Human Subjects Section of Shed MEDS Grant Proposal

Human Subjects Involvement, Characteristics, and Design. In this study, we estimate that we will consent 1,356 adult medical or surgical ward inpatients that are 65 or older, taking at least 5 medications, and are referred to one of our 14 participating SNFs. As stated in the Research Plan (Anticipated Enrollment and Attrition), we estimate that 170 patients/year will be randomized into the intervention group to yield a total of 680 patients in the intervention phase of the study. 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. This study does not contain any exclusion criterion based on race, gender, or ethnicity. Patients 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 5. This study will involve one acute care hospital (VUMC) and 14 participating regional SNFs (see Letters of Support). The planned enrollment table provides demographic data regarding gender, race, and ethnicity of anticipated enrolled patients 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 Vanderbilt University IRB; and,
- NIH Human Subjects training

Study Group Assignment. As described in the Research Plan, patients will be screened daily for eligibility criteria. Vanderbilt IRB permits a record review to screen patients for research studies, similar to a limited HIPAA waiver. All patients who meet criteria will be approached for consent. Following enrollment and the completion of baseline assessments, patients will be randomized into the intervention or usual care control group (see Randomization in the Data Analysis section). The research team member who completes the initial deprescribing medical record review and the research staff who administer outcome assessments will be blind to group assignment.

Follow-up and Retention Plan. In order to maximize the 90-day participation of randomized patients, 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 patients 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 letters will be sent 2 weeks prior to the 60-day phone call and 2 weeks prior to the 90-day in-person visit.
- The 60-day phone follow-up will serve as an additional reminder of study participation.
- Weekly team meetings will be conducted with study personnel to assess study enrollment and follow-up rates, with in-depth discussions related to barriers and enablers to follow-up participation.

Specific Vulnerable Populations

Dementia Patients: Patients 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. 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 Seizure History: 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.

Sources of Research Material

Data Sources. All materials will be collected and recorded for research purposes. The sociodemographic, clinical, and outcome data collected during this investigation will be obtained from multiple sources, including subjects (or proxies) directly via standardized interview protocols, medical records (both hospital and SNF), hospital databases, and pharmacy records. The main source of data for the hospitalization will be chart abstraction utilizing the patient'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 patient assessment and medical records will be entered directly into the study database via electronic case report forms (eCRFs) using the secure Research Electronic Data Capture (REDCap) database on the Vanderbilt username/password protected server. Data will be entered into the database using a computerized tablet that synchronizes to a central server via a secure web channel. Paper CRFs will be used in situations when access to the electronic database is not available (e.g., home visits). Data from paper will be directly entered into the electronic database, and all paper CRFs will be maintained in a secure and locked file cabinet, in a secure and locked office.

Follow-up and Record Retention. All data collected in this study will be maintained at VUMC on a secured server. Information in the database will be stored for an indefinite period of time 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% 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 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.[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.

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 Vanderbilt's 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 patient 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 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. During the informed consent process (including surrogate and patient consent) the following techniques will be employed:

- Study staff will describe the study protocol to patients 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 patient's routine hospital or out-patient care provided by Vanderbilt or the SNF.
- Patients 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 patient/surrogate wishes to withdraw from the study.
- The patient and family will be provided with a written copy of the consent form and ample time to have questions answered prior to enrollment.
- For eligible patients who have cognitive impairment based on the BIMS, 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 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 patients inability to consent is temporary (e.g., delirium, drug effects), the patient 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 patients will have an alert placed in their medical record to identify them as a study participant, along with contact information for the study personnel.

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 patient 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 pharmacist or nurse practioner deprescriber, 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 (see Efficacy and Safety Monitoring). To provide an additional safeguard, we also have created 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 usual 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 patient, after considering the input from the pharmacy/NP expert, the patient, 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 patients 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.) All protocols, consent forms, and research materials have been submitted to the Vanderbilt IRB as part of the pilot intervention and have been approved.

10.) We have in place close monitoring and reporting of adverse events, including Adverse Drug Withdrawal Events. Serious Adverse Events (SAEs) and Suspected Unexpected Serous 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 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. Study tables for data gathering will have two layers of password protection. The first layer activates the device itself, and the second layer accesses the database software. Data will be synchronized from the electronic tablet to the secure server. Patient data will be removed from the electronic tablet once data has been transferred securely to the VUMC 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 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 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 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.