FDA-CATALYST STATISTICAL ANALYSIS PLAN

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

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FDA-Catalyst Statistical Analysis Plan

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

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I. OVERVIEW

This is the statistical analysis plan (SAP) for **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 **F**ibrillation (IMPACT-AFib) study. The purpose of this document is to provide an overview of the study design and study objectives, outline the types of analyses and data presentations relevant to the study objectives, and to provide a detailed description of the methods in which the statistical analyses will be conducted to meet protocol objectives. This plan is a supplement to the materials provided in the IMPACT-AFib protocol. This SAP does not contain all the protocol details and is intended to be read in conjunction with the full protocol. Only analytic decisions are documented here.

A. PRIMARY ENDPOINT

IMPACT-AFib is a prospective randomized controlled clinical trial that will evaluate whether a patient and provider education intervention increases the proportion of patients with atrial fibrillation (AF) who fill at least one oral anticoagulant (OAC) over the course of follow-up. Follow up is through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time. As described in the protocol, there is an "early intervention" arm (who receive patient and provider mailings) and a "delayed intervention" arm (who receive provider mailings only, ~12 months after the early intervention mailings occur).

B. SECONDARY ENDPOINTS

We will evaluate the impact of the patient and provider education intervention on the endpoints listed below at the end of follow-up (i.e., the date on which at least 80% of eligible study participants have at least 12 months of follow-up time):

- The incidence rate of stroke or transient ischemic attack (TIA) hospitalizations
- The incidence rate of stroke hospitalizations
- The time to first OAC prescription fill
- The proportion of days covered by OAC prescription fills
- Proportion of patients actively on OAC at 12 months of follow-up
- The incidence rate of hospitalization for any bleeding
- All-cause in-hospital mortality rates
- All-cause mortality rates among patients with accurate out-of-hospital mortality data, if data are available (such as Medicare Advantage patients)
- Health care utilization, reported as counts of number of health care utilization events (outpatient visits, days hospitalized, number of emergency department visits, etc.)

Depending on the review of preliminary data, the primary endpoint and some secondary endpoints may be examined separately by warfarin and novel OAC. This will be descriptive only and will not include formal statistical testing.

C. EXPLORATORY ENDPOINTS

We will evaluate the effect of the early and delayed education interventions on the primary and secondary endpoints once at least 80% of eligible study participants have at least 24 months of follow-up time (the early intervention includes mailing to the patient and provider while the delayed intervention, at ~12 months follow-up, only includes a provider mailing). Note that we may not conduct

these analyses if the results of the primary outcome are null in the earlier assessment. Therefore, this statistical analysis plan does not include the details of analyses for a 24 months assessment.

D. DATA SOURCE

The data used for the study are claims data from the five participating sites, transformed into the Sentinel Common Data Model. At the time of analysis, the data available in the Sentinel Distributed Database (i.e., those approved and in use for Sentinel routine surveillance activities) will be used to assess the primary and secondary endpoints.

As background, the identification and creation of the study cohort was based on the claims data in the Sentinel Distributed Database plus linked "fresh" data (i.e., about 1 month old) for pharmacy claims and enrollment information. The target population for the study was those members enrolled in the sites who did not have evidence of an OAC medication dispensing in the 12 months prior to randomization; the fresh and production data ensured we identified those eligible for the trial. The data used for routine Sentinel activities are several months old – hence the need for certain "fresh" data – and the date of the last available claims varies by site.

E. PATIENT INCLUSION CRITERIA

All inclusion and exclusion criteria were determined by claims data. For entry into the study, the following criteria MUST be met at the date of randomization:

1. Two or more diagnoses of AF (ICD-10-CM codes I48.0, 148.1, 148.2, 148.4, or I48.91; ICD-9-CM codes 427.3 or 427.31) 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 at the time of the randomization (i.e., as of the last date in the current approved data used for cohort identification). The ICD-9/10-CM coding for CHA_2DS_2-VASc is shown in Table 1. 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).
3. Medical and pharmacy insurance coverage as identified via administrative claims data 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

Table 1. Coding for CHA2DS2-VASc components

	Component	Codes
C	Congestive heart failure (or left ventricular systolic dysfunction)	**ICD-10-CM:** I09.81, I11.0, I13.0, I13.2, I42.0, I42.5-I42.9, I43, I50.1, I50.20-23, I50.30–I50.33, I50.40-43; I50.9; **ICD-9-CM:** 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.2, 425.4, 425.5, 425.7, 425.9, 428.0-428.4, 428.20-428.23, 428.30-428.33, 428.40-428.43, 428.9
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	**ICD-10-CM:** I10–I16 and subcodes, I67.4, N26.6; **ICD-9-CM:** 401-405, 401.0, 401.1, 401.9, 402.0, 402.1, 402.9, 403.0, 403.1, 403.9, 404.0, 404.1, 404.9, 405.0, 405.1, 405.9, 437.2, 402.**, 403.**, 404.**, 405.**; **CPT:** 4050F
A_2	Age ≥75 years	
D	Diabetes Mellitus	**ICD-10-CM:** E08.31- E08.36, E08.3**, E08.40, E08.42, E08.51, E08.52, E08.59, E08.65, E09.31-E09.36, E09.3**, E09.40, E09.42, E09.51, E09.52, E09.59, E10.1–E13.9 and subcodes; **ICD-9-CM:** 250.*, 357.2, 362.0, 249.7*, 250.**, 362.0*, 366.41
S_2	Prior stroke or TIA or thromboembolism	**ICD-10-CM:** I60.**, I60.2, I60.4, I60.6-I60.9, I61.*, I62.9, I63.0*, I63.0**, I63.1*, I63.1**, I63.2*, I63.2**, I63.3*, I63.3**, I63.4*, I63.4**, I63.5*, I63.5**, I63.6, 163.8, I63.9, I69.00, I69.0**, I69.10, I69.1**, I69.30, I69.3**, I69.8** except I69.898, I69.9** except I69.998, S06.34, S06.34*A, and S063.34*D, S06.35, S06.35*A, and S063.35*D, S06.36, S06.36*A, and S063.36*D, S06.6, S06.6X*A, S06.6X*D, Z86.73, H34.00, H34.219, H34.239, H34.9, I67.82, I74.**, I74.2-I74.9, K76.3, N28.0, T81.718A, G45.8, G45.9; **ICD-9-CDM:** 438.0-438.8, 852.0, 853.0, 433.*1, 434.*1, 438.1*, 438.2*, 438.3*, 438.4*, 438.5*, 438.81-428.85, 852.0*, 853.0*, V12.54, 444, 444.*, 444.**, 453.9, 573.4, 362.30-362.34, 434.00, 435, 435.8, 435.9; **CPT:** 34101, 34111, 34201, 34203
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	**ICD-10-CM**[1]**:** E08.51, E08.52, E09.51, E09.52, E10.51, E10.52, E11.51, E11.52, E13.51, E13.52, I21.0*, I21.1*, I21.2*, I21.3, I21.4, I22.*, I25.7, I25.70-I25.73, I25.70*, I25.71*, I25.72*, I25.73*, I25.79, I25.79*, I25.810, I73.8, I73.9, I77.1, T82.2, T82.21 and subcodes, Z95.820, Z95.82
A	Age 65–74 years	
Sc	Sex category (i.e. female sex)	

[1] Only ICD-10-CM codes are presented for the vascular disease component given size of the list; complete code list, which includes ICD-9-CM, ICD-10-PCS, ICD-9-PCS, CPT, and HCPCS codes, is available on the Sentinel website.

Patients are excluded if they meet any of the following criteria:

1. Evidence of OAC medication fill during the 12 months prior to randomization (the delayed intervention group's treatment status will be assessed at the end of the 12 month follow-up period)
2. Conditions other than AF that require anticoagulation such as ever having mechanical prosthetic valve, deep venous thrombosis, or pulmonary embolism prior to the last date in the current approved data used for cohort identification ("ever" is operationalized as -6000 days from the index AF code)
3. Pregnancy identified 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, or ticagrelor within 90 days of prior to randomization)

F. STUDY DESIGN AND DURATION

As described in detail in the protocol, the study is a prospective, randomized, and open-label educational intervention trial. Patients with AF and a CHA_2DS_2-VASc score of 2 or greater were 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 was an OAC medication dispensing or at least 4 INR tests in the claims data.[2] The claims records of the patients randomized to the early intervention cohort were then 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 were 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 were excluded from the trial). In addition to usual care, these patients and their providers received a one-time mailing at trial start. There were two waves of mailing for the early intervention cohort at most sites due to the practical challenges of claims data: the patients were assigned to wave 1 if they had a provider easily identified in the data (i.e., the provider associated with the most recent AF diagnosis is indeed an individual provider), and they were assigned to wave 2 if it was difficult to identify a provider (e.g., the first identified provider is actually a facility). Follow-up time started on the date of the respective wave 1 and wave 2 mailings for the early intervention patients.

The delayed intervention cohort will have received usual care over the initial study period. After the date on which at least 80% of all eligible study participants have at least 12 months of follow-up time, the treatment status of the delayed intervention group will be assessed via the Sentinel data available at that time, in addition to "fresh" pharmacy claims data. The providers of patients in the delayed cohort who did not receive OAC medication during the course of follow-up and still meet all inclusion criteria

[2]Not all OAC dispensings are captured in pharmacy claims, particularly, for warfarin due to some patients paying for medication out of pocket. INR tests are assumed indicative of OAC fills that were not billed through the claims. Four 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.

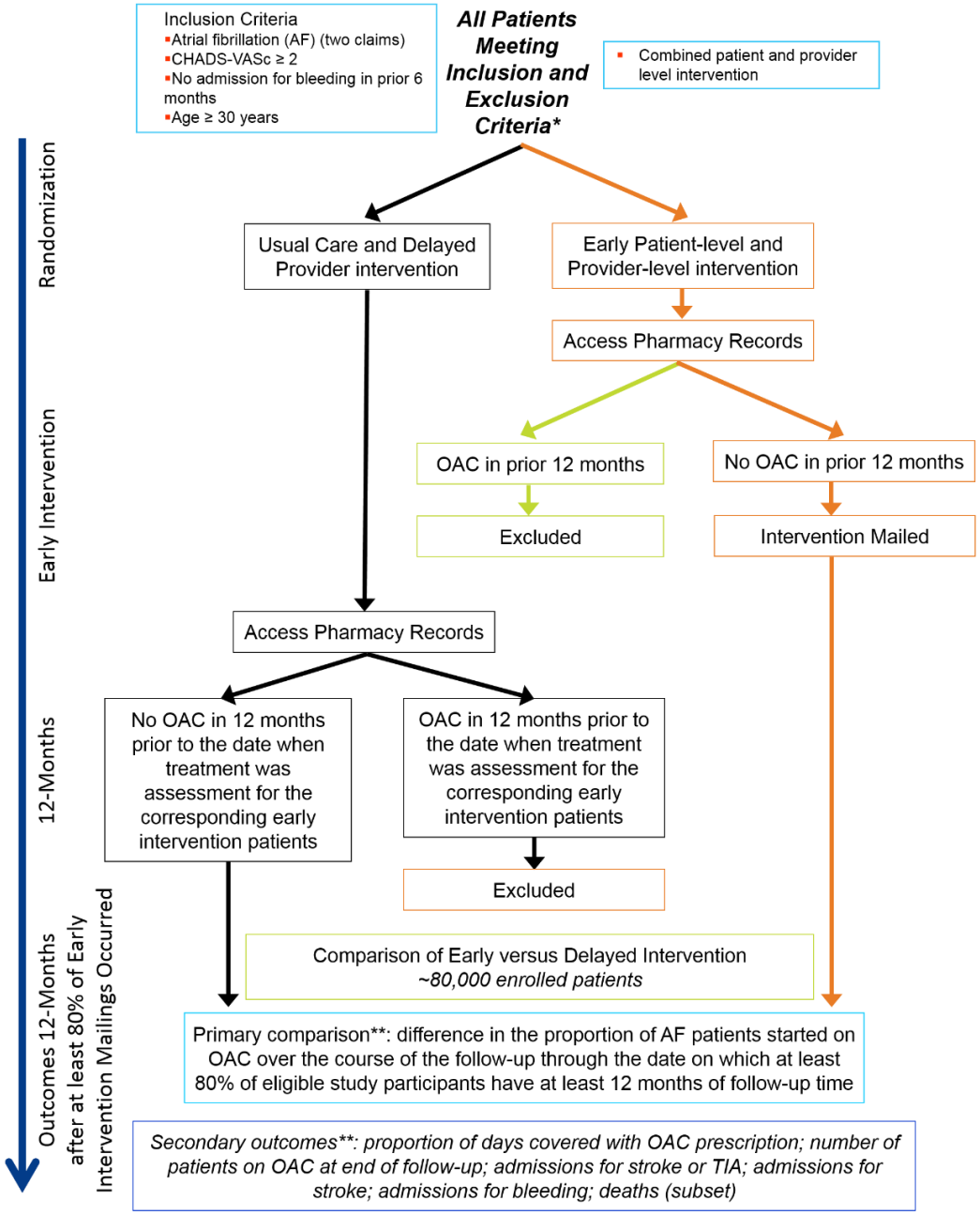
will receive the provider-only education intervention (patients will not receive the educational materials unless no provider can be identified for a mailing).

Details on the analyses are provided in Section II. Here we describe the data sources for the **modified intention-to-treat** (primary) and **as-randomized** (sensitivity) analyses. Similar to 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, for the modified intention-to-treat analysis). The follow-up for the delayed intervention patients will start on the date the wave 1 or 2 mailings took place for a given Data Partner's early intervention cohort. For both early and delayed intervention cohorts, any patients who die, are disenrolled, or get started on OAC between the randomization and early intervention mailing will be excluded from the analysis at each Data Partner. For both the early and delayed arms, exclusion criteria that are based on member medical history were assessed at the time of randomization. For the early intervention cohort, enrollment and treatment status were assessed at randomization for all and re-assessed at the wave 2 time point at some of the sites (this was at site discretion, in response to the lag between wave 1 and 2 mailings). The enrollment and treatment status of the delayed intervention cohort will be examined for eligibility at the same time point as the early intervention patients, meaning at the time of mailing per Data Partner, via the locked data (using the wave 1 and 2 dates).

Because the Sentinel Distributed Database will be used for analyses, and this information is refreshed approximately quarterly on different timetables for the different health plans, it is likely that when the required follow-up time is available for at least 80% of patients, there will be more than 12 months of follow-up for over 80% of patients. 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. Note that if the 24 month analysis is conducted, we will do that when at least 80% of members have at least 24 months of follow-up time.

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 (see the protocol for the full study design and details):

Figure 1. Design of the early intervention period portion of the study

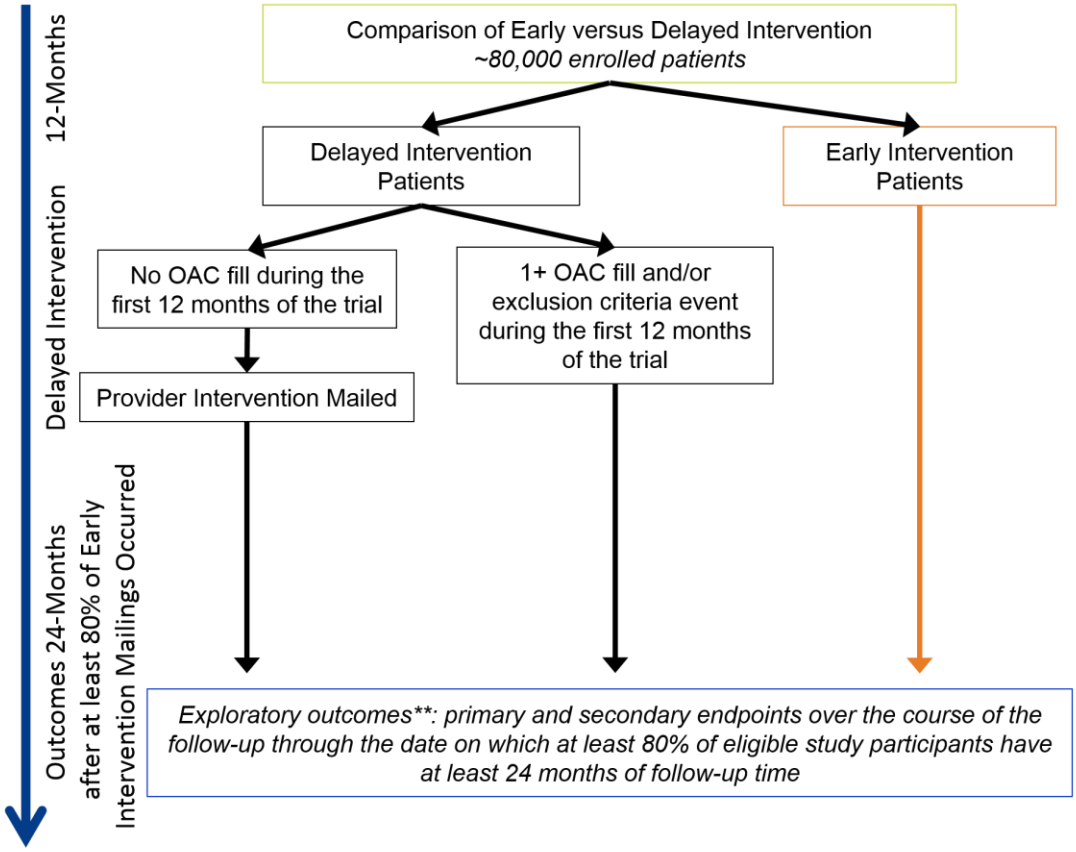


*Baseline characteristics of delayed and early intervention cohorts will be taken from the same time point at randomization from a dataset that is archived at randomization, while exclusion criteria for evidence of OAC medication fill or P2Y12 antagonist use was determined at randomization for the early 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:

Figure 2. 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.

G. SAMPLE SIZE JUSTIFICATION

1. Primary Endpoint

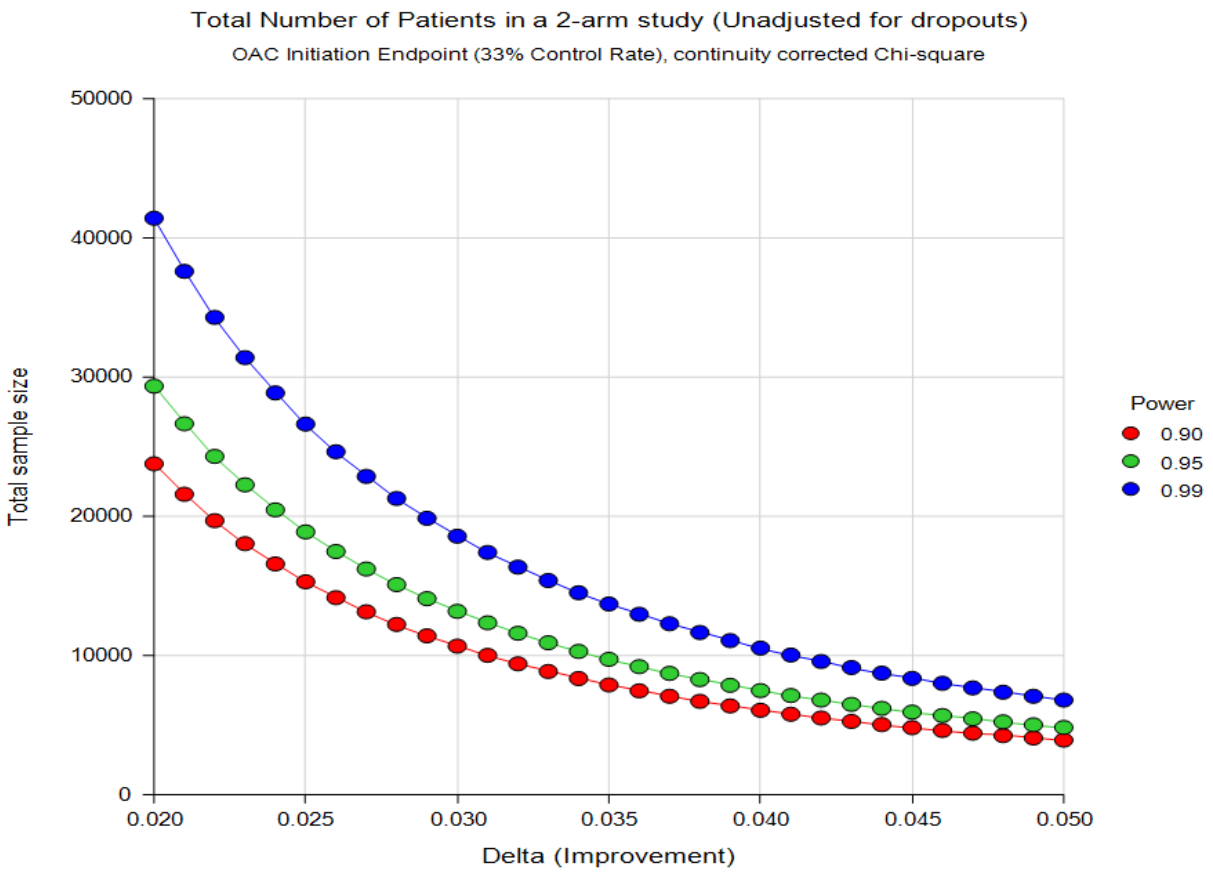
The following assumptions were used to determine the sample size and power for the primary endpoint assessing the proportion of AF patients with evidence of at least one OAC prescription fill through the date on which at least 80% of eligible study participants have at least 12 months of follow-up time:

1. 33% OAC initiation rate in the delayed intervention arm
2. 38% OAC initiation rate in the early intervention arm (5% absolute improvement in OAC initiation over the 33% OAC initiation expected in the delayed intervention arm over 1-year follow-up)
3. 1-year attrition rate: 30% dropout or lost-to-follow-up
4. Two-sided type I error rate of 0.05
5. Roughly 10,000 patients who meet the inclusion/exclusion criteria will yield more than 99% power to detect a 5% absolute difference

Table 2. Sample size and power for the primary endpoint

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

Figure 3. Total number of patients in a 2-arm study



2. Important Secondary Outcome of Stroke or TIA

A study with approximately 80,000 patients could provide reasonable power for stroke or TIA outcome under certain assumptions listed below:

1. 1-year stroke or TIA rate: 18% among patients not treated with OAC
2. 1-year stroke or TIA rate: 7% among patients treated with at least 1 OAC fill
3. Duration of follow-up: 1 year
4. 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%
5. 1-year attrition rate: 30% dropout or lost-to-follow-up
6. Two-sided type I error of 0.05
7. 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.
8. 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. STATISTICAL ANALYSIS

All primary analyses will be based on modified intention-to-treat (mITT) principle (i.e., all identified early intervention patients who met eligibility and were mailed the intervention will be included; using "pseudo" wave assignments, all identified delayed intervention patients who met eligibility at the time of corresponding early mailings will be included). Since the additional exclusions after randomization will be applied in the same way, using the same time points for both the early and delayed intervention groups, we expect there will be no effect from these additional exclusions on the randomization. The mITT analysis will include the following:

- Early intervention members who were mailed a letter, with follow-up beginning on the date of mailing (up to two dates per site and the dates varied by site).
- Delayed intervention members who were not on treatment at the date of mailing (wave assignments were made for the delayed as described earlier in section I.F) with follow-up beginning on that date.

An as-randomized analysis will be performed for the primary endpoint as a sensitivity analysis. Randomization occurred prior to treatment status assessment per the study design. Therefore, the as-randomized analysis will include people who were on treatment as well as others who were not truly eligible for the study (i.e., people who disenrolled, were transitioned to a plan that does not permit their inclusion, had incomplete or invalid addresses, died, or had a "do not contact" status).

Potential sensitivity analysis for mITT analysis: There may be differential loss to follow up between the early and delayed intervention groups because some members did not have valid mailing addresses,

though we did not assess the addresses of the members in the delayed intervention arm at the time of early intervention mailings. It is not possible to retrospectively ascertain the address status of the delayed intervention group as of the date on which mailing would have occurred for that group. We can estimate the magnitude by referring to the early intervention group, and in the early intervention group, we can compare the baseline characteristics and experience of the individuals who had no valid address to those who do.

All possible person-time will be used to assess participants' outcomes. For the time-to-event analysis, 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.

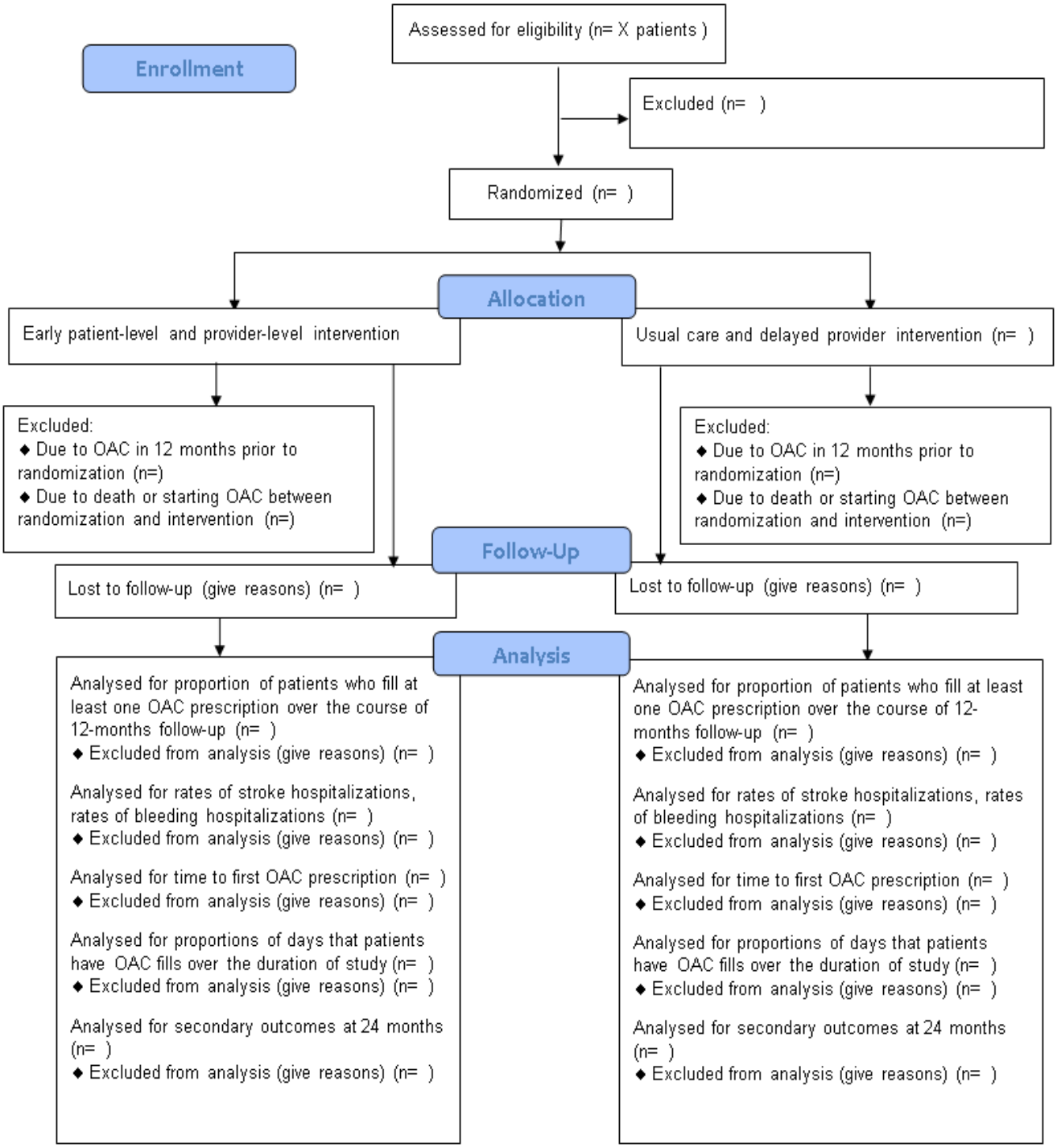
Providers may have more than 1 patient in the study – either within the same arm or in both the early and delayed intervention arms. The frequency of this, when provider overlap can be identified, will be reported descriptively and it is expected to be a low proportion of whole population. Depending on the number of patients in this scenario, a sensitivity analysis may be considered to examine the effect.

There were a few variations in the implementation of the early intervention across the Data Partners due to pragmatic issues. The intervention per the protocol is targeted at both member and provider (i.e., the provider who gave most recent AF diagnosis). If the AF provider was a facility in the source data, the educational intervention was applied to the member only, unless the site chose an alternate provider. In the latter case, the intervention was sent to both the member and the alternate provider. The number of patients in each of these variations to the intended intervention will be reported.

A detailed Consort flow diagram will be provided showing the number of patients randomized to the early and delayed intervention groups, the numbers of subjects lost to follow up or excluded from analyses, and the number of subjects evaluable for the key study endpoints (Figure 1). [1]

All analyses will be conducted using SAS version 9.4 or higher software (SAS Institute Inc., Cary, NC). However, version and modules to be used could vary from one Data Partner to another. All tests will be two-sided and a p-value of <0.05 will be considered statistically significant. No multiplicity adjustment will be made.

Figure 4. Consort Flow Diagram



A. METHODS FOR ANALYSIS IN DISTRIBUTED DATA NETWORKS

Patient-level data will be maintained by the Data Partners for all or most analyses. Therefore, analyses specified in this document will be conducted via a distributed SAS programming code developed by the Duke statistical team in collaboration with the study coordinating center at HPHCI as specified in the study table and figure shells. These SAS programs will be shared with HPHCI trial coordinating center for validation, beta testing, and software version compatibility as specified by each Data Partner. Results are expected to be returned by Data Partner to HPHCI and shared with the data coordinating center (DCC) at Duke to conduct an overall statistical analysis across all Data Partners' results. The Duke DCC will have a data use agreement with each Data Partner as necessary in order to receive/access aggregate summary data, which are housed at HPHCI. No Data Partner-specific tables will be shared beyond the coordinating center and Duke DCC, if agreed upon by Data Partners, the analytic team; only data aggregated across sites will be published or made public.

There are several analytic approaches that can be used to perform analysis in a distributed database without requiring patient-level information.[2 3 4 5 6 7 8] Each of these methods requires different types of summary-level information from the participating sites but they generally provide comparable results. We describe these approaches in Appendix D: 1) meta-analysis, 2) case-centered logistic regression, 3) distributed regression. The analysis of primary and secondary outcomes in this study will require using both logistic regression and time-to-event approach. The heterogeneity across Data Partners will need to be assessed. A fixed-effects meta-analysis approach will be the primary statistical method for integrating the findings from each Data Partner. Because case-centered logistic regression and distributed regression methods require a more granular level of data as compared to meta-analysis approach, these methods could be explored as sensitivity analyses depending on the level of data provided by the five Data Partners.

Hereafter, the statistical analysis details will be described based on patient-level data with the understanding that each Data Partner will run these analyses separately and return the results to the HPHCI coordinating center for further analyses.

B. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics of the early intervention and delayed intervention cohorts will be based on the claims data at the time of randomization (among those eligible for inclusion in the analysis). 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 (Table 1 in Appendix A). Key demographic and baseline variables to be summarized include: geographic region, age, sex, risk factors for stroke, risk factors for bleeding, and selected comorbid conditions. Depending on the data availability and effort required by Data Partners, a sensitivity analysis may be conducted to examine the number of patients associated with different provider types (examination of outcomes by provider type may also be considered). 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 if the count in any cell is less than 5. 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 data within each Data Partner. For the continuous variables in combined study population, only the mean will be summarized. Each Data Partner will run the SAS program(s) distributed by HPHCI, developed with the statistical team at Duke, to generate a summary table for their cohort of patients shown in Tables 1a – 1e in Appendix A (one for each Data Partner) and return the summary table to HPHCI. The same summary table will be generated for entire study population by HPHCI, as shown in Table 1 in Appendix A.

As part of the provider intervention materials, providers had the opportunity to respond and provide an explanation for why their patients were not being treated with OAC. The data collected from these responses will be aggregated by rationale for non-treatment and reported as counts (percentages) by the coordinating center.

C. PRIMARY ENDPOINT DATA ANALYSES

The proportion of patients with evidence of at least one OAC medication 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) is the primary endpoint. The definition for OAC medication fill will be an OAC medication billing in the outpatient pharmacy claims or at least 4 INR tests or results in the laboratory claims (indicative of OAC use that was not billed through the pharmacy claims data). The primary endpoint will be summarized and compared between the early intervention and delayed intervention arms. Both unadjusted and adjusted (based on available baseline risk factors) analyses will be conducted for the difference in the primary endpoint between the early intervention and delayed intervention arms using the data shown in Table 3. The adjusted analysis will be considered the primary analysis.

1. Adjusted Analysis Model

The logistic regression model will be used for analyzing primary endpoint. Let binary indicator variable T denotes randomized treatment groups, i.e. T=1 indicates early intervention; T=0 indicates delayed intervention. Let π denotes the probability that a patient filling at least at least one OAC medication over the course of the 12-months post intervention. The primary analysis model has the form

$$logit(\pi) = \log\left(\frac{\pi}{1-\pi}\right) = \alpha + \beta_0 \, T + \boldsymbol{\beta}'\boldsymbol{\chi}$$

where α is the intercept parameter, $\boldsymbol{\chi}$ is the vector of baseline covariates to be adjusted in the model, listed in Appendix A Table 2. The same set of covariates will be used in the analysis performed by each data partner on their cohort of patients. $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_s)'$ is the vector of slope parameters. $\frac{\pi}{1-\pi}$ is the odds of a patient filling at least one OAC medication prescription 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. This model assumes observations are correlated within each Data Partner "cluster" but not across Data Partners, a "working" correlation structure will be used via generalized estimating equation (GEE).[10]

2. Analysis Results Interpretation

The estimate of β_0 in the model in section C.1 is the logarithm of odds ratio of treatment groups (i.e., the odds of an average patient in the early intervention group filling at least one OAC medication prescription as compared to the odds of an average patient in the delayed intervention group filling at least one OAC prescription 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). To evaluate whether the early patient-level and provider-level educational interventions increases the proportion of patients with evidence of at least one OAC medication fill over the course of the 12-months post intervention, we will calculate the odds ratio using logistic regression model adjusted for baseline risk factors listed in Appendix A Table 2, with GEE to account for the correlation of responses among the patients from a same service provider. The odds ratio, 95% confidence interval (CI), and p-value will be presented to show whether there is a statistically significant difference in the proportion of patients who fill at least one OAC prescription 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 between the early intervention and

delayed intervention groups. Each Data Partner will run the SAS program(s) distributed by HPHCI, developed with the statistical team at Duke DCC, to perform logistic regression on their cohort of patients and return the parameter estimate (standard error [SE]), estimated of odds ratio, 95% CI, and p-value, shown in Table 3a – 3e in Appendix A (one for each Data Partner), to HPHCI. Meta-analysis methods with inverse-variance weighting on log scale will be used to integrate the results and obtain the estimate of the overall odds ratio, 95% CI and p-value for entire study population, as shown in Table 3 in Appendix A.

There are patients for whom a provider was not identified, and therefore the provider letters were not mailed out. The primary endpoint will be summarized and compared between the patients with provider letter and the patients without provider letter. Each Data Partner will return the descriptive data, shown in Table 4a – 4e in Appendix A to HPHCI. Similar summary table will be generated for entire intervention arm by HPHCI, as shown in Table 4 in Appendix A. To evaluate whether the intervention effect is different between the patients with provider letter and the patients without provider letter, an interaction term between treatment and provider status (an indicator variable of Yes/No for the provider letter received) will be tested in the above multivariable model. Each Data Partner will return the p-value of interaction term to HPHCI. Fisher's method as described below will be used to combine the p-values of test for the interaction term from each Data Partner and generate the p-value for the interaction term for entire cohort.

$$\chi 2_{2k} = -\sum_{i=1}^{k} \ln(p_i)$$

Where p_i is the p-value from *ith* Data Partner.

D. SECONDARY ENDPOINTS DATA ANALYSES

1. OAC Initiation

The time to first OAC initiation, is 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 tests or results documented over the study period, the date of the first INR measurement would be used for initiation of OAC. A Cox proportional hazards[11] model with early intervention vs. delayed intervention as the main effect will be used to model the time to first OAC initiation, after adjusting for baseline risk factors listed in Appendix A Table 2. A robust sandwich covariance estimate or a frailty model will be used to account for the correlation of responses among the patients from a same service provider. The hazard ratio, 95% CI and p-value will be summarized for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin. Each Data Partner will run the SAS program(s) distributed by HPHCI, developed with the statistical team at Duke DCC, to perform Cox regression model[11] on their cohort of patients and return the estimated hazard ratio, 95% CI and p-value, shown in Table 5a – 5e in Appendix A (one for each Data Partner), to HPHCI. Meta-analysis methods with inverse-variance weighting on log scale will be used to integrate the results and obtain the overall estimate of the hazard ratio, 95% CI and p-value for the entire study population, as shown in Table 5 in Appendix A.

2. OAC Adherence

OAC adherence will be assessed by the proportion of days covered by OAC prescription fills over the duration of the study, or the proportion of days covered. 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. Overlapped prescription days will be counted only once, and the days prescribed beyond censor date will be censored accordingly in calculating the total days

covered by OAC. Patients will only be included in this secondary analysis if they had a prescription fill for apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin. Proportion of days covered will be summarized as mean (±SD), and median (25^{th}, 75^{th} percentiles) by early vs. delayed intervention, the comparison between the two groups will be conducted using Wilcoxon rank-sum test, as shown in Table 6 in Appendix A. Each Data Partner will run the SAS program(s) distributed by HPHCI, developed with the statistical team at Duke, to generate a summary table for their cohort of patients shown in Tables 6a – 6e in Appendix A (one for each Data Partner) and return the summary table to HPHCI. For entire study population, the mean of two groups will be generated using meta-analysis methods. Fisher's method as described in Section C will be used to combine the p-values of Wilcoxon rank-sum test from each Data Partner and generate the p-value for entire cohort.

3. Proportion of Patients Actively on OAC at the End of Follow-up

The proportion of patients actively on OAC at the end of follow-up will be summarized and compared between the early intervention and delayed intervention arms. Last Observation Carry Forward will be used if the patient is censored. To evaluate whether the early patient-level and provider-level educational intervention increases the proportion of patients being actively on OAC at the end of follow-up, we will calculate the odds ratio (i.e., the odds of an average patient in the early intervention group being actively on OAC at the end of follow-up as compared to the odds of an average patient in the delayed intervention group being actively on OAC at the end of follow-up) using logistic regression model adjusted for baseline risk factors listed in Appendix A Table 2, with GEE to account for the correlation of responses among the patients from a same service provider. The odds ratio, 95% confidence interval (CI) and p-value will be presented to show whether there is a statistically significant difference in the proportion of patients who are actively on OAC at the end of follow-up between the early intervention and delayed intervention groups. Each Data Partner will run the SAS program(s) distributed by HPHCI, developed with the statistical team at Duke DCC, to perform logistic regression analysis on their cohort of patients and return the parameter estimate (SE), estimated odds ratio, 95% confidence interval (CI) and p-value, shown in Table 7a – 7e in Appendix A (one for each Data Partner), to HPHCI. Meta-analysis methods with inverse-variance weighting on log scale will be used to integrate the results and obtain the estimate of the overall odds ratio, 95% confidence interval and p-value for entire study population, as shown in Table 7 in Appendix A.

4. Clinical Outcomes

Claims data (ICD-10-CM codes used for defining these outcomes are listed in Appendix C) will be used to define the following clinical outcomes:

- Hospitalization for ischemic stroke or unknown stroke
- Hospitalization for hemorrhagic stroke
- Hospitalization for any bleeding
- Composite of ischemic or hemorrhagic stroke
- Composite of ischemic stroke, hemorrhagic stroke, and hospitalization for any bleeding
- All-cause in-hospital death

For each of these outcomes, time-to-event methodology will be implemented. Kaplan-Meier estimator[12] will be used to estimate the probability of occurrence at 12 months of follow-up and the log-rank test[13] will be used to compare the survival curves. The Cox proportional hazards model with early intervention vs. delayed intervention as main effect will be used to model the time to event, after adjusting for baseline risk factors listed in Appendix A Table 2. The hazard ratio, 95% CI and p-value will be presented to summarize the difference in the risk of clinical outcome between early intervention and delayed intervention groups. In-hospital death or medically attended death will be collected through claims data.

Depending on number of patients and events, the comparison of the stroke rate between early and delayed intervention may be examined separately in patients who have 1 OAC fill and multiple OAC fills. This will be descriptive only and will not include formal statistical testing.

Each Data Partner will run SAS program(s) distributed by HPHCI, developed with the statistical team at Duke DCC, to perform analysis on their cohort of patients and return the results to HPHCI. For the comparison of probability of occurrence, each Data Partner will return the estimate of probability of occurrence, standard error, 95% CI by early intervention vs. delayed intervention, and p-value, as shown in Table 8a - 8e in Appendix A (one for each Data Partner). For the comparison of risk, each Data Partner will return the parameter estimate (SE), hazard ratio, 95% CI and p-value, as shown in in Appendix A Table 9a - 9e (one for each Data Partner). The statistical team will use meta-analysis methods to integrate the results and obtain the results for entire study population, as shown in Tables 8 and 9 in Appendix A.

5. Health Care Utilization

The total counts of health care utilization (number of outpatient visits, emergency department visits, hospital admissions, and days hospitalized) at the end of follow-up time, including AF and non-AF related care, will be summarized by early intervention and delayed intervention group, as shown in Table 10 in Appendix A.

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IV. APPENDIX

A. TABLES

For all tables below, the study coordinating center at HPHCI will receive Data Partner-specific tables. The coordinating center will generate aggregated tables across Data Partners (shown below), using meta-analysis methods where appropriate (for continuous variables in aggregated tables, only mean will be generated); these will be shared with the Duke DCC statistical team. Duke DCC will have a data-use agreement with each Data Partner as necessary in order to receive/access aggregate summary data, which are housed at HPHCI. No Data Partner-specific tables will be shared beyond the coordinating center and Duke DCC, if agreed upon by Data Partners, the analytic team; only data aggregated across sites will be published or made public.

Appendix A Table 1. Baseline characteristics of all patients by early intervention vs. delayed intervention

	Early intervention (N=XXXX)	Delayed intervention (N=XXXX)	Overall (N=XXXX)
Demographics			
Age			
N			
Mean (SD)			
Median (Min, 25th, 75th, Max)			
30-34 yr, %			
35-39, %			
40-44, %			
45-49, %			
50-54, %			
55-59, %			
60-64, %			
65-69, %			
70-74, %			
75-79, %			
≥ 80, %			
Sex			
N			
Female, %			
Region			
New England, %			
Mid-Atlantic, %			
South-Atlantic, %			
Midwest, %			
Mountain, %			
Pacific, %			
Unknown, %			
Medical history			
History of anemia?			

	Early intervention (N=XXXX)	Delayed intervention (N=XXXX)	Overall (N=XXXX)
N			
Yes, %			
History of hypertension?			
N			
Yes, %			
History of diabetes?			
N			
Yes, %			
History of hospitalization for any bleeding?			
N			
Yes, %			
History of peripheral vascular disease?			
N			
Yes, %			
History of prior cerebrovascular disease?			
N			
Yes, %			
History of heart failure?			
N			
Yes, %			
History of kidney disease?			
N			
Yes, %			
History of MI			
N			
Yes, %			
History of CABG			
N			
Yes, %			
CHA_2DS_2 VASc score			
N			
Mean (SD)			
Median (25th, 75th)			
0, %			
1, %			
2, %			
3, %			
4, %			
5, %			
6, %			
7, %			
8, %			
9, %			

	Early intervention (N=XXXX)	Delayed intervention (N=XXXX)	Overall (N=XXXX)
Bleeding risk score: ATRIA score			
Low (≤3), %			
Intermediate (4), %			
High (≥5), %			
Hospitalization in the prior 6 months			
0, %			
1, %			
2, %			
≥3, %			

For Tables 3 through 10: The SAP workplan(s) run at each Data Partner sites will generate Partner-specific tables of events (per outcome, for early vs delayed intervention) and unadjusted and adjusted model results. These will be returned to the coordinating center; results will be aggregated and meta-analyses will be run on site-specific models to generate final aggregated results.

Appendix A Table 2. Baseline covariates to be adjusted in the models described in Sections II.C, II.D.1, II.D.2, II.D.3, and II.D.4

Demographics
Age (continuous)
Sex (male vs. female)
Region (New England vs. Mid-Atlantic vs. South-Atlantic vs. Midwest vs. Mountain vs. Pacific)
Medical history
History of anemia (yes vs. no)
History of hypertension (yes vs. no)
History of diabetes (yes vs. no)
History of hospitalization for any bleeding (yes vs. no)
History of peripheral vascular disease (yes vs. no)
History of prior cerebrovascular disease (yes vs. no)
History of heart failure (yes vs. no)
History of kidney disease (yes vs. no)
History of MI
History of CABG
Bleeding risk score: ATRIA score (Low (≤3) vs. Intermediate (4) vs. High (≥5))
Hospitalization in the prior 6 months (0 vs. 1 vs. 2 vs. ≥3)

Appendix A Table 3. Odds ratio of filling at least one OAC medication prescription over the course of the 12-months of follow-up: early intervention vs. delayed intervention (replicated at each Data Partner)

	Early Intervention, n/N (%)	Delayed Intervention, n/N (%)	Parameter Estimate (SE)	Odds Ratio (95% CI)	p-value
OAC Prescription at 1-year					

Appendix A Table 4. Numbers and proportions of filling at least one OAC medication prescription over the course of the 12-months of follow-up in intervention arm: patients with provider letter vs. patients without provider letter (replicated at each Data Partner)

	Patients with Provider Letter, n/N (%)	Patients without Provider Letter, n/N (%)	p-value
OAC Prescription at 1-year			

Appendix A Table 5. Hazard ratio of OAC initiation: early intervention vs. delayed intervention (replicated at each Data Partner)

	Early Intervention, n/N (%)	Delayed Intervention, n/N (%)	Parameter Estimate (SE)	Hazard Ratio (95% CI)	p-value
OAC initiation					

Appendix A Table 6. Proportion of days covered: early intervention vs. delayed intervention (replicated at each Data Partner)

	Early Intervention	Delayed Intervention	p-value
N			
Mean (SD)			
Median (Min, 25th, 75th, Max)			

Appendix A Table 7. Proportion of patients actively on OAC at the end of follow-up: early intervention vs. delayed intervention (replicated at each Data Partner)

	Early Intervention, n/N (%)	Delayed Intervention, n/N (%)	Parameter Estimate (SE)	Odds Ratio (95% CI)	p-value
Actively on OAC at the end of follow-up					

Appendix A Table 8. Probability of occurrence at 1-year: early intervention vs. delayed intervention (replicated at each Data Partner)

Outcomes	Early Intervention, n/N (%)	Delayed Intervention, n/N (%)	Early Intervention, Probability (SE) (95% CI)	Delayed Intervention, Probability (SE) (95% CI)	p-value
Hospitalization for ischemic stroke or unknown stroke					
Hospitalization for hemorrhagic stroke					
Hospitalization for any bleeding					
Composite of ischemic or hemorrhagic stroke					
Composite of ischemic stroke, hemorrhagic stroke, and hospitalization for any bleeding					
All-cause in-hospital death					

Appendix A Table 9. Hazard ratio of each outcome: early intervention vs. delayed intervention (replicated at each Data Partner)

Outcomes	Early Intervention, n/N (%)	Delayed Intervention, n/N (%)	Parameter Estimate (SE)	Hazard Ratio (95% CI)	p-value
Hospitalization for ischemic stroke or unknown stroke					
Hospitalization for hemorrhagic stroke					
Hospitalization for any bleeding					
Composite of ischemic or hemorrhagic stroke					
Composite of ischemic stroke, hemorrhagic stroke, and hospitalization for any bleeding					
All-cause in-hospital death					

Appendix A Table 10. Health care utilization at 12 months: early Intervention vs. delayed Intervention (replicated at each Data Partner)

	Early Intervention	Delayed Intervention	p-value
Visit Type			
N (Total visits)			
Patients with outpatient visits, % (total outpatient visits)			
Patients with emergency department visits, % (total ED visits)			
Patients with hospital admissions, % (total hospitalizations)			
Days hospitalized			
N (Total)			
Mean (SD)			
Median (25^{th}, 75^{th})			

B. CONSORT 2010 WORKSHEET FOR RANDOMIZED TRIALS

CONSORT 2010 checklist of information to include when reporting a randomized trial

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomization; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	

Section/Topic	Item No	Checklist item	Reported on page No
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome	
	13b	For each group, losses and exclusions after randomization, together with reasons	
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	
Generalizability	21	Generalizability (external validity, applicability) of the trial findings	
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

C. ICD-10 CODES FOR DEFINING CLINICAL OUTCOMES

The below ICD-10-CM codes will be used to define clinical outcomes during analyses (list is not final).

a. **Ischemic stroke or unknown stroke:** diagnosis of
   1. I63.x Cerebral infarction, including
      i. I63.0 Cerebral infarction due to thrombosis of precerebral arteries
      ii. I63.1 Cerebral infarction due to embolism of precerebral arteries
      iii. I63.2 Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries
      iv. I63.3 Cerebral infarction due to thrombosis of cerebral arteries
      v. I63.4 Cerebral infarction due to embolism of cerebral arteries
      vi. I63.5 Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries
      vii. I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
      viii. I63.8 Other cerebral infarction
      ix. I63.9 Cerebral infarction, unspecified
   2. I67.81 Acute cerebrovascular insufficiency
   3. I67.82 Cerebral ischemia
   4. I67.89 Other cerebrovascular disease
   5. I67.9 Cerebrovascular disease, unspecified
   6. G45.x Transient cerebral ischemic attacks and related syndromes, including
      i. G45.0 Vertebro-basilar artery syndrome
      ii. G45.1 Carotid artery syndrome (hemispheric)
      iii. G45.2 Multiple and bilateral precerebral artery syndromes
      iv. G45.3 Amaurosis fugax
      v. G45.4 Transient global amnesia
      vi. G45.8 Other transient cerebral ischemic attacks and related syndromes
      vii. G45.9 Transient cerebral ischemic attack, unspecified
   7. without primary diagnosis of Intracranial injury (S06.x)

b. **Hemorrhagic stroke:** diagnosis of
   1. I60.x Nontraumatic subarachnoid hemorrhage
   2. I61.x Nontraumatic intracerebral hemorrhage
   3. I62.x Other and unspecified nontraumatic intracranial hemorrhage
   4. without primary diagnosis of Intracranial injury (S06.x)

c. **Hospitalization for any bleeding:** see ICD-10-CM codes in "any hemorrhage" category in cohort identification code list (of which GI bleeding is a subset)

d. **Hospitalization for GI bleeding:**
   1. I85.01 Esophageal varices with bleeding
   2. I85.11 Secondary esophageal varices with bleeding
   3. K22.11 Ulcer of esophagus with bleeding
   4. K22.6 Gastro-esophageal laceration-hemorrhage syndrome
   5. Gastric ulcer
      i. K25.0 Acute with hemorrhage
      ii. K25.2 Acute with hemorrhage and perforation
      iii. K25.4 Chronic or unspecified with hemorrhage
      iv. K25.6 Chronic or unspecified with hemorrhage and perforation
   6. Duodenal ulcer
      i. K26.0 Acute with hemorrhage

   ii. K26.2 Acute with hemorrhage and perforation
   iii. K26.4 Chronic or unspecified with hemorrhage
   iv. K26.6 Chronic or unspecified with hemorrhage and perforation
7. Peptic ulcer, site unspecified
   i. K27.0 Acute with hemorrhage
   ii. K27.2 Acute with hemorrhage and perforation
   iii. K27.4 Chronic or unspecified with hemorrhage
   iv. K27.6 Chronic or unspecified with hemorrhage and perforation
8. Gastrojejunal ulcer
   i. K28.0 Acute with hemorrhage
   ii. K28.2 Acute with hemorrhage and perforation
   iii. K28.4 Chronic or unspecified with hemorrhage
   iv. K28.6 Chronic or unspecified with hemorrhage and perforation
   v. K29.01 Acute gastritis with bleeding
   vi. K29.21 Alcoholic gastritis with bleeding
   vii. K29.31 Chronic superficial gastritis with bleeding
   viii. K29.41 Chronic atrophic gastritis with bleeding
   ix. K29.51 Unspecified chronic gastritis with bleeding
   x. K29.61 Other gastritis with bleeding
   xi. K29.71 Gastritis, unspecified with bleeding
   xii. K29.81 Duodenitis, with bleeding
   xiii. K29.91 Gastroduodenitis, unspecified, with bleeding
9. K31.811 Angiodysplasia of stomach and duodenum with bleeding
10. K31.82 Dieulafoy lesion (hemorrhagic) of stomach and duodenum
11. K57.01 Diverticulitis of small intestine with perforation and abscess with bleeding
12. K57.11 Diverticulosis of small intestine without perforation or abscess with bleeding
13. K57.13 Diverticulitis of small intestine without perforation or abscess with bleeding
14. K57.21 Diverticulitis of large intestine with perforation and abscess with bleeding
15. K57.31 Diverticulosis of large intestine without perforation or abscess with bleeding
16. K57.33 Diverticulitis of large intestine without perforation or abscess with bleeding
17. K57.41 Diverticulitis of both small and large intestine with perforation and abscess with bleeding
18. K57.51 Diverticulosis of both small and large intestine without perforation or abscess with bleeding
19. K57.53 Diverticulitis of both small and large intestine without perforation or abscess with bleeding
20. K57.81 Diverticulitis of intestine, part unspecified, with perforation and abscess with bleeding
21. K57.91 Diverticulosis of intestine, part unspecified, without perforation or abscess with bleeding
22. K57.93 Diverticulitis of intestine, part unspecified, without perforation or abscess with bleeding
23. K62.5 Hemorrhage of anus and rectum
24. K63.81 Dieulafoy lesion of intestine
25. K92.0 Hematemesis
26. K92.1 Melena
27. K92.2 Gastrointestinal hemorrhage, unspecified

D. ANALYSIS METHODS FOR DISTRIBUTED NETWORKS

1. Meta-analysis

In meta-analysis, each Data Partner estimates the effect and their variance (or other information needed to calculate the weight) using pre-specified models on their own individual-level data and send these to the coordinating center. Then, the overall estimated effect and 95% confidence interval is derived by pooling site-specific estimates. A commonly used weight is inverse of variance on the log scale of the estimate. Meta-analysis method requires the least amount of data sharing and is flexible with respect the types of study design and analysis. However, it is the least flexible with respect to the subgroup and sensitivity analyses and requires greatest degree of programing/analysis ability at each participating site.

2. Case-centered Logistic Regression

In this method, each Data Partner transfers an aggregated dataset to the coordinating center that includes 1 record per risk set. Each risk set is anchored by a case (patient with the outcome of interest) and comprised of the cases and comparable individuals at risk of the outcome at the time the case occurs. Each record includes a binary variable indicating whether the patient diagnosed with the outcome is exposed to the treatment and the log odds of the site-specific proportion of exposed patients in the risk set. Confounding adjustment will be conducted through stratification. Specifically, if the number of imbalanced covariates is small, we will create strata that are defined by these covariates within each site; the risk set for a given case will be at-risk individuals who are within the same covariate stratum as the case. If the number of imbalanced covariates is large, we will create propensity score (PS) strata. The PS will be estimated within each site, and the risk set for a given case will be at-risk individuals who are within the same propensity score stratum as the case. The statistical team fits a logistic regression model with indicator variable as the dependent variable and log odds as the independent variable. It is shown that this method maximized the same likelihood as a stratified Cox model using patient–level data. Thus, it is appropriate for study designs that needs to be analyzed using Cox proportional hazards model.

3. Distributed Regression

Distributed regression is a suite of methods that enable researchers to conduct multi-database multivariable-adjusted regression analysis without the need to centrally combine all individual-level data from participating sites. It performs the same numeric algorithm as standard ordinary least squares regression but uses only summary statistics for computation. By following the same computation process, distributed regression and pooled individual-level data analysis produce statistically equivalent results. With distributed regression, we can adjust for imbalanced covariates directly in the outcome regression models.