Standardized Patient-Centered Medication Review in Home Hospice

This title should include, where possible, information on the participants, condition being evaluated, and intervention(s) studied.

Unique Protocol Identification Number:

National Clinical Trial (NCT) Identified Number: NCT03972163

Principal Investigator: Jennifer Tjia

Sponsor:

"Sponsor" indicates an institution, foundation, or individual who takes responsibility for and initiates a clinical investigation; often times this is the university with which the Principal Investigator is affiliated.

Grant Title: PILOT STUDY OF STANDARDIZED PATIENT-CENTERED MEDICATION REVIEW (SPECTORX) IN HOME HOSPICE

Grant Number: R21 AG060017

Funded by: NIA

Version Number: v.1.004

30 January 2020

All versions should have a version number and a date. Use an international date format (e.g.,YYYY-MM-DD [2017-12-21] or write out the month (e.g., 21 December 2017).
For the initial submission of a protocol to the IRB, indicate "Not applicable; this is the first version of the protocol." in the table below. For any subsequent amendment being submitted to the IRB, add details of the specific changes that are being implemented in the amendment. Please note that Section 10.4 is a high-level summary of <u>all</u> formal protocol versions/amendments.

Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
8.4 - Unanticipated problems	Included language to address possible situation that participants may use telephone surveys to ask clinical questions	To ensure participant safety, this change establishes a procedure to escalate clinical questions to the clinical hospice team in a timely and systematic manner

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STATEMENT OF COMPLIANCE

Provide a statement that the trial will be conducted in compliance with the protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP) and applicable state, local and federal regulatory requirements. Each engaged institution must have a current Federal-Wide Assurance (FWA) issued by the Office for Human Research Protections (OHRP) and must provide this protocol and the associated informed consent documents and recruitment materials for review and approval by an appropriate Institutional Review Board (IRB) or Ethics Committee (EC) registered with OHRP. Any amendments to the protocol or consent materials must also be approved before implementation. Select one of the two statements below. If the study is an ***intramural*** *NIH study, use the second statement below:*

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

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

    National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.
    OR
2. The trial will be conducted in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the [specify NIH Institute or Center (IC) [Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), and the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, if applicable, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.
    For either option above, the following paragraph would be included:
    The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

Principal Investigator or Clinical Site Investigator:

Signed: Date:
Name*: Jennifer Tjia
Title*: Principal Investigator

Investigator Contact Information:

Affiliation*: UMass Medical School
Address: 368 Plantation Street, Worcester, MA 01605
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For multi-site studies, the protocol should be signed by the clinical site investigator who is responsible for the day to day study implementation at his/her specific clinical site:

Signed: Date:
Name: Jennifer Tjia
Title: Principal Investigator
Affiliation: UMass Medical School

Signed: Date:
Name: Margaret Clayton
Title: Co-Investigator
Affiliation: University of Utah

Signed: Date:
Name: Susan DeSanto-Madeya
Title: Co-Investigator
Affiliation: Boston College

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: **Standardized Patient-Centered Medication Review in Home Hospice**

Grant Number: R21 AG060017

Study Description:

Background

Over 1.3 million Americans aged 65 years and older receive hospice services annually and 45% are cared for at home.[5] These patients are prescribed an average of 10-12 medications daily[6 7 8]and have progressively declining organ function that increases their risk of drug-related harm[9 10]. Furthermore, many take questionably beneficial medications[11 12 13]until death while simultaneously being prescribed an increasing number of end-of-life (EOL) symptom management drugs. This changing combination of medications contributes to stress and confusion for family caregivers (FCG) who are responsible their management and administration.[14 3]

Study Design

This protocol describes a pilot multi-site cluster randomized trial of a behavioral education intervention to standardize hospice clinician approach to medication management support for family caregivers of patients in home hospice vs attention control of an educational handout about medication management for older adults education from the NIA. The primary outcome if feasibility and acceptability of the trial as measured by trial enrollment and completion. Secondary outcomes include family caregiver medication administration burden, family caregiver satisfaction with care, polypharmacy, medication regimen complexity, patient quality of life, patient symptom burden, adverse events including hospitalizations and emergency department and adverse drug withdrawal events.

Objectives*:

Primary Objective:	To determine, among patients admitted to home hospice with life-limiting illness, the acceptability and feasibility of enrollment and completion of a trial of a medication support program delivered by home hospice clinical staff.

Secondary Objective:

Secondary analysis will investigate the following outcomes:

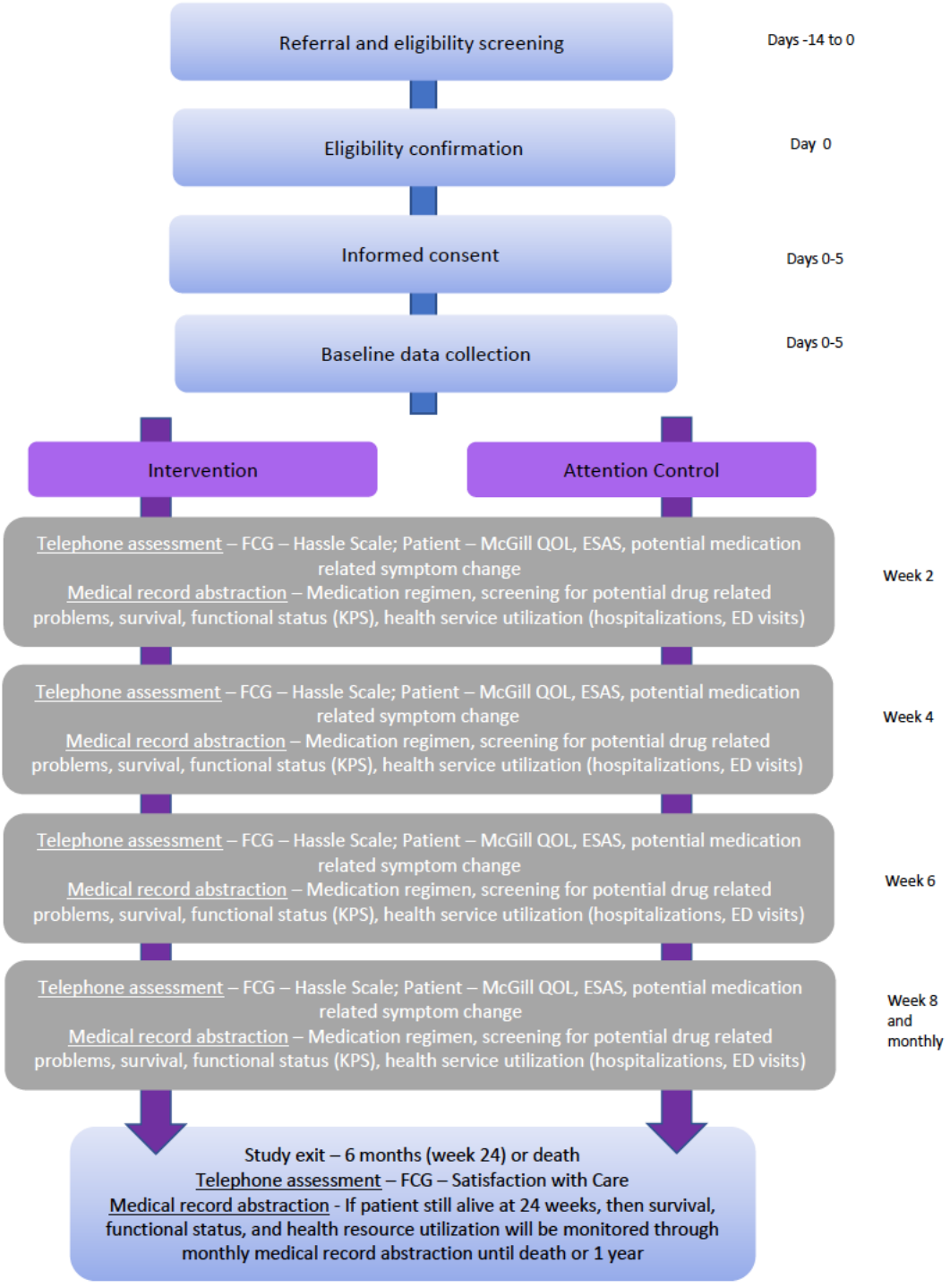
- Family caregiver medication burden, as measured by the Family Caregiver Medication Administration Hassle Scale.
- Family caregiver satisfaction with care, as determined by likelihood to recommend
- Polypharmacy
- Potentially inappropriate medication use, as determined by a modified Medication Appropriateness Index
- Medication regimen complexity, as measured by the Medication Regimen Complexity Scale
- Medication changes
- Adverse drug withdrawal events, as measured by a single item single item measure of change in medication since last visit and associated symptom change
- Patient Quality of life (QOL), as measured by the McGill QOL Questionnaire (MQOLQ)
- Patient Symptoms, as measured by the Edmonton Symptom Assessment System (ESAS)
- Performance status, as measured by the Karnofsky Performance Status sale (KPS)
- Unanticipated Events (whether study-related or not), as measured by time to first important event, consisting of:
    - admission to a hospital for any reason
    - admission to an emergency department for any reason

- Overall survival, as measured by time-to-death

Endpoints*:	Primary Endpoint:	Trial completion
	Secondary Endpoints:	As described in Secondary Objectives
Study Population:	Eligible participants are adults aged 65 years and older with advanced life-limiting illness with an estimated prognosis of 1-6 months who are prescribed 5 or more medications and their family caregivers.	
Phase* or Stage:	Feasibility Trial	
Description of Sites/Facilities Enrolling Participants:	**Hospice Sites.** EOL practices vary regionally.[13 15]Thus, we are partnering with two large, geographically distinct home hospice agencies to begin exploring the generalizability of SPECTORx nationally. Each agency has multiple offices serving different	

	local regions within their states. Care Dimensions (Massachusetts) has 2 offices serving 4 counties in Eastern MA, and CNS Home Health & Hospice (Utah) has 10 offices throughout Utah.
Description of Study Intervention/Experimental Manipulation:	The study intervention is a patient-centered medication review and FCG support program called "Standardized PatiEnt-CenTered medicatiOn Review (SPECTO*Rx*) in Home Hospice". This intervention combines 3 innovative, complementary, educational programs that, together, train hospice staff to create a comprehensive, patient-centered, medication management plan. These evidence-based tools equip hospice staff: 1. to systematically identify medications that can be stopped or tapered using STOPPFrail (Screening Tool of Older Persons Prescriptions) criteria; 2. to discontinue medications appropriately; and 3. to educate and support FCGs with medication administration and management challenges. The SPECTORx program also creates an online learning community for hospice clinicians to promote ongoing education and practice change.
Study Duration*:	Estimated study duration from earliest enrollment to completion of data collection is 12 months.
Participant Duration:	Estimated time it will take for each individual participant to complete all study-related tasks (i.e. time from enrollment to patient death, discharge from hospice, or end of study) is 6 months.

1.2 SCHEMA


Referral and eligibility screening
Days -14 to 0
Eligibility confirmation
Day 0
Informed consent
Days 0-5
Baseline data collection
Days 0-5
Intervention
Attention Control
Telephone assessment – FCG – Hassle Scale; Patient – McGill QOL, ESAS, potential medication related symptom change
Medical record abstraction – Medication regimen, screening for potential drug related problems, survival, functional status (KPS), health service utilization (hospitalizations, ED visits)
Week 2
Telephone assessment – FCG – Hassle Scale; Patient – McGill QOL, ESAS, potential medication related symptom change
Medical record abstraction – Medication regimen, screening for potential drug related problems, survival, functional status (KPS), health service utilization (hospitalizations, ED visits)
Week 4
Telephone assessment – FCG – Hassle Scale; Patient – McGill QOL, ESAS, potential medication related symptom change
Medical record abstraction – Medication regimen, screening for potential drug related problems, survival, functional status (KPS), health service utilization (hospitalizations, ED visits)
Week 6
Telephone assessment – FCG – Hassle Scale; Patient – McGill QOL, ESAS, potential medication related symptom change
Medical record abstraction – Medication regimen, screening for potential drug related problems, survival, functional status (KPS), health service utilization (hospitalizations, ED visits)
Week 8 and monthly
Study exit – 6 months (week 24) or death
Telephone assessment – FCG – Satisfaction with Care
Medical record abstraction - If patient still alive at 24 weeks, then survival, functional status, and health resource utilization will be monitored through monthly medical record abstraction until death or 1 year

1.3 SCHEDULE OF ACTIVITIES

	STUDY PERIOD					
	Screening / Enrollment	Post-allocation				Close-out
TIMEPOINT	Baseline (Day 0-3)	2 weeks	4 weeks	6 weeks	8 weeks and monthly	24 weeks or death
ENROLLMENT						
Eligibility screening	x					
Informed consent	x					
FEASIBILITY						
SPECTORx Intervention						
Attention Control						
ASSESSMENTS (Source/Items)						
FCG/Demographics	x					
FCG/Family Caregiver Medication Administration Hassle Scale	x	x	x	x	x	
FCG/Potential medication related symptom change		x	x	x	x	
FCG/Patient Centered Medication Communication	x	x	x	x	x	
FCG/Satisfaction with Care (Likelihood to recommend)						x
EMR/ PT Demographics	x					
EMR/ PT Primary Hospice Admitting Diagnosis*	x					
EMR/ PT Comorbid Illness*	x					
EMR/PT Medications*	x	x	x	x	x	
EMR/PT KPS*	x	x	x	x	x	
EMR/PT Survival*		x	x	x	x	
EMR/PT Health resource utilization (hospital admissions, emergency department visits)*		x	x	x	x	

EMR/Potential Drug Related Problem Screen	x	x	x	x	x
Patient/Potential Drug Related Problem		x		x (& monthly thereafter)	
Patient/MQOLQ	x	x	x	x	x
Patient/ESAS	x	x	x	x	x

2 INTRODUCTION

2.1 STUDY RATIONALE

Need for a Comprehensive, Patient-Centered, Medication Review and FCG Support Program

A tremendous challenge in *home hospice care is ensuring that medication prescribing is appropriately aligned to patients' goals of care and that medications are appropriately managed by FCGs.*

There are no intervention studies addressing medication appropriateness in home hospice. Our literature review[16] found one uncontrolled, retrospective study in geriatric palliative care that **reviewed and simplified** regimens by reducing unnecessary drug use by 65% (from 1.7 to 0.6 per patient).[17] Investigators reported that 74% of patients used at least 1 unnecessary medication (defined as drugs with lack of indication, lack of effectiveness, or prolonged duration of therapy). Their study provided "proof of concept" that it is possible to systematically review and simplify medications in geriatric palliative care.[17] However, such studies have focused on geriatrics[18 19 20 21 22 23]and nursing homes,[24 25] and not home hospice.

Few studies examine FCG medication management needs.[14 3 26 27] FCGs have many challenges, including dealing with patients' non-adherence, deciding which medications to give, juggling administration times and monitoring for side effects.[14 3] Furthermore, patient symptom outcomes depend on appropriate medication administration. (Figure 1) The implication is that high-quality, patient-centered care needs to address *both* medication appropriateness and FCG medication management support.

*Therefore, we propose a novel approach that trains hospice staff to (a) regularly **review, simplify, and align** patients' prescribed medications with their goals of care as their illness progresses*, [16] *and (b) **support** FCGs' with education that empowers them to understand each medication's use, develop skills for safe administration, and understand when stopping medications may be beneficial*.[3 26]

2.2 BACKGROUND

Polypharmacy for Home Hospice Patients is Burdensome, Harmful and Costly

Over 1.3 million Americans aged 65 years and older receive hospice services annually and 45% are cared for at home.[5] These patients are prescribed an average of 10-12 medications daily[6 7 8] and have progressively declining organ function that increases their risk of drug-related harm.[9] Furthermore, many take questionably beneficial medications[11 12 13] until death while simultaneously being prescribed an increasing number of end-of-life (EOL) symptom management drugs.[8] This changing combination of medications contributes to stress and confusion for family caregivers (FCG) who are responsible who are responsible for patient medication management and administration.[14 3]

Family (Informal) Caregivers Find Managing Complex Home Hospice Medication Regimens Stressful
Family (informal) caregivers are defined as "any relative, partner, friend or neighbor who has a significant personal relationship with, and provides a broad range of assistance for [an older person]". [4] Hospice is a particularly challenging setting for FCGs because they are responsible for complicated medication administration tasks that are *usually reserved for licensed healthcare professionals*.[28] An estimated 44 million adults, mostly women, provide this informal (i.e. unpaid) care. [29] They often feel inadequately prepared for this responsibility [30] and have fears about doing something wrong.[28] [30]

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The risks and costs vs benefits of reducing polypharmacy for patients with advanced disease and their family caregivers remains a genuine clinical uncertainty. Multiple studies support the use of myriad individual chronic disease medications, such as statins, in elderly adults with appropriate indication. However, the benefit of continuing chronic disease medications after hospice admission on quality of life, family caregiver medication hassle, or patient survival is unknown. Simplifying medication regimens through a process of depresribing is one remedy to medication complexity as death approaches, but may be associated with potential risk of stress to family caregivers about making decisions regarding stopping medications and additional potential risk of adverse drug withdrawal events after stopping medications - a particular concern when abruptly stopping medications with long half lives that are known to require tapering protocols.

2.3.2 KNOWN POTENTIAL BENEFITS

Multiple studies support reduction of polypharmacy in elderly patients with multi-morbidity. Less is known to support the benefit of medication discontinuation among patients in hospice. One exception is the question of benefit from stopping statins used for primary prevention among eldelry patients with advanced illness, a question addressed in a randomized controlled trial of statin discontinuation by Kutner et al. These data show that statin discontinuation does not contribute to shorted survival, and may be associated with improved quality of life.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Polypharmacy has known patient burden and associated patient side effects. This is attributable to the accumulation of individual medication effects, and known drug-drug interactions resulting from complex medication regimens. For patients with life-limiting conditions who take one or more chronic disease medications along with symptom directed therapies, the balance of medication efficacy vs burden remains unclear. Finally, the psychological impact of using or discontinuing chronic disease medications in the setting of advanced life-limiting illness is largely unknown. Patients may feel relief when not

taking as many pills, anticipating the potential for fewer side effects, and paying less medication costs for medications not covered by hospice yet desired by the family. Conversely, there may be increase worry or distress when discontinuing a medication that a patient and their family was told would need to be taken for the rest of their lives.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
Feasibility and Acceptability	• Intervention Delivery to Hospice Staff • Patient and Family Caregiver Recruitment Goals • Completion of FCGs Assessments • Completion of Patient Assessments • Time for completing FCG assessments • Time for completing Patient Assessments • Yield of FCG Eligibility Criteria • Yield of Patient Eligibility Criteria	• Measurements of Intervention Uptake • Measures of Recruitment Yield • Measure of Outcome Assessment Success	
Secondary			
Efficacy and Safety	• FCG Burden • Medication Regimen Complexity • Patient-Centered Medication Communication	• Primary Outcome for trial • Patient medication burden • Quality of prescribing for patients	

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	• Potentially Inappropriate Medications, as measured by modified Medication Appropriateness Index • Medication changes • Patient QOL, as measured by McGill QOL Questionnaire • Patient Symptoms, as measured by Edmonton Symptom Assessment System (ESAS) • Overall Survival • Suspected Unexpected Serious Adverse Reactions (SUSAR) • Drug Related Problems	• Key patient outcome • Key patient outcome • Key patient outcome • Assessment of risk for study population • Risk assessment for intervention	
Tertiary/Exploratory			

4 STUDY DESIGN

4.1 OVERALL DESIGN

A pilot, single-blinded, cluster randomized, pragmatic trial of the SPECTO*Rx* intervention.
We will compare outcomes within and across 2 large, multi-office, hospice agencies from Utah and Massachusetts. Within each hospice agency, we will randomize 1 office to intervention and 1 office to attention control. Target enrollment is 30 FCG-patient dyads per agency (n=15 intervention, n=15 control), for a total trial target of n=60 FCG-dyads of patients aged ≥65 years, with an estimated life expectancy of >1 month, and polypharmacy (defined as ≥5 regularly scheduled daily medications).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a controlled study to evaluate the effect of a medication review, education and communication intervention on improving medication administration burden by family caregivers in home hospice. The unit of randomization is the team within a hospice agency, the intervention is aimed at the hospice clinicians, and patient and family caregivers are the units of analysis. We randomize at the level of the hospice to reduce cross-contamination at the clinician level.

Study Design. We will compare outcomes within and across 2 large hospice agencies using a cluster randomized trial study design. Within each hospice agency, we will recruit 30 eligible FCG-patient dyads (total n=60) of patients ≥65 years old, an estimated life expectancy >1 month, and polypharmacy (defined as ≥5 regularly scheduled daily medications). [**Eligibility Criteria** for details]
Hospice Sites. EOL practices vary regionally.[13 15] Thus, we are partnering with two large, geographically distinct home hospice agencies to begin exploring the generalizability of SPECTORx nationally. Each agency has multiple offices serving different local regions within their states. Care Dimensions (Massachusetts) has 2 offices serving 4 counties in Eastern MA, and CNS Home Health & Hospice (Utah) has 10 offices throughout Utah. Combined, they had over 5,000 hospice admissions in 2016. Both have recently participated in a research studies. (see Letters of Support)
Randomization and Attention Control. Within each of the 2 hospice agencies, we will randomize 1 office to intervention and 1 to control status. Target enrollment is 15 FCG-patient dyads at each office (total 30 FCG-patient dyads per hospice agency). As the attention control, we will refer staff in control offices to the NIA's website on "Medicines and Medication Management" [37] to review content and materials for use in FCG support.

4.3 JUSTIFICATION FOR INTERVENTION

High-quality, patient-centered care about medication management in hospice needs to address both medication appropriateness and FCG medication management support. We propose a novel approach that trains hospice staff to (a) regularly **review, simplify, and align** patients' prescribed medications with their goals of care as their illness progresses, [16] and (b) **support** FCGs' with education that empowers them to understand each medication's use, develop skills for safe administration, and understand when stopping medications may be beneficial. [3] [26]

4.4 END-OF-STUDY DEFINITION

A FCG participant is considered to have completed the study if he or she has completed the baseline assessment, and at least the 2 week assessment and the post-death follow-up assessment (or at 6 months if patient survives 6 months after hospice admission).

A patient participant is considered to have completed the study if he or she has completed the baseline assessment, and at least the 2-week assessment.

The end of the study is defined as completion of the 6-month follow-up assessment shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Participants (patients, FCGs, and clinical hospice staff) will be recruited for both intervention and control arms.

FCG-Patient Dyads.

Patient - Eligible patients are newly admitted home hospice enrollees, aged ≥65 years old with: 1. advanced life-limiting illness; 2. an estimated life expectancy of >1 month; 3. recent functional status decline (defined as change in Karnofsky Performance Status [KPS] [1] to < 80% in prior 3 months); 4. polypharmacy (defined as ≥ 5 regularly scheduled medications [excluding antimicrobials]); 5. cognitive ability to provide informed consent based on a Short Portable Mental Status Questionnaire (SPMSQ) score ≥6 [2] OR, with a legally authorized representative who is willing and able to provide proxy consent. These variables are easily assessed on hospice intake forms on admission.

FCG – FCGs are eligible if: they self-identify as "usually" or "always" providing care to the eligible patient; are English-speaking; have telephone access; and have cognitive ability to participate. [3] Family is operationally defined "any relative, partner, friend or neighbor who has a significant personal relationship with, and provides a broad range of assistance." [4]

Hospice Clinicians -

Hospice clinicians are eligible if : nurses, social workers, chaplains and medical directors deliver care or communicate with home hospice patients in the course of their primary hospice-related job responsibility; pharmacists are eligible if their primary responsibility is to oversee safety of prescribing of medications to home hospice patients or coordination of medication-related decisions with hospice prescribers.

5.2 EXCLUSION CRITERIA

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

1. Life expectancy of < 1 month
2. Age < 65 years old
3. Cognitively unable to provide informed consent AND no legally authorized representative (LAR) to who is willing to provide proxy consent

4. No family caregiver

5.3 LIFESTYLE CONSIDERATIONS

5.4 SCREEN FAILURES

We will not consent participants to do not meet eligibility criteria. It is possible that consenting, enrolled patients may die quickly after enrollment despite meeting eligibility criteria. This is not unexpected for this study population.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Patient and family caregiver participants will be recruited through the participating home hospice clinical sites. Each site minimally includes a dedicated Site Investigator and Research Assistant capable of enrolling in and conducting the study.

The total enrollment is up to 60 consenting patient-FCG dyads. Within each of the 2 hospice agencies, we will randomize 1 office to intervention and 1 to control status. Target enrollment is 15 FCG-patient dyads at each office (total 30 FCG-patient dyads per hospice agency).

Hospice clinician participants will be recruited at each hospice site. In cooperation with hospice administrative leaders, we will present the study to the hospice clinical teams and invite teams randomized to the intervention to complete the online education training intervention about medication review, education, and deprescribing.

The Site PI will develop study-specific recruitment strategies in consultation with the local hospice administration. Site RA and CRCs and other study staff will attend an introductory training program covering research related-communication, ethics, recruitment planning and implementation.

The screening and recruitment algorithms will be developed for each site, delineating expected processes and highlighting potential hurdles so that effective solutions can be developed. Key messages for the recruitment call/visit, supporting study diagrams, recruiting scripts, strategies for working with

bereaved family members, and simplified consent language will be developed. Tools will be practiced through role plays: refresher role plays will be repeated periodically during the study to ensure quality and consistency. Recruitment metrics will be monitored on a regular basis and will including screening eligibility, study completion, study withdrawal rates; progress will be presented to Site Investigators and staff. If a study site should encounter particular difficulty with enrollment, the study team may conduct a site visit to review obstacles and devise solutions, presenting results for review to the existing study stakeholder panel.

Site specific screening will follow this general scheme, but may be adapted (as described herein) to local workflow procedures to minimize impact on clinical care delivery:
In general, hospice staff (i.e. front-line hospice nurses or local administrative staff) will preliminarily screen eligible patients on their daily hospice census list and, at their discretion within the first week after the hospice admission visit, provide an *IRB-approved generic brochure* about research in hospice and palliative care; if there is interest in learning more about the study, the patient and family caregiver will also be given an IRB-approved study-specific brochure. A variation at some hospices routinely places an *IRB-approved generic brochure* about research in hospice and palliative care in the hospice admission packet along with information about how to contact the hospice to opt-out of being screened and contacted for research, or similarly routinely provides patients and families to opt-out of being screened for research based on the local hospice's forms and policies. We will work with local hospice leadership to identify the most appropriate approach for their system. Then, a list of eligible participants will be identified and confirmed by a CITI-trained RA who will examine the daily admissions for hospice to identify participants who meet eligibility criteria among patients who have indicated interest in hearing about the study to front-line staff (or, as applicable, has not opted-out to being screened for research. This will generate a final list of eligible patient and family, and the hospice will then forward contact information to the study team among eligible participants indicating in the form of an authorization to contact form.

The Site RA will follow-up to lead recruitment efforts.

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

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

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

Intervention: We will present the SPECTORx educational intervention to clinical hospice staff randomized to the intervention. This is comprised of 3 x 20-25 minute online in-service modules about systematic, patient-centered, medication review, educational support for family caregivers about medication administration, and deprescribing of potentially inappropriate medications. The intervention patient and family caregiver participants will be given a study-specific notebook including a blank notepad, a blank medication tracking sheet, and printed information about the Medications in Older Adult website, as well as printed guidance from the NIA's Medicine's and Medication Management website (https://www.nia.nih.gov/health/topics/medicines-and-medication-management) about "What Do I Need to Tell the Nurse and Doctor?", and clinical information handouts about medications commonly used in hospice (e.g. Haldol, Morphine, Understanding Nausea, Understanding Pain and Symptoms).

Attention control: We will refer clinical hospice staff randomized to control offices to "Medications in Older Adults" website sponsored by the American Geriatrics Society's Health in Aging Foundation. (https://www.healthinaging.org/medications-older-adults) Based on personal preferences, these materials can be shared via electronic link or the information can be printed and distributed in paper form to patients and their family caregivers. The attention control patient and family caregiver participants will be given a study-specific notebook including a blank notepad, a blank medication tracking sheet, and information about the Medications in Older Adult website.

At the end of the trial, staff in control offices will be offered the SPECTORx educational intervention training.

6.1.2 ADMINISTRATION AND/OR DOSING

Staff will be referred to this attention control resources one time, but will be able to access the resources as many times as they deem clinically appropriate for the care of their patients.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

We will track completion of online learning of the three 20-25 minute SPECTORx educational modules, including self-assessment quizzes by tracking completion online and by asking consenting participants to complete brief self-assessments before and after the educational intervention. Study staff will periodically check in with hospice clinical staff to inquire about adherence to the study intervention. We will also track fidelity be asking FCGs of consenting hospice nurses brief questions about whether hospice staff conducted medication reviews, offered education and support about medication administration and management, and discussed the option of deprescribing medications that are potentially inappropriate.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization is at the level of the office location within each hospice agency.

Outcomes assessments will be blinded with withholding intervention assignment data from the clinical research coordinator responsible for data collection related to the measurement of patient and family-caregiver outcomes and from the adjudication team responsible for measuring ADE and ADWEs.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

The intervention is a medication support care intervention delivered by hospice clinical team, led by the hospice nurse. Hospice teams are randomized to SPECTORx intervention or attention control of standard American Geriatric Society/NIA funded educational materials of medication management for older adults.

6.5 CONCOMITANT THERAPY

6.5.1 RESCUE THERAPY

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

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

The study intervention, which targets hospice clinical staff, will be delivered one time at the beginning of the study and will be delivered to any new clinical staff joining the intervention site teams. We will inform the clinical sites of the end of the study when we 3 months after completion of study enrollment to allow for adequate, uncontaminated, collection of outcome data for all participants.

When a subject discontinues study procedures will be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected at the time of study intervention discontinuation will include the following:

- The reason(s) for discontinuing the participant from the intervention, and methods for determining the need to discontinue
- If the participant is due to complete assessments within 2 weeks of being discontinued from the study intervention, those assessments will be administered at the time of discontinuation; if the next scheduled assessments are more than 2 weeks from the discontinuation date, the discontinued participant will wait for the next scheduled assessment. Thereafter, the participant will be included in all future scheduled assessments, even though not participating in the intervention.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants (family caregivers and patients) are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue a participant from the study for the following reasons:

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

The reason for participant discontinuation or withdrawal from the study will be recorded on the [specify] Case Report Form (CRF).

Clinical staff participants (nurses, social workers, chaplains, physicians, pharmacists) area also free to withdraw from the study at any time. Consenting clinical participants who are randomized but do not receive the study intervention may be replaced. Consenting participants who are randomized and receive the study intervention, and subsequently withdraw, or are discontinued from the study, will be replaced when possible.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if study staff are unable to contact the participant after at least 3 attempts.
The following actions must be taken if a participant fails complete study assessments:

- The site will attempt to contact the participant and ascertain if the participant wishes to and/or should continue in the study
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

The endpoint of the study is either patient death, disenrollment from hospice, or completion of 6 months of follow-up after study enrollment.

8.2 SAFETY ASSESSMENTS

In accordance with applicable regulatory requirements and principles for the ethical conduct of research, a Safety Officer will be appointed by the NIA to oversee the safety of study participants.

Because the study population has, per the eligibility criteria, a limited expected prognosis of less than one year, death and the preceding associated development of symptoms related to the natural progression of disease are expected. Because the study setting is home hospice, hospitalizations related to the natural progression of disease are expected to be unusual. However, deaths, hospitalizations, and emergency department visits will be monitored.

Because the focus of the trial educational intervention focuses on medication-related management, review and support, medication changes and symptom changes potentially related to drug related problems (DRPs) will be monitored, including potential DRPs present upon study enrollment which, by definition, are not related to the research.

Medication changes will be identified by collecting medication lists every 2 weeks and iteratively identifying changes between lists. DRPs will be monitored by a trained research assistant who will screen the medical record using a Screening Algorithm of Potential Drug Related Problems at *study enrollment and every 2 weeks up to 2 months* for a retrospective chart review, and then monthly up to 6 months. These medical record will be reviewed for new clinical events, symptoms, abnormal lab events and drug levels, new reported drug allergies or drug associated problems identified by clinicians. Secondarily, a trained research assistant will also conduct a screening telephone interview with patients (or their caregiver, if patient is unable to participate) for potential DRPs using a method by Chrischilles[31] *at 2 weeks and monthly* thereafter.

To ensure that potential DRPs, emergency department visits, hospitalizations and deaths are indeed unrelated to the research, these will be closely monitored by the study's Event Classification Pharmacist (ECP) comprised of a pharmacist using a procedure described below in Section 8.3.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 ADVERSE EVENTS

Any event due to the presence or progression of illness that a patient had on study enrollment will not be considered an adverse event (AE), including changes in symptoms, hospitalizations, emergency department presentations, and death more likely related to disease progression than not related to disease progression. Only events more likely not related to known underlying illness will be considered an AE.

If such an event is also related to the research and is unanticipated, regardless of its level of severity, this would require expedited (prompt) reporting to the local IRB in keeping with its reporting requirements for a suspected unanticipated problem involving risks to subjects or others (suspected UPIRTSO).

AEs are classified as to whether or not they are serious (SAE), namely life threatening (resulting in hospitalization, emergency department presentation or death), leading to permanent disability or judged a SAE by the site PI. AEs will be graded according to seriousness, and then designated as more likely expected or unexpected (yes/no), and more likely related or unrelated to the research (yes/no). Other characteristics of the AE to be recorded include date identified, diagnosis, outcome and date resolved.

SAEs will be classified as to whether or not they are a Suspected Unexpected Serious Adverse Reaction. (SUSAR) SUSARs are defined as events that are a suspected adverse reaction AND serious AND unexpected. This approach focuses the Safety Officer's and IRB's attention on potentially study participating-related events rather than on a large number of anticipated events that are part of normal disease progression and unrelated to the intervention. If a SUSAR, then expedited reporting and processes must be followed, as outlined below. If not a SUSAR, standard reporting for AEs is followed (for all AEs and SAEs), unless, as described above, the event meets the definition of a suspected Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO). An event can be a SAE, but not a SUSAR (e.g. a person hospitalized for hip fracture and not attributable to underlying known illness, but not suspected to be related to the study intervention).

The ECC will review a pre-specified proportion of all hospitalizations and deaths. The ECC will determine if the hospitalization/death or drug related problem (DRP) was an expected event, SAE, or SUSAR. Results will be reported to the Safety Officer and the NIA Project Officer.

Cumulative aggregated AE data will be presented to the Safety Officer and the NIA Project Officer, along with tabulated outcomes data. This includes AEs, SAEs and SUSARs, plus survival, health resource utilization, and patient reported outcomes.

The Study PI is also responsible for contacting the NIH grant program officer in the event that any action resulting in temporary or permanent suspension of the trial occurs. (Because this trial does not involve any investigational medication, the action would be limited to an IRB- or investigator-initiated suspension or discontinuation of the study.)

8.4 UNANTICIPATED PROBLEMS

See discussion of UPIRTSO above in 8.3.

Further, there is the possibility that the patient and/or family caregiver will ask clinical questions (e.g. about symptom management) of the study research assistant during a telephone interviews for study-related outcomes assessment. If this occurs, the research assistant will 1. provide the hospice triage phone number to the participant and direct him/her to call about their clinical questions and 2. call the hospice triage phone number directly, inform hospice that the participant had clinical questions, and request a call back to the patient/family caregiver.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

- Primary Endpoint(s): For this exploratory study, the primary endpoints are: acceptability and feasibility of the SPECTO*Rx* intervention by hospice stakeholders; feasibility of a brief, standardized, 'interest in research' screen upon hospice admission to refer FCG-patient dyads for recruitment; acceptability, burden and completion of FCG assessments (FCG Medication Administration Hassle Scale [32] at baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and monthly).
- Secondary Efficacy Endpoint(s): medication regimen complexity index scores[33] *for chronic daily medications* and prevalence of potentially inappropriate medications (baseline, 2 weeks, 4 weeks, 6 weeks, 8 weeks, and monthly and death), patient quality of life, patient symptom burden

9.2 SAMPLE SIZE DETERMINATION

Sample Size Justification. In this exploratory study, we chose a sample size sufficient to enable a decision about feasibility.[34] This sample size is larger than many pilot palliative care trials and sufficient to determine acceptability in each of the two hospice agencies.[35] This sample size is also attainable. Target enrollment is 30 FCG-dyads at each hospice agency who, combined, have over 400 admissions a month. We lack power to establish efficacy for the intervention on outcomes.

9.3 POPULATIONS FOR ANALYSES

While we aim to enroll dyads of family caregivers and patients, the population for analysis include family caregiver outcome separate from patient outcomes.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Feasibility and Acceptability. We will use descriptive statistics to analyze *quantitative feasibility outcomes*. We will calculate the mean number of eligible patient-FCG dyads screened and enrolled per week, accrual, retention, and training completion. We will use Chi-square (for comparisons of rates and

proportions) and t-tests (for mean comparisons) to explore differences by site and participant characteristics, including sex.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

A secondary goal of this pilot is to estimate preliminary intervention treatment effect size for a large-scale, R01-funded trial. Comparisons will be made between the baseline and follow-up assessments, both within and across intervention and control sites. Descriptive analyses will establish data distributions for continuous outcomes (e.g. FCG Hassles Scale). We will use linear mixed effects models to account for cluster randomization for continuous outcomes. Clusters are hospice agencies, offices within agencies, clinicians within office, and patients within clinicians/nurses. Even with small samples, we can explore the relationship between change in measures (e.g. # PIMs) and FCG/patient factors. Mixed effects models are robust with small sample sizes and adjust for correlations from repeated measures within individuals and from clustering.

Missing Data. Descriptive analyses will characterize missing data frequency and examine associations with key characteristics (e.g. admitting diagnosis, race). Variables associated with missingness will be included in analyses as covariates to account for possible effects from the missing pattern (missing at random). [36]

9.4.4 SAFETY ANALYSES

Safety reports will be sent to the Safety Officer and Project Officer at every 3 months and will include a detailed analysis of study progress, data and safety issues, including interim analyses as described in 9.4.6.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

1. Baseline characteristics of the patients and family caregivers.

9.4.6 PLANNED INTERIM ANALYSES

1. Recruitment by week/month;
2. Treatment phase of patients & family caregivers (screened, enrolled, follow-up phase);
3. Completeness of data (assessments completed, % of expected forms submitted, % of submitted forms passing edit);
4. Missed assessments and missing information within assessments;
5. Summary of adverse events by type;

6. Summary of adverse events by body system;
7. Summary of actual medication changes;
8. Listing of adverse events (including duration, severity, seriousness, relatedness, action taken, resolution);
9. Descriptive information for each endpoint without statistical testing except at designated interim monitoring points if requested by the DSMB, including # and details of medication changes for each patient during the study;
10. Compliance information (completion of intervention training by clinical staff); and
11. Quality control analyses.

9.4.7 SUB-GROUP ANALYSES

Analyses by intervention and control status.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

9.4.9 EXPLORATORY ANALYSES

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

To alleviate the burden of obtaining written consent from these typically home-bound patients and their family caregivers, we will use a telephone based consent procedure. That is, we will obtain a waiver of written documentation of informed consent for this minimal risk participation study for family caregivers and patients, since their involvement requests only access to medical records and completion of telephone questionnaires.

If a patient and family caregiver a potentially interested in study participation, they will be given a Fact Sheet by the hospice staff that summarizes the relevant information about the study, including the risks, benefits, and rights as a study participant. Hospice staff will not answer questions about the study consent, but will refer all questions to trained study staff who will be scheduled to call the patient within 1 week of referral to the study staff. The fact sheets will describe the study in detail the study intervention, study procedures, and risks.

Potentially eligible patients will be referred to the study team. To minimize burden of making a unnecessary study enrollment calls to ineligible patients, we will request a HIPAA waiver for medical record review for the express purpose of confirming eligibility by the study team. If confirmed to be eligible, the study team will call the patient and family caregiver to explain the study, answer any question about participation and the fact sheet, and to obtain telephone recorded consent.

Persons with dementia will be given the opportunity to consent for themselves because cognitive impairment is not always associated with the lack of capacity to provide informed consent to participate in research. Study staff will explain the study and assess capacity to consent based on the standard decision-making capacity criteria of: (a) ability to communicate a yes or no decision; (b) ability to understand relevant information; (c) ability to appreciate the situation and its likely consequences; and (d) ability to manipulate information rationally. If the patient is unable to meet all 4 of these criteria, we will obtain consent from a legally authorized representative (LAR). Further, study staff will obtain consent from the LAR for persons with a documented dementia severity of FAST 6 or greater as this indicates severe dementia with limited speech ability, or individuals has been ruled incompetent by a court of law or with documentation by a qualified practitioner in the medical record that the individual lacks capacity to make the decision to participate in the proposed study.

Utah and Massachusetts hospice sites will provide lists of individuals who are authorized to consent when the patient ins unable to consent on their own behalf. In Utah this includes any married person for

a spouse and any person 18 years of age or older for his or her parent who is unable to reason of age, physical or mental condition, to provide such consent. In Massachusetts this includes a health care agent or guardian.

The LAR will be provided with the description of the research study and informed of their role and obligation to protect the rights and welfare of the patient participant. The LAR must be informed that the obligation as a surrogate decision maker is to try to determine what the participant would decide if the participant were able to make such decisions. In the case of this study, the patient's participation would be limited to providing HIPAA waiver for access to the medical record for data collection.

The following consent materials are submitted with this protocol.

- Study fact sheet for patients
- Study fact sheet for family caregivers
- Telephone consent script
- Assessing Capacity to Consent Form

10.1.2 STUDY DISCONTINUATION AND CLOSURE

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

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

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

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, or Safety Officer.

10.1.3 CONFIDENTIALITY AND PRIVACY

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

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

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

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

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

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see https://grants.nih.gov/policy/sharing.htm). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

Certificate of Confidentiality

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

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Massachusetts Medical School Data Coordinating Center. After the study is completed, the de-identified, archived data will be transmitted to and stored at the Palliative Care Research Collaborative Data Repository, for use by other researchers including those outside of the study. Permission to transmit data to the Palliative Care Research Collaborative Data Repository will be included in the informed consent.

During the conduct of the study, an individual participant can choose to withdraw consent to have data stored for future research. However, withdrawal of consent with regard to data storage may not be possible after the study is completed.

When the study is completed, access to study data will be provided through the Palliative Care Research Collaborative Data Repository.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Safety Officer (SO) who is a physician with relevant study and disease-specific expertise appointed by the study sponsor/NIA. The SO is independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The SO will review the safety and data monitoring plan, informed consent documents, and participant recruitment and retention milestones. At predetermined intervals (e.g. every 3 months) the study team will prepare safety reports to be reviewed by the SO and the NIA for recommendations for or against the trial's continuation, as well as any modification to the study. The SO will be unblinded to safety data.

10.1.7 CLINICAL MONITORING

Clinical site monitoring will be conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Council on Harmonization Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s). Monitoring activities will be as follows:

- **Data Coordination and Quality Control**. Data will be entered into REDCap data capture software, and then extracted to SAS for analysis. For all assessments, RAs will complete CRFs on paper for subsequent entry into REDCap. One part of the CRF will remain at the local site and the other part will be sent to the UMMS central study site for quality checking. The project biostatistician will conduct regular quality control analyses for missing data, internal consistency reliability, the number and type of forms failing to edit, and data distribution looking for outliers. We will conduct data audits by reviewing select, high-risk, data [e.g. patient characteristics and medications] against source documents from every 5th patient enrolled (i.e. ~10% sample). If systematic errors are detected, further data will be audited to determine the cause(s) and monitoring reports will be generated and distributed accordingly.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. All sites will follow a common quality management plan.

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

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

Source documents and the electronic data - Data will be initially captured on source documents (see **Section 10.1.9, Data Handling and Record Keeping**) and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

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

Protocol Deviations The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern. Should independent monitoring become necessary, the PI will provide direct access to all trial

related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.
Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into RedCAP, a 21 CFR Part 11-compliant data capture system provided by the University of Massachusetts Medical School DCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

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

These practices are consistent with ICH GCP:

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

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation, or within 10 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the UMass Med Data Coordinating Center. Protocol deviations must be sent to the reviewing IRB per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:
National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

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

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the University of Massachusetts Medical School has established policies and

procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

Determination of ADE and ADWE

10.3 ABBREVIATIONS AND SPECIAL TERMS

ADE	Adverse Drug Event
ADWE	Adverse Drug Withdrawal Event
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
ED	Emergency Department
FCG	Family Caregiver
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices

GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QOL	Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

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