Document Coversheet

Study Title: Assessment of Medication Optimization in Rural Kentucky Appalachian Patients With Mild Cognitive Impairment or Dementia: The AMOR Kentucky Study

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Study overview: The current proposal includes a single arm, unblinded feasibility study of the MTM describing intervention in rural/underserved Kentucky Appalachian populations with MCI and/or dementia. Our well-established experience in providing MTM deprescribing interventions to the aging population with and without cognitive decline has allowed us to develop routine practices of assessment of medication appropriateness using the MAI, as well as implementation of a multidisciplinary physician-pharmacist team targeting improvement in cognitive outcomes in the aging population. This approach will be carried forward through a telemedicine practice that is comprised of approximately 500 patient-caregiver dyads throughout rural areas of Appalachian Kentucky. The methods for cognitive assessment and assessment of other health related issues have been well-established through an initial grant from the Alzheimer's Association in 2007 and have been in practice for 16 years here at UK.

We intend to use this system and these experiences to assess medication appropriateness in 50 research participants over the one-year funding. In this trial, each participant will be evaluated for medication appropriateness, and a deprescribing intervention will be provided by our multidisciplinary team. Reassessment of the proposed medication changes, as well as the potential impact on cognition will be determined at the six-month evaluation for each of these participants. Participants will be age greater than 60 years, with mild cognitive impairment, and/or in the early stages of dementia. Participants will be enrolled and followed for 6 months to determine the impact of the telemedicine-delivered deprescribing intervention in improving medication-related outcomes (i.e., medication appropriateness, number of medication/PIM) in rural/underserved Kentucky Appalachian populations with cognitive impairment and/or dementia. As secondary outcome measures, we will evaluate the impact of the deprescribing intervention on cognitive function and caregiver burden using validated assessment instruments (see description of outcome measures below).

Table 3. Timeline of study events

Study procedures	Baseline evaluation	4 weeks	3 months	6 months
Complete medical evaluation	X			X
MTM intervention		X	X	
Assessment of medications	X	X	X	X
Assessment of AE/SAEs		X	X	X
Participant outcome measures	X			X
Caregiver outcome measures		X		X

Abbreviations: MTM, Medication Therapy Management Intervention; AE, adverse event: SAE, serious adverse event.

Study Design. This preliminary feasibility study will use an unblinded, single-arm design. See study table for timing of specific procedures and intervention (Table 3).

Study population. Participants will all be enrolled from rural Appalachian referrals to the UK telemedicine Cognitive Clinic. All people enrolled in this clinic receive a standardized cognitive evaluation and treatment plan, described below. Immediately after completing their first remote visit, eligibility for participating in the study intervention – which comprises specific medication-focused evaluation and recommendations, also described below – will be assessed. Eligibility includes: (1) 60 years or older, (2) diagnosed with mild cognitive impairment or dementia, (3) using at least one PIM, (4) living in the community, (5) willing to participate in this intervention study (both the patient and the caregiver). Subjects meeting eligibility criteria will be contacted, informed about the study, and invited to participate. The informed consent process will be performed remotely with the participant and or legally authorized representative using IRB-approved protocols (see Human Participants Section for details).

AMOR-KY MTM Intervention. The proposed deprescribing intervention is using a patient-centered framework by: (1) balancing the risks and benefits, and addressing the specific needs of each individual patient, (2) considering the individual patient and their caregiver's preferences and values, and (3) empowering the patient and their caregiver to take responsibility and fully participate in the decision-making process as equal team players.[28-30] The proposed MTM deprescribing intervention will be developed on an individualized basis, taking into account specific medications and medical conditions for each unique participant, and delivered in an interdisciplinary fashion by the pharmacist-physician team working closely with the patient and their caregiver.

After enrollment, we will conduct an interview with the participant and their caregiver to collect information on all the medications the participant is taking, including prescription and over-the-counter medications, vitamins and supplements. These data will include health history, indication for treatment, duration of therapy, dose and mode of administration, and adherence to therapy. In addition, we will assess the potential for adverse drug effects by asking the participant and their caregiver to recall any side effects, unwanted reactions, or other problems with their medications in the last year or since the medication was initiated, whichever is shorter.[31] For patients reporting adverse effects, additional information will be collected to include the name of the

medication they suspected, a description of the symptomatology experienced, and whether they modified the use of the medication in question on their own or after discussing with their primary care physician.[31]

Based on the data collected, the pharmacist will review the information and will prepare prioritized written recommendations to include the 'problem-list' of medications that are potentially inappropriate (based on indication, adverse events, drug-drug or drug-disease interaction, or as described by the Beers 2019 criteria, specifically focusing on medications like anticholinergics, benzodiazepines, or Z-drugs that are of importance to patients experiencing MCI or dementia).[36,37] The pharmacist will also provide recommendations on the proposed action for each of these medications including: 1) discontinuation; 2) modification of therapy to switch to suggested safer alternative, or to change the dose; or 3) continuation of treatment due to treatment necessity and favorable outcomes under treatment. Where appropriate, the proposed alternatives will include medications listed in an adjunct to the Beers 2019 criteria as "Alternative Medications for Medications in the Use of High-Risk Medications in the Elderly and Potentially Harmful Drug-Disease Interactions in the Elderly Quality Measures".[36-38]

Following this review, the pharmacist-physician team will meet during case conferences to discuss all the problems identified and decide on final recommendations for discontinuation or change related to inappropriate medications. The final recommendations and their rationale, along with general drug information will be discussed by the pharmacist with the patient and their caregiver. Attention will be given to explaining the rationale behind each recommendation and allowing the patient and the caregiver to ask clarification questions, and to express concerns. The written recommendations and the proposed changes will be shared with the patient's primary care physician who will be consulted on the best approach to improve the patient's outcomes. At 4 weeks and 3 months after the initial intervention was delivered, we will follow up with the participant and their caregiver to determine the need for additional evaluations by the pharmacist and/or physician. If necessary, the pharmacist-physician team will provide the following for the participant: (1) comprehensive medication list, updated each time there is a medication change; (2) monitoring for patient concerns or adherence issues; (3) targetted additional evaluation and recommendations for interim medication changes. The intervention will be administered using the existing tele-medicine infrastructure at UK.

Table 4. Description of components of the standard telemedicine evaluation used in this proposal

Instrument	Description & Rationale
Alzheimer disease 8 questions scale (AD8)	Brief 8 item screening questionnaire validated for the detection of MCI and/or dementia
Past Medical History	Includes medical/surgical/family/social history components of the standard clinical evaluation. Used to determine MAI and identify covariates
Neuropsychiatric inventory (NPI)	Used to assess behavioral and psychiatric symptoms of dementia. These may serve as exploratory measures and are important for AE/SAE issues.
Functional Assessment Questionnaire (FAQ)	Used to assess functional consequences of MCI/dementia. These may serve as exploratory measures and are important for AE/SAE issues.
Kokmen Short Test of Mental Status (KSTMS)	Global assessment of cognitive function that allows cross comparisons between other commonly used global assessment tools such as the Folstein Mini-Mental State examination (MMSE) and the Montreal Cognitive Assessment (MOCA). Used to define cognitive state, diagnosis, and to track longitudinal change.
5 Word Free & Cued Recall Test	Memory test that assesses learning, free-delayed recall, and recall augmented by category and choice cuing. Used to define memory components, assist with diagnosis, and to track longitudinal change.
Category Fluency (animal naming)	Number of animals one can name in 60 seconds. Semantic fluency measure used to assess verbal capacity that has been shown to high predictive ability for early clinical cognitive decline and for tracking longitudinal change.
Phonemic Fluency (letter fluency)	Number of words starting with the letter "S" one can name in 60 seconds. Phonemic fluency measure used to assess verbal capacity that has been shown to high predictive ability for early clinical cognitive decline and for tracking longitudinal change.
Physical Examination	Extraocular movements, AMRs (alternating motion rates) in all 4 extremities, Praxis in all 4 extremities, Gait and postural stability, Frontal release signs (glabellar, snout, palmomental).
Clinical Dementia Rating (CDR) scale	The CDR is a fundamental staging system for MCI and dementia stage determination including both global as well as sum of box scores spanning 6 domains of cognition and function. Scores will allow determinations of inappropriate medication use and success of the intervention as well as serving as a covariate in the secondary and exploratory and outcome measures described.

***Telemedicine Evaluation Protocol*.** All study participants will receive the standard telemedicine evaluation for the UK Telemedicine Cognitive Clinic, which includes a 1-hour initial visit and a 30 minute follow up telemedicine evaluation (as noted above, after the first clinic visit, patients will be evaluated for eligibility for the "add-on" MTM intervention we seek to study, and thereafter invited to participate in this research). In the initial evaluation, a diagnosis is made or diagnostic testing is pursued, which may include routine laboratory blood tests to evaluate for reversible causes of dementia and brain imaging studies (CAT scan or MRI) according to the AAN practice parameter on the initial workup and diagnosis of dementia (AAN practice parameter on initial evaluation of dementia). Details of the standard telemedicine evaluation used in this study are provided in Table 4. These assessment scales are ideal for telemedicine assessment providing insights into diagnosis as well as gait, balance and fall risk that are important outcomes of deprescribing interventions. They will serve as appropriate clinical diagnostic and research outcome measures supporting the proposed protocol.

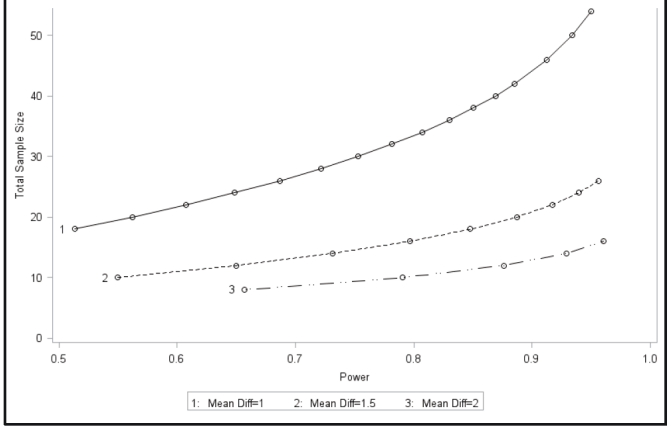
Following the Telemedicine evaluation, a tentative diagnosis will be made in relation to the research participant's cognitive status, that will be used as an important covariate in the analysis. Ultimate clinical diagnosis and disease staging will follow currently approved National Alzheimer Coordinating Center criteria and guidelines.

Outcome variables (Aims 1 and 2). **Primary outcomes of interest** include change from baseline to the 6 months follow-up in the **Medication Appropriateness Index** (MAI) and in **number of medications** (total number and number of PIM), with a focus on medications targetted by the MTM deprescribing intervention. MAI rates each medication based on 10 different criteria (Table 5), each of them with explicit instructions and examples to guide evaluation; the evaluator rates whether the particular medication is "appropriate", "marginally appropriate", or "inappropriate".[39] The reliability of MAI assessments made by a clinical pharmacist and a physician (i.e., internist and geriatrician) demonstrated high inter-rater (kappa = 0.83) and intra-rater reliability (kappa = 0.92).[39] We will also measure the reduction in the number of potentially inappropriate medications,[36] from baseline to the end of the study period. **Secondary outcome measures** will include deprescribing and caregiver assessments to explore the acceptability of deprescribing and caregiver burden that may be associated with inappropriate medication use and the correction of potential medication misuse that may be influenced through our interventional strategy (Table 6); these will also be collected at the beginning and end of the study (see Table 3). Additional secondary and exploratory outcome measures include **cognitive assessments** collected as part of the routine telemedicine cognitive assessment are described earlier. To assess **acceptability of the intervention**, at the last study visit, patients and caregivers will be surveyed using several Likert scale questions and will be given the opportunity to share their opinions of the intervention, including what they liked and disliked about it and what they might do differently.[24] Responses to this survey will be used to inform the planned subsequent iteration of the study for a major future RCT.

Table 6. Deprescribing and Caregiver assessments not described previously that extend beyond the routine telemedicine cognitive assessment.

rPATD scale	The caregiver version of the questionnaire will collect information on patient's and caregiver's attitudes and believes about deprescribing, information that will inform the approach in deprescribing.
Zarit's Caregiver Burden Inventory	Caregiver burden may be directly impacted by inappropriate medication use. The Zarit Burden scale is a well validated instrument that has not been used previously in describing studies.
Appraisal of Self-care Agency scale	"Caring for the Caregiver" is a common phrase we hear frequently. The assessment of self care by caregivers may be an important variable for study in the caregivers of persons with inappropriate medication use.

Figure 3:
Sample size needed to detect different changes in mean MAI



Statistical Analysis Plan and Power Calculations: Descriptive statistics will be used to describe the demographics of the study participants. The pre- and postintervention changes will be analyzed using the Wilcoxon signed-rank test. Based on previous studies using MAI as outcome of interest we calculated the sample size to detect a mean difference of 1.0 between baseline and follow-up assessment. We will need 34 participants to detect this difference with 80% power at a significance level of 0.05 (Figure 3). This is a rather conservative approach as previous studies showed that medication reconciliation interventions can determine a mean MAI change ranging between 1.9 and 17,[40] with our previous study showing a change in MAI of 3.6 after the intervention.[24] In order to account for the potential loss to follow-up, we will plan to enroll 50 participants. Despite the use of an open label, unblinded intervention that precludes definitive proof of efficacy for our deprescribing interventions, this study will provide valuable feasibility, and acceptability data regarding our interventional strategy. The data derived will further provide estimations of intervention effect size that will enable the

Table 5. Medication Appropriateness Index (MAI) criteria

Criterion	Weight
Is there an indication for the drug?	3
Is the medication effective for the condition?	3
Is the dosage correct?	2
Are the directions correct?	2
Are there clinically significant drug-drug interactions?	2
Are there clinically significant drug-disease interactions?	2
Are the directions practical?	1
Is this the east expensive alternative compared with others of equal utility?	1
Is there unnecessary duplication with other drugs?	1
Is the duration of therapy acceptable?	1

development of our planned larger scale R01 interventional study focused on remote deprescribing interventions in rural and underserved communities throughout distributed US populations.

Expected results & alternative approaches. As this is a single-arm pilot study, we will not be able to distinguish effects of usual care from the additional MTM intervention. However, because usual care in the Cognitive Clinic does not place substantial focus on medications, it is likely that any observed changes will be plausibly attributable to the MTM intervention, and evaluations of feasibility and acceptability will also be distinguishable. Relevant concerns to this study include technology and access issues that may be prohibitive for our rural population. This should be minimized through the availability of telemedicine in their local community health care facilities that afforded the initial telemedicine consultation. Should we discover such barriers to engagement we will leverage internal funding to provide appropriate internet connectivity and or devices as need to ensure the conduct of the trial is not compromised by such concerns or issues. Another possible barrier to the study's conduct and execution of our planned deprescribing intervention includes issues in regard to coordination and acceptability of our proposed medication modifications with the rural primary care providers. This has not been a problem previously but maintaining close communication on our intervention and recommendations is needed to ensure our success. Should this prove an obstacle, further develop initiatives to enhance our integration and cooperativity with the rural primary care physicians that are involved in our participant's care.