A Randomized Controlled Trial to Deprescribe for Older Patients with Polypharmacy Transferred from the Hospital to Skilled Nursing Facilities (Shed-MEDS)

Study Protocol

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PRÉCIS

Overview and Objectives

Geriatric syndromes are clinical conditions common in older adults that are multifactorial in origin and involve several organ systems.[1] The co-occurrence of multiple syndromes within the same patient is prevalent and associated with adverse health outcomes.[2] Older patients are likely to experience new onset of geriatric syndromes during hospitalization. Patients discharged from the hospital to skilled nursing facilities (SNF), which comprises 1.7 million Medicare beneficiaries per year, are a particularly high risk group for loss of independence.[3, 4] Recent data show that only 28% of SNF patients are living at home 100 days after SNF discharge.[5] We report novel preliminary data that patients discharged from the hospital to SNF, and ultimately SNF to home, experience an average of two geriatric syndromes in both care settings, with 57% experiencing three or more. Unfortunately, there is little recognition of these syndromes in each setting. Effective management of geriatric symptoms across this continuum could improve outcomes in SNF patients.

There is a dearth of evidence related to efficacious interventions to manage geriatric syndromes because it is difficult to implement a multifactorial intervention that addresses all of the syndromes experienced by an older patient. An alternative approach is to intervene on a common factor contributing to multiple geriatric syndromes. Our preliminary data, as well as the published literature, strongly suggests that one common factor is polypharmacy. Polypharmacy and a variety of drug indices that quantify drug burden[6, 7] are associated with the development of long-term cognitive impairment,[8-10] delirium,[11, 12] falls,[13-18] frailty,[18-20] urinary incontinence,[21-23] and weight loss.[24-26] The number of syndromes related to polypharmacy supports our hypothesis that polypharmacy is a common mechanistic cause of multiple geriatric syndromes.

Although the published literature has strongly associated polypharmacy with geriatric syndromes, it is unknown if deprescribing, as defined by medication dose or number reductions, leads to improvements in geriatric syndromes. We prospectively collected data on 904 Medicare patients discharged to SNF and found that 98% met criteria for polypharmacy (≥ 5 medications) with an average 14 and15 medications at hospital and SNF discharge, respectively. A systematic review was then conducted by clinicians and pharmacists of all discharge medications for 156 of these patients using explicit review criteria to link medication side effects with geriatric syndromes. An average of 5.9 discharge medications per patient was determined to be associated with one or more geriatric syndromes in these patients. We also pilot-tested a patient-centered deprescribing intervention ("Shed-Meds") wherein we successfully engaged patients and providers to reduce the number or dose of medications prior to hospital discharge. Based on these preliminary data, we propose a randomized, controlled trial to evaluate the effects of the Shed-Meds deprescribing intervention on polypharmacy, geriatric syndromes, and other outcomes during the care transitions from hospital to SNF to home. Our overarching hypothesis is that reducing medications for older patients across the continuum of care will favorably impact geriatric syndromes is at home.

Specific Aim 1: Implement a patient-centered deprescribing intervention (Shed-Meds) that spans the continuum of hospital and post-acute care to reduce the total number of medications patients are prescribed in each care setting and at home after SNF discharge.

- Hypothesis 1a: The Shed-Meds intervention will result in a significant increase in the total number of medications deprescribed, as defined by termination or dose reductions, at hospital discharge, SNF discharge and 90 days after SNF discharge.
- Hypothesis 1b: Shed-Meds will result in a significant reduction in the number of potentially inappropriate medications (PIMs) and medications associated with geriatric syndromes at hospital discharge, SNF discharge and 90 days after SNF discharge.
- Hypothesis 1c: Shed-Meds will result in a significant decrease in the anticholinergic and sedative drug burden of prescribed medications at hospital discharge, SNF discharge and 90 days after SNF discharge.

Specific Aim 2: Document the effects of the patient-centered deprescribing intervention (Shed-Meds) on geriatric syndromes, medication adherence, and health status.

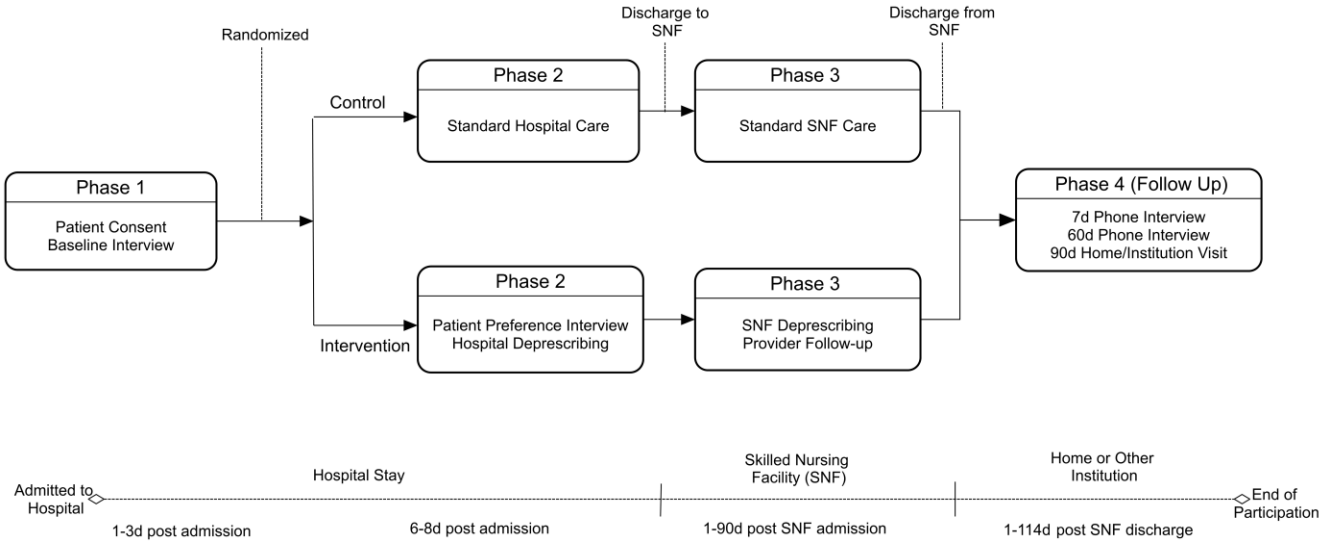
Hypothesis 2a: Shed-Meds will result in a significantly lower prevalence and severity of geriatric syndromes 90 days after SNF discharge.

Hypothesis 2b: Shed-Meds will result in a significant improvement in medication adherence and self-rated health status after SNF discharge.

Study Design and Outcomes

Overview of Design

Figure 1. Schematic of Study Design



Study Setting

Vanderbilt University Medical Center (VUMC) is a private, non-profit, tertiary care teaching organization located in Nashville, Tennessee. We will work with patients discharged to 22 post-acute care (PAC) facilities within a nine-county radius of VUMC.

Interventions and Duration

There are two phases to the intervention: in-hospital and during post-acute care (PAC) stay (Figure 1: Phases 2 & 3). The hospital phase of the intervention includes identification of medications for deprescribing, a patient preference interview, and discussion with patients' primary treatment teams (outpatient and inpatient). At the point of hospital discharge, the intervention continues at the PAC facility via warm hand-off and weekly monitoring calls by the study team. The intervention ends at PAC discharge, and participants will be contacted for follow-up assessments at 7, 60, and 90 days after PAC discharge.

Study Population and Sample Size

The eligible patient population is patients age $\geq$ 50 with polypharmacy as defined by $\geq$ 5 medications based on the pre-hospital admission; able to self-consent or has a proxy; home residence within the nine-county radius of VUMC; does not reside in long-term care and is not hospice eligible. All eligible patients will be approached for consent. We anticipate enrolling approximately 144 patients per year, or 576 across all four years of enrollment. Among those, we estimate that 27.5% will either die or become unreachable prior to 90-day follow up. Thus, across all four years of enrollment, 420 patients will contribute measurements at 90 days. Although 567 is the expected enrollment, we conservatively use 420 to estimate the statistical power

associated with our hypotheses based on overall completion rate, rather than enrollment rate, to account for attrition.

BACKGROUND AND SIGNIFICANCE

Background on Condition, Disease, and Primary Study Focus

Geriatric syndromes represent clinical conditions that share underlying causative factors and involve multiple organ systems.[1] The most commonly cited geriatric syndromes include incontinence, depression, cognitive impairment, delirium, weight/appetite loss, mobility impairment, pressure ulcers and falls. However, there are no published studies that include measurements of all these conditions in one patient population.

The presence of multiple syndromes is common in older adults and predictive of poor health outcomes, even when controlling for age and illness severity.[2] For example, approximately 50% of hospitalized patients aged 65 and older experience two or more syndromes, with one or more syndromes either developing or worsening during the acute care episode.[27-31]

Patients discharged from the hospital to SNF are at higher risk for loss of independence relative to patients discharged to home, and our preliminary data showed that 57% of patients discharged to SNF had three or more syndromes. We also report data that each patient had an average of 5.9 medications associated with one or more geriatric syndromes. Thus, we propose that polypharmacy represents a common factor contributing to multiple geriatric syndromes. These data provide a strong rationale for our overarching hypothesis that reducing medications for older patients across the continuum of care will favorably impact geriatric syndromes.

Polypharmacy is common among older patients. The epidemiology differs according to the definition and the population to which it is applied. Among hospitalized patients, polypharmacy has been commonly defined as five medications[13, 32-34] to as many as 10 or more, sometimes described as, "hyper-polypharmacy".[35-37] In published studies, about 45% of older hospitalized patients are discharged on five or more medications.[38-40] Older patients have an increased prevalence of multi-morbidity; thus, it is not surprising polypharmacy is common. However, a substantial number of medications prescribed to these patients may be unnecessary. Studies have found that > 90% of inpatients are taking at least one inappropriate medication.[41-43] Several studies have shown that up to 43%[41, 43] of medications taken by older patients lacked a clear indication. In addition, 5% to 11% of medications may be unintentionally prescribed for the same indication.[41, 43] Even when a clear indication exists, medications may be inappropriate when considering drug-drug interactions[44, 45] or drug-disease interactions.[44, 45] These medications, also known as potentially inappropriate medications (PIMs), have been defined by multiple explicit criteria such as the Beer's list,[46, 47] the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)[48, 49] and variations of STOPP.[50] Beyond medical appropriateness, some medications may be costly or may have inconvenient dosing[43] that decreases adherence.[41, 43] Finally, prescribed medications may be inconsistent with a patient's goals of care.[51, 52]

The prevalence and inappropriateness of polypharmacy is of major concern and leads to multiple harmful outcomes among older community-dwelling and hospitalized populations. Outcomes include, but are not limited to, decreased medication adherence,[53] increased adverse drug events,[53-55] and increased health care utilization and costs.[56-59] Polypharmacy and a variety of drug indices that quantify drug burden[6, 7] have additionally been found to be associated with the development of geriatric syndromes. Notably, polypharmacy is associated with long-term cognitive impairment,[8-10] delirium,[11, 12] falls,[13-18] frailty,[18-20] urinary incontinence,[21-23] and weight loss.[24-26] The number of syndromes related to polypharmacy supports our hypothesis that polypharmacy is a common mechanistic cause of multiple geriatric syndromes.

Study Rationale

Interventions to Deprescribe Medications and Knowledge Gaps

In recognition of the potential harms of polypharmacy, numerous studies have evaluated efforts to improve medication prescribing for older patients.[60, 61] Most interventions have applied the use of explicit criteria to reduce inappropriate prescribing with tools such as the Beers list or STOPP criteria, while a few considered other patient-centered factors (e.g., drug-disease interactions, cost, convenience, life expectancy). Trials commonly use pharmacists, physicians or inter-disciplinary teams to implement deprescribing protocols.[62] However, there are several important gaps in knowledge, which this proposal will address. First, few interventions have been initiated in the hospital setting, and no interventions have deprescribed across the continuum of acute and post-acute care. Second, few trials have incorporated patient preferences into the decision-making process. These latter trials have been disease-focused on deprescribing anticoagulants and acid suppressive medications for the treatment of atrial fibrillation and reflux disease.[63, 64] Finally, although most of the trials reported improvements in medication appropriateness,[62] there has been no study to date to evaluate the effects of deprescribing on health outcomes, such as geriatric syndromes.

Preliminary Data

Our interdisciplinary research team has performed innovative, critical preliminary work which supports the rationale and feasibility of the proposed study. In preparation for this project, we implemented a structured patient-centered intervention protocol (Shed-Meds) to reduce the total number of medications prior to hospital discharge. As part of the pilot intervention, both groups received a standardized medical record review by a research team physician or pharmacist to identify medications for potential deprescribing (i.e., stop or dose reduction). However, only intervention patients received a structured interview about their medication preferences, and only intervention patients received deprescribing recommendations based on those preferences. Any deprescribing in the control group was conducted by the hospital team as part of routine care. Both groups were assessed for the following outcomes at hospital discharge, which correspond to the hypotheses of the present proposal: total number of medications, PIMs, medications associated with geriatric syndromes, anticholinergic and sedative burden using the Drug Burden Index.

Across both groups, the research team identified an average of 12.75 (± 6.08) medications per patient for potential deprescribing based on initial chart review. Team reviewers were able to achieve agreement on all deprescribing recommendations following discussion. The standardized patient preference interview (intervention patients only) resulted in an average of 10.2 (± 4.5) *changes* (e.g., adjustments in dose) to the initial deprescribing recommendations based on chart review only. The large number of changes in recommendations demonstrates the importance of involving the patient in the decision process. Recommendations were communicated to the hospital team and other prescribers (outpatient providers) for the intervention group only.

The Shed-Meds pilot resulted in an average of 12.6 total deprescribed medications in the intervention group ($P<.001$), which included 6.1 pre-hospital medications. The control group had an average of 6.5 total deprescribed medications as part of routine hospital care, of which 4.0 were pre-hospital medications. The number of PIMs was reduced for both groups from hospital enrollment to discharge, although the reduction was greater in the intervention group. Both the number of medications associated with geriatric syndromes and the DBI showed a significant reduction in the intervention group relative to the control group.

Innovation

There are several innovative aspects of this study:

1) The Shed-MEDS study reflects one of the first controlled intervention trials to improve post discharge outcomes for the high-risk population of older patients transitioning from hospital to SNF to home. Medicare costs are increasing faster for this group relative to any other Medicare population, and they are at high risk for medication-associated complications and newly acquired geriatric syndromes.
2) Although the number of medications is strongly associated with increases in geriatric syndromes,[24] it is unknown whether reducing medications will improve geriatric syndromes. This trial will specifically evaluate the impact of medication reduction on health outcomes.

3) Several expert groups have requested the development of interventions to simultaneously address multiple chronic conditions in older patients. The proposed intervention will determine the feasibility and efficacy of addressing multiple geriatric syndromes within one intervention framework.
4) The intervention is one of the first to explicitly incorporate patient preferences into deprescribing efforts, which is consistent with patient-centered care initiatives. Moreover, we have preliminary evidence that incorporating patient preferences significantly changes these clinical decisions.

STUDY DESIGN

The study is a 5-year, randomized controlled clinical intervention trial at a singular academic medical center.

Primary Outcomes are change in total number of medications including the number of potentially inappropriate medications, number of medications associated with geriatric syndromes, and medications that contribute to anticholinergic and sedative drug burden.

Secondary Outcome is the impact of deprescribing on prevalence and severity of geriatric syndromes, medication adherence, and functional health status.

Eligible patient population is aged 50 years or older, experiencing polypharmacy as defined by 5 or more home medications, and hospitalized at VUMC with a referral to partner post-acute care facility.

Exclusion criteria include limited life expectancy (less than 6 months), non-English speaking, no telephone, homeless or incarcerated, enrolled in another drug trial, and expected to discharge from VUMC in less than 48 hours.

The primary study setting is Vanderbilt University Medical Center (VUMC), a private, non-profit, tertiary care teaching organization located in Nashville, Tennessee. The medical center is a principal referral center for physicians and patients throughout the Southeast, and it serves a diverse population in terms of income, geography, and education level. We will work with patients discharged to 20 SNFs and 2 IPRs within a nine-county radius of Nashville. The target PACs are all for-profit and comparable to PACs in the middle TN area based on publicly reported staffing and quality indicators (www.medicare.gov).

The timeline for the study is 5 years with enrollment beginning in March 2017 and enrollment closing at the end of October 2020.

The Shed-MEDS intervention is a multistep deprescribing protocol which considers patient and disease factors, life expectancy, goals of care, and appropriate treatment targets. Medication-specific factors such as drug-drug interactions, drug-disease interactions, and drug-specific safety profiles are also incorporated. Finally, patient preferences and primary prescriber input are key to final deprescribing actions by identifying the medications patients are willing to deprescribe and seeking their primary prescriber's agreement. In this intervention, deprescribing is defined as either stopping a medication or reducing the dose/frequency of a medication.

PARTICIPANT RECRUITMENT AND ENROLLMENT

Eligibility Screening and Recruitment

Vanderbilt Institutional Review Board (IRB) permits a record review to screen patients for research studies, similar to a limited HIPAA waiver. Screening is conducted every weekday by the project coordinator, data

manager, or research assistant. The screening process begins with a structured query of the medical record system (EMR). The physical therapy department (PT) developed a report specifically for the Shed-MEDS team that queries every patient in Vanderbilt University Hospital (regardless of 'inpatient' or 'observation' status) aged 50 and over who has been evaluated by PT and recommended for SNF placement. All new patients on this report are added to a screening panel in the EMR and subsequently reviewed for the following inclusion and exclusion criteria:

Inclusion Criteria: (1) we confirm that all patients are over the age of 50. The original criteria included patients 65 years and older, but the age limit was lowered to age 50 after four months of initial study enrollment due to a large proportion of hospitalized patients aged 50-64 meeting all eligibility criteria. (2) Next the "Prior to Admission List" in the EMR is reviewed to confirm the patient has five or more medications administered via oral, sublingual, nasal, inhaled, ophthalmic, transdermal, subcutaneous, rectal, intramuscular, intravenous, and peg tube routes. (3) The patient's county of home residence appears on the screening panel, and they must reside in one of nine surrounding counties.

Exclusion Criteria: (1) The patient's primary language is listed on the patient screening panel; any patient with a primary language other than English is excluded. (2) The patient's case management or social work intake assessment is reviewed to confirm the patient has a valid telephone number and is not homeless, incarcerated or a long-term care resident of a nursing home. In the instance the EMR is unclear, the patient's social worker or case manager is contacted to confirm. (3) The EMR is reviewed for life expectancy of less than 6 months by searching key terms 'hospice' and 'stage 4' to find referrals to hospice care or notes indicating the patient has a stage 4 metastatic cancer, which would exclude them from participation. (4) The 'research' tab of the EMR is reviewed to determine if the patient is on another drug trial that excludes them. (5) Finally, the chart is reviewed for any indication the patient will be discharged in less than 48 hours (i.e., presence of transfer orders, etc.), which would not allow the study team sufficient time to complete assessments or the intervention.

After it is determined the patient meets all of the above inclusion criteria and is demographically eligible, the study team reviews the social work referral system (AllScripts or AIDEN) to determine if the patient has a referral to one of the 22 partner SNFs or IPRs. If the patient has no referrals, the coordinator will continue to monitor in case a partner referral is made.

For patients who have multiple hospitalizations during the trial period, they are re-screened at each admission to determine eligibility for enrollment unless they were previously enrolled in the trial.

Enrollment Procedures

All patients who meet eligibility criteria are approached for consent. Eligible patients can be approached by any study team personnel but are typically approached by a study team nurse practitioner (NP) who provides an overview of the study and intervention in lay terminology. Emphasis is made that data collection will be for research purposes and refusal to participate will have no effect on a patient's routine hospital or outpatient care provided by Vanderbilt or the PAC facility. The patient and/or surrogate is offered time to review an IRB approved brochure and the consent document. Study personnel answer patient and/or surrogate questions and provide contact information if the patient wants to discuss with a family member or friend before enrolling. The consent process also includes a release of information form to allow study team members access to participant's health records at other institutions to monitor and assess safety of the intervention.

As we are enrolling older hospitalized patients, we expect that many patients will be incapable of providing informed consent due to cognitive impairment secondary to their severity of illness, underlying comorbid conditions (e.g., advanced dementia), or use of psychoactive medications (e.g., active use of benzodiazepines). When a patient is unable to provide informed consent, we will seek consent from the patient's legally authorized representative, per the healthcare decision-maker policy at VUMC. To determine capacity to sign the consent

form, all patients will complete a "standardized evaluation to sign an informed consent", as done in prior studies, wherein a research team member provides a hard copy of the consent form and also offers to read the consent form aloud to the patient and then asks five structured questions to determine their level of understanding of study procedures (e.g., "What is one potential risk of being in this study?"; "What would you do if you decided you no longer wanted to participate?"). A patient must answer all questions correctly to be deemed capable of informed consent. Otherwise, their assent is sought along with their permission to contact their surrogate for consent. In the case that a patient's inability to consent is temporary (e.g., delirium, drug effects), the patient will be asked to provide verbal assent in the trial once they are deemed competent to consent (via our standardized evaluation form). Research subjects will have full disclosure of who provided surrogate consent for their participation and retain the right to re-consent or withdraw at the time that they are able to consent for themselves.

The patient consent process will be supplemented with the use of a REDCap-based electronic consent form. The hardcopy consent form has been recreated in the HIPAA-compliant REDCap, and similar to the hardcopy form, it is reviewed and approved annually by the IRB. Additionally, it has embedded videos of a study team NP explaining each portion of the consent form. Potential participants will participate in the consent process by –

1. Being approached in-person at Vanderbilt University Medical Center and reviewing a hardcopy consent form with key study personnel. During the in-person consent process, patients or their surrogates will be consented by a member of the study team (First Preference).
2. If a patient is interested in participation but unable to pass the evaluation to self-consent and a surrogate is not present at the hospital, with the patient's permission, key study personnel will call the surrogate to explain the study and address any questions. A member of the study team will send the surrogate a link to the REDCap consent form for the surrogate to review and sign. The surrogate will also be provided with key study personnel contact information in case they have additional questions. Upon completion of e-consent, surrogates will be able to download a pdf copy of the consent, and key study personnel also print a copy of the signed e-consent and deliver to the patient's room.
3. *During COVID-19 restrictions, the electronic consent process was used for patients who were on isolation precautions.*

All enrolled patients have an alert placed in their medical record to identify them as a study participant, along with a brief study description and contact information for the study personnel (e.g., study coordinator and PI). Additionally, the study team enters an Informed Consent note utilizing VUMC's EMR template to indicate time of consent, IRB number, staff member consenting, patient or surrogate who signed consent, and who witnessed the consent. Upon enrollment, the participant is added to an EMR panel for enrolled patients.

Following enrollment, patients will be randomized into the intervention or usual care control group (see Randomization in the Data Analysis section) using the REDCap randomization feature wherein the randomization schedule is uploaded then automatically assigns allocations to authorized users. Participants will be randomized in a 1:1 ratio using permuted blocks of two or four, where the size for each block is selected uniformly at random. This type of randomization ensures balance across the intervention and control groups after every second or fourth randomization (depending on the size of the current block). This randomization scheme will be generated by computer using the Mersenne-Twister pseudo random number.

STUDY PROCEDURES

Data collection includes patient descriptive data as well as three groups of outcomes: geriatric syndromes, medications and health status, safety and healthcare utilization. Table 1 shows a summary of the study timepoints along with the corresponding assessments. Upon enrollment, hospitalized participants complete interviewer-administered questionnaires, which require approximately 45 minutes per participant. Following

discharge to SNF, facility staff is required to assess all residents upon SNF admission and discharge using the standardized Minimum Data Set (MDS), which includes an assessment of these same geriatric syndromes using similar scales. The baseline hospital questionnaires are repeated by research staff via telephone 7-10 days after PAC discharge and in-person in the participant's place of residence at 90-days after PAC discharge. *(During the COVID-19 pandemic, the VUMC IRB allowed the 90-day visits to be completed as telephone calls or using Vanderbilt's HIPAA compliant video technology to limit exposure risks to both participants and staff).* A telephone interview is also conducted at 60-days post SNF discharge to assess medications and health-related measures. If a participant has a follow-up outpatient visit scheduled at VUMC during any of these time frames, an effort is made to conduct the interview in-person during that visit, if they prefer. For assessments completed in-person, the study team provided hearing and visual aids if necessary (e.g., hearing amplifiers and large font printed response cards with Likert scale categories). Both the intervention and control groups will be monitored using the same data collection schedule and measures. All interview assessments are completed by trained research personnel on our multidisciplinary team which includes a social worker, geriatric nurse practitioners, clinical pharmacists, geriatrician, hospitalist, and psychologist.

In the event a participant is unable to complete assessments due to delirium or cognitive impairment, their designated surrogate or caregiver (e.g., child, spouse, assisted living facility nurse) is interviewed to complete assessments which are validated for use with surrogates. Assessments that can be completed by surrogates include the ICIQ (urinary incontinence), Determine, falls, pressure ulcers, medication history, and demographics.

Patients are compensated upon completion of the baseline (hospital) interview ($10) and again upon completion of the in-residence follow-up interviews ($40). *Due to home visits being stopped during COVID-19, participants were still compensated the appropriate amount, but they received a pre-paid gift card in the mail as opposed to cash.*

Schedule of Assessments

Table 1. Data Collection Schedule

Measures	Baseline Hospital	SNF*	Post SNF Discharge 7-Days Telephone	60-Days Telephone	90-Days In-Person
Descriptives					
Demographics and Length of Stay	X	X			
Charlson Comorbidity Index	X				
Adverse Drug Event Risk Score	X				
Walter Index (Life Expectancy)	X				
Patient Attitudes Toward Deprescribing (PATD)	X				
Primary Outcome – Medications					
Total number of Routine & PRN Medications	X	X	X	X	X
Total number of potentially inappropriate medications (PIMs) and medications associated with geriatric syndromes (MAGS)	X	X	X	X	X
Drug Burden Index (DBI)	X	X	X	X	X
Secondary Outcomes – Geriatric Syndromes, Adherence, Functional Health					
Cognitive Impairment (BIMS)	X	X	X		X

Delirium (BCAM)	X	X			X
Depression (PHQ-9)	X	X	X		X
Urinary Incontinence (ICIQ-UI SF)	X	X	X		X
Unintentional Weight Loss (DETERMINE)	X	X	X		X
Pain (Brief Pain Inventory, BPI-short form)	X	X	X		X
Falls	X	X	X	X	X
Pressure Ulcers	X	X			X
Medication Behavior (ARMS)	X			X	X
Functional Health Status (VES-13)	X		X		X
Safety and Healthcare Utilization Outcomes					
Unplanned Healthcare Utilization (Hospitalizations, emergency room visits)		X	X	X	X
Adverse Drug Withdrawal Events & Adverse Drug Events	X	X	X	X	X
Status: Long-Term Care, Hospice, Death		X	X	X	X

*Secondary outcome measures at SNF phase were assessed by SNF personnel as part of their routine MDS assessments

Descriptions of Assessments

Demographic and Administrative Data: The sociodemographic data collected during this investigation is obtained from multiple sources, including subjects (or proxies) directly via standardized interview protocols and medical records review. Utilizing a standardized form to abstract information from the electronic medical record, a member of the project team collects age, gender, race/ethnicity, home address/telephone contact information, insurance status, outpatient providers and pharmacies, brief health literacy score, and highest education level. We also abstract from the site immediately prior to hospital admission, hospital admission and discharge dates (length of stay), admission diagnoses, hospital service/team, and discharge destination (SNF name/location). Social security number is abstracted and recorded to process the participant payment. These data are verified with the patient or surrogate during the bedside baseline interview. We also track SNF discharge date and length of stay.

Charlson Comorbidity Score[77] ranges from 0 to 31, with a higher score indicating more comorbid illness. There is an additional one-unit increase in the weighted score for every decade starting from age 50. Data sources for comorbidities are the ICD-9 and ICD-10 diagnostic criteria from the 12 months prior to hospital discharge found on the patient's Problem List in the EMR.[78]

GerontoNet Adverse Drug Event risk assessment calculates the older patient's risk for an adverse drug event. The components of the risk assessment include certain medical diagnoses or comorbidities (e.g., chronic kidney disease), which are assessed through ICD-10 codes, notations on patient's problem list, and patient's medical history on their hospital intake and assessment form. The other component is a previous adverse drug reaction, which is included in the bedside baseline interview.

Walter Index is a prognostic tool to predict one-year mortality among older adults after hospital discharge with a higher score indicating a greater likelihood of mortality. The comorbidities and lab values are abstracted from the medical record review, and the activities of daily living assistance is completed based on both medical record review and patient interview.

Patients' Attitudes Toward Deprescribing (PATD) is a 15-item survey of which the first 10 items are part of a 5-point Likert scale ranging from 'strongly agree' to 'strongly disagree.' Examples include: "I feel that I am taking a large number of medicines" and "I believe that all my medications are necessary." The remaining five

questions are related to patient's perception of their total number of medications, history and comfort level with stopping a medication. If the patient is unable to answer, the questionnaire can be administered to the surrogate.

Primary Outcomes - Medications

Total number of Medications: Data sources include the participant's VUMC 'pre-hospital medication list', patient/family interview, pharmacy refill records, Controlled Substance Monitoring Database (CSMD), and outside hospital/PAC medical records. We include both prescription and over-the-counter medications (OTC) (vitamins, herbal supplements also included) administered by the following routes: oral, intravenous, intramuscular and ophthalmologic medications. All participants and/or their surrogates receive a baseline structured interview and chart review to determine any medication that has the potential to be continued at the time of hospital discharge to including pre-hospital medications and active in-hospital medications not on the pre-hospital medication list. Pre-hospital medications are confirmed by patient/ family interview and pharmacy refill records (including mail-order pharmacies) for the three months prior to hospitalization. Patient/surrogate are given specific prompts if they report no OTC usage, for example, asking them if they take anything for sleep disturbances, constipation, or allergies. If a patient is admitted from SNF or an outside hospital, we will request a copy of the MAR for the past 30 days. Current medications are defined as those taken within 30 days prior to hospitalization.[72] At PAC discharge, the discharge medication list serves as the outcome data source. During follow-up calls at 7 and 60 days, study team asks the patient or surrogate for the status of each medication on the enrollment medication list to determine if and how they are taking it. Then the study team prompts for any new medications the patient may be using. In preparation for the 90-day visit, the study team completes a pharmacy record review similar to enrollment. At the 90-day visit, the study PharmD or NP reviews all the medication bottles in the home and asks the patients if and how they are using each.

PIMs are defined by previously published lists including the recently updated Beers criteria,[47] the STOPP criteria,[48, 49] as well as the RASP list,[50] for which there is a large degree of overlap. The total number of PIMs is the sum of medications that are found on any of these explicit lists. The total number of medications related to geriatric syndromes will be based on the detailed lists of specific medications we developed in preparation for this proposal. We also sought to determine the total number of medications that may be contributing to or exacerbating geriatric syndromes in this patient population. To enable this, we developed a unique Shed-Meds knowledge base. Our research team consisted of: PhD Gerontologists, Geriatricians, Hospitalists, Pharmacists, Geriatric Nurse Practitioners, and Specialists (e.g., Urologist, Geriatric Psychiatrist). Based on an extensive literature review, we first compiled a list of all medications potentially contributing to the following six geriatric syndromes: cognitive impairment, delirium, depression, urinary incontinence, unintentional weight loss/appetite decrease and falls. Next, we held a series of team meetings to review each medication list in the context of each syndrome with the goal of reaching consensus based on the following criteria: (1) evidence-based recommendations (randomized controlled trials, meta-analysis, systematic review articles); (2) expert clinical opinion (care practice guidelines, expert consensus, review articles); (3) associated with $\geq$ 5% side effect incidence per the Lexicomp Online® database and/or FDA approved package inserts; and, (4) the potential for over-prescribing in this population.

Drug Burden Index (DBI): A DBI score is calculated separately for anticholinergic (DBI_{AC}) and sedative medications (DBI_S), which have been strongly linked to functional impairment,[6, 7, 16, 84] falls[85-87] and delirium.[88-92] The drug burden is the sum of each individual anticholinergic/sedative medication's prescribed daily dose divided by the sum of the minimum effective dose (as estimated by the FDA minimum recommended dose) and the patient's daily dose. The DBI includes over-the-counter medications. We will calculate the DBI at the time of randomization, hospital discharge, PAC discharge, and all follow-up timepoints. Importantly, the DBI captures reductions in dose, even when total number of medications is not reduced.

Secondary Outcomes - Geriatric Syndromes, Medication Adherence, Functional Health Status

Delirium: The Brief Confusion Assessment Method (bCAM) is a brief screening tool for delirium and has been validated among hospitalized, older patients.[67, 68] If the participant screens positive for delirium, no other participant interviews are conducted at that time. Research personnel continue to re-assess delirium daily during hospitalization; and, when the participant screens negative for delirium via the bCAM, the remaining assessments are administered to the participant. If delirium continues throughout the hospital stay or the participant is otherwise unable or unwilling to complete the assessments, the surrogate is approached for a sub-set of the geriatric syndrome assessments (i.e., incontinence, nutrition and fall history). The bCAM is not repeated by research personnel at 7-day follow-up because it has limited validity when administered via the telephone; thus, it is repeated only at 90-day follow-up during the in-person home visit. Additionally, PAC personnel use the CAM (i.e., the Confusion Assessment Method, [CAM]), which is a modified version of the bCAM, to assess delirium during the PAC stay via the MDS assessment.

Cognitive Impairment: The Brief Interview for Mental Status (BIMS) is a short, validated assessment of cognitive impairment with a total score range from 0 to 15 (0-7: severe impairment; 8-12: moderate impairment; 13-15: cognitively intact).[65, 66] The BIMS is routinely used in the SNF care setting as part of required MDS assessments for all SNF patients upon admission and discharge and following a hospitalization event.

Depression: The Patient Health Questionnaire (PHQ)[79] is a validated tool to assess depression symptoms and severity. Each item is scored from 0 ("not at all") to 3 ("nearly every day") to yield a total score range from 0 (no depressive symptoms) to 27 (severe depression). In the event that a participant reports severe depression or thoughts of self-harm, the study team elicits more information to evaluate their immediate safety then contacts the primary treatment team to address this with the participant. The PHQ-9 is routinely used in the SNF care setting as part of required MDS assessments.

Urinary Incontinence: The International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF)[80] consists of four items that assess the symptoms, frequency and impact of urinary incontinence on quality of life. This tool has well established reliability (Crohnbach's alpha = .95) and validity, including sensitivity to treatment.[80] The MDS has one item for incontinence frequency scored 0 'always continent' to 3 'always incontinent'.

Unintentional Weight Loss and Poor Appetite: We use the same structured interview used in our prior study to assess recent changes in weight and/or appetite in addition to the 10-item "Determine Your Nutritional Health checklist", which yields a total nutritional risk score of: 0-2 ("low"), 3-5 ("moderate"), or $\geq$ 6 ("high"). The DETERMINE checklist has been validated in a longitudinal study of community-dwelling older adults.[81] If the participant endorses a weight change of 10 pounds or more on the DETERMINE item, a structured follow-up question is posed to clarify whether the weight change reflects a gain versus a loss. The MDS has one item for unintentional weight loss, defined as 5% or more in 30 days or 10% or more in 180 days.

Pain: Pain will be assessed using the Brief Pain Inventory (BPI) Short-Form, which is a validated instrument for assessing pain location, severity, and interference with daily activities among older adults.[82, 83] Pain severity is based on four questions wherein participants use a 0 (no pain) to 10 (worse pain imaginable) scale to rate their pain in the last 24-hours under four conditions: at its worst, at its least, on average, and now. Pain is assessed in the PAC setting via the MDS, which includes items related to pain frequency, effect on function and intensity.

Falls: The patient/surrogate is asked if the patient has fallen in the last month or since the previous timepoint during the follow-up phase. If the response is 'yes,' then the patient is asked how many times they have fallen, and that number is recorded. Finally, the study team asks if any of the falls led to either an emergency room visit or hospitalization.

Pressure Ulcers: The presence of pressure ulcers (Stages 0 – 4) will be abstracted from the hospital medical record (flowsheets) at baseline and confirmed via direct interview with the patient and/or family. Similarly, this same information will be, again, abstracted from the PAC medical record and confirmed via patient/family interview during an in-person visit 7 and 90-days post PAC discharge.

Adherence to Refills and Medications Scale (ARMS): The ARMS consists of 12 items to assess overall medication adherence, with a total score range of 12 to 48. A lower score is indicative of better medication adherence.[91] Example questions include: "How often do you forget to take your medicines?", "How often do you miss taking your medicines when you feel better?", and "How often do you put off refilling your medicines because they cost too much money?" Response options are on a 4-point Likert scale that ranges from "none of the time" to "all of the time."

Vulnerable Elders Survey (VES-13) is a functional measure of health status that assesses a patient's cognitive, physical and self-care activities and which also includes an item for self-rated health status. Scores range from 1 to 10, with lower scores indicative of better health.[94, 95]

Safety and Healthcare Utilization Outcomes

Unplanned Healthcare Utilization and Patient Status: We will request a release of healthcare information as part of our consent, which will provide permission to track healthcare utilization (ER visits, hospitalizations) at VUMC or elsewhere during the study period. We will contact the PAC care providers weekly during each participant's PAC stay to track their status and will follow-up 7, 60, and 90 days after PAC discharge with each participant. If a participant has been moved to hospice care, they will be withdrawn from the study.

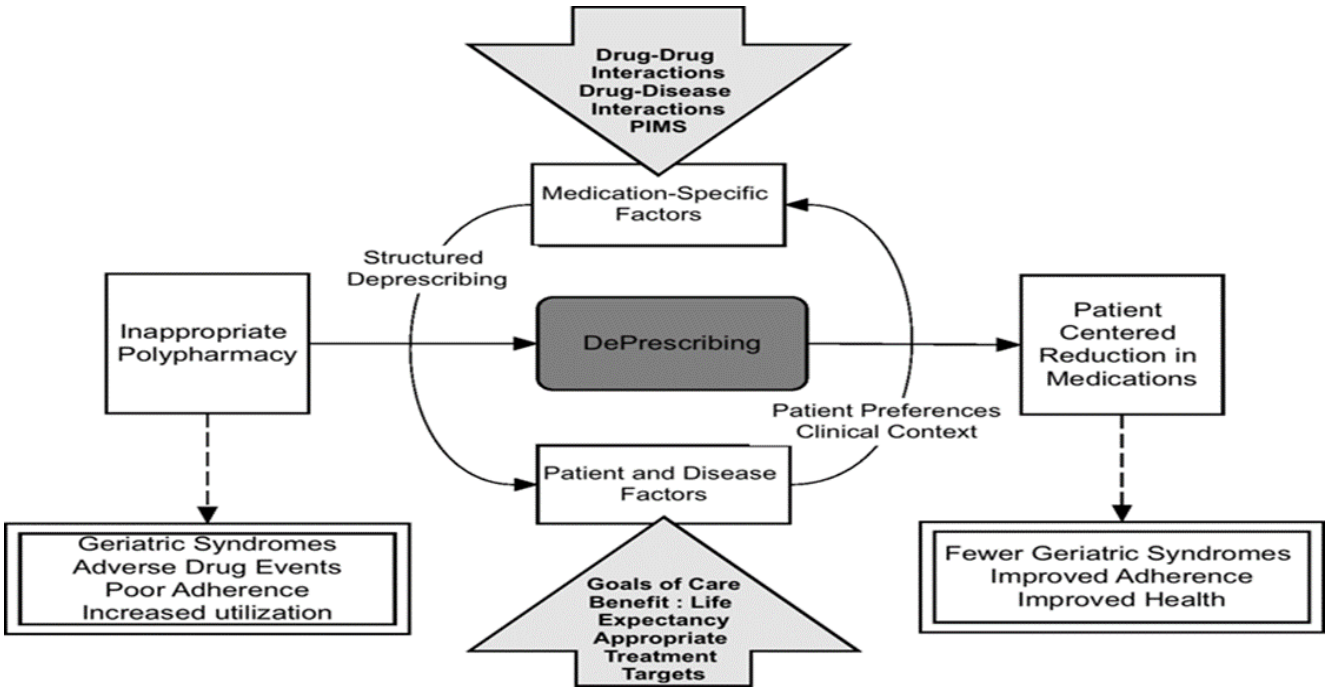
Adverse Drug Withdrawal Events (ADWEs): Any unplanned healthcare utilization event (i.e., acute hospitalization, emergency room visit) will be assessed by blinded physician co-investigators for ADWEs. This assessment will include validated scales such as the Naranjo. A detailed description of the adjudication procedures can be found in the *Safety Assessments* section of this protocol.

STUDY INTERVENTION

Our deprescribing protocol is based on a conceptual framework by Holmes that considers patient and disease factors, goals of care, appropriate treatment targets, and the duration of treatment required for benefit (Figure 2).[52] We also incorporated medication-specific factors from Scott's framework for minimizing inappropriate medication use, such as drug-specific safety profiles and drug-drug and drug-disease interactions.[71] Finally, patient preferences were viewed as a key component that informs final deprescribing actions by identifying medications the patient is willing to deprescribe (e.g., due to lack of efficacy, poor compliance, side effects, or cost burden) as well as potential barriers to deprescribing (e.g., concerns about worsening of symptoms). Specifically, our goal was to identify opportunities for deprescribing wherein clinical evidence aligned with patient preferences.

Conceptual Model

Figure 2. Deprescribing Framework

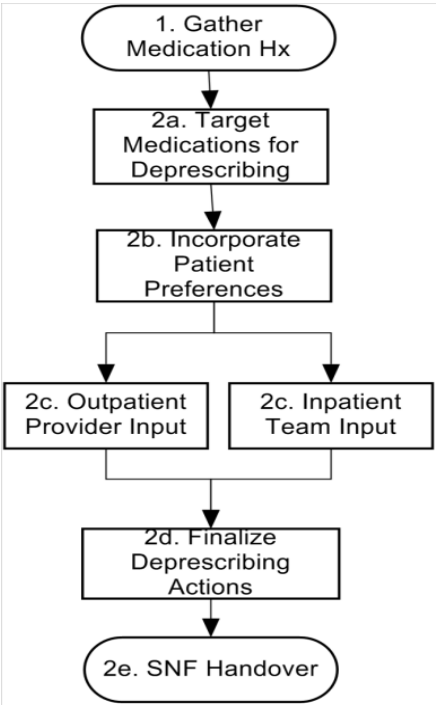


The intervention has five steps after the initial medication history is collected during baseline assessments. Each step is described in detail below, and the Figure 3 shows the order of the intervention. While patients randomized to the intervention group receive this protocol, patients randomized to the control group receive usual care from the hospital and PAC treatment teams.

Pre-Review (Target Medications for Deprescribing)

Following the baseline patient/surrogate interview, a study clinical reviewer (pharmacist, geriatric nurse practitioner, or physician) receives the reconciled total enrollment medication list. Using medical record data only such as the history and physical, lab values, physician notes, etc., reviewers will first identify a Medication – Indication pairing for each medication (i.e., clinical reviewers try to establish an indication diagnosis or symptom which the medication treats). If an indication does not exist, "no indication indicated" is specified. For each medication recommended for deprescribing, the reviewer chooses one of the following actions: (1) Stop prior to hospital discharge without need for monitoring; (2) Stop prior to hospital discharge with symptoms/physiologic monitoring; (3) Stop at specified time point following hospital discharge; (4) Reduce over time with monitoring until medication is stopped; (5) Reduce to lower dose without need for monitoring; (6) Reduce to lower dose with symptoms /physiologic monitoring. Then the clinician selects a de-prescribing rationale, and they may select more than one rationale (i.e., choose all applicable rationales) from Table 2.

Figure 3. Deprescribing Protocol



All medications, both prescription and OTC including vitamins and herbal supplements, are reviewed for potential deprescribing. Select medication classes will not be under consideration for active deprescribing, which include the following:

- Anti-rejection medications for organ/ bone-marrow transplantation
- Chemotherapeutic medications for the treatment of known solid organ or hematologic malignancy.

The above medications may be deprescribed during the study period; however, it would solely be under the direction and recommendation of the primary treatment team or primary prescriber of the medication.

Table 2. Deprescribing Rationale

A. No indication for medication / Indication not clear B. Wrong dose or directions for medication C. Inappropriate for current indication due to: 1. Indication has resolved 2. Patient is below treatment threshold 3. Treating guidelines have changed, medication no longer indicated 4. Wrong Indication for medication D. Medication is ineffective as evidenced by no change in symptom or condition E. Duplicate medication for same indication	F. High risk medication based on: 1. Potential drug-drug interaction 2. Potential drug-disease interaction (e.g. associated with geriatric syndrome) 3. On Explicit list of PIMs (i.e., Beer's list[47], STOPP list[48, 49], and/or RASP list[50]) G. Medications are inconsistent with goals of care H. Risk > benefit given patients limited life expectancy I. Evidence of poor adherence or high risk of poor adherence (directions impractical, high cost) J. Medication currently indicated, however is time-limited and expect indication to resolve

Although any rationale may be appropriate for deprescribing medications, clinician-reviewers will establish a priority level of 1 (low) to 10 (high) for discussing deprescribing recommendations. Priority will take into consideration the potential harm of the medication and their relation and potential effect on geriatric syndromes. Deprescribing prioritization will be performed for several reasons. First, in some circumstances, it may be inappropriate to deprescribe multiple medications simultaneously; thus, prioritization may guide the deprescribing

order. Second, the above rationales may not have equal influence on deprescribing decisions and prioritization provides an opportunity to weigh the potential value.

Incorporate Patient Preferences

Following medication targeting (Figure 3. 2a) intervention participants or their surrogates receive a structured interview by the intervention pharmacist (PharmD) or nurse practitioner (NP) to elicit their preferences regarding medications identified for deprescribing. Surrogates are included in the conversation if the patient's cognitive deficits preclude their ability to fully participate, if the patient prefers to have the surrogate involved in decision making, or if the surrogate has a role in the patient's medication management. The following is assessed for each targeted medication: medication adherence, possible side effects, perceived benefit (or harm) of the medication, cost, and agreement/ disagreement to stopping or reducing the medication. As part of this interview the PharmD or NP may need to provide patient education about individual medications (e.g., side effects, risk-benefit, current evidence) and address any questions or concerns before asking if the patient agrees to deprescribe. If the patient raises a concern about a medication which the study team did not target for deprescribing, the PharmD or NP should still address these concerns and note them in communications with the treatment team. Finally, if a patient agrees to deprescribe a medication for which they have refills, the PharmD or NP informs them that we will be canceling the refills if their provider agrees.

Study clinicians take field notes during the interview in which they detail the patient's general comments about medications and prescribers as well as the rationale for the patient's agreement/disagreement with each deprescribing recommendation. After the interview these comments are coded into pre-set barriers and enablers (e.g., appropriateness, fear, process, influences, pragmatic, and dislike) from an established framework. Patient/ surrogate comments can align with more than one category for each medication and should be coded as such. A second study team member, usually the study coordinator or data manager, independently reviews the interview comments and coded for agreement. If there is disagreement related to categorization, the team discuss the theme assignment until a consensus is reached.

Outpatient Provider Input

Intervention PharmDs or NPs inform patients and in-hospital providers of our intent to engage primary prescribers (Figure 3. 2c) in the deprescribing decisions and ensure they have the final medication list at the time of PAC discharge to incorporate into their medical records for continued medication management. The goal of these conversations is to obtain provider feedback about the proposed changes and facilitate medication updates in the medical record. Additionally, these conversations will hopefully lead to sustained deprescribing by engaging the primary provider early in the process.

Study team clinicians can contact VUMC providers through the EMR messaging service or by paging their clinic. Outside providers are engaged via telephone. In either case, the study clinician provides a brief description of the study, the medication for deprescribing and the rationale, and finally explains the patient's willingness to deprescribe. Much like the patient preference interview, the study PharmD or NP documents the original prescriber's agreement/disagreement and rationale for their decision. These field notes are coded into pre-set barrier and enabler categories (e.g., inertia, self-efficacy, feasibility) from a published framework.

Inpatient Provider Input

The inpatient treatment team is responsible for the final deprescribing actions of the hospital phase of the intervention. The study team PharmD pages the treatment team at enrollment to notify them that the study team will contact them to provide medication recommendations. After contacting outpatient providers, the study PharmD or NP contacts the inpatient team and explains the recommendations and rationales Figure 3. 2c). Again agreement/disagreement and provider reasoning are documented and classified in the same manner as with outpatient providers.

Final Hospital Deprescribing Actions

The final in-hospital phase of the deprescribing protocol requires that the study PharmD or NP assimilate the data from all three phases (Figure 3. 2a, 2b, 2c) to finalize deprescribing actions. Deprescribing can begin at any time after randomization and following step 2a – 2c. All deprescribing actions are executed by the inpatient treatment team using recommendations from the study PharmD or NP. Recommendations include input from the intervention team, patient, inpatient treatment team, and the original prescriber(s) when available.

We anticipate that there will be disagreement between clinical reviewers, inpatient teams, primary prescribers and patients. The incidence and nature of the disagreement will be monitored closely. In anticipation of disagreement the following guidelines will be in place. First, deprescribing of pre-hospital medications will not be recommended to the treatment team (acute or post-acute) without patient agreement. Deprescribing of medications will be recommended against a patient's preferences when there is a clear indication of imminent safety threats as determined by the intervention pharmacist / NP, inpatient clinical team, or primary prescriber. Otherwise, we will first counsel the patient regarding the rationale for the deprescribing recommendation and seek consensus. If disagreement continues, we will monitor the medication throughout the intervention phase for side effects. In addition, we will highlight this medication at discharge for follow-up by the primary prescriber. All final deprescribing actions will be carried out by the inpatient treatment team.

PAC Handover and Ongoing Deprescribing at PAC Facility

Within 24-hours of transition to PAC, a study pharmacist or NP has a phone conversation with a designated PAC provider with prescribing authority (NP or physician) to review the Transfer Medication List, highlight deprescribed medications and the need for medication-specific monitoring. In addition, all medications recommended for deprescribing may not be stopped prior to hospital discharge in the interest of first monitoring symptoms and ensuring safety or due to delayed contact and input from the outpatient prescriber. Medications for additional deprescribing at the PAC may be highlighted during this initial handover and discussed again in weekly follow-up calls while the patient remains in PAC (Phase 3).

Following PAC handover, we initiate a weekly conversation via telephone with the designated PAC provider to review intervention participants' medication administration record (MAR) and any drug withdrawal events. Reasons for modifying the Transfer Medication List during the PAC stay will be discussed and intervened upon as necessary. The intervention also will continue for participants readmitted to VUMC directly from PAC (estimated 20%) and continue upon transfer back to the PAC. The study PharmD or NP may also continue to communicate with the original prescriber/ outpatient provider during the PAC stay to confirm their agreement with medication changes. At the time of discharge from the PAC facility, a final reconciled medication list will be sent to the patient's primary outpatient providers along with suggestions for continued medication management and deprescribing as well as any explanations for other medication changes made.

For analytical and feasibility purposes, the intervention ends at the point of discharge to home. If a patient discharges to home instead of a partner PAC facility, they will be withdrawn from the study and only considered to have one phase of the intervention. For safety reasons, the study team provides their outpatient provider with the final discharge medication list highlighting any symptom monitoring required.

SAFETY MONITORING AND ASSESSMENTS

We have established a system to report and track adverse events (AEs) including adverse drug withdrawal events (ADWEs), serious adverse events (SAEs), and Suspected Unexpected Serious Adverse Reaction (SUSARs). In this study, an AE is defined as any unplanned healthcare utilization or unexpected death (i.e., patient not receiving hospice services at time of death). These AEs are considered SAEs if they include any untoward medical outcome that results in the following: inpatient hospitalization or prolongation of existing hospitalization, life threatening

condition with immediate risk of loss of life (including escalation of hospital care to Intensive Care Unit), or unexpected death. A SUSAR is an SAE that is suspected to be secondary to the drug withdrawal and is unexpected. Study personnel will monitor the safety of subjects and follow them until the event resolves or is explained.

Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Notification of Unplanned Healthcare Utilizations and Deaths

Unplanned healthcare utilization (intensive care unit transfers, emergency department visits and/or hospitalizations) and deaths are monitored throughout all study phases for each participant. Both the study coordinator and the data manager have access to a study patient panel in the electronic health record. As such, any time a participant is admitted to the VUMC Emergency Room, VUMC Inpatient Services, or the participant's medical record is updated to indicate death, the coordinator and data manager receive a notification. To determine if a participant had an unplanned healthcare utilization at an outside hospital (OSH), the participants are asked at each follow-up time point if they have been to an emergency room or had an inpatient stay, and if so, at what facility. The study coordinator and data manager are responsible for requesting medical records from OSHs (and SNFs) relevant to the utilization.

Review of Unplanned Healthcare Utilizations and Deaths

Any unplanned healthcare utilization (e.g., hospitalization, ER visit) or unplanned death (e.g., patient not receiving hospice care) is reviewed to determine if it was an adverse event that was serious, related to the study, and unexpected (SUSAR). Once all necessary records have been obtained and collated by the study coordinator, the case is assigned to a physician co-investigator (adjudicator) blinded to group assignment. Through a structured review protocol of all relevant medical records from both within and outside of VUMC (e.g., admission medication lists, discharge lists, SNF MAR, available outpatient notes, laboratory results, etc.), the adjudicator uses an established methodology to determine the presence of serious medication errors.

Clinician-adjudicators will decide whether the unplanned healthcare utilization is related to medication withdrawal (i.e., ADWE) using the 10-question Drug Withdrawal Probability Scale,[96] a scale based on the Naranjo algorithm,[97] which is a validated scoring system to assess causality of adverse drug events. ADWE will be coded as definite (>8), probable (5-8), possible (1-4), and doubtful (<1). For all ADWEs, clinician-adjudicators will then determine whether it was avoidable by any change in management. Differences between adjudicators will be resolved through discussion or, when necessary, the involvement of a third adjudicator.

After review by the clinician-adjudicator, the case is sent to the Principal Investigator to review. Both the PI and a co-investigator appointed by the DSMB review to determine if the event was unexpected and/or study related. Should the event be determined as SUSAR (serious, unexpected, and study related) it will be reported as such to the DSMB and IRB as outlined below.

Serious Adverse Events and Reporting Procedures

To ensure proper and timely reporting of adverse events, the following communication plan is utilized. The project coordinator is responsible for reporting adverse events to the NIA/DSMB and the IRB in a timely manner and in accordance with each group's guidelines. Our procedures are as follows:

1. NIA/DSMB: The NIA project officer and chair of the DSMB will receive a monthly listing of all adverse events, including a brief synopsis, by type of event and group. The NIA project officer will receive a semi-annual report with enrollment updates, attrition numbers, and adverse events data (i.e., group comparisons, individual case listings), which he then distributes to DSMB members in advance of the semi-annual meeting. The project officer will be notified of all participant deaths, regardless of study relatedness, within 48 hours of PI notification of the death.
2. IRB: PIs will notify the IRB of any Serious, Unexpected, Study Related Adverse Event within 7 days of PI notification of the event. Any noncompliance with the IRB approved protocol that increases the risk or

affects the patient's rights, safety, or welfare also need to be reported within one week. At the time of the IRB annual continuing review, the IRB receives copies of the reports generated from DSMB meetings. If the DSMB meeting report identifies a new risk to or a change in the risk benefit ratio, the IRB will be notified within 10 days of PIs receipt of the report.

STATISTICAL CONSIDERATIONS

Sample Size and Randomization

Figure 1 illustrates the flow of participants through the study and estimated total sample sizes during each study phase based on prior data. The overall effectiveness of the intervention will be evaluated based on the primary outcome measure, which is total medication count. Based on current enrollment rate, we estimate that approximately 144 patients per year will enroll in the study, or 576 across all four years of enrollment. Among those, we estimate that 27.5% will either die or otherwise be lost from the study prior to the 90-day post PAC discharge follow up period. Thus, across all four years of enrollment, an estimated 420 patients will contribute measurements at 90 days. Although 567 is the expected total enrollment, we conservatively use 420 to estimate the statistical power associated with the assessment of overall effectiveness (i.e., overall completion rate) rather than enrollment rate, to account for estimated attrition across all study phases.

Preliminary data is available for the effect of deprescribing on the reduction in the counts of total medications.[97] Our pilot intervention (N=40) was associated with roughly a 50% reduction in the count of total medications from enrollment to hospital discharge, whereas a roughly 25% reduction was observed in the control group receiving routine hospital care. Using these preliminary data and mixed-effects Poisson regression methods, we implemented a simulation-based power analysis wherein we assumed that this effect would be attenuated by 20% at SNF discharge, and again by 20% at the 90-day follow up. Using a sample size of 420, there is greater than 95% power to detect a 50% versus 25% reduction in total medications. There is approximately 90% power to detect a 30% versus 25% reduction in total medications, and 80% power to detect a 27.5% versus 25% reduction in total medications. Thus, the target sample size provides some protection against effects that are substantially smaller than that observed in our preliminary data.

Participants will be randomized in a 1:1 ratio using permuted blocks of two or four, where the size for each block is selected uniformly at random. This type of randomization ensures balance across the intervention and control groups after every second or fourth randomization (depending on the size of the current block). This randomization scheme will be generated by computer using the Mersenne-Twister pseudo random number.

Interim analyses and Stopping Rules

Interim analyses will be conducted to evaluate safety endpoints but will not be conducted to evaluate conditional power (futility) or to assess efficacy.

Safety is evaluated by examining group differences in death and serious adverse events semi-annually in conjunction with scheduled DSMB meetings to evaluate the safety of the study intervention, and the associated risk-to-potential benefit ratio. The Principal Investigators will address study efficacy only at the end-of-study, and thus will not consider terminating the trial early on the basis of conditional power (futility) or evidence of efficacy. This is because firm evidence will be required to change current clinical practice, and because trials that have stopped early for efficacy often report implausibly large effect sizes (and therefore should be considered with skepticism).[41] At the conclusion of each DSMB meeting, the Board should take into account the statistical evidence (as summarized by the relative hazard of safety endpoints and the corresponding 95% confidence interval) as well as practical and clinical considerations to make one of the following recommendations based on safety:

1. Suspend enrollment due to safety concerns secondary to study intervention including:

a. A difference in all-cause mortality between patients randomized to the deprescribing intervention versus usual care such that the DSMB deems the difference to be study-related and excessive.
b. A difference in drug related SAEs between patients randomized to the deprescribing intervention versus usual care such that the DSMB deems the difference to be study-related and excessive.

2. Continue enrollment

Outcomes

Hypotheses 1a-1b: The effect of the intervention on the total number of medications, PIMs, and medications associated with geriatric syndromes at hospital discharge, SNF discharge, and at 90-days following SNF discharge will be assessed using mixed effects Poisson regression, allowing for overdispersion (more or less variability than is expected under the Poisson regression model), and adjusting for measurement time point (as a categorical covariate) and the total number of medications at participant enrollment. The within-subject correlation among repeated measurements will be modeled using a random intercept term, indexed by subject. The intervention effect at each time point will be summarized using a Wald-type 95% confidence interval. Statistical significance will be indicated if the 95% confidence interval excludes the value zero (i.e., the Poisson regression intervention effect under the null hypothesis). Model fit will be assessed by examining the associated Pearson residuals and using other graphical methods. Alternative regression techniques may be used in the case of poor fit, for example, negative-binomial regression.

Hypothesis 1c: The effect of intervention on the anticholinergic and sedative medication drug burden scores at hospital discharge, SNF discharge, and 90-days following SNF discharge will be assessed using linear mixed effects regression, adjusting for measurement time point, and using a random intercept term indexed by subject. Intervention effects will be summarized using 95% confidence intervals. Model fit will be assessed using residual diagnostics and graphical methods. Due to the constrained nature of the score values (0-1 for anticholinergic and sedative drug burden scores), an alternative method may be required, such a 'beta' regression, which is suitable when such scores frequently occur at a boundary (0 or 1).

Hypothesis 2a: The prevalence and severity of geriatric syndromes will be analyzed at each time point following SNF discharge. The effects of intervention on the prevalence of each type of geriatric syndrome will be assessed using mixed-effects logistic regression, adjusting for measurement time point (categorical). The severity of each geriatric syndrome is measured on an ordinal scale. Thus, severity will be analyzed using mixed-effects proportional odds logistic regression, also adjusting for measurement time point. For either method, the correlation among repeated measures will be modeled using a random intercept term indexed by subject. The effects of intervention at each time point will be summarized using the odds ratio with Wald-type 95% confidence intervals. Statistical significance will be indicated when the 95% confidence interval excludes the value one (i.e., null hypothesis value for both types of logistic regression). Model fit diagnostics and alternative analysis strategies will be considered as described for Hypotheses 1a-1c.

Hypothesis 2b: Patient medication adherence will be measured using selected questions from the ARMS, based on an ordinal scale. Functional health status will be measured using the VES-13 total score, which is also an ordinal outcome. The effects of intervention on these outcomes will be assessed at 7 and 90-days following SNF discharge using mixed-effects logistic regression or proportional odds logistic regression in a manner that is analogous to that described for Hypothesis 2a.

Safety Analyses

All-cause mortality will be quantified by the count of deaths per person-months (28 days) of observation by intervention/usual care group. These values will be computed overall and stratified by study phase. Thus, the maximum follow-up period for mortality (and other safety outcomes) is 90 days after SNF discharge. Cox proportional hazards regression will be used to quantify statistical uncertainty about the effect of intervention on

the hazard of death (overall and separately within study phase), which will be summarized using the hazard ratio and corresponding Wald-type 95% confidence interval.

The incidence and timing of (potentially recurrent) adverse events will be quantified, for each type of event both overall and stratified by study phase, by counting the number and fraction of affected participants, by tabulating the number of events per participant, and the total number of events per person-months. The effect of the intervention on the hazard of each adverse event type (overall and separately within study phase) will be quantified using Cox proportional hazards regression in a recurrent events (frailty) configuration, which accounts for between-subject heterogeneity in the baseline hazard of recurrent events. In other words, this approach accounts for the within-subject correlation among recurrent event times. The hazard ratio will be summarized using a Wald-type 95% confidence interval.

If there are sufficiently many events, the Nelson-Aalen estimator of the baseline hazard will be used in conjunction with the estimated hazard ratio to estimate median survival with Wald-type 95% confidence interval, for each type of adverse event. Graphical regression diagnostics will be used to evaluate model fit and modeling assumptions of the Cox proportional hazards method.

Data Analyses

Missing Data: We have extensive preliminary data describing attrition due to mortality which should not differ between the intervention and control groups. However, we cannot exclude the possibility that missing data will be associated with intervention. We will examine the incidence of missing data by group. If imbalances are found, we will implement a series of sensitivity analyses, using multiple imputations, to assess the degree of bias that might be induced by missing data.

Randomization, intent-to-treat, and safety outcomes: Participants will be assigned to the usual care control group or the intervention group in a completely randomized fashion (i.e., without blocking or stratification). The effectiveness of randomization will be assessed by summarizing the balance of baseline demographic and clinical factors across randomization groups. The sample mean, standard deviation, and five-number summary will be used to summarize continuous variables. The count and proportion will be used to summarize categorical variables. All randomized patients who complete Phase 2 (i.e., discharged to a partner SNF) will be included in analyses. We will implement both intent-to-treat and per-protocol analyses.

Repeated measures: Barring study withdrawal or death, each participant will be assessed at multiple time points. We anticipate that such repeated measurements will exhibit correlations across time points. Our statistical plan takes full advantage of this information by using a mixed-effects framework for each analysis. In the event that a mixed-effects technique cannot be implemented, an alternative method will be used and the standard errors of effect estimates will be adjusted using the Huber-White ‘sandwich’ method.

Limitations: The proposed intervention will be implemented during hospitalization and will continue during the patient’s SNF stay because there is a high probability that new medications, including PIMs, will be added during these care transitions. However, we acknowledge that new medications also might be added after PAC discharge; thus, we have incorporated intervention components that should, at least partially, mitigate this problem. Specifically, we will communicate with pharmacies and known community providers so that they are aware of the patient’s preferences and final discharge medication list. We also will determine during the 7-day post PAC follow-up if intervention patients are taking medications that were previously stopped but which are still in the home. We will assess changes in medications for both intervention and control patients for 90 days post PAC discharge and, thus, be able to determine if intervention components need to be extended past PAC discharge.

The randomization of patients prior to hospital discharge, as opposed to randomization by PAC discharge location, has numerous advantages and is necessary because it is not possible to determine which PAC a patient

will ultimately go prior to implementing the deprescribing intervention. This approach does, however, increase the risk of contamination because both intervention and control group participants will be discharged to the same PACs; thus, there is a possibility that PAC providers will change their medication practices for control participants as a result of our active monitoring of medication changes for the intervention participants. We will be able to detect such contamination effects by comparing changes in the medication lists from hospital to PAC discharge for both intervention and control groups, with the expectation of fewer changes in the intervention group. We believe the risk for contamination is minimal as there was no evidence of contamination effects in our pilot intervention, and PAC providers will not be asked to actively deprescribe beyond following the deprescribing actions recommended by the research team, many of which will be initiated prior to hospital discharge. Finally, PAC and hospital providers may not be equipped to overcome many of the barriers to deprescribing that will be addressed with our Shed-MEDS protocol.

DATA COLLECTION AND QUALITY ASSURANCE

Data Collection Forms

Data is obtained from multiple sources including subjects (or surrogates) directly via standardized interview protocols, electronic medical records (both hospital and PAC), hospital databases, and pharmacy records. All patient assessments, both interviews and medical record reviews, are recorded on paper forms stamped by the Vanderbilt IRB. Hardcopy forms should use the participant's randomly assigned ID number. Utilizing case report forms allows for quality assurance reviews of data entered in the electronic (REDCap) databases.

Data Management & Storage

All paper case report forms are maintained in a secure and locked file cabinet in a secure and locked office. Data collected from patient assessment and medical records are entered directly into Research Electronic Data Capture (REDCap) databases on the Vanderbilt username/password protected server. Use of REDCap outside the Vanderbilt server is allowable; however, it requires two factor authentication for security purposes. Assessment and interview forms are entered within the same week of data collection, and if possible, the same day.

Study coordinators will maintain SPSS databases for study tracking purposes. These databases along with data exported from REDCap for reporting and analysis purposes are maintained on a password protected VUMC secure server, which is only accessible to key study personnel registered with the IRB. Information in the REDCap databases and the secure server will be stored for an indefinite period of time to allow for subsequent data analysis and future reference.

Quality Assurance

No quality assurance training or metrics are required beyond IRB training and VUMC confidentiality standards. To reduce data entry errors, the REDCap databases have been created in a longitudinal model to match the paper case report forms and including branching logic and automated syndrome scoring. Additionally, to ensure integrity of the data, the project coordinator and data manager conduct weekly data reviews to check for both completion and accuracy.

PARTICIPANT RIGHTS AND CONFIDENTIALITY

Shed-MEDS deprescribing intervention meets the criteria for human subjects research and, as such, is subject to a standard review by the institution's review board. All protocols, consent forms, and research materials were submitted to the Vanderbilt IRB as part of the pilot intervention and were approved. The study is subject to annual review by the IRB. In accordance with VUMC policy, all key study personnel complete human subjects training

annually and Good Clinical Practice training every three years. Below is a description of the key human subjects materials submitted to the IRB.

Rationale for studying a potentially vulnerable population

Patients with cognitive impairment or dementia represent a population at potentially increased risk for worsened outcomes associated with polypharmacy. Thus, it is important to understand the effect of deprescribing on this vulnerable population. Patients with moderate impairment will likely need a surrogate to provide consent and complete some study measures. Patients with mild impairment may (not) need a surrogate to provide consent. We will complete a "standardized evaluation to sign informed consent" for all eligible patients with cognitive impairment based on the BIMS (see *Recruitment and Informed Consent Procedures*). Based on the distribution of BIMS scores, we may examine intervention effects by cognitive status via sub-group analyses.

Patients with a history of seizures on and off antiepileptics who otherwise meet study eligibility criteria will be considered eligible for enrollment. Antiepileptic medications are commonly used in the treatment of non-epileptic conditions. Although, the presence of a seizure disorder will not be a contraindication to deprescribing, patients who are currently on a therapy specifically for this indication will be continued on antiepileptic medications and managed by the medical team, as per usual care practice.

Approach to potential risks of the proposed study

The potential risks of deprescribing medications include, but are not limited to, adverse drug withdrawal reactions, pharmacokinetic and pharmacodynamic changes in other medications, and return of a medical condition.

Physiologic Drug Withdrawal: In retrospective studies of medication cessation, 1 in 5 older outpatients experienced an adverse withdrawal reaction, however only 12% of these reactions were assessed to be physiological reactions to medication withdrawal. These included B-blockers, benzodiazepines, clonidine, nortriptyline, and prednisone.[96] The only risk factor for ADWE found in this study was the number of medications stopped (OR = 1.90, 95% CI 1.33 to 2.67). All reactions occurred within 30 days of discontinuation. Patient age, baseline comorbidities, and number of baseline medications were not associated with ADWEs. A separate study showed that only 1% of unplanned emergency department visits were due to withdrawal reactions.[98] We will mitigate the potential for physiologic withdrawal by identifying those medications with the highest likelihood of physiological withdrawal, including benzodiazepines, opiates, B-blockers, alpha blockers, and tricyclic antidepressants. Any medication believed to have increased potential for physiologic withdrawal will undergo a prescribed drug taper, where the identified drug will not be reduced by more than 25% during any 1 week interval when a patient is receiving greater than the minimum therapeutic dose. In addition to staged tapering of the medication, patients will be receiving continued care in a post-acute care facility, where patients are observed daily by licensed nurses for vital sign and symptom changes. Medications can be restarted or increased at any time should a physiologic drug withdrawal effect be detected.

Pharmacokinetic and Pharmacodynamic Changes: Medication cessation may additionally alter pharmacokinetic and pharmacodynamic profile of medications. This may include medications that inhibit or potentiate the cytochrome P450 enzyme inhibitor, thus alerting clearance of specific medications. Alternatively, some medications may have opposing effects on blood pressure or electrolytes (e.g., potassium). All deprescribing actions will be made by a trained pharmacist and clinicians. In the case that there is believed to be a potential change in pharmacokinetics or pharmacodynamics, deprescribing pharmacists / NPs will alert the primary medical team and make recommendations for surveillance of symptoms, signs (e.g., vital signs), labs (e.g., electrolytes, INR), or follow-up tests (e.g., EKG). Medications can be restarted or increased at any time should adverse pharmacokinetic or pharmacodynamics effects be detected.

Medical Condition Exacerbation: The most expected side effect of deprescribing is the return of the condition for which the medication was initially prescribed. A medication may be intentionally reduced or discontinued in the

absence of symptoms or signs to determine if the medication is still required to maintain control of a medical condition. In the Graves et al. study, 88% of all ADWEs were due to medical condition recurrence. Published data, however, does suggest that medication deprescribing for specific conditions (e.g., hypertension, osteoporosis, hyperlipidemia, angina) can be done without serious adverse effects.[99-102] A strength of this trial is that we will be able to monitor for exacerbations of medical conditions in a post-acute care setting (mean length of stay = 26.9 days), where monitoring of vital signs and symptoms are done daily by licensed nurses. In addition, during the "SNF handover" process, all discontinued medications will be clearly delineated along with any expected signs or symptoms that may be expected to return. In addition, any necessary laboratory or diagnostic study follow-up will be recommended, as necessary. Medications can be restarted or increased at any time should condition signs or symptoms recur.

In addition, our deprescribing intervention protocol is a carefully developed, multi-stage process that includes the independent review by multiple clinicians, each of whom can stop a recommended deprescribing action. This includes the study team pharmacist or nurse practitioner, the primary hospital team, the outpatient prescribing clinician, as well as the patient/proxy. Each recommended medication for deprescribing will be considered for its potential for physiologic withdrawal, pharmacokinetic/pharmacodynamic effects, and medical condition exacerbation. For each medication for which any one of these is a potential concern, a medication titration protocol will be recommended, rather than full drug withdrawal, with appropriate monitoring of signs and symptoms. In addition, following the deprescribing intervention, explicit and systematic safety assessments and data recording will occur during Phase 2 – 4.

Additional protections against risk include the nature of the informed consent process and safeguards built into the intervention. As described above in *Enrollment Procedures*, the consent process enumerates the study risks in lay terminology and reminds patients that they are under no obligation to participate and choosing not to participate will not impact their routine care at VUMC or PAC. Additional protections for persons with cognitive impairment and/or delirium exist in the informed consent process. To mitigate risks of the deprescribing intervention, certain safeguards are built into the intervention protocols beginning with the well-grounded conceptual framework and the input of a broad range of disciplines including geriatrics, gerontology, pharmacology, hospital medicine, post-acute care medicine, psychiatry, and clinical trial methodologists. The intervention protocol is general in its approach, however all deprescribing decisions are individualized to the patient, after considering the input from the pharmacy/NP expert, the patient, the hospital care team, and outpatient prescribers. Finally, robust monitoring of adverse events at both PAC stay and follow-up provide both the study team and DSMB the data to determine if the risk benefit profile changes.

Participant Confidentiality

Research subjects' identities will be kept confidential. Subject identifiers will never be revealed in publication, presentation, or other scientific purpose. All data obtained with subject identifiers will be maintained in locked file cabinets and locked offices on the VUMC campus. All study subjects will be assigned a unique study identification number for use in computer database and analytic work. Linkage of patient study IDs to patient identifiers will be maintained by the PIs and Project Coordinator only, with username/password protected access. All electronic data is kept in password-protected computer files on secured VUMC servers.

Potential Benefits of the Proposed Research to the Subject and Others

The risks to study participants are reasonable in relation to the anticipated benefits. Although deprescribing is a well-known concept, the safety of such practice has not been closely evaluated as will be done in this study, which will advance our knowledge of how best to manage polypharmacy in clinical practice. In the absence of this study, a hospital medical team may elect to deprescribe without consideration of withdrawal effects, pharmacokinetic / pharmacodynamic changes or exacerbation of an underlying medical condition. We will proactively consider these potential risks and actively mitigate risks with protocolized tapers of medication, surveillance, and communication of changes to the next care provider. Because most polypharmacy goes

unaddressed in routine care practice, patients who do not undergo active deprescribing would be the same as receiving placebo (i.e., usual care). Thus, the risk is not greater than current standard practice.

Importance of Knowledge to Be Gained

Older patients are the fastest growing hospital demographic. Older patients are likely to experience new onset and/or worsening of geriatric syndromes during hospitalization, and patients discharged from the hospital to SNF (1.7 million Medicare beneficiaries per year) are a particularly high risk group for loss of independence and other poor clinical outcomes. Recent data shows that only 28% of SNF patents are living at home 100 days after SNF discharge.5 Our data show that these patients also experience multiple geriatric syndromes (e.g. delirium, cognitive impairment, falls, incontinence). A number of these syndromes are acquired during the hospitalization and continue to be acquired during the post-acute care stay. We have shown that patients discharged from the hospital to SNF, and ultimately SNF to home, experience an average of two geriatric syndromes across both care settings, with 57% experiencing three or more syndromes. The majority of these patients admitted to the hospital and discharged to SNF are experiencing polypharmacy, and our preliminary data showed that patients are discharged with average of 14 medications from the hospital and 15 medications from the SNF. This practice occurs despite well documented associations between polypharmacy and geriatric syndromes. This is, in large part, due to the lack of evidence to suggest that the act of deprescribing improves outcomes. Although more medications are associated with geriatric syndromes, it is unclear if fewer medications are associated with clinical health benefits, including reductions in the number and/or severity of geriatric syndromes. This study will answer this important question, with major implications for future clinical practice and future trials in medication management among older patients.

Data and Safety Monitoring Plan

The DSMB is independent, and acts in an advisory capacity to the NIA Director to monitor participant safety, data quality and evaluate the progress of the study. Monthly safety reports are submitted to NIA and semi-annual DSMB meetings are held to review safety data. The NIA Program Official or designee attend each meeting. An emergency meeting of the DSMB may be called at any time by the Chair or by the NIA should participant safety questions or other unanticipated problems arise. In the case of a serious adverse event that results in death, the Principal Investigators are required to inform the NIA within 48 hours of notification (see *Serious Adverse Events and Reporting Procedures* above).

DSMB Membership

The DSMB consists of five members, and 3 members constitute a quorum. Members were selected by an NIA Program Official in consultation with the investigators, and the NIA Director approved the composition of the DSMB and its membership. The DSMB includes experts in the fields of relevant clinical expertise in geriatrics, clinical trial methodology, and biostatistics. Membership consists of individuals who have no financial, scientific, or other conflict of interest with the trial. Collaborators or associates of the investigators are not eligible to serve on the DSMB. Written documentation attesting to the absence of a conflict of interest is required and each DSMB member will sign a Conflict of Interest Statement. The DSMB members are responsible for notifying the PI of any changes in their Conflict of Interest. If there are new potential significant conflicts of interest as determined by the NIA Program Official or the Principal Investigators, the DSMB member will have to resign from the DSMB. *In 2019, two new members were added to the DSMB due to a new conflict of interest as noted below.*

1. **Rosanne M. Leipzig MD, PhD [Chairperson]**
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5. **Heather G Allore, PhD**
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6. **Joseph Hanlon, PharmD** ***(joined in 2019)***
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7. **Jack Guralnik, MD, PhD** ***(joined in 2019)***
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Communications

To avoid the appearance of conflict of interests, neither the investigators nor the DSMB members should directly communicate on any study-related issues. This includes any protocols, manual of procedures, reports, recommendations and other study-related correspondence. All such communications should be conducted exclusively through the NIA Program Official as described elsewhere. The only exception is that the Chairperson should receive the monthly safety reports.

Meeting Processes and Outcomes

Meetings are closed to the public because discussions may address confidential participant data. All Closed Session Meetings have an open session attended by the Board members, study investigators and NIA Program Official prior to and immediately following the Closed Session. The Closed Session will be attended by only the Board members, NIA Program Official and unblinded study biostatistician. The DSMB also has an option to hold an Executive Session attended exclusively by the DSMB members.

Following the initial meeting, the DSMB will meet at least twice a year to review blinded or unblinded data as needed and appropriate, including data on recruitment, randomization, compliance, retention, protocol adherence, intervention effects, gender and minority inclusion, and subject safety. The reports list and summarize safety data (adverse events) and describe the status of the study (e.g., participants screened, enrolled, completed, and discontinued). The DSMB is responsible for identifying problems related to safety (including all SAEs/SUSARs), requesting additional data relevant to safety (including all SAEs/SUSARs), proposing analyses of safety endpoints as needed, and considering the rationale for continuation of the study in light of safety data, progress of randomization, retention, protocol adherence, and data management. Reports of SAEs and SUSARs for two interim looks at the data will initially be provided to the DSMB in a blinded fashion (i.e., treatment group assignment will not be revealed), but the DSMB will retain the right to request an unblinded report. Only DSMB members will have access to unblinded data in order to preserve the integrity of data and minimize potential for bias while maintaining appropriate safety monitoring.

After each DSMB meeting, the chairperson will provide a written report including any formal recommendations to the PIs and the NIA program official. In turn, the PIs will provide all reports to the Vanderbilt IRB. Each meeting must include a recommendation to continue or terminate the study and whether the DSMB has any concerns about participant safety made by a formal DSMB majority or unanimous vote. A recommendation to terminate the study may be made by the DSMB at any time by majority vote. The Chair should provide such a recommendation to the NIA immediately by telephone and email.

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