FDA-CATALYST PROTOCOL

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

Final Draft Posted for Public Comment

Deadline for responses: March 15, 2017

An individually randomized trial of a practice and patient level educational intervention to increase anticoagulant use for individuals with atrial fibrillation and increased risk of stroke (i.e. CHA_2DS_2-VASc score ≥2). This project is a proof of concept effort, the first trial conducted using Sentinel Infrastructure, and will inform future interventional studies that are designed to utilize existing healthcare data as part of their design.

The Sentinel Operations Center has posted this final draft surveillance plan for public comment. **Comments must be received by the Sentinel Operations Center no later than March 15, 2017.**

Submit comments by clicking on the Submit Comments link on the details page associated with this project (https://www.sentinelinitiative.org/content/implementation-randomized-controlled-trial-improve-treatment-oral-anticoagulants-patients) and filling out the Comment Form or by sending an email directly to info@sentinelsystem.org. Please include the following information along with your comments:

- Surveillance plan title
- Section(s) and page number(s) of surveillance plan, if appropriate
- Optional (but preferred):
  - Your name
  - Your organization and title
  - Your email address

Workgroups will consider all comments, but under most circumstances will not reply directly to commenters.

Any revisions done to this surveillance plan after it is posted for public comment will be noted in the change log document posted along with the amended surveillance plan. Posting of both documents will be listed on the Sentinel homepage, on the relevant assessments project details page, and in the Sentinel RSS feed.

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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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March 1, 2017

FDA-Catalyst Protocol

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

Table of Contents

I. PROTOCOL SYNOPSIS

Protocol Title:	IMplementation of a randomized controlled trial to imProve treatment with oral AntiCoagulanTs in patients with Atrial Fibrillation (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 12 months. Duration of follow-up for the primary outcome (OAC treatment) will be 12 months from the date that the materials are mailed to the study participants; secondary outcomes will also be evaluated at this time.
Study Objectives:	**Primary:** evaluate the effect of the patient and provider education interventions 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 12-months of follow-up.
	Secondary: evaluate the impact of the patient and provider education interventions on:
	1. Rates of stroke/transient ischemic attack (TIA) hospitalization at 12 months
	2. Rates of hospitalization for stroke at 12 months
	3. Time to first OAC prescription fill within 12 months
	4. Proportion of days covered by OAC prescription fills over 12 months
	5. Proportion of patients on oral anticoagulation at the end of 12 months follow-up
	6. Rates of hospitalization for bleeding at 12 months
	7. All-cause in-hospital mortality rates at 12 months
	8. All-cause mortality rates among patients with accurate out-of-hospital mortality data (such as Medicare Advantage patients) at 12 months
	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.) at 12 months
	Exploratory:
	10. Evaluate the effect of the early and delayed education interventions on the primary and secondary endpoints at 24 months after enrollment
	11. Demonstrate that the Clinical Trials Transformation Initiative (CTTI) and the FDA supported Sentinel data partnership can

	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 intervention arm: early patient and provider educational interventions for those patients identified at the time of randomization and (b) the control arm: usual care followed by delayed provider education intervention (these patients' eligibility for the study will be assessed 12 months after randomization). 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 12-month trial. A total of approximately 40,000 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 enrollment. 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 24 months after enrollment to assess the durability and longer-term outcomes of the effect of the education intervention.
Accrual Goal (Total number of participants):	Approximately 40,000 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. Patients with 2 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 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 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 randomization) [determined at randomization for the early intervention cohort and 12 months post-randomization for the delayed intervention cohort]
Criteria for Evaluation (Effectiveness, safety, stopping rules, etc.):	The primary outcome is the proportion of patients with evidence of at least one OAC prescription fill over 12-months after the early education intervention.
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 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 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, pod casts, and case studies targeted at improving the appropriate use of OAC for AF

	- Information sheet with 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 over the course of 12-months of follow-up 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 in the early versus delayed intervention arm at 1-year) - Duration of follow-up: 1 year 1-year attrition rate: up to 30% dropout or lost-to-follow-up - Two-sided type I error of 0.05 - Total 6,910 patients needed for 95% power Important secondary outcome: stroke or transient ischemic attack (TIA) over 12-months of follow-up. A study with approximately 40,000 patients will provide reasonable power 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, resulting in a 1 year stroke or TIA rate in the delayed intervention group of 14.4% 43% of early intervention patients will have at least 1 fill of OAC, resulting in a 1 year stroke or TIA rate in the early intervention group of 13.3% 1-year attrition rate: 30% dropout or lost-to-follow-up - Two-sided type I error of 0.05 A total of 40,000 patients will result in 75% power to detect a reduction in stroke or TIA of 1.1%

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 prognosis 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 education interventions 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 12-months of follow-up.

B. SECONDARY OBJECTIVE

The secondary objectives are to evaluate the impact of the patient and provider education interventions on:

1. Rates of stroke/transient ischemic attack (TIA) hospitalization at 12 months
2. Rates of hospitalization for stroke at 12 months
3. Time to first OAC prescription fill within 12 months
4. Proportion of days covered by OAC prescription fills over 12 months
5. Proportion of patients on oral anticoagulation at the end of 12 months follow-up

6. Rates of hospitalization for bleeding at 12 months
7. All-cause in-hospital mortality rates at 12 months
8. All-cause mortality rates among patients with accurate out-of-hospital mortality data (such as Medicare Advantage patients) at 12 months
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.) at 12 months

VI.   EXPLORATORY OBJECTIVES

The exploratory objectives are to:

1. Evaluate the effect of the early and delayed education interventions at 24 months on the primary and secondary endpoints that were evaluated 12 months after enrollment.
2. Demonstrate that the Clinical Trials Transformation Initiative (CTTI) and the FDA supported Sentinel data partnership can successfully conduct a pragmatic trial to answer important questions to improve public health.
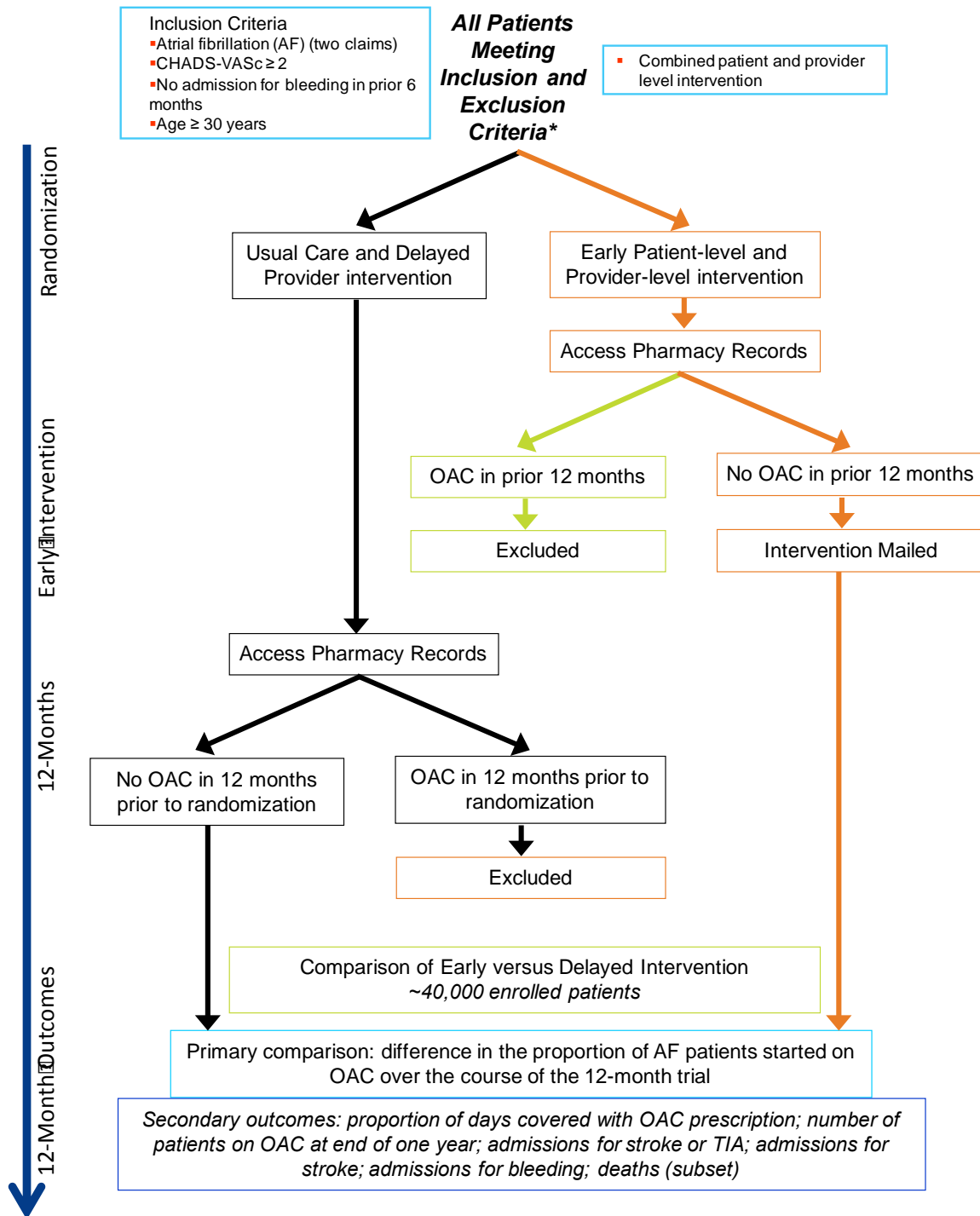
VII.   STUDY DESIGN AND DURATION

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. The definition for OAC medication fill will be an OAC medication dispensing or at least 4 INR tests in the claims data (INR tests are assumed indicative of OAC use that was not billed through the claims). The claims records of the patients randomized to the early intervention cohort will then be linked to "fresh" (i.e. about 1 month 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 early intervention with evidence of an OAC medication fill during the 12 months prior to randomization will be excluded from the trial.

The delayed intervention cohort will receive usual care over the initial 12-month study period. After the first 12 months of the study, "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 (not at the time of patient eligibility 12 months after enrollment). 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 a 12-month study period in the early versus the delayed intervention arm. A total of approximately 40,000 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. The follow-up time for the primary outcome will be 12 months from enrollment (date on which early intervention materials are mailed).

The intervention for the patients identified in the delayed cohort who did not receive OAC medication over the course of the 12-month study period will be the provider-level education only; the patients will not receive any educational materials. We intend to assess the primary and secondary endpoints again at 2 years after enrollment 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 at the 12-month time point are consistently null.

A schematic diagram below shows the design of the first 12 months of the study:

Inclusion Criteria
- Atrial fibrillation (AF) (two claims)
- CHADS-VASc ≥ 2
- No admission for bleeding in prior 6 months
- Age ≥ 30 years

All Patients Meeting Inclusion and Exclusion Criteria*

- Combined patient and provider level intervention

Randomization

Usual Care and Delayed Provider intervention

Early Patient-level and Provider-level intervention

Access Pharmacy Records

Early Intervention

OAC in prior 12 months → Excluded

No OAC in prior 12 months → Intervention Mailed

12-Months

Access Pharmacy Records

No OAC in 12 months prior to randomization

OAC in 12 months prior to randomization → Excluded

12-Month Outcomes

Comparison of Early versus Delayed Intervention
~40,000 enrolled patients

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 TIA; admissions for stroke; admissions for bleeding; deaths (subset)

*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 12 months post-randomization for the delayed intervention cohort.

A schematic diagram below shows the design of the second 12 months of the study:
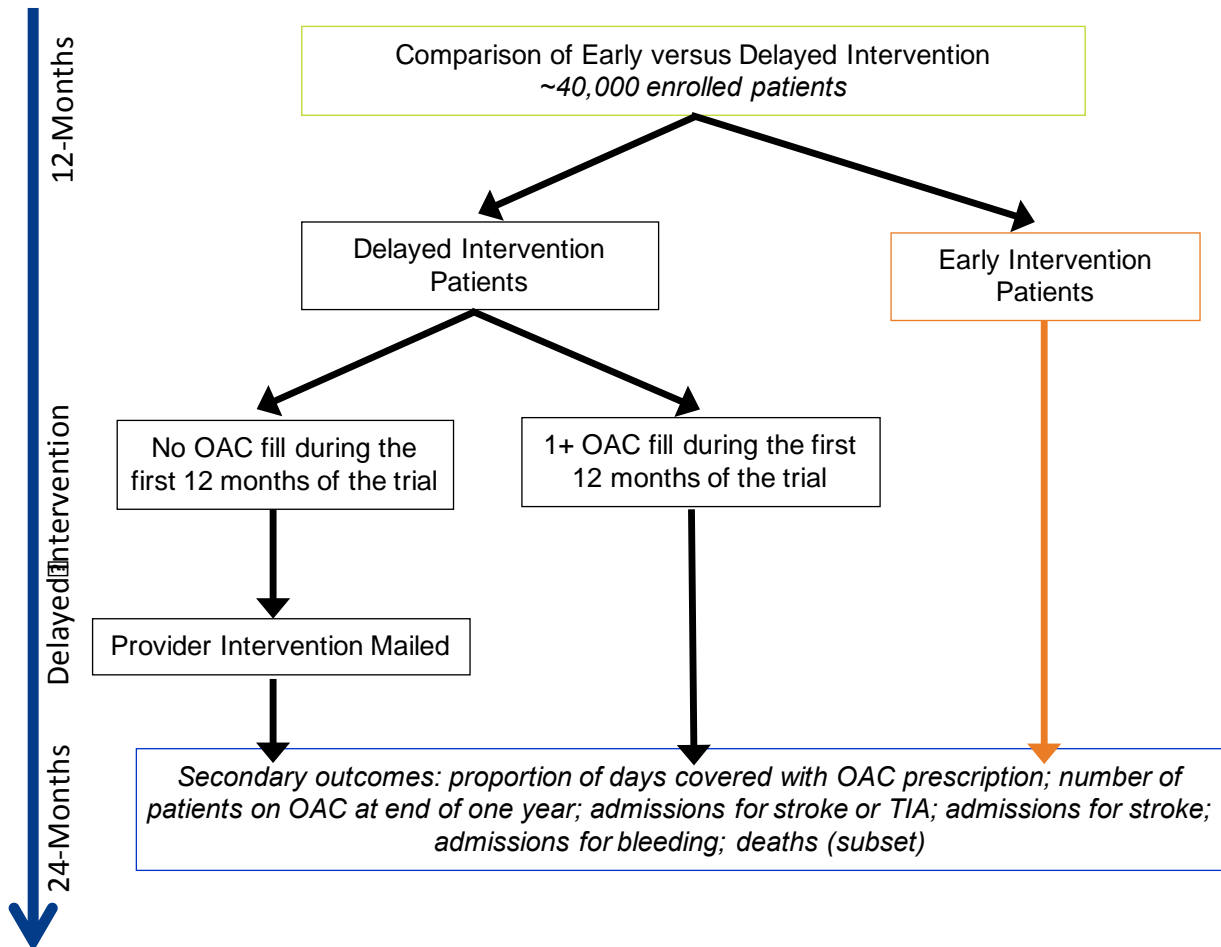
VIII. STUDY POPULATION

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. Patients with 2 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 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 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 randomization) [determined at randomization for the early intervention cohort and 12 months post-randomization for the delayed intervention cohort]

IX. INTERVENTIONS

A. PATIENT-LEVEL INTERVENTIONS (EARLY INTERVENTIONS 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

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

- Letters to providers:
    - Early intervention letters to providers 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 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, pod casts, and case studies targeted at improving the appropriate use of OAC for AF

- Information around 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

X.   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 criteria 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 not until 12 months later in the delayed intervention group. 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. 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; this is the provider who will receive the intervention letter. 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.

XI.   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 will receive an intervention, as they will either be in the early intervention or the delayed intervention cohort.

XII.   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.

XIII.   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)

XIV.   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 (Appendix 1).
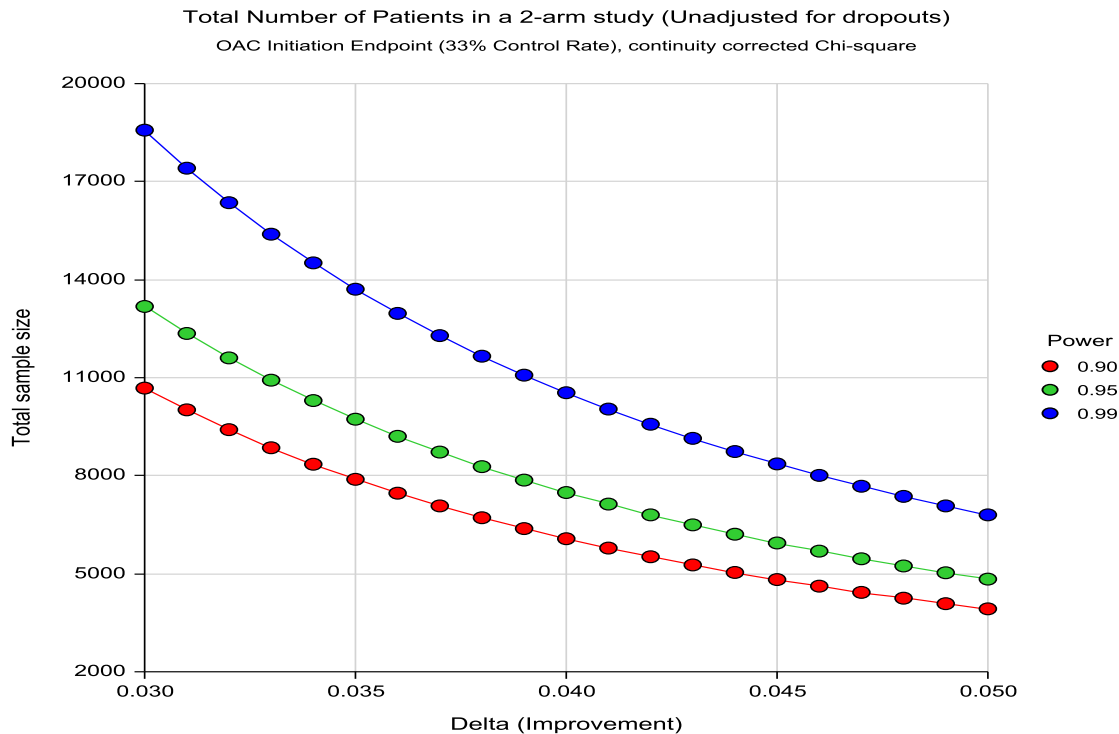
XV.   STATISTICAL CONSIDERATIONS

A. SAMPLE SIZE AND POWER CALCULATIONS

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 over the course of the 12-month trial:

- 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 in the early versus delayed intervention arm at 1-year)
- Duration of follow-up: 1 year
- 1-year attrition rate: up to 30% dropout or lost-to-follow-up
- Two-sided type I error of 0.05
- Total 6,910 patients needed for 95% power

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

Total Number of Patients in a 2-arm study (Unadjusted for dropouts)
OAC Initiation Endpoint (33% Control Rate), continuity corrected Chi-square

2. Important Secondary Analysis of Stroke or TIA

A study with approximately 40,000 patients could provide reasonable power for stroke or TIA outcome 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, resulting in a 1 year stroke or TIA rate in the delayed intervention group of 14.4%
- 43% of early intervention patients will have at least 1 fill of OAC, resulting in a 1 year stroke or TIA rate in the early intervention group of 13.3%
- 1-year attrition rate: 30% dropout or lost-to-follow-up
- Two-sided type I error of 0.05
- A total of 40,000 patients will result in 75% power to detect a reduction in stroke or TIA of 1.1%

B. POPULATIONS FOR ANALYSIS

All analyses will be based on intention-to-treat principal (i.e., all randomized patients who meet eligibility criteria will be included). 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 12-months of follow-up. Patients will be censored from the analysis at the time of disenrollment from the health plan that was in place at the time of trial enrollment, at the time of pregnancy, or at the time of death. The statistical analysis plan will outline in detail how granular aggregate data will be received from each data partner in lieu of patient-level data.

XVI. 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 12-months of follow-up

2. Time 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 one-year follow-up.

5. Rate of stroke or TIA: the rate of stroke or TIA related hospitalizations; stroke, excluding transient ischemic attacks (TIAs), will also be assessed

6. Rate of bleeding related hospitalization: the rate of hospitalizations for 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

XVII. STATISTICAL ANALYSES

A. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics of delayed and early 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, select comorbid conditions, and baseline medications. Continuous variables will be summarized as mean (±SD) and median (25th, 75th percentiles), the comparison between the two groups will be conducted using Wilcoxon rank-sum test. 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 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.

C. EFFECTIVENESS ANALYSES

The proportion of patients with evidence of at least one OAC medication fill over the course of the 12-months of 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 logistical regression to account for the effect of data partner 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 12-months of 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 bleeding
- Composite of ischemic or hemorrhagic stroke
- Composite of ischemic stroke, hemorrhagic stroke, and hospitalization for 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. For the clinical outcomes such as, stroke or TIA, hospitalization for bleeding etc., death is the competing risk. Thus, Fine and Gray model will be used to assess each of these outcomes with death as competing risk.[41] In-hospital death or medically attended death will be collected through claims data.
Analyses will be performed using SAS software version 9.3 or higher (SAS Institute, Inc., Cary, NC).

More details on the statistical methods and analyses will be provided in the statistical analysis plan (SAP). The SAP will be finalized prior to study database lock, 12 months after the early intervention mailing. 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.

XVIII.   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 12 months of follow-up, and separately at 24 months of follow-up (if conducted). Finally, data partner-specific results will be shared with each data partner at the 12 and 24 month time points.

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