Implementing and Evaluating the Comprehensive Integration of Physical Activity into a Major Health System and Connecting Patients to Community-Based Physical Activity Programs

- Study Protocol -

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1.0 LIST OF ABBREVIATIONS

ACSM	American College of Sports Medicine
BMI	Body Mass Index
CITI	Collaborative Institutional Training Initiative
DSMB	Data Safety and Monitoring Board
EHR	Electronic Health Records
EIMG	Exercise is Medicine Greenville
ERS	Exercise Referral Scheme
Ex Pros	Exercise Professionals
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICD-10	International Classification of Diseases, Tenth Revision
i-PARIHS	Integrated-Promoting Action of Research Implementation in Health Services
IRB	Institutional Review Board
LDL	Low Density Lipoprotein
NCCA	National Commission for Certifying Agencies
NHLBI	National Heart, Lung, and Blood Institute
PA	Physical Activity
NIH	National Institutes of Health
PAVS	Physical Activity Vital Sign
PHQ-9	Patient Health Questionnaire-9
PROMIS	Patient Reported Outcomes Measurement Information System
RE-AIM	Reach, Effectiveness, Adoption, Implementation, Maintenance
REDCap™	Research Electronic Data Capture
RPE	Rating of Perceived Exertion
SAE	Serious Adverse Event
U.S.	United States

2.0 STUDY SYNOPSIS

Protocol Title	Implementing and Evaluating the Comprehensive Integration of Physical Activity into a Major Health System and Connecting Patients to Community-Based Physical Activity Programs
Principal Investigators	Jennifer Trilk, PhD; Mark Stoutenberg, PhD, MSPH
Study Sponsor	National Heart Lung and Blood Institute (NHLBI)
Study Design	Multiple case study trial examining the adoption, implementation, and reach of eligible patients visiting participating Prisma Health primary care clinics and receiving a referral to a 12-week evidence-informed physical activity (PA) program hosted at local community PA facilities.
Duration of Study Participation	• Prisma Health primary care clinics will have the opportunity to adopt Exercise is Medicine Greenville (EIMG) • Adopting clinics will be provided with an introductory video and have EIMG activated upon study entry (baseline) • After approximately three months, clinics will receive a more in-depth EIMG onboard training (months 0-3) • Clinic referral rates will be tracked for an additional six months after receiving the EIMG onboard training (months 4-9) • During the 9-month study period, eligible patients referred to participating community PA centers will have the option of enrolling in a 12-week, evidence-informed PA program
Summary of Investigational Intervention	• Implementation: our sequential design will test provider referral rates with eligible patients after: 1) an initial instructional video, and 2) more in-depth EIMG onboard training • Effectiveness: we will examine the effectiveness of a 12-week evidence-informed physical activity (PA) on patient PA levels and health outcomes
Summary of Key Eligibility Criteria	• Prisma Health primary care clinics not yet onboarded to EIMG • Clinic managers at all Prisma Health primary care clinics eligible for the study (adoption) • Healthcare providers at the Prisma Health primary care clinics that chose to adopt EIMG (implementation) • Patients, age 18 or older, attending participating Prisma Health primary care clinics for whom exercise is not contraindicated (effectiveness)
Primary Outcome Measure	• Referral rates of eligible patients to the evidence-informed PA program
Secondary Outcome Measure	• Variables impacting adoption of EIMG at Prisma Health primary care clinics • Effectiveness of the 12-week evidence-informed PA program on patient PA levels and health outcomes • Cost of implementing EIMG in a Prisma Health primary care clinic • Cost effectiveness of EIMG on patient healthcare expenditures

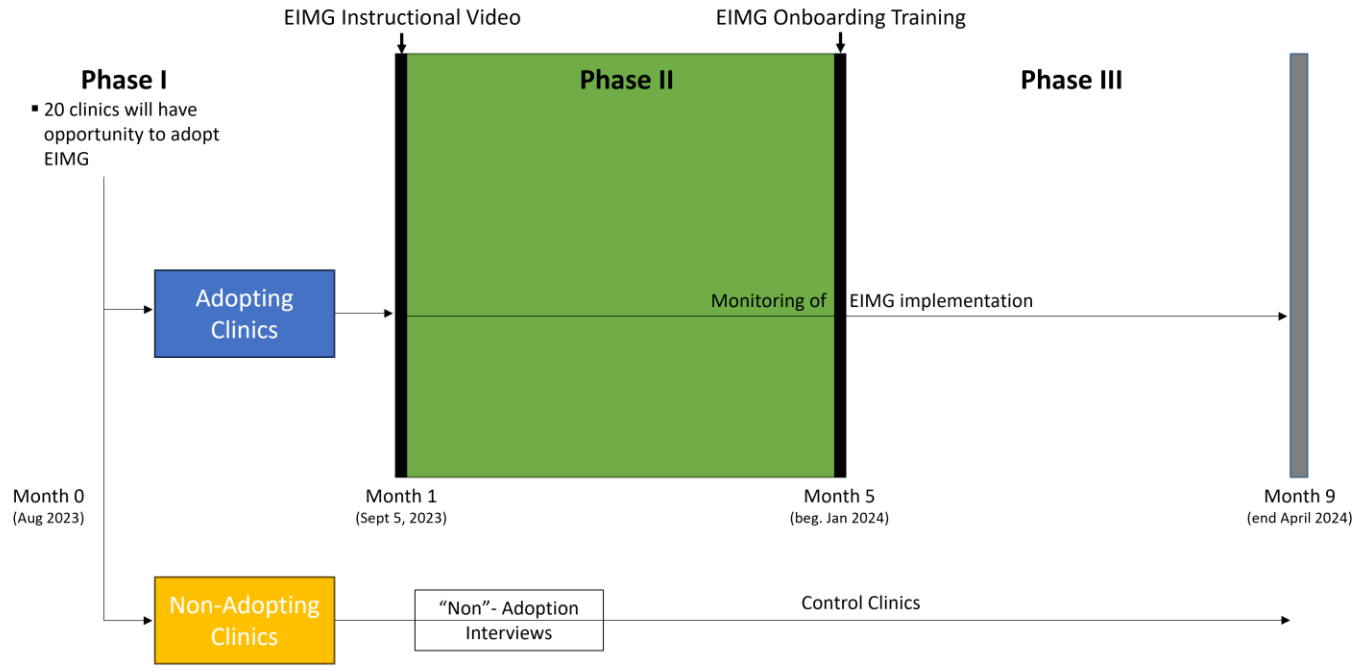
NARRATIVE: The U.S. healthcare sector has great potential for promoting physical activity (PA) for chronic disease prevention and treatment; however, implementation barriers exist, ranging from practice integration to information flow. In 2016, the first multi-organizational partnership between a large academic healthcare system and a national PA organization launched *Exercise is Medicine Greenville (EIMG)*, a comprehensive clinic-to-community approach that involves PA assessment, prescription, and referral of patients with chronic diseases to tailored, community-based PA programs. EIMG strategically leverages resources across a medical school (University of South Carolina School of Medicine Greenville), healthcare system (Prisma Health-Upstate), and community organization (YMCA of Greenville) to connect patients, who are physically inactive and have chronic diseases, to partnering community PA centers. Clinics adopting EIMG typically receive standardized training to: 1) assess patient PA levels, 2) provide brief PA counseling, and 3) initiate a referral process connecting patients to the community PA centers. Referred patients are then guided by credentialed EIMG professionals in a 12-week evidence-informed PA program. Since launching in 2016, EIMG has grown to include 27 provider clinics and 7 community PA facilities covering >400 urban/rural miles^2. Even though EIMG onboard training is standardized across clinics, a high degree of variability exists in its implementation, impacting patient reach, referral rates, and engagement in the community-based PA programs. As EIMG expands across Prisma Health, additional strategies are needed to enhance EIMG adoption, dissemination, and scale up.

This multiple case study design will examine the adoption, implementation, and reach of EIMG (i.e., clinic workflow, referral process) across Prisma Health primary care clinics. Twenty Prisma Health primary care clinics will have the opportunity to adopt EIMG beginning in August 2023. Adopting clinics will receive a standardized instructional video and have the EIMG referral process activated, allowing providers to refer eligible patients to the 12-week evidence-informed PA program. In January 2024, adopting clinics will receive an in-depth, tailored EIMG onboard training. At EIMG adopting clinics, we will track referral rates of eligible patients over two phases lasting a total of eight months (months 1-4 after instructional video, months 5-8 after tailored onboard training).

We will use a mixed methods approach to explore factors related to the adoption of EIMG (i.e., characteristics of adopting versus non-adopting clinics), achieving optimal implementation (i.e., clinic workflow, referral process), reach (i.e., proportion of eligible patients receiving a referral, characteristics of referred versus non-referred patients), and patient enrollment in evidence-informed PA programs at participating community PA facilities. The RE-AIM framework will inform the assessment of implementation outcomes, while the i-PARIHS framework will be used to understand contextual factors (i.e., determinants) influencing patient- and clinic-level outcomes. Careful attention will be paid to issues of health equity across all RE-AIM dimensions over the course of the study. Finally, this work will examine the impacts of EIMG implementation on healthcare costs and patient outcomes to assess the cost-effectiveness associated with implementing EIMG in a major health system.

Integrating the EIM model in health systems to connect patients with available community resources has the potential to significantly alter clinical practice and improve population health outcomes. Information gained from this study will lead to the development of a generalizable approach and materials that will inform future implementation strategies on optimizing and scaling up the integration of comprehensive PA models in U.S. health systems. Study findings will also provide cost estimates of potential savings to health systems integrating PA as a population health management tool through clinic-community linkages.

Figure 1. Overall study schematic.



3.0 BACKGROUND

In 2016, Prisma Health[1] began the process of integrating a physical activity (PA) pathway as a primary prevention strategy, connecting patients to six community partners who offer an evidence-informed PA program tailored for patients with chronic diseases. Prisma Health (with eight inpatient hospitals and more than 100 outpatient facilities and affiliated doctor offices) is the first large health system committed to a multi-level process of promoting PA with patients through a model called Exercise is Medicine Greenville (EIMG).[2] This study will generate vital information on optimizing this pathway and developing clinic-community linkages that engage patients in a community-based, evidence-informed PA program. Our work will also provide data on cost savings related to integrating PA in a health system as a key prevention strategy.

3.1 Health Benefits of Physical Activity

The evidence around the benefits of PA are irrefutable; PA is unquestionably a "best buy" for overall health and is effective in reducing a broad array of health conditions.[3] Exercise training is equally (or more) effective as drug therapy on mortality outcomes, secondary prevention of coronary heart disease, treatment of heart failure, and diabetes prevention.[4] Globally, physical inactivity causes 6-10% of all major non-communicable diseases and is responsible for 9% of premature deaths, rates similar to other established cardiovascular disease risk factors, such as smoking and obesity.[5] Conversely, PA acutely improves blood pressure,[6] glycemic control,[7] and inflammation.[8] Regular PA reduces the risk of developing chronic conditions, such as stroke, hypertension, heart disease, type 2 diabetes, and several types of cancer.[9,10] Given the benefits of PA, it is remarkable that only 54.2% of U.S. adults meet aerobic activity recommendations, while only 22.9% meet both aerobic and strength training recommendations.[11]

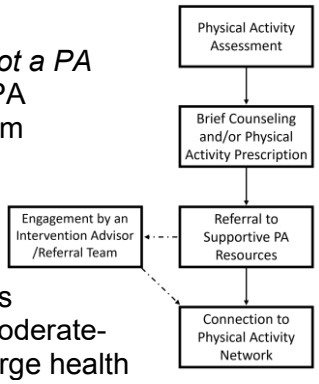
3.2 Physical Activity in the Health Sector

Engagement of the health sector is essential in increasing population PA levels with strategies well-described in the U.S. National PA Plan.[12,13] Healthcare providers see a large portion of the general population, often several times a year. These ongoing, multiple contacts offer the ideal opportunity to provide brief, impactful PA counseling. The Toronto Charter,[14] a global call to action for population-based approaches, outlines several strategies for increasing PA in health settings including: reorienting health services and funding systems, screening of patient PA levels at primary care consultations, and referral to community programs for insufficiently active patients. These overarching guidelines have been supported by calls to action by medical societies[15] and leading health professionals.[16,17] Yet, integration lags because health systems are not properly equipped/designed to promote PA.

3.3 Integrating Physical Activity Pathways into Health Systems

Similar to the SBIRT model[18] (Screening, Brief Intervention, and Referral to Treatment), an evidence-based, clinical strategy for addressing substance use disorders, Exercise is Medicine (EIM)[19] is a comprehensive model for integrating PA in the clinic workflow. *EIM is not a PA intervention*, but a framework to improve the reach of evidence-based PA interventions by identifying and engaging patients that would benefit from increased PA. The individual components of the EIM model include: 1) assessing PA levels of patients, 2) providing brief PA counseling and/or a PA prescription, and 3) referring patients to PA resources for further guidance. In some instances, a 'navigator' or referral team is involved to increase referred patient engagement levels (Figure 2). As described below, the individual components of the "EIM model" have moderate-to-strong evidence bases. Prisma Health-Upstate is the first and only large health system in the world to attempt to integrate all EIM components into their clinic workflow, connecting patients with chronic diseases to community-based PA programs.

Figure 2. Comprehensive model for physical activity integration into health systems.



3.3.1 Assessing Patient Physical Activity Levels

The assessment of PA in clinic settings has been noted as a catalyst to subsequent prescription and referral.[20] The PA 'Vital Sign' (PAVS) is used by multiple U.S. health systems,[21,22] demonstrating strong face and discriminant validity in identifying inactive individuals across gender, age groups, and disease conditions.[23] Significant associations exist between PA levels and cardiometabolic risk factors, body mass index (BMI), and patient disease burden.[23,24] PAVS integration into the electronic health records (EHR) leads to greater PA progress note documentation, PA counseling, and referral compared to patient visits without PAVS administration.[25] Despite PAVS integration in a limited number of U.S. health systems, none have adopted any of the following steps (4.3.2 and 4.3.3) to address low patient PA levels.

3.3.2 Providing Physical Activity Prescriptions

The New Zealand Green Prescription is the best-known program involving health professionals giving patients a written/electronic PA prescription, leading to increased PA levels compared to verbal advice alone.[26] Patients receiving a prescription, compared to usual care, were more likely to meet PA guidelines and achieve higher energy expenditure[27] with benefits extending out 2-3 years.[28] Outside of a few small trials, PA prescriptions have not been systematically integrated into U.S. health systems.

3.3.3 Referring Patients to Physical Activity Resources

The largest exercise referral schemes (ERS) exist in the United Kingdom, involving health professionals referring patients to community-based PA programs.[29] ERS increase patient PA levels, lower levels of depression and anxiety, and is moderately cost effective, particularly in older patients and those with greater cardiovascular disease risk factors.[30,31] However, ERS do not often involve a standardized PA assessment. In the U.S., no system-wide PA referral efforts have been established to date.

3.4 Cost-Effectiveness of Physical Activity Promotion in Health Systems.

Physical inactivity costs healthcare systems $53.8 billion worldwide and contributes to $13.7 billion in productivity losses.[32] In the U.S., inadequate PA, independent of BMI levels, is associated with 11.1% of aggregated, direct healthcare expenditures.[33] Conversely, PA interventions are cost-effective in improving population health outcomes.[34,35] Cost savings have been noted when examining PA interventions introduced in healthcare settings. A review found that linking primary care patients to community PA resources was likely to be cost-effective, *but that evidence was sparse*.[36] To date, no studies have examined costs associated with integrating a PA referral pathway into a U.S. health system and associated cost effectiveness of the PA referral pathway.

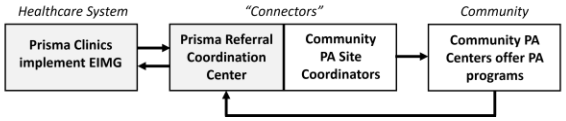
4.0 EXERCISE IS MEDICINE GREENVILLE (EIMG)

The EIMG model is a joint effort involving the University of South Carolina School of Medicine Greenville (UofSC SOM Greenville), Prisma Health, and the YMCA of Greenville. An EIMG Advisory Board, led by Jennifer L. Trilk, PhD, FACSM, provides oversight and direction for EIMG implementation and ensures compliance with program rules and regulations.[2]

4.1 Implementing EIMG into the Prisma Health System

EIMG implementation started in 2016 with the testing of EHR functionality, onboarding of two clinics, PAVS integration into the EHR, best practice alerts, risk assessment, EIMG order sets and electronic referrals to community PA facilities. By April 2023, 27 Prisma Health practices, including family and internal medicine, as well as specialty clinics (i.e., bariatrics, cancer), had adopted EIMG (Figure 3) covering, >400 miles[2] in Greenville and Oconee counties.

Figure 3. EIMG model for connecting patients from health systems to community PA facilities to participate in physical activity programs.



4.2 Patient Eligibility

Patients are eligible to participate in EIMG if they are between the ages of 18-80, physically inactive (<150 minutes per week of moderate intensity aerobic activity) and with or without a chronic condition (i.e., overweight/obese, hypertension, type 2 diabetes) that is positively impacted by PA. Patients with uncontrolled hypertension or diabetes, and those at increased fall risk are ineligible to participate in EIMG until symptoms are controlled and physician approval is provided.

4.3 EIMG Clinic Workflow

The EIMG Clinician Decision Modules are incorporated into the EHR as part of clinical workflow. The three Decision Modules include: 1) PA assessment, 2) PA prescription (through patient order sets), and 3) referral to a community PA facility.

Module 1: PA Assessment. Front office or nursing staff capture the patient's current PA behavior via the PAVS programmed into the EHR. The PAVS consists of two questions ("how many minutes per day do you exercise?" and "how many days per week?") to determine if the patient is meeting national PA guidelines of 150 minutes of moderate intensity aerobic activity a week. The PAVS identifies 'eligible' patients, provides a best practice alert (BPA) through the EHR stating that the patient may qualify for EIMG, and prompts providers to discuss lifestyle behavior change.

Module 2: PA Prescription. The healthcare provider informs eligible patients about the EIMG program, reviews risks, and provides basic PA and health education by providing them with *EIM Rx for Health* handouts for exercising with chronic disease (e.g., obesity, diabetes, hypertension, peripheral artery disease), developed by experts in the field.[37] The healthcare provider then electronically starts an 'EIMG Order Set' leading to the patient referral.

Module 3: Patient Referral. Through a series of EHR prompts confirming patient eligibility, the healthcare provider sends a referral to the *EIMG Referral Team*. All aspects of the EHR referral process are electronic, except a paper version of the EIMG Consent to Treat and the Release of Information that the patient must sign (either while in the clinic room or at the checkout counter) in order to continue.

4.4 The EIMG Referral Team

The *EIMG Referral Team* consists of an EIMG Care Coordinator employed by Prisma Health, who reviews the patient's EHR, contacts them via telephone, confirms their eligibility and interest, identifies their preferred location and ability to pay (e.g., scholarship eligibility), and electronically sends all HIPAA-compliant patient information to the EIMG Site Coordinator at the selected community PA facilities for a warm "hand off".

4.5 Interface Between Prisma Health and Community PA Facilities

The EIMG Community Interface consists of: 1) EIMG Community PA Facilities, and 2) EIMG Community PA Facility Site Coordinators.

4.6 EIMG Community PA Facilities

The EIMG community PA facilities include one Prisma Health medical fitness facility and seven YMCA sites across Greenville and Oconee Counties, with a reach of >400 miles^2. The PA facilities have a like-minded mission to serve as an extension of health care to improve community health and decrease geographical barriers to participation. Upon joining the EIMG network, each facility is educated on program operations and all associated administration and staff undergo standardized EIMG training.

4.7 EIMG Community PA Facility Site Coordinators

Upon receiving a patient referral from the EIMG Referral Team, the EIMG Site Coordinator at the patient's preferred community PA facility contacts the patient, reviews logistic and financial needs, and schedules the patient for onboarding with an EIMG Professional (EIMG Pro) at their facility. The EIMG Site Coordinator informs the EIMG Pro about the incoming patient. The EIMG Site Coordinator also is responsible for HIPAA protocols, implementing EIMG protocols, oversight of EIMG Pros responsibilities, communicating timelines, and audit reporting.

4.8 Evidence-Informed PA Programming at Community PA Facilities

The final step involves patient enrollment in the PA program at a community PA facility. Three key activities take place at each community PA facility: 1) EIMG Pro selection and training, 2) patient onboarding, and 3) conducting the 12-week evidence-informed PA program.

4.9 EIMG Professionals (EIMG Pros) Selection and Training

EIMG Pros are community PA facility employees selected based on their experience and desire to work with clinical populations. All EIMG Pros have a B.S. in exercise science or health-related field, possess a NCCA-accredited personal training certification, obtain the EIM Credential,[38] complete HIPAA and CITI training for the protection of human subjects, and receive training on using REDCap™ (Research Electronic Data Capture) database. Continuing education is provided to all EIMG Pros twice per year and all training materials are archived on an EIMG Pro site. EIMG Pros are responsible for leading the 12-week PA program over one-hour sessions, two times per week, in the community PA facilities.

4.10 Patient Onboarding

Patient onboarding with EIMG Pros takes approximately one hour and includes completing: 1) appropriate paperwork (i.e., health history forms), 2) pre-participation surveys (i.e., PHQ-9, PROMIS Scale), and 3) measurement of height, body weight (in duplicate), blood pressure (after 10 minutes seated in triplicate), and heart rate (in triplicate). The assessments are also completed at the end of the 12-week program. A rolling enrolment feature allows patients to onboard in <10 business days to maximize readiness for behavior change, with new patients learning from current program participants.

4.11 The Evidence-Informed PA Program

The evidence-informed PA program used by EIMG was created based on evidence-based research and ACSM Position Stands around meeting national PA guidelines of 150 min/week of moderate intensity aerobic activity. Patients are referred to either the: 1) Cardiometabolic or 2) Musculoskeletal/ Pain modules based on their primary diagnosis and referral. Training sessions are guided by the following social-cognitive theory principles that: 1) all training is progressive, 2) training should include full body movements, and 3) active education is incorporated into training. In lieu of a fixed curriculum, program "essential" and "recommended" building blocks provide a foundation and allows for flexible and adaptive delivery by EIMG Pros based on their

individual strengths, their unique participants, and limitations of their specific facility (i.e., equipment, space, scheduling). This program model is consistent with key concepts for adaptive and flexible health promotion interventions.[39,40] Patients also are provided with EIMG Patient Education Handouts to increase their understanding about adopting a healthy lifestyle (i.e., PA, nutrition, stress management, goal setting, social support). Data from PA program sessions (i.e., patient attendance and progress, pre-post metrics) are tracked using REDCap that is accessible to the EIMG Site Coordinators, EIMG Pros, and the research team.

4.12 Closing the Loop: Interfacing Back to Prisma Health

All pertinent patient activity (e.g., contraindications to exercise notifications, Patient Consult Summary Form when a patient graduates or drops out from the program) is documented by EIMG Pros and sent by secure email to the EIMG Referral Team. The EIMG Referral Team then provides the patient's summary to the healthcare provider through the EHR.

4.13 Program Cost and Financial Assistance

Understanding that EIMG only succeeds as a population health tool if it is affordable and delivered equitably, the YMCAs of Greenville developed a program in which a percentage of their annual giving campaign goes to EIMG so that no patient is turned away due to their inability to pay. To date, >$350,000 has been set aside for patient scholarships, a model that can be replicated by other YMCAs and community PA facilities outside of Greenville, SC. Patients receive scholarships covering 5-100% of program costs with as many as 75% of patients receiving some sort of financial assistance to participate in the EIMG.

4.14 Initial Results from EIMG Implementation

From launch in 2016, EIMG expanded to 18 Prisma Health practices and six community PA facilities across Greenville County by 2019. Over time, referral numbers have been consistent within a clinic, demonstrating initial sustainability of the EIMG model. Yet, large variations exist in referral patterns between participating clinics.

As of the end of 2022, a total of 1471 patients had been correctly referred to the EIMG Referral Team (Figure 4) with 520 enrolling in the PA programs. Variation in referral patterns between clinics, as well as system level gaps in connecting patients to the PA programs, provides substantial rationale for investigating strategies to optimize the clinical implementation of the EIMG model.

Figure 4. Results for EIMG clinic-to-community referrals, 2016-22.

Number of Correct Patient Referrals	Referrals to Community PA Centers	Patients Enrolled in PA Program	Patient Graduation (2016-19)
1471	1049	520	273
	71.3% referred patients connected to nurse navigator	35.4% of referred patients enrolled in a PA program	18.6% of referred patients graduated from a PA program
52.5% of enrolled patients graduated (273/520)			

Patients enrolled in the PA program graduated at rates of 48%, 63%, and 68% in 2016 through 2018, with a projected 72% in 2019/2020 (prior to shut down during coronavirus pandemic).[41] Analysis of a subgroup of patients (n=173) demonstrated a significant decrease in bodyweight (1.5±4.1 kg, $p<0.001$). Patients referred for hypertension (n=106), lost an average of 1.2±3.8 kg ($p=0.002$) and decreased their systolic (n=100) and diastolic blood pressure by 7±15 ($p<0.001$) and 3±8 mmHg ($p=0.001$), respectively. In an exit survey (n=153 graduates), all program components received high satisfaction scores (5-point Likert scale, 5 = "highly satisfied"). All provider ratings were above 4.75 and all satisfaction scores were above 4.9.

Despite the existence of a standardized framework for integrating EIM in Prisma Health clinics, variability in implementation fidelity has emerged over the initial years of the EIMG program. This underscores the need to understand the contextual factors and processes at both clinic- and provider-levels to enhance implementation of the EIMG model.

5.0 STUDY OBJECTIVES

5.1 Primary Objectives

Primary Aim. To determine differences in clinic- and provider-level adoption (i.e., proportion and characteristics of clinics that adopt and initiate use of EIMG), implementation (i.e., delivery fidelity), and reach (i.e., number, proportion, and representativeness of patients) before and after EIMG integration at newly adopting Prisma Health primary care clinics.

5.2 Secondary Objectives

Secondary Aim 1. To assess the effectiveness of participating in the evidence-informed, 12-week PA program at the community PA facilities on patient health outcomes (i.e., body weight, blood pressure, hemoglobin A1c, lipid profiles) captured in their electronic health records.

Secondary Aim 2. To evaluate, from a health system perspective, the cost of implementing EIMG to estimate the effort of EIMG vs. standard care on costs and outcomes (effectiveness). We will use these estimates to obtain the incremental cost-effectiveness of EIMG vs. standard of care.

5.3 Significance to the Field

The completion of this study and achievement of our study aims has the potential to significantly advance understanding of how to optimally integrate a PA referral pathway into clinical settings that involves the prescription, referral, and engagement of patients in community-based PA programs. This study will enhance the operationalization of future large-scale, PA models in health systems that have diverse policies, practices, and patients. Study findings and resources will be made available to health systems for broad scale up with the goal of increasing patient engagement in community-based PA programs as an extension of healthcare systems. Finally, the achievement of our study aims will provide an economic evaluation that has the potential to impact coverage decisions made by insurance companies and adoption/implementation decisions made by health systems when determining the design and uptake of clinical/ community health promotion programs.

6.0 STUDY DESIGN

6.1 Overview of Study Design

This study will employ a single arm, multiple case study design using a mixed methods approach to examine the adoption, implementation, and reach of EIMG across Prisma Health primary care clinics (i.e., clinic workflow, referral process), leading to patient enrollment in a community-based, evidence-informed PA program. Eligible Prisma Health primary care clinics that have not yet received EIMG onboard training and activation will be provided with the opportunity to adopt EIMG as a part of their clinic practice and patient workflow process. A mixed methods approach will examine contextual factors influencing decisions to adopt/not adopt EIMG.

Clinic champions at clinics adopting EIMG will be provided with a brief pre-recorded training video to disseminate to their clinic staff (e.g., physicians, nurses, medical assistants, administrative assistants) on how to provide their patients with an EIMG referral. All providers at the clinic will have the ability to screen and identify physically inactive patients and provide them with an EIMG referral. Initial implementation and reach of EIMG at adopting clinics will be tracked for approximately four months following the dissemination of the pre-recorded training video. After four months, the EIMG team will provide a more in-depth, standardized clinic onboard training following established protocols iteratively developed and refined through the initial addition of EIMG clinics between 2016-19. The onboard training, which consists of an overall presentation of the EIMG program and specific information on placing the referral order and patient workflow, has been adapted for virtual environments due to its notable added benefits, including its recording to serve as an ongoing reference tool for those who cannot attend initial training and incoming staff. Implementation and reach of EIMG will be tracked for an additional four months after the onboard training.

Referred patients will have the opportunity to enroll in an evidence-informed, 12-week PA program at local community PA facilities (e.g., YMCAs) that partner with EIMG. Upon enrollment and at the completion of the 12-week PA program, patients will undergo an assessment battery that includes the completion of a patient health questionnaire, anthropometric assessments (i.e., height, weight, waist circumference) and an evaluation of their mental and emotional health (i.e., PROMIS tool, PHQ-9). The RE-AIM framework will inform the assessment of implementation outcomes (i.e., adoption, implementation, and reach), while the i-PARIHS framework will be used to examine contextual factors (i.e., determinants) influencing clinic level outcomes. Patient demographics, health outcomes, healthcare utilization and costs of eligible patients at participating primary care clinics, both before and after EIMG onboarding, will be extracted from the Prisma Health EHR. Data will be compared between patients that receive EIMG referrals and matched controls at clinics that do not adopt EIMG: 1) the impact of EIMG on changes in health outcomes, and 2) the impact of EIMG on healthcare costs. These estimates will be used as the basis for cost-effectiveness analyses of EIMG and serve as the foundation for long-term evaluation modeling approaches to incorporate changes in longer-term secondary health outcomes (e.g., stroke, acute myocardial infarction) on healthcare costs.

6.2 Rationale for Study Design

6.2.1 Choice of Primary Outcome

Referral rates of eligible patients was chosen as our primary outcome because we wish to: 1) specifically examine clinic-community linkages for which the referral is the linchpin, and 2) on evaluating the implementation of a PA referral pathway integrated within a health system. The ultimate indicator of provider-patient 'engagement' in the clinic setting is the delivery of a complete and accurate EIMG referral to eligible patients. We considered examining patient engagement in the evidence-informed PA program, but this occurs further downstream, involving several additional steps on the periphery and outside of the healthcare setting. However, as part of a secondary aim (effectiveness of the evidence-informed PA program), we will examine patient enrollment rates and factors influencing their decisions (i.e., barriers and facilitators).

6.2.2 Study Population

Our study population will consist of: 1) clinic staff at participating Prisma Health primary care clinics, and 2) all patients eligible to receive an EIMG referral to participate in the evidence-informed PA program at local community PA facilities.

6.2.3 Inclusion of Women

We expect that approximately equal numbers of men and women will be eligible to receive an EIMG referral and have the opportunity to participate in the study. We therefore might expect to enroll women at a similar (or greater) proportion as they appear in the underlying population of ambulatory care. However, in our previous work involving EIMG, women received a greater proportion of referrals (75%) and participated in the PA program at a greater rate (81% to 19%) than men. Therefore, we expect to see levels of participation in the study that reflect these past trends.

Patients that are pregnant are not eligible for participation in EIMG and, therefore, will not be eligible to participate in the study. The PA program is designed for patients with chronic diseases and are not tailored for the specific needs and considerations of pregnant women. A future goal of EIMG, beyond the scope of this study, is to develop, offer, and test an EIMG model specifically tailored for pregnant women and other higher risk populations.

6.2.4 Inclusion of Minorities

This study focuses on the identification of physically inactive patients with chronic disease and their referral to the PA program. The study will include patients regardless of their race, ethnicity, or any other underrepresented status. Conducting the study in Prisma Health primary care clinics, a major health system serving a large and diverse population in Greenville, South Carolina, ensures that we will have a high representation of minority patients. Based on the current patient population served by Prisma Health, we anticipate that approximately 25% of the study participants will be African American, 62% will be White, and approximately 8% will be Hispanic/Latino. It is our intention to pay particular attention to issues of health equity across all dimensions of the study, examining determinants and contextual factors that may potentially impact the participation of vulnerable populations at any point in the EIMG model.

6.2.5 Selection of Eligible Prisma Health Primary Care Clinics

We elected to use the clinic as the unit of observation, rather than individual providers or patients within a clinic. Clustering is preferred when the target of an intervention is a collective or system rather than a particular person or patient, allowing us to evaluate a new standard of care or practice-wide change that may affect patient outcomes. Further, the use of clusters (at the clinic level) reduces potential contamination between groups as patients within a clinic are more likely to be treated similarly and exhibit similar outcomes. Our unit of analysis will be a

compilation of provider-level metrics, aggregated across all providers within a clinic. The negative to clustering at the clinic level includes requiring more participants to obtain equivalent statistical power, more complex analyses, and not being able to blind groups.

6.2.6 Selection of Primary Care Settings

The primary care setting, as opposed to acute and urgent care centers or specialty clinics, was selected for this study as most patient contacts originate and end in primary care. In many cases, primary care is the only place that individuals have access to care. The primary care setting is the cornerstone of health systems in meeting the broader needs of patients, families, and communities. Primary care practices are tasked with providing high quality care for patients on a long-term basis, many of them with co-morbid conditions that are all positively impacted by greater PA levels. The primary care setting is the first point of contact for patient populations (inactive, with diabetes, hypertension, obesity, and dyslipidemia) requiring primary and/or secondary disease prevention, such as PA promotion and counseling. Further, the primary care setting allows for the ongoing observation of the trajectory of chronic diseases through multiple visits over time.[42] Lastly, the patients seen in primary care settings are representative of the surrounding population, allowing for a greater examination of interventions that reduce health disparities and improve health equity.

6.2.7 Rationale for Control Condition

The selection of our control group was influenced by several factors. There are currently only 20 Prisma Health primary care clinics that have not received EIMG onboarding and activation and that are within 15 miles or less of a participating community PA facility. There are no other equivalent Prisma Health primary care clinics to serve as matched controls (i.e., via a stepped wedge design). We are then left with two groups of clinics to serve as controls. The first of these is using a within-clinic design and comparing patient health outcomes before and after the dissemination of the initial EIMG Instructional Video. Secondly, from past experiences, we anticipate that several of the 20 clinics will choose not to adopt EIMG and/or will be non-responsive to our invitation. As one of our study aims, we will evaluate contextual factors and differences between adopting and non-adopting clinics. Clinics that do not adopt EIMG will not be ‘activated’ and can therefore serve as control clinics, particularly when evaluating patient-level outcomes, as none of their patients will have had the opportunity to participate in EIMG.

7.0 STUDY POPULATION

7.1 Prisma Health - Clinic Eligibility

As the unit of randomization, we will offer the opportunity to adopt EIMG to 20 Prisma Health primary care clinics that have not yet implemented EIMG. The department chairs for Internal and Family Medicine (Drs. Peter Tilkemeier and Peter Carek) have provided their support for EIMG expansion across these primary care clinics.

Eligibility criteria for clinics to participate in this study include the following:

- Prisma Health primary care clinics (i.e., family or internal medicine) located in the Upstate of South Carolina
- Have not received EIMG onboarding or activation in the past;
- Consist of at least two attending providers;
- Be located 15 miles or less from a participating community PA facility.

All potentially eligible Prisma Health primary care clinics were geographically coded to determine the distance to the nearest participating community PA facility. Clinics >15 miles will be ineligible for study participation as previous research consistently demonstrates that engagement in leisure time PA and enrollment in fitness centers is negatively correlated with distance to PA destinations.[43,44]

7.2 Prisma Health – Patient Eligibility

Adult patients (≥18 years of age) will be deemed eligible for the study through two different approaches. First, patient eligibility to receive an EIMG referral is determined in real time through a series of steps that are integrated within the patient workflow process in the Prisma Health primary care clinics. Patients that receive an EIMG referral will have the opportunity to enroll in the community-based PA programs and will be considered as the numerator in our 'reach' calculations. Second, all patients that were eligible for an EIMG referral (whether they received one or not) at participating clinics will be identified through a retrospective data extraction process from the Prisma Health EHR that will occur at the end of the study period (end of month 8). These broader sample of patients that were eligible for an EIMG referral will be considered as the denominator in our 'reach' calculations.

7.3 Patient Eligibility – Participating in the PA Program

Healthcare providers at participating Prisma Health primary care clinics that adopt EIMG will have the ability to identify eligible patients and provide them with an EIMG referral during the patient visit through a process embedded in the patient care workflow at each clinic.

The first step in determining patient eligibility to receive an EIMG referral will involve identifying potentially eligible patients that would benefit the most from participating in an exercise training program. As part of EIMG adoption (both with the EIMG Instructional Video [phase I] and the EIMG Onboard Training [phase II]), clinicians will be guided to identify and refer patients with low physical activity levels with or without any of the following: overweight/obesity, high blood sugar, high blood pressure, or dyslipidemia. Although the provision of referrals is left to the judgement of each clinician, general guidelines for referring patients will be as follows:

- >150 minutes per week of moderate intensity PA (as determined by the PAVS)
- BMI ≥30kg/m^2
- Impaired fasting glucose
- Prediabetes
- Types 2 diabetes mellitus
- Essential hypertension
- Dyslipidemia (including hyperlipidemia, hypertriglyceridemia, hypercholesteremia)

Once a clinician has deemed that a patient would benefit from participating in EIMG, to complete the referral process they will be asked to:

i. Complete a Risk Severity Assessment to ensure that participating in an exercise training program will be safe and that it is appropriate for their patients;
ii. Upload the consent and release of information forms signed by the patient (these forms allow the transfer of a limited amount of HIPAA-protected patient health information to the site coordinator at the community PA facility).

This information is electronically sent to a member of the EIMG Referral Team, who checks for completeness and ensures patient eligibility to participate in the PA program. EIMG Referral Team members will contact referring clinicians if any required information is missing or to clarify any safety concerns.

The final number of patients referred to the EIMG Referral Team will serve as the 'numerator' in our Reach calculations (see 13.2 and 13.3).

7.4 Determining Patients Eligible for EIMG Referral

During the data extraction process, a list of patients that were eligible for an EIMG referral (regardless of whether they received a referral or not) will be extracted from the Prisma Health EHR. The research study team will retrospectively identify patients that could have received an EIMG referral based on a list of pre-determined ICD-10 codes.

Inclusion Criteria. The study team will develop a list of ICD-10 codes (based off the criteria presented in section 7.2.1.) to identify all potentially eligible patients that could have received an EIMG referral. The ICD-10 codes were selected a-priori by the study team based on the priority health conditions identified by Prisma Health leadership in partnership with the EIMG Advisory Board. These conditions include patients that are physically inactive and/or who have obesity, diabetes, hypertension, or dyslipidemia. The list of ICD-10 codes was selected by the research team and verified by: a) the EIMG Advisory Board, and b) Prisma Health primary care clinicians.

Exclusion Criteria. During phase I and II of the study (prior to any extraction of patient data from the Prisma Health EHR), the research team will engage in a process to develop a list of exclusionary criteria. Patients seeking medical assistance with any of these criteria would be deemed ineligible to receive an EIMG referral and will be removed from the denominator of our implementation, reach, and effectiveness analyses. To develop the list of exclusionary criteria, we will engage in a three-step process. First, we will identify published guidelines and existing tools (e.g., PAR-Q+) that list health conditions that are contraindications for physical activity. Second, we will seek the opinions of 8-12 primary care physicians to identify conditions for which they would not refer their patients to a physical activity program. Combining these findings, we will develop a list of ICD-10 codes that will serve as exclusionary criteria for which exercise training is either inappropriate or contraindicated.

The final list of patients deemed eligible for a referral (inclusion criteria – exclusion criteria) will serve as the 'denominator' in our Reach calculations (see 14.1 and 14.2).

	Definition	Description
Numerator	# of eligible patients that receive an EIMG referral	• Determined through a real time patient workflow process in Prisma Health primary care clinics participating in the study
Denominator	# of patients that were eligible to have received an EIMG referral	• Retrospectively pulled from the Prisma Health EHR • Determine number of eligible patients based in ICD-10 inclusion criteria (Appendix A) • Remove ineligible patients based off ICD-10 exclusionary criteria

8.0 STUDY PROCEDURES

8.1 Waves of Enrollment

All eligible Prisma Health primary care clinics will be invited to adopt EIMG at the same time. Prisma Health primary care clinics will not enter clinics into the study via stepped approach. Within this one wave, three distinct study phases will be conducted.

8.2 Phase I – EIMG Adoption

The first phase of this study will involve inviting all eligible Prisma Health primary care clinics to adopt EIMG through a three-step approach, as described below.

8.2.1 Step One – Department Chair Email

The department chairs for family and internal medicine at Prisma Health will, on behalf of the research team, send a brief email to all physicians and practice managers at eligible Prisma Health primary care clinics. The email will briefly introduce EIMG, discuss its compatibility, complexity, relative advantage, observability, trialability and how adopting it will benefit their clinic, and provide a link to the EIMG website. If a practice manager responds to this email, they will be invited to schedule a brief introductory meeting (section 8.2.3.) to discuss the process of adopting EIMG. If a physician responds to this email, they will be encouraged to reach out to their practice manager so that they can both be jointly involved in the EIMG adoption process. We decided that the practice manager must be included in the adoption process as they are most likely to disseminate information and materials to the clinic staff and serve as the best point of contact for the research team.

8.2.2 Step Two – Communication with Practice Manager

Approximately one-week after the department chair email, a study coordinator will send a follow up email to each practice manager to gauge their interest in adopting EIMG. Practice managers that express interest in adopting EIMG will be asked to schedule a brief introductory email (section 8.2.3.). If a practice manager expresses that their clinic is not interested in adopting EIMG, the clinic will be considered as a 'non-adopter'. If the practice manager does not respond to the email within one week, the study coordinator will attempt to call the practice manager up to three times over the following ten days. If the study coordinator is unable to get in touch with the practice manager, they will be considered unresponsive and their clinic will be classified as a 'non-adopter'.

8.2.3 Step Three – Brief Introductory Meeting with Practice Managers

A study coordinator will conduct a brief, 15-minute meeting with practice managers at clinics interested in adopting EIMG. The meeting will be held in-person or virtually at the request and convenience of the practice manager. During the meeting, the study coordinator will provide an overview of the adoption process (phase II and phase III), discuss the EIMG Introductory Video and the timeline for its dissemination and EIMG activation at the clinic, explain the optional research components accompanying EIMG adoption (adoption interview, section 9.1.1; online ORCA questionnaire, section 9.1.2; individual interviews with clinic staff, section 9.1.3), and answer any questions from the practice manager.

8.3 Phase II – EIMG Instructional Video

Phase II will start with disseminating the EIMG Instructional Video to adopting clinics, followed by EIMG activation. The EIMG Instructional Video is intended to be a low-intensity strategy for disseminating information and guidance on EIMG and the PA referral pathway connecting Prisma Health primary care clinics and the community PA facilities. The EIMG Instructional Video is a brief (11-minute), voice-over PowerPoint presentation that provides information on: a) the origins of EIMG, b) the 12-week, community-based PA program, c) initial patient effectiveness results, and d) process for placing an EIMG referral. The EIMG Instructional Video will be sent to the practice managers at EIMG-adopting clinics for broader dissemination to all

clinic staff. After delivery of the EIMG Instructional Video to the practice managers, access to the EIMG referral process in the EHR is '*turned on*' (aka – EIMG activation) allowing clinic staff to electronically identify and engage with eligible patients.

8.4 Phase III – EIMG Onboard Training

Phase III will consist of a more in-depth standardized EIMG onboard training that will take place with EIMG-adopting Prisma Health primary clinics (section 8.2). The EIMG onboard training will be scheduled in collaboration with the clinic practice manager on a day and time most convenient for the clinic staff. The scheduling of the EIMG onboard training will occur during the second half of month 4, with the trainings taking place during the first half of month 5. The onboarding process will follow an established protocol that has been iteratively developed and refined from lessons learned through the addition of EIMG clinics between 2016-21. Due to the coronavirus pandemic, the onboard training process was adapted for virtual environments and will be used moving forward due to its notable benefits, including recording the training to serve as an ongoing reference tool for clinic staff who cannot attend initial training, as well as new and incoming staff. The standardized, yet flexible and adaptable training is targeted to practice managers, healthcare providers, nurses, and front-office staff at clinics. The training includes a detailed explanation of the EIMG Clinical Education Workflow, a breakdown of responsibilities for each part of the EIMG process (i.e., conducting the PAVS, obtaining the consent and release of information forms), and completing the risk severity assessment. Strategies used in the onboard training will be mapped to implementation strategies compiled as a part of the Expert Recommendations for Implementing Change (ERIC).

9.0 STUDY EVALUATION AND ASSESSMENTS

This study is evaluating the adoption and implementation of an existing program (EIMG), which has previously been adopted and is in use by >27 Prisma Health clinics, at Prisma Health primary care clinics that have not yet had the chance to adopt this program. Our study will conduct research activities examining adoption, implementation, and effectiveness across three different groups of individuals:

- Practice managers at Prisma Health primary care clinics that are eligible to adopt EIMG;
- Clinic staff at Prisma Health primary care clinics that adopt EIMG;
- Patients at primary care clinics that adopt EIMG and receive an EIMG referral.

All individuals that agree to participate in research activities will go through an informed consent process as described in section 14.3. A timeline for the following research activities is summarized in section 10.

9.1 Evaluating EIMG Adoption

The adoption of EIMG at eligible Prisma Health primary care clinics will be examined through two strategies. First, we will compare key characteristics (e.g., proximity to the PA facilities, number of patients seen, patient insurance distribution, number and type of providers) between clinics that adopt versus those that do not adopt EIMG. Second, during the first month of Phase II, we will seek to conduct semi-structured interviews with practice managers from each Prisma Health primary care clinic that was offered the chance to adopt EIMG, regardless of whether their clinic adopted EIMG or not. The semi-structured interview will be guided by an interview script mapped to the i-PAHRIS framework,[45] exploring decisions to adopt (or not) EIMG at their clinic.

9.2 Evaluating EIMG Implementation

Two assessments will be utilized to examine contextual factors influencing the implementation and reach of EIMG at the clinic level. First, we will conduct the Organizational Readiness to Change Assessment (ORCA)[46] with clinic staff (administrators, providers, and staff) at EIMG-adopting clinics. The ORCA tool operationalizes constructs defined in the original PARIHS framework to measure organizational readiness to change in clinic settings. The ORCA consists of three major scales that measure the strength of evidence for the proposed innovation, organizational support for change, and organizational capacity to facilitate the change. In previous work, we adapted and pilot-tested the ORCA as an online questionnaire with Prisma Health primary care clinics (not included in this study) to assess contextual factors related to EIMG adoption and implementation. In the current study, we will conduct the ORCA as an online questionnaire with a representative sample of clinic staff from each clinic after the dissemination of the EIMG Instructional Video (months 2-3) and again after the EIMG Onboard Training (months 6-7).

Second, we will conduct brief (~30 minutes), semi-structured interviews with clinic staff to gain a more nuanced understanding of EIMG implementation across clinics. While self-administered questionnaires or structured interviews cost less and reduce interviewer bias, semi-structured interviews foster rapport and are preferred when seeking information on respondents' attitudes and perceptions on a topic.[47] Semi-structured interviews also allow exploration of issues through extensive probing.[48] The interview scripts will be mapped to the i-PAHRIS framework[45] and structured to complement the quantitative data gained through the ORCA. We will attempt to conduct interviews with a representative sample of staff (e.g., four staff per clinic) approximately 1-2 months after the EIMG Onboard Training (months 6-8).

9.3 Evaluating the Effectiveness of the 12-week, Community-Based PA Program

9.3.1 Changes in Patient PA Levels

Changes in patient PA levels will be evaluated through two strategies. First, patients will be screened for their PA levels during clinic visits using the PAVS. Patients that enroll in the 12-week PA program will continue to complete the PAVS (to ensure consistency of assessment) at baseline (week 1), midpoint (week 6), conclusion (week 12), and 12 weeks after the completion of the PA program by the EIMG Pros. As a secondary data source, we will extract patient PAVS data from the Prisma Health EHR. We will use this data to monitor patient PA levels prior to receiving the EIMG referral through six months after completing the PA program.

9.3.2 Changes in Patient Health Outcomes

Primary data for assessing changes in patient health outcomes (i.e., body weight, blood pressure, hemoglobin A1c, lipid profiles) will be extracted from the Prisma Health EHR to allow comparisons between eligible patients that received an EIMG referral and participated in the PA program and eligible patients that do not receive an EIMG referral. Disease incidence, burden, and complications (i.e., the Charlson Comorbidity Index) will be calculated from extracted data.

9.3.3 Individual Interviews with Patients

As part of our mixed methods approach, we will conduct semi-structured individual interviews, based on the COM-B (Capability, Opportunity, Motivation – Behavior) framework, with patients receiving an EIMG referral. Patients from each of the following three categories will be interviewed: 1) patients who received an EIMG referral from their provider, but chose not to enroll in the PA program, will be queried about their awareness and reasons for not enrolling (i.e., perceived challenges to participation); 2) patients who received an EIMG referral and enrolled, but dropped out, will be asked about their perceptions and satisfaction with the PA program, motivations for enrolling, and reasons for discontinuation; and 3) patients who enrolled and completed the PA program will be queried about their motivations for enrolling, perceptions of and satisfaction with the program, and challenges encountered. Where possible, responses from the individual interviews will be linked to our EIMG implementation strategies, such as clarifying places for additional support and improvements to provider-patient interactions, to add to our comprehensive evaluation of the EIMG referral pathway. We will contact all patients that received an EIMG referral during Phase II (EIMG Introductory Video) to conduct an individual interview. We will conduct a similar number of patient interviews, matching for gender and referring clinic, in Phase III (EIMG Onboard Training).

10.0 STUDY TIMELINE

This study will be conducted over three phases: 1) EIMG Adoption; 2) EIMG Introductory Video; and 3) EIMG Onboarding Training. *Phase I* will occur over the first month of this project in which practice managers and their clinic will be offered the opportunity to adopt EIMG, No research activities will take place during this phase. *Phase II* will occur between months 2 through 5, beginning with the dissemination of the EIMG Introductory Video to practice managers and EIMG activation at adopting clinics. This phase will involve several study activities including conducting individual (adoption) interviews with practice managers, clinic staff completing the online ORCA questionnaire, and conducting individual interviews with patients receiving an EIMG referral. *Phase III* will occur from months 6 through 9, beginning with the EIMG onboard training. This phase will involve clinic staff completing the online ORCA questionnaire, conducting individual (implementation) interviews with clinic staff, and continuing the individual interviews with patients receiving an EIMG referral.

10.1 Timetable - Clinic Assessment of EIMG Referral Pathway

		Month								
	Estimated Time	1	2	3	4	5	6	7	8	9
Practice Manager Assessments										
Individual Interviews (Adoption)	20		X							
Clinic Staff Assessments										
ORCA Questionnaire	10			X	X			X	X	
Individual Interviews (Implementation)	20							X	X	X
Patient Assessments										
Individual Interviews (Enrollment)	30		X	X	X	X	X	X	X	X
EHR Patient Information Extraction	n/a		X	X	X	X	X	X	X	X

10.2 Timetable - Evaluating the Effectiveness of the Community-Based PA Program

		Week													
	Estimated Time	0	1	2	3	4	5	6	7	8	9	10	11	12	13
Patient Assessments															
Informed Consent	10	X													X
Participant Intake Form (Demographics)	20	X													X
Anthropometric Biometrics		X													X
Patient Health Questionnaire		X													
Food Behavior Survey		X													X
PROMIS Scale		X													X
Physical Activity Levels		X			X			X			X				X
PA Session Participation	2		X	X	X	X	X	X	X	X	X	X	X	X	
PA Exit (Satisfaction) Survey	15														X

* Note: patients enroll in the 12-week PA program on a rolling basis. The above timetable is relative to their individual enrollment, not the overall study timeline.

10.3 Overall Study Timetable

Milestones and Tasks	Month										
	1	2	3	4	5	6	7	8	9	10	11
Study Start Up											
Hire and train research staff											
Finalizing study protocol and study forms											
Obtaining approval of study documents (i.e., IRB, NIH)											
Register trial with ClinicalTrials.gov											
Establish study databases, finalize study tools											
Finalize the EIMG Instructional Video											
Determine clinics eligible for study participation											
Phase I – Adoption of EIMG											
Email from department chairs to eligible clinics											
Follow up email to clinic practice managers											
Brief, in-person meeting with practice managers											
Phase II – EIMG Instructional Video											
Dissemination of EIMG Instructional Video											
Activation of EIMG to allow EIMG referrals											
Conduct individual (adoption) interviews											
Tracking of EIMG patient referrals for phase II											
Tracking PA program effectiveness											
Begin individual interviews with patients											
EHR data extraction at end of phase II											
Phase III – EIMG Onboard Training											
Conducting standardized EIMG Onboard Training											
Tracking of eligible EIMG patients for phase III											
Conduct individual interviews with clinic staff											
Tracking patient PA program effectiveness											
Continue individual interviews with patients											
EHR data extraction at end of phase II											
Study Wrap Up											
Package and disseminate implementation resources											
Distribute findings to stakeholders/health system											
Manuscript preparation, submission, and publication											
Attend national meetings to present study findings											

11.0 ATTENTION TO HEALTH EQUITY

When examining the adoption and implementation of EIMG, we will pay particular attention to questions of health equity across all dimensions of RE-AIM, including:

1. ADOPTION: We will examine the ability of lower resource clinics to adopt EIMG to the same extent as high resource clinics; necessary adaptations to EIMG at lower resource clinics for more equitable adoption of EIMG; and adapting clinic context to better support staff efforts to utilize EIMG with their patients.
2. IMPLEMENTATION: We will examine characteristics of providers implementing EIMG with a high vs low proportion of patients; differences in clinics and staff capacity; resources to deliver EIMG on an ongoing basis; EIMG implementation strategies distribution among various clinic staff; the impact of setting characteristics on successful EIMG implementation.
3. REACH – We will examine the representativeness of patients reached (i.e., across race/ethnicity, education) compared to all eligible patients; equitableness of the reach of EIMG; which population subgroups are not being equitably reached; barriers to participation in the community-based PA programs.
4. EFFECTIVENESS – We will examine whether the health benefits of EIMG are experienced equitably across subgroups based on social dimensions and social determinants of health; certain subgroups experience higher levels of barriers, negative effects, or burden due to EIMG participation.
5. COST – Participation may present considerable burden to patients, resulting in unintentional inequities. We will examine patient participation in the PA program, paying consideration to cost, time, resources, and unintended social consequences, discussing findings with the EIMG Advisory Board to develop more equitable and sustainable outcomes.

12.0 STATISTICAL ANALYSES

12.1 Primary Outcome

To determine differences in implementation (i.e., delivery fidelity) and reach (i.e., number, proportion, and representativeness of patients) before and after EIMG integration at Prisma Health clinics.

12.2 Statistical Methods for Primary Analysis

Clinic level nominal characteristics will be summarized as count and proportion; quantitative characteristics (e.g., patient census, provider census, etc) will be summarized as using the median and interquartile range. Patient level data will be summarized monthly by clinic using count and proportions for categorical data and mean (standard deviation) or median (interquartile range) as appropriate.

Clinic level characteristics will be compared between adopting and non-adopting clinics to look for indicators that may be leveraged to improve the adoption of EIMG into the patient care workflow. Similarly, there may be providers within participating clinics that choose not to adopt EIMG (refer eligible patients to the physical activity program); characteristics of the providers will be compared to look for ways to adopt / improve EIMG referral.

The primary endpoint will be analyzed on an intent-to-treat basis. This means that clinics will be analyzed according to their agreement to adopt regardless of their subsequent participation. For analyses at the patient level, patients within EIMG-adopting clinics that receive referrals will be analyzed as EIMG participants regardless of their subsequent actions / participation. Referred patients will be considered as part of the "EIMG group" even though they may not be perfectly compliant or follow the prescribed dose of exercise in the physical activity program.

The effect of EIMG on outcomes for overall reach will be analyzed using generalized linear mixed models (GLMM). The use of the GLMM accounts for the variability between clinics (random intercept) and the random effect of time within each clinic. The right-hand side of the model will have the same form. The left-hand side of the model may require the use of different link functions. Our experimental units are the clinics themselves with the observational units being the EIMG eligible patients nested within each clinic. The analytical models will have the following form:

$$g(Y_{ijk}) = (\beta_0 + \mu_{0i}) + \beta_1 EIMG_j + (\beta_2 + \mu_{2i})X_i + (\beta_3 + \mu_{3k})\,T_k + (\beta_4 + \mu_{4jk})EIMG_j T_k + e_{ijk}$$

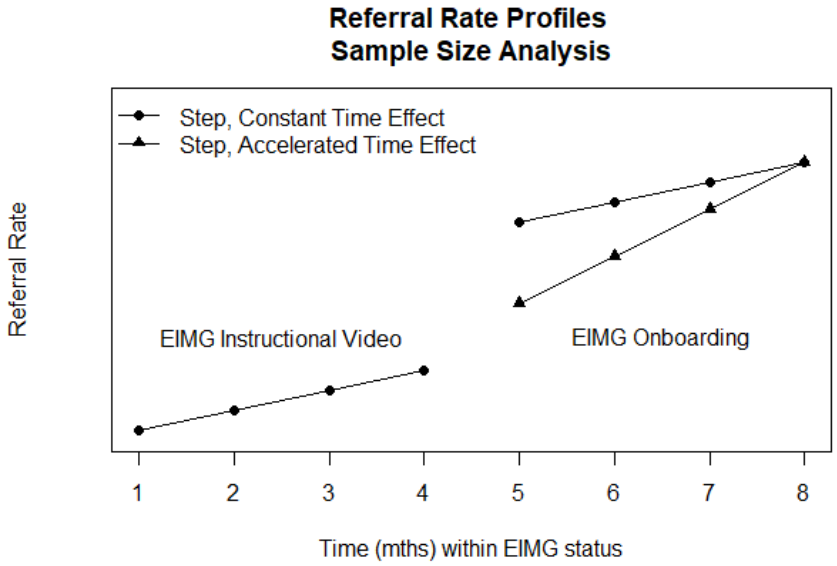
The subscripts i, j and k refer to clinic, EIMG status and time (monthly), respectively. Y_{ijk} is the clinic level outcome measure; $g(Y_{ijk})$ is the link function; β_0 is the mean response across clinics; $\beta_1$is the effect of EIMG; β_2 is the mean effect of clinic level covariates controlling for EIMG status; β_3 is the effect of time; β_4 is the effect of the interaction between EIMG status and time. The remaining terms in the model represent random variability and are assumed to have an expected value of 0 and associated non-zero variance. Specifically, μ_{0i} is the uncertainty term for the intercepts between clusters; μ_{2i} is the uncertainty term for clinic level covariate slopes between clusters; μ_{3k} is the uncertainty term for the effect of time; μ_{4ijk} is the uncertainty term for EIMG by time interaction between clusters; and e_{ijk} is the unexplained residual.

12.3 Rationale for Sample Size and Statistical Power

Sample size was established via simulation in R version 4.2.3 (R Core Team, 2023) utilizing preliminary data from clinics participating in a pilot study. This analysis is based on a within clinics, repeated measures design with two levels of EIMG exposure: Instructional Video and Onboard Training. The outcomes (e.g., referral rates) will be measured 4 times (once per month) under each level of EIMG, for a total of 8 observations per outcome per clinic. Two marginal referral rate profiles were considered in determining the sample size: a step effect of

EIMG onboarding with parallel time effect (main effects model) and a step plus accelerated time effect. A generic plot showing the two marginal rate profiles considered is presented in Figure 5.

Figure 5. Referral rate profiles considered in sample size analysis.



Pilot data from 12 previously onboarded EIMG-clinics indicate the marginal referral rate (reach with eligible patients) prior to onboarding to EIMG is approximately 0.01. The following assumptions were made for both referral rate profiles. The standard deviation for the random effect of clinic, and random deviation is 0.01, the significance level for each comparison is 0.05. For the step with constant time effect, it was assumed that there was a linear change from 0.001 to 0.01 over the four months following the EIMG Instructional Video, a step-jump of 0.02, followed by a linear and parallel time effect achieving 0.04 (4%) referral rate at 8 months. For the step with accelerated time effect profile, the profile for the first 4 months was assumed to be the same as for EIMG Instructional Video with a step-jump of 0.01 followed by a linear increase to 0.04. Simulations (n=100) under each profile were conducted to compute a single empirical power, this was repeated 100 times. The power reported corresponds to the minimum empirical power observed. For a step with constant time effect a total of 10 clinics are needed to achieve a power of 92% to detect the EIMG Onboarding effect of 0.02. For the step plus accelerated time effect profile, a total of 20 clinics achieves 78% power to detect the time by EIMG status interaction when using a significance level of 0.05. Ten clinics provide 40% power to detect the step plus accelerated time effect profile.

12.4 Secondary Aim 1

To assess the <u>effectiveness</u> of participating in the community-based, 12-week evidence-informed PA program on EIMG-referred patient health outcomes (i.e., body weight, blood pressure, hemoglobin A1c, lipid profiles).

Hypothesis 1: Patients participating in the 12-week evidence-informed, community-based PA program will experience increased PA levels that is associated with a dose-response, significant reduction in body weight, systolic and diastolic blood pressure, hemoglobin A1c level, as well as improvements in their lipid profiles.

<u>Effectiveness</u> is the degree to which participating in the evidence-informed PA programs improves patient physical activity levels and health outcomes (i.e., changes in cardiometabolic biometric values). Primary data for assessing effectiveness will be extracted from the Prisma

Health EHR to allow comparisons between patients that are engaged in EIMG and participate in the evidence-informed PA programs and patients that do not participate (either those that are not engaged in EIMG by their providers or those who choose not to participate). Disease incidence, burden, and complications (i.e., the Charlson Comorbidity Index) may also be calculated from data captured in the EHR. Secondary assessment of patient-level effectiveness (e.g., blood pressure, blood glucose, cholesterol concentrations) will be collected by the EIMG Ex Pros at the community PA facilities.

Qualitative Data Collection. As part of our mixed methods approach, we will conduct semi-structured individual interviews with patients from each participating clinic. Patients will be randomly selected from one of three categories:

i. Patients who received a referral from their provider, *but chose not to enroll in the evidence-informed PA program*, will be queried about their awareness of and reasons for not enrolling (i.e., perceived challenges to participation)

ii. Patients who received a referral and enrolled, *but dropped out of the evidence-informed PA program*, will be asked about their perceptions of and satisfaction with the program, motivations for enrolling, and reasons for discontinuation, and

iii. Patients who *enroll and complete the program* will be queried about their motivations for enrolling, perceptions of and satisfaction with the program, and challenges encountered.

Analysis of Qualitative Data. Dr. Leah Schumacher will oversee the collection and analysis of the patient interviews. We will employ a rigorous approach to the analysis of the qualitative data. Open-ended responses will be uploaded to a qualitative software program (e.g., Dedoose) to create and apply codes to textual data, write analytic memos, and conduct analyses by question and respondent. Individual responses will be analyzed as follows: responses will be reviewed to develop an initial coding scheme for each question. Codes will be developed deductively from the questions posed and inductively from responses.[49] As new codes emerge, they will be incorporated into the schemes for each question. A coding manual with definitions for each code will ensure high levels of intercoder reliability (>80%) are achieved throughout the coding process.[50,51] Disagreements in the application of codes will be resolved by Drs. Schumacher and/or Stoutenberg. The analyses will catalogue facilitators, barriers, and challenges to EIMG® implementation in each phase, as well as strategies for overcoming those barriers.

12.5 Secondary Aim 2

To evaluate, from the health system perspective, the cost of implementing EIMG, employing variation from the step-wedge design to estimate the effect of EIMG vs. standard care on costs and outcomes (effectiveness). These estimates will be used to obtain the incremental cost-effectiveness of EIMG vs. standard of care.

Hypothesis 2: Patients receiving an EIMG referral and participating in the 12-week, community-based PA program will experience improved health outcomes, decreased healthcare service utilization, and a reduction in health care expenditures compared to patients that do not receive an EIMG referral and the opportunity to participate in the PA program.

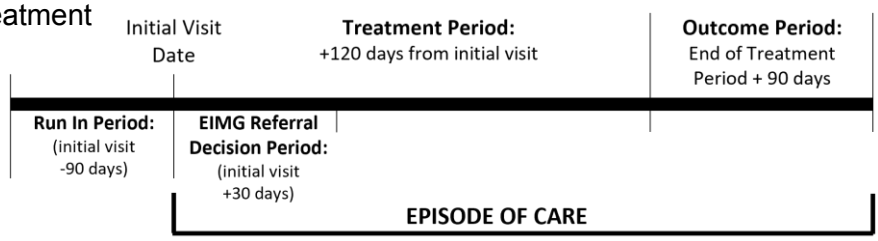
12.5.1 Study Observations.

The first observed visit for each patient with an EIMG-eligible diagnosis will be designated the index visit date for “candidate” care episodes within each study period. To ensure consistent episodes across periods, candidate episodes will be excluded if the index date is within 90 of the end of a previous care episode for that patient.

12.5.2 Episode of Care

For each patient, a 90-day Run-in-Period prior to the index date will be used to calculate baseline patient baseline covariates. The EIMG Referral Decision Period is the 30 days after the index visit date. The Treatment Period is 120 days from the initial visit date, providing sufficient time for patient referral, entry into and completion of the 12-week PA program. The Outcome Period is the 90 days following the treatment period.

Figure 6. Defining the Episode of Care



12.5.3 Data Sources

Resource Activity Logs: Prisma employment records by-labor-type (i.e., physician, nurse care coordinator, referral coordinator).

Patient-Specific Healthcare Resources Used: For EIMG-eligible patients, we will collect from the Prisma Health Epic EHR during the episode of care:

1) All healthcare utilization received by Healthcare Common Procedure Coding System (HCPCS), Diagnosis Related Group (DRG), and National Drug (NDC) codes; and
2) REDCap-based provider surveys to assess the resources used by EIMG and the 12-week PA program.

Resource Unit Price Data: Medicare standard pricing files for HCPCS, DRG and NDCs, and Prisma average wage rates of Prisma labor resources.

Patient-Specific Health Outcomes: From the Prisma Epic EHR we will collect: 1) blood pressure; 2) body weight; 3) hemoglobin A1c; 4) full lipid profiles, and 5) PA levels for each patient at the index visit and across the episode of care.

12.5.4 EIMG Training Costs Per Eligible Patient

Analysis will be performed from the perspective of a healthcare system interested in the costs of initiating EIMG across system clinics (i.e., physician nurse care coordinator, referral coordinator) for implementing the EIMG model. Toward this end we will calculate: 1) Total Fixed Cost (TFC) to develop the EIMG implementation toolkit; 2) Total Variable Cost (TVC) of providing the EIMG onboard training and EIMG activation at participating clinics; and (3) number of EIMG eligible-patients (N) over the study period. Retrospective analysis of the Prisma Employment records will be used to estimate the labor hours by labor type used to develop the fixed costs associated with developing the EIMG implementation toolkit (TFC). For the TVC, we will calculate the labor hours by labor type for those performing and attending the standardized EIMG training classes. TFC and TVC will be estimated by multiplying hours by Prisma wage rates by labor type. TFC and TVC will be combined with the number of eligible patients (N) to calculate:

$$(1)\ EIMG\ Training\ Costs\ Per\ Patient = \frac{TFC+TVC}{N}$$

12.5.5 Assessing the Effects of EIMG

We will use episode of care level data generated using the quasi-experimental stepped wedge design[52–56] to estimate the relationship between EIMG referral and study outcomes. Outcomes will include:

Episode Healthcare Costs – the price-weighted sum of all healthcare resources used by patient “i” during the episode of care

Episode-Specific Health Outcomes - Change in health outcomes (blood pressure; body weight; hemoglobin A1c; full lipid profile and physical activity for patient "i") between the index visit and the first provider visit in the episode in the Outcome Period (Figure 6) in which this information is collected.

We will initially regress whether patients in an episode were referred to EIMG on variables representing whether the patient's clinic had received standardized EIMG training, patient clinical and demographic characteristics, time trends, and clinic specific fixed effects represented by:

$$(2) \qquad E_{ijk} = \beta_0 + \beta_1 \cdot X_{ijk} + \beta_2 \cdot L_j + \beta_3 \cdot M_k + \boldsymbol{\beta_4} \cdot C_{ijk} + \omega_j + u_k + \epsilon_{ijk}\,, where$$

E_{ijk} equals 1 if patient "i" in the episode at clinic "j" in the "k-th" month after study initiation was referred to EIMG, 0 otherwise; X_{ijk} represents patient-specific baseline demographic, clinical, and socioeconomic factors, L_j are a series of binary variable for each Prisma clinic "j", M_k is a count variable representing the number of months since the beginning the study that contains patient "i's" index date, and C_{ijk} equals 1 if the episode occurred in a period in which the clinic "j" received or had previously received EIMG activation, 0 otherwise. The parameters $\omega_j, u_k, and\ \epsilon_{ijk}$ represent the model random effects associated with site "j", month "k", and patient "i", respectively. We will estimate equation (1) using a generalized linear mixed model.[57] The estimate of parameter $\boldsymbol{\beta_4}$ equals the effect of standardized EIMG training on the probability of the patient within the episode being referred to EIMG. Variables within X_{ijk} will include patient history of EIMG use. Our stepped wedge design will enable us to directly control for unmeasured factors associated with site and time.[58] Secondary analyses will assess differences in the impact of standardized EIMG training by stratifying by eligible conditions (i.e., overweight/obese, hypertension, type 2 diabetes).

While EIMG activation will be randomly assigned to clinics using the stepped wedge design, actual EIMG referral decisions will remain at the discretion of provider and patient. As a result, referral decisions for some patients will be "non-compliant" at the clinical level. Providers may refer patients into EIMG based on factors unmeasured by the researcher that are related to study outcomes which can confound estimation of the effect of EIMG on study outcomes. With non-compliance, it is problematic to use "as treated" EIMG referral variation to assess the effects of EIMG referrals on study outcomes.[59] Instrumental variable (IV) methods using randomized EIMG activation as an "instrument" will be used to avoid confounding problems. In this scenario IV estimation will yield consistent estimates of the effect of EIMG referral on study outcomes for the subset of patients whose referrals are responsive to the randomized clinical-level EIMG activation. This is known as the Complier Average Causal Effect (CACE).[60–64] The CACE model is specified as:

$$(3) \qquad Y_{ijk} = \alpha_0 + \alpha_1 \cdot X_{ijk} + \alpha_2 \cdot L_j + \alpha_3 \cdot M_k + \boldsymbol{\alpha_4} \cdot \hat{E}_{ijk} + \rho_j + \tau_k + \vartheta_{ijk}\,,$$ where

$\hat{E}_i$ equals the *predicted probability of* that patient "i" is referred to EIMG from equation (2); and the other variables defined as in equation (2). The parameters $\rho_j, \tau_k, and\ \vartheta_{ijk}$ represent the random effects associated with site "j", month "k", and patient "I", respectively. The estimated parameter $\boldsymbol{\alpha_4}$ on $\hat{E}_{ijk}$ is the CACE or the average treatment effect for patient subset whose EIMG referral was influenced by EIMG activation at the clinic. C_{ijk} in equation (2) serves as the "instrument" and only the portion of variation in $\hat{E}_{ijk}$ stemming from C_{ijk} is used to estimate $\boldsymbol{\alpha_4}$. Because C_{ijk} will be randomly assigned, EIMG referral variation stemming from this assignment will be independent of unmeasured confounding variables. Two-stage least squares (2SLS) IV estimators will be used to estimate the effects of EIMG referrals induced by clinical-level EIMG activation on study outcomes. For each study outcome, equation (2) will serve as the first stage

equation of 2SLS, and second stage model will be equation (3). Because our expected sample sizes will be greater than 500 *our 2SLS estimates will be distributed normally via the central limit theorem regardless of the distribution of the underlying error term*.[58,65,66] Each 2SLS model will be estimated with robust standard error methods appropriate for 2SLS models using STATA to account for error structure in equation (3).

Define $\boldsymbol{\alpha_{4C}}$ as the 2SLS estimate when episode healthcare cost is the dependent variable in equation (3) and $\boldsymbol{\alpha_{4H}}$ as the 2SLS estimate when a health outcome change is the dependent variable in equation (3). Combining these estimates with the estimates of average patient EIMG training costs from Section F3.2 yields the following cost-effectiveness ratio of EIMG relative to standard care:

$$(4)\ EIMG\ Cost\ Effectiveness\ Ratio = \left[\frac{(EIMG\ Training\ Costs\ per\ Patient + \alpha_{4c})}{\alpha_{4H}}\right]$$

The ratio in equation (4) equals the incremental cost per patient associated with the EIMG referral induced by clinical-level EIMG activation per average change in health outcome associated with the EIMG referral induced by clinical-level EIMG activation. Separate estimates of equation (4) will be calculated by clinical diagnosis using the health outcome change in the denominator most relevant to the specific diagnosis (e.g., change in hemoglobin A1c for type 2 diabetes).

12.6 Poolability of Data

We intend to perform the primary treatment effect analysis by pooling data from all clinics. It is possible that treatment effect will differ across clinics and this will be investigated. We will fit a model with site by treatment interaction and if significant (at 0.05 level), we will present treatment effects by clinic. Although the study is not powered for detection of different treatment effects across clinics, this analysis will provide insight into possible varied treatment effects across sites or reassure that data can reasonably be pooled over sites with respect to the treatment effect.

13.0 PARTICIPANT SAFETY MEASURES

13.1 Patient Safety Screening

Even though referral through EIMG and participation in the community-based physical activity program is not part of the research study, we will monitor and track patient safety in the physical activity program as we are tracking participant (effectiveness) outcomes as a part of the study.

13.2 Healthcare Provider Screening of Patient

Prior to receiving an EIMG referral, participants are screened by the ordering provider to determine eligibility in the program. Upon opening the referral order set, the provider is shown a list of conditions that excludes a patient from participating in EIMG. The list of exclusion criteria is as follows:

- Patients <18 years
- Patients >350 lbs (evaluated on a case-by-case basis)
- Obstetric patients
- Patients paralyzed and/or have inability to move
- Patients on daily oxygen use
- Using ambulatory aid (cane, walker, wheelchair, etc.)
- Patients on dialysis
- Patients with several High Risks and/or Comorbidities
- Patients with high-risk behavior health issues: acute suicidal ideation, acute psychiatric or psychological disorders not resolved within 90 days prior to EIMG referral
- Patients receiving chemotherapy within the past 3 months
- Patients with a concurrent referral to PT or OT

Prior to signing the referral, the ordering provider completes a risk severity assessment evaluation of asthma, chronic obstructive pulmonary disease, hypertension, and congestive heart failure to document if the patient has one or multiple of these diagnoses. A patient will become ineligible for the program if any of the listed diagnoses are uncontrolled.

13.3 EIMG Care Coordinator Screening of Patients

The EIMG Care Coordinator will complete a chart review in the electronic health record (EHR) of the patient upon receipt of the referral. The medical history and referral diagnosis will be reviewed to ensure the patient is eligible to participate.

13.4 Safety Assessment at the Community PA Facility

Prior to every physical activity session, patients complete a “Contraindications to Exercise” worksheet (see Appendix B). The EIMG Professional (EIMG Pro) reviews the worksheet and if any signs or symptoms are marked as positive, a safety protocol (Patients Exhibiting Contraindications to Exercise Workflow; see section 13.5) is initiated. If any signs or symptoms develop during the exercise session, the session ends immediately and the EIMG Pro initiates the safety protocol.

13.5 Patient Exhibiting Contraindications to Exercise

If there is a contraindication to exercise, the participant is ineligible to participate in the exercise session or, if already engaged, they will stop the activity immediately. An email will be sent to the Facility Coordinator and the EIMG Care Coordinator with a copy of the “Contraindications to Exercise” worksheet, which will be subsequently uploaded into the patient’s EHR. A message is sent to the referring provider via the EHR messaging system notifying them of the contraindication. An EIMG Release Form is required from the provider for the participant to resume the program.

13.6 Emergent Events

In the event of an emergency, the EIMG Pro will follow the facility emergency action plan and then notify the EIMG Care Coordinator. The participant will be evaluated by the referring physician after the acute event. If the patient requires further work-up and is not cleared for exercise, the patient will be released from the program and require another referral in the future if they wish to continue the program. If it is determined the participant may continue, the EIMG Release Form will be completed by the referring provider.

13.7 Non-Emergent Events

In the case of a non-emergent event, the EIMG Pro will evaluate the participant to determine the severity of the event. The “Contraindications Worksheet” will be reviewed by the participant if appropriate and the Patients Exhibiting Contraindications to Exercise Workflow will be activated as needed. For mild or moderate events, the EIMG Pro will document the reported symptoms in REDCap.

13.8 Exercise Session Absences

Any unplanned absence from an exercise session will require an EIMG Pro to contact the patient by phone if they have not already notified the EIMG team of their absence. The reason for their absence will be documented in REDCap.

14.0 HUMAN SUBJECTS PROTECTION

All requirements relating to obtaining institutional review board (IRB) review and approval and informed consent will be met. Written informed consent will be obtained from each study participant utilizing the local IRB-approved informed consent form. Appropriate research personnel will explain all aspects of the study to each participant, answering all questions and ensuring that all basic elements of the informed consent process are covered. All study personnel will be required to complete Human Subject Protection, Good Clinical Practice and HIPAA training (as required) and will be instructed to act under those guidelines at all times when working with participants, participants data or protected participant health information.

14.1 Defining EIMG Research Participants

The Exercise is Medicine Greenville (EIMG) program (the referral of patients to the community-based physical activity program and their participation in the program) is part of a clinical workflow process that is not considered as a part of the research study. The research study consists of gathering data from surveys, individual interviews with clinic staff and patients that have been referred to EIMG and evaluating the effectiveness of the physical activity program (using data that is already collected as a part of the program). There will be minimal risk to the participants with study activities and all available measures will be taken to protect privacy of participant responses.

14.2 The Informed Consent Process

Prior to consenting to participate in the study, a copy of the informed consent will be mailed or emailed to prospective participants to review ahead of the consent process and to keep as a reference. At a scheduled study meeting, a member of the research staff will explain the study to the potential participant, reviewing all sections of the informed consent in detail and answer any of the participant's questions. During the informed consent process (for all study participants), details of the study will be explained, including participant burden, potential risks and benefits, names and contact information for the study PIs, and other local individuals (i.e., IRB staff) that can be contacted for additional study details. All participants will be asked if they want a copy of the consent form (either a hard or electronic copy) for their personal records. There will be no coercion to participate or prejudice against those who choose not to take part in the study and potential participants will be encouraged to ask any questions they have regarding study procedures. Informed consent will be obtained prior to any participation in the study. Proxy consent will not be accepted as we anticipate that all individuals eligible to participate in the study will be able to provide their own informed consent.

Study participation is voluntary and there are no benefits lost (e.g., ability to participate in the PA program) if an individual declines participation. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent form will be updated and revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect a participants' participation in the trial.

14.3 Documenting Informed Consent

14.3.1 Written Informed Consent

Individuals involved with in-person study activities (e.g., individual interviews) will be asked to provide their written consent by signing and dating the consent form. The person obtaining consent will also sign and date the consent document. The consent must be properly executed and complete to be valid. Another research staff member will review the consent form after it is signed to ensure that the consent is properly executed and complete. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Participants will be given the option of having a signed copy of

the informed consent form. The original version will be stored in a secure location at each study site. Members of the research team will inspect the informed consent forms periodically to ensure that correct signatures and dates were obtained on valid informed consent forms.

14.3.2 Verbal Informed Consent

Individuals conducting virtual study activities (i.e., telephone or virtual interviews) will be asked to provide their verbal consent to participate in the study. The research team member will follow the same informed consent process as with the written informed consent process. However, the participant will not be asked to sign a consent form, only to verbally agree to participate in the study after the informed consent process. The final page of the informed consent form will have a page for documentation of verbal consent that the research team member will check off (if provided) and date.

14.4 Obtaining Participant Consent

A description of how informed consent will be obtained from study participants is described below:

14.4.1 Individual (Adoption) Interviews with Practice Managers

All practice managers at clinics eligible to adopt EIMG will receive an email inviting them to participate in an individual (adoption) interview. Practice managers that wish to participate in the individual (implementation) interviews will undergo the informed consent process to obtain either their written (for in-person interviews) or verbal (for virtual interviews) consent immediately prior to conducting the interview.

14.4.2 Online ORCA Questionnaire with Clinic Staff

All staff at participating clinics that adopted EIMG will receive an email inviting them to complete the online ORCA questionnaire. The email will contain an electronic link to the online questionnaire. The first page of the online questionnaire will be a consent form providing a detailed explanation of the study (both the online survey and the individual (implementation) interview and potential risks of participation. At the bottom of the webpage, participants will be asked to provide their consent to participate in the study before continuing to the online questionnaire. Individuals that do not agree to participate in the study will be thanked for their time and exited from the questionnaire.

14.4.3 Individual (Implementation) Interviews with Clinic Staff

All staff at participating clinics that adopted EIMG will receive an email inviting them to participate in an individual (implementation) interview. If an individual provided their consent to participate in the online ORCA questionnaire, they will not undergo an additional informed consent process prior to conducting the individual interview as verbiage in the online consent will also describe participation in this individual interview. Eligible clinic staff that did not complete the online ORCA questionnaire will undergo the informed consent process to obtain either their written (for in-person interviews) or verbal (for virtual interviews) consent.

14.4.4 Individual Interviews with Patients

Patients that received an EIMG referral at a participating clinic will be invited to participate in an individual interview. Patients that wish to participate in the individual interviews will undergo the informed consent process virtually (over the phone) to obtain their verbal consent immediately prior to conducting the phone interview.

14.5 Participant Discontinuation

Participants will have the right to discontinue study participation at any time. This includes stopping the individual interviews at any time or not responding to questions they do not wish to answer, closing out the online ORCA questionnaire, or declining to have their PA program data included in the research study. Females participating in the PA program who become pregnant

during the study will be required to discontinue participation. Additionally, participants may be asked to stop their participation in the PA program if any situation arises that, in the investigator's judgment, poses a safety risk. Participants who must stop the PA program will not continue completing program assessments.

14.6 Participant Remuneration

Participants (practice managers, clinic staff, and patients) will receive monetary remuneration (gift cards) for participating in the individual interviews to compensate them for their time, travel, and burden of participation. Clinic staff will not be compensated for completing the online ORCA questionnaire and patients will not be compensated for participating in the 12-week, community-based PA program or any of the program assessments.

15.0 REPORTING AND MONITORING

15.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, appropriate ICH guidelines (including current Good Clinical Practice [GCP]), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment will be obtained by the Prisma Health institutional review board (IRB) prior to study initiation. Any amendments to the protocol or consent materials will be approved before they are implemented. Annual progress reports and Serious Adverse Event (SAE) reports will be submitted to the IRB according to its usual procedures.

15.2 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all communications. Regulatory files will be reviewed for compliance prior to study initiation, throughout the study, as well as at the study closure.

15.3 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will have an up-to-date signed financial disclosure form on file with their respective institutions.

15.4 EIMG Exercise Session Monitoring

Study team members may periodically audit, at mutually agreed upon times, EIMG exercise sessions and source documents for each participant. Monitoring will take place as specified by the research team and occur as often as needed to help prevent, detect, and correct issues at the community PA facilities. Research staff will verify that procedures for the exercise sessions are properly followed and that EIMG Pros are trained and able to conduct the protocol as intended. If the review of exercise session documentation indicates that additional training is needed, research staff arrange for that training.

15.5 Study Documentation

Study documentation includes all exercise session report forms, data correction forms, questionnaires, monitoring logs, sponsor-investigator correspondence, signed protocol and amendments, Institutional Review Committee correspondence, approved consent forms, and signed participant consent forms. Source documents include all (audio) recordings of individual interviews, notations of interviews or exercise sessions, and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original (audio) recording of an observation should be retained as the source document. Transcripts should provide a clear and exact duplication of the recordings, but are not considered source documentation.

15.6 Records Retention and Requirements

All research records will be stored by the PI in a secure location to be accessed only by authorized research personnel. Study records will be stored in accordance with local IRB, state, and federal regulations and will be kept for a minimum of 3 years following study completion.

15.7 Participant Confidentiality/Privacy

Participant records will be made confidential by using study codes for identifying participants, secure and separate storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. All research information obtained on participants is confidential, and disclosure to any third parties without specific authorization is strictly prohibited. To maintain subject privacy, all study forms and reports will

be identified by a coded study identification number only. No subject identifying information will be included in any presentations or publications resulting from the study. Study records may be inspected by the sponsor and its authorized representatives, other government agencies such as the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP), authorized Node Staff, or the local IRB for quality assurance purposes.

15.8 Confidentiality Breach

In the event of a confidentiality breach with our survey and/or interview data, reporting to the site IRB will be done within 10 business days of the co-Principal Investigators (PI) becoming aware of the breach.

15.9 Data and Safety Monitoring Board (DSMB)

As required by the National Institutes of Health (NIH), this study will develop and maintain an IRB-approved data and safety monitoring plan. In discussion with the funding agency (the National Heart, Lung, and Blood Institute), it was determined that an independent DSMB for this study is not necessary for this study. NIH policy states that monitoring activities of all NIH-sponsored or -conducted clinical studies are commensurate with their risks, nature, size, and complexity. Given that the nature of this research study involves conducting individual interviews and online surveys with participants, none of whom would be considered vulnerable subjects, this trial was deemed to be a low-risk behavioral study.

15.10 Protocol Deviations & Violations - Reporting and Management

A protocol departure is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored for: 1) significance, 2) frequency, and 3) impact on the study objectives, to ensure that violations do not compromise the integrity of the trial. Any protocol deviations that are substantive and affects rights, safety, or welfare of subjects or willingness to continue in study or the integrity of the research data will be reported within 10 business days from the date either of the co-PIs becoming aware. The decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation will be made by the multiple PIs.

15.11 Adverse Events (AEs)

15.11.1 Definitions of AEs

Any unfavorable or unintended medical or psychological event experienced by a study participant. This can represent a new symptom or an exacerbation of an existing condition. The event does not necessarily have to be causally related to the research study intervention.

15.11.2 Classification of AEs

An AE will be classified as one of the following:

i. *Mild*: events that do not interfere with the participants daily activities (i.e., muscle soreness, fatigue, anxiety).
ii. *Moderate*: events that have a low level of inconvenience for the participant. This may cause some interference with EIMG participation but is not a contraindication.
iii. *Severe*: events that interrupt the normal daily activities of a participant. Events would include, but are not limited to, those listed on the Contraindications to Exercise worksheet.

15.11.3 Reporting of AEs

Mild and moderate AEs will be documented but need not be reported to the site IRB or sponsor (NHLBI) unless a trend appears. If an adverse event is classified as severe and is expected and related to study participation, IRB guidelines indicate this will be reported periodically (annually).

15.11.4 Expectedness of AEs

Adverse events will be reviewed weekly by the co-PIs and determined if it was expected within the described study procedures.

15.12 Serious Adverse Events (SAEs)

15.12.1 Definition of Serious Adverse Events (SAEs)

Any AE occurring, which results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability, incapacity, a congenital anomaly, or birth defect.

15.12.2 Reporting of SAEs

Per IRB guidelines, serious adverse events (SAE) related to study participation will be reported promptly. The Prisma Health IRB does not require reporting of unrelated SAEs. In the case of fatal or life-threatening events, reporting will take place within 7 calendar days of initial receipt of information by either of the co-PIs. For any other unanticipated SAE that is non-fatal, reporting to the site IRB and sponsor (NHLBI) will take place within 10 business days from the time that either of the co-PIs are aware of the event. Expected and related SAEs will be reported annually.

15.13 Unanticipated Problems

15.13.1 Definition of Unanticipated Problems

Any incident, experience, or outcome that meets all the following criteria:

i. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures described in the protocol-related documents, and (b) the characteristics of the subject population.
ii. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
iii. Suggest the research places the subject or any others at greater risk of harm than was previously recognized.

15.13.2 Relatedness to Study

Adverse events will be reviewed weekly by the co-PIs and determined whether the event was related or possibly related to the research study.

15.13.3 Reporting of Unanticipated Problems

Any unanticipated problem that is not a SAE will be reported to the site IRB and sponsor (NHLBI) within 10 calendar days from the time either of the co-PIs are aware of the event.

16.0 DATA MANAGEMENT AND PROCEDURES

16.1 Field-Based Data Collection Forms

The data collection process consists of direct data entry at the community PA facilities into the REDCap system. In the event that the REDCap system is not available, the study team will provide EIM Ex Pros at the community PA facilities with a set of source documents (i.e., hard copies) and completion instructions. Data entry into REDCap will be completed according to the EIMG program instructions provided during facility onboard training and established manuals of operation. The EIMG Ex Pros are responsible for maintaining accurate, complete, and up-to-date records, and for ensuring the completion of data entry for each participant at every exercise session. An EIMG research team member will conduct regular quality control checks ensuring that participant data is being regularly collected and properly entered into the REDCap system.

16.2 Field-Based Data Editing

Completed data will be entered into REDCap system. If incomplete or inaccurate data are found, a data query will be generated to resolves inconsistencies and errors, and all corrections and changes will be entered into and documented in REDCap system in accordance with the data management plan.

16.3 Field-Based Data Quality Assurance

To address the issue of data entry quality, we will follow a standard data monitoring plan. An acceptable quality level prior to study closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the study.

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APPENDIX A – Patient Eligibility for EIMG Referral: Inclusion Criteria

Condition	Data Variables (per ICD code)	
Physical Inactivity		
	Z71.3	Encounter for weight loss counseling
	Z71.82	Exercise counseling
	Z72.3	Inactivity
	Z91.89	Sedentary lifestyle
Obesity		
	E66.01	Obesity
	E66.09	Obesity
	E66.9	Obesity
	Z68.30	BMI 30.0-30.9, adult
	Z68.31	BMI 31.0-31.9, adult
	Z68.32	BMI 32.0-32.9, adult
	Z68.33	BMI 33.0-33.9, adult
	Z68.34	BMI 34.0-34.9, adult
	Z68.35	BMI 35.0-35.9, adult
	Z68.36	BMI 36.0-36.9, adult
	Z68.37	BMI 37.0-37.9, adult
	Z68.38	BMI 38.0-38.9, adult
	Z68.39	BMI 39.0-39.9, adult
	Z68.41	BMI 40.0-44.9, adult (HCC)
	Z68.42	BMI 45.0-49.9, adult (HCC)
	Z68.43	BMI 50.0-59.9, adult (HCC)
	Z71.3	Encounter for weight loss counseling
Diabetes		
	E11.8	Type 2 DM with complication, without long-term current use of insulin (HCC)
	E11.9	Type 2 DM
	E11.65	Type 2 diabetes with hyperglycemia
	R73.01	Impaired fasting glucose (covered by prediabetes and diabetes)
	R73.03	Prediabetes
Blood Pressure		
	I10	Essential hypertension
Dyslipidemia		
	E78.5	Dyslipidemia
	E78.5	Hyperlipidemia, unspecified hyperlipidemia type
	E78.2	Mixed hyperlipidemia
	E78.2	Combined hyperlipidemia
	E78.2	Moderate mixed hyperlipidemia not requiring statin therapy
	E78.1	Hypertriglyceridemia
	E78.00	Pure hypercholesterolemia
	E78.00	Hypercholesteremia

Appendix B. Patient Checklist for Contraindications to Exercise.

Exercise is Medicine Greenville®: Patient Checklist for Contraindications to Exercise

Patient Name:_____ **Date of Birth:**_____/_____/_____

Session Number:	Orientation	1	2	3	4	5	6	7	8	9	10	11	12
Date:	/	/	/	/	/	/	/	/	/	/	/	/	/
Did patient attend this session:		Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Please circle Y (yes) or N (no) if experienced recently or currently:													
Have you been hospitalized or diagnosed with any new health problems since your last session?	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Abnormal leg pain or cramps	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Angina or chest pain	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Unusual or increased shortness of breath	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Uncontrolled blood sugar at home	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Nausea, vomiting or diarrhea in past 24 hours	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Fever	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Dizziness or faintness	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
New or increased back or joint pain	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
Patient initials at each session:													
	I have read and understood the list of symptoms above and <u>do not</u> exhibit any said symptoms at this time												

Patient signature:_____

EIMG® Pro Trainers only:

Did the participant exhibit any unusual symptoms during their exercise session?		Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
	If Yes, refer to the EIMG® Procedure for Patients Exhibiting Contraindications to Exercise												
If patient exhibited any unusual symptoms, document details regarding symptoms (include date/time):													

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