Study Protocol: Pragmatic Randomized Controlled Evaluation of a Quality Improvement Program to Reduce Hyperpolypharmacy

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Abstract

Background: Ten to fifteen percent of Medicare patients experience hyperpolypharmacy (use of ≥10 prescription drugs) and are at risk of adverse drug effects. Health systems have started bundling deprescribing of multiple drugs into a single intervention. However, knowledge about the effectiveness and safety of bundled deprescribing is inadequate.

Methods: Kaiser Permanente is performing a randomized quality improvement project to evaluate a bundled, deprescribing intervention targeted to patients aged ≥76 years using ≥10 prescription drugs. The intervention includes collaborative drug therapy management, standard-of-care treatment protocols, shared decision-making, and deprescribing protocols. Ambulatory care pharmacists work over multiple cycles from days 1-180 after allocation to deprescribe medications while monitoring for adverse drug withdrawal effects. Primary effectiveness endpoints include change in the number of medications and diagnosis of geriatric syndrome conditions. Safety endpoints possibly resulting from loss of disease control include emergency room visits, hospitalizations, and deaths. Endpoints will be obtained from the electronic medical record during days 181 to 365 after allocation. Differences will be tested using intention-to-treat analyses.

Results: Approximately 8,500 patients were eligible during the recruitment phase. After physician authorization, obtained for 94% of those sampled, 2,470 patients were randomized: 1,237 to the intervention and 1,233 to usual care. To date, 92% of patients were reached, the average time to reach was 23 days, and 93% agreed to participate. To date, the pharmacist's recommendation to deprescribe a medication was accepted in

65% of instances, about 30% had no medication deprescribed, one-quarter had 3 or more medications deprescribed, proton pump inhibitors accounted for 11% of deprescribed medications, and medication was restarted in 13% of instances.

Conclusions: The study will provide essential information on the effectiveness, safety, and implementation of a bundled deprescribing initiative to address hyperpolypharmacy in older adults.

INTRODUCTION

Hyperpolypharmacy, the use of ≥10 prescription drugs, is prevalent in about 5-15% of patients aged ≥65 years.[1, 2] It is associated with frailty, physical and cognitive dysfunction, medication interactions (drug-drug, drug-patient, drug-disease), unfavorable benefit-risk tradeoffs, and increased healthcare costs.[3] Deprescribing is the supervised withdrawal of drugs with the goal of providing guideline-consistent care and improved outcomes. It has been developed as an intervention to reduce hyperpolypharmacy and improve outcomes.[4] Past studies of the effectiveness of deprescribing focused on single drug classes and examined disease management as the outcome.[5] However, single-drug approaches result in patients being enrolled into multiple programs and receiving potentially conflicting interventions. Bundling is a proven implementation strategy,[6] and in recent years, health systems have sought to bundle deprescribing into a single intervention.[5] However, randomized controlled trials of bundled deprescribing have included relatively few patients, included patients with limited prognoses, or assessed drug counts and not adverse drug effects (ADEs) nor adverse drug withdrawal effects (ADWEs).[7-11]

In 2017, the Pharmacy department at Kaiser Permanente Northern California began developing a quality improvement intervention, *Bundled Hyperpolypharmacy Deprescribing*. The intervention uses collaborative drug therapy management and was designed for patients aged ≥76 years using ≥10 prescription drugs and integrates pharmacist review of >20 drug classes into a single workflow. This protocol for a pragmatic randomized controlled evaluation was developed to evaluate program effectiveness and safety.

METHODS

The Research Determination Committee for the Kaiser Permanente Northern California region determined the project does not meet the regulatory definition of research involving human subjects per 45 CFR 46.102(d).

Setting

Kaiser Permanente Northern California provides care to persons aged ≥65 years largely through its capitated Medicare Advantage program. Encounters are recorded into the electronic medical record (EMR) using smart-text and drop-down menus that link the reason for the encounter to ICD-10 diagnostic codes. For each patient, the EMR opens to a screen that summarizes key medical information with hyperlinks enabling rapid and comprehensive clinician review. Clinicians can also search the EMR using text-strings. The health system owns its pharmacies, and pharmacy information is integrated into the EMR. For reasons of cost and convenience, more than 95% of patients use the health

plan's pharmacies to obtain their medications. Physicians sometimes record orders for over-the-counter medications, however because many of these medications are uninsured, patients often purchase them outside the system and electronic capture of these purchases is incomplete.

Overview

Figure 1 provides a design schematic of the randomized controlled evaluation, with details provided in later sections. Briefly, the evaluation was designed during 2018-2019 by a multidisciplinary team (pharmacists, adult and family medicine physicians, geriatrician, epidemiologist, biostatistician, project manager, data analyst) that consulted closely with the quality department, specialty physicians, Adult and Family Medicine, and the Pharmacy and Therapeutics Committee. Design decisions were informed by a preliminary analysis, and in late 2019, the protocol was critiqued by an external Stakeholder Advisory Committee. In response to the pandemic, the project was paused from March-July 2020. The project was then piloted in August 2020. In brief, the intervention was designed for patients aged ≥76 years using ≥10 prescription drugs. Eligibility for the intervention is determined algorithmically from information recorded in the EMR and requires physician authorization. The intervention is administered over multiple deprescribing encounters over a window of 180 days. The drug treatment protocols are standard-of-care for older, complex patients. This evaluation has the goal of accruing 1,000 intervention patients and 1,000 usual-care controls over 10 waves scheduled over 10 months. Accrual started in October 2020 and ended in July 2021. All deprescribing encounters, decisions, and actions are recorded into the EMR using

smart-text and drop-down menus designed for the intervention. Consistent with the pragmatic design, outcomes are obtained from clinical information routinely recorded in the EMR. Primary outcomes include (1) change in the average numbers of medications dispensed and (2) a diagnosis of ≥1 condition for geriatric syndrome (a composite measure of known ADEs). Secondary outcomes include the average number of encounters for any reason and ADWEs. Effectiveness outcomes are assessed over the period starting from day 181 and ending on day 365 after allocation. Safety outcomes are assessed at 6, 12, 18, and 24 months after randomization, with an internal Data Safety and Monitoring Committee meeting at each of these time points.

Population Eligible for the Intervention

Patients eligible for the intervention include those aged ≥76 years, with ≥12 months enrollment, ≥10 non-topical prescription drugs filled ≥2 times in the past year, and with the most recent fill within the past 180 days. Translation services are used to include non-English speakers. Patients with a history of transplant or on dialysis, in hospice, or with a cancer diagnosis in the past year or with an oncology visit or under active treatment for cancer during the past 12 months are not eligible for the intervention because these patients are especially complex and require frequent interventions by multiple teams.

Physician Authorization

The intervention is administrated by ambulatory care pharmacists using collaborative drug therapy management, defined as a formal partnership between the pharmacist and

physician to allow the pharmacist to manage a patient's drug therapy by augmenting the physician.[12] To obtain physician authorization, a pharmacy technician sends a staff message to each patient's primary care physician, explaining the intervention and evaluation, asking for authorization to randomize the patient and to perform deprescribing should the patient be randomized to the intervention arm. Physicians who do not respond within one week receive a second message. For the purpose of this evaluation, the physician-authorization process is closed at 2 weeks, when the pharmacy technician sends the list of authorized patients to the research data analyst, who re-checks eligibility and uses randomization to allocate patients to intervention or usual care at a ratio of 1:1.

Patient Allocation and Participation

For each patient with physician authorization who has been randomized to the intervention, a pharmacy technician uses the EMR and patient interview to obtain and document the complete medication list for the pharmacist, schedules the initial pharmacist appointment, helps the patient prepare for a telephone or video visit, and mails the patient a decision aid. If the technician is unable to reach the patient, they immediately follow-up with a secure electronic message through the patient portal and place another telephone call 1 week later. During the encounter, the pharmacist performs a medication reconciliation by reviewing the EMR for current and past medications (including refill history and any documentation of intolerance or ADEs), appropriate indications, and recent encounters that may indicate a change in the patient's medical condition. Patients without a deprescribing opportunity are disenrolled

from the intervention although they are retained in the evaluation for the intention-to-treat analysis.

Intervention

The intervention, *Bundled Hyperpolypharmacy Deprescribing*, is delivered by ambulatory care pharmacists during a telephone call or virtual visit with the patient using a playbook containing the Hyperpolypharmacy Program Tool, drug-specific deprescribing protocols, workflow guidance book, and other resources. Patients are not deprescribed if they have an appropriate indication for a drug and the benefits outweigh the risks, or if the patient prefers to continue the medication. The key drugs and drug classes targeted for deprescribing include antiemetics, antihypertensives, antipsychotics, non-narcotic antitussives, aspirin, clopidogrel, asthma medications, bisphosphonates, chronic obstructive pulmonary disease medications, diabetes medications, digoxin, ezetimibe, fibrates, gabapentin, glucose test strips, gout medications, histamine H2-receptor antagonists, levothyroxine, long-acting nitrates, non-steroid anti-inflammatory drugs, potassium supplements, proton pump inhibitors, skeletal muscle relaxants, statins, tricyclic antidepressants, urinary antispasmodics, and prescribed vitamin D. Opioids are not included because Drug Enforcement Agency licensing is required to prescribe opioids and other controlled substances. In addition, since 2013, the health plan has implemented multiple interventions to reduce opioid prescribing through separate clinical pharmacy programs.

The Hyperpolypharmacy Program Tool (Figure 2) includes the Agency for Healthcare Research and Quality SHARE Approach for shared decision-making[16] and the CEASE deprescribing framework.[17-19] Training on the SHARE Approach is supported by a curriculum and accredited webinars. The CEASE deprescribing framework includes medication reconciliation; assessment of benefits, harms, and side effects; consideration of individual factors; prioritization; changing, discontinuing, or adding orders; documentation; communication with physicians; and monitoring.[14-16] The deprescribing protocols are standard of care and were restated, in collaboration with physicians specialists, pharmacists, and with the Pharmacy and Therapeutics Committee, to highlight guidance for older complex patients.

During the encounter, the pharmacist performs a full medication review with the patient, discussing medication adjustments and adherence, providing education, and elucidating the patient's experience with the drug including ADEs. Next, the pharmacist and patient prioritize drugs to be deprescribed and the order of deprescribing. Depending on appropriateness and patient understanding, medications may be deprescribed one or more at a time, starting with the initial encounter. Encounters are scheduled about 3 weeks apart, depending on the drug-specific withdrawal protocol. Deprescribing actions may include educating the patient, ordering laboratory monitoring, communicating with the primary care provider, and changing medication orders. Before closing out deprescribing of a medication, the pharmacist schedules a follow-up encounter with the patient to assess ADWEs, disease management, the results of laboratory monitoring, and proper disposal of unused pills.

Documentation of all deprescribing encounters is recorded into the EMR. Data elements include who the pharmacist spoke with and their agreement to the medication review and possible deprescribing. For each medication considered for deprescribing, the pharmacist reviews the Problem List and ascertains relevant symptoms the patient may be experiencing with their medication. They also assess the patient's understanding of their medication, adherence, and preference for using the medication. The pharmacist's reasons for deprescribing, patient agreement, and deprescribing actions are recorded. Reasons for deprescribing may include unnecessary therapy, ineffective medication, dosage too high, ADEs, adherence or cost, or needs additional monitoring. Deprescribing actions include the following: discontinue medication, reduce medication dose, change to alternative medication, re-start/initiate or increase medication dose, recommendation to prescriber, and patient education. The patient can accept, decline, or defer each deprescribing recommendation. During follow-up encounters, the pharmacist records ADWEs and reasons for re-prescribing if the medication needs to be restarted, ideally at the lowest necessary dose. Reasons for disenrollment are documented.

Usual Care

Physicians and pharmacists use collaborative drug therapy management to provide deprescribing services at various touchpoints and transitions using single drug approaches. Some patients may also be eligible to receive deprescribing as part of Medicare's Medication Therapy Management (MTM) and other clinical pharmacy

programs.[17] Finally, deprescribing is performed by physicians during ambulatory care visits when time allows, and patients often receive medication reconciliation upon discharge from the hospital and skilled nursing care.

Outcomes, including ADEs and ADWEs

Primary effectiveness endpoints include (1) change in the average numbers of medications dispensed and (2) a diagnosis of ≥1 condition for geriatric syndrome (a composite measure of ADEs). (Table 1), while the average number of encounters for any reason will be examined as a secondary outcome. Geriatric syndrome was used as a concept based on the work of Inouye,18 Vasilevskis,19 and others, who developed evidence about the associations of polypharmacy with falls, cognition, urinary incontinence, weight loss, and pain. Specific outcomes to be grouped under geriatric syndrome were selected with consideration of frequency of drug use, severity and frequency, and responsiveness to deprescribing. These judgments were made by clinicians and investigators with specialty expertise in pharmacy, family medicine, geriatrics, cardiology, gastroenterology, and pulmonology over a period of several weeks using an iterative process. Weight loss was removed from the concept because its prevalence was only 1%. Types of encounters include telephone and video encounters, as well as clinic, emergency room, and hospital visits.

Primary safety endpoints (ADWEs) possibly resulting from loss of disease control include emergency room visits and hospitalizations for lower respiratory, cardiovascular, and gastrointestinal disease, and death from any cause, as well as total number of

emergency room visits and hospitalizations. The internal Data Safety Monitoring Committee[20] includes a biostatistician, cardiologist, gastroenterologist, and pulmonologist. The committee meets at 6, 12, 18, and 24 months after allocation of the first wave to compare the rate of ADWEs in the intervention and usual care groups, taking into consideration the consistency of findings with respect to the drugs that were deprescribed in the patients who experienced the outcomes.

Process measures clarify facilitators and barriers and include, for example, the number of deprescribing telephone encounters, the time needed to administer the intervention, specific drugs that are deprescribed, deprescribing actions, and the time-course of deprescribing.

Statistical Methods

Outcome data missing because of death or disenrollment is expected in 7% of usual care subjects. In addition, after randomization, approximately 5% of patients enter skilled nursing for an average of 15 days. Imputation algorithms will be used in relation to each outcome to assess whether data are missing at random.[21]

Primary analyses will use intention-to-treat and will include all randomized patients, including patients who were not reached, had no deprescribing recommendation identified, chose not to pursue deprescribing, or were re-prescribed during follow-up. In addition, we will perform secondary analyses focused on patients who received an intervention (‘as-treated’). Endpoints will be obtained from the EMR during the 6-month

period before allocation (baseline) and the 6-month period from days 181 to 365 after allocation. Mean change in the number of medications used from 181-365 days after allocation compared with the 6-month baseline before allocation will be treated as a continuous variable. Based on preliminary data, we anticipate that change in the number of medications will be normally distributed, but will test this assumption, using the Kolmogorov-Smirnov test if needed. We will report baseline characteristics of the usual care and intervention groups in means and standard deviations for continuous variables and number and percent for categorical and binary variables. Differences in baseline characteristics will be tested using t-tests for continuous variables and using chi-square tests for categorical and binary variables. Following CONSORT guidelines, we will not use statistical tests of baseline covariate imbalance to choose adjustment covariates.

We will account for having two primary outcomes by using a Bonferroni correction when assessing the statistical significance of the primary outcomes such that the level of α will be 0.025. Secondary outcomes will be tested at a level of α=0.05, and we will clearly state the number of statistical tests performed. For effectiveness outcomes (ADEs), we plan a single interim analysis after the 500th intervention patient completes their follow-up, with the final analysis performed after all patients complete their follow-up. Safety outcomes (serious ADWEs) will be assessed at 6, 12, 18, and 24 months using all available follow-up time. Repeated interim analyses are prone to an increased false positive error rate. Therefore, when conducting interim analyses, we will control for multiple testing using the O'Brien-Fleming bounds for sequential testing.[22] If the safety analysis provides evidence that the risk of a serious deprescribing harm is increased, we will work with physicians to re-prescribe the patients.

Statistical Power

Preliminary data collected from the EMR during the design phase, before study initiation, were used to estimate expected outcome rates. The data showed that eligible patients used an average of 11.3 medications at the time of identification and 10.5 medications after 365 days, with a mean change in the number of medications used of -0.8 (standard deviation, 2.2). The minimum detectable difference between the usual care and intervention groups was estimated with 90% power, using the full sample in intention-to-treat analyses, with two-sided with $\alpha=0.05$, and for the two primary outcomes, with a Bonferroni correction and correction for the interim analysis using O'Brien-Fleming bounds. We estimate that we can detect a difference of 0.3 medications (corresponding to a change in the number of medications used of -0.8 in the usual care group and -1.1 in the intervention group) (Table 2). Thus, we are well-powered to detect any clinically meaningful effect of this intervention. The Table also presents the power of the secondary outcomes as well as the safety analyses at the time of the second interim analysis at 12 months after allocation of Wave 1.

RESULTS

The number of eligible patients is about 8,500, which represents <5% of members aged ≥76 years. Drugs used by at least half of the study population include statins, beta-blockers, aspirin and clopidogrel, loop diuretics, and albuterol. Drugs used by one-quarter of patients include calcium channel blockers, proton pump inhibitors, diabetes medications, angiotensin receptor antagonists, levothyroxine, ACE inhibitors, H2-

receptor inhibitors, gabapentin, potassium replacement, anticonvulsants, inhaled glucocorticoids, and combinations of inhaled beta-adrenergic and glucocorticoid.

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Study Protocol Table 1. Operational definitions of primary and secondary outcomes and potential deprescribing harms

Endpoints	ICD-10 Definition
	Serious Adverse Drug Effects (ADEs)
Number of medications (primary outcome)	From dispensed medications recorded in the comprehensive, integrated pharmacy information system
≥1 encounter for a geriatric syndrome condition[a] (primary outcome)	Fracture (S32, S42, S52, S62, S72); hip fracture (S79); lower leg fracture (S82); osteoporosis with fracture (M80), pathologic fracture (M84[.3-.7]), osteonecrosis (M87); gait (R26); repeated falls (R29.6); syncope (R55); tripping (W00-W19); reduced mobility (Z74.0)
	Somnolence (R40); awareness (R41); dizziness (R42); malaise (R53)
	Unspecified urinary incontinence (R32); retention of urine, unspecified (R33.9); functional urinary incontinence (R39.81); stress incontinence (N39.3); other specified urinary incontinence (N39.4)
	Drug induced headache (G44.4); joint pain (M25.5); muscle weakness, rhabdomyolysis, spasm (M62.81-.83), myalgia (M79.1)
	Any of the above
Number of visits, any reason (secondary outcome	Includes telephone encounters with the advice nurse and other clinicians, clinic, emergency room, hospital, and laboratory visits.
	Serious Adverse Drug Withdrawal Effects (ADWEs)[b] *(secondary outcomes)*
Lower respiratory disease	Chronic lower respiratory diseases including acute exacerbations (J40-J47); influenza (J09-J11); pneumonia (J12-J18); bronchitis (J20-J22)
Cardiovascular	Transient ischemic attack (G45); ischemic heart disease (I20-I25); atrial fibrillation (I48); other arrhythmias (I49); heart failure (I50); stroke (I63); peripheral vascular dis (I73); arterial embolism/thrombosis (I74); septic arterial embolism (I76); chest pain (R07.9); tachycardia (R00.0); edema (R60); essential hypertension (I10); hypertensive heart

	disease, (I11); hypertensive chronic kidney disease (I12); hypertensive heart and chronic kidney disease (I13); secondary hypertension (I15); hypertensive crisis (I16); rheumatic heart failure (I09.81); nontraumatic subarachnoid hemorrhage (I60); nontraumatic intracerebral hemorrhage (I61); other and unspecified nontraumatic intracranial hemorrhage (I62); other cerebrovascular disease (I67)
Gastrointestinal	Gastroesophageal reflux disease (K21); upper gastrointestinal bleed due to gastritis (K29.71); gastric ulcer, gastritis, hemorrhage (K25[.0, .2, .4, .6]); duodenal ulcer hemorrhage (K26[.0, .2, .4, .6]); peptic ulcer, site unspecified, with hemorrhage (K27[.0, .2, .4, .6]); gastrojejunal ulcer with hemorrhage (K28[.0, .2, .4, .6]); gastrointestinal hemorrhage unspecified (K92.2); hematemesis (K92.2); melena (K92.1); acute hemorrhagic gastritis (K29); angiodysplasia of stomach, small intestine, or duodenum with hemorrhage (K31.80, K31.88, K55.8, K63.80, K63.88, K91.80); esophagitis (K20); other diseases of esophagus (K22); disorders of esophagus in diseases classified elsewhere (K23); gastric ulcer (K25); duodenal ulcer (K26); peptic ulcer, site unspecified (K27); gastrojejunal ulcer (K28); gastritis and duodenitis (K29)
All-cause deaths	Administrative information
Emergency department visits	Any cause
Hospitalizations	Any cause[c]

[a]Types of encounters used to capture geriatric syndrome include telephone encounters with the advice nurse and other clinicians, as well as clinic, emergency room, and hospital visits. For the latter, we use the admitting diagnosis. We require that encounters be separated by at least 48 hours.

[b]Emergency room visit or hospital discharge with a relevant diagnosis code.

[c]90% of hospitalizations are unscheduled.

STUDY PROTOCOL TABLE 2. Power estimates

Endpoint	Usual care (ratio 1:1)	Intention-to-treat	
		Intervention N=1,000	Minimum detectable difference[b, c]
Primary Effectiveness Outcomes: ADEs -- at final analysis			
Mean (SD) change in the number of medications	-0.80 (2.2)	-1.1	-0.3
Proportion with ≥1 geriatric syndrome condition[b]	46%	39%	8%
Secondary Effectiveness Outcome: ADEs – at final analysis			
Mean (SD) number of encounters	13.1 (9.8)	9.8	3.3
Safety outcomes: Serious ADWEs – at 2nd interim analysis			
Proportion with ≥1 lower respiratory disease	20%	29%	9%
Proportion with ≥1 cardiovascular	30%	40%	10%
Proportion with ≥1 gastrointestinal	17%	25%	8%
Proportion with death from any cause	5%	11%	6%
Proportion with ≥ ED visit	39%	49%	10%
Proportion with ≥1 hospitalization	18%	27%	9%

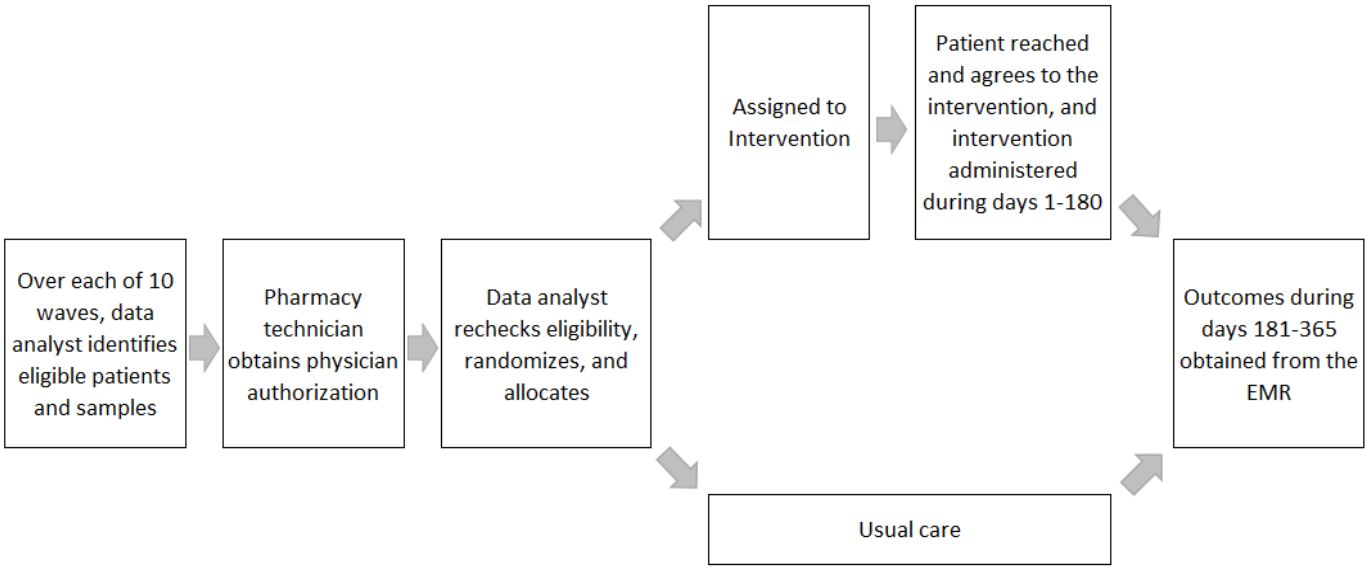
Abbreviations: ADE, adverse drug effect; ADWE, adverse drug withdrawal effect; ED, emergency department; SD, standard deviation.

[a]Expect loss of 6.5% of patients before 180 days due to death and disenrollment.

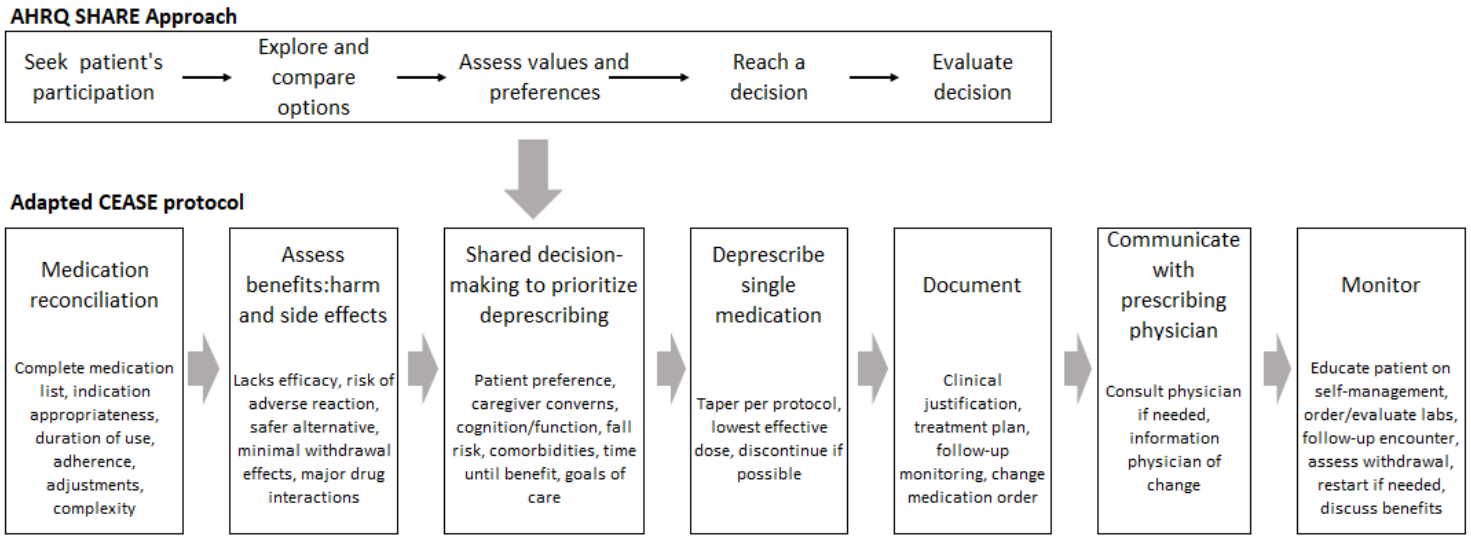
[b] We accounted for having two primary outcomes by using a Bonferroni correction to address multiple testing, such that an α level of 0.025 would be required for statistical significance of the primary outcomes. However, we also plan an interim analysis, and the final analysis of the primary outcomes would use a p-value of 0.024, accounting for both multiple testing of 1 primary outcome and 1 interim analysis. Per O'Brien-Fleming bounds for sequential testing, the interim analyses would use a p-value of 0.0026. (April 25, 2023 correction: The two-sided Bonferroni and O'Brien-Fleming bounds result in a significance level of alpha = 0.0015 for the interim analysis and 0.0244 for the final analysis.)

[c]The secondary outcomes of mean number of encounters and serious ADWEs will be tested at a level of α=0.05.

Study Protocol Figure 1. Study Schematic



Study Protocol Figure 2. Hyperpolypharmacy program tool [a,b]



[a] AHRQ Share from https://www.ahrq.gov/health-literacy/curriculum-tools/shareddecisionmaking/index.htm

[b] Patient was able to decline or withdraw consent for participation at any point