FDA-CATALYST PROTOCOL

IMPLEMENTATION OF A RANDOMIZED CONTROLLED TRIAL TO IMPROVE TREATMENT WITH ORAL ANTICOAGULANTS IN PATIENTS WITH ATRIAL FIBRILLATION (IMPACT-AFib)

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The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I.

History of Modifications

Version	Date	Modification	By
V5.0	03/07/2019	• Updated text throughout to match decisions made during development of the statistical analysis plan (SAP) • Annotated change in study design – early intervention mailing occurred in two waves (*VI. Study Design & Duration*) • Updated Figures 1 and 2 for accuracy • Added link to code list for inclusion and exclusion criteria • Included reasons eligible members and providers might not be mailed the intervention (*IX. Method of Assigning Patients to an Intervention*)	IMPACT-AFib Workgroup

V4.0	04/19/2018	• Each Data Partner conducted its own mailing to trial participants. Due to the early intervention launch (start of follow-up) spanning multiple months:
		  ○ Clarified that the follow-up period for primary and secondary objectives will be calculated based on the date on which at least 80% of eligible study participants have at least 12 months of follow-up time
		  ○ Clarified that the follow-up period for exploratory objectives will be calculated based on the date on which at least 80% of eligible study participants have at least 24 months of follow-up time
		  ○ Noted that all possible person-time will be used to assess outcomes (*VI. Study Design & Duration*)
		• Updated Figures 1 and 2 for accuracy
			IMPACT-AFib Workgroup

V3.0	11/03/2017	• Updated anticipated trial size and power calculations • Included more detail about provider identification process for mailing (*IX. Method of Assigning Patients to an Intervention)* • Clarified population eligible for primary analyses (*XIV. Statistical Considerations, B. Populations for Analysis*)	IMPACT-AFib Workgroup

V2.0	10/02/2017	• Clarified descriptions of the early and delayed intervention arms, including timing of mailings; noted that both arms include usual care and reiterated that those with recent OAC treatment will be excluded from mailings • Updated schematic diagrams based on improved descriptions of the early and delayed interventions • Updated Sentinel-CTTI partnership objective (*V. Study Objectives, C. Exploratory Objectives*) • Clarified medical and pharmacy coverage requirement (*VII. Study Population, A. Inclusion Criteria)* • Included more details about sample size and power calculations (*XIV. Statistical Considerations, A. Sample Size and Power Calculations*) • Added rationale for using INR tests/values as a proxy for anticoagulant dispensing(s) (*VII. Study Population*) • Added description of patient written education materials and clarified that information regarding top misperceptions will be provided for providers (*VIII. Interventions*) • Noted that feedback from the provider response mailers will not be linked to specific patients or providers (*XVI. Statistical Analyses, B. Responses from Providers*) • Made many less substantive changes in the interests of completeness, accuracy, and flow	IMPACT-AFib Workgroup

FDA-Catalyst Protocol

Implementation of a Randomized Controlled Trial to Improve Treatment with Oral Anticoagulants in Patients with Atrial Fibrillation (IMPACT-AFib)

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I. PROTOCOL SYNOPSIS

Protocol Title:	**IM**plementation 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 (IMPACT-AFib)
Research Hypothesis:	Education on stroke prevention in atrial fibrillation (AF) among AF patients and their providers can result in increased use of oral anticoagulants (OAC) for stroke prevention among those AF patients with guideline-based indications for oral anticoagulation (CHA_2DS_2-VASc score of 2 or greater)
Study Schema and Length of Trial:	Early patient and provider* education interventions versus usual care (with delayed provider* education intervention at the date on which at least 80% of eligible study participants have at least 12 months of follow-up time). Duration of follow-up for the primary outcome (OAC treatment) will be from the date that the early intervention materials are mailed through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time; secondary outcomes will also be evaluated at this time.
Study Objectives:	**Primary:** evaluate the effect of the patient and provider education interventions (versus usual care with delayed provider education intervention) on the proportion of patients with evidence of at least one OAC prescription fill (defined as one OAC dispensing or 4 INR tests) over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time. **Secondary:** evaluate the impact on outcomes of the patient and provider education interventions over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time: 1. Incident rate of stroke or transient ischemic attack (TIA) hospitalization 2. Incident rate of hospitalization for stroke 3. Time to first OAC prescription fill 4. Proportion of days covered by OAC prescription fills 5. Proportion of patients actively on OAC at 12 months of follow-up 6. Incident rate of hospitalization for any bleeding 7. All-cause in-hospital mortality rates

*Where it is possible to identify an individual provider. See Section IX. Method of Assigning Patients to an Intervention for further information.

	8. All-cause mortality rates among patients with accurate out-of-hospital mortality data (such as Medicare Advantage patients) 9. Health care utilization for AF patients, which would be reported as counts of number of health care utilization events (outpatient visits, days hospitalized, number of emergency department visits, etc.) **Exploratory:** 10. Evaluate the effect of the education interventions on the primary and secondary endpoints over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 24 months of follow-up time. 11. Explore the Clinical Trials Transformation Initiative (CTTI) and the FDA supported Sentinel Data Partners' ability to successfully conduct a pragmatic trial to answer important questions to improve public health
Study Design:	Prospective, randomized, open-label education intervention trial. Patients with AF and a CHA_2DS_2-VASc score of 2 or greater will be randomized in a 1:1 ratio to (a) the early intervention arm: early patient and provider educational interventions for those patients identified at the time of randomization and (b) the delayed intervention arm: usual care followed by provider education intervention 12 months after at least 80% of early intervention mailing has occurred (eligibility status of these patients will be assessed at time of delayed mailing). All inclusion criteria, exclusion criteria, and outcomes will be determined through claims data. The primary outcome is the proportion of AF patients with evidence of at least one OAC prescription fill over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time. A total of approximately 80,000 patients will be enrolled within multiple major health plans across the United States. Follow-up for the primary outcome and secondary outcomes will be assessed 12 months after the date on which at least 80% of eligible early intervention participants were mailed the early intervention materials. The randomization will be performed by the central coordinating center (Harvard Pilgrim), and statistical analyses will be performed by the Duke Clinical Research Institute. A second exploratory assessment of the primary and secondary endpoints will be performed once at least 80% of participants have at least 24 months of follow-up time to assess the durability and longer-term outcomes of the effect of the education intervention. Because the Sentinel Distributed Database will be used for follow-up information, and this information is refreshed approximately quarterly and this is done on separate timetables for the different health plans, it is likely that when at least the required follow-up

	time is available for at least 80% of people, there will be more than 12 or 24 months of follow-up for over 80% of people. All possible person-time will be used to assess participants' outcomes (patients will have different duration of follow-up).
Accrual Goal (Total number of participants):	Approximately 80,000 patients across all participating Data Partners (Aetna, Harvard Pilgrim, HealthCore, Humana, and Optum)
Accrual Rate (Number of participants expected per month):	All patients and providers will be randomized prior to the initiation of the early intervention. The enrollment date for all patients (early and delayed intervention patients) will be the date that the letters are mailed out to early intervention patients and providers by their respective health plans.
Inclusion Criteria:	1. Two or more diagnoses of AF (ICD-9 and/or ICD-10 codes) at least one day apart and with at least one diagnosis within the last 12 months prior to the last date in the current approved data used for cohort identification 2. CHA_2DS_2-VASc score of 2 or greater 3. Medical and pharmacy insurance coverage of at least the prior year as identified via administrative claims databases of one of the participating Data Partners as of the date of randomization 4. Age 30 years or greater as of the last date in the current approved data used for cohort identification
Exclusion Criteria:	1. Evidence of OAC medication fill during the 12 months prior to randomization (determined at randomization for the early intervention cohort and 12 months post-randomization for the delayed intervention cohort) 2. Conditions other than AF that require anticoagulation, including treatment of deep venous thrombosis, pulmonary embolism, or ever having had a mechanical prosthetic heart valve prior to the last date in the current approved data used for cohort identification 3. Pregnancy within 6 months of the last date in the current approved data used for cohort identification 4. Any known history of intracranial hemorrhage prior to the last date in the current approved data used for cohort identification 5. Hospitalization for any bleeding within the last 6 months of the last date in the current approved data used for cohort identification 6. Patients with recent P2Y12 antagonist use (i.e. clopidogrel, prasugrel, ticlopidine, or ticagrelor) within 90 days of the last date in the current approved data used for cohort identification
Criteria for Evaluation (Effectiveness, safety, stopping rules, etc.):	The primary outcome is evidence of at least one OAC prescription fill through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time.

Patient-Level Interventions (early intervention arm):	• Letters to patients that (1) explain to the patient that he or she appears to have AF, characterize the risk of stroke, and emphasize that although there may be a medical reason, the patient does not seem to be on an anticoagulant and (2) encourage the patient to discuss this with his or her provider to ask if he or she might benefit from OAC therapy to prevent stroke • Written education materials • Website with the patient-focused information contained in the letters to patients

Provider-Level Interventions (early intervention and delayed intervention arms):	• Letters to providers:
	  ○ Early intervention letters to providers that explain this project, the nature of the problem, and identify a list of the provider's patients who have been contacted, as the provider and patient letters will be sent at approximately the same time; describe evidence and guidelines regarding oral anticoagulation
	  ○ Delayed intervention letters to providers that explain this project, the nature of the problem, and identify a list of the provider's patients who are at risk for stroke and have not been treated with an oral anticoagulant; describe evidence and guidelines regarding oral anticoagulation
	• Response mailer that gives the provider the opportunity to share the rationale for his or her patient(s) not being on OAC
	• Web portal with access to clinical practice guidelines, decision support tools including from professional societies, podcasts, and case studies targeted at improving the appropriate use of OAC for AF
	• Information sheet describing top misperceptions of barriers to OAC use
	  ○ Misperception of benefit and risk of aspirin: it is neither safe nor effective
	  ○ Misperception around risk of resuming OAC (months) after bleeding
	  ○ Misperception regarding risk of OAC regarding patients who fall
	  ○ Opportunities with novel OACs (NOACs) for patients who have not tolerated warfarin
	  ○ Concern about lack of an antidote for the NOACs

Statistics and Power Calculations:	Primary outcome: proportion of AF patients with evidence of at least one OAC prescription fill through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time Sample size and power determination assumptions:

	• 33% OAC initiation rate in the delayed intervention arm over the first year of the study • 38% OAC initiation rate in the early intervention arm (a 5% improvement in OAC initiation over the 33% OAC initiation expected in the delayed intervention arm over 1-year follow-up) • 1-year attrition rate: 30% dropout or lost-to-follow-up • Two-sided type I error of 0.05 • Roughly 10,000 patients will yield more than 99% power to detect a 5% absolute difference Secondary outcome: stroke or transient ischemic attack (TIA) over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time. A study with approximately 80,000 patients is reasonably powered to detect a reduction in stroke or TIA under assumptions listed below: • 1-year stroke or TIA rate: 18% among patients not treated with OAC • 1-year stroke or TIA rate: 7% among patients treated with at least 1 OAC fill • Duration of follow-up: 1 year • 33% of delayed intervention patients will have at least 1 fill of OAC, meaning the 1 year stroke or TIA rate in the delayed intervention group would be 14.4% • If 38% of early intervention patients have at least 1 fill of OAC (meaning the 1 year stroke or TIA rate in the early intervention group would be 13.82%, i.e., an absolute reduction of 0.55%), the study will have 46% power to detect this 0.55% reduction. However, if 40.5% of early intervention patients have at least 1 fill of OAC (meaning the 1 year stroke or TIA rate in the early intervention group would be 13.54%, i.e., an absolute reduction of 0.83%), the study will have 80% power to detect this 0.83% reduction. • 1-year attrition rate: 30% dropout or lost-to-follow-up • Two-sided type I error of 0.05 • The sample size has 80% power to detect a 0.5% absolute reduction in stroke, assuming a cumulative 1-year incidence of stroke of 4.2% in control (delayed intervention arm) patients and 3.7% in intervention (early intervention arm) patients. The assumption is that patients not on oral anticoagulation have an annual stroke rate of 5%, and stroke will be reduced by 50% (HR=0.5) in the treated (anticoagulated) population. The 80% power requires that 52% of early intervention arm patients are treated at 1-year as compared to 33% in the control arm.

II. INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical practice, accounting for one-third of rhythm-related hospitalizations.[1] The prevalence of AF in the United States is 1% overall and more than 10% in people over age 80 years, with approximately 70% of cases in patients between 65 and 85 years of age.[2] As Americans age, the number of patients with AF is expected to increase 150% by 2050, with more than 50% of patients being octogenarians or older.[3-8] The increasing burden of AF is expected to lead to a higher incidence of stroke, as patients with AF have a five to seven fold greater risk of stroke than the general population.[9-11] The incidence of stroke in AF patients is 4 to 5% per year.[12] Patients with a stroke due to AF have worse prognoses than patients with stroke without AF.[13,14] Oral anticoagulants (OACs) are an important therapy for patients with AF as they decrease the rate of stroke by more than two-thirds.[15]

The clinical benefit of warfarin is only seen in patients who consistently maintain their international normalized ratio (INR) values within the therapeutic range (2.0-3.0).[16] The median times in the therapeutic range in the ARISTOTLE[17], ROCKET AF[18], RE-LY[19], and ENGAGE[20] trials were 62%, 55%, 64%, and 68%, respectively. As part of quality improvement efforts, there is significant interest in measuring and improving performance of physicians in prescribing anticoagulation for patients with AF. The $CHADS_2$ and CHA_2DS_2-VASC scores have been developed to support providers in identifying patients with AF who are at an increased risk for stroke.[21,22] Paradoxically, anticoagulation use is no higher, or declines, as the risk of stroke, as measured by these scores, increases.[23] This is in large part due to the fact that physicians and patients are concerned about the risk of bleeding in higher-risk populations, and they may underappreciate the net benefit from anticoagulants, including stroke prevention. In any case, approximately 40-60% of patients with AF at risk of stroke are not prescribed anticoagulation therapy.[15,24-30] This translates to over 50,000 preventable strokes each year in the United States with a number needed to treat of approximately 25 patients to prevent 1 stroke.

The specific reasons for not using an anticoagulant in eligible AF patients are poorly defined. The AVERROES trial provided some insight into reasons for patients deemed "unsuitable for warfarin" with 42% unable to maintain therapeutic INR, 43% unlikely to monitor INR, and 37% refusing warfarin.[31] The reasons for underuse of oral anticoagulation are likely related to three types of barriers: patient-level barriers (i.e. overestimation of risk of bleeding, underestimation of risk of stroke, misperceptions of adverse events from OACs), provider-level barriers (i.e. overestimation of risk of bleeding, underestimation of risk of stroke, misperceptions of adverse events from OACs, misperceptions about a patient's fall risk, misperceptions of the benefits of aspirin in stroke prevention), and system-level barriers (i.e. lack of time in a clinic visit to discuss stroke prevention, access to care such as an anticoagulation clinic, cost of OACs, feasibility of warfarin monitoring).

Another issue driving under-treatment with oral anticoagulants is poor medication adherence, which may be driven by patient barriers or system-level barriers. Medication non-adherence is defined as a patient's passive failure to follow a prescribed drug regimen. An average of 50% of patients are non-adherent to their prescribed treatment regimens for chronic diseases, such as AF.[32] Non-adherence rates are similar across disease states, treatment regimens, and age groups, with the first several months of therapy characterized by the highest rates of discontinuation.[33] Interventions to support patient management of medications have fallen short, and sustainable adherence rates have not improved.[34,35]

The cost to the health care system of hospitalizations due to medication non-adherence for all disease states may be as high as approximately $100 billion annually.[36] Patient-provider communication regarding medication use is poor, and opportunities to document and provide feedback on metrics for medication adherence are not readily available in EMR applications.[37] Meaningful and measurable improvements in adherence require a comprehensive, multifaceted intervention in which all participants, including physicians, play an active part.

III. RESEARCH HYPOTHESIS

Among AF patients with guideline indications for OAC for stroke prevention who have not received any OAC dispensing for at least one year, an education intervention at the patient-level and the provider-level will increase the proportion of patients started on OAC for stroke prevention.

IV. STUDY RATIONALE

Preliminary data from three Sentinel Data Partners between 1/1/2006 and 6/30/2015, identified 231,696 patients (1.4%) with at least 2 diagnoses of AF (ICD-9 codes of 427.31 or 427.32) over the study period, among 16.2 million covered lives. Within the 231,696 AF patients, there were 201,882 with a CHA_2DS_2-VASc score of 2 or greater (based on administrative claims data in the Sentinel Distributed Database), which is an American Heart Association (AHA)/American College of Cardiology (ACC) guideline indication for OAC. Over the study period from 2006 through 2015, 52% (n=105,256) patients filled at least one prescription for anticoagulation, meaning that 48% of patients with CHA_2DS_2-VASc score of 2 or greater never had a pharmacy claim submitted for an OAC during the study period. While there may be clinical or health system related reasons for not treating some of these patients, this apparent significant gap of guideline-based adherence is a public health issue of interest. The presented protocol is an opportunity to test the potential for developing and testing a health plan (Data Partner) based education intervention to improve the quality of care.

V. STUDY OBJECTIVES

A. PRIMARY OBJECTIVE

The primary objective is to evaluate the effect of the patient and provider education interventions (versus usual care with delayed provider education intervention) on the proportion of patients with evidence of at least one OAC prescription fill (defined as one OAC dispensing or 4 INR tests) over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time.

B. SECONDARY OBJECTIVE

The secondary objectives are to evaluate the impact on outcomes of the patient and provider education interventions over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time:

1. Incident rate of stroke or transient ischemic attack (TIA) hospitalization
2. Incident rate of hospitalization for stroke
3. Time to first OAC prescription fill
4. Proportion of days covered by OAC prescription fills
5. Proportion of patients actively on OAC at 12 months of follow-up
6. Incident rate of hospitalization for any bleeding
7. All-cause in-hospital mortality rates
8. All-cause mortality rates among patients with accurate out-of-hospital mortality data (such as Medicare Advantage patients)
9. Health care utilization for AF patients, which would be reported as counts of number of health care utilization events (outpatient visits, days hospitalized, number of emergency department visits, etc.)

C. EXPLORATORY OBJECTIVES

The exploratory objectives are to:

1. Evaluate the effect of the early and delayed education interventions on primary and secondary endpoints over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 24 months of follow-up time.
2. Explore the CTTI and the FDA supported Sentinel Data Partnership's ability to successfully conduct a pragmatic trial to answer important questions to improve public health.

VI. STUDY DESIGN AND DURATION

The study is a prospective, randomized, and open-label education intervention trial. Patients with AF and a CHA_2DS_2-VASc score of 2 or greater will be randomized in a 1:1 ratio to an early intervention cohort and a delayed intervention cohort within each participating health plan. The definition for OAC medication fill will be an OAC medication dispensing or at least 4 INR tests in the claims data.[1] The claims records of the patients randomized to the early intervention cohort will then be linked to "fresh" (i.e. about 1-4 months old) pharmacy claims data at the time of randomization. Patients without evidence of an OAC medication fill during the 12 months prior to randomization will be included in the patient-level and provider-level early educational intervention (patients randomized to this early intervention with evidence of an OAC medication fill during the 12 months prior to randomization will be excluded from the trial.). In addition to usual care, these patients and their providers[2] will receive a

[1]Not all OAC dispensings are well captured in pharmacy claims, particularly, for warfarin. INR tests are assumed indicative of OAC fills that were not billed through the claims. 4 INR tests or values within a 12-month period will be used as a proxy since that is roughly the number of tests administered in the process of stabilizing dose.
[2]See Section IX. Method of Assigning Patients to an Intervention for detail regarding provider identification. In certain circumstances, a member or provider may not receive the one-time mailing.

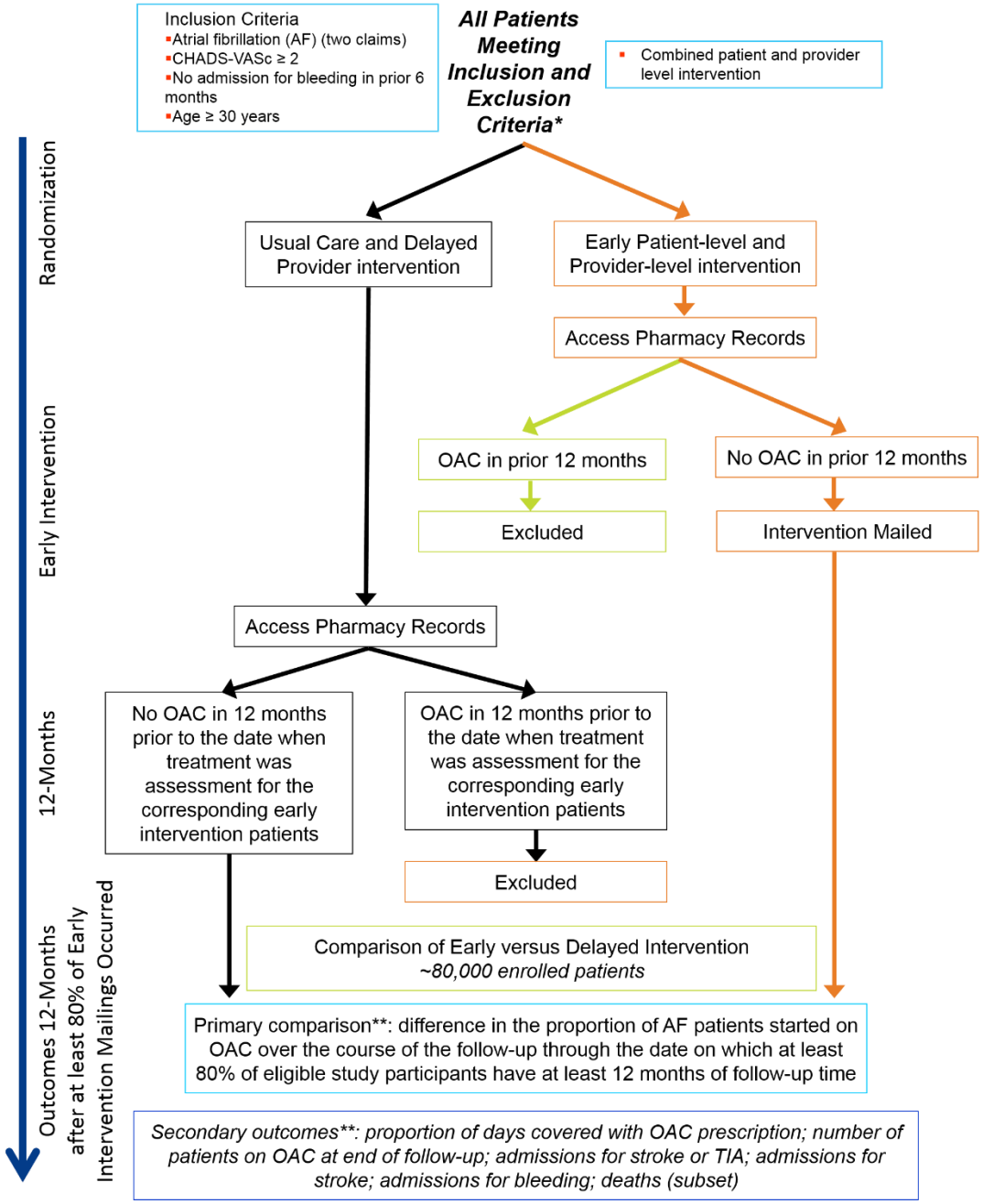
one-time mailing at trial start. There will be two waves of mailings for the early intervention cohort at most sites due to the practical challenges of claims data: the patients are assigned to wave 1 if they have a provider easily identified in the data (i.e., the provider associated with the most recent AF diagnosis is an individual provider), and they are assigned to wave 2 if it is difficult to identify a provider (e.g., the first identified provider is a facility). Follow-up time will start on the date of the respective wave 1 and wave 2 mailings for the early intervention patients

The delayed intervention cohort will receive usual care over the initial study period. After the date on which at least 80% of eligible study participants have at least 12 months of follow-up time, "fresh" pharmacy claims data for the delayed intervention cohort that was generated and locked at the time of randomization will be used to assess trial eligibility, and those patients without evidence of an OAC medication fill during the 12 months prior to randomization will be included in the primary and secondary analyses as the delayed intervention arm. Patients randomized to the delayed intervention arm with evidence of an OAC medication fill during the 12 months prior to randomization will be excluded from the trial and will not be included in analyses. The baseline characteristics of the delayed intervention patients will be examined at the same time point as the early intervention patients, meaning at the time of randomization. The primary outcome is a comparison of the proportion of patients not on OAC during the 12 months prior to randomization, who were started on OAC over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time in the early versus the delayed intervention arm. A total of approximately 80,000 patients (randomized 1:1) across all participating Data Partners (Aetna, Harvard Pilgrim, HealthCore, Humana, and Optum) will be enrolled from participating Data Partners across the United States. Similar to the early intervention cohort, the patients in the delayed intervention cohort will be assigned to wave 1 or wave 2 ("pseudo" wave assignments) depending on the difficulty in identifying the patient's provider (the intent is to handle them the same way as was done for the early intervention arm). The follow-up for the delayed intervention patients will start on the date the wave 1 or 2 mailings take place for a given Data Partner's early intervention cohort. The follow-up time for the primary outcome will be 12 months from the date at which at least 80% of eligible study participates are enrolled (date on which early intervention materials are mailed).

The providers of patients in the delayed cohort who did not receive OAC medication during the course of the 12-month study period and meet our inclusion criteria will receive the delayed intervention: the provider-only education intervention, a one-time mailing administered 12 months after at least 80% of early intervention mailing have occurred (patients will not receive any educational materials unless no provider can be identified for a mailing). We intend to assess the primary and secondary endpoints again once at least 80% of patients have at least 24 months of follow-up time to assess the durability and longer-term outcomes of the effect of the patient- and provider-level education intervention, as well as the use of OAC following the delayed provider-level education intervention. However, as this second assessment is exploratory, we may not conduct these analyses if the results of the primary outcome are null.

Because the Sentinel Distributed Database will be used for follow-up information, and this information is refreshed approximately quarterly and this is done on separate timetables for the different health plans, it is likely that when at least the required follow-up time is available for at least 80% of people, there will be more than 12 or 24 months of follow-up for over 80% of people. All participants' outcomes will be assessed using all possible person-time; patients will have different duration of follow-up and that will be accounted for in the analyses.

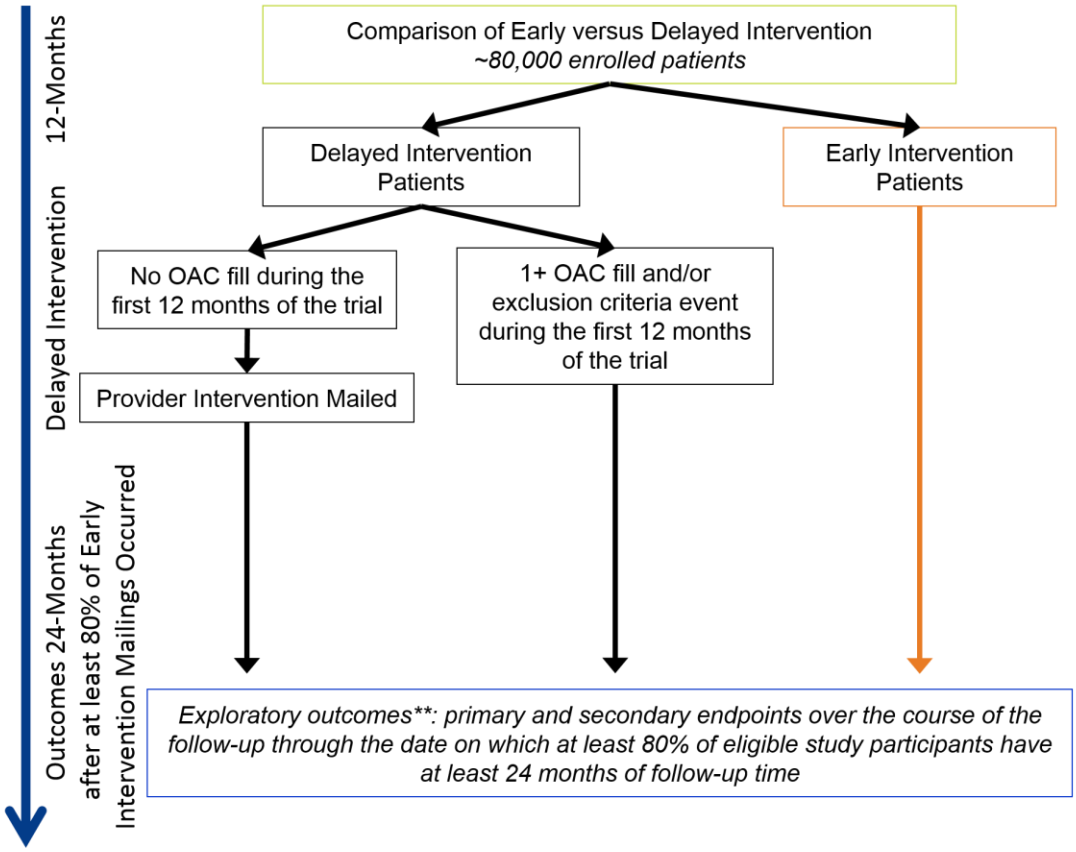
A schematic diagram below shows the design of the early intervention period of the study over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time:



*Baseline characteristics of delayed and early intervention cohorts will be taken from the same time point at randomization from a dataset that is archived at randomization, while exclusion criteria for evidence of OAC medication fill or P2Y12 antagonist use was determined at randomization for the early intervention cohort and approximately 12 months post-randomization for the delayed intervention cohort.
**All possible person-time will be used to assess participants' outcomes (patients will have different duration of follow-up).

For analysis, treatment status is at time of randomization or corresponding early intervention mailing; for the delayed intervention mailing it is prior to mailing.

A schematic diagram below shows the design of the delayed intervention portion of the study:



*All possible person-time will be used to assess participants' outcomes (patients will have different duration of follow-up).

For analysis, treatment status is at time of randomization or corresponding early intervention mailing; for the delayed intervention mailing it is prior to mailing.

VII. STUDY POPULATION

All inclusion and exclusion criteria will be determined by claims data. For entry into the study, the following criteria will be met:

A. INCLUSION CRITERIA

1. Two or more diagnoses of AF (ICD-9 and/or ICD-10 codes) at least one day apart and with at least one diagnosis within the last 12 months prior to the last date in the current approved data used for cohort identification
2. CHA_2DS_2-VASc score of 2 or greater
3. Medical and pharmacy insurance coverage of at least the prior year as identified via administrative claims databases of one of the participating Data Partners as of the date of randomization
4. Age 30 years or greater as of the last date in the current approved data used for cohort identification

B. EXCLUSION CRITERIA

1. Evidence of OAC medication fill (defined as 1 OAC dispensing or 4 INR tests) during the 12 months prior to randomization (determined at randomization for the early intervention cohort and 12 months post-randomization for the delayed intervention cohort)
2. Conditions other than AF that require anticoagulation, including treatment of deep venous thrombosis, pulmonary embolism, or ever having had a mechanical prosthetic heart valve prior to the last date in the current approved data used for cohort identification
3. Pregnancy within 6 months of the last date in the current approved data used for cohort identification
4. Any known history of intracranial hemorrhage prior to the last date in the current approved data used for cohort identification
5. Hospitalization for any bleeding within the last 6 months of the last date in the current approved data used for cohort identification
6. Patients with recent P2Y12 antagonist use (i.e. clopidogrel, prasugrel, ticlopidine, or ticagrelor within 90 days of the last date in the current approved data used for cohort identification

The complete code list for inclusion and exclusion criteria is accessible on the Sentinel website (https://www.sentinelinitiative.org/FDA-catalyst/projects/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients).

VIII. INTERVENTIONS

A. PATIENT-LEVEL INTERVENTIONS (EARLY INTERVENTION ARM)

- Letters to patients that (1) explain to the patient that he or she appears to have AF, characterize the risk of stroke, and emphasize that although there may be a medical reason, the patient does not seem to be on an anticoagulant and (2) encourage the patient to discuss this with his or her provider to ask if he or she might benefit from OAC therapy to prevent stroke.
- Written education materials about AF and anticoagulants, including answers to commonly asked questions
- Website with the patient-focused information contained in the letters to patients

B. PROVIDER-LEVEL INTERVENTIONS (EARLY INTERVENTION AND DELAYED INTERVENTION ARM)

- Letters to providers:
    - Early intervention letters to providers that explain this project, the nature of the problem, and identify a list of the provider's patients who have been contacted, as the provider and patient letters will be sent at approximately the same time; describe evidence and guidelines regarding oral anticoagulation
    - Delayed intervention letters to providers that explain this project, the nature of the problem, and identify a list of the provider's patients who are at risk for stroke and have not been treated with an oral anticoagulant; describe evidence and guidelines regarding oral anticoagulation
- Response mailer that gives the provider the opportunity to share the rationale for his or her patient(s) not being on OAC

- Web portal with access to clinical practice guidelines, decision support tools including from professional societies, podcasts, and case studies targeted at improving the appropriate use of OAC for AF
- Information sheet describing top misperceptions of barriers to OAC use
    1. Misperception of benefit and risk of aspirin: it is neither safe nor effective
    2. Misperception around risk of resuming OAC (months) after bleeding
    3. Misperception around risk of OAC regarding patients who fall
    4. Opportunities with NOACs for patients who have not tolerated warfarin
    5. Concern about lack of an antidote for the NOACs

IX. METHOD OF ASSIGNING PATIENTS TO AN INTERVENTION

An electronic program, developed by the central coordinating center (Harvard Pilgrim), will be used by the participating Data Partners to identify their eligible member-patients who meet the inclusion and exclusion criteria for this trial. The patient billing claims records will not be linked to pharmacy data until after randomization, so the inclusion criterion of no OAC medication fill during the 12 months prior to randomization will not be applied until after randomization. This will be done immediately for the early intervention group, and in the delayed intervention group, not until 12 months after at least 80% of early intervention mailing have occurred. Patients will be randomly assigned in a 1:1 ratio, via the program, to early patient-level and provider-level intervention versus delayed provider-level intervention. A list of eligible member-patients will stay at each Data Partner, and identifiable patient-level data will not be shared with the central coordinating center (Harvard Pilgrim) or the statistical analysis center (Duke Clinical Research Institute). The Data Partners will remove any individuals who cannot be included in research studies, which includes certain Centers for Medicare and Medicaid Services and Administrative Services Only patients. There are several other reasons that could prevent mailing of the intervention, to members and/or their providers (list may not be exhaustive):

- Member is now deceased
- Member disenrolls from health plan
- Member transitions to a plan that does not allow for inclusion in research
- Member has a recent anticoagulant dispensing
- Member has an incorrect/missing/bad address
- Member is added to a do-not-contact list at the health plan

The list of randomized individuals will include the provider on each patient's most recent encounter with an AF diagnosis as of the last date in the current approved data used for cohort identification. When the identified provider is an individual, this provider will receive the provider intervention materials. When the identified provider is a facility, Data Partners will select an alternate provider or conduct a member only mailing based on their health plan policies and the decision of the health plan's leadership. An alternative provider may be a patient's PCP or other recent clinician who provided care. At least one health plan intends to mail letters to the member only when an individual provider is not identified with the most recent AF diagnosis given the large volume of members.

As with the member-patient list, the provider list will be kept by each Data Partner and not shared, as each Data Partner will be mailing the intervention materials to their respective patients and providers.

X. ETHICAL CONSIDERATIONS

This study will be conducted, where appropriate, in accordance with good research practice as outlined by Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The study will be conducted in compliance with the protocol. The protocol and any amendments will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study. Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks. This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (e.g., loss of medical licensure; debarment).

Insurance companies do not ordinarily identify their members with AF who might be appropriate candidates for OACs, and they perform no standard outreach to either clinicians or members regarding treatment of AF. Individuals who are identified for this trial will have had their health care providers bill under the diagnosis code of AF at least twice, with at least one billed diagnosis within the last 12 months. Thus, this trial involves no new identification of AF, since the method of ascertainment is through billing by providers based on their diagnosing AF. The current standard of care is for clinicians and their patients with AF to decide together whether anticoagulation for the diagnosed atrial fibrillation is appropriate. All Data Partners collaborating in the IMPACT-AFib trial are insurers (or affiliates of insurers), not care providers, and the clinicians are not employees of the Data Partners.

There is no current evidence that the communications by insurers (like those being assessed in this trial) will have any effect on use of anticoagulation. All eligible patients included in the trial who do not appear to fill an OAC prescription will receive an intervention, as they will either be in the early intervention or the delayed intervention cohort.

XI. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the co-principal investigators must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, and any other written information to be provided to prospective participants.

The investigators should provide the IRB/IEC with reports, updates, and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

XII. INFORMED CONSENT

Consent will be waived. The reasons for the waiver include:

1. The contacting of the delayed intervention patients for consent would be an intervention by itself and might affect the results of the trial.
2. The intervention is entirely consistent with a quality improvement initiative that the health plans could initiate on their own. Thus, the intervention is very low risk for harm.
3. The intervention only adds on to the existing care of and programs for patients. There are no restrictions placed on the delayed intervention group, as a result of the trial.
4. It would be impractical to collect informed consent on the patients included in this trial.

The waiver of informed consent is consistent with the approach that has been taken in several similar clinical trials, the first using individual patient randomization, the others cluster randomized:

1. UH3 Pragmatic Trial of Population-based Programs to Prevent Suicide Attempt (NCT02326883)
2. The HMO Research Network CERT: A randomized trial of direct-to-patient communication to enhance adherence to beta-blocker therapy following myocardial infarction (NCT00211172)
3. MI FREE: A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Prevention Therapies (NCT00566774)
4. STOPCRC: Strategies and Opportunities to Stop Colon Cancer in Priority Populations (NCT01742065)

XIII. INDEPENDENT ADVISORY COMMITTEE

An independent advisory committee (IAC), consisting of members independent from the study team and with expertise in statistics, anticoagulation for atrial fibrillation, engagement, health plan management, and/or in practical clinical trials, will serve to enhance patient safety and trial integrity. The IAC will meet with study leadership at least twice. The first meeting will occur before intervention materials are mailed, and the second will take place two months after all mailings are sent. In addition, other meetings will occur if deemed necessary by the IAC chair, study leads and/or the FDA. The study team will provide the IAC with the study protocol before any intervention materials are mailed and will brief the IAC on any issues (or lack thereof) that have been raised 2 months after the last mailing has occurred. The IAC will advise on concerns that arise. An IAC charter describes the roles, responsibilities, and operations of the IAC.

XIV. STATISTICAL CONSIDERATIONS

A. SAMPLE SIZE AND POWER CALCULATIONS

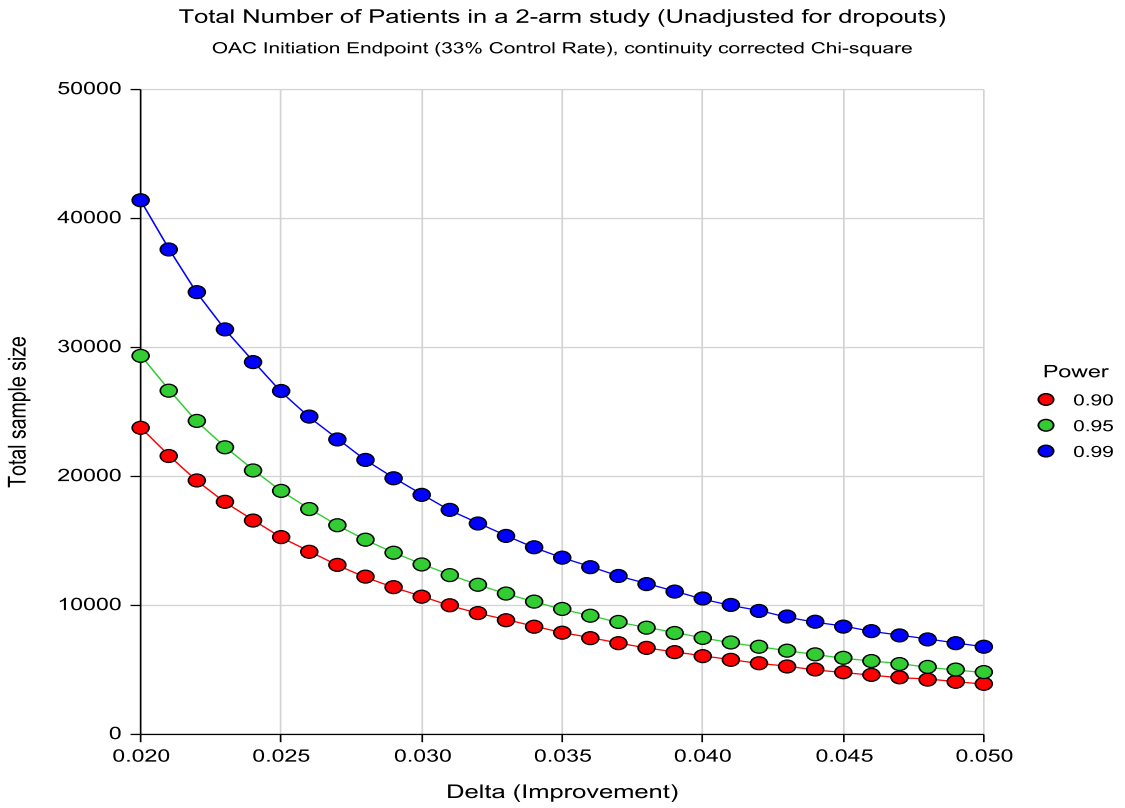
Our target sample size is 80,000 patients. All enrolled patients and/or their providers will be targeted by mailing (early or delayed) provided they are eligible at time of mailing and able to be contacted.

1. Primary Endpoint

The following assumptions were used to determine the sample size and power for the primary endpoint assessing the proportion of AF patients with evidence of at least one OAC prescription fill through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time:

- 33% OAC initiation rate in the delayed intervention arm over the first year of the study
    - In a Sentinel feasibility assessment of identified health plan members meeting similar inclusion and exclusion criteria as this trial, 33% had evidence of OAC initiation in a 1 year period of follow-up.
- 38% OAC initiation rate in the early intervention arm (a 5% absolute improvement in OAC initiation over the 33% OA initiation expected in thedelayed intervention arm over 1-year follow-up)
- 1-year attrition rate: 30% dropout or lost-to-follow-up
- Two-sided type I error of 0.05
- Roughly 10,000 patients (Table below) will yield more than 99% power to detect a 5% absolute difference

Power	Total sample size (2-arm)	Early Intervention	Delayed Intervention
90%	5610	2805	2805
95%	6910	3455	3455
99%	9718	4859	4859



2. Important Secondary Analysis of Stroke or TIA

A study with approximately 80,000 patients is well powered for the outcome of stroke or TIA over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time, under certain assumptions listed below:

- 1-year stroke or TIA rate: 18% among patients not treated with OAC
- 1-year stroke or TIA rate: 7% among patients treated with at least 1 OAC fill
- Duration of follow-up: 1 year
- 33% of delayed intervention patients will have at least 1 fill of OAC, meaning the 1 year stroke or TIA rate in the delayed intervention group would be 14.4%
- If 38% of early intervention patients have at least 1 fill of OAC (meaning the 1 year stroke or TIA rate in the early intervention group would be 13.82%, i.e., an absolute reduction of 0.55%), the study will have 46% power to detect this 0.55% reduction. However, if 40.5% of early intervention patients have at least 1 fill of OAC (meaning the 1 year stroke or TIA rate in the early intervention group would be 13.54%, i.e., an absolute reduction of 0.83%), the study will have 80% power to detect this 0.83% reduction.

- 1-year attrition rate: 30% dropout or lost-to-follow-up
- Two-sided type I error of 0.05
- The sample size has 80% power to detect a 0.5% absolute reduction in stroke, assuming a cumulative 1-year incidence of stroke of 4.2% in control (delayed intervention arm) patients and 3.7% in intervention (early intervention arm) patients. The assumption is that patients not on oral anticoagulation have an annual stroke rate of 5%, and stroke will be reduced by 50% (HR=0.5) in the treated (anticoagulated) population. The 80% power requires that 52% of early intervention arm patients are treated at 1-year as compared to 33% in the control arm.

B. POPULATIONS FOR ANALYSIS

All analyses will be based on a modified intention-to-treat principle (i.e., all identified early intervention patients who meet eligibility and are mailed the intervention will be included; using "pseudo" wave assignments, all identified delayed intervention patients who meet eligibility at the time of corresponding early mailings will be included in the analysis). The primary endpoint will be calculated based on the proportion of patients with evidence of at least one OAC prescription fill over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time. An as-randomized analysis will be performed for the primary endpoint as a sensitivity analysis. All possible person-time will be used to assess participants' outcomes; patients will have different duration of follow-up and that will be accounted for in the analyses. Patients will be censored from the analysis at the time of death, disenrollment from the health plan, loss of medical or pharmacy coverage, or change in eligibility for inclusion in research based on health plan membership. The statistical analysis plan (SAP) provided more information and outlines in detail how granular aggregate data will be received from each Data Partner in lieu of patient-level data.

XV. OUTCOME DEFINITIONS

All outcome definitions will be based on available claims data.

1. Evidence of OAC start: the proportion of AF patients who have at least 4 INR values measured or who fill at least one OAC prescription for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin over the course of the follow-up through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time
2. Time to OAC start: the time to first OAC initiation, as defined by the first fill date for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin. If there was no prescription fill for these medications, but the patient had 4 or more INR values measured over the study period, the date of the first INR measurement will be used for initiation of OAC.
3. OAC prescription coverage: the proportion of days that AF patients have OAC prescription fills over the duration of the study. The assumption is that a 30-day or 90-day supply will last for the planned period, even in the case of warfarin, when the length of time that a prescription lasts may be less well defined. Patients will only be included in this secondary analysis, if they had a prescription fill for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin.
4. OAC rates at follow-up: proportion of patients with an active oral anticoagulant dispensing at the end of the one-year follow-up. This will include patients with apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin medication fills that encompass the end of the study period. If there was no prescription fill for these medications, this will also include patients with 4 or

more INR values measured over the study period, who had an INR value measured within 60 days of the end of the approximately one-year follow-up.

5. Rate of stroke or TIA: the incident rate of stroke or TIA related hospitalizations; stroke, excluding transient ischemic attacks (TIAs), will also be assessed
6. Rate of bleeding related hospitalization: the incident rate of hospitalizations for any bleeding
7. Health care utilization: the total counts of health care utilization (number of outpatient visits, emergency department visits, hospital admissions, etc.) for AF patients, including AF and non-AF related care
8. In-patient all-cause mortality: patients with in-hospital death
9. All-cause mortality: in a subset of patients with mortality status

XVI. STATISTICAL ANALYSES

A. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics of eligible early and delayed intervention cohorts will be based on the claims data at the time of randomization. Frequency distribution and summary statistics for demographic and baseline variables will be presented by early intervention group, delayed intervention group, and for the overall study population. Key demographic and baseline variables to be summarized include: geographic region, age, sex, risk factors for stroke, risk factors for bleeding, and select comorbid conditions. Continuous variables will be summarized as mean (±SD) and median (25^{th}, 75^{th} percentiles); the comparison between the two groups will be conducted using Wilcoxon rank-sum test. For the continuous variables in combined study population, the mean will be summarized. Categorical variables will be presented as counts (percentages) and will be compared between groups by using Pearson's chi-square or Fisher's exact test, as appropriate.

B. RESPONSES FROM PROVIDERS

As part of the provider intervention materials, providers will have the opportunity to respond to the patient's health plan and give an explanation for why their patients were not being treated with OAC via a postage paid postcard. The data collected from these responses will be aggregated by rationale for non-treatment and reported as counts (percentages) by the coordinating center. Data will not be linked to specific patients or providers.

C. EFFECTIVENESS ANALYSES

The proportion of patients with evidence of at least one OAC medication fill over the course of the follow-up, the primary endpoint, will be summarized and compared between the early intervention and delayed intervention arms. The definition for OAC medication fill will be an OAC medication billing in the pharmacy claims or at least 4 INR tests billed in the laboratory claims (indicative of OAC use that was not billed through the pharmacy claims data). To evaluate whether the comprehensive evaluation and customized multilevel (patient-level and provider-level) educational interventions increases the rate of use of oral anticoagulants at one year post intervention, we will evaluate the odds ratio (i.e. the odds of an average patient in the early intervention group taking OAC at 1 year compared to the odds of an average patient in the delayed intervention group taking OAC at 1 year) using logistic regression to account for the effect of Data Ppartner and adjust for other potential baseline risk factors.[38] We will

present the odds ratio, 95% confidence interval, and p-value to show whether there is a difference in rate of use of OAC at one year post intervention between the early intervention and delayed intervention groups. Similarly, we will analyze the proportion of days covered with an OAC prescription fill over the course of the follow-up. Patients will only be included in this analysis, if they had a prescription fill for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin.

Event rates for the following secondary outcomes will be summarized by treatment group, as defined by claims data:

- Stroke or TIA
- Ischemic stroke or unknown stroke
- Hemorrhagic stroke
- Hospitalization for any bleeding
- Composite of ischemic or hemorrhagic stroke
- Composite of ischemic stroke, hemorrhagic stroke, and hospitalization for any bleeding

For time-to-event outcomes, Kaplan-Meier cumulative incidence estimates and log-rank test will be utilized.[39] In addition, Cox proportional hazards model with early intervention vs. delayed intervention as main effect will be used to assess the clinical outcomes, after adjusting for baseline risk factors.[40] A robust sandwich covariance estimate or a frailty model will be used to account for effect of Data Partner. The hazard ratio, 95% confidence interval and p-value will be presented to summarize the difference in the risk of clinical outcome between early intervention and delayed intervention group. In-hospital death or medically attended death will be collected through claims data. Analyses will be performed using SAS software version 9.4 or higher (SAS Institute, Inc., Cary, NC).

More details on the statistical methods and analyses will be provided in the SAP. The SAP will be finalized prior to study database lock, 12 months after at least 80% of the early intervention mailings. Of note, all patient-level data will be maintained by the Data Partners, so analyses are expected to be conducted via a distributed SAS programming code developed by the coordinating center and results are expected to be returned, by Data Partner, in aggregate to the coordinating center. Analyses will be examined by Data Partner and across Data Partners.

XVII. DISSEMINATION PLAN OVERVIEW

A manuscript describing the study design will be published. A manuscript will also be written describing the results on the primary and secondary endpoints based on the date on which at least 80% of eligible study participants have at least 12 months of follow-up time, and separately once at least 80% of members have at least 24 months of follow-up time (if 24-month aanalysis is conducted). Finally, Data Partner-specific results will be shared with each Data Partner at both time points.

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