STrategies to
Reduce
Injuries and
Develop confidence in
Elders

STRIDE

TITLE: RANDOMIZED TRIAL OF A MULTIFACTORIAL FALL INJURY PREVENTION STRATEGY

STUDY PROTOCOL

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APPLICANT CONSORTIUM: THE PEPPER CENTERS CONSORTIUM FOR PREVENTION OF SERIOUS FALL-RELATED INJURIES

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RANDOMIZED TRIAL OF A MULTIFACTORIAL FALL INJURY PREVENTION STRATEGY

Summary of Changes from Protocol Version 2.1 to Version 2.2

In addition to corrections to typographical errors and spelling mistakes, the following changes were made to convert version 2.1 to version 2.2:

1. Eliminate the postal questionnaire to ascertain fall/fall injury data. Instead, obtain these data through telephone calls from the RAC to all participants. (Note: all STRIDE participants will continue to use the fall calendars as a memory aid).

2. Change the timing of follow-up calls to patients to inquire about falls/fall injuries from every 3 months to every 4 months.

3. To comply with Pennsylvania state law, the list of people who are eligible to serve as proxy respondents for people who are unable to provide informed consent due to cognitive or hearing impairment has been adjusted.

Summary of Changes from Protocol Version 2.2 to 2.3

1. Changed the lower age limit for eligibility from 75 to 70.

Summary of Changes from Protocol Version 2.3 to 2.4

2. Clarification to the Adjudication process with CMS

Summary of Changes from Protocol Version 2.4 to 2.5

1. Duration of the study changed from 36 months (18 months of recruitment and 18 months of follow-up) to 40 months (20 months of recruitment and minimum 20 months of follow-up).

2. Target sample size adjusted to n = 5,322 for a 40-month study instead of n = 6000 for a 36-month study.

3. Interim monitoring was changed from efficacy and futility to efficacy or futility, if necessary.

Summary of Changes from Protocol Version 2.5 to 2.6

1. The definition of the primary outcome has been modified to reflect the recommendations of the DSMB working group

Summary of Changes from Protocol Version 2.6 to 2.7

1. Extend the study from a minimum of 20 and maximum of 40 months follow-up to a minimum of 24 and maximum of 44 months of follow-up. Final end date of the study, including the analytic phase is now extended to April 30 2020.

Summary of Changes from Protocol Version 2.7 to 2.8

1. Addition of new and updated information to the description of the statistical analysis plan in the protocol document.

STUDY SUMMARY FOLLOWS

Title	RANDOMIZED TRIAL OF A MULTIFACTORIAL FALL INJURY PREVENTION STRATEGY
Study Design	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	5 years
Trial Sites	10 trial sites: The Partners' Health Care System; Essentia; Hopkins Health Care System; HealthCare Partners; Reliant Health Care System; Mount Sinai Health Care System; University of Pittsburgh Health Care System; University of Texas Medical Branch Health Care System; University of Iowa Health Care System; University of Michigan Health Care System.
Objective	Conduct a cluster-randomized trial to determine the effectiveness of an evidence-based, patient-centered multifactorial fall injury prevention strategy.
Number of Subjects	The original target sample size was 6,000 participants enrolled from 86 practices to provide 90% power to detect a 20% reduction in the rate of the primary outcome with intervention relative to control. Later, the duration of the trial was extended to a total of 40 months (20 months of recruitment and an additional 20 months of follow-up), which reduced the target sample size to 5,322 participants. Recruitment ended after 20 months on March 31, 2017, with a total of 5,451 participants enrolled.
Main Inclusion Criteria	Community-living persons, 70 years or older, who are at increased risk for serious fall injuries.
Intervention	An evidence-based patient-centered intervention that will combine elements of a multifactorial, risk factor-based, standardly-tailored fall prevention strategy developed at Yale, practice guidelines offered by the CDC's "STEADI" toolbox and the joint American Geriatrics Society/British Geriatrics Society guidelines, and ACOVE practice change approach.

Duration of Intervention	A minimum of 20 months and a maximum of 40 months.
Primary Outcome	The primary outcome is serious fall injuries, operationalized as a fall resulting in: (1) (fracture other than thoracic/lumbar vertebral; joint dislocation; or cut requiring closure) AND any medical attention; OR (2) (head injury; sprain or strain; bruising or swelling; or other) requiring hospitalization.
Primary Analysis	The risk of any serious fall injury (i.e., time to first event) 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.
Secondary Outcomes	Number of falls, number of all fall injuries, and measures of well-being.
Adaptive Components	**Adaptive components of the trial** include: 1) monitoring the accrual rate to determine whether the study eligibility criteria need to be reconsidered if recruitment is lower than expected, taking into account that any changes could affect the inferences; 2) monitoring the potential for ascertainment bias because of interactions between the FCMs and study participants and changing the primary outcome definition if necessary; 3) monitoring the primary outcome rate to determine whether the outcome needs to be adapted, e.g., from time to first serious fall-related injury to time to all recurrent serious fall-related injuries if the former rate is too low, affecting the power of the study; 4) interim monitoring for efficacy or futility, if necessary; and 5) refining the analytic methods based on the validity of the assumptions; such an adaptation will be done blinded to treatment, e.g., if the death rate is low, competing risks could be considered as a secondary, rather than a primary, analysis.
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.

ABBREVIATIONS

ACOVE	Assessing Care of Vulnerable Elders Project
AE	Adverse Event
AGS	American Geriatrics Society
AHRQ	Agency for Healthcare Research & Quality
BGS	British Geriatrics Society
CAT	Computer Adaptive Testing
CDC	Centers for Disease Control and Prevention
CDRN	Clinical Data Research Network
CTSA	Clinical Translational Science Award
CCFP	Connecticut Collaborative Falls Program
CMS	Centers for Medicare and Medicaid Services
CPMC	Central Project Management Center
D & I	Dissemination and Implementation
DCC	Data Coordinating Center
DE	Design Effect
DSMB	Data and Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
EDC	Electronic Data Capture
EHR	Electronic Health Record
EMR	Electronic Medical Record
FCS	Falls Care Software
FCM	Falls Care Manager
FICSIT	Frailty and Injury Cooperative Studies of Intervention Technologies
FRID	Fall Risk Increasing Drug
FES	Falls Efficacy Scale
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act

ICC	Intracluster Correlation
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IT	Information Technology
ITS	Information Technology Services
LIFE	Lifestyle Interventions and Independence for Elders
LPSC	Local Patients and Stakeholders Council
LL-FDI	Late Life Function and Disability Instrument
MAR	Missing at Random
MMSE	Mini-Mental State Examination
MOP	Manual of Procedures
MSO	Medical Safety Officer
NP	Nurse Practitioner
NPSC	National Patients and Stakeholders Council
OAC	Outcomes Adjudication Committee
OAIC	Claude D. Pepper Older Americans Independence Centers
OHRP	Office of Human Research Protections
OT	Occupational Therapist
PCORI	Patient-Centered Outcomes Research Institute
PCORTF	Patient-Centered Outcomes Research Trust Fund
PCP	Primary Care Provider
PDC	Publications and Dissemination Committee
PHI	Personal Health Information
PPRN	Patient Powered Research Network
PreFIT	A Fall Injury Prevention Trial in the UK
ProFaNE	Prevention of Falls Network Europe
PROMIS	Patient Reported Outcomes Measurement Information System
PVQ	Pre-visit Questionnaire

PT	Physical Therapist
RAC	Recruitment and Assessment Center
RCT	Randomized Clinical Trial
RN	Registered Nurse
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SPPB	Short Physical Performance Battery
STEADI	Stopping Elderly Accidents, Deaths, and Injuries
STRIDE	Strategies to Reduce Injuries and Develop Confidence in Elders
UP	Unanticipated Problem
VA	Veterans Administration

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1. INTRODUCTION

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

2. STUDY OBJECTIVES

The proposed multi-site randomized clinical trial will determine the effectiveness of an evidence-based, multifactorial patient-centered intervention to reduce the risk of serious fall injuries among non-institutionalized older persons. The project is a collaboration among investigators, patients, and other key stakeholders from the 14 Claude D. Pepper Older Americans Independence Centers (OAICs) and 10 healthcare systems where patients will be recruited. The OAIC investigators bring decades of research experience in developing, implementing, and testing interventions to treat and prevent complex geriatric conditions, including falls. The patients and stakeholders bring their unique personal perspective of how falls and fall injuries affect their lives, the difficulties they face in adhering to interventions, what outcomes are important to them, and what attributes of the interventions render them feasible, scalable, and sustainable. The clinical sites bring participants, clinical environments, and expertise in patient-centered research and implementation. The investigators, patients, and other stakeholders planned and prepared this proposal jointly; these partners will continue to be collaboratively engaged in all aspects of the trial's implementation.

Our integrated strategy to reduce serious fall injuries, guided by continuous input from our patient advisors and stakeholders during conference calls and focus groups, encompasses several patient-centered components, including screening to identify persons at high risk for falls and injuries, assessing high risk individuals to define their risk factors, individualized intervention based on each person's risk factors, and intervening to implement appropriate care processes and behavioral changes. Because the contributors to fall injuries are multifactorial, the proposed interventions to reduce serious fall injuries also comprise multiple components, including:

- Changing organizational and provider behavior (quality improvement through ACOVE-2 practice redesign model) to initiate care processes, based on an individual patient's identified risk factors;
- Treating or mitigating medical and environmental risk factors specific to each individual (e.g., orthostatic hypotension, multiple medications, visual impairment, foot problems, hazards at home);
- Providing exercise and rehabilitation interventions (e.g., physical therapy and community-based multimodality exercise programs) tailored to the participant's physical and cognitive ability, to improve balance, gait, and other motor functions;
- Reducing the risk of injury if person does fall (e.g., osteoporosis treatment; preventing long lie after a fall);
- Patient engagement throughout the trial's implementation, including ascertainment of individual goals, and patient activation based on successful approaches developed at Yale to prevent falls and injuries.

Accordingly, we will conduct a randomized trial to determine the effectiveness of an evidence-based, intervention that will combine elements of ACOVE-2 practice redesign, a multifactorial, individually-tailored intervention developed at Yale, and practice guidelines offered by the CDC's "STEADI" toolbox and the joint American Geriatrics Society/British Geriatrics Society guidelines, and will utilize a cluster randomization strategy for participant allocation. The primary outcome is serious fall injuries operationalized as a fall resulting in: (1) (fracture other than thoracic/lumbar vertebral; joint dislocation; or cut requiring closure) AND any medical attention; OR (2) (head injury; sprain or strain; bruising or swelling; or other) requiring hospitalization. The trial originally had a slightly different primary outcome definition. The first primary outcome definition will be explored as a secondary outcome as explained below. The definition was changed based on the recommendation of a DSMB working group. Secondary outcomes, based on input from patients and stakeholders, include all injurious falls and all falls regardless of injury. The pre-existing operationalized primary outcome which was "a fall resulting in (fracture other than thoracic/lumbar vertebral; joint dislocation; or

cut requiring closure; head injury; sprain or strain; bruising or swelling; or other) AND any medical attention" is now a secondary outcome. Other secondary outcomes are indicators of well-being, including fall efficacy, physical function and disability, anxiety, and depressive symptoms.

Collaboratively, the investigators, patient advisors, and stakeholders will accomplish the following **Specific Aims:**

1. To conduct in partnership with patients and stakeholders a cluster randomized trial of the intervention in a sample of 5322 participants from 86 practices in 10 health care systems that reflect geographic and sociodemographic diversity. The trial will include features of an adaptive design, to facilitate "learning", including a pre-specified, mid-term analysis.
2. To identify and evaluate jointly with patients and stakeholders the obstacles and facilitators of the post-trial scalability, sustainability, and dissemination of the fall injury prevention strategy.

3. BACKGROUND

Approximately one in three older Americans falls each year and 20-30% of those who fall suffer moderate to severe injuries such as lacerations, hip fractures, or head trauma.[1,2] The problem is important particularly among those 75 years and older when the incidence of falls rises dramatically.[3] Among older adults, falls are the leading cause of both fatal and nonfatal injuries. In 2010, 2.3 million nonfatal fall injuries were treated in emergency departments and more than 662,000 of these patients were hospitalized.[4] These numbers will rise with the aging of the baby boomers. In addition, many who do not sustain injuries develop fear of falling,[5] which may result in self-limiting their activities, leading to reduced mobility and loss of physical fitness, further increasing their risk of falling.[6]

Despite decades of research that has demonstrated conclusively that many falls in the elderly can be prevented,[7-10] quality of care for falls remains low. Fewer than half of those who fall each year discuss their falls or fall prevention with a health care provider.[11] Moreover, only a third of elderly patients in primary care practice are screened for falls and the quality of care for those who are at risk for falling has not improved in the past decade.[12,13]

Accordingly, this project funded jointly by the National Institute on Aging and the Patient Centered Outcomes Research Institute (PCORI) is a multi-site cluster randomized clinical trial (RCT) of an evidence-based, multifactorial individually-tailored intervention to reduce the risk of serious fall injuries among non-institutionalized older persons.

4. STUDY DESIGN

The proposed trial 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. This avoids the potential for contamination of controls, allows staff to be trained efficiently, and improves the feasibility of applying the intervention practice-wide. The primary outcome is time to first serious fall injury assessed at the patient level. This outcome was selected as primary because the initial event is associated strongly with subsequent

adverse outcomes[14] regardless of the occurrence of another event; however, all serious fall injuries will be evaluated in a supportive analysis.

Adaptive features will include:

1. Monitoring the accrual rate to determine whether the eligibility criteria should be altered if enrollment is lower than expected (e.g., by lowering the age entry criterion);
2. Monitoring the potential for ascertainment bias and changing the primary outcome definition if necessary
3. Monitoring the primary outcome rate to determine whether the outcome needs to be adapted, e.g., from first serious fall injury to all serious fall injuries if the former rate is too low, affecting the power of the study;
4. Interim monitoring for efficacy or futility, if necessary; and
5. Refining the analytic methods (blinded to treatment) based on the validity of the assumptions (e.g., models that consider non-proportional hazards). Because the recruitment period will be relatively short, other commonly used adaptive features are not feasible, such as adapting the randomization, intervention or sample size (based on nuisance parameters (e.g., intracluster correlation [ICC] and/or observed treatment effect).[15]

4.1 Number of Subjects

The original protocol had planned for randomization of 80+ practice sites – each randomizing an average of 75 participants, for a total of 6,000 randomized participants in a study of 36 months duration (18 months of recruitment and a further 18 months of follow up). Later, the duration of the trial was extended to a total of 40 months (20 months of recruitment and a minimum 20 months of follow-up), which reduced the target sample size to 5,322 participants. Recruitment ended after 20 months on March 31, 2017, with a total of 5,451 participants enrolled.

4.2 Subject Selection and Withdrawal

4.2.1 Inclusion and Exclusion Criteria

Table 1 lists the inclusion and exclusion criteria for screening patients for participation in the trial.

Table 1: Inclusion and Exclusion Criteria	
Inclusion Criteria	
i.	The patient is at least 70 years of age.
ii.	The patient must answer 'yes' to one or more of the following questions:
ii.a	Have you fallen and hurt yourself in the past year?
ii.b	Have you fallen 2 or more times in the past year?
ii.c	Are you afraid that you might fall because of balance or walking problems?
Exclusion Criteria	
i.	The patient is enrolled in hospice.
ii.	The patient resides in a nursing home.
iii.	The patient is not capable of providing informed consent (or assent), and a proxy is not available.
iv.	The patient does not speak English or Spanish

Because participants must be able to provide consent (or assent) over the phone, it is not feasible to enroll participants who do not speak English or Spanish.

4.3 Screening, Recruitment, and Enrollment

Our procedures have been designed to maximize efficiency and have been vetted with our stakeholders. As described in Human Subjects, we are committed to enrolling ethnic minorities and disadvantaged populations, including those for whom Spanish is their primary language.

4.3.1 Screening

From each practice, patients aged 70 or older will be identified via the electronic health record (EHR) and subsequently screened to identify those at increased risk for falls and fall-related injuries. Based on our pilot testing, the primary strategy will be centralized screening. The clinic sites will provide the Yale Recruitment and Assessment Center (RAC) with the names and addresses of patients in the practice who are aged 70 years or over. These people will be sent a letter addressed from their primary providers asking them to

complete the fall screening questionnaire, which will include the three questions in **Table 1**, and mail it back to the RAC. If needed, a second mailing may be sent out to non-responders to improve response rates.

To allow some flexibility, we will also use a clinic screening strategy, as needed. Practice staff will screen all age-eligible patients during routine primary care visits. Those responding positively to any of the 3 screening questions in **Table 1** will be deemed to have "screened in" and will be recruited into the study. As part of a practice change, the screening questions will be imbedded in the usual work flow, as a part of standard vital signs. This approach has been implemented successfully in Assessing Care of Vulnerable Elders (ACOVE) program,[16-18] and was successfully pilot-tested during Year 1 at practices across each of the 10 clinical sites.

During the trial, the age of eligibility was lowered from 75 to 70 to expand our pool of eligible patients. Based on data available from the Center for Disease Control injury data and other studies, the reduction in the outcome rate will likely be relatively modest for ages down to 72, and this reduction will be obviated, at least in part, by the need to meet one or more of the three fall-injury screening criteria.[8,19,20] We will implement the enrollment of people with a lower age eligibility age in steps. EHR data will be obtained for people aged 70 and above. The study team will proceed to screen patients who are 74 years or older. The study team will monitor the impact of lowering the eligibility age to 74 on the recruitment pool, recruitment yield, and the proportion of patients enrolled based solely on the "fear of falling" criterion. If the study team determines that further lowering of the age criterion is required, the study team will request Steering Committee's approval, based on its evaluation of the afore mentioned monitoring results. While it is unlikely that we would need to enroll participants younger than 72, the age of eligibility was lowered to 70 to allow efficient enrollment if needed.

The screening questions were selected based on evidence indicating that persons meeting these criteria are at significantly elevated risk for injurious falls.[8,19] Evidence from the ACOVE prime study suggests that nearly 40% of persons aged 75 or older screen positive for any one of screening questions.[17] Comparable results were obtained during our pilot testing.

4.3.2 Recruitment and Enrollment

For the centralized screening strategy, patients who screen positive will be sent a recruitment packet. For the clinic screening strategy, screen-positive patients will be handed (or mailed) the recruitment packet. For each strategy, the recruitment packet will include an invitation letter from their primary provider and an information sheet about the study. The letter will indicate that they can opt out from being contacted about the study by returning a self-addressed, pre-stamped postcard to the RAC within two weeks.

Screen-positive patients in both intervention and control practices who do not opt out will be called by a study staff member at the RAC. During this telephone interview, the recruiter will confirm the absence of any exclusion criteria, review the purpose of the study, answer any questions and, after obtaining verbal consent, collect baseline data on: key demographic characteristics – including ethnicity, marital status, living situation, and educational attainment; a cognitive screen using the Callahan 6-item screener;[21] health insurance and other PHI; chronic conditions; fall history; self-rated health; height and weight; functional status; and other secondary outcomes (among a random subset of 720 participants based on our sample size estimates).

Screen-positive patients will be recruited until the desired number (average n=75) has been enrolled in each practice.

Because randomization of practices will occur prior to participant enrollment, it will be important to minimize any potential bias due to lack of allocation concealment. The central recruitment staff will be kept blinded to randomization status of the practices and will be rigorously trained to reduce potential bias. Although practice

staff cannot be kept blinded to intervention status, we will carefully monitor performance at practices that implement clinic screening to ensure that all age-eligible patients are screened for fall risk.

4.3.3 Patients with Cognitive Impairment

Patients with cognitive impairment will be included in the study because: (1) cognitive impairment is a risk factor for fall injuries;[22] (2) patients with cognitive impairment may benefit from several components of the multifactorial intervention, including physical exercise;[23] (3) patients with cognitive impairment are more susceptible to the adverse consequences of fall injuries;8 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. Patients with significant cognitive impairment/dementia will be required to have a caregiver/proxy willing to: (1) provide consent; (2) facilitate adherence to the study protocol, and (3) assist with implementing the intervention as needed.

Significant cognitive impairment will be defined as 4 or more errors on the Callahan 6-item cognitive screener. The six-item screener is a brief and reliable instrument for identifying participants with cognitive impairment and its diagnostic properties are comparable to those of the full Folstein Mini-Mental State Examination (MMSE). 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. Additional information about the inclusion of patients with cognitive impairment is provided in the Informed Consent section.

4.3.4 Rescreening

Patients who screened out initially as low risk for the centralized strategy will not be rescreened. Because screening will be imbedded in the usual work flow for the clinic strategy, patients who screened out initially as low risk will be rescreened during subsequent clinic visits. However, screen positive patients who had previously opted out or declined to participate will not be re-contacted, even if they screen positive during a subsequent clinic visit.

4.3.5 Early Withdrawal of Participants

Because this trial is based on the principle of “intent-to-treat”, all participants in a particular practice will be analyzed in the group to which that practice was randomly assigned, regardless of whether they complete the intervention or are noncompliant. This preserves the effect of randomization. Because the intervention will be integrated into the work flow of the practice, we expect withdrawals from the intervention will be limited. Nonetheless, we plan to follow participants for the study outcomes even if they elect to stop the study intervention. For participants who are lost to follow-up, we will be able to obtain some information from the electronic health record or from the utilization or claims data on the primary outcome of serious fall injuries.

If the participant elects full withdrawal from the study, this will be recorded on the Participant Final Disposition Form and all contact with the participant will cease, as will any acquisition of participant data (e.g., CMS claims, clinical trial site encounter data, or medical records).

5. STUDY INTERVENTION

The intervention **focuses on quality improvement** and includes a multifactorial risk assessment and individually tailored set of recommendations/interventions. The intervention will utilize a primary care co-management model with nurse Falls Care Managers (FCM) that follows four steps:

- Risk assessment by a FCM using a standardized structured visit note.
- Use of structured visit notes and algorithms to develop an individualized Falls Care Plan by the FCM that will be presented to the patient’s primary care physician (PCP) for modification and approval, to include:

  - Fall risk reduction interventions that the FCM can directly implement;
  - Recommendations that the PCP can implement (e.g., medication changes);
  - Referrals to health providers or community-based organizations for more detailed assessment or implementation of specific components identified in the Risk Assessment.
- Explanation of identified risks to the patient (and caregiver, when appropriate) and suggested interventions, using motivational interviewing to elicit patient preferences and readiness to participate in treatments.
- Ongoing monitoring of response to treatment as indicated in the Care Plan and reassessment of risk factors at scheduled intervals by the FCM with revision of the Care Plan as needed.

The broad pillars of the intervention (e.g., the FCM), the linkage with health care system providers, and referrals to community-based programs) are consistent across practices. Moreover, the content of the individual components is consistent across sites. **As with all quality improvement efforts**, implementation depends upon local resources; accordingly, the precise approach to implementation will vary from site to site and sometimes from practice to practice.

Below are the specific activities to be implemented for each patient. The detailed information and procedures relating to Intervention fidelity and quality assurance are contained in the Manual of Procedures.

5.1 Activities Prior to Initial Visit

a. Identification of Participants. Eligible participants (i.e., those who have met eligibility criteria and consented to the study) are identified by the RAC and their names are transmitted to sites as well as information regarding cognition to determine whether the patient or caregiver is the informant for the pre-visit call, initial visit, and subsequent communication. For patients with significant cognitive impairment/dementia, defined as 4 or more errors on the Callahan 6-item cognitive screener, the caregiver/proxy will be interviewed for the pre-visit call and will need to accompany the patient to the initial visit to provide clinical information.

b. Scheduling and sending pre-visit forms to patients.

c. Pre-visit calls. FCMs will conduct the pre-visit phone call and obtain additional information.

5.2 Activities During and Immediately After Initial Visit

a. Initial visit.

i. **Determining individual risk factors based on findings from Pre-Visit Questionnaire (PVQ) and initial assessment.** All risk factors will be assessed through PVQ review and physical examination. Some specific risk factor protocols will be applied to all participants whereas others will be applied only to patients who meet specified criteria (triggers).

ii. **Linking risk factors to possible interventions.** For each risk factor, standard of care interventions will be identified and a template will be used to communicate the recommendation; the template will include several different messages depending upon what the risk factor-specific protocol determines is appropriate for the patient. Risk factors and triggers include:

1. **Medications.**
   a. **Triggers.** Fall Risk Increasing Drugs (FRIDs) or symptoms identified from PVQ.
2. **Osteoporosis.**
   a. **Triggers.** All patients.
3. **Vitamin D.**

a. **Triggers.** Only patients who have had a vitamin D level drawn within the last year. (Vitamin D recommendations for all others will be covered in Osteoporosis).

4. **Home safety.**
   a. **Triggers.** All patients complete a home safety checklist prior to initial visit that is reviewed with the FCM.
5. **Orthostatic hypotension.**
   a. **Triggers.** Patients identified with orthostatic hypotension during initial visit.
6. **Visual impairment.**
   a. **Triggers.** Patients who have not been seen by eye doctor in past year or have vision risk factors (macular degeneration, glaucoma, diabetic eye disease, near or far vision loss) even if they have seen an eye doctor within the past year.
7. **Unsafe feet and footwear.**
   a. **Triggers.** All patients.
8. **Strength, balance, gait impairment.**
   a. **Triggers.** All patients.

iii. **Patient engagement/motivational interviewing.** Patients identify 1-3 recommendations to initially work on and develop action items with FCM.

iv. **Care Plans will be developed based on action items**.

v. **Approval of Care Plans by Primary Care Provider (PCP)**.

b. Follow up with FCM. For each participant, the frequency and timing of follow-up visits to reassess risk factors and monitor progress towards risk factor reduction will be determined by the patient's individual needs as defined in the Care Plan and initial visit EHR note. During the time when components of the intervention are being implemented actively, many participants will need to see or communicate with the FCM frequently to monitor progress and change the treatment plan and implement alternative interventions if there is failure to improve.

c. Documentation of care will be site specific and will include**:**

i. Initial visit and referrals.

ii. **Follow-up (in-person, telephone, e-mail) contacts**.

iii. **Storage of clinical documents (e.g., PVQ, home safety checklist**).

5.3 Activities After Initial Visit and Between Visits

a. Referrals to other health providers will be based on the individual patient's specific risk factors and chosen action items. Referrals include resources:

i. Within health system.

ii. Home health.

iii. Community-based falls prevention programs.

b. Acute and recent falls will be managed by the practice and FCM according to standards of care.

c. Follow-up visits.

i. **Routine.** During the first year of the intervention, all participants will be seen by the FCM at least twice and after the first year at least annually to mitigate new risk factors, consistent with AGS/BGS guidelines. During scheduled follow-up visits, the FCM will re-assess risk factors and repeat physical performance (SPPB) assessments.

ii. **Triggers for additional follow-up visits.** Because acute illness can precipitate deconditioning and place participants at higher risk of falling, all participants will be scheduled to see the FCM for a reassessment following discharge from the hospitalization or after an Emergency Department visit.

6. CONTROL INTERVENTION

6.1 Activities after Screening

Eligible patients (i.e., those who have met eligibility criteria and consented to the study) are identified by the RAC (see **4.3.2**), and their names are transmitted to the relevant clinical sites.

6.2 Activities Conducted at the Sites

a. Providers in the control group practices, i.e. usual care, will receive the results from the screening questions to identify age-eligible patients at high risk for falls.
b. Patients receiving care at Control group practices will receive a falls informational booklet and will be encouraged to discuss fall prevention with their primary provider at their next clinic visit. This booklet, entitled “Stay Independent”, is part of the STEADI tool kit.
c. A webinar about falls and fall prevention will be available to providers and staff in the control practices. This will be based on the existing fall prevention webinar, which is part of the STEADI tool kit.

6.2.1 Rationale

All patients enrolling in STRIDE will be told that their practices are delivering fall prevention programs. The control group needs to receive some fall prevention information that is part of the current standard of care for the following reasons: (1) all participants will be at increased risk for falls, so there is an ethical obligation to inform their PCP; (2) to increase adherence to using the fall calendars (and avoid differential reporting of the study’s primary outcome between the two groups), the control group needs to believe that they are part of some program to prevent falls; (3) to avoid cross-overs to the intervention group (i.e. patients choosing to change their practice if they believe other patients in their health system are receiving superior care at practices located near their home) or drop-outs from the study (i.e. patients refusing to report falls and/or to allow their health information to be shared), it is important that the control group does not perceive that they are receiving a clearly inferior intervention.

STRIDE will provide the control participants with materials that are part of the STEADI tool kit. These materials have been produced by the CDC to raise awareness about falls in primary care. These materials can be considered part of standard of care since they are currently being disseminated widely in primary care practices around the country.

7. OUTCOME MEASURES

7.1 Definition and Ascertainment of Outcomes

Our approach to choosing outcome measures and assessment methods has been informed by discussion with our patients and stakeholders. With their help, we reviewed measurement domains from the Prevention of Falls Network Europe (ProFaNE) consensus.[24] Based on these discussions and review of the literature, we will assess outcomes in two domains: 1) fall-related and 2) well-being, as summarized in **Table 2.**

Table 2. Primary and Secondary Outcome Measures, assessed centrally by Yale RAC		
Domain	**Measure (1˚ & 2˚)**	**Source, Frequency, and Sample**
Fall-related	Serious fall injuries (1˚)	Telephone interview every 4 months, supplemented by administrative claims/encounter data (including data from clinical trial sites and Medicare) for date and type of injury; medical record adjudication for discrepancies with fall-injury claims
	All fall injuries (2˚)	Telephone interview every 4 months: serious fall injuries plus other injuries that may not come to medical attention
	Original operationalized definition of primary outcome (2˚)	Telephone interview every 4 months, supplemented by administrative claims/encounter data (including data from clinical trial sites and Medicare) for date and type of injury
	All falls (2˚)	Telephone interview every 4 months
Well-being	Concern about falling (2˚)	Modified FES at baseline, 12 m and 24 m (telephone) in 720 participants, representing a random sample of participants enrolled in first 12 months
	Physical function and Disability (2˚)	LL-FDI via CAT at baseline, 12 m and 24 m (telephone) in 720 participants
	Anxiety/Depressive symptoms (2˚)	PROMIS scales measured at baseline, 12 m and 24 m (telephone) in 720 participants
CAT: Computer Adaptive Testing; FES: Fall Efficacy Scale; LL-FDI: Late-Life Function and Disability Instrument; PROMIS: Patient Reported Outcomes Measurement Information System		

7.1.1 Fall-Related Outcomes

The primary outcome of serious fall injuries is defined as: a fall resulting in: (1) (fracture other than thoracic/lumbar vertebral; joint dislocation; or cut requiring closure) AND any medical attention; OR (2) (head injury; sprain or strain; bruising or swelling; or other) requiring hospitalization.

A fall is defined as “an unexpected event in which the participant comes to rest on the ground, floor, or lower level.”[24] To ensure that this definition is met, participants are asked, “Did you fall all the way fall to the floor, ground or other lower level when you fell?”

All fall injuries, a secondary outcome, include serious fall injuries as well as less severe falls that result in bruises, cuts, persistent pain, and restricted activities, but not necessarily medical attention. The importance of these less severe injuries was recognized and articulated by our stakeholders. We propose to collect data on falls, serious fall injuries (both as defined by the current primary outcome and as defined by the original definition of the primary outcome) and other fall injuries every four months in all participants using a structured telephone interview. This interview will ask about falls, injuries, hospitalizations, emergency department (ED) visits, and other health care utilization. To facilitate recall, participants will be instructed to record their falls/injuries on a monthly fall calendar.[25,26] To enhance efficiency and consistency, ascertainment of these outcomes will be conducted centrally at Yale, which has an unparalleled track record for falls surveillance and participant retention.

To confirm participant reports of the primary outcome (serious fall injuries) and identify instances of the primary outcome that were not reported by participants, we have developed a verification system based on administrative health care claims and encounter data that will be provided by sites and by Medicare, and medical records that will be provided by sites. Participants reporting a fall-related injury that led to medical attention will have this injury confirmed in administrative claims/encounter data; we will request medical records when administrative claims/encounter data do not confirm the injury. Once appropriate data have been assembled as noted above, fall-related injuries will be reviewed independently by two members of the

Outcomes Adjudication Committee (OAC), which will be masked to group assignment. These physicians will use available data to confirm: a) the occurrence of a fall; b) whether a fall-related injury has occurred; and c) the type of injury. For cases where the two initial reviewers disagree and cannot reconcile their differences, the OAC as a whole will review the case masked to group assignment to make a final designation. Similar procedures have been used successfully in the Lifestyle Interventions and Independence for Elders (LIFE) Study, under the direction of Dr. Gill.[27] This triangulation approach will ensure that the primary outcome is captured accurately and completely.

Process for Linking to Data from Medicare: The Medicare ID/SSN are needed as the link to the patient's Medicare data. Subjects provided consent for us to review their medical records at the time of enlistment into STRIDE. The 10 Clinical Trial Sites (CTSs) will be instructed to supply enrolled participants' Medicare ID, SSN or both if they have both along with the STRIDE ID directly to a third-party vendor. To prevent a mismatch, the CTS will send two additional identifiers, date of birth and gender, which the third-party vendor can compare against lists provided by the Yale DCC (i.e., STRIDE ID, date of birth, gender) to make sure there is no mismatch between the STRIDE ID and Medicare ID/SSN.

The SSN/Medicare ID will have two legs to its journey. The first leg is from the STRIDE CTS to Health Information Solutions. The second leg is from Health Information Solutions to General Dynamics Information Technology (GDIT). GDIT, acting as a contractor for the Centers for Medicare and Medicaid Services, will then use the Medicare ID and/or SSN to identify patients' Medicare enrollment and claims data that is needed, after which GDIT will strip out the Medicare ID/SSN so the central STRIDE team researchers never see it. Because the Medicare ID/SSN are sent to GDIT with the STRIDE ID next to each Medicare ID/SSN, when the Medicare ID/SSN are stripped out, we still have the STRIDE ID left, which we can use to identify our patients.

Health Information Solutions is acting as a third-party intermediary to save STRIDE researchers from responsibility to manage the SSN's/Medicare ID's themselves. GDIT is the CMS' contractor that handles CMS data for researchers. It should be noted that while ResDAC and GDIT are acting on behalf of CMS, Health Information Solutions is acting on behalf of STRIDE. Since Health Information Solutions is providing a technical service to STRIDE, they are being treated as a vendor by Yale and are considered covered under the entity to whom they are providing the service (in this case, Yale).

The Centers for Medicare and Medicaid Services Privacy Board approved the use of their data to be able to complete this linkage process.

7.1.2 Well-Being Outcomes (assessed by phone at baseline, 12m, and 24m in random sample of 720 participants enrolled in first 12 months)

Based on input from stakeholders, the four indicators of well-being will include: fall efficacy, physical function/disability, anxiety, and depressive symptoms. We identified instruments that were brief and could be administered by phone. We gave preference to computerized adaptive testing (CAT), when available, and to demonstrated responsiveness to change in studies of comparable populations. Fall efficacy will be operationalized as the level of concern for falling (4-point scale: not at all, somewhat, fairly, very) when performing a series of activities, using a modified version of the Fall Efficacy Scale (FES).[28] While fall efficacy had been operationalized originally as degree of confidence,[29] more recent work by the ProFaNE group has asked about level of concern. Fall efficacy has been used previously as an outcome in two successful interventions to reduce falls[30] and improve falls care in primary care.[17]

The Late-Life Function and Disability Instrument (LL-FDI) measures two areas that stakeholders viewed as important consequences of sustaining a fall injury (physical function and disability). The LL-FDI has been validated psychometrically[31] and can be administered efficiently by phone via CAT.[32] The physical function area includes items such as going up a flight of steps, getting in/out of a car, and walking around one's home; while the disability area includes items such as visiting friends/family, taking part in organized social activities, taking care of personal errands and preparing meals. The LL-FDI is responsive to interventions designed to improve physical function, and effect sizes of .3-.45 SD units are considered minimally important differences.[33]

We will use the Patient Reported Outcomes Measurement Information System (PROMIS) to assess anxiety and depressive symptoms.[34] The eight-item anxiety short scale asks about the frequency of feeling fearful, worried or anxious (among others), while the eight-item depression short scale asks about the frequency of feeling worthless, hopeless or having nothing to look forward to (among others). Somatic items are not included because they are confounded with symptoms of frailty, do not fit the item response theory model well, and exhibit differential item functioning by age.[34] The brevity of these measures obviated the use of CAT. These measures are responsive to clinically meaningful changes over time,[35] using both mixed methods and anchor-based effects. Changes of 0.33 to .5 SD units have been observed[36] in very similar PROMIS cancer instruments, and an effect size of 0.33 is considered a minimally important difference.[37]

7.1.3 Tertiary Outcomes

Tertiary outcomes will include hospitalizations (from interviews and claims), long-term nursing home admissions[14] (from interviews and claims), and deaths.

8. STUDY PROCEDURES AND VISITS

8.1 Randomization

The trial has a cluster randomized design. The unit of randomization is the practice. This avoids the potential for contamination of controls, allows staff to be trained efficiently, and improves the feasibility of applying the intervention practice-wide.

8.2 Schedule of Events

The trial Schedule of Events is shown in **Table 3**.

The STRIDE Study will follow subjects for up to 44 months through contacts every four months to inquire about falls. At 12 and 24 months, selected participants will have a longer contact for the Wellbeing outcomes subsample (n=720).

Activity/assessment	**Screen / Enroll**	**BL**	**4 mon**	**8 mon**	**12 mon**	**16 mon**	**20 mon**	**24 mon**	**28 mon**	**32 mon**	**36 mon**	**40 mon**	**44 mon**
Screening for high fall risk	X												
Recruitment packet mailed	X												
Enrollment - Verbal Consent / Assent	X	X											
Telephone interview	X	X	X	X	X	X	X	X	X	X	X	X	X
Demographic characteristics		X											
Cognitive screen		X											
Chronic conditions		X											
Fall history		X											
Self-rated health, height/weight		X											
Physical function and disability*		X			X			X					
Concern about falling*		X			X			X					
Anxiety/depressive symptoms*		X			X			X					
Falls, fall injuries, serious fall injuries			X	X	X	X	X	X	X	X	X	X	X
Health care utilization			X	X	X	X	X	X	X	X	X	X	X

BL: Baseline; mon: months

*Among a random subset of 720 participants

9. STATISTICAL ANALYSIS, SAMPLE SIZE AND POWER CALCULATIONS

9.1 Design Overview

STRIDE is designed as 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 to avoid the potential for contamination of controls, which could occur more easily if randomization was at the level of the participant or physician. The primary outcome is time to first adjudicated serious fall injury assessed at the patient level. The target sample size is 5,322 participants enrolled in 86 practices to provide 90% power to detect a 20% reduction in the rate of the primary outcome with intervention relative to control.

Adaptive design features will include: 1) monitoring the accrual rate to determine whether the eligibility criteria need to be reconsidered if recruitment is lower than expected, e.g. by lowering the age entry criterion; 2) monitoring the potential for ascertainment bias because of interactions between the FCMs and study participants and changing the primary outcome definition if necessary; 3) monitoring the primary outcome rate to determine whether the outcome needs to be adapted, e.g., from first serious fall injury to all serious fall injuries if the former rate is too low, affecting the power of the study; 4) interim monitoring for efficacy or futility; and 5) refining the analytic methods based on the validity of the assumptions; such an adaptation will be done blinded to treatment, e.g., if the death rate is low, competing risks could be considered as a secondary, rather than a primary analysis. Because the recruitment period will be relatively short, other commonly used adaptive features were deemed to be infeasible, such as adapting the randomization, intervention or sample size (based on nuisance parameters, e.g., intracluster correlation [ICC]) and/or observed treatment effect).[38]

9.2 Subject Allocation to Treatment Arms

All participating clinical practices will be randomized at one time using a stratified randomization approach with stratification by clinical site to control for potential site differences. Practices will not be added after trial initiation. The method of randomization will balance practice characteristics within and across the clinical sites to enhance homogeneity and to provide some control for the ICC to maintain the power of the trial. The balancing covariates include practice size, geography (urban/rural), and race/ethnicity.

An important consideration, particularly in cluster trials, is allocation concealment to control for selection bias. Potential approaches include 1) randomizing after enrollment, 2) blinding the recruiters, 3) standardizing the enrollment process with adequate training of screeners and recruiters, and 4) covariate adjustment in the analysis. Because enrollment must occur after practices have been randomized in STRIDE, the first approach is not feasible. However, as discussed under Recruitment, we will mitigate the possible effects of selection bias through approaches 2 and 3, along with covariate adjustment in the analysis, if necessary.

9.3 Sample Size

Sample Size estimates were informed by preliminary data from MOBILIZE Boston, a longitudinal study of 765 community-living seniors, with monthly ascertainment of serious fall injuries.[39] Although based solely on self-report, the operational definition of serious fall injury was otherwise the same as in the proposed trial. Analyses were restricted to 135 participants meeting our entry criteria, with a median follow-up of 2.8 y. The annual rate of first serious fall injury was 18% (95%CI: 14%-24%); a preliminary estimate of the overall serious fall injury rate (including recurrent events) was comparable, at 21% (95%CI: 16%-24%). For the proposed trial, we project an annual outcome rate in the control group of 14% to 18%, since fall injuries will be assessed every four months rather than monthly, and our protocol requires that serious fall injuries be confirmed by data from claims or medical records. We project a 20% reduction in serious fall injuries (intervention relative to control, assuming constant and proportional hazards). This reduction, which would have considerable clinical and public health impact, is intermediate between that found in Yale FICSIT (31% reduction in all falls) and Connecticut Collaborative Falls Program (CCFP) (9% reduction in serious fall injuries), two prior multifactorial

fall prevention studies.[30,40] Because many aspects of our intervention will be implemented at the level of the patient (as in FICSIT) rather than geographic region (as in CCFP), our effect size should be closer to that of FICSIT than CCFP, making the sample size estimates given here conservative.

Sample size estimates were determined for a clustered design for time to first serious fall injury (the primary outcome) based on the logrank statistic in the presence of competing risk due to death.[41-43] **Table 4** provides sample size estimates for a trial duration of 3 y assuming: 1) type I error = 5% (2-sided) and 90% power; 2) uniform accrual with periods of 1, 1.5 and 2 y; 3) equal allocation to intervention and control groups; 4) no adjustment for non-adherence to intervention (accounted for with conservative treatment effect); 5) all patients followed to end of the trial (max = 3 y); 6) 7% annual death rate without experiencing a serious fall injury (i.e., competing risk); 7) 3% annual loss to follow-up in the absence of serious fall injury or death (expected to be low due to the use of multiple sources, including claims data, but will be examined in Year 1 due to potential impact of migration out of the healthcare system; 8) 3% inflation for the proposed interim monitoring for efficacy and futility;[44] and 9) 57% inflation for the design effect (DE) of clustering, assuming an average of 75 participants enrolled per practice and an ICC of 0.0076 estimated from an analysis of serious fall injuries in the LIFE Study.[45] Based on **Table 4**, we had selected a target sample size of 6000 participants to be accrued from 80+ practices, each enrolling an average of 75 participants over a 1.5 year recruitment period. The target number of serious fall injuries to detect a 20% reduction for intervention relative to control at 90% power is 845 (unadjusted for clustering or interim monitoring). When the duration of the study was extended to 40 months, sample size was revised to 5,322 participants.

Data from the pilot study indicate that recruiting the desired number of participants is feasible. First, to achieve the targeted sample size, we will need to enroll about 4 participants per month per practice. During the pilot study, 164 participants who met the inclusion/exclusion criteria described in **Table 1** were enrolled from 10 practices (1 from each clinical site) over an average of about 1 month, a rate of about 16 participants per month per practice. The target rate was exceeded by all practices. Second, central screening will be the primary method of enrolling age-eligible participants. The probability of being enrolled using central screening was 0.08 in the pilot, which included a 50% nonresponse rate. To increase the response rate, we will send out a second mailing to nonresponders. A few sites will use a clinic screening strategy that had a probability of enrollment of 0.16 in the pilot. Therefore, we conservatively estimate that about 10% of screened patients will be enrolled in the trial. Thus, to enroll 6000 participants, we initially estimated a pool of 60,000 age-eligible patients would be required.

Table 4. Sample size estimates.

Accrual Period (Years)	Annual Event Rate, Control Group	Total Sample Size
1	**0.14**	**5680**
	0.16	**5036**
	0.18	**4535**
1.5	**0.14**	**6190**
	0.16	**5474**
	0.18	**4920**
2	**0.14**	**6844**
	0.16	**6046**
	0.18	**5426**
	0.18	**5426**

9.4 Sample size and power for secondary outcomes

Power for all fall injuries and all falls (regardless of injury) was calculated using the same assumptions as above, but with a 1% Type I error to control for multiplicity and no adjustment for interim analysis. Annual rates of first fall and first fall injury from MOBILIZE Boston are 0.92 (95%CI: 0.75, 1.10) and 0.57 (95%CI: 0.46, 0.69), respectively. Using conservative rates of 0.70 and 0.40, and based on the targeted sample size of 6000, power is > 99% to detect a 20% reduction with intervention relative to control for both of these secondary outcomes. For the indicators of well-being, an unadjusted sample size of 524 participants is required to detect

a standardized effect size of 0.3 between intervention and control at 1 and 2 years with 80% power and 1% type I error. The sample size adjusted for missing outcomes due to death (10%/y) and lost to follow-up (5%/y with or without a serious fall injury), and for clustering (DE = 6% assuming ICC = 0.0076 with 80 practices each enrolling 9 participants) is 720 (360 per group), a 12% subsample of the 6000 participants.

9.5 Interim Monitoring

Interim monitoring will focus on patient accrual, baseline comparability of treatment groups, protocol adherence, loss to follow-up, data completeness and quality, accrual of fall events, safety, efficacy, and futility. A risk-based monitoring approach[15] will be taken focusing on centralized monitoring that will include: 1) monitoring data quality in real time (e.g. values out of range, missing data); 2) conducting statistical analyses to identify trends in the data; and 3) developing metrics for monitoring practice performance (e.g., practice report cards) based on the aggregated data, such as enrollment of ineligible patients, protocol violations, timeliness and quality of the data, losses and withdrawals. The inter-practice variation will be measured by the intracluster correlation coefficient (ICC) calculated for the primary outcome, serious fall injuries. Because the ICC has a direct impact on the power of the trial, it will be carefully monitored by the DCC and reported to the DSMB in closed session to ensure that power is adequate, recognizing that early estimates based on limited data may be unstable. A set of data monitoring tables will be developed as part of the Statistical Analysis Plan (SAP) that includes the above elements for presentation to a Data Safety Monitoring Board (DSMB) at approximately 6-month intervals. Per RFA, a "preliminary statistical analysis of the effects of the preventive strategy on the rate of serious fall injuries must be reported in March 2017." At this time, recruitment will have ended and about 55% of the expected number of primary events will have been accrued, sufficient for an interim look.[46] (The expected number of events is based on the ratio of average follow-up time at the interim look [1.25 y] relative to the average total follow-up time for the study [2.25 y, assuming recruitment begins on June 1, 2015].) Thus, we propose consideration of stopping the trial at this time only for compelling evidence of efficacy (~$p<0.008$) or a trend in the wrong direction (i.e., futility) taking into account trends in secondary outcomes. Future looks will be left to the purview of the DSMB based on emerging trends in the data; however, by March 2017, there will be less than one year left in the trial and it may be impractical to conduct another interim look before it ends in February 2018. Interim monitoring boundaries will be established using an alpha spending approach.[44,46]

The original proposal to the DSMB included an interim look in March 2017, but that date was considered unrealistic because of the trial's late start and the accrual of insufficient numbers of adjudicated events by that date. Accordingly, the sponsors and the DSMB left the exact timing and content of the interim monitoring to the discretion of the investigators. At its May 31, 2017 meeting, the trial's DSMB approved a revision to the interim monitoring plan specifying "that a formal interim analysis for efficacy or futility with the potential for early termination may not be necessary, and that a final decision about a formal interim analysis can be made sometime in 2018."

9.6 Statistical Analysis Plan

This section provides an overview of the analytic plan for the final analysis, which consists of **comparability of treatment groups, safety, and treatment efficacy.** Per protocol, the analytic plan will be refined based on the validity of the assumptions; such an adaptation will be done blinded to treatment, e.g., if the death rate is low, competing risks could be considered as a secondary, rather than a primary, analysis. The analysis of the primary and secondary outcomes will be according to the principle of intent-to-treat (i.e., practices/participants will be analyzed according to their original treatment assignment regardless of adherence to protocol). All analyses will account for the cluster design with the participant as the unit of analysis. SAS 9.4 and R 3.6.1 software will be used for all analyses. Comparability of treatment groups will be assessed by comparing the distribution of baseline characteristics in the two groups using appropriate graphical procedures, summary statistics and multivariate methods. The randomization is designed to produce balance on important covariates at the practice level (unit of randomization) but not necessarily at the patient level. Therefore, in a secondary analysis, the following pre-specified set of baseline covariates will be selected for adjustment to determine their influence on the treatment comparisons: age, sex, race/ethnicity, education, number of chronic conditions, and

number of positive screening items (out of three) for serious fall injuries.[47] Analysis of safety will involve tabulating the occurrence of serious adverse events (SAEs) between the two groups using methods appropriate for discrete and continuous measures. SAEs will be tabulated both on a per event and per patient basis. Survival rates will be monitored and calculated by the method of Kaplan-Meier.

Analysis of the primary outcome will be done using a survival model that incorporates competing risks (due to death) and clustering. [48,49] The model will be adjusted for the randomization of practices by healthcare system and include the covariates used for the constrained-covariate randomization (practice size, location and race/ethnicity). Participants lost to follow-up without a prior serious fall injury will be censored at their date last seen. In a sensitivity analysis, we will also adjust for the pre-specified set of baseline covariates to examine their influence on the treatment comparisons. Standard approaches (e.g., examination of Martingale residuals and the proportional hazards assumption) will be used to examine the fit of the models. The effect of intervention relative to control will be estimated as a hazard ratio with corresponding 95% confidence intervals. Also, in a supplementary analysis, we will obtain an estimate of the intervention effect at the practice level. The effect of intervention will be evaluated in the following five pre-specified subgroups of participants using appropriate tests of homogeneity (e.g., interaction): age (70-79, 80+), sex (male, female), fear of falling alone (yes, no), multimorbidity (0-1 chronic conditions, 2+ chronic conditions), and hip fracture or other fracture since age 50 (yes/no) adjustment for multiplicity will be done using the method of Hochberg.[50] The cumulative incidence of serious fall injuries will be estimated using non-parametric maximum likelihood methods (Aalen-Johansen estimator) [48] and will be used to estimate freedom from falling over the entire follow-up period. Also, in a supportive analysis, we will evaluate serious fall injuries as a recurrent outcome using a joint frailty model that accounts for clustering, competing risk and recurrent events. [51] An overall type-I error rate of 0.05 (2-sided) will be used as the level of statistical significance for the primary endpoint.

Analysis of the secondary and tertiary outcomes. All fall injuries and all falls (regardless of injury) will be analyzed both as time to first event and as recurrent events similar to the primary outcome. Indicators of well-being (fall efficacy, physical function, anxiety and depressive symptoms) will be analyzed using generalized linear mixed models assuming missing at random (MAR) with adjustment for baseline indicator of well-being and factors that are predictive of missingness. Sensitivity analyses will be conducted to investigate the MAR assumption, such as methods that model jointly the missingness and outcome distributions.52 To provide some control for multiplicity, we will test the secondary outcomes using a significance level of 1% (2-sided) and report 99% confidence limits. Hospitalizations will be analyzed using a Poisson regression model accounting for practice-level clustering with follow-up time as an offset. Time to first long-term nursing home admission will be analyzed using a multistate model accounting for clustering (as described for the primary outcome). Death will be analyzed using the marginal Cox model.49 No control for multiplicity will be done for analysis of tertiary outcomes.

10. DATA MANAGEMENT

Components required to screen and recruit participants, collect baseline assessments, and obtain outcome data are managed centrally by the Data Coordinating Center (DCC). Field operations, including interviewing and mailings, are carried out by Recruitment and Assessment Center (RAC) staff following workflows that are supported closely by DCC systems.

The main components of DCC support are:

- An Electronic Data Capture (EDC) system and database (REDCap) to support RAC field operations;
- A “portal” website to disseminate STRIDE information to the public, provide access to STRIDE resources, and to support intra-project communications;
- A website tool to support clinic screening;
- A website tool to support adjudications;
- A software application to support Falls Care Managers (FCMs);
- An administrative tracking application to support RAC office activities; and

- A data mart of de-identified data in SAS format, for use by DCC programmers for conduct-of-study monitoring and analyses.

These components are described below, in the context of the support they provide.

10.1 Field Operations Support

Almost all STRIDE data collection and data entry is based on REDCap, an NIH-supported electronic data capture (EDC) application that is used at more than 1000 institutions in 60 countries (http://project-redcap.org). The DCC hosts Yale's implementation of REDCap and has the expertise to employ thoroughly its many features, and to extend REDCap's capabilities as required to meet special study needs.

10.1.1 Screening

Central Screening will be the primary strategy for recruitment. To maintain flexibility, clinic-based screening will also be available on a limited basis. Under Central Screening, age-eligible patient contact data are imported from EHR data warehouses at each site and stored in a patient information database. Patients are randomly selected for screening from this database. The clinic screening protocols require clinic staff to administer the fall risk screen. The recruitment materials may either be handed directly to the patient or mailed by the RAC.

10.1.2 Baseline Interviews

The recruitment, consent and enrollment or “baseline” interviews will be managed using REDCap with extensions designed by DCC to better support the interviewers’ workflow. The Administrative Tracking application will identify newly enrolled participants and will provide tools to manage the post-enrollment mailings.

10.1.3 Outcome Surveillance

The Administrative Tracking application will identify participants nearing the end of their 4-month surveillance cycles so that they can be called for telephone interviews,.These data will then be made available to the outcomes adjudication team via a secure web-based tool designed by DCC.

10.2 Website Tools

10.2.1 STRIDE Portal (stridestudy.org)

An important website developed and maintained by DCC is stride-study.org, which serves two main functions. First, it includes a public section that is used for disseminating STRIDE information.

The second main function is to support STRIDE project activities. This section requires login authentication, and provides role-specific pages (Site Coordinator, FCM, etc.), blogs, study resources (including the screening and adjudication-support tools), discussion forums and other features.

10.2.2 Screening Support

DCC has developed a secure website tool for use by site coordinators to help them manage clinic screens and to monitor patient study status. Through this website, a site coordinator can identify patients for screening, enter screening data, and enter or update patient contact information. Specialized views are provided, such as lists of screen-positive patients and enrolled patients.

10.2.3 Adjudication Support

Another secure website tool will support adjudication activities. Features offered will include:

- Access to claims/encounter data acquired from site EHR data warehouses;
- A means to request medical records;
- A means to enter claims and encounter data if unavailable from EHR systems;
- Access to scanned medical record documents (a PDF browser); and
- An administrative module for assigning interviewers and tracking the status of each adjudication.

10.2.4 Intervention Support

An important component of the intervention is specialized software that supports the Fall Care Managers (FCMs). This software has two major components: an electronic data capture module that is designed and maintained by DCC, and a workflow support module that is designed and maintained by an external vendor (High5LA).

10.3 Administrative Tracking Application

The Administrative Tracking Application will track each patient's progress through the study, and provide lists and alerts for patients requiring action by the RAC. It will also provide support for RAC office procedures. These include initiating and tracking all mailings, preparing and emailing monthly site "report cards," managing gift card acquisition, distribution and replenishment, and other functions that are identified during the STRIDE field operations phase. Many of these functions are based on tools already developed by DCC for other national studies.

10.4 The Data Mart

To facilitate the production of conduct-of-study reports, error-check reports and interim analyses, a read-only SAS "data mart" is maintained and updated weekly. The data mart is a well-documented, read-only snapshot of administrative and research data, in a format readily accessible to data managers and statisticians. The data mart is the basis for all conduct-of-study reports, which will be generated by SAS programs and posted on the Study Website. Permanent copies of the data mart will be created for DSMB reports and interim analyses.

10.5 Data Security

All of the databases described in this section are maintained on very strongly firewalled servers managed jointly by Yale Information Technology Services (ITS) and DCC. These servers are not accessible outside the Yale internal network, and access to the databases are further restricted to a carefully controlled set of authorized DCC and RAC users. Servers are physically secured in environmentally-controlled server facilities to which access is limited to ITS and DCC systems staff. Implementation of the DCC and REDCap database and application server is monitored by the Yale Information Security Office, and are certified as following Yale and NIH HIPAA guidelines.

10.6 Protection from Data Loss and Downtime

Secure, encrypted daily backups of all databases and applications are maintained by the DCC. All servers are configured with RAID 10 drive arrays that will survive the simultaneous loss of two drives. To protect against downtime, the REDCap and STRIDE application and database servers will be duplicated in virtualized environments in two separate data centers, with documented failover procedures that will minimize downtime caused by a critical component failure in the primary system.

11. SAFETY AND ADVERSE EVENTS

11.1 Background

This section describes the requirements and processes for reporting adverse events (AE), serious AE (SAE) and unanticipated problems to the Central IRB, National Institute on Aging (NIA), and DSMB. It incorporates guidelines provided by the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) reporting requirements. NIH is obligated to ensure that researchers comply with their approved reporting procedures. Clinical trial investigators funded by NIA are obligated under federal regulations to appropriately inform the Institute of adverse events and unanticipated problems, and NIA is required to ensure that the appropriate procedures are in place to support this reporting.

11.2 Definitions

Adverse Event: Because 45 CFR 46 does not provide a specific definition for an adverse event (AE), the definition of an AE will conform to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The same definition is used by the U.S. Food and Drug Administration (FDA) except that "drug" is typically used instead of the term "intervention." An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational intervention, whether or not related to the intervention.

Serious Adverse Event (SAE): Any AE 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 the investigators judge to represent significant hazards.

Unanticipated Problem: 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 IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- related or possibly related to participation in the research; in this guidance document, 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;
- 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.

Adverse Event Reporting Period: The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

Preexisting Condition: A preexisting condition is one that is present at the time of providing the consent for the study. A preexisting condition is considered an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

11.3 Responsibilities

Both the NIA and the investigators it funds have responsibilities with respect to safety reporting.

NIA program staff members are responsible for providing:

- Assistance to extramural investigators in understanding and applying adverse event and serious adverse event guidelines and for ensuring compliance with OHRP guidance in all NIA-funded clinical research.
- Oversight of these guidelines, which includes periodic review and revision as relevant rules and regulations change.
- Assurance that the Data and Safety Monitoring Plan (DSMP) addresses reporting of adverse events, serious adverse events, and unanticipated problems.
- Verification that all corrective action plans have been adequately implemented.
- Assurance that the study has an independent safety monitoring body commensurate with study risk (Data and Safety Monitoring Board or Medical Safety Officer).
- Ongoing oversight of the safety reporting process to assure that potential safety issues are addressed.

Investigators conducting clinical research are responsible for:

- Assurance that their procedures are conducted in compliance with these guidelines.
- Submission of IRB-approved protocol to the NIA program office. A DSMP that is commensurate with the study risks and reflects these guidelines will also be submitted to the NIA program staff.
- DSMP describes the plans for adverse events, serious adverse events, and unanticipated problems commensurate with the nature and complexity of the study.
    - Recipients of Serious Adverse Event and Unanticipated Problem reports must include the IRBs, DSMB or Medical Safety Officer, and NIA.
    - Adherence to the DSMP with respect to timely submission of adverse events, serious adverse events, and unanticipated problems.

11.4 Level of Monitoring in this Study

General Description/Overview: 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. Indeed, the consent form does not include language for consent to an intervention, only for collecting data. Thus, the definitions of research and therefore AE, SAE, Unanticipated Problems and Pre-existing conditions do not apply to the intervention. However, this appraisal does not preclude the need to monitor the study and its impact on participant safety. There are no study visits; the only data collection methodologies are interviews, EMR review, and examination of claims data. Therefore, our safety monitoring procedures focus on data collection via the methodologies available 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) need 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.

5) The primary and secondary study outcomes will not require additional SAE reporting even though they are likely to meet the definition of an SAE.

11.5 Ascertainment of AE, Unanticipated Problems (UP), and SAE

11.5.1 Adverse events

As noted in 11.4, 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 in 11.5.3.

11.5.2 Unanticipated Problems (UP)

Investigator institutions must have written procedures for ensuring prompt reporting to the IRB and NIA, and others as appropriate, of any Unanticipated Problem involving risks to study participants or others (45 CFR 46.103(b)(5)). As shown in **Table 6**, if the site PI or study coordinator has an individual concern, they will be required to contact the Medical Safety Officer (MSO) within 48 hours of first knowledge of the event. An UP form must be completed by the investigator and faxed to the MSO within 48 hours. The investigator/ coordinator will keep a copy of this UP form on file at the study site. The MSO will confirm that the UP is an anticipated event and, if confirmed, report the UP to the DSMB and NIA within 48 hours of its notification. An UP will result in corrective plans and measures to prevent reoccurrence. An electronic record of such concerns and the action plan will be filed by the MSO with the DCC so that concerns can be tabulated and reported as outlined below.

Table 6. Methods to ascertain safety concerns and SAEs

- Site PI or FCM has specific concern → contact MSO directly;
- Hospitalizations:
  - Four-monthly telephone interview reported hospitalization –assessed as one of the following:
    - Intra-health system → confirmed by MSO via EHR data;
    - Extra-health system → not confirmed, but tallied for separate reporting;
    - EHR data – reported in aggregate;
- Deaths:
  - Four-monthly telephone interview - non-response will result in telephone call from the RAC to the designated contact person to assess status;
  - EHR data;
  - Death certificates (if needed for confirmation).

11.5.3 Ascertainment of SAEs and Deaths

Given the principles in **11.4**, our plan focuses on a limited set of SAEs for acquisition and monitoring with data derived from the interviews, EHR data downloads and claims data. Only hospitalizations and deaths will be collected, which will ensure the protection of participants from potential harm but remain feasible within the study design. The vast majority of SAE ascertainment will occur from telephone interviews every 4 months and/or in aggregate via biannual data downloads from the EHR and claims data as described below If the event occurred within the same health care system where the participant usually receives care, it also will be confirmed via EHR review by the MSO. The aggregate claims data will be collated separately (to avoid double

counting of events). Self-reported hospitalizations will be reviewed quarterly by the Medical Safety Officer (MSO), as described in the Safety Plan.

Participants who die within the participating health care systems will be verified by EHR review by the MSO from routine data transfers utilized for outcomes monitoring. However, participants, who die during the interval between their visits, at home or outside the participating health care systems, may be missed in this process. Therefore, when a participant is lost to follow-up we will ask their designated contact person whether s/he has died. If a death cannot be confirmed through the EHR, we will ask the relevant clinical site to obtain a death certificate. These procedures worked well in the recent multi-center NIA-sponsored LIFE Study. The National Death Index cannot be used routinely because of substantial delays in recording deaths, but will be considered as a back-up option. We will also consider querying the CMS Master Beneficiary Summary File if needed.

As outlined in the safety plan below, SAEs will be reported to the DSMB, cIRB and local IRBs in accordance with the NIH and local regulations, and in conformity with the Data and Safety Monitoring Plan developed by the DSMB and approved by NIA and PCORI.

11.6 Safety Personnel

Medical Safety Officer (MSO): The MSO will coordinate reporting of the safety data. The MSO will monitor and evaluate all collected UPs and SAEs from all sites efficiently and effectively by regular review/monitoring of reports of monitored SAEs or UP reported directly by site PIs/personnel. The MSO will have a critical role, ensuring that all participants receive the highest quality care and that safety concerns are foremost in the conduct of this trial. The MSO may suggest measures to the PIs to improve monitoring or prevent risk to participants. Upon approval by the DSMB, these modifications may be submitted as protocol modifications to the cIRB with communication to the local IRBs. The MSO will review reports of UPs and SAEs (in total, but not segregated by treatment assignment) and submit these to the DSMB, NIA, cIRB and the DCC for distribution to Reporting of Unanticipated Problems and Serious Adverse Events.

A summary report of the UP and SAE collected by all methods of ascertainment will be prepared by the MSO and DCC for submission to the DSMB, NIA and cIRB in accordance with the Safety Monitoring Plan.

12. ETHICAL AND REGULATORY CONSIDERATIONS

12.1 Good Clinical Practice Statement

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and all federal as well as local regulatory requirements.

12.2 Informed Consent

The principles of informed consent are described in ICH guidelines for GCP (ICH E6[R1]). The ICH used by the investigators at the trial sites will be reviewed and approved by the Trial's DSMB prior to submission to the site's IRB and Informed Consent.

As noted previously in the screening procedures outlined above, participants identified by age and screening eligibility will be contacted by phone if they do not otherwise opt out. 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 surveillance evaluations, along with the study specific evaluations. Importantly, written consent was not considered necessary to implement specific components of the 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. The cIRB agreed with this premise in the pilot phase of the study and is anticipated to do so for this phase. Further, given the cluster randomized design, extensive discussion of the intervention for a specific individual may bias substantially the sample from site to site. Of course, data

collection does require consent and thus will be the primary focus of the consenting process. Verbal consent should be adequate per the learned opinion of two IRB Chairs (at Yale and Wake Forest) and approval of the process by the cIRB (Brigham and Women's) in the pilot phase.

Decisional capacity and proxy consent: It is likely that potential participants with impaired decisional competency will be identified for this study by the Callahan 6-item screener as described previously. It is recognized that such participants need to be identified – not to exclude them from participation, but to identify those who require added processes to participate in an ethical manner. Therefore, at the time any potential participant is approached, professional judgment will be used to determine the need for alternate consent with assent by the participant. Study personnel responsible for recruitment and consent will be highly trained and experienced 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 the score on the Callahan 6-item screener, if they: 1) have an inability to express or communicate a preference/choice; 2) cannot understand the consequences of a potential situation – e.g. cannot understand the implications of releasing their personal health information (PHI); 3) are unable to provide a logical rationale for participation/non-participation; 4) have a legal guardian or have been identified legally as incompetent to make decisions for themselves. If there is any uncertainty, study personnel will be instructed to obtain proxy consent.

When proxy consent is deemed necessary, the proxy will be approached for consent. Potential participants deemed not to have decisional capacity will be informed that their proxy is going to be approached. If permission is granted by the proxy to enroll the participant, the potential participant will then be notified and asked to provide verbal assent, using the following items defined clearly to the potential participant:

- A simplified description of the purpose of the research study including risks/benefits;
- A description of the measures/outcomes to be collected and their method of collection;
- An explanation of the procedures involved and how long the study will last;
- An indication that the study is voluntary;
- A question/answer opportunity in which the potential participant will be encouraged to ask questions.

If verbal assent is granted, the participant will be enrolled.

12.3 Institutional Review Board

A central IRB (cIRB; Brigham and Women's) will be responsible for review and approval of the protocol, any amendments, the informed consent form (ICF) and any other materials provided to participants. Delegation agreements to the cIRB have been signed for all clinical study sites; however, at each trial site, an appropriately constituted IRB as described in ICH guidelines for GCP will also be responsible for needed review and approval of the study protocol, ICF and any other materials provided to the participants within the terms of the delegation agreement. The site IRB will also review any amendment to the study protocol or ICF

unless the change is necessary to remove an immediate danger to the participant, in which case the IRB will be informed as soon as possible.

The cIRB and site IRBs also will be informed of any event likely to affect the safety of the participant or the continued conduct of the trial. Records of IRB review and approval of study protocol, ICF, and amendments will be kept by the site PI.

12.4 Protocol Amendments

Any change in the study protocol must be approved by the DSMB, NIA, and the Project's Steering Committee and approved by the cIRB and trial sites' IRBs before it can be implemented.

12.5 Risks to Human Subjects

The risks associated with participation in the study intervention itself are deemed to be minimal because: 1) the intervention is aimed at maximizing participation in components of current standard of care; and 2) the intervention is being implemented by trained professionals in the care setting in which they typically provide care. Our assessment of minimal risk does not, however, preclude the possibility that adverse events, and serious adverse events could occur. Therefore, a comprehensive data safety monitoring plan is outlined in the following sections. Authority for monitoring the safety of the protocol will reside in an independent DSMB responsible for holding the PIs accountable for data quality and completeness, and assessing the ongoing safety of the trial participants through periodic meetings/review. Ongoing participant safety monitoring is the responsibility of site PIs who will report adverse events to a Medical Safety Monitor appointed by the PIs. The Medical Safety Monitor has the authority to directly report concerns to the DSMB if they arise.

There are potential risks associated with data collection and information management and, in fact, these risks are the major reason consent will be required in this trial. These include inadvertent disclosure of personal health information or research data collected. Every effort will be made to inform the participant of this potential and minimize the risks as outlined below.

12.5.1 Protection Against Risks

Minimizing Risks: The study protocol will be implemented at each clinic only after the PI, Falls Care Manager (FCM), and study coordinator have undergone rigorous protocol training. The training and monitoring of performance in accordance with the Manual of Procedures for the study will be the responsibility of the study PIs (Drs. Bhasin, Gill and Reuben). All efforts will be made to minimize risks and participant inconvenience, and mitigate interruptions of therapy. Risks will be minimized by: 1) adequate training of all staff with proficiency testing; 2) ensuring participants are verbally informed of the details of the interventions as they are delivered; 3) frequently encouraging participant questions throughout the interventions; and 4) Serious Adverse Event (SAE) Reporting and monitoring overall study safety by a DSMB as outlined below.

12.5.2 Potential Benefits of the Proposed Research to Human Participants and Others

There are a number of potential benefits of the study for the participants including: 1) close monitoring of the participant during the trial; 2) identification of fall risk factors during the customized risk assessment; and 3) medication reconciliation by trained professionals with experience in the care of seniors.

The potential societal benefits from this protocol are also substantial. Optimizing models of care for reducing the risk of serious fall injuries has the potential to greatly enhance patient care – including the potential to

reduce both morbidity and mortality, as well as reduce costs. Further, quality of life benefits may be derived from reducing injurious fall risk, particularly as one's confidence in balance and mobility is increased.

12.5.3 Importance of the Knowledge to be Gained

The knowledge to be gained from this trial is substantial. Injuries that result from falls pose a substantial public health burden, especially among older persons with risk factors for falling. Serious injuries, including hematomas, broken bones and lacerations may be important factors that contribute to older persons' loss of independence. This research proposal aims to mitigate this public health burden by rigorously evaluating whether the multifactorial intervention reduce the risk of serious fall injuries. Our major goal is to address the obstacles of effectively reducing falls risk including: 1) establishing an effective method for control over implementation of preventive interventions; 2) enhancing provider knowledge/expertise/adherence to guidelines; 3) overcoming geographic, racial, ethnic, and cultural barriers; 4) enhancing patient adoption of self-management risk modification; and 5) organizational structure and support needed to implement and coordinate multifactorial strategies. The sustainability and effectiveness of scalable, multifactorial strategies have not been assessed previously, but are goals of this clinical trial.

12.6 Safety Monitoring Protocol

Safety monitoring will be accomplished in accordance with Safety Monitoring Manual of Procedures (MOP) to be approved by the DSMB and NIA. NIA will endorse all members of the DSMB, and the DSMB will determine reporting procedures and meeting frequency outlined in the Safety Monitoring MOP.

12.7 Inclusion of Women and Minorities

As shown in **Table 7**, women are expected to constitute nearly 60% of the overall sample, consistent with the higher prevalence of falls among older women than among older men, and the higher life expectancy of women than men. Also, women are more likely to participate in clinical trials than men. **Table 7** also summarizes the racial and ethnic background of the potential participants at each of the ten trial sites. In aggregate, based on the 2012 census data from the trial sites, 12.3% of potential participants >75 years of age at the trial sites are expected to be African-Americans, 11.0% Hispanics, and 4.3% Asian-Americans. These proportions are higher for each of these racial/ ethnic groups than those in the general US population.

Table 7. Projected enrollment by sex, race and ethnicity

Site	Male	Female	Hispanic	Black	American Indian	Asian	Native Hawaiian/ Pacific Islanders	White
Essentia	252	348	3	3	6	3	0	588
Health Care Partners	300	300	360	180	4	122	24	270
Hopkins	240	360	12	150	1	18	0	431
Iowa	218	327	16	16	5	5	0	518
Mount Sinai	200	400	149	75	9	39	0	477
Partners	245	355	36	60	1	24	0	515
Pittsburgh	222	378	12	71	0	11	0	518
Reliant	245	355	41	17	1	16	0	566
UTMB	240	360	6	41	2	35	2	520
Michigan	226	374	66	126	2	6	0	466
Total	2410	3590	703	741	32	280	26	4921
Percent	40.2	59.8	11.7	12.3	0.5	4.7	0.4	82.1

Site-specific cell counts represent projected sex, race and ethnicity totals assuming 600 randomized patients at each of the ten trial sites, for a total of the original target of 6000 participants enrolled.

Some of the rural health care systems have a lower proportion of minorities than the US population by virtue of their location and demography. In contrast, other participating health care systems centers in urban areas, such as Johns Hopkins Health Care System in Baltimore, MD, and Health Care Partners in Los Angeles, CA have a substantially higher proportion of African-Americans and Hispanics in their patient population. Thus, 60% of patients at Health Care Partners describe themselves as Hispanic, 24% of patients at the Mount Sinai Health Care System in New York, NY describe themselves as Hispanic, while 25% of patients attending the Johns Hopkins Health Care System describe themselves as African-American.

We will utilize the help of our patient advisors and stakeholders to effectively recruit older men, and men and women in the minority communities.

13. STUDY DOCUMENTS

13.1 Retention of Records

The site PI will retain all study-related documents for at least seven years following the completion or discontinuation of the study. If the site PI's personal situation is such that such archiving can no longer be ensured, the PI will inform the Central Project Management and the relevant records will be transferred to a central secure location for storage.

14. PUBLICATION AND DISSEMINATION POLICY

The project PIs in discussion with the Steering Committee will establish a Publication and Dissemination Committee, which will set the rules for publication of the data and authorship in conformity with PCORI and NIH policies. In accordance with PCORI's legislative mandate on public dissemination, we will collaborate with NIH and PCORI in order to make the study's findings available to clinicians, patients, and the general public not later than 90 days after the completion of the study.

14.1 Dissemination

The findings of this trial have important implications for public health and policy, requiring wide dissemination; additionally, several aspects of this trial's approach and implementation will shape clinical practice and form the basis for dissemination after the trial. First, the screening methods will be built to interface with major EHR vendor software and will be readily transferable to any site using similar software. Second, instruments used for risk assessment and intervention management by the FCM can be used in any primary care practice. Third, patient materials will be adapted and used in the program and will be exportable after the trial. Fourth, training materials and procedures will be available for propagating "train the trainer" programs.

A Publication and Dissemination Committee (PDC) will be established to oversee the dissemination of the study's findings. The PDC will include members of the National Patients and Stakeholders Council (NPSC) and investigators with content expertise. This structure will allow the stakeholders and investigators to jointly address how to disseminate study findings to impact clinicians, patients, policy makers, communities, CMS and other third party payers. Also, local councils will work with investigators from the trial site to plan dissemination and implementation in local communities.

Dissemination of study results will be accomplished through traditional routes (e.g. scientific meeting presentations, publications), but also through novel routes felt to be most effective by our patients and other stakeholder partners using the PCORI Dissemination and Implementation Action Plan begun through a recent roundtable.

In the PCORI roundtable, the Agency for Healthcare Research & Quality (AHRQ) efforts in dissemination and implementation (D&I) were highlighted, with particular reference to AHRQ's work with the Patient-Centered Outcomes Research Trust Fund (PCORTF) and its legislative role in assisting PCORI with D&I of research findings in this space. The framework for the PCORTF investments by AHRQ include prioritization and topic

development, message development and strategy selection, audience identification, training and career development, and infrastructure. Further, AHRQ has products and tools for D&I activities that could be utilized to disseminate widely the successful tools developed during this project. These tools include consumer and clinician summaries, decision aids, and publicly focused instruments such as public service announcements that can be leveraged to engage patients, consumers, and caregivers in shared decision making. Producing these materials is well beyond the budget of this project. However, since D&I is a key activity for PCORI after sponsored research is completed, we will enlist our PCORI partners to access and optimize use of these resources for dissemination.

A particularly valuable asset for dissemination of this project is the Pepper Older Americans Independence Centers, which form a network of fourteen key academic institutions and thought leaders who are likely to be early adopters of this program if proven effective. Two other major resources for dissemination will be the recently formed PCORI Patient Powered Research Network (PPRN) and the Clinical Data Research Network (CDRN). Because this is a multifactorial fall-related injury prevention intervention, it will be important to determine the readiness of specific research findings for D&I through these networks. As best as can be gleaned from *a priori*-defined outcomes, D&I efforts should focus on communicating what works, and what does not work, particularly tailoring the message to key relevant stakeholder groups. The proper balance between benefits vs. potential risks must be struck and clear guidance provided to stakeholders.

15. ORGANIZATIONAL FRAMEWORK OF AN INTERDISCIPLINARY TEAM OF INVESTIGATORS, PATIENTS, AND STAKEHOLDERS

This program will be a cooperative agreement with substantial NIH and PCORI programmatic involvement anticipated throughout the project.

The project is led by three joint PIs – Bhasin, Gill and Reuben. The PIs have the primary responsibility for all aspects of the study, but will accept close coordination, cooperation, and participation of NIA and PCORI staff. The Steering Committee is the primary high-level decision-making body for the study with overall responsibility for the final approval of the study protocol, monitoring the study's progress, approving revisions to the protocol, and deciding whether to advance the study from protocol development and refinement to the implementation phase. Members of the steering committee include the three PIs, the Director of the Data Coordinating Center, a representative of PCORI, NIA scientific officer, two clinical trial site PIs, a nurse scientist, the Safety Officer, three content experts, and an IT and Data Management expert. Additionally, the NIA Program Officer, the Study Director, the Study's Communications Director, the Study Manager, a PCORI Officer, and a patient representative will serve as nonvoting members.

The Operations Committee is responsible for overall operational management and coordination of the entire project, synthesizing information from various committees, preparing and executing operational plans, identifying problems and disseminating information throughout the operation. The Operations Committee includes the three Joint PIs, Director of the OAIC Coordinating Center, and the Study Director.

15.1 Committees

Table 8 displays the functions of the current committees. The committees include scientific chairs, other highly regarded experts in the area of falls prevention, and patient and stakeholder representatives. The Committees conduct their business through regularly scheduled conference calls; their approved minutes are posted in the STRIDE Study Box.

15.2 Reporting Structure

As shown in **Figure 2**, the various committees, DCC, and IT Management Group report to the Operations Committee, which in turn reports to the Steering Committee, which is the highest decision making body. The leadership of NIA and PCORI interfaces with the Stride Study leadership through the Steering Committee or directly with the PIs through the Operations Committee.

Table 8. Functions of the Committees

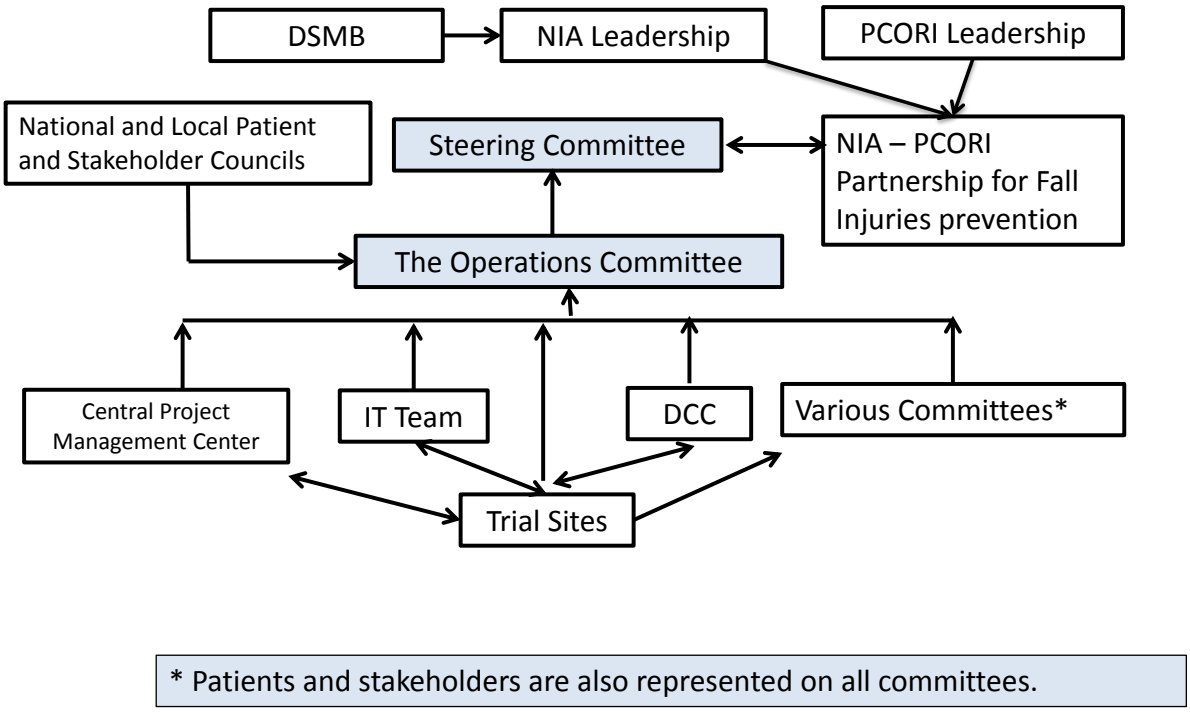
Committee	Committee Function
Steering	The primary high-level decision-making body for the study with overall responsibility for the final approval of the study protocol, monitoring the study's progress, approving revisions to the protocol, and deciding whether to advance the study from protocol development and refinement to the implementation phase.
Operations	Consists of the three Joint PIs, OAIC Coordinating Center Director, and the Study Director. Responsible for overall operational management and coordination of the entire project, synthesizing information from various committees, preparing and executing operational plans, identifying problems and disseminating information throughout the study.
Clinical Trial Sites	Provides venue for bidirectional flow of information between site PIs and the study's leadership. Provides high-level guidance for the trial's implementation at the trial sites. Includes all site PIs.
Screening and Recruitment	Responsible for high-level guidance on screening and recruitment activities.
Intervention	Responsible for developing the protocols for the intervention, FCM evaluation and training, and overseeing the implementation of the intervention at the trial sites.
Physical Components/ Rehabilitation Subcommittee	Responsible for developing the protocols for physical intervention, training of the rehabilitation and exercise staff at sites, and evaluation of CBE programs.
Self-management Subcommittee	Responsible for developing programs to train FCMs and study staff to encourage patient self-management.
Training Subcommittee	Responsible for developing training plans and programs for the FCMs and physical intervention/ rehab staff at the sites.
National Patient Stakeholders Council	Responsible for developing protocols for patient and stakeholder engagement, overseeing the formation and training of local patient and stakeholder councils, providing input into protocol development and all aspects of trial's implementation.
Biostatistics	Responsible for sample size estimation, power calculation, practice randomization, and data analyses.
Data Management and IT Platform	Responsible for building the IT infrastructure for data collection and management, staff training in data recording, building appropriate interfaces with the EHRs at sites to allow data collection, creating data forms, ensuring data security, and overseeing FCM software development.
Assessments and Study Outcomes	To develop the procedures for the baseline assessment, ascertainment of study outcomes and a plan for collection and analyses of outcomes data
Protocol	Develop the study protocol for the pilot and main study.
Ancillary Studies	To review the ancillary studies proposals and make recommendations to the Steering Committee and NIA on the approval of ancillary studies to the trial.
Publication	To review publications and major presentations from the study.

15.3 Meeting Schedule and Functions of the Leadership

The Operations Committee [three PIs, Study Director, and PI of the OAIC Coordinating Center] hold a conference call weekly to review progress, establish work objectives, and discuss operational problems. The Steering Committee meets by conference call every two weeks to ensure integration and oversight. In addition, we held two investigator's meetings in year 01, and a third meeting is planned in late May. We plan to hold an investigators' meeting once yearly in subsequent years.

When necessary, individuals from the broader group of Co-Investigators and/or co-chairs of various committees will join the Steering Committee with regard to specific agenda items.

Figure 2. The Organizational Structure of the STRIDE Study Team



15.4 Additional Committees

As implementation progresses, the PIs and Steering Committee will consider forming additional committees to include Publications and Dissemination, as well as several operational committees. These committees will be co-chaired jointly by senior investigators with content expertise. All committees will include patient/stakeholder representation.

15.5 Integration of Patient and Stakeholders in the Trial's Planning, Implementation, Analyses and Dissemination

In accordance with the model set forth by Curtis et al (**Figure 3**),[53] patient engagement will occur at two levels – locally, at the clinical trial sites, and nationally, at the central project management level. To provide integration between the local and national patient and stakeholder councils, the local councils at the 10 trial sites have chosen representatives to serve on the National Patient and Stakeholder Council (NPSC). The NPSC is comprised of 10 to 12 members, half of whom are patients. The NPSC is representative in terms of the type of stakeholder, sex, race, ethnicity, and geographic region. Each Local Council is engaging with

investigators at its respective trial site and reports to the NPSC. The NPSC engages with all committees, PIs and Co-Is.

As described below, we have planned for a systematic and robust process of patient and stakeholder engagement throughout all phases of the study.

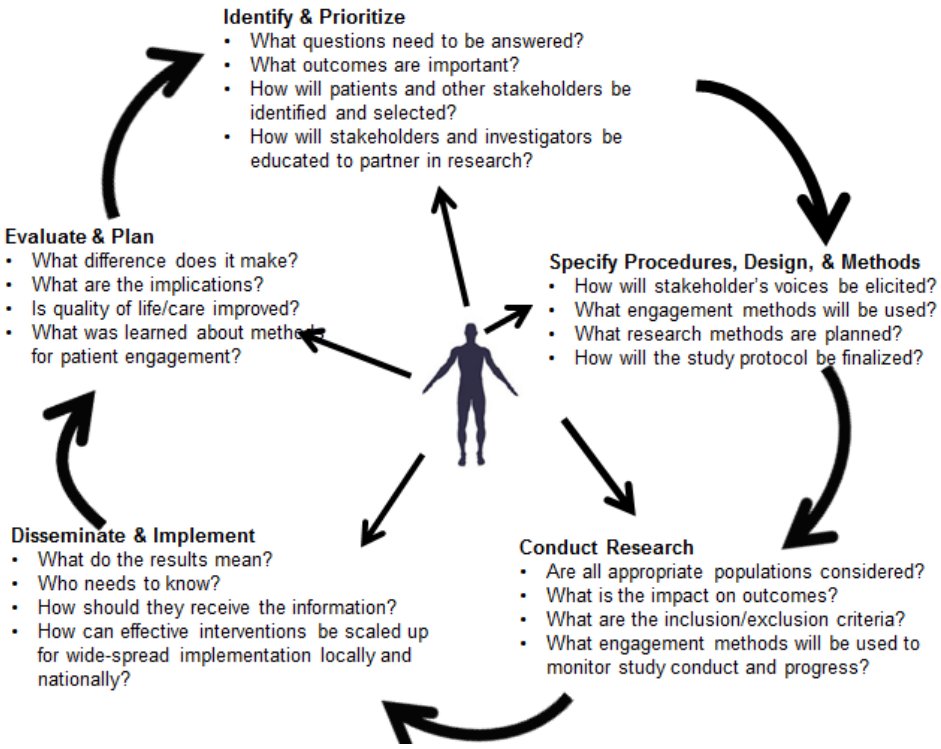


Figure 3. The Conceptual Framework for Patient and Stakeholder Engagement (Based on model developed by Curtis et al.)

The Year 1 Pilot Period focused on 1) development of local patient and stakeholder councils; 2) development of national patient and stakeholder council (NPSC; 3) training of investigators and stakeholders to work in partnership; 4) refining methods for eliciting patients' and stakeholders' voices, and 5) setting up structures to assure patients and stakeholders engagement with investigators to: (a) formulate the final research questions; (b) finalize study design with attention to screening and recruitment of participants, the planned intervention, the comparators, and the outcomes; (c) monitor study's progress and interim results; and (d) help disseminate the results of the study.

15.5.1 Local Patient and Stakeholder Councils

The criteria for selection of local patients and stakeholders are described in **Table 9**.

Table 9. Composition of the Local Patient and Stakeholder Councils (LPSCs). At least half the members of each local council are patients. Not all stakeholders will be represented on every local council but there is broad representation from each of these stakeholder groups across the ten local councils.

Term	Number	Definition
Patients	2 to 3	Have a history of a fall or fall related injury or are at risk for a fall or fall related injury, are from the local community served by the clinical study site, and have no specialized training or experience in health advocacy or health research.
Caregiver	1	Have provided care as a nonhealth professional to a friend or family member who is at risk for falling or has experienced a fall or fall related injury.
Public/Community	1 to 2	Representatives from the local geographic communities that the health systems of the clinical sites serve, e.g. YMCA.
Engagement professional – health	1	Representative from local patient and family centered care programs from the clinical sites.
Clinician	1	Those providing care at the sites in which the study will be done (clinical sites). (e.g. NPs, physicians, PT).
Government	1	Representative of local or state health department.
Advocate/consumer group	1	Local area agency on aging.

The chair of the NPSC and 2 patient advisors from the NPSC worked with trial site PIs to identify potential participants, assure representativeness (e.g. race, sex, ethnicity), and prepare invitations, which included processing group expectations, the importance of their authentic participation, and resources available to enable their participation (e.g. payment; e-mail access). Each Local Patient and Stakeholder Council (LPSC) designed their group to include 8 to10 members and a facilitator with experience in engaging patients and stakeholders in research. The Local Patient and Stakeholder Councils are being co-chaired by the facilitator and a patient stakeholder. Members of the NPSC travelled to all the trial sites to train the council members.

15.5.2 National Patient and Stakeholder Council

The NPSC is comprised of 10 to 12 persons, at least half of whom are patients (**Table 10**). The members of each local council recommended individuals for inclusion in the NPSC, giving attention to diversity of stakeholder type, sex, race/ ethnicity, and geographic location. The NPSC: 1) serves in a consultative capacity to local councils and site PIs, various work group committees and study leadership; 2) integrates the input from the 10 local councils and communicates that to the trial's PIs and committees; and; 3) coordinated activities initially for a) formulating the final research questions; b) finalizing study design; c) monitoring study progress, and suggesting changes and editing of all participant-facing print materials and d) recommendations for disseminating the results.

Table 10. Composition of the National Patient and Stakeholder Council (NPSC). The NPSC include 10 to 12 members, at least half of whom will be patients.

Term	Number	Description
Patients	5 to 6	Are from a local stakeholder group, have a history of a fall or fall related injury or are at risk for a fall or fall related injury, and have no specialized training or experience in health advocacy or health research.
Caregiver	1 to 2	Are from a local stakeholder group and have provided care as a nonhealth professional to a friend or family member who is at risk for falling or has experienced a fall or fall related injury.
Public/Community	1 to 2	Representatives from a Pepper Center Community group or CTSA Community Engagement group from the participating clinical sites.
Engagement professional – health	1	Representatives from a patient and family centered care programs – may or may not be on a local stakeholder group.
Clinician	1 to 2	Individuals who provide health care or related services to older adults on a regular basis (over 80% in clinical care).
Government	2	Representative from NIA/ PCORI.
Advocate/consumer group	1	National Area Agency on Aging.

15.5.3 Training patients, stakeholders, and investigators

During Year 1, investigators, patients and stakeholders underwent training, focusing on communicating what it means to be partners in patient-centered research. The training emphasized an authentic communication paradigm that builds and maintains trust, respect, and mutual understanding. An interactive *Partners in Research* (PIR) program was used that is part of the University of Michigan CTSA (MICHR) and has been delivered to over sixty communities including patients, stakeholders and investigators. During this training, the patients and stakeholders from the local council and the investigators from the trial site met to develop common understandings of research from the perspective of others and discussed methods for developing effective partnerships in addressing research issues related to injurious fall prevention. These discussions were led jointly by the NPSC chair and NPSC patient advisors.

15.5.4 Engaging patients and other stakeholders as partners in all phases of the research:

The bidirectional process of engaging patients and other stakeholders will take place in local councils and the NPSC throughout the duration of the project. Initially, the local councils are meeting monthly, until the LPSC's have established a high functioning participatory group. The NPSC will continue to meet twice a month throughout the duration of the study.

After the planning year, the local councils will focus on refining their trial sites' local resources that support screening and recruitment strategies, the intervention(s), assessment and outcomes, and strategies for disseminating the trial's findings. These local councils will provide recommendations to the NPSC and to site PIs and continually support the local Falls Care Manager(s). The NPSC will collate the information from all local councils and provide guidance to the PIs and various committees [See **Figure 4**].

15.5.5 Eliciting patients' and stakeholders' voices through focus groups

To gain the patients' and stakeholders' perspectives on specific issues, the NPSC will continue to work with local councils to organize focus groups at each trial site. The local focus groups will be led by the facilitator and co-chair of the local council. Each of the local stakeholders will be asked to invite one or two individuals who have roles similar to theirs (e.g. patient, caregiver, clinician) to participate in a focus group. The focus groups will be planned for 10 participants. With the permission of the participants, focus groups will be tape-recorded and analyzed using standard qualitative methods.[54] If focus group participants are averse to tape-recording conversations, a scribe will prepare a summary of the discussion. Topics for discussion will include overall study progress, review of interim analyses, and dissemination of the trial's findings. Focus group summaries will be provided to NPSCs, which will collate the findings from the 10 sites and communicate them to Joint-PIs and committee chairs.

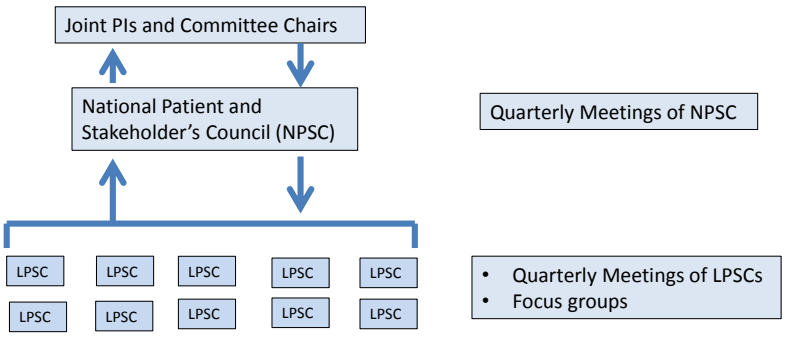


Figure 4. The organizational framework of the 10 Local Patient and Stakeholder Councils (LPSCs) at the trial sites and the National Patient and Stakeholder Council (NPSC). The LPSCs and NPSC will meet quarterly throughout the trial. The NPSC will collate the reports from the LPSC meetings and focus groups and communicate them to the Joint PIs and the Committee Chairs. Focus groups will address specific design issues, as described in the text.

15.5.6 Monitoring the study's progress

The local councils and site investigators will meet quarterly to review study progress and address, collectively, any potential issues in implementation. These meetings will be led by the local facilitator. Summations of these meetings will be forwarded to the site PIs and the NPSC. The NPSC will review and collate the recommendations of the 10 local councils and communicate these to the Joint PIs and committee chairs to inform protocol revisions, which will be presented to the Steering Committee and DSMB for approval.

15.5.7 Dissemination and implementation of study findings

A Publication and Dissemination Committee (PDC) will be established to oversee the dissemination of the study findings. The PDC will include members of the NPSC and investigators with content expertise. This structure will allow the stakeholders and investigators to jointly address 1) how to disseminate the study findings to impact clinicians, patients, policy makers, communities, CMS and other payers; and 2) how study interventions can be scaled up for wider implementation. Also, local councils will work with site investigators to plan dissemination in their local communities. The patients and stakeholders can be effective particularly in influencing the policies of CMS and other payers, which can facilitate the adoption of the intervention. In addition to publications in scientific journals, the PDC will plan presentations at scientific meetings, and orchestrate presentations to stakeholders, the media, payers, and policymakers.

15.5.8 Ongoing Evaluation and Feedback

This study provides an outstanding opportunity for formative and summative evaluation of patient and other stakeholder engagement in research. Formative evaluation will be performed by all stakeholders annually. We

will use the *Partnership Trust Tool Survey*, developed by the CDC (www.cdc.gov/prc), to elicit stakeholders' perceptions about 12 components of partnerships in research such as communication, willingness to listen to the ideas of others, relationship building, sharing of power and decision-making, truthfulness, and valuing of differences. These surveys will elicit information such as 1) what were the barriers to your engagement in this research; 2) what made the intervention helpful; 3) were there challenges in implementing the intervention in some groups of participants, such as ethnic groups and those living in rural areas; 4) what would you recommend to other investigators who plan to engage patients and stakeholders; 5) what would you recommend for large-scale use of the intervention(s) in your community; and 6) what are the lessons learned by engaging in this research.

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