Protocol Title: Leveraging behavioral economics to equitably implement cascade screening in individuals with familial hypercholesterolemia in partnership with the Family Heart Foundation (R33 Phase)

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1 Introduction

Familial hypercholesterolemia (FH) is a genetic disorder of cholesterol metabolism that affects one in 250 (more than 1.3 million) American men, women, and children of all races and ethnicities. FH causes lifelong elevation of low-density lipoprotein cholesterol (LDL-C) (over 190 mg/dL) and increased risk for premature atherosclerotic cardiovascular disease (ASCVD), and is associated with a 10- to 20-fold increase in risk of major adverse cardiac events (myocardial infarction, coronary revascularization, stroke, or transient ischemic attack). Early diagnosis followed by proactive treatment can prevent or delay the onset of ASCVD and save lives. National Heart, Lung, and Blood Institute (NHLBI), and American Academy of Pediatrics recommend evidence-based guidelines for FH screening, diagnosis, and treatment, but despite this broad consensus, up to 90% of FH patients remain undiagnosed. Cascade screening is an evidence-based practice of contacting and screening relatives of individuals after their FH diagnosis; it improves timely diagnosis, reduces morbidity, and has been shown to be cost-effective in other countries. However, implementation in the U.S. is challenging due to regulatory restrictions and lack of a national healthcare system and thus, usual care in the U.S. relies on the proband (i.e. the first person in the family who receive an FH diagnosis) to contact family members and encourage FH screening. Improving implementation of cascade screening may have particular promise for subgroups of patients at risk of, or already experiencing, health inequities. Although improved identification and treatment of FH is needed for all groups, there is evidence of inequities in diagnosis and effective treatment among several sociodemographic groups, including Black or African American and Asian people, and women.

The NHLBI awarded our team an R61/R33 grant to refine and test two promising approaches to implement cascade screening in partnership with the Family Heart Foundation (i.e. FHF), a nonprofit research and advocacy organization. As part of the R61 phase, we will co-design two patient-facing implementation strategies using behavioral economics in partnership with Family Heart Foundation and key partners from diverse backgrounds. We will then pilot our strategies with 20 patients with high cholesterol and/or FH to ascertain feasibility, acceptability, and appropriateness. As part of the R33 phase, we will conduct a 3-arm hybrid Type 3 effectiveness-implementation randomized controlled trial.

By testing sustainable and scalable implementation approaches, our study results will be poised to guide future wide-scale implementation of cascade screening for FH and other genetic conditions within and outside large health systems while also answering important questions related to equitable implementation.

1.1 Background and Relevant Literature

FH is a genetic disorder of cholesterol metabolism that affects more than 1.3 million American men, women, and children of all races and ethnicities.[1] One in 250 Americans have FH. It causes lifelong elevation of low-density lipoprotein cholesterol (LDL-C; >190 mg/dL in adults, >160 mg/dL in children) and increased risk for premature atherosclerotic cardiovascular disease (ASCVD), and is associated with a 10- to 20-fold increase in risk of major adverse cardiac events (myocardial infarction, coronary revascularization, stroke, or transient ischemic attack).[2,3] Atherosclerosis begins in childhood, and in untreated patients, major cardiovascular events are common in middle adulthood.[4,5] Early diagnosis followed by aggressive treatment can prevent or delay the onset of ASCVD and save lives. The American Heart Association, American College of Cardiology, Centers for Disease Control and Prevention (CDC), NHLBI, and American Academy of Pediatrics recommend evidence-based guidelines for FH screening, diagnosis, and treatment, but despite this broad consensus, up to 90% of FH patients remain undiagnosed.[6] When a diagnosis is made, it often comes decades late. The Family Heart Foundation's national longitudinal CASCADE FH® Registry initiative, the only one of its kind in the U.S., shows that the average ages of statin initiation and FH diagnosis are 39 and 47, respectively, even though diagnosis and treatment can and should begin at ages 2 and 10, respectively.[7]

Cascade screening—an evidence-based practice of contacting and screening relatives of individuals after their FH diagnosis—improves timely diagnosis, reduces morbidity, and has been shown to be cost-effective in other countries[8,9,10,11,12,13,14] First-degree biological relatives (parents, siblings, children) have a 50% chance of having FH, and systematic testing facilitates early diagnosis and connection to care.[15] Each newly identified case becomes a proband for broader cascading.[10] Family cascade screening is recommended by national and international bodies, and is a CDC Tier 1 genomic application with Grade A evidence-based recommendations.[2,10,16] The most successful approach to cascade screening was implemented in the Netherlands.[17] When a proband was identified and genetically confirmed, their contact information was shared with the Foundation for Tracing Hereditary Hypercholesterolemia, which served as a centralized coordinating body that contacted the proband to identify family members and then directly contacted family members for screening. The program identified 70% of FH cases nationwide. Its success is attributed, in part, to the direct contact with family members, which involved significant outreach outside of a visit-based healthcare model.[17]

Despite the proven effectiveness of cascade screening in other countries and broad consensus on its importance, implementation in the U.S. is challenging.[18] Due to regulatory restrictions and lack of a national healthcare system, usual care in the U.S. relies on probands to contact family members and encourage FH screening.[19] In one of the few studies available,[20] we randomized 240 individuals with a clinical diagnosis of FH to genetic testing for FH (n=160) or usual care with lipid testing alone (n=80). The primary study endpoint was the proportion of probands with at least one relative enrolled in the study within 1 year after notification of results. Despite active attempts to encourage cascade screening, only 38 (15.8%) probands overall had at least one family member contact the study team and of these, only 28 probands (11.7%) had at least one family member enroll. Overall, a total of only 43 family members (0.2 family members per proband) were enrolled over the 12-month study period. These data demonstrate the challenges of cascade screening. The reasons for this include the need for the proband to be responsible for contacting and communicating medical information to family members, geographical and sometimes emotional dispersion of families, and the lack of incentive for the health system in which the proband is treated to ensure screening of family who are not a part of that system.

Improving implementation of cascade screening may have particular promise for subgroups of patients at risk of, or already experiencing, health inequities. Although improved identification and treatment of FH is needed for all groups, there is evidence of inequities in diagnosis and effective treatment among several sociodemographic groups, including Black or African American people and Asian people, and women.[21] For example, Black people (across genders) and women were found to be diagnosed with FH several years later than average, and Black and Asian people were 50% less likely to achieve LDL-C<100 mg/dL.[21] This is especially concerning because racial and ethnic minorities already experience notable inequities in incidence and treatment of other cardiovascular risk factors such as hypertension and diabetes, and women experience other inequities in cardiac care, such as less timely and accurate diagnosis of heart attacks.[22,23,24,25,26,27,28,29] Low income is also a major risk factor for poor cardiovascular health.[30,31] As a result, undetected FH likely represents compounded risk for these groups.46 At the same time, concerns among certain communities such as medical mistrust among those who have experienced discrimination[32] may influence acceptability of implementation approaches to cascade screening. For example, prior research in other areas of health behavior suggests that messaging from health systems may be less effective for Black men.[33] Yet 74% of studies in a scoping review of the cascade screening literature did not include information on participants' race or ethnicity, and none of those that did focused on racial and ethnic minority populations.[34] In order to ensure that cascade screening efforts do not exacerbate existing inequities, special attention to these concerns is warranted.[35] Attending meaningfully to racial and ethnic inequities in FH identification and treatment is a key priority.[36]

The latest advances in implementation science and behavioral economics have great potential to improve cascade screening by directly addressing identified barriers. Maximizing the effectiveness of cascade screening requires best practices from implementation science; attention to patient/family, clinician, and health system perspectives; effective engagement and utilization of strategies that facilitate contact with patients and their families outside of health care settings; and inclusion of key principles related to decision-making and behavior. The proposed project will integrate these fields to develop and pilot two implementation strategies that promote a centralized, direct contact approach: a health system-mediated strategy using automated text messages and a Family Heart Foundation-mediated strategy delivered by a navigator, outside of the healthcare setting.[36] Prior to testing in an RCT during the R33 phase, both active conditions will be piloted and refined in the R61 phase using both partner feedback and behavioral economics principles that have been shown to increase uptake of desired health behaviors. By testing and directly comparing two scalable approaches, our study results will help to answer important questions about what strategies work for whom and will be poised to guide future wide-scale implementation of cascade screening for FH and other genetic conditions in large health systems as well as nationally outside of usual healthcare settings. Our strong partnership with the Family Heart Foundation will help successful strategies be taken to scale nationally to save lives.

2 Study Objectives

We will design, refine, and pilot the two implementation approaches using behavioral economics and then seek further feedback prior to our proposed R33 clinical trial, consistent with these recommendations. Then, we will conduct a three-arm hybrid Type 3 effectiveness-implementation randomized controlled trial of different strategies to encourage family cascade screening for familial hypercholesterolemia.

- **R61 Aim 1**. Co-design both implementation strategies using behavioral economics in partnership with the Family Heart Foundation and key partners from diverse backgrounds.
- **R61 Aim 2**. Pilot strategies with 20 patients with high cholesterol and/or with FH to ascertain feasibility, acceptability, appropriateness.
- **R33 Aim 1**. Compare the effect of the three arms on:
  - Reach (*primary outcome*): proportion of probands who have at least one family member who completes a lipid panel and/or a FH genetic test within 6 months of proband randomization.
  - We also include a *co-primary outcome of engagement*, defined as the number of probands who respond to at least one outreach contact attempt divided by the number of probands outreached.
  - We will also explore *secondary endpoints*: absolute number of family members screened *and* absolute number of family members with a new FH diagnosis *6 months after proband randomization*, and proband LDL-C levels *(12 months after proband randomization)*.
- **R33 Aim 2**: Use mixed methods to identify implementation strategy mechanisms with a focus on health equity.
  - *Aim 2a*. Conduct interviews to understand proband perspectives on mechanisms using the Consolidated Framework for Implementation Research, oversampling for populations at risk for disparities.
  - *Aim 2b*: Explore disparities quantitatively by evaluating differential strategy effectiveness by race/ethnicity and gender; and descriptively explore differential strategy effectiveness by income and medical mistrust.

3 Investigational Plan & Design

- **R61 Aim 1**. We will engage in interviews with patients with high cholesterol and/or FH, family members, and clinicians to identify common barriers and facilitators for individuals to engage in cascade screening. These activities will occur in the first 6 months and will serve as inputs into the design of the implementation strategies to ensure that strategies address determinants identified in the interviews.

- **R61 Aim 2**. To maximize success, we will pilot test the implementation strategies and our planned data collection approaches.
- **R33 Aim 1**. We will enroll 300 Penn Medicine patients with FH and/or high cholesterol ("probands") in a three-arm RCT (100 per arm: Penn [health system] mediated-strategy, Family Heart Foundation-mediated strategy, usual care). The arms are described in detail below in **Study Procedures**.
- **R33 Aim 2**. We will conduct qualitative interviews with a purposive sample of RCT (Aim 1) proband participants, as well as Family Heart Foundation staff, to identify potential mechanisms of implementation strategy effectiveness.

3.1 Study Measures

- **R61 Aim 1**. We developed a semi-structured interview guide, which received IRB approval.
- **R61 Aim 2**. We developed a semi-structured interview guide to use after each mini pilot. We will assess feasibility, acceptability, and appropriateness of the implementation strategies via 3 questionnaires that will be administered verbally during the interview (12 items total): Feasibility of Intervention Measure, Acceptability of Intervention Measure, and Intervention Appropriateness Measure. These 4-item psychometrically-validated measures capture the extent to which people believe an implementation strategy is feasible, acceptable, and appropriate. We will also ask participants open-ended questions that elaborate on their responses to the quantitative measures. We will also ask about their perceptions of and experience with cascade screening, including barriers and facilitators. We will iterate to improve on each component during each mini-pilot based on responses during the qualitative interviews.
- **R33 Aim 1**. Data for the RCT will be gathered via several platforms: the Penn Medicine EHR (e.g., proband race/ethnicity, gender), Way To Health and REDCap (e.g., self-report of lipid and/or genetic test results via REDCap survey link sent via Way To Health), and phone call (e.g., self-report of lipid and/or genetic test results by family members in the Penn and Family Heart Foundation arms to the study clinician during a telemedicine call). See below description of study arms (**Study Procedures**) for more details.
- **R33 Aim 2**. We will develop a semi-structured interview guide and informed consent form, and **will submit them for IRB approval before beginning this activity**. The guide will also contain quantitative measures (to be administered verbally) regarding medical mistrust and income.

4 Study Population and Duration of Participation

- **R61 Aim 1 (Interviews)**. We will conduct interviews with three groups (patients with high cholesterol and/or FH, family members, and clinicians [MDs, APPs]) to understand barriers and facilitators to cascade screening. 10 clinicians are being interviewed currently through our sister protocol 849516 (MPIs: Volpp, Beidas, Rader); in an effort to reduce interview burden on clinicians, the 849516 study team submitted a modification to add questions to their interview guide about barriers and facilitator for individuals to engage in cascade screening. ***As part of this protocol, we will focus on conducting interviews with 15 Penn Medicine patients with high cholesterol and/or FH and 10 family members.*** Duration of participation will last the length of one qualitative interview. *Aim 1 interviews will be completed by research team members at Penn.*
- **R61 Aim 1 (Meeting – NOT HUMAN SUBJECT RESEARCH).** We will convene a group of 10 experts to review and discuss these findings, including people that represent the following perspectives: patients with high cholesterol and/or FH, family members, clinicians, setting leaders, implementation scientists, behavioral economists, and Family Heart Foundation leaders. We will prioritize diversity in the selection of people with regard to racial/ethnic minority background, gender, and income. We are not conceptualizing these 10 experts as research subjects, i.e. we will not be collecting any research data from these individuals. We are simply convening this meeting to help us discuss and refine the data collected during interviews to produce the

behavioral roadmap that describes barriers to implementation of cascade screening and facilitates the development of the two implementation strategies we will pilot in Aim 2.

- **R61 Aim 2 (Pilot Testing Strategies).** Participants will include 20 patients with high cholesterol and/or FH. At least half will identify as racial and/or ethnic minorities (i.e., Black or African American, Asian), female, and/or have low income. Patients will be randomized to receive the health system-mediated strategy or the Family Heart Foundation-mediated strategy. Duration of participation will last up to 1-2 months for each participant. Our goal is to have 20 patients *complete* the mini-pilots; we anticipate more than 20 patients will need to be enrolled in order to reach our target of 20 completed participants (e.g., due to loss to follow-up and subject dropout). Study team members at Penn and Northwestern will collaborate closely to outreach participants and conduct these activities. Participants will be identified via Penn's EHR and/or using the CASCADE FH registry (see more info here: https://familyheart.org/cascade-fh-registry-clinical), which is a registry of patients who have FH and is maintained by the Family Heart Foundation. We would only outreach individuals from the registry who are Penn Medicine patients.
- **R33 Aim 1 (RCT).** We will enroll **300 Penn Medicine patients** with high cholesterol and/or FH ("probands") in the RCT. Probands will be randomized to one of the three study arms (n=100 per arm) and will receive outreach according to the study arm they are randomized to (described below in **Study Procedures**). In the health system- and Family Heart Foundation-mediated arms, probands will be invited to reach out directly, or give permission for the health system or FHF staff (respectively) to reach out, to their eligible **family members (first-degree biological relatives)**. With either approach, family members will be provided education about cascade screening and given information about how to obtain lipid and/or genetic testing for FH. In the usual care arm, probands will not receive any contact at baseline. We will collect lipid and/or genetic testing data from **family members** in the Penn and FHF arms for **up to 6 months from proband randomization**. We will also send a REDCap survey to *probands* in all study arms at approximately 6 months post-proband randomization to collect: family member testing and diagnosis data (from the usual care arm), or additional family member testing and diagnosis data not yet collected via the Penn Medicine and Family Heart Foundation implementation strategies. Family members in the usual care arm will **not** be contacted by the research team and will not be enrolled in this study. Probands in all arms will be outreached approximately 10 months after initial randomization to invite them to complete a lipid panel within 12 months of their initial randomization date. **Proband participation will be completed after: this 12-month lipid testing is completed, participants do not respond to our lipid testing invitations, or participants decline to participate in the 12-month lipid testing**.
- **R33 Aim 2 (Interviews).** A purposive sample of **60 RCT (Aim 1) proband participants**, as well as **8 Family Heart Foundation staff/leadership**, will be invited to participate in **one-time** qualitative interviews at that seek to understand potential mechanisms of implementation strategy effectiveness. Probands will be invited to participate at approximately 6 months post-randomization; Family Heart Foundation staff/leadership will be interviewed in Year 4-5 of the grant period (March 2025-February 2027).

4.1 Eligibility Criteria

- **Patients with high cholesterol and/or FH (i.e., "probands;" R61 Aims 1 and 2 Interviews and R61 Aim 2 Pilot Testing Strategies)**. Adults aged 18 and older with clinically diagnosed FH who are treated within Penn Medicine
- **Family Members (R61 Aims 1 and 2 interviews)**. Adults aged 18 and older who have a family member who has been identified as a patient with high cholesterol and/or FH who is treated within Penn Medicine

- **Probands (R33 Aim 1 and Aim 2 interviews).** Adults aged 18 and older with clinically diagnosed FH and/or high cholesterol who are treated within Penn Medicine who: (1) are the first person in their immediate family to be diagnosed with FH, and have not previously participated in cascade screening attempts with first-degree biological relatives (i.e., parent, sibling, child); (2) have contact information for at least one living, first-degree biological relative in the U.S.; and (3) have a cell phone with texting capabilities.
- **Family Members (R33 Aim 1, Penn Medicine and Family Heart Foundation arms only).** Adults aged 18 and older who have a family member who has been identified as a patient with high cholesterol and/or FH who is treated within Penn Medicine (i.e., adult relatives of probands). (Family members in the usual care arm will **not** be contacted by the research team and will not be enrolled in this study.)
- **Family Heart Foundation staff and leadership (R33 Aim 2 interviews).** All Family Heart Foundation staff and leadership will be eligible to participate in an interview.

4.2 Subject Recruitment

R61 Phase.
Our recruitment strategy does not target any populations defined by HHS regulations 45 CFR 46 subparts B, C, or D as vulnerable (i.e. children, pregnant women, fetuses, neonates, or prisoners) as part of this research study and thus this protocol does not require additional protection consideration. Our recruitment strategy also does not target participants who are likely to be vulnerable to undue influence or coercion. Once all study documents are finalized and approved by the IRB, potential participants will receive an initial contact via email or phone by a research staff. We will follow-up no more than six additional times to recruit them to participate in this research protocol.

- **Patients with high cholesterol and/or FH (R61 Aims 1 and 2 Interviews and R61 Aim 2 Pilot Testing Strategies)**. Patients with high cholesterol and/or FH will be recruited from the University of Pennsylvania Health System (UPHS) which consists of six large hospitals including the Hospital of the University of Pennsylvania, Penn Presbyterian Medical Center, Pennsylvania Hospital, Chester County Hospital, Princeton Health, and Lancaster General Hospital. We will be recruiting from primary care and cardiology practices at UPHS throughout Pennsylvania and New Jersey. Target population: The UPHS population includes patients of mixed socioeconomic status. It is estimated that there are 18,000 patients at UPHS with FH (based on the national FH prevalence of one in 250). This will provide an ample population from which to perform the proposed clinical trial. Potentially eligible patients will be identified using data from the electronic health record (PennChart) and Clarity, PennChart's reporting database.
- **Family Members (R61 Aims 1 and 2 interviews)**. Patients with high cholesterol and/or with FH will be asked to identify family members who would be willing to engage in an interview with our study team.

R33 Phase.
Our recruitment strategy does not target any populations defined by HHS regulations 45 CFR 46 subparts B, C, or D as vulnerable (i.e., children, pregnant women, fetuses, neonates, or prisoners) as part of this research study and thus this protocol does not require additional protection consideration. Our recruitment strategy also does not target participants who are likely to be vulnerable to undue influence or coercion.

R33 Aim 1.

- **Patients with high cholesterol and/or FH ("probands")**. Patients with high cholesterol and/or FH (probands) will be recruited from the University of Pennsylvania Health System (UPHS) which consists of six large hospitals including the Hospital of the University of Pennsylvania, Penn

Presbyterian Medical Center, Pennsylvania Hospital, Chester County Hospital, Princeton Health, and Lancaster General Hospital. We will identify probands using two approaches: (a) a search of the Penn Medicine EHR for the FH ICD-10 code (E78.01); and (b) application of the FIND FH® tool (outlined in sister protocol #849516; MPIs: Volpp, Beidas, Rader) to the Penn Medicine EHR to find patients with "highest probability" scores; only patients who have already been notified of their diagnosis via sister protocol #849516 will be recruited for the present study.

- For the Penn Medicine and Family Heart Foundation arms, potential proband participants will receive initial contact via text message, email, patient portal message, and/or phone by research staff at Penn and/or Northwestern. We will follow-up no more than five additional times (six attempts total) to invite them to participate in this study. We will use these same methods to reach out to probands to invite them to complete the 6-month Follow-Up survey, described below in **Study Procedures.**
- For the usual care arm, we will not reach out to probands at baseline. We will contact usual care probands via email, text, phone, and/or patient portal message to invite them to participate in a REDCap survey that asks about our Aim 1 outcomes (6-month Follow-Up Survey) at approximately 6 months post-randomization. We will reach out no more than 6 times to invite them to participate.
- At approximately 10 months post-randomization (for all arms), we will reach out to probands via phone, email, text message, and/or patient portal to invite them to complete a new lipid panel and ask them to self-report a lipid panel (obtained as part of their routine medical care) from before their date of randomization. We will reach out no more than 6 times to invite probands to participate in this activity.

- **Family Members**. Probands who do not opt-out of the study will be asked to identify first-degree biological relatives ("family members") whom either a) the proband is willing to reach out to directly, or b) the proband is willing to have Penn/Northwestern research staff (on behalf of Penn Medicine) / FHF staff reach out to. For option (a), probands will be given educational information and information about obtaining a lipid and/or genetic test for FH, which they can share with family members. For option (b), family members will be contacted directly by the Penn/Northwestern research or FHF staff via the contact information shared by the proband. Probands will be given the option to give their family members a "heads up" before Penn Medicine / FHF reaches out. We will reach out to the family member no more than 6 times to invite them to participate. A link to an opt-out letter will also be sent to the family members during this initial recruitment; only those who do not opt out will continue on to receive the implementation strategy.

R33 Aim 2.

- **Probands**. We will recruit a purposive sample of R33 Aim 1 probands via the same methods used in the RCT (i.e., text, email, patient portal, and/or phone) to invite them to complete a one-time qualitative interview.
- **Family Heart Foundation members**. We will recruit FHF staff / leadership via email to invite them to participate in a one-time qualitative interview.

5 Study Procedures

- **R61 Aim 1 (Interviews)**.
  - Individuals will be invited to complete an eligibility screen either through REDCap or the Way to Health platform along with an electronic consent (which will contain a contact phone number in case of questions), in keeping with prior studies. Patients can register electronically or directly with the study coordinator.
  - Interviews will occur either by phone or videoconference to maximize convenience and participant preference. We will use purposive sampling to recruit 15 patients with high

cholesterol and/or FH and 10 family members to ensure diversity in responses; however, we will continue interviewing until we reach thematic saturation. We will oversample for the following patient populations given established inequities: Black or African American individuals, Asian individuals, women of all races, and people with low income. We will also ensure diversity in age, given that privacy and health concerns may vary based on an individual's stage of life or generation. Interviews will be digitally recorded with the participants' permission.

- Interviews will be 30-60 minutes in length and will focus on how individuals understand cascade screening, barriers to engagement including reasons why individuals do and do not share health information with family members, and preferred approaches to engaging family members, with a focus on acceptability, appropriateness, and feasibility of our planned implementation strategies. We will attend to structural factors such as medical mistrust and experiences of racism in health care, and ask about preferences and logistics to incorporate preference into our R33 trial design. Our approach is consistent with the gold-standard approach that we have used in other studies. Acknowledging that individuals are not always able to report accurately on factors influencing their behavior, we will also deploy an approach used in previous work to infer behavioral barriers driving suboptimal implementation behavior.
- Participants will be compensated $25 via e-Clincard for engaging in this one time interview.
- Aim 1 interviews will be conducted by members of the Penn research team.

- **R61 Aim 1 (Behavioral Roadmap and Development of implementation strategies (NOT HUMAN SUBJECT RESEARCH)**.
  - Using the interview results and behavioral insights to understand clinician and patient decision-making, consistent with previous work, we will produce a behavioral roadmap that describes barriers to implementation of cascade screening. We will lay out the steps in the process where there appear to be hurdles and the behavioral biases that might be contributing to low rates of cascade screening. This roadmap will additionally account for organizational and system-level factors known to potentially hinder implementation of evidence-based practices. We anticipate developing two centralized direct contact implementation strategies leveraging interview insights and behavioral economics, one deployed within the health system context using an automated solution, the other deployed through Family Heart Foundation outside of healthcare settings using a navigator. We will use our findings from Aim 1 and begin the process of matching the observed barriers to implementation strategies informed by the implementation mapping approach (i.e. a systematic procedure we have successfully used in previous studies), to incorporate key literature, inputs from Aim 1, and partner input. We will convene a half-day retreat with partners to present and refine our implementation strategies in anticipation of the R33 phase. ***Note, we do not conceptualize these activities as human subject research***; rather these are activities that are required to produce the implementation strategies we will be testing in the Aim 2 pilots and ultimately in the R33 phase.
- **R61 Aim 2 (Pilot Testing Strategies)**.
  - To "learn quickly and fail fast," we will use rapid cycle approaches method, which is intended to accelerate development, initial testing, and refinement of an innovation (e.g., a new implementation strategy) to avoid investing potentially unnecessary time and resources at scale before determining whether that approach is effective. For example, in testing whether a wireless device could improve glycemic control, we first tested ways to increase initial engagement with the device. Rapid cycle approaches leverage observation and mini-pilots to learn how to design innovations to fit into real-world circumstances in an efficient, cost-effective, and reliable way. The typical development and refinement process involves several cycles of concept definition, implementation of a minimally viable product, evaluation, and

concept refinement. Given the cost of developing fully functioning implementation strategies, this is an ideal way to prototype strategies.

- We will refine the development of the content and delivery components of our two implementation strategies following mini-pilots. These mini-pilots will be conducted with approximately 4 patients per condition per week (n = approximately 8 per week). Following the establishment of the procedure, we anticipate that this process will unfold for up to six months and include up to 10 mini-pilots, where we will make systematic alterations to the implementation strategies following each pilot, based on feedback. One change will be made per mini-pilot. For example, during the first mini-pilot, a clinical research coordinator, acting as a "fake back end" for the Way to Health platform that delivers automated text messages, will deploy text messages with two patients and their family members and rapidly obtain their feedback on the timing, content, and tone of the messages. The other patients will engage with the Family Heart Foundation navigator and provide feedback on the timing, content, and tone of the discussions. During the next mini-pilot, we would enroll approximately 4 new patients with high cholesterol and/or FH per condition and make modifications based on the previous mini-pilot. The goal of this will be to refine our 2 active implementation strategies. Both active implementation strategies will include centralized outreach to patients with high cholesterol and/or FH and direct contact with family members if preferred. Key differences include delivery modality (automated SMS messages vs. navigator) and centralization scheme (health system vs. a national organization).
- Regardless of implementation strategy, family members will be offered FH screening at no cost via a blood lipid panel or genetic test. The 'no cost' test will be provided by reimbursing the participant for the cost of the LabCorp lipid test (via ClinCard; $59); we give them instructions on how to obtain the test via LabCorp. Although this implementation strategy is automated, study participants will also have the opportunity to directly contact research staff with questions.
- Aim 2 pilot testing strategies will be conducted by the Penn and Northwestern study teams working in close collaboration.

- **R61 Aim 2 (Interviews).**
  - We will invite patients and family members who participated in the mini-pilots to complete a one-time post-pilot interview. Interviews will occur either by phone or videoconference to maximize convenience and participant preference. Interviews will be digitally recorded with the participants' permission. During interviews, participants will be asked questions from the Aim 2 interview guide as described above. We will obtain verbal informed consent before beginning the interviews. Interviews will be conducted by the Penn and/or Northwestern study teams. Interviews will last approximately 15-30 minutes.
- **R33 Aim 1 (RCT).** We plan to conduct this study as a pragmatic trial. First, we will randomize participants to one of the 3 study arms (n=100 per arm). Participants randomized to the Penn and Family Heart Foundation arms will be asked to confirm their identity through the Way To Health platform (text and/or email) and via phone and/or patient portal if initial Way To Health outreach is unsuccessful. They will also be given information about how to opt-out. All participants who do *not* opt-out will receive further engagement via the Penn or Family Heart Foundation strategies (described below). Participants randomized to the FHF arm will be given the opportunity to opt out of having their information shared with FHF. Participants randomized to the usual care arm will not receive outreach at baseline. The first outreach will be done via Way To Health (text and/or email) and via phone and/or patient portal if initial Way To Health outreach is unsuccessful, ahead of the 6-month Follow-Up survey (described below). Probands in this arm will be asked to confirm their identity and will be given information about how to opt-out (using the same messaging as is used for the Penn and Family Heart Foundation arms) before they are invited to complete the survey.

- *Penn (health system)-mediated*. After confirming the proband's identity and giving information about how to opt-out, the Penn and/or Northwestern research teams will conduct the Penn Medicine (health system-mediated) study activities with probands who didn't opt out. Probands receive a series of automated SMS messages, patient portal messages, and/or emails through the Way to Health platform containing information about FH and cascade screening from Penn Medicine. Participants may also receive a phone call informing them of the program and directing them to the text and/or email messages. Probands will be invited to complete a genetic test for FH if they haven't had genetic testing previously. They will have multiple options for completing genetic testing: requesting the test from their PCP or having the study clinician order a genetic test via a testing company called LabCorp. Test completion and results will be shared with the study team via self-report by the proband (via REDCap survey) and/or will be received directly from LabCorp by the study clinician who ordered the test. Tests ordered by the study clinician will be offered at no cost to the participant (i.e., the cost of the test will be covered by LabCorp and/or paid to LabCorp from study funds; the participant will not be charged). Participants will be informed before they sign up for LabCorp testing that for tests ordered by the study clinician, their results will be shared directly back with the study clinician. Probands will also receive a request for them to identify first-degree biological relatives. We provide an opportunity for customization whereby probands have a choice of whether to contact family members themselves or share contact information so that automated text / email messages can be sent directly by Penn Medicine via Way to Health; and what communication modalities to use (e.g., text message or email). If participants opt to contact family directly, they receive tips on how to do this effectively (e.g., committing to a date/time to make contact) and informational materials that they can share. If the proband selects health system-mediated outreach, identified family members will be asked to confirm their identity through the Way To Health platform (text and/or email) or via phone if initial Way To Health outreach is unsuccessful, and will be given information about how to opt-out. They will also receive a link to an opt-out letter containing passive informed consent language and reiterating information about how to opt-out. Then, family members who *don't* opt out will receive educational information about FH and instructions for obtaining lipid and/or genetic testing. To mimic real world settings, we will allow family members to select how they would like to complete their screening from a range of mechanisms. This includes sharing results from a recent lipid panel and/or genetic test, requesting a lipid panel and/or genetic test from their PCP, or having the study clinician order the test for them (testing via this option will be free for family members). Test completion and results will be shared with the study team via self-report by the family member (during a phone call or telemedicine visit with study clinician; and/or via REDCap survey) or will be received directly by the study clinician if they ordered the test. Family members will be informed before they sign up for LabCorp testing that for tests ordered by the study clinician, their results will be shared directly back with the study clinician. Family members that complete lipid and/or genetic testing (or are willing to share recent test results) will be invited to complete a follow-up phone call or telemedicine visit with the health system arm's study clinician to review their results. If a proband's initial choice of pathway is not successful (e.g., proband chose to contact relatives directly and they did not respond), they will have the option of initiating the other contact approach. Probands will receive an invitation to complete a REDCap survey at approximately 6 months post-randomization to report on the outcomes of their program participation (i.e., whether their family members received FH testing and/or were diagnosed with FH; 6-month Follow-Up Survey).
- *Family Heart Foundation-mediated*. After confirming the proband's identity and giving information about how to opt-out, probands randomized to this arm (and who didn't opt out) will be given the opportunity to opt out of having their information shared with FHF (as

described above). For probands who do not opt out of having their contact information shared, FHF will be provided with the proband's name and contact information securely via REDCap. (This data sharing is covered under the Master Collaboration Agreement between FHF, Penn, and Northwestern.) Then, FHF will reach out directly via an FHF-employed navigator, making multiple contact attempts if needed. The navigator is trained and supervised by FHF leadership (Dr. McGowan) and a genetic counselor. During an initial call, the navigator introduces the proband to navigation services, conducts a social history, obtains contact information for family members the proband gives permission to contact, and initiates a plan for contacting family members. Probands will also be invited to complete a free genetic test for FH if they haven't had genetic testing already; details and logistics of this testing will mirror those described for the Penn Medicine arm above. As with the health system-mediated approach, probands will choose whether to contact family members themselves or have FHF contact relatives directly, with similar choice architecture and the same consent procedures as described above. Those who choose to contact family members themselves receive personalized coaching to address barriers and concerns, including follow-up calls as needed. They also receive informational materials that they can share with their relatives. If family contacts are successful, the family member will be offered FH screening (lipid and/or genetic test) at no cost; the details and logistics of this testing will mirror those described above for the Penn Medicine arm. Family members that complete lipid and/or genetic testing will be invited to complete a follow-up phone call or telemedicine visit with the FHF arm's study clinician or genetic counselor to review their results. If a proband participant's initial choice of pathway is not successful (e.g., proband chose to contact relatives directly and they did not respond), they will have the option of initiating the other contact approach. Probands will receive an invitation to complete a REDCap survey at approximately 6 months post-randomization to report on the outcomes of their program participation (i.e., whether their family members received FH testing and/or were diagnosed with FH; 6-month Follow-Up Survey).

    - *Usual Care*. Probands randomized to the usual care arm will not receive outreach at baseline. At approximately 6 months post-randomization, we will reach out to the proband via Way To Health (text/email) and patient portal and/or phone if Way To Health outreach is unsuccessful (as described above), to confirm identity and give the option to opt-out. Participants who confirm their identity and do not opt out will be sent an invitation to complete a survey via REDCap (i.e., 6-month Follow-Up Survey). The survey will ask questions about whether they have participated in family cascade screening and if so, the results (i.e., whether their family members received FH testing and/or were diagnosed with FH).
    - *12-month LDL-C levels*. At approximately 10 months after initial randomization, probands in all arms will be invited to complete lipid testing at no cost to them. Lipid testing logistics and procedures will mirror those described above for proband genetic testing and family member genetic/lipid testing in the Penn and Family Heart Foundation arms. Probands who complete lipid testing and share their results with the study team either by a) self-report via REDCap; and/or b) having their test ordered by a study clinician, which automatically sends the test results back to the ordering clinician, will receive a letter from Penn Medicine summarizing and interpreting their results and encouraging them to discuss their results with their primary care provider. Participants in all arms will also be asked to report results from their last lipid panel before randomization (obtained as part of their routine care) via a REDCap survey, so we can compare their lipid panel numbers before and after program participation as part of study data analyses.
- **R33 Aim 2 (Interviews).**
    - We will invite probands who participated in the RCT and Family Heart Foundation staff / leadership to complete a one-time qualitative interview. Interviews will be conducted by the

Penn and/or Northwestern research teams, and will occur either by phone or videoconference to maximize convenience and participant preference. We will obtain verbal informed consent before beginning the interview (**the consent form will be submitted for IRB approval before interviews begin**). Interviews will be audio-recorded with the participant's permission. During interviews, participants will be asked questions from an interview guide **that will be submitted for IRB approval before interviews begin**. Interviews will last approximately 30 minutes.

5.1 Subject Compensation

- **R61 Aim 1 (Interviews)**. Participants will be compensated $25 via e-ClinCard for engaging in this one time interview.
- **R61 Aim 2 (Interviews)**. Participants will be compensated $25 via e-ClinCard each time they complete an interview. Family members who complete a lipid panel or genetic test will also be compensated $25 via e-ClinCard.
- **R33 Aim 1 6-month Follow-Up Surveys**. Probands in all arms will be offered a $25 e-ClinCard for completing the 6-month Follow-Up Survey in REDCap. Probands (usual care arm only) who complete part 2 of the 6-month Follow-Up survey will be offered an additional $25 e-ClinCard.
- **R33 Aim 1 12-month LDL-C.** Probands in all arms who complete a 12-month lipid panel (and share results via self-report in a REDCap survey or via the study clinician ordering the test, which sends the results directly to the study clinician) *and* share pre-randomization lipid panel results (via REDCap survey) will be compensated $25 via e-ClinCard.
- **R33 Aim 2 interviews.** Probands will be compensated via $25 e-ClinCard for participating in the qualitative interview. FHF staff/leadership will not be compensated for completing an interview.

5.2 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to study instructions or unanticipated problems. The Investigator or the funding agency may also withdraw subjects who violate the study plan, to protect the subject for reasons related to safety, or for administrative reasons. It will be documented if any subject is withdrawn and reason why. If participants request their data be destroyed, the study team will honor all requests. Otherwise, previously collected data will be used. The consent form will clearly state this information.

6 Statistical Plan

- **R61 Aim 1 & Aim 2 (Interview Analysis)**. Interview recordings will be professionally transcribed and loaded into QSR NVivo software for data management and analysis. Analysis will be guided by an integrated approach that includes identification of a priori attributes (i.e., constructs from the CFIR, Health Equity Framework, and behavioral economics) and modified grounded theory, which provides a rigorous, systematic approach to identifying emergent codes and themes. This integrated approach uses an inductive process of iterative coding. After initial exploration of data, a comprehensive coding scheme will be developed and applied to all data to produce a fine-grained descriptive analysis. Overseen by qualitative experts on the study team, a sample of transcripts will be separately coded and their application of the coding scheme compared to assess the scheme's reliability. Any disagreements in coding will be resolved through team discussion.
- **R33 Aim 1**. For testing hypotheses related to our primary clinical and implementation outcomes of reach (yes/no) we will conduct two-sample Z-tests and report the proportion of reach and 95% confidence interval in each arm. To assess potential imbalance in variables that we use for stratified sampling (e.g., race/ethnicity) on the dependent variable, we will conduct logistic regression analysis with reach (1 = yes, 0 = no) as the outcome and a binary variable for indicating

implementation strategy (1 = FHF; 0 = health system) as the covariate of interest, adjusting for these stratification variables. The odds ratio parameter for the binary study arm indicator approximates the ratio between the proportion of reach in the two arms, and we will assess whether the odds ratio parameter is significantly greater than one. To assess potential impact on results due to proband clustering within clinic, we will repeat the same logistic regression analysis but additionally include clinic as a random effect. As exploratory analyses, if data allow, we will repeat the above analysis but with "reach" redefined as "whether a proband had at least two family members who completed a lipid panel or FH genetic test within 6 months of proband randomization." For continuous outcomes (number of family members screened, number of family members diagnosed with FH, proband LDL-C), we will conduct similar analyses but substitute a two-sample t-test and linear regression models. All tests will be two-sided at the 0.05 significance level. For missing data, we will use multiple imputation as we have in other trials.

- **R33 Aim 2a (Interviews).** As in previous work, we will query around specific mechanisms through which our implementation strategies operate (e.g., shifting responsibility from proband to technology or FHF, shifting engagement to non-health system related staff, changing motivation), using the CFIR to identify key mechanisms at multiple ecological levels. We will also include questions about social and structural factors that may contribute to health inequities such as experiences of discrimination, health care access, language barriers, and how these relate to the success of the implementation strategy conditions and if they differ across populations. We will also collect responses to quantitative measures of income and medical mistrust verbally during interviews. Analysis of this quantitative data will occur as part of Aim 2b, described below. We will interview FHF team members to understand how this approach might be scaled up at the national level. We will load all transcripts into QSR NVivo for data management and analysis of the qualitative data. Analysis will be guided by an integrated approach that includes identification of a priori attributes (i.e., constructs from the CFIR, Health Equity Framework, and behavioral economics) and modified grounded theory, which provides a rigorous, systematic approach to identifying emergent codes and themes. This integrated approach uses an inductive process of iterative coding. After initial exploration of data, a comprehensive coding scheme will be developed and applied to all data to produce a fine-grained descriptive analysis. Overseen by qualitative expert Dr. Klaiman (Co-I), a sample of transcripts will be separately coded and their application of the coding scheme compared to assess the scheme's reliability. Any disagreements in coding will be resolved through team discussion.
- **R33 Aim 2b (Quantitative Analyses).** This analysis is exploratory. We will conduct stratified analysis by repeating the Aim 1 analysis separately in subgroups defined by each candidate effect modifier (race/ethnicity, gender). This will allow us to examine the difference in effect sizes (e.g., difference in reach) between subgroups. To test the significance of such a difference, for the primary outcome, we will fit a logistic regression model that uses the reach status (yes/no) as the outcome variable and includes three covariates, a binary variable indicating the study arm (1 = FHF; 0 = health system), the effect modifier (e.g., race/ethnicity), and a cross term between the study arm and effect modifier. A significant modification effect is indicated if the p-value for the cross term by the Wald test is less than 0.05. We will use the same statistical methods to assess modification effects of the stratification variables in the comparison between the two active strategies and usual care. We understand that power is limited given the sample size; therefore, we will carefully examine the size and direction of the effect. We will perform interaction analysis for the secondary outcomes also, substituting linear regression models for continuous variables (e.g., LDL-C levels). Lastly, we will conduct exploratory, descriptive analyses to understand the differential effects of participant income and medical mistrust.

7 Safety and Adverse Events

Data Safety and Monitoring. Diligent data and safety monitoring will be conducted by the PI and research team throughout the conduct of this study. This monitoring plan includes tracking participant safety and demographics, monitoring the safety of data, and monitoring and appropriately reporting adverse event activity. The PI and appropriate co-investigators will review data collected to ensure that no study findings warrant immediate intervention. We believe this research poses no greater than minimal risk and have proposed a monitoring plan that reflects this risk level.

The PI will be responsible for oversight of potential adverse events. An adverse event (AE) is any untoward medical occurrence in a subject during participation in the clinical study. We anticipate two potential types of AEs that could be directly related to study participation. These include distress experienced with regard to research participation and breach of confidentiality and privacy. With regard to the former, we have protocols in place that include conferring with one of the PIs (who is a licensed clinical psychologist) or a staff psychologist. With regard to the latter, we have appropriate safeguards to reduce risk of breach of confidentiality and privacy. Any risks related to additional potential AEs are not expected because this protocol poses minimal risk to subjects.

All members of the research team who will be involved in the design and conduct of the study must receive education in human research subjects protection through the CITI program. The PI will be responsible for ensuring project faculty and staff have the equipment and training required to protect privacy and confidentiality and will monitor and document that these individuals are properly certified. If new personnel and staff become involved in the research, they will be required to engage in the same CITI program.

DSMB. We have identified a four-member DSMB from faculty outside of Penn and Northwestern. The DSMB composition includes individuals with expertise in: implementation science, behavioral economics, FH, and biostatistics. The DSMB will be an independent group of experts charged with reviewing study data for data quality and integrity, adherence to the protocol, participant safety, and study conduct and progress. They will also make determinations regarding study continuations, modifications, and suspensions/terminations. DSMB members will be independent from any professional or financial conflict of interest with the research project and/or study investigators. The DSMB will meet annually via phone/video conference calls for the duration of the project. The DSMB will elect a Chair to moderate the meetings. At the initial meeting, the DSMB will review and approve all study protocols before study initiation to ensure participant safety. Protocols will include formal procedures for reporting and tracking all adverse reactions to the NIH and IRBs; tracking progress in the study; and identifying any need for premature termination of the protocol. At subsequent meetings, the DSMB will be provided with summary study progress reports and adverse events. The DSMB will provide a summary report following each meeting. We will not require the DSMB to conduct interim analyses of data prior to the end of the study.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. All PHI that will be collected as part of this study include:

- Name
- Address
- Date of Birth
- Phone number
- Email address
- Medical record number

8.2 Data Collection and Management

As outlined in the Master Collaboration Agreement (MCA) between Northwestern, Penn, and Family Heart Foundation, all data saved and stored at Northwestern and FHF will be stored in accordance with the federal privacy and security regulations set forth at 45 CFR Parts 160 and Part 164 (i.e., HIPAA). Data will only be shared between parties as outlined in the MCA, via secure file transfer methods. All members of the study teams at Northwestern and FHF have completed human subjects training.

At the University of Pennsylvania, we will use secure, encrypted servers to host the data and conduct the analysis to minimize the risk of breach of data and confidentiality. The Penn Medicine Academic Computing Services (PMACS) will be the hub for the hardware and database infrastructure that will support the project. The PMACS provides a secure computing environment for a large volume of highly sensitive data, including clinical, genetic, socioeconomic, and financial information. PMACS requires all users of data or applications on PMACS servers to complete a PMACS-hosted cybersecurity awareness course annually, which stresses federal data security policies under data use agreements with the university. The curriculum includes Health Insurance Portability and Accountability Act (HIPAA) training and covers secure data transfer, passwords, computer security habits and knowledge of what constitutes misuse or inappropriate use of the server. We will implement multiple, redundant protective measures to guarantee the privacy and security of the participant data. All investigators and research staff with direct access to the identifiable data will be required to undergo annual responsible conduct of research, cybersecurity, and HIPAA certification in accordance with University of Pennsylvania regulations. Data will be stored, managed, and analyzed on a secure, encrypted server behind the University of Pennsylvania Health System (UPHS) firewall. All study personnel that will use this data are listed on the Penn IRB application and have completed training in HIPAA standards and the Collaborative IRB Training Initiative (CITI) human subjects research. Data access will be password protected. Whenever possible, data will be de-identified for analysis.

Audio recordings from the interviews will be digitally recorded and stored in REDCap. Audio recordings will be sent to TranscribeMe, a professional transcription service. TranscribeMe services include multiple safeguards designed to protect the privacy and security of personal health information, along with utilizing workers specifically cleared to work with this type of sensitive information. TranscribeMe maintains crowd worker teams that are vetted, trained, and authorized to work on content containing PHI/PII. Data submitted to TranscribeMe is stored on servers located inside secure, dedicated Microsoft Azure data centers, with state-of-the-art physical and online intrusion prevention measures in place. Data is submitted and maintained through a secure file transfer protocol (SFTP) platform that has been set up specifically for HIPAA compliance. The service limits the amount of internal staff that has access to customer data within this SFTP only to essential personnel. Transcripts will be loaded into NVIVO qualitative data analysis software for management and analysis. Qualitative analysis is described in the Statistical Analysis section below.

A number of procedures will be utilized to ensure confidentiality of participant data. First, all qualitative interview participants will be assigned a random ID number. This ID number will be used on all data collected from participants. The names that correlate to those ID numbers will be kept separate, i.e. identifiable data will be stored in one file and de-identified research data will be kept in a separate file. The key linking ID numbers to participant names will only be kept in REDCap. Only the research team outlined in this application will have access to the participant's identifiable data. Electronic records (e.g., digital audio files) will be stored in REDCap as well as on a PMACS HIPAA-compliant server. All requests to use the data will be reviewed by the PI. Any data files provided to other individuals will be de-identified and contain only the random ID numbers. Participants will be notified of the above procedures during informed consent.

8.3 Risks

Participants may experience discomfort when asked to answer questions or complete questionnaires with the Penn and/or Northwestern team, Family Heart Foundation navigator, or via the REDCap or Way to Health platform. These activities may make them feel temporarily uncomfortable or experience an emotional response (e.g., anxiety, frustration). Participants may also experience possible embarrassment, distress, or inconvenience related to questions regarding personal information. The risk level is low and these risks will be minimized by letting participants know that they can choose not to answer a question or discontinue their participation at any time; one of the PIs is a licensed clinical psychologist (Beidas) and can provide support around distress and appropriate referrals.

Participants will also be informed that their responses will be kept private and not be shared with anyone outside of the research team, within the limits to confidentiality in research studies. There is also the potential risk of breach of confidentiality. While there is always the possibility of a breach of confidentiality when conducting research and while the likelihood of such is very low, we take a number of precautions to minimize the possibility of breach of confidentiality, including that: 1) all research team staff will be well trained in confidentiality and data security procedures; 2) data will be rendered anonymous to the degree possible to minimize likelihood of any individual being identified; 3) all data will be kept locked at all times in a secure office building; and 4) all electronic records and audio recordings will be password protected. Another possible type of breach of confidentiality is if an organization learns about some of the impressions a staff person has about their health system. To minimize this risk, we will de-identify all interview transcripts and questionnaires and maintain them in a confidential manner. We will ensure there are protections in place so that data are only accessible by the appropriate members of the research team.

All risks and the ways in which the research team will minimize them will be explained during the consenting of all potential participants. Participants will not be required to complete research measures or interviews and lack of participation will not impact the care they receive at Penn Medicine.

The research team at Penn Medicine and/or Northwestern will reach out on behalf of Penn Medicine (via Way To Health, patient portal, and/or phone) to confirm **probands'** identity and provide information about how to opt out of participation. Additionally, if randomized to the Family Heart Foundation strategy (and if the proband doesn't opt out of having their contact information shared), the proband's information will be shared with Family Heart Foundation so that their navigator can reach out directly to the patients with high cholesterol and/or FH to discuss cascade screening. For **family members** who receive direct outreach from Penn or FHF, we will confirm their identity, and will share an opt-out consent form with them. Only participants who do not opt out will receive additional messaging as part of the implementation strategy. We will work closely with the Penn IRB to mitigate any risks related to this agreement, and we will outline this information clearly in the consent. The Family Heart Foundation and Northwestern teams will take precautions similar to the above to mitigate the possibility of breach of

confidentiality. All activities will fall under the Master Collaboration Agreement established between the Family Heart Foundation, Northwestern University, and the University of Pennsylvania Office of Research Services.

Regardless of implementation strategy, probands and family members will be offered FH screening at no cost via a blood lipid panel or genetic test as described above. If a family member or proband receives a blood lipid panel, the risks of venipuncture for blood drawing (for lipid panel) include pain, bleeding, bruising, infection, and inflammation at the site. The risk level is minimal and unlikely to impact subjects as blood draws are very common and will be performed by trained phlebotomists. If the proband or family member receives a genetic test, the physical risk of saliva genetic test is minimal. However, genetic tests that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. The risks of genetic tests will be discussed at length with participants and participants are not required to get genetic tests in order to participate in this study.

8.4 Benefits

There are no direct benefits of the proposed research to the participants. Participants may indirectly benefit from participation. Patients with high cholesterol and/or FH and family members may learn about FH, risks related to this disorder, and ways to minimize health risks. Discussing their experiences with the implementation strategies may contribute to participants reflecting on how to reduce their risk of cardiac events as it relates to FH.

8.5 Risk Benefit Assessment

Cascade screening is an evidence-based practice of contacting and screening relatives of individuals after their FH diagnosis and improves timely diagnosis, reduces morbidity, and has been shown to be cost-effective in other countries. Improving implementation of cascade screening may have particular promise for subgroups of patients at risk of health inequities. Behavioral economic approaches, which include the use of ‘choice architecture’ to harness the power of the environment to support behavior change, have been effectively leveraged to change behavior in multiple areas of medicine. Study results will help us determine promising strategies to increase equitable implementation of cascade screening with the ultimate goal of improving detection and outcomes for individuals with FH. Participants may indirectly benefit from participation by knowing that their participation is contributing to the improvement of detection and outcomes for individuals with FH. The ratio of risks to benefit is reasonable given the importance of the information to be gained by this research.

8.6 Informed Consent Process / HIPAA Authorization

Waiver of Written Documentation of Consent. We are requesting a waiver of written documentation of consent for participants who agree to participate in the R61 Aim 1 and 2 interviews and R33 Aim 2 interviews. Because all interviews will be conducted remotely and all surveys will be completed via REDCap, it is not feasible to collect a signed copy of the combined consent and HIPAA document. These research activities present no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

Individuals will be informed that the study is 100% voluntary and not mandatory. It will be clearly stated that patients do not have to participate in this research in order to get care at Penn Medicine. The research team will ensure that the potential participant has all the additional necessary information (e.g., the research objectives, procedures, duration, risks, benefits, etc.) to make an informed decision about whether or not they want to participate in the study. Family Heart Foundation staff will be informed that their decision of whether or not to participate in an interview will not impact their employment.

- For R61 Aim 1 and Aim 2 qualitative interviews and R33 Aim 2 qualitative interviews, consent and HIPAA authorization will be obtained either by phone or via videoconference. The study team member (from Penn and/or Northwestern) will ask the participant to be in a private location during the call. We will schedule the interview at a time most convenient to the participant. The interviews will be audio-recorded. We will review the required elements of informed consent and HIPAA authorization and answer any questions the potential participant might have before any research questions are asked and audio-recorded. Potential participants will be encouraged to ask questions about the project. Participants will be emailed a copy of the IRB approved consent document for their records. If they agree to participate, the interview team will document the consent process in REDCap.

- ***For R61 Aim 2 and R33 Aim 1 (RCT) family member outreach (for the Penn Medicine and Family Heart Foundation arms)***, we will use passive consent language in the form of an "opt out" letter that explains FH, primes them that someone will reach out to them about cascade screening, and provides instructions on how to opt out of being contacted. (Family members in the usual care arm will *not* be contacted by the research team or be participants in the study.)

Waiver of Consent.

For patients (probands) enrolling in Aim 2 mini-pilots and the R33 Aim 1 (RCT), we are requesting a waiver of consent and HIPAA authorization. The research activities are minimal risk and involve minimal collection of PHI. Because we are studying the effect of communicating about cascade screening and we are planning to conduct a pragmatic trial, we do not want to send a primer letter for probands to opt out because we do not want to add another layer of communication that could impact the effect we are seeing from the implementation strategies or the usual care arm. We believe additional communication in the form of a consent would affect the organic response of probands and alter the research results. A primary goal of ours is also to improve equitable delivery of cascade screening, and so understanding the real-life challenges healthcare providers would face when trying to contact probands about cascade screening is at the heart of this research.

Similarly, for the usual care arm, our goal is to collect our study outcomes while intervening minimally on participants, in order to minimize the impact the data collection activities have on these participants' behavior. Our goal is to maintain the integrity of the care that is received by these participants as part of Penn Medicine's usual care for FH (i.e., our goal is for our data collection activities to have as little impact as possible), so we can understand the impacts and outcomes of usual care for FH at Penn Medicine. Similar to the active arms, we do not want to send a primer letter for probands to opt out because we do not want to add another layer of communication that could impact the effect we are seeing in the usual care arm. We believe additional communication in the form of a consent would affect the organic response of probands and alter the research results, and/or could negatively impact our ability to achieve the equity goals of this study. We are gathering the same information in the usual care arm as we are in the active arms; these research activities are all minimal risk and involve minimal collection of PHI.

You will also note in the implementation strategy language we uploaded that some elements of consent are naturally contained in the outreach language – we are striving to integrate as much communication into the implementation strategies as possible to mimic what we believe would happen outside of a research study. In summary and in accordance with 45 CFR § 46.116, this research:

1) involves no more than minimal risk to subjects;
2) could not be carried out practicably without the waiver or alteration;
3) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and,
4) the subjects will be provided with additional information about their participation.

9 Study Finances

This study is financed through an R61/R33 grant from the US National Heart, Lung, and Blood Institute. No investigators have any conflicts of interest.

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