A Program to Reduce Inappropriate Medications Among Older Adults With Alzheimer's Disease

NCT05147428

Study Protocol and Analysis Plan: Version 11 May 2023

Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD).

Principal Investigator: Jerry H. Gurwitz, MD

Sponsor: University of Massachusetts Medical School

Grant Title: Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD).

Grant Number: 4R33AG069794-02

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11 May 2023

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol and all participant materials will be submitted to the IRB for review and approval. Approval of the protocol must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: [redacted] Date: 23 Nov. 2021

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1 PROTOCOL SUMMARY

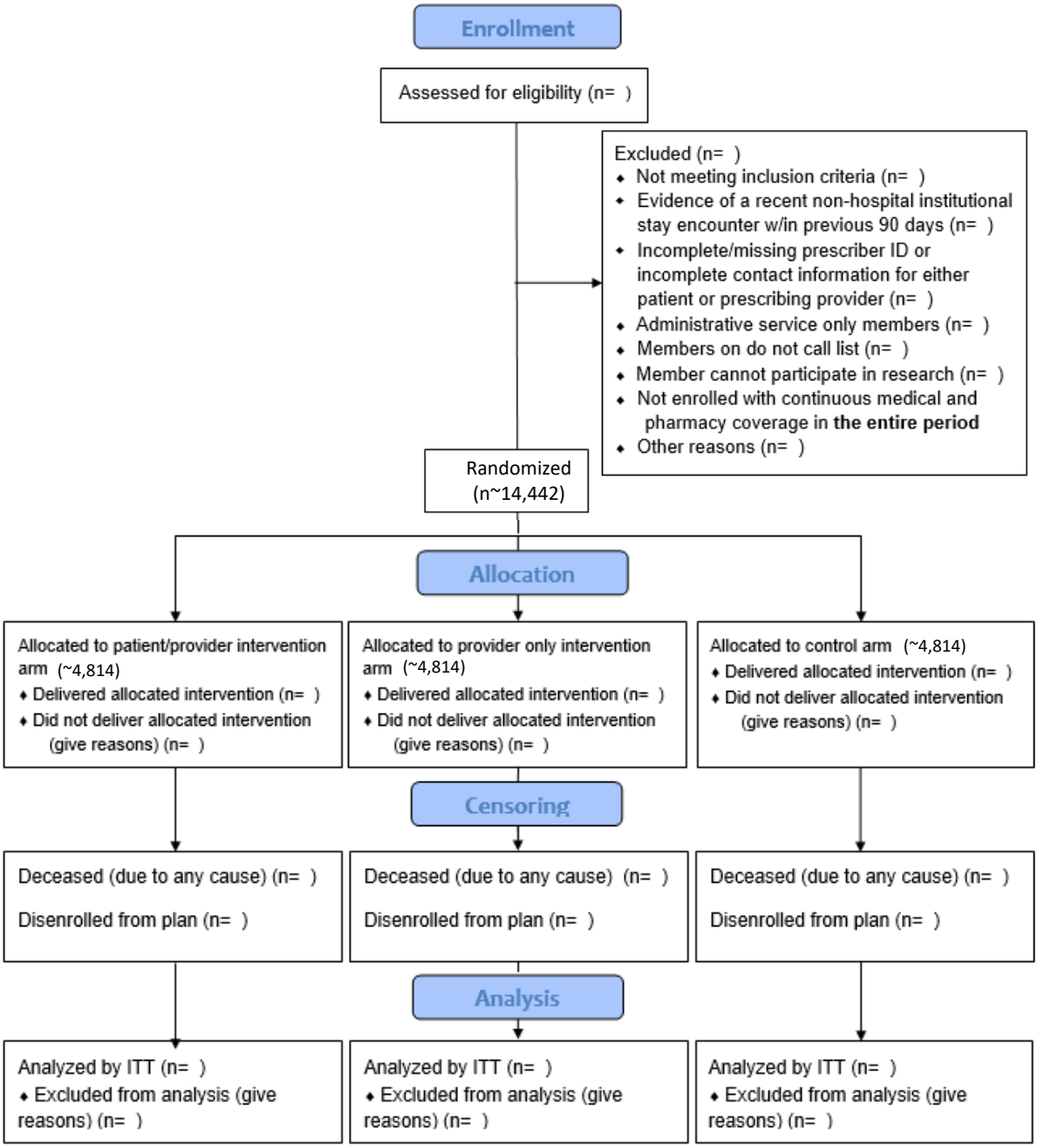
1.1 SYNOPSIS

Title:	Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD).
Grant Number:	4R33AG069794-02
Study Description:	This will be a large, randomized, pragmatic trial to test a health plan-based intervention leveraging the NIH Collaboratory's Distributed Research Network, which uses the Food and Drug Administration (FDA) Sentinel Initiative infrastructure. Our study population will include community-dwelling patients with AD/ADRD, identified based on diagnosis codes of AD/ADRD or use of a medication for Alzheimer's Disease, who have evidence of inappropriate prescribing of antipsychotics, /sedative-hypnotics, or strong anticholinergics. We will evaluate the effect of educational interventions designed to stimulate patient/caregiver-provider communication about medication safety (versus usual care) on the primary outcome defined as absence of any dispensing of the targeted inappropriate prescription class from day 91 to day 270 during the 9 months following receipt of intervention. The trial will be conducted in two large, national health plans. The study design will be a prospective, randomized, comparative effectiveness intervention trial with three arms: (1) a combined patient/caregiver and provider educational intervention; (2) a provider only educational intervention; and (3) usual care. Our research hypothesis is that education on inappropriate prescribing among patients/caregivers and their providers can reduce medication-related morbidity in patients with AD/ADRD and lead to an improvement in medication safety for this vulnerable population. We plan to conduct two separate, consecutive pragmatic trials. This sequential approach will allow us to adapt the second trial based on the findings and experience gained in the first trial, with an expectation of increasing efficiency and effectiveness. Adaptations could include dropping the provider only arm and/or or further limiting the classes of inappropriate medications targeted.
Objectives*:	**Primary Objective**: To assess the impact of the patient/caregiver educational intervention on inappropriate prescribing to AD/ADRD patients. **Secondary Objectives**: To create: (1) a plan for disseminating study findings to stakeholders who might implement the intervention or make decisions about its future use; and (2) an implementation toolkit for health plans and health systems wishing to implement the intervention.

Endpoints/Outcomes:	**Primary Endpoint**: We will evaluate the effect of educational interventions designed to stimulate patient/caregiver-provider communication about medication safety (versus usual care) on the primary outcome. The primary outcome will be defined as absence of any dispensing of the targeted medication from day 91 to day 270 during the 9 months following receipt of intervention. **Secondary Endpoints**: Secondary outcomes are listed below. These will also be assessed specific to the 6-month observation period (days 91-270 following mailing/intervention) based on health plan claims data including: a) Any dose reduction (defined as ≥ 50% reduction in dose of the targeted medication), assessed at the participant level using health claims data (outpatient dispensing). b) Percentage of patients with polypharmacy. (defined as >5 active prescriptions for different oral agents) c) Decline in the rates of: emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); and overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, and non- acute institutional days). d) In-hospital all-cause mortality. (We can only study in-hospital all-cause mortality due to a delay in receipt of comprehensive death data.) We will use administrative claims data to identify encounters of interest (ED visits, hospitalizations, non-acute institutional stays, outpatient visits) and only assess oral formulations for medications. e) Among study subjects who discontinue the targeted medication, we will determine if another agent within the targeted class has been dispensed over the period of observation (day 91-270).
Study Population:	The patients in a randomized open label pragmatic trial D-PRESCRIBE-AD will be randomly selected from the membership of the two participating health plans (HealthCore/Anthem and Humana) who meet eligibility criteria determined through administrative claims data as defined below. 1. Eligibility criteria: To be eligible for enrollment in the study, the following inclusion criteria will be met: diagnosis of AD/ADRD based on the Chronic Conditions Data Warehouse codes,[1] or treatment with a pharmacologic therapy used for AD (e.g., donepezil, rivastigmine, galantamine, or memantine) in the 365 days prior to or on cohort entry date (e.g., Jan 1 2022). The two AD/ADRD ICD-10 diagnosis codes must be ≥7 day apart and at least one of the codes must be within 365 days of the cohort entry date. Treatment is defined as use of an ADRD drug based on either: (1) days' supply of one or more dispensing, or (2) a dispensing in the 365 days prior to cohort entry date; (b)

	evidence of prescribing with the selected inappropriate medication classes including antipsychotics, sedative-hypnotics, and strong anticholinergics within the past 3 months prior to or on the cohort entry date; (c) age >50 years of age as of cohort entry date; and (d) continuous medical and pharmacy insurance coverage for at least the prior year. Exclusion criteria include evidence of a recent institutional stay encounter in a Skilled Nursing Facility, hospice, rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays within the previous 90 days prior to or on cohort entry date; incomplete/missing prescriber ID or incomplete contact information for either patient or prescribing provider, or on "do not contact" list. In our feasibility study during the planning year, we identified 130, 682 participants with AD/ADRD diagnosis codes or prescription dispensing for ADRD medications, approximately 20% (n=26,259) also had current evidence of inappropriate prescribing and met our eligibility criteria. These individuals had a mean age of 78.8 years (SD +/- 9.2); 92% were age 65 or older and 28% were age 85 or older; 68.2% were women. Based on available data on race/ethnicity, we estimated that 82% were White, 15% Black or African American, 1% Asian, <1% Native Hawaiian or Pacific Islander, <1% American Indian or Alaska Native, and <1% more than one race.
Phase* or Stage:	N/A
Description of Sites/Facilities Enrolling Participants:	Our study will be conducted in two national health plans (HealthCore/Anthem and Humana). The study will not include sites outside of the United States.
Description of Study Intervention/Experimental Manipulation:	The study design will be a prospective, randomized, comparative effectiveness intervention trial with three arms: (1) a combined patient/caregiver and provider educational intervention; (2) a provider only educational intervention; and (3) usual care.
Study Duration*:	Data collection will take 24 months overall from the cohort identification mailing until statistical analysis of data.
Participant Duration:	The observation period will extend 9 months (following a 3-month "blackout" period following the mailing) for each participant.

1.2 SCHEMA


Enrollment
Assessed for eligibility (n=)
Excluded (n=)
Not meeting inclusion criteria (n=)
Evidence of a recent non-hospital institutional stay encounter w/in previous 90 days (n=)
Incomplete/missing prescriber ID or incomplete contact information for either patient or prescribing provider (n=)
Administrative service only members (n=)
Members on do not call list (n=)
Member cannot participate in research (n=)
Not enrolled with continuous medical and pharmacy coverage in the entire period
Other reasons (n=)
Randomized (n~14,442)
Allocation
Allocated to patient/provider intervention arm (~4,814)
Delivered allocated intervention (n=)
Did not deliver allocated intervention (give reasons) (n=)
Allocated to provider only intervention arm (~4,814)
Delivered allocated intervention (n=)
Did not deliver allocated intervention (give reasons) (n=)
Allocated to control arm (~4,814)
Delivered allocated intervention (n=)
Did not deliver allocated intervention (give reasons) (n=)
Censoring
Deceased (due to any cause) (n=)
Disenrolled from plan (n=)
Deceased (due to any cause) (n=)
Disenrolled from plan (n=)
Deceased (due to any cause) (n=)
Disenrolled from plan (n=)
Analysis
Analyzed by ITT (n=)
Excluded from analysis (give reasons) (n=)
Analyzed by ITT (n=)
Excluded from analysis (give reasons) (n=)
Analyzed by ITT (n=)
Excluded from analysis (give reasons) (n=)

1.3 SCHEDULE OF ACTIVITIES

Timeline	**Year 1**				**Year 2**				**Year 3**				**Year 4**				**Year 5**			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
R61 Planning Phase																				
R33 Implementation Phase																				
Identification of cohort #1					X															
Randomization #1					X															
Mailing of Intervention Materials						X														
Blackout period							X													
6-month observation period								X	X											
Primary and Secondary Outcome ascertainment										X	X									
Statistical analysis of 1st mailing												X								
Meeting with DSMB												X								
Implementation Phase 2																				
Identify Study Cohort #2												X								
Randomization #2												X								
Mailing of Intervention Materials													X							
Blackout period														X						
6-month observation period															X	X				
Primary and Secondary Outcome ascertainment																	X	X		
Analysis of 2nd Mailing																			X	
Meet with DSMB		X		X		X		X		X		X		X		X		X		X
Prepare manuscript	Ongoing																			
Dissemination															X	X	X	X	X	X
Engagement with stakeholders and advisors	Throughout the study																			

2 INTRODUCTION

2.1 STUDY RATIONALE

Potentially inappropriate prescribing includes the use of medications that may no longer be necessary or that may increase the risk of harm. Inappropriate prescribing can lead to adverse drug events, falls, worsening cognitive impairment, and emergency hospitalizations. Inappropriate prescribing is a "morbidity multiplier," increasing overall symptom burden, and adversely affecting health-related quality of life and function. Inappropriate prescribing of certain drug categories, such as sedative-hypnotics, antipsychotics, and strong anticholinergic agents, poses particular risks for older adults and may be more prevalent among those with Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) due to a higher prevalence of multimorbidity and associated polypharmacy.[2]

Enhancing patient/caregiver communication with the healthcare provider about medications may help reduce inappropriate prescribing to persons with AD/ADRD. The overarching goal of our proposal is to develop, implement, and evaluate the effect of a patient/caregiver-centered, multifaceted educational intervention on inappropriate prescribing in patients with AD/ADRD. The Developing a PRogram to Educate and Sensitize Caregivers to Reduce the Inappropriate Prescription Burden in Elderly with Alzheimer's Disease Study (D-PRESCRIBE-AD) will be a large, randomized, pragmatic trial to test a health plan-based intervention leveraging the NIH Collaboratory's Distributed Research Network, which uses the Food and Drug Administration (FDA) Sentinel Initiative infrastructure. In this study, we will enroll community dwelling AD/ADRD patients (based on a diagnosis of AD/ADRD or use of a medication for AD), who have evidence of inappropriate prescribing. We will evaluate the effect of educational interventions designed to stimulate patient/caregiver-provider communication about medication safety (versus usual care) on the cessation of inappropriate prescribing, **the primary outcome** of this study. The educational intervention will be an adaptation of an intervention proven effective in reducing the use of inappropriate medications in older adults,[3] modified for the AD/ADRD population and their caregivers.

2.2 BACKGROUND

Polypharmacy, commonly defined as use of five or more medications, is directly associated with multimorbidity and is prevalent among persons with AD/ADRD.[4-7] Polypharmacy substantially increases the likelihood of being exposed to inappropriate medications and the likelihood that inappropriate medications will lead to adverse drug events, falls, worsening cognitive impairment, and emergency hospitalizations.[8] Inappropriate prescribing includes the use of medications that may no longer be necessary or that may increase the risk of harm. While the characterization of a medication as "inappropriate" might be considered by some as absolutist, for the purpose of this application, the designation "inappropriate prescribing" or "inappropriate medication" indicates the need to carefully assess the risks of continued use versus the benefits. In a sense, inappropriate prescribing can be thought of as a "morbidity multiplier," increasing overall symptom burden, and adversely affecting health-related quality of life and function. Certain drug categories, such as sedative-hypnotics, antipsychotic medications, and strong anticholinergic agents, pose special risks for older adults.[9] Patients with AD/ADRD are at particularly increased risk for inappropriate prescribing due to high levels

of multimorbidity and polypharmacy, superimposed on the challenges and complexities of their care. Patient/caregiver communication with the healthcare provider regarding medications is often suboptimal. Addressing this challenge requires an intervention in which patients, caregivers, providers, and health systems can play an active role.

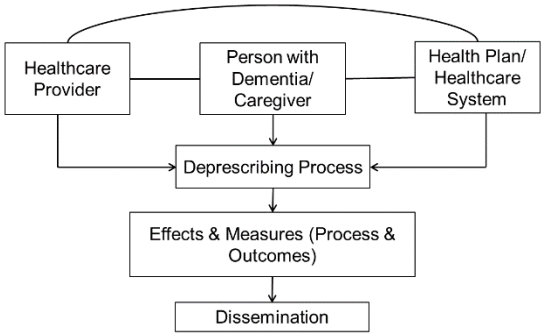
Patients and family caregivers have important insights into their care, but often do not speak up about these concerns. Consequently, if healthcare providers are unaware of these concerns, they are unable to correct misperceptions or to address and correct actual care breakdowns, including medication safety issues. Some healthcare systems have sought to address this challenge, through a campaign called "*We Want to Know*"[10] (conceived by Dr. Kathleen Mazor, a co-investigator on this application) that seeks to address patient concerns and questions about their care in real-time. While this initiative has been focused on engaging patients and families to speak up if they have a concern about their care in the hospital, *"We Want to Know"* serves as a model for activating patients and caregivers to engage providers with the purpose of identifying and addressing situations like inappropriate prescribing. The Alzheimer's Association has also sought to activate patients and their caregivers through the use of a "Doctor's Visit Checklist" that includes: (1) taking a list of concerns to the visit with the healthcare provider; (2) taking a medication list or medicine bottles to the visit; and (3) asking questions until you understand everything.[11]

Several direct-to-patient educational efforts have been shown to be effective in improving the quality and safety of pharmacotherapy. Dr. Cara Tannenbaum, a consultant on our application, has led a number of Canadian studies focused on reducing inappropriate prescribing to older adults through direct patient education designed to elicit shared decision-making.[12-14] Most relevant to our proposed study, Dr. Tannenbaum's team conducted a consumer-focused educational intervention, targeting the inappropriate prescribing of several Beers Criteria medications in older adults (D-PRESCRIBE).[3] In D-PRESCRIBE, educational materials were distributed by pharmacy-based pharmacists by mail or in-person, and contained information about why the medication may be inappropriate, potential alternative treatment options, and tapering protocols for sedative-hypnotics. In this modest-sized trial, at 6 months, 106 of 248 patients (43%) in the intervention group no longer filled prescriptions for inappropriate medication compared with 29 of 241 (12%) in the control group (risk difference 31% [95% confidence interval, 23% to 38%]). We will adapt Dr. Tannenbaum's proven approach, modified specifically for the AD/ADRD population and their caregivers, for implementation in two national health plans. Our efforts will represent a substantial scaling-up of prior efforts focused on reducing inappropriate prescribing.

Deprescribing is the clinically supervised process of stopping medications that could cause harm or that no longer provide benefits that outweigh potential risks.[15-17] It is not an action that the patient and/or caregiver takes independent of the prescriber, as it occurs under the guidance and direction of the healthcare provider. Recognizing the multiplicity of factors that influence and challenge deprescribing efforts, Linsky and colleagues recently published a unifying deprescribing conceptual framework, generalizable across healthcare settings, to advance the science of deprescribing research and to foster the design, conduct, and dissemination of deprescribing trials.[18] Importantly, this new conceptual framework emphasizes the roles of the patient/caregiver, prescriber, and healthcare system, all of

which influence the decision and ability to deprescribe. Linsky's framework emphasizes that the deprescribing process (including the decision to deprescribe) is ideally shared by patients and healthcare providers. It takes into account effects and measures, including process measures of the performance of the intervention, and outcomes including ongoing use of inappropriate medications, hospitalization, and mortality. Linsky and colleagues also recognize the challenges and delays involved in disseminating and implementing effective interventions, highlighting that the findings of deprescribing studies "will be limited in impact unless successful approaches are broadly taken up across healthcare systems." The figure below adapts and applies Linsky's deprescribing conceptual framework to our proposed D-PRESCRIBE-AD Study. **(Figure 1)**

Figure 1. Deprescribing Framework



Our overarching **hypothesis is that inappropriate prescribing of antipsychotics, sedative-hypnotics and strong anticholinergics in AD/ADRD patients can be addressed through enhanced communication between the patient/caregiver and the provider, facilitated by the patient's health plan**. The evidence of medication-related morbidity as a public health issue justifies large scale efforts to reduce inappropriate prescribing in vulnerable patient populations, such as those with AD/ADRD. Evidence also exists that simple direct-to-patient educational interventions can impact positively on medication use patterns, including discontinuation of potentially harmful therapies. However, existing evidence certainly does not prove effectiveness, or even the feasibility, of large-scale, simple educational interventions targeting persons with AD/ADRD and caregivers, in addition to their healthcare providers. New research is needed to: (1) demonstrate the feasibility of population-based outreach to AD/ADRD patients at high-risk for inappropriate prescribing and their family caregivers; (2) demonstrate the feasibility and effectiveness of a low-intensity educational intervention focused on reducing inappropriate prescribing involving AD/ADRD patients, their family caregivers, and healthcare providers; (3) demonstrate the value and efficiency of capitalizing on routinely collected health plan data to identify high-risk populations and to assess primary and secondary outcomes; and (4) demonstrate the potential to adapt, spread, and scale-up[19] a proven intervention (D-PRESCRIBE[3]) to address inappropriate prescribing at a national level.

Our proposed D-PRESCRIBE-AD study will take advantage of the **NIH Collaboratory Distributed Research Network, which uses the FDA Sentinel Initiative infrastructure**. The FDA Sentinel Initiative has

previously initiated proof-of concept endeavors employing direct-to-patient strategies using the Sentinel infrastructure and the network of participating health plans.[20]

Potential Public Health Impact. The proposed research will represent a rigorous evaluation of a large scale, health plan-based, educational intervention to improve medication safety and reduce preventable medication-related morbidity among high-risk AD/ADRD patients. By design, the proposed intervention will be transportable to other large health plans and healthcare systems.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The proposed study poses minimal risks to the participants. The primary risks to participants are **risks associated with potential loss of confidentiality** and **risks associated with the research content area**. There is a slight risk that research data files might be compromised and obtained or viewed by unauthorized persons and we also recognize that the content of the educational materials may be **emotionally sensitive** (related to health conditions and side effects of medications). Our procedures for protecting against such risks are described below:

Risks associated with potential loss of confidentiality. The organizations proposing this study have systems, oversight, experienced personnel, and organizational cultures that support the appropriate use, access, and storage of confidential information. All persons collecting or handling data will be trained in human subjects' procedures, confidentiality, and privacy protection. All investigators and project staff are required to receive and complete IRB and HIPAA training.

Data for all participants will be kept strictly confidential. All hard copies of research files will be kept in locked file cabinets or a locked file room. Participants will be assigned a numerical code (Study ID) for identification in the files. Individual identifier information will be removed from study data files as soon as possible in the data processing steps. All computerized data will be kept on secured computers or networks. These data will be accessible only to research staff using confidential usernames and passwords. Statistical analyses will be performed using only limited datasets and only de-identified data will be reported. All data will be used for research purposes only; published data will not contain any individual identifiers.

All patient-level electronic data will be maintained by the health plans which have routine access to these data. Investigators who prepare reports, presentations, and publications based on this study will never have had access to identifiers of the complete study population. Investigators outside of the health plans will never have had access to any identifiers and will only receive deidentified data and results.

HIPAA Authorization
Electronic Data. Electronic data from the administrative health plan systems will only be collected with the appropriate HIPAA Waiver as approved by the IRB. Electronic data will be collected for the purposes

of: (1) recruitment for the clinical trial and to contact eligible patients with the intervention educational materials; and (2) outcomes assessment for those enrolled in the Clinical Trial. We believe the study meets the following criteria to obtain a waiver of HIPAA Authorization (followed by a rationale):

1. *The use or disclosure of protected health information involves no more than a minimal risk to the privacy of individuals.*
   Rationale: The release of individual PHI will be only to the health plan entities which readily have access to those data. The intervention is also entirely consistent with a quality improvement initiative that the health plans could initiate on their own.
2. *There is an adequate plan to protect the identifiers from improper use and disclosure.*
   Rationale: Identifiers will remain with the participating health plans; no disclosure of individual-level patient data will occur beyond the health plan of origin. Data will remain behind secure firewalls at the health plans and will not be accessed by any personnel who do not already have routine access as part of normal business operations.
3. *There is an adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research unless there is a health or research justification for retaining the identifiers or such retention is otherwise required by law.*
   Rationale: Identifiers, which will remain at the health plan of origin, will be destroyed as soon as all data are collected, verified, and analyzed.
4. *There are adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the protected health information would be permitted.*
   Rationale: PHI will not be disclosed beyond the health plan of origin nor for use beyond the scope of the research aims of this study. The Sentinel System has established systems for data management and security.
5. *The research could not practicably be conducted without the waiver or alteration.*
   Rationale: There are several reasons why the research would be impractical without the waiver of authorization. First, contacting "control" and "provider only intervention" patients for authorization would be an intervention by itself and might affect the results of the study. Secondly, given the number of subjects to be included in the pilot and the trials, it would be impractical to collect authorization from the total study population included in the research.
6. *The research could not practicably be conducted without access to and use of the protected health information.*
   Rationale: The research could not practicably be conducted without access to and use of the PHI as some PHI is required to identify eligible patients (e.g., date of birth, date of dispensing); PHI is further required to contact eligible patients with the intervention educational materials (name, address), and PHI is required to assess the outcomes (e.g., dates of dispensings of medications of interest).
7. *Access to the protected health information is necessary*.
   Rationale: As described above, access to the PHI is necessary to conduct the research.

We will be requesting a waiver of consent from the IRB for the Randomized Clinical Trial; see section 10.1.1.1 for details.

The waiver of informed consent is consistent with approach taken in several similar large clinical trials such as:

- IMPACT-Afib (NCT03259373);
- The HMO Research Network CERT: Acute Myocardial Infarction (NCT 00211172),

- Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial: A Randomized Evaluation of First-dollar Coverage for Post-MI Secondary Preventive Therapies NCT00566774.

Emotional Distress. Regarding the minor risk of **emotional distress** from the content of the educational materials, we have developed the materials in collaboration with advisors and stakeholders and with feedback obtained through interviews with patients, caregivers, and providers to attempt to induce as little emotional distress as possible. All materials will be submitted to the IRB for review and approval prior to use with study participants in this study.

2.3.2 KNOWN POTENTIAL BENEFITS

It is uncertain whether individual participants will directly benefit from participation. Some participants may learn something new about their health condition and/or treatment. Some participants may become motivated to specifically discuss medication management questions with their providers.

The potential societal benefits from this study are substantial. Optimizing models of care for reducing inappropriate prescribing among AD/ADRD patients has the potential to enhance patient care greatly – including the potential to reduce both morbidity and mortality, as well as reduce costs. Further, quality of life benefits may be derived from reducing risk of adverse drug effects caused by inappropriate prescribing. Society may benefit in the future, as this study may contribute to improving communication related to best prescribing practices for the AD/ADRD population, and results may be generalizable to other conditions and to the general population overall. The benefits to society and the medical practice community are seen to outweigh the minimal risks of participating in this study.

Importance of the Knowledge to be Gained
The products of this study will enhance scientific understanding of how to communicate with and educate patients and providers about inappropriate prescribing. These findings will likely be generalizable to other health conditions and diseases among older adults. In addition, the products which we will produce will be made publicly available for dissemination. The benefits of the knowledge to be gained are seen to outweigh the minimal risks of participating in this study.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The D-PRESCRIBE-AD intervention poses a low risk of harm to patients.

The probability and magnitude of harm or discomfort anticipated in the research study are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The intervention is entirely consistent with a quality improvement initiative that the health plans could initiate on their own. Health plans regularly conduct patient safety initiatives and remind physicians about the appropriate use of medications.

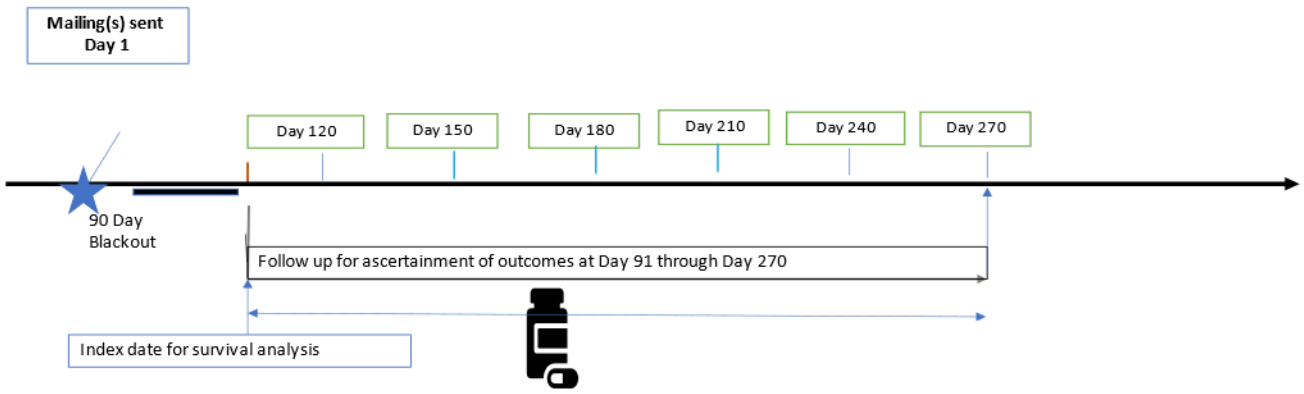
The intervention only adds to the existing care of patients focusing on a high priority list of drugs in patients with AD/ADRD. There are no restrictions placed on the control group as a result of the trial. Additionally, the substantial potential benefits to participants in this study make for a favorable benefit to risk ratio.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
Primary			
To assess the impact of the patient/caregiver educational intervention on inappropriate prescribing to AD/ADRD patients.	The primary outcome will be defined as absence of any dispensing of the targeted inappropriate prescription from day 91 to day 270 following receipt of intervention.	We selected this endpoint because the absence of any dispensing for the selected inappropriate drug during the study window is likely to reflect a clinically meaningful effect of the intervention.	Our research hypothesis is that education on inappropriate prescribing among patients/caregivers and their providers can reduce inappropriate prescribing in patients with AD/ADRD.
	Secondary Outcome: a) Any dose reduction defined as a ≥ 50% decrease in the mean daily dose of the targeted medication, assessed at the participant level using health claims data (outpatient dispensings). b) Percentage of patients with prevalence of polypharmacy (defined as >5 active prescriptions for different oral agents). c) Rates of emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, and non- acute institutional days). d) In-hospital all-cause mortality. e) Substitution within classes	We selected the endpoint of dose reduction as a secondary outcome because some of these potentially inappropriate medications require gradual taper and the effect of the intervention may only be reflected as a dose reduction. We set the threshold at 50% for dose reduction. We selected the endpoint polypharmacy which has been shown to be associated with adverse outcomes in this	Education on inappropriate prescribing among patients/caregivers and their providers can reduce medication-related morbidity in patients with AD/ADRD and lead to an improvement in medication safety for this vulnerable population.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS	PUTATIVE MECHANISMS OF ACTION
	We will use administrative claims data to identify encounters of interest (ED visits, hospitalizations, non-acute institutional stays, outpatient visits) and only assess oral formulations for medications.	population. We selected the endpoint of ER visits and health care utilization measures to assess whether a change in use of the targeted medications will have an impact on these metrics.	
Secondary			
To create: (1) a plan for disseminating study findings to stakeholders who might implement the intervention or make decisions about its future use; and (2) an implementation toolkit for health plans and health systems wishing to implement the intervention.	Secondary aims will be measured by tracking website visits and downloads of website materials. The study team will also track dissemination by tracking presentations, publications, and any other dissemination activities.	NA	*NA*
Tertiary/Exploratory			
N/A			

PRIMARY OUTCOME



4 STUDY DESIGN

4.1 OVERALL DESIGN

Overview of intervention and methods: The overarching goal of D-PRESCRIBE-AD is to develop, implement, and evaluate the effect of a patient/caregiver-centered, multifaceted educational intervention on inappropriate prescribing in patients with AD/ADRD. For the purpose of our study, inappropriate prescribing will include sedative-hypnotics, antipsychotics, and strong anticholinergic agents. Our research hypothesis is that education on inappropriate prescribing among patients/caregivers and their providers can reduce medication-related morbidity in patients with AD/ADRD and lead to an improvement in medication safety for this vulnerable population. We will evaluate the effect of educational interventions designed to stimulate patient/caregiver- provider communication about medication safety (versus usual care) on the cessation of inappropriate prescribing, **the primary outcome** of this study. The educational intervention will be an adaptation of an intervention proven effective in reducing the use of inappropriate medications,[3] modified specifically for the AD/ADRD population and their caregivers.

Our study will be conducted in two national health plans and will represent a substantial scaling-up of prior educational interventions focused on inappropriate prescribing. The study design will be a **prospective, randomized, "open-label" educational intervention trial with three arms: (1) a combined patient/caregiver and provider educational intervention; (2) a provider only educational intervention; and (3) usual care**.

It has two sequential phases. **Planning phase (R61/phase).** We have conducted a one-year R61 planning phase to precede a four-year R33 implementation phase. During the one-year R61 planning phase, we have finalized the intervention and conducted feasibility testing, and stakeholder engagement and met the required milestones. The activities are described below.

Planning phase Activities.
Development and Finalization of Educational Intervention
We conducted interviews with patients with AD, caregivers of such patients, and providers of such patients, to solicit feedback about educational materials pertaining to deprescribing from potentially harmful medications. We additionally met two times with an advisory panel and three times with a stakeholder panel to gather feedback on these materials. The feedback gathered from participants, advisors, and stakeholders was used to iteratively develop the materials. Intervention materials were piloted to 200 patients at each of the two participating health plans. We are currently receiving responses to these mailings.

R33 phase. During the R33 phase we will sequentially implement **two separate pragmatic trials** (Implementation Phase 1 and Implementation Phase 2), the first enrolling **up to 15,000 patients**, with the second trial to be adapted based on the findings and experience gained in the first trial. Adaptations could include dropping the provider only arm and/or or further limiting the classes of inappropriate medications targeted.

Study setting: The study will leverage the NIH Collaboratory Distributed Research Network, which uses the FDA Sentinel Initiative infrastructure. The FDA Sentinel Initiative, established in 2009, is a long-term public health surveillance program designed to create a national electronic system for monitoring the

safety of FDA-regulated drugs and other medical products. The Sentinel Initiative includes a wide array of collaborating organizations across the United States including health plans, which are referred to as Health Plans. The electronic data used in this initiative is accessed, maintained, and protected, as part of a "distributed network." In a distributed network, data remain in their existing secure environments, rather than being consolidated into a single database; Health Plans maintain physical and operational control over their electronic health data behind their institutional firewalls. Health Plans transform their data into the Sentinel Common Data Model, execute standardized analytic queries distributed by the Sentinel Operations Center, which is based at Harvard Pilgrim Health Care Institute (HPHCI), then share the output of queries, with the Operations Center via a secure network portal. This system protects the privacy and confidentiality of individual-level health information and is preferred by participating health plans over a centralized data repository approach. The FDA Sentinel Initiative infrastructure has previously been leveraged to pursue novel efforts relevant to advancing population health such as IMPACT-AFib, the first large randomized pragmatic trial employing the Sentinel Initiative infrastructure.[21]

Definition of Inappropriate Prescribing: We will target inappropriate prescribing of specific drug categories such as sedative-hypnotics, antipsychotics, and strong anticholinergic agents. While the characterization of a medication as "inappropriate" might be considered by some as absolutist, for the purpose of this study, the designation "inappropriate prescribing" or "inappropriate medication" indicates the need to carefully assess the risks of continued use versus the benefits.

Study population: The patients in D-PRESCRIBE-AD will be randomly selected from the membership of the two participating health plans (HealthCore/Anthem and Humana) who meet inclusion and exclusion criteria determined through health plan administrative claims data as defined below. See Section 4. 1 and 4.2 in our manual of procedures for the eligibility criteria and cohort identification from this study setting.

Eligibility criteria. To be eligible for enrollment in the study, the following inclusion criteria will be met:

1.	Diagnosis of AD/ADRD based on a modified list of the Chronic Conditions Data Warehouse codes, or treatment with a pharmacologic therapy used for AD (e.g., donepezil, rivastigmine, galantamine, or memantine) in the 365 days prior to or on cohort entry date. • The two AD/ADRD ICD-10 diagnosis codes must be ≥7 day apart and at least one of the codes is within 365 days of the cohort entry date. • Treatment is defined as use of an ADRD drug based on at least two dispensings in the 365 days prior to or cohort entry date.
2.	Evidence of prescribing within the past 3 months prior to or on the cohort entry date
3.	Age ≥50 years of age as of cohort entry date
4.	Continuous medical and pharmacy insurance coverage for at least the prior year.

Exclusion criteria:

1. Evidence of a recent institutional stay encounter in a skilled nursing facility, hospice, rehab center, nursing home, residential, and other non-hospital stays within the previous 90 days prior to or on cohort entry date..

2. Incomplete/missing prescriber ID or incomplete contact information for either patient or prescribing provider.
3. On "do not contact" list

Provider Inclusion Criteria:

1. Prescribing provider associated with most recent prescribing of a target drug

Feasibility analysis. We conducted a feasibility analysis using data from January 1, 2019 to January 31, 2021. During the study period, there were 99,826,441 unique members identified in the two health plans, of whom 66,862,829 were ineligible for research and excluded. After further excluding 32,832,930 members due to exclusion criteria (lacking pharmacy and medical coverage, < 50 years, or no diagnosis codes of ADRD drug or dispensing for ADRD), there were 130,682 members with AD/ADRD. We additionally excluded 104,423 patients without current evidence of inappropriate prescribing, resulting in a cohort of 26,259 trial-eligible patients. **The selection of participants for the feasibility analysis is shown in Figure 2. The flow diagram of participants is shown in Figure 3.**

Figure 2. Selection of participants for the feasibility analysis

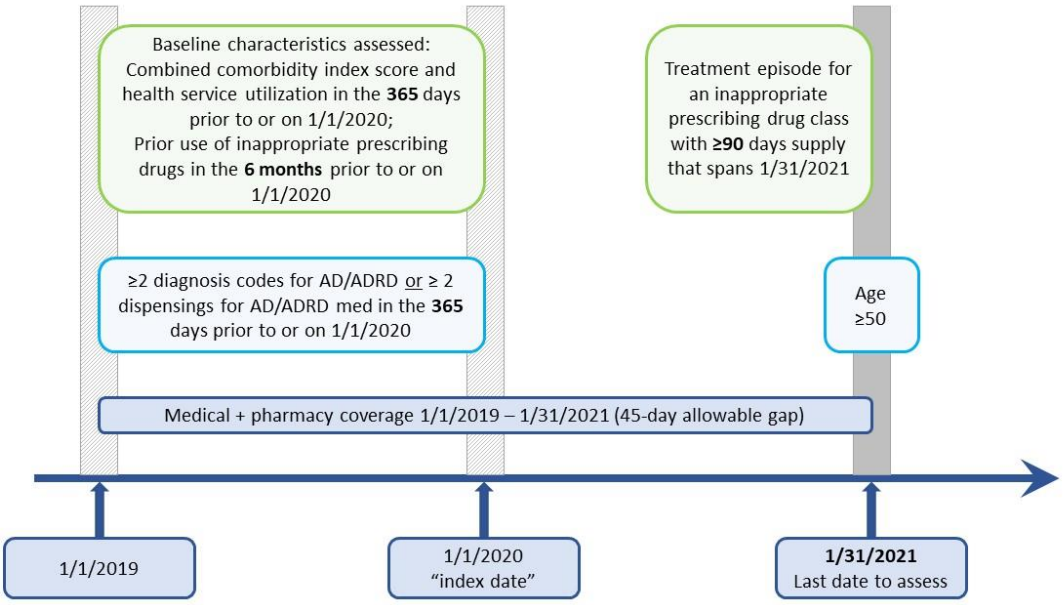
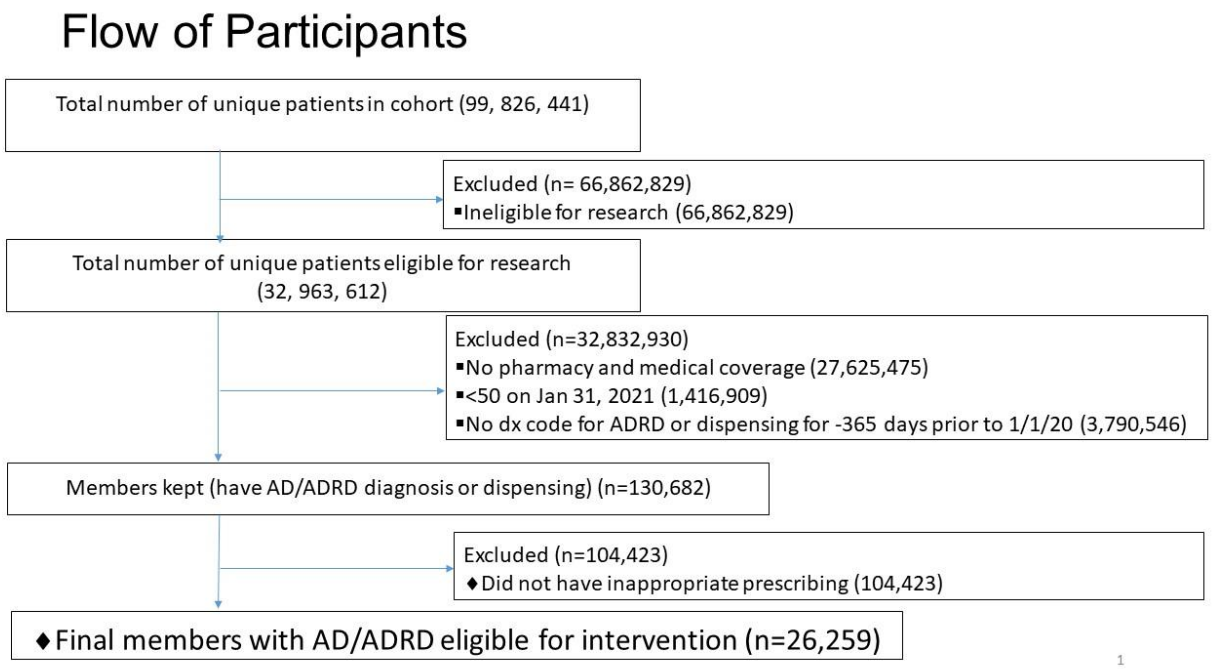


Figure 3. Flow diagram of participants



Eligible Study Population and Demographic Characteristics for the Feasibility Analysis. We identified a total of **26,259** trial-eligible members who were living with AD/ADRD and had current evidence of prescribing of antipsychotics, sedative-hypnotics, and strong anticholinergics. This corresponds to approximately 20% of the 130,682 members with AD/ADRD (having diagnosis codes for AD/ADRD or dispensing's for ADRD drugs). These individuals had a mean age of 78.8 years (SD 9.2); 92% were age 65 or older and 28% were age 85 or older; 68% were women. They had a Charlson Comorbidly Score of 5.1 (SD 3.2). Based on available data on race/ethnicity, we estimate that 82% were White, 15% were Black or African American, 1% were Asian, <1% were Native Hawaiian or Pacific Islander, <1% were American Indian or Alaska Native, and <1% were more than one race. Approximately 3% were Hispanic.

Proportion of AD/ADRD participants with Inappropriate Prescribing. Among members with AD/ADRD (n=130, 682) 9.6% were dispensed antipsychotics, 5.1% were dispensed sedative-hypnotics, and 8.6% received strong anticholinergics. These findings which allowed patients to be on multiple inappropriate medication classes are shown **(Table 1 A)**

Table 1A. Characteristics of AD/ADRD Population with current evidence of potentially inappropriate prescribing in Health Plans Jan January 2019-January 2020*	
Number of health plan members with AD/ADRD	130,682
Number of health plan members with AD/ADRD and evidence of potntially inappropriate prescribing N, %	**26,259, 20.1%**
Antipsychotics N, %	12,581, 9.6%

Sedative hypnotics N, %	6,617, 5.1%
Strong anticholinergics N, %	11,228, 8.6%

**Members could be on multiple classes of medications and so sum of total inappropriate percentage > 20.1%*

Several patients in the study were on more than one class of inappropriate medications. We plan to evaluate the effect of the intervention on a single class of targeted inappropriate prescriptions in the trial. In consultation with our Advisory panel and based on relevance and importance for this study population, for patients who were on multiple medication we will prioritize antipsychotics (9.6%) over sedative-hypnotics (3.9%) and sedative-hypnotics over strong anticholinergics (6.5%) as shown in **Table 1B**. As a result, this analysis displays patients based on this hierarchy.

Table 1B. Characteristics of AD/ADRD Population with current evidence of inappropriate prescribing in Health Plans Jan January 2020-January 2021 after prioritization of Medication Classes #	
Number of health plan members with AD/ADRD	**130,682**
Antipsychotics N, %	12,581, 9.6%
Sedative hypnotics N, %	5,122, 3.9%
Strong anticholinergics N, %	8,556, 6.5 %
Number of health plan members with AD/ADRD and evidence of inappropriate prescribing N, %	**26,259, 20.1%**

Members prioritized with Antipsychotics > sedative-hypnotics>strong anticholinergics; Total inappropriate percentage=20.1

R33 Implementation Phase Aims: The R33 Implementation Phase aims are:

Aim 1: To assess the impact of the patient/caregiver educational intervention on the primary outcome of cessation of inappropriate prescribing among AD/ADRD patients, employing a prospective, randomized trial design with three arms: (1) a combined patient/caregiver and provider educational intervention; (2) a provider only educational intervention; and (3) usual care. Secondary outcomes will include any dose reduction of inappropriate medications, prevalence of polypharmacy; rates of emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, and non-acute institutional days); and inpatient mortality.

Aim 2: To create: (1) a plan for disseminating study findings to stakeholders who might implement the intervention or make decisions about its future use; and (2) an implementation toolkit for health plans and health systems wishing to implement the intervention.

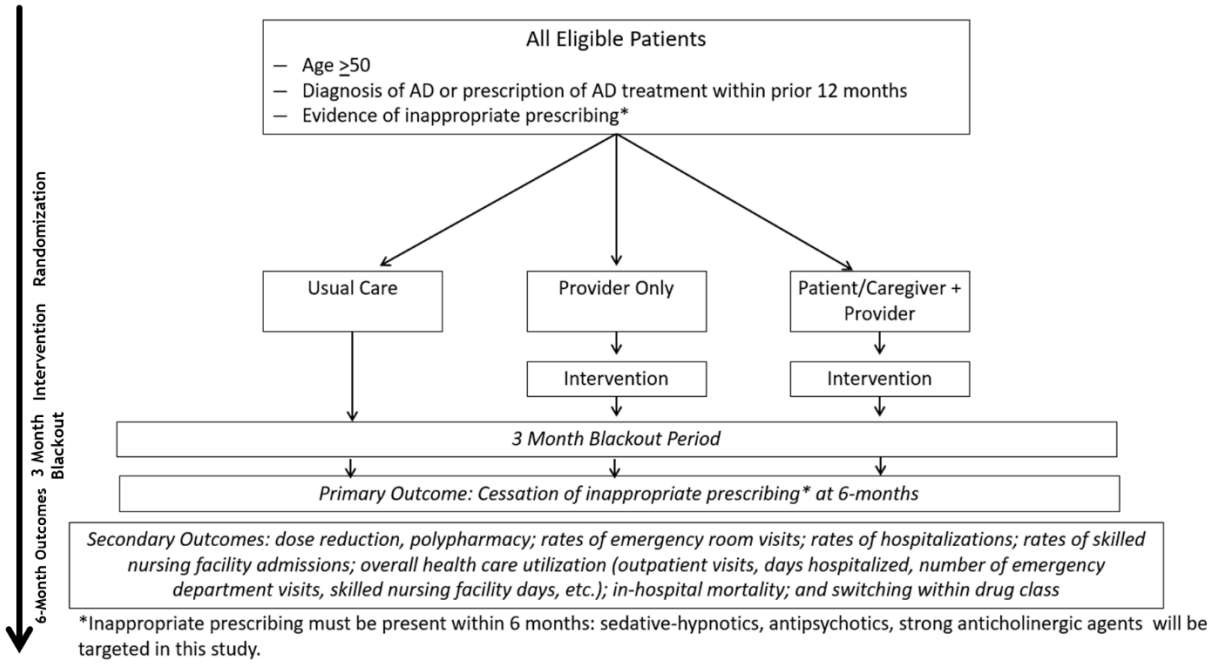
R33 Phase (Aim 1): D-PRESCRIBE-AD is a **prospective, randomized, "open-label" educational intervention trial**.

Patients with a diagnosis of AD/ADRD based on the Chronic Conditions Data Warehouse algorithm,[1] or a prescription fill for a pharmacologic therapy used in the treatment of AD/ADRD (e.g., donepezil, rivastigmine, galantamine, and memantine) within the last 12 months, and who meet the additional inclusion (evidence of inappropriate prescribing, , age ≥50 years, and continuous medical and pharmacy insurance coverage of at least the prior year and exclusion criteria (no evidence of a recent institutional stay encounter in a Skilled Nursing Facility, hospice, rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays within the previous 90 days prior to or on cohort entry date; *; incomplete contact information for patient or prescribing provider),* will be randomized to **the three treatment arms: usual care; provider only education; and patient/caregiver plus provider education.**

In the provider only arm, only the provider of the patient will receive intervention materials; in the patient/caregiver plus provider education arm, both the patient/caregiver plus the provider will receive intervention materials. Providers and patients/caregivers will receive applicable educational materials through a one-time mailing at trial start. In instances where a patient has been prescribed more than one inappropriate medication, only one educational intervention will be mailed based on the hierarchy described above (antipsychotics first, followed by sedative-hypnotics, and then strong anticholinergics). Within each of the three target drug categories, we included any drug that had a prevalence of 0.5% use or higher among potentially eligible subjects in either of the two plans. (see appendix A)

Relevant to the provider only and the patient/caregiver plus provider arms of the trial, a dedicated D-PRESCRIBE-AD study website will be available for patients, caregivers, and healthcare providers. The website will provide online access to all mailed educational materials. It will also include stories/testimonials of patients/caregivers who successfully engaged in collaborative conversations with healthcare providers about inappropriate prescribing. The website will provide a study telephone number for the "Know Your Meds" study team so that patients, caregivers, and healthcare providers will be able to discuss any questions they have about mailed educational materials with a study clinical pharmacist.

Over the course of the four-year R33 phase we will sequentially implement two separate pragmatic trials (Implementation Phase 1 and Implementation Phase 2, respectively), with the first enrolling upto 15,000 patients; the second trial will be adapted based on the findings and experience gained in the first trial. Adaptations could include dropping the provider only arm and/or or further limiting the classes of inappropriate medications targeted.



Method of assigning patients to treatment arms: A program, developed by the analytic coordinating center (HPHCI), will be used by the participating health plans to identify active members who meet eligibility criteria for the trial. Patients will be randomly assigned to the three treatment arms via the program.

Each participating health plan site will identify its eligible health plan members via a distributed SAS program run on their electronic administrative claims data organized according to the Sentinel Common Data Model. Individuals who cannot be included in research studies for any reason will be excluded. A programmer at each participating health plan site will use its locally stored patient ID numbers to identify the names and contact information (home addresses) of patients and utilize the locally stored provider ID numbers to identify the names and contact information of the prescribing provider. For patients with a dispensing of a target drug associated with a prescriber who is also associated with dispensings to other eligible patients, only one patient associated with each provider will be randomly selected. The list of eligible patients, along with the provider list will stay with the health plans and will be used by the health plan for the mailing of the intervention materials. The identifiable, patient-level data will not be shared with the analytic coordinating center, based at HPHCI.

R 33 Phase (Aim 2): **Dissemination**: In the final phase of the project, we will develop a plan to promote study findings and resources, including the study website, placing a particular emphasis on dissemination beyond usual academic circles in order to reach policy and practice audiences whose efforts are most likely to be influenced by study findings. The research team will create an initial dissemination plan and will present it to the Advisory Committee and Stakeholder Panel for feedback and input. Dissemination activities will take advantage of Dr. Gurwitz's leadership of the NIA-funded Advancing Geriatrics Infrastructure and Network Growth ("AGING") Initiative (R33AG057806), a collaborative endeavor of the Health Care Systems Research Network (HCSRN) and the NIA-funded Claude D. Pepper Older American Independence Centers (OAICs or "Pepper Centers"), which has dissemination of research findings relevant to multimorbidity as a core

function and key to its mission.[22] Dissemination efforts will also be aligned with and facilitated by the NIA IMPACT Collaboratory and the NIA-funded US Deprescribing Research Network. Recognizing the potential impact and interest in the results of our project, we also plan for dissemination of our experience, tools, and research findings through various entities including the NIH Collaboratory Distributed Research Network, as well as professional, industry, and advocacy organizations such as, but not limited to, the American Geriatrics Society, Alzheimer's Association, the American Pharmacists Association, the Academy of Managed Care Pharmacy, the American Society of Health-System Pharmacists, and America's Health Insurance Plans. To facilitate widespread adoption of the intervention, we will create an implementation toolkit. The toolkit will provide detailed documentation, and practical "tips" on implementation. All interventional materials will be included in the toolkit. Our team has extensive prior experience in creating and distributing toolkits as part of dissemination efforts relevant to a number of studies focused on improving medication safety and outcomes in older adults.[23,24]

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The D-PRESCRIBE-AD study design, planning phase, implementation phase, and experimental approach will build on experience gained through IMPACT-AFib, an ongoing large scale pragmatic clinical trial, which uses the FDA Sentinel platform to implement an educational intervention targeting patients with atrial fibrillation and their providers to increase evidence-based use of oral anticoagulants for stroke prevention.[21] In IMPACT-AFib, patient-level interventions include letters to patients with atrial fibrillation, who are not using oral anticoagulant therapy, encouraging them to discuss this with their healthcare providers. IMPACT-AFib has randomized over 80,000 patients; cohort identification and analysis of outcomes is using health plan claims data, a model which will be emulated in our D-PRESCRIBE-AD Study.

With funding from the National Institute on Aging (R56AG061813, PI Gurwitz), we have leveraged the NIH Collaboratory Distributed Research Network, which uses the FDA Sentinel System's distributed data network architecture and established collaborative relationships with the participating health plans (HealthCore/Anthem and Humana) to identify and capture baseline information on inappropriate prescribing (including prescribing cascades). The health plans executed queries that characterized a cohort of health plan members with AD/ADRD as of January 1, 2020, defined using Chronic Condition Data Warehouse (CCW) codes[1] for ADRD or use of medications specific for AD, excluding health plan members with an institutional stay.

These efforts have provided a population-level assessment of the prevalence of inappropriate prescribing in the AD/ADRD population. This information serves to inform our description of the study population for our proposed D-PRESCRIBE-AD Study. As shown above in Tables 1A and 1B, we identified 130,682 health plan members with a diagnosis of AD/ADRD or with use of a medication for AD at some time during the previous 12 months of whom 20% (n= 26,259) had evidence of inappropriate prescribing and were eligible for inclusion.

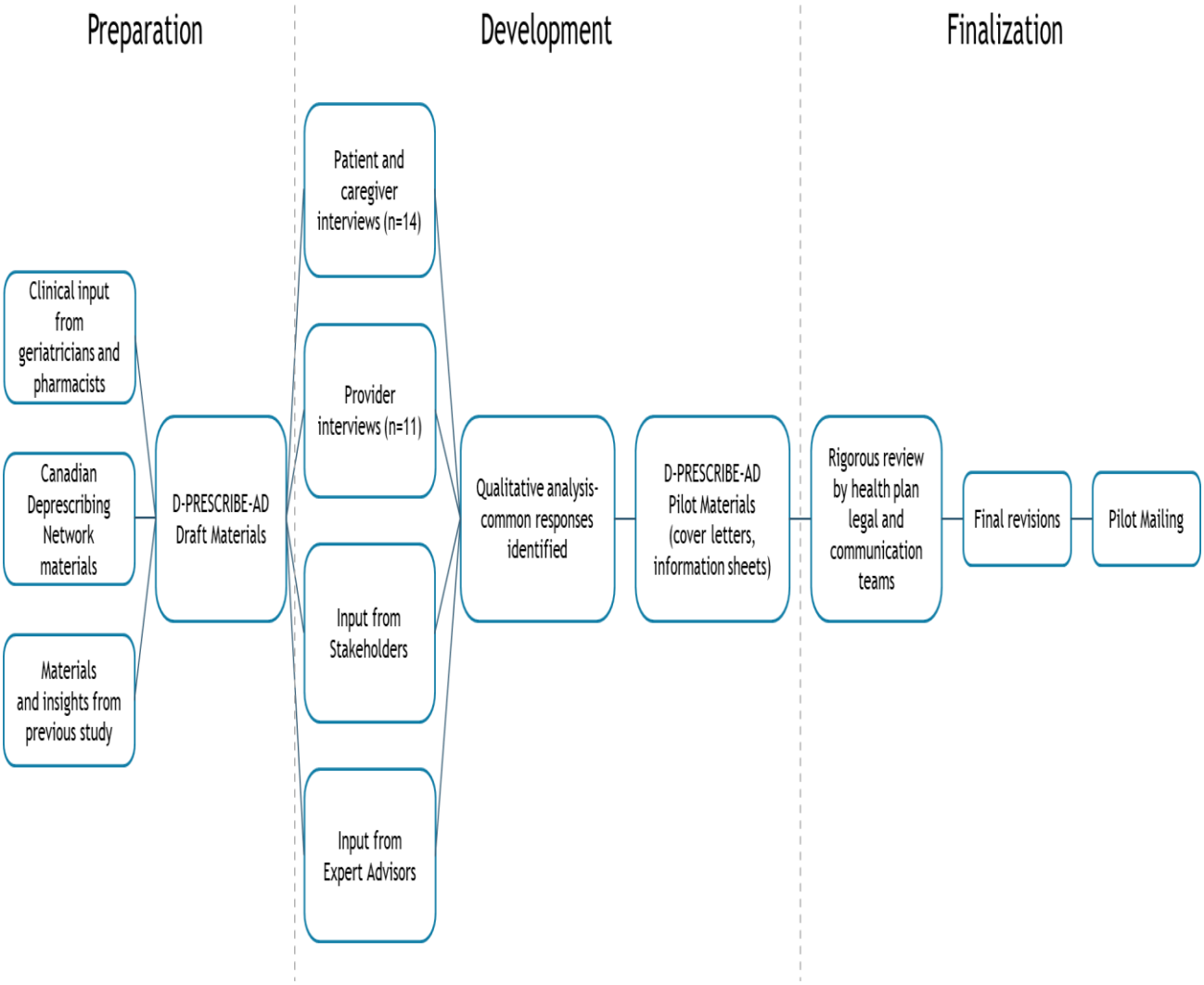
Once the study population was identified, we used an iterative process to develop and evaluate patient materials for patients with AD/ADRD (see below Figure 4). We modeled our patient materials on

materials developed by Dr. Cara Tannenbaum (consultant on our D-PRESCRIBE-AD application), the Canadian Deprescribing Network, and materials developed from previous research.[13,25] The patient materials include: a) a cover letter presenting the subject of deprescribing and suggesting a conversation with one's provider; and b) an informational sheet with the potential side effects and best courses of action. We iteratively revised the materials based on interviews with patients with AD/ADRD and their caregivers (9 caregivers, 2 independent patients, and 3 patient-caregiver dyads (n=17)). Interviewees were receptive to the idea of bringing the materials to their next healthcare visit to initiate a conversation, and most indicated a caregiver would see the materials. The revised materials were reviewed by a Stakeholder Panel comprised of 3 caregivers of family members with AD/ADRD, 3 geriatricians, and 2 national health plan leaders.

We also conducted interviews with primary care providers (5 family medicine, 3 internal medicine, and 3 geriatric medicine (n=11)) to review provider materials. These materials included: a) a cover letter presenting the subject of deprescribing and stating which patients received materials; b) a deprescribing algorithm; and c) a tapering guide. Providers were supportive of patients receiving the materials. The patient and provider materials were also reviewed and approved by collaborating national health plans (HealthCore/Anthem and Humana) prior to mailing. This foundational work created educational materials that gain patients', caregivers', and providers' attention, are easily understood, address critical beliefs and attitudes, motivate conversations about inappropriate prescribing, and promote patient/caregiver discussions with prescribers that may ultimately result in deprescribing. The patient materials were reviewed and approved by the two collaborating national health plans (HealthCore/Anthem and Humana).

See figure 4 which illustrates the process for creating educational materials.

Figure 4. Material Development Process



4.3 JUSTIFICATION FOR INTERVENTION

We have planned for a single educational intervention to be mailed by the health plan to patients/caregivers and providers. We chose this mode and frequency of delivery in this pragmatic trial based on replicating the usual mode and delivery of contacting providers by health plans, lessons learned from our provider and patient/caregiver interviews, and the potential for replication of this intervention. Health plans often mail letters to providers about medication use issues. We plan to replicate the usual mode, delivery and frequency used by health plans in contacting providers in this pragmatic trial and extend a similar a mode and frequency to the combined patient/caregiver and provider arm. Additionally, we want to minimize the number of mailings to providers based on feedback from interviews with providers (and patients/caregivers) who are already overburdened with the number of mailings from various sources. Although a single educational intervention may appear to be 'light touch', it is more likely to ultimately be scalable.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 270-day review of health claims data as shown in the Schedule of Activities (SoA), **Section 1.3**.

5 STUDY POPULATION

Study population: The patients in D-PRESCRIBE-AD will be randomly selected from the membership of the two participating health plans (HealthCore/Anthem and Humana) who meet inclusion and exclusion criteria determined through health plan administrative claims data as defined below.

5.1 INCLUSION CRITERIA

Eligibility criteria: To be eligible for enrollment in the study, the following inclusion criteria will be met: a) diagnosis of AD/ADRD based on the Chronic Conditions Data Warehouse codes, or treatment with a pharmacologic therapy used for AD (e.g., donepezil, rivastigmine, galantamine, and memantine) in the 365 days prior to or on cohort entry date. (N.B. The two AD/ADRD ICD-10 diagnosis codes must be ≥7 day apart and at least one of the codes must be within 365 days of the cohort entry date. Treatment is defined as exposure to an AD drug based on either: (1) days' supply of one or more dispensing; or (2) a dispensing in the 365 days prior to cohort entry date.) (b) evidence of inappropriate prescribing within the 3 months prior to cohort entry date; (c) age ≥50 years of age as of cohort entry date; and (d) continuous medical and pharmacy insurance coverage for at least the prior year.

Exclusion Criteria:

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Evidence of a recent institutional stay encounter in a Skilled Nursing Facility, hospice, rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays within the previous 90 days prior to or on cohort entry date.
2. Incomplete/missing prescriber ID or incomplete contact information for either patient or prescribing provider.
3. On "do not contact" list

5.2 LIFESTYLE CONSIDERATIONS

N/A

5.3 SCREEN FAILURES

N/A

5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Each participating health plan will send approved intervention materials to their respective patients and providers as appropriate according to their random group assignment. Providers and patients/caregivers

will receive applicable educational materials through a one-time mailing at trial start. All patients who are assigned to a group will be considered enrolled. Participants enrolled in the clinical trial will not receive a stipend.

Trial participants will only be contacted once as detailed above. Outcomes of interest will be provided by the health plan to the Analytic Coordinating Center at Harvard Pilgrim Health Care Institute (HPHCI), with identifiable patient-level data removed, relating to the 6-month observation period that follows a 3-month "blackout" period after the initial mailing. Retention of participants will be determined by their continued enrollment with their respective health plan, and as such, the study team will not require a specific plan for retention.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

The study will have two intervention arms; educational intervention to provider only and educational materials to patients/caregivers *plus* educational materials to providers. Educational materials will be distributed through a one-time mailing. The two intervention arms are described below.

Provider Only Arm

- *Patients do not receive any materials*
- *Providers receive:*
  - *Letter referencing a specific patient and drug*
  - *Algorithm to guide decision making about deprescribing*
  - *Patient information sheet*
  - *Sample "Tapering Plan" to help patients track dose reductions*
  - *Main messages: this drug may be inappropriate for this patient; consider deprescribing*
- *Materials reference the study **website***

Patient/Caregiver & Provider Arm

- *Patient/caregivers receive:*
  - *Letter referencing a specific drug*
  - *Information sheet referencing the drug class*
  - *Main messages: this drug may be inappropriate for you; talk to your provider*
- *Providers receive:*
  - *Letter referencing a specific patient and drug*
  - *Algorithm to guide decision making about deprescribing*
  - *Patient information sheet*
  - *Sample "Tapering Plan" to help patients track dose reductions*
  - *Main messages: this drug may be inappropriate for this patient; consider deprescribing*
- *Both sets of materials reference the study **website***

Study specific website. Relevant to the provider only and the patient/caregiver plus provider arms of the trial, a dedicated D-PRESCRIBE-AD study specific website will be available for patients, caregivers, and healthcare providers. The website will provide online access to all mailed educational materials. It will also include stories of patients/caregivers who successfully engaged in collaborative conversations with healthcare providers about deprescribing. The website will provide a study telephone number for patients, caregivers, and healthcare providers to discuss any study-related questions they have with a study clinical pharmacist.

6.1.2 ADMINISTRATION AND/OR DOSING

Providers and patients/caregivers will receive applicable educational materials through a one-time mailing at trial start. *In instances where a patient has been prescribed more than one inappropriate medication, educational materials will be sent for one selected medication class according to the following hierarchy: antipsychotics, then sedative-hypnotic, then strong anticholinergic.*

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Level of Fidelity	Procedures to Ensure Fidelity	Monitoring
Study Design	• Protocol based on prior successful studies and builds upon well-established protocols.	• Careful protocol review and regular monitoring to ensure accuracy. • Monitoring of all study documents after changes to ensure consistency. • Distribution of updated documents to all participating sites after any changes are made
Intervention Delivery	• Detailed Standard Operating Procedures (SOP) will be followed for identification and randomization of cohort. • SOPs will also be followed for actual mailing of intervention materials.	• Regular meetings between research team and participating health plans to ensure version control and maintain consistency in cohort identification and intervention delivery. • Ad hoc meetings take place as needed for interim communication.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Blinding is not required for this study as the intervention is delivered via mail and does not pose a risk for bias. As there may be the potential for within-provider "contamination," such that some providers would be treating patients who are randomized to different study arms, for any provider with more than one eligible patient, only one patient will be randomly enrolled.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

N/A

6.5 CONCOMITANT THERAPY

N/A

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

N/A

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Patients will be censored from the analysis at the time of disenrollment from the health plan to which they were enrolled at the start of the trial, or at the time of death. We will use survival analysis to account for censoring of participants. Due to the limitations of health plan data, information on important variables such as reasons for disenrollment are not available on censored participants.

7.3 LOST TO FOLLOW-UP

N/A

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Following a "blackout" period of 3 months after the mailing of the intervention materials to providers and patients/caregivers, outcomes will be assessed over a 6-month observation period. Outcomes will be identified in health plan claims data via a distributed program, similar to how the eligible members were initially identified. We will evaluate the effect of educational interventions designed to stimulate patient/caregiver-provider communication about medication safety (versus usual care) on the primary outcome defined as absence of any dispensing of targeted medication from day 91 to day 270 following receipt of intervention. Secondary outcomes will also be assessed specific to the 6-month observation period based on health plan claims data including: dose reduction, prevalence of polypharmacy (defined as >5 active prescriptions for different oral agents); rates of emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, comparison by drug class, and non-acute institutional days); switching within drug class, and in-hospital mortality. All outcomes will be ascertained from health plan claims data.

8.2 SAFETY ASSESSMENTS

The Principal Investigator and research team will comply with the University of Massachusetts Institutional Review Board requirements for defining, collecting and reporting any unanticipated problems, adverse events, or serious adverse events during the conduct of research.

All study procedures and recruitment procedures will undergo review by the Institutional Review Board at the University of Massachusetts prior to initiating research, and will be subject to annual and other required reviews. Investigators will work with NIA to convene a Data Safety and Monitoring Board to oversee the human subjects' safety and adverse event reporting for this trial.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

In the context of this study there is no ascertainment of adverse events, either actively or passively. There will be information on clinical outcomes but that will not be available to the investigators until at least 12 months or more after the mailing as there are no interim analyses planned.

8.3.1 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

As this study consists only of a mailed intervention, there will be no direct interaction with participants to be able to assess adverse events.

In the context of this study there is no ascertainment of adverse events, either actively or passively. There will be information on clinical outcomes, but that will not be available to the investigators until at least 12 months after the mailing.

8.3.2 ADVERSE EVENT REPORTING

In the context of this study there is no ascertainment of adverse events, either actively or passively. Adverse event reporting will be refined with input from the DSMB during its initial meeting, to address any specific concerns related to this study protocol.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). Events will be reported to the DSMB at periodic intervals.

Clinical information is not available to us to assess for presence of AEs. There is no contact at all with third arm (usual care) precluding any meaningful between- group comparisons. Phone line is available only for questions about mailing. The only way to become aware of an AE would be serendipitously on receiving a phone call or email from the patients/caregivers or providers which encourages them to contact us with any questions about the mailed educational materials. The message and information provided to patients regarding the contact information is presented below.

IMPORTANT: Do not stop taking this medication or change this medication without talking to your doctor first. Bring this letter and enclosed information sheet with you to your next doctor's appointment so you can discuss.

We encourage you to speak with your doctor regularly about your medications. Only you and your doctor can decide whether this medication remains the best choice for you.

We know that managing your medications can be challenging, and we want you to get the care that is best for you. Thank you for considering this information. Should you have any questions about this letter or information sheet, you can contact the University of Massachusetts medication safety team at 1-833-739-1374 (TTY: 711), Monday-Friday, 9am – 5pm, Eastern time. You can also email questions to knowyourmeds@umassmed.edu.

Study personnel will report Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)s to the PI in a timely manner.

When a UPIRSO or AE is present, the PI and Project Manager will submit a report to the UMMS IRB within 3 working days of receipt of this information. Generally, the report will contain the following:

- Detailed information about the event or issue, including relevant dates. The report will not identify study participants by their names or other personal identifiers.
- An assessment of whether any subjects or others were placed at risk or suffered any harm (e.g., physical, social, financial, legal, or psychological) as a result of the event.
- If the event involves noncompliance, describe the result of the root cause analysis
- Any corrective and preventative actions planned or already taken.
- Any other information requested by UMMS IRB, if applicable.
- If the report cannot be completed in its entirety within the required time period, the report will describe what information is still needed and when the investigator anticipates that a follow-up report will be submitted.

Information previously unknown to the IRB that suggests new or increased risk to subjects or others (hereinafter referred to as New Safety Information) is promptly reportable to UMMS IRB within 7 calendar days of the investigator becoming aware of the information.

- Information for which the sponsor requires reporting to the IRB, may be summarized and submitted to the IRB at continuing review.
- Protocol deviations that did not harm subject(s) or others or place subject(s) or others at

increased risk will be summarized and reported to the IRB at continuing review.
- Researchers may consult with the UMMS IRB Director if they are uncertain about what information is reportable.

8.3.3 SERIOUS ADVERSE EVENT REPORTING

In the context of this study there is no ascertainment of adverse events, either actively or passively.

8.3.4 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.5 EVENTS OF SPECIAL INTEREST

N/A

8.3.6 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given: (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied.
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Data Coordinating Center (DCC)/lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number.
- A detailed description of the event, incident, experience, or outcome.
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP.
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB and to the DCC/study sponsor/funding agency within 48 hours of the investigator becoming aware of the event
- Any other UP will be reported to the IRB and to the DCC/study sponsor/funding agency within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 business days of the IRB's receipt of the report of the problem from the investigator]

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

We hypothesize that, compared to patients in the control group, patients who are in either intervention arm and receive information around inappropriate prescribing themselves along with their provider, or who have a provider that received the mailing, will have reduced inappropriate prescribing. Alternatively, our null hypothesis is that there will be no difference in the effects of the educational intervention at the end of the observation period.

Secondary Endpoint(s):

We hypothesize that education on inappropriate prescribing among patients/caregivers and their providers can reduce medication-related morbidity in patients with AD/ADRD and lead to an improvement

in medication safety for this vulnerable population. This will be measured by assessing evidence of dose reduction of the selected inappropriate medication, reduction in the prevalence of polypharmacy; reduction in the rates of emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, and non-acute institutional days); and in-hospital mortality.

9.2 SAMPLE SIZE DETERMINATION

Sample Size and Power. Our target sample size for the first trial is 14,442 patients, 4814 patients in each of the three study arms. The calculations below employ 80% power, overall Type I error rate of .05 with a Bonferroni correction for 3 pairwise comparisons of study arms (.05/3=.0167), and 2-sided hypothesis testing. Based on our prior analyses,[26,27] we anticipate death or health plan disenrollment in 9.9% of sampled patients within 3 months of the intervention (receipt of the letter), with the remaining 90.1% contributing data in the 6-month interval of interest (days 91-270 post-intervention) – that is, we anticipate a per-arm sample size of 4814 × .901 = 4337.

For analyses of the primary outcome, absence of dispensing of targeted inappropriate prescription classes in days 91-270, we anticipate censoring in this interval for 13.5% of participants based on prior data. To make maximal use of observed data, we will use survival analysis to model time until an inappropriate prescription (a "failure") in days 91-270. Detectable pairwise between-arm differences (e.g., between usual care and an intervention arm) are presented in Table 2 below for a range of possible percentages for "failure" = inappropriate prescribing of the targeted drug.

Table 2. Detectable pairwise between-arm differences in hazard of inappropriate prescription classes in days 91-270

Percent with inappropriate prescribing of targeted drug ("failure"), Study Arm 1	Detectable hazard ratio for inappropriate prescribing, Arm 2 versus Arm 1
40	.8860
50	.8979
60	.9067
70	.9136
75	.9165
80	.9192
85	.9216
90	.9239
95	.9260
99	.9267

For the range of "failure" percentages examined here, which reflect those seen in Martin et al,[3] detectable hazard ratios range from 0.89 to 0.93. For example, if 75% of participants randomized to Arm 1 are observed to have a "failure" (prescription for a targeted inappropriate medication) by day 270, the detectable hazard ratio for an inappropriate prescription for Arm 2 versus Arm 1 is 0.9165, a

8.35% reduction in risk; the corresponding detectable "failure" probability for Arm 2 = 0.7193, a difference smaller – i.e., more precise – than that seen in Martin et al.[3] Calculations for the secondary outcome of ≥50% reduction in dose are parallel.

For additional secondary outcomes, such as per-patient number of hospitalizations or ED visits, based upon prior data (mean of 0.35 hospitalizations per 6-month period and 0.4 ED visits per 6-month period), we will be able to detect rate ratios of 0.8856 and 0.8927, respectively (corresponding to intervention-related reductions of 11.4% and 10.7%), accounting for censoring due to death or disenrollment. For between-arm differences in mortality, assuming usual care 6-month mortality of 6.3% – likely an underestimate given a lag in ascertainment – and 7.6% censoring due to disenrollment based on information provided by the participating health plans, the detectable hazard ratio is 0.7356 corresponding to per-arm survival percentages of 93.7% versus 95.33% (absolute difference of 1.63%).

9.3 POPULATIONS FOR ANALYSES

Intention-to-Treat (ITT) Analysis Population (all randomized participants):
All analyses will be intention to treat. We do not expect differential loss to follow up between the three arms of the study. For the time to event analysis patients will be censored from the analyses at the time of death, disenrollment from the health plan, loss of medical or pharmacy coverage, or change in eligibility for research based on health plan membership.

We will construct a detailed consort diagram showing the number of patients randomized to the three arms, the number of patients lost to follow up, excluded from analyses and the number of subjects included in the primary and secondary analysis. [See consort Draft. In section 1.2 (schema)]

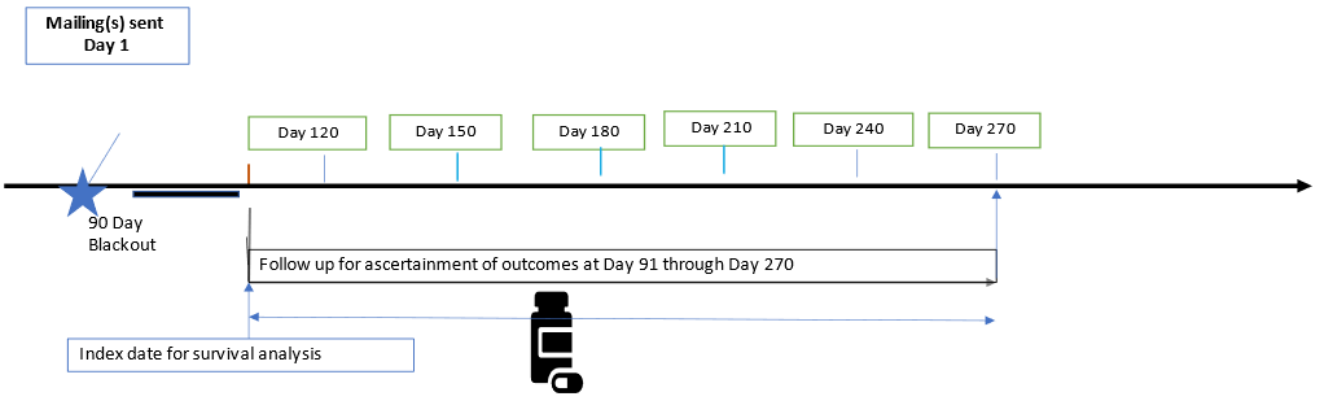
9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

In descriptive analyses, treatment arms will be compared regarding key patient characteristics, including age, gender, and renewal of inappropriate prescriptions in days 1-90, using percentages for categorical characteristics and means (standard deviations) or medians (interquartile range) for continuous characteristics, depending on the observed distributions. Analyses of study outcomes will employ two-sided hypothesis testing and an overall Type I error of 0.05, applying a Bonferroni correction to accommodate three pairwise comparisons of the three study arms. Covariates of *a priori* interest include patient age, gender, and renewal of inappropriate prescriptions in the blackout period. In addition, we will adjust for characteristics that are found to predict study outcomes, in order to increase precision for the comparison of study arms,[28] as well as for characteristics found to be related to censoring or other missing data, in order to reduce possible nonresponse bias.[29] All analyses will be intention-to-treat. Sex as a biological variable will be factored into all analyses.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

PRIMARY OUTCOME



Statistical Analysis of Primary Outcome:

1. The primary outcome will be defined as absence of any dispensing of the targeted inappropriate prescription class from day 91 to day 270 following the day of mailing. Educational interventions will be targeted towards one specific drug class so participants who switch within one class (e.g, clonazepam to lorazepam) will not be considered as having met primary outcome**. The intervention will only target one potentially inappropriate medication class for patients who are on more than one class of potentially inappropriate medication**.

2. **Timing of Ascertainment**: The timing of ascertainment is over a 6-month period beginning 3 months after mailing/intervention – i.e., we will assess evidence of a dispensing in days 91 through 270 after the date of mailing.

3. **Method of Aggregation: Hazard ratio**. The data on primary outcome will be measured as the relative hazard of time to dispensing of any new incident inappropriate prescription of

their initial drug class in the intervention vs control group. The index date for the survival analysis will be Day 91 for the trial. We chose the hazard ratio as method of aggregation as this allows the statistical analysis to account for censoring due to death or disenrollment.

4. Any prescriptions dispensed during the **blackout period** will not be counted towards measurement of the primary outcome but may affect subsequent dispensing. In covariate-adjusted survival analyses, we will adjust for whether any prescription for the same inappropriate medication class was dispensed during the blackout period and the duration of such dispensing because dispensing during the blackout period is an important factor which may affect the primary outcome. A blackout period was needed to allow time for the mailing and receipt of the intervention after randomization, and the opportunity to set up the appointment with or contact their provider to discuss the use of the potentially inappropriate medication. Alternatively, we may also consider stratification of survival analyses by prescriptions dispensed during the blackout period.

For the primary outcome (i.e., any post-intervention discontinuation of inappropriate prescribing during the 6-month period beginning 3 months after the mailing), as a first step, we will calculate crude arm-specific percentages, as well as Kaplan-Meier curves and log-rank testing. Covariate-adjusted comparisons of arms will be estimated using Cox proportional hazards modeling. Comparing active intervention arms to usual care, we hypothesize a hazard ratio of less than 1, indicating lower risk of an inappropriate prescription in days 91-270 in the active intervention arms. The index date for the survival analysis will be day 91. We chose the hazard ratio as method of aggregation as this allows the statistical analysis to account for censoring due to death or disenrollment. To account for mortality, anticipated to be approximately 6%, we also will conduct competing risk analyses [30] as well as cause-specific hazards modeling.[31]

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Secondary outcomes. These will also be assessed specific to the 6-month observation period (days 91-270 following mailing/intervention) based on health plan claims data including:

a) Any dose reduction of each of the targeted medications, assessed at the participant level using health claims data (outpatient dispensings).

b) Percentage of patients with prevalence of polypharmacy (defined as >5 active prescriptions for different oral agents)[32]

c) Rates of emergency room visits; rates of hospitalizations; rates of non-acute institutional stays (e.g., skilled nursing facilities); overall health care utilization (number of outpatient visits, days hospitalized, emergency department visits, and non- acute institutional days).

d) In-hospital all-cause mortality

e) Switching within classes

We will use administrative claims data to identify encounters of interest (ED visits, hospitalizations, non-acute institutional stays, outpatient visits) and only assess oral formulations for medications.

Measurement of Dose Reduction. We will consider dose reduction for each selected drug as being a ≥ 50% decrease in the mean daily dose comparing the 6 months immediately prior to the randomization with the 6-month study window period. (day 91-day 270). We will measure average daily dose using dates of prescription dispensing, duration of prescription dispensing and strength of the prescription. We will measure the dose reduction as a dichotomous variable defined as the proportion of patients who achieved a more than 50% dose reduction in the daily dose during the study window period (day 91 to day 270) compared to the 6-month period prior to randomization. Measurement of dose reduction over 6 month follow-up requires participants to complete follow-up through end of observation period (day 270). Censored participants – that is, those who have less than 6 months in days 91-270 – will be excluded for the analysis of dose reduction. Analyses will adjust for correlates of missing data. Analyses for post-intervention polypharmacy prevalence will be analogous. We will identify participants with evidence of dispensings of ≥5 oral medications over the respective 6-month periods [during the study window period (day 91 to day 270) compared to the 6-month period prior to mailing]. AD medications and the three potentially inappropriate medication classes will contribute to measure of polypharmacy. Injectables and topical or ocular medications will not be counted as evidence of polypharmacy.
A combination drug will be considered a single medication for the purpose of this analysis.
Additional analyses will examine within-patient change in number of inappropriate medications, where the maximum possible decrease equals the pre-intervention number of inappropriate medications. We will accommodate this between-patient heterogeneity as follows: within-patient changes will be ranked separately by pre-intervention number of inappropriate medications, ranks will be transformed using normal scores to obtain comparable distributions across these strata, and treatment arms will be compared regarding transformed ranks[34] using analysis of covariance. In analyses of other secondary outcomes, count outcomes such as per-patient number of emergency department (ED) visits will be analyzed using Poisson or negative binomial regression, accounting for "excess" zeros if warranted based on observed distributions.[35]

Among study subjects who discontinue the targeted medication, we will determine if another agent within the targeted class has been dispensed over the period of observation (day 91-270).
For sedative/hypnotics: dispensing of a new generic agent within the class of sedative/hypnotics.
For antipsychotics: dispensing of a new generic agent within the class of antipsychotics.
Analyses will be analogous to those for dose reduction.

Mortality will be analyzed using survival analyses, including Kaplan-Meier curves, log-rank testing, and Cox proportional hazards (PH) modeling, accounting for censoring due to disenrollment

9.4.4 SAFETY ANALYSES

N/A

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Demographics and baseline characteristics. Baseline and demographic characteristics will be based on claims data at the time of randomization. Frequency distribution and summary statistics will be presented by three intervention groups. Key demographics to be summarized include age in 5-year categories, sex, ethnicity, geographic region, Combined Comorbidity score, health care utilization indices and current use of inappropriate prescribing drugs. Categorical variables will be presented as frequencies and continuous variables as mean and SD. We will not use inferential statistics at baseline.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

We will conduct analyses stratified by sex and we do not anticipate sex related differences in within- group correlations (ICC). We will also conduct analyses of primary and secondary outcomes stratified by each individual drug class. Pre-specified analyses of primary and secondary outcomes will be conducted according to levels of polypharmacy at baseline (5+ medications at baseline; 7+ medications at baseline).

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

No individual participant data will be listed by measure.

9.4.9 EXPLORATORY ANALYSES

Analyses parallel to those conducted for the primary outcome will be conducted by targeted inappropriate medication class**.**

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

We will be requesting a waiver of consent from the IRB for the Randomized Clinical Trial. We believe the study meets the following criteria to obtain a waiver of consent (followed by a rationale):

1. *The research involves no more than minimal risk to the subjects.*
   Rationale: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. The intervention is entirely consistent with a quality improvement initiative that the health plans could initiate on their own. The intervention only adds to the existing care of patients. There are no restrictions placed on the control group as a result of the trial.
2. *The waiver or alteration will not adversely affect the rights and welfare of the subjects.*
   Rationale: The waiver of consent will not impede on any rights or the welfare of subjects; the waiver will solely allow the research team to implement the educational intervention by mail which subjects may choose to entirely ignore.
3. *The research could not practicably be carried out without the waiver or alteration.*
   Rationale: There are several reasons why the research would be impractical without the waiver of consent. First, contacting "control" and "provider only intervention" patients for consent would be an intervention by itself and might affect the results of the study. Secondly, given the number of subjects to be included, it would be impractical to collect informed consent from the total study population included in the trial.
4. *Whenever appropriate, the subjects will be provided with additional pertinent information after participation.*
   Rationale: If necessary, we will provide additional information to patients, as deemed appropriate by the IRB.
5. *The research is not FDA-regulated.*
   Rationale: The research does not include any FDA-regulated activities; there are no pharmaceutical agents or medical devices being implemented as part of the intervention.
6. *The research does not involve non-viable neonates as subjects.*
   Rationale: The research only includes living adult patients aged 50 years of age or older and/or their medical providers.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

N/A

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator and funding agency. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and the sponsor/funding agency and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)
- Data that are not sufficiently complete and/or evaluable

The study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the funding agency, sponsor, IRB, Food and Drug Administration (FDA), or other relevant regulatory or oversight bodies (OHRP, DSMB).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence and will not be shared beyond the health plan. No personally identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator.

The study participant's contact information will be securely stored at each study site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Harvard Pilgrim Health Care Institute (HPHCI) and University of Massachusetts Chan Medical School and will not include the participant's contact or identifying information. No individual level data will be shared with HPHCI; only aggregate level data will be shared for analysis. Deidentified individual level data will be shared with UMass Chan; a Data Use Agreement will be executed between both plans and UMass Chan. The study data entry and study management systems used by sites, UMass Chan and by Harvard Pilgrim Health Care Institute research staff will be secured and password protected. At the end of the study, all study databases will be archived at the UMass Chan Medical School.

Measures Taken to Ensure Confidentiality of Data Shared per the NIH Data Sharing Policies
It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

The organizations proposing this study have systems, oversight, experienced personnel, and an organizational culture that supports the appropriate use, access to, and storage of confidential

information. All persons collecting or handling data will be trained in human subjects' procedures, confidentiality and privacy protection. All investigators and project staff are required to receive and complete IRB and HIPAA training.

Data for all participants will be kept strictly confidential and will remain at the health plans. All hard copies of research files will be kept in locked file cabinets or a locked file room. Participants will be assigned a numerical code (Study ID) for identification in the files. Individual identifier information will be removed from study data files as soon as possible in the data processing steps and prior to receipt by Harvard Pilgrim Health Care Institute. All computerized data will be kept on secured computers or networks. These data will be accessible only to research staff using confidential usernames and passwords. Statistical analyses will be performed using only limited datasets and only de-identified data will be reported. All data will be used for research purposes only; published data will not contain any individual identifiers.

All patient-level electronic data will be maintained by the health plans which have routine access to these data. Investigators who prepare the reports, presentations, and publications that will be based on this study will never have had access to identifiers of study subjects. Investigators outside of the health plans will never have had access to any identifiers.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Query results returned to Harvard Pilgrim Health Care Institute (HPHCI) are retained onsite for a minimum of six years after the close of the study, followed by six years at an offsite storage facility. For file security, all desktops and laptops run encryption software from Credant Technologies, Inc. to prevent accidental loss or theft of data on computers or removable media from being usable. Network file storage is on a password protected server. Remote access to the Harvard Pilgrim network is available on Harvard Pilgrim laptops using the VPN software.

The data extracted for this study will be stored on the health plans' secured, encrypted, password-protected servers accessible only by staff. Access to the data requires a secured login and password. Paper documents will be stored in a locked file. Electronic data for the research will remain secured and destroyed once the required retention period has been completed per IRB guidelines, state and federal laws, and according to the health plan IT and data security policies.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Jerry Gurwitz, MD, Executive Director
Meyers Primary Care Institute, UMMS
385 Grove St. Worcester, MA 01605

508-791-7392
jerry.gurwitz@umassmed.edu

The research team will be led by Dr. Jerry Gurwitz (PI). The PI and Project Manager will provide administrative leadership and study coordination, to ensure timely completion of research tasks and consistency with protocol standards.

The research team will be complemented by an Advisory Committee with specific expertise relevant to the D-PRESCRIBE-AD pragmatic clinical trial and will meet on a quarterly basis.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including geriatric medicine, primary care, prescribing in clinically complex older adults, testing of clinical quality measures. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The SMC will meet at least semiannually to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to National Institutes of Health staff.

The DSMB members are listed below:

Chiang-Hua Chang, PhD, MS
Research Assistant Professor
University of Michigan

Laura C. Hanson, MD, MPH
Professor, Geriatric Medicine
Medical Director, UNC Palliative Care Program
University of North Carolina, Chapel Hill

Michael Steinman, MD
Professor of Medicine, School of Medicine
University of California, San Francisco, CA

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

All health plans for this study are participants of the FDA Sentinel project and will use their approved local implementation of the Sentinel Common Data Model (SCDM) for querying. As participants in the

Sentinel project, all health plans must undergo a rigorous data management and quality assurance process before their data is approved for use in querying. The frequency of each health plan's quality assurance approval process depends on their specific contract with Sentinel, but occurs at a minimum on an annual basis. In addition to quality assurance of data elements, Harvard Pilgrim Health Care Institute (HPHCI) adopts standard SAS programming quality assurance and quality control processes used by the Sentinel System to check SAS programs and deliverables.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The electronic data used in this protocol will be accessed, maintained, and protected, as part of a "distributed system." In a distributed system, data remain in their existing secure environments, rather than being consolidated into a single database. Health plans maintain physical and operational control over their electronic health data behind their institutional firewalls. Health plans transform their data into the Sentinel Common Data Model, execute standardized analytic queries distributed by the Sentinel Operations Center, which is based at Harvard Pilgrim Health Care Institute (HPHCI), then share the output of queries, with the Operations Center and UMass Chan via a secure portal.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years and will comply with all NIH and NIA data retention standards.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the investigators to use continuous vigilance to identify and report deviations within seven working days of identification of the protocol deviation, or within seven working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to National Institute on Aging Program Official and UMMS IRB. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator will be

responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

Protocol deviations will be recorded in the Protocol Deviation Log, including the following information:

- Text description
- Protocol deviation category

All deviations will be reported quarterly to National Institute on Aging Program Official and University of Massachusetts IRB and will be summarized for each meeting of the study DSMB.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 3 years after the completion of the primary endpoint by contacting Harvard Pilgrim Health Care. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute on Aging has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

ADRD	Alzheimer's disease and Alzheimer's disease-related dementias
AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Section of Protocol	Description of Change	Rationale
1.1	June 16, 2021	1. Protocol Summary 9.4 Analysis of the secondary endpoint(s)	Assessment of polypharmacy will be limited to "oral" medications.	On the recommendations of the DSMB at the meeting on June 1, 2021 we will now limit our assessment of polypharmacy to oral medications only as opposed to medications administered via other routes (e.,g., topical, ocular routes etc). These orally use medications were most clinically relevant to the assessment of polypharmacy
1.2	Nov. 22, 2021	6.3 Measures to minimize bias: randomization and blinding 9.2 Sample size determination	Randomize patients at the individual-level, as opposed to the cluster-level by MSA.	This was necessitated by the unique privacy, data source and proprietary constraints of this pragmatic trial. The analytic program for identification of participants and randomization will be developed by the Data Coordinating Center at the HPHCI, and will be implemented in a distributed environment across the two participating national health plans (Humana and Health Core/Anthem). To operationalize block randomization and ensure balance across clusters in a cluster RCT, we need to determine the number of participants within each MSA prior to randomization. These data are proprietary to the health plans. Although our Data Coordinating Center can have access to this data in a masked format, this complicates programming efforts increasing the chance for errors that will possibly lead to delays in implementing the trial. Preliminary work also indicates the potential for a significant imbalance in the number of participants that are likely to be randomized from each plan if cluster-level randomization by MSA is employed. In addition, all geographic areas across the U.S. are not encompassed within MSAs, potentially adversely impacting the number of eligible subjects available for the trial. In summary, we have weighed the benefits of cluster randomization against

				pragmatic considerations and the need to operationalize a robust, consistent distributed analytic randomization scheme across the health plans, with adequate quality checks and quality control measures. We have chosen to randomize patients at the individual-level. To address potential within-provider contamination, for providers with medication dispensings of target medications to more than one eligible patient, only one patient per provider will be selected (randomly) for inclusion. This strategy allows us to operationalize quality control measures early in the process, and address the operational challenges identified above.
2.0	July 18, 2022	4.1 Overall Design 9.2 Sample Size and Power	Updated sample size for trial 1 and updated associated power calculations.	When unexpected data issues arose at one health plan and we were not certain they would be resolved in time for intervention implementation (the mailing), we were able to increase the sample size for the other health plan to 11,250 to ensure that we would maintain the planned sample size for the study (n=11,250). Fortunately, the issues at the first health plan have been resolved and we were able to randomize the originally planned number of subjects from that site. This has resulted in an increase in our overall sample size from 11,250 to 14,442.
3.0	May 11,2023	2.3.1 Known potential risks 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S) 10.1.3 Confidentiality and Privacy 10.1.9.1 Data Collection and	Updated text to reflect that UMass will receive deidentified patient level data from both plans.	The complex multivariate nature of the analyses requires deidentified individual level data for analyses rather than just deidentified aggregate data. For this reason, we will be executing Data Use Agreements between UMass Chan Medical School and the health plans in order to receive the data directly at UMass for analyses. We have also added a secondary outcome to investigate switching between classes, at the request of the DSMB.

		Management Responsibilities		

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