

**Randomized Evaluation to Measure Improvements in Nonadherence from Low-Cost Developed**

**(REMIND Trial)**

FINAL STUDY PROTOCOL

---

## Background

---

Long-term adherence to essential prescription medications for the treatment of diabetes, hypertension, high cholesterol, and other chronic diseases is only 50%.<sup>1</sup> Poor adherence results in preventable morbidity and mortality as well as an estimated \$290 billion of avoidable healthcare spending annually.<sup>2</sup> Potential reasons for non-adherence include cost, medication burden, side-effects, and simple forgetfulness.

Several simple and inexpensive devices have been created to remind patients to take their medications by providing visual cues and helping with habit formation. For example, Take-N-Slide is a plastic strip that attaches to the side of a pill bottle with tabs for each day of the week that patients toggle from green to red each day after taking their medication. The RxTimer Cap is a digital timer on the cap of a pill bottle that shows the amount of time since the bottle was last opened and thus provides a time-based visual reminder for medication taking.

While these products have intuitive appeal and a number of them are commercially available, their ability to improve adherence remains unknown. Further, standard pillboxes are also inexpensive and have been used for decades, and the comparative effectiveness of these alternative products has not been evaluated.

---

<sup>1</sup> World Health Organization. Adherence to Long-Term Therapies: Evidence for Action. Geneva, Switzerland: World Health Organization; 2003. Available at: [www.who.int/chronic\\_conditions/en/adherence\\_report.pdf](http://www.who.int/chronic_conditions/en/adherence_report.pdf). Accessed October 21, 2013.

<sup>2</sup> National Community Pharmacists Association. Medication Adherence in America: A National Report: National Community Pharmacists Association; 2013. Available at: [http://www.ncpanet.org/pdf/reportcard/AdherenceReportCard\\_Abridged.pdf](http://www.ncpanet.org/pdf/reportcard/AdherenceReportCard_Abridged.pdf). Accessed October 22, 2013.

---

## Research Goal and Objectives

---

The objective of this study is to determine whether adherence to oral maintenance medications differ for patients who are randomized to receive a Take-N-Slide, a RxTimer Cap, a pillbox, or none of these devices. Because care recommendations and treatment durations for depression differ from other chronic conditions, the primary outcome will evaluate adherence among patients sub-optimally adherent to targeted medications excluding antidepressants.

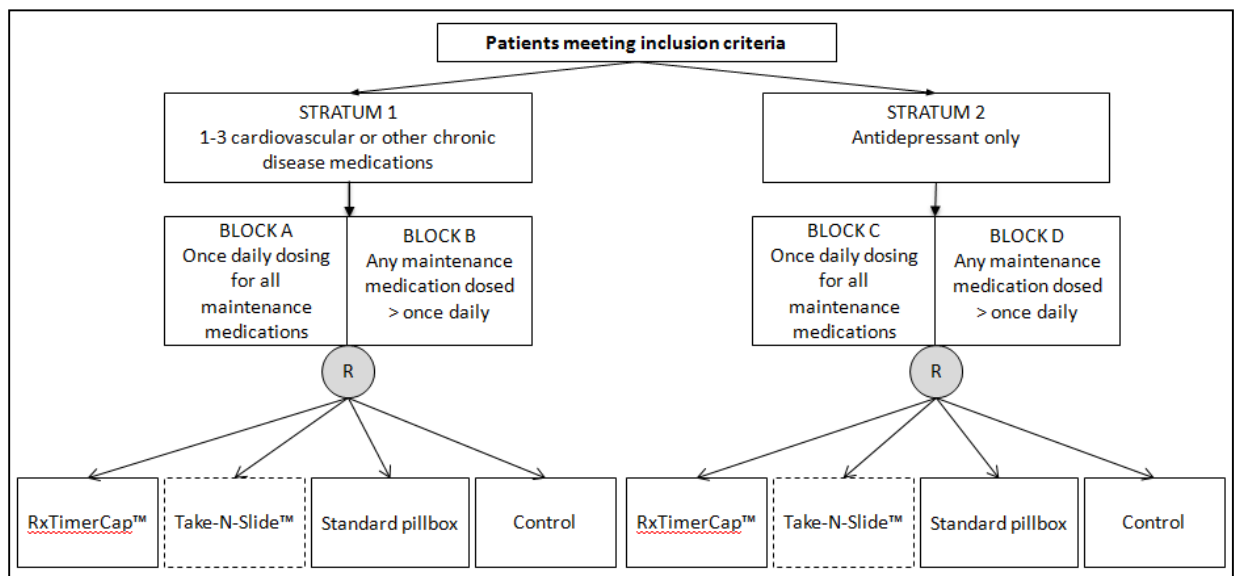
---

## Overall Design

---

Figure 1 illustrates the overall study design

**Figure 1: Study Design**



This study is a prospective, intent-to-treat, randomized control trial that will evaluate the impact of the three devices on medication adherence. Randomization will be stratified based upon which medications subjects had filled prior to randomization: (1) cardiovascular or other chronic disease medications or (2) an antidepressant. Within these strata, all patients meeting

the inclusion criteria described below will be randomized in two blocks based upon the number of times per day filled medications were intended to be taking.

---

### **Patient Inclusion and Exclusion Criteria**

---

The eligible member pool will consist of patients whose prescription drug benefits are administered by CVS Caremark, whose plan sponsor (i.e. the entity that provides the individual with insurance benefits) is a commercial plan, and whose sponsor has provided CVS Caremark with permission to contact their members with regard to this study.

Specific inclusion criteria are:

- 18 to 64 years of age at the time of identification for study eligibility;
- Have 1 to 3 oral maintenance medications with at least one medication intended to a chronic condition (defined as hypertension; hyperlipidemia; coronary artery disease; congestive heart failure; diabetes; breast cancer; benign prostatic hypertrophy; schizophrenia, bipolar disorder, anxiety; Parkinson's disease; seizure and epilepsy) or depression that has been filled via mail order or at a retail pharmacy within 150 days prior to being identified as being eligible for the study;
- Poorly adherent to at least one targeted drug class a member is taking, defined as MPR or 30%-80% in at least one targeted drug class a member is taking during the 12 months preceding identification of study eligibility;
- For patients taking antidepressants in addition to other targeted medications, patients need only be poorly adherent to their non-antidepressant medications;

- Eligible for pharmacy benefits during the 12 months prior to being identified as being eligible for the study and expected to be eligible for pharmacy benefits through the end of the evaluation period

Specific exclusion criteria are:

- Not enrolled in Ready Fill at Mail (a pharmacy benefit program whereby members elect to have medications shipped automatically to them at the time of refill due date or prescription renewal).

These criteria will be evaluated using routinely collected administrative pharmacy claims data.

---

## **Randomization**

---

All members meeting the inclusion and exclusion criteria will be enrolled in the study (see below got consent) stratified based on the frequency with which their medications are (or could possibly be) taken.

Individuals whose medications are all intended for once daily use (Blocks A and C) will be randomized in a 1:2:2:2 ratio to one of the following four groups:

- (1) Control group: usual care;
- (2) Intervention 1: Take-N-Slide;
- (3) Intervention 2: PillMinder;
- (4) Intervention 3: Rx Timer Cap.

Because the Take-N-Slide only has a yes/no toggle for each day of the week, patients who are on a medication that is or could be used more than once per day (Blocks B and D), will be randomized in a 1:2:2 ratio to one of the following three groups:

- (1) Control group: usual care;
- (2) Intervention 1: PillMinder;
- (3) Intervention 2: Rx Timer Cap.

Randomization will be carried out using a random number generator. More patients will be randomized to the intervention than the control groups to maximize our ability to detect differences between the devices (see Sample Size Estimations, below). Once a member is assigned to a study group, s/he will remain assigned into the given arm for the duration of the study.

---

### **Study Devices (Appendix A)**

---

The Take-N-Slide can be affixed onto any pill bottle. The patented strip has toggles for each day of the week which are meant to be slid after taking a medication. The device is intended to provide visual cues to remind patients if they have forgotten to take their medication and may also reduce “double dosing” patient errors. Each Take-N-Slide can be removed and reused for the next prescription bottle.

The RxTimerCap is a pill bottle with a digital timer on the cap that shows the time elapsed since

the medication was last taken. The cap works like a stopwatch, automatically resetting the timer after the cap has been opened. Patients can immediately see when the last dosage was taken in order to prevent unnecessary or missed dosing.

The pillbox is a plastic organization box with one compartment for every day of the week.

---

### **Study Procedures**

---

Patients randomized to one of the devices will receive a one-time mailing with the appropriate device(s) along with an information card explaining its use. Patients will receive a device for each of the maintenance medications when they were using at the time of identification for study eligibility. For example, a patient on 3 maintenance medications randomized to the RxTimer Cap arm will receive 3 RxTimer Caps. If patients have questions about their devices, the information card that arrives with it will provide a dedicated CVS Caremark telephone number at which they can get additional information. Patients will receive no other study-specific communication nor will they receive additional devices during follow-up. Controls will not receive a device and will not be contacted.

As a quality control measure, a subset of 600 intervention group participants will be surveyed via telephone or, upon follow-up, email regarding the delivery, function, and satisfaction of the devices. Survey participants will be randomly selected at 2 weeks, 3 months, and 6 months following product shipment.

---

## Outcomes and Analysis

---

### *(a) Outcomes*

The primary study outcome will be optimal adherence to all cardiovascular or non-depression chronic disease medications (defined in Patient Inclusion and Exclusion Criteria above) over the 12-month period beginning from the date of randomization in Stratum 1. This outcome will be assessed using highly standard methods applied to administrative pharmacy claims that are routinely collected as part of CVS Caremark's business practices.<sup>3</sup> Optimal adherence will be defined as a Medication Possession Ratio (MPR) equal to or greater than 0.80. MPR is the ratio of the total number of days on which the participant had medications available (numerator) 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 maintenance medication identified at the start of the study and patients will be defined as optimally adherent if their MPR is equal to or greater than 0.80 for each of their therapies.

Secondary outcomes will assess (a) optimal adherence to antidepressants among patients whose only targeted therapy is an antidepressant (i.e. patients in Stratum 2); (b) optimal adherence to the targeted therapies in each study block (A through D), independently; (c) optimal adherence to cardiovascular medications among patients who are poorly adherent to these medications at the time of randomization (i.e. a subset of patients in blocks A and B).

---

<sup>3</sup> Brennan TA, Dollear TJ, Hu M, Matlin OS, Shrank WH, Choudhry NK, Grambley W. An integrated pharmacy-based program improved medication prescription and adherence rates in diabetes patients. *Health Aff.* 2012;31:120-9



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.

*(b) Analysis Plan*

All analyses will be conducted based on intention-to-treat principles. The baseline characteristics of patients will be compared with t-tests and chi square tests, and their non-parametric analogues, as appropriate.

The primary (optimal adherence in Stratum 1) and secondary (optimal adherence in Stratum 2, optimal adherence to cardiovascular medications and optimal adherence in each study block independently) outcomes will be compared between study arms using standard logistic regression, adjusting for study block in the regression model.

In supplemental analyses, all outcomes will be compared between study arms using a generalized estimating equation (GEE) with a logit or linear 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.

---

## Sample Size Estimations

---

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 3,050 in control and 6,100 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 poorly-adherent at baseline will become optimally adherent during follow-up.<sup>45</sup>

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.<sup>6</sup>

---

<sup>4</sup> Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. *Archives of internal medicine*. 2007;167(8):847-52. doi:10.1001/archinte.167.8.847

<sup>5</sup> Franklin JM, Shrank WH, Pakes J, Sanfelix-Gimeno G, Matlin OS, Brennan TA, Choudhry NK. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. *Med Care*. 2013;51(9):789-96

<sup>6</sup> Choudhry NK, Glynn RJ, Avorn J, Lee JL, Brennan TA, Reisman L et al. Untangling the relationship between medication adherence and post-myocardial infarction outcomes: medication adherence and clinical outcomes. *American heart journal*. 2014;167(1):51-8 e5. doi:10.1016/j.ahj.2013.09.014

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.

---

### **Recruitment and Informed Consent**

---

Because of the extremely low risk nature of this study and the study devices being tested, all of which are currently available for commercial use and the fact that patients will receive these devices via mail and may choose not to use them, no patient-level consent will be sought.

Further, given the size and nature of the study obtaining formal informed consent will be impractical and will substantially reduce the statistical power of the study as well as limit its generalizability to a small subset of individuals to whom it might ultimately be applied.

If patients have questions about their devices, the information card that arrives with it will provide a dedicated CVS Caremark telephone number at which they can get additional information (Appendix B).

---

### **Study Risks, Safety, Monitoring**

---

Each intervention device presents minimal known additional risk to members. Each of the intervention devices is intended to supplement in adherence to medications that have been prescribed by their treating physicians and are filled at a pharmacy (mail-order or retail) of their choosing. The devices will not prevent the member from accessing his/her medications.

Included in the introductory study participation materials will be contact information should the member have any questions or concerns regarding the study or intervention devices.

All study members (including controls) will have their refills monitored using administrative pharmacy claims. Analysis will be conducted using a HIPAA limited identifiable dataset. These data come from previously collected claims and no information will be attached to any subject's medical record. As such, the analysis of these data poses no risk to subjects.

---

## Appendix A: Intervention Devices

---

### Take-N-Slide



### RxTimer Cap



### Standard pillbox (example)



---

## Updates to original research protocol from 01/02/2014

---

Several minor changes were made to the trial design after the original trial protocol was finalized. The published trial protocol contains these changes (Contemporary Clinical Trials 2015; 43: 53-59). The specific modifications are summarized below:

1. The randomization ratios were changed from 1:1.3 for control to each intervention arm to 1:2 to optimize statistical power based upon pilot data of the number of potentially eligible subjects.
2. A survey of 600 intervention group participants regarding the delivery, function, and satisfaction of the devices was added as a quality control measure.
3. The original protocol described the trial as consisting of two parallel RCTs distinguished by the dosing frequency of eligible medications (i.e. once a day [Trial 1] v. more than once per day [Trial 2]) and study blocks with these trials based upon medication type (i.e. chronic disease medications [Block A in Trial 1 and Block C in Trial 2] v. antidepressant only [Block B in Trial 1 and Block D in Trial 2]). The primary outcome was defined based upon adherence to non-antidepressant chronic disease medications (i.e. one block [Block A] from Trial 1 and one block [Block C] from Trial 2). To clarify this approach while keeping the pre-specified primary outcome unchanged, the description of the study was changed to consider it as single trial with 2 strata based upon the types of medication patients had filled at baseline and blocks based upon dosing frequency. The primary outcome remained unchanged (now clarified as being optimal adherence in Stratum 1 [previously Block A in Trial 1 and Block C in Trial 2]). Adherence in Stratum 2 (antidepressant medication only) was redefined as a secondary

outcome. Additional secondary outcomes (optimal adherence in each of the study blocks independently and optimal adherence to cardiovascular medications) were added. Mean adherence was changed from a secondary to a tertiary outcome.