Contemporary Clinical Trials 43 (2015) 53–59

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Rationale and design of the Randomized Evaluation to Measure Improvements in Non-adherence from Low-Cost Devices (REMIND) trial

Niteesh K. Choudhry [a,*], Alexis A. Krumme [a], Patrick M. Ercole [b], Charmaine Girdish [b], Danielle L. Isaman [a], Olga S. Matlin [b], Troyen A. Brennan [b], William H. Shrank [b], Jessica M. Franklin [a]

[a] Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 1620 Tremont Street, Suite 3030, Boston, MA 02120, United States
[b] CVS Health, One CVS Drive, Woonsocket, RI 02895, United States

ARTICLE INFO

Article history:
Received 11 March 2015
Received in revised form 9 May 2015
Accepted 11 May 2015
Available online 12 May 2015

Keywords:
Medication adherence
Cardiovascular disease
Low-cost reminder system

ABSTRACT

Background: Long-term adherence to prescription medications for the treatment of chronic disease remains low. While there are many contributors to suboptimal medication use, simple forgetfulness is widely believed to be central. Relatively simple devices may be a particularly cost-efficient and scalable way to promote adherence, however limited data exists about their ability to improve adherence in real-world settings.

Methods/design: The REMIND trial is a prospective, intent-to-treat randomized control trial to evaluate the impact on medication adherence of three simple, low-cost devices (Take-N-Slide™, the RxTimerCap™, and a standard pillbox). In March 2014, we enrolled 53,480 individuals 18 to 64 years old taking one to three medications to treat chronic disease whose prescription drug benefits were administered by CVS Caremark. The study's primary outcome is optimal adherence over the 12-month period after randomization. Using a randomization ratio of 1:2 between control and each intervention arm, the study has more than 80% power with an alpha of 5% to detect a 1% difference in the rate of optimal adherence between intervention and control groups and across intervention arms.

Discussion: The REMIND trial is the first randomized study to rigorously evaluate the impact of simple, low-cost reminder devices on medication adherence. The results will inform comparative cost effectiveness studies of reminder systems in improving medication adherence and clinical outcomes.

1. Background

Long-term adherence to essential prescription medications for the treatment of diabetes, hypertension, high cholesterol, and other chronic diseases remains extremely low [1]. Poor adherence results in preventable morbidity and mortality as well as an estimated $290 billion of avoidable healthcare spending annually [2]. While there are many contributors to suboptimal medication use, including medication cost, side-effects, medication burden, and patient perceptions, simple forgetfulness is widely believed to be central [3–5]. In surveys, 45%–60% of patients have reported forgetting to take their medications as the primary reason for non-adherence to their chronic disease medications [6,7].

Devices that remind patients to take their medications as prescribed may help address non-adherence by providing visual or auditory cues and can help with habit formation. Currently-available devices vary widely in cost and complexity and include standard plastic pill organizers, electronic pill bottles with visual cues and wireless monitoring, [8] and electronic boxes that interact with patients and caregivers and/or scan and send images of medications to remote staff members. Relatively simple devices, such as standard pillboxes or bottle caps with a digital timer, may be a particularly efficient and widely scalable way to promote adherence for the millions of patients who require only a few medications to manage their chronic conditions. In other words, even if their impact on adherence is relatively modest, the low cost of these devices means that they have the potential to be highly cost-effective.

* Corresponding author at: Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120, United States.
E-mail addresses: nchoudhry@partners.org (N.K. Choudhry), akrumme@partners.org (A.A. Krumme), patrick.ercole@CVSCaremark.com (P.M. Ercole), charmaine.girdish@CVSCaremark.com (C. Girdish), disaman@partners.org (D.L. Isaman), olga.matlin@CVSHealth.com (O.S. Matlin), troyen.brennan@CVSHealth.com (T.A. Brennan), william.shrank@CVSHealth.com (W.H. Shrank), jmfranklin@partners.org (J.M. Franklin).

http://dx.doi.org/10.1016/j.cct.2015.05.006
1551-7144/

While small studies have found that low-cost adherence reminder devices significantly improve adherence among patients on antiretroviral therapy, there is limited data about the ability of such devices to improve adherence in other therapeutic areas, especially in real-world naturalistic settings [9–11]. Further, the comparative effectiveness of these alternative solutions remains unevaluated.

2. Methods/design

2.1. Trial design

The Randomized Evaluation to Measure Improvements in Non-adherence from Low Cost Devices (REMIND) trial is a prospective, intent-to-treat randomized control trial to evaluate the impact on medication adherence of three simple and low-cost devices (the Take-N-Slide™, the RxTimerCap™, and a standard pillbox) among patients with one to three medications used to treat a chronic disease who were sub-optimally adherent to their prescribed treatment. The devices were mailed between March 19 and 24, 2014 and all patients will be followed for 12 months. The study is registered with clinicaltrials.gov (NCT02015806).

2.2. Study devices

The REMIND trial evaluates three adherence devices (Fig. 1). Take-N-Slide™, produced by i-c Innovations, Inc., is a patented strip that can be affixed to any pill bottle and has toggles for each day of the week that can be slid from red to green after each day's dose has been taken. The device provides visual cues that remind patients to take their medications and may also reduce "double dosing" patient errors. It can be removed and reused on a new prescription bottle. Commercially, a pack of 10 strips costs less than $5 through online mail order.

The RxTimerCap™ is a pill bottle cap with a digital timer that displays the time elapsed since the medication was last taken. The cap works like a stopwatch, resetting the timer after the cap has been opened, and thereby allowing patients to determine when the last dosage was taken. This device was developed by RxTimer Cap, LLC and is available commercially on their website for $14.95 for a pack of two.

The standard pillbox is a plastic organization box with one compartment for every day of the week, available for purchase online and at most pharmacies for as little as $2.50 [12]. Subjects randomized to the control arm were not contacted and did not receive any of the devices.

A: RxTimerCap™

B: Take-N-Slide™

C: Standard pillbox

Fig. 1. Three low-touch devices evaluated in REMIND Trial: Take-N-Slide™ (Panel A); RxTimerCap™ (Panel B); standard pillbox (Panel C).

2.3. Participants and randomization

We enrolled individuals 18 to 64 years of age whose prescription drug benefits were administered by CVS Caremark, a large pharmacy benefits manager that serves over 65 million individual members nationally [13]. We included only commercially-insured patients whose plan sponsor had given us permission to contact their members for this study and who were continuously eligible for pharmacy benefits in the 12 months prior to the start of the study. Patients enrolled in CVS Caremark's auto-refill at mail program, in which members elect to have medications shipped automatically to them at the time that refills are due, were excluded from the study.

Eligible subjects were identified using prescription claims data. To be included, patients must have filled between one and three oral maintenance medications for chronic disease in the 12-month period before February 2014, when eligibility for the study was evaluated (Appendix Table 1). Included chronic disease medications were those intended for the treatment of cardiovascular disease (defined as hypertension, hyperlipidemia, coronary artery disease, congestive heart failure, or diabetes), another non-depression chronic condition (defined as breast cancer; benign prostatic hypertrophy; schizophrenia, bipolar disorder, and anxiety; arrhythmia; Parkinson's disease; seizure and epilepsy) or depression. Because antidepressants, unlike the other medication classes in this study, are often not intended for life-long use [14,15], subjects were stratified prior to randomization based upon whether the only eligible medication was an antidepressant (see Fig. 2). Subjects in Stratum 1 may or may not have been on an antidepressant in addition to up to three medications to treat cardiovascular disease or another non-depression chronic disease.

Based upon prior research demonstrating larger effects from interventions targeting non-adherent patients than those that were more broadly applied [16], subjects were required to be suboptimally adherent to their qualifying medications. This was defined as a medication

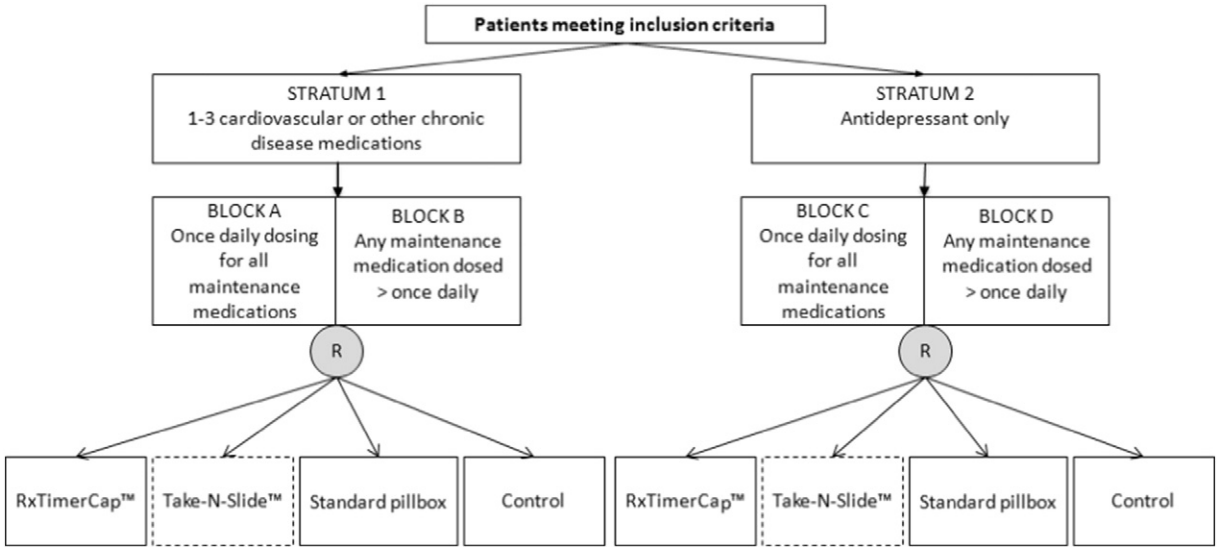

Fig. 2. Study design. Patients were stratified based upon the medications they were taking. Stratum 1 consisted of patients on one to three medications for cardiovascular or other non-depression chronic conditions who were suboptimally adherent to these therapies. Stratum 2 consisted of patients only taking an antidepressant and suboptimally adherent to this therapy. Within strata, randomization was conducted within blocks, based upon how many times per day their medications were dosed. Subjects in Blocks A and C were randomized to one of four arms (RxTimeCap, Take-N-Slide, pillbox or control), whereas subjects in Blocks B and D were randomized to one of three arms (RxTimeCap, pillbox or control), since the Take-N-Slide can only be used for medications that are dosed once per day.

possession ratio between 30% and 80% during the 12 months before the identification of study eligibility and was assessed using prescription claims data [17]. All drugs within a given class (e.g. sulfonylurea oral hypoglycemic agents) were considered interchangeable. Those subjects in Stratum 1 who were also taking an antidepressant were only required to be suboptimally adherent to their non-antidepressant medications. Patients in Stratum 2 were taking only antidepressant medications and no other chronic medications, and were required to be non-adherent to this drug.

Within each Stratum, the study cohort was block randomized to account for the fact that the Take-N-Slide™ can only be used for medications intended for once daily administration. In Block A and Block C, randomization was carried out in a 1:2:2:2 ratio of control to each of the three Low Touch Devices. In Block B and D, subjects were randomized in a 1:2:2 ratio of control to RxTimerCap™ and pillbox.

2.4. Study procedures

Once randomization was complete, subjects randomized to a study device arm were provided with devices free of charge distributed by mail along with an information card explaining their use. These subjects were provided with their assigned device for all of the chronic disease medications identified at the time of study eligibility, and were also given a dedicated telephone number to obtain additional information for the duration of the trial. Subjects do not receive additional devices during follow-up. Subjects randomized to control arm were not contacted.

2.5. Institutional review board and ethical approval

Because the study devices being tested are currently available for commercial use, and the fact that subjects receive the devices by mail and may choose not to use them, this study was considered to pose minimal risk to participants. As a result, no patient-level consent was sought. The institutional review board of Brigham and Women's Hospital and the Chesapeake Institutional Review Board approved this strategy and the use of a HIPAA Limited Dataset for the purpose of analysis.

2.6. Outcomes

The study's primary outcome (see Table 1) is optimal adherence over the 12-month period beginning from the date of randomization. The primary outcome will be optimal adherence to all cardiovascular or non-depression chronic disease medications in subjects only in study Blocks A and B. Secondary outcomes will assess: (a) optimal adherence to antidepressants among subjects whose only targeted therapy is an antidepressant and who are suboptimally adherent to this therapy (i.e. subjects in Blocks C and D); (b) optimal adherence to the targeted therapies in each block independently and (c) optimal adherence to cardiovascular medications among subjects who are suboptimally adherent to these medications at the time of randomization (i.e. a subset of subjects in Blocks A and B).

Optimal adherence will be evaluated by calculating a medication possession ratio (MPR) with CVS Caremark's administrative pharmacy claims [18]. The MPR is a highly valid and widely used measure of long-term adherence. It is calculated as the ratio of the total number of days on which the participant had medications available (numerator)

Table 1
Primary and secondary study outcomes and their measurement.

Outcome	Description
Primary	Optimal adherence to cardiovascular and non-depression chronic disease medications among subjects in Blocks A and B.
Secondary	Optimal adherence to antidepressants among subjects in Blocks C and D. Optimal adherence among patients in each of the study blocks individually. Optimal adherence to all cardiovascular medications among patients on these medications at the time of randomization (i.e. a subset of Blocks A and B).

Table 2
Baseline characteristics, Stratum 1.

Characteristic	Block A: medications dosed 1× daily				Block B: at least one medication dosed ≥1× daily		
	TakeNSlide N = 6330	RxTimerCap N = 6331	Pillbox N = 6334	Control N = 3167	RxTimerCap N = 6147	Pillbox N = 6148	Control N = 3075
Demographic							
Age, mean (SD)	48.1 (10.3)	48.2 (10.1)	48.1 (10.1)	48.1 (10.1)	45.0 (11.5)	44.9 (11.6)	45.0 (11.4)
Female gender	45.1%	46.3%	44.6%	46.2%	56.2%	54.8%	56.4%
Income (median in ZIP)[a]							
<$50,000	38.5%	38.5%	39.2%	38.8%	40.9%	40.5%	41.9%
$50,000 +	60.8%	60.6%	59.9%	60.6%	58.1%	58.8%	57.2%
Race, mean (SD) % black in ZIP[a]	10.5 (16.7)	10.3 (16.1)	10.6 (16.8)	10.8 (17.3)	10.7 (16.6)	10.4 (16.2)	10.7 (16.4)
Region							
Midwest	17.3%	16.6%	17.6%	16.0%	17.8%	17.9%	17.5%
Northeast	51.3%	50.5%	49.8%	51.7%	49.0%	48.5%	48.6%
South	25.9%	27.3%	27.1%	28.7%	27.4%	27.4%	27.9%
West	5.4%	5.6%	5.4%	5.6%	5.8%	6.2%	5.9%
Number of medication classes							
1	78.3%	79.0%	78.6%	78.3%	68.9%	70.4%	70.2%
2	20.6%	19.8%	20.3%	20.6%	28.8%	27.2%	27.7%
3	1.1%	1.1%	1.1%	1.1%	2.3%	2.5%	2.1%
Medication classes							
Breast cancer, %	1.2%	1.5%	1.3%	1.0%	0.9%	0.7%	0.7%
MPR, mean (SD)	0.60 (0.14)	0.58 (0.15)	0.58 (0.14)	0.58 (0.14)	0.60 (0.15)	0.56 (0.17)	0.61 (0.13)
High cholesterol	39.0%	39.3%	39.1%	38.0%	19.8%	20.7%	20.4%
MPR, mean (SD)	0.59 (0.14)	0.59 (0.14)	0.59 (0.14)	0.60 (0.14)	0.59 (0.14)	0.58 (0.15)	0.58 (0.15)
Benign prostatic hypertrophy	3.7%	3.5%	3.5%	3.5%	2.1%	2.1%	2.1%
MPR, mean (SD)	0.54 (0.15)	0.55 (0.15)	0.53 (0.15)	0.55 (0.15)	0.54 (0.15)	0.55 (0.15)	0.54 (0.15)
Coronary artery disease	0.4%	0.3%	0.4%	0.3%	0.1%	0.1%	0.1%
MPR, mean (SD)	0.57 (0.14)	0.56 (0.17)	0.56 (0.14)	0.49 (0.15)	0.55 (0.15)	0.62 (0.14)	0.48 (0.20)
Diabetes	2.0%	2.5%	2.3%	2.6%	16.7%	17.6%	16.8%
MPR, mean (SD)	0.55 (0.15)	0.56 (0.14)	0.56 (0.15)	0.57 (0.14)	0.55 (0.15)	0.56 (0.15)	0.56 (0.15)
Heart failure	2.3%	2.3%	2.5%	2.6%	4.4%	4.8%	4.4%
MPR, mean (SD)	0.54 (0.15)	0.53 (0.15)	0.53 (0.15)	0.52 (0.14)	0.55 (0.14)	0.55 (0.15)	0.55 (0.15)
Hypertension	56.1%	55.6%	56.0%	57.2%	41.6%	40.3%	40.5%
MPR, mean (SD)	0.60 (0.14)	0.60 (0.14)	0.60 (0.15)	0.60 (0.14)	0.59 (0.15)	0.58 (0.15)	0.58 (0.15)
Mental health	1.6%	1.5%	1.4%	1.6%	2.2%	2.4%	2.4%
MPR, mean (SD)	0.55 (0.14)	0.56 (0.15)	0.54 (0.15)	0.55 (0.15)	0.56 (0.15)	0.54 (0.15)	0.56 (0.16)
Arrhythmia	0.03%	0.03%	0.05%	0.03%	0.3%	0.3%	0.4%
MPR, mean (SD)	0.44 (0.01)	0.60 (0.15)	0.64 (0.07)	N/A	0.56 (0.17)	0.61 (0.17)	0.53 (0.14)
Parkinson's disease	0.00%	0.02%	0.03%	0.00%	0.1%	0.1%	0.1%
MPR, mean (SD)	N/A	N/A	0.49 (0.15)	N/A	0.53 (0.12)	0.59 (0.20)	0.61 (0.21)
Seizure	4.3%	3.5%	3.9%	3.5%	24.7%	24.3%	24.9%
MPR, mean (SD)	0.54 (0.14)	0.53 (0.15)	0.54 (0.15)	0.55 (0.14)	0.54 (0.15)	0.55 (0.15)	0.55 (0.15)

[a] <1% of data missing for these variables due to unavailability in 2010 Census data.

and the total number of possible days the participant could have had the medication on hand (denominator). The denominator is the total number of days within the measurement period (12 months), and is therefore the same for all participants. MPR will be calculated for each medication identified at the start of the study. Medications with similar molecular structures and/or which are never used additively (e.g. two

Table 3
Baseline characteristics, Stratum 2.

Characteristic	Block C: medications dosed 1× daily				Block D: at least one medication dosed ≥1× daily		
	TakeNSlide N = 2766	RxTimerCap N = 2768	Pillbox N = 2770	Control N = 1385	RxTimerCap N = 2503	Pillbox N = 2503	Control N = 1253
Demographic							
Age	38.5 (11.8)	38.8 (12.1)	38.7 (12.1)	39.0 (11.9)	40.0 (11.7)	39.1 (11.9)	39.1 (11.8)
Female gender	70.4%	73.1%	69.8%	69.0%	72.2%	71.5%	71.3%
Income (median in ZIP)[a]							
<$50,000	32.4%	33.5%	33.0%	33.5%	35.0%	34.9%	35.1%
$50,000 +	67.1%	65.7%	66.1%	66.0%	64.0%	64.5%	64.4%
Race (mean % black in ZIP)[a]	0.07 (0.11)	0.07 (0.11)	0.07 (0.12)	0.07 (0.12)	0.07 (0.12)	0.07 (0.12)	0.08 (0.12)
Region							
Midwest	22.7%	21.6%	22.1%	20.9%	20.1%	19.3%	20.9%
Northeast	51.2%	51.0%	50.2%	52.1%	52.6%	52.3%	52.0%
South	20.9%	21.6%	21.3%	22.3%	20.5%	21.5%	19.6%
West	5.2%	5.7%	6.4%	4.7%	6.8%	6.9%	7.4%
Medication class							
Depression	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Mean MPR	0.57 (0.15)	0.57 (0.15)	0.57 (0.15)	0.57 (0.15)	0.56 (0.15)	0.57 (0.15)	0.57 (0.15)

[a] <1% of data missing for these variables due to unavailability in 2010 Census data.

different statins) will be considered to be interchangeable and are accounted for in the MPR metric. Subjects will be defined as optimally adherent if their MPR is equal to or greater than 80% for each medication considered for that outcome.

Tertiary outcomes will evaluate adherence as a continuous measure. In this case, adherence will be assessed based upon the mean MPR of all medications considered for that outcome.

2.7. Analytic plan

We will report means and frequencies of prerandomization variables separately for intervention and control subjects. Comparison of these values will be made with t-tests and chi square tests and their non-parametric analogs, as appropriate.

Outcomes will be evaluated based on intention-to-treat principles. In the primary analysis, all outcomes will be compared between study arms using standard logistic or linear regression, depending on the outcome. In a secondary analysis, all outcomes will be compared between study arms using a generalized estimating equation (GEE) with a logit or identity link, depending on the outcome, to account for clustering of subjects within plan sponsors and will be adjusted for any differences in baseline characteristics between study groups that are believed, through analytical assessment and subject-matter expertise, to be confounders of the intervention–outcome association.

2.8. Sample size considerations

A sample size calculation was conducted to estimate sufficient statistical power to detect relatively small changes in study outcomes. For the primary outcome, using a randomization ratio of 1:2 between control and each intervention arm and assuming a rate of optimal adherence of 2% in the control group, we will have 80% power with an alpha of 5% to detect a 1% difference in the rate of optimal adherence between intervention and control and among each of the intervention arms with 3050 in control and 6100 in each intervention arm, for a total of 21,350 and 15,250 in Block A and Block B, respectively. The assumption of a 2% adherence improvement in the control arm is based on the observation that adherence is dynamic, and thus that some patients in this population of subjects suboptimally-adherent at baseline will become optimally adherent during follow-up [19,20]. Under the assumption that approximately 20% of patients in intervention arms would use the devices, a 1% adherence improvement relative to control translates into a 7% improvement in the rate of optimal adherence among those intervened upon. Improvements of this magnitude have been observed in other adherence-improvement interventions and are believed to be clinically meaningful [21]. Pilot data collected in January 2014 indicated that 22,197 and 15,410 subjects would be eligible for Blocks A and C, and Blocks B and D, respectively.

2.9. Baseline characteristics

The study was launched in March 2014 with mailings over 4 days of all study devices, with a final sample size of 22,162, 15,370, 9689, and 6259 in Blocks A, B, C, and D, respectively (see Appendix Table 2).

Baseline characteristics of the study participants are presented by Stratum in Tables 2 and 3. Across all study arms patients had a mean age of 45 years (SD = 12) and were 56% female; patients in Blocks C and D were generally younger and more likely to be female. Based on zip code level information, average median income was $59,920 (SD = $22,166) and 9.5% (SD = 15.3%) were black. On average, 78.6% and 69.8% of patients in Blocks A and B, respectively, were taking medications for only one chronic disease.

2.10. Limitations

There are several limitations to this trial. Patients randomized to interventions will receive the devices free of charge, and thus, the extent to which the results from this study may be attenuated by cost-related non-adherence should these devices be instead offered at a small charge is unknown. In addition, the devices were delivered by mail and therefore we are unable to measure actual device use and their barriers to utilization. For patients randomized to the RxTimerCap intervention, investigators used pharmacy data to predict which size cap would fit over members' existing bottle(s). While we anticipate differences in predicted versus actual cap size to be rare, a discrepancy could potentially prevent a patient from using the device.

While the magnitude of the effect used in the power calculation does not impact the likelihood of false positives for an individual test, cumulatively, the chance of finding at least one false positive among several tests is greater than 5%. However, the multiple comparisons among the treatment arms share the same four exposure groups; therefore, we do not expect the familywise error rate to differ greatly from 5%. In fact, a recent review of multi-arm trials showed that more than half of all randomized trials with multiple exposure groups do not adjust for multiple comparisons, reasoning that if each exposure was compared with control in a separate trial, no adjustment would be necessary [22].

Finally, this study measures statistically significant improvements in medication adherence and not the extent of clinical benefit subjects derive from appropriate management of their chronic condition. Nonetheless, expected improvements in observed adherence in these trials are consistent with the literature and most quality measures, which establish a threshold of 80% MPR as a clinically meaningful level of adherence [20,21,23–25]. The results may not be fully generalizable to older and/or Medicare-insured populations and those with greater maintenance medication complexity.

3. Discussion

The REMIND trial is the first randomized study to rigorously evaluate the impact of reduced medication therapy complexity through simple, low-cost reminder systems on medication adherence. This study is powered to detect differences between devices and usual care as well as between devices in three adherence-related outcomes. Because of the pragmatic nature of this study, we anticipate relatively low average utilization rates of the study devices. As a result, if we are to detect small average treatment effects it will likely be the case that the improvements in adherence for those individuals that do use the devices will be clinically meaningful. Further, should there be any improvement in adherence from the studied devices, their low cost will likely mean that their use is cost-effective or perhaps even cost-saving. Results from this study may inform future comparative cost-effectiveness studies of the wide variety of alternative strategies for improving medication adherence and may identify which of the low-cost devices may be more efficient to use in conjunction with other patient engagement strategies.

Competing interests

This work was supported by an unrestricted grant from CVS Health to Brigham and Women's Hospital. The trial was designed collaboratively by investigators from the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School and CVS Health.

Authors' contributions

All authors were involved with the conduct and design of the trial. Investigators from CVS Health are responsible for the day-to-day operations of the trial, as described above. All data analysis and outcomes assessment will be performed independently of the trial sponsor.

Appendix A

Appendix Table 1
Oral maintenance medications.

Maintenance medication for the treatment of chronic disease	Medication classes
Cardiovascular	
High cholesterol	Statin and statin combinations
	Bile acid sequestrants
	Fibrates
	Nicotinic acid derivatives
Coronary artery disease	Isosorbide
	Ranolazine
	Platelet inhibitors
Diabetes	Amylin analogs
	GLP-1 receptor agonists
	Sulfonylureas
	Biguanides
	Meglitinide analogs
	Alpha-glucosidase inhibitors
	DPP-4 inhibitors
	Thiazoledinediones
Heart failure	Cardiac glycoside
	Selective aldosterone receptor agonists
	Nitrate and vasodilator combinations
	Spironolactone
	Diuretics
Hypertension	Angiotensin-converting enzyme inhibitors
	Angiotensin II receptor blockers
	Direct renin inhibitors
	Anti-adrenergic antihypertensives
	Beta-blockers
	Diuretics
	Calcium-channel blockers
Non-cardiovascular	
Breast cancer	Tamoxifen
	Aromatase inhibitors
	Toremifene
Benign prostatic hypertrophy	Alpha-blockers
	Finasteride
	Combination BPH agents
Schizophrenia, bipolar disorder, anxiety	Antipsychotics – atypical
	Antianxiety medications
Arrhythmia	Antiarrhythmics
Parkinson's disease	Carbidopa – Levodopa combination
	COMT inhibitors
	Monoamine oxidase inhibitors
	Carbidopa
Seizure or epilepsy	Anticonvulsants
Additional maintenance medication condition	Medication classes
Depression	Alpha-2 receptor antagonists
	Monoamine oxidase inhibitors
	Modified cyclics
	Tricyclic agents
	Selective serotonin reuptake inhibitors
	Serotonin and norepinephrine reuptake inhibitors
	Thienbenzodiazepine and SSRI combination

References

[1] P.M. Ho, C.L. Bryson, J.S. Rumsfeld, Medication adherence: its importance in cardiovascular outcomes, Circulation 119 (23) (2009) 3028–3035, http://dx.doi.org/10.1161/CIRCULATIONAHA.108.768986.

[2] National Community Pharmacists Association, Medication adherence in America: a national report card, National Community Pharmacists Association, Alexandria, 2013. (http://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Abridged.pdf. Accessed 19 Jun 2014).

[3] World Health Organization, Adherence to long-term therapies: evidence for action, World Health Organization, Geneva, 2003. (http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1. Accessed 19 Jun 2014).

[4] A. Bardel, M.A. Wallander, K. Svardsudd, Factors associated with adherence to drug therapy: a population-based study, Eur. J. Clin. Pharmacol. 63 (3) (2007) 307–314, http://dx.doi.org/10.1007/s00228-006-0246-4.

[5] J.A. Gazmararian, S. Kripalani, M.J. Miller, K.V. Echt, J. Ren, K. Rask, Factors associated with medication refill adherence in cardiovascular-related diseases: a focus on health literacy, J. Gen. Intern. Med. 21 (12) (2006) 1215–1221, http://dx.doi.org/10.1111/j.1525-1497.2006.00591.x.

[6] A.S. Gadkari, C.A. McHorney, Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Serv. Res. 12 (2012) 98, http://dx.doi.org/10.1186/1472-6963-12-98.

[7] B.M. Egan, D.T. Lackland, N.E. Cutler, Awareness, knowledge, and attitudes of older Americans about high blood pressure: implications for health care policy, education, and research, Arch. Intern. Med. 163 (6) (2003) 681–687.

[8] K.D. Checchi, K.F. Huybrechts, J. Avorn, A.S. Kesselheim, Electronic medication packaging devices and medication adherence: a systematic review, JAMA 312 (12) (2014) 1237–1247, http://dx.doi.org/10.1001/jama.2014.10059.

[9] S.C. Kalichman, D. Cain, C. Cherry, M. Kalichman, H. Pope, Pillboxes and antiretroviral adherence: prevalence of use, perceived benefits, and implications for electronic medication monitoring devices, AIDS Patient Care STDS 19 (12) (2005) 833–839, http://dx.doi.org/10.1089/apc.2005.19.833.

[10] M.L. Petersen, Y. Wang, M.J. van der Laan, D. Guzman, E. Riley, D.R. Bangsberg, Pillbox organizers are associated with improved adherence to HIV antiretroviral therapy and viral suppression: a marginal structural model analysis, Clin. Infect. Dis. 45 (7) (2007) 908–915, http://dx.doi.org/10.1086/521250.

[11] S. Kripalani, L.E. Henderson, T.A. Jacobson, V. Vaccarino, Medication use among inner-city patients after hospital discharge: patient-reported barriers and solutions, Mayo Clin. Proc. 83 (5) (2008) 529–535, http://dx.doi.org/10.4065/83.5.529.

[12] Pill organizers, Walgreens, Deerfield, 2014. (http://www.walgreens.com/store/c/medicines-and-treatments-pill-organization-pill-organizers/ID=361563&Eon=361563-tier3. Accessed 8 Sept 2014).

[13] CVS Caremark, Corporate social responsibility report, CVS Caremark, Woonsocket, 2012. (http://www.cvshealth.com/sites/all/modules/custom/csr_report/files/2012-CVS-Caremark-CSR-Report.pdf. Accessed 8 Sept 2014).

[14] G.A. Fava, Can long-term treatment with antidepressant drugs worsen the course of depression? J. Clin. Psychiatry 64 (2) (2003) 123–133.

[15] R.S. El-Mallakh, Y. Gao, J.R. Roberts, Tardive dysphoria: the role of long term antidepressant use in inducing chronic depression, Med. Hypotheses 76 (6) (2011) 769–773, http://dx.doi.org/10.1016/j.mehy.2011.01.020.

[16] S.L. Cutrona, N.K. Choudhry, M.A. Fischer, A.D. Servi, M. Stedman, J.N. Liberman, T.A. Brennan, W.H. Shrank, Targeting cardiovascular medication adherence interventions, J. Am. Pharm. Assoc. (2003) 52 (3) (2012) 381–397, http://dx.doi.org/10.1331/JAPhA.2012.10211.

[17] R. Sikka, F. Xia, R.E. Aubert, Estimating medication persistency using administrative claims data, Am. J. Manag. Care 11 (7) (2005) 449–457.

[18] T.A. Brennan, T.J. Dollear, M. Hu, O.S. Matlin, W.H. Shrank, N.K. Choudhry, W. Grambley, An integrated pharmacy-based program improved medication prescription and adherence rates in diabetes patients, Health Aff. (Millwood) 31 (1) (2012) 120–129, http://dx.doi.org/10.1377/hlthaff.2011.0931.

[19] M.A. Brookhart, A.R. Patrick, S. Schneeweiss, J. Avorn, C. Dormuth, W. Shrank, et al., Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use, Arch. Intern. Med. 167 (8) (2007) 847–852, http://dx.doi.org/10.1001/archinte.167.8.847.

[20] J.M. Franklin, W.H. Shrank, J. Pakes, G. Sanfelix-Gimeno, O.S. Matlin, T.A. Brennan, N.K. Choudhry, Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence, Med. Care 51 (9) (2013) 789–796, http://dx.doi.org/10.1097/MLR.0b013e3182984c1f.

[21] N.K. Choudhry, R.J. Glynn, J. Avorn, J.L. Lee, T.A. Brennan, L. Reisman, et al., Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes, Am. Heart J. 167 (1) (2014) 51–58, http://dx.doi.org/10.1016/j.ahj.2013.09.014 (e5).

Appendix Table 2
Final sample sizes for primary and secondary outcomes.

Outcome	Medications dosed 1× daily				At least one medication dosed ≥1× daily			Total			
	Take-N-Slide	RxTimer Cap	Pillbox	Control	RxTimer Cap	Pillbox	Control	Take-N-Slide	RxTimer Cap	Pillbox	Control
Primary	6330	6331	6334	3167	6147	6148	3075	6330	12,478	12,482	6242
Secondary (1)	2766	2768	2770	1385	2503	2503	1253	2766	5271	5273	2638
Secondary (2)	5716	5757	5761	2893	4451	4478	2228	5716	10,208	10,239	5121

[22] J.M. Wason, L. Stecher, A.P. Mander, Correcting for multiple-testing in multi-arm trials: is it necessary and is it done? Trials 15 (2014) 364, http://dx.doi.org/10.1186/1745-6215-15-364.
[23] T.J. Bramley, P.P. Gerbino, B.S. Nightengale, F. Frech-Tamas, Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations, J. Manag. Care Pharm. 12 (3) (2006) 239–245.
[24] C.J. Hope, J. Wu, W. Tu, J. Young, M.D. Murray, Association of medication adherence, knowledge, and skills with emergency department visits by adults 50 years or older with congestive heart failure, Am. J. Health Syst. Pharm. 61 (19) (2004) 2043–2049.
[25] HEDIS, Summary table of measures, product lines and changes, NCQA, Washington, 2014. (http://www.ncqa.org/Portals/0/HEDISQM/HEDIS2014/List_of_HEDIS_2014_Measures.pdf. Accessed 8 May 2014).