Agenda

- **CTTI overview**
  - Pamela Tenaerts, MD, MBA
    Clinical Trials Transformation Initiative

- **Sentinel IMPACT-AFib: Transforming Pragmatic Clinical Trials Using a Nationwide Distributed Claims Database**
  - Christopher Granger, MD
    Duke Clinical Research Institute
    Co-PI, IMPACT-Afib
  - Sean Pokorney, MD, MBA
    Duke Clinical Research Institute
    Investigator, IMPACT-AFib

CTTI Overview

Pamela Tenaerts, CTTI

Clinical trials in crisis

REPORT TO THE PRESIDENT

TRANSFORMATION AND OPPORTUNITY: THE FUTURE OF THE U.S. RESEARCH ENTERPRISE

Executive Office of the President

President's Council of Advisors on Science and Technology

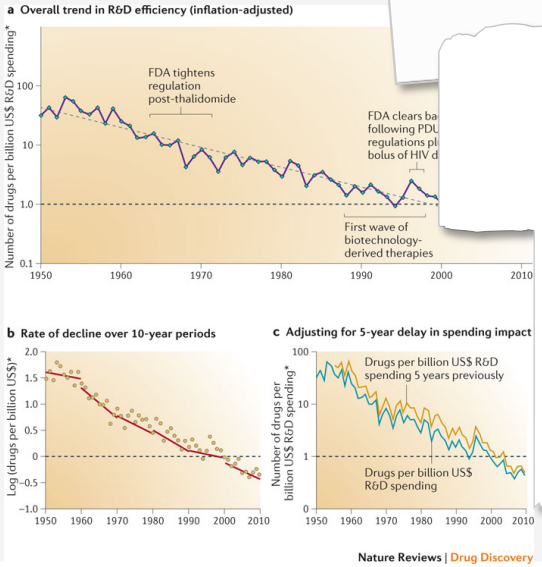
NOVEMBER 2012

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION

ENVISIONING A TRANSFORMED CLINICAL TRIALS ENTERPRISE IN THE UNITED STATES

ESTABLISHING AN AGENDA FOR 2020

WORKSHOP SUMMARY



Addressing This Need

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

Public-Private Partnership
co-founded by Duke University & FDA
involves all stakeholders
90+ members

Mission: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

CTTI Membership

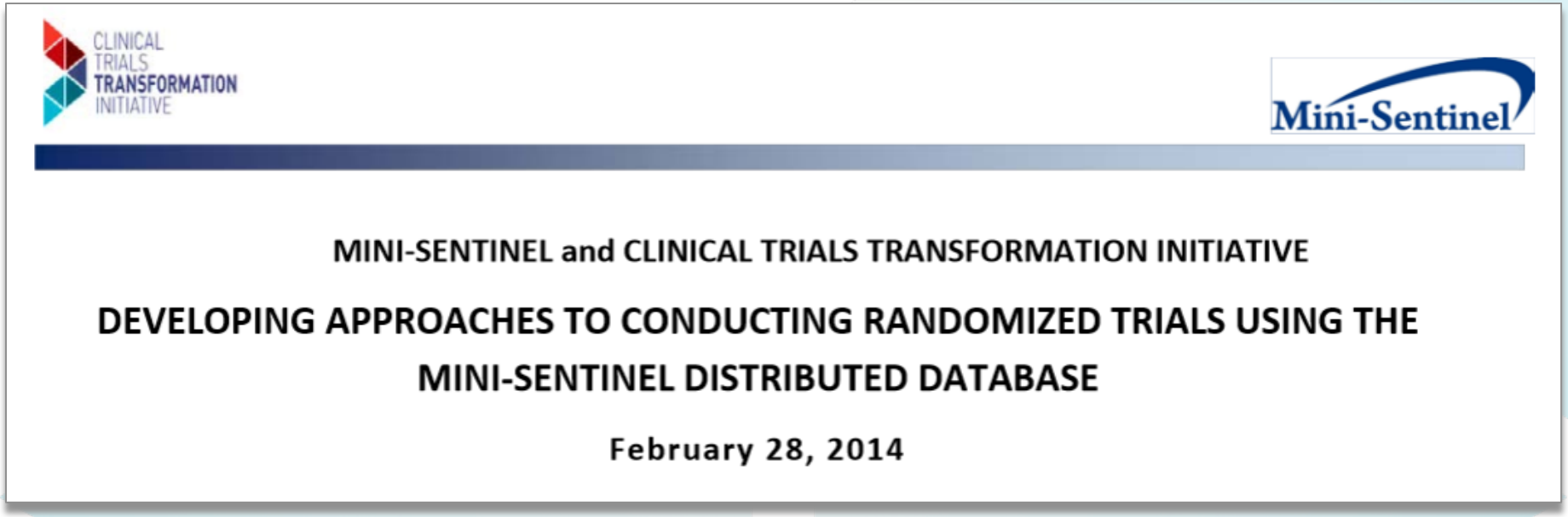
CTTI Methodology

PROJECT PORTFOLIO *November 2016*	Systematic Evidence Generation	Patients as Equal Partners	Efficient & Quality Trials	Public Health Concern	Safe & Ethical Trials
Complete Projects	Large Simple Trials		GCP Training Monitoring Quality by Design Recruitment Site Metrics	ABDD Streamlining HABP/VABP Trials Long-Term Opioid Data	Central IRB Central IRB Advancement DMCs Informed Consent IND Safety SAE Reporting
Active Projects	MCT Legal & Regulatory MCT Mobile Devices MCT Novel Endpoints MCT Stakeholder Perceptions Registry Trials State of Clinical Trials	Patient Groups & Clinical Trials	GCP Follow On Investigator Turnover	ABDD HABP/ VABP Studies ABDD Peds Trials ABDD Unmet Need	IND Safety Advancement Pregnancy Testing

CTTI

COLLABORATIONS PORTFOLIO November 2016	Systematic Evidence Generation	Patients as Equal Partners	Efficient & Quality Trials	Public Health Concern	Safe & Ethical Trials
Completed Collaborations	Clinical Trials for Comparative Effectiveness Electronic Healthcare Data	Patient Engagement Survey	Clinical Trials Poll FDA Training Course Patient Engagement Survey	Cardiovascular Endpoints	
Active Collaborations	**Sentinel** **IMPACT-AFib**	Patient Engagement Collaborative		ABDD PTN	

Electronic HealthCare Data:



- Sentinel IMPACT-Afib

Sentinel IMPACT-Afib Project team

- Team Leaders
  - Christopher Granger (Duke)
  - Richard Platt (Harvard)
  - Melissa Robb (FDA)
- Team Members
  - Hussein Al-Khalidi (Duke)
  - Sana Al-Khatib (Duke)
  - Noelle Cocoros (Harvard)
  - Tom Harkins (Humana)
  - Kevin Haynes (HealthCore)
  - Robert Jin (Harvard)
  - Daniel Knecht (Aetna)
  - Daniel Lane (Humana)
  - Nancy Lin (Optum)
  - Debbe McCall (Patient Rep)
  - Vinit Nair (Humana)
  - Emily O'Brien (Duke)
  - Lauren Parlett (HealthCore)
  - Nick Patel (Humana)
  - Sean Pokorney (Duke)
  - Jennifer Rymer (Duke)
  - Ryan Saliga (Harvard)
  - Robert Temple (FDA)
  - Cheryl Walraven (Aetna)
  - Yunping Zhou (Humana)
- Project Managers
  - Crystal Garcia (Harvard)
  - Jennifer Goldsack (CTTI)

The Sentinel IMPACT-Afib Study

Christopher Granger, DCRI

Sean Pokorney, DCRI

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

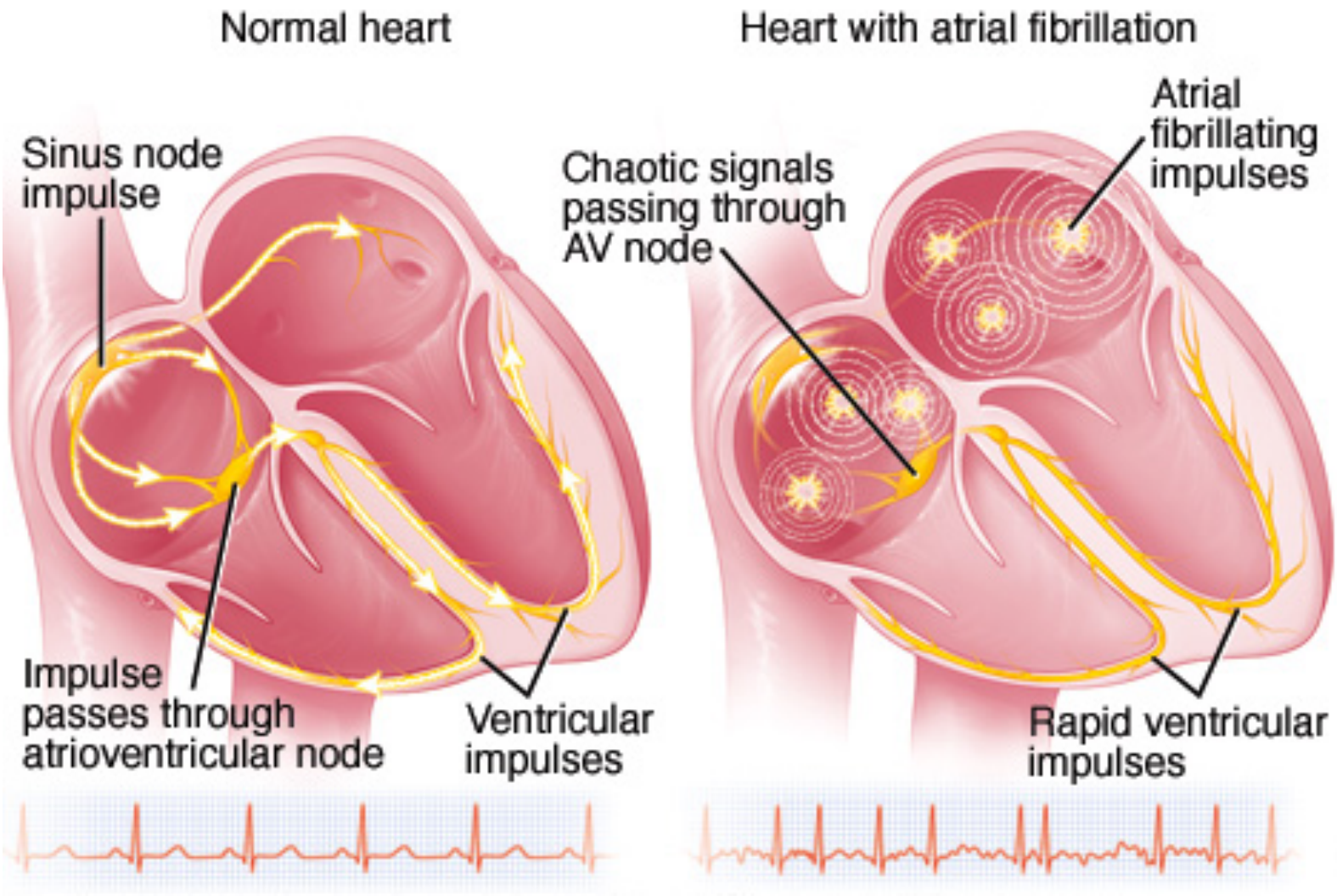
November 17, 2016

Sean Pokorney MD and Chris Granger MD
Duke Clinical Research Institute

Outline

- Background on atrial fibrillation and stroke risk
- Underuse of oral anticoagulants
- Efforts to increase use of oral anticoagulants
- FDA-Catalyst
- Sentinel data partners and randomization
- Sentinel IMPACT-AFib

What is Atrial Fibrillation?

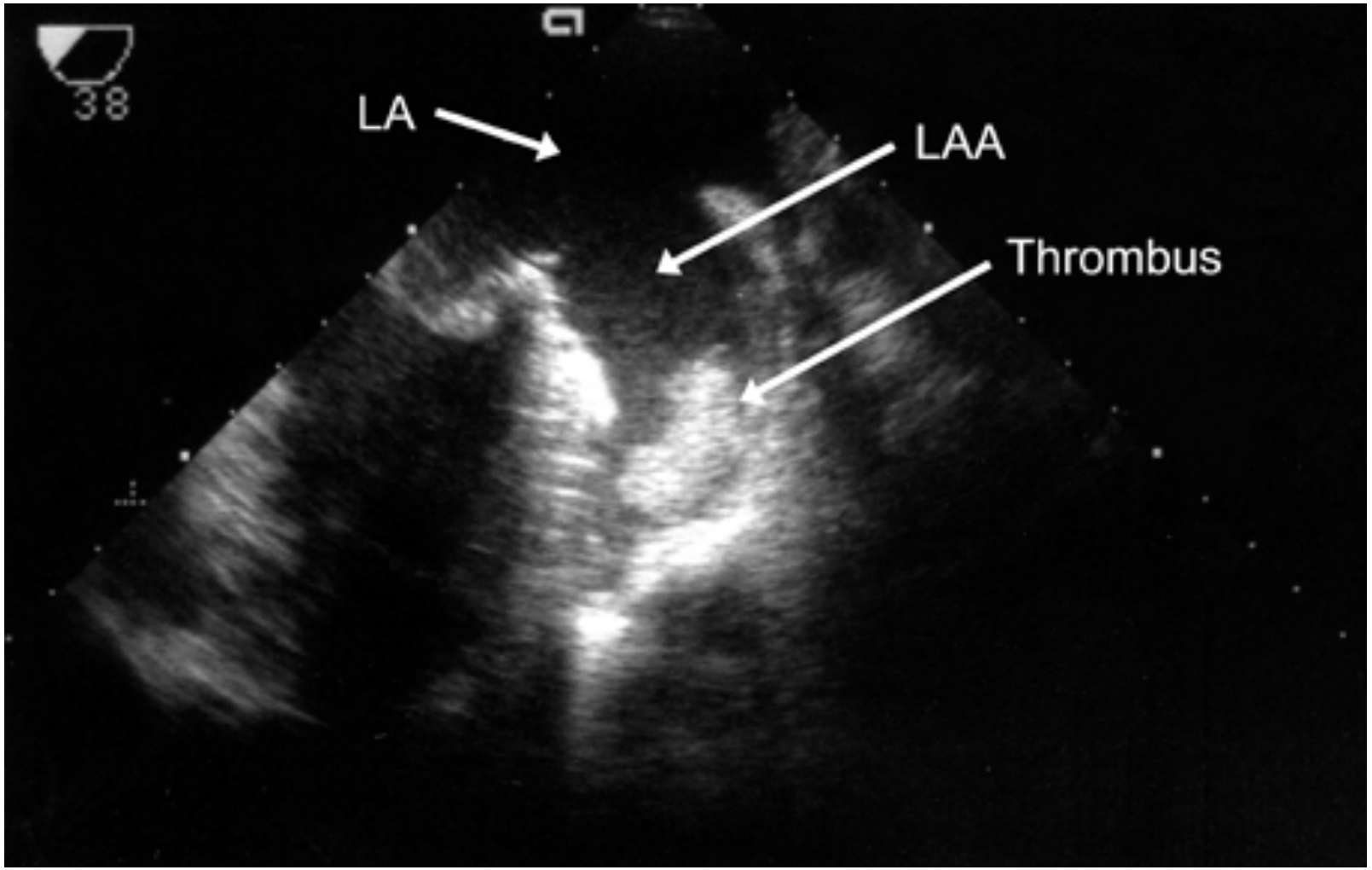


Atrial Fibrillation, a common and important problem

- 2.7–6.1 million people in the United States have AFib
  - 2% of people younger than age 65
  - 9% of people aged ≥65 years
- 4-5 fold increase in risk of stroke
  - 750,000 added strokes per year in U.S.
  - Contributes to 130,000 deaths
  - $6 billion added annual cost ($8,700 per person with AFib)

www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm

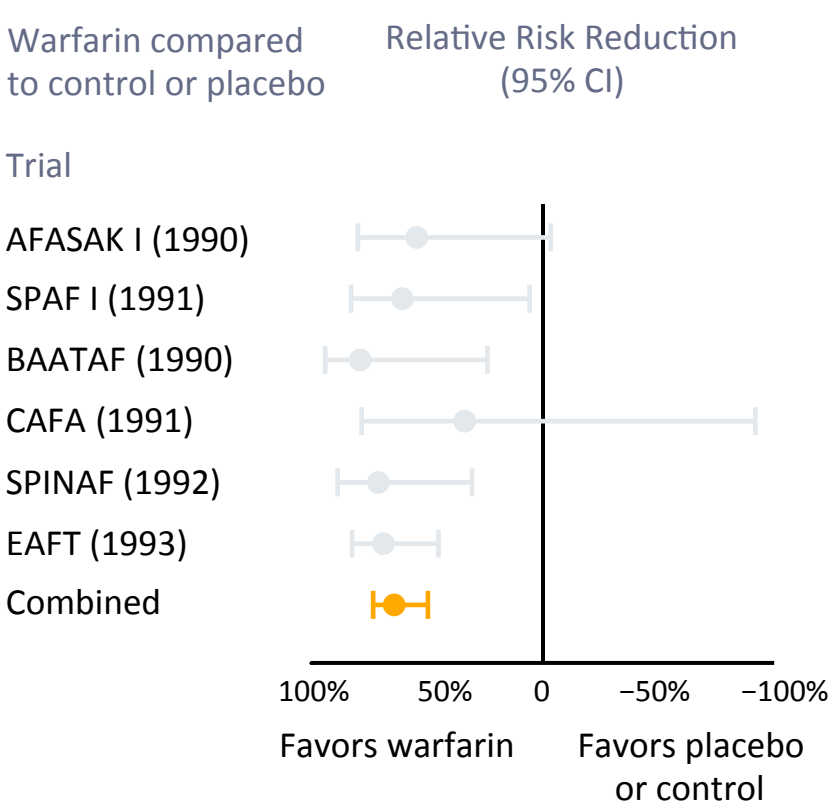
Why Is Atrial Fibrillation Associated with Stroke



Good News:

Medications are very effective at preventing stroke

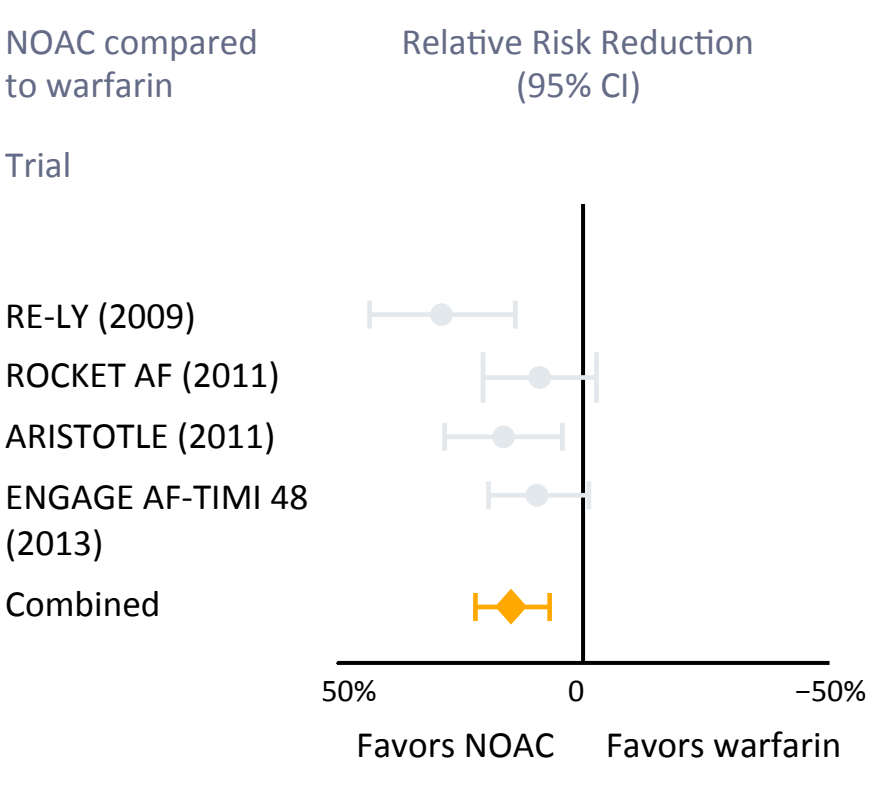
Anticoagulation for stroke prevention



RRR 64%

Warfarin vs. Placebo or Control
(6 trials, total n=2,900)

Hart R, et al. Ann Intern Med. 2007;146:857-867.



RRR 19%

NOAC vs. Warfarin
(4 trials, total n=71,683)

Ruff C, et al. Lancet. 2014;383:955–962.

Bad News:

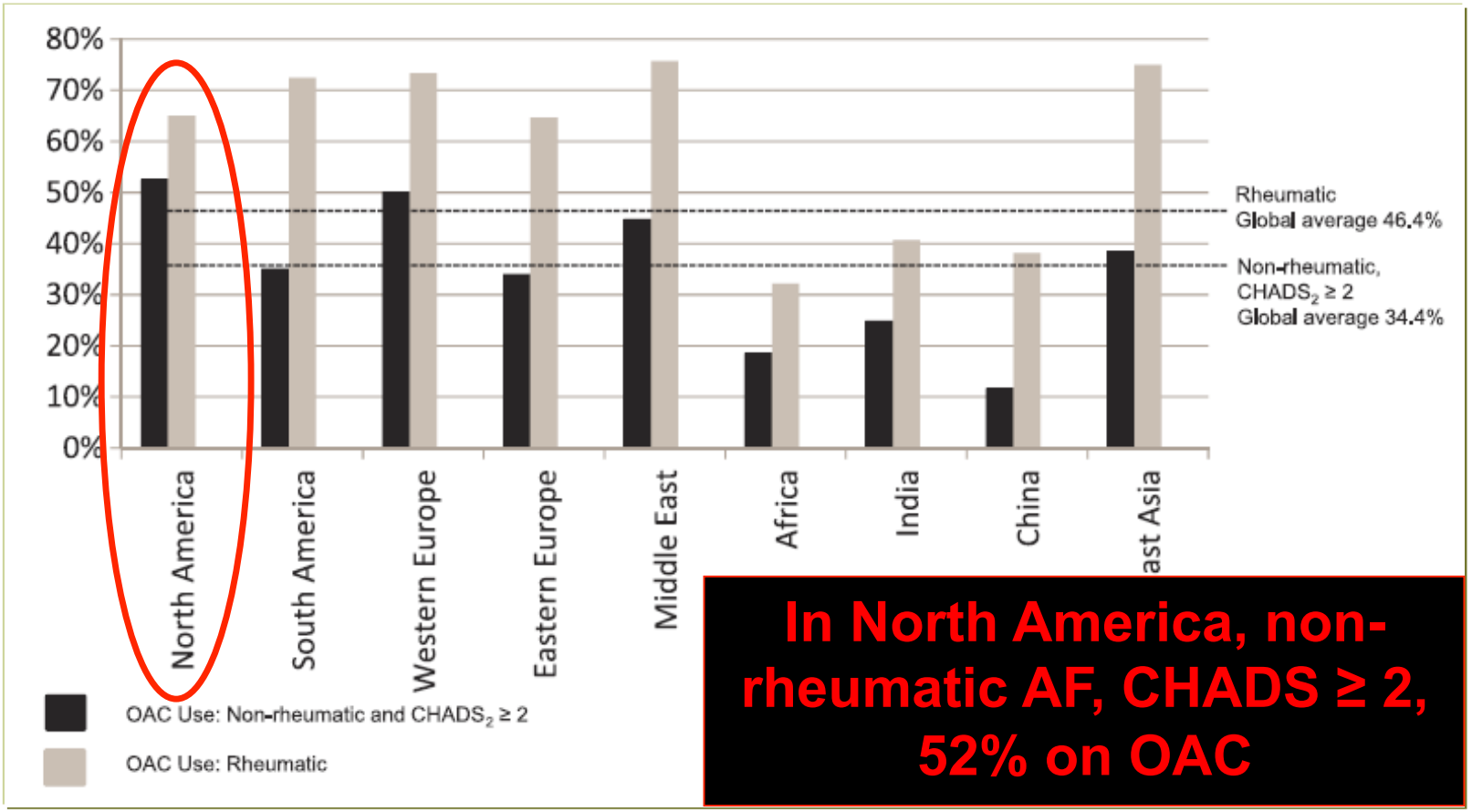
Anticoagulation is commonly not used in AF patients at risk for stroke

RE-LY Registry

47 countries; 163 sites; 15,174 patients

Region	Sites	Patients	Middle East	8	896
North America	18	1802	Africa	20	1089
South America	23	1127	India	22	2520
Western Europe	19	1975	China	20	1951
Eastern Europe	22	2536	Asia	11	1278

Anticoagulation Use in RE-LY Registry



In North America, non-rheumatic AF, CHADS ≥ 2, 52% on OAC

Circulation. 2014;129:1568-1576

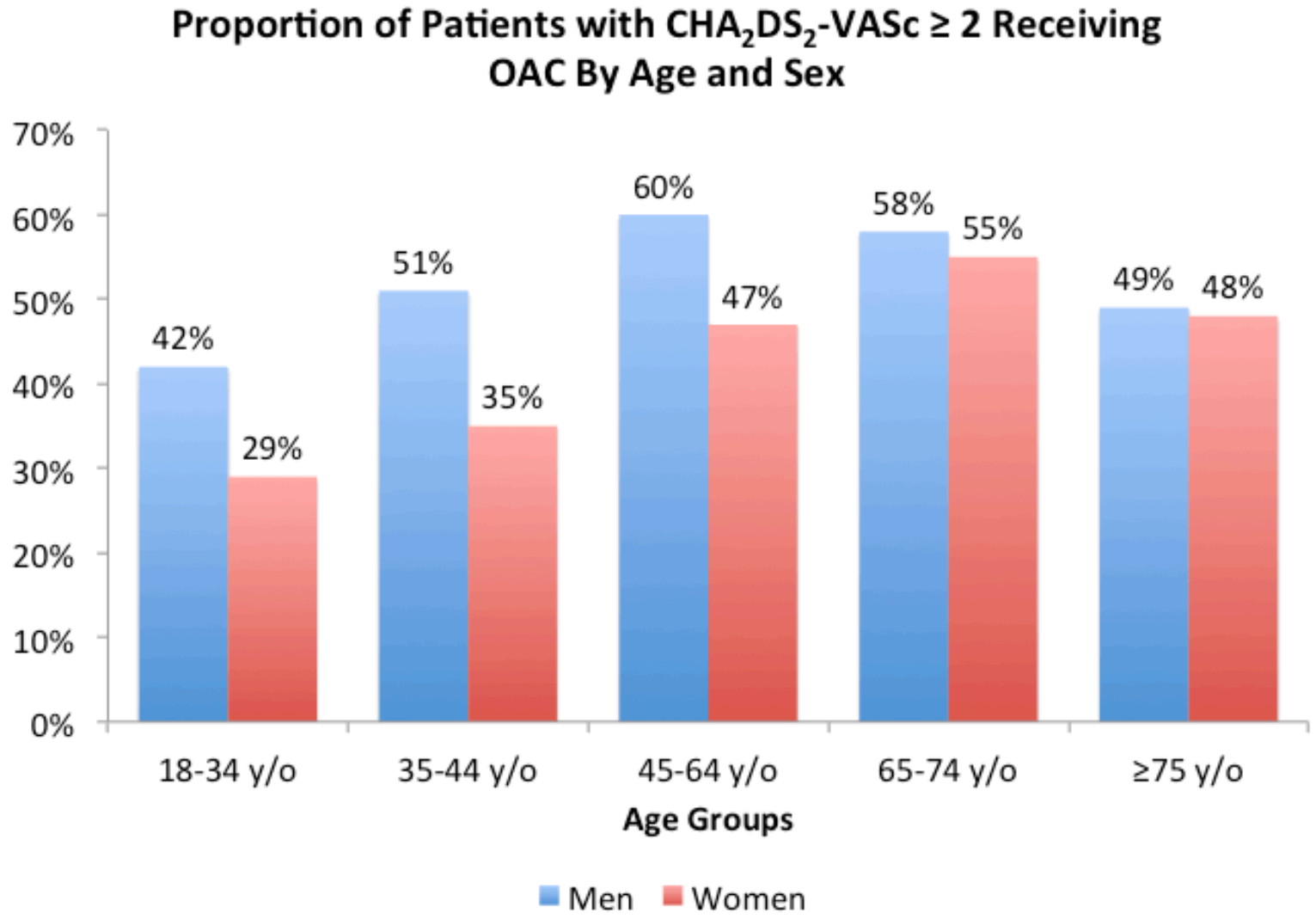
How about recent data from commercially insured patients from Sentinel?

Rates of Anticoagulation for Atrial Fibrillation

Criteria	Patients
Total number of patients (Aetna, Humana, Harvard Pilgrim)	16.2 million
Patients with AF	231,696 (1.4% of all patients)
AF pts with CHA_2DS_2-VASc ≥ 2	201,882 (87% of AF patients)
Patients with at least one oral anticoagulation fill	105,256 (52% of AF patients with CHA_2DS_2-VASc ≥ 2)
Proportion of days covered by anticoagulation in AF patients	32%

Pokorney S et al. Am College of Cardiol 2016

Initial Sentinel Data



How about at a top medical center like Duke?

Anticoagulation rates at Duke

Accuracy and validation of an automated electronic algorithm to identify patients with atrial fibrillation at risk for stroke

Ann Marie Navar-Boggan, MD, PhD, Jennifer A. Rymer, MD, MBA, Jonathan P. Piccini, MD, MHS, Wassim Shatila, MD, Lauren Ring, BS, Judith A. Stafford, MS, Sana M. Al-Khatib, MD, MHS, and Eric D. Peterson, MD, MPH *Durham, NC*

- In 2011-2012, 6,397 patients with AF.
- Chart reviews confirmed AF in 95.7%
- Assessment of CHA_2DS_2-VASc score category about 80% accurate
- Anticoagulation **rate 56% for CHA_2DS_2-VASc scores ≥2**

Navar-Boggan AM. Am Heart J 2015 169, 39-44.e2

What do these low rates of oral anticoagulant use mean from a public health perspective?

Preventable Strokes from AF Per Year

- > 5 million people in the US have AF
- Of those with additional risk factors for stroke, more than half are not treated with oral anticoagulants
- Of these, 5% stroke per year
- Of these, 70% are preventable
- Hundreds of thousands of preventable strokes each year world wide

What do the guidelines say?

Atrial Fibrillation Guidelines

Risk	Recommended Therapy	
	ESC 2012	AHA/ACC/HRS 2014
No risk factors CHA_2DS_2-VASc= 0	No antithrombotic therapy (I)	No antithrombotic therapy (IIa)
CHA_2DS_2-VASc= 1	OAC (IIa) (NOAC > VKA)	None or OAC or ASA (IIb)
CHA_2DS_2-VASc≥ 2	OAC (I) (NOAC > VKA)	OAC (I) (NOAC or VKA)
Mechanical valve, mitral stenosis	VKA	

ESC Guidelines. Eur Heart J 2012
AHA/ACC/HRS Guidelines. Circulation 2014

Why do only 50% of patients with AF get treated?

Contraindications to Anticoagulation

ORBIT AF (n= 10,130; 13% with contraindication)

Contraindication†	Overall (n = 1330)	Age (y) <75 (n = 493)	Age (y) ≥75 (n = 837)	P§
Prior bleed	27.7	21.1	31.7	<.0001
Patient refusal	27.5	31.6	25.1	.01
High bleeding risk	18.0	15.4	19.5	.06
Frequent falls/frailty	17.6	5.9	24.5	<.0001
Need for dual APT	10.4	12.0	9.4	.14
Unable to adhere	6.0	7.3	5.3	.13
Comorbid Illness	5.3	6.1	4.8	.30

Obrien E AHJ 201467:601-609.e1

Reasons for not using OAC for AF with risk factors

Legitimate

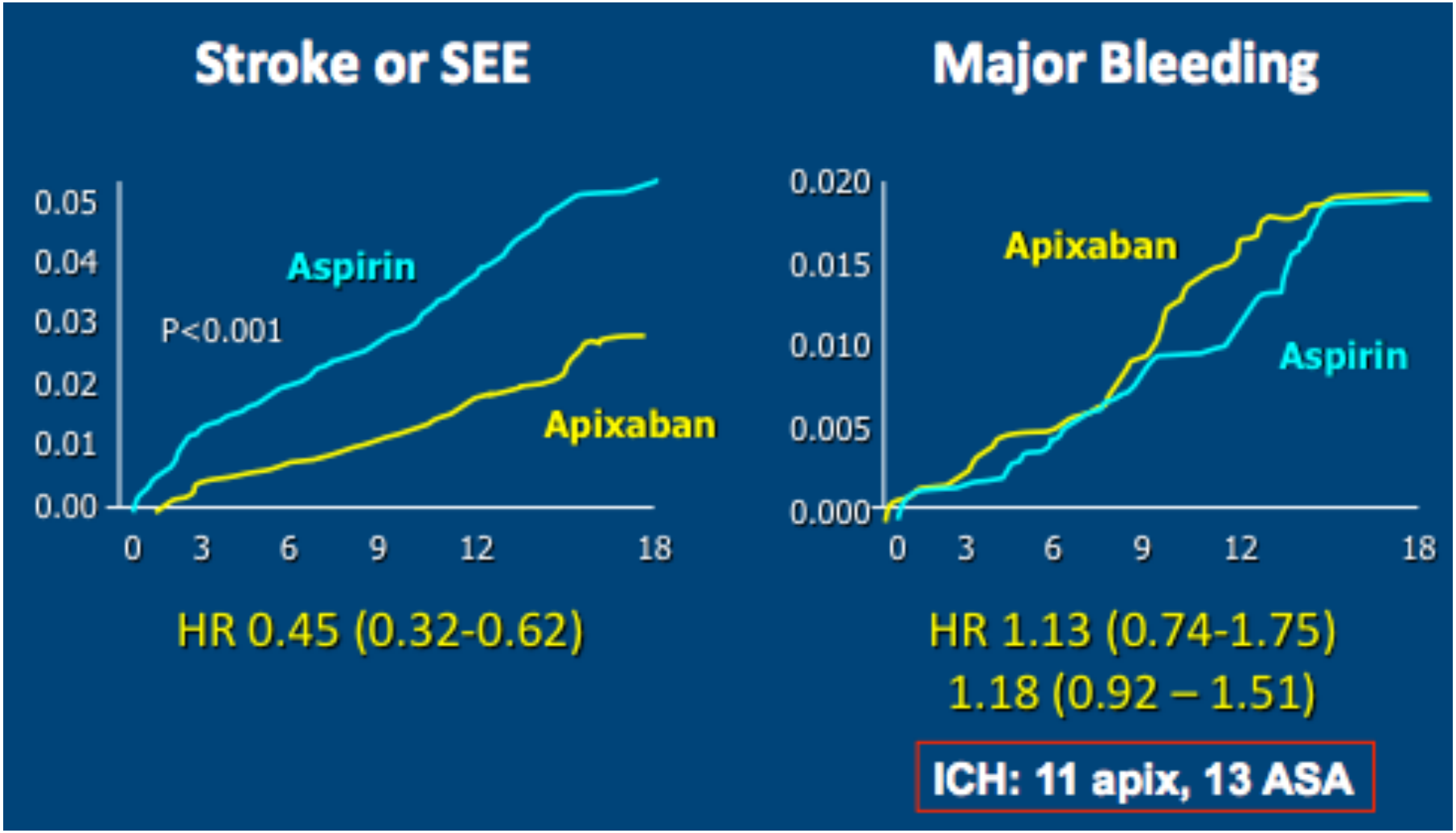
- Very high risk of major/life-threatening bleeding
- Unable to tolerate warfarin and unable to afford NOAC
- Patient decision after thorough review of risks, benefits, concerns

Illegitimate

- Aspirin is effective
- Belief that asymptomatic or minimal AF has a low stroke risk
- Some risk of bleeding that does not outweigh stroke reduction benefit (prior bleeding, typical falls, etc)
- Lack of a reversal agent

How do the novel drugs compare to aspirin?

AVERROES Efficacy and Safety



Connolly SJ, et al. N Engl J Med 2011

Efforts to reduce undertreatment

IMPACT-AF Cluster Randomized Trial
Argentina, Brazil, China, India, Romania

Argentina	Cecilia Bahit	INECO	Rosario
Brazil	Renato Lopes	Federal University	Sao Paulo
India	Denis Xavier	St. John´s	Bangalore
China	Huo Yong	Peking University	Beijing
Romania	Dragos Vinereanu	Carol Davila University	Bucharest

Duke Clinical Research Institute

Rao MP et al. Am Heart J. 2016;176:107-13

IMPACT AF

IMPACT-AF Cluster Randomized Trial

50 Centers in Argentina, Brazil, China, India, Romania

Patients (40-70 per center)
- AF
- CHADS-VASc ≥ 2
- Stable
- No clear contraindication to oral anticoagulation
- Able to give consent
- Able to have 1 year follow-up

Randomize 50 centers

- Cluster randomized design
- Multifaceted educational and systems improvement intervention with data feedback
- Endorsed by each national cardiology society
- Investigator-initiated, multi-industrial sponsorship

Intervention

Control

One year follow-up

Primary comparison: difference in percentage change of patents taking oral anticoagulants from baseline to one year

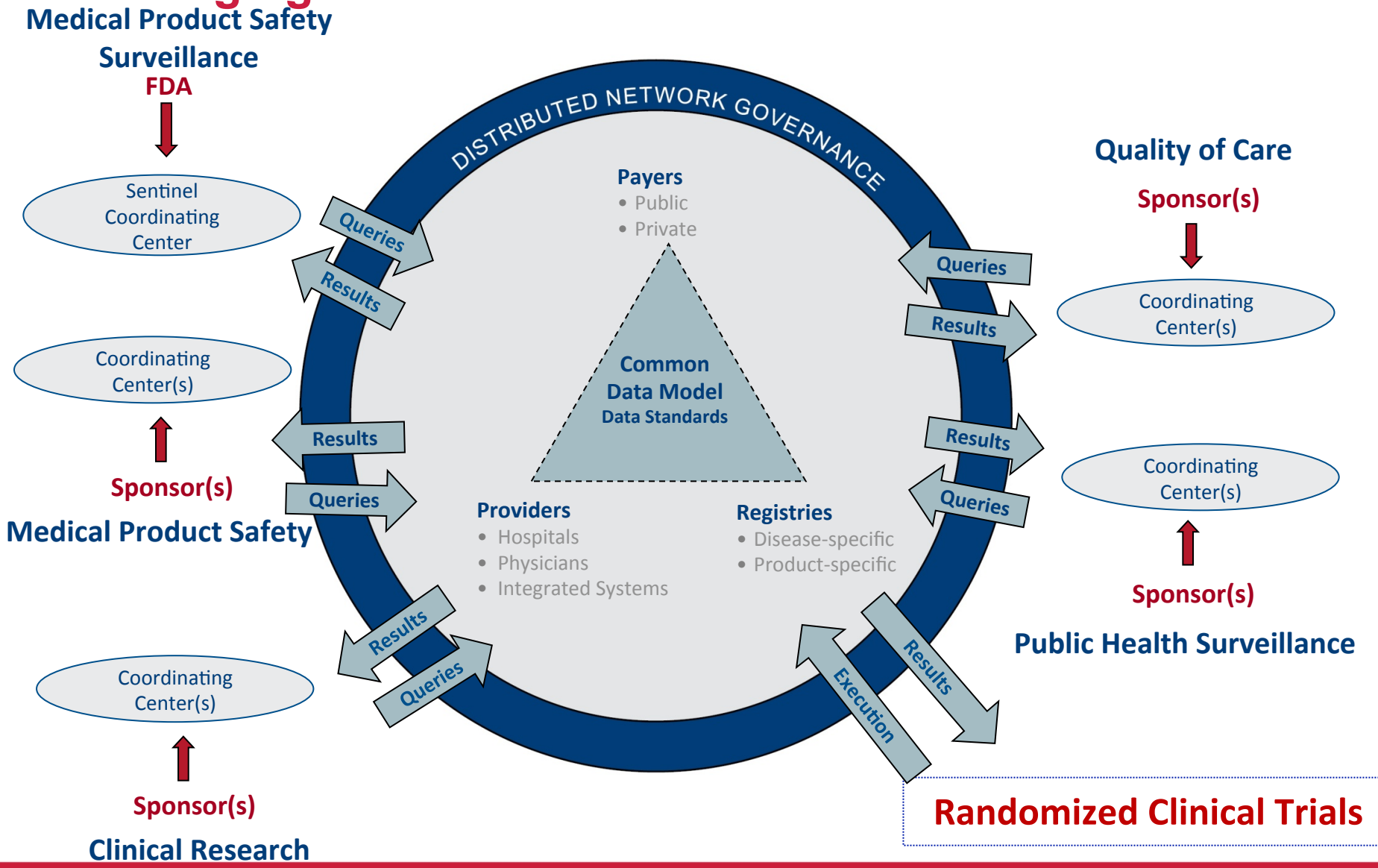
Baseline oral anticoagulant use of 60%, post-intervention 70%
intra-cluster correlation coefficient of 0.25, 80% power

IMPACT-AFib

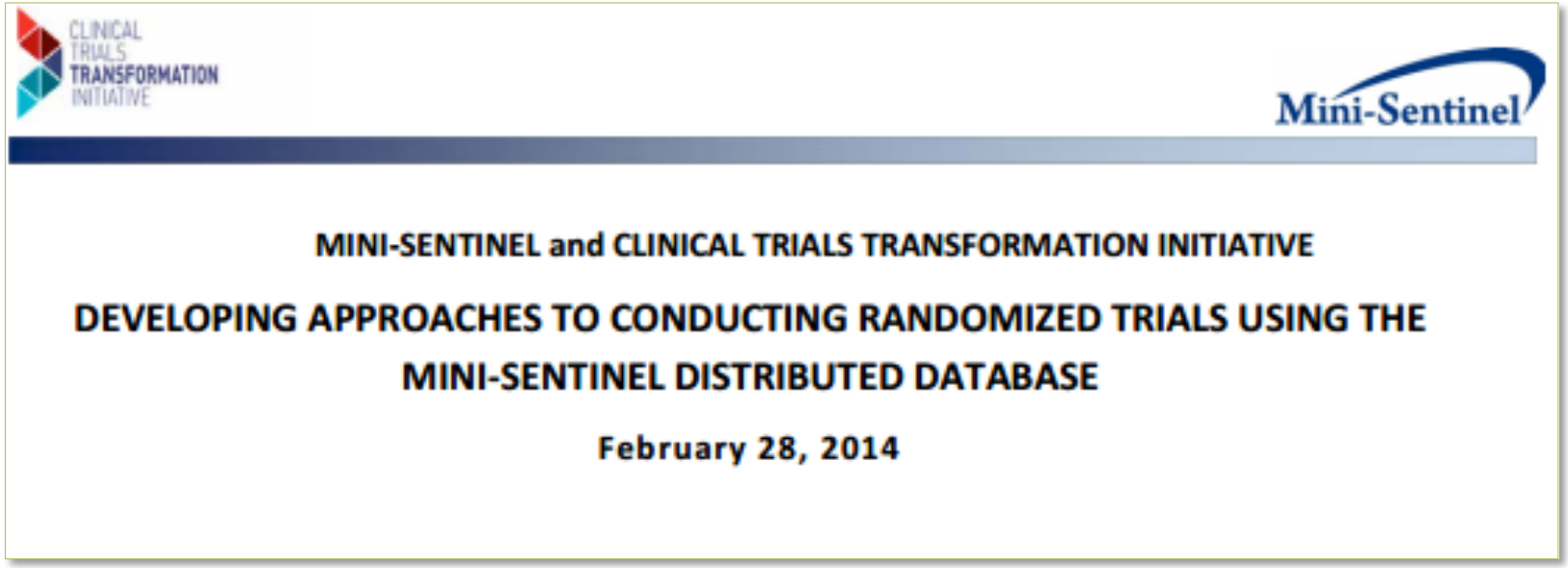
Rao MP et al. Am Heart J. 2016;176:107-13

Sentinel IMPACT-Afib: A Test Case

Leveraging Distributed Database



Initiatives for Clinical Trials with Distributed Database



Sentinel Initiative

- Sentinel Distributed Database
  - Routinely collected health data (health plan enrollment, claims, pharmacy dispensing, etc.)
- Sentinel System
  - Uses Sentinel Distributed Database
  - Operates under FDA's public health authority
- FDA-Catalyst
  - Directly contacts health plan members/providers or changes care (request more information, randomize care, etc.). May also use the Sentinel Distributed Database.
  - Common Rule applies – IRB oversight

Data Partners' Trial Experience

- Nearly all had experience in randomized trials
- Experience contacting patients and providers via various methods
- ~Half had internal research departments

Information from 13 data partners, Aug 2013

Data Partners' Trial Interest

- 3 primary factors:
  - Topic must align with organizational or provider priorities
  - Could not compete for resources
  - Adequate financial support
- 7 interested in future trials

Data Partners' Other Considerations

- Turnover of population
- Ability to engage providers varies
- Varied structure / approval requirements

Rationale for IMPACT-AFib trial

- OAC underuse is a public health priority
- Also a priority of health plans
- Interventions (mailings!) are consistent with routine health plan interventions
- Eligible population and major outcomes measurable using Sentinel Distributed Database

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

- Randomized controlled trial of direct mail to health plan members with AFib and to their providers to encourage consideration of oral anticoagulation
- Proof of concept randomized trial using Sentinel Initiative infrastructure

IMPACT-Afib Workgroup

aetna℠

Duke Clinical Research Institute

Harvard Pilgrim HealthCare

Patient representative

HealthCore® Anthem®

FDA U.S. FOOD & DRUG ADMINISTRATION

HUMANA®

OPTUM™

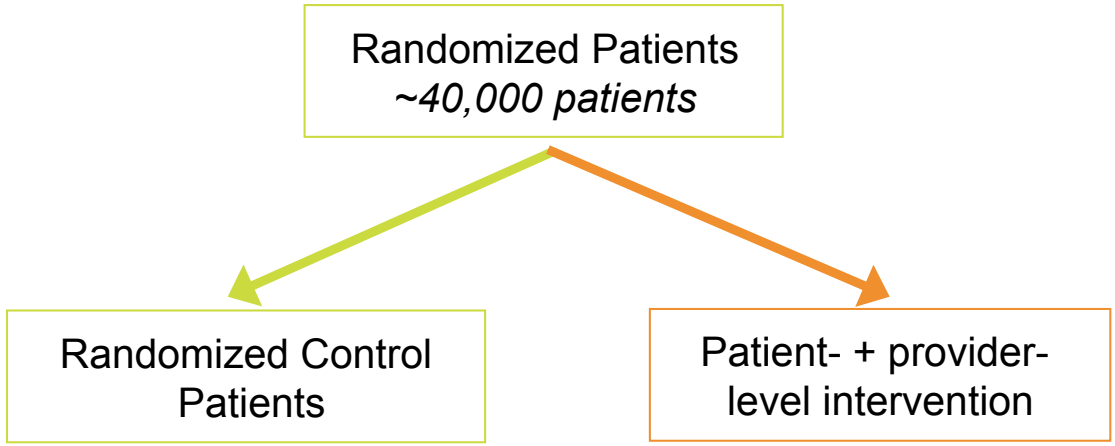
CLINICAL TRIALS TRANSFORMATION INITIATIVE

Trial Overview

Patients
- Atrial fibrillation (AF) (two claims)
- CHADS-VASc ≥ 2
- No admission for bleeding in prior 6 months
- Not prescribed anticoagulant for prior 12 months
- Age ≥ 30 years

All Patients Meeting Inclusion and Exclusion Criteria

- Aim to increase the use of oral anticoagulation (OAC) among patients with AF and risk of stroke
- Combined patient and provider level intervention



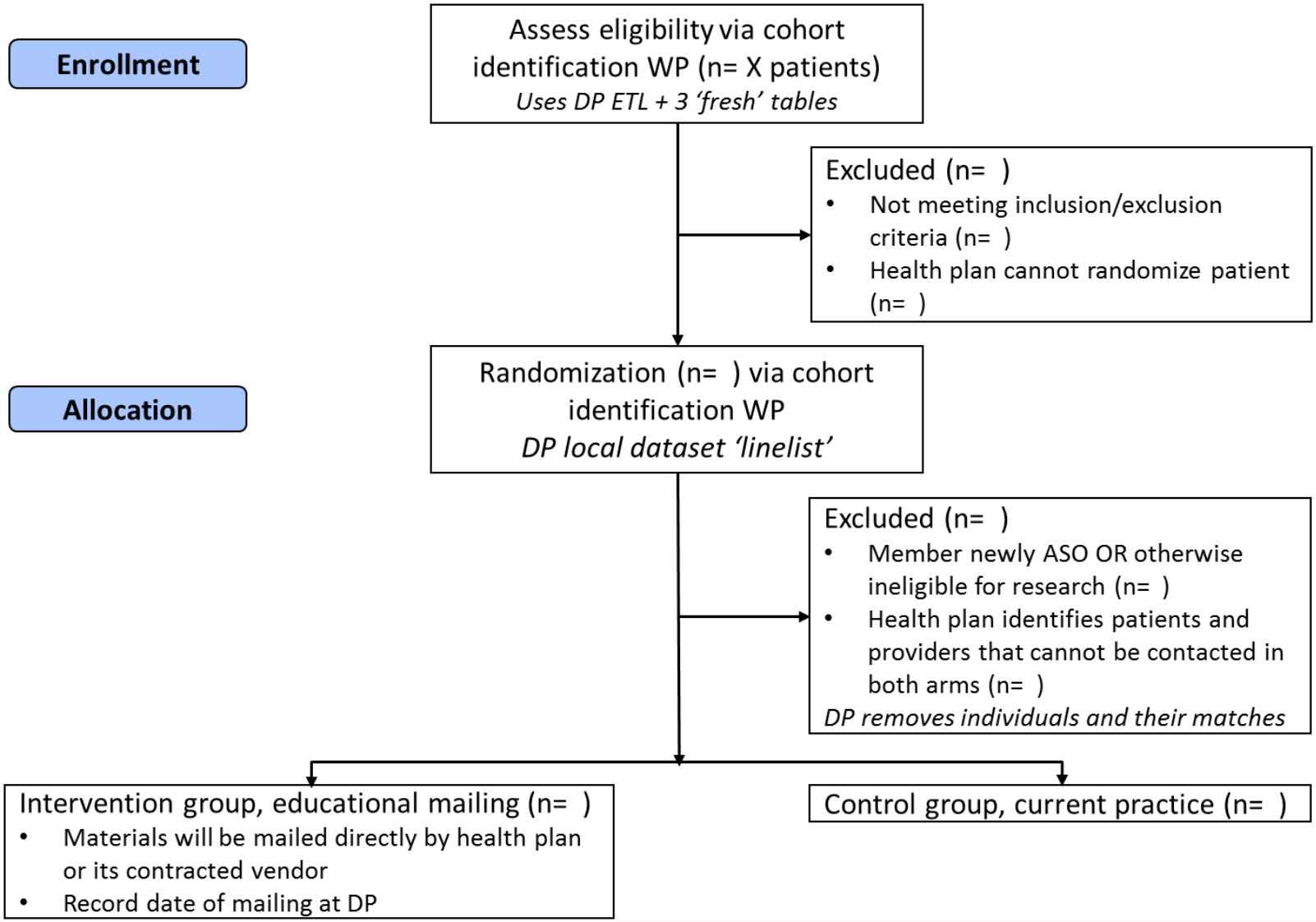
Primary comparison: difference in the proportion of AF patients started on OAC over the course of the 12-month trial

Secondary outcomes: proportion of days covered with OAC prescription, number of patients on OAC at end of one year; admissions for stroke or bleeding; deaths (subset)

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
- All-cause mortality in Medicare Advantage patients
- In-hospital mortality
- Outcomes will be assessed 12 and 24 months after mailings

Flow Diagram



Inclusion Criteria

- Adult ≥30 years old
- Medical & pharmacy coverage for ≥365 days
- ≥2 atrial fibrillation diagnosis codes with 1 in the last year
- No OAC fill within the previous 12 months
- CHA_2DS_2-VASc score ≥2

Exclusion Criteria

- Any OAC dispensing within the last year (or ≥4 INRs)
- Conditions other than AF that require anticoagulation
  - Mechanical prosthetic valve, DVT, pulmonary embolism
- Any history of intracranial hemorrhage
- Bleeding related hospitalization in the last 6 months
- Current pregnancy
- P2Y12 inhibitor treatment, e.g., clopidogrel within 90 days

Sample size estimate using Sentinel tools

- Run March 2016 at 5 Data Partners
- Overview:
  - Identify patients with AF in 2013 and no prior OAC use
  - Estimate CHA_2DS_2-VASc scores
  - Assess subsequent treatment with OAC in 1 year follow-up
  - Assess rates of stroke and bleeding among those treated and not
- 38,759 patients identified

Power to detect initiation of anticoagulant

- 11,000 subjects (total of both arms) has 95% power to detect increase from 20% to 24%
- Two sided type I error rate of 0.01
- Assumes 30% attrition during 1 year observation

Power	Total sample size (2-arm)	Intervention arm	Control arm
85%	8136	4068	4068
90%	9256	4628	4628
95%	11052	5526	5526

Power to detect decrease in stroke

- 40,000 subjects (total of both arms) has 85% power to detect a decrease in one year stroke rate from 4.4% to 3.8%
- This assumes a 60% reduction in hazard ratio among treated group

Intervention Materials for Patients

- Sample intervention materials shared during presentation and will be made available here after the study period concludes

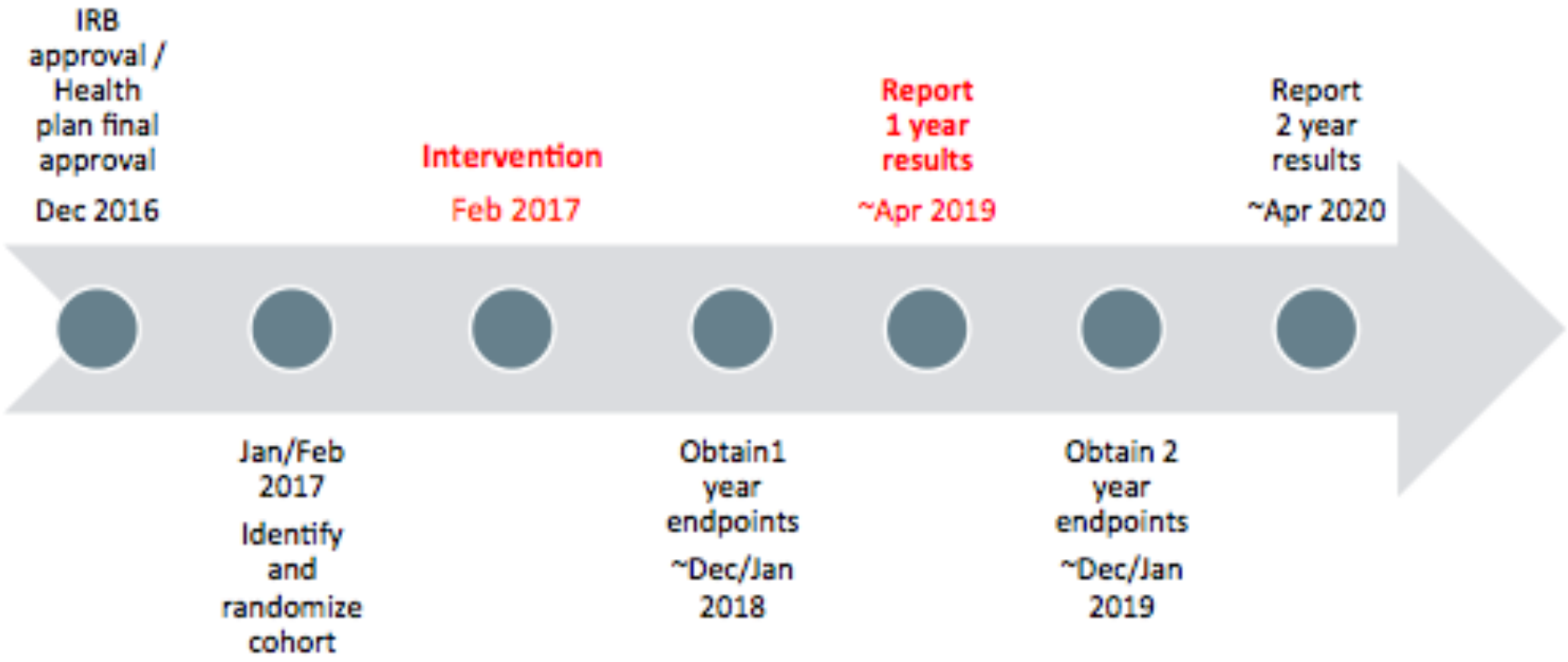
Intervention Materials for Providers

- Provider letter - sent from health plan CMO, describes call to action
- Response mailer - way for providers to share feedback
- Provider enclosure – myths and facts on use of OACs

Surprises along the way

- Medicare Advantage member enrollment concerns
- Similar outreach initiatives at health plans as part of routine care

Timeline


IRB approval / Health plan final approval
Dec 2016
Jan/Feb 2017
Identify and randomize cohort
Intervention
Feb 2017
Obtain1 year endpoints
~Dec/Jan 2018
Report 1 year results
~Apr 2019
Obtain 2 year endpoints
~Dec/Jan 2019
Report 2 year results
~Apr 2020

Substantial discussions about:

- Unit of randomization (individual, practice, metropolitan statistical area)
- Intervention designs (one vs multiple contacts, feedback to clinicians)
- Content of intervention materials
- Identifying low cost warfarin dispensings
- Health plan leadership review of intervention materials
- Timing of mailing (open enrollment and HEDIS)
- Appropriateness of requesting waiver of consent
- Need for Independent Advisory Committee

Thank you!