

# Randomized Clinical Trial Using FDA's Sentinel Infrastructure: An Analysis Assessing Feasibility

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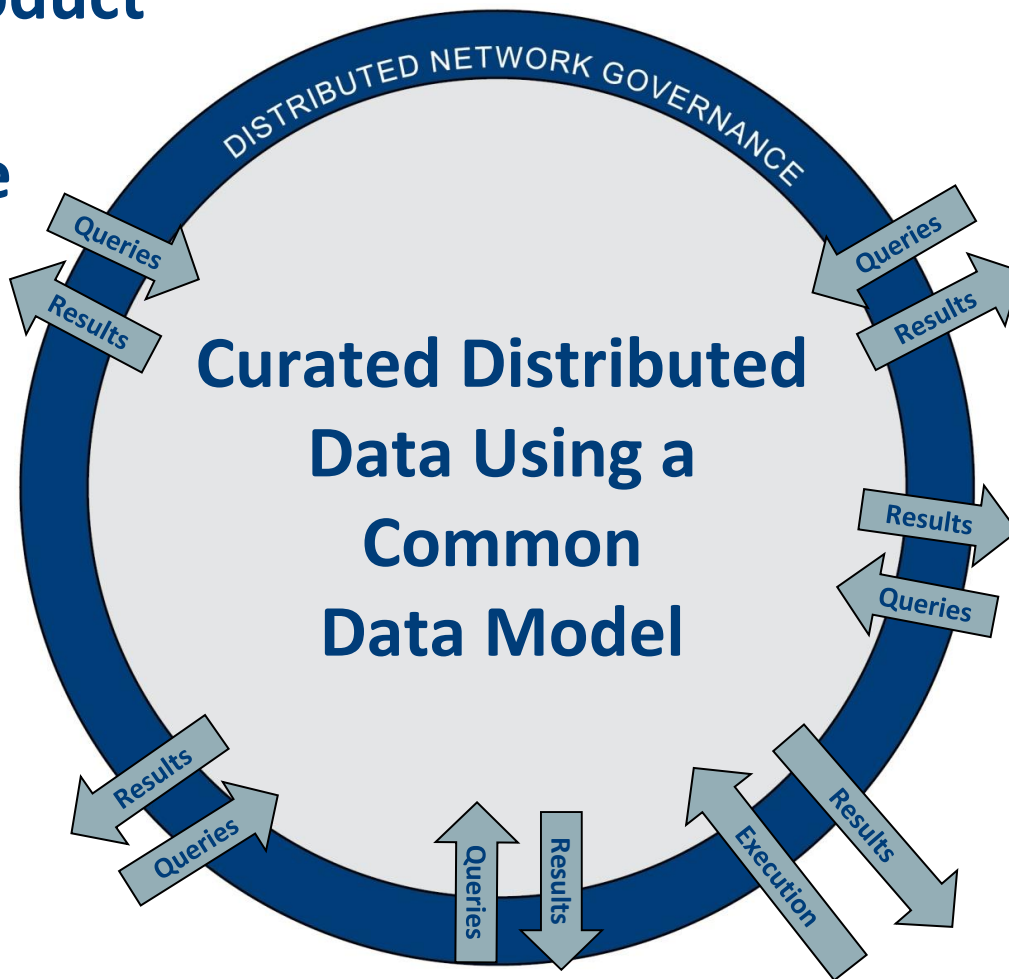
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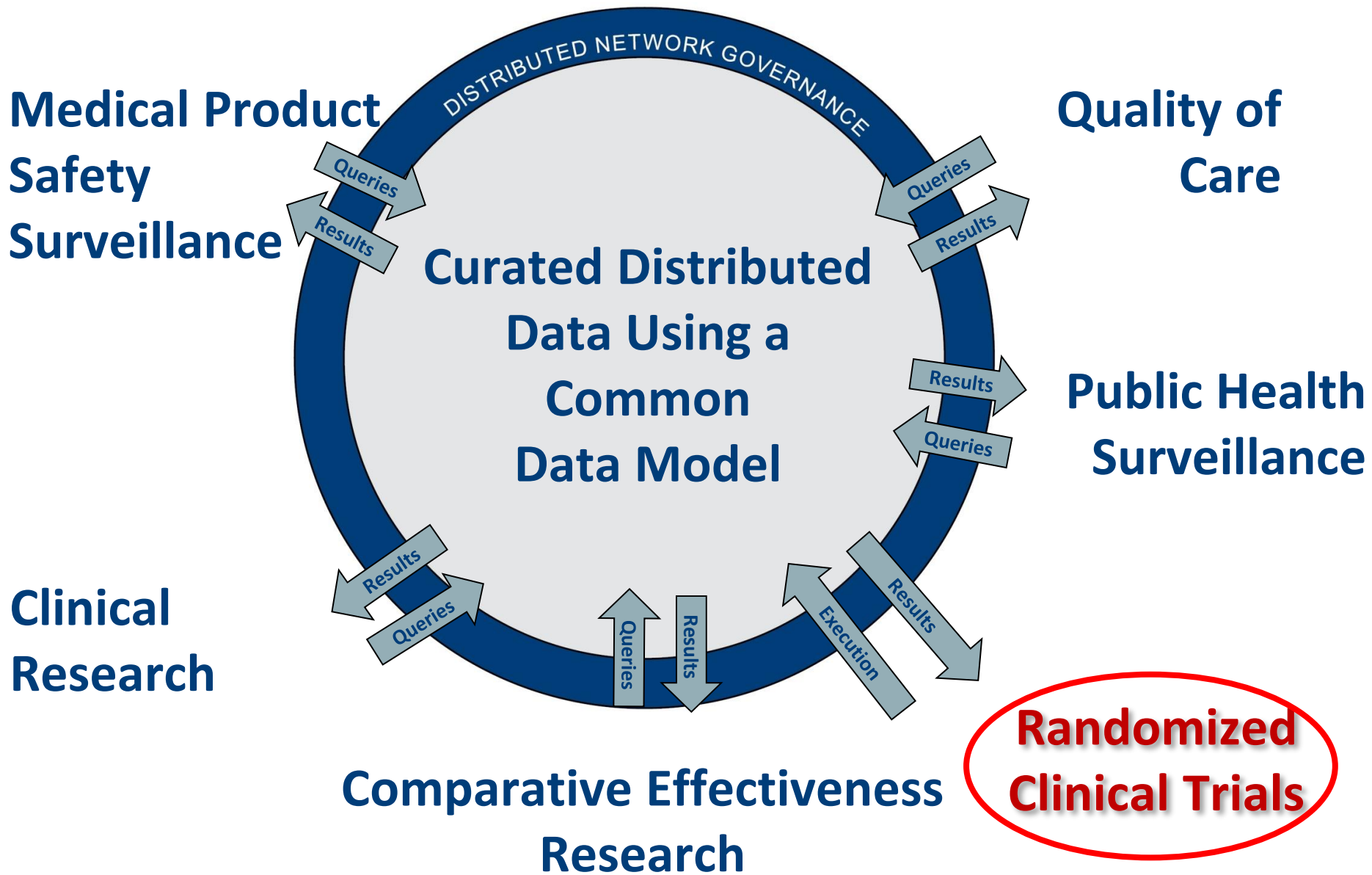
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6. Optum Epidemiology, Boston, MA
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- No relationships to disclose

# Medical Product Safety Surveillance







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# FDA-Catalyst: IMPACT-AFib randomized trial

**IM**plementation of a randomized controlled trial to im**PR**ove treatment with oral **AntiCoagulanTs** in patients with **Atrial Fib**rillation

- Direct mailer to 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 Participating Sites



# Atrial fibrillation, a common and important problem

- 2.7–6.1 million people in the U.S. have atrial fibrillation (AFib)
- 4-5 fold increase in risk of stroke
  - 750,000 added strokes per year in U.S.
  - Contributes to 130,000 deaths
- ~2/3 of AFib related stroke is preventable with oral anticoagulants (OACs)
- 40-60% of AFib patients at risk of stroke are not on OAC therapy

Birman-Deych et al 2006; CDC Afib Fact Sheet; Connolly et al 2011; Go et al 1999; Nieuwlaat et al 2006; Partington et al 2007; Waldo et al 2005; Walker et al 2008; Wilke et al 2012



# Objective

To estimate the number of health plan members with AFib at risk for stroke without evidence of OAC use

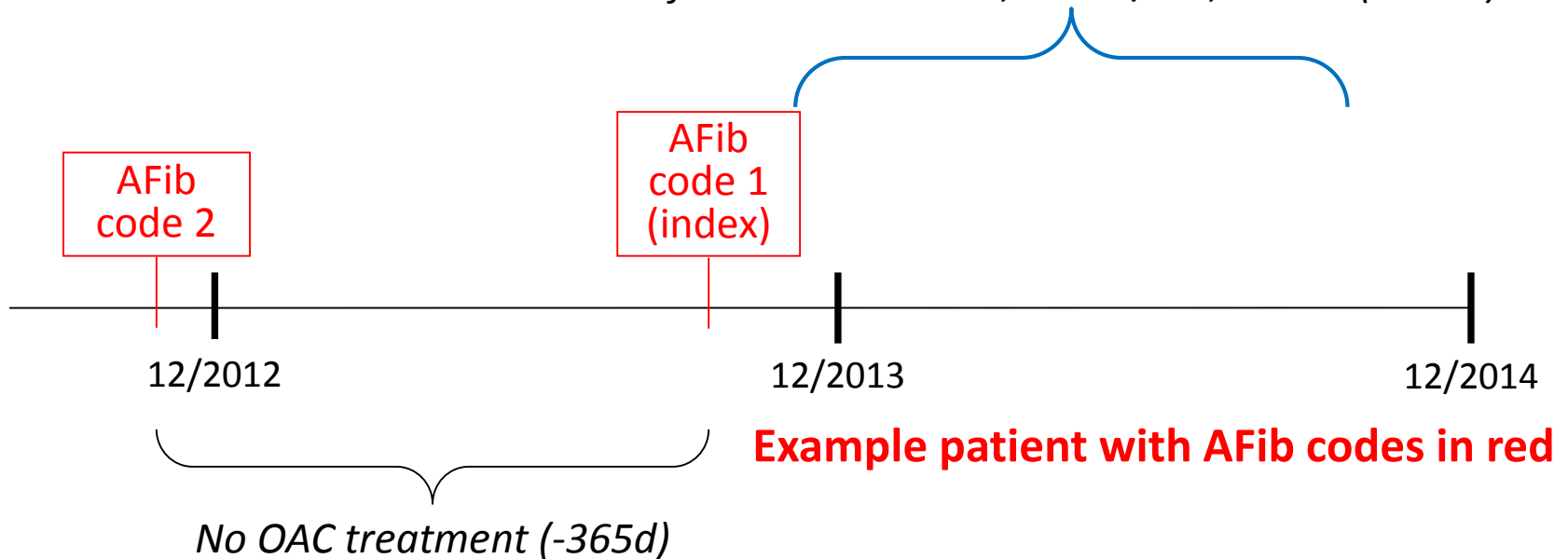
# Trial cohort eligibility

- Adult  $\geq 30$  years old
  - Medical & pharmacy coverage for  $\geq 365$  days
- $\geq 2$  AFib diagnosis codes
- No OAC dispensing (or  $\geq 4$  INR measurements) within the last year
- High risk for stroke (CHA2DS2-VASc score  $\geq 2$ )
- 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<sub>2</sub>DS<sub>2</sub>-VASc in feasibility query

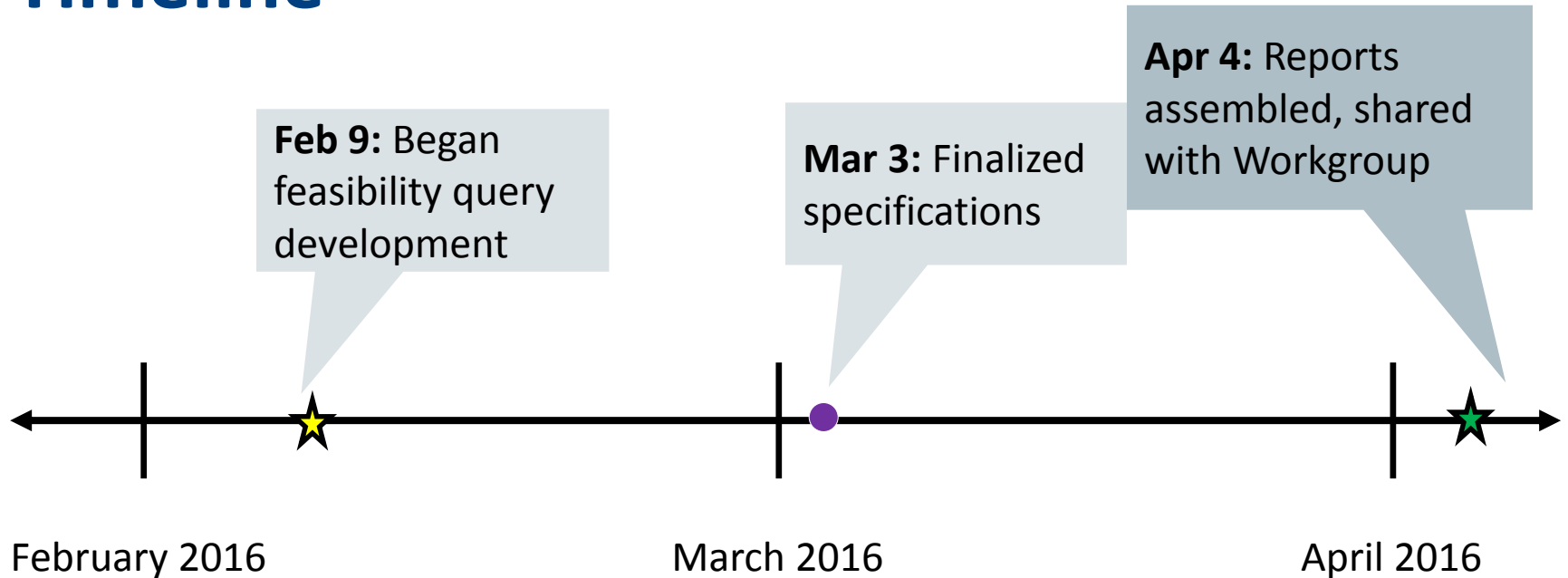
CHA <sub>2</sub> DS <sub>2</sub> -VASC CALCULATOR		
	Risk factor	If patient has risk factor, add points
<b>C</b>	Congestive Heart Failure	+1
<b>H</b>	High Blood Pressure (hypertension, including normal blood pressure on blood pressure medications)	+1
<b>A<sub>2</sub></b>	Age 75 years old or older	+2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

Look for OAC treatment, stroke/TIA, bleeds (+365d)



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

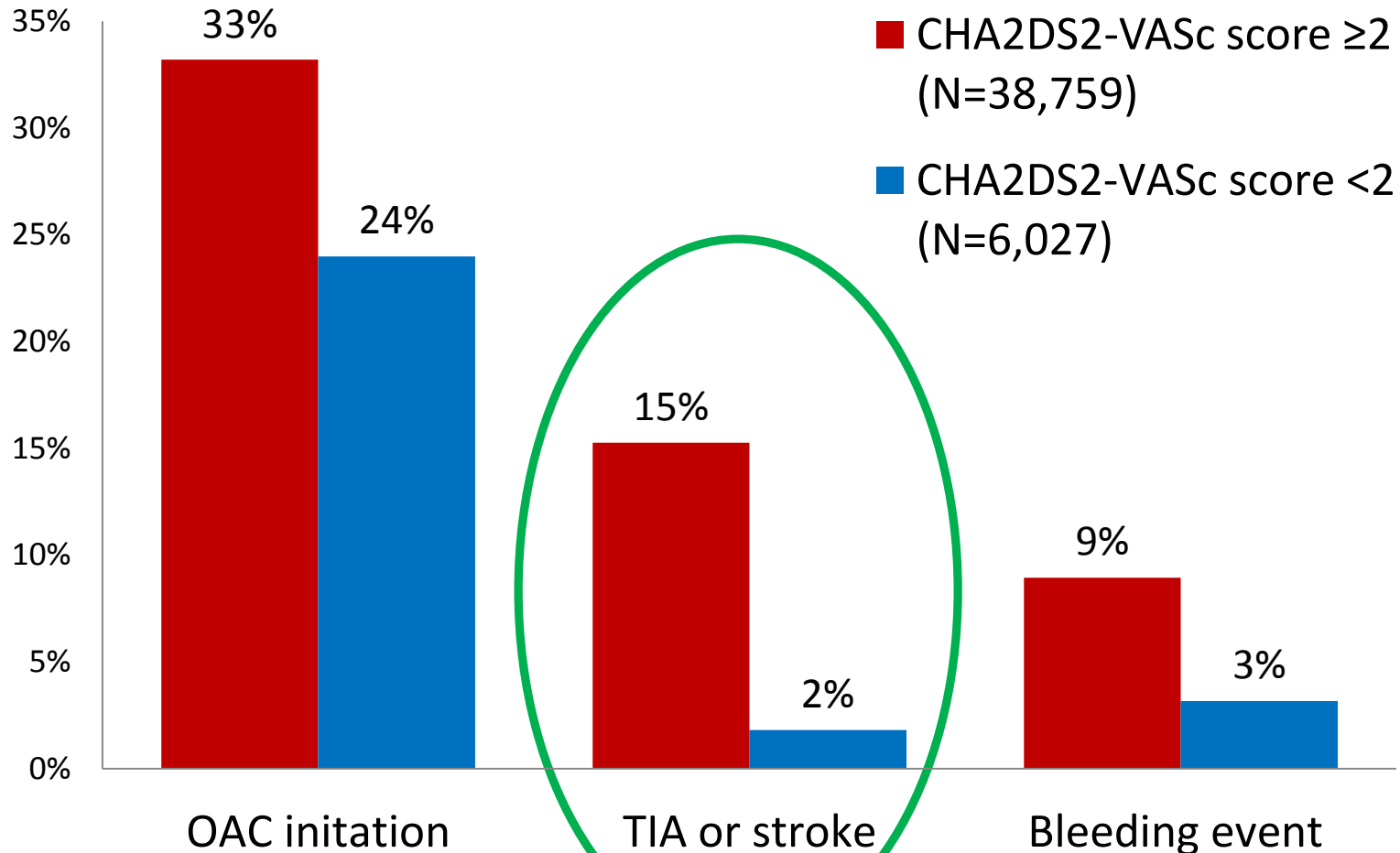
# Timeline



## Results 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
- Demonstrated capability (and speed!) of Sentinel infrastructure to support assessment of trial feasibility
- Limitations
  - Crude estimates due to analytic limitations of tool
  - Misclassification associated with claims data



# Where are we now?

IMPACT AFib address  
IMPACT AFib address

[Date]  
[Member Name]  
[Member Address]  
[Member City, St, zip]

Dear [Member Name],

According to our records, you may have been diagnosed with atrial fibrillation. We know that managing your health can be a challenge and hope this information about how to lower your risk for stroke will help.

## People who have the heartbeat irregularity known as "atrial fibrillation" are at an increased risk of having a stroke.

Please visit [IMPACT-AFib.org](http://IMPACT-AFib.org), to learn more about atrial fibrillation, stroke risk, and anticoagulant medications. More information about the IMPACT-AFib initiative is available by calling [XXX-XXX-XXXX] or emailing [contact@IMPACT-AFib.org](mailto:contact@IMPACT-AFib.org)

If you have questions about your benefits, call the number on the back of your health plan ID card.

### Talk to your doctor about anticoagulant medications.

This packet contains information about the benefits of taking anticoagulant medications, also called blood thinners, to lower your risk of having a stroke. We recommend that you bring this information packet to your next doctor's appointment. We sent similar information to your doctor.

Anticoagulant medications may not be right for all patients, but they might be right for you. Even if you have talked about this with your doctor in the past, we encourage you to have another conversation about these medications. New anticoagulant medications are safe and effective options for many patients.

### Protecting your health information

We take protecting your health information seriously. None of your health information has been shared with other healthcare organizations. Only you and your doctor were sent this information.

Sincerely,

Chief Medical Officer  
Enclosures

If you have any questions, please contact [name] at [phone #] or [email]

**You can lower your risk of stroke.**  
Bring this letter and pocket card to your next doctor's appointment.  
**Talk to your doctor about the use of anticoagulant medications to prevent stroke.**

**Should I be taking an anticoagulant medication?**

## Patient Information

You may have atrial fibrillation and may be at risk of a stroke.

### Taking an anticoagulant medication may prevent a stroke.

Atrial fibrillation (AFib) is a heartbeat irregularity. If you have AFib your blood can pool, which increases the risk of a blood clot forming in your heart. The blood clot can travel to your brain, causing a stroke.

Anticoagulant medications, also called blood thinners, can prevent most strokes in patients with AFib. If you are not taking an anticoagulant medication, you may suffer a stroke that could have been prevented.

Please review this information and talk with your doctor to find out if you should be on an anticoagulant medication to prevent a stroke.



### How do I know if I'm at a high risk for stroke?

If you have AFib, you are at a higher risk of stroke.

You are at additional risk if you:

- Have high blood pressure
- Have high blood sugar
- Have weak heart function
- Have had a stroke or mini-stroke
- Have had a heart attack or a blocked vessel in your leg
- Are over 64 years old
- Are a woman

### I have AFib only sometimes. Am I still at risk for a stroke?

Yes, the risk is similar whether your AFib is all the time, often, or only occasionally.

### What is an anticoagulant?

Anticoagulants are medications that:

- Prevent blood clots
- Keep existing clots from moving

Examples include: Coumadin®, Eliquis®, Pradaxa®, Savaysa®, warfarin, and Xarelto®.\*

\*The information in this mailing is NOT sponsored by any drug company.

For more information, please visit [IMPACT-AFib.org](http://IMPACT-AFib.org)

### If my doctor prescribes an anticoagulant, how should I take it?

- Take your medication exactly as directed by your doctor
- Take it at the same time each day
- If you forget to take your medication one day, take a dose as soon as possible on the same day
- Do not take a double dose the following day to "catch up"

Tell your doctor if you are pregnant or plan to become pregnant, are breastfeeding or plan to breastfeed, if you have liver or kidney problems, or are planning to have surgery.

### Will anticoagulant medications prevent strokes?

- Anticoagulant medications reduce the risk of stroke by 70% in patients with atrial fibrillation.

### What about aspirin?

- Aspirin is **not** an effective medication for decreasing the risk of stroke caused by atrial fibrillation.



## IMPACT-AFib

Dear Patient,

Talk with your doctor to find out if taking an anticoagulant medication is right for you. Anticoagulant medications prevent blood clots and are sometimes called blood thinners.

**Not sure where to start?** Here is a way to start the conversation with your doctor:  
*I received this letter, information sheet, and card in the mail from my health plan. My health plan suggests that I talk with my physician about taking an anticoagulant to help prevent a stroke.*

### QUESTIONS TO ASK YOUR DOCTOR:

1. Do I have atrial fibrillation?
2. What are my risk factors for stroke?

Based on my CHA<sub>2</sub>DS<sub>2</sub>-VASc score from the other side of this card, should I be taking an anticoagulant medication?

3.
  - If no, why not?
  - If yes, what kind of anticoagulant would work best for me?

Is aspirin good for me to take? The information I received said it was not effective in preventing stroke caused by AFib.

5. Should I be concerned with bleeding if I take an anticoagulant?

Most anticoagulant medications are covered by your health plan. Check with your health plan's information or call the phone number on your health plan card to determine which of the following drugs are covered: Coumadin®, Eliquis®, Pradaxa®, Savaysa®, warfarin, and Xarelto®.\*

For additional information, please visit [IMPACT-AFib.org](http://IMPACT-AFib.org).

\*This mailing is NOT sponsored by any drug company.



## IMPACT-AFib

Dear Doctor,

As you know, patients who have atrial fibrillation and a CHA<sub>2</sub>D<sub>2</sub>-VASc score of 2 or more are at risk of a stroke and would likely benefit from taking an anticoagulant medication.

The CHA<sub>2</sub>DS<sub>2</sub>-VASc calculator shows a patient's risk of a stroke. The score helps determine whether a patient would benefit from an anticoagulant.

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

Patients with a score of 2 or greater are at high risk for stroke. Strokes may be prevented with an anticoagulant medication.

Is IMPACT-AFib new to you? For more information, please visit [IMPACT-AFib.org](http://IMPACT-AFib.org).



Dear Provider:

As part of our effort to improve the use of oral anticoagulant medications for stroke prevention in patients with atrial fibrillation (AFib), we would like to introduce you to the IMPACT-AFib initiative. The objective of the IMPACT-AFib initiative is to increase awareness and education among you and your patients. This FDA-sponsored initiative is being conducted by [HEALTH PLAN] in collaboration with researchers at Harvard and Duke.

Educational materials were sent to patient(s) who appear to have AFib, have high stroke risk (CHA<sub>2</sub>DS<sub>2</sub>-VASc score ≥ 2), and have no record available to us of having filled a prescription for an anticoagulant in the past year. Please see the following page for a list of patients who received these materials.

**Facts about AFib**

- Patients with AFib have a five times higher stroke risk relative to patients without AFib (*Circulation* 2011;123(10):e269-367)
- More than two-thirds of strokes caused by AFib are preventable with anticoagulation (*Annals of internal medicine* 146.12 (2007): 857-867)
- 50 percent of patients with AFib and high stroke risk have not filled an anticoagulant prescription (*Circulation* 2014; 129 (15),1568-1576)

**Common misperceptions about stroke prevention**

<b>Aspirin is good enough</b>	<ul style="list-style-type: none"> <li>• Aspirin reduces stroke by &lt; 20%, if at all, compared with 70% reduction with anticoagulation; therefore, aspirin is not sufficiently effective for stroke prevention<sup>1</sup></li> </ul>
<b>Patients with AFib are at greater risk of bleeding than stroke</b>	<ul style="list-style-type: none"> <li>• 30% of elderly patients fall in a year, but a patient would need to fall nearly every day before the risk of intracranial bleeding outweighs the benefits of anticoagulants.<sup>2</sup></li> <li>• The risk of recurrent GI bleeding averages 1.2% per year but would have to exceed 10% before the risk of GI bleeding outweighs the benefit of anticoagulants.<sup>3</sup></li> </ul>

There are appropriate reasons for patients to not take an anticoagulant, including pregnancy and history of intracranial hemorrhage. A response mailer is enclosed for you to share these reasons, should they exist for your patient(s).

<sup>1</sup> European Heart Journal 2015; 36: 653-656    <sup>2</sup> Arch Intern Med 1999;159:677-685    <sup>3</sup> Arch Intern Med 2002;162:541-550

**IMPACT-AFib**

If they are not taking oral anticoagulants, patients with AFib can have strokes that are PREVENTABLE.

Myth vs. Reality
<p><b>Myth:</b> Aspirin prevents stroke and is safe</p> <p><b>Reality:</b> Aspirin is neither safe nor effective (<i>Eur Heart J</i> 2015;36:653-6)</p>
<p><b>Myth:</b> It is risky to resume oral anticoagulation therapy in the months after bleeding</p> <p><b>Reality:</b> Benefits generally outweigh risks (<i>Arch Intern Med</i> 2002;162:541-550)</p>
<p><b>Myth:</b> It is risky to prescribe oral anticoagulants to patients who are at risk of falling</p> <p><b>Reality:</b> "... persons taking warfarin must fall about 295 times in 1 year for warfarin to not be the optimal therapy." (<i>Arch Intern Med</i> 1999;159:677-685)</p>
<p><b>Myth:</b> Patients who don't tolerate warfarin won't tolerate any oral anticoagulant</p> <p><b>Reality:</b> Most patients tolerate novel oral anticoagulants (<i>N Engl J Med</i> 2011;364:806-17)</p>
<p><b>Myth:</b> Patients with paroxysmal AFib are low risk of stroke</p> <p><b>Reality:</b> Risk is about the same for paroxysmal or permanent AFib, indicating need for anticoagulation (<i>Circulation</i> 2014;130: e199-e267)</p>
<p><b>Myth:</b> There is no antidote for novel oral anticoagulants</p> <p><b>Reality:</b> An injectable reversal agent (Praxbind) is available for the novel oral anticoagulant Pradaxa (dabigatran). (<i>N Engl J Med.</i> 2015;373:511-20)</p>

**IMPACT-AFib**

Patients with atrial fibrillation (AFib) are at five times higher risk of stroke (*Circulation* 2011;123(10):e269-367)

- Two-thirds of strokes in patients with atrial fibrillation are preventable with anticoagulation, as recommended in clinical practice guidelines (*Annals of internal medicine* 146.12 (2007): 857-867)
- Despite this guideline, at least 50% of patients with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score of 2 or higher are not being prescribed an oral anticoagulant (*Circulation* 2014; 129 (15), 1568-1576)

**You can help change these statistics by—**

- Educating all of your patients with AFib about anticoagulant use
- Stopping the use of aspirin as an anticoagulant

**For more information, please visit IMPACT-AFib.org**

Patient name: \_\_\_\_\_

Date of birth: \_\_\_\_ / \_\_\_\_ / 19\_\_\_\_  
Month Day Year

Should not be prescribed an oral anticoagulant because— (please check all that apply)

- He/she is not my patient and/or I am not the prescribing physician
- Patient does not have atrial fibrillation
- Patient already takes an anticoagulant
- An anticoagulant has already been prescribed
- Very high risk of major/life-threatening bleeding
- Unable to tolerate warfarin
- Unable to afford a non-vitamin K oral anticoagulant
- Patient decision after thorough review of risks, benefits, concerns
- Other (please explain): \_\_\_\_\_

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- **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

**Thank you!**

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