Drug Reduction in Older Patients (The DROP Trial)

Study Protocol

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PRÉCIS

Overview and Objectives

Polypharmacy, defined as five or more medications,[1, 2] is common in older patients discharged to skilled nursing facilities (SNFs) and is associated with adverse health outcomes.[3-5] As part of a recent VA project, we prospectively collected medication data for 134 hospitalized, older Veterans. These data showed that, on average, 14.2 medications were ordered for Veterans discharged to SNF, which included 2.5 medications newly prescribed in the hospital that met criteria for being potentially inappropriate medications (PIMs). Moreover, 75% of these Veterans had two or more geriatric syndromes. Geriatric syndromes are clinical conditions common in older adults such as cognitive impairment, unintentional weight loss and falls.[6, 7] The co-occurrence of multiple syndromes is associated with loss of independence and higher healthcare utilization.[8] All Veterans with polypharmacy also had one or more medications associated with geriatric syndromes. The prevalence of polypharmacy and multiple geriatric syndromes may partially explain why these patients often have poor health outcomes after SNF discharge. Recent data suggests that only 28% of patients discharged from SNF are living at home 100 days later, and 35% experience an adverse drug event.[9]

There is a dearth of evidence related to the management of multiple co-existing geriatric syndromes, and few interventions have been implemented to reduce medications while also monitoring health outcomes. The relationship between polypharmacy, adverse drug events and geriatric syndromes in the VA population supports the rationale for an intervention focused on deprescribing medications before hospital discharge. We have pilot-tested a multifaceted intervention (Drug Reduction in Older Patients, DROP) to engage patients and providers to reduce the number and/or dose of medications prior to hospital discharge. The proposed randomized, controlled trial is powered to evaluate the effect of this intervention on a reduction in medications as defined by the total number of prescribed medications, the number of PIMs, anticholinergic and sedative drug burden and the number of medications associated with geriatric syndromes. In addition, we will collect relevant data on the prevalence and severity of geriatric syndromes and other clinical outcomes. We also will use a hybrid research design to evaluate both effectiveness and implementation issues to better inform future adoption and sustainability.[10] Our overarching hypothesis is that a hospital-based intervention to safely reduce the total number of medications represents the most feasible way to impact multiple health-related outcomes among older Veterans. Our Specific Aims reflect the primary outcomes that are the focus of the analyses, although we also will measure secondary outcomes related to VA healthcare utilization and patient safety:

Specific Aim 1: Implement a patient-centered deprescribing intervention (DROP) in the hospital to reduce the total number of medications Veterans are prescribed at hospital discharge.

- Hypothesis 1a: DROP will result in a significant reduction in total medication exposure due to discontinuations and dose reductions at hospital discharge, SNF discharge and 90-days after SNF discharge.
- Hypothesis 1b: DROP will result in a significant reduction in the number of potentially inappropriate medications (PIMs) at hospital discharge, SNF discharge and 90-days after SNF discharge.
- Hypothesis 1c: DROP will result in a significant reduction in the anticholinergic and sedative drug burden at hospital discharge, SNF discharge and 90-days after SNF discharge.
- Hypothesis 1d: DROP will result in significantly fewer medications associated with geriatric syndromes at hospital discharge, SNF discharge and 90-days after SNF discharge.

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

- Hypothesis 2a: DROP will result in a significant improvement in medication adherence and self-rated health status at 7 and 90 days after SNF discharge.
- Hypothesis 2b: DROP will result in a lower prevalence and severity of geriatric syndromes at 7 and 90 days after SNF discharge.

Specific Aim 3: Evaluate intervention implementation to inform future adoption and sustainability.

Aim 3a: Identify patient-level barriers and facilitators of DROP.

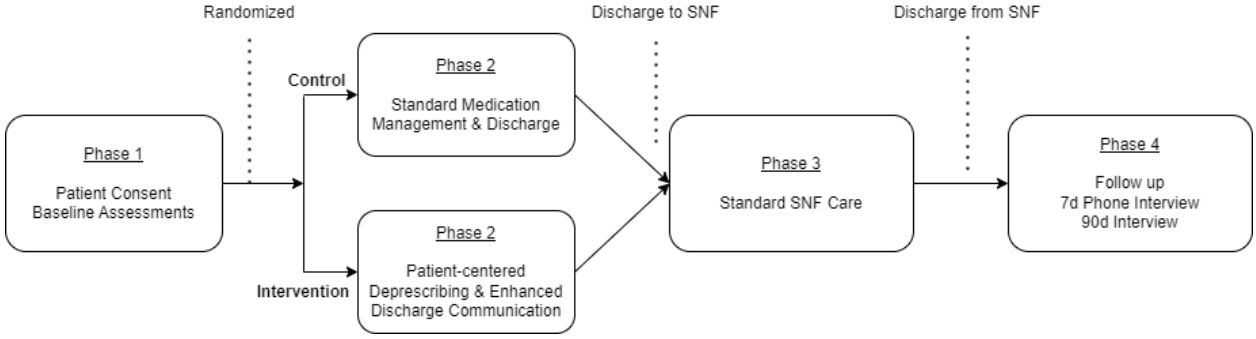
Aim 3b: Identify VA and Non-VA provider-level barriers and facilitators of DROP.

Aim 3c: Identify system-level factors that influence sustainability after hospital discharge.

Study Design and Outcomes

Overview of Design

Figure 1. Schematic of Study Design



Study Setting

The Nashville VA Medical Center is part of the Tennessee Valley Healthcare System (TVHS), which serves a diverse Veteran population in terms of income, geography and education level. We will target Veterans discharged from the Nashville VA hospital to any SNF, although the most common SNF locations include the TVHS York campus and 20 contract VA homes in surrounding areas.

Interventions and Duration

The intervention occurs during the Veteran's hospital stay (Figure 1: Phase 2). This phase includes identification of medication for deprescribing, an interview to determine Veteran preference for deprescribing, and discussion with the Veteran's inpatient treatment team. The inpatient treatment team incorporates the agreed upon final deprescribing actions in the Veteran's hospital discharge orders. The intervention ends at the point of hospital discharge.

Study Population and Sample Size

Eligible Veterans are age ≥ 50 with polypharmacy as defined by ≥ 5 medications based on the pre-hospital admission; ability to provide consent (or proxy); speaks English; does not reside in long-term care or receive hospice services; have a recommendation or referral to a skilled nursing facility (SNF). All eligible Veterans will be approached for consent with an original enrollment goal of 540.

The population and sample size were adjusted mid-study due to the significant enrollment and retention challenges caused by the COVID-19 pandemic. It was determined that a sample of 260 Veterans was sufficient to provide power greater than 93% for both the primary and secondary outcomes. Additionally, Veterans who were recommended SNF placement but ultimately discharged from hospital to home were approved to remain in study, which improved the study retention rate.

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.[6, 7] The most commonly cited geriatric syndromes include: incontinence, depression, cognitive impairment, delirium, unintentional weight/appetite loss, mobility impairment, pressure ulcers and falls. However, no published studies include measures of all these conditions in one patient population. Multiple syndromes are common in older adults and predictive of poor health outcomes, even when controlling for age and illness severity.[8] Approximately 50% of hospitalized patients aged 65 and older experience two or more syndromes,[12] with one or more syndromes either developing or worsening during the acute care episode.[13-15] Patients discharged from the hospital to SNF are at higher risk for loss of independence relative to patients discharged home, and our preliminary data showed that 47% of hospitalized Veterans discharged to SNF had two or more geriatric syndromes. Moreover, each Veteran was prescribed an average of 5.4 medications associated with one or more geriatric syndromes (*Preliminary Studies*). A separate study of community-dwelling Veterans aged 65 and older with polypharmacy, as defined by five or more medications, showed that 43% had one or more geriatric syndromes, and the strongest predictor of an adverse drug event was the number of medications added to their regimen during a 12-month timeframe.[16] These data provide a strong rationale for our overarching hypothesis that reducing medications for older Veterans will favorably impact geriatric syndromes and other health-related outcomes, such as adverse drug events.

Polypharmacy is common among older patients. Among hospitalized patients, polypharmacy has been most commonly defined as five or more medications[1, 2] to as many as 10 or more, also described as, "hyper-polypharmacy".[17] About 45% of older hospitalized patients are discharged on five or more medications.[18, 19] Older patients have an increased prevalence of multi-morbidity; thus, it is not surprising polypharmacy is common. However, a substantial number of prescribed medications may be unnecessary. Studies have found that > 90% of inpatients are taking at least one inappropriate medication.[20, 21] Several studies have shown that up to 43%[20] of medications taken by older patients lacked a clear indication, and 5%-11% of medications may be unintentionally prescribed for the same indication.[20] Even when a clear indication exists, medications may be inappropriate when considering drug-drug or drug-disease interactions.[22, 23] These medications, also known as potentially inappropriate medications (PIMs), have been defined by multiple criteria such as the Beers list[24] and the Screening Tool of Older Persons' potentially inappropriate Prescriptions (STOPP)[25, 26] Beyond medical appropriateness, some medications may be costly or have inconvenient dosing that decreases adherence.[20, 27] Finally, prescribed medications may be inconsistent with a patient's goals of care.[28, 29]

Although most studies have been conducted in non-VA hospital settings, two studies reveal similar rates of polypharmacy and prescribing problems among VA patients. Most recently, a large study involving 462,405 Veterans aged 65 and older examined prescribing quality using VA pharmacy data. Results showed that Veterans were prescribed a median of five medications, and 50% were identified as having one or more types of 'prescribing problems' as defined by the following categories: inappropriately high dose (12%), drug-drug interactions (30%), drug-disease interactions (3%), potentially inappropriate per the Beers list (26%) or other high-risk drugs (26%, e.g., warfarin, insulin, and/or digoxin). This study also showed that the total number of medications was the strongest predictor of each type of prescribing problem.[30] Similarly, an earlier study with 196 community-dwelling Veterans aged 65 and older prescribed 5 or more medications showed that 65% were taking one or more medications deemed clinically inappropriate and 57% were taking at least one medication deemed ineffective, not indicated or duplicative. Most importantly, however, the frequency of inappropriate medications increased as the total number of medications increased from a mean of 0.4 per Veteran among those taking five to six medications, to 1.1/Veteran among those taking seven to nine medications, and 1.9/Veteran among those taking 10 or more medications (i.e., hyper-polypharmacy). Underuse also occurred but was much less common, especially for those taking more than eight medications.[31]

These studies demonstrate the prevalence and potential inappropriateness of polypharmacy among older patients in (non)VA healthcare settings. Other studies have shown that polypharmacy can lead to multiple harmful outcomes among older community-dwelling and hospitalized populations. These outcomes include decreased medication adherence,[32] increased adverse drug events,[16, 32] and increased health care utilization and costs.[3-5] Polypharmacy and a variety of drug indices that quantify drug burden[33, 34] also have been associated with the development of geriatric syndromes including long-term cognitive impairment,[35, 36] delirium,[37, 38] falls,[1, 39-41] frailty,[42, 43] urinary incontinence,[44] and weight loss.[45] The number of syndromes related to polypharmacy supports our hypothesis that polypharmacy may be contributing to geriatric syndromes.

Study Rationale

Alignment with VA Priorities

The study will examine the quality of care for hospitalized Veterans as they transition from acute to post-acute care and, subsequently, to home. The focus of this study is on polypharmacy among a vulnerable group of older Veterans who typically experience frequent care transitions and high healthcare utilization. The intent of the Veteran-centered intervention is to deprescribe unnecessary and potentially inappropriate medications to improve adherence and health status, which aligns with VA HSR&D research priority B, topic #3: *assesses an intervention that encourages Veterans to be more actively engaged participants in their health care and decision-making by improving communication and interactions between providers and Veterans*.

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.[46, 47] Most interventions have applied the use of explicit criteria to reduce inappropriate prescribing with tools such as the Beers or STOPP, while a few considered other patient-centered factors (e.g., cost, convenience, life expectancy). Trials commonly use pharmacists, physicians or inter-disciplinary teams to implement deprescribing protocols.[48] 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 deprescribing interventions have targeted older patients transitioning from acute to post-acute care, which may be an opportune time to deprescribe. The few trials that have been conducted have been disease-focused on deprescribing specific types of medications.[49, 50] Second, few trials have incorporated patient preferences into the decision-making process. A recent VA study implemented an electronic health record algorithm to identify medications for deprescribing; however, patients were not explicitly involved in the decision process.[51] A recent qualitative study that included community-dwelling Veterans aged 65 and older with polypharmacy (mean = 13 medications/Veteran) demonstrated that most Veterans expressed a desire to take fewer medications.[52] Finally, although most of the trials reported improvements in medication appropriateness,[48] *there has been no study to evaluate the effects of deprescribing on health outcomes*.

Preliminary Data

Our interdisciplinary research team has performed innovative, critical preliminary work that supports the rationale and feasibility of the DROP trial. This work includes (1) a determination of the prevalence of multiple geriatric syndromes in Veteran hospitalized older patients discharged to SNF; (2) identification of the potential link between polypharmacy and specific medications with contributing side effects to geriatric syndromes; and (3) a pilot-tested patient-centered deprescribing intervention (DROP).

We examined geriatric syndrome and polypharmacy prevalence in a predominately male (96%), White (86%) Veteran sample (average age 74±10) discharged to SNF (N=134). Overall, 75% endorsed symptoms for two or more syndromes and 43% endorsed symptoms for three or more syndromes, with an average of 2.6 syndromes per Veteran. Polypharmacy was almost universal among both Veterans. Specifically, 99% of Veterans were prescribed $\geq$ 5 medications and 80% were prescribed $\geq$ 10, with a mean of 14.2 (± 5.3) per person at hospital discharge to SNF. Discharge medication lists included an average of 2.5 medications per patient that met criteria for being potentially inappropriate (PIMs), with 1.0 newly prescribed PIM during their hospital stay.

We implemented a structured patient-centered intervention protocol (DROP) to reduce the total number of medications prior to hospital discharge among a sample of non-Veterans. Our deprescribing protocol was based on a conceptual framework that considers patient and disease factors, goals of care, treatment targets and the duration of treatment required for benefit.[29] This framework also considers the clinical context of the patient's care and providers' willingness to deprescribe (provider barriers and facilitators). 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., including facilitators such as poor compliance, side effects or cost burden) and potential barriers (e.g., concern about symptoms worsening). The results of two recent qualitative studies revealed that most Veterans with polypharmacy expressed a desire to take fewer medications[52] and the importance of involving the patient in the decision process related to medication changes to improve adherence.[59] In addition, a survey of VA providers showed that assistance with follow-up, which a SNF care setting provides, and increased patient involvement in prescribing decisions were rated as two of the most preferred interventions to improve provider ability to discontinue medications.[60,61]

The DROP intervention was implemented for 20 hospitalized patients referred to SNF and a control group of 20 patients, who received routine hospital care. The intervention and control groups had a comparable number of total medications upon hospital enrollment. Overall, the research team identified an average of 12.75 (± 6.08) medications/patient for potential deprescribing based on initial chart review. The patient preference interview (intervention patients only) resulted in an average of 10.2 (± 4.5) *changes* (e.g., dose adjustments) to the initial 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 inpatient team and outpatient provider(s) for the intervention group only. The DROP pilot resulted in an average of 12.6 total deprescribed medications in the intervention group ($P<.001$), which included 6.1 pre-hospital medications (Table 3. Total deprescribed). The control group had an average of 6.5 total (4 pre-hospital) deprescribed medications as part of routine hospital care.

The results of the DROP intervention demonstrate our ability to reduce the total number of medications, PIMs, and medications associated with geriatric syndromes through a patient-centered deprescribing protocol implemented during the hospital stay. Because our protocol included dose reductions, we were able to reduce the DBI from enrollment to hospital discharge. The intervention also demonstrates the importance of involving the patient in the decision-making process along with the inpatient team and outpatient providers. Our patient preference interview is a unique component of our intervention and one that is absent from most prior studies.

Innovation:

This trial is advancing science in multiple ways:

1) One of the first controlled intervention trials designed to improve post discharge outcomes for the high-risk population of older Veterans transitioning from hospital to SNF to home. Healthcare costs are increasing for this patient 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,[45] it is unknown whether reducing medications will improve geriatric syndromes. This trial will generate data to evaluate the impact of medication reduction on Veteran health outcomes.
3) To date, there have been no controlled intervention trials focused on reducing the number of medications prescribed for hospitalized patients discharged to SNF, and the proposed intervention is one of the first to explicitly incorporate Veteran preferences into deprescribing efforts, which is consistent with Veteran-centered care initiatives. Moreover, our preliminary data show that incorporating patient preferences in the intervention protocol significantly changes these clinical decisions.
4) The proposed trial will evaluate both clinical effectiveness and implementation to inform the potential for DROP to be adopted into VA clinical practice.[10]

STUDY DESIGN

The study is a 3-year, randomized controlled clinical intervention trial at a singular VA medical center.

Primary Outcomes are change in total number (and/or dose) of medications including 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 geriatric syndromes, medication adherence, and self-rated health status.

Implementation Science Outcomes are to identify patient and provider level barriers and facilitators as well as system-level factors required for sustainability.

Eligible Veteran population is aged 50 years or older, experiencing polypharmacy (based on pre-hospital medications), and hospitalized at Nashville VA Medical Center with a recommendation for skilled nursing facility care. Exclusion criteria include limited life expectancy (less than 6 months or hospice admission), non-English speaking, no telephone, admitted from long-term care facility, incarcerated, no valid surrogate (if unable to consent), or enrolled in another drug trial.

The timeline for the study is 3.5 years with enrollment beginning October 2019 with enrollment closing in November 2022. Final follow-up ends in March 2023.

The DROP intervention is a deprescribing protocol that 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, Veteran preferences are key to final deprescribing actions by identifying the medications Veterans are willing to deprescribe. The inpatient (hospital) treatment team makes the final decision on deprescribing and incorporates the changes in the hospital discharge orders. 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

The Nashville VA Institutional Review Board permits a record review to screen patients for research studies. Screening is conducted every weekday by the project coordinator or research assistant. The screening process starts with a structured query of the VISTA reporting system. The Physical Therapy Consult Report allows the study team to identify Veterans recommended for SNF care after hospital discharge. All Veterans on this report are added to the screening panel in the electronic medical record then reviewed for the following inclusion and exclusion criteria:

Inclusion Criteria: (1) Confirm that the Veteran is aged 50 years or older. (2) Next review the Essential Medication List Review to confirm the Veteran has 5 or more home medications excluding topical agents. (3) Review the inpatient social work admission note to verify that the Veteran speaks English, has a working telephone, and was admitted from the community (i.e., non-LTC location).

Exclusion Criteria: (1) The EMR is reviewed for indication of life expectancy less than 6 months by searching for palliative care consults with hospice recommendations, referrals to hospice agency, and diagnoses of Stage IV

cancer. (2) Lastly, the research flags are reviewed to determine whether the Veteran's current trial enrollment(s) include a pharmaceutical trial.

For Veterans who have multiple hospitalizations during the trial period, they are re-screened at each new admission to determine eligibility for participation.

Enrollment Procedures

All Veterans meeting eligibility requirements are approached for consent. While any member of the research team can obtain informed consent, we preferred to have a study clinician, either Nurse Practitioner (NP) or Pharmacist (PharmD), provide an overview of the study and intervention in lay terminology. The Veterans and/or their surrogates were given time to review the study brochure and informed consent document then study personnel answered any questions. Prior to signing the consent documents, all Veterans were asked to complete a four question 'evaluation to sign consent' (approved by the IRB) to ensure they were capable of providing consent.

In the event that the Veteran was not capable of providing consent due to cognitive impairment, underlying comorbid conditions, or use of psychoactive medications, the study team sought the Veteran's legally authorized representative. In the case that a Veteran's inability to consent is temporary, the Veteran will be asked to provide verbal assent once they are deemed competent to consent. Participants will have full disclosure of who provided consent on their behalf and retain the right to re-consent or withdraw.
The process to obtain consent can occur in-person or via telephone. Study team's first preference is to meet with the Veteran and/or their surrogate in person.

1. However, in the event that study personnel cannot enter the Veteran's hospital room (due to COVID-19 precautions), the IRB approved a verbal consent process via the telephone in the Veteran's room. At the point the Veteran is no longer isolated, study staff will enter the room to provide the Veteran with a hardcopy of the study informed consent documentation and to have the Veteran sign a release of information form.
2. If the Veteran does not pass the evaluation to sign consent and their surrogate is not at the hospital, the IRB approved a verbal surrogate consent documentation. After verbal consent is given, study personnel mail a copy of the consent form to the surrogate for their records.

All enrolled Veterans will have a research flag placed in their medical record to identify them as a study participant. The research alert includes a brief description of the study and contact information for key study personnel. After enrolling, the Veteran will be added to an enrollment panel in the electronic medical record.

Following enrollment, Veterans are randomized to either intervention or control groups using the REDCap randomization feature which automatically assigns allocations based on a schedule (computer generated using Mersenne-Twister), which is uploaded by the team statistician. Veterans are randomized using permuted blocks of two or four where the size of each block is selected uniformly at random. This randomization ensures balance between the groups after every second or fourth randomization.

STUDY PROCEDURES

Data collection includes Veteran descriptive data along with geriatric syndromes, medications, health status, safety, and implementation science as noted in the table below. Upon enrollment, the Veteran will complete interviewer-administered questionnaires (marked with an asterisk below) with interviews conducted by trained study personnel. In the event the Veteran is unable to complete assessments (e.g., delirious, cognitively impaired), their designated surrogate will be asked to complete the assessments for which surrogate responses have been validated. Assessments that can be completed by surrogates are the ICIQ (urinary incontinence), DETERMINE, falls, pressure ulcers, medication history, and demographics. The remainder of the data will be abstracted from each patient's medical record; however, total number and type of medications will be determined based on a

combination of patient interview, medical record and pharmacy refill history to ensure an accurate, complete medication list.

The data shown in the below table for the "SNF" column is abstracted from SNF medical records; thus, research personnel will not interview the participant again during their SNF stay. However, participants will be contacted via telephone by research personnel at 7 and 90 days after they leave the SNF. If the Veteran is willing to also complete our implementation evaluation interview to assess barriers and enablers of deprescribing during their routine 7-day follow-up call, we will conduct this additional interview at the current 7-day follow-up timepoint in conjunction with other 7-day assessments. However, in consideration of Veteran response burden, we will provide the Veteran with the option to schedule the implementation evaluation interview component anytime during the initial 14-days following SNF discharge, based on the preference and convenience of the Veteran, so that they may choose to complete this interview separately. Both the intervention and control group will be monitored using that same data collection schedule and measures.

Schedule of Assessments

Measures and Data Collection Timeline	**Baseline Hospital**	**SNF Discharge**	**Post SNF Discharge**	
			7-Days	**90- Days**
Descriptives			**Telephone Interviews**	
Demographics and Length of Stay	X	X		
Elixhauser Comorbidity Index	X			
Patient Attitudes Toward Deprescribing (PATD)*	X			X
Primary Outcome – Medications				
Total number and type of Routine and PRN Medications, including PIMs	X	X	X	X
Pharmacy Calls to Verify Refill History	X			X
Drug Burden Index (DBI)	X	X		X
Medication Adherence (ARMS)*	X		X	X
Secondary Outcome – Geriatric Syndromes				
Cognitive Impairment (BIMS)*	X		X	X
Delirium (BCAM)*	X		N/A	N/A
Depression (PHQ-9)*	X		X	X
Urinary Incontinence (ICIQ-UI SF)*	X		X	X
Unintentional Weight Loss (DETERMINE)*	X		X	X
Pain (Brief Pain Inventory, BPI-short form)*	X		X	X
Falls	X		X	X
Pressure Ulcers	X		X	X
Secondary Outcome – Health Status				
Functional Health Status (VES-13)*	X		X	X
Secondary Outcomes – Safety				
Unplanned Healthcare Utilization (hospitalizations, emergency room visits)		X	X	X
Adverse Drug / Withdrawal Events	X	X	X	X
Status: Long-Term Care, Hospice, Death		X	X	X
Implementation Evaluation				

Veteran & Provider Barriers and Facilitators	X		X	X
System-Level Factors related to Sustainability		X	X	X
Staff Time for Intervention Implementation	X	X	X	X
Stakeholder Input	X			

Description of Assessments

Demographic and Administrative Data: The sociodemographic data is obtained primarily obtained from medical record abstraction then verified with the Veteran (or their surrogate). Using a standardized abstraction form, study personnel collects and records age, gender, race, ethnicity, home address, telephone number, insurance status, outpatient providers, and pharmacies. We also abstract key information related to this hospitalization including site prior to hospitalization, admission date, admission diagnoses, hospital service/team, and discharge date and disposition. Data is verified with the Veteran, and participants are also asked their highest level of education and complete the Brief Health Literacy Screen.

GerontoNet Adverse Drug Event risk assessment calculated the Veteran's risk for experiencing an adverse drug event. The assessment contains items related to certain comorbid conditions or diagnoses, which are assessed via the Veteran's problem list. The other component is previous adverse drug reactions, which are assessed in the baseline demographic interview.

Walter Index is a prognostic tool to predict mortality within one year of hospital discharge. A higher score indicates a greater likelihood of mortality. The components of this tool are comorbid conditions and lab values which are abstracted from the Veteran's problem list and hospital intake assessment. The component assessing assistance with activities of daily living is completed by both medical records review (physical therapy notes) and during the baseline demographic 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 collection begins with the Veteran's Essential Medication Review List (EMLR). After this list is abstracted from the medical record, a study NP or PharmD pulled the Controlled Substance Monitoring Database report, called non-VA pharmacies for recently filled prescriptions, reviewed non-VA medical records (i.e., outside hospital or SNF records), and interviewed the Veteran or their surrogate. We included all medications, either prescription or over-the-counter (OTC) that were administered by the following routes: oral, intravenous, intramuscular, sublingual, or ophthalmologic. Veterans (or their surrogate) were given specific prompts if they reported no OTC usage, for example, asking them if they take anything for constipation or allergies. If a patient was admitted from an institutional setting (e.g., outside hospital, SNF, ALF), we request a copy of the medication administration record from the previous 30 days. Medications are considered current/active if the Veteran took it within 30 days of hospitalization. The hospital discharge and SNF discharge medication lists, serve as the outcome data for those respective time points. During the follow-up calls, the study NP or PharmD systematically asked the Veteran for the status of each medication on the enrollment list and discharge lists to determine if and how they are taking it. Afterwards the study clinician prompted the Veteran for any new medications they may be taking.

Potentially Inappropriate Medications (PIMs): We used previously published and validated lists including the Beers criteria, the STOPP criteria, and the RASP list, which have a large degree of overlap. The total number of PIMs is the sum of medications that are found on these lists.

Drug Burden Index (DBI): This score is calculated separately for anticholinergic and sedative medications, which have been linked to functional impairment, falls, and delirium. The DBI is the sum of each individual anticholinergic/sedative medication's prescribed daily dose divided by the sum of the minimum effective dose (per the FDA minimum recommended dose) and the patient's daily dose. The DBI is calculated for all medications including OTCs. We will calculate the DBI at each timepoint, and this will capture dose reductions even when the total number of medications is not reduced.

Secondary Outcomes – Geriatric Syndromes, Medication Adherence, and Functional Status
Delirium: is assessed via the Brief Confusion Method (bCAM), a screening tool validated for use with hospitalized older adults. If the participant screens positive for delirium, no other participant interviews are conducted. Members of the research team will re-assess delirium daily during the remainder of the hospitalization; if/when the Veteran screens negative, the remaining assessments will be administered to the Veteran. If delirium persists throughout the hospitalization, the Veteran's surrogate is approached for syndrome assessments. The bCAM is not repeated at any other time point as it cannot be completed via telephone.

Cognitive Impairment: is assessed by the Brief Interview for Mental Status (BIMS), which has a total score range from 0 to 15 (0-7: severe impairment; 8-12 moderate impairment; 13-15 cognitively intact).

Depression: The Patient Health Questionnaire-9 (PHQ-9) is a validated screen to assess for depressive symptoms and their severity. Each item is scored from 0 ("not at all") to 3 ("nearly every day") to produce a cumulative score between 0 (no depressive symptoms) and 27 (severe depressive symptoms). If a Veteran reports severe depression or thoughts of self-harm, the study team elicits more information on their immediate safety then contacts the primary treatment team to close the loop for follow-up. The study team also offers to connect the Veteran with the VA's emergency helpline.

Urinary Incontinence: The International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) has four components and measures symptoms, frequency, and impact of urinary incontinence on quality of life. This tool has well established reliability and validity including sensitivity to treatment.

Unintentional Weight Loss and Poor Appetite: Nutritional concerns are assessed through the Determine Your Nutritional Health checklist, which is a 10-item tool utilized by the state government to determine nutritional risk in older adults receiving meal assistance. The checklist has 10-items which yields a nutritional risk score of 0-2 (low), 3-5 (moderate), and ≥ 6 (high). One item asks if they experienced a 10-pound weight change; if the Veteran indicates they had experienced a weight change, the study team will ask a structured question to clarify if the weight change was a gain or a loss.

Pain: is assessed with the Brief Pain Inventory (BPI) short form, which has three primary components: location, pain severity, and pain interference with daily activities. The pain severity score is comprised of four questions (e.g., worst, best, average, current) in which the Veteran rates their pain on a 0-10 scale in the last 24 hours.

Falls: The Veteran (or their surrogate) is asked if they have fallen in the last month or since the previous timepoint during follow-up phase. If the response is 'yes,' then the patient is asked how many times they have fallen, and if any of the falls led to an emergency room visit or hospitalization.

Pressure Ulcers: At enrollment, the medical record is reviewed (via flowsheets and free text search) for the presence of pressure ulcers, including the staging (Stages 0-4). During the follow-up timepoints, the Veteran and/or their surrogate are interviewed directly about the presence of a pressure ulcer.

Medication Adherence: The Adherence to Refills and Medications Scale (ARMS) is 12 items on a Likert scale with the options ranging from "none of the time" to "all of the time." Example questions include "How often do you forget to take your medicines?" and "How often do you put off refilling your medicines because they cost too much money?". The assessment's score range is 12 to 48 points with lower scores indicating better medication adherence.

Functional Health Status: The Vulnerable Elders Survey (VES-13) is a measure of health status that assesses a patient's cognitive, physical and self-care activities, and self-rated health status. Scores range from 1 to 10, wherein lower scores indicate better health.

Safety Outcomes

Unplanned Healthcare Utilization: The study team will monitor Veterans' healthcare utilization, both at the VA and outside the VA system, after study enrollment. During the consent process, Veterans sign a release of information form that allows the team to request records from non-VA entities. We will track all emergency room visits, hospitalizations, and deaths, and these events will be adjudicated by a blinded clinician (see Safety Assessments section).

Adverse Drug Withdrawal Events (ADWEs): any unplanned healthcare utilization is reviewed by a blinded physician co-investigator to determine if the event was medication related, and more specifically if it was related to medication withdrawal. The standardized adjudication form includes validated scales such as the Naranjo.

Implementation Science

Veteran Barriers & Enablers: Veteran level barriers and enablers to deprescribing are assessed for every Veteran randomized to the intervention group. For every medication recommended to the Veteran for deprescribing, the study NP or PharmD records the agreement to deprescribing and field notes of the Veteran's reasoning for agreement/disagreement. The field notes are later coded into pre-set categories of barriers/facilitators created through a systematic review by the creators of the PATD. This will allow the study team to compare the barriers and enablers of Veterans with non-Veteran populations from other deprescribing trials.

To gain additional insight into Veteran preferences for deprescribing, Veterans both treatment arms will be asked to complete a semi-structured interview at the 7-day follow-up call. This interview broadly discusses changes to medication regimens including the Veteran's perception of how medication changes are currently made and if they have ever initiated a medication change. Then the interview gauges the Veteran's comfort with having medication conversations with their provider, and finally ends with how they would prefer medication and deprescribing conversations take place (e.g., what type of provider, inpatient v. ambulatory setting).

Provider Barriers & Enablers: Similar to the Veteran level barriers and enablers, provider level barriers and enablers are documented at the medication level during the deprescribing conversation. These field notes are coded using pre-set categories: awareness, inertia, self-efficacy, and feasibility. Study team members probe the inpatient provider for a rationale, but in the event that a provider offers a one-word agreement (e.g., sure, yes, okay) to deprescribe, we have added 'tacit' as an enabler category.

System Level Factors: The study team engages both inpatient pharmacists and physicians as part of the deprescribing protocol. The adoption of a deprescribing intervention into clinical practice would likely be the responsibility of inpatient pharmacists; therefore, we chose to conduct semi-structured interviews with pharmacists who interacted with the study team. The pharmacists were explicitly asked about the feasibility of incorporating the intervention into their workflow and workload, how it would change their work processes, and what organizational support (or factors) would be necessary to routinely implement a deprescribing intervention.

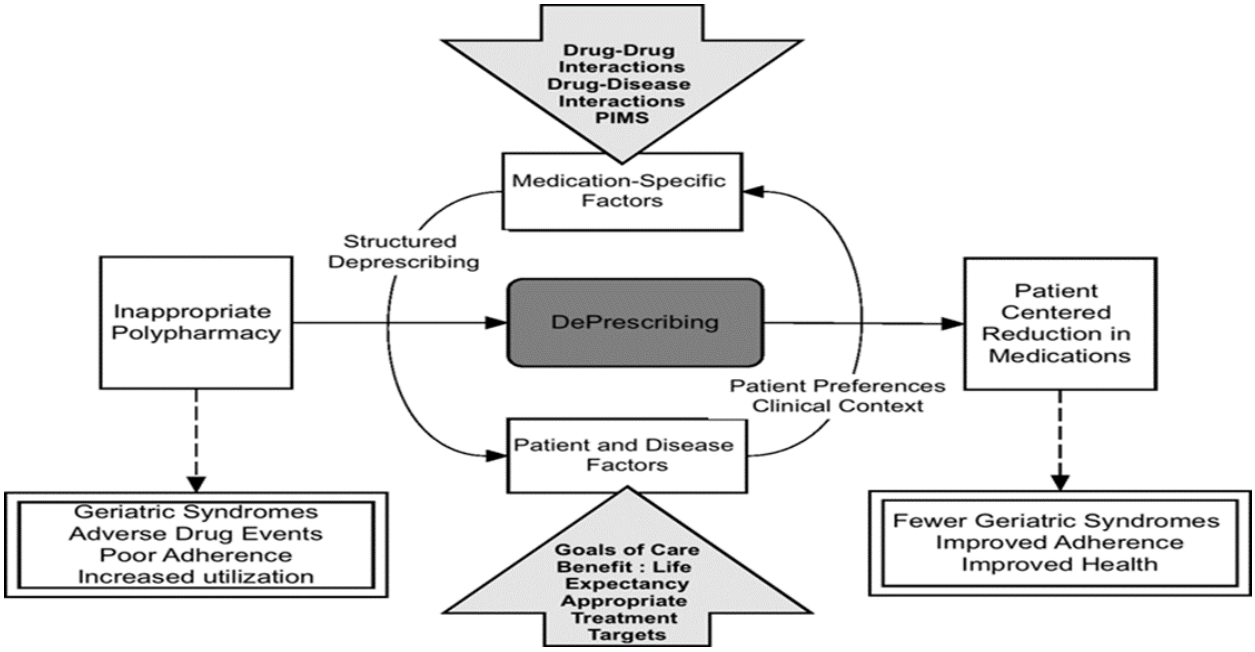
Staff Time to Implement Intervention: To understand the resources necessary to implement the intervention (and thus provide feedback to the organization), we time certain components of the intervention to calculate staff time. Specifically, we document the time required for calling outside pharmacies for refill information, reviewing the medication list and assigning every medication and indication and deprescribing recommendation, and conducting a deprescribing conversation with the Veteran and/or their surrogate.

STUDY INTERVENTION

The deprescribing protocol is based on a conceptual framework that considers patient and disease factors, goals of care, treatment targets and the duration of treatment required for benefit (Figure 2). We also incorporated medication-specific factors for minimizing inappropriate medication use (drug-drug and drug-disease interactions). Additionally, this framework considers the clinical context of the patient's care and providers' willingness to deprescribe. Lastly, patient preferences are a key component that informs final deprescribing actions by identifying medications the patient is willing to deprescribe (e.g., including facilitators such as poor compliance, side effects or cost burden) and potential barriers (e.g., concern about symptoms worsening).

Conceptual Model

Figure 2. Deprescribing Framework



Pre-Review (Target Medications for Deprescribing)

Following baseline assessments and medical record review, a study Pharmacist or Nurse Practitioner will review the total enrollment medication list. Using medical record data, the following information will be ascertained for each medication: (1) Medication Indication**:** If an indication (i.e. diagnosis or symptom) cannot be identified, "no indication indicated" will be specified; and, (2) Deprescribing rationale: Rationales for deprescribing (i.e., stopping or reducing dose) will be assessed for each medication as summarized below in Table 2. For each medication recommended for deprescribing, the deprescribing action will be specified as: (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.

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

Incorporating Veteran Preferences

Following medication targeting, intervention Veteran (and/or their surrogate) will receive a structured interview by the study pharmacist or nurse to elicit their preferences regarding medications identified for deprescribing. The following will be assessed for each targeted medication: adherence, side effects, perceived benefit (or harm), cost, and willingness to stop or reduce the medication. We also will document patient barriers (e.g., concern about increased pain) and facilitators (e.g., high dose frequency, cost) that influence their willingness to deprescribe. If the Veteran 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. As noted in the Description of Assessments, field notes were categorized into specific barriers and enablers.

Inpatient Provider Communication

After completing the deprescribing interview with the Veteran, the study NP or PharmD will reach out the Veteran's inpatient treatment team including both the pharmacist and the resident physician. The study clinician will present the team with the deprescribing recommendations that the Veteran agreed to along with the rationale for deprescribing. Similar to the Veteran deprescribing interview, the study NP or PharmD will record field notes and team agreement to deprescribing, which will be coded into barriers and enablers (see Description of Assessments).

Final Deprescribing Actions

A crucial component to successful intervention is the Veteran leaving the hospital with an accurate medication list that reflects all the agreed upon deprescribing actions. The study NP or PharmD will remain in communication with the treatment team to ensure that final agreed upon recommendations are included on Veteran's final discharge list. Ultimately any medication changes are at the discretion of the inpatient treatment team.

SNF Handover

Within 24-hours of hospital discharge the study team will contact the SNF admissions nurse to review the Transfer Medication List in conjunction with the list of deprescribed medications and the need for medication-specific monitoring, if applicable. In addition, recommended dose titrations may be highlighted during this SNF handover.

Post-Intervention Follow-Up

The intervention ends at hospital discharge. Originally, if the Veteran discharged to any location other than SNF, they were discontinued from study. Due to retention concerns, the IRB approved the retention of Veterans who discharged home (beginning in March 2021).

Skilled Nursing Facility (SNF)

The study team will contact the SNF weekly to monitor the Veteran's expected discharge date and monitor for any unplanned healthcare utilization. At the point of SNF discharge, the study team will request the Veteran's discharge medication list.

7- and 90-Day Follow-Up

The 7-Day follow-up call occurs 7 days after SNF discharge (±3 days), and the 90-Day call occurs 90 days after SNF discharge (±10 days). The study NP or PharmD asks the Veteran to have their medication bottles, pill organizer, and list nearby during the call. If a surrogate assists with medication management, we also ask that person to be available. The Veteran lists of the medications they are currently taking with the dose and frequency information. Afterwards, the study clinician will inquire about medications from enrollment or discharge lists that the Veteran did not address in order to confirm their usage or discontinuation. After the medication history is obtained, the study team administers the geriatric syndrome and medication adherence assessments.

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 Veteran. The study coordinator and research assistant share a study patient panel in the electronic health record. Any time a participant is admitted to the Nashville VA Medical Center, they are alerted. To identify if a Veteran experience an unplanned healthcare utilization at an outside hospital (OSH), the Veterans 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. Additionally, the research assistant or study clinician reviews VISTA for any uploaded OSH records at the time of the follow-up calls. The research assistant is responsible for requesting medical records from OSHs (and SNFs) relevant to the utilization.

Review of Unplanned Healthcare Utilizations and Deaths
Any unplanned healthcare utilization or unexpected 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 by the research assistant, 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 VA, 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.

After review by the clinician-adjudicator, the case is sent to the Principal Investigator to 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.

Adverse Event Reporting Procedures
The Principal Investigators (PIs) are responsible for reporting to the respective governing bodies in accordance with their prescribed timelines and regulations.

Institutional Review Board
PIs will notify the IRB of any Serious, Unexpected, Study Related Adverse Event within 7 days of PI notification of the event. All deaths regardless of study relatedness will be reported to the IRB within 7 days of PI notification. At the time of the IRB annual continuing review, the IRB will receive (1) a listing of all adverse events, and (2) 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 5 days of PIs receipt of the report.

Data Safety Monitoring Board (DSMB)
The Health Services Research and Development Service (HSR&D) Data and Safety Monitoring Board convenes annually in March. The PI will submit a report to the VA Program Officer and DSMB coordinator by January 31st each year. This report will include case listings for all deaths, serious adverse events, and non-serious adverse events regardless of unexpectedness or study relatedness. At the conclusion of the closed session meeting, the DSMB will note any concerns about Veteran safety and issue an approval for study continuation. In the event that the DSMB has additional concerns, issues a conditional approval, or requests a temporary study stoppage, the PIs will be given 30 days to respond to the DSMBs concerns.

STATISTICAL CONSIDERATIONS

Sample Size and Randomization
Existing data indicate that approximately 600 to 700 hospitalized Veterans are referred to SNF annually. Thus, we conservatively estimate that 40% (or, 240 per year) will provide consent, complete baseline assessments and discharge to SNF to yield a total consented sample of 540 across all study months. During the SNF stay, we anticipate ~5% will die, which will leave 513 (or ~256 per group) discharged from SNF. Based on preliminary data, ~15% of patients die within 90 days of SNF discharge. Thus, ~85% (or 393 total) will be alive at 90 days. In addition, we estimate we will be unable to reach ~10%, which will leave ~354 total participants (~177/group) for 90-day follow-up. The population and sample size were adjusted mid-study due to the significant enrollment and retention challenges caused by the COVID-19 pandemic.

It was determined that a sample of 260 Veterans was sufficient to provide power greater than 93% for both the primary and secondary outcomes. Finally, the study enrollment was continued for an additional 10 months beyond the original project timeline.

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 Analysis 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 will be 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 well as practical and clinical considerations to make one of the following recommendations based on safety:

a. Suspend enrollment due to safety concerns secondary to study intervention including:
    1. 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.
    2. 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.
b. Continue Enrollment

Outcomes

Hypotheses 1a -1b: Among participants assigned to the intervention group, we will summarize both the number of deprescribing *recommendations* and the number of actual medication *changes* at hospital and SNF discharge and 90-days following SNF discharge. The effect of the intervention on the total number of medications, PIMs, and medications associated with geriatric syndromes at hospital discharge, SNF discharge, and 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 enrollment and the interaction of intervention and time point. The heterogeneity in outcome measures across participants will be modeled using a random intercept term, indexed by subject. Heterogeneity among VA providers and SNFs in the effectiveness of intervention will be modeled using a random intervention effect, indexed by VA provider and SNF. The overall intervention effect will be evaluated using a Wald-type multiple degree-of-freedom test against the null hypothesis of no effect at any time point. The intervention effect at each time point will be summarized using a Wald-type 95% confidence interval. Model fit will be assessed by examining the associated Pearson residuals and other graphical methods. Alternative regression techniques may be used in the case of poor fit, for example, negative-binomial regression. A secondary analysis to explore the possibility of intervention effect modification by hospital length of stay (e.g., longer stay may result in more deprescribing) will be implemented by considering the interaction of hospital length of stay with intervention.

Hypothesis 1c: The effect of intervention on the anticholinergic and sedative drug burden index 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, its interaction with intervention and using random effects, testing and summary methods as described for Hypotheses 1a, 1b and 1d. Model fit will be assessed using residual diagnostics and graphical methods. Due to the constrained nature of the DBI values, a 'beta' regression method may be required, which is suitable for scores that often occur at a boundary.

Hypothesis 2a: Medication adherence will be measured using the ARMS based on an ordinal scale. Functional health status will be measured using the VES-13 total score, also an ordinal outcome. Patient attitudes toward deprescribing (PATD) also will be measured on an ordinal scale. The effects of intervention on these outcomes will be assessed at 7 (except PATD) and 90-days following SNF discharge using mixed-effects logistic regression or proportional odds logistic regression similar to analyses for Hypothesis 2b.

Hypothesis 2b: The prevalence and severity of geriatric syndromes will be analyzed at baseline, 7 and 90 days 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) and its interaction with intervention. 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 and its interaction with intervention. For either method random effects, testing, summary and diagnostic methods will be used as described for Hypotheses 1a, 1b and 1d.

Hypotheses 3a-c: Descriptive analyses will be performed to examine implementation outcomes: anticipated barriers and facilitators, medication changes per patient following hospitalization, and staff time required for each intervention component. Unanticipated barriers and facilitators and stakeholder input responses will be analyzed using qualitative methods. A research assistant will generate clean versions of the data collection notes. We will code notes using NVivo11® software based on a two-pronged approach that relies on: a) a priori factors, and b) emergent themes or "grounded theory", an inductive approach in which the categories used for the analysis are derived from the data. The a priori factors include the categories of anticipated barriers and facilitators as well as constructs from CFIR. Analyses will then compare all cases to identify the range among and differences between respondents. Themes will be noted, counted, and documented by illustrative quotations from the notes. Data collection will continue until saturation of themes are reached, likely requiring 20-25 respondents. Ten percent of the notes will be double coded (first by PI then by the study coordinator) to calculate a reliability statistic.]

Data Analyses

Missing Data

We have extensive preliminary data describing attrition due to mortality, which should not differ between 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, & Safety Outcomes

Participants will be assigned to the usual care control or intervention group in randomly permuted blocks of size two or four, where block sizes are selected uniformly at random. This type of randomization ensures balance across groups after every second or fourth randomization (depending on block size). The effectiveness of randomization will be assessed by summarizing the balance of baseline demographic and clinical factors across 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 Veterans discharged from the hospital to SNF rather than to home or hospice will be included in analyses. We will implement both intent-to-treat and per-protocol analyses.

Repeated Measures
Barring study withdrawal or death (or hospice transfer), each participant will be assessed at multiple time points. Participants may be clustered by VA provider and/or SNF discharge location. Thus, outcome measurements may exhibit heterogeneity across participants and clusters. 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 robust Huber-White 'sandwich' method.

DATA MANAGEMENT AND QUALITY ASSURANCE

Data Collection Forms & Data Entry

The study team chose to utilize hard copy case report forms to allow for quality assurance reviews of entered data. The standardized interview and abstraction forms were approved by the IRB. Data recorded on the case report forms are entered into a VA REDCap database. Assessment and interview forms are entered within the same week of data collection, and if possible, the same day.

Data Storage

Paper data collection forms are stored in locked filing cabinets in the academic partner's offices. Upon study completion, each Veterans files are moved to the local VA research offices where they are stored in a locked filing cabinet. Electronic data is stored in the VA REDCap and on a shared project folder only accessible to study team members. With permission of the IRB, de-identified data is allowed to be temporarily stored on the secure server of the academic partner. All electronic files are username and password protected. Data in the REDCap databases and secure server will be stored indefinitely to all for subsequent data analyses.

Quality Assurance

No quality assurance training or metrics are required beyond standard IRB Human Subjects training. To ensure data integrity, the project coordinator will conduct weekly data reviews to check for completion and accuracy.

PARTICIPANT RIGHTS AND CONFIDENTIALITY

The DROP trial's intervention is considered human subjects research and is subject to standard review by the local institutional review board (IRB). All protocols, consent forms, and other research materials were submitted and approved prior to the recruitment of any Veterans. As noted above, the study is subject to an annual safety review by the IRB. All study personnel complete annual human subjects and good clinical practice training. Below is a summary of key human subjects information submitted to the IRB.

Protection Against Risks

The deprescribing intervention protocol is a carefully developed, multi-stage process that includes the independent review of multiple clinicians, each of whom can stop any recommended deprescribing action. This includes the research team pharmacist or nurse practitioner, primary hospital team, and the Veteran or their surrogate. Each medication recommended for deprescribing will be considered for its potential for physiologic withdrawal, pharmacokinetic/pharmacodynamic effects, and medical condition exacerbation. Strategies to protect against risks are as follows:

- 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% to 50% during any 1-week interval when a patient is receiving greater than the minimum therapeutic dose.

- Deprescribing pharmacists / NPs will alert the primary medical team and make recommendations to the post-acute care for surveillance of symptoms, signs (e.g., vital signs), labs (e.g., electrolytes, INR), or follow-up tests (e.g., EKG).
- 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.
- Medications can be restarted or increased at any time should adverse pharmacokinetic/ pharmacodynamics effects or a physiologic drug withdrawal effect be detected.

Veteran Confidentiality

Research subjects' identities will be kept confidential at all times. 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 VA Medical Center (GRECC offices) campus or the academic partner. 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 with username/password protected access.

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