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

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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. Family Heart), 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 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. **PLEASE NOTE: this protocol only outlines the R61 activities as this is a multiphase award from NHLBI. Before we begin any R33 activities, we will submit a modification to the IRB for review and approval.**

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.

- **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.

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.

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.

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.

4.1 Eligibility Criteria

- **Patients with high cholesterol and/or FH (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

4.2 Subject Recruitment

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.

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 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 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. 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.
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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.

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.

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. 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, all data saved and stored at Northwestern and Family Heart 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 Family Heart 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 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 team at Penn Medicine and/or Northwestern will consent participants and, if randomized to the Family Heart strategy, the participant's information will be shared with Family Heart so that their navigator can reach out directly to the patients with high cholesterol and/or FH to discuss cascade screening. 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 agreements established between the Family Heart Foundation, Northwestern University, and the University of Pennsylvania Office of Research Services.

Regardless of implementation strategy, family members may be offered FH screening at no cost via a blood lipid panel or genetic test. If a family member 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 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 Aim 1 and 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.

- For Aim 1 and 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 Aim 2 family member outreach***, 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.

Waiver of Consent.

For patients enrolling in Aim 2 mini-pilots, 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 ultimately 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 these strategies. 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. 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

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