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TITLE: Familial Hypercholesterolemia in the United States: Evaluating a Centralized Cascade Screening Model to Improve Early Diagnosis

PRINCIPAL INVESTIGATOR: Zahid Ahmad, MD

CONTRACTING ORGANIZATION: UT Southwestern Medical Center, Dallas, TX

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Zahid Ahmad, MD

E-Mail: Zahid.ahmad@utsouthwestern.edu

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

UT Southwestern Medical
Center
5323 Harry Hines Blvd
Dallas, TX 75390

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14. ABSTRACT

Cascade (family) screening remains the best method to identify individuals with Familial Hypercholesterolemia. The purpose of this project is to use implementation science methods to test a centralized approach to cascade screening, similar to the most successful program in the world (Netherlands), and assess its cost-effectiveness. Our scope includes two centers in the Dallas, TX, area from which FH patients will be recruited to participate. Thus far, we are nearly complete in developing semi-structured patient and provider questionnaires to assess barriers and facilitators for cascade screening in the US. We have assembled a Panel of Advisors that includes individuals from a diverse backgrounds and expertise to guide the work proposed. In the next few weeks, we will begin interviewing patients and providers. These interviews will be analyzed, and we will then use intervention mapping to adapt a centralized cascade screening model.

15. SUBJECT TERMS
Familial Hypercholesterolemia; Cascade screening; family screening; hypercholesterolemia; cholesterol; lipids; LDLR; LDL-C; LDL-receptor; cost-effectiveness; cardiovascular disease

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1. **INTRODUCTION:** Familial hypercholesterolemia (FH) is an autosomal dominant condition affecting ~1:250 individuals, characterized by markedly elevated low-density lipoprotein-cholesterol (LDL-C) and an increased risk of premature atherosclerotic cardiovascular disease (ASCVD). Less than 15% of FH cases in the US are identified despite a Tier 1 indication from the Centers for Disease Control and Prevention for early detection, cascade screening (i.e., screening blood relatives), and early intervention. In contrast, the Netherland's national FH screening program detected > 70% of FH cases – many as children - thanks to a systematic approach to cascade screening (i.e. the Dutch model). The key components to their approach were centralized coordination of family interactions and patient engagement outside of usual healthcare settings by their "Foundation for Tracing FH." These efforts were cost-effective and led to early interventions (i.e. lipid lowering therapies) for individuals with FH, reducing their ASCVD risk to levels similar to the general population. An ***urgent need*** exists to establish a feasible and cost-effective cascade screening model in the US, without which upwards of 1 million FH individuals will remain undiagnosed and undertreated, leaving them at high risk for ASCVD events (and their high costs to the healthcare system), early death, and lost productivity as young and middle-aged adults. Currently, only 4-25% of families participate in cascade screening as evidenced by data we aggregated from existing US research efforts to do cascade screening (at UT Southwestern Medical Center, University of Pennsylvania, Geisinger, West Virginia University, and Mayo Clinic). To improve this low uptake, the centralized Dutch model is promising but has not been tested in the US. Before broader implementation the centralized cascade screening model requires further adaptation to account for differences between the Dutch and US context, especially as it relates to barriers and facilitators experienced by US FH patients – including underrepresented populations (i.e., rural and racial/ethnic minority populations) and the diverse healthcare system of the US (i.e. multiple payers, varying public health policies). Our ***overall objective*** is to further develop our centralized cascade screening model for implementation in the US and demonstrate its feasibility and cost effectiveness. **Our central *hypothesis* is that an adapted, centralized approach will show efficacy and value as a cascade screening model for the US FH population.** To test this hypothesis, we propose following ***specific aims***: **Aim 1. Utilize intervention mapping techniques to adapt the centralized cascade screening model for FH populations in urban and VA settings. Aim 2. Implement centralized cascade screening at two sites (UT Southwestern and North Dallas VA). Aim 3. Evaluate the value of centralized cascade screening in the US.**

2. **KEYWORDS:** Familial Hypercholesterolemia; Cascade screening; family screening; hypercholesterolemia; cholesterol; lipids; LDLR; LDL-C; LDL-receptor; cost-effectiveness; cardiovascular disease

3. **ACCOMPLISHMENTS:**

- **What were the major goals of the project?**

Specific Aim 1: Utilize intervention mapping techniques to adapt the centralized cascade screening model for FH populations in urban and VA settings.	Timeline	1	2	3	4	5
Major Task 1 Perform qualitative interviews of human patients and providers to assess barriers and facilitators of cascade screening the US	Months					
Subtask 1: Obtain (centralized) IRB/ HRPO approval for entire study (all Aims)	1	X				
Subtask 2: Develop interview guides	1-3			X		
Subtask 3: Recruit patients (n = 20) and providers (n = 10) to participate in telephone interviews	3-9	X	X		X	
Subtask 4: Perform Telephone Interviews (n = 30)	3-9			X		
Subtask 5: Key summary report of interviews	9-12			X		
Major Task 2: Apply intervention mapping to develop implementation strategies overcoming the barriers and facilitators						
Subtask 1: Adapt centralized model with panel of advisors	9-15	X	X	X	X	X
Milestone(s) Achieved:	Major task 1, Subtask 1 100% completed; Major Task 1 Subtask 2 80% complete (interview guides currently in final revision); Major Task 1 Subtask 3 10% complete (potential patients and providers identified); Major Task 2, Subtask 1 10% complete (Panel of Advisors assembled)					
Specific Aim 2: Implement centralized cascade screening at two sites (UT Southwestern and North Dallas VA)populations in urban and VA settings.	Timeline	1	2	3	4	5
Major Task 1 Perform centralized cascade screening.	Months					
Subtask 1: Recruit FH Probands (n = 100)	12-42	X			X	

Subtask 2: Recruit relatives of FH Probands for FH screening	12-42		X			
Subtask 3: Screen relatives with lipid measurements and genetic testing	12-42	X			X	
Major Task 2: Evaluate processes and outcomes of centralized cascade screening utilizing the RE-AIM framework.						
Subtask 1: Evaluate "Reach": number of family members screened (statistical analyses)	42-48	X				
Subtask 2: Develop interview guides for study participants (n = 20) and study staff (n = 2)	36			X		
Subtask 3: Recruit study participants (n = 20) for telephone interviews	36-42	X			X	
Subtask 4: Conduct telephone interviews (n = 22)	36-42			X		
Subtask 5: Key summary report of telephone interviews	42			X		

Specific Aim 3: Evaluate the value of centralized cascade screening in the US.	Timeline	1	2	3	4	5
Major Task 1 Perform cost-effectiveness analyses	Months					
Subtask 1: Model cost-effectiveness of FH cascade screening in the US.	42-48					X

- **What was accomplished under these goals?**
    - Major task 1, Subtask 1 100% completed; Major Task 1 Subtask 2 80% complete (interview guides currently in final revision); Major Task 1 Subtask 3 10% complete (potential patients and providers identified); Major Task 2, Subtask 1 10% complete (Panel of Advisors assembled)
    - IRB/HRPO approval was finalized in April 2022, and due to some confusion with funding transfer, funds were available 1-2 months later. Thus, study activities started in June 2022. Per the SOW, we immediately began working on the semi-structured telephone questionnaires for Aim 1 (Major Task 1, Subtask 1). The questionnaires are nearly complete, requiring a few pilot interviews and then IRB approval. We anticipate these to be completed within the next 2-4 weeks, at which time we will immediately begin interviewing patients and providers (Aim 1, Major Task 1, Subtask 2). We have also put together a Panel of Advisors as part of Aim 1, Major Task 2, Subtask 1, to help with activities of this subtask.
- **What opportunities for training and professional development has the project provided?**
    - Nothing to report
- **How were the results disseminated to communities of interest?**
    - Nothing to Report
- **What do you plan to do during the next reporting period to accomplish the goals?**
    - Finalize the semi-structured telephone questionnaires and obtain IRB approval for them.
    - Conduct the interviews of both patients and providers.
    - Apply intervention mapping to develop implementation strategies overcoming the barriers and facilitators for FH cascade screening in the US. The Panel of Advisors will meet quarterly to assess progress, give direction, and help with intervention mapping.

4. IMPACT:

   - What was the impact on the development of the principal discipline(s) of the project?
     - Nothing to Report
   - What was the impact on other disciplines?
     - Nothing to Report
   - What was the impact on technology transfer?
     - Nothing to Report
   - What was the impact on society beyond science and technology?
     - Nothing to Report

5. CHANGES/PROBLEMS:

   - Changes in approach and reasons for change
     - No major changes were made in the approach.
   - Actual or anticipated problems or delays and actions or plans to resolve them
     - The project was delayed by roughly 1 year due to IRB/HRPO approval process, which was a lengthy since the study includes 5 sites. We will focus on conducting Aim 1 faster and we may begin the tasks involved in Aim 3 (originally planned for year 4) now so that the project may still finish on time.
   - Changes that had a significant impact on expenditures
     - None
   - Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
     - None
   - Significant changes in use or care of human subjects
     - None
   - Significant changes in use or care of vertebrate animals.
     - None
   - Significant changes in use of biohazards and/or select agents
     - None

6. PRODUCTS:

   - Publications, conference papers, and presentations

- Nothing to report

- Website(s) or other Internet site(s)
  - Nothing to report
- Technologies or techniques
  - Nothing to report
- Inventions, patent applications, and/or licenses
  - Nothing to report
- Other Products
  - Nothing to report

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

1. What individuals have worked on the project?

Key Study Personnel (Include Degrees and Credentials)	Study Roles and Responsibilities
Name: Zahid Ahmad, MD Affiliated Institution: UT Southwestern Medical Center	Study Role(s): Principal Investigator Responsibilities: Provide leadership in all aspects of the study
Name: Chul Ahn, PhD Affiliated Institution: UT Southwestern Medical Center	Study Role(s): Co-Investigator Responsibilities: Provide statistical support
Name: Marina Cuchel, MD, PhD Affiliated Institution: University of Pennsylvania	Study Role(s): Consultant Responsibilities: Serve as advisor and provide guidance for methodology
Name: Laney Jones, PharmD, MPH Affiliated Institution: Geisinger Clinic	Study Role(s): Consultant Responsibilities: Development and analyses of qualitative interviews
Name: Paul Kolm, PhD Affiliated Institution: Medstar Health Research Institute	Study Role(s): Co-Investigator Responsibilities: Define outcomes and interpret results
Name: Mary McGowan, MD Affiliated Institution: FH Foundation	Study Role(s): Co-Investigator Responsibilities: Overall coordination and supervision of all aspects of the study for the FH Foundation
Name: Megan Roberts, PharmD	Study Role(s): Co-Investigator Responsibilities: Overall coordination and supervision of implementation science activities

- Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

  1. Nothing to Report.

2. What other organizations were involved as partners?

Family Heart Foundation
959 E. Walnut Street, Suite 220. Pasadena, CA 91106
Site PI/POC: Mary McGowan
Contribution: Collaboration

University of North Carolina at Chapel Hill
104 Airport Drive, Suite 2200, Chapel Hill, NC 27599
Site PI/POC: Megan Roberts
Contribution: Collaboration

Medstar Health Research Institute, Inc.
6525 Belcrest Road, Suite 700, Hyattsville, MD 20782
Site PI/POC: William Weintraub
Contribution: Collaboration

FH Foundation
959 E. Walnut Street, Suite 220, Pasadena, CA 91106
Site PI/POC: Mary McGowan
Contribution: Collaboration

Dallas VA Research Corporation
4500 S. Lancaster Road, 151C, Dallas, TX 75216
Site PI/POC: Kyaw Soe
Contribution: Collaboration