

eSTEPS RCT Protocol and SAP

**eSTEPS (electronic Strategies for Tailored Exercise to Prevent Falls): Pragmatic
Randomized Controlled Trial of Fall Prevention**

Protocol Number: IRB 2022P001055

Study Protocol and Statistical Analysis Plan

National Clinical Trial (NCT) Identified Number: NCT04993781

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

Protocol Modifications

1. This protocol was modified after the first DSMB meeting based on the request of the DSMB to change the Safety Officer to someone who had no research collaborations with the study team. Protocol version 1.4 was updated to reflect this change.
2. The protocol was modified after the second DSMB meeting to document that two sites were withdrawn prior to patient enrollment because one site had problems sharing electronic health record data with the research team, so both this site and its matching pair were removed. As reported to the DSMB, we continue to have adequate power to complete the trial with 22 sites. We will report this site change in our site consort diagrams in our future study reports. Protocol version 1.5 was modified to reflect this change.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed:



Date: 06 01 2024

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title	eSTEPS (electronic Strategies for Tailored Exercise to Prevent Falls): Pragmatic Randomized Controlled Trial
Grant Number	4R33AG068926-03
Study Description	The design is a cluster randomized, parallel group superiority trial with practices stratified by healthcare system and patients nested within practices. The unit of randomization is the practice.
Study Duration	3 years
Trial Sites	24 MGB Primary Care Practices
Objective	Conduct a cluster-randomized trial to determine the effectiveness of a fall prevention strategy.
Number of Subjects	The target sample size for our primary outcome is 8352 participants (4176 in each arm) enrolled from 24 practices to provide 90% power to detect a 20% reduction in the rate of the primary outcome with intervention relative to control.
Main Inclusion Criteria	People aged 65 years or older, who are attending a primary care visit at a participating MGB practice and are at increased risk for serious fall injuries.
Intervention	The eSTEPS clinical decision support application and related tools to support fall prevention exercises conducted by participants at home, including hand-outs, a website and a patient app.
Participant Duration	A minimum of 12 months and a maximum of 23 months.
Endpoints	The primary outcome is falls. Secondary outcomes are falls leading to fractures and death, exercise self-efficacy and falls self-efficacy.
Primary Analysis	The risk of any fall will be analyzed using a survival model that incorporates competing risks (due to death) and clustering. In this analysis, participants who are lost to follow-up without a prior serious fall-related injury will be censored at their date last seen. In a secondary analysis, we will adjust for the pre-specified set of baseline covariates to examine their influence on the intervention effect.
Interim Analysis	Interim monitoring will focus on patient accrual, baseline comparability of treatment groups, protocol adherence, data completeness and quality, accrual of fall events, safety, and efficacy or futility.

1.2 SCHEMA

Figure 1: Randomization at the Practice Level

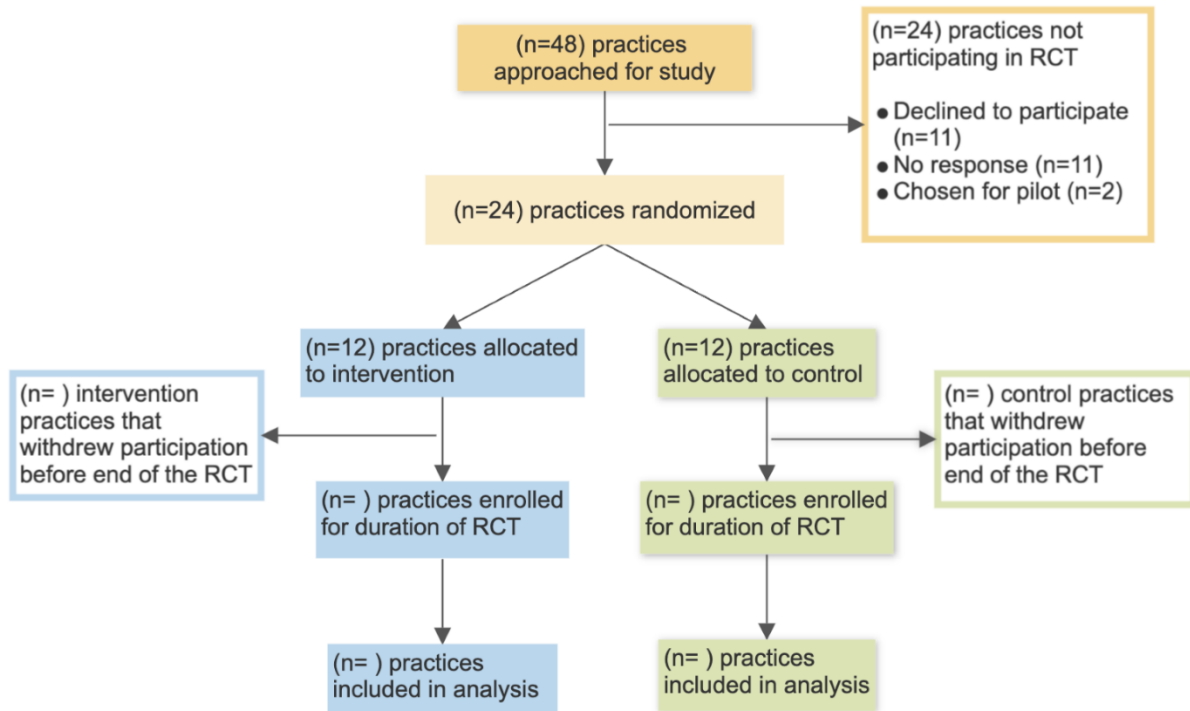


Figure 2: Main Cohort Study

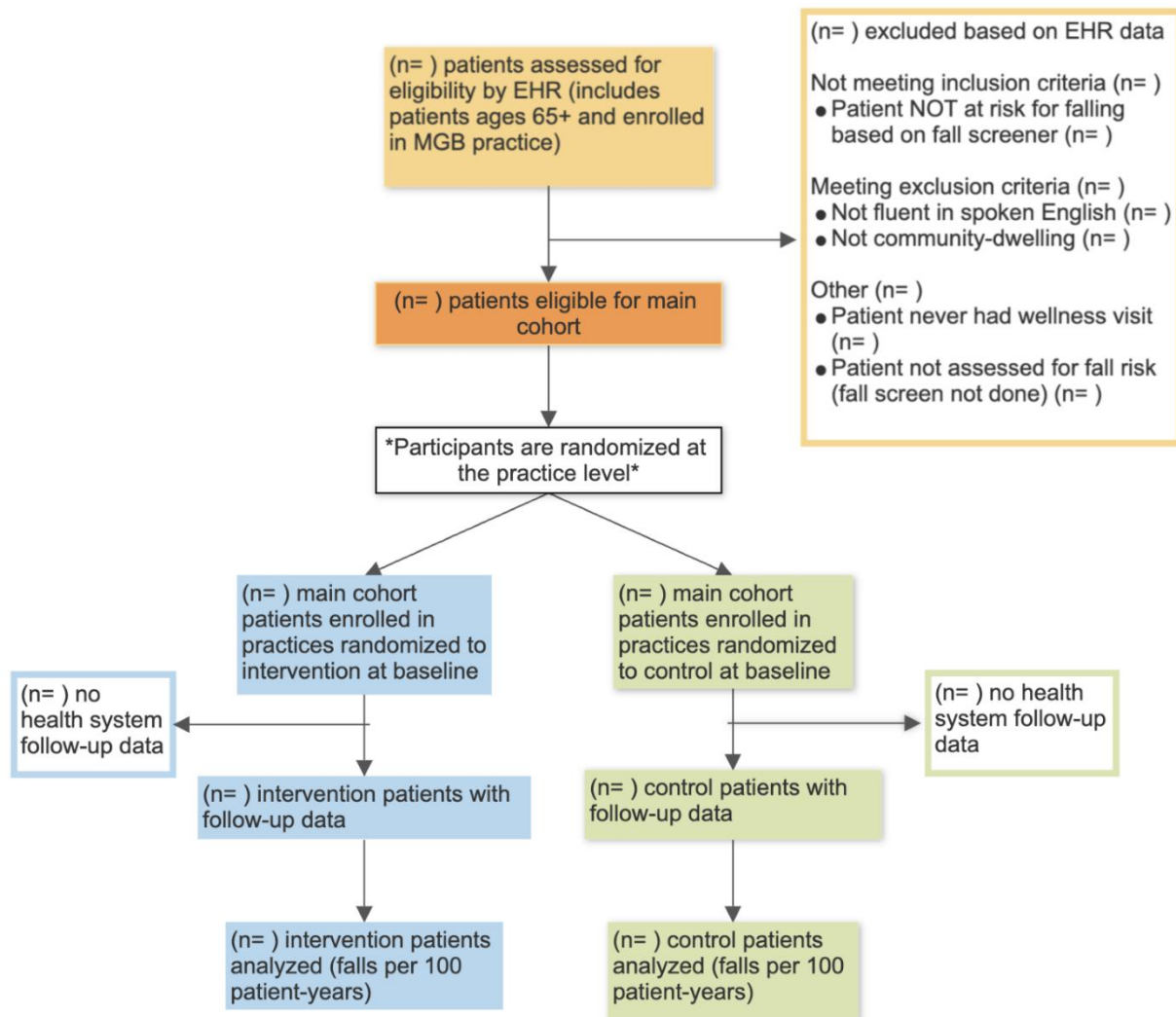
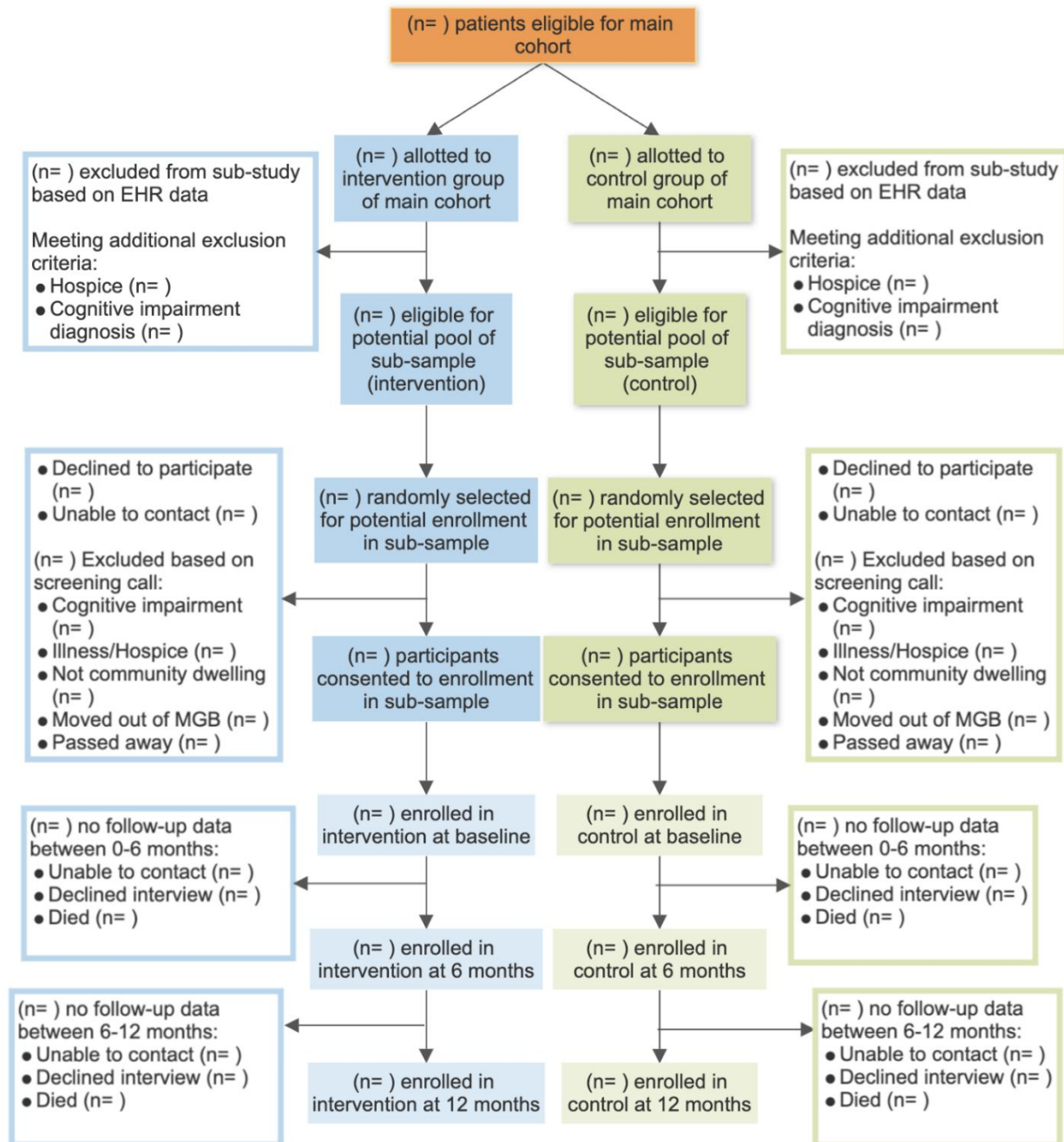


Figure 3: Sub-sample Study



1.3 SCHEDULE OF ACTIVITIES

Activity/assessment	Central EHR Data Collection	Subsample Outcomes		
		Baseline	6 months	12 months
Qualitative Interviews				x
iTUES (providers only)				
Letter from practice/optout postcard*		x		
Chronic conditions	x			
Screening for high fall risk	x			
Demographic characteristics	x			
Health care utilization	x			x
Fall history	x			x
Assessments	x			
Diagnoses	x			
Medications	x			
Computer log files re: eSTEPS CDS	x			
Callahan cognitive assessment		x		
Verbal consent**		x		
Telephone interview**		x	x	x
Fear of falling**		x	x	
Exercise Self-efficacy **		x	x	
Falls, fall injuries**	x	x	x	x
eSTEP exercise CDS during Medicare Wellness Visit		x	x	x
Patient use of eSTEPS Exercise App or other exercise resources		x	x	x

2 INTRODUCTION

2.1 STUDY RATIONALE

Every hour, three older Americans die because of a fall¹. There are 29 million falls in the United States annually resulting in 2.8 million emergency department visits and 800,000 hospital stays² with a cost of \$49.5 billion.³ Recent meta-analyses have found that participation in the appropriate fall-prevention exercise program for an older adult reduces the risk of falls by 23% in relative terms, for an absolute reduction of 0.20 falls per person per year.⁴ Many guidelines, including the US Preventive Service Task Force (USPSTF) recommend that older adults at risk of falls are referred to appropriate fall-prevention exercise programs (USPSTF Level B).⁵ Fall prevention is inadequately addressed in primary care and disparities exist. Many primary care providers (PCPs) are unaware of their patients' falls, as half of older people do not discuss falls with them.^{6,7} Older people living in rural areas are more likely to fall and experience fall-related injuries, but are less physically active overall⁸ and less likely to participate in fall prevention programs.^{9,10,11,12,13}

The challenge is to ensure that fall prevention guidelines are implemented and that older adults at risk of falling receive appropriate exercise prescriptions and referrals from their PCP. Advances in computing technology can help to identify older people at risk of falls and disseminate guidance about the most effective interventions using clinical decision support (CDS). Well-implemented CDS that is integrated into the electronic health record (EHR) can support prescribing or recommending exercise programs and engaging patients in fall prevention decision-making thus integrating evidence-based guidelines into clinical practice.^{14,15} Patients can be supported in their exercise programs through the use of technology.¹⁶

The long-term goal of our research program is to enhance the safety of community-based older adults by reducing falls through an effective patient-centered CDS system, eSTEPS (electronic Strategies for Tailored Exercise to Prevent FallS). With eSTEPS, an exercise algorithm will be integrated into the widely implemented Epic EHR which will trigger a Best Practice Alert (BPA) and/or Care Gap and Smart Set to provide actionable CDS within primary care clinic workflows and facilitate the use of CDS with older patients during their annual wellness visit, ensuring that evidence-based recommendations are tailored to patients' preferences. The tailored exercise prescription will also be available through printouts, a website, and an app for use by patients at home. The eSTEPS intervention includes a machine learning algorithm for improving traditional fall risk screening, the provider CDS, and the patient resources (printouts, website, exercise app) that will support primary care providers and patients with personalized exercise care planning during an annual Medicare Wellness visit.

The objectives of this proposal are to evaluate the eSTEPS CDS (eSTEPS) in a cluster randomized control trial. The intervention includes the following

(**Figure 1**): 1) A machine learning-based fall injury risk screening algorithm to improve traditional fall risk screening. 2) Provider BPA and/or Care Gap and Smart Set to provide CDS that helps primary care providers develop a tailored fall prevention exercise plan in the context of a Medicare Wellness Visit and 3) eSTEPS Patient App and exercise tools to provide older patients continued access to their interactive, tailored exercise plan.

We will conduct a pragmatic cluster randomized control trial in diverse urban primary care clinics (Mass General Brigham, MGB) to test the efficacy of the eSTEPS CDS intervention.

Development of the eSTEPS CDS within the widely adopted Epic EHR will support dissemination of evidence for older adults and the focus on a diverse cohort of elders will reduce disparities.

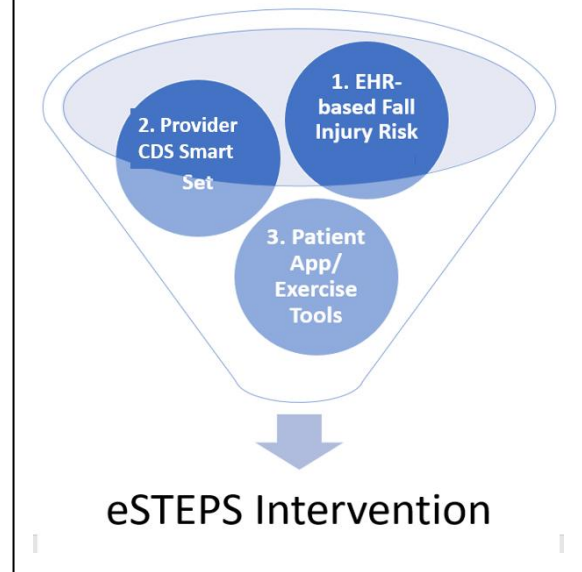
2.2 BACKGROUND

Falls are a common event among older persons and are associated with significant long-term consequences. More than one in four adults age 65 or older fall each year.² Injuries from falls, such as hip fractures, can cause long-term functional impairment and even death.²⁰ Despite growing evidence that falls can be prevented, deaths from falls continue to rise -- a recent report found that fall-related deaths more than doubled for U.S. adults age 75 and older between 2000 and 2016.¹ Currently, three older adults die from a fall every hour in the U.S.²¹ The CDC projects that if fall rates continue to rise at the current rate, by 2030 there will be 7 fall deaths every hour in the U.S.²¹

A single fall frequently results in a fear of falling that can begin a downward spiral of reduced mobility, leading to loss of function, activity restriction and further risk for falls.^{22,23} The majority of falls are preventable.^{24,25} Many fall risk factors and treatment strategies have been identified in numerous studies and meta-analyses with high levels of evidence, but exercise is the single intervention that on its own significantly reduces the risk of falls and fall-related injuries.²⁶⁻²⁸ Deficits in gait and balance are the most prominent predisposing risks at the population level and all older adults at-risk for falling require exercise. Many guidelines, including the US Preventive Service Task Force (USPSTF) recommend that older adults at risk of falls be referred to appropriate fall-prevention exercise programs (USPSTF Level B).^{5,6} However, the type and level of exercise must be individually tailored to patient factors; exercise must also be selected to maximize an individual's adherence, considering personal preferences, abilities and access.^{5,6} The wrong exercise approach might have no effect, or even increase the risk of falls.²⁹ Direct implementation of the exercise intervention by PCPs conducting the risk assessment, or facilitation of the interventions by qualified healthcare professionals, is strongly recommended for community dwelling older adults (level A evidence).²⁶⁻²⁸

The challenge is to ensure that older adults at risk of falling receive appropriate exercise referrals, education and support from their PCP. Many PCPs are unaware of their patients' falls, as half of older adults do not discuss falls with their PCP.^{7,8} Further fall prevention disparities exist in rural areas where older adults are more likely to fall, but are less likely to participate in fall prevention programs and less likely to be physically active.⁹⁻¹² Advances in computing technology can help to identify older people at

Figure 4: 3-Component eSTEPS Intervention



risk of falls and disseminate guidance about the most effective exercise interventions using CDS. Given the many decisions that must be made to identify the most appropriate exercise plan for individual patients, PCPs need CDS to guide them and to facilitate engaging patients in their decision-making process. CDS would ensure that the exercise prescription is evidence-based and consistent with patients' needs and preferences. An EHR intervention based on the CDC's STEADI fall prevention program has been created to screen older adults and support a multifactorial intervention.³⁰ Because this intervention focuses on many fall risk factors, it is time consuming to implement. In follow-up surveys, more than 75% of providers said that time constraints were barriers to implementation and 71% said that the fall screening does not fit in easily within a Medicare Wellness visit.^{31,32} By focusing on the single most effective fall prevention strategy, exercise, this project will create a more efficient intervention but also allow the individualization and incorporation of behavioral approaches needed for a successful exercise program.

Health IT in primary care can enable workflow and well-integrated evidence-based CDS ensures the right information is delivered to the right people in the right formats through the right channels at the right time. In the first phase of this project, we developed tools for engaging older adults in decision making related to developing an evidenced-based, tailored exercise plan. Throughout each phase of the project, we identified and addressed gaps in the CDS Framework³⁵ to ensure that the eSTEPS CDS is meaningful to PCPs and patients.

In the first phase of this project, we translated the existing evidence-based fall prevention exercise decision algorithms³⁶ into the "right information." We will work with end-users to iteratively develop a BPA and/or Care Gap and Smart Set within the Epic EHR to ensure that PCPs' access the eSTEP CDS within their clinical workflow ("right people"/"right time").

The BPA and/or Care Gap and Smart Set will be used by PCPs during a patient's annual wellness visit to engage the patient in developing an evidence-based fall prevention exercise plan that will be saved as a note in the Epic HER ("right format"). The Health Level 7 (HL7) Fast Health Interoperability Resources (FHIR) standard and the Substitutable Medical Applications and Reusable Technology (SMART) Health IT platform ("right channel") will allow us to share a fall prevention exercise prescription and associated content to the patient via a smart phone App and other exercise resources where they can be viewed after the visit and any time it is needed, ("right people"/"right time").^{37,38}

Given the rigor of previous community-based fall prevention studies, systematic reviews, and fall prevention guidelines and their consensus regarding tailored exercise programs,^{4,26,39} there is a clear need to integrate fall prevention knowledge related to tailored exercise prescriptions into clinical practice. Primary care CDS will routinely identify older adults at risk of falling, support rapid clinical decisions by linking the decades of fall prevention evidence to practice, and engage patients in this process. This study builds on our team's pragmatic clinical trial, *Strategies to Reduce Injuries and Develop Confidence in Elders (STRIDE) [5U01AG048270]*, that tested an intervention integrating patient-centered fall prevention evidence into primary care.^{18, 40} We will translate existing *STRIDE* evidence-based fall prevention exercise decision rules into computable eSTEPS CDS. To ensure success, we have formed a highly qualified interdisciplinary scientific and clinical team to make these important scientific and translational contributions.

The goal of this phase of the eSTEPS study is to test the eSTEPS CDS for use by primary care providers and patients across primary care settings.

We will first implement the eSTEPS intervention within the Epic EHR including CDS for providers (PCPs) and an exercise app (for patients) that will ensure PCPs' access to the eSTEPS CDS within their clinical workflow. The CDS (BPA and/or Care Gap and Smart Set), will be used by PCPs during a patient's annual wellness visit to engage the patient in developing an evidence-based fall prevention exercise plan, which will be shared with the patient/family using a range of low-tech to high tech tools (printouts, website, smartphone App). The App will provide the tailored exercise prescription and leverage evidence-based behavior change strategies to support older people initiating and adhering to fall prevention exercise recommendations. In addition to the App, eSTEPS includes exercise tools including a web portal and printable handouts for patients who are less tech savvy and in accordance with patient learning needs and preferences.

We will recruit 24 primary care practices within MGB and conduct a cluster randomized trial. We will develop matched pairs and randomize half of the practices to the eSTEPS intervention and half to usual care. We will then conduct a pragmatic cluster randomized controlled trial of eSTEPS to determine the effectiveness, safety, and acceptability of the intervention in decreasing fall frequency and fear of falling, and improving exercise self-efficacy by older people and as compared to usual care.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Potential risks to subjects are minimal. Participation is voluntary, and during any point of the data collection process, participants can refuse to answer any question or may terminate their participation.

The eSTEPS intervention is not physically invasive and is currently recommended by clinical practice guidelines. Therefore, any patient subject participating in this research will be at no greater risk for physical harm than usual care.

Potential risks include (1) breach of confidentiality (i.e., we will collect protected health information via the EHR, however all data will be de-identified for analysis), and (2) the additional burden that the intervention may pose to patients (i.e., information overload during interviews, becoming tired of answering interview/survey questions).

Risks of the intervention may include the burden of receiving additional communications and information regarding fall prevention risk/interventions. Risks related to data collection activities include the inconvenience of participating in surveys, pilot testing, and interviews.

Due to the quality improvement nature of the intervention, it is unlikely that a patient will be harmed. If there is any concern that a significant patient harm event was observed, the principal investigator will discuss with the IRB within 48 hours of discovery and report the event to the NIA as per the NIH protocol.

Adequacy of Protection Against Risks

Inconvenience of participation (interviews/surveys) by patients and caregivers will be minimized through the opt-out process and the voluntary nature of the data collection instruments. We will attempt to minimize potential adverse events due to the intervention by carefully monitoring study outcomes

We will handle protection against breach of confidentiality in several ways. First, data collection will follow established procedures in full compliance with HIPAA regulations. Second, data will be stored in a locked office or password-protected computer. Third, data collected on paper will be shredded upon completion of data analysis, manuscript publication and record-keeping requirements. Finally, data will be analyzed and presented in aggregate. These steps are likely to be effective in protecting confidentiality.

2.3.2 KNOWN POTENTIAL BENEFITS

If successful, patients receiving the intervention may receive safer and better quality of care due to the clinician's improved ability to mitigate their fall risk factors through the implementation of appropriate exercise interventions. Patients who choose not to participate by using the patient-centered eSTEPS CDS in the study will have no benefits from these tools, although they may benefit from the CDS and parallel efforts to increase awareness around the importance of conducting an accurate fall risk assessment linked to tailored prevention exercise interventions for older adults in the primary care setting.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The eSTEPS CDS is the result of translating the STRIDE fall prevention exercise algorithm into computer-readable language and integrating our experience from that study into the exercise resources. The patient data will be passed through the eSTEPS CDS (BPA and/or Care Gap and Smart Set) within existing EHR workflows and then populate the patient-facing App. The goal is to provide an evidence-based fall prevention exercise intervention, accounting for patient preferences, within existing EHR workflows that can be widely disseminated to primary care practices. If the intervention is successfully implemented, then the study findings may be used to refine and improve the eSTEPS intervention. Effort can be shifted to ensure that more patients, caregivers, and health professionals have access to the eSTEPS intervention and understand the best practices for sustaining use and changing patient and clinician behavior. Additionally, efforts can be focused on expanding the scope of the intervention and adapting the intervention to additional healthcare systems and EHRs. If the intervention is not successful, then lessons learned from the study will inform the design of future interventions and help develop other strategies for primary care practices to help reduce the incidence of preventable falls in community-dwelling older adults using tailored exercise interventions. Given the high incidence of serious fall-related injuries and deaths caused by falls, this intervention could be of great benefit to many older people. Either way, the knowledge gained from this study will lead to future improvements in communication, collaboration among team members (including the patient), as well as improving alignment with promoting interoperability tools.

3 OBJECTIVES AND ENDPOINTS

The objective of this study is to conduct a pragmatic cluster randomized controlled trial of eSTEPS in MGB primary care practices to determine the effectiveness, safety, and acceptability of the eSTEPS intervention in improving appropriate referrals of exercise programs, exercise participation by older people, and fall frequency compared to usual care.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the effect of the eSTEPS intervention on falls)	Falls rate per 100 patient years	Primary outcome
Secondary		
To determine the effect of the eSTEPS intervention on falls self-efficacy (fear of falling)	Falls self-efficacy	Secondary outcome
To determine the effect of the eSTEPS intervention on self-efficacy for exercise	Self-efficacy for Exercise	Secondary outcome
Tertiary/Exploratory		
To explore the effect of the eSTEPS intervention on the rate of death	Death	Exploratory outcome
To determine the effect of the eSTEPS intervention on fall injuries	Fall injuries	Exploratory outcome

4 STUDY DESIGN

4.1 OVERALL DESIGN

The goal of this study is to conduct a pragmatic cluster randomized controlled trial of the eSTEPS intervention to determine the effectiveness, safety and acceptability of the intervention in improving appropriate referrals for exercise programs, exercise participation by older people and fall frequency as compared to usual care.

This project is a matched-pair cluster randomized trial. The unit of randomization is the primary care practice (n=24). Twelve primary care practices randomized to the intervention will have eSTEPS CDS integrated in the EHR system, and the other 12 primary care practices will continue with usual care. Due to the quality improvement nature of the intervention (all components are evidence-based, recommended by current clinical practice guidelines, and do not increase risk to participants), the eSTEPS intervention will be turned on in Epic for all primary care providers and patients in the intervention practices. Providers and staff in intervention practices will receive training on how to use the eSTEPS CDS to provide individualized exercise prescriptions to older patients at risk for falls during an annual wellness visit. Note: prior to enrollment of participants, 1 of the randomized sites was found to be unable to fully share EHR data with the study team. This site and its matched pair with withdraw from the trial, and not patients were enrolled from these sites, so the trial continued with 22 practices. We will report this site withdrawal in all future study reports.

Prescreening (primary care practices): Randomization is at the primary care practice level and outcomes are at the patient level. We will use MGB organizational data to identify all primary care practices with at least 348 Medicare Wellness Visits per year for patients ≥ 65 . A meeting will be scheduled with the practice director to explore interest in participating in the clinical trial. We will make it clear that if they

agree to participate, the practice will have an equal chance of being assigned to intervention or control conditions.

Practices that agree to participate will be matched and then randomized to intervention or control conditions. Pair matching of facilities will be based on key available background characteristics (size of the practice and academic/community health center). Matching minimizes variability in paired differences between intervention and comparison practices, which in turn tends to deflate the sample size required to detect expected differences between treatment arms. Matching of practices will be conducted by coarsened exact matching, a monotonic imbalance bounding matching method that estimates causal effects by reducing imbalance in matching variables between treated and comparison groups.¹⁷ Before using the coarsened exact matching algorithm, we will screen out 'outlier' practices (those where matches are not feasible). Then, we will pair match the remaining practices. We will then randomly choose the pairs that are broadly representative of the full population of practices with at least 348 Medicare Wellness Visits e.g., practices in which the baseline patient characteristics mirror the full population after removing the outliers.

Prescreening (primary care patients for participation in telephone calls/surveys): Patients who meet inclusion criteria (aged 65 or older, scheduled for Medicare Wellness Visit and screen positive for fall risk) will be identified via an electronic health record (EHR). These people will be sent a letter via postal mail from their practice informing them that their practice, working in co-operation with BWH/Harvard Medical School, is trying to learn more about how to improve uptake of regular exercise to decrease risk for falls in older adults. This will include a cover letter from the practice, a brochure describing the eSTEPS Study and an opt-out postcard. If people do NOT want to be contacted by the research team, people are asked to return this postcard. In approximately (but no less than) two weeks' time, the trained eSTEPS study staff member will call the potential subject. Patients will be eligible for recruitment if the opt-out postcard from a clinic-screened patient is not received by the eSTEPS team within two weeks.

Detailed Consent Process: Each eligible patient will be called by a trained eSTEPS study staff member. The interviewer will administer a REDCap-based, computer-assisted telephone interview (CATI) that will include verbal consent for data collection. Informed, verbal consent will be obtained by trained study personnel with all potential participants receiving a general description of the study, including the baseline and follow-up questionnaires, along with the study specific evaluations. Importantly, we do not feel written consent needs to be obtained to implement specific components of the exercise intervention that will vary by risk assessment in any given individual since it is facilitating standard of care in a consistent fashion, not providing an experimental intervention, and it is not practical to obtain written consent from all subjects in this pragmatic trial. Further, given the cluster randomized design, extensive discussion of the intervention for a specific individual may bias the sample from site to site. However, the survey data collection does require consent, and this will be the emphasis in the consenting process.

Decisional capacity: Patients with cognitive impairment will be included in the main trial because: (1) cognitive impairment is a risk factor for fall injuries; (2) patients with cognitive impairment may benefit from the intervention (a personalized physical exercise plan); (3) patients with cognitive impairment are more susceptible to the adverse consequences of fall injuries; and (4) the inclusion of patients with cognitive impairment will enhance the generalizability of this pragmatic trial, facilitate the subsequent translation of results into clinical practice, and reduce the likelihood of selection effects. However, patients with significant cognitive impairment/dementia, defined as 4 or more errors on the Callahan 6-item cognitive screener, will not be eligible to participate in telephone calls/surveys as altered cognition could adversely impact a participant's ability to accurately report these study outcomes. We will use the Callahan, a six-item, brief and reliable instrument for identifying participants with cognitive impairment

and its diagnostic properties are comparable to those of the full Folstein Mini-Mental Status Examination (MMSE).¹⁸ The six-item screener can be administered by telephone and is easily scored by a simple summation of errors. The six items include the three-item recall (apple, table, penny) and three-item temporal orientation (day of the week, month, year) from the MMSE. This screener will only be used during the RCT phase of the study.

Study personnel responsible for recruitment and consent will be highly trained in determining decisional capacity in senior populations. In addition, specific assessment of decisional capacity will be part of study training. For example, potential participants will be considered impaired with regard to decisional capacity, regardless of Callahan cognitive score, if they: 1) have an inability to express or communicate a preference/choice; 2) are unable to provide a logical rationale for participation/non-participation; 3) have a legal guardian or have been identified legally as incompetent to make decisions for themselves.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This pragmatic trial will use a matched-pair cluster RCT design with the intervention at the MGB primary care practice group level, and the outcomes measured at the patient level. Cluster randomization is appropriate because eSTEPS is a facility-level intervention. Of the eligible primary care practices within MGB (have on average 950 Medicare Wellness Visits per year), a total of 24 primary care practices will be enrolled in the study.

We will match pairs of practices based on size of the practice and whether the practice is an academic or community health center, based on 2021 and 2022 annual encounter data and patient characteristics. Within each pair, one practice will be randomized to eSTEPS intervention and one to usual care. Within the practices randomized to the eSTEPS intervention, all patients ≥ 65 who receive a Medicare Wellness Visit and screen positive for fall risk will receive the intervention and all patients who receive a Medicare Wellness Visit and screen positive for fall risk in practices randomized to control will receive usual care. Pair matching of practices will be based on key available background characteristics (size of the practice and academic/community health center) prior to randomization.

4.3 JUSTIFICATION FOR INTERVENTION

The rationale for the eSTEPS intervention is that by using a CDS integrated into the EHR of primary care providers, information and materials to support older people at risk of falls to take part in evidence-based fall prevention exercises can be efficiently delivered to many older patients during their annual wellness visit. The eSTEP CDS provides an individually tailored set of exercise recommendations based on patient characteristics. The tailoring of the exercise intervention is necessary so that it can provide safe but effective exercises to people.

Development of the eSTEPS CDS within the widely adopted Epic EHR will support dissemination of evidence for older adults. The PCP will receive an eSTEPS BPA and/or Care Gap and Smart Set for all patients aged 65 and older who screen positive for fall risk during their annual Medicare Wellness Visit. The BPA and/or Care Gap and Smart Set will display when the PCP opens the patient's record and provides a preliminary recommendation for exercise based on patient characteristics documented in the EHR. After discussing the importance of exercise for fall prevention and documenting patient exercise preferences, an exercise plan of care will be automatically documented as a note in the EHR and an exercise prescription with pertinent content will be sent to the patients' after visit summary. The app will be available for download at the PCPs office and/or information can be transmitted to the patient via email, and/or after visit summary that provides a link to the app and/or to a website with training video for the

app. In addition to the app, patients and providers will have access to an exercise website with videos and printed handouts in English and Spanish for patients who choose not to use the app. The rationale for providing this range of materials is so that it can meet the needs of older people who have a range of access and comfort using different technologies.

4.4 END-OF-STUDY DEFINITION

Participants will be considered to have completed the study at the end of the study follow-up. This will range from a minimum of 12 to a maximum of 23 months of follow-up.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Age 65 or above
2. Patients enrolled in participating primary care intervention and control practices at MGB
3. Positive screen for fall risk at annual wellness visit.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

Not community-dwelling (i.e., residents of long-term care facilities, prisoners etc.)

Enrollment in the Subsample for Patient Reported Outcomes (PROs):

A subsample of patients will be recruited and consented to participate in follow-up phone calls and surveys. Additional exclusion criteria for the subsample participants are:

1. Unwilling or unable to provide verbal consent
2. Not able to participate due to cognitive impairment (i.e., 4 or more errors on the Callahan Cognitive Screen assessment)
3. Has a terminal illness or other condition that indicates that the participant is not expected to survive for 1 year, such as receiving hospice or palliative care services.
4. Not fluent in spoken English
5. Does not have access to a working telephone

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

N/A

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

In this pragmatic trial, eligible patients at primary care practices assigned to the intervention group will be considered to be enrolled in the trial.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION.

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The intervention is the eSTEPS CDS, an individually tailored set of exercise recommendations/interventions based on patient specific factors and preferences that will be built directly into the Epic EHR system at study sites. PCPs will be trained to use the eSTEPS CDS using the approach described in the pilot phase. The PCP will receive a BPA and/or Care Gap and Smart Set with an exercise prescription Smart Set for all patients aged 65 and older who screen positive for fall risk during their annual Medicare Wellness Visit. The BPA and/or Care Gap and Smart Set will display when the PCP opens the patient's record to provide a preliminary recommendation for exercise based on patient characteristics documented in the EHR. After discussing the importance of exercise for fall prevention and documenting patient exercise preferences, an exercise plan of care will be automatically documented as a note in the EHR and an exercise prescription with pertinent content will be sent to the patient after visit summary and smart App. The App will be available for download at the PCPs office and/or information can be transmitted to the patient via email, and/or after visit summary that provides a link to the App and/or to a website with training video for the App. In addition to the app, patients and providers will have access to an exercise website with videos and printed handouts in English and Spanish for patients who choose not to use the app.

Table 3. Fall risk assessment and exercise care planning in primary care without and with the eSTEPS CDS		
	Present State	Future State with eSTEPS
Fall Risk Assessment and Care Planning Process	- Recommended by practice guidelines, but not routinely done - Completeness/accuracy dependent on individual provider competency - Evidence available but not accessible in the context of primary care workflows - No standardized approach to ensure patient and/or family engagement	- eSTEPS CDS drives consistent evidence-based fall prevention assessment and tailored exercise care planning - eSTEPS CDS accessed within existing EHR workflows - Patient and family engaged in the fall risk assessment and exercise planning process
Fall Prevention Care Plan/Exercise Prescription	- Rarely available in primary care - Rarely accessible by patient - Usually includes only generic recommendations	- Fall prevention exercise plan is personalized to each individual patient's risk factors and patient preferences - Saved as a note in the EHR for care team access - Provided to patient/family in smart App, access to a website and printed resources (low to high-tech tools to address varying levels of digital and health literacy)

As part of the Medicare Wellness Visit, the primary care provider or clinic staff will recommend a personalized exercise plan and encourage the patient to use the App or other resources (we have

developed a website and printable handouts that are available in Epic). Following the Medicare Wellness Visit, the patient will receive regular exercise reminders via the App (if they choose to use it). They will also receive exercise instructions via their Epic after visit summary.

6.1.2 ADMINISTRATION AND/OR DOSING

N/A

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

In this pragmatic trial, the intervention will be delivered by the primary care team at participating practice sites as part of routine care. There are no interventionists in this trial.

We will provide structured training and re-training of the project teams at the intervention trial sites, and of the investigators and staff who are partners in this project. We will provide training for the site physicians and practice staff whose patients will be enrolled in the trial. Clinicians will need to understand both the trial and exercise interventions that the eSTEPS CDS will be recommending. Dr. Dykes and the core study team who are unblinded will hold on-site or Zoom training sessions for physicians and staff in the intervention practices.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

In this cluster-randomized study, it is not possible to blind the practices to their treatment group assignment. It is also necessary for some study team members to be unblinded to help manage the implementation of the intervention, including training of practices, troubleshooting problems with the technology, etc.

The following team members will be blinded to the assignment of the practices into intervention or control group:

- All research assistants who are conducting the interviews to obtain the patient-reported outcomes in the sub-sample
- Dr. Latham, the co-PI who is overseeing the regulatory aspects of the conduct of the clinical trial
- The Safety Officers who are helping to oversee the assessment of AEs

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

Drs. Dykes and Latham will monitor and assure the validity and integrity of the data and will adhere to the procedures outlined in this protocol. In accordance with NIH/NIA's recommendation, a Data Safety Monitoring Board will be instituted. The DSMB will closely track any adverse events. In addition, study PIs will report them to the MGB IRB and to NIA, and notify patients' primary care clinicians. If the primary care clinician feels that it is appropriate, the patient can be withdrawn from the study. In the event that adverse events seem to occur more frequently in either of the two intervention groups, however, we will alert the Partners IRB and NIA as soon as we are aware and take further action as needed.

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

This trial uses an intent to treat analysis. When a subject discontinues from the eSTEPS intervention but not from the study, remaining study procedures will be completed as indicated by the study protocol. Participants will be included in the final analysis regardless of their compliance with the eSTEPS intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-compliance, unless varying compliance is an aspect of the study objectives
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant or might require an additional treatment that would confound the interpretation of the study
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF) documenting Participant Discontinuation or Withdrawal.

7.3 LOST TO FOLLOW-UP

For the primary outcome, data will be obtained from the EHR from any contact with the health system. Participants will only be considered lost to follow-up if they move out of the health system.

For the subsample surveys, a participant will be considered lost to follow-up for that phase of the study if he or she fails to complete the final 12-month interview and study staff are unable to contact the participant after at least 5 attempts. This will not affect the participant's enrollment in the main phase of the trial.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The **Table 4** below summarizes the study procedures that will be conducted during the eSTEPS study for evaluating the effectiveness of the eSTEPS intervention.

Activity/assessment	Central EHR Data Collection	Subsample Outcomes		
		Baseline	6 months	12 months
Qualitative Interviews				x
iTUES (providers only)				
Letter from practice/optout postcard*		x		
Chronic conditions	x			
Screening for high fall risk	x			
Demographic characteristics	x			
Health care utilization	x			x
Fall history	x			x
Assessments	x			
Diagnoses	x			
Medications	x			
Computer Log files re: eSTEPS CDS	x			
Callahan cognitive assessment		x		
Verbal consent**		x		
Cognitive screen**		x		

Telephone interview**		x	x	x
Fear of falling**		x	x	
Exercise Self-efficacy **		x	x	
Falls, fall injuries**	x	x	x	x
eSTEP Exercise CDS during Medicare Wellness Visit		x	x	x
Patient use of eSTEPS Exercise App or other exercise resources		x	x	x

Outcomes are summarized in **Table 5**. Study staff blinded to patients' intervention/control status will call a randomly selected subset of participants at baseline, six and at 12 months. The primary outcome is a fall, defined as an unexpected event in which the participant comes to rest on the ground, floor, or lower level. The total number of falls will be evaluated based on EHR data and patient-reported falls in the subsample. The subsample participants will record falls and fall-related injuries in monthly calendars to improve recollection during interviews. In addition to fall-related outcomes, other secondary outcomes include self-report measures of fear of falling, self-efficacy for exercise, using instruments that have been validated for telephone-based use with older adults (see **Table 5**). We will also use the EHR data to report on use of the recommended exercise program.

Table 5. Primary and Secondary Outcomes				
Primary, Secondary, or Exploratory	Name of Outcome	Specific measure to be used	Timepoints	Powered? Yes or No
Primary	Falls	Self-reported and from EHR	Patient-days follow-up, minimum 12 months	Yes
Secondary	Fear of falling	Modified Falls Efficacy Scale (mFES)	Baseline and 6 months	Yes
Secondary	Exercise Self-efficacy	Self-Efficacy for Exercise (SEE) Scale	Baseline and 6 months	Yes
Secondary	Fall injuries	Self-reported and from EHR	Minimum 12 months	No
Secondary	Mortality	As recorded in EHR	Minimum 12 months	No

The outcome measures will be obtained centrally via enterprise electronic health record (EHR) systems (falls, injuries) as expressed as events per 100 patient-years; patients will contribute patient-years

follow-up to the denominator even if they are lost to follow-up with less than the minimum 12 months follow-up. Telephone interviews (patient-reported outcome data) of enrolled patients will be conducted by blinded outcome assessors at baseline, 6- and 12 months post- Medicare Wellness Visit. There will be two patient-reported outcomes: Fear of Falling and Self-Efficacy for Exercise. Fear of Falling will be measured using the Modified Falls Efficacy Scale (mFES) Score and self-efficacy for exercise will be measured using the Self Efficacy for Exercise (SEE) Scale as described above.

8.2 SAFETY ASSESSMENTS

Level of Monitoring in the eSTEPS Study

This pragmatic trial differs from a typical randomized, controlled trial (RCT) in important ways. First, no experimental interventions are used. All interventions are standard of care and not research. For this reason, the consent for this study only relates to the outcome assessment procedures since the intervention is not considered to be research. Thus, the definitions of research and therefore AE, SAE, Unanticipated Safety Events and Pre-existing conditions do not apply to the intervention.

The BWH IRB has decided that this is a “minimal risk” study. However, this appraisal does not preclude the need to monitor the study and its impact on participant safety. The data collection methodologies include questionnaires, telephone interview and EHR review. Therefore, our safety monitoring procedures focus on data collection via the methodologies described in the protocol design. Our plan is based upon the following principles:

1. It is not feasible or necessary for participant safety to monitor AEs, as the definitions above do not apply because the intervention is not research.
2. Limited monitoring is justified for serious adverse events (SAEs) as many of these will not occur in our study population (e.g. congenital anomalies) AND this is not a trial that has implications for FDA approval. Thus, only Good Clinical Practice (GCP) needs dictate the level of monitoring in accordance with Federal Registry Title 21.
3. It is not necessary to assign monitored SAEs as “related” or “unrelated” to the study protocol because there is inherent bias in this assessment, attribution of “relatedness” would be a tremendous burden, and whether a difference in SAE burden is considered “related” or not, a significant difference between groups would be treated with similar concern by the DSMB.
4. Mechanisms for timely reporting after SAE ascertainment are important, but collective totals of monitored SAEs at assigned intervals will meet “timeliness” for the purposes of this study.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of adverse event from 21 CFR 312.32 (a): any untoward medical occurrence associated with the use of an intervention in humans, ***whether or not considered intervention-related.***

As noted in above, AEs will not be collected in this trial since “any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention” will be occurring in the course of routine care, not research. Limited SAEs will be collected and reported as outlined below.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

This protocol uses the following definition of a Serious Adverse Event (SAE): Any adverse event that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

Our plan focuses on the acquisition and monitoring of a limited set of SAEs with data derived from the following sources:

- Regularly scheduled EHR data downloads
- Telephone interviews with the subsample of participants who are having self-reported outcomes assessed

Only hospitalizations and deaths will be collected, which will ensure the protection of participants from potential harm but remain feasible within the study design. SAE ascertainment will occur from either the telephone interviews or from the regularly scheduled data downloads from the EHR.

The participants who die within the participating health care systems will be verified by EHR review by the biostatistics team from regularly scheduled EHR data downloads. However, participants who die at home or outside the participating health care systems, may be missed in this process. Therefore, we will survey the primary care providers for any deaths of their enrolled patients that have occurred in a 6-month period.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

It is not necessary to assign monitored SAEs as “related” or “unrelated” to the study protocol because there is inherent bias in this assessment, attribution of “relatedness” would be a tremendous burden, and whether a difference in SAE burden is considered “related” or not, a significant difference between groups would be treated with similar concern by the DSMB.

8.3.3.3 EXPECTEDNESS

A clinician with appropriate expertise in older adults and fall prevention will be responsible for determining whether a serious adverse event (SAE) is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of a serious adverse event (SAE) may come to the attention of study personnel during review of EHR data or interviews with a study participant who is participating in the surveys as part of our subsample, or upon review by a study monitor.

SAEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF) in REDCap. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study will be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical or psychiatric condition that is present at the time that the participant is screened will be considered as baseline and not reported as an SAE. However, if the study participant's condition deteriorates at any time during the study such that it results in hospitalization or death, it will be recorded as an SAE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. Documentation of onset and duration of each episode will be maintained for AEs characterized as intermittent.

Research coordinators will record events with start dates occurring any time after informed consent is obtained until 30 days after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

As stated above, this trial will not be monitoring AEs.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

In consultation with the PI, a trained member of the study team will be responsible for conducting an evaluation of a serious adverse event and shall report the results of such evaluation to the NIH and the reviewing Institutional Review Board (IRB) as soon as possible, but in no event later than 10 working days after the investigator first learns of the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- 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); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI’s name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the funding agency within 48 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the funding agency within 5 days of the investigator becoming aware of the problem
- All UPs should be reported to appropriate institutional officials (as required by an institution’s written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within <insert timeline in accordance with policy> of the IRB’s receipt of the report of the problem from the investigator]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint:

We hypothesize that, compared to patients who receive usual care, older patients at risk of falls who are in primary care practices that are using the eSTEPS intervention will have fewer falls in the 12-23 months of follow-up. Alternatively, our null hypothesis is that there will be no difference in the effects of the eSTEPS intervention compared to usual care on falls at 12-23 months of follow-up.

- Secondary Endpoints:

We hypothesize that, compared to patients who receive usual care, older patients at risk of falls who are in primary care practices that are using the eSTEPS intervention will have improved exercise self-efficacy and reduced fear of falling.

9.2 SAMPLE SIZE DETERMINATION

Power analysis for the primary outcome

Based on 2018 data from all participating facilities, the estimated fall rate was approximately 29 falls per 100 patient years. We expect to reduce falls by 20% (to 23.2 falls per 100 patient years) with the intervention. As seen previously¹ we assume the intra-class coefficient (ICC) for patients in the same practice is approximately 0.0076, with the ICC for two patients in different practices in the matched clinics to be half that of patients in the same practice (0.0038). Using a generalized estimating equations z-test² to account for clustering of patients within the same practice and different practices in matched pairs, an average of at least 348 patients in each of the 24 practices (12 pairs) followed for a minimum of 12 months are needed to detect the projected 20% drop in the fall rate for the intervention practices versus control practices with a two-sided type 1 error rate of $\alpha=.05$ and with 90% power. In particular, 8352 total patients (4176 in each arm) will give 90% power to detect the expected 20% decrease in the fall rate.

Based on 2022 data, in which there were 15410 age-eligible people who screened positive for falls at the 24 participating primary care practices, we will have adequate accrual in these practices in a 9-month period followed by a minimum of 12 months of follow-up (follow up range of 12-23 months). This will also account for a 10% drop-out or missing data (patients not followed for a full 12 months). Note that patients who drop-out with less than 12 months follow-up will still be used in the person-year calculation, so that our power calculation here will be conservative. Additionally, patients accrued at the beginning of the study period will have more than 12 months follow-up, up to a maximum of 23 months of follow-up, which also makes our power calculation conservative.

Power analysis for secondary (survey) outcomes

Our goal is to detect clinically important improvements in the patient reported outcomes (fear of falling and self-efficacy for exercise) at 6 months post Medicare Wellness Visit. Fear of Falling will be measured using the Modified Falls Efficacy Scale (mFES) Score²³ and self-efficacy for exercise will be measured using the Self Efficacy for Exercise (SEE) Scale²³ as described above. Using the guidelines of Cohen, we want to detect a clinically meaningful effect size in the 0.2-0.5 range, where 'effect size' is defined as the standardized difference in treatment group means. For power purposes, we (conservatively) choose the

lower end of the range (.25) of clinically important differences. For patient fear of falling, a 0.25 effect size translates to an improvement from 103.7 (usual care) to 129.6 (eSTEPS) on the mean mFES score, since the SD of the mFES score is estimated from previous studies to be SD=36.2.³³ An effect of 0.25 for the mFES is a conservative estimate of the expected effect on this outcome, based on the standardized mean difference of 0.56 for fear of falling measured using the Falls Efficacy Scale, mFES or similar measures that was found in a systematic review of fall prevention exercise programs for older people.³² For patient reported self-efficacy for exercise, a 0.25 effect size translates to an improvement from 58.7 (usual care) for older adults to 73.4 (eSTEPS) on the mean SEE scale since the SD of the SEE scale score is estimated from previous studies to be SD= 21.5.³³ An effect of 0.25 for the SEE Scale is a reasonable estimate for this trial, based on the effect size of 0.27 that was found in a trial of an exercise program in older people at risk of falls after hip fracture.³³

9.3 POPULATIONS FOR ANALYSES

Intention-to-treat (ITT) analysis will be used, meaning that all eligible patients in the participating primary care practices will be included in the analysis.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

In this study, descriptive statistics will be used to summarize the characteristics of the study participants, and to summarize the utilization of different components of the eSTEPS intervention by both PCPs and patients. Both categorical and continuous data will be obtained and will be presented using the most appropriate method for the type of data, such as percentages, means with standard deviations or 95% confidence intervals and/or medians and ranges.

An overall type I error rate of 0.05 (two-sided) will be used as the level of significance for the primary endpoint. The effect of intervention relative to control will be estimated as a rate ratio with corresponding 95% confidence intervals. A prespecified set of baseline covariates to examine their influence on treatment effect: age, race/ethnicity, number of chronic conditions (e.g., Charlson Comorbidity Score), and risk for fall injury based on our computer-based algorithm. For all statistical analyses, an evaluation of any assumptions (e.g., normality) underlying the statistical procedures will be performed and appropriate procedures will be utilized (e.g., transformation or the use of nonparametric tests).

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

All analyses will consider practices (and sampled patients) according to their randomized assignment regardless of adherence to protocol and will account for matched-pair cluster design with the participant as the unit of analysis.

The primary outcome will be the fall rate (per 100 patient-years). Data for this outcome will be obtained from the fall risk screening questions routinely collected and recorded in the EHR when a patient is seen in an outpatient area within the healthcare system. We will also provide calendars to the subsample of patients who will participate in the surveys as a fall rate validation check. We will use Poisson regression for rates (allowing for over-dispersion, e.g., variance greater than expected under an exponential time to fall) to model the fall rates in the two arms. In the Poisson regression, we use a log link and offset for follow-up time, to estimate rate ratios. The primary analyses were adjusted for prespecified covariates: baseline covariates to examine their influence on treatment effect: age, race/ethnicity, number of chronic

conditions, and risk for fall injury based on our computer-based algorithm. Generalized estimating equations (GEE) will be used to adjust for the clustering within and across matched pairs in the matched pair RCT design. Participants enter the study at their first wellness visit during the study period and participants without a fall will be censored either at the date of their withdrawal or at the end of study follow-up. (Thus, patients who are lost to follow-up with fewer than the minimum 12 months follow-up will still contribute patient-years to the denominator of the fall rate).

In an important secondary analysis of the primary end-point, a subgroup analysis was conducted to compare the rate per 100 person years of patients with one or more ICD-10 coded falls or fall injuries in younger (aged 65-75 at baseline) versus older patients (aged 76 and above). This was performed using an interaction between age group and treatment arm in the Poisson regression model. The effect of intervention relative to control will be estimated as a rate ratio with corresponding 95% confidence intervals. An overall type I error rate of 0.05 (two-sided) will be used as the level of significance for the primary endpoint.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Analytic Plan for Survey Outcomes

Patient-reported fear of falling and self-efficacy for exercise measured at baseline and 6 months post Medicare Wellness Visit will be collected on a sample of patients from each practice. This subsample will also complete fall/fall-injury calendars and report falls/injuries at baseline, 6- and 12-month calls.

Because a linear improvement on both scales of the patient-reported outcomes at 6 months is of interest, we will fit a robust linear regression model (robust in not assuming normality) to model both patient-reported outcomes at 6 months in the two arms. GEEs will be used to account for the clustering within and across matched pairs in the matched pair cluster RCT design. The sample of participants selected for the interviews to collect patient-reported outcomes will be enrolled after their Medicare Wellness Visit (ensuring diverse patient mix) and continue for one year follow-up. If patients miss the 6-month follow-up interview, their baseline data will still be used in the GEE to reduce the bias if sicker (or better) patients at baseline dropout.²⁶ If there are baseline differences in mean patient-reported outcomes across the two arms, we will adjust for baseline outcomes in the robust linear regression model. Besides the GEE approach to accounting for missing data, missing data will be dealt with using multiple-imputation procedures, and sensitivity analysis. The missing mechanism will be examined to identify explicit factors associated with missingness and whether there are apparent differences between some groups and to document primary reasons leading to data missing. Under the assumption of missing-at-random, all the missing outcomes at 6 months will be imputed with multiple imputation.²⁷

Sensitivity analysis will be conducted to investigate the robustness of the statistical findings to the missing mechanism, assuming missing-not-at-random.²⁶ We will also perform subgroup analyses to examine if any particular value(s) of these baseline covariates preferentially benefit from our intervention. We will use an interaction term (i.e., covariate*intervention) in the GEE robust linear regression model to develop subgroup-specific effects, and report these in publication. Prespecified subgroups of interest are those in which disparities in fall-related outcomes have previously been found: men vs women^{28,29}, Black vs white patients^{29,30,31}, rural vs urban patients²⁹ and age (65-75 vs >75 years of age)²⁹. The effect of intervention relative to control on patient reported outcomes will be estimated as a mean difference in scores, with corresponding 95% confidence intervals.

9.4.4 SAFETY ANALYSES

Safety endpoints will be analyzed as summary statistics, overall and by treatment group.

SAEs will be presented in a table, where each SAE will be counted once only for a given participant. The table will include the key information described in the safety reporting section, including the type of event, date, expectedness, severity, frequency, and relationship of SAEs to study intervention.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Intervention groups should be compared on baseline characteristics (e.g., demographics, laboratory measurements, behavioral characteristics) using descriptive statistics. Descriptive statistics include frequencies and percentages for categorical variables; means and standard deviations as well as median and inter-quartile range (IQR; 25th-75th percentile) for continuous variables. Both categorical and continuous Patient Baseline Demographic and clinical characteristics, will be compared across arms using the appropriate GEE (GEE for binary, categorical, or continuous variables) clustered by matched pair and practice within pair.

9.4.6 PLANNED INTERIM ANALYSES

The trial will be monitored for possible early stopping due to a large intervention effect using a Haybittle–Peto approach.^{24,25} Specifically, one interim GEE z-test will be performed after approximately 30% (2505 patients) of the total patients are enrolled, which should occur approximately 3 months after baseline. In order to stop the study at this point in favor of the intervention, the P-value for this GEE z-test must be ≤ 0.001 . We note here that we used a simpler, conservative interim analysis approach (Haybittle–Peto) because the less conservative approaches (e.g., O'Brien-Fleming) require independent increments of data, but the data will not likely come to us in independent increments because of matched-pairs cluster randomized design. *Final Analysis*. If the study is not stopped, the final analysis will be performed when 4176 patients have been accrued in each arm (8352). Using the Haybittle–Peto approach, the P-value for this GEE z-test must be ≤ 0.05 for the intervention and comparison groups to be declared significantly different. The final analysis is expected to occur 54 months after the study begins.

9.4.7 SUB-GROUP ANALYSES

The **primary endpoint and secondary endpoints** will be analyzed based on age, sex, race/ethnicity, chronic conditions and fall history at time of screening. Because this is a cluster randomized trials, these sub-group analyses will reflect the expected positive within-group correlation and will take into account heterogeneity in that correlation among study arms as a function of the study design. We will use an interaction term (i.e., covariate*intervention) in the GEE regression model to develop subgroup-specific effects.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

Exploratory analyses will be conducted for two outcomes, fractures and death. These outcomes will be estimated as rates (per 100 patient-years).

Data for these outcomes will be obtained from the EHR when a patient is seen in an outpatient area within the healthcare system. We will use Poisson regression for rates (allowing for over-dispersion, e.g., variance greater than expected under an exponential time to fall) to model the event rates in the two arms. Generalized estimating equations (GEE) will be used to adjust for the clustering within and across matched pairs in the matched pair RCT design. Participants enter the study at their first wellness visit during the study period and participants who do not experience these events will be censored either at the date of their withdrawal or at the end of study follow-up

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Verbal consent will be obtained from participants in the subsample. A verbal consent script, describing in detail the study intervention, study procedures, and risks will be read to the study participants and documentation of informed consent will be electronically recorded prior to starting the study procedures for the subsample. In addition, an information letter which summarizes the information provided in the verbal consent will be mailed to study participants.

The following consent materials are submitted with this protocol: verbal consent script, information sheet, brochure.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Interviews: In accordance with our IRB's standards, we will not approach any patients for participation in interviews before we first use the EHR diagnosis/information to exclude people who have dementia or other cognitive impairments. Consent will be confirmed verbally at the time any patient subject is approached by study staff. At any time, patient subjects have the right to refuse to participate or to opt out of the study, and we will clearly state this at the time of consent. The same will apply to clinician subjects.

Evaluation: Given the nature of the study intervention (minimal risk/quality improvement) and the fact that it would not be feasible to consent every patient to receive the evidence-based, guideline recommended eSTEPS intervention, we have obtained a waiver of written informed consent from our Institutional Review Board (IRB).

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigators, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor/funding agency and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance of study staff to the protocol (ie, significant protocol violations)
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or other relevant regulatory or oversight bodies (DSMB).

A planned Interim Analyses will be performed after approximately 30% (2505 patients) of the total patients are enrolled the study.; the statistical details of the Interim Analyses are described in section 9.4.6 PLANNED INTERIM ANALYSES.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Brigham and Women's Hospital. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by Brigham and Women's Hospital research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the NIA AgingResearchBiobank.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see <https://grants.nih.gov/policy/sharing.htm>). The PI will ensure all mechanisms used to

share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see <https://humansubjects.nih.gov/coc/index>). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at BWH. After the study is completed, the de-identified, archived data will be transmitted to and stored at the NIA Biorepository, for use by other researchers including those outside of the study. Permission to transmit data to the NIA biorepository will be included in the informed consent.

When the study is completed, access to study data and/or samples will be provided through the NIA AgingResearchBiobank.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Provide the name and contact information of the Principal Investigator and the Medical Monitor or Independent Safety Monitor. Update table heading to remove non-relevant role.

Principal Investigator	Medical Monitor or Independent Safety Monitor
Patricia Dykes, PhD, RN	Julia Lowenthal, MD
Brigham and Women's Hospital	Brigham and Women's Hospital
1620 Tremont Street, 3 rd Floor, Boston, MA 02120	Phyllis Jen Center for Primary Care 45 Francis St, 2 nd Floor, Boston MA 02115
(617) 525-3003	(617) 732-6040
pdynes@bwh.harvard.edu	jlowenthal@bwh.harvard.edu

The Steering Committee is the primary high-level decision-making body for the trial. Members of the Steering Committee include the two PIs, at least 3 clinical trial site PIs (including at least two from UTMB), the trial Safety Officer, the Director of the Data Coordinating Committee (DCC) and two experts in fall prevention in older people. Additionally, the NIH Program Officer and the Study Manager will serve as nonvoting members. The Steering Committee will have the overall responsibility for: final approval of

study protocol, approval of study aims and methods, monitoring study progress, and approving revisions to the protocol. When necessary, individuals from the broader group of Co-Investigators and/or Committee members or clinical site representatives will join the Steering Committee for specific agenda items. The Steering Committee will meet by video conference once each month.

The **Operations Committee** will provide overall operational management and coordination of the trial, synthesizing information from various committees, preparing and executing operational plans, identifying problems and disseminating information throughout the operation. The Operations Committee includes the two Joint PIs, the DCC Director, Dr. Volpi, and the Study Manager.

Other Committees: We will establish a Recruitment and Retention Committee; a Safety Committee; a Clinical Trial Site Committee; and, in the final year, a Publication and Dissemination Committee. The functions of the committees are shown in **Table 6** below.

Table 6: Functions of the Committees

Committee Name	Committee Function
Steering Committee	Overall decision-making body
Operations Committee	Responsible for the overall operational management and maintaining integration across all aspects of the trial operations; works closely with the DCC in developing and finalizing the study protocol, Manual of Operations; oversees the study progress, including recruitment and retention, safety reporting; intervention implementation; budget management, scheduling committee meetings, and collating and maintaining minutes of committee meetings;
Clinical Trial Site Committee	Provides venue for bidirectional flow of information between clinical trial sites and the Study's leadership. Provides high level guidance for trial's implementation and conduct at the trial sites.
Recruitment and Retention Committee	Responsible for overseeing recruitment, retention and outcome assessment issues; monitoring enrollment and retention rates; preparing and implementing contingency plans should the enrollment start to fall behind schedule
Data Safety Monitoring Board (DSMB)	Responsible for data safety monitoring and ensuring appropriate reporting of AE, SAE or unanticipated problems in the trial. Ensuring timely reporting of SAEs and SUSARs to the DSMB, sIRB, and to the NIA through appropriate channels.
Data Coordinating Center	Responsible for building the database, DSMB reports, and data analyses. Responsible for building the IT infrastructure for data collection and management, staff training in data recording, building appropriate interfaces with the EMRs at sites to allow data collection, creating data forms, ensuring data security, ongoing management all data systems and providing tracking reports of recruitment and other study processes.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including clinical trial, statistical and aging research. Members

of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to National Institutes of Health staff and the MGB IRB.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed consent — Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

The electronic data — Data will be entered into electronic case record forms (eCRF) in the study database.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations — The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical trial staff under the supervision of the site investigator. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Clinical data (including serious adverse events (SAEs), and clinical laboratory data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the NIA AgingResearchBiobank. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or

contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to the NIA Program Official and the BWH Data Coordinating Center. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting Dr. Patricia Dykes. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest

will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the NIA has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
ANCOVA	Analysis of Covariance
BPA	Best practice alert
BWH	Brigham and Women's Hospital
CDS	Clinical Decision Support
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
EHR	Electronic health record
eSTEPS	Electronic strategies for tailored exercises to prevent falls
FFR	Federal Financial Report
GCP	Good Clinical Practice
GEE	General estimating equation
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
mFES	Modified Falls Efficacy Scale
MGB	Mass General Brigham
MMSE	Mini-mental state examination
MOP	Manual of Procedures

NCT	National Clinical Trial
NIA	National Institute of Aging
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PCP	Primary Care Provider
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

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