PILOT STUDY OF ALIGN: A PRAGMATIC DEPRESCRIBING TRIAL FOR PATIENTS WITH DEMENTIA IN PRIMARY CARE

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PRÉCIS

Study Title

ALIGN: Aligning Medications with What Matters Most

Objectives

The overarching goal of this proposal is to refine and pilot a workflow in which a clinical pharmacist makes deprescribing recommendations to the primary care provider (PCP) to reduce medication regimen complexity for people living with dementia (PLWD) and their care partners. To accomplish our main objective above, we propose the following specific aims:

1) To assess the feasibility and acceptability of ALIGN in two different health care systems, to guide the subsequent evaluation of the effectiveness of the intervention in an embedded pragmatic trial (ePCT).

2) To determine the feasibility of the primary and secondary outcome measures for the subsequent ePCT:

2a) To determine the feasibility of measuring the primary outcome, the patient-level Medication Regimen Complexity Index (pMRCI)[1-4], within the existing EHR systems, and to compare it with a more pragmatic measure, chronic medication count, as the primary outcome measure for the ePCT.

2b) To determine the feasibility of measuring the secondary outcome, the Family Caregiver Medication Administration Hassles Scale (FCMAHS)[5], a caregiver-reported outcome measure.

Design and Outcomes

This is a pilot study of a pragmatic intervention consisting of the following strategies: 1) direct-to-consumer deprescribing educational materials designed to activate the care partner and PLWD; 2) a telehealth visit in which a clinical pharmacist discusses benefits and harms of the patient's medications with the patient and care partner in the context of their goals and preferences; and 3) pharmacist-PCP communication in which the pharmacist provides tailored deprescribing recommendations designed to be useful and actionable for the PCP. The study will assess the feasibility and preliminary efficacy of the intervention in two healthcare systems, to guide the subsequent evaluation of the intervention in an ePCT.

Patient eligibility criteria will be: age ≥65 years with a diagnosis of Alzheimer's disease or related dementia (ADRD) from ICD-9 or ICD-10 visit codes or from the electronic health record (EHR) problem list and ≥5 chronic medications. Patients and care partners will be enrolled as dyads and randomized to the intervention group and a delayed intervention control group that will receive the pharmacist-led component 3 months after the educational mailing.

Interventions and Duration

Dyads at each pilot site will be randomly assigned to receive the pharmacist-led intervention immediately after the educational mailing or to a delayed intervention control group that will receive the pharmacist-led component 3 months after the mailing. Piloting with a delayed intervention control group will allow for a more realistic examination of the differential effect of a low-touch control arm (educational mailing only) vs. the pharmacist-led process. Each participant will be on study (intervention period and additional follow-up) for 3 months.

Sample Size and Population

The eligible patient population for the pilot study will be all patients at the two pilot clinics who are age 65 or greater with a diagnosis of Alzheimer's disease and related dementias (ADRD) from either ICD visit codes or documentation on the problem list. Patients must also be taking 5 or more chronic medications, and active patients, defined as having $\geq$1 visit to the primary care clinic within the past year. We will enroll 60 patient-care partner dyads (15 dyads per arm at each site).

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1 STUDY OBJECTIVES

1.1 Primary Objective

To assess the feasibility and acceptability of ALIGN in two different health care systems, to guide the subsequent evaluation of the effectiveness of the intervention in an embedded pragmatic trial (ePCT).

1.2 Secondary Objectives

To determine the feasibility of the primary and secondary outcome measures for the subsequent ePCT:
a) To determine the feasibility of measuring the primary outcome, the patient-level Medication Regimen Complexity Index (pMRCI)[1-4], within the existing EHR systems, and to compare it with a more pragmatic measure, chronic medication count, as the primary outcome measure for the ePCT.
b) To determine the feasibility of measuring the secondary outcome, the Family Caregiver Medication Administration Hassles Scale (FCMAHS)[5], a caregiver-reported outcome measure.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

PLWD use more medications and have more complex medication regimens than people without dementia. Medication regimen complexity is a major source of burden for family caregivers of PLWD in the community.[6-9]It has been associated with adverse drug events,[10] poor adherence,[11] hospital discharge to non-community settings,[12] and hospital readmission,[10] suggesting that "the cure may have become the disease."[13,14] Regimen complexity strains patients, caregivers, and healthcare systems due to the time and stress associated with administering medications (eg, due to swallowing difficulties or confusion), monitoring and direct medication costs. The key principle of person-centered care is that people should be on the medicines that will help them achieve their goals – but not medicines that are either likely to be harmful or unhelpful.[15]

Few prior deprescribing studies have targeted caregivers of PLWD, despite the enormous strain caregivers face due to medication-related tasks[16] and their specific informational and decisional needs and conflicts.[17] Most deprescribing interventions have focused on specific drug classes or the number of medications only, not addressing dosing schedule and additional directions for medication use – critical factors that determine regimen complexity and caregiver burden. Furthermore, interventions to reduce medication regimen complexity have primarily occurred in hospitals,[18] long-term care facilities,[19] or skilled home healthcare,[20] not in primary care – typically the first point of contact with the health care system for PLWD and their caregivers. Another knowledge gap is that health systems rarely collect data on outcomes that reflect the lived experience of dementia caregivers.[21] Both the Alzheimer's Association and the 2017 NIA National Research Summit on Dementia Care identified the development and use of patient/caregiver-reported outcome measures (PCROs) as a priority for dementia research.[21]

2.2 Study Rationale

In preliminary work by our team and others, PCPs cite time pressure during office visits and lack of published guidance of when and how to stop medications as barriers to optimizing prescribing.[22-24] Deprescribing statins, antihypertensives, and psychotropic medications in older adults has been shown to be safe, and may lead to improved quality of life, reductions in falls, and improvements in cognitive and psychomotor function.[25-28] Pharmacists are ideally suited to help address the barriers to deprescribing by lessening demands on PCP time and providing concrete, individualized deprescribing recommendations. Previous research has shown that providers have high acceptance rates for medication therapy management services provided by community pharmacists.[29,30] Our qualitative research has revealed that patients, caregivers and PCPs have a high degree of trust in clinical pharmacists embedded within primary care clinics.[31]

ALIGN: Aligning Medications with What Matters Most is informed by learnings from OPTIMIZE, our team's patient-centered, pragmatic deprescribing intervention for PLWD in primary care that is currently being prospectively evaluated with a cluster-randomized trial at 18 clinics within KPCO.[32] OPTIMIZE is based on the Chronic Care Model, in which patients and families are empowered through approaches such as education and self-management support, and practice teams are bolstered by tools such as decision support and clinical information systems.[33] OPTIMIZE consists of two components: A patient-level intervention comprised of a deprescribing educational brochure, and a PCP-level intervention comprised of an in-person deprescribing educational session, deprescribing "tip sheets" and tailored feedback at the level of the clinic on rates of potentially inappropriate medication (PIM) prescribing in PLWD. Although OPTIMIZE materials encourage patients and caregivers to discuss deprescribing with PCPs, the intervention does not require such conversations. ALIGN builds on OPTIMIZE by more explicitly addressing the informational and decisional needs of caregivers through a shared decision making process facilitated by **clinical pharmacists, who are already embedded in both pilot clinics and throughout their parent healthcare systems**. ALIGN leverages existing pharmacist-led comprehensive medication management programs in both healthcare systems. The goal of the pharmacist-led process in ALIGN is to optimize prescribing and reduce medication regimen complexity by focusing on what matters most to the patient and caregiver, beyond rigid adherence to clinical practice guidelines. ALIGN is responsive to the COVID-19 outbreak in that it can be delivered entirely via telephone.

3 STUDY DESIGN

The proposed pragmatic intervention consists of the following strategies: 1) direct-to-consumer deprescribing educational materials designed to activate the care partner and PLWD; 2) a telehealth visit in which a clinical pharmacist discusses benefits and harms of the patient's medications with the patient and care partner in the context of their goals and preferences; and 3) pharmacist-PCP communication in which the pharmacist provides tailored deprescribing recommendations designed to be useful and actionable for the PCP. The study will assess the feasibility and preliminary efficacy of the intervention in two healthcare systems, to guide the subsequent evaluation of the intervention in an ePCT.

We will enroll 60 patients and their care partners as dyads (15 dyads per arm at each site). Patient eligibility criteria will be: age ≥65 years with a diagnosis of ADRD from ICD-9 or ICD-10 visit codes or from the EHR problem list and ≥5 chronic medications. In

Baltimore, the study site will be 1-4 clinics that are part of Johns Hopkins Community Physicians (JHCP). In Denver, the study sites will be KPCO greater Denver metro primary care practices. Dyads at each pilot site will be randomly assigned to receive the pharmacist-led intervention immediately after the educational mailing or to a delayed intervention control group that will receive the pharmacist-led component 3 months after the mailing. (Please see the Consent section for a discussion of consent options for consenting patients as part of pragmatic trials.)

This protocol employs a pragmatic design. **The intervention is delivered by clinical pharmacists who are already integrated in primary care clinics at JHCP and KPCO. The pharmacists are trained in complex geriatric medication management and routinely provide comprehensive medication management to Medicare beneficiaries.**

Aim 1 is to assess the feasibility and acceptability of ALIGN in two different health care systems, to guide the subsequent evaluation of the effectiveness of the intervention in an ePCT. Data to measure feasibility will be acquired from the EHR, checklists completed by the pharmacists, and audiorecordings of pharmacist phone calls with care partners. We will collect the following measures:
• Proportion of dyads that opt out of the intervention;
• Proportion of pharmacist messages to the PCP that receive an acknowledgement or response;
• Number of contacts between pharmacist and PCP and between pharmacist and dyad;
• Time required by the pharmacist to complete the intervention;
• Proportion of dyads who complete 2 of 2 pharmacist phone calls based on documented status reports.

To evaluate intervention acceptability, we will track the following:
• Type of recommendations made by the pharmacist and acceptance rates for those recommendations (we will look in the chart for notation of patient/care partner and PCP acceptance).

Aim 2 is to determine the feasibility of the primary and secondary outcome measures for the subsequent ePCT:
In Aim 2a, we will determine the feasibility of measuring the primary outcome, the patient-level Medication Regimen Complexity Index (pMRCI)[1-4], within the existing EHR systems, and compare it with a more pragmatic measure, chronic medication count, as the primary outcome measure for the ePCT.

In Aim 2b, we will determine the feasibility of measuring the secondary outcome, the Family Caregiver Medication Administration Hassles Scale (FCMAHS)[5], a caregiver-reported outcome measure.

We will develop the procedures for collecting both outcomes for the full trial.

In Aim 2a, feasibility will be measured as follows:
• Proportion of participants with data elements available vs. unavailable to calculate the pMRCI.

To compare it with chronic medication count as the primary outcome measure for the ePCT, we will measure:
• Change in chronic medication count; and
• Change in pMRCI from baseline to 3 months.
Chronic medication count will be obtained from the EHR using algorithms refined in OPTIMIZE.

In Aim 2b, feasibility will be measured as follows:
• Response rate and completion time for the FCMAHS using each mode of administration.

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Participants must meet all of the following inclusion criteria to participate in this study:

- Care partners will be defined as family or other companions ≥21 years who regularly help the patient with managing medications. We will ask patients to identify the person who helps them the most with tasks such as picking up medications at the pharmacy, requesting refills, filling the pill box and administering medications.
- Patient eligibility criteria will be: age ≥65 years with a diagnosis of ADRD from ICD-9 or ICD-10 visit codes or from the EHR problem list and ≥5 chronic medications. We will include only active patients, defined as having ≥1 visit to the primary care clinic within the past year.

4.2 Exclusion Criteria

Candidates meeting any of the following exclusion criteria at baseline will be excluded from study participation:
- As both the pilot and the planned pragmatic trial will be based in primary care, individuals residing in long term care facilities or enrolled in hospice will be excluded.
- Individuals who cannot converse comfortably in English will be excluded because the FCMAHS has not been validated in other languages.

4.3 Study Enrollment Procedures

1) Using clinical and claims data under a waiver of HIPAA Authorization, the data analytics team at each institution will identify all patients at each of the two clinics who meet inclusion criteria. This list will be routed to the project assistant via a HIPAA-compliant method.

2) The project assistant will perform administrative roles for the study. This includes: Mailing study materials with opt-out provisions to the homes of 30 randomly selected patients from this list. Patients will be entered into a study database for tracking and to avoid repeated mailings. Study materials will include a phone number that patients or care partners can call to opt out. We will continue mailing materials to eligible patients until 30 have been recruited at each clinic. Materials will also provide dyads the opportunity to opt *in* by calling the phone number. To emphasize that the study is for

care partners, the envelope and introductory letter will be addressed to the patient and family (eg, "Mr. John Smith and family").

Scheduling virtual visits with the clinical pharmacist. Dyads who do not opt out (and those who opt in) within 14 days of the study mailing will be randomized using computer-generated random numbers to either the intervention group or the delayed intervention control group, and called by the project assistant.

If the patient and care partner do not opt out, the project assistant will call the patient's phone number listed in the EHR and use an IRB-approved script (attached) to identify the care partner:

- The project assistant will briefly explain that they are calling about "a program for family members and friends who are caring for someone with memory problems."
    - If the patient answers the phone, the project assistant will say, "I'm calling about your medicines. Many people have someone who helps them manage their medicines on a daily basis." They will then ask to speak with the care partner.
    - If the care partner answers the phone, the project assistant will ask, "Are you the person who helps [PATIENT] the most to manage their medicines?" **This is the standard approach that clinic staff use to call patients with dementia on the phone and identify their care partners during the course of clinical care.** As the intervention is designed to address the needs of care partners and requires their participation, the project assistant will ask to speak with the care partner first. Because some patients with mild or moderate dementia may be interested in hearing about the program, the project assistant will offer to describe it to the patient as well.
- Patients who are unwilling or unable to identify a care partner who helps them manage their medicines will be excluded. The project assistant will document the reasons for ineligibility in a REDCap Screening Log.
- The project assistant will briefly describe the pharmacist consult to the care partner. If the care partner agrees, the project assistant will schedule the pharmacist call, which will occur immediately (within 4 weeks) for the intervention group and at approximately 3 months for the delayed intervention control group.

4) If patients or care partners opt out during the phone call, the project assistant will document the reason (eg, no time to participate, not interested) in a REDCap Screening Log.

5) Dyads randomized to the delayed intervention group will be told that they will receive another phone call from the project assistant in approximately 3 months to remind them of their appointment with the clinical pharmacist.

6) After scheduling the pharmacist consult, project assistants will offer care partners in both groups the option of completing the secondary outcome measure, the Family Caregiver Medication Administration Hassles Scale (FCMAHS). For care partners who are interested in completing the FCMAHS, project assistants will obtain verbal consent when administering the measure over the phone (see script). If the care partner does not wish to complete the FCMAHS over the phone during the scheduling phone call, the project

assistant will offer to call back before the pharmacist visit (up to 28 days) or to later e-mail the care partner a link to an electronic version.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

1) The mailing sent to patients' homes will be no more than 3 pages and will consist of an informational brochure introducing the idea of discontinuing unnecessary or potentially inappropriate medications. This approach is based on an established model of patient-centered deprescribing and is adapted from a direct-to-consumer deprescribing intervention for older adults on benzodiazepines.[34,35] Materials are designed to engage care partners and invite them to discuss medication-related concerns with the pharmacist. The informational brochure will include mention of how to plan for a telehealth visit with a clinical pharmacist to discuss medication optimization and reasons why some people may benefit from taking fewer medicines. It will encourage care partners to discuss their key health outcome goals for the patient, and medication-related activities that the dyad finds helpful and feasible vs. unhelpful or difficult. The brochure will include instructions NOT to discontinue any medications without talking to the clinical pharmacist or the patient's primary care clinician.

2) As described in Section 4.3, dyads who do not opt out (and dyads who opt in) will be called by the project assistant to assess interest and schedule the pharmacist consult approximately 14 days after mailing the intervention materials.

Intervention group:
3) The project assistant will schedule the telehealth visit with the clinical pharmacist to occur within the next 4 weeks.

4) After scheduling the pharmacist consult, the project assistant will offer care partner the option of completing the secondary outcome measure, the Family Caregiver Medication Administration Hassles Scale (FCMAHS). They will obtain verbal consent for the FCMAHS when administering it over the phone (see script). If the care partner does not wish to complete the FCMAHS over the phone during the scheduling phone call, the project assistant will offer to call back before the pharmacist visit (up to 28 days) or to later e-mail the care partner a link to an electronic version. The FCMAHS will be administered again 3 months after the enrollment phone call.

5) Using comprehensive medication management (CMM) as a foundation, the pharmacist will call the patient-care partner dyad to assess for medication-related problems, such as issues with adherence, potential adverse effects and caregiver strain related to medication management. **Clinical pharmacists are already embedded in both pilot clinics and throughout their parent healthcare systems, and are conducting CMM phone calls with patients. The clinical pharmacists in ALIGN have considerable experience doing medication reviews with older adults, patients with dementia and care partners. They will use a script that was closely adapted from templates that are currently being used by embedded clinical pharmacists in both healthcare systems.** The pharmacists will use these guiding questions to elicit the dyad's goals and priorities for the patient's health in

order to align medications with goals of care (see attached template). We anticipate that the intervention phone call will take up to 1 hour.

6) The pharmacist will then develop an evidence-based deprescribing communication, which will be routed to the PCP via the EHR using a standardized template (see attached). The pharmacist will contact the PCP as per usual clinical practice. The template will encourage the PCP to respond to the pharmacist either to accept the recommendations, to ask questions or to raise concerns.

7) With the PCP's approval, the pharmacist will call the dyad to implement the recommendations and document the changes in the EHR. An updated medication list will be mailed to the dyad. All decisions about discontinuation or continuation of medications will be made by the PCP and patient/ care partner.

Delayed intervention group:
Steps 1-2 will be identical to the intervention group. For participants randomized to the delayed intervention control group, the project assistant will schedule the pharmacist consult in approximately 3 months.

After scheduling the pharmacist consult, project assistants will offer care partners in the delayed intervention group the option of completing the Family Caregiver Medication Administration Hassles Scale (FCMAHS). They will obtain verbal consent for the FCMAHS when administering it over the phone (see script). If the care partner cannot complete the FCMAHS over the phone during the scheduling phone call, the project assistant will offer to call back before the pharmacist visit (up to 28 days) or to later e-mail them a link to an electronic version. The FCMAHS will be administered again 3 months after the enrollment phone call.

The project assistant will call the care partner again closer to the date of the pharmacist visit to remind them of the appointment. Steps 4-6 will be identical the intervention group but will occur 3-4 months after study enrollment.

5.2 Handling of Study Interventions

Due to the nature of the intervention, participants, pharmacists and PCPs cannot be masked. Project assistants will enter data into a REDCap database so that the researchers can analyze it without having access to group assignment.

We will use multiple strategies to implement and measure fidelity in the study:

Training Fidelity: Training materials for pharmacists will consist of guiding questions to help elicit patient/care partner health outcome goals, communicate about deprescribing with patients and care partners, and align medications with goals of care, and an Epic template for communicating deprescribing recommendations to the PCP (attached). **This document was developed in collaboration with 3 clinical pharmacists at JHCP and KPCO and closely adapted from the approach and language they use when calling patients with dementia and their care partners on the phone.**

Intervention Fidelity:

1. Intervention adherence will be measured using a REDCap survey, which will enable us to monitor in real time and address issues immediately. The survey will be sent to pharmacists electronically together with the appointment information for each intervention telehealth visit. It will consist of a checklist that pharmacists will use to report which intervention elements occurred, any protocol deviations beyond their control (eg, dyads canceling a meeting), and the time required to complete each task in the intervention. We will calculate intervention fidelity as the proportion of dyads who participate in 2 of 2 pharmacist phone calls based on documented status reports.

2. We will calculate the proportion of eligible dyads that opt out of the intervention, and the proportion of pharmacist messages to the PCP that receive an acknowledgement or response (captured in the EHR).

3. To evaluate the content of the intervention being delivered, we will analyze a random sample of audiorecorded phone calls between pharmacists and dyads. We will use a fidelity checklist to determine the extent to which the pharmacists deliver the key elements of the intervention: 1) Assessing for medication-related problems (adherence issues, potential adverse effects, care partner strain); 2) Eliciting the dyad's key health outcome goals for the patient's health; and 3) Aligning medications with goals of care. We will also review the pharmacist-physician communication in the EHR to calculate the proportion of templates that are properly completed. This will enable us to provide feedback to the pharmacists in real time to address barriers to achieving high fidelity.

5.3 Concomitant Interventions

We do not have any concomitant interventions. All medical care will proceed in according to the decisions of the patient, care partner and primary care provider.

5.4 Adherence Assessment

There is no planned adherence assessment given the nature of the intervention.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

Assessment	Identify eligible population	Baseline: scheduling phone call (Day 0 ± 28 days)	3 months post enrollment (Day 90 ± 45 days)
Inclusion/Exclusion Criteria	**X**		
Patient demographics and diagnoses	**X**		
Care partner demographics		**X**	
Chronic medication count		**X**	**X**
Patient-level Medication Regimen Complexity Index (pMRCI)		**X**	**X**
Family Caregiver Medication Administration Hassles Scale (FCMAHS)		**X**	**X**

Feasibility measures			
Proportion of dyads that opt out	**X**		
Proportion of participants with data elements available to calculate pMRCI		[redacted] **Throughout intervention**	
Response rate and completion time for FCMAHS		**X**	**X**
Proportion of pharmacist messages to PCP that receive acknowledgement or response		[redacted] **Throughout intervention**	
Number of contacts between pharmacist and PCP and between pharmacist and dyad		[redacted] **Throughout intervention**	
Time required by pharmacist to complete intervention			**X**
Type of recommendations made by pharmacist, acceptance rates for recommendations			**X**
Fidelity measures			
Proportion of intervention elements successfully completed by pharmacist			**X**

6.2 Description of Evaluations

Pilot study evaluations will consist of: 1) assessing baseline eligibility criteria; 2) assessing the intervention for feasibility and acceptability; 3) assessing outcomes of the future pragmatic trial for measurement feasibility; and 4) assessing intervention fidelity.

Definitions of the data elements and sources are itemized below. Unless otherwise mentioned, all data at JHCP will be extracted from the EHR. All data at KPCO will be extracted from the KPCO Virtual Data Warehouse, a quality controlled, common data model that includes data from multiple KPCO data sources covering enrollment, utilization, pharmacy, demographics, mortality, problem list diagnoses, and social history, among other domains.[36]

Inclusion/ exclusion criteria: As previously described (section 4.1). Data elements will include age, diagnosis codes, current medications on the date of enrollment (see definition "chronic medication count" below). Chronic diagnoses will be from a list of 86 chronic conditions itemized in the Multiple Chronic Conditions Chartbook.[37] We have developed a method of counting chronic medications that uses a consensus-based list of Generic Product Index (GPI) categories to be included for polypharmacy estimates.

Patient demographics and diagnoses: Age, gender, and race/ethnicity will be collected from the EHR. ICD-10 codes will be used to identify diagnoses from visit billing codes, hospital and emergency department claims diagnoses, and problem list diagnoses.

Care partner demographics: Age, gender, race/ethnicity, relationship to patient, and health literacy ("How confident are you filling out medical forms by yourself?") will be asked by the project assistant during the scheduling phone call.

Chronic medication count: We will use the approach refined in Optimize to define chronic medication use as any prescription medication for which the patient had at least a 28-day supply on the assessment date.[32] We selected a 28-day supply (rather than a supply for a longer time period) because some medications (such as opioid medications) are mostly dispensed in 28-day supplies. Chronic medications exclude the following domains identified by 2-digit GPI codes: vaccines, toxoids, allergenic extracts, oxytocics, local anesthetics—parenteral, general anesthetics, antiseptics and disinfectants, antidotes, diagnostic products, chemicals, and medical

devices. We are examining different methods of identifying chronic medications in the Johns Hopkins EHR.

Patient-level Medication Regimen Complexity Index (pMRCI): Scores are derived from weighted values of regimen components (eg, dosage formulations, frequencies, and specific instructions).[2] We will adapt an algorithm developed and tested by Dr. Boyd's team to extract pre-specified variables from the EHR and calculate pMRCI scores in REDCap.[20] The data analytics teams at both institutions will determine the steps necessary to further adapt the pMRCI for use within the existing EHR systems. In doing so, we will build on methods developed by JHU researcher, Dr. Hadi Kharazzi, who automated the pMRCI within an EHR and calculated pMRCI scores for 70,000 patients.[3,38] Similar EHR adaptations of the pMRCI by other researchers will also serve as a foundation for our work.[109]

Family Caregiver Medication Administration Hassles Scale (FCMAHS): Collected from family care partners at baseline by the project assistant and again at approximately 3 months after enrollment. For care partners who are unable to complete the FCMAHS by phone, we will examine the feasibility of administering it electronically by e-mailing them a link. See attached patient intervention materials. Project assistants will record administration time when the FCMAHS is administered over the phone. Care partners will be asked to record administration time when it is self-administered electronically.

Feasibility measures:

Proportion of dyads that opt out: Will be assessed from the patient recruitment/ tracking log completed by project assistants.

Proportion of participants with data elements available to calculate pMRCI: Will be calculated based on the algorithm developed above.

Response rate and completion time for FCMAHS: Completion time will be collected by project assistants when they administer the FCMAHS on the telephone, and via self-report when it is administered electronically. The response rate using both modes of administration will be assessed.

Proportion of pharmacist messages to PCP that receive an acknowledgement or response; number of contacts between pharmacist and dyad; number of contacts between pharmacist and PCP: Project assistants will extract these data from the EHR at 3 months.

Time required by pharmacist to complete the intervention: Pharmacists will be asked to complete a REDCap survey. The link will be sent to them via e-mail to complete after each patient-care partner telehealth visit.

Fidelity measures:

Proportion of intervention elements successfully completed by pharmacist: A sample of audiorecorded telehealth visits between pharmacists and dyads will be scored by project assistants using a fidelity checklist.

6.2.1 Screening Evaluation

Consenting Procedure

As described in section 4.3, initial eligibility will be determined based on available clinical and claims data under a waiver of HIPAA Authorization.

Project assistants will serve as scheduling coordinators for the pilot study. Dyads who do not opt out (and those who opt in) will be called by the project assistant approximately 14 days after the study materials are mailed. Using the same approach that clinic staff use to call patients with dementia on the phone and identify their care partners during the course of clinical care, the project assistant will use an IRB-approved script (attached) to describe the pharmacist consult and assess interest. If the patient declines to identify a care partner and does not have a care partner listed in the EHR, the dyad will not be eligible. This phone call is described in section 4.3.

Participation in the pharmacist consult is not contingent on completion of the secondary outcome measure, FCMAHS. After scheduling the pharmacist consult, project assistants will offer care partners the option of completing the FCMAHS. They will obtain verbal consent for the FCMAHS when administering it over the phone (see script). If the care partner cannot complete the FCMAHS over the phone during the scheduling phone call,

the project assistant will offer to call back before the pharmacist visit (up to 28 days) or to later e-mail them a link to an electronic version.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Project assistants will mail study materials with opt-out provisions to the homes of 60 patients (30 at each site). Dyads who do not opt out (or who opt in) will be called by the project assistant approximately 14 days later to describe the pharmacist consult and assess interest. Enrollment will be defined as the date of this phone call.

Baseline Assessments

The baseline point will be defined as the date of the enrollment phone call, whether or not dyads are randomized to the intervention or delayed intervention control group.

Randomization

Dyads who do not opt out (or who opt in) will be randomized to the immediate or delayed intervention group prior to the enrollment/scheduling phone call using computer-generated random numbers. The intervention group will be scheduled to have the pharmacist telehealth visit immediately (within 4 weeks) after enrollment. The delayed intervention group will receive the pharmacist-led component 3-4 months after enrollment. For dyads randomized to the delayed group, the project assistant will say, "I will call you back in about 3 months to remind you of the call with the pharmacist."

6.2.3 Follow-up Visits

As described in the Evaluations Table, dates for follow up measurements will be relative to baseline/enrollment. This is defined as the date of the enrollment phone call. Data will be extracted from the EHR and VDW as described above. There will be one follow up call/e-mail to administer the FCMAHS 3 months after enrollment for care partners who have opted to complete it.

6.2.4 Completion/Final Evaluation

As described above, there will be one follow up phone call/e-mail to administer the FCMAHS 3 months after enrollment. Care partners who do not wish to complete the FCMAHS by phone will be offered an electronic version and will be e-mailed a link. All

other data will be extracted from the EHR and VDW. If participants discontinue the intervention early (eg, by opting out during the pharmacist phone call), we will still extract their data from the EHR and VDW but will not offer the FCMAHS.

7 SAFETY ASSESSMENTS

7.1 Specification of Safety Parameters

Comprehensive medication management is already part of the KPCO and JHCP standard of care, and any changes in medication regimens will be made by the pharmacist, PCP and patient/care partner through shared decision making. This is consistent with usual care. There is no requirement for patients, care partners, or PCPs to engage in discussions about medication optimization upon receipt of intervention materials. The intervention is educational and designed to offer care partners the opportunity to discuss optimal medication use. The intervention does not in itself alter patient medication prescribing.

There is still the potential for adverse effects or unintended consequences from the intervention including: inadvertent stopping of necessary medications by patients or care partners and associated effects of those potential discontinuations, longer patient-PCP visit encounters devoted to medication discussions or clarifying misunderstandings, and lower satisfaction of patients/ care partners about medication management. If PCPs and patients or care partners elect to discontinue specific medications, there is the potential for recurrent symptoms, adverse drug withdrawal events, and anxiety about the deprescribing process. Potential risks can be minimized or prevented by using a patient-centered, pharmacist-led, structured deprescribing process, such as ALIGN. The intervention brochure and template for the pharmacist visit will include language that instructs the dyad not to stop any medications without talking to the pharmacist or PCP.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Throughout the study period any physician, pharmacist or health care staff member will be able to report concerns about a safety issue that arises via a dedicated, monitored study email address and phone number as well as via contacting the PIs at each site (Green at Johns Hopkins; Boxer at KPCO). In addition, during the pilot study, study staff will review medical records of all patient participants who have ED visits, hospitalizations, or

observation admissions to assess whether any emergency services were likely to have resulted from medication discontinuation. We will also assess whether emergency services were likely to have resulted from adverse effects of non-discontinued medications. Information on use of emergency services will inform the development of safety procedures for the future pragmatic trial.

7.3 Adverse Events and Serious Adverse Events

We define adverse events as any new negative diagnosis or symptom during the study period that results in seeking medical care. Serious adverse events will be those requiring the use of emergency hospital services. In the ADRD-MCC population we anticipate a baseline hospitalization rate of approximately 30% due to morbidity burden. As described above, we will review medical records of all patients who use emergency hospital services during the pilot study period and use this information to inform adverse event monitoring for the future pragmatic trial. Each month, project assistants will also review the list of enrolled patients who have received intervention materials for any uses of hospital emergency services. These cases will be targeted for record review by the site PI.

7.3.1 Reporting Procedures

We will provide contact information for the JHU and KPCO Project Managers (TBD) and the JHU and KPCO PIs (Green and Boxer) to all clinical pharmacists and PCPs at the pilot study sites and ask them to report any perceived adverse events resulting from the trial.

7.3.2 Follow-up for Adverse Events

For each report, the JHU and KPCO PI will contact the clinical pharmacist and/or PCP to review the potential concern. All potential concerns will be noted and discussed with the Safety Officer as part of reviewing pilot study results and will be reported to the IRB. Duration of follow-up will extend until discharge from the hospital for hospitalizations or completion of any acute care services associated with an adverse event.

7.4 Safety Monitoring

An independent Safety Officer will be appointed to serve as the data safety monitor.

8 INTERVENTION DISCONTINUATION

For this pilot study of a pragmatic intervention, we do not have intervention discontinuation criteria.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

This is a pilot of a future pragmatic, cluster randomized trial. The pilot aims to assess feasibility and acceptability of the intervention. There are no statistical hypotheses. Our conceptual hypotheses are that the pilot intervention will be acceptable to patients and clinicians and feasible to conduct. In Aims 1 and 2a, our focus will be on descriptive statistics (counts and proportions). In Aim 2b, the primary analyses will rely on intention-to-treat analysis to present the comparative results of the trial. All events following randomization will be counted. Analyses using post-randomization data (eg, intervention compliance) will be discussed as secondary analyses. We will distinguish non-compliance with intervention from non-compliance with follow-up (ie, missing data).

For our primary outcome measure, pMRCI, we will first perform correlation analyses between chronic medication count and pMRCI scores at baseline. We will analyze changes in pMRCI before and after intervention and evaluate the impact of intervention assignment on the change scores using linear regression. The cluster by health system effect will be accounted for in the calculation of robust standard errors. Given the pilot nature of this trial, we will focus on estimates of precision in detecting treatment effects that will aid in the planning of a larger, sufficiently powered ePCT. We will also explore treatment effects by gender, age strata and race/ethnicity, again focusing on estimates of with-stratum variabilities instead of statistical significance. We will use multiple imputation to account for missing data.

For our secondary outcome measure, FCMAHS, we will first construct summary scores of the FCMAHS subscales using principal components analysis. We will then analyze changes in FCMAHS before and after intervention and evaluate the impact of intervention assignment on the change scores using linear regression.

9.2 Sample Size and Randomization

Sample size calculation: With an attrition rate of 10%, a sample size of 30 dyads per arm will produce a 2-sided 95% confidence interval with a width equal to 0.4 standard deviation (SD) when the SD of the study outcome (ie, based on normalized score) is 1.

9.2.1 Treatment Assignment Procedures

Enrolled dyads will be randomized prior to the scheduling phone call using computer-generated random numbers to either the intervention group or the delayed intervention group. The intervention group will then be scheduled to have the pharmacist telehealth visit immediately (within 4 weeks) after enrollment. The delayed intervention group will be scheduled to receive the pharmacist-led component 3-4 months after enrollment. For dyads randomized to the delayed group, the project assistant will say, "I will call you in about 3 months to remind you of your appointment with the pharmacist." Due to the nature of the intervention, participants, pharmacists and PCPs cannot be masked. Project assistants will enter data into a REDCap database so that the researchers can analyze it without having access to group assignment.

9.3 Interim analyses and Stopping Rules

There are no interim analysis planned or stopping rules.

9.4 Outcomes

Aim 1 is to assess the feasibility and acceptability of ALIGN in two different health care systems, to guide the subsequent evaluation of the effectiveness of the intervention in an embedded pragmatic trial. Data to measure feasibility will be acquired from the EHR, REDCap surveys completed by the pharmacists, and audiorecordings of pharmacist phone calls with care partners. We will collect the following measures:

• Proportion of dyads that opt out of the intervention;

• Proportion of pharmacist messages to the PCP that receive an acknowledgement or response;

• Number of contacts between pharmacist and PCP and between pharmacist and dyad;

• Time required by the pharmacist to complete the intervention;

• Proportion of intervention elements, including pharmacist phone calls, successfully completed.

To evaluate intervention acceptability, we will track the following:

• Type of recommendations made by the pharmacist and acceptance rates for those recommendations (project assistants will review the EHR for notation of patient/care partner and PCP acceptance). The pharmacists will document each phone call with the dyad in the EHR and will record whether the patient and care partner have agreed to the recommendations. The template for the pharmacist message to the PCP (attached) includes a routing comment that asks the PCP to respond via secure chat or staff message – either to indicate acceptance or ask questions about the recommendations.

Aim 2 is to determine the feasibility of the primary and secondary outcome measures for the subsequent ePCT:

Aim 2a is to determine the feasibility of measuring the primary outcome, the patient-level Medication Regimen Complexity Index (pMRCI)[1-4], within the existing EHR systems, and to compare it with a more pragmatic measure, chronic medication count, as the primary outcome measure for the ePCT.

Aim 2b is to determine the feasibility of measuring the secondary outcome, the Family Caregiver Medication Administration Hassles Scale (FCMAHS)[5], a caregiver-reported outcome measure.

As described in Section 6.2, we will develop the procedures for collecting the pMRCI and FCMAHS. In Aim 2a, feasibility will be measured as follows:

• Proportion of participants with data elements available vs. unavailable to calculate the pMRCI.

To compare it with chronic medication count as the primary outcome measure for the ePCT, we will measure:

• Change in chronic medication count; and

• Change in pMRCI from baseline to 3 months.

Chronic medication count will be obtained from the EHR using algorithms refined in OPTIMIZE.

In Aim 2b, feasibility will be measured as follows:

• Response rate and completion time for the FCMAHS using each mode of administration.

• Change in FCMAHS from baseline to 3 months.

9.5 Data Analyses

In Aims 1 and 2a, our focus will be on descriptive statistics (counts and proportions). In Aim 2b, the primary analyses will rely on intention-to-treat analysis to present the comparative results of the trial. All events following randomization will be counted. Analyses using post-randomization data (eg, intervention compliance) will be discussed as secondary analyses. We will distinguish non-compliance with intervention from non-compliance with follow-up (ie, missing data).

For our primary outcome measure, pMRCI, we will first perform correlation analyses between chronic medication count and pMRCI scores at baseline. We will analyze changes in pMRCI before and after intervention and evaluate the impact of intervention assignment on the change scores using linear regression. The cluster by health system effect will be accounted for in the calculation of robust standard errors. Given the pilot nature of this trial, we will focus on estimates of precision in detecting treatment effects that will aid in the planning of a larger, sufficiently powered ePCT. We will also explore treatment effects by gender, age strata and race/ethnicity, again focusing on estimates of with-stratum variabilities instead of statistical significance. We will use multiple imputation to account for missing data.

For our secondary outcome measure, FCMAHS, we will first construct summary scores of the FCMAHS subscales using principal components analysis. We will then analyze changes in FCMAHS before and after intervention and evaluate the impact of intervention assignment on the change scores using linear regression.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

The majority of the study data will be collected from the Johns Hopkins EHR and the KPCO VDW as described in Evaluation Section 6. Demographic, health and medication data will be automatically merged into REDCap on enrolled patients or will be manually entered by the project assistant (there will be some site-specific differences). Patient interactions will be documented in the EHR and data from those interactions will be entered into REDCap for descriptive analyses.

Responses from care partners to the FCMAHS will be collected by a project assistant on the telephone or electronically (self-administered) via a link sent through e-mail.

Intervention fidelity measures will be collected from clinical pharmacists via a REDCap survey that will be e-mailed to them, and from audiorecordings of telehealth visits between pharmacists and patient-care partner dyads.

10.2 Data Management

Unless otherwise mentioned, all data will be extracted from the Johns Hopkins EHR and the KPCO Virtual Data Warehouse, a quality controlled, research common data model that includes data from multiple KPCO data sources and includes the following domains: Pharmacy data, demographics, problem list diagnoses, and social history. Two identical instances of the REDCap database will be used for data collection – one at each site. Data from VDW will be pulled directly into REDCap; data from EHR will be manually entered into REDCap, downloaded and cleaned; data from pharmacist fidelity measures will be manually entered.

10.3 Quality Assurance

Multiple strategies will be used to ensure accuracy of the data, including (but not limited to) the following:

- The REDCap database will incorporate field validation (eg, format type, valid range) whenever possible to increase accuracy of data entry.
- After every 3rd dyad is enrolled, the project assistants will download data from the REDCap database into Excel or SAS to assess for missingness.
- We will use double input for any key variables that are manually entered. These variables will be re-entered into an empty database by someone other than the individual who completed the first data entry. The reliability of the entered data will then be assessed by comparing the first and second round of data entry so that any errors can be identified and corrected.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and patient/care partner-facing materials will be reviewed and approved by the IRB responsible for oversight of the study.

11.2 Informed Consent Forms

This pragmatic intervention adheres to standard clinical practice for older adults with dementia. The intervention is delivered by clinical pharmacists who are already integrated in primary care clinics at JHCP and KPCO and have considerable experience doing medication reviews with older adults, patients with dementia and care partners. The pharmacists are trained in complex geriatric medication management and routinely provide comprehensive medication management to Medicare beneficiaries. ALIGN provides structured templates for these existing comprehensive medication management phone calls, to focus them around dementia and to align medications with goals of care.

Options for pragmatic trial consent range from 1) full individual level recruitment and written informed consent, to 2) recruitment information sent to all eligible candidates with an 'opt out' clause, to 3) general information on the intervention provided to all eligible patients with an option for further inquiry. We request a waiver of informed consent (option 2) as an acceptable approach for the intervention, audio-recording of the pharmacist visit, and data collection from the EHR. This is based on the following factors:

(i) The research involves no more than minimal risk to the subjects.
- Any changes in medication regimens will be made by the pharmacist, PCP and patient/care partner through shared decision making. This is consistent with usual care.
- Comprehensive medication management is already part of the KPCO and JHCP standard of care.
- There is no requirement for patients/ care partners or PCPs to engage in discussions about medication optimization upon receipt of intervention materials.
- Potential risks of deprescribing can be minimized or prevented by using a patient-centered, pharmacist-led, structured process, such as ALIGN. Any medication believed to have increased potential for physiologic withdrawal, such as benzodiazepines, will undergo a prescribed drug taper under the clinical pharmacist's supervision according to standard clinical procedure. In addition, patients and care partners will be told that they can contact the pharmacist with any concerns about drug withdrawal effects or medical condition exacerbation. Further, medications can be restarted or increased at any time should concerns arise on the part of the patient, care partner or PCP. The intervention brochure and template for the pharmacist visit will include language that instructs the dyad not to stop any medications without talking to the pharmacist or PCP.

(ii) The research could not practicably be carried out without the requested waiver or alteration. Requiring full individual level recruitment and written informed consent would be highly burdensome to the target population, older adults with dementia, and would outweigh the minimal risks of the intervention itself. The standard procedures for assessing capacity, identifying a legally authorized representative and obtaining surrogate consent would likely cause many patients to opt out or become ineligible, which would compromise the scientific

validity of any evaluation of the intervention. Even if we consented care partners, the research cannot practicably be carried out without enrolling patients and care partners as dyads.

(iii) If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format:
The intervention is pragmatic and designed to test a scalable process that can be implemented across multiple clinics to improve care for PLWD. For this reason, our initial eligibility criteria and our primary outcome, the patient-level Medication Regimen Complexity Index, are derived from the EHR data under a waiver of HIPAA Authorization. The data need to be identifiable in order to recruit individual patients and care partners and to link subject data over time.

(iv) The waiver or alteration will not adversely affect the rights and welfare of the subjects:
Intervention materials will include an informational cover letter that will indicate that dyads may wish to discuss medication discontinuation with the pharmacist but are under no obligation to do so. It will explain that because this is a new clinical program, appointments are limited and the pharmacist consult may be scheduled up to 3 months out. This is consistent with usual care, in which non-urgent appointments are typically made at least 3 months out.

(v) Whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.
We do not currently have plans to provide study subjects with information after the study ends. However, we could provide a summary of the study and its main findings to the individual clinics and they may distribute it through patient newsletters if they wish. We may also share the key findings with both health care systems and they may disseminate the information to their patients as they see fit.

For Aim 2b, we will obtain verbal informed consent to administer the Family Caregiver Medication Administration Hassles Scale (FCMAHS). After scheduling the pharmacist consult with interested care partners, project assistants will offer the FCMAHS. They will explain that **the pharmacist consult is not contingent on completion of the questionnaire**. If the care

partner is interested in completing the FCMAHS, the project assistant will obtain verbal informed consent for either the telephone or web version, according to the care partner's preference (see attached script). The project assistant will offer to administer the FCMAHS as part of the same phone call or to call back before the pharmacist visit (up to 28 days later). They will tell care partners that they will call back to administer the FCMAHS once more about 3 months after enrollment, defined as the date of the scheduling phone call.

11.3 Participant Confidentiality

Data Management

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

For all sources of data, names and other identifiers will be kept in REDCap, a secure, HIPAA complaint web-based application for clinical data collection with secure authentication options for multi-site projects. Statistical analyses will be performed on de-identified data; participants will never be individually named. All computerized data will be kept on secured computers or networks at KPCO and Johns Hopkins. Once the data are cleaned and verified, there will be no further changes to the dataset. We will merge our de-identified data sets and Johns Hopkins will be responsible for analysis. These data will be accessible only to the research team, using confidential usernames and passwords.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the NIA, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

All research conducted at Johns Hopkins and KPCO 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. Johns Hopkins and KPCO each have approved Federal-wide

Assurance Compliance filed with the Office for Human Research Protections (OHRP). Both institutions have agreed to cede to Advarra for IRB oversight and study approval. Advarra will also serve 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).

13 COMMITTEES

NIA Program Officers:

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Stakeholder Panel: ALIGN builds off OPTIMIZE, our team's ongoing cluster-randomized deprescribing pragmatic trial at KPCO. OPTIMIZE has two stakeholder panels comprised of patients/care partners and clinicians. We will extend these panels and develop similar ones at JHCP to provide insight on study design, intervention materials, implementation, results interpretation and dissemination. Their contributions will ensure that the intervention is relevant to patients and care partners, generalizable across health systems and culturally-tailored to promote health equity. Stakeholder panels will meet quarterly by teleconference. Dr. Green will lead these efforts.

14 PUBLICATION OF RESEARCH FINDINGS

Publication of the evaluation of the pilot study will be determined by the study team. Our primary purpose is to inform a subsequent cluster randomized controlled trial. Publication of the results of this pilot study will be governed by the policies and procedures developed by the study team.

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16 SUPPLEMENTS/APPENDICES

Items in this list are not included in this document, but are external documents included in the application.

A. Patient/care partner intervention materials

a. Cover letter for intervention materials

b. Patient/care partner brochure

c. Web-based Family Caregiver Medication Administration Hassles Scale

d. Template for pharmacist telehealth visit and pharmacist-PCP communication

B. Recruitment materials

a. Telephone script for scheduling phone call

b. Oral consent script for FCMAHS