Title: Implementing Prescriber-Pharmacist Collaborative Care for Evidence-based Anticoagulant Use

NCT: NCT05351749

Protocol IRB Approval Date: 8/11/2022

Implementing Prescriber-Pharmacist Collaborative Care for Evidence-based Anticoagulant Use

National Clinical Trial (NCT) Identified Number: NCT05351749

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

Agency for Healthcare Quality and Innovation (AHRQ)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of AHRQ-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the any relevant consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: Implementing Prescriber-Pharmacist Collaborative Care for Evidence-based Anticoagulant Use

Study Description: Direct oral anticoagulant medications are commonly used to treat or prevent thrombotic conditions, such as pulmonary embolism, deep vein thrombosis, and atrial fibrillation. However, up to 10-15% of patients receiving these medications get unsafe doses based on a patient's kidney or liver function, potential interactions with other medications, and indication for taking the medication. Medication alerts and notifications directed to prescribers may be beneficial for improving evidence-based prescribing, but can be burdensome. This study will improve upon the existing systems by testing augmentations that encourage collaboration between prescribing health care providers (e.g., physicians, nurse practitioners) and expert pharmacists working in anticoagulation clinics and incorporating dynamic long-term monitoring of patient needs, as well as updates to evidence-based guidelines. The target participant for this trial is the DOAC prescriber (physician, physician assistant, nurse practitioners). We will specifically test two different clinical situations: (1) a medication alert at the time an inappropriate new direct oral anticoagulation (DOAC) prescription is written, and (2) a medication notification that is sent anytime a new prescribing error develops *after* the initial DOAC prescription is written. This project will implement and evaluate an Electronic Health Record (EHR) medication alert and notification system to improve safe DOAC prescribing through prescriber-pharmacist collaboration. Findings from this project will establish a framework for implementing prescriber-pharmacist collaboration for high risk medications, including anticoagulants.

Objectives:

Primary Objective:	Implement and evaluate EHR medication alert and notification systems to improve safe DOAC prescribing through prescriber-pharmacist collaboration.

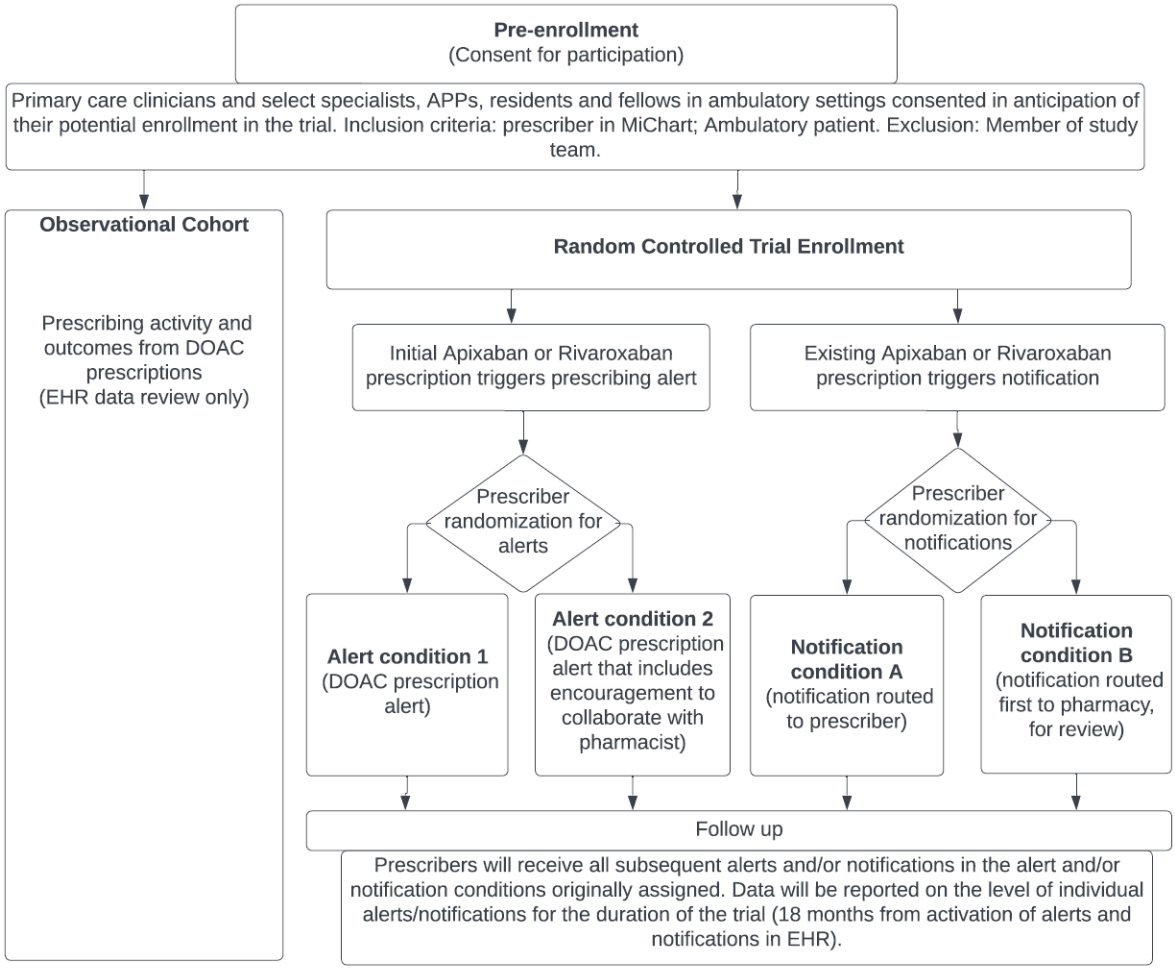
Endpoints:

Primary Endpoint:	The number (proportion) of notifications (in the existing-prescription notification conditions) that are addressed within 7 days.
Secondary & Exploratory Endpoints:	The number (proportion) of alerts (in the newly prescribed DOAC alert conditions) that are addressed within 7 days. Change in magnitude of improvement for the existing-prescription notification over time, reported on at the institution level (not individual level).

	Change in magnitude of improvement for the new-prescription alert over time, reported on at the institution level (not individual level).
Study Population:	300 (minimum) prescribers of DOACs
Phase:	NA
Description of Sites Enrolling Participants:	This single center clinical trial will be conducted at the University of Michigan. Participants (DOAC prescribers) will be recruited from Michigan Medicine prescribers.
Description of Study Intervention:	The study examines the effects of medication alerts and notifications in the EHR regarding problems with the DOAC medications Apixaban and Rivaroxaban. Alerts and notifications vary only in the degree to which pharmacists are involved. For alerts (for new prescriptions), prescribers will be randomly assigned to receive either an alert at the time of prescribing that includes an explicit option to consult with a pharmacist or one that does not include an explicit option to consult with a pharmacist. (Pharmacy consults are always available.) For notifications (related to existing prescriptions), a notification will be initially routed to either a pharmacist (who can consult the prescriber) or to the prescriber (who can consult a pharmacisit).
Study Duration:	18 months
Participant Duration:	Up to 18 months
Source of funding:	AHRQ grant: R18HS028562

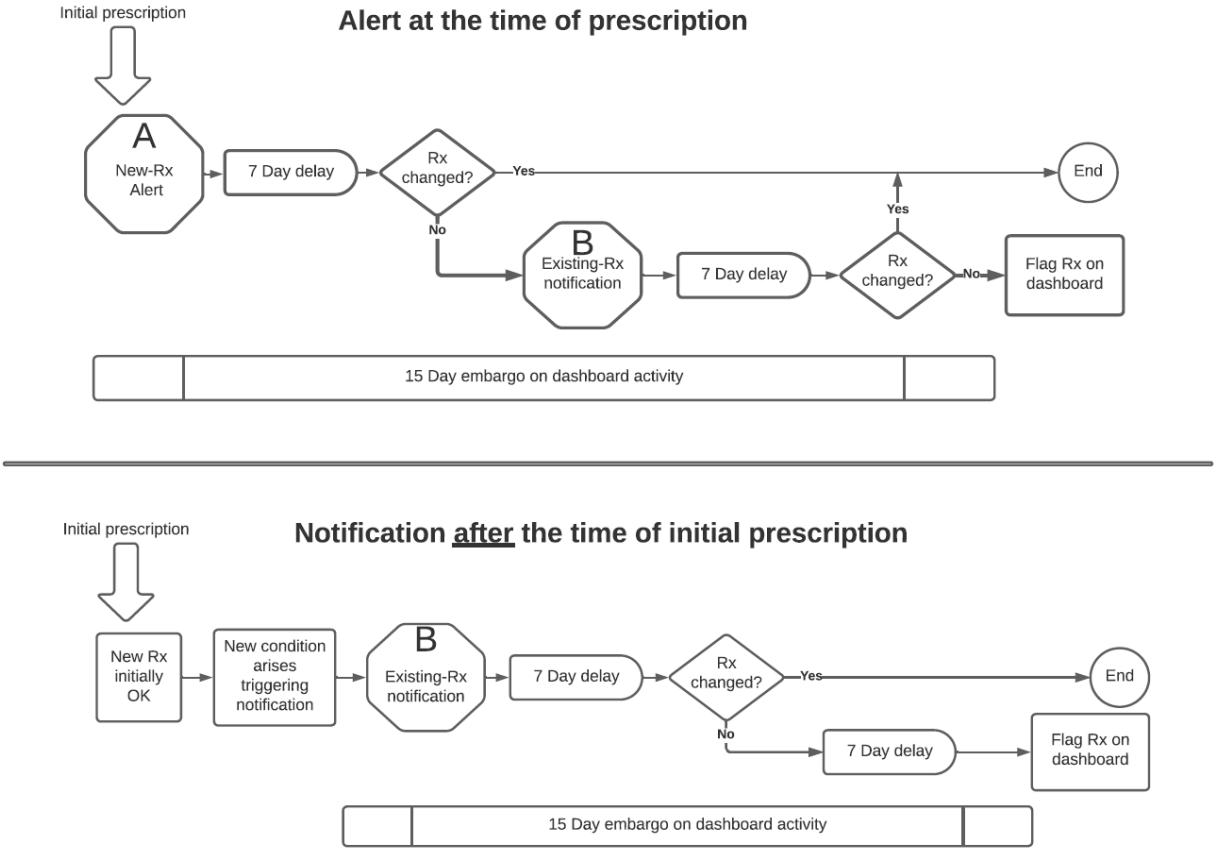
1.2 SCHEMA

Schema for enrollment and participation



Note that prescribers can be enrolled in just one or both the alert and notifications arms of the randomized controlled trial if they are eligible.

Representation of alerts and notifications in protocol



Note: Reference to the “dashboard” relate to a current tracking system used by anticoagulation clinic pharmacists to identify when potentially inappropriate DOAC prescriptions exist. These will be embargoed for 15 days to measure the effect of an alert and/or notification on prescriber behavior before reverting to the usual care pathway (display alert on dashboard).

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	**Screening and Enrollment**	**At time of first triggered alert or notification**	**At time of subsequent alerts or notifications**	**6 & 12 months of trial**	**18 months of trial**
Informed Consent (waived documentation per IRB)	X				
Inclusion/exclusion		X			
Randomization		X			
Collection of EHR alert data		X	X		
Conclusion of data collection					X
Event review and DSMB ● Adverse events (See appendix A) ● Appropriateness of Rx				X	X
Final Status					X

Key: EHR = electronic health record

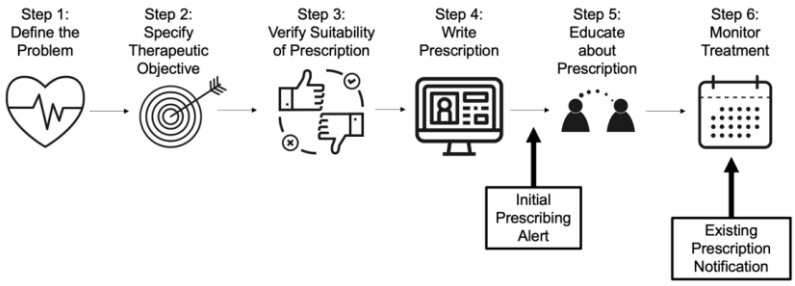
2 INTRODUCTION

2.1 BACKGROUND AND STUDY RATIONALE

Direct Oral Anticoagulant (DOAC) use is rapidly expanding for six million Americans with common thrombotic conditions. Atrial fibrillation (AF) and venous thromboembolism (VTE) are the leading indications for chronic anticoagulation therapy. Since 2010, four DOAC medications (apixaban, dabigatran, edoxaban, and rivaroxaban) have rapidly overtaken warfarin as first-line therapy for AF and VTE.[1–3] DOAC therapy is critical to prevent life-threatening stroke and thromboembolic complications.

Unsafe DOAC prescribing is common and dangerous. While initially heralded as easier to prescribe than warfarin, in real-world settings 10-20% of DOAC prescriptions do not follow the Federal Drug Administration (FDA) evidence-based package label instructions.[4–6] The most common reasons for unsafe DOAC use include inappropriate dosing based on renal or liver function, overlooked drug-drug interactions, and dosing based on the wrong indication (e.g., using AF dosing for VTE). These prescribing errors occur both at the time of initial prescription and in the months to years of follow up (**Figure 1**). Data from both large national registries[4,5] and our local studies[7] confirm a higher rate of bleeding, hospitalization, and death for patients with unsafe DOAC use as compared to evidence-based prescribing. Despite these common prescribing errors, most health systems only provide alerts for potential drug-drug interactions, not for other (more common) causes of inappropriate DOAC prescribing.

Figure 1



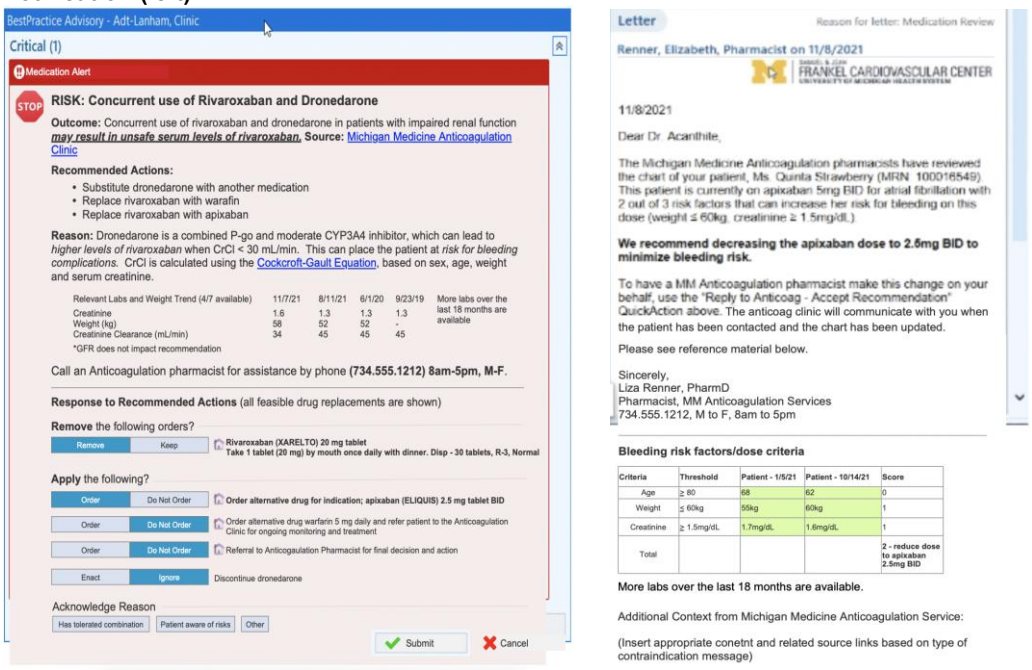
Prescriber-pharmacist collaboration is an underutilized resource. Prescribers have long collaborated with more than 3000 anticoagulation clinics nation-wide to manage warfarin. The majority of these clinics rely on pharmacists with anticoagulation expertise to manage complex patients and their high-risk medications safely. Our 2017 survey of these clinics found that most anticoagulation clinics offer collaborative DOAC care.[15] In this collaborative mode, the pharmacists review prescriptions for appropriateness and for potential drug-drug interactions and recommend appropriate drug/dose selection. However, despite their high volume, DOAC-treated patients accounted for a small fraction (~10%) of the overall anticoagulation clinic volume, indicating prescriber underutilization. One exception is the Veterans Health Affairs system, where pharmacist collaboration is common for DOAC prescribing and rates of unsafe DOAC prescribing are significantly lower than outside the Veterans Health Affairs system.[16]

Most medication alerts do not follow key design principles and fail to improve patient care. Studies have shown that well-designed medication alerts in the EHR can reduce adverse drug events by up to 50%.[17] However, these promising results are too often not realized. In fact, poorly implemented

Table 1. Medication Alert Design Principles[18,19]

- Improve signal-to-noise ratio by *incorporating clinical context* into alert logic
- Support *collaborative work*, including pharmacists
- Fit within prescriber workflow and mental model, which includes *non-interruptive alerts*
- Display relevant data on why alert occurred
- Ensure system transparency
- Include *actionable tools* within the alert

Figure 2. Sample Medication Alert with Pharmacist Referral Option and notification (right), and notification (left)



medication alerts frequently lead to clinician dissatisfaction from alert fatigue and habitual override.[17,18] Currently available DOAC medication alerts suffer from three fundamental design flaws, which together lead to incorrect DOAC dosing both at the time of the initial prescription and at subsequent moments in time where clinical changes should lead to modification of the DOAC medication or dose: (1) alerts intrude or interrupt prescriber work flow with low-yield information without actionable tools, often leading to alert dismissal without action; (2) alerts occur only at the time of prescribing, ignoring changes to the clinical scenario that may occur after the initial prescription is written; and (3) alerts do not promote collaboration between prescribers and pharmacists. As a result, many patients receive unsafe prescriptions that can cause significant harm. Medical informatics experts have proposed key design principles to address these issues (**Table 1**).[18,19] Key among these is supporting collaborative work between prescribers and pharmacists.

Many prescribers have multiple patients with unsafe DOAC prescriptions. DOAC prescribing has rapidly accelerated between 2012 and 2020, to more than 19,000 unique patients at Michigan Medicine alone with active DOAC use. A single-day (Dec 21, 2020) cross-sectional analysis at Michigan Medicine found 9,325 patients had DOAC use documented by 1,002 primary care, cardiology, hematology, or surgery prescribers (median 23 patients/prescriber, interquartile range 7-47). Of these, 670 (7.2%) patients (among 250 unique prescribers) clearly did not follow evidence-based guidelines, a median of 2 (IQR 1-5) unsafe DOAC prescriptions per prescriber observed on that single day snapshot.

Prescribers change when alerted. During a recent pilot study that we conducted, when prescribers were contacted about unsafe DOAC use they made meaningful changes in 51/81 (63%) cases.[20] Actions taken included changing the medication, changing the dose, or discontinuing an interacting medication. When changes were not made, a thoughtful discussion usually occurred between the prescriber and an anticoagulation expert focusing on unique patient factors.

Proposed Intervention. We propose two different interventions to improve DOAC prescribing. The first intervention is an automated EHR alert that occurs at the time a DOAC medication is prescribed but some potential error exists (e.g., drug-drug interaction, wrong dose for given renal function). Prescribers will be randomized to receive a detailed alert, but half will include a referral link for optional pharmacist review and the other half will receive an alert that does not include the pharmacist review referral link.

The second intervention is an EHR notification that is sent to the inbox of either the DOAC prescriber or an anticoagulation pharmacist anytime *after* a DOAC medication is prescribed when a new potential issue develops (e.g., worsened renal function that impacts dosing, new drug-drug interactions).

2.2 Risk/Benefit Assessment

2.2.1 Known Potential Risks

There are minimal risks to the subjects (prescribers).

- Confidentiality
- Risk to reputation if "errors" are revealed to Michigan Medicine administrators
- Alert fatigue
- The alert and notifications may recommend a medication change that is harmful for the patient

2.2.2 Known Potential Benefits

Participation in this study will help prescribers of anticoagulants perform their job better by providing them with clinical decision support that they do not currently have. There are no current DOAC alerts or notifications in the EHR relative to prescribing other than for drug-drug interactions.

The current EHR drug-drug alerts will be improved to provide better rationale for why the drug-drug interactions exists and recommendations on how to address the problem (e.g., dose change, alterantive medication)

Patients (who are not the primary participants in the protocol) may benefit from reduced probability of having a prescription error related to DOAC medications.

2.2.3 Assessment of Potential Risks and Benefits

We assess the potential risks to be minimal. Our preliminary data shows that an overwhelming majority of prescribers are happy to receive feedback and suggestions on how to correct inappropriate DOAC prescriptions.

We assess the potential benefits to be moderate-large. Prescribers are likely to improve the evidence-based use of DOAC medications and gain knowledge about how to safely prescribe DOACs. Patients are likely to experience the benefit of evidence-based DOAC use while minimizing the risk of harm (e.g., bleeding from excessive anticoagulant effect).

2.3.4. Risk Mitigation Strategies

The likelihood of breach of confidentiality is rare. Every possible effort will be made to keep the research information in the strictest confidence. We will de-itendify all records as soon as possible. This includes the use of a dummy "ID" variable in the primary data set that requires a separate linking database to gather medical record numbers. All data will be stored on secured servers at the University of Michigan and will be password protected. Any paper records will be destroyed using University of Michigan secure processes.

Materials informing prescribers about the study will include reassurances that data will be de-identified prior to analyses, and any results shared through publications, presentations, or with administrators will only use aggregated information. They will also be reminded that existing systems used by Michigan Medicine already monitor inappropriate prescriptions for medications such as DOACs, thus the only new information being generated relates to their receipt and engagement with the alerts.

All alerts and notifications have undergone a rigorous, multi-stage user-centered design process to improve readability, actionability, and acceptability by the end users. This should minimize any alert fatigue issues.

All alert and notifications are based on FDA-approved dosing recommendations and nationally trusted sources (Michigan Anticoagulation Quality Improvement Initiative and Anticoagulation Forum). All logic has been reviewed by at least two clinical experts (anticoagulation physician and pharmacist) to ensure accuracy.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATIONS
Primary		
Determine the effect of notifications regarding existing DOAC prescriptions on prescriber behavior	The number (proportion) of notifications (in the existing-prescription notification conditions) that result in any prescription change within 7 days.	The goal of alerts and notifications is to bring about corrections in prescription errors. Given that "correct" is not always an absolute assessment, our primary outcome measure will capture any change to the DOAC prescription that results from the notification.
Secondary		
Determine the effect of alerts regarding newly prescribed DOACs on prescriber behavior	The number (proportion) of alerts (in the newly prescribed DOAC alert conditions) that result in any prescription change within 7 days.	The goal of alerts and notifications is to bring about corrections in prescription errors. Given that "correct" is not always an absolute assessment, our primary outcome measure will capture any change to the DOAC prescription that results from the notification.
	Change in magnitude of effect for the existing-prescription notification over time. This is reported on at the institution level (not individual level).	The effectiveness of notifications should be sustained over time. This measure examines longitudinal trends in effectiveness.

	(This outcome measure analysis is based on the primary outcome)	
	Change in magnitude of effect for the new-prescription alert over time, reported on at the institution level (not individual level).	The effectiveness of alerts should be sustained over time. This measure examines longitudinal trends in effectiveness.
Tertiary/Exploratory		
Determine the effectiveness of promoting pharmacist-prescriber collaboration in new DOAC prescriptions through the design of CDS alerts	The difference in outcome measures (primary and secondary outcomes) between Notification A and B conditions	While alerts are expected to reduce prescription errors, variations in alert and design to encourage pharmacy collaboration may provide added benefit
Determine the effectiveness of promoting pharmacist-prescriber collaboration in existing prescriptions through routing of DOAC prescription error notification	The difference in outcome measures (primary and secondary outcomes) between Alert 1 and 2 conditions	While notifications are expected to reduce prescription errors, automatically routing notifications to pharmacy may provide added benefit

4 Study Design

4.1 Overall Design and Scientific Rationale

This prospective randomized clinical trial will determine the effectiveness of alerts (for newly prescribed DOAC) and notifications (for existing prescriptions) in reducing prescription errors. We have two central hypotenses: (1) alerts and notifications will reduce prescription errors; and (2) involving pharmacists in the prescribing process through alerts and notifications will increase the efficacy of the alerts and notifications. These two hypotheses will be evaluated by the proportion of prescriptions that are changed following an alert (for a new prescription) or notification (for an existing prescription).

This study is 18-month prospective, randomized, controlled clinical trial of medication alerts and notifications in the ambulatory settings. See section 1.2 for an overview of the schema. Prescribers will be randomized into one of four conditions upon triggering a DOAC alert or notification (see figure 4.1-1, below).

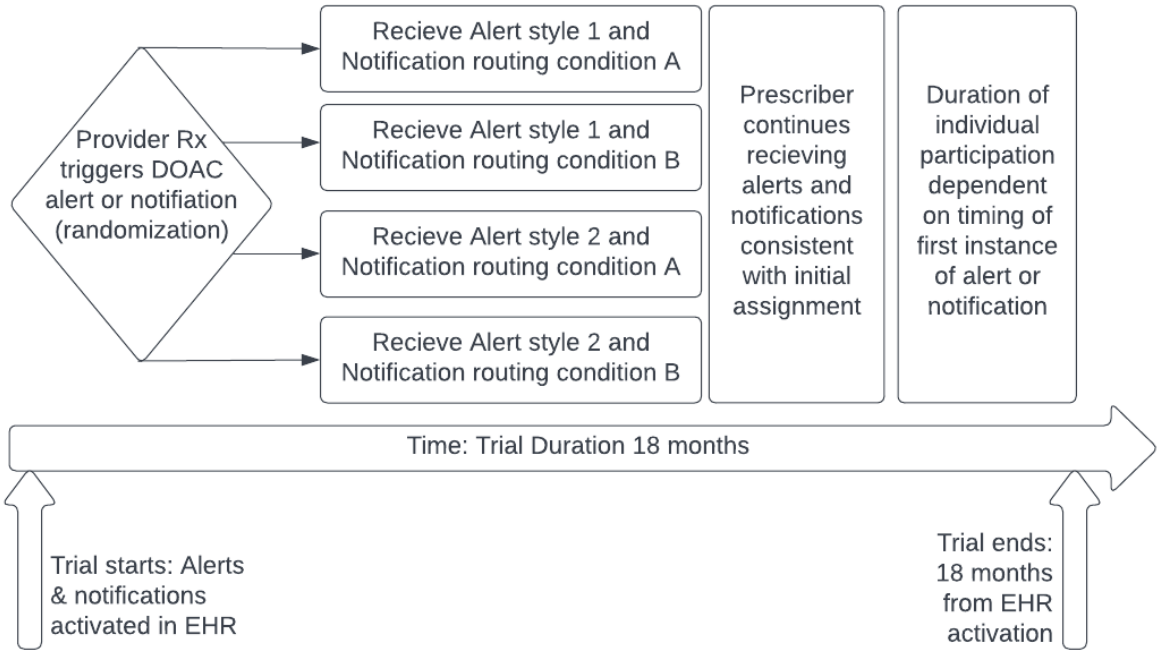


Figure 4.1-1: Timeline of trial protocol.

Alert styles 1 and 2 (for newly prescribed DOACs) will differ only in the inclusion or exclusion of a pharmacy consult (i.e. there will or will not be an option to click to automatically receive a consult). Notifications (for existing DOAC prescriptions) will differ in that the notification will either be routed directly to the pharmacist, who will then consult the prescriber if need be, or be routed to the prescriber directly.

4.2 End of Study Definition

The study will end after 18 months of the alerts and notifications being active in the EHR. The duration of any individual prescriber will vary, as an individual's participation is dependent on triggering a DOAC medication alert or notification.

We will perform a one-time interim analysis after 12 months. This will asses only for safety outcomes. We will not assess for effectiveness outcomes to avoid overestimation of the effect size for effectiveness.

5 Study Population

5.1 Inclusion Criteria

The overarching study will include all ambulatory DOAC prescriptions by a primary care clinician, cardiologist, hematology, or vascular surgeron at the University of Michigan. Within that overarching study, a randomized trial will be conducted to explore the impact of medication alerts and notifications on prescriber behavior. This observational dataset will be used for secondary analyses only to better describe the context of DOAC use within the institution.

For the randomized trial, we will enroll prescribers who meet all the following criteria

1. Michigan Medicine providers with prescribing privileges (including attending physicians, house officers, nurse practitioners, and physician assistants)
2. Prescribing DOAC to a patient in an ambulatory setting
3. Trigger a DOAC alert or notification for an ambulatory patient

5.2 Exclusion Criteria

1. Member of the study team
2. Prescriptions written in Emergency Department or hospital setting (including upon discharge)
3. Prescriptions written in a skilled nursing facility or other institutionalized setting.

The reason for the exclusions for #2 and #3 is because these prescribers typically do not follow patients longitudinally and therefore are not eligible to receive notifications when new medication prescribing issues develop *after* the initial prescription is written.

5.3 Screen Failures

N/A

5.4 Strategies for Recruitment and Retention

All prescribers using MiChart will be included in the observational data portion of the study. For the randomized trial, any prescriber of a DOAC medication will be considered for recruitment. Prescribers, not patients, are the primary subjects of this study.

Prescribers will be recruited through a message sent to MiChart users (prescribers) at least 1 week before being enrolled, as part of the regularly occurring messages to MiChart users regarding important changes and updates to MiCHart.

The message will describe the protocol, and include a link to the IRB-approved consent form. It will also inform prescribers about how to "opt-out" of the protocol by replying to the email. Any prescriber who does not “opt-out” will be included in the study through a waiver of documented informed consent as approved by the IRB. All potential participants will be contacted. Only those who prescribe an anticoagulant in a manner that triggers a medication alert will be "enrolled."

Prescribers’ participation will consist of receiving medication error alerts through MiChart as appropriate. The specific alert they receive will be randomly assigned. Note: all alerts will contain the same valid and clinically relevant warning about a potential prescribing error, and the alert will vary only as to whether or not there is a link/button to automatically consult a pharmacist. Similarly, notifications of an existing prescription (longitudinal) that triggers a medication alert will be routed initially to a pharmacist or initially to the prescriber's MiChart inbox..

6 Study Intervention

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

The intervention consists of an EHR alert that is presented to prescribers at the time that they are prescribing a DOAC, OR a notification in the EHR that indicates that an existing prescription for a DOAC does not meet the prescribing guidelines (a potential medication error). Existing prescription notifications are triggered once daily through an EHR registry that is updated continuously.

The **alerts** were designed through a user-centered design process to ensure that they are clear and usable. There will be two versions of the alerts that are identical other than except for one aspect: One alert will include a ‘button’ to click to automatically get a pharmacy consult; one will not include such a button.

The **notifications** were designed through a user-centered design process to ensure that they are clear and usable. Alerts will be identical, but will be routed one of two ways:

1. They will be routed initially to a pharmacist, who may then contact the prescriber to request/recommend a prescription change.
2. They will be routed directly to the prescriber, who may change the prescription, contact a pharmacist, or opt to keep the prescription unchanged.

6.1.2 Administration

Alerts and notificaitons will fire through automated mechanisms using best practice advisory logic and registries in the EHR, and therefore will not require intervention from the research coordinator to function properly.

The PIs will monitor announcements from the FDA regarding the drugs apixaban and rivaroxaban for announcements and label changes to ensure that alerts and notifications adhere to up-to-date guidance. Members of the study team and steering committee also help to lead the Michigan Medicine Anticoagulation Pharmacy and Therapeutics subcommittee on anticoagulation and will ensure harmonization between institutional prescribing protocols and those used in this study.

Opt-out requests will be processed by the research coordinator and relevant study team members within 7 days of the request. Upon receipt, the requesting prescriber will be entered into the EHR database such that all study-related alerts and notifications will be suppressed. Usual care activities will not be impacted if a prescriber opts out of the study alerts and notifications.

Other than changes in participation (opt out) and changes in FDA guidance regarding the relevant medication, administration of this research will be conducted through the EHR (MiChart). No direct contact between the study team and the participants is anticipated.

6.2 Acquisition and Accountability

N/A – No devices will be acquired.

6.3 Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized by computer based solely on the sampling algorithm, so unintended selection bias by the study team will not be a factor. The randomization algorithm will stratify by:

1. Trainee vs non-trainee specialist vs non-trainee pcp
2. Alert vs notification

This clinical trial is not fully blinded. Participants randomized to the different alert and notification conditions and will be blinded to the specifics of their assignment. However, they may be able to discern which condition they have been assigned to owing to the specifics of the alerts and notifications they receive. During the data analysis, study team members will be blinded to the alert and notification condition of the participants.

6.4 Study Intervention Compliance

There are no discrete participant-initiated activities associated with participation in this protocol, so compliance is not an issue. Participants will receive alerts or notifications generated by the EHR, based on their routine clinical prescribing activities. Receipt of the notification constitutes participation and compliance. Prescribers' responses to the alerts and notifications are measured as an outcome, not as compliance.

7 Study Intervention Discontinuation and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Discontinuation of a particular alerts or notification does not mean discontinuation from the study, and remaining study procedures (e.g., adverse event review) should be completed as indicated by the study protocol. If a clinically significant finding is identified after enrollment, the investigator or qualified designee will determine if any change in participant management is needed.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from the study at any time. Data collected prior to the withdrawal may be used for analysis and publications. The study coordinator will ensure that the participant is removed from the EHR's categorization to receive alerts and notification (i.e. will no longer receive alerts and notifications) within 7 business days.

An investigator may discontinue or withdraw a participant from the study at his/her discretion. The reason for participant discontinuation or withdrawal from the study will be recorded on the study team's logs. Adverse events of special interest will be collected from the time of discharge through study completion or study withdrawal/discontinuation.

Participants who are randomized and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

7.3 Lost to Follow-Up

- Participants who leave the institution or are otherwise no longer eligible to prescribe DOAC medications will be considered "lost to follow-up."
- No actions will be taken by the study team to prevent their loss to the study.
- At the end of the trial period, the study team will compare the list of enrolled prescribers against a list of potentially eligible prescribers to determine if any enrolled prescribers have left the institution. These providers status will be noted in the data. Analysis of their prescribing patterns will be included in analysis as appropriate.

8 Study Assessments and Procedures

8.1 Efficacy Assessments

Outcome Measurements:

Our **primary** outcome measure (adoption) is the proportion of DOAC notifications that lead to a change in the prescription within seven days. The denominator is the total number of DOAC prescription notifications that are sent to either the prescriber or pharmacist (per randomization). The numerator is the number of DOAC notifications that result in any change to the DOAC prescription within seven days after the notification has been sent.

Secondary

Our **secondary** outcome measure (adoption) is the proportion of DOAC alerts that lead to a change in the prescription within seven days. The denominator is the total number of DOAC prescription alerts with or without a visible option for pharmacist sonsultation (per randomization). The numerator is the number of DOAC alerts that result in any change to the DOAC prescription within seven days after the alert has occurred.

Effectiveness: We will evaluate the effectiveness of our DOAC alert system components by examining patient level 30-day clinical adverse event rates (bleeding and thrombotic). This time period was selected to minimize potential contamination from the safety review mechanism described above, and we recognize that rates for the adverse events will be low. Supplementary analyses will also examine the effect of the alert system overall on adverse events.

Clinical adverse events assessed will include major[21] and clinically-relevant non-major bleeding (CRNMB)[22] events, as defined by the International Society on Thrombosis and Haemostasis (ISTH), new or recurrent VTE events, and stroke or systemic arterial embolic events. Each of these events will be captured using health informatics tools (described below) and independently adjudicated by two expert clinicians (one pharmacist, one prescriber) who meet once in Y1 and twice in Y2 to adjudicate any potential adverse events. We will use two Michigan Medicine-developed health informatics tools, DataDirect and EMERSE,[23] to identify adverse events and capture clinical data (e.g., notes, labs, imaging, procedure reports) for adjudication. These tools allow for rapid identification of populations based on granular clinical details (e.g., demographics, diagnosis, medication use) and for textbased searches of the medical record for key terms (e.g., “bleeding”, “stroke”) across pre-defined patient populations. The adjudicators will be blinded as to which alert the patient’s prescribing clinician was randomized. Using these EHR search tools, we can also capture all ICD10 diagnosis and procedure codes for longitudinal system-level analyses. [See Appendix A for current list of ICD10 codes used.]

8.2 Implementation outcomes

Our exploratory analysis of outcomes will follow the RE-AIM implementation evaluation framework.

Reach: All alerts for unsafe DOAC use will be categorized based on the prescriber specialty and patient characteristics (e.g., demographics, comorbidities). These will be described both independently for the both the alerts and the notifications separately, as well as in aggregate. We will also examine the proportion of patients on DOACs that had alerts or notifications fire, as well as the propotion of prescribers that received alerts and/or notifications. Finally, we will examine the frequency of unsafe DOAC prescribing for prescribers who opt out of the alert system.

Adoption: In addition to our primary outcome measure of prescriber-level adoption of evidence-based DOAC prescription, secondary adoption measures will examine the frequency and clinical predictors of prescribers who dismiss the new-prescription alert or ignore the existing-prescription notification (defined as no action within seven calendar days). We will also identify the frequency and predictors of prescribers who use anticoagulation clinic pharmacist referrals in new-prescription alerts.

Implementation (including fidelity): To address how various EHR alerts impact implementation of evidence-based DOAC prescribing, we examine process measures related to prescriber and pharmacist alert and notification receipt.

For prescribers, we will examine how often they order (or do not order) the recommended medication (and whether they provide a reason when they do not order) for both new-prescription alerts and existing prescription notifications. For pharmacists, we will measure how often they respond to referrals at the time of initial prescribing or to existing-prescription notifications, as well as the time from referral/alert until the pharmacist documents a recommendation in the EHR. For existing-prescription notifications, we also will measure the time from notification until the notification is read as well as time until any DOAC prescription change or related EHR documentation occurs (automated chart abstraction using EMERSE, validated by random manual chart review) as well as the number of times a existing-prescription notification is read before being acted on.

Maintenance: To measure maintenance and sustainment, we will assess all “reach” and “adoption” outcomes after 6 and 12 months for all patients, and after 18 months for the subset of prescribers enrolled prior to the second quarter of Year 2. This will also allow us to investigate whether treatment effects for prescribers are maintained after the initial adoption.

8.3 Safety and Other Assessments

Participants (prescribers) will not undergo any procedures. Prescribers’ patients will be monitored for adverse events through the DSMB review.

DSMB will monitor for adverse events every 6 months. Adverse events will be measured up to 30 days after the alert or notification occurred. The safety outcomes being monitored by the DSMB include bleeding and thromboembolic events (including stroke and venous thromboembolism). These will be identified through diagnostic code searches within the EHR (see appendix A) and will undergo adjudication as described below.

Investigators will report serious adverse events in accordance with IRBMED requirements. The investigator will follow usual clinical practices at UM for reporting to regulatory authorities serious, unexpected events related to standard of care medications and devices.

8.4 Adverse Events and Serious Adverse Events

8.4.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward or unfavorable medical occurrence associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice) (from OHRP "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (1/15/07)"http://www.hhs.gov/ohrp/policy/advevntguid.html#Q2).

8.4.2 Classification of an Adverse Event

AEs will be graded for severity and relationship to the intervention by the investigator according to the guidelines to be specified below.

8.4.2.1 Severity of Event

The following guidelines will be used to grade severity of AEs:

Bleeding related events, as defined by the International Society on Thrombosis and Haemostasis (ISTH):

- Major,
- clinically relevant, non major
- minor

Thrombotic (stroke and venous thromboembolism):

- There will be no severity grading of thrombotic events.

Any bleeding or new thrombotic event that occurs within 30 days of a study alert or notification will be included as an adverse event.

Serious adverse events include any death or life threatening outcome. This includes ISTH major bleeding event and any new thrombotic event that occurs within 30 days of a study alert or notification.

8.4.2.2 Relationship to Study Intervention

Our protocol is intended to increase adherence to evidence based prescribing. Adverse outcomes will be assessed in relation to the degree to which prescribers adhered to evidence-based prescribing.

Use of evidence based prescribing (Appendix B) will be evaluated by blinded adjudicators (one pharmacist, one prescribing clinician) at the time of any adverse event as well as randomly selected cases. The following categories will be used:

Initially, each adverse event will be examined with regard to medication management. Cases will be classified into one of the following 5 categories:

1. **Definitely appropriate medication management** – There is clear evidence to suggest that prescribers considered the appropriate clinical factors and prescribed medication in accord with evidence based prescribing. (Example: Rivaroxaban dose changed from 15->20mg daily in a patient with atrial fibrillation, creatinine clearance 75 ml/min, and no drug drug interactions)

2. **Probably appropriate medication management** – There is some evidence to suggest that prescribers considered the appropriate clinical factors and prescribed medication in accord to evidence based prescribing. (Example: Rivaroxaban dose changed from 15->20mg daily in a patient with atrial fibrillation, creatinine clearance of 51ml/min [previously 48 ml/min], and no drug-drug interactions)

3. **Probably inappropriate medication management** – There is some evidence to suggest that the prescriber may have deviated from evidence based prescribing. (Example: Rivaroxaban dose changed from 15->20mg daily in a patient with atrial fibrillation, creatinine clearance of 48 ml/min [previously 55 ml/min], and no drug-drug interactions)

4. **Definitely inappropriate medication management** – There is clear evidence to suggest that the prescriber deviated from evidence based prescribing. (Example: Rivaroxaban dose changed from 15->20mg daily in a patient with atrial fibrillation, creatinine clearance of 35 ml/min, and no drug-drug interactions)

5. **Unable to assess appropriateness of medication management**: Due to lack of information in the medical record, it is not possible to assess the appropriateness of the medication management.

Adverse events that are classified in the Medication Management categories 3, 4 or 5 above will then be reviewed with regard to whether the adverse event is related to the prescription. The following 5 categories will be used:

A. **Definitely not related**–The clinical event, despite occurring in a plausible time relationship to study intervention administration, can be explained by concurrent disease or mechanism, or other other drugs or chemicals, or is a non-preventable medication adverse event.

B. **Probably not related** –The clinical event, despite occurring in a plausible time relationship to study intervention administration, is **more likely than not** explained by concurrent disease or mechanism, or other other drugs or chemicals, or is a non-preventable medication adverse event.

C. **Probably related** – It is **more likely than not** that a causal relationship exists between the adverse event and the prescription. However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events).

D. **Definitely related** –There is no significant evidence that suggests other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

E. **Unable to assess relatedness of medication management**: Due to lack of information in the medical record, it is not possible to assess the relationship between the adverse event and the prescription.

Adverse events that are classified into categories of C, D, or E (as well as categories 3, 4, and 5) will be reviewed by the DSMB. This includes all cases in which the medication management was more likely than not inappropriate medication management, and adverse events which are more likely than not related to the medication. It also includes all cases where the medication management and the relationship of the medication to the adverse event is unknown.

All adverse events (serious and non-serious) will further be assessted based on the time from medication error until the adverse event occurred. This will be done to determine if the 15 day embargo on the existing dashboard may have contributed to patient harm. Specifically, we will look to see if medication alerts or notifications were not addressed through the study interventions that may have been addressed via the dashboard if no embargo were in place.

8.4.3 Adverse Event Reporting

All reporting comply with Michigan Medicine IRB guidelines (https://az.research.umich.edu/medschool/guidance/adverse-event-reporting).

Any serious adverse event that are adjudicated as being definitely or possibly related to the study intervention will be reported to the IRB within 7 calendar days of the study team becoming aware of the event.

All non-serious adverse events that are adjudicated as being definitely or possibly related to the study intervention will be reported to the IRB in aggregate at least annually.

All serious adverse events that are adjudicated as being definitely or possibly unrelated to the study intervention will be reported to the IRB in aggregate at least annually.

All non-serious adverse events that are adjudicated as being definitely or possibly unrelated to the study intervention will be collected for analysis but not reported to the IRB.

All adverse events in which the adjudication team is unable to assess the relatedness to the study intervention will be reported to the IRB in aggregate at least annually.

8.4.4 Reporting Events to Participants

Not applicable

8.5 Unanticipated Problems

8.5.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.5.2 Unanticipated Problem Reporting

The investigator will report unanticipated problems (UPs) to the reviewing institutional review board (IRB) and to the DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are adverse events will be reported to the IRB and to the study sponsor within 24 hours of the investigator becoming aware of the event.
- Any other UP (e.g., study protocol deviations) will be reported to the IRB and to the study sponsor within 2 weeks or 10 business days of the investigator becoming aware of the problem.

8.5.3 Reporting Unanticipated Problems to Participants

Not applicable.

9 Statistical Considerations

9.1 Sample Size Determination

This study is powered for our primary comparison, which is the comparison of our two different notitifications. We will use mixed-effects binary logistic regression to model the proportion of inappropriate DOACs that are changed within 7 days following an alert.

We anticipate randomizing 300 prescribers to different notifications over the course of the study, allowing for a main effect comparison of 150 prescribers randomized to each of Notification A vs. B. This estimate for prescribers is pulled from 2019 preliminary data indicating Michigan Medicine had more than 1000 unique DOAC prescribers, and a one-day pull in February 2020 that indicated more than 250 prescribers on that day had one or more patients currently receiving an inappropriate DOAC, thus eligible for randomization to a longitudinal notificaiton. For our secondary aim, examining the main effect of alerts, we also anticipate randomzing 300 prescribers to initial prescription alerts over the study period, or 150 to each of Alert 1 and Alert 2, respectively.

For our patient-level main effects analyses, we estimate that prescribers will average 2 patients that trigger an inappropriate DOAC alert over the 12-month trial period. As of June 14, 2022, Michigan Medicine currently has 11,590 patients receiving a DOAC. Pilot data indicates that about 40% of prescribers changed prescriptions following an notication that did not involve a pharmacist; notificaitons that did involve pharmacists resulted in change approximately 60% of the time. Using a base rate of 40% and assuming a patient n=600, alpha of 0.05 and prescriber-level ICC of 0.1, we will have 80% power to detect a difference in proportions of 0.12 (or 40% vs. 52%).Table 3 shows power for several other risk ratios, baseline rates, and number of patients per prescriber. All estimates were computed in Stata 17.

Table 3. Power Calculations (Prescriber N=300)

Table 3. Power Calculations (Prescriber N=300)				
Patient n=2	**Base Proportion**			
Risk Ratio	**0.3**	**0.4**	**0.5**	**0.6**
1.2	32%	47%	65%	84%
1.3	44%	63%	83%	96%
1.4	67%	87%	98%	>99%
1.5	84%	97%	>99%	>99%
1.6	94%	>99%	>99%	>99%
Patient n=3				
Risk Ratio				
1.2	42%	60%	79%	94%
1.3	74%	91%	99%	>99%
1.4	93%	>99%	>99%	>99%
1.5	>99%	>99%	>99%	>99%
1.6	>99%	>99%	>99%	>99%

For our secondary prescriber-level outcomes, we will have 94% power to detect a difference in proportions of 0.4 to 0.6. For longitudinal outcomes (e.g., maintenance), this calculation is conservative as it does not account for repeated measures. For our clinical effectiveness secondary outcome, we will have 63% power to detect a difference of 1% vs. 0.5% in adverse event rates for each factor, again assuming 300 prescribers with an average of 2 patients each, and assuming a prescriber-level ICC of 0.03 (for clinical adverse events). A less conservative estimate of 3 patients per prescriber increases this power to 79%

For our exploratory moderation analyses, described below in Section 9.3.5, again assuming 300 prescribers with 2 patients each and an ICC of 0.1, we will have 80% power to detect a minimum effect size of 0.34 for our binary prescriber-level moderators, using a two-sided test with [alpha] = 0.05. If our average number of patients per prescriber is 3, this minimum detectable effect size decreases to 0.29 under the same assumptions. For our binary cross-level (patient-level) moderators, assuming a non-randomly varying slope, with an average of 2 patients per prescriber, we will have 80% power to detect a minimum effect size of 0.34; assuming 3 patients per prescriber decreases this minimum detectable effect size to 0.27. Minimum detectable effect sizes for cross-level moderators that also include a random slope are slightly larger at 0.36 and 0.28 respectively

9.2 Populations for Analyses

Our population for analysis is prescribers of DOACs for ambulatory patients. All eligible participants will be randomized. (Randomization by prescriber, not by patient.) All randomized participants who received an intervention will be included in safety analyses. All analyses, primary or secondary, will be reported by sex/gender and race/ethnicity as reported in the EHR.

9.3 Statistical Analyses

9.3.1 General Approach

The main effect analyses will allow us to determine the impact of different alert- and notification types on evidence-based DOAC prescribing in both newly prescribed DOAC prescriptions and existing DOAC prescriptions in order to understand under what contexts prescriber-pharmacist collaboration is an effective implementation strategy. In both our primary and secondary outcomes, our analyses will compare the main effects of each intervention, i.e., new prescription alerts (Alerts 1 vs 2) and existing-prescription notifications (Notifications A vs B), to determine which are most effective. For both interventions, the outcome of interest will be whether the patient whose prescription triggered the alert/notification (i.e., is receiving a non-evidence based DOAC) has their prescription changed following the alert or notification.

For the primary intervention outcome (existing-prescription notifications), main effect analyses will compare the proportion of patients receiving an evidence-based DOAC prescription within seven business days following the notification between prescribers randomized to receive the notifications themselves vs. prescribers for whom notifications were sent directly to anticoagulation clinic pharmacists.

For the secondary intervention outcome (new DOAC prescription alerts), main effect analyses will compare the proportion of patients receiving an evidence-based DOAC seven business days following the notification between prescribers randomized to receive enhanced alerts vs. enhanced alerts plus pharmacist referral.

The treatment interaction will allow evaluation of whether certain alerts and notifications work better when provided in tandem.

The main outcome analysis will use mixed-effects logistic regression models to account for the binary patient-level outcome variable of evidence-based DOAC receipt after an alert. The two treatment factors and their interaction will be included as fixed effects, as well as any stratification variables and baseline patient- and/or prescriber-level characteristics that are unbalanced. A prescriber-level random effect will account for patient clustering within prescribers, and an unstructured covariance matrix will be used for residual errors. Similar mixed-effects regression analyses will be conducted for secondary outcomes, adapted for different outcome measures or levels of analysis.

Missing Data. Patients will contribute primary outcome data through EHRs as long as they stay with Michigan Medicine. Patient attrition due to leaving Michigan Medicine also discontinues the ability for their Michigan Medicine prescribers or pharmacists to affect their medication prescription, so does not induce missing data under intent-to-treat principles. Similarly, data on prescribers (e.g., secondary outcome/process data) will continue to be captured via EHR as long as they are employed at Michigan Medicine. Prescribers that leave Michigan Medicine during the study will be lost to follow-up; however, the Michigan Medicine prescriber population (attending physicians, nurse practitioners, and physician assistants) is generally quite stable and, given the nature of the intervention, we expect attrition to be entirely unrelated to treatment assignment. House officers, while less stable in longevity, do have predictable start and stop dates for patient care, such that missingness is predictable and not related to

treatment. Proposed mixed-effects analyses produce valid inferences for data that is missing at random, and multiple imputation will be used as appropriate. If multiple imputation is employed, all analyses will be performed with and without imputed data. Further sensitivity analyses will evaluate robustness of results under informative missingness scenarios, as appropriate.

9.3.2 Analyses Of Primary Outcomes

The primary outcome will be the number (proportion) of prescriptions triggering notifications that were changed within 7 days, among all prescriptions that triggered a notification.

As noted in the general approach, for the primary factor (existing-prescription notifications), main effect analyses will compare the proportion of DOAC prescriptions that were changed within seven business days following the notification between prescribers randomized to receive the notifications themselves vs. prescribers for whom notifications were sent directly to anticoagulation clinic pharmacists.

9.3.3 Analyses Of Secondary Outcome

Secondary outcomes will be the number (proportion) of new DOAC prescriptions triggering alerts that were changed within 7 days, among all prescriptions that triggered an alert.

As noted in the general approach, for the secondary outcome factor (new DOAC prescription alerts), main effect analyses will compare the proportion of DOAC prescriptions that were changed within seven business days following the notification between prescribers randomized to receive enhanced alerts vs. enhanced alerts plus pharmacist referral.

9.3.4 Analyses Of Implementation

Reach: To assess reach, we will examine the proportion of patients on DOACs that had alerts or notifications fire, as well as the propotion of prescribers that received alerts and/or notifications. To futher understand reach, we will also report the proportion and clinical predictors of prescribers who dismissed alerts or notififcations (defined as no action within seven calendar days). We will also identify the proportion and predictors of prescribers who used anticoagulation clinic pharmacist referrals in new-prescription alerts. We will also categorize all DOAC alerts based on prescriber and patient characteristics (e.g., demographics, comorbidities).

Effectiveness: Analysis of Effectiveness will be the focus of the primary and secondary outcome measures (as noted above). We will evaluate the effectiveness of our DOAC alert system components by examining patient-level clinical adverse event rates (bleeding and thrombotic) within 30 days of triggering the alert. This time period was selected to minimize potential contamination from the safety review mechanism described above, and we recognize that rates for the adverse events will be low.

However, as a T4 implementation study, the primary goal is implementing the evidence-based practice for which efficacy is already established. Supplementary analyses will also examine the effect of the alert system overall on adverse events.

Clinical adverse events assessed will include major[21] and clinically-relevant non-major bleeding (CRNMB)[22] events, as defined by the International Society on Thrombosis and Haemostasis (ISTH), new or recurrent VTE events, and stroke or systemic arterial embolic events objectively identified by imaging and identified as a new event by their primary clinical provider. Transient Ischemic Attacks (TIAs) that do not result in findings on imaging (such as CT or MRI) will not be included. Each of these events will be captured using health informatics tools (described below) and adjudicated every six months. Adjudication will occur at least one month prior to six month DSMB meetings to allow for the DSMB to review findings in advance of the meeting. We will use Michigan Medicine-developed health informatics tools to create a report that identifies all patients whose prescribers have received an alert or notification and any adverse event diagnosis codes within 30 days thereafter. These cases will then be reviewed by the adjudicators to determine if an adverse event occurred and if it was associated with medication management, as defined in Section 8.4.2.2. The adjudicators will have access to all laboratory and medication data as well as clinical notes, but will be blinded to group allocation. The report, created by Michigan Medicine health informatics research team, will undergo a validation process for accuracy by the study team leads, including a cardiovascular physician and pharmacist.

Implementation (including fidelity): To address how various EHR alerts impact implementation of evidence-based DOAC prescribing, we examine process measures related to prescriber and pharmacist alert receipt. For prescribers, we will examine how often they order (or do not order) the medication recommended by the alerts (and, for the latter, whether they provide a reason) for both new-prescription alerts and existing-prescription notifications. For pharmacists, we will measure how often they respond to referrals at the time of initial prescribing or to existing prescription notifications, as well as the time from referral/alert until the pharmacist documents a recommendation in the EHR. For existing prescription notifications, we also will measure the time from notification until the notification is read as well as time until any DOAC prescription change or related EHR documentation occurs as well as the number of times a existing-prescription notification is read before being acted on.

Maintenance: To measure maintenance and sustainment, we will assess all “reach” and “adoption” outcomes after 6 and 12 months for all patients, and after 18 months for the subset of prescribers enrolled prior to the second quarter of Year 2 (approximately N=225, or 75% of the total prescriber enrollment). This will also allow us to investigate whether treatment effects for prescribers are maintained after the initial adoption.

Other implemention outcomes: We will also estimate the resource utilization by the pharmacists using a combination of EHR tool tracking (measured in hours) and self-reported weekly hours dedicated to study activities using a study provided tracking sheet similar to those used in our prior implementation trials (R01MH099898; R01MH114023).

9.3.5 EXPLORATORY ANALYSIS

Interrupted time-series analyses (comparison to usual care).
While our trial and analyses are designed to determine the best approach for improving evidence-based DOAC prescribing through EHR alerts via comparative effectiveness analyses, observational analyses can also evaluate the impact of the introduction of the DOAC EHR alert system overall on patient receipt of evidence-based DOACs, relative to prior to the trial. Using EHR data, we will compute the proportion of patients that were receiving an inappropriate DOAC for each quarter, starting 24 months prior to randomization and continuing 18 months after randomization. Interrupted time series analyses (ITSA) will then be used to compute the change in inappropriate DOAC prescriptions, pre- and post-system introduction, to determine whether the system implemented via the trial resulted in a significant decline in patients on inappropriate DOACs. We will also assess for system-level changes in adverse event rates, as defined in the Measures section. As a further check on changes in DOAC prescribing behaviors in response to the alerts and/or increased prescriber-pharmacist collaboration, we will also use ITSA models to assess for changes in the rate of new-prescription alerts (per total number of DOACs prescribed) over the 18-month study period, relative to the 24-month period prior to study start.

Moderator analyses.
Moderator analyses will be used to help pinpoint the prescriber- and patient-characteristics that most benefit from alerts designed to facilitate prescriber-pharmacist collaboration for both the new-prescription alerts and existing-prescription notifications. We hypothesize that for both new-prescription alerts and existing-prescription notifications, alerts and notifications that engage pharmacists will be more effective at improving patient receipt of evidence-based DOACs for prescribers that (1) are based in primary care vs. medical specialists and/or (2) have prescribed fewer DOACs in the six months preceding randomization; and for patients that (1) are aged 70+; (2) have a VTE (as opposed to AF) diagnosis, as the former has more complex dosing that many clinicians are less familiar with; (3) have 5+ concurrent medication prescriptions; and/or (4) have moderate or worse renal function (creatinine clearance ≤ 60 ml/min). Moderators will be assessed by adding interaction effects between the treatments and the moderator(s) of interest to the primary analysis model described above. All tested moderators will be reported and those that show both clinical and statistical significance will be considered for use in tailoring alert delivery.

Sensitivity analyses.

Carryover effects for new-prescription alerts: Primary analyses will be conducted as intent-to-treat analyses among prescriber-patient dyads for whom an alert was triggered. This allows investigation of the best types of alerts given the need for an alert. However, for new-prescription alerts, it is also possible that alerts that include the option for pharmacist referral vs. those that don't also differentially affect how many future DOAC prescribing errors are made. Specifically, prescriber-pharmacist collaboration may provide the prescriber with new knowledge about evidence-based DOAC prescribing that could be applied to future DOAC prescriptions, avoiding the occurrence of an alert altogether. To

explore these effects, we will also evaluate the main effect of the two new-prescription alerts on the proportion of DOAC patients that receive a new prescription for an evidence-based DOAC using the model described above, but including all patients to whom they prescribed a DOAC from the point they received their first new-prescription alert through the end of the 18-month study period. This will allow us to evaluate whether correct DOAC prescribing improved overall by type of new-prescription alert.

Treatment-as-received analyses: In line with intent-to-treat clinical best practices, prescribers will be randomized to both types of alerts at the time of their initial receipt of either type of alert. This approach was chosen for both good clinical practice and pragmatic reasons, but also with the support of our preliminary data, which showed that on one day, more than 1/4 of Michigan Medicine prescribers had one or more DOAC patients receiving a non-evidence-based prescription (see Power and Sample Size, above). There is a possibility that during trial period, some prescribers will only ever receive one type of alert, never exposed to their second randomized treatment—i.e., they made an initial prescribing error but never had a DOACreceiving patient need a change in prescription, or vice versa. While we believe that this will be the case for only a minority of enrolled prescribers, sensitivity analyses will examine treatment-as-received effects and will re-assess main effects for the two factors including only patients for prescribers who received that type of alert.

Changes in patient population: While unlikely, it is also possible that a prescriber's patient panels may change directly or indirectly as a result of their assigned treatment. To account for this, sensitivity analyses will also rerun models including only patients that were affiliated with the prescriber prior to randomization.

9.3.6 Safety Analyses

The number of and proportion of participants with SAEs and non-serious AE'swill be presented, overall, and by randomization group. These presentations will be descriptive, with no formal inferential methods used.

If the number of adverse events reaches a statistically significant level at $p<0.01$ as compared to other arms of the study, the trial may be halted or otherwise modified as appropriate at the time of DSMB review.

10 Supporting Documentation and Operational Considerations

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/assent and Other Informational Documents Provided to participants

IRB approved information sheets describing in detail the study intervention, study procedures, and risks are made available for the participant. Written documentation of informed consent is not required prior to starting the study intervention (waiver of documentation of consent approved by IRB).

10.1.1.2 Consent Procedures and Documentation

The IRB has approved a detailed information sheet which will be provided to all eligible prescribers simultaneously through an electornic mail notification (weekly Epic notice sent to all Michigan Medicine clinicians). Participants will have the opportunity to carefully review the information sheet (available through a link on the weekly Epic electronic mail notification) and ask questions for at least 7 days before potentially being enrolled. For the randomized trial component of the study, enrollment occurs when prescriptions written by the individual trigger a medication alert or notification in the EHR. Participants are informed in writing that participation is voluntary and that they may withdraw from the study at any time, without prejudice.

If the protocol is amended and requires a change in the consent form, determination of whether a participant is re-consented will be based on IRB discretion.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform study participants, the IRB, and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and/or the IRB.

The role of the DSMB to advise suspension, resumption, and termination of the study is detailed below.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, DSMB, representatives of the IRB, and regulatory agencies may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participants' contact information will be securely stored for internal use during the study in a password protected file on a secure University of Michigan server. At the end of the study, all records will continue to be kept on a secure University of Michigan server for at least 3 years beyond the completion of the study.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be stored on secure servers at the University of Michigan.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored on a secure server at the University of Michigan. After the study is completed, the data will be de-identified and archived for a minimum of 6 years. Details shared with prescribers about data retention and use is included in the IRB-approved information sheet.

10.1.5 Key Roles and Study Governance

Principal Investigator	**Principal Investigator**
Geoffrey Barnes, MD, MSc	Shawna Smith, PhD
University of Michigan	University of Michigan
Frankel Cardiovascular Center and Institute for Healthcare Policy and Innovation 2800 Plymouth Rd, B14 G214 Ann Arbor, MI 48109-2800, USA	Department of Health Management and Policy School of Public Health University of Michigan 1415 Washington Heights Ann Arbor 48109
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10.1.6 Safety Oversight

Safety oversight will be under the direction of an internal Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including members with expertise in cardiology, statistics, pharmacy, and/or research ethics. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet twice a year to assess safety and efficacy data on each arm of the study. The DMSB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. The DSMB will provide its input to the sponsor (AHRQ), the PIs, and the governing IRB at the University of Michigan through a report issued after each meeting.

The DSMB will act in an advisory capacity to the study team, the IRB, and the sponsor (AHRQ) to monitor patient safety and data quality. They will review the study protocol, monitor all aspects of the study (e.g., recruitment, adverse events, protocol adherence, data quality, attrition, demographic and baseline characteristics) and recommend protocol modifications, including early study termination. All proposed changes to the study protocol will be reviewed by the DSMB.

In the event that the DSMB believes the study should be suspended or terminated due to safety or data management concerns, the DSMB will make a specific and written recommendation to the study investigators, sponsor (AHRQ), and IRB. In the case of a temporary suspension, the DSMB will subsequently make a written recommendation to the study investigators, sponsor, and IRB prior to resuming study activities.

Reports will be prepared by the PIs prior to each meeting of the DSMB. These will minimally include recruitment, adherence, attrition, adverse events, data quality, and descriptive characteristics of the study sample both in aggregate and according to randomization assignment (unblinded if specifically requested by the DSMB). The DSMB will meet at least twice a year via teleconference/webinar to review the cumulative data. A recording secretary will be available for all DSMB meetings. The sponsor or the chairman of the DSMB in consultation with the sponsor may convene additional meetings. Based on the data presented, the DSMB will make recommendations including continuation or termination of the study.

A report containing the recommendations for continuation or modification of the study will be prepared. The draft report will be sent to the DSMB members for review and approval no later than three weeks after the meeting. It is the responsibility of the Principal Investigator to distribute the DSMB recommendation to all co-investigators and to ensure that copies are submitted to the IRB that reviewed and approved the study documents.

10.1.7 Data Handling and Record Keeping

10.1.7.1 Data Collection and Management Responsibilities

The investigator is responsible for ensuring the accuracy, completeness, and timeliness of the data reported. Clinical data (including adverse events (AEs), concomitant medications, and specific prescribing data) and clinical laboratory data will be stored on HIPAA compliant servers provided by the Michigan Clinical Outcomes Research and Reporting Program (MCORRP) using password-protected CSV files.

10.1.7.2 Study Records Retention

Paper and electronic data for the study will be retained for at least 3 years after the study ends.

10.1.8 Protocol Deviations

All protocol deviations (e.g., data breach, receipt of incorrect alert or notification) that significantly impact the integrity of the study or subject safety must be reported within 7 days through IRBMED. Any event that requires immediate action will be brought to the attention of the IRB Chair. Events that meet the criteria of serious and/or continuing noncompliance will be communicated to IRBMED.

10.1.9 Publication and Data Sharing Policy

AHRQ policy requires that unique research data be made available to the scientific community after the conclusion of a study. In accordance with NIH NOT-OD-16-149 and DHHS rule 81 FR 64922, our trial is registered with clinicaltrials.gov [ClinicalTrials.gov Identifier: NCT05351749]. We report our results to clinicaltrials.gov as well as present our findings through conventional dissemination routes like publications and presentations at specialty societies.

Resource sharing may include sharing of study documents (e.g., recruitment materials, protocols, SOPs, and informed consents that may be useful as starting points for other studies).

10.1.10 Conflict of Interest Policy

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

None

10.3 Abbreviations

AE	Adverse Event
AF	Atrial Fibrillation
AESI	Adverse Event of Special Interest
AHRQ	Agency for Healthcare Research and Quality
CDS	Clinical Decision Support
CFIR	Consolidated Framework for Implementation Research
CFR	Code of Federal Regulations
DOAC	Direct Oral Anticoagulant
DSMB	Data and Safety Monitoring Board
EHR	Electronic Health Record

ERIC	Expert Recommendations for Implementing Change
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IQR	Interquartile Range
IRB	Institutional Review Board
IRBMED	Institutional Review Board for Michigan Medicine
ISTH	International Society on Thrombosis and Haemostasis
MAQI^2	Michigan Anticoagulation Quality Improvement Initiative
MiChart	EHR used in Michigan Medicine
MOP	Manual of Procedures
NIH	National Institutes of Health
NHLBI	National Heart Lung and Blood Institute
OHRP	Office for Human Research Protections
PHI	Patient Health Information
PI	Principal Investigator
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood pressure
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
VTE	Venous thromboembolism

10.4 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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12 APPENDICES

Appendix A: < ICD10 diagnosis and procedure codes for longitudinal system-level analyses >
[This appendix will be included and updated in coordination with or data analyst, as needed.]

Appendix B: Appropriate DOAC prescribing guidelines