

VA DROP Human Subjects Section

Human Subjects Involvement, Characteristics, and Design. In this study, we estimate that we will consent 540 adult medical inpatients aged 50 or older, who are taking at least 5 medications and are referred to SNF. As stated in the Research Plan (Anticipated Enrollment and Attrition), we estimate that 270 Veterans will be randomized into the intervention group across all study years. In order to meet inclusion requirements, study participants will be taking at least five medications, although we anticipate that the majority will experience hyper-polypharmacy at the time of inclusion, taking 10 or more medications, based on our preliminary data. This study does not contain any exclusion criterion based on race, gender, or ethnicity. Veterans who are blind, deaf, or unable to understand or speak English will not be enrolled because they cannot be assessed appropriately using the instruments highlighted in the Measures section, Table 7. In addition, Veterans admitted to the VA hospital from long-term care or who are receiving end-of life (hospice) services will be considered ineligible for study participation. This study will involve one acute care VA hospital. The Planned Enrollment Table provides demographic data regarding gender, race, and ethnicity of anticipated enrolled Veterans based on our extensive preliminary data for the target population. There are several training requirements that study staff must complete. These include all local institution IRB-required courses on Human Subjects Protection, including protected health information required by the VA and Vanderbilt University IRBs.

Study Group Assignment. As described in the Research Plan, Veterans will be screened daily (Monday – Friday) for eligibility criteria. VA IRB permits a record review to screen Veterans for research studies, similar to a limited HIPAA waiver. An attempt will be made by research personnel to approach all Veterans who meet study inclusion criteria. Following enrollment, Veterans will be randomized into the intervention or usual care control group (see Randomization in the Data Analysis section).

Follow-up and Retention Plan. In order to maximize the 90-day participation of randomized Veterans, our study team will enact strategies that have enabled follow-up success rates in excess of 80% in other studies involving co-investigators. Study staff will be instructed to obtain as much contact information as possible (e.g. multiple phone numbers, addresses) of both Veterans and surrogates, when required. The following strategies will be used to further increase retention:

- One week post-discharge follow-up, with confirmation of contact information at that visit.
- Reminder postcard will be sent 2 weeks prior to the 90-day phone call.
- Weekly team meetings will be conducted with study personnel to assess study enrollment and follow-up rates, with in-depth discussions related to strategies to support follow-up participation.

Specific Vulnerable Populations

Dementia Patients: Veterans with cognitive impairment 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. Veterans with moderate impairment will likely

need a surrogate to provide consent and complete some study measures. Veterans with mild impairment may (not) need a surrogate to provide consent. We will complete a “standardized evaluation to sign informed consent” for all eligible Veterans to determine if a surrogate consent is required.

Patients with Seizure History: Veterans 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, Veterans 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.

Sources of Research Material

Data Sources. All materials will be collected and recorded by trained research personnel for research purposes. The sociodemographic, clinical, and outcome data collected during this investigation will be obtained from multiple sources, including subjects (or surrogates) directly via standardized interview protocols, medical records, hospital databases and pharmacy records. The main source of data for the hospitalization will be chart abstraction utilizing the Veteran’s electronic medical record. Progress notes, nursing notes, and pharmacy notes will also be used to collect data. Communication with participants and/or their families will be conducted in person and over the phone. There will be no collection of biologic specimens for this study.

Database. Data collected from Veteran assessment and medical records will be entered directly into the study databases via electronic case report forms (eCRFs) using a VA version of Research Electronic Data Capture (REDCap) database.⁷⁵ Data recorded on paper forms will be directly entered into the electronic databases, and all paper CRFs will be maintained in a secure and locked file cabinet, in a secure and locked office located within our local TVHS GRECC offices. Access to the VA REDCap database is available only via a secured web-based interface behind the VA firewall and is username/password protected. Only the VA investigative team will have access to all participant data.

Follow-up and Record Retention. All data collected in this study will be maintained at the VA on a secured server. Information in the database will be stored for an indefinite period of time, or as otherwise required by the VA IRB and VA HSR&D funding, to allow for subsequent data analysis and future reference.

Potential Risks

Side Effects of Medication Deprescribing. The 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% to 50% during any 1 week interval when a patient is receiving greater than the minimum therapeutic dose (See Medication Suggested Tapers table below). 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 that would be expected for the withdrawn medication. 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 altering 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 commonly 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.⁷⁷⁻⁸⁰ A strength of this trial is that patients will be discharged to 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 condition signs or symptoms recur.

Adequacy of Protection Against Risks

Recruitment and Informed Consent. We have designed this study and all of its components in keeping with published ethical standards for clinical research. Informed consent guidelines of the VA Institutional Review Board (IRB) will be employed, as done in numerous prior studies of this investigative team. Prior to participant enrollment, we will notify all hospital attending physicians of Veteran enrollment into the

deprescribing study. The medical team will be fully informed of the nature of the study and any risk and benefits. Study coordinators will follow IRB-approved and HIPAA-compliant procedures to identify potential candidates for enrollment utilizing the inclusion and exclusion criteria per our protocol.

As we are enrolling older hospitalized Veterans, we expect that some Veterans 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 Veteran is unable to provide informed consent, we will seek consent from the Veteran's legally authorized representative, per the healthcare decision-maker policy at the VA. During the informed consent process (including surrogate and Veteran consent) the following techniques will be employed:

- Study staff will describe the study protocol to Veterans in lay terminology.
- Emphasis will be made that data collected will be for research purposes and refusal to participate will have no effect on a Veteran's routine hospital or out-patient care provided by the VA or the SNF.
- Veterans and families will be informed that there is no obligation to participate in the study.
- Staff will provide a name and contact information for further questions or if the Veteran/surrogate wishes to withdraw from the study, which may be done at any time.
- The Veteran and family (and SNF) will be provided with a written copy of the consent form and ample time to have questions answered prior to enrollment.
- For eligible Veterans, we will perform 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 Veteran 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 Veteran 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 Veteran's inability to consent is temporary (e.g., delirium, drug effects), the Veteran will be re-consented 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. All enrolled Veterans will have an alert placed in their medical record to identify them as a study participant, along with contact information for the study personnel.

As part of the consent process, we also will obtain the patient/surrogate's signed permission for "Release of Medical Information", which will allow the research team to access their medical records if they are admitted to an emergency room or hospital other than the Nashville VA. The medical release of

information will allow the research team access to the necessary clinical information to determine if a hospitalization event meets criteria for an adverse event, per review by our Clinician reviewers (see Adverse Event Reporting section)

Protections Against Risk. The proposed research study has been designed based on input of experts in geriatrics, pharmacology, psychiatry, hospital medicine, and clinical trials. In order to assure appropriate research subject selection and high quality data collection, all study personnel will undergo training in the study protocols. Exclusion criteria have been carefully considered to help minimize Veteran risk prior to enrollment. In addition, our deprescribing intervention protocol is a carefully developed, multi-stage process that includes the independent review of multiple clinicians, each of whom has the ability to stop any recommended deprescribing action. This includes the study pharmacist, the primary hospital team, the SNF provider team, the outpatient prescribing clinician, as well as the Veteran/surrogate. 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 recommendations to the SNF for monitoring of signs and symptoms. In addition, following the deprescribing intervention, explicit and systematic safety assessments and data recording will occur (see Efficacy and Safety Monitoring). To provide an additional safeguard, we also will create a Data Safety Monitoring Plan to ensure data quality and integrity.

Steps Taken to Reduce Risks and Increase Impact of Study. The following are actions to minimize risk for the study population and maximize the impact of this study in deprescribing:

- 1.) Intervention protocols included in this study are supported by a well-grounded conceptual framework, clinical evidence and, although not yet proven, the potential to benefit older hospitalized adults experiencing both polypharmacy and geriatric syndromes.
- 2.) The intervention has established clinical equipoise, with the absence of clear evidence in favor of one intervention (deprescribing) over another (current routine VA care).
- 3.) The study protocol has been informed by a broad range of expertise including geriatrics, gerontology, pharmacology, hospital medicine, post-acute care medicine, psychiatry, and clinical trial methodologists.
- 4.) Deprescribing actions and decisions will be guided by a clear and explicit protocol that will enable transparency and explanation of results and allow for broader generalizability.
- 5.) The intervention protocol is general in its approach, however all deprescribing decisions are individualized to the Veteran, after considering the input from the study pharmacy expert, the Veteran, the hospital care team, and outpatient prescribers.
- 6.) In the event that medications have increased potential for physiologic withdrawal, pharmacokinetic / pharmacodynamics effects, or medical condition exacerbation we will implement a titration protocol to minimize risk.

- 7.) We have designed our trial with extensive follow-up of Veterans extending to 90 days after SNF discharge, thus allowing for robust follow-up for any potential adverse drug withdrawal events.
- 8.) An independent and qualified Data Safety Monitoring Board (DSMB) will be established to review the research protocol prior to the start of the study and conduct interim analyses for safety and review data on serious adverse drug withdrawal events.
- 9.) We have in place close monitoring and reporting of adverse events, including Adverse Drug Withdrawal Events. Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Drug Withdrawal Reactions (SUSADWR) will be conducted to monitor safety during the trial.

Privacy and 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 campus. All study subjects will be assigned a unique study identification number for use in computer databases and analyses. Linkage of participant study IDs to Veteran identifiers will be maintained by the PIs and Project Coordinator only, with username/password protected access. All electronic data will be kept in password-protected computer files on a secured VA server.

Potential Benefits of Proposed Research to Human Subjects 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 VA clinical practice. In the absence of this study, a VA 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, Veterans 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 the 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 patients are living at home 100 days after SNF discharge.¹¹ 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 to three geriatric syndromes across both care settings. 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 patient 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 VA clinical practice and future trials in medication management among older patients.

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