Pragmatic Trial of Messaging to Providers about Treatment of Hyperlipidemia (PROMPT-Lipid)
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Protocol and SAP
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HRP-503B – BIOMEDICAL RESEARCH PROTOCOL
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Protocol Title

Pragmatic Trial of Messaging to Providers about Treatment of Hyperlipidemia (PROMPT-Lipid)

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INSTRUCTIONS

This template is intended to help investigators prepare a protocol that includes all of the necessary information needed by the IRB to determine whether a study meets approval criteria. **Read the following instructions before proceeding:**

1. Use this protocol template for a PI initiated study that includes direct interactions with research subjects. Additional templates for other types of research protocols are available in the system Library.

2. If a section or question does not apply to your research study, type “Not Applicable” underneath.

3. Once completed, upload your protocol in the “Basic Information” screen in IRES IRB system.

SECTION I: RESEARCH PLAN

Statement of Purpose
To evaluate the efficacy of automated electronic alerts containing guideline-based recommendations built into the EPIC electronic health record to improve rates of best practices in the treatment of patients with hyperlipidemia who present in the setting of outpatient internal medicine and cardiology practices at four teaching hospitals within the Yale New Haven Health System.

This study is being funded by Amgen because of its vested interested in the aim of the planned research, which is to improve the quality of hyperlipidemia care and management. However, this is an investigator-initiated study, and the Yale study team has full jurisdiction over the protocol, conduct, analysis, and publication of the research, of which Yale has full ownership. No medication is being explicitly provided to subjects as a result of this study.

Probable Duration of Project:
15 months (12 months for alerting and data collection, 3 months for data analysis and publication submission) for primary outcomes. There can be an optional additional 2 year follow up for long-term clinical outcome ascertainment and data analysis.

Background:
In the United States and most developed countries, cardiovascular disease (CVD), which includes coronary heart disease (CHD), stroke, and peripheral artery disease, is and will remain the leading cause of death in men and women. A key risk factor for CVD is dyslipidemia, in particular elevations in low-density lipoprotein cholesterol (LDL-C), treatment of which has been shown to dramatically reduce downstream risks of adverse cardiovascular events.[1, 2]

Recent professional society guidelines outline the use of pharmacological therapies for the reduction of LDL-C in very high risk patients, defined as patients with multiple ASCVD events or one ASCVD event and multiple clinical comorbidities (diabetes, hypertension, age > 65, among others).[6] These guidelines support the use of high intensity statin therapy, and then addition of non-statin therapies including ezetimibe and PCSK9 inhibitors if the LDL-C remains ≥70 mg/dL based on favorable results from several large clinical trials.

Despite these clear guideline recommendations, implementation of lipid lowering therapy has been poor across health care systems and there is substantial underuse of evidence based lipid lowering therapies.[7] Data from registries in the United States, Canada, and Europe show that <35% of eligible patients attain an LDL-C <70 mg/dL.[8] Since the benefit of lipid-lowering treatment seen in studies and recommended in the guidelines on cardiovascular prevention can only be fully realized if all patients are treated appropriately, there is a strong need for strategies aimed at improving adoption of the practice guidelines and the recommended therapies therein.

Several studies have found that real-time alerting to important clinical conditions, when fired in an appropriate and timely manner and with actionable interventions, can positively impact patient outcomes through increased physician awareness and adherence to best practices.[9, 10] Our group has extensive experience in the study of best practice alerts, and is currently enrolling the largest randomized trial of alerts for Acute Kidney Injury (N=6,030 patients). In the proposed study, we seek to evaluate whether automated electronic alerts that contain guideline-based recommendations and are

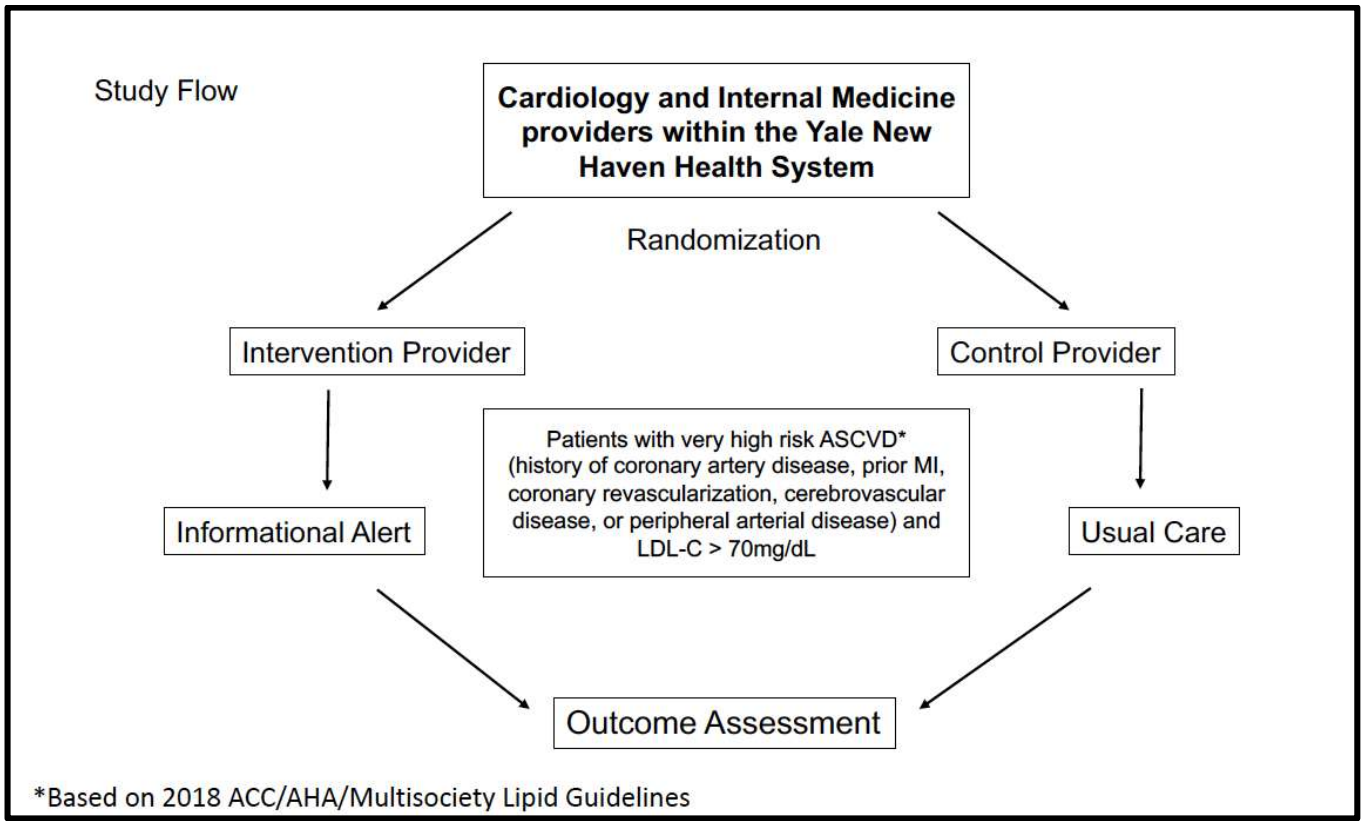
built into the Epic electronic health record can improve the management of hyperlipidemia among patients at very high risk for future ASCVD events who are seen in outpatient internal medicine and cardiology practices associated with four teaching hospitals within the Yale New Haven Health System, the 4th largest health system in the US. One hundred internal medicine and cardiology physicians will undergo cluster randomization to either the alert group or the control (usual care) group. Upon opening the order entry screen of a patient with hyperlipidemia, the alert group will receive an informational alert informing the provider that the patient has hyperlipidemia and is at very high risk for future ASCVD events and providing ACC/AHA-guideline-directed actionable items, including a link to a hyperlipidemia "order set" to include both diagnostic and therapeutic options. The primary outcome will be the proportion of patients who have intensification of their lipid lowering therapy (increase in statin dose or addition of ezetimibe or addition of a PCSK9 inhibitor) at 90-days. The secondary outcomes will be achieved LDL-C at 6-months and rates of hospitalization for myocardial infarction, stroke, unstable angina, coronary or peripheral artery revascularization.

Research Plan:

This study will be a randomized, parallel-group, single blind interventional trial designed to determine the efficacy of automated electronic alerts built into the EPIC electronic health record to improve the management of hyperlipidemia among patients at very high risk for future ASCVD events. The intervention will target outpatient cardiology and internal medicine providers associated with four teaching hospitals within the Yale New Haven Health System (including Greenwich Hospital, Bridgeport Hospital, Yale New Haven Hospital and St. Raphael's Campus).

Study Population: Patients with very high risk atherosclerotic cardiovascular disease (based on 2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol) and most recent LDL-C > 70mg/dL.

One hundred outpatient cardiology and internal medicine providers practicing at four teaching hospitals within the Yale New Haven Health System will undergo randomization to either an intervention (alert) group or a control (usual care) group. Those in the intervention group will receive an informational alert containing guideline-based recommendations for their eligible adult outpatients. Our study flow is the following:



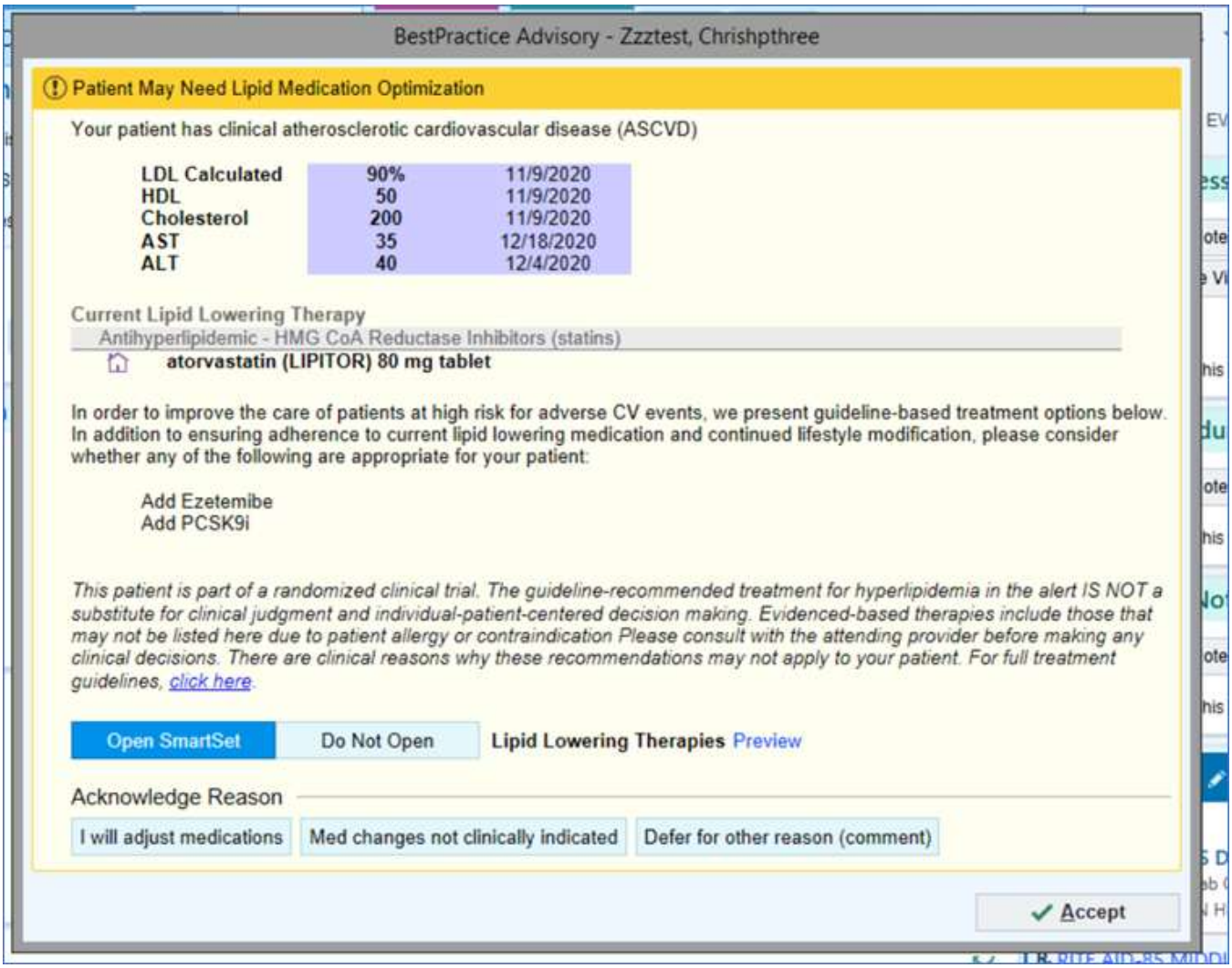
Outpatient cardiology and internal medicine providers in the Yale health system will be selected for potential participation in the study based on the frequency with which they see patients who meet the inclusion criteria (must see at least 10 potentially eligible patients per week). They will be identified based on a retrospective review of clinical encounters that include patients at very high risk for ASCVD events based on clinical guidelines within Epic and approached for consent to participate in the study. Once consented, we will determine baseline prescribing patterns for lipid lowering therapy (over 3-months) specifically looking at the proportion of very high risk ASCVD patients on high-intensity statin therapy, ezetimibe, or PCSK9 inhibitor as well as distribution of LDL-C. All physicians will then be randomized within Epic to either the intervention group or the control (usual care) group via a permutated block randomization scheme to ensure an equal number of providers in each study arm. Logic checks within the alerts ensure that once a provider is assigned to an arm, they remain in that arm for the remainder of the study. This will create 100 clusters (providers) to which eligible patient participants will be assigned upon their outpatient visit. In other words, any patient seen by a provider randomized to the intervention (alert) group will have an informational alert generated when their provider opens the order entry screen in the patient's medical record. On the contrary, any patient seen by a provider randomized to the control arm will not generate an alert and will receive usual care. Instead, a "silent alert" that simply registers the patient into the trial by the study team is generated. Because it is likely that providers may internalize the best practice metrics once repeatedly exposed to the alert, cluster randomization of patients at the level of the provider will ensure that providers consistently receive an alert or not, which will reduce contamination between study arms. It will also minimize the chance that providers get so accustomed to seeing an alert for hyperlipidemia that they will become less attentive to the condition in patients not generating an alert. Additional pre- and post-intervention analyses in the control group, leveraging the three-month baseline period, can assess the level of contamination and the effect of secular trends towards better care over time.

Once a patient is seen by an enrolled-provider, they will not generate further alerts. This ensures that the rare patient who is seen by two providers from different arms of the study cannot be enrolled twice.

Identification of patients to be involved in the study and generation of an alert (or not) will be performed entirely within the Epic medical records system based on inclusion and exclusion criteria outlined below. This will be done using a best-practice alert build developed by the data analytics team at Yale that will, upon opening the order entry screen in the patient's chart by a enrolled provider, examine the medical record to identify the patient as having very high risk for ASCVD (see ICD-10 codes below) as well as an LDL-C > 70mg/dL without a recent change in lipid lowering therapy (dose escalation or addition of new therapy). If these conditions are met, the patient will be included in the study and then depending on whether the provider is randomized to the alert or usual care arm, will determine whether an alert is shown upon entering the order screen within the medical record.

Providers in the intervention (alert) group will have an alert generated within the electronic medical record system for all patients who meet criteria. The alert will fire once per patient, during the patient's first eligible outpatient visit, when the provider opens the order entry screen in the patient's electronic medical record. This will maximize the chance that the alert appears at the most relevant place in the provider's workflow. There will be a 1-hour lockout feature such that a provider randomized to receiving alerts will not receive another alert within 1 hour but outside that window would receive another alert for the patient if they enter the order page of the record.

The alert will consist of a "pop-up" that notifies the physician that the patient is at very high risk for ASCVD events, displays the most recent cholesterol values and current lipid lowering therapy. In addition to noting that the provider should ensure adherence to both current lipid-lowering therapy and lifestyle modifications, a link to full treatment guidelines for hyperlipidemia is also provided and includes a continuing medical education (CME) option to obtain CME credits. An example of what this alert will look like is as follows:



At the bottom of the alert, there will be an option to “dismiss” or accept the alert. If a provider chooses to dismiss the alert, a drop-down menu will appear that will display options for the reason for dismissing the alert from which the provider can select, including that the alert was not germane to the patient, or that another clinical reason precludes them from intensifying the patient’s lipid-lowering therapy. Providers can choose to accept or dismiss the alert and act accordingly based on their own clinical judgement. They can decide at their own discretion whether or not following the guidelines included in the alert is appropriate or not for their patient and are not obligated or required to take any specific action relating to this alert. This alert and its associated guidelines are not a substitute for a clinical consultation and recommendation.

Engaging Providers: The study team will be blinded to the treatment assignment until the end of the trial period. We will engage in pre-trial outreach to all eligible providers, informing them of the background and rationale of the study, reviewing evidence-based guidelines, and outlining the randomized nature of the study and the alert intervention. We will additionally inform them that limited data is being collected regarding provider behavior. However, we will also make it clear that such data will not be linked to individual clinicians and no clinicians will be linked to any specific outcome.

Our primary outcome will be proportion of patients with intensification of lipid lowering therapy, defined by an increase in statin dose, addition of ezetimibe, or addition of PCSK9 at 90-days. The key secondary endpoint will be the achieved LDL-C (fasting or non-fasting[11]) at 6-months. Other outcomes

of interest will be the proportion of patients with an LDL-C <70 mg/dL and the proportion with an LDL-C < 55 mg/dL. An exploratory endpoint, in an optional extension phase, we will assess the rates of long-term outcomes, specifically the rate of major adverse cardiac events (MACE) defined as hospitalization for myocardial infarction, cerebrovascular accident/transient ischemic attack, or coronary or peripheral arterial revascularization. All outcomes will be abstracted from the patient chart via medical record review.

Additional outcomes will collect provider education and experience metrics. We will assess the percentage of providers who visit the guideline site via the link provided within the alert. Further, all providers will be asked to complete both a pre- and post- study survey that will assess their knowledge of and the level of comfort with the ACC/AHA guidelines for hyperlipidemia. The post survey will also include questions that will allow us to assess provider approval and overall acceptance of the alert, assessing their opinions on user friendliness, usefulness versus disruptiveness, and overall user experience. Analysis of responses will allow us to assess which aspects of the alert were most helpful and which could be improved in possible future iterations of this alert and others.

Alerts will no longer be seen by providers and removed from Epic once enrollment is complete but may be reinstated should our data and further study prove that such alerts are useful and beneficial to the patient population.

Objectives and Endpoints: The objective of this study is to evaluate the efficacy of targeted electronic alerts to improve rates of best practices in the treatment of patients with hyperlipidemia who are seen by outpatient cardiology and internal medicine physicians. The primary outcome will be the proportion of patients who have intensification of their lipid lowering therapy (increase in statin dose or addition of ezetimibe or addition of a PCSK9 inhibitor) at 90-days. The secondary outcomes will be achieved LDL-C (fasting or non-fasting) at 6-months and rates of hospitalization for myocardial infarction, stroke, unstable angina, coronary or peripheral artery revascularization.

Consent and Survey distribution: Provider consent will be collected in one of several ways, and we are requesting a waiver of documentation of consent for providers in this study, as the study poses minimal risk. The first method for provider outreach and consent will be done through university email in which a link to the consent and provider survey will be provided. In this method, the consent and survey will be administered electronically via REDCap (Research Electronic Data Capture) and an electronic signature will be captured. This link to the consent form will be sent to all eligible providers that will direct them to our online consent form in REDCap for review and signature. If the provider consents, we will follow up and send a survey link that will direct them to the survey form in REDCap.

Should provider outreach via email prove difficult, we will use other means to contact eligible providers. The first will be via an Epic inbasket message, where the informed consent will be copied directly into the body of an Epic message that is then sent to the eligible provider. The provider can then read through the consent and reply back to the inbasket message with “Yes I do consent” or “No I do not consent”, without requiring a signature on the consent document. This response will be document, and consented providers will then be sent further instructions and a link for the REDCap survey.

We will also contact providers via telephone, where study personnel will describe the study via phone, answer questions, and receive and document provider verbal consent. Consented providers will then be sent further instruction and a link for the REDCap survey.

If/when feasible, study coordinators will also conduct in-person recruitment to obtained signed consent.

Data for this study (consent and survey only) will be collected, recorded and stored using REDCap. REDCap is a secure, web application designed to support data capture for research studies. It includes features for HIPAA compliance including real-time data entry validation (e.g. for data types and range checks), a full audit trail, user-based privileges, de-identified data export mechanism to statistical packages (SPSS, SAS, Stata and R), and integration with the institutional Active Directory. Access to study data in REDCap will be restricted to the members of the study team with authentication through University NetID credentials. The REDCap@Yale database and web server are housed on secure platforms that are backed up daily. REDCap@Yale meets the security standards for use with high risk data as set forth by the Yale Information Security Office. Electronic data will be kept in password-protected files located within REDCap™. Access to the study's data in REDCap™ will be restricted to the members of the study team by username and password.

1. Genetic Testing N/A ☒

A. Describe
   i. the types of future research to be conducted using the materials, specifying if immortalization of cell lines, whole exome or genome sequencing, genome wide association studies, or animal studies are planned *Write here*
   ii. the plan for the collection of material or the conditions under which material will be received *Write here*
   iii. the types of information about the donor/individual contributors that will be entered into a database *Write here*
   iv. the methods to uphold confidentiality *Write here*

B. What are the conditions or procedures for sharing of materials and/or distributing for future research projects? *Write here*
C. Is widespread sharing of materials planned? *Write here*
D. When and under what conditions will materials be stripped of all identifiers? *Write here*
E. Can donor-subjects withdraw their materials at any time, and/or withdraw the identifiers that connect them to their materials? *Write here*
   i. How will requests to withdraw materials be handled (e.g., material no longer identified: that is, anonymized) or material destroyed)? *Write here*
F. Describe the provisions for protection of participant privacy *Write here*
G. Describe the methods for the security of storage and sharing of materials *Write here*

2. **Subject Population:**

We will recruit and consent 100 providers who practice Cardiology and Internal Medicine at or associated with one of the 4 teaching hospitals of the Yale New Haven Health System (to include Yale New Haven Hospital and St. Raphael's Campus, Bridgeport Hospital, and Greenwich Hospital). These practices may be located on site or at satellite offices across the health care system. Providers will be selected based on the number of hyperlipidemia patients seen, on average, to increase efficiency of our study and more quickly reach our target patient enrollment number (see below). These providers will be selected through retrospective review of records from outpatients within the Yale New Haven system and must see a minimum of 10 eligible patients per week. While providers will be recruited to the study and randomized, the aim of the study is to assess the efficacy of alerts on improving the care of patients with hyperlipidemia. Thus, this population of patients will be participants in the study. Our best practice alert will identify patients who meet specific inclusion and exclusion criteria (outlined below), for a target sample size of 2500. These patients will then either receive usual care, or, if seen by a physician randomized to the intervention group, will have an alert

generated in their medical record to inform their provider of the presence of very high risk for ASCVD events and elevated LDL-C. Because the study presents minimal risk to patients, we will be requesting a waiver of informed consent at the patient level.

3. **Subject classification:** Check off all classifications of subjects that will be specifically recruited for enrollment in the research project. Will subjects who may require additional safeguards or other considerations be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐Children	☐ Healthy	☐Fetal material, placenta, or dead fetus
☐Non-English Speaking persons	☐ Prisoners	☐Economically disadvantaged
☐Decisionally Impaired	☐ Employees	☐Pregnant women and/or fetuses
☐Yale Students	☐ Females of childbearing potential	

NOTE: Is this research proposal designed to enroll children who are wards of the state as potential subjects?
Yes ☐ No ☒

4. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion?

For patients:
Inclusion Criteria
- Adults 18 years old or greater
- Currently being seen as an outpatient of a cardiology or internal medicine practice associated with a teaching hospital within the Yale New Haven Health System (Yale New Haven Hospital, St. Raphael's Campus, Bridgeport Hospital and Greenwich Hospital). Clinics may be on site or a satellite office associated with the hospital.
- Very high risk for ASCVD defined as history of a major ASCVD event (at least one ICD-10 code below) AND most recent lipid profile with LDL-C > 70mg/dL with or without other high-risk features (diabetes, chronic kidney disease, or age > 65).

Exclusion Criteria
- Heart transplant
- Left Ventricular Assist Device
- Hospital inpatient status
- Pregnancy
- Have opted out of clinical research via MyChart

Providers must be practicing at an outpatient cardiology and internal medicine practices at or associated with one of the four teaching hospitals within the Yale New Haven Health System (located on site or at a satellite office) and will be selected for study participation based on the frequency with which they see patients who meet the above criteria, based on a retrospective review (must see a minimum of ten eligible patients per week).

Table outlining conditions that comprise the definition of a history of major ASCVD event (adapted from Colantonio LD et al. JACC 2019;74: 2496-2507).

Condition	Algorithm	List of diagnosis and procedure codes

History of myocardial infarction	• ≥1 overnight inpatient claim with a discharge diagnosis code for acute myocardial infarction in any discharge diagnosis position. • ≥1 inpatient claim with a discharge diagnosis code for old myocardial infarction in any discharge diagnosis position. • ≥2 outpatient claims with a diagnosis code for old myocardial infarction at least 30 days apart, but less than 365 days apart.	*Diagnosis codes for acute myocardial infarction:* ICD9: 410.x0, 410.x1. ICD10: I21.x, I21.xx, I22.x. *Diagnosis codes for old myocardial infarction:* ICD9: 412. ICD10: I25.2.
Unstable angina	≥1 inpatient claim with a discharge diagnosis code for unstable angina in any discharge diagnosis position within past 12 months.	ICD9 diagnosis codes: 411.1, 411.81, 411.89. ICD10 diagnosis codes: I20.0, I24, I24.0, I24.8, I24.9, I25.110, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790.
Ischemic stroke	≥1 overnight inpatient claim with a discharge diagnosis code for ischemic stroke in any discharge diagnosis position	ICD9 diagnosis codes: 433.x1, 434.x1. ICD10 diagnosis codes: I63, I63.x, I63.xx, I63.xxx.
Peripheral artery disease	• ≥1 inpatient claim with a discharge diagnosis code for peripheral artery disease in any discharge diagnosis position. • ≥2 outpatient claims with a diagnosis code for peripheral artery disease at least 30 days apart, but less than 365 days apart.	ICD9 diagnosis codes: 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.3, 440.30, 440.31, 440.32, 440.4, 443.9. ICD10 diagnosis codes: I70.2, I70.20, I70.201, I70.202, I70.203, I70.208, I70.209, I70.21, I70.211, I70.212, I70.213, I70.218, I70.219, I70.22, I70.221, I70.222, I70.223, I70.228, I70.229, I70.23, I70.231, I70.232, I70.233, I70.234, I70.235, I70.238, I70.239, I70.24, I70.241, I70.242, I70.243, I70.244, I70.245, I70.248, I70.249, I70.25, I70.26, I70.261, I70.262, I70.263, I70.268, I70.269, I70.29, I70.291, I70.292, I70.293, I70.298, I70.299, I70.3, I70.30, I70.301, I70.302, I70.303, I70.308, I70.309, I70.31, I70.311, I70.312, I70.313, I70.318, I70.319, I70.32, I70.321, I70.322, I70.323, I70.328, I70.329, I70.33, I70.331, I70.332, I70.333, I70.334, I70.335, I70.338, I70.339, I70.34, I70.341, I70.342, I70.343, I70.344, I70.345, I70.348, I70.349, I70.35, I70.36, I70.361, I70.362, I70.363, I70.368, I70.369, I70.39, I70.391, I70.392, I70.393, I70.398, I70.399, I70.4, I70.40, I70.401, I70.402, I70.403, I70.408, I70.409, I70.41, I70.411, I70.412, I70.413, I70.418, I70.419, I70.42, I70.421, I70.422, I70.423, I70.428, I70.429, I70.43, I70.431, I70.432, I70.433, I70.434, I70.435, I70.438, I70.439, I70.44, I70.441, I70.442, I70.443, I70.444, I70.445, I70.448, I70.449, I70.45, I70.46, I70.461, I70.462, I70.463, I70.468, I70.469, I70.49, I70.491, I70.492, I70.493, I70.498, I70.499, I70.5, I70.50, I70.501, I70.502,

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Endovascular stent graft placement	• ≥1 inpatient claim with a diagnosis-related group code or a current procedure terminology code for endovascular stent graft placement. • ≥1 outpatient claim with a current procedure terminology code for endovascular stent graft placement.	Diagnosis-related group codes: 237, 238. Current procedure terminology code: 34802, 34825, 34826.

5. How will **eligibility** be determined, and by whom?

Eligibility of the patients will be assessed electronically, without human intervention, within the Epic best practice alert framework. Upon the opening of the order entry screen in the patient's chart, this framework will automatically assess inclusion criteria. Those patients that meet the inclusion criteria and who have no exclusion criteria will be automatically enrolled and will be placed in the randomization group according to the physician they are being cared by. Selection of providers will be performed via retrospective review of past outpatients with hyperlipidemia and based on the frequency with which they care for such patients (must see a minimum of 10 eligible patients per week to be included).

6. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

The risk to patients in this study is minimal, as patients will receive usual care regardless of the randomization group of their primary care provider. The informational alert simply synthesizes data that is already present in the medical record and available to providers. Potential risks include:

- Loss of confidentiality, as with any study that collects patient information and data.

- Overtreatment: If alerts affect physician behavior, then providers randomized to the alert arm may be more likely to order certain tests or interventions. These interventions fall within the standard-of-care and may benefit patients, but it is also possible that additional interventions may not benefit patients and could incur additional costs.

The risk to providers is also minimal, as they are simply receiving an alert containing information already available to them. Potential risks include:

- Disturbance to workflow
- Alert fatigue: These studies represent an additional alert to which providers will be exposed and prior research has demonstrated that more frequent alerting may lead to less attention to other alerts. While a potential risk, this is also a major motivation of this line of research, as it is only via randomized trials that truly effective alerts can be discovered and ineffective ones be discarded.

7. **Minimizing Risks:**

There is limited risk to the loss of confidentiality, as only de-identified data is being stored for analysis. All data in this study will be stored on a secured central server within the Program of Applied Translational Research. The server is only accessible from within the Yale intranet (or via VPN remotely) and additionally requires separate logon username and password. Data abstracted from the medical record will be de-identified, with a linking file retained in a separate location that will allow for merging of longitudinal outcomes into our dataset and for future linking of de-identified data to protected health information (PHI) for the purpose of potential future studies. Studies that require the use of PHI (for example, linking patient info to national outcomes databases) will require approval of both the manuscript and executive committees and a separate IRB approval. De-identified data will be stored on a secure server, accessed via "dumb" terminals, and all analyses will proceed on that server alone. De-identified data will be transmitted to outside investigators using secure, encrypted channels upon approval of the manuscript committee. The study is not causing any novel data to be gathered about any patient; it only gathers data from already-existing electronic health records. No PHI is included in the data being analyzed or published. Study participants therefore face no greater dangers of loss of confidentiality than they already face as patients. This data is not subject to any data sharing agreements. As this will be a large and useful data set that may be utilized in future research protocols, we plan to maintain both the de-identified data set and the linking dataset for at least the duration of IRB approval, and will seek permission to maintain those files on a yearly basis from the IRB if the research protocol is renewed. We will attempt to minimize disruption to workflow by creating an alert with a simple, user-friendly interface that links directly to actionable items. The alert will appear when the physician opens the order entry system, the most relevant place in the workflow. The alert will only appear once per patient, so we do not anticipate a large contribution to alert fatigue.

8. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.)
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? This protocol presents minimal risk to all subjects.
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? N/A
    c. Include an appropriate Data and Safety Monitoring Plan. Examples of DSMPs are available here http://your.yale.edu/policies-procedures/forms/420-fr-01-data-and-safety-monitoring-plans-templates for
        i. Minimal risk
        ii. Greater than minimal

The principal investigators (PI) is responsible for monitoring the data, assuring protocol compliance, and conducting the safety reviews at the specified frequency regularly. During the review process the PIs will evaluate whether the study should continue unchanged, require modification/amendment, or close to enrollment. The PIs or the Institutional Review Board (IRB) has the authority to stop or suspend the study or require modifications.

Despite this being a minimal risk study, we reviewed results of the AKI-Alert study that was recently completed that showed a small signal of harm at a non-teaching hospital within the YNHS. We realize that heart failure is an entirely different disease state and the intervention being tested in PROMPT-LIPID is strictly guideline based. Out of an abundance of caution, we decided to include an independent DSMB that will review the study results at 25% and 50% enrollment. These have been made in partnership with the leadership at both Yale School of Medicine/Yale Center for Clinical Investigation (YCCI) and Yale New Haven Hospital: Drs. Brian Smith (YCCI), Teisha Johnson (YCCI), Allen Hsaio (YNHS), and Nitu Kashyap (YNHS) who believe that studies of decision support tools continue to pose minimal risk to patients. Of note, we are also restricting the study to teaching hospitals within the YNHS: Yale New Haven, Greenwich, Bridgeport, Saint Raphael.

This protocol presents minimal risks to the subjects and Unanticipated Problems Involving Risks to Subjects or Others (UPIRSOs), including adverse events, are not anticipated. In the unlikely event that such events occur, Reportable Events (which are events that are serious or life-threatening and unanticipated (or anticipated but occurring with a greater frequency than expected) and possibly, probably, or definitely related) or Unanticipated Problems Involving Risks to Subjects or Others that may require a temporary or permanent interruption of study activities will be reported immediately (if possible), followed by a written report within 5 calendar days of the Principal Investigator becoming aware of the event to the IRB (using the appropriate forms from the website) and any appropriate funding and regulatory agencies. The investigator will apprise fellow investigators and study personnel of all UPIRSOs and adverse events that occur during the conduct of this research project through regular study meetings and via email as they are reviewed by the principal investigator.

d. For multi-site studies for <u>which the Yale PI serves as the lead investigator</u>:
   i. How will adverse events and unanticipated problems involving risks to subjects or others be reported, reviewed and managed? The PI will oversee the safety of the study and all adverse and unanticipated events will be reported to the IRB using standard reporting protocols.
   ii. What provisions are in place for management of interim results? Interim results will be managed by Yale study personnel.
   iii. What will the multi-site process be for protocol modifications? IRB approval will be obtained at all sites not covered by Yale's IRB and we will make modifications accordingly.

In addition, the following safety reporting processes will be implemented:

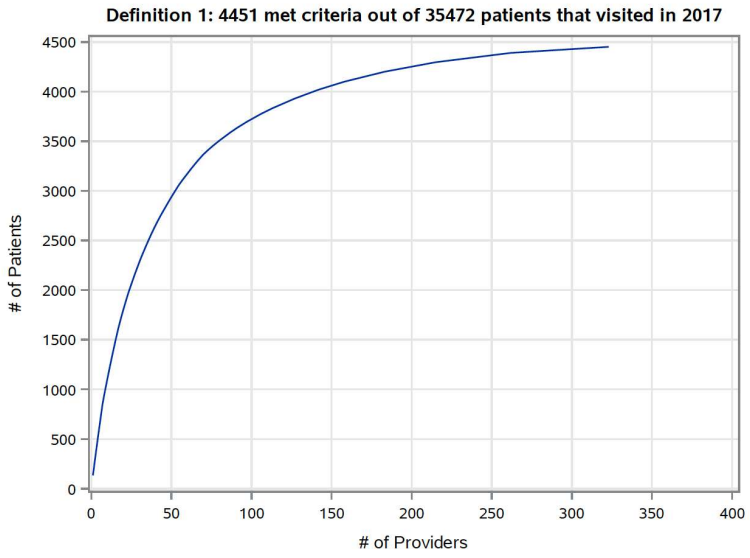
Safety Data	**Timeframe for submission to Amgen**
Adverse events considered related to Amgen drug	Per contractual agreement, send ONLY to Regulatory Agency per local regulatory requirements (spontaneous reporting)

Safety Data	**Timeframe for submission to Amgen**	**Send to**
Listing for Safety data reconciliation[b]	Once per year and at the end of the study	NASCR Manager
<u>Annual Safety Report</u>	Annually	

(eg, EU Clinical Trial Directive DSUR and US IND Annual Report)		NASCR Manager
Other aggregate analyses (any report containing Safety data generated during the course of the study)	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.)	NASCR Manager
Final (End of Study Report, including): • Unblinding data for blinded studies • Reports of unauthorized use of a marketed product	At the time of Sponsor submission to any body governing research conduct (eg. RA, IRB etc.) but no later than 1 calendar year of study completion	NASCR Manager

9. **Statistical Considerations:**

Initial review of retrospective data for calendar year 2017 revealed 35,472 unique individuals who underwent LDL testing at a Yale-affiliated practice. Of those, 4,451 had ASCVD (one ICD-10 code) and LDL-C > 70mg/dL. The following graphic displays the cumulative number of unique eligible patients attained (y-axis) by interfacing with a given number of providers (x-axis), starting with the provider who sees the most patients meeting inclusion criteria.



As displayed above, cluster-randomization of the top 100 providers (in terms of number of patients with high-LDL seen; at least 10 per week) would include approximately 3700 unique patients and we are proposing to enroll 2500 patients over 9 months. Randomizing 100 providers (50 in the alert group and 50 in the control group with an equal number of cardiology and internal medicine providers in each arm – 25 patients per provider) would give 80% power to detect a difference in intensification of lipid lowering therapy from 5% (current ezetimibe rate) to 9.3% and 90% power to detect a difference from 5% to 10.7%, assuming a conservative intra-class correlation coefficient of 0.05. Similarly, we would have 80% power to detect an increase in PCSK9 inhibitor use from <0.2% to 1.9% and 90% power to detect an increase from <0.2% to 2.4%. The primary analysis will be conducted using logistic regression where the independent variable (primary endpoint) is the proportion of the patients who have intensification of their lipid lowering therapy and the primary dependent variable is randomization status. The regression will be clustered at the provider level.

SECTION II: RESEARCH INVOLVING DRUGS, BIOLOGICS, RADIOTRACERS, PLACEBOS AND DEVICES

If this section (or one of its parts, A or B) is not applicable, check off N/A and delete the rest of the section.

A. RADIOTRACERS ☒N/A

B. DRUGS/BIOLOGICS ☒N/A

B. DEVICES ☒N/A

SECTION III: RECRUITMENT/CONSENT AND ASSENT PROCEDURES

1. Targeted Enrollment: Give the number of subjects: 100 providers, 2500 patients

a. Targeted for enrollment at Yale for this protocol: 100 providers, 2500 patients

b. If this is a multi-site study, give the total number of subjects targeted across all sites: N/A

2. Indicate recruitment methods below. Attach copies of any recruitment materials that will be used.

☐ Flyers	☐ Internet/web postings	☐ Radio
☐ Posters	☒ Mass email solicitation (providers only)	☒ Telephone (providers only)
☐ Letter	☐ Departmental/Center website	☐ Television
☒ Medical record review*	☐ Departmental/Center research boards	☐ Newspaper
☐ Departmental/Center newsletters	☐ Web-based clinical trial registries	☐ Clinicaltrails.gov
☐ YCCI Recruitment database	☐ Social Media (Twitter/Facebook):	
☐ Other:		

* **Requests for medical records should be made through JDAT as described at** http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx

3. Recruitment Procedures:

a. Describe how potential subjects will be identified. Patient subjects will be identified using an electronic algorithm that interfaces with Epic databases. Provider subjects will be identified using retrospective review and based on frequency with which providers see hyperlipidemia patients.

b. Describe how potential subjects are contacted. There will be no formal contact between patient subjects and study personnel and we will be requesting a waiver of informed consent for patients. Providers will be contacted and asked to consent for study participation via one of the methods described above (via email, Epic in basket messaging, and telephone). Pre-trial education during the consent process will be performed, as well periodic outreach to all participating providers. Who is recruiting potential subjects? For patients, this will be done electronically via the electronic health record. Patients will be identified if they are seen in outpatient general medicine or cardiology clinic and meet the inclusion and exclusion criteria stated above. Providers will be recruited and contacted by study coordinators and the principle investigator.

4. Assessment of Current Health Provider Relationship for HIPAA Consideration:

Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐Yes, all subjects

☐Yes, some of the subjects

☒No

If yes, describe the nature of this relationship. *Write here*

5. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only. Note: if you are collecting PHI as part of a phone or email screen, you must request a HIPAA waiver for recruitment purposes.)
   Choose one:
   ☒ For entire study – for patient subjects
   ☐ For recruitment/screening purposes only
   ☐ For inclusion of non-English speaking subject if short form is being used and there is no translated HIPAA research authorization form available on the University's HIPAA website at hipaa.yale.edu.

   i. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data: Consent would not be practical, as it would require informing patients in the control arm that they have hyperlipidemia. This could substantially alter the patient-physician relationship as well as bias the results, as patients could essentially act as an "alert" to physicians in the control arm. Further, because the alert fires in real-time at the time of the patient's office visit and as soon as the algorithm assess the patient's inclusion/exclusion criteria, it would be impractical to be able to reach all 2500 patients for consent, who will be at various outpatient settings throughout the Yale New Haven Health System. Because the study poses minimal risk, no procedures are being conducted that require consent outside of the research paradigm, not does a waiver violate the rights or welfare of patients, a waiver of HIPAA authorization is requested.

   ii. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data: *Write here*

The investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

6. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.
   Process of Consent/Assent: Eligible providers will be approached for consent by one of the methods described above. In cases where signed consent can occur, providers will be emailed a linkto the electronic REDCap consent form. The email will be sent by one of the study team members. The providers consent to participation by typing in their first and last name, include date/time of consent, and by signing the electronic consent. It will also have providers give their address, telephone number, and date of birth for purposes of payment through the OnCore system. Following that, the providers click on the "submit" button and the study team will then send a copy of the signed form to the provider along with a link to the REDCap survey.

   Should this method prove difficult, consent with waiver of documentation will be attempted via either Epic inbasket messaging or via telephone with verbal consent.

Patient subjects will not be informed of their randomization status or participation in this trial as the trial could not be feasibly performed if subjects were told they were enrolled.

All investigators will be blinded to treatment assignment until the end of the trial period. Care providers will, obviously, not be blinded to the intervention as they are receiving the alert.

7. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.
   The principle investigator and study coordinators obtaining consent will answer any and all questions posed by the subject and will ask questions regarding their participation and understanding of the study in order to ensure that the subject knows the purpose of the study, its risks, and benefits.

8. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. If enrollment of these subjects is anticipated, translated copies of all consent materials must be submitted for approval prior to use.
   N/A

As a limited alternative to the above requirement, will you use the short form* for consenting process if you unexpectedly encounter a non-English speaking individual interested in study participation and the translation of the long form is not possible prior to intended enrollment? YES ☐ NO ☐

Note* If more than 2 study participants are enrolled using a short form translated into the same language, then the full consent form should be translated into that language for use the next time a subject speaking that language is to be enrolled.

Several translated short form templates are available on the HRPP website (yale.edu/hrpp) and translated HIPAA Research Authorization Forms are available on the HIPAA website (hipaa.yale.edu). If the translation of the short form is not available on our website, then the translated short form needs to be submitted to the IRB office for approval via modification prior to enrolling the subject. ***Please review the guidance and presentation on use of the short form available on the HRPP website.***

If using a short form without a translated HIPAA Research Authorization Form, please request a HIPAA waiver in the section above.

9. Consent Waiver: In certain circumstances, the HIC may grant a waiver of signed consent, or a full waiver of consent, depending on the study. If you will request either a waiver of consent, or a waiver of signed consent for this study, complete the appropriate section below.

☐**Not Requesting any consent waivers**

☒**Requesting a waiver of signed consent: (for provider subjects only)**

☐ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ **Entire Study (**Note that an information sheet may be required.)

For a waiver of signed consent, address the following:

- Would the signed consent form be the only record linking the subject and the research? **YES ☒ NO ☐**
- Does a breach of confidentiality constitute the principal risk to subjects? **YES ☒ NO ☐**

OR

- Does the research pose greater than minimal risk? **YES ☐ NO☒**
- Does the research include any activities that would require signed consent in a non-research context? **YES ☐ NO ☒**

☒ Requesting a waiver of consent: (for patient subjects only)

☐ **Recruitment/Screening only** *(if for recruitment, the questions in the box below will apply to recruitment activities only)*

☒ **Entire Study** for patient subjects only

For a full waiver of consent, please address all of the following:

- Does the research pose greater than minimal risk to subjects?
  ☐ **Yes** ***If you answered yes, stop. A waiver cannot be granted.***
  ☒ **No**
- Will the waiver adversely affect subjects' rights and welfare? **YES ☐ NO☒**
- Why would the research be impracticable to conduct without the waiver? Consent would not be practical, as it would require informing patients in the control arm that they have hyperlipidemia. This could substantially alter the patient-physician relationship as well as bias the results, as patients could essentially act as an "alert" to physicians in the control arm. Further, because the alert fires in real-time at the time of the patient's office visit and as soon as the algorithm assess the patient's inclusion/exclusion criteria, it would be impractical to be able to reach all 6000 patients for consent, who will be at various outpatient settings throughout the Yale New Haven Health System. Because the study poses minimal risk, no procedures are being conducted that require consent outside of the research paradigm, not does a waiver violate the rights or welfare of patients, a waiver of informed consent is requested.
- Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date? Results of the study will not be returned to the subject at a later date, as they will not be pertinent to the subjects. Post-hoc disclosure of the nature of the study to the subjects may generate undue stress and concern on the part of the subject as to the quality of their overall clinical care.
  We will update all clinicians of the results of this trial after trial completion but will not collect data that would tie a specific clinician to an outcome. For example, while we would inform clinicians if the alerts increased the use of certain drugs, we will not be able to tell them what their specific rate of drug initiation was.

SECTION IV: PROTECTION OF RESEARCH SUBJECTS

Confidentiality & Security of Data:

1. What protected health information (medical information along with the HIPAA identifiers) about subjects will be collected and used for the research? Patient information to be collected includes name, SSN, zip code, DOB, outpatient visit date, medical record number, laboratory values, provider notes, medical procedures, medical history, and medication lists.

2. How will the research data be collected, recorded and stored? All data, both patient and provider, will be collected electronically by an automated algorithm that interfaces with the EPIC user database system, developed by JDAT. Data will be skimmed from the EHR, processed electronically, encrypted, deidentified, and transferred to a secure server for storage and later analysis. As discussed above, the primary dataset will contain no PHI. We will maintain a separate "linking file" that contains all PHI and will be stored on a separate server to limit the risk of accidental disclosure. The linking file is being maintained for merging of longitudinal outcomes into our dataset and for potential future linking to national databases of death and dialysis.

   We also plan to share de-identified data with Amgen under the appropriate data sharing agreements. We will provide periodic transfer of this data via encrypted secure file transfer.

3. How will the digital data be stored? ☐CD ☐DVD ☐Flash Drive ☐Portable Hard Drive ☒Secured Server ☐Laptop Computer ☐Desktop Computer ☐Other

4. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during and after the subject's participation in the study? All data will be stored on an encrypted, HIPAA-Compliant server with 2-factor authentication. Data will not be stored on personal computing devices of any kind. The server will only be accessible from within the Yale firewall or via VPN. No portable devices will be used to store study data at any time.

All portable devices must contain encryption software, per University Policy 5100. If there is a technical reason a device cannot be encrypted please submit an exception request to the Information Security, Policy and Compliance Office by clicking on url http://its.yale.edu/egrc or email it.compliance@yale.edu

5. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured. PHI will be deleted by study personnel within one year of closing of the study.

6. If appropriate, has a Certificate of Confidentiality been obtained? *N/A*

SECTION V: POTENTIAL BENEFITS

Potential Benefits:
Patient subjects in this study may benefit from their provider being given information about the presence of hyperlipidemia. This benefit may be derived from closer monitoring of their condition, and increased use of best practices to diagnose and treat their condition. Regardless of the outcome for participants, the results of these studies may lead to significant societal benefit, as positive results would lead to broader adoption of an effective alerting system that would lead to improved treatment for hyperlipidemia patients, and a negative study would lead to less enthusiastic adoption of ineffective alerting that would otherwise contribute to alert fatigue.

SECTION VI: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?
   Usual care
2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects, the amount and schedule of payments, and the conditions for receiving this compensation.
   Patient subjects will not receive any payment. Provider subjects will receive payment in the form of a gift card for their completion of the pre- and post-trial surveys assessing their knowledge of ACC/AHA guidelines for hyperlipidemia and their overall experience with the alert. Providers will receive $50 for completion of the pre-trial survey and $200 for the completion of the post-trial survey. There is no payment directly connected to their experience with the alert itself (i.e. whether they accept or dismiss the alert, acknowledge or ignore the alert, etc). All enrolled providers, regardless of randomization status, will partake in the study surveys and receive payment.
3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.
   N/A
4. **In Case of Injury:** This section is required for any research involving more than minimal risk, and for minimal risk research that presents the potential for physical harm (e.g., research involving blood draws).
   N/A

    a. Will medical treatment be available if research-related injury occurs? *Write here*

    b. Where and from whom may treatment be obtained? *Write here*
    c. Are there any limits to the treatment being provided? *Write here*
    d. Who will pay for this treatment? *Write here*
    e. How will the medical treatment be accessed by subjects? *Write here*

IMPORTANT REMINDERS

Will this study have a billable service? **Yes** ☐ **No**☒

A billable service is defined as any service rendered to a study subject that, if he/she was not on a study, would normally generate a bill from either Yale-New Haven Hospital or Yale Medical Group to the patient or the patient's insurer. The service may or may not be performed by the research staff on your study, but may be provided by professionals within either Yale-New Haven Hospital or Yale Medical Group (examples include x-rays, MRIs, CT scans, specimens sent to central labs, or specimens sent to pathology). Notes: 1. There is no distinction made whether the service is paid for by the subject or their insurance (Standard of Care) or by the study's funding mechanism (Research Sponsored). 2. This generally includes new services or orders placed in EPIC for research subjects.

If answered, "yes", this study will need to be set up in OnCore, Yale's clinical research management system, for Epic to appropriately route research related charges. Please contact oncore.support@yale.edu

Are there any procedures involved in this protocol that will be performed at YNHH or one of its affiliated entities? **Yes** ☐ **No** ☒

If Yes, please answer questions a through c and note instructions below.

a. Does your YNHH privilege delineation currently include the **specific procedure** that you will perform? **Yes** ☐ **No** ☐

b. Will you be using any new equipment or equipment that you have not used in the past for this procedure? **Yes** ☐ **No** ☐

c. Will a novel approach using existing equipment be applied? **Yes** ☐ **No** ☐

If you answered "no" to question 4a, or "yes" to question 4b or c, please contact the YNHH Department of Physician Services (688-2615) for prior approval before commencing with your research protocol.

IMPORTANT REMINDER ABOUT RESEARCH AT YNHH

Please note that if this protocol includes Yale-New Haven Hospital patients, including patients at the HRU, the Principal Investigator and any co-investigators who are physicians or mid-level practitioners (includes PAs, APRNs, psychologists and speech pathologists) who may have direct patient contact with patients on YNHH premises must have medical staff appointment and appropriate clinical privileges at YNHH. If you are uncertain whether the study personnel meet the criteria, please telephone the Physician Services Department at 203-688-2615. **By submitting this protocol as a PI, you attest that you and any co-investigator who may have patient contact has a medical staff appointment and appropriate clinical privileges at YNHH.**

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