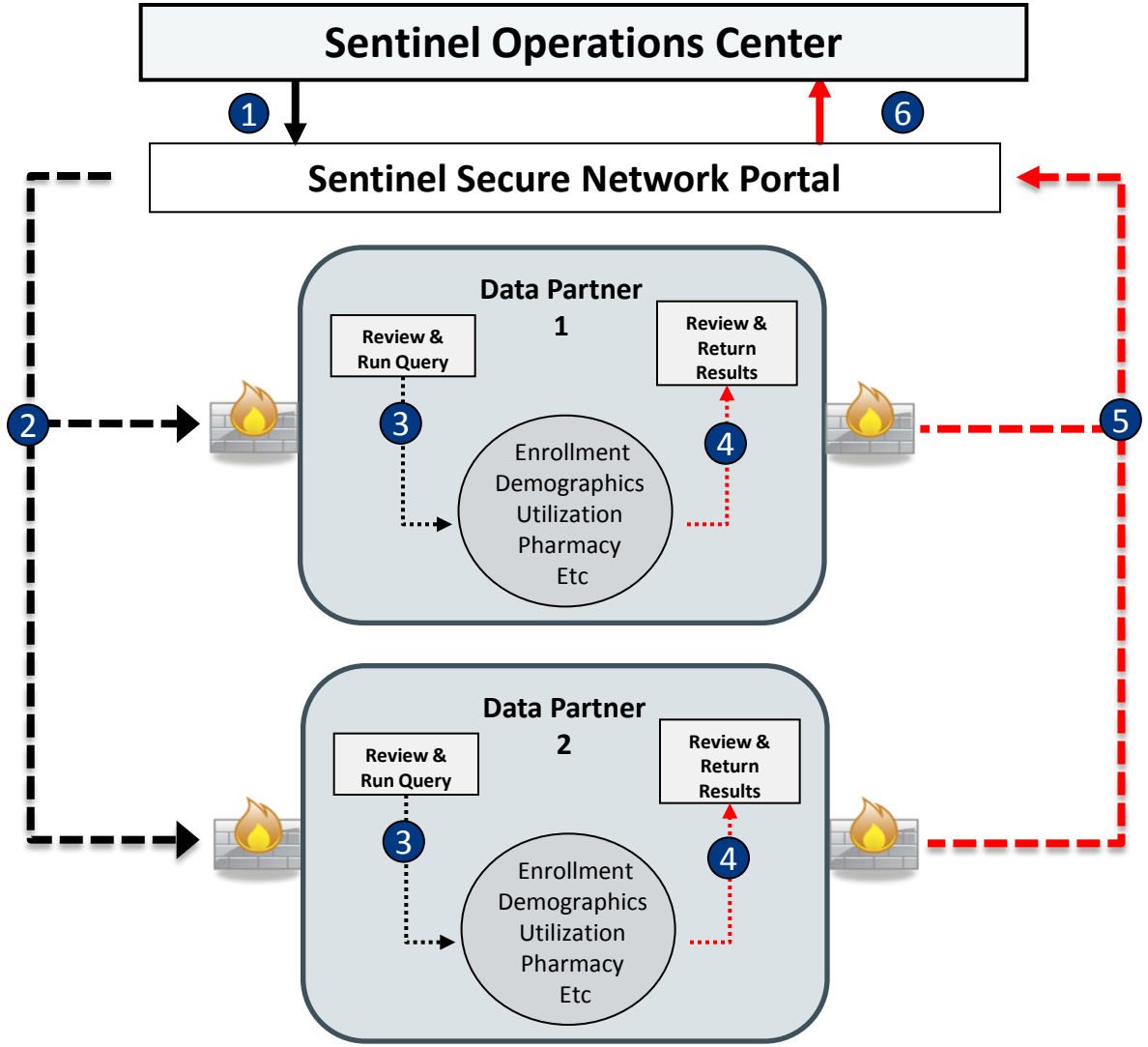
Level 2: Cross-variable and cross-table integrity

Judgment Call Checks

Level 3: Trends: consistency

Level 4: Logical: plausibility, convergence

Sentinel distributed analysis



1- User creates and submits query

2- Data Partners retrieve query

3- Data Partners review and run query against their local data

4- Data Partners review results

5- Data Partners return results via secure network

6 Results are aggregated and returned

Sentinel distributed database*

Population with well-defined person-time for which most medically-attended events are known

- 425 million person-years of observation time
- 43 million people currently accruing new data
- 5.9 billion dispensings
- 7.2 billion unique encounters
- 42 million people with ≥1 laboratory test result

* As of January 2017

Sentinel and effectiveness/efficacy

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials

Sentinel distributed data alone

Prospective Surveillance Pilot of Rivaroxaban Safety

Elizabeth Chrischilles

College of Public Health, University of Iowa

Workgroup

- Leads: Elizabeth Chrischilles, Ryan Carnahan
- Co-investigators: Joshua J. Gagne, Bruce Fireman, Jennifer Nelson, Sengwee Toh, Azadeh Shoaibi, Marsha E. Reichman, Shirley Wang, Michael Nguyen, Rongmei Zhang, Rima Izem, Margie R. Goulding, Mary Ross Southworth, David J. Graham, Candace Fuller, Hannah Katcoff, Tiffany S. Woodworth, Catherine Rogers, Ryan Saliga, Nancy D. Lin, Cheryl N McMahill-Walraven, Vinit P. Nair, Nandini Selvam
- Many thanks are due to Data Partners who provided data used in the analysis

Propensity Score Matching (1/2)

- Variable ratio propensity score (PS) matching (each new rivaroxaban user matched to up to 10 new warfarin users)
- Using nearest neighbor algorithm, matching caliper 0.05
- PS estimation and matching within Data Partner

Propensity Score Matching (2/2)

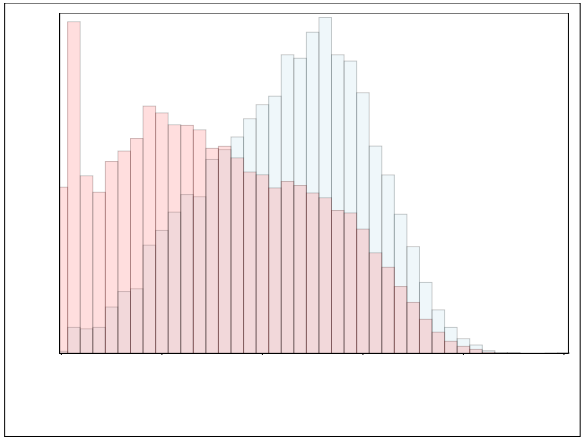
- 70+ confounders:
  - Age, sex, year of index date
  - Combined comorbidity score
  - Health service utilization
    - Counts of encounters by setting
    - Number of drugs
  - Procedures and diagnoses:
    - Risk factors for bleeding and schemic stroke
  - Medications:
    - Oral cardiovascular agents,
    - Medications that increase bleeding risk,
    - Interacting medications

Statistical Analysis

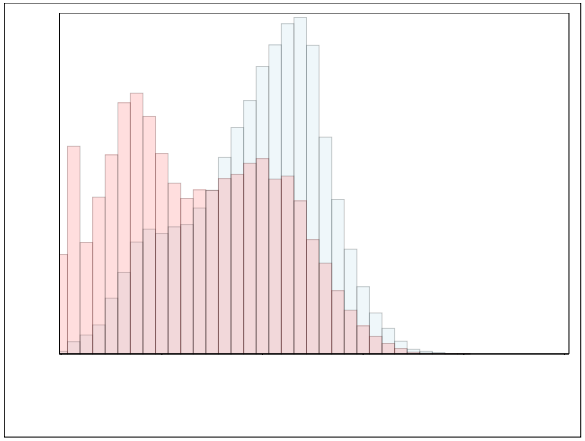
- Cox regression stratified by Data Partner and matched set to estimate hazard ratio
- Sequential testing
  - Group sequential design, multiple looks, flat boundary
  - Initial threshold for signal (5 looks): Wald z-score > 2.37 (P<0.018)
  - Revised signaling threshold (2 looks): Wald z-score >2.06 (P<0.039)
    - To reflect change of number of looks and amount of information at each look
    - Delay due to tool refinements
- End-of-surveillance analysis (one-time estimation)
  - Included only diagnosis codes in primary position

Histograms of Propensity Scores, Unmatched Cohort, 4 Data Partners, Gastrointestinal Bleeding Analysis Cohort

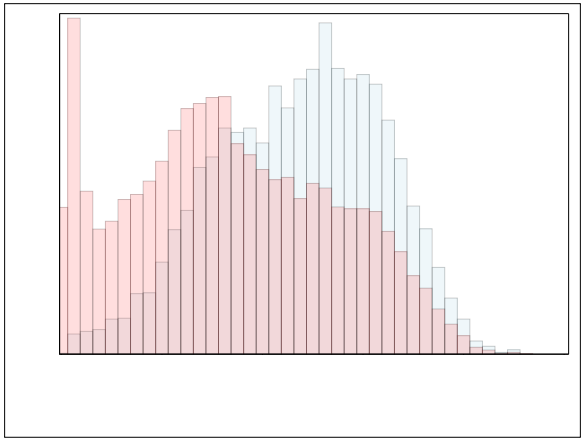
Data Partner 1



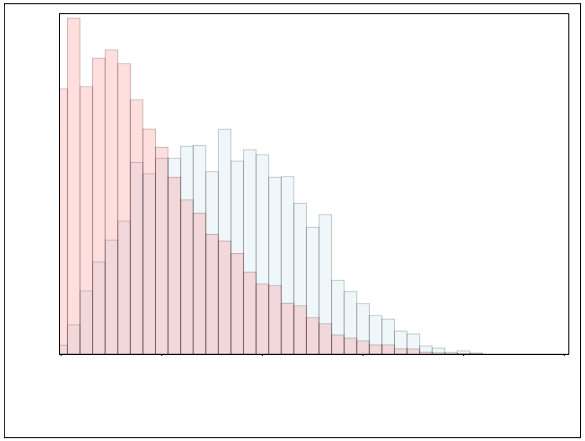
Data Partner 2



Data Partner 3



Data Partner 4



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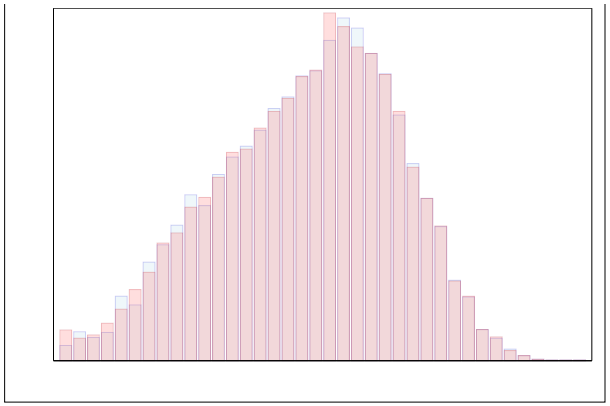
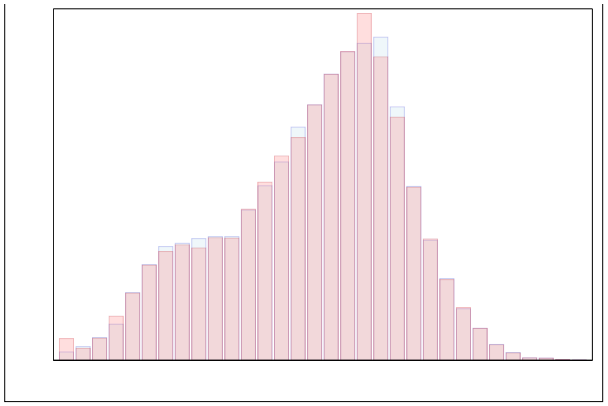
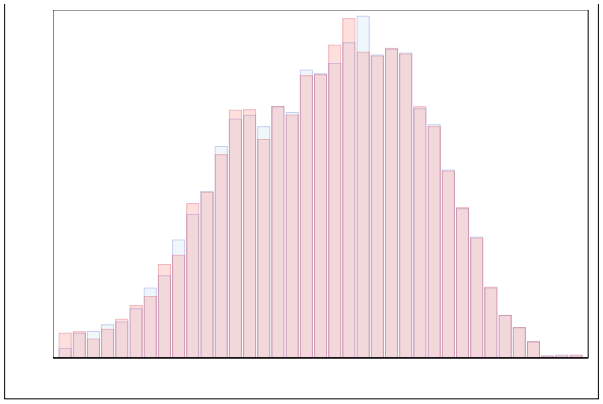


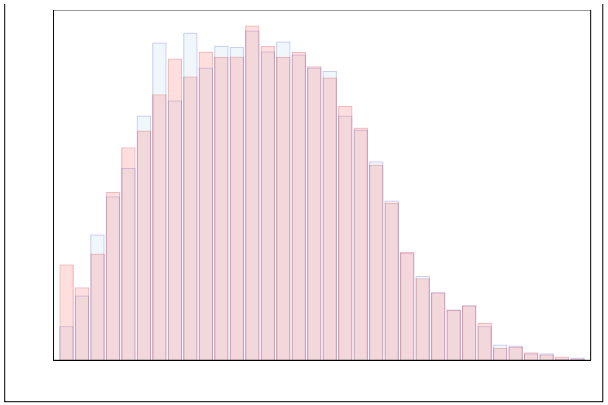
Data Partner 2



Data Partner 3



Data Partner 4

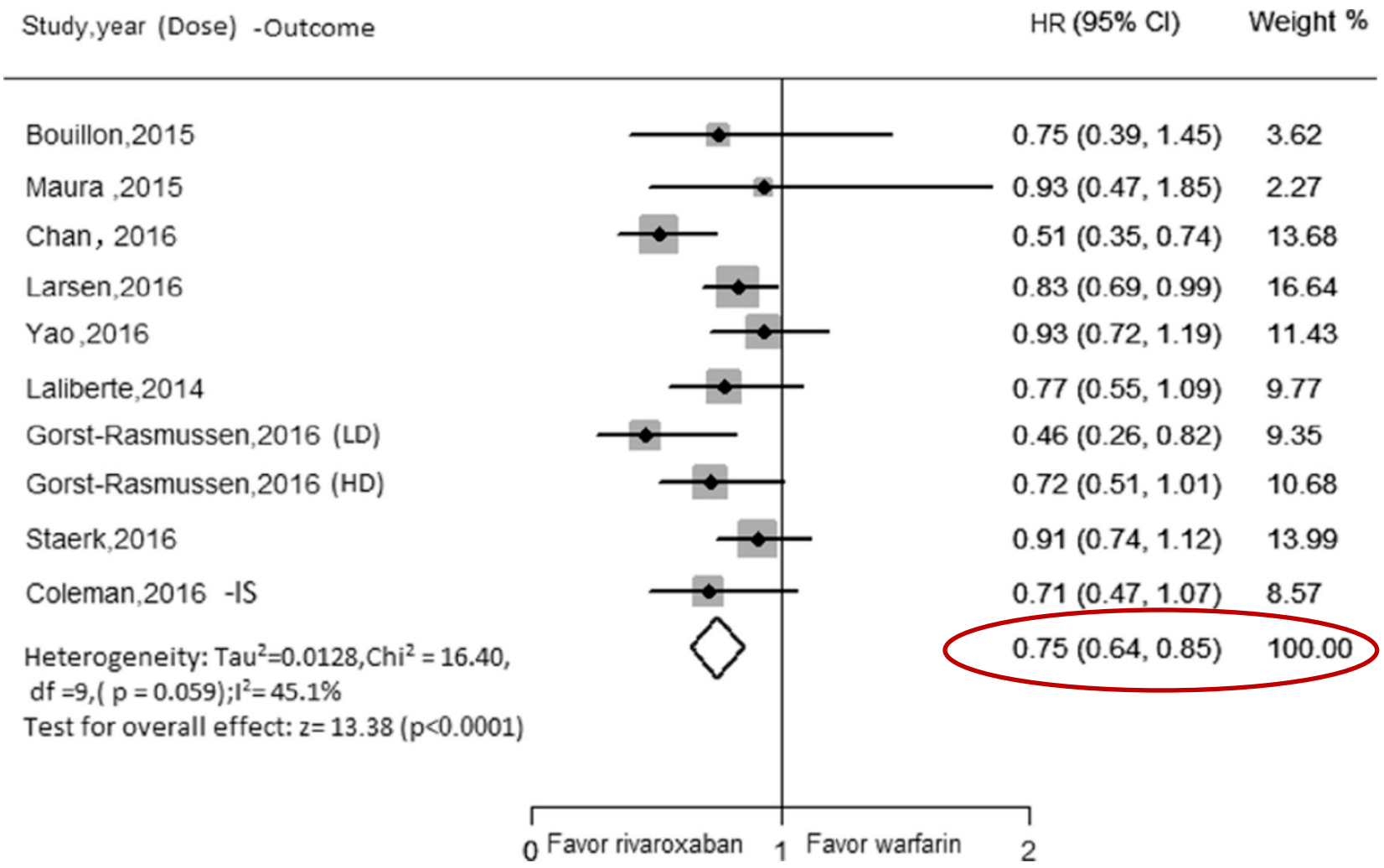


Rivaroxaban vs Warfarin: Comparing Sentinel to ROCKET-AF

	Hazard Ratio (95% CI)	
	ROCKET-AF[1]	Sentinel
GI Bleed	1.61 (1.30-1.99)	1.47 (1.29-1.67)
Intracranial hemorrhage	0.67 (0.47-0.93)	0.71 (0.50-1.01)
Ischemic stroke	0.94 (0.75-1.17)	0.61 (0.47-0.79)

[1]ROCKET-AF compared rivaroxaban with warfarin for stroke prevention in non-valvular atrial fibrillation Patel NEJM 2011;364:883

Rivaroxaban compared with warfarin in risk of stroke/TE in AF patients.



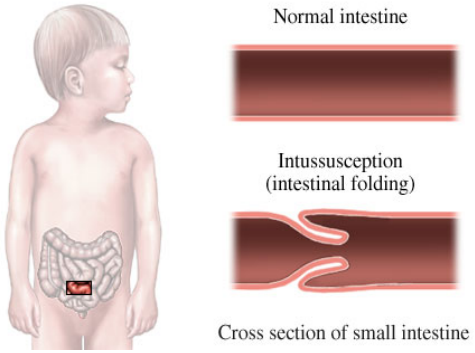
Ying Bai et al. Stroke. 2017;48:970-976

Sentinel with chart review

Risk of Intussusception after Rotavirus Vaccination: Results of the Mini-Sentinel/PRISM* Study

W. Katherine Yih, PhD, MPH

Sentinel Initiative Public Workshop 2014



* Post-licensure Rapid Immunization Safety Monitoring

Background

- RotaShield, first vaccine for prevention of rotavirus infection in infants, licensed in 1998
  - Withdrawn in 1999 due to risk of intussusception, a form of bowel obstruction
- For RotaTeq and Rotarix, no increased risk in clinical trials of >60,000 children each
  - But post-licensure studies in other countries later suggested increased risk of intussusception after both
- In 2010, FDA's Center for Biologics Evaluation and Research (CBER) initiated this study to quantify the possible risk among U.S. infants

Source data and chart review

- Data partners: Aetna, HealthCore, Humana
- Date range: 2004 - mid-2011
- CPT-4 codes for immunization:
  - CPT-4 codes 90680 (RotaTeq) and 90681 (Rotarix)
- CPT-4 and ICD-9 codes for outcomes:
  - ICD-9 codes 560.0 (intussusception), 543.9;
    CPT-4 code 74283 (therapeutic enema…)
- **Chart review to validate both outcome and exposure**
  - **Pediatrician adjudicators classified cases using Brighton Collaboration criteria**

Intussusception confirmation

Algorithm-identified potential cases = 343

Potential cases are from whole population aged 5-36 weeks and include unexposed

Intussusception confirmation

Algorithm-identified potential cases = 343

Those for whom chart obtained =267 (78%)

Potential cases are from whole population aged 5-36 weeks and include unexposed

Intussusception confirmation

Algorithm-identified potential cases = 343

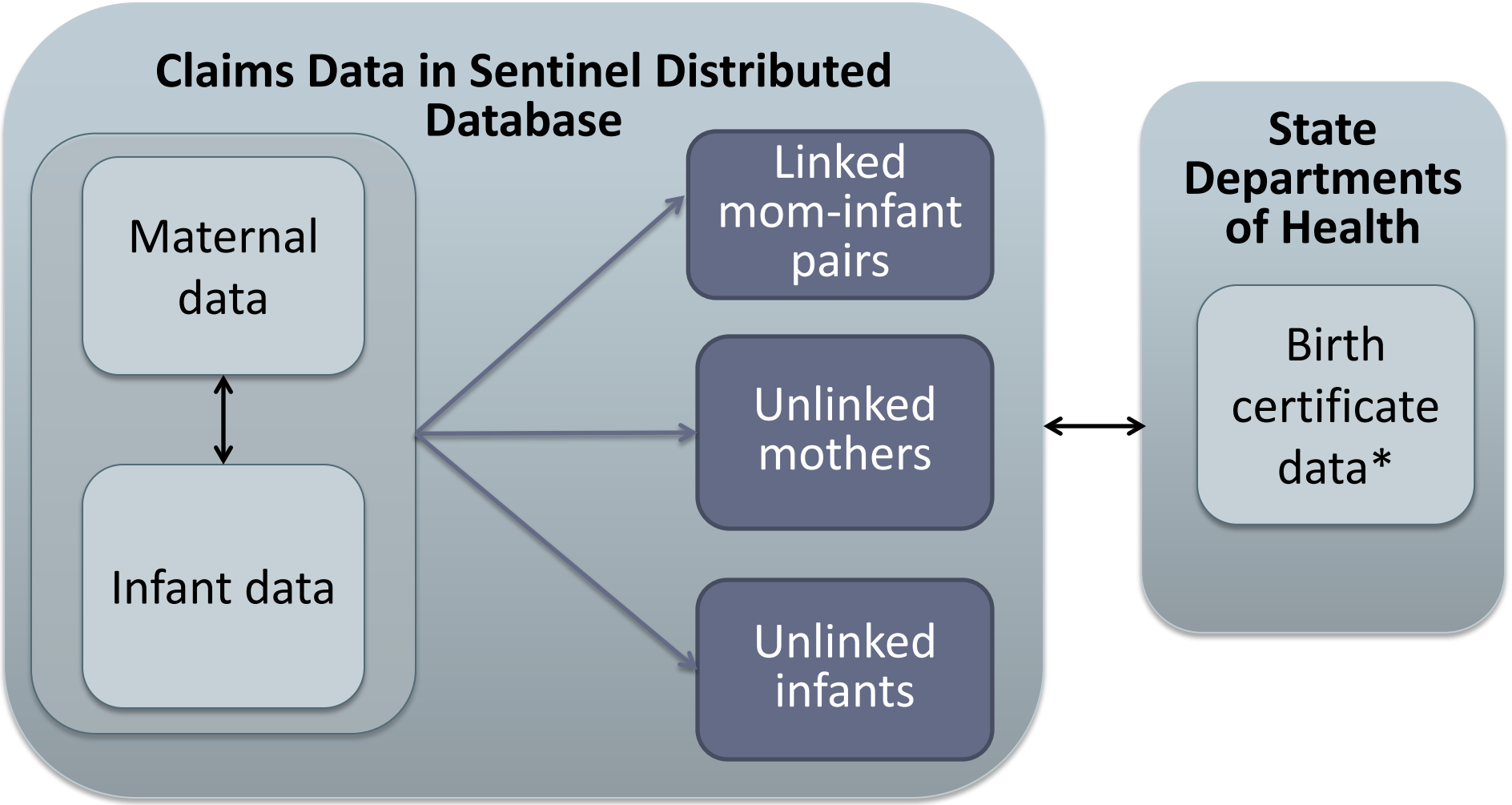
Those for whom chart obtained =267 (78%)

Confirmed as intussusception, Brighton Level 1 = 124 (46%)

Classified as Brighton Level 2 = 20 (7%)

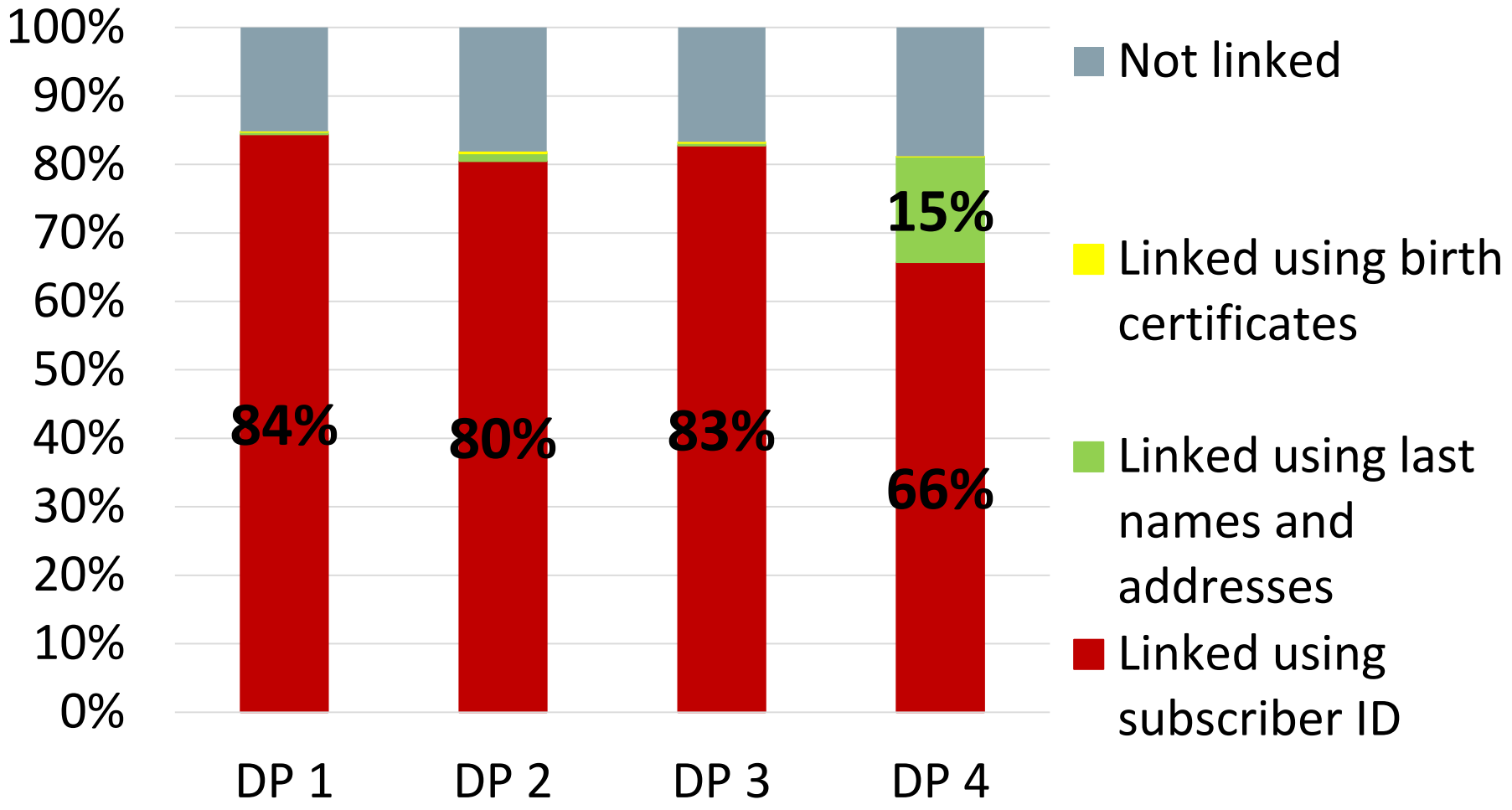
Potential cases are from whole population aged 5-36 weeks and include unexposed

Sentinel linked to registries



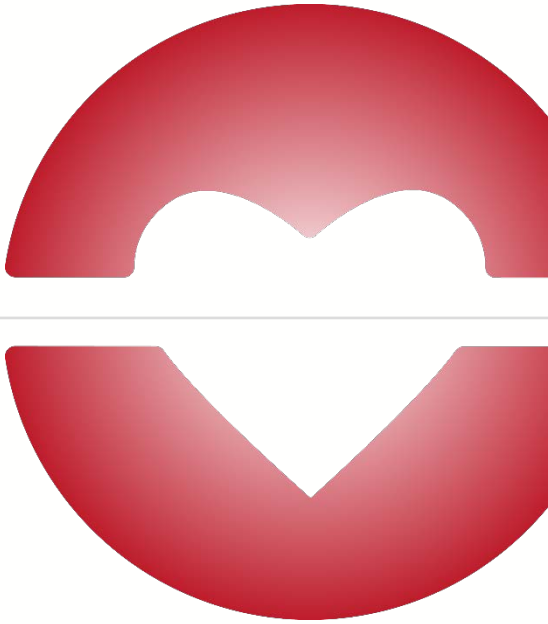
*Birth certificates available for 9 states

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



Sentinel linked to EHRs

ADAPTABLE Trial



Adaptable

The Aspirin Study

pcornet

Follow us on Twitter @**ADAPTABLEstudy**

ClinicalTrials.gov: NCT02697916

ADAPTABLE Study Design

Patients with known ASCVD + ≥ 1 "enrichment

Identified through EHR (computable phenotype)

Electronic follow-up: Every 3–6 months
Supplemented with EHR/CDM/**claims** data

Primary endpoint:
Composite of all-cause mortality, hospitalization for MI or stroke

Primary safety endpoint:
Hospitalization for major bleeding

† Participants without internet access may be consented and followed via a parallel system.

Adaptable

ADAPTABLE Computable phenotype

History of CAD

- Prior MI

  OR

- Prior angiogram showing significant CAD

  OR

- Prior revascularization (PCI/CABG)

At least one:

- Age >65 years
- Creatinine >1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Current cerebrovascular disease and/or peripheral artery disease
- Known ejection fraction<50%
- Current smoker

Enabling Pragmatic Research: eScreening, eEnrollment and eFollowup

ADAPTABLE Enrollee

Baseline Data

OR

Adaptable
The Aspirin Study

DCRI FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

Portal FOLLOW-UP
- *Patient Reported Outcomes*
- *Medication use*
- *Health outcomes*

4 8 12 16 20 …. 30

PCORNet Coordinating Center FOLLOW-UP
- *Via Common Data Model*
- *Longitudinal health outcomes*

CMS & Payer Virtual Data Warehouse FOLLOW-UP
- *Longitudinal health outcomes*

Adaptable

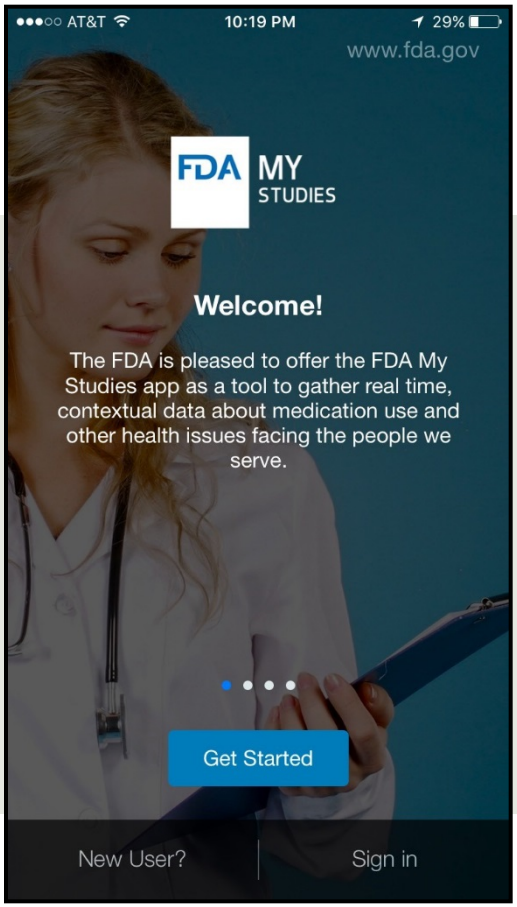
Sentinel linked with patient reported data

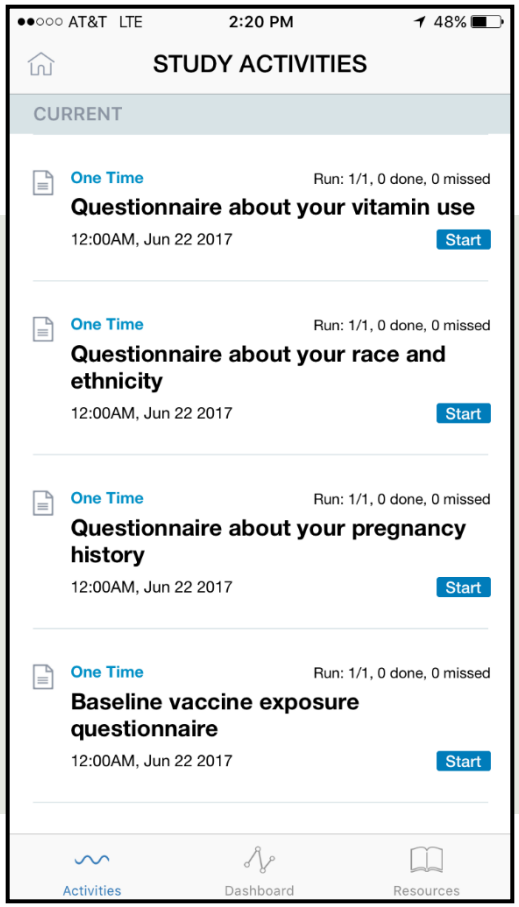
Developing a Mobile App for Studies of Medication Safety

Sascha Dublin, MD, PhD, Kaiser Permanente Washington

August 2017

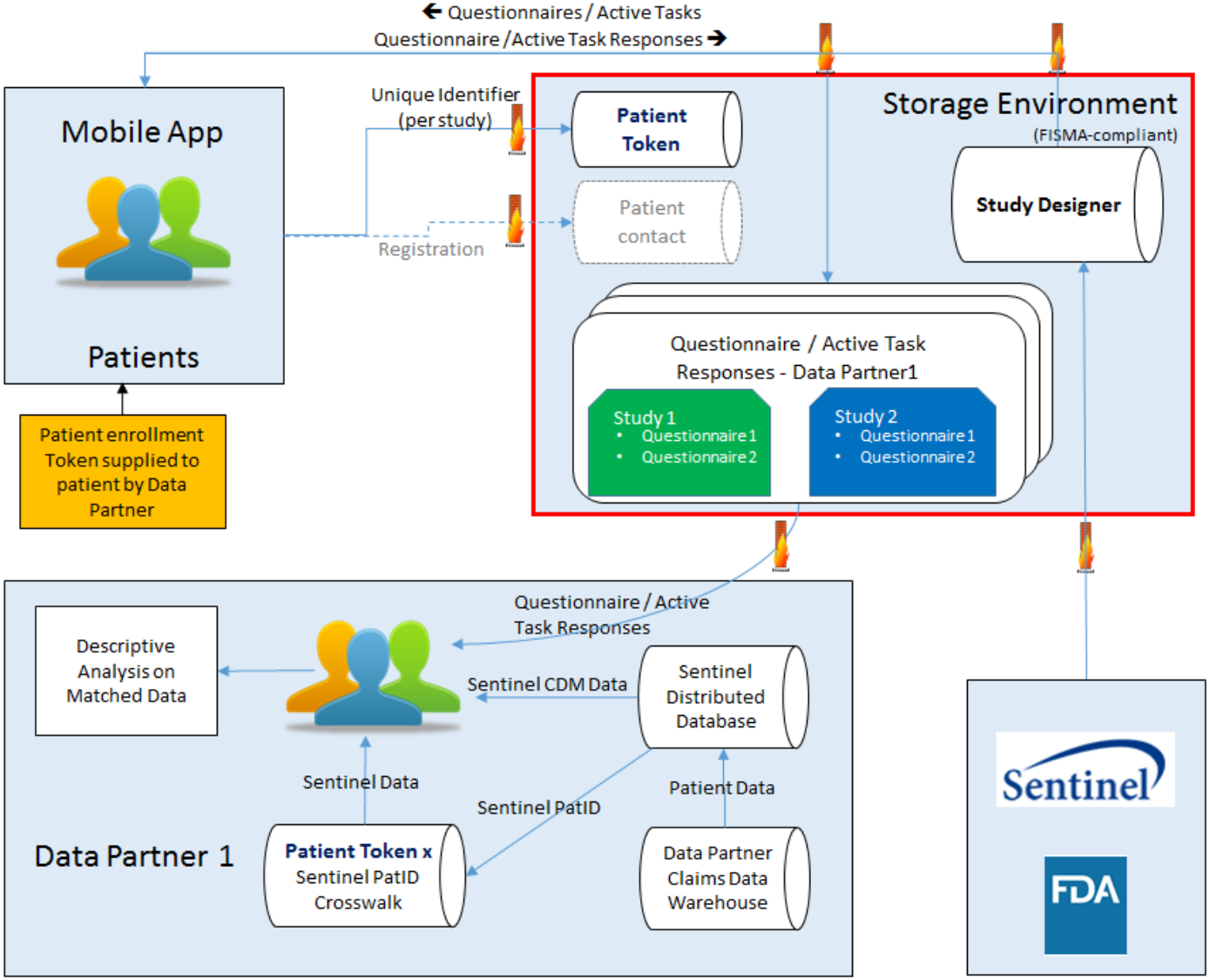
Screenshots from App





info@sentinelsystem.org

Link Primary and Secondary Data



Sentinel and randomized trials

Sentinel IMPACT-AFib: Transforming Pragmatic Clinical Trials Using a Nationwide Distributed Claims Database

IMPACT-AFib

IMPACT-Afib Participating Sites

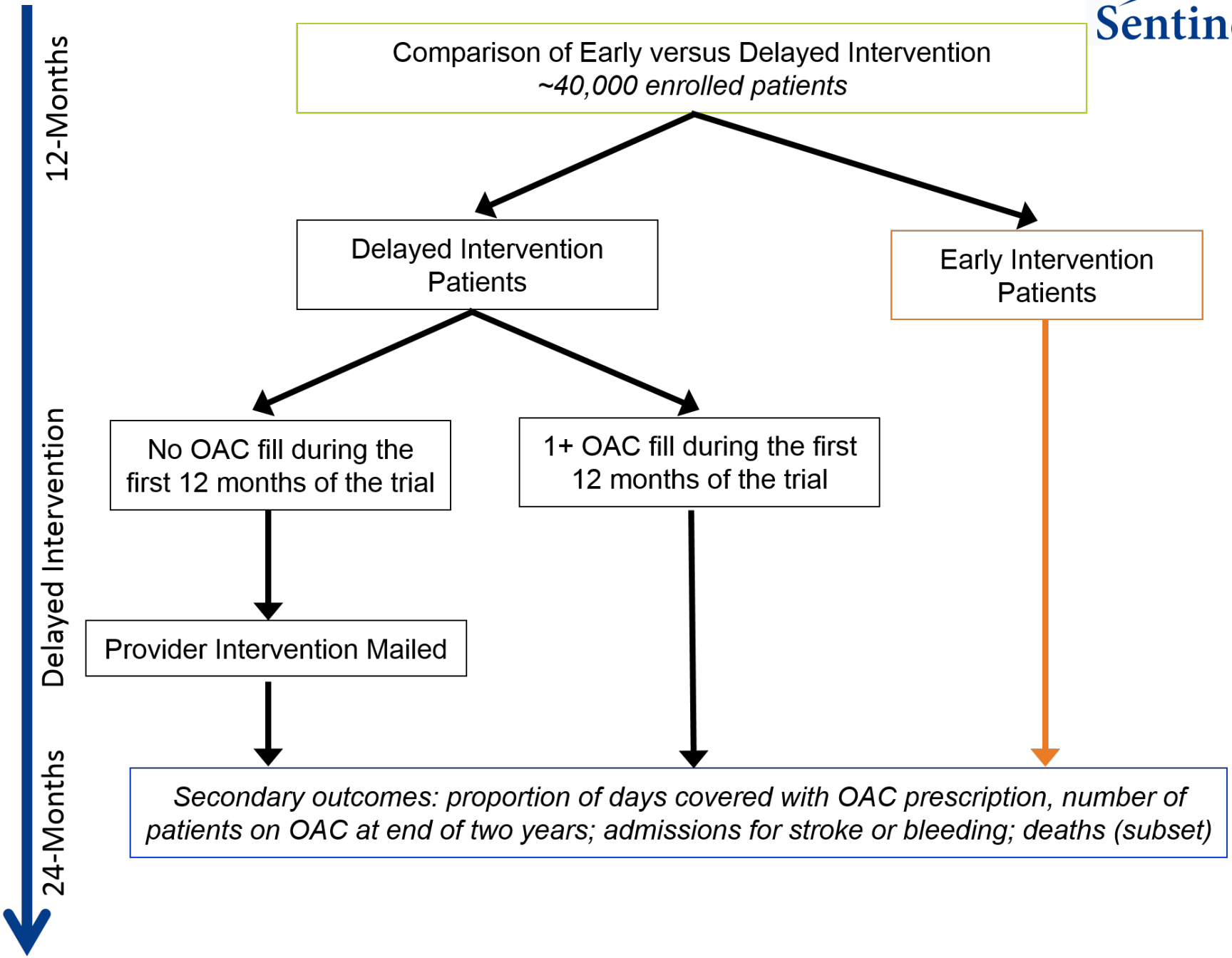
FDA-Catalyst: IMPACT-AFib randomized trial

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 40,000 health plan members with AFib, high risk for stroke, and no oral anticoagulant (OAC) treatment, and their providers to encourage consideration of OACs

IMPACT-AFib Outcomes

- Primary outcome: Proportion who fill ≥1 OAC prescription within 12 months
- Secondary outcomes:
  - Rates of stroke hospitalizations
  - Time to first OAC dispensing
  - Proportion of days with OAC days supplied
  - Proportion of patients on OAC at end of follow up
  - Rates of bleeding hospitalizations
  - Health care utilization
  - Hospital mortality
- Outcomes will be assessed 12 and 24 months

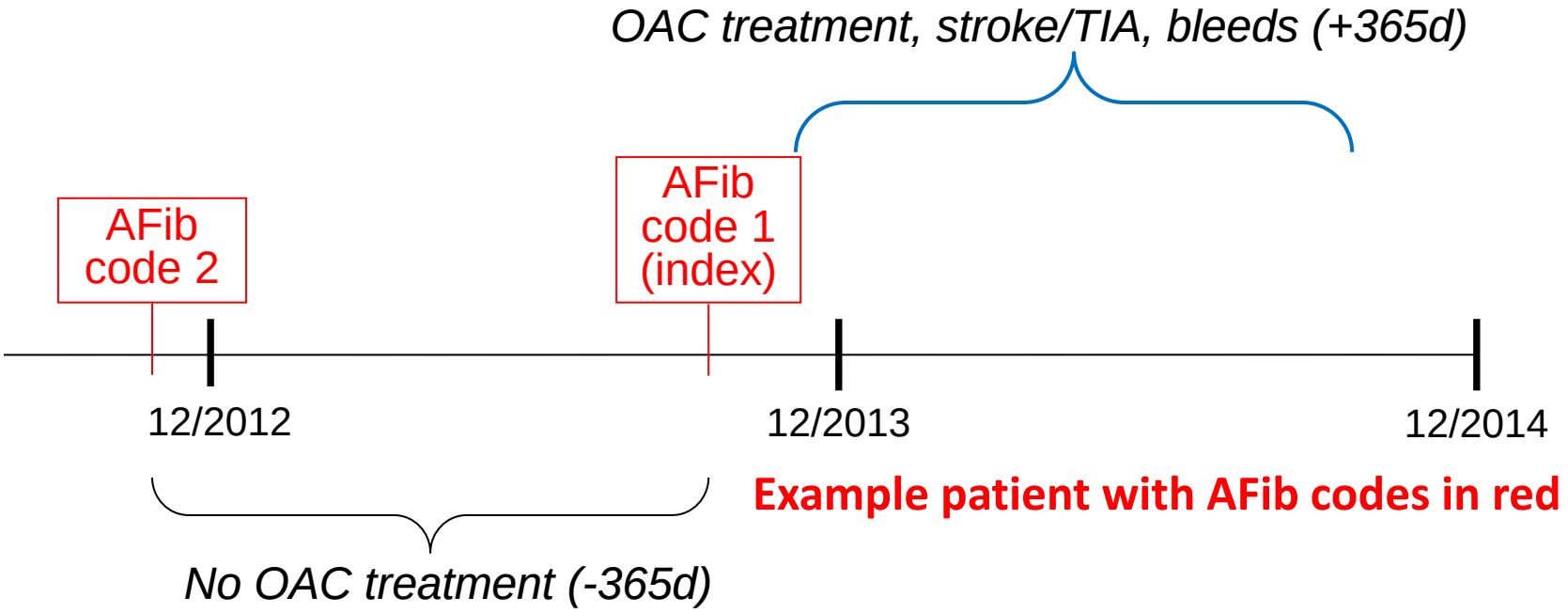


Trial cohort eligibility

- Adult ≥30 years old
  - Medical & pharmacy coverage for ≥365 days
- ≥2 AFib diagnosis codes
- No OAC dispensing (or ≥4 INR measurements) within the last year
- High risk for stroke (CHA2DS2-VASc score ≥2)
- Exclusions:
  - History of mechanical prosthetic valve, deep vein thrombosis, pulmonary embolism, intracranial bleed
  - Hospitalized bleed in last 6 months
  - Current pregnancy
  - Current P2Y12 inhibitor treatment, e.g., clopidogrel

Estimating CHA_2DS_2-VASc in feasibility query

CHA_2DS_2-VASC CALCULATOR		
	Risk factor	**If patient has risk factor, add points**
C	Congestive Heart Failure	+1
H	High Blood Pressure (hypertension, including normal blood pressure on blood pressure medications)	+1
A_2	Age 75 years old or older	+2
D	Diabetes	+1
S_2	Stroke or TIA (mini-stroke)	+2
V	Vascular Disease (prior bypass surgery, heart attack peripheral artery disease, or aortic plaque)	+1
A	Age 65-74 years	+1
Sc	Sex Category: Female sex	+1
	TOTAL	

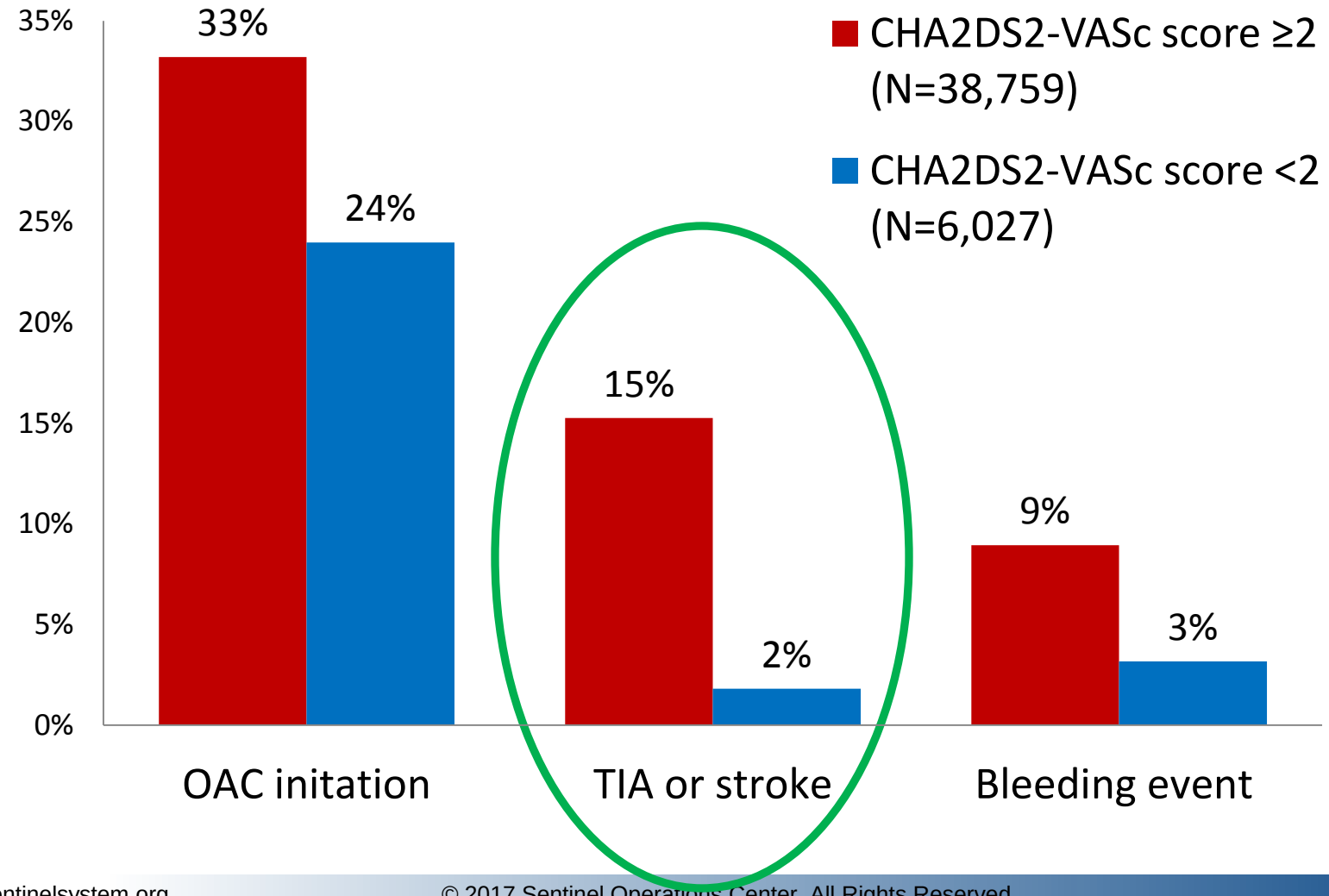


- Follow-up period: 365 days after 2013 diagnosis or until an event or disenrollment
- Event definitions:
  - Anticoagulant treatment (≥1 NDC or ≥2 INR CPT codes)
  - Stroke or TIA (≥1 ICD-9-CM code in any care setting)
  - Bleeding (≥1 ICD-9-CM code in any care setting)

Preliminary Data from Five Data Partners

- **44,786** individuals identified with AF with no evidence of current or recent OAC use
- **38,759** (87%) eligible for anticoagulant treatment
- Among those, by end of follow up:
  - 12,867 (33%) had evidence of anticoagulant dispensing
  - 5,917 (15%) had a documented TIA or stroke
  - 3,469 (9%) had a documented bleeding event

Proportion of AFib members at five Data Partners with an event at end of follow up



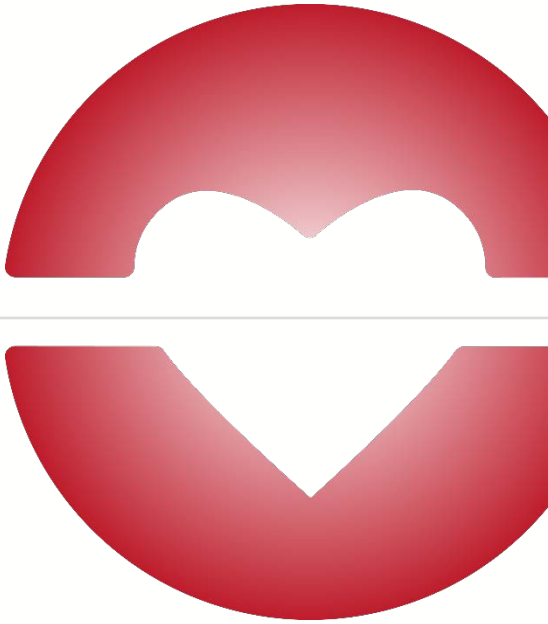
Conclusions

- Identified a large number of health plans members potentially eligible for IMPACT-AFib
- Confirmed public health importance
- Sentinel infrastructure able to support
  - Assessment of trial feasibility
  - Implementation
  - Followup

Acknowledgements

- **Aetna:** Cheryl Walraven, Daniel Knecht
- **Clinical Trials Transformation Initiative:** Jennifer Goldsack
- **Duke Clinical Research Institute:** Christopher Granger, Sean Pokorney, Hussein Al-Khalidi, Emily O'Brien, Jennifer Rymer, Sana Al-Khatib
- **Harvard Pilgrim Health Care Institute:** Crystal Garcia, Richard Platt, Ryan Saliga, Robert Jin, Jeff Brown, Hannah Katcoff
- **HealthCore:** Kevin Haynes, Lauren Parlett
- **Humana:** Vinit Nair, Thomas Harkins, Daniel Lane, Yunping Zhou
- **Optum:** Nancy Lin
- **Patient Representative:** Debbe McCall
- **U.S Food & Drug Administration:** Melissa Robb, Patrick Archdeacon

ADAPTABLE Trial



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  OR

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  OR

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- Creatinine >1.5 mg/dL
- Diabetes mellitus
- Known 3-vessel CAD
- Current cerebrovascular disease and/or peripheral artery disease
- Known ejection fraction<50%
- Current smoker

HealthCore Anthem Research Network (HCARN)

- **Identified 150,000 eligible members** from 30,000 providers with PCORnet Computable Phenotype Common Data Model code
- Provider letters will go out informing providers of ADAPTABLE
- Two weeks after provider letters three batches of member mailers
  - Initial email or mailing
  - Reminder mailing
  - Telephone call
- Eligible patients will be instructed to the ADAPTABLE web recruitment portal
- For enrolled patients Duke will conduct reminders and further outreach

ClinicalTrials.gov: NCT02697916

Sentinel and effectiveness/efficacy

- Plain Sentinel
- Sentinel with full text medical record adjudication
- Sentinel linked to registries
- Sentinel linked to EHRs
- Sentinel and patient generated data
- Sentinel as a home for clinical trials

Thank you!