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Interruptive Versus Non-Interruptive Reminders for Statin tHerApy in Primary Care (INIRSHA-PC). A Randomized Trial.

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Study Schema

Study Protocol. Version August 9, 2024
Full Study Title: Interruptive versus Non-Interruptive Reminders for Statin tHerApy in Primary Care (INIRSHA-PC). A Randomized Trial.
Primary Investigator: Aileen Wright, MD, MS

History of Protocol Amendments

Version	Submission Date	Changes Made
1	3/7/2024	N/A
2	8/12/2024	- Study title changed to "Interruptive versus Non-Interruptive Reminders for Statin tHerApy in Primary Care (INIRSHA-PC)"
3	11/12/2024	- Addition of exploratory outcomes and expanded detail and minor corrections on the statistical analysis approach

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1.0 Study Summary

Title: Interruptive versus Non-Interruptive Reminders for Statin tHerApy in Primary Care (INIRSHA-PC). A Randomized Trial.

Background: Statins reduce cardiovascular events and mortality, but only 30% of eligible primary care patients nationally are on statins. Clinical decision support (CDS) interventions in the electronic health record (EHR) can deliver education to providers and increase adherence to guideline recommendations via many potential forms of delivery. Interruptive alerts are an effective form of CDS but disrupt clinician workflow and increase alert fatigue in an age of clinician burnout and frustration with the EHR. Non-interruptive reminders are proposed as an alternative method of delivering CDS; however, they require active pursuit by the provider, and their effectiveness compared to interruptive alerts has not been rigorously studied. We propose a randomized trial comparing the effect of interruptive vs. non-interruptive reminders displayed to clinicians to increase statin prescribing in primary care clinics.

Primary Aim:

- To compare the effect of delivering education via interruptive or non-interruptive reminders versus routine care (i.e., fully unprompted) on statin prescribing in primary care clinics within the first 24 hours of alert firing.

Primary Hypothesis:

- Interruptive reminders to providers will be more effective at increasing statin prescriptions within 24 hours of alert firing compared to routine care. Non-interruptive reminders will have no effect on statin prescription rate within 24 hours of firing compared to routine care.

Inclusion Criteria:

1. Patients age ≥ 18 and <75
2. Seen in primary care visit within Vanderbilt University Medical Center
3. Eligible for statin therapy due to: 1) Atherosclerotic cardiovascular disease (ASCVD) 10-year risk ≥ 10%, 2) Type 1 or 2 diabetes and age ≥ 40, or 3) ASCVD diagnosis.

Exclusion Criteria:

Patient records within the EHR indicate:

1. Already on statin, ezetimibe, bempedoic acid, or PCSK9 inhibitor
2. Last low-density lipoprotein cholesterol (LDL-C) < 100 mg/dL
3. Known to be pregnant or lactating
4. Palliative care
5. Statin allergy or adverse effect of statin
6. Rhabdomyolysis
7. Statin contraindicated due to liver disease, defined as 1) Decompensated liver disease, 2) AST or ALT >5 times the upper limit of normal, or 3) Total bilirubin > 1.5 mg/dL.
8. Statin contraindicated due to kidney disease, defined as 1) Dialysis or 2) Estimated glomerular filtration rate < 15 ml/min/1.73 m^2.
9. Has had coronary calcium computerized tomography
10. Less than 3 months since lipid panel resulted
11. Acute visit

- **Consent:** Given that best practice advisories (BPAs) are regularly encountered by providers in daily practice, provider autonomy is not impeded, as providers are freely able to prescribe statins at their own discretion. Furthermore, these BPAs will introduce no additional risk to patients as they will merely be reminding clinicians to apply evidence-based practices and guideline-concordant care. The Adult Clinician Taskforce, which provides consent on behalf of primary care providers at VUMC, reviewed and approved this study, so a waiver of informed consent will be requested.

Randomization:

- The educational intervention that the provider receives is randomized in a 1:1:1 ratio to display either an interruptive BPA, non-interruptive BPA, or no BPA (routine care) during primary care visits with patients meeting all inclusion and no exclusion criteria.

Comparator Arms:

- Interruptive reminder group: Providers will receive education via a pop-up alert at the time that the chart is opened for eligible patient visits assigned to the interruptive reminder group.
- Non-interruptive reminder group: Providers will be able to seek out education at their own initiative via an on-demand reminder within a section of the chart for eligible patient visits assigned to the non-interruptive reminder group.
- The reminder will have the same format for both groups, but the manner in which it is displayed will differ between the two groups (i.e., interruptive vs. non-interruptive.)
- The reminder will alert clinicians that a statin is recommended for the patient and list the reasons the statin is indicated. It will give the clinicians a defaulted option for statin prescription as well as alternatives. If the clinician accepts the alert, an order for a statin will be placed in their "shopping cart" for convenience, and the order can be signed to prescribe the medication. If the clinician does not wish to prescribe a statin from the reminder, they can choose an acknowledgement reason.
- No reminder group: No alert recommending a statin will be displayed/available to the provider. The system will record eligibility through triggering a "silent" BPA, which is not displayed to the clinician and exists solely for data collection purposes.

Primary Effectiveness Outcome:

- The primary outcome is statin prescription within 24 hours of BPA firing (either interruptive, non-interruptive, or silent/hidden reminder).

Secondary Effectiveness Outcome:

- The secondary outcomes are statin prescription within 12 months post-BPA firing, and the first post-BPA firing LDL-C level.

Exploratory Outcomes:

- The exploratory outcomes are any non-statin lipid lowering agent prescription within 12 months post enrollment BPA firing, any statin prescription filled within 12 months of enrollment BPA firing, any new ASCVD event occurrence within 12 months of enrollment BPA firing, and time from enrollment BPA firing to statin prescription.

Sample Size Considerations:

- Using retrospective data from 3,931 patients eligible for the alert and seen in a primary care visit over 6 months, we calculated that enrolling 3,006 total patients would give 90% power to detect an increase in statin prescribing rate from 3% (baseline) to 6%. However, due to uncertainty in the effect size for the study interventions, we have leveraged an adaptive study design with a maximum sample size constraint of 6,000 total patients.

2.0 Background

Statins have been shown to reduce LDL-C and the rate of adverse cardiac events[1]. National guidelines recommend initiation of statin therapy for patients based on LDL-C level and baseline cardiovascular disease risk; however, many patients who are eligible for statins do not receive them[2]. Lack of statin therapy can be caused by providers failing to offer statins, patients declining statins, or patients discontinuing statins due to adverse effects. Previous studies exploring CDS-based education delivery and its impact on guideline-concordant prescribing have shown mixed results[3–8].

2.1 Statin therapy to lower LDL-C and reduce risk of ASCVD

Death due to cardiovascular disease (CVD) remains the leading cause of death in the United States. Lowering LDL-C can reduce the risk of death from ASCVD, both in patients without established CVD (primary prevention) and those with established CVD, such as after a myocardial infarction (MI) or ischemic stroke (secondary prevention). Statins competitively inhibit hydroxymethylglutaryl (HMG) CoA reductase, which is the rate-limiting step in cholesterol production. This leads to a decrease in LDL-C, and typically an increase in high-density lipoprotein (HDL) cholesterol. In addition to reducing LDL-C, which is a component of the plaques which build up within arteries and cause adverse cardiac outcomes such as myocardial infarction (MI), statins have also been found to act through nonlipid mechanisms, such as reduction of inflammation. Currently available statins include atorvastatin, rosuvastatin, pravastatin, pitavastatin, fluvastatin, simvastatin, and lovastatin.

A meta-analysis of the benefits of statins for primary prevention conducted by the United States Preventive Services Task Force (UPSTF) found significant benefits when looking at outcomes of all-cause mortality, cardiovascular mortality, stroke, myocardial infarction, and revascularization[1]. It also found convincing evidence that any harms of statin use in adults aged age 40 to 75 are small. Accordingly, the UPSTF recommends moderate-intensity statins for primary prevention in patients aged 40 to 75 years who have 1 or more CVD risk factor (i.e., dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD risk of 10% or greater.

In addition, the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines recommend high-intensity statin therapy in all patients with clinical ASCVD, or with severe primary hypercholesterolemia (LDL-C level ≥ 190 mg/dL), based on multiple meta-analyses and randomized trials showing a reduction in major ASCVD with lowering of LDL-C.

Adherence to clinical guidelines which recommend statins in eligible patients is suboptimal. One study among 5,445 statin-eligible patients across 74 US practices found the median guideline-recommended treatment rate to be 42.5%[2]. They also found wide variation among practices, suggesting that in addition to patient-specific reasons for under-use, clinician-specific approaches to statin prescribing may explain some gaps in guideline adherence.

2.2 CDS to Improve Guideline Adherence

CDS systems which are integrated into the EHR are now a standard method of improving quality of care, having been incentivized by the Health Information Technology for Economic and Clinical Health (HITECH) Act in 2009, which includes CDS within its core requirements of meaningful use. CDS includes, but is not limited to, interventions such as computerized alerts and reminders, reports, patient summaries, and clinical guidelines embedded within the EHR. Multiple studies have demonstrated that CDS interventions are effective in increasing guideline adherence, such as in areas of cancer care delivery[3], antibiotic stewardship[4], and antithrombotic therapy in patients with atrial fibrillation[5]. Results are often modest; one meta-analysis of CDS interventions found an average improvement in the percentage of patients receiving the desired care element by 5.8%[6]. CDS reminders have been employed to attempt to increase statin prescribing with mixed results. One meta-analysis looked at 5 studies implementing CDS statin reminders and found that 2 had positive results, both of which were electronic rather than paper-based interventions[7].

2.4 Interruptive Alerts and Alert Fatigue

Interruptive pop-up alerts, which are the main type of CDS with proven effectiveness[8], by definition interfere with clinical workflow and can lead to alert fatigue[9]. Introducing more frustrations into the clinician experience with the EHR raises concerns in an age where the rapid adoption of EHRs has been linked to clinician burnout[10]. Non-interruptive reminders, such as those which must be accessed by the clinician in an on-demand manner, may be suggested as an alternative to interruptive pop-up alerts, but the effectiveness of non-interruptive alerts to improve guideline adherence is unclear. One meta-analysis found that providing CDS automatically versus on demand led to large improvements in adherence[8]. However, this was based on only 3 studies, with low certainty of evidence. One 3 arm cluster-randomized controlled trial of interruptive vs non-interruptive alerts recommending statins in cardiology clinics showed no significant effect of either alert[11]. However, cardiologists already place a high importance on statin therapy, making reminders for statin therapy potentially less effective in this group. The effectiveness of interruptive vs. non-interruptive alerts to recommend statin prescribing in primary care clinics has not been studied.

2.5 Rationale for a Trial of Interruptive vs. Non-Interruptive Alerts Recommending Statins in Primary Care

With the widespread use of EHRs and the implementation of reminders, the decision to build an alert as interruptive or non-interruptive is an important one which must balance potential alert

fatigue with potential positive effects on adherence to clinical guidelines which improve quality of care for patients. Rigorous studies are needed to gather evidence to help clinical informaticians when making decisions about the design of CDS interventions. Findings from such studies would have implications for the thousands of alerts displayed to clinicians each year.

To address this knowledge gap, we will conduct a prospective, randomized trial of reminders delivered to clinicians seeing patients in primary care clinics, comparing interruptive vs. non-interruptive reminders in outcomes of statin prescriptions.

3.0 Rationale, Aims, and Hypotheses

In order to determine the effect of interruptive reminders, compared to non-interruptive reminders, on the rate of statins prescribed in primary care clinics, a randomized trial is needed.

Study Aims:

- Primary:
  - To compare the effect of interruptive versus non-interruptive reminders on statin prescribing in primary care clinics within the first 24 hours of BPA firing.
- Secondary:
  - To compare the effect of interruptive versus non-interruptive reminders on statin prescribing in primary care clinics within a year after BPA firing.
  - To compare the effect of interruptive versus non-interruptive reminders on patients' first post-intervention LDL-C level.
- Exploratory:
  - To compare the effect of interruptive versus non-interruptive reminders on any non-statin lipid lowering agent prescribing within a year after BPA firing.
  - To compare the effect of interruptive versus non-interruptive reminders on statin prescription filling within a year after BPA firing.
  - To compare the effect of interruptive versus non-interruptive reminders on incidence of new ASCVD events within a year of BPA firing.
  - To compare the effect of interruptive versus non-interruptive reminders on the time from BPA firing to statin prescribing.

Study Hypotheses

- Principal Hypothesis:
  - Interruptive alerts to providers will lead to a significant increase in statin prescriptions within 24 hours of BPA firing as compared to no alert.
- Ancillary Hypothesis
  - Non-interruptive alerts will not lead to a significant increase in statin prescriptions within 24 hours of BPA firing as compared to no alert.

4.0 Study Description

In order to address the aims outlined above, we propose a pragmatic randomized controlled trial evaluating the impact of interruptive versus non-interruptive reminders recommending

statin prescriptions during primary care visits. All primary care providers caring for patients who are eligible for statin prescribing as defined herein will be included in this study. In the control arm, providers will not receive any additional education beyond what is normally provided. Providers in the interruptive alert arm will receive additional statin prescribing education via a pop-up reminder that will be automated and displayed to the provider in the moment. Providers in the non-interruptive alert arm will be able to access the same supplementary education via an on-demand reminder within the BPA section of the medical record should they choose to seek this out. Arm assignment will be based on 1:1:1 randomization ratio anchored to the patient's record. Randomization, group assignment and delivery of the intervention will occur within the electronic health record (details in section 7). Data will be collected prospectively from the medical record to determine the effect of the assigned interventions on provider behavior via clinical and physiologic outcomes, such as statin prescriptions and cholesterol levels.

5.0 Inclusion/Exclusion Criteria

5.1 Inclusion Criteria:

1. Patients age ≥ 18 and <75
2. Seen in primary care visit at VUMC
3. Eligible for statin therapy due to: 1) Atherosclerotic cardiovascular disease (ASCVD) 10-year risk ≥ 10%, 2) Type 1 or 2 diabetes and age ≥ 40, or 3) ASCVD diagnosis.

5.2 Exclusion Criteria:

Patient records within the EHR indicate:

1. Already on statin, ezetimibe, bempedoic acid, or PCSK9 inhibitor
2. Last low-density lipoprotein cholesterol (LDL-C) < 100 mg/dL
3. Known to be pregnant or lactating
4. Palliative care
5. Statin allergy or adverse effect of statin
6. Rhabdomyolysis
7. Statin contraindicated due to liver disease, defined as 1) Decompensated liver disease, 2) AST or ALT >5 times the upper limit of normal, or 3) Total bilirubin > 1.5 mg/dL.
8. Statin contraindicated due to kidney disease, defined as 1) Dialysis or 2) Estimated glomerular filtration rate < 15 ml/min/1.73 m^2.
9. Has had coronary calcium computerized tomography
10. Less than 3 months since lipid panel resulted
11. Acute visit

6.0 Enrollment/Randomization

6.1 Study Sites:

Primary care clinics at Vanderbilt University Medical Center

6.2 Study Population:

Primary care providers of adult patients who are eligible for statin therapy but not currently on a statin unless determined to meet exclusion criteria.

6.3 Enrollment:

All primary care providers at Vanderbilt University Medical Center primary care clinics treating patients eligible for statin prescriptions as defined herein will be enrolled in the study. This provider population is aware of the study and has agreed to participate through review and approval of the study by the Adult Clinician Taskforce. The time of randomization will be defined as "time zero" on "study day 0."

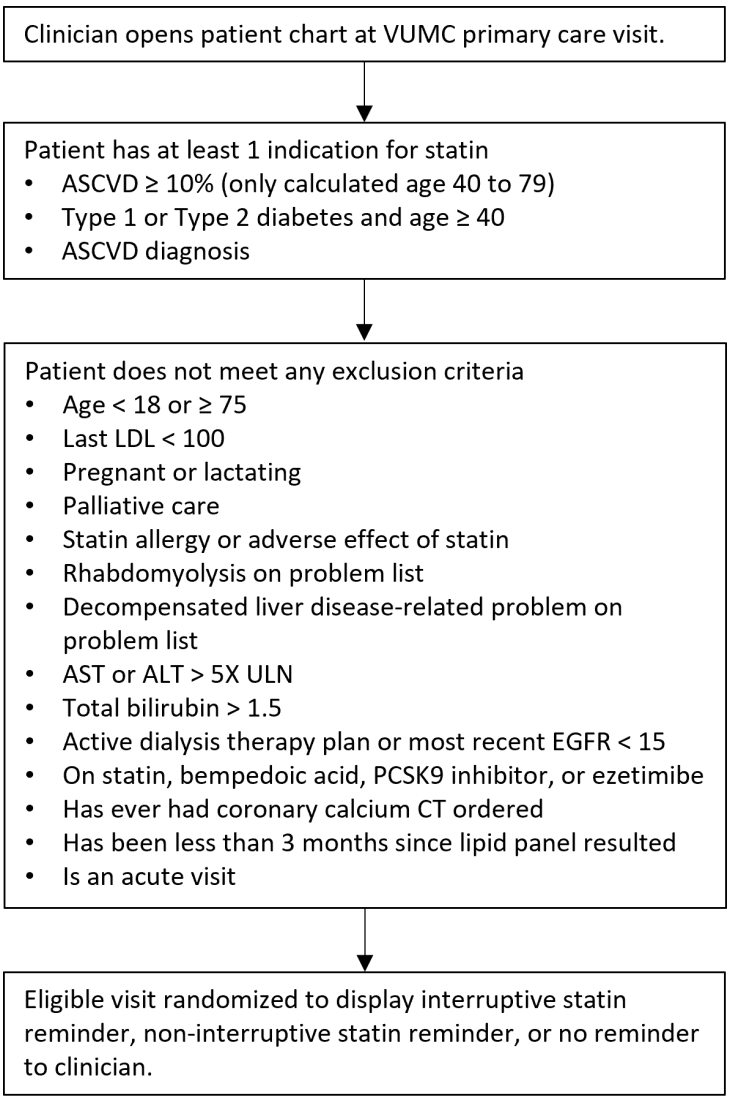

Figure 1: Randomization Schema – When a clinician first opens the chart during a primary care clinic visit, a tool within the electronic health record (details in section 7) will evaluate whether the patient being seen meets any inclusion and no exclusion criteria. If so, a randomization tool

anchored to the patient record will assign the provider to receive an interruptive alert recommending statin, non-interruptive alert recommending statin, or no alert.

6.4 Consent:

Prescription of statins in eligible patients is the standard of care. In each case that the clinician is shown a reminder, the decision to prescribe a statin will be left up to that clinician in discussion with the patient. Because (1) the interventions studied are used as part of routine care, (2) statins are recommended by national guidelines for eligible patients, and (3) all decisions about whether to prescribe the statin will be left to the provider and patient, we feel the study presents minimal risk.

The study has received approval from the VUMC Adult Clinician Taskforce on behalf of the participating primary care providers. It is impracticable to obtain consent for all providers in the moment through the interruptive alert, as it would be impossible to do so without introducing further bias. Only one arm will be receiving the interruptive BPA, thus this information/consent would not be available in the no-alert group or non-interruptive alert group. Furthermore, attempting to consent providers in the non-interruptive alert or no-alert groups would inherently reduce the ability to study the effects of these BPAs as deployed in usual practice. The interplay of interruptive reminders and alert fatigue is of critical interest in this study and additional interruptive reminders to obtain consent could bias outcomes and decrease generalizability of the study. Moreover, providers implicitly consent to receiving interruptive alerts through use of the EHR at a research institution. Providers additionally have the freedom to choose not to act on the interruptive reminder's guidance. In the non-interruptive alert arm, providers also imply consent by actively seeking out the available education.

Primary care providers routinely encounter electronic reminders in clinical care, presented in both interruptive and non-interruptive forms. The patient record-based randomization schema ensures that all participating providers will be exposed to each treatment arm throughout the study, preventing any subset of providers from experiencing undue alert burden. Importantly, all providers maintain autonomous decision-making rights concerning statin prescribing, irrespective of their intervention assignment. Thus, we propose that the study does not introduce adverse effects on the rights or welfare of the participants.

At the core of this study is the imperative to educate providers and promote guideline-concordant patient care. This study necessitates accessing PHI in an identifiable form to ensure that both the interruptive and non-interruptive educational reminders offer appropriate, accurate, and patient-specific guidance. Accessing PHI is also essential for capturing clinical outcomes relevant to the provision of care. All outcome measures assessing changes in provider behavior and resulting impacts, such as statin prescription status and post-intervention LDL-C, are abstracted from the EMR and linked to identifiers. Consequently, the practical execution of the study is dependent on the use of identifiable PHI.

Because the study presents minimal risk, would not adversely affect the welfare or privacy rights of the participants, and consent to perform the trial within the primary care clinician space has been received, a waiver of informed consent will be requested.

6.5 Randomization:

A series of study group assignments will be generated by computerized randomization in a 1:1:1 ratio of (1) interruptive statin reminder, (2) non-interruptive statin reminder, and (3) no alert. Assignment will carry forward to apply to patients' future primary care visits during the study period, provided that they still meet inclusion and exclusion criteria.

7.0 Study Procedures

7.1 Electronic Health Record (EHR) Based Screening for Eligible Patients

For the duration of the study, when a patient presents to a primary care visit, a software tool in the EHR will assess if the patient is eligible for statin prescribing by meeting at least one inclusion criteria and no exclusion criteria. If the patient is determined to be eligible for a statin, a silent BPA will perform the randomization and their provider will be enrolled in the study and receive either (1) interruptive statin reminder, (2) non-interruptive statin reminder, or (3) no alert.

7.2 Alert format

An example of an alert is shown in Figure 2. The alert education information is customized to the provider based on their patient's clinical characteristics such as 1) the specific reasons that the patient is eligible for a statin (for example, ASCVD risk score or other diagnoses), 2) whether a moderate or high-intensity statin is recommended, 3) whether the patient has liver disease, and 4) whether the patient may have familial hypercholesterolemia based on their cholesterol level. The alert also displays liver testing results for the patient and provides options for statin medications to prescribe. One statin prescription is defaulted, such that if the provider accepts the reminder, the statin medication will be prepared for signing. The clinician also has the opportunity to choose a different statin or a referral to a specialist such as a lipid or gastroenterology specialist. If the clinician does not wish to prescribe a statin at this time, they may select an "acknowledge reason" which specifies the reason for declining statin prescription. The alert also has a feedback link where the clinician can provide feedback about the alert.

The text and information displayed in the alert will remain identical whether the provider receives the interruptive reminder or the non-interruptive alert. The only way that the alert will differ between interruptive and non-interruptive arms is the place in the workflow in which the clinician encounters it.

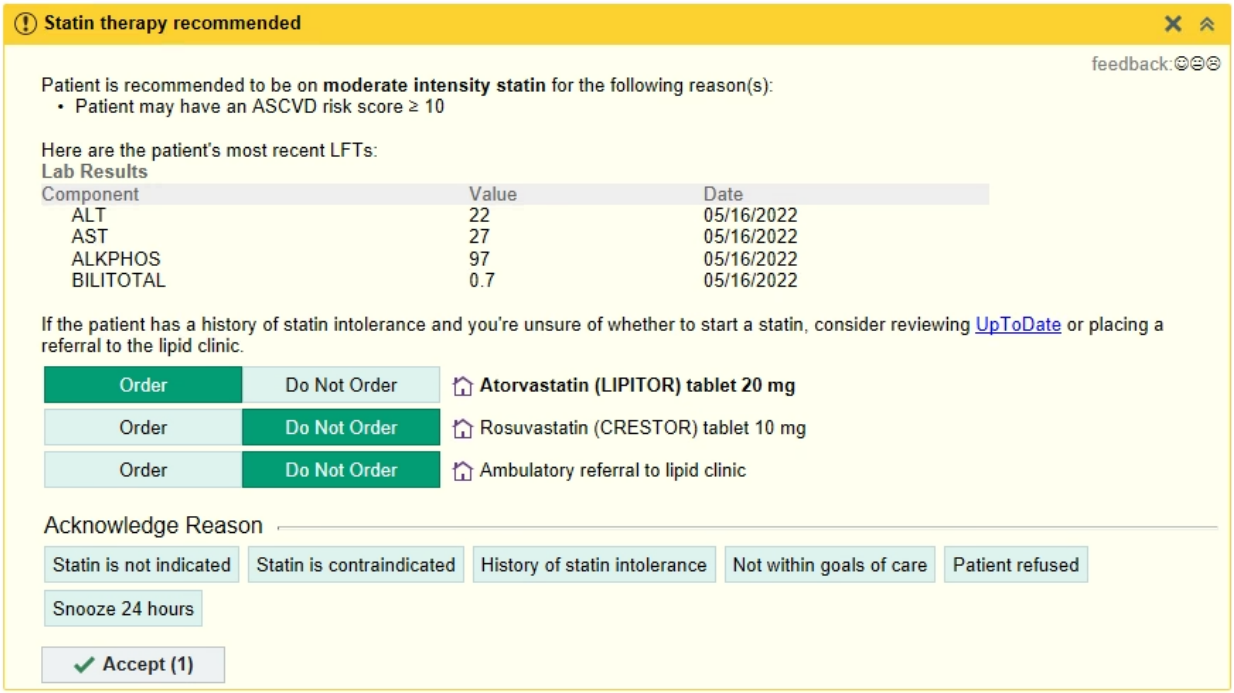

Figure 2. Example of a reminder recommending statin therapy

7.3 Interruptive Reminder

Interruptive reminders will be displayed to providers as pop-up alerts at the time of opening the patient chart. These alerts need to be resolved (either through accepting or acknowledging the alert) before the clinician can proceed with interacting with the rest of the patient's chart.

7.4 Non-Interruptive Reminder

Non-interruptive reminders will be available on-demand if the clinician prefers to seek them out. To look for a non-interruptive reminder, the clinician must click on the "Plan" section of the patient's chart and select "BestPractice" to open the BestPractice Advisory (BPA) navigator, which shows a list of all the reminders the patient is eligible for (Figure 3). This section will be highlighted in yellow if the patient has reminders for review. Depending on the number of other reminders the patient is eligible for, the clinician may need to scroll down to see the statin reminder.

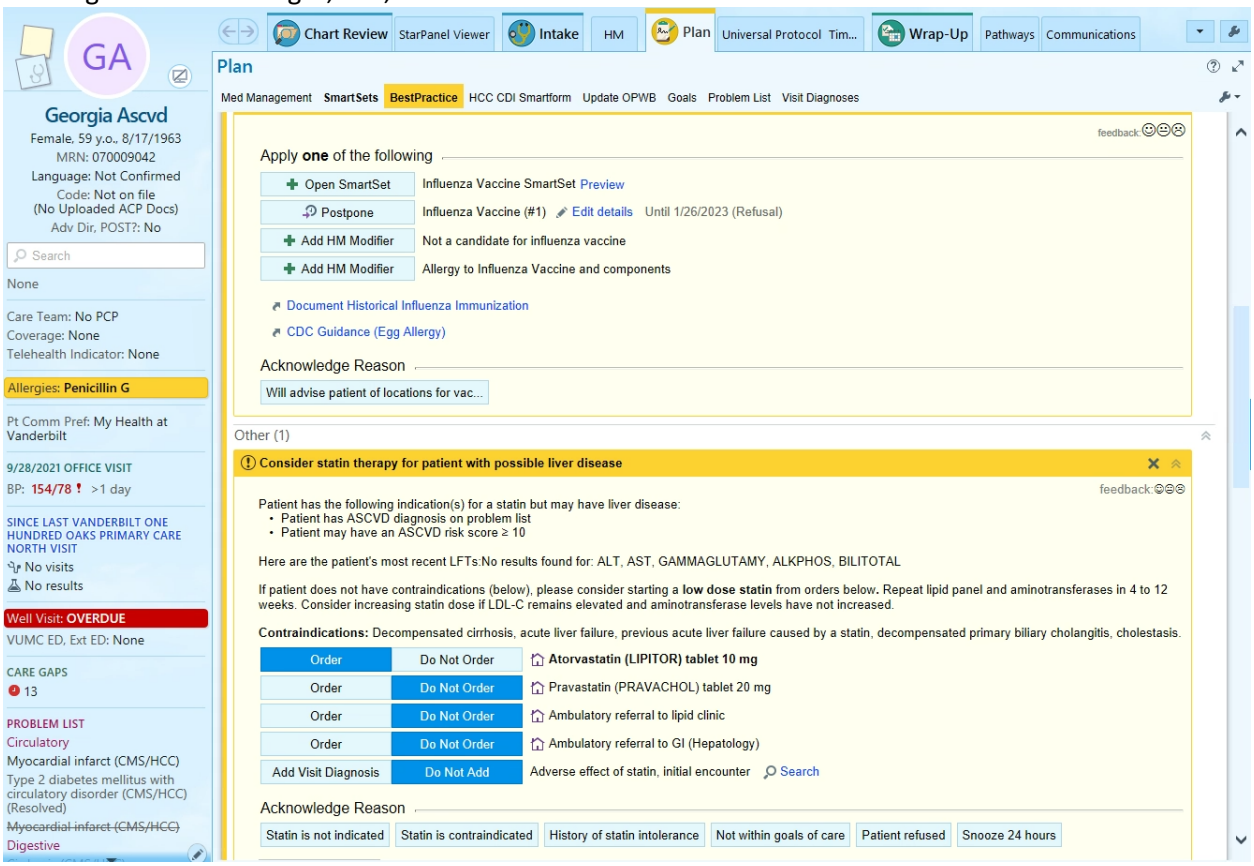

Figure 3. Example of a Non-Interruptive Alert Recommending Statin. This alert is shown within a test patient's chart. The clinician must select the "Plan" tab and then click on the "BestPractice" Navigator to see a list of on-demand reminders. Depending on the number of other non-interruptive reminders the patient is eligible for, the clinician may need to scroll through other reminders to find the statin reminder.

7.5 Control Group

For patients who are randomized to the control (routine care) arm, the system will record that the patient's provider was eligible for an alert. This will be done by triggering a "silent" alert which is not displayed to the clinician. This "silent alert" exists for data collection purposes. No alert recommending a statin will be displayed to the clinician, either in an interruptive or non-interruptive format.

7.6 Duration of the Intervention

As the randomization is anchored to the provider's patient, the provider will receive the same educational intervention for a given patient throughout the course of the study. For interruptive and non-interruptive alert arms, clinicians may or may not still be eligible for a repeat alert depending on how they interacted with the initial alert. If the patient is on a statin, the clinician will not be shown a repeat alert. If the clinician did not prescribe a statin and chose an acknowledgement reason such as "statin is contraindicated", the alert will not be shown again. If the clinician simply closed or "canceled" the alert during the first visit, or if the clinician did not interact with a non-interruptive alert, the alert will be displayed again at the next visit.

Any alert shown will be customized according to the patient's current clinical characteristics. For example, if the dose intensity indicated for the patient has changed, the reminder will display the currently recommended dose intensity.

7. 6 Blinding:

It would be impractical to pursue blinding for the study since the format of the alert is obvious when the alert is displayed. Given the nature of the study intervention, clinicians and investigators will not be blinded to group assignment.

8.0 Data Collection:

8.1 Outcomes:

Primary Effectiveness Outcome: The primary outcome is statin prescription within 24 hours of BPA firing.

This outcome will be measured within the first 24 hours after the interruptive, non-interruptive, or silent BPA is fired. Only prescriptions for statins which are signed by the provider, and not canceled, will be included in this measurement.

Justification for the Primary Effectiveness Outcome
The primary purpose of the reminder is to encourage statin prescription. Most prescribing as a result of the reminder is likely to occur within the first 24 hours after the alert.

Secondary Effectiveness Outcome:
The secondary outcomes are statin prescription within 12 months post-intervention, and the first post-intervention LDL-C level.

Exploratory Outcomes:
The exploratory outcomes are any non-statin lipid lowering agent prescription within 12 months post enrollment BPA firing, any statin prescription filled within 12 months of enrollment BPA firing, any new ASCVD event occurrence within 12 months of enrollment BPA firing, and time from enrollment BPA firing to statin prescription.

8.2 Baseline data:

Age, sex, height, weight, body mass index, race, ethnicity, active medical problems at the time of visit, active comorbidities, comorbidities contraindicating statin prescription (such as rhabdomyolyis, decompensated liver disease, active dialysis statin intolerance), pregnancy or lactation status, palliative care, ASCVD risk score, ASCVD diagnoses, diabetes, LDL-C, liver function tests (AST, ALT, alkaline phosphatase, bilirubin), glomerular filtration rate, orders for coronary calcium CT, status of current visit (acute or routine).

8.3 Data from enrollment to study end:

LDL-C, liver function tests (AST, ALT, alkaline phosphatase, bilirubin.) Date of visits to primary care, hepatology clinic, or lipid clinic. Record of statin reminder, including whether it is displayed, trigger for display, date and time, number of times displayed, role of clinician to whom it is displayed, whether reminder is accepted, acknowledgement reason selected if applicable, free-text comment if applicable. Date, time, and dose of prescription of lipid lowering agent such as statin, ezetimibe, bempedoic acid, PCSK9 inhibitor. Presence of prior statin prescription. Visit type (in person or telemedicine).

8.4 Outcome Data:

Primary Outcome: All statin prescriptions signed in the first 24 hours after intervention. Secondary Outcome: All statin prescriptions signed in the first 365 days after intervention. All LDL-C values resulting from samples collected after intervention and during study period. Exploratory Outcome: Ezetimibe, PCSK9 inhibitor, or bempedoic acid prescriptions signed in the first 365 days after the intervention. Filling of statin prescriptions within 365 days after the intervention. New ASCVD events recorded within 365 days after the intervention. Date and time of statin prescription signing within 365 days after the intervention.

9.0 Risks and Benefits

Lipid-lowering therapy with statins has been shown to reduce relative cardiovascular disease risk by approximately 30 percent. Thus, statin therapy in eligible patients is standard of care to reduce ASCVD risk, and multiple guidelines recommend statin therapy in eligible patients. While adverse reactions such as adverse muscle events and hepatic dysfunction are possible with stain therapy, randomized trials have shown only a slight increased risk of side effects with statin therapy as compared with placebo, and no increased risk of discontinuing therapy[12,13]. The study intervention is a reminder to clinicians to prescribe guideline-based care. BPAs are not new technology and are encountered on a daily basis by providers. Thus, there is no reason to believe that participation in this study would expose providers or patients to greater risk than those experienced as a part of routine care. This study has a greater benefit to society in the form of improved understanding of how to increase the following of guideline recommendations with EHR interventions.

A potential risk to patients participating in this study involves the collection of protected health information (PHI). In order to limit the associated risks, the minimum amount of PHI necessary for study conduct will be collected. After collection, the data will be stored in a secure, password-protected database only accessible by the investigators. After publication, a de-identified database will be generated to protect participant privacy.

10.0 Reporting of Adverse Events or Unanticipated Problems

Assuring participant safety is an essential component of this protocol. Electronic clinical reminders are standard within clinical practice, and statins are approved by the Food and Drug

Administration and used and recommended in clinical practice with an established safety profile. Accordingly, this trial does not plan to collect non-serious adverse events related to statin prescribing as suggested in FDA guidelines for Investigator Reporting (21 CFR 312.64(b)) for post-marketing outcome trials.

As the intervention is a reminder directed at clinicians to recommend an eligible patient receives guideline-based care, the study procedures do not represent a direct risk to providers or their patients above what would be incurred during usual care. Adverse events (AEs) associated with participating in this study are predominately limited to those resulting from loss of PHI confidentiality. To minimize this risk, a minimal amount of PHI will be collected to perform the study, and collection and storage will occur through secure online databases with access restricted to KSP. After data analysis is complete, PHI will no longer be accessed.

Adverse Event Reporting and Communication.

A system has been established to report and track interactions with the EHR-based reminder. Study personnel will monitor the integrity of data confidentiality to protect the safety of subjects and follow any breaches in confidentiality until the event resolves or is explained. Any loss of privacy will be recorded in the AE case report form in the electronic database and reported to the PI within 3 days of occurrence. The PI will report all reportable events to the IRB within 7 calendar days from the PI's knowledge of the event.

11.0 Study Withdrawal/Discontinuation

Because this intervention is targeting providers, does not force changes in clinical practice, and has no direct interaction with patients, patients will generally not have the option to self-withdraw from the study.

12.0 Statistical Considerations

Study Design and Sample Size Consideration

If we assume that the statin prescribing rate for the control arm (i.e., routine care, or "silent" alert) is 3%, an estimate derived from current clinical data, and the statin prescribing rate for the interruptive statin reminder arm is 6%, a total of 3,006 patients (1,002 patients per arm) would provide 90% power to detect the difference in the statin prescribing rates between the two arms at a type I error rate of 0.05. With a conventional study design, our planned sample size could be a total of 3,000 patients (1,000 patients per arm).

However, considering that this study is a 3-arm trial with substantial uncertainty on the effect size for both the interruptive statin reminder arm and the non-interruptive statin reminder arm, we designed an adaptive clinical trial with sample size adaptation. When sample size reaches 2,250 patients (750 patients per arm), we will conduct an interim analysis to re-estimate the sample size. At the interim, we will calculate the conditional power and re-estimate the sample size that will provide sufficient power. Should the interim analysis confirm that the originally

planned sample size of 3,000 patients (1,000 patients per arm) is sufficient, we will proceed without further adjustment and stop recruiting patients when the sample size reaches 3,000 patients (1,000 patients per arm) or the stopping decision is made, whichever occurs later. However, if the interim analysis indicates the need for an increased sample size, we will adjust accordingly based on the re-estimated sample size with the constraint of the maximum sample size of a total of 6,000 patients (2,000 patients per arm).

More specifically, at the interim, the statin prescribing rates for three arms will be estimated, and we will calculate the conditional powers for pairwise comparisons between all pairs of arms – i.e., A-B, B-C, C-A (as they will be still blinded) using the estimated statin prescribing rates. If the conditional powers for all pairs are less than 50% (i.e., the study is unfavorable), or the conditional powers for at least 2 of these pairwise comparisons are greater than 90% (i.e., the study is favorable), the study will continue until the planned sample size is reached. Otherwise, the sample size will be re-estimated so that the study is 90% powered to detect the largest and the second largest differences in the statin prescribing rates from the pairwise comparisons. The sample size will be increased to either the re-estimated sample size or the maximum sample size of a total of 6,000 patients, whichever is larger.

To examine the operating characteristics of the trial design, we performed simulations with 10,000 repetitions using various scenarios of the statin prescribing rate of the non-interruptive statin reminder arm between 3% (same as the control arm) and 6% (same as the interruptive statin reminder arm). Based on our simulation, our adaptive clinical trial design with the sample size adaptation controls a type I error rate under 0.05 and the power is at least 90% to detect the increase of 3% of the statin prescribing rate from the baseline statin prescribing rate of 3%.

Baseline Characteristics

To assess randomization success, we will summarize the distribution of baseline variables across the study arms. Categorical variables will be reported as frequencies and proportions while continuous variables will be summarized as mean with standard deviations (SD) or median with range and interquartile ranges (IQR). Variables reported will be specified in a formal Statistical Analysis Plan (SAP).

Primary Effectiveness Outcome Analysis

The primary outcome is a binary outcome of statin prescription at 24 hours post-randomization. To compare the primary outcome between the interruptive reminder arm, non-interruptive reminder arm, and control arm, a logistic regression will be performed with indicator variables for randomized group without adjusting for any other covariates. An overall test regarding whether at least one arm is different from other arms will be performed. If the overall test is significant at the level of 0.05, then additional test will be performed to determine which arm(s) are different compared to the control arm. The analysis set for the primary outcome will be described in the SAP.

Secondary Outcomes Analysis

The secondary outcomes include a binary outcome of statin prescription within 12 months post-randomization and first post-randomization LDL-C level. To compare each outcome between the interruptive reminder arm, non-interruptive reminder arm, and control arm, a logistic regression will be used to analyze the binary outcome of statin prescription within 12 months post-randomization while a linear regression analysis will be performed to compare LDL-C level between the arms. If the distribution of LDL-C levels is highly skewed, an ordinal logistic regression analysis will be used in place of a linear regression. The analysis set for the secondary outcomes will be described in the SAP.

Exploratory Outcomes Analysis

A logistic regression will be performed to compare the binary outcomes between intervention arms. Time from enrollment BPA firing to statin prescription will be compared between intervention arms using a Cox proportional hazard model and the differences in the outcome between arms will be visualized using a Kaplan-Meier curve.

Secondary Analysis

A secondary, covariate-adjusted analysis will be performed for the primary and the secondary outcomes using the same regression analysis methods as listed above. The selected covariates for each outcome will be detailed in the formal SAP.

13.0 Privacy/Confidentiality Issues

At no time during the course of this study, its analysis, or its publication will patient or provider identities be revealed in any manner. The minimum necessary data containing patient or provider identities will be collected. As quickly as feasible, all data collected will be stored on secure, password-protected servers with user-level access control. All patients will be assigned a unique study number for use in the computerized database. At the time of publication all identifiers will be removed.

14.0 Follow-up and Record Retention

Clinician BPA interactions, statin prescription status, and patient LDL-C outcomes will be followed after the intervention for one year. All data will be stored on secure servers with user-level access control until the time of study publication. At the time of publication, a de-identified version of the database will be generated. After study close, the PI will retain study data for a minimum of 3 years, consistent with institutional and federal policies.

15.0 Data and Safety Monitoring

Given the minimal risk of the study intervention, which is a reminder directed at clinicians to recommend an eligible patient receives guideline-based statin prescription, the principal investigator with serve as the Data and Safety Monitor. The PI will regularly monitor data from this trial, review and assess the performance of its operations, and consult with co-investigators and the IRB with respect to:

- Review of adverse events

- Possible modifications in the clinical trial protocol

16.0 References

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