Anticoagulation with Enhanced Gastrointestinal Safety (AEGIS): A pilot quality improvement trial to evaluate clinician- and patient-facing strategies to reduce upper gastrointestinal bleeding risk in patients on combination antithrombotic therapy

Protocol Number: 1.0
National Clinical Trial (NCT) Identified Number: NCT05085405
Principal Investigator: Jacob E. Kurlander, MD, MS
Sponsor: NIDDK
Grant Title: Using Intervention Mapping and the Multiphase Optimization Strategy to Develop Multilevel Interventions to Prevent Upper GI Bleeding
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Version Number: v.1.5
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AMENDMENTS

Date	Version	Section(s)	Changes
9/22/2021	V.1.1	1.1 7.1.1 7.2.2 9.1	Protocol was amended to remove all mentions of the anticoagulation clinic LPN and RN and revise language to show that anticoagulation clinic nursing staff (RN or LPN) will deliver the quality improvement strategies for this study. The language about the role of the LPN and the RN are being removed following feedback from the clinic staff about LPN staffing shortages (e.g., maternity leave, part-time staff) and concerns about the feasibility of the LPN having the time and bandwidth to deliver the strategies in the desired timeframe. However, as it is possible that either LPNs or RNs may deliver these strategies while covering for other staff members, the language in the protocol was revised to be inclusive of all anticoagulation clinic nursing staff.
10/13/2021	V.1.2	1.1 1.3 6.1 6.4 9.1 9.2.1	Protocol was amended to reflect an increase in clinician and patient participant enrollment numbers. The number of clinician participants was increased from 10 to 12 in order to allow for a balanced number of cardiologists and non-cardiologists to be included in each clinician-facing intervention arm. As all eligible patients cared for by a clinician participant will be included in this pilot trial, the number of patient participants increased as a result of the increase in clinicians. All informed consent documents for clinician and patient participants have been revised to reflect this increase in enrollment.
11/04/2021	V1.3	1.1 1.2 1.3 2.1 4 5.1 5.2 7.1.1 7.3	Protocol was amended to reflect a semantic name change for the more resource-intensive clinician-facing implementation strategy. The “clinician notification and information relay” implementation strategy was renamed to “clinician notification and nurse facilitation” following feedback from topic experts in the implementation science field.
1/26/2022	V.1.4	1.1 1.4 2.2	Protocol was amended to reflect the addition of participant group 2, a convenience sample of 8 primary care clinicians and their eligible patients, and

		2.3 3.1 3.2 4 5.4 6.1 6.2 6.3 6.4 6.6 7.2 8.1 8.2 8.3 9 11 12.1	the outcomes being assessed for group 2 participants. This group was added to the study to elicit feedback from this specialty group about the feasibility and appropriateness of the implementation strategies after only 1 primary care clinician was included in group 1 and did not respond to invitations to participate in the qualitative research interview. Protocol was additionally amended to change the timing of assessment #3 for group 1 patient participants from week 9-12 to week 15-17.
3/31/2022	V.1.5	1.1 2.3 4.2 9.4.2 9.7 11.2.1 11.4.2 11.5.2	Protocol was amended to clarify that all endpoints associated with group 2 participants are exploratory endpoints, and no primary or secondary endpoints will be evaluated or uploaded to clinicaltrials.gov for this participant group.

STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with research best practices, applicable United States Code of Federal Regulation, and the terms and conditions of the sponsor. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All research personnel involved in the conduct of this study have completed Human Subjects Protection and research best practices training.

1 PROTOCOL SUMMARY

1.1 Synopsis

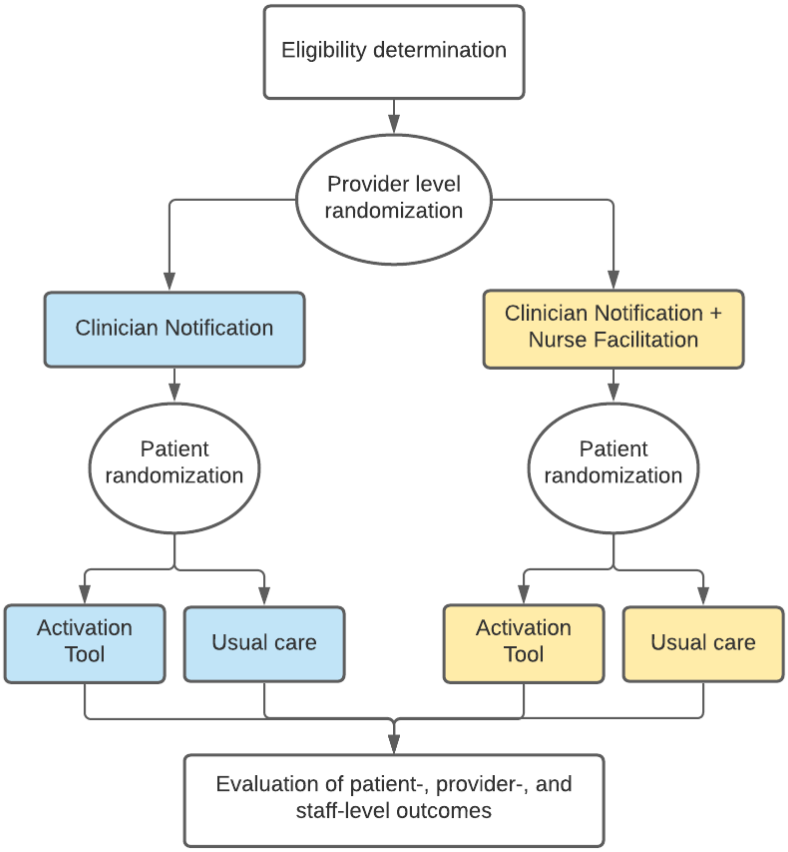
Title:	Anticoagulation with Enhanced Gastrointestinal Safety (AEGIS): A pilot quality improvement trial to evaluate clinician- and patient-facing strategies to reduce upper gastrointestinal bleeding risk in patients on combination antithrombotic therapy
Grant Number:	K23 DK118179
Background	Patients who use an anticoagulant together with an antiplatelet drug (combination antithrombotic therapy, or CAT) are at increased risk for serious bleeding, which most commonly occurs in the gastrointestinal tract. For patients on CAT, there are two evidence-based medication optimization strategies to reduce upper gastrointestinal (GI) bleeding risk. Many of these patients may safely discontinue the antiplatelet drug. For patients who must continue the antiplatelet drug, proton pump inhibitors (PPIs) effectively reduce upper GI bleeding risk. Both of these strategies are underused. The aim of this trial is to evaluate the feasibility of conducting a future large-scale randomized quality improvement trial of quality improvement (QI) implementation strategies to increase medication optimization for patients on CAT at high risk for upper GI bleeding.
Study Population:	Group 1: Quality improvement strategy components will be directed at both patients and clinicians. Patients will be eligible for inclusion if they are prescribed warfarin and an antiplatelet drug without a PPI and are enrolled in the Michigan Medicine anticoagulation monitoring service. See section 6.1 for additional inclusion and exclusion criteria. Clinicians will be eligible for inclusion if they are the clinician of record for a patient meeting inclusion criterion (i.e., the clinician who receives routine communications from the anticoagulation service), or if they are a cardiologist who has had a visit with the patient in the prior year. We anticipate including 12 clinicians and 51 patients. All participating anticoagulation clinic staff, who will deliver the QI strategies, will also be included to assess their perceptions of program feasibility and acceptability. Group 2: Quality improvement strategy components will be directed at both patients and clinicians. Patients will be eligible for inclusion if they are prescribed warfarin and an antiplatelet drug without a PPI, are enrolled in the Michigan Medicine anticoagulation monitoring service, and have a physician in Group 2 as their clinician of record for the anticoagulation clinic. See section 6.1 for additional inclusion and exclusion criteria.

	Clinicians will be eligible for inclusion if they are the clinician of record for a patient meeting inclusion criterion (i.e., the clinician who receives routine communications from the anticoagulation service), and are a primary care specialist. We anticipate including 8 primary care clinicians and 8-16 of their patients.
Study Description:	The study is designed as a pilot cluster randomized quality improvement trial. For each patient, a target clinician will be identified, defined as either a cardiologist at Michigan Medicine, if the patient has seen one in the past year, or else the clinician of record on file with the anticoagulation service. For each patient, assignment to one of two clinician-level QI strategies will be done at the cluster level according to the identity of the target clinician. Each clinician (cluster) will be randomized 1:1 to receive either clinician notification (consisting of a notification message sent in the electronic health record) or clinician notification + nurse facilitation (consisting of a similar notification, but which additionally includes provision of clinically relevant information identified on chart review, along with other steps to facilitate appropriate care). Separately, patients will be individually randomized to receive an activation guide that provides patient education and encouragement to discuss medication optimization with their clinicians, or to usual care. Following delivery of the QI strategies, patients, clinicians, and anticoagulation staff will be invited to participate in semi-structured interviews about their experiences with and perceptions of the QI strategies.
	Group 1: Primary Objective: To explore the feasibility of patient participation in a one-time assessment of medication use following delivery of the QI strategies. **Group 1: Secondary Objectives:** To explore the feasibility of delivering QI strategy components to clinicians and patients as intended. **Group 2: Primary Exploratory Objective:** To explore the feasibility and appropriateness of the QI strategies from the perspective of primary care clinicians to inform a future clinic-wide trial.
Endpoints*:	**Group 1: Primary Endpoint**: The proportion of randomized patients who complete a brief phone assessment (patient assessment #1) at week 5. **Group 1: Secondary Endpoints**: The proportion of patients and clinicians who received the QI strategies to which they were randomized. **Group 1: Exploratory Endpoints**: Multiple additional quantitative endpoints will be evaluated, as documented in the section 4 of the protocol.

	Group 2: There is no quantitative endpoint. The primary exploratory objective is to conduct a qualitative evaluation of primary care providers' perceptions of the intervention strategies. **Group 2 Exploratory endpoints:** Multiple exploratory endpoints will be evaluated, as documented in section 4.
Phase or Stage:	This project is a pilot feasibility quality improvement trial.
Description of Sites/Facilities Enrolling Participants:	Participants will be included from a single site (the Michigan Medicine anticoagulation monitoring service in Ann Arbor, Michigan, USA).
Description of Study Intervention/Experimental Manipulation:	**Quality improvement implementation strategies to be delivered:** Two clinician-facing QI strategies will be evaluated, both of which are intended to assist the clinician in making an appropriate decision to optimize patients' medications: 1. **Clinician Notification:** A protocol-driven QI strategy in which an anticoagulation clinic nurse sends a templated message to the patient's target clinician that identifies the patient as high risk for upper GI bleeding, summarizes options for medication optimization, and asks that the clinician manage any medication changes. 2. **Clinician Notification +Nurse Facilitation:** A protocol-driven QI strategy in which an anticoagulation clinic nurse sends a templated message to the patient's target clinician, similar to clinician notification, but which also includes clinical information about the patient identified by the nurse during chart review, along with a concise evidence summary relevant to the patient. In addition, once clinicians decide on a medication optimization plan, the nurse will facilitate execution of the plan and communicate recommendations to the patient. Two patient-facing strategies s will be evaluated: 1. **Patient Activation Guide:** A guide to educate patients about their risk for bleeding and activate them to talk with their clinician about medication changes to reduce their bleeding risk. 2. **Usual care:** No additional education or activation strategies outside of usual care will be included.
Assessments	Group 1: Semi-structured interviews will be conducted with patients, clinicians, and anticoagulation staff to evaluate perceptions of the QI strategies, as described in the body of the

	protocol. Data will also be extracted from the medical record at multiple timepoints. Group 2: Semi-structured interviews will be conducted with primary care clinicians to evaluate perceptions of the QI strategies, as described in the body of the protocol. Data will also be extracted from the medical record for included patients.
Human subject's protection:	A waiver of informed consent will be sought for delivery of the QI strategies, as well as for patient assessment #1, since they constitute minimal risk, the waiver will not adversely affect the rights or welfare of participants, and the research could not practically be carried out otherwise.
Study Duration:	Group 1: 28 weeks Group 2: 12 weeks
Participant Duration:	Group 1: 12 weeks Group 2: 12 weeks

1.2 Schema



1.3 Schedule of Activities – Group 1

It is anticipated that 12 clinicians will be included in the study, and up to 51 patients who are cared for by those clinicians. Eight to ten patients will enter the study cohort each week for 6 weeks.

For informational purposes, whether the research team performs the activity, or the anticoagulation clinic staff performs the activity is indicated in bold. Failure of the anticoagulation clinic staff to follow the clinical protocols for delivery of the patient and clinician level QI strategies will not be considered study deviations.

Schedule of Patient-Targeted Activities

Activity	Screening and randomization	Week 1	Week 2-4	Week 5-8	Week 9-12	Week 15-17	Week 13-28
Eligibility determination by chart review **(research team)**	X						
Randomization of patient to QI strategy **(research team)**	X						
Delivery of education and activation guide for patients randomized to receive it **(anticoagulation staff)**		X					
Possible outreach to the patient by their clinical care team and/or anticoagulation clinic staff as per usual clinical care **(no research team activity)**		X	X	X			
Administration of patient assessment #1 by phone, with waiver of informed consent **(research team)**				X			
Verbal informed consent followed by patient assessment #2 **(research team)**				X			
Administration of patient assessment #3 by phone, with verbal informed consent **(research team)**						X	
Chart review to ascertain exploratory outcomes **(research team)**	X	X	X	X	X	X	X

Activity	Screening and randomization	Week 1	Week 2-4	Week 5-8	Week 9-12	Week 15-17	Week 13-28
Chart review to determine appropriateness of initial and subsequent use of antiplatelet therapy **(research team)**							X

Schedule of Clinician-Targeted Activities

Activity	Screening, selection, and randomization	Week 1-5	Week 6-10
Eligibility determination **(research team)**	X		
Randomized selection of 12 clinicians to be included **(research team)**	X		
Randomization of selected clinicians to either clinician notification arm or clinician notification + nurse facilitation arm **(research team)**	X		
Delivery of clinician-facing QI strategies, synchronized with patient-level strategies **(anticoagulation clinic staff)**		X	
Additional outreach, communication, or facilitation steps as per anticoagulation clinic protocol for clinician notification and clinician notification + information relay strategies **(anticoagulation clinic staff)**		X	
Verbal informed consent and semi-structured interviews with clinicians **(research team)**. This may occur as soon as week 5 if the clinician has already responded to messages for all of their patients involved in the trial.		X	X

Schedule of Anticoagulation Clinic Staff-Targeted Activities

Activity	Week 1-5	Week 6-8	Week 9-16
Anticoagulation clinic staff receive weekly list of up to 10 patients starting trial each week, and the name of the target clinicians **(research team)**	X		
Anticoagulation staff initiate clinician and patient facing QI strategies synchronously **(anticoagulation clinic staff)**	X		
Additional outreach, communication, or facilitation steps as per anticoagulation clinic protocol for clinician notification and clinician notification + nurse facilitation strategies **(anticoagulation clinic staff)**	X	X	
Verbal informed consent and semi-structured interviews with anticoagulation staff **(research team)**			X

1.4 Schedule of Activities – Group 2

A convenience sample of 8 primary care clinicians will be selected. Additionally, all eligible patients for whom the primary care clinician is the responsible provider on record for the anticoagulation clinic will be included in group 2. We anticipate that each included primary care clinician will have 1-2 eligible patient included in group 2, for a total of 8-16 patient participants.

For informational purposes, whether the research team performs the activity, or the anticoagulation clinic staff performs the activity is indicated in bold. Failure of the anticoagulation clinic staff to follow the clinical protocols for delivery of the patient and clinician level QI strategies will not be considered study deviations.

Schedule of Patient-Targeted Activities

Activity	Screening and randomization	Week 1	Week 2-4	Week 5-8	Week 9-12
Eligibility determination by chart review **(research team)**	X				

Activity	Screening and randomization	Week 1	Week 2-4	Week 5-8	Week 9-12
Randomization of patient to QI strategy **(research team)**	X				
Delivery of education and activation guide for patients randomized to receive it **(anticoagulation staff)**		X			
Possible outreach to the patient by their clinical care team and/or anticoagulation clinic staff as per usual clinical care **(no research team activity)**		X	X	X	
Chart review to ascertain exploratory outcomes **(research team)**			X	X	X

Schedule of Clinician-Targeted Activities

Activity	Screening, selection, and randomization	Week 1	Week 2-6
Eligibility determination **(research team)**	X		
Selection of 8 primary care clinicians **(research team)**	X		
Randomization of selected clinicians to either clinician notification arm or clinician notification + nurse facilitation arm **(research team)**	X		
Delivery of clinician-facing QI strategies, synchronized with patient-level strategies **(anticoagulation clinic staff)**		X	

Additional outreach, communication, or facilitation steps as per anticoagulation clinic protocol for clinician notification and clinician notification + information relay strategies **(anticoagulation clinic staff)**			X
Verbal informed consent and semi-structured interviews with clinicians **(research team)**. This may occur as soon as week 3 if the clinician has already responded to messages for all of their patients involved in the trial.			X

2 INTRODUCTION

2.1 Study Rationale & Background

Increasing numbers of patients in the United States are prescribed oral anticoagulants to treat or prevent a range of thromboembolic conditions [1]. The main risk with anticoagulants is major bleeding, most commonly from the gastrointestinal tract [2,3]. Many patients prescribed anticoagulants are co-prescribed an antiplatelet drug (aspirin or a thienopyridine), and these patients are at particularly high risk for major bleeding. In an observational study of patients prescribed warfarin, use of an antiplatelet drug increased the risk of major bleeding (5.7% vs. 3.3%), emergency department visits for bleeding (13.3% vs. 9.8%), and hospitalizations for bleeding (8.1% vs. 4.1%), but did not reduce the rate of thrombosis [4].

Medication optimization can substantially reduce bleeding risk for patients prescribed combination antithrombotic therapy (CAT). One evidence-based practice is to discontinue antiplatelet therapy in patients for whom it is inappropriate. Based on recent clinical trial data, the indications for CAT are increasingly narrow, and most patients prescribed anticoagulants should only use antiplatelet drugs for a limited time after acute coronary syndrome, coronary stenting, or other vascular procedures [5]. A second evidence-based practice is the use of a proton pump inhibitor (PPI gastroprotection) for patients in whom CAT is truly indicated, a strategy recommended by professional guidelines [5,6]. A meta-analysis showed PPIs reduce the risk of UGIB by up to 79% in patients using aspirin or non-steroidal anti-inflammatory drugs [7]. Both of these evidence-based practices are underused [8]. In an observational study of six anticoagulation clinics, 45% of patients prescribed warfarin were co-prescribed an antiplatelet drug. Of these, 44% had no identifiable indication for antiplatelet therapy, and 36% were appropriately prescribed CAT but without a PPI [8].

There are multiple barriers to use of these evidence-based practices. Clinicians may lack knowledge of appropriate use of medication optimization strategies, have inadequate time or prioritization, or lack “ownership,” since many patients are co-managed by a PCP and a subspecialist (typically a cardiologist) [9]. In many cases, a clinician may be prepared to assess

use of one of the evidence-based practices but not the other, which may lead to suboptimal care. Clinicians may also have concerns about provoking a cardiovascular event when deprescribing antiplatelet drugs, and about possible PPI adverse effects when initiating a PPI [Kurlander AFM, in press].

There is a critical need for implementation strategies to improve medication optimization for upper GI bleeding risk reduction in patients prescribed CAT. Importantly, to ensure the most appropriate care, any implementation strategy should simultaneously address both evidence-based practices, determining first the appropriateness of antiplatelet therapy, then of PPI gastroprotection. Previous one- or two- component clinician-facing interventions aimed at improving use of PPI gastroprotection (including decision support tools, electronic alerts, audit and feedback, and clinician education) have had limited success [10–13]. Several European studies that have tested multi-component interventions involving professional education, incentive payments, clinician feedback, and pharmacist support have effectively reduced the proportion of high-risk patients without gastroprotection (odds ratios 0.55-0.72) [15–17]. However, such multicomponent strategies are resource intensive and challenging to implement in the fragmented US healthcare system. There have been limited efforts to activate patients to enhance the quality of their care in this clinical domain [14].

As part of a quality improvement program through the Michigan Medicine anticoagulation service, three potential implementation strategies have been identified to improve the safety of patients using CAT, including clinician notification by electronic health record (EHR) message, a multi-faceted nurse facilitated process involving clinician notification + nurse facilitation, and activation of patients to discuss medication optimization with their clinicians using a newly developed guide. The anticoagulation clinic intends to undertake a clinic-wide randomized quality improvement trial in the near future to evaluate the effectiveness of these strategies. This protocol describes plans for a pilot randomized evaluation of the quality improvement project, focused on feasibility, which will provide essential information for planning the future quality improvement trial.

2.2 Objectives - Group 1

Primary Objective: To explore the feasibility of patient participation in a one-time assessment of medication use following delivery of the quality improvement implementation strategies.
Secondary Objectives: To explore the feasibility of delivering QI strategy components as intended.

2.3 Objectives - Group 2

Primary Exploratory Objective: To explore primary care providers' perceptions of the QI strategies.

3 RISK/BENEFIT ASSESSMENT

3.1 Known Potential Risks to Randomized Patients in Group 1

No novel therapeutic medications or devices are being tested in this study and participants are not required to discontinue an antiplatelet agent, initiate a PPI, or make any other medication changes as part of study participation. The risks and benefits discussed here relate to the implementation strategies and assessments of the implementation strategies, but not any possible medication changes undertaken by their clinicians, which are done as part of usual clinical care.

1. **Potential Psychological Discomfort due to Subject Content.** The patient activation guide and patient assessments will deal with the topic of their potential for bleeding. This could cause them to be upset or concerned. All efforts will be made to discuss these topics in a careful and thoughtful manner.
2. **Inconvenience.** Participants may feel inconvenienced by the attempts to reach them and send them educational materials, or the time it takes to engage in study assessments.
3. **Breach of Data Confidentiality.** It is possible that the identity of the participant or protected health information (PHI) could be unintentionally revealed to persons outside of the research team. As this study does not deal with sensitive or stigmatized behavior (i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.
4. **Potential questions about the quality of their clinical care.** It is possible that patient participants may have questions about their clinical care. During creation of the patient activation guide, steps were taken to mitigate this risk by including language throughout that this project is being conducted in response to evidence from newer research studies and they are being contacted as part of a new patient safety initiative.
5. **Patient-initiated changes in medications without clinician consultation**. Patients who receive the patient-facing activation guide may make a change in their medications without first consulting one of their clinicians for input. Because antiplatelet drugs like aspirin and some PPIs are available over-the-counter, it is possible that a patient may choose to discontinue aspirin therapy or initiate a PPI on their own in response to the information included in the activation guide. To discourage patients from making medication changes on their own, language has been included throughout all patient-

facing materials to regularly remind the patient to speak with their clinician before making any medication changes and that their clinician will have to carefully consider which change would be most beneficial.

3.2 Known Potential Risks to Randomized Patients in Group 2

No novel therapeutic medications or devices are being tested in this study and participants are not required to discontinue an antiplatelet agent, initiate a PPI, or make any other medication changes as part of study participation. The risks and benefits discussed here relate to the implementation strategies and assessments of the implementation strategies, but not any possible medication changes undertaken by their clinicians, which are done as part of usual clinical care.

1. **Potential Psychological Discomfort due to Subject Content.** The patient activation guide will deal with the topic of their potential for bleeding. This could cause them to be upset or concerned. All efforts will be made to discuss these topics in a careful and thoughtful manner.
2. **Inconvenience.** Participants may feel inconvenienced by the attempts to send them educational materials.
3. **Breach of Data Confidentiality.** It is possible that the identity of the participant or protected health information (PHI) could be unintentionally revealed to persons outside of the research team. As this study does not deal with sensitive or stigmatized behavior (i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.
4. **Potential questions about the quality of their clinical care.** It is possible that patient participants may have questions about their clinical care. During creation of the patient activation guide, steps were taken to mitigate this risk by including language throughout that this project is being conducted in response to evidence from newer research studies and they are being contacted as part of a new patient safety initiative.
5. **Patient-initiated changes in medications without clinician consultation**. Patients who receive the patient-facing activation guide may make a change in their medications without first consulting one of their clinicians for input. Because antiplatelet drugs like aspirin and some PPIs are available over-the-counter, it is possible that a patient may choose to discontinue aspirin therapy or initiate a PPI on their own in response to the information included in the activation guide. To discourage patients from making medication changes on their own, language has been included throughout all patient-facing materials to regularly remind the patient to speak with their clinician before making any medication changes and that their clinician will have to carefully consider which change would be most beneficial.

3.3 Known Potential Risks to All Anticoagulation Clinic Patients who Undergo Chart Review

Chart review of all anticoagulation clinic patients who are documented in the electronic health record as using CAT without PPI gastroprotection at study initiation will be completed to provide information about the number of patients who may require medication optimization in the future clinic-wide trial and about the use of the evidence-based medication optimization strategies in usual practice to assess feasibility of completing the future clinic-wide trial. Anticipated risks to patients who are not randomized to receive a QI strategy and solely undergo chart review are minimal.

1. **Breach of Data Confidentiality.** It is possible that the identity of the participant or protected health information (PHI) could be unintentionally revealed to persons outside of the research team. As this study does not deal with sensitive or stigmatized behavior (i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.

3.4 Known Potential Risks to Clinicians and Staff (Group 1 and Group 2)

1. **Potential Psychological Discomfort due to Subject Content.** The clinician messages and assessment will deal with the topic of clinical care practices, including opportunities for clinical care improvement. This could cause clinicians to be upset or concerned. All efforts will be made to discuss these topics in a careful and thoughtful manner.
2. **Inconvenience.** Clinician participants may feel inconvenienced by the attempts to reach them or the time it takes to engage with communications from anticoagulation clinic staff or in the clinician assessment.
3. **Breach of Data Confidentiality.** It is possible that the identity of the participant could be unintentionally revealed to persons outside of the research team. However, no PHI will be sought from clinicians. As this study does not deal with sensitive or stigmatized behavior (i.e., illicit drug use), a potential data breach is anticipated to cause minimal harm to the participant if it were to occur.

3.5 Known Potential Benefits to Randomized Patients (Group 1)

Potential benefits associated with study participation include:

1. **Increased knowledge and understanding of personal risk** for GI bleeding, which will be discussed in the patient activation guide and during research interviews.
2. **Increased sense of self-efficacy** to discuss risk status and medication optimization with their clinicians.
3. **Reduced risk of upper GI bleeding events** if patients have medication optimization as a result of participation.

4. **Self-Satisfaction** – participants may derive a sense of personal satisfaction and purpose from contributing new knowledge to help advance science and medicine.

3.6 Known Potential Benefits to Randomized Patients (Group 2)

Potential benefits associated with study participation include:

1. **Increased knowledge and understanding of personal risk** for GI bleeding, which will be discussed in the patient activation guide.
2. **Increased sense of self-efficacy** to discuss risk status and medication optimization with their clinicians.
3. **Reduced risk of upper GI bleeding events** if patients have medication optimization as a result of participation.

3.7 Known Potential Benefits to All Anticoagulation Clinic Patients who Undergo Chart Review

Potential benefits for all patients who receive care from the anticoagulation clinic service who are not randomized to receive one of the QI strategies but are identified as being at high-risk for upper GI bleeding through a workbench report in MiChart at baseline and undergo chart review include:

1. **Increased knowledge and understanding of the prevalence of CAT use without PPI gastroprotection** among patients cared for by the anticoagulation clinic will help gain clinic leadership buy-in to allocate resources to lower bleeding risk and improve patient safety through wide-scale implementation of the QI strategies being tested.

3.8 Known Potential Benefits to Clinicians and Staff (Group 1 and Group 2)

1. **Increased knowledge** of risk factors for upper gastrointestinal bleeding and of evidence-based practices to reduce the risk.
2. **Self-Satisfaction** – clinicians and anticoagulation clinic staff may derive a sense of satisfaction and purpose from working to prevent bleeding and adverse events related to warfarin use in their patient population.

3.9 Assessment of Potential Risks and Benefits

The risks to patients, clinicians and staff are all minimal and justified by the value of the potential benefits and knowledge gained. Risks of confidentiality breach will be mitigated by separation of personal identifiers (consent forms, enrollment forms) from data source documents. All data

source documents and any personally identifying information for trial participants will be stored on a secure drive or in a locked file cabinet and will be accessible only to the study team.

4 OBJECTIVES AND ENDPOINTS

4.1 Objectives and Endpoints (Group 1)

OBJECTIVES	ENDPOINTS
Primary	
To explore the feasibility of patient participation in a one-time assessment of medication use following delivery of the QI strategies.	Proportion of patient participants who are able to be contacted by phone and are willing to participate in and fully complete patient assessment #1, related mainly to medication use (week 5 interview).
Secondary	
To explore the feasibility of delivering QI strategy components as intended.	Proportion of participants who received all implementation components to which they were randomized in the appropriate time frame.
Exploratory	
To explore additional aspects of the feasibility of recruitment.	Proportion of randomized patients able to be reached by phone after three attempts for patient assessment #1 at week 5. Average number of phone call attempts to reach each patient for patient assessment #1 at week 5. The number of anticoagulation clinic patients who meet eligibility criteria for the AEGIS trial on the first day of the pilot study according to the EHR workbench report.
To explore changes in the proportion of eligible patients during the study duration.	The proportion of all patients in the anticoagulation clinic who meet eligibility criteria for the study, regardless of whether they are included, who discontinued warfarin or were otherwise closed to the anticoagulation service during the study period. The proportion of patients who were randomized who discontinued warfarin or were closed to the anticoagulation clinic service during the participants' study duration.

OBJECTIVES	ENDPOINTS
To explore the accuracy of the electronic health record's medication list for ascertaining inclusion criteria	The proportion of randomized patients who, retrospectively, report that they had been using antiplatelet therapy at baseline during patient assessment #1 at week 5. The proportion of randomized patients who, retrospectively, report that they had been using PPI at baseline during patient assessment #1 at week 5. The proportion of randomized patients who met inclusion criteria based on retrospective medication use in patient assessment #1 at week 5.
To explore the accuracy of the electronic health record's medication list for ascertaining medication changes	The accuracy, positive predictive value, and negative predictive value of the electronic health record for use of antiplatelet therapy, and for use of PPIs at the time of assessment #3. The accuracy, positive predictive value, and negative predictive value of the electronic health record for "medication optimization" at the time of assessment #3. A patient will be considered to have had medication optimization if they are either no longer using combination antithrombotic therapy or are using a PPI.
To explore the feasibility of complete collection of study data	The proportion of patients with complete data entry in RedCAP database at study completion Average duration of interviews on medication use/adherence during patient assessment #3 at week 15-17.
To explore the feasibility of delivering the clinician-level QI strategies	Proportion of patients whose clinician was sent the clinician-level strategy by the anticoagulation clinic staff in the prescribed time period per the clinic protocol. We will also separately calculate this endpoint for the two levels of the clinician QI strategy.
To explore the feasibility of delivering the patient activation tool	The proportion of patients randomized to receive the activation guide who were sent the guide in the prescribed period of time, as determined by chart review. The proportion of patients randomized to receive the guide who recalled receiving the guide during patient assessment #1 at week 5. The proportion of patients randomized to receive the guide who recalled reviewing the guide in patient assessment #1 at week 5.

OBJECTIVES	ENDPOINTS
To explore the feasibility of prompting patient-clinician communication about medication optimization	The number of days after delivery of the clinician-facing QI strategy at which the patient and the target clinician (or their healthcare team) had communication (either by phone, in person visit, or portal message) about medication optimization, based on chart review. This will be calculated overall and separately for each QI strategy. The proportion of patients who had a communication about medication optimization with their clinicians based on patient recall at week 5 (patient assessment #1) and at week 9-12 (patient assessment #3). This will be calculated overall and separately for each QI strategy. For patients who had a communication with their clinician about medication optimization, the proportion in whom initial contact was made by the clinician vs. by the patient, according to chart review. This will be calculated overall and separately for each of the QI strategies. This will be assessed based on week 5 call. For patients who had a communication with their clinician about medication optimization, the proportion in whom initial contact was made by the clinician vs. by the patient, according to patient recall. This will be calculated overall separately for each QI strategy. For patients who contacted a clinician about medication optimization, the specialty of the clinician and whether the clinician who was sent the clinician notification was the target clinician. This will be determined separately based on chart review and patient recall. For patients who had communication with their clinician documented in the electronic health record, whether this occurred by phone, portal, or in-person/telehealth visit based on chart review.
To explore process measures associated with clinician notification	**For clinicians randomized to clinician notification:** Number of days taken for clinicians to send a response message to anticoagulation staff after first receiving the clinician QI strategy. Proportion of clinicians who documented their plan-of-care for the patient in the response message to the anticoagulation staff. The number of clinicians who appropriately documented changes in antiplatelet drugs or PPI in the EHR medication list.

OBJECTIVES	ENDPOINTS
To explore process outcomes associated with the clinician notification + nurse facilitation implementation strategy	**For patients randomized to clinician notification + nurse facilitation:** Number of days taken for clinicians to send a response message to anticoagulation staff after first receiving the clinician notification. Proportion of clinicians who documented their plan-of-care for the patient in the response message to the anticoagulation staff. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse provided patient education. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse pended the PPI order.
To explore aspects of effectiveness of the implementation strategies.	For anticoagulation clinic patients who meet inclusion criteria but are not randomized to a QI strategy in the pilot trial, whether or not they initiate PPI or discontinue antiplatelet therapy over the study period, as determined using electronic health record data, which will provide data on use of the evidence-based practices in usual care. For randomized patients, initiation of either a PPI or discontinuation of all antiplatelet therapy at week 5 (patient assessment #1), and at week 15-17 (patient assessment #3), as determined by patient interview. For randomized patients, the level of adherence to the recommended medication change (either PPI initiation or antiplatelet discontinuation) at week 15-17 measured using the Wilson questionnaire, as determined by patient assessment #3. Documentation of a recommendation by one of the patient's Michigan Medicine clinicians to discontinue antiplatelet therapy or initiate a PPI as indicated by a clinical documentation or by a change in the EHR medication list, ascertained by EHR review.
To explore the appropriateness of antiplatelet therapy used by patients at the time of study randomization.	The clinical appropriateness of antiplatelet therapy at the time of study initiation, classified as either (probably guideline concordant, probably not guideline concordant, or uncertain), based on detailed chart review and in reference to practice recommendations (Appendix 1).

OBJECTIVES	ENDPOINTS
To explore the appropriateness of medication changes in antiplatelet therapy during the trial.	For patients who either stopped antiplatelet therapy or initiated a PPI during the trial, to explore the appropriateness of antiplatelet management according to patient-reported use in patient assessment #3 at week 15-17. The clinical appropriateness of antiplatelet management will be determined according to pre-specified criteria (probably guideline concordant, probably not concordant, uncertain). See appendix 1 for criteria.

Additional objectives to be explored in qualitative interviews with patients, clinicians, and anticoagulation clinic staff:

- Acceptability of the implementation strategy components
- Perceptions of the implementation strategies
- Barriers to successful implementation

Please see associated interview guides. The interview guides used to complete patient, clinician, and anticoagulation clinic staff assessments will be iteratively revised throughout the pilot study, allowing initial findings from assessments to inform subsequent assessments and ensuring capture of all relevant information necessary for effective planning of the future clinic-wide quality improvement trial.

4.2 Objectives and Endpoints (Group 2)

OBJECTIVES	ENDPOINTS
Primary Exploratory	
To explore perceptions of the QI strategies from the perspective of primary care clinicians.	No quantitative endpoint. Clinician perceptions will be assessed qualitatively.
Secondary Exploratory	
To explore aspects of effectiveness of the implementation strategies.	For randomized patients, initiation of either a PPI or discontinuation of all antiplatelet therapy based on chart review at week 3.
To explore the feasibility of delivering the patient activation tool	The proportion of patients randomized to receive the activation guide who were sent the guide in the prescribed period of time, as determined by chart review.

OBJECTIVES	ENDPOINTS
To explore the feasibility of delivering the clinician-level QI strategies	Proportion of patients whose clinician was sent the clinician-level strategy by the anticoagulation clinic staff in the prescribed time period per the clinic protocol. We will also separately calculate this endpoint for the two levels of the clinician QI strategy.
To explore process outcomes associated with the clinician notification + nurse facilitation implementation strategy	**For patients randomized to clinician notification + nurse facilitation:** Number of days taken for clinicians to send a response message to anticoagulation staff after first receiving the clinician notification. Proportion of clinicians who documented their plan-of-care for the patient in the response message to the anticoagulation staff. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse provided patient education. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse pended the PPI order.
To explore the feasibility of prompting patient-clinician communication about medication optimization	The number of days after delivery of the clinician-facing QI strategy at which the patient and the target clinician (or their healthcare team) had communication (either by phone, in person visit, or portal message) about medication optimization, based on chart review. This will be calculated overall and separately for each QI strategy. For patients who had a communication with their clinician about medication optimization, the proportion in whom initial contact was made by the clinician vs. by the patient, according to chart review. This will be calculated overall and separately for each of the QI strategies. For patients who contacted a clinician about medication optimization, the specialty of the clinician and whether the clinician who was sent the clinician notification was the target clinician. This will be determined separately based on chart review. For patients who had communication with their clinician documented in the electronic health record, whether this occurred by phone, portal, or in-person/telehealth visit based on chart review.

OBJECTIVES	ENDPOINTS
To explore process measures associated with clinician notification	**For clinicians randomized to clinician notification:** Number of days taken for clinicians to send a response message to anticoagulation staff after first receiving the clinician QI strategy. Proportion of clinicians who documented their plan-of-care for the patient in the response message to the anticoagulation staff. The number of clinicians who appropriately documented changes in antiplatelet drugs or PPI in the EHR medication list.
To explore process outcomes associated with the clinician notification + nurse facilitation implementation strategy	**For patients randomized to clinician notification + nurse facilitation:** Number of days taken for clinicians to send a response message to anticoagulation staff after first receiving the clinician notification. Proportion of clinicians who documented their plan-of-care for the patient in the response message to the anticoagulation staff. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse provided patient education. Proportion of patients randomized to clinician notification + nurse facilitation for whom the anticoagulation nurse pended the PPI order.
To explore aspects of effectiveness of the implementation strategies.	For randomized patients, initiation of either a PPI or discontinuation of all antiplatelet therapy at week 3 as determined by chart review. Documentation of a recommendation by one of the patient's Michigan Medicine clinicians to discontinue antiplatelet therapy or initiate a PPI as indicated by a clinical documentation or by a change in the EHR medication list, ascertained by EHR review.

OBJECTIVES	ENDPOINTS
To explore the appropriateness of antiplatelet therapy used by patients at the time of study randomization.	The clinical appropriateness of antiplatelet therapy at the time of study initiation, classified as either (probably guideline concordant, probably not guideline concordant, or uncertain), based on detailed chart review and in reference to practice recommendations (Appendix 1).
To explore the appropriateness of medication changes in antiplatelet therapy during the trial.	For patients who either stopped antiplatelet therapy or initiated a PPI during the trial, to explore the appropriateness of antiplatelet management according to chart review at week 3. The clinical appropriateness of antiplatelet management will be determined according to pre-specified criteria (probably guideline concordant, probably not concordant, uncertain). See appendix 1 for criteria.

Additional objectives to be explored in qualitative interviews with clinicians:

- Acceptability of the implementation strategy components
- Barriers to successful implementation

Please see associated interview guide. The interview guide used to complete clinician assessments will be iteratively revised throughout the pilot study, allowing initial findings from assessments to inform subsequent assessments and ensuring capture of all relevant information necessary for effective planning of the future clinic-wide quality improvement trial.

5 STUDY DESIGN

5.1 Overall Design

This is a pragmatic, single center, feasibility pilot of a cluster randomized quality improvement trial with embedded individual randomization to evaluate implementation strategies to increase the use of evidence-based practices (EBPs) to reduce bleeding in patients who are using combination antithrombotic therapy and who are managed by the Michigan Medicine anticoagulation monitoring service. Two clinician-level strategies will be evaluated: (1) a clinician notification that identifies the patient as high-risk for upper GI bleeding and suggests discontinuing the antiplatelet agent or initiating a PPI; and (2) a clinician notification + nurse facilitation strategy in which a nurse undertakes multiple steps in an effort to overcome barriers to medication optimization. In addition, two patient-level strategies will be evaluated: (1) a patient activation tool; and (2) usual care. Clinicians will be cluster randomized, such that all the patients cared for by a single clinician will receive the same clinician-level notification.

Simultaneously, patients will be individually randomized to one of the two patient-level strategies.

Since this is a pilot study to assess feasibility of delivering all QI implementation strategies and acceptability of the strategies, the study design may be modified during the study period if problems are identified. Any study design modifications will be submitted to the IRB at Michigan Medicine as study amendments and documented in the amendment section on page 6 of this document.

5.2 Scientific Rationale for Study Design

The current study is a pilot quality improvement trial that will inform the design of a larger quality improvement trial with a similar design that will take place in the Michigan Medicine anticoagulation service in the near future. The justification for conducting the pilot study is to ensure that all study components can be feasibly executed. Indeed, it is recommended that pilot studies be undertaken prior to larger scale evaluations.

There are several additional justifications for the study design. Both clinician notification, as well as mailed patient education and activation tools, are commonly used by the anticoagulation service as part of routine clinic practice to improve the safety of patients using warfarin. For example, the anticoagulation clinic previously undertook a quality improvement project that consisted of notifications to clinicians about the potential benefits of discontinuing aspirin in certain patients. The anticoagulation clinic has also produced and distributed materials for patients on self-management of nosebleeds. However, even though these clinician- and patient-facing strategies are considered standard practices, it remains important for the clinic to understand whether such strategies are effective, and whether they justify the significant resource investment of the anticoagulation clinic staff. The study design will help to answer that question in the context of medication optimization to reduce upper GI bleeding.

The study design selected, which can be classified as a factorial study design, is well suited to the objectives of this quality improvement trial because it will allow the simultaneous investigation of two important questions: (1) How a relatively simple notification message to clinicians (“clinician notification”) compares to a simple notification paired with additional steps by the anticoagulation nurse to facilitate medication optimization (“clinician notification with nurse facilitation”). Prior studies have shown that clinician alerts often have weak and inconsistent effects, justifying a more comprehensive clinician-level quality improvement strategy. However, the more comprehensive QI strategy is also more labor intensive for anticoagulation clinic staff, and so it is therefore important to know how effective it is. (2) How effective is a patient-level education and activation tool? While these tools are often used by the anticoagulation service, it is important to confirm their effectiveness and gain a better understanding of how patients use and perceive such tools.

Patients will be cluster randomized within clinicians for the clinician-level QI strategy because if the same clinician received clinician notification for some of their patients and clinician

notification + nurse facilitation for others, this would likely cause some confusion about what services the clinician could expect to receive from the anticoagulation service for any individual patient. The justification for the individual level randomization for the patient level randomization is that it is the best design to make causal inference about the effect of the patient education and activation tool.

Ultimately, this future large-scale cluster randomized trial will identify which combination of QI implementation strategies is most effective in reducing UGIB risk, and that strategy will be used in the future as a part of usual care by the anticoagulation service.

5.3 Justification for Intervention

Upper GI bleeding is a serious risk to patients who use combination antithrombotic therapy. However, both of the available evidence-based medication optimization strategies to reduce upper GI bleeding risk are underused.

This trial will rigorously evaluate strategies that are used by the anticoagulation service to address safety issues that arise surrounding the safe use of warfarin.

5.4 End-of-Study Definition

5.4.1 Group 1

Patient and anticoagulation clinic staff are considered to have completed the study after week 28.

Clinicians are considered to have completed the study 10 weeks after trial entry of the last of the patients within the clinicians' cluster once they have completed the clinician interview (or decline to do so).

5.4.2 Group 2

Patient and clinician participants are considered to have completed the study after week 12.

6 STUDY POPULATION

6.1 Sample size

6.1.1 Group 1

The target sample size for group 1 in the pilot study is 40-51 patients cared for by 12 target clinicians. See sample size determination (below) for a justification of the size.

6.1.2 Group 2

The target sample size for group 2 is 8-16 patients cared for by 8 target clinicians who specialize in primary care.

6.2 Inclusion Criteria

6.2.1 Group 1

For patients:

- Enrollment with the Michigan Medicine anticoagulation monitoring service
- Currently prescribed warfarin with anticipated use for ≥90 days on day 1 of trial enrollment, according to the MiChart documentation.
- Currently prescribed an antiplatelet drug (aspirin, clopidogrel, ticagrelor, or prasugrel) according to the MiChart medication list

For clinicians:

- Practicing cardiologists at Michigan Medicine who in the prior year had a face-to-face or virtual visit with a patient who meets eligibility criteria for this study
- Practicing clinicians in any specialty who are designated as the clinician of record with the anticoagulation clinic for a patient who meets eligibility criteria

For anticoagulation clinic staff:

- Participated in the quality improvement project to deliver implementation strategies

6.2.2 Group 2

For patients:

- Enrollment with the Michigan Medicine anticoagulation monitoring service
- Currently prescribed warfarin with anticipated use for ≥90 days on day 1 of trial enrollment, according to the MiChart documentation.
- Currently prescribed an antiplatelet drug (aspirin, clopidogrel, ticagrelor, or prasugrel) according to the MiChart medication list

For clinicians:

- Practicing primary care or family medicine clinicians at Michigan Medicine who in the prior year had a face-to-face or virtual visit with a patient who meets eligibility criteria for this study

6.3 Exclusion Criteria

6.3.1 Group 1

For patients:

- Age less than 18
- Currently prescribed a PPI
- Documented intolerance or allergy to PPI use
- Left ventricular assist device
- Heart transplant

For clinicians:

- Cardiologists specializing in electrophysiology unless they are the clinician of record for a patient followed by the anticoagulation service.

For anticoagulation clinic staff

- None

6.3.2 Group 2

For patients:

- Age less than 18
- Currently prescribed a PPI
- Documented intolerance or allergy to PPI use
- Left ventricular assist device
- Heart transplant

For clinicians:

- None

6.4 Patient and Clinician Selection

6.4.1 Group 1

At random, we will choose 12 Michigan Medicine clinicians who either serve as the cardiologist for (n=6), or the (non-cardiologist) clinician of record (n=6) for patients in the anticoagulation clinic. For each of these clinicians, we will include all of their patients who meet eligibility criteria based on chart review. We anticipate the number of included patients will be 40-51. Eligibility will be determined based on information in the electronic health record. All participants will be screened for eligibility in the week prior to study entry.

6.4.2 Group 2

We will select a convenience sample of 8 Michigan Medicine clinicians who are the clinician of record for patients in the anticoagulation clinic and specialize in primary care from a convenience sample. For each of these clinicians, we will include all of their patients who meet eligibility criteria based on chart review. Eligibility will be determined based on information in the electronic health record. All participants will be screened for eligibility in the week prior to study entry.

6.5 Screen Failures

Patients who are ineligible for the study at the time of screening will not be included.

6.6 Strategies for Recruitment and Retention

6.6.1 Group 1

This trial will be conducted as a pragmatic quality improvement initiative in partnership with the Michigan Medicine anticoagulation clinic service. As knowledge of their participation in this study prior to receipt of the QI implementation strategies could result in unintended reactivity, in which the participant changes their behavior in response to knowing they are being observed, and harm the integrity of the study, patient and clinician participants will not be actively recruited for this study prior to delivery of the implementation strategies and no strategies will be used for participant retention. However, to complete the assessments for the study to evaluate the feasibility and acceptability of the Qi strategies, we will contact patients by phone up to 3 times over the period of 2 weeks to administer a brief 5-10 minute phone assessment to assess the accuracy of the electronic health record and determine whether the patient received the implementation strategies. Patient phone numbers will be obtained from the electronic health record and a voicemail will be left for the patient if they are unable to be reached at any of the 3 contact attempts. The research team will also contact clinician and anticoagulation clinic staff participants at their institutional email address to invite them to participate in a one-time, hour long qualitative assessment to elicit feedback about their experience with the implementation strategies and feasibility of continuing the project. Clinician and staff email addresses will be obtained from Michigan Medicine departmental websites or the University directory.

6.6.2 Group 2

This trial will be conducted as a pragmatic quality improvement initiative in partnership with the Michigan Medicine anticoagulation clinic service. As knowledge of their participation in this study prior to receipt of the QI implementation strategies could result in unintended reactivity, in which the participant changes their behavior in response to knowing they are being observed, and harm the integrity of the study, patient and clinician participants will not be actively recruited for this study prior to delivery of the implementation strategies and no strategies will be used for participant retention. The research team will, however, contact clinician participants at their institutional email address to invite them to participate in a one-time, hour long qualitative assessment to elicit feedback about their experience with the implementation strategies and feasibility of continuing the project. Clinician email addresses will be obtained from Michigan Medicine departmental websites or the University directory.

7 STUDY QUALITY IMPROVEMENT STRATEGIES

7.1 Study Implementation Strategy Administration

7.1.1 Quality Improvement Strategy Descriptions

All of the implementation strategies have been documented into clinical protocols approved by the anticoagulation clinic to address upper GI bleeding risk. All study QI strategies will be delivered by anticoagulation clinic staff as part of routine care.

Two clinician-facing implementation strategies will be evaluated.

1. **Clinician Notification:** An anticoagulation clinic nurse sends a templated message to the patient's target clinician that points out the patient's high risk for upper GI bleeding, summarizes guidelines on appropriate antiplatelet drug use and PPI gastroprotection, and recommends that the clinician consider either discontinuing the patient's antiplatelet drug or initiating a PPI for gastroprotection.
2. **Clinician Notification + Nurse facilitation:** An anticoagulation clinic nurse sends a templated message to the target clinician, similar to the clinician notification strategy. However, the message also includes clinical details about the patient's indication for antiplatelet therapy, ascertained by the nurse during chart review, and is intended to streamline decision-making by the clinician. In addition, the nurse will pend orders for medication changes if given instructions by the clinician and will communicate any recommendations to the patient on the clinician's behalf.

In addition, two patient-facing implementation strategies will be evaluated:

1. **Patient Activation:** A written guide to educate patients about their risk for bleeding and encouraging patients to talk with their clinician about medication changes to reduce their bleeding risk. This will be sent to patients through their preferred mode of communication (mail or patient portal). All patients will only be sent the guide once.
2. **Usual care:** With usual care, the anticoagulation clinic will not send the patient activation guide or other project-specific materials to the patient.

7.1.2 Administration and/or Dosing

N/A

7.2 Fidelity

7.2.1 Anticoagulation Nurse Training

Prior to the start of the study, the participating anticoagulation clinic staff will attend an instructional meeting with a research team member on how and when to administer the QI strategy components and how to document delivery of strategies in the electronic health record. This training is anticipated to be 90 minutes long.

For anticoagulation clinic staff, the implementation strategies and how to perform them are additionally described in anticoagulation clinic protocol documents.

7.2.2 Quality Improvement Strategy Delivery

Anticoagulation clinic nurses will have pre-scripted messages to use as part of clinician-facing implementation strategies.

Nurses will also have an example script available to use when talking with patients about medication changes.

7.2.3 Quality Improvement Strategy Receipt & Enactment

7.2.3.1 Group 1

Chart review will be performed for all patients to ensure that they received the implementation strategies to which they were randomized.

For patients randomized to the activation brochure, they will be questioned about receipt of the brochure, their understanding of the brochure and its purpose during patient assessment #2 at week 5-8.

7.3 Measures to Minimize Bias: Randomization and Blinding

Assignment to one of two clinician-level QI strategies will be done at the cluster level according to the identity of the clinician to be contacted. The cluster of patients cared for by each anticoagulation clinic target clinician will be randomized 1:1 to get either clinician notification (CN) or clinician notification + nurse facilitation (CN+NF). Patients will also be individually randomized to receive the patient activation guide or to a usual care arm.

Neither patients nor clinicians can practically be blinded.

As this is a pragmatic, quality improvement trial, there is no intention to blind anticoagulation clinic staff or research team members to group assignment.

7.4 Concomitant Therapy

Patients in this study will continue to receive all other usual care through the anticoagulation clinic. They will not be prevented from seeking or being exposed to any other medications or information from other sources during the study period or from seeking care from other clinicians.

7.5 Rescue Therapy

N/A

8 END-OF-INTERVENTION/END-OF-STUDY

8.1 Discontinuation of Intervention

8.1.1 Group 1

Use of the implementation strategies will be discontinued for patients who discontinue warfarin therapy or are closed to the anticoagulation clinic service during the first 5 weeks of study participation. Such patients will not be included in the analyses, and will not receive patient assessment #1, #2, or #3.

For patients who discontinue warfarin or are closed to the anticoagulation clinic between week 5 and the end of the study, they will be contacted for patient assessment #1 and #2 but not #3. They will be included in the analysis of the primary and secondary outcomes, as well as the

exploratory outcomes, except those related to patient assessment #3 (e.g., medication adherence, appropriateness of antiplatelet therapy at week 15-17).

8.1.2 Group 2

Use of the implementation strategies will be discontinued for patients who discontinue warfarin therapy or are closed to the anticoagulation clinic service during the first 3-5 weeks of study participation. Such patients will not be included in any analyses.

8.2 Participant Discontinuation/Withdrawal from the Study

8.2.1 Group 1

Patients or clinicians who wish to discontinue any study interview will have the interview discontinued.

8.2.2 Group 2

Clinicians who wish to discontinue any study interview will have the interview discontinued. No patient outreach or assessments will be conducted with group 2 participants.

8.3 Lost to Follow-Up

8.3.1 Group 1

If a patient is unable to be reached for assessment #1, #2, or #3, the data for the variables associated with that assessment will be coded as missing. If a patient is unable to be reached for assessment #1, no attempt will be made to reach them for assessment #2 or assessment #3. Even if patients are unable to be reached for assessment #1, #2, or #3, chart review will still be performed for that patient to evaluate the exploratory outcomes.

8.3.2 Group 2

Not applicable as no patient assessments will be conducted with group 2 participants. Chart review will be performed for patients in group 2 between study initiation and week 6.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Eligibility Assessment

9.1.1 Group 1

Before identifying eligible patients, the 12 participating clinicians will be selected at random. Next, the patients who fall into each clinician cluster, and who meet eligibility criteria, will be identified. These two tasks will be accomplished using a MiChart workbench report (previously developed by the anticoagulation clinic) that contains data on relevant eligibility criteria. All eligible patients and clinicians will be identified prior to commencement of the interventions.

Each week, 8-10 patients from the list of eligible patients will enter into the study, after confirming that they still meet eligibility criteria. These patients will be added to a separate MiChart report for the participating anticoagulation clinic nurses, identifying the patients and the QI implementation strategies to which they have been randomized.

9.1.2 Group 2

A convenience sample of 8 primary care clinicians who meet eligibility criteria for group 2 will be selected . Next, the patients who fall into each clinician cluster, and who meet eligibility criteria, will be identified. These two tasks will be accomplished using a MiChart workbench report (previously developed by the anticoagulation clinic) that contains data on relevant eligibility criteria. All eligible patients and clinicians will be identified prior to commencement of the interventions.

Each week, up to 12 patients from the list of eligible patients will enter into the study, after confirming that they still meet eligibility criteria. These patients will be added to a separate MiChart report for the participating anticoagulation clinic nurses, identifying the patients and the QI implementation strategies to which they have been randomized.

9.2 Qualitative Assessments with Participants in Group 1

Qualitative assessments will be conducted with clinicians, patients, and anticoagulation clinic staff to elicit feedback on the appropriateness and feasibility of the implementation strategies. Semi-structured interview guides have been developed to guide each assessment. These interview guides will be iteratively revised throughout the study to allow initial assessments to inform later assessments and ensure capture of all relevant information.

9.2.1 Clinicians:

One-time semi-structured qualitative interviews will be conducted with up to 12 clinicians who received communications from the anticoagulation clinic as part of this project. The interviews will be conducted 5-10 weeks after the last patient in the clinician-cluster entered into the study. Clinicians will be sent an invite to participate in an hour-long phone or zoom interview at their institutional email address by a research assistant. Clinicians will be offered a $100 gift card as an incentive for participation. Qualitative interviews with clinicians will focus on clinicians'

perceptions of the acceptability of the QI strategies and on feasibility of responding to the messages and initiating medication changes for GI bleeding risk reduction. Written informed consent will be obtained using SignNow software.

9.2.2 Patients:

- **Patient Assessment #1 (Week 5)**: A research assistant will contact all patient participants by phone at week 5 to administer patient assessment #1, expected to take no more than 10 minutes to complete, with the patient's permission. This questionnaire will ask patients about the medications they used ~30 days prior and the medications that they currently use. All patients will be asked whether they have had any changes in their medications in the past month, or if they have had a discussion with a healthcare provider about any medication changes or their risk of bleeding. Patients who were randomized to receive the activation tool will additionally be asked whether they recall receiving any educational materials about bleeding risk from the anticoagulation clinic to assess the feasibility of delivering patient education and activation materials. If the patient self-reports any use or non-use of medications that contradicts the information in their MiChart medication list, the research assistant will send a MiChart message to the patient's anticoagulation clinic nurse so that the nurse can reconcile the chart. No remuneration will be offered with this patient contact. We request a waiver of informed consent for patient contact #1. **Data on the ability to reach patients for this evaluation will be used to assess the pilot trial's primary outcome. Up to three contact attempts over a period of 2 weeks will be made to reach each patient for assessment #1.**
    - At the end of this call, patients who self-report having had a discussion with their clinician and those who were randomized to receive the patient activation tool will be invited to take part in a second 60-minute phone research interview within the next 3 weeks(patient assessment #2). All patients who complete assessment #1 will additionally be invited to participate in another medication review call at week 15-17 to assess durability of medication changes (patient assessment #3).
- **Patient Assessment #2 (Week 5-8):** A research assistant will contact a subset of participants (as described above) to participate in an hour-long semi-structured qualitative phone or zoom interview for patient assessment #2. The interview will elicit patient perceptions about the patient activation tool and about any discussions the patient may have had with one of their clinicians about their risk of bleeding and/or ways to reduce that risk. Prior to the interview, patient's will be provided with an informed consent document approved by the IRB at the University of Michigan and given the chance to ask any questions they may have. Patient's will then be asked to provide verbal consent before the interview may begin. Patient's will be advised that participation is entirely voluntary and choosing not to participate will not affect the care they may receive at Michigan Medicine. They will also be instructed that they can decline to answer any questions or end the interview at any time shall they wish. As all interviews will be conducted over the phone or zoom, and do not deal with sensitive or stigmatized subjects, we request a waiver of documentation of written informed consent for patient

assessment #2. Patients will receive a $20 gift card as remuneration for participating in this assessment. Patient remuneration will be sent through the University of Michigan treasurer's office human subjections incentives payment program gift card payment option.

- **Patient Assessment #3 (Week 15-17):** A brief 15-20 minute medication phone interview that asks patients about their use of antiplatelet drugs and PPIs at the time of the call, instructions they received from their clinician on how to use any of these medications, and about adherence to any antiplatelet drugs or PPIs the patient self-reports using. If the patient self-reports any use or non-use of medications that contradicts the information in their MiChart medication list, the research assistant will send a MiChart message to the patient's anticoagulation clinic nurse so that the nurse can reconcile the chart. Prior to the interview, patient's will be provided with an informed consent document approved by the IRB at the University of Michigan and given the chance to ask any questions they may have. Patient's will then be asked to provide verbal consent before the interview may begin. Patient's will be advised that participation is entirely voluntary and choosing not to participate will not affect the care they may receive at Michigan Medicine. They will also be instructed that they can decline to answer any questions or end the interview at any time shall they wish. As all interviews will be conducted over the phone, do not deal with sensitive or stigmatized subjects, we request a waiver of documentation of written informed consent for patient assessment #3. Patients will receive a $10 gift card as remuneration for participating in this assessment. Patient remuneration will be sent through the University of Michigan treasurer's office human subjections incentives payment program gift card payment option.

9.2.3 Anticoagulation clinic staff:

One-time semi-structured qualitative interviews will be conducted with all anticoagulation clinic staff members who participated in the pilot project. Anticoagulation clinic staff members will be sent an invite to participate in an hour-long phone or zoom interview at their institutional email address by a research assistant at the conclusion of the pilot study. Interviews with staff will be conducted during normal work hours and anticoagulation clinic staff will not receive additional remuneration above their regular pay for participating in the research interview. Qualitative interviews with anticoagulation clinic staff will focus on eliciting staff members' perceptions of the acceptability of the implementation strategies and on feasibility of delivering the implementation strategies to both patients and clinicians. Written informed consent will be obtained using SignNow software.

9.3 Qualitative Assessments with Participants in Group 2

Qualitative assessments will be conducted with clinicians to elicit feedback on their perceptions of the implementation strategies. A semi-structured interview guide has been developed to guide the assessment. The interview guide will be iteratively revised throughout the study to

allow initial assessments to inform later assessments and ensure capture of all relevant information.

9.3.1 Clinicians:

One-time semi-structured qualitative interviews will be conducted with up to 8 primary care clinicians who received communications from the anticoagulation clinic as part of this project. The interviews will be conducted 3-6 weeks after the last patient in the clinician-cluster entered into the study. Clinicians will be sent an invite to participate in an hour-long phone or zoom interview at their institutional email address by a research assistant. Clinicians will be offered a $100 gift card as an incentive for participation. Qualitative interviews with clinicians will focus on clinicians' perceptions of the acceptability of the QI strategies and on feasibility of responding to the messages and initiating medication changes for GI bleeding risk reduction. Written informed consent will be obtained using SignNow software.

9.4 Assessment of the Primary Endpoint

9.4.1 Group 1

The primary endpoint, defined as the proportion of patients able to be contacted and willing to participate in patient assessment #1, will be determined based on up to three contact attempts with the patient over the course of 2 weeks. Patients will be counted as meeting the primary endpoint if they complete the entirety of assessment #1. A brief message stating the research assistant’s name and affiliation with the anticoagulation clinic and asking the patient to call back at the earliest convenience will be left for the patient if they do not answer the phone during any of the three contact attempts.

9.4.2 Group 2

N/A

9.5 Assessment of the Secondary Endpoint

9.5.1 Group 1

The proportion of patients who received all implementation strategies to which they were assigned will be determined by EHR chart review in the 6 months following the trial.

9.5.2 Group 2

N/A

9.6 All Other Study Assessments – Group 1

Assessment of all exploratory study endpoints will be performed by a research assistant using chart review or semi-structured interview assessments conducted by phone or zoom call with patients,

clinicians, and anticoagulation clinic staff. There will be no assessments that require physical exams, radiology, biological specimens or laboratory evaluations.

9.6.1 Chart Review for Randomized Patients

For each patient participating in the trial, review of the electronic health record will be performed by a research team member to ascertain documentation of delivery of the quality improvement strategy components, documentation of medication changes, documentation of contact between clinicians and anticoagulation staff, appropriateness of antiplatelet therapy prior to and after the QI strategies, as well as other variables required for evaluation of exploratory outcomes.

To evaluate the appropriateness of antiplatelet therapy for randomized patients, a study team member who has training in internal medicine will conduct a detailed chart review for each patient. The team member will determine, first, whether the antiplatelet therapy initially prescribed was either probably appropriate, probably inappropriate, or uncertain, and second, whether continuation or discontinuation of antiplatelet therapy at the time of chart review was either probably appropriate, probably inappropriate, or uncertain.

9.6.2 Chart Review for All Anticoagulation Clinic Patients who Meet Eligibility Criteria at Baseline

For all patients who are enrolled with the anticoagulation clinic monitoring service at Michigan Medicine at the time of study initiation, review of the electronic health record will be performed by a research team member to determine (1) the total number of patients who meet eligibility criteria for the study, (2) the proportion of patients who met eligibility criteria at study initiation who discontinued warfarin therapy or were closed to the service during the study period, and (3) the number of patients who were eligible at study initiation and made one of the two medication-optimization changes during the study period. This data will provide necessary information about the number of patients who may require medication optimization in the future full-scale trial and also about the use of evidence-based strategies to reduce upper GI bleeding risk in usual practice without use of the implementation strategies being tested. This data would be obtained using workbench reports developed specifically to identify patients at high-risk for upper GI bleeding and through review of the electronic health record for additional data when needed. As these assessments are of patients who were not randomized to a QI strategy in this pilot trial and this data will be used solely for assessing feasibility of a future larger scale trial, we are seeking a waiver of consent and a waiver of HIPAA authorization to obtain this data.

9.7 All Other Study Assessments – Group 2

Assessment of the primary exploratory endpoint will be completed by the research team using semi-structured interview assessments with primary care clinicians who received one of the clinician-level strategies for a patient they care for. Assessment of all secondary exploratory study endpoints will be performed by a research assistant using chart review. There will be no

assessments that require physical exams, radiology, biological specimens or laboratory evaluations.

9.7.1 Chart Review for Randomized Patients

For each patient participating in the trial, review of the electronic health record will be performed by a research team member to ascertain documentation of delivery of the quality improvement strategy components, documentation of medication changes, documentation of contact between clinicians and anticoagulation staff, as well as other variables required for evaluation of exploratory outcomes.

10 ADVERSE EVENTS

Since this trial constitutes a quality improvement trial intended to improve the use of evidence-based practices to reduce bleeding in patients using CAT, and since all decisions regarding changes in drug treatment will be made by patients' own clinicians as part of usual care, the study will not proactively monitor for adverse events. No experimental drug is being investigated. However, any adverse events that are identified will be logged in an adverse event database.

11 STATISTICAL CONSIDERATIONS

11.1 Sample Size Determination

11.1.1 Group 1

The sample size was determined in consideration of the primary endpoint, which is the rate of participant recruitment and participation in assessment #1. With a sample size of 40, we will be able to estimate a recruitment rate of 80% to within a 95% confidence interval of +/- 13%, using normal approximation to the binomial calculation.

11.1.2 Group 2

N/A

11.2 General Statistical Approach

11.2.1 Group 1

For the primary and secondary analyses, all participants who undergo randomization will be analyzed. Proportions with confidence intervals will be calculated.

11.2.2 Group 2

For the primary and secondary exploratory analyses, all participants who undergo randomization will be analyzed. Proportions with confidence intervals will be calculated.

11.3 Descriptives

11.3.1 Group 1

We will calculate descriptive statistics (means and proportions) for all patient variables.

11.3.2 Group 2

We will calculate descriptive statistics (means and proportions) for all patient variables obtainable through chart review.

11.4 Hypotheses

11.4.1 Group 1

We hypothesize that the rate of participant recruitment and participation in assessment 1 (the primary endpoint) will exceed 66%.

Similarly, we hypothesize that the rate of delivery of intended quality improvement strategies will exceed 66%.

11.4.2 Group 2

N/A for qualitative primary exploratory endpoint.

11.5 Analysis of the Primary Endpoint(s)

11.5.1 Group 1

We will calculate the proportion of randomized patients that complete the patient assessment at week 5. We will estimate the confidence interval using the normal approximation to the binomial distribution. We will accept this hypothesis if the two-sided confidence interval (alpha=0.05) for the primary endpoint excludes 0.66.

11.5.2 Group 2

Qualitative analysis will be performed to explore clinician perceptions of the intervention strategies for the primary exploratory endpoint.

11.6 Analysis of the Secondary Endpoint(s)

11.6.1 Group 1

We will calculate the proportion of randomized patients that received all implementation components to which they were randomized in the appropriate time frame. We will estimate the confidence interval using the normal approximation to the binomial distribution. We will accept the hypothesis if the two-sided confidence interval (alpha=0.05) for the secondary endpoint excludes 0.66.

11.7 Exploratory Analyses

11.7.1 Group 1

Exploratory analyses will mainly consist of descriptive analyses using cross-tabulations, means, standard deviations and proportions. The accuracy, positive predictive value, and negative predictive value will be calculated for antiplatelet use, PPI use, and “medication optimization” at multiple time points, comparing the EHR medication list to self-report (reference standard).

11.7.2 Group 2

Exploratory analyses will mainly consist of descriptive analyses using cross-tabulations, means, standard deviations and proportions.

11.8 Other Analyses

N/A

11.9 Safety Analyses

N/A

11.10 Planned Interim Analyses

None planned.

11.11 Subgroup Analyses

N/A

12 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

12.1 Regulatory, Ethical, and Study Oversight Considerations

12.1.1 Informed Consent Process

12.1.1.1 Quality improvement strategy delivery (Both Group 1 and Group 2)

The types of quality improvement strategies (clinician notifications and patient educational handouts) described in this document are routinely used by the anticoagulation clinic as part of clinical care to improve the safety of patients using warfarin. The quality improvement strategies used in this pilot trial were developed specifically for use as part of a quality improvement effort to promote the use of evidence-based practices and reduce bleeding risk among the anticoagulation clinic's patient population.

We request a waiver of informed consent for delivery of the quality improvement strategies. This is justified on the grounds that the study presents only minimal risk to participants (and is likely to be beneficial), the waiver does not adversely affect the rights and welfare of participants, and the research could not practically be carried out without the waiver. The study could not practicably be carried out if patients and clinicians are consented because the intent of the pilot quality improvement trial is to evaluate the feasibility of a large scale quality improvement project, which would not include informed consent, i.e., if patients were consented, the pilot would diminish the validity of the results.

12.1.1.2 Patient assessment #1 (Group 1 only)

Obtaining informed consent from patient and clinician participants prior to delivery of the implementation strategies could harm the integrity of the study by priming participants to respond to communications or notifications from the anticoagulation service or initiate a medication change for bleeding risk reduction.

Patients and clinicians will not be consented prior to receipt of any implementation strategies delivered as part of the quality improvement project in an attempt to reduce reactivity and the Hawthorne Effect and ensure integrity of the study. Additionally, we request a waiver of informed consent for assessment #1 with patients. Patient assessment 1 will consist of a one-time phone questionnaire anticipated to take 10 minutes or less to complete and will solely include questions that will allow the anticoagulation clinic to ensure that information in MiChart related to medications that influence bleeding risk are accurately documented in the patient's EHR both at baseline and at the time of the call and to assess whether the patient-facing

implementation strategy (activation tool) was received by the patient. Accurate patient medication information in MiChart and knowledge of whether the tool was received by the patient are necessary to correctly identify patients at high-risk for adverse events associated with warfarin use and ensure that patient education and activation materials can be delivered in a timely-fashion, and as such are in-line with quality improvement efforts.

As consenting patients and/or clinicians prior to their randomization or receipt of the implementation strategies may result in unintended reactivity or the Hawthorne Effect which could harm the integrity of the study and influence study results, the study team will seek a waiver of informed consent from the IRB at the University of Michigan for patient assessment #1.

12.1.1.3 Patient Assessment #2 (Group 1 only)

Patients who, during patient assessment #1, self-report having had a conversation with a clinician about strategies to reduce bleeding risk or who were randomized to receive the patient activation guide will be invited at the end of assessment #1 to participate in patient assessment #2. Patients who agree to participate in assessment #2 will be provided with an IRB approved informed consent document prior to the interview and will be required to provide verbal consent to participate in the assessment before any interview questions are asked. Patients who agree to complete assessment #2 at week 5-8 will receive a $20 gift card as remuneration. Remuneration gift cards will be sent to patients by mail through the human subject incentives payment program. As these interviews will be conducted over the phone or zoom and will not deal with any sensitive or stigmatized subjects, the study team will seek a waiver of written informed consent from the IRB at the University of Michigan for patient assessment #2. Patients will not be required to consent to video or audio recording in order to complete assessment #2, though interviews will be recorded for all patients who do consent to audio or video recording.

12.1.1.4 Patient Assessment #3 (Group 1 only)

All patients who complete patient assessment #1 will be asked at the end of assessment #1 whether the research team can contact them for a brief, 15-20 minute follow-up questionnaire approximately 10-12 weeks after assessment #1. Patients who agree to participate in assessment #3 at week 15-17 of the study will be provided with an IRB approved informed consent document prior to initiation of assessment #3 and will be required to provide verbal consent to participate in the assessment before any assessment questions are asked. Patients who agree to complete assessment #3 at week 15-17 will receive a $10 gift card as remuneration. Remuneration gift cards will be sent to patients by mail through the human subject incentives payment program. As this assessment will be conducted over the phone or zoom and will not deal with any sensitive or stigmatized subjects, the study team will seek a waiver of written informed consent from the IRB at the University of Michigan for patient assessment #3. Patients will not be required to consent to video or audio recording in order to complete assessment #3.

12.1.1.5 Clinician Qualitative Semi-Structured Interviews (Group 1 and 2)

Any Michigan Medicine clinicians who participate in the research interview will be provided with an IRB approved informed consent document, reminded that their decision to participate or not participate will not impact their employment at Michigan Medicine in any way, given the opportunity to ask any questions, and asked to provide written informed consent using SignNow prior to the start of the interview. All clinician interviews will be completed during normal work hours at a time convenient to the clinician. Michigan Medicine clinicians will receive a $100 gift card incentive to promote participation in these semi-structured interviews. Remuneration gift cards will be sent to patients by mail through the human subject incentives payment program.

12.1.1.6 Anticoagulation Clinic Staff Qualitative Semi-Structured Interviews (Group 1 Only)

Any anticoagulation clinic staff members who participate in this interview will be provided with an IRB approved informed consent document, reminded that their decision to participate or not participate will not impact their employment at Michigan Medicine in any way, given the opportunity to ask any questions, and asked to provide written informed consent using SignNow prior to the start of the interview All staff interviews will be held during normal work hours at a time that is convenient to the staff member. As this project is being done in collaboration with the anticoagulation clinic service and staff members are delivering the implementation strategies as part of normal clinic activities, no remuneration will be offered to clinic staff .

12.1.1.7 Chart Review for Randomized Participants (Group 1 and 2)

A waiver of informed consent will be sought for the chart review component of this study as it poses minimal risk to participants, does not adversely affect the risks and benefits of participation for the participant, and the study could not practically be completed without a waiver.

12.1.1.8 Chart Review for All Anticoagulation Clinic Patients who Meet Eligibility Criteria at Baseline (other than having a participating clinician) (Group 1)

No outreach will be made to patient participants whose charts will be reviewed for this portion of the study and this data would solely be used to assist with planning for a future large-scale trial to test the same implementation strategies trialed in this pilot study. As review of patient's charts to assess their bleeding risk with warfarin is a minimal risk to participants and the knowledge obtained from this data will be used to promote future patient safety efforts, a waiver of informed consent and a waiver of HIPAA authorization will be sought from the IRB.

12.1.2 Consent Procedures and Documentation

All patient participants will be required to provide verbal consent before beginning the patient assessment #2 or patient assessment #3 and will be provided with an IRB approved informed consent document for their records no later than 2 business days after the associated

assessment is completed. Michigan Medicine clinicians and staff members will be required to provide written consent using SignNow to participate in the qualitative semi-structured phone interviews prior to the start of the interview. An informed consent document will be provided to all participants prior to any of the aforementioned assessments, and this script will address the voluntary nature of participation, participants' rights, the risks of participation, limits to confidentiality, and procedures for reporting complaints and/or adverse events to the investigators, the UM IRB, and the funding agency. Consent will occur over the phone or zoom with a trained study team member following reading of a comprehensive informed consent script. All participants will be given the opportunity to ask any questions or voice any concerns prior to participation and will be asked to provide verbal consent before any interview or assessment questions are asked. While a waiver of documentation of consent is sought from the IRB for patient assessments #2 and #3, documentation of the consent process will be entered into the RedCap database to allow the study team to track and verify that consent was obtained from all patients who participate in the research interview components of the study.

A waiver of documentation of written informed consent for patient assessment #2 and patient assessment #3 is justified as the clinic provides all of its care to patients virtually and no patients are physically seen in the clinic to allow for written informed consent during a patient visit. Additionally, the clinic's patient population is generally older and less technologically savvy, resulting in concerns about the use of SignNow software for patient participants. The study team previously conducted a preliminary evaluation of the patient activation guide to be used in this study and recruited patients who used antithrombotic medications from the UMHealthResearch.org website to participate in semi-structured zoom interviews in which the patient was provided with the activation guide and asked to provide feedback on the guide by "thinking aloud". During this study, the research team found that despite recruiting from the UMHealthResearch.org site where participants were generally more technologically savvy as they had to use the internet and complete screening questions to indicate their interest in participating, it was difficult for many of the participants to use the SignNow software. Many of the participants in the prior study either could not figure out how to complete the consent form on SignNow, while others were able to complete the form but incorrectly filled out certain lines (i.e., patient entered correct month and date for birthday, but left the current year [2021] in the birth date line), requiring the team to re-do consent multiple times and placing a burden on the patient. Due to difficulties encountered with the consent process, some participants ended up not completing the interview. We believe that a waiver of written informed consent for patient assessments #2 and #3 will allow the study team to obtain a better response rate and prevent any unnecessary burden on the behalf of the patients being contacted.

12.2 Confidentiality and Privacy

12.2.1 Future Use of Stored Specimens and Data

The data from this study may be used for future studies by the investigator team. During the conduct of the observational study, an individual participant can choose to withdraw consent to have their data stored for future research.

12.2.2 Data sharing

This study will be conducted in accordance with the National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication. This study will also comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting Dr. Kurlander.

12.3 Safety Oversight

This study will not have a Data and Safety Monitoring Board or Safety Monitoring committee since it constitutes quality improvement.

12.4 Key Roles and Study Governance

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Jacob E. Kurlander, MD, MS Assistant Professor
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1500 E. Medical Center Drive, SPC 5362 Ann Arbor, MI 48109
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12.5 Clinical Monitoring

N/A

12.7 Data Handling and Record Keeping

The source materials will include self-report questionnaires completed during phone encounters and audiotapes of qualitative interviews. Each study subject will be given a unique numeric identifier upon study entry. We will have audiotapes transcribed, and any identifying information

will be removed. All individuals who wish to access the information system will need to pass through two levels of username and password authentication. All data will be stored on secured, password-protected UM computers. To access these data, approval must be obtained from the PI. These data will be kept only as long as specific use requires and then will be destroyed when all necessary linkages between data collection instruments have been accomplished.

Any paper records associated with this study will be stored at 2800 Plymouth Road, Ann Arbor MI in a locked cabinet.

12.8 Data Collection and Management Responsibilities

Data collection will be the responsibility of the research staff at the site under supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of the data.

12.9 Study Records Retention

As this trial will involve collection of health related data through interaction with participants, all study documents will be retained for at least 7 years after the trial is completed in accordance with the University of Michigan's Human Research Protections Program (HRPP) Operations Manual Part 6.II.B.

12.10 Protocol Deviations

Deviations from the clinic protocol by anticoagulation clinic staff members when sending or delivering the implementation strategies as part of the quality improvement project will not constitute protocol deviations and will not be reported. This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, related only to the research evaluation components. The noncompliance may be either on the part of the investigator, or research staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly. Since the proposed research is a formative pilot study that will inform the design of a future larger quality improvement trial, the design of the pilot may be modified during the study period if feasibility issues are identified early on. Any study design modifications that affect the risks and benefits of study participation will be submitted to the IRB at Michigan Medicine as study amendments and documented in the amendment section on page 6 of this document.

All major protocol deviations or protocol amendments which affect the risks and benefits of participation will be reported to the IRB per the IRBMED reporting guidelines. It will be the responsibility of the site investigator to use continuous vigilance to identify and report major deviations or recurring minor deviations within 1 week of identification of the protocol deviation

or deviation trend, or within 1 week of the scheduled protocol-required activity. Any protocol changes will be submitted to the IRB as a study amendment and will require IRB approval prior to implementation of the protocol change. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements.

13 DATA SAFETY MONITORING PLAN

As this trial constitutes a low-risk study with a small number of participants, participant safety will be monitored by the study PI and there will be no data safety monitoring board or independent safety monitor for this project. Any unanticipated adverse events associated with the implementation strategies tested in this study will be identified by the study team and PI through participant self-report during any of the study assessments. During each assessment, the study team member conducting the phone or zoom call will ask the participant whether they have experienced any negative reactions or adverse events since the time when they entered the study and document and review any reported events with the PI. Adverse events related to any medication changes made by the patient's clinician will not be tracked or reported and the patient would be expected to discuss any such side effects with the clinician who initiated the medication change. The justification for not monitoring for adverse events related to a medication change is that participants in this study are not required to make a medication change as part of their participation and all medication changes will be made by the patient's clinician as part of usual care. Any unanticipated problems or adverse events self-reported by participants will be reported to the PI immediately and communicated to the IRB according to the policies described in the Human Research Protection Program Operations Manual. No individual stopping rules will apply to any participants as all quality improvement strategies will be delivered one-time only. However, any participants who request to no longer be contacted by the study team for study assessments will not be contacted again and will be considered to have withdrawn from the study. Any participants who complete patient assessment #1 but not any further assessments will be considered lost to follow-up and no data will be recorded for future assessments for that participant, though chart review may still be completed to assess appropriateness of antiplatelet therapy unless the participant explicitly requests that their data not be accessed. Data completeness is one outcome for this feasibility pilot trial and will be evaluated at the end of the study period.

13.1 Study Leadership Roster

A study leadership roster is included herein. All CVs and licenses for investigators and staff members included on the roster will be filed in the essential document binder for this study.

Name	Study Team Role	Contact Information	Responsibilities
Jacob E. Kurlander	Principal Investigator (PI)	734-647-9252, jkurland@umich.edu	• Identification and enrollment of participants • Obtaining informed consent from participants • Collection of study data through chart review, patient surveys, and qualitative interviews • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Geoffrey D. Barnes	Co-Principal Investigator (Co-PI)	734-763-0047, gbarnes@umich.edu	• Identification and enrollment of participants • Obtaining informed consent from participants • Collection of study data through chart review, patient surveys, and qualitative interviews • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Danielle Helminski	Study Coordinator	734-615-3952, dhelmins@umich.edu	• Identification and enrollment of participants • Obtaining informed consent from participants • Collection of study data through chart review, patient surveys, and qualitative interviews • Development and maintenance of study materials and protocols • Maintenance of regulatory and study related documents
Kelley Kidwell	Statistician	734-764-6724, kidwell@umich.edu	• Develop randomization procedure • Assign participants to groups • Maintain the master randomization list • Notify PIs and study coordinator when participants have

			been randomized ● Perform statistical analyses ● Develop and present routine reports throughout the trial period for review by the DSMP
Michael Lanham	Co-Investigator	934-936-1644, mlanham@umich.edu	● Develop randomization procedure ● Assign participants to groups ● Maintain the master randomization list ● Notify PIs and study coordinator when participants have been randomized ● Develop EMR tools to assist with identifying participants and sending quality improvement strategy components
Sameer D. Saini	Faculty Mentor	734-936-4785, sdsaini@umich.edu	● Provides expert advice on research conduct and study design ● Monitor study progress to ensure completion of project
Caroline Richardson	Faculty Mentor	734-998-7120, caroli@umich.edu	● Provides expert advice on research conduct and study design ● Monitor study progress to ensure completion of project
Sarah L. Krein	Faculty Mentor	734-845-3621, skrein@umich.edu	● Provides expert advice on research conduct and study design ● Monitor study progress to ensure completion of project
Raymond De Vries	Faculty Mentor	734-936-1644, rdevries@umich.edu	● Provides expert advice on research conduct and study design ● Monitor study progress to ensure completion of project

13.2 Protocol Amendment Procedures and Approvals

Protocol amendments require approval by both the PI and the Co-PI, Jacob E. Kurlander and Geoffrey D. Barnes, prior to submitting the amendment to the IRB. Written IRB approval of protocol amendments is required prior to implementation. Any amendment to the protocol will be adhered to by all study staff and will apply to all subjects.

13.3 Clinical Trial Registry and Publication Policy

Prior to subject enrollment, this clinical trial will be registered with clinicaltrials.gov by a University of Michigan's Michigan Institute for Clinical and Health Research (MICHR) representative. After the trial has been registered, the Co-PIs and study coordinator will be responsible for providing study updates and posting study results within 1 year of the primary completion date for the study on clinicaltrials.gov. Results from this trial will additionally be presented at cardiology or gastroenterology conferences and manuscripts of findings will be submitted for publication in relevant journals. As this study is being funded by the NIDDK through Dr. Kurlander's K23 award, all journal articles that arise from this study will be submitted to PubMed Central in accordance with NIH Public Access Policy.

14 APPENDICES

14.1 Appendix 1. Criteria for determining appropriateness of antiplatelet therapy.-

<u>Recommended duration of anti-platelet therapy for patients using anticoagulation, by indication.</u>
Clinicians should use their judgment in applying these recommendations to patients depending on the specific clinical scenario.

Indication for antiplatelet drug		Recommended management of antiplatelet drug	Notes	Ref.
Primary prevention of coronary artery disease				
Primary prevention		Stop antiplatelet drug		[1]
Treatment of coronary artery disease with atrial fibrillation (AF)				
	PCI ≤ 6 months ago	Continue antiplatelet drug	Clopidogrel preferred	[1]

PCI for stable CAD	PCI 6-12 months ago	Continue antiplatelet drug	Consider switch to aspirin 81mg	
	PCI >12 months ago	Stop antiplatelet drug		
CABG for stable CAD	CABG ≤12 months ago	Continue aspirin 81mg		
	CABG >12 months ago	Stop aspirin		
Acute Coronary Syndrome (ACS) +/- PCI	ACS +/- PCI ≤12 months ago	Continue antiplatelet drug	Clopidogrel preferred	
	ACS +/- PCI >12 months ago	Stop antiplatelet drug		
Treatment of coronary artery disease with venous thromboembolism (VTE)				
PCI for stable CAD	PCI <3 months ago	Continue antiplatelet	Clopidogrel preferred	[1]
	PCI 3-6 months ago	Continue antiplatelet drug	-Clopidogrel preferred -Consider stopping anticoagulant if reversibly provoking risk factors	
	PCI >6 months ago	Continue antiplatelet drug	-Consider switch to aspirin 81mg -Consider stopping anticoagulant if reversibly provoking risk factors	
	PCI >12 months ago	Stop antiplatelet drug	-Consider stopping anticoagulant if reversibly provoking risk factors	
CABG for stable CAD	CABG ≤12 months ago	Continue aspirin 81mg		
	CABG >12 months ago	Stop aspirin		
Acute coronary	ACS +/- PCI <3 months ago	Continue antiplatelet drug	Clopidogrel preferred	

syndrome (ACS) +/- PCI	ACS +/- PCI 3-12 months ago	Continue antiplatelet drug	-Consider switch to aspirin 81mg -Consider stopping anticoagulant if reversibly provoking risk factors	
	ACS +/- PCI >12 months ago	Stop antiplatelet drug	-Consider stopping anticoagulant if reversibly provoking risk factors	
Cerebrovascular disease				
History of TIA, CVA, or CEA		Stop antiplatelet drug		1
Carotid stent ≤ 3 months ago		Continue antiplatelet drug	Clopidogrel preferred	
Carotid stent > 3 months ago		Stop antiplatelet drug		
Peripheral arterial disease				
Endovascular intervention or surgical repair ≤ 1-3 months ago		Continue antiplatelet drug	Clopidogrel preferred	1
Endovascular intervention or surgical repair > 1-3 months ago		Stop antiplatelet drug		
Valve replacement				
Mechanical Heart Valve		Stop antiplatelet drug unless another indication is present		2
Bioprosthetic Heart Valve ≤ 3 months ago		Continue aspirin 81mg only if high thromboembolic risk		
Bioprosthetic Heart Valve > 3 months ago		Stop aspirin		
TAVR ≤ 3 months		Continue antiplatelet drug only if high thromboembolic risk		3
TAVR > 3 months		Stop antiplatelet drug		

Venous Intervention (including IVC and Iliofemoral venoplasty/stenting)			
Venous procedure ≤2 months prior	Continue dual antiplatelet therapy		
Venous procedure >2 months prior	Stop P2Y12 inhibitor Continue aspirin 81mg indefinitely		

PCI=Percutaneous coronary intervention.

1. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. *Journal of the American College of Cardiology*. 2021;77(5):629-658. doi:10.1016/j.jacc.2020.09.011
2. Writing Committee Members, Otto CM, Nishimura RA, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77(4):e25-e197. doi:10.1016/j.jacc.2020.11.018
3. Saito Y, Nazif T, Baumbach A, et al. Adjunctive Antithrombotic Therapy for Patients With Aortic Stenosis Undergoing Transcatheter Aortic Valve Replacement. *JAMA Cardiol*. 2020;5(1):92-101. doi:10.1001/jamacardio.2019.4367

15 ABBREVIATIONS AND SPECIAL TERMS

Abbreviation	**Term**
CAT	Combination Antithrombotic Therapy
CFR	Code of Federal Regulations
EHR	Electronic Health Record
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation

IRB	Institutional Review Board
MOP	Manual of Procedures
NCT	National Clinical Trial
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institute of Health
NSAID	Non-Steroidal Anti-Inflammatory Drug
PCP	Primary Care Provider
PI	Principal Investigator
PPI	Proton Pump Inhibitor
PUD	Peptic Ulcer Disease
UGIB	Upper Gastrointestinal Bleeding
UM	University of Michigan
US	United States

16 REFERENCES

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National Trends in Ambulatory Oral Anticoagulant Use. *The American Journal of Medicine*. 2015;128(12):1300-1305.e2. doi:10.1016/j.amjmed.2015.05.044

2. Lamberts M, Staerk L, Olesen JB, et al. Major Bleeding Complications and Persistence With Oral Anticoagulation in Non-Valvular Atrial Fibrillation: Contemporary Findings in Real-Life Danish Patients. *J Am Heart Assoc*. 2017;6(2). doi:10.1161/JAHA.116.004517

3. Hippisley-Cox J, Coupland C. Predicting risk of upper gastrointestinal bleed and intracranial bleed with anticoagulants: cohort study to derive and validate the QBleed scores. *BMJ*. 2014;349. doi:10.1136/bmj.g4606

4. Schaefer JK, Li Y, Gu X, et al. Association of Adding Aspirin to Warfarin Therapy Without an Apparent Indication With Bleeding and Other Adverse Events. *JAMA Intern Med*. 2019;179(4):533-541. doi:10.1001/jamainternmed.2018.7816

5. Kumbhani Dharam J., Cannon Christopher P., Beavers Craig J., et al. 2020 ACC Expert Consensus Decision Pathway for Anticoagulant and Antiplatelet Therapy in Patients With Atrial

Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease. *Journal of the American College of Cardiology*. 0(0). doi:10.1016/j.jacc.2020.09.011

6. Bhatt DL, Scheiman J, Abraham NS, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2008;52(18):1502-1517. doi:10.1016/j.jacc.2008.08.002

7. Scally B, Emberson JR, Spata E, et al. Effects of gastroprotectant drugs for the prevention and treatment of peptic ulcer disease and its complications: a meta-analysis of randomised trials. *The Lancet Gastroenterology & Hepatology*. 2018;3(4):231-241. doi:10.1016/S2468-1253(18)30037-2

8. Kurlander JE, Gu X, Scheiman JM, et al. Missed opportunities to prevent upper GI hemorrhage: The experience of the Michigan Anticoagulation Quality Improvement Initiative: *Vascular Medicine*. Published online February 27, 2019. doi:10.1177/1358863X18815971

9. Anderson K, Stowasser D, Freeman C, Scott I. Prescriber barriers and enablers to minimising potentially inappropriate medications in adults: a systematic review and thematic synthesis. *BMJ Open*. 2014;4(12):e006544. doi:10.1136/bmjopen-2014-006544

10. Gill JM, Mainous AG, Koopman RJ, et al. Impact of EHR-Based Clinical Decision Support on Adherence to Guidelines for Patients on NSAIDs: A Randomized Controlled Trial. *Ann Fam Med*. 2011;9(1):22-30. doi:10.1370/afm.1172

11. Laine L, Connors L, Griffin MR, Curtis SP, Kaur A, Cannon CP. Prescription rates of protective co-therapy for NSAID users at high GI risk and results of attempts to improve adherence to guidelines. *Aliment Pharmacol Ther*. 2009;30(7):767-774. doi:10.1111/j.1365-2036.2009.04090.x

12. Avery AJ, Rodgers S, Cantrill JA, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial and cost-effectiveness analysis. *Lancet*. 2012;379(9823):1310-1319. doi:10.1016/S0140-6736(11)61817-5

13. Lanas A, Esplugues J-V, Zapardiel J, Sobreviela E. Education-based approach to addressing non-evidence-based practice in preventing NSAID-associated gastrointestinal complications. *World J Gastroenterol*. 2009;15(47):5953-5959.

14. Wallis KA, Elley CR, Lee A, Moyes S, Kerse N. Safer Prescribing and Care for the Elderly (SPACE): Protocol of a Cluster Randomized Controlled Trial in Primary Care. *JMIR Research Protocols*. 2018;7(4):e109. doi:10.2196/resprot.9839

15. Avery AJ, Rodgers S, Cantrill JA, et al. A pharmacist-led information technology intervention for medication errors (PINCER): a multicentre, cluster randomised, controlled trial

and cost-effectiveness analysis. *The Lancet*. 2012;379(9823):1310-1319. doi:10.1016/S0140-6736(11)61817-5

16. Dreischulte T, Donnan P, Grant A, Hapca A, McCowan C, Guthrie B. Safer Prescribing--A Trial of Education, Informatics, and Financial Incentives. *N Engl J Med*. 2016;374(11):1053-1064. doi:10.1056/NEJMsa1508955

17. Guthrie B, Kavanagh K, Robertson C, et al. Data feedback and behavioural change intervention to improve primary care prescribing safety (EFIPPS): multicentre, three arm, cluster randomised controlled trial. *BMJ*. 2016;354:i4079.