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Design of a pragmatic RCT of a pharmacist-led hyperpolypharmacy deprescribing intervention

Presenters:

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Disclosures

I have no disclosures to report.

Background

- 10-15% of Medicare patients use ≥10 prescription drugs -- increased risk of adverse drug events.
- *Ad hoc* deprescribing of single drug classes results in patients receiving multiple, potentially conflicting interventions.
- Health systems have started bundling deprescribing of multiple drug classes into a single intervention.
- However, knowledge about the outcomes of bundled deprescribing is inadequate.

Leadership, Design and Hypotheses

- Leadership
  - The intervention was developed by clinical leaders, pharmacists, and physician specialists under executive direction.
  - About midway, recruited an embedded researcher and team.
- Design
  - Designed over a two-year period.
  - Randomized performance improvement project.
  - Determined not to be research because the implementation was planned regardless of the evaluation.
  - Design was reviewed by an Stakeholder Advisory Committee.

Members of the External Stakeholder Committee

Name and Position	Engagement
Cynthia M. Boyd, MD MPH, Prof of Med, Epidemiol, and Health Policy Management at Johns Hopkins.	As co-PIs of the Deprescribing Network, Drs. Steinman and Boyd will assure sharing of knowledge, methods, and approaches between the present project and others under development in the Network. Drs. Boyd and Steinman are also active with Am Geriatric Soc (AGS) committees and will assist with dissemination to AGS members.
Michael Steinman, MD, Prof of Medicine, UCSF.	
Don Goldmann, MD, Chief Medical and Scientific Officer, Inst for Healthcare Improvement; Professor, Harvard University	Dr. Goldmann will provide liaison between the research group and the IHI, which has worked to bring improvement science into healthcare delivery for the past 25 years.
Sandra Simmons PhD, MA. Director of Vanderbilt Center for Quality Aging; Vanderbilt University Medical Center	Drs. Simmons and Vasilevskis are currently engaged in an RCT of deprescribing focused on patients undergoing care transitions. They will provide a broad perspective to assure relevance, scientific rigor, feasibility, and dissemination.
Eduard Vasilevskis, MD, MPH, Asst Prof; Vanderbilt University Medical Center	
Shannon Brownlee, MSc, Sr Vice President, Lown Institute; Co-founder, Right Care Alliance	Dr. Brownlee has extensive connects with leaders in healthcare transformation and with patient advocacy groups. She will assure relevance and clarity and assist with dissemination to her network.
Wade Thompson, PhD, Pharmacist, Fellow; University of Southern Denmark	Dr. Thompson understands the Canadian and Danish national healthcare systems for which he has been involved in developing deprescribing concepts, methods, and approaches.
Elizabeth Bayliss, MD, MSPH, Senior Clinician Investigator, Kaiser Permanente Colorado; Deprescribing Lead for the Measures Working Group	Dr. Bayliss has worked on complex patients and implementation for years. She straddles key academic and professional audiences as well as Kaiser Permanente researchers. She will help translate the findings to other audiences.

Overview

- Population
  - Patients aged ≥76 years using ≥10 prescription drugs
- Intervention
  - Collaborative practice agreements
  - Standard-of-care treatment protocols
  - AHRQ's SHARE approach to shared decision-making
  - CEASE deprescribing protocol
- Comparison group
  - Usual Care
- Outcome
  - Reduction in medication count
  - Reduction of Adverse Drug Effects (ADE)
  - Reduction in healthcare utilization
  - Adverse Drug Withdrawal Effects (ADWE) evaluated for safety

Population

- Include English- and non-English-language patients aged ≥76 years, with ≥12 months enrollment, ≥10 non-topical drugs filled ≥2 times in the past year.
- Exclude patients with history of transplant (estimated, 1%), on dialysis (2%), in hospice (1%), or under active treatment for cancer (2%).
- The expected number of eligible patients estimated to be was 8,660, representing 5% of members aged ≥76 years.

Table 1. Characteristics of Patients Identified for the Feasibility Study (N=8,660).

Characteristic		%
Age, years	76-79	39
	80-84	34
	≥85	27
Race/ethnicity	White	65
	Hispanic	9
	African-Am	7
	Asian/Pac Isl	10
	Other	9
	Unknown	1
Body mass index, kg/m2	<18.5	1
	18.5-24.9	22
	25-29.9	32
	≥30	42
	Not recorded	2
Cognition	Dementia/delirium	11
	Alzheimer's	4
	Mild cognitive imp	5
	Any of the above	14

Characteristic		%
Charlson comorbidities*	0	3
	1-2	16
	3-4	28
	5-6	29
	≥7	24
Number of drugs filled ≥2 times in the past year	10	41
	11	26
	12	15
	≥13	18
Number of ambulatory visits in 180 days	0-2	29
	3-4	16
	5-7	20
	≥8	33
Emergency dept visits in 180 days	No	62
	Yes	38
Hospitalization in 180 days	No	82
	Yes	18

Drug use

Statins (88%)

Beta-blockers (73%)

Aspirin and clopidogrel (54%)

Loop diuretics (52%)

Albuterol (51%)

Calcium channel blockers (47%)

Proton pump inhibitors (42%)

Insulin (36%)

Angiotensin receptor antagonists (35%)

Thyroid hormone (34%)

ACE inhibitors (30%)

Metformin (28%)

H2-receptor inhibitors (28%)

Insulin-release stimulators (26%)

Gabapentin (25%)

Potassium replacement (25%)

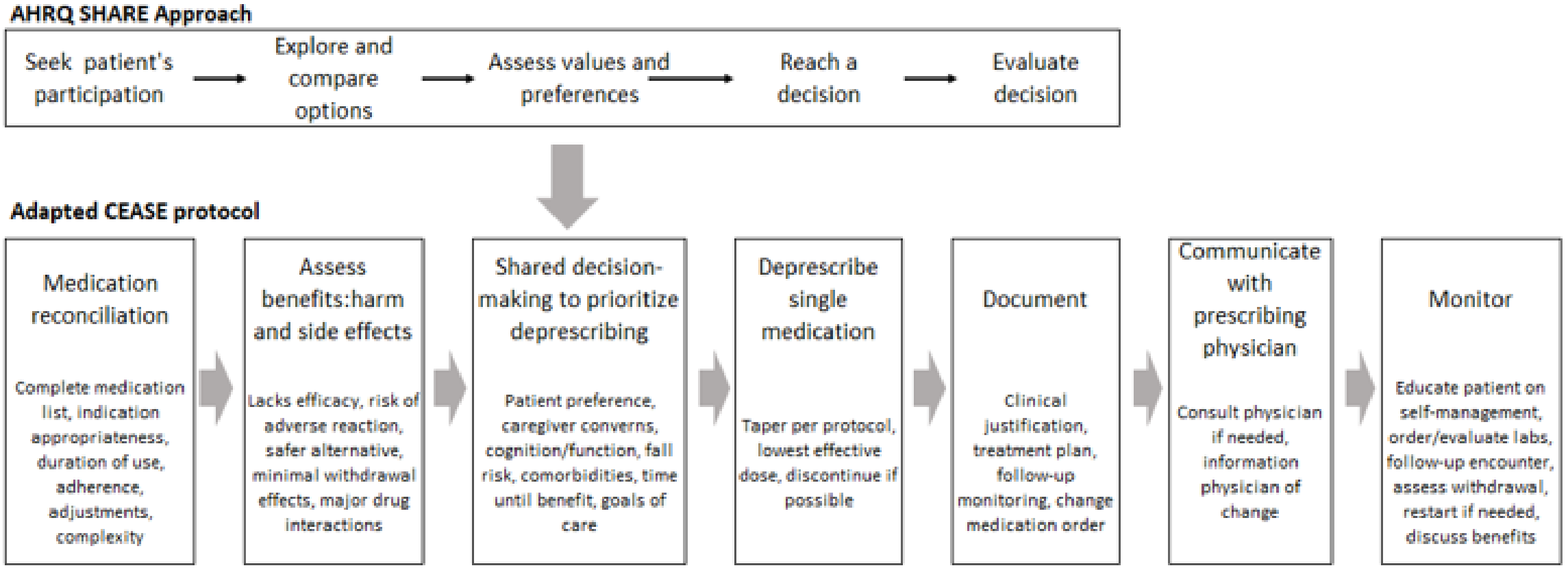
Anticonvulsants (25%)

Inhaled glucocorticoids (24%)

Combinations of inhaled beta-adrenergic and glucocorticoid (23%)

Other drugs (<20%)

INTERVENTION



*AHRQ Share from https://www.ahrq.gov/health-literacy/curriculum-tools/shareddecisionmaking/index.html.

Deprescribing protocols

- All guidelines are standard of care.
- Restated, in collaboration with specialists and with approval by the Pharmacy and Therapeutics Committee, to highlight guidance for older complex patients.
- For example, the guideline for coronary artery disease is a 2,500-word document largely directed to younger patients with relatively few comorbidities. Guidance for older complex patients is summarized in 134 words separated across antiplatelet therapy, blood pressure treatment, and lipid therapy, mostly at the end of the document.
- Relevant sections of the guideline were written into the intervention playbook.
- To assure safety, the deprescribing guidelines that will be used for the present project are conservative. For example, for antihypertensives, deprescribing will be performed for patients aged ≥85 years, while for antihyperglycemics, the HgA1c threshold is 9%. We will consider broadening indications for deprescribing in future studies.

Usual care

- Physician-directed deprescribing

- Existing pharmacy deprescribing programs
  - Targeted deprescribing of single drug class (e.g. diabetes, NSAIDs)
  - Drug use management initiatives (e.g. opioid reduction, polypharmacy)
  - Medication Therapy Management (MTM)

Outcome

- Obtained from the electronic medical record only.
- We will not use information recorded from days 0 to 179 after randomization to allow time for several deprescribing cycles.
- Primary outcomes:
  - Change in the average numbers of medications dispensed
  - A diagnosis of ≥1 condition for geriatric syndrome (next slide)
  - The average number of encounters for any reason
- Process measures (change in eligibility after consent, number of deprescribing telephone encounters, the time needed to administer the intervention, names of drugs deprescribed, deprescribing actions, time-course of deprescribing, etc.) to clarify facilitators, barriers, and opportunities to improve the intervention.

ADE and ADWE

Table 2. Operational definitions of primary outcomes and potential deprescribing harms

Endpoints	ICD-10 Definition	Frequency
	Primary Outcomes	
Number of medications	From dispensed medications recorded in the comprehensive, integrated pharmacy information system	Average, 11.3
≥1 encounter for a geriatric syndrome condition[a]	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 (Z74.0x)	17%
	Somnolence (R40), awareness (R41), dizziness (R42), malaise (R53)	20%
	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)	10%
	Drug induced headache (G44.4); joint pain (M25.5); muscle weakness, rhabdomyolysis, spasm (M62.81-.83), myalgia (M79.1)	21%
	Any of the above	46%
Avg no. of visits, any reason[b]	Includes telephone encounters with the advice nurse and other clinicians, clinic, emergency room, hospital, and laboratory visits.	13.1
	Serious Adverse Drug Withdrawal Effects (ADWEs)**	
Lower respiratory disease	Chronic lower respiratory diseases including acute exacerbations (J40-J47)	20%
Cardiovascular	Transient ischemic attack (G45); ischemic heart disease (I20-I25); afib (I48); other arrhythmias (I49), heart failure (I50); stroke (I63); peripheral vascular dis (I73); arterial embolism/thrombosis (I74); atheroembolism (I75); septic arterial embolism (I76); chest pain (R07.9), tachycardia (R00.0); edema (R60)	30%
Gastrointestinal	Gastroesophageal reflux disease (K21), upper gastrointestinal bleed due to gastritis (K29.71)	17%
All-cause deaths	Administrative information	5%
ED visits	Any cause	39%
Hospitalizations	Any cause[d]	18%

[a] Types of encounters used to capture geriatric syndrome will include telephone encounters with the advice nurse and other clinicians, as well as clinic, emergency room, and hospital visits. For the latter, we will use the admitting diagnosis. We will require that encounters be separated by at least 48 hours.
[b] Emergency room visit or hospital discharge with a relevant diagnosis code.
[c] Varies by symptom, with most averaging 0.5 to 1.5 with standard deviation 1.0 to 1.25.[38, 39]
[d] 90% of hospitalizations are unscheduled.

Analytic Approach

- Intention-to-treat includes all randomized patients, including patients who were not reached, were not offered a deprescribing recommendation, chose not to pursue deprescribing after discussion with the pharmacist, or were re-prescribed during follow-up.
- Per-protocol analyses.
- Medications and healthcare encounters: Mean change in the number from 180-365 days after allocation compared with the 6-month baseline before allocation. T-tests will be used to compare intervention and usual care groups.
- Proportion of patients with ≥1 encounter for geriatric syndrome from 180 to 365 days, chi-square test.
- Serious ADWEs will be assessed in four analyses, at 6, 12, and 18 months. Repeated interim analyses are prone to an increased false positive error rate, control for multiple testing using the O'Brien-Fleming bounds for sequential testing.
- If the analysis provides evidence that the risk of a serious deprescribing harm is increased, we will work with the physician to re-prescribe the patient.

Table 3. Minimum detectable differences of primary outcomes with 90% power

Endpoint	Usual care (ratio 1:1)	Intention-to-treat	
		Intervention N=1,000	Minimum detectable difference
Primary Outcomes			
Mean (SD) change in the number of medications	-0.80 (2.2)	-1.1	-0.3
Mean (SD) number of encounters	13.1 (9.8)	9.8	3.3
Mean (SD) EQ-5D health status**	81 (15)	84	3.0
Mean (SD) PATD**	2.40 (1.1)	2.56	0.16
Mean (SD) PRO-CTCAE***	1.00 (1.25)	0.89	0.11
Proportion with ≥1 geriatric syndrome condition	46%	39%	7%
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%

*Expect loss of 6.5% of patients before 180 days due to death and disenrollment.
**Expected values obtained from published literature for EQ-5D[44] and PATD.[45]
***Varies by symptom, with most averaging 0.5 to 1.5 with standard deviation 1.0 to 1.25.[38, 39]

Threats to Validity

Threat	Explanation	Strategy
Learning effect	The effectiveness of the pharmacist for deprescribing may improve over the course of the project.	Pharmacists will be trained and monitored, and we plan an analysis examining change in treatment effect over time.
Misspecification of timing of treatment effect	The benefits and harms of deprescribing various drugs may range from short to long, and misspecification of timing may result in a spurious negative finding.	We plan an analysis examining the timing of deprescribing and outcomes.
Data quality	Use of routinely collected information in the EMR may lack some standardization.	Should not differ between the intervention and usual care groups.
Missing variable	OTCs are not routinely recorded into the pharmacy data,	None, the effect is expected to be minimal and randomization should enable comparability.
Misspecification of outcome	Deprescribing may impact severity, but not cause the syndrome to resolve completely.	Analysis of healthcare utilization will address this threat.

Status

- Pilot study in October, pharmacists gained muscle memory, no changes to protocol
- Currently in Wave 2: 180 patients allocated to intervention, 180 to usual care
- No results yet

Thank you

Pharmacy

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- Chris Chang
- Andrew Fung
- Kerri Butler
- Virginia Chu

Researchers

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- Stephanie Prausnitz (project manager)
- Mubarika Alavi (data analyst)

Physicians

- Maisha Draves
- Carter Chang
- Michael Mason
- Ashok Krishnaswami

- Rita Hui (pharmacy researcher, reviewer)

- External stakeholder advisors

Questions?