Protection of Human Subjects—Revised

Clinical trial criteria

As a research study in which one or more human subjects are prospectively assigned to one or more interventions to evaluate the effects of those interventions on health related biomedical or behavioral outcomes, the current study meets criteria for a clinical trial. The study will be conducted as a clinic level cluster pragmatic trial at …….

Risk to Subjects-Overview

…….. Institutional Review Board

This study involves human subjects research which will be undertaken at ……. All research conducted at….. complies with the Department of Health and Human Services requirements for safeguarding the rights and welfare of human subjects, regardless of the source of funding. ……. has an approved Federal-wide Assurance Compliance filed with the Office for Human Research Protections (OHRP). All human subjects research undertaken in .... is reviewed and approved by the .... IRB in accordance with this Assurance. The .... IRB also serves as the Research Privacy Board, and ensures that the privacy and confidentiality or protected health information is maintained, as required by the Health Insurance Portability and Accountability Act (HIPAA).

Rationale for studying a potentially vulnerable population

The proposed study addresses medication management in a potentially vulnerable population, individuals with Alzheimer's Disease and Related Dementia (ADRD). For older individuals with ADRD, taking more medications is associated with greater risk of adverse drug events, drug interactions, treatment burden, and cognitive changes from medication side effects. The combination of ADRD plus other conditions (ADRD-MCC) leads to more medication use, more complex medication regimens for patients, and is associated with higher rates of hospitalization and mortality. Clinical guidelines developed for people with single conditions (e.g. hypertension), rather than for people with multiple chronic conditions (e.g. hypertension and heart disease and dementia and incontinence) tend to exacerbate polypharmacy and complexity of medication regimens and increase the risk of drug interactions and inappropriate prescribing. The key principle that should guide person- and family-centered care is that people take medicines to help them achieve their goals – but not medicines that are either likely to be harmful or unhelpful. Optimizing medication through deprescribing (the process of reducing or stopping the use of inappropriate medications or medications unlikely to be beneficial) can help avoid adverse drug effects and improve outcomes for MCC patients, particularly for those with ADRD. Therefore, the rationale for studying deprescribing in the potentially vulnerable ADRD population is that this population is at risk for adverse effects from inappropriate medication use and may attain improved health outcomes from discontinuing unnecessary or inappropriate medications.

Approach to potential risks of the proposed study

Potential risks associated with deprescribing include an adverse drug withdrawal event, return of symptoms, and anxiety about the deprescribing process. However, potential risks can be minimized or prevented by using a patient-centered, structured deprescribing process. Additionally, potential risks of deprescribing need to be weighed against potential risks of

continuing an inappropriate medication. Deprescribing studies, where the intervention involves withdrawal of medications which have been determined to be inappropriate in the individual (which is what our intervention will involve) have been generally shown to be safe. Our intervention involves providing tools (including patient/caregiver and clinician education) and opportunities (through patient/ caregiver and clinician engagement) to identify medications which are suitable for withdrawal in an individual and to assess individuals' willingness to consider deprescribing. The decision to deprescribe a medication will be made by the primary care physician and the patient/family caregiver through shared decision making.
The following additional measures also address this concern:

- A limited number of medications will be selected during Aim 1 for potential deprescribing during Aim 3.
- Potential side effects of deprescribing will be integral to stakeholder discussions of medication selection during Ami 1 and will inform medication selection. These discussions will include evidence-based information on risks and benefits of medication continuation.
- The protocol for the pragmatic trial will be a) developed with clinician and patient and caregiver input, b) pilot tested, and c) approved by the independent Data Safety Monitoring Board (DSMB) before it is submitted to the IRB for review.

It is possible that discussing deprescribing of medications may lead to anxiety and stress to the patient. However, previous qualitative studies indicate that where there is a discussion of the reasons why the medication is being recommended for withdrawal and shared decision making about deprescribing, this anxiety is minimal.
Strategies to mitigate this concern in our study include:
- Emphasis on shared-decision making between patients, caregivers and their primary care physician
- Patient and caregiver directed education
- Determining the method of broaching the subject will be a key investigation in the R21 phase through discussions with the National Advisory Panel and local Stakeholder Advisory group and a specific interview question in the qualitative interviews with patients and caregivers.
- Pilot testing of the approach prior to the pragmatic trial.

<u>Human Subjects involvement, characteristics, and design</u>

<u>Aim 1</u>: Aim 1 involves interviewing patient/caregiver dyads and clinicians to inform refinement of the proposed intervention. One-on-one interviews will be held with 10 patients with Alzheimer's disease or related dementia (ADRD) and/or their caregivers at their usual clinic. We also will separately conduct interviews with 10 clinicians. Interview questions will address stakeholders' understanding of, and potential interest in, deprescribing; specific drug classes of interest (a limited number of medications will be selected during Aim 1 for potential deprescribing during Aim 3.), potential side effects of deprescribing; and suggestions for approaching this topic with patients and families or with primary care physicians (depending on the stakeholder's perspective). We will also seek input on the design and content of proposed patient/ family caregiver educational materials. Clinicians and health system leaders will additionally be queried on proposed components of the clinician portion of the intervention including case-based learning, clinic level feedback on PIM prescribing patterns, potential side effects of deprescribing as well as the risks and benefits of medication continuation, and appropriate engagement of the overall practice team to refine patient / caregiver and clinician intervention materials and provide input on intervention design.

Aim 2: After refining the intervention protocol based on Aim 1 feedback, receiving DSMB approval of the revised protocol, and confirming support from leadership at the pilot clinic, 20 patients / family caregivers from a single clinic and their primary care physicians (PCPs) will be recruited to pilot test the intervention for feasibility. ……. (Please see discussion of DSMB involvement and discussion of consent process below.) ……..

Aims 3-4: Aims 3-4 involve a clinic-level cluster randomized pragmatic trial with a delayed control group. …….. After appropriate consent (see discussion of consent process for Aims 3-4 below), we will send the estimated … eligible participants across …clinics mailed intervention materials ….it will contain IRB approved language that indicates that by returning the assessment a participant is consenting for assessment responses to be used in research. PCPs of eligible patients will receive a continuing medical education (CME) case-based learning intervention on the topic of deprescribing which will include a short (9 question) assessment of clinicians' attitudes towards deprescribing. The CME and clinician attitudes assessment will be completed in a web-based format. The clinician attitudes assessment will also contain IRB approved language that indicates that by returning the assessment a participant is consenting for deidentified response data to be used in research.

Aim 5. Aim 5 methods will be similar to Aim 1 qualitative methods. Up to 20 patients / caregivers will be recruited by mailed letter with routine opt out provisions and telephone follow up. Interviews will take place by phone (unless the participant prefers in person). We will request verbal consent for Aim 5 interviews. Up to 10 PCPs will be recruited by email based on enrollment of their patients in the pilot study. Interviews will take place by phone at a time convenient for the physician. The goal of Aim 5 interviews is to explore the mechanisms of intervention effectiveness including intervention fidelity and sustainability.

The following inclusion and exclusion criteria will be implemented:
……..

Sources of Materials:

Electronic Health Record (EHR): We will use a list of validated ICD codes applied to EHR diagnosis data to identify patients who have a diagnosis of ADRD, 1 or more additional chronic condition, and are using 5 or more prescription medications. A waiver of HIPAA authorization will be obtained from the IRB to identify possible study participants.

……. *personnel and data:* Clinicians will be identified through snowball sampling starting with recommendations from geriatric and primary care clinical leadership. EHR administrative data will be used to identify the clinicians at the pilot clinic who are PCPs for the pilot study participants.

Qualitative interviews: Aim 1: Patients / caregivers will be recruited by mailed letter with routine opt out provisions and telephone follow up.(See recruitment details below.) In-person interviews will take place in locations convenient to the participants, specifically before or after an upcoming appointment at the participant's usual clinic. Clinician stakeholders will be recruited by snowball sample starting with clinical leadership. Interviews will take place at times and locations convenient to the clinician, specifically at the clinician's home office. The strictly voluntary nature of the study will be clearly stated in the recruitment materials and in the consent form. Participants will be consented in person at the time of the interview with written consent materials. Research staff will use an IRB-approved script to describe the study when

contacting potential participants. Potential participants will be encouraged to ask questions about the project. For Aim 5: Patients / caregivers will be recruited by mailed letter with routine opt out provisions and telephone follow up. Interviews will take place by phone (unless the participant prefers in person). We will request verbal consent for Aim 5 interviews. PCPs will be recruited by email based on enrollment of their patients in the pilot study. Interviews will take place by phone at a time convenient for the physician.

Chart Reviews: Charts of the potential participants identified for the Aim 1 interviews will be reviewed to assess cognitive function and notation of a Legally Authorized Representative (LAR)—see recruitment process below. Charts of the 20 patients in the pilot study will be reviewed after the intervention to understand the content of the most recent patient-PCP visit with regards to discussion of medication prescribing and discontinuation.

Adequacy of Protection from Risks

Data Safety Monitoring Board (DSMB)—Please see the Data and Safety Monitoring Plan below and attached DRAFT DSMB Charter.

Data management

EHR data: Eligible patient/ caregiver participants will be identified by the study statistician or analyst using EHR data under a waiver of HIPAA Authorization. The study staff have successfully completed HIPAA and human subjects research trainings as required by .... will comply with our institutions' policies regarding data sharing, data protection, and data file destruction at the earliest date.

Names and other identifiers will be kept in separate locked files. Statistical analyses will be performed on de-identified data; participants will never be individually named. All computerized data will be kept on the secured computers or networks at ..... These data will be accessible only to research staff, using confidential usernames and passwords.

Recruitment

Aim 1: Patients / caregivers will be identified through the electronic medical record based on the eligibility criteria above and recruited by mailed letter with routine opt out provisions and telephone follow up. Just prior to the telephone follow up to enroll potential interviewees, study staff will conduct a brief chart review to assess the potential participant's level of cognitive function. For individuals with EHR documentation of lower cognitive function (as indicated by documented assessment of low cognitive function or documentation of medical decision making by an LAR) who are interested in participating, study staff will require that the participant be accompanied by a caregiver who is a legally authorized representative (LAR) to provide Consent for the interview, while the participant will provide Assent (see consent processes below). Similarly, during the follow up call, if study staff believe a patient may not be able to provide Consent, they will make the request for the LAR to as above. In-person interviews will take place in locations convenient to the participants, specifically before or after an upcoming appointment at the participant's usual clinic. Clinician stakeholders will be recruited by snowball sample starting with clinical leadership. Interviews will take place at times and locations convenient to the clinician, specifically at the clinician's home office. The strictly voluntary nature of the study will be clearly stated in the recruitment materials and in the consent form. Clinician participants will be consented in person at the time of the interview with written consent materials. Research staff will use an IRB-approved letter for initial recruitment and approved

script to describe the study when contacting potential participants. Potential participants will be encouraged to ask questions about the project.

Aim 2: The pilot clinic will be identified in conjunction with operations and clinical leadership and with support from leadership at the individual clinic. Clinicians at the pilot clinic will be educated on the pilot project by study staff at a clinic team meeting and will be consented in person after all questions are addressed. Patients / caregivers from the single clinic participating in the pilot study will be recruited by mailed letter with routine opt out provisions and telephone follow up. Study staff will follow the same procedures as for Aim 1 to ensure that participants with low cognitive function are recruited in conjunction with their LARs. Consent for the pilot study will include consent to complete the PATD and consent for debriefing interviews. (See consent process below.) Debriefing interviews for patients/ caregivers will take place by phone (unless the participant prefers in person). Clinician interviews will take place by phone at a time convenient for the physician.

Aims 3-4: The intervention will be delivered at the level of the clinic with a delayed control group. … Following appropriate consent (see below), we will send all patients meeting eligibility criteria at intervention clinics the intervention informational materials on deprescribing.
We will request a waiver of informed consent for the clinicians in the intervention clinics with the intervention consisting of offering physicians case-based learning on deprescribing for Continuing Medical Education credit and clinic level feedback on prescribing patterns. The clinician case-based learning module will include a 9 question assessment of Physician Perceptions of Medication Discontinuation (PPMD). We will request IRB approval to include a statement of implied consent physician deprescribing attitudes assessments as responses to these questions will be used in the study analyses.

Aim 5: Aim 5 recruitment will follow the same processes as Aim 1. Patients / caregivers will be recruited by mailed letter with routine opt out provisions and telephone follow up. Interviews will take place by phone (unless the participant prefers in person). PCPs will be recruited by email based on enrollment of their patients in the pilot study. Interviews will take place by phone at a time convenient for the physician.

<u>Consent Process</u>

Overview of the consent process:

We have discussed the proposed project with a .... Institutional Review Board (IRB) representative. The IRB representative anticipates that Aim 1 (stakeholder engagement) will likely be considered minimal risk. Aim 2 will involve individual level informed consent for pilot project participants. The protocol for the pragmatic trial (Aims 3-4) will be revised as needed following Aims 1 and 2 and approved by the DSMB prior to being submitted to the .... IRB as a modification to the original IRB submission. The pragmatic trial will be conducted at the level of the clinic with 9 intervention clinics and 9 control clinics. Options for pragmatic trial consent range from full individual level recruitment and written informed consent, to recruitment information sent to all eligible candidates with an ‘opt out’ clause, to general information on the intervention provided to all eligible patients with an option for further inquiry. The IRB has recently considered this spectrum of consent options for a pragmatic trial on lung nodule surveillance. The IRB representative also suggested that stakeholders and interviewees engaged during Aim 1 be invited to discuss consent options for Aim 3 so that they can inform a recommendation for consent during the pragmatic trial. (Although stakeholders would contribute information to the Aim 3 modification, the determination of consent requirements would rest with

the IRB.) This would align with stakeholder input on protocol development and with stakeholder input on selecting medications for potential deprescribing.

Consent process: Aims 1, 2, 5

The following process will apply to Aims 1, 2, and 5 and are specifically relevant to working with study participants with ADRD and their family/ caregivers.

Following recruitment as described above, trained study staff will obtain informed consent for either interviews or for the pilot study. (Consent documents for each aim will reflect the activities of that aim.) Patient and Companion Informed Consent will be obtained by research staff trained in human subject research at the time of the scheduled interviews. Upon review of the informed consent form, we will evaluate patient and companion capacity to give consent by asking potential participants about the study protocol. We will ask: "What is the main purpose of the study?", "What are the benefits of the study?", "What are the risks of the study?", "Are you able to withdraw from the study at any time?" Based on answers to these questions, research staff will document whether the person may provide informed consent. Among patients who are determined to lack capacity to provide informed consent, we will seek to obtain written or oral assent from the patient, and proxy consent from their LAR. In such cases, the research staff will complete a form that specifies how informed consent was obtained.

Those who consent to study participation will be given a detailed description of their potential involvement in the study, and a copy of the consent form. The interviewer will explain the purpose of the study, protections provided by the Federal Certificate of Confidentiality, and study procedures. The interviewer will have the participant read the consent form, or read it to him/her if necessary, and answer questions before the participant consents. All participants will be informed that they have the right to decline to answer any question for any reason without providing an explanation. The participant's understanding of the study will be assessed by asking them to explain the research procedure, research purpose, possible risks, possible benefits, and that participation is voluntary in their own words. Participants will be given as much time as they would like to ask questions regarding the study. They will be asked not to provide any identifiable information about non-consented persons in this reporting form. No interviews will be conducted until informed consent is obtained.

Once consent is obtained, in-person subjects will receive a copy of the signed consent form. Participants will be informed that they can withdraw from the study at any time. Participants will be directed to the phone number of the PIs (listed in the consent form) if further questions arise. The contact information for the IRB will also be in the consent document for further questions concerning their rights as study subjects. Aim 1 participants will receive a $100.00 gift card for completion of the in-person interview. For aim 2, participants who complete the telephone debrief will receive a $25 gift card.

Aims 3-4

We have discussed with the IRB approaches to informed consent for Aims 3 and 4. A final approach to consent for Aims 3 and 4 will be determined after the final protocol has been completed and reviewed by the DSMB after the Aim 2 pilot study. As a cluster randomized pragmatic trial, all eligible patients and their PCPs will receive either the initial or the delayed intervention. Per the IRB discussions, options for Aim 3 consent range from full individual level recruitment and written informed consent, to recruitment information sent to all eligible candidates with an 'opt out' clause, to general information on the intervention provided to all

eligible patients with an option for further inquiry. The IRB has recently considered this spectrum of consent options for a pragmatic trial on lung nodule surveillance. In the event that the IRB requires informed consent of Aim 3 participants we will still be able to conduct the proposed study. The number of potential participants is large, but participants can be identified under a waiver of HIPAA authorization for the initial contact through electronic data, contacted in advance of the intervention, and offered study information including risks, benefits, alternatives to participation, and assurances that participation will not affect their medical care. Since potential participants by definition have some degree of cognitive impairment, the study team will seek assent from the patient if they lack the capacity to provide informed consent through the process described for Aims 1,2, and 5 above, and will obtain any required consent from caregivers or others with legal authority to act on behalf of the potential participant as documented in the electronic medical record.

2. Potential benefits of the proposed Research to the subject and others

Clinician guided deprescribing has been shown to be safe, effective, and improve outcomes for older patients. There is no direct benefit to those included into the study for Aim 1. However, this research will improve the design of the pragmatic deprescribing intervention. Participants in the Aim 2 pilot study may benefit from learning about potential deprescribing as part of medication management and may benefit from shared decision making with their PCPs regarding medication management. Participation in the study as part of Aims 3 and 4 has the potential to improve health outcomes for patients by decreasing rates of adverse events that result from potentially inappropriate or unnecessary medications.

3. Importance of Knowledge to be Gained

Information gathered from this research has the potential to improve outcomes for patients with ADRD-MCC. For older individuals with ADRD, taking more medications is associated with greater risk of adverse drug events, drug interactions, treatment burden, and cognitive changes from medication side effects. Educating patients and clinicians on optimal medication management can improve health outcomes. If the intervention is successful, the simple, scalable, pragmatic study design can be replicated in other healthcare systems and settings.

4. Data and Safety Monitoring Plan

At the start of the study (prior to Human Subjects recruitment) both co-PIs will work with the National Institute on Aging (NIA) to create a DSMB to monitor the study and report to the .... IRB. The DSMB will be comprised of individuals with expertise in clinical management of dementia and specific expertise on medication management in the ADRD population: research scientists, physicians and pharmacists not associated with the study. The DSMB will monitor of the progress and safety of all study participants, promptly report all adverse events, and oversee the validity and integrity of the data and protocol compliance. PIs will attend all DSMB meetings. The DSMB will have the final decision of whether individual participants should be removed from the study due to safety concerns.

The DSMB will meet twice by teleconference during the R21 phase of the project: First to review the pragmatic trial protocol prior to the pilot study and again to review the results of the pilot study and approve the final protocol for the full pragmatic trial. If the R33 phase of the project is funded, the DSMB will remain in effect and will meet at least semi-annually with additional ad hoc meetings as needed. The DSMB will determine if modification or cessation of the study

protocol will be necessary. DSMB responsibilities will include evaluating study progress, adequacy of recruitment, any (intended or unintended) deviations from study protocol, interim study analyses and results, performance of individual study sites (clinics), and data quality. Information on these factors and any additional requested information will be summarized and provided to the DSMB in advance of each meeting. PIs will conduct and report to the DSMB interim analyses addressing possible safety outcomes (study terminations, AE), and data quality.