Electronic Medication Adherence Reporting and Feedback During Care Transitions

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Organization: Brigham and Women's Hospital

Inclusive Dates of Project: 05/01/2016 – 04/30/2019 (NCE)

Federal Project Officer: Steve Bernstein

Acknowledgment of Agency Support: This study was supported by a grant from the Agency for Healthcare Research and Quality, R21 HS024587 (Dr. Schnipper). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The contents do not represent the views of the United States Government.

Grant Award Number: R21 HS024587

Structured Abstract:
Purpose: Implement and evaluate a "smart pillbox" intervention for patients discharged from the hospital to the community; determine barriers and facilitators of implementation of the intervention.
Scope: Adverse drug events (ADEs) are very common after hospitalization, from 11-30% in the 30 days after discharge. Novel information technology has the potential to minimize medication discrepancies, improve adherence, and reduce post-discharge ADEs in this patient population. Participants included patients admitted to the medical service of a single academic medical center, on 5 or more chronic medications, spoke English or Spanish, with a plan to be discharged home.
Methods: This was a cluster-randomized controlled trial, with clustering at the level of the primary care practice. The intervention consisted of a "smart pill-box" with pre-filled medication trays and several HIT features, including ability to send alerts if medication wells in the pillbox were not accessed; and the generation of adherence reports accessible by providers. Primary outcomes included medication discrepancies between dispensed medications and the regimen documented in the EHR, and medication adherence based on prescription fill data. Semi-structured qualitative interviews of a sample of patients, caregivers, and providers were conducted to identify barriers and facilitators of implementation.
Results: Barriers included challenges to patient enrollment in the study, logistical issues with coordinating the intervention at the time of hospital discharge, logistical issues after discharge, and technical problems with pillbox connectivity. We also found that some patients may not be ideal candidates for this intervention, such as patients with frequently changing medication regimens. Preliminary results suggest that patients who used the pillbox had fewer medication discrepancies and better adherence, but these results are subject to confounding. The lessons learned can be applied to the design and implementation of future technologies to help patients take their medications correctly and safely after discharge.

Key words: medication safety, health information technology, care transitions, medication adherence, drug packaging

Purpose

The goals of this study were to: 1) Implement a smart pill-box intervention for patients discharged from the hospital to the community; 2) Evaluate the effects of the intervention on post-discharge medication discrepancies, medication adherence, and chronic disease management; and 3) Determine barriers and facilitators of implementation of the intervention.

Scope:

Background, Context, Incidence and Prevalence

The period following hospital discharge is a vulnerable time for patients who are transitioning home from the acute care setting, especially regarding medication use. Patients often have difficulty managing their medications after hospital discharge, due in part to changes in the regimen, challenges in reconciling new medications with what they were taking previously, inadequate discharge instructions, and inadequate follow-up. Unintentional medication discrepancies (i.e., between the prescribed medication regimen and what patients think they should be taking) occur in up to 30% of patients in the days after discharge, and medication non-adherence (i.e., between what patients think they should be taking and what they actually take) occurs in approximately 25% of patients.[1] This includes "primary non-adherence," failure to fill the initial prescription of a medication, which occurs in 10% of patients despite counseling by a pharmacist at discharge.[2] Such errors in medication use can lead to unnecessary side effects and poor disease control as well as hospital readmission and even death. Several studies have shown that post-discharge adverse drug events (ADEs, injury due to a medication in the 30 days after discharge) make up 70% of all post-discharge adverse events, at a rate of 0.30 ADEs per patient; it is estimated that 11-30% of hospitalized patients suffer an ADE within 30 days of discharge, of which 2/3 are preventable or ameliorable.[3-6] Several studies of interventions designed to reduce post-discharge ADEs, such as pharmacist counseling and follow-up, have had variable success, including several at our own institution.[1 5]

Research has found that some health information technology (HIT)-related interventions can enhance adherence and reduce discrepancies. Recent advances include the development of smart medical devices that can track patient outcomes and communicate this information with providers. These devices include "smart pillboxes" that can remind patients to take their medications, track adherence, and send adherence reports to providers. Evaluations of smart pillboxes are emerging in the ambulatory setting but have yet to be deployed or evaluated in the transitions setting, where there are unique logistical challenges, e.g., due to time pressures at discharge, but also tremendous opportunities to engage patients, caregivers, and providers in medication safety and to improve care during a high-risk period in their lives.

Settings and Participants

The Smart Pillbox Transition Study was conducted at Brigham and Women's Hospital (BWH), a 793-bed teaching hospital in Boston, MA, from January 2017 to December, 2018. Eligible patients included adults admitted to any inpatient medical service (including general medicine, cardiology, and oncology services) with a BWH primary care provider (PCP), on 5 or more chronic medications, spoke English or Spanish, and had a plan for discharge home. Patients who were pregnant, incarcerated or institutionalized were excluded from the study. The study took place in the hospital, the hospital's attached ambulatory pharmacy, in PCPs' clinics, and in patients' homes.

Methods:

Trial design

This was a cluster-randomized controlled trial, with randomization of patients at the level of the primary care practice. The study was approved by the Partners Healthcare Institutional Review Board and by the BWH Primary Care Practice-Based Research Network.

Interventions

The smart pillbox (TowerView, Philadelphia, PA) is a system that accommodates pre-filled weekly medication trays that work in tandem with a connected device that measures real-time medication adherence (**Figure 1**). Compartments of the medication trays are heat-sealed with a label that can be peeled back to reveal individual medication compartments for each day of the week and time of day. Each compartment is labeled with the name and dosage of the medications in it. In addition, there is a tear-off with each tray that has a detailed description of each medication and directions for use. Non-oral medications (e.g., inhalers, nasal sprays, injectables), as-needed (PRN) medications, and opioids and other controlled substances were not included in the medication trays.

Once the medication regimen and times of day for medication usage are entered into the pillbox's secure online application and the medication labels are printed and applied to the filled medication tray, the pillbox is ready for use. When it is time for a patient to take their medications, an alarm chimes and the appropriate compartment of the tray lights up. The pillbox optically senses if all the medications have been removed from the compartment. If not, the alarm chimes again and a text message, phone, or email reminder can be sent to the patient and/or a designated caregiver. Information regarding whether medications were removed from each compartment and the time of removal are stored and then transmitted on a cellular network (Verizon Communications, New York, NY) to a central server. The data are aggregated into an adherence report by week or by month. The list of a provider's patients is prioritized by those patients with low adherence (<80% in the prior 3 days) at the top. Clicking on a patient's name displays adherence rates (proportion of doses taken) over time. A second view, known as the "heatmap," shows which doses have been missed or taken late. These data can be viewed for any week or aggregated monthly to produce summaries by date and time (e.g., 2 of 4 doses taken on Friday afternoons, average of 14 minutes late; **Figure 2**).

The initial medication tray was created by the BWH ambulatory pharmacy (see below for enrollment process), while subsequent medication trays were filled either by the BWH ambulatory pharmacy or by a dedicated third-party pharmacy (Curant Health, Smyrna, Georgia), depending on the patient's insurance. These trays were mailed to the patient every 2-4 weeks. Prior to refilling these trays, the pharmacy would review the medication regimen according to the patient's electronic medical record (Epic, Verona, WI) to identify any new discrepancies with their list of prescriptions. A pharmacist would also contact the patient to confirm the regimen. Any discrepancies were then resolved by contacting the patient's PCP or other prescribers as needed.

A pharmacist at the filling pharmacy also reviewed each patient's medication adherence report on a weekly basis. In event of <80% adherence for 3 days in a row, the pharmacist would call the patient to discuss possible barriers to medication adherence and create a plan to overcome these barriers. Documentation of these actions were added to each patient's electronic medical record. We also created a link to the adherence report within the EHR's environment and provided access to each patient's PCP. Whenever possible, we provided the same log-in and password for each PCP as the one used for network and EHR access within BWH/Partners Healthcare. PCPs (or their practice managers) were encouraged to periodically review these reports and to take action as they saw fit.

Patient Enrollment

Prior to the start of the study, researchers met with each BWH primary care practice to explain the intervention, the study, and their role in it, and were given the option to participate or not. We also addressed any questions (e.g., what to do if they change the medication regimen after discharge). Practices that those to participate were then randomized to the smart pillbox, simple pillbox, or usual care.

Patients who met study criteria were identified shortly after admission by a research assistant using a report generated by our EHR. The order in which patients were approached was randomized to avoid biased enrollment. Once eligibility criteria were confirmed by targeted medical record review and discussion with the inpatient medical team, patients were asked to provide informed written consent and to complete a brief intake questionnaire. Once enrolled, patients' PCPs and inpatient providers were contacted informing them of study enrollment and were given an opportunity to opt the patient out of the study prior to discharge if they felt the patient was a poor candidate for the intervention. Allocation was concealed from patients until after the consent process was complete.

For patients assigned to the intervention, the RA contacted their responding clinician (usually an intern or physician assistant) by email and then page, notifying them of the patient's participation and providing instructions about their role in the study: 1) to perform discharge medication reconciliation and send prescriptions to the BWH ambulatory pharmacy as early in the discharge process as possible (ideally the day prior) to allow sufficient time for the pharmacy to create the medication trays; 2) complete a bedside medication delivery form within Microsoft Outlook (Redmond, WA), already in use at BWH, including the estimated date and time of discharge, a note of any anticipated last-minute changes to the discharge medication regimen, and a note of any medications that should be withheld from the pillbox due to unexpected future changes to the regimen (e.g., warfarin, or furosemide in a patient with unstable congestive heart failure).

RAs contacted each subject's inpatient unit each weekday to identify those being discharged that day. Based on the patient's discharge regimen and their insurance, the patient's total medication copayments were determined and then conveyed to the patient. Because copayments could in theory increase, e.g., if 90-day mail-order prescriptions were changed to 30-day prescriptions, patients were given the option to withdraw from the study at that time (contractually, patients are expected to pay their copayments, and the pharmacy cannot routinely waive copayments). Because medications cannot be repackaged (i.e., in a medication tray) by a pharmacist, any medication recently filled prior to admission and to be prescribed at discharge could be declined by insurance as an early refill. We therefore set up a fund as part of the grant to reimburse the pharmacy for any uncovered medications.

On the day of discharge, a pharmacy technician contacted the patient, verified the times of day they take medications and elicited information about any caregivers to be contacted in the event of missed/late medication doses. A trained BWH pharmacist entered this information in the pillbox software and created the first two medication trays. While the Epic EHR and the pillbox software were not compatible with each other, we programmed the EHR to create a CSV file of the discharge medication regimen that could be imported into the pillbox software to facilitate this process.

Immediately prior to discharge, a member of the ambulatory pharmacy delivered the pillbox and the medication trays to the patient's bedside, demonstrated how to use the intervention, and answered any questions. Patients were also provided with a Frequently Asked Questions brochure and "Let's Get Started" booklet. Patients were provided with a number to call for any technical or medication-related

issues. Finally, the patient's pharmacy was updated in the EHR and the patient was associated with the study in the EHR so that their participation in the study was visible on the top line of their medical record.

For patients discharged on weekends, when the ambulatory pharmacy was closed, plans were made for patients to be given a 3-4 day supply of medications in pillboxes and for them to return to the ambulatory pharmacy to pick up their pillbox and receive instructions in its use on Monday. This process was facilitated by communication between the RA, responding clinician, and ambulatory pharmacy on the Friday prior to discharge.

Patients continued to use the pillbox for up to 6 months after discharge. At that point, participation in the study ended, and patients were given the option to go back to their former way of managing medications with their prior pharmacy, to continue using the medication trays without the pillbox, or with permission from TowerView, to continue to use the intervention.

Usual Care and Simple Pillbox Arms

Patients in the usual care arm had their medication prescriptions electronically transmitted to the community pharmacy of their choice or to the BWH ambulatory pharmacy if they preferred. Medical teams could still opt for medication bedside delivery by the BWH ambulatory pharmacy if desired, although this was not common.

Patients assigned to the simple pillbox were given a weekly pillbox on the day of discharge and provided instructions on how to fill it, including how to use the discharge medication list as a guide, and how to use it on a daily and weekly basis.

All patients in the study, regardless of arm, received counseling on their discharge medication regimen from their nurse or a unit-based pharmacist. In addition, most patients admitted to medicine through the Emergency Department had a "best possible medication history" taken by a trained pharmacy technician or resident, who documented that history in Epic so that it could be used for discharge medication reconciliation. Lastly, the medication reconciliation screens in Epic were previously optimized to maximize the accuracy of the medication orders at hospital discharge.

Outcomes

<u>Primary Outcomes</u>

Our primary medication safety outcomes were medication discrepancies and adherence:

• Medication discrepancies: each month after discharge for 6 months, the medications dispensed (based on SureScripts pharmacy data) were compared with the medication regimen as documented in the Epic EHR that same day. SureScripts is a repository of pharmacy and pharmacy-benefit-manager (PBM) data to which BWH/Partners has a license. In a study of post-discharge management of patients with diabetes mellitus discharged on insulin, we found SureScripts data to be available for 67.8% of patients discharged from BWH in February 2012 through March 2013,[7] and this number increases each year, currently estimated at over 80%. Discrepancies per patient per month can then be calculated.

• Medication adherence: this will also be based on SureScripts data, using 80% of Proportion of Days Covered (PDC) as the threshold for adherence. PDC is the number of days a medication is filled divided by the days between fills. For example, if a 30-day supply of a medication is filled every 40 days, then PDC would be 75%. PDC for an entire regimen is the mean PDC of every medication in that regimen. PDC is a widely used measure and is easy to calculate. However, average PDC across a number of medications tends to overestimate adherence because it does not fully account for polypharmacy, the

frequency of therapeutic switching and duplication, overlapping supplies, or unexpected same-day refills.[8] Because of limitations of PDC, we also used an alternate measure of adherence known as the Daily Polypharmacy Possession Ratio (DPPR).[9] The DPPR measures the proportion of all prescribed medications available each day of the measurement period, averaged across all days in the period. It considers therapeutic switching and therapeutic duplication as one medication and accounts for changes in dosing and for carrying over excess medication from one interval to the next interval. Thus the DPPR is a more realistic measure of adherence.

Secondary Outcomes

• Implementation: we collected data on a number of process measures to evaluate the extent to which the intervention was successfully implemented in the transitions setting. For example, we measured the proportion of each patient's regimen was included in medication trays; the proportion of biweekly time periods for which patients received a supply of medication trays from the BWH or TowerView central pharmacy; the use of adherence reports by patients, by caregivers, and by providers; and the proportion of cases for which downstream actions to address adherence issues are documented by PCPs.
• Patient Outcomes: in addition to the proximal measures of medication discrepancies and adherence, we measured disease control in patients with hypertension (blood pressure), hyperlipidemia (LDL cholesterol), and diabetes mellitus (A1c), three chronic conditions in which disease control is closely related to medication adherence. We obtained these data from the Epic EHR (last values during the 6-month post-discharge period) as they are collected and documented as part of routine medical care as compared with results in the 3 months prior to the time of hospital admission. Consensus guidelines on disease control were used for each parameter to allow for measurement both of improvement over time and maintenance of control.[10-12]
• Adherence Data: for patients in the intervention arm, we analyzed the characteristics of the adherence data produced by the smart pillbox itself. These data provide a precise view of the extent to which patients are or are not adherent with their medications.
Table 1 below describes how each of these outcomes are measured.

Analysis Plan

The number of discrepancies per patient (mean per month) was analyzed using multivariable Poisson regression. Potential confounders to be adjusted for included data from administrative data sources (patient age, sex, marital status, insurance, median income by zip code, and number of medication changes from preadmission to discharge) and variables from the intake interview (Morisky score,[13] presence and relationship of caregivers, health literacy using the s-TOFHLA).[14] The number of discharge medications was used as a model offset, and general estimating equations were used to cluster by primary care practice. Medication adherence (>80% PDC or DPPR) were analyzed in a similar manner using multivariable logistic regression, as were secondary outcomes that are dichotomous in nature (e.g., achievement of a disease control goal). Use of the intervention were analyzed in several ways. First, we examined use of adherence reports by patients and caregivers. Secondary outcomes based on proportions (e.g., proportion of medications filled using medication trays) were calculated using binomial logistic regression (e.g. X/N, where N would be the number of medications in the regimen and X would be the number of those medications filled using medication trays). Secondary outcomes based on pre-post improvement in a continuous variable (e.g., LDL cholesterol) were analyzed using multivariable linear regression.

A number of statistics were used to describe the unique adherence data derived from the smart pillbox adherence reports. Besides simple descriptive statistics (mean (SD), median (IQR), total range), we

examined proportion adherent using various thresholds, as well as within-patient vs. inter-patient variation. For example, we examined how similar adherence is between different medications taken by the same patient, as well as changes in adherence over time. The GLIMMIX procedure in the SAS package, which allows for the simultaneous analysis of multiple outcomes (following different distributions) for the same patient and also for correlation over time and within practice, were used extensively for these more sophisticated analyses.

Power and Sample Size

We assumed, as has been shown in previous studies,[7 8] that 50% of patients would have a PDC >80%, then we estimated a required effective sample size of 170 patients in each arm to see an increase to 65% adherence with 80% power, assuming an alpha of 0.05. Assuming a cluster size of 17 patients in each of 10 practices in each arm and an intra-class correlation coefficient of 0.01 (based on previous studies of this type),[1] then the required actual sample size was estimated to be approximately 200 patients per arm (i.e., 400 patients total, or 20 patients per practice). We originally planned to achieve this by enrolling 50 patients a month for 8 months. This same sample size also allowed us to detect a decrease in medication discrepancies from 0.35 per patient (based on our previous studies[1] and assuming a Poisson distribution) to 0.20 discrepancies per patient.

Unless otherwise stated, two-sided p values < 0.05 were used to determine significance, and all analyses were conducted using SAS v9.4 (SAS Institute, Cary, NC). All analyses are on an "intention-to-treat" basis unless otherwise stated.

Qualitative Data Collection

To better understand barriers and facilitators of implementation, we collected data from a variety of sources: 1) minutes from weekly research team minutes; 2) logs of technical issues with the pillbox sent to TowerView; and 3) patient satisfaction surveys sent to intervention patients at the end of the 6-month follow-up period. Themes were generated from this information and reviewed with all study authors until consensus was reached.

In addition, a random sample of patients and their caregivers were contacted by phone at the end of the 6-month postdischarge period to determine their interest in participating in qualitative interviews. We obtained verbal consent from interested subjects and scheduled a time for interviews to take place. Patients and caregivers were interviewed separately. Using a semi-structured interview guide, we asked a series of questions regarding issues of usability of the pillbox, the associated reminders, and the adherence reports, as well as barriers to and facilitators of implementation of the intervention. A random sample of providers were also invited to participate in similar interviews focused on the usability of the adherence reports, and barriers and facilitators of accessing adherence reports and taking action based on their results. Interviews were recorded, transcribed, and then analyzed using NVivo qualitative analysis software. Under the guidance of Anna Revette, our qualitative research expert, Drs. Schnipper and Shannon performed dual coding of all themes, and all differences were discussed and reconciled. We used an *a priori* analytic framework based on the Systems Engineering Initiative for Patient Safety Model (SEIPS)[15]. We planned to interview approximately 10 of each group (patients, caregivers, and providers), or until thematic saturation was reached.

Limitations

One limitation of this study is the nature of adherence measures based on pharmacy prescription fill data, which assumes patients take all dispensed doses of medications at home. In particular, it could be

argued that our intervention was designed specifically to lead to 100% adherence using this measure given the biweekly delivery of medication trays to patients. However, it is still possible for measured adherence to be lower in the intervention arm, for example, due to logistical problems with filling or delivering trays, and the use of medications that need to be filled outside of trays. This is also a fair comparison with the usual care arm, where we will made the same assumptions about adherence. Measures like PDC have been used in many previous studies and are well understood by clinicians, they have been validated, and they are inexpensive to collect, making them ideal for a proof-of-concept study like this one. Lastly, we complemented this outcome with several others, including measures of medication discrepancies and measures of disease control. Another limitation is generalizability, since we will conducted this study in one academic medical center. Again, we believe this was appropriate for a proof-of-concept study of this scale and scope.

Results

Enrollment and Patient Flow

The flow diagram of patients assigned to the intervention arm is shown in **Figure 3**. Enrollment of patients was difficult throughout the study, and we therefore decided, in conjunction with AHRQ, to reduce our target sample size to 266 patients and eliminate Arm 2 of the study, focusing the analysis on usual care vs. the smart pillbox. In the end, 207 patients were randomized, including 24 assigned to Arm 2 who were later withdrawn from the study. Of the 73 patients allocated to receive the intervention, 33 did not receive it. This was for a variety of reasons, but the most common was that the patient was discharged before the pillbox could be provided (or over a weekend, when the ambulatory pharmacy was closed) and they chose not to return to pick it up after discharge (e.g., Monday morning). In 15 cases, patients no longer met eligibility criteria and were post-enrollment exclusions (e.g., discharged to hospice or rehabilitation, on fewer than 5 medications). In 12 cases, patients stopped the intervention early because the patient, their PCP, or study staff opted them out of the study after enrollment. The cost of copayments was the specified reason for patient withdrawal in 4 cases.

Barriers to Study Conduct

Barriers to the conduct of the study and implementation of the intervention could be divided into three major categories: patient enrollment, logistics at the time of discharge, and post-discharge issues (**Table 2**). For example, regarding patient enrollment, many patients declined to be in the study because they denied any problems with medication adherence in the past (whether true or not) and/or stated they were content with their current method of managing their medications. Others were simply overwhelmed by their hospitalization and did not want any additional changes to their routine. Others perceived portability issues with the pillbox, had too many medications dispensed outside the pillbox (e.g., non-oral medications, controlled substances, as needed medications, medications at risk for frequent changes), were concerned about their copayments going up, or were simply resistant to participating in research studies.

At discharge, the overriding theme was the conflict between the many processes that normally have to occur prior to discharge, the unpredictable nature of the discharge decision, and the rushed nature of discharge on the one hand, and the many steps that needed to occur for the smart pillbox and medication trays to be given to the patient prior to them leaving the hospital. For example, the ambulatory pharmacy often received the final discharge prescriptions less than two hours before the anticipated discharge time, which was not sufficient time to complete all the required tasks related to the intervention. The time required for the pharmacy to dispense the initial medication trays and enter information into the pillbox application was also an issue, especially since several tasks normally automated (like entering the pill description and the NDC number) had to be completed manually due to

incompatibility with the pharmacy's dispensing software. As noted above, the BWH ambulatory pharmacy was closed on weekends, thus creating a separate workflow for patients discharged over the weekend, a process that did not always work.

After discharge, logistical issues included difficulty reaching patients to confirm regimens prior to mailing new medication trays and difficulty obtaining prescription renewals from providers. Technical issues included poor signal in some locations, leading to failure to record adherence data, and the occasional inability for the optical reader to detect the removal of medications, e.g., if only one small pill was in the compartment.

Several solutions to these barriers were implemented during the course of the study, while others were planned (**Table 2**). For example, we revised our enrollment scripts several times to reduce the perceived stigma of participating in the study, and when patients were unsure about enrolling, we enlisted the help of the patient's inpatient and outpatient providers and their caregivers to gently encourage participation if appropriate. We worked with the pillbox vendor to create a system of text reminders for medications outside the pillbox to remove the disparity between those medications that could and couldn't leverage the intervention. We made several changes to our protocol to improve communication between study staff and the inpatient medical team to facilitate the completion of pre-discharge tasks. We also improved our procedures to identify the correct prescriber for each outpatient medication in order to obtain prescription renewals as efficiently as possible. Planned improvements included pillbox software interfaces compatible with the hospital's EHR and medication dispensing software, and technical improvements regarding signal strength and optical detection of pill removal.

Despite these obstacles, exit surveys with patients who used the pillbox were extremely positive. They often noted the convenience of their medications being mailed to them, increased confidence knowing it was the correct regimen, and no longer having the burden (or their family's burden) to fill their own pillbox or use pill bottles to organize their regimens. Opinions were mixed on the reminder system, but some patients found it helpful.

Principal Findings

The analysis of medication adherence is shown in **Table 3**. Patients assigned to the smart pillbox had a higher mean proportion of days covered (PDC) of their medications, 0.70 vs. 0.61. These results just missed statistical significance in unadjusted analyses (0.076) but were significant in adjusted analyses (adjusted mean difference 0.11, 95% CI 0.01-0.21, p=0.038). The same is true of the proportion of patients with a PDC > 80%: 45.7% vs. 30.5%, p=0.055 in unadjusted analyses, adjusted odds ratio 2.56, 95% CI 1.10-5.96, p=0.030 in adjusted analyses.

Other Outcomes

In terms of disease control (**Table 4a and 4b**), those assigned to the smart pillbox overall had better blood pressure control. The results were significant for the proportion of those meeting targets for diastolic BP but not systolic BP, and were significant when analyzing the absolute pre-post improvements in systolic and diastolic BP levels between the two arms (i.e., a difference in differences analysis). There were no significant differences in disease control of LDL cholesterol or diabetes (Hgb A1c) levels.

Use of adherence reports by patients, caregivers, and PCPs was virtually non-existent, although they were used extensively by the pharmacy study staff, who contacted patients in the event of non-adherence.

Discussion, Significance, and Implications

In summary, we identified several obstacles to enrolling patients in this study and successfully providing intervention patients with the smart pillbox prior to hospital discharge. One major theme was the tension between a rushed and sometimes unpredictable hospital discharge process on the one hand and the time required to set up a smart pillbox on the other. Other obstacles were related to the intervention being provided in the context of a cluster-randomized study (e.g., the need to get patient consent, some patients' resistance to participating in research studies), while others were more technical in nature (e.g., software incompatibility, issues with signal strength). A final set of obstacles were related to financial and regulatory issues (e.g., inability to repackage medications, waive copayments, or do early refills). Those who used the intervention were pleased with it, but obviously there is selection bias among those who chose to go through the obstacles to use it and liked it enough to continue to use it.

Discharge planning can be a complicated process involving much logistical planning, and adding a process such as a smart pillbox in a short amount of time can create many unforeseen barriers. The intervention required approximately 2 hours from the time prescriptions were received to when the pillbox was filled and delivered. Tasks included obtaining pharmacy benefits information, processing prescriptions, troubleshooting insurance issues, entering medication information into the TowerView platform, printing patient specific labels, filling the pillbox, and coordinating delivery and education to the patient. Often, prescriptions were sent to the pharmacy less than 2 hours prior to the expected time of discharge, resulting in a rush to provide the intervention and sometimes in an ability to provide it at all. Competing priorities, such as reducing length of stay or discharging patients before noon, also complicated these logistics.

Patients who were being discharged on medications that were too soon to fill could not have previously dispensed medications added to the pillbox by the pharmacy due to regulations against repackaging of medications. The study provided grant coverage for these medications to ensure they were in the pillbox, but this is not a long-term realistic solution.

One of the major barriers faced by the pharmacy was using the software for inputting the information into the TowerView platform. There was no interface between the Towerview platform and either the hospital's EHR or the pharmacy's medication dispensing software. While a CSV file of the discharge medication regimen could be created by the EHR and then uploaded to the TowerView system, it still required double-checking to make sure all the information was accurate. And as noted above, medication information such as NDC number and pill appearance had to be manually entered, unlike usual care. These were extremely time-consuming steps and the biggest barrier faced by the pharmacy for a timely turnaround and providing this as a long-term service. Lastly, the adherence reports were rarely used by any group (patients, caregivers, PCPs) except for the pharmacy study staff, who used them extensively in patients with evidence of non-adherence. This also has implications for long-term sustainability of the intervention.

However, despite the obstacles to its use and the relatively small number of patients assigned to the intervention who actually received it, the intervention was associated with better medication adherence and in improvements blood pressure control, especially diastolic blood pressure (arguably the more important of the two measures) in fully adjusted intention-to-treat analyses. This suggests that the intervention was potent enough in those who received it to overcome the effects of dilution in those who did not. We are currently looking at "on-treatment analyses" to further explore this hypothesis.

The lack of effect on diabetes control may have been due to the fact that many of these patients were taking insulin, which was not in the pillbox; in some ways, this served as an internal control. We did offer to provide smart phone reminders for patients in the intervention arm to take their insulin, but either they did not accept this offer and/or there are other barriers to taking insulin besides a simple reminder. Analyses regarding LDL control were limited by the small number of test results during the study period. Pending analyses, including a detailed look at discrepancy rates, implementation fidelity, adherence patterns in the intervention arm, and a complete analysis of the qualitative data, are likely to provide additional insights.

Given the known problems with medication safety after hospital discharge and the potential of interventions like these to address these problems, the larger question is what would it take for this kind of intervention to become part of usual care? First, if no longer part of a research study, several obstacles (such as the need for consent or resistance to participating in research) would be resolved by themselves. However, issues of patient denial of prior medication problems may persist: we frequently noted feelings of shame and guilt around prior medication-taking behavior, and offering this intervention as an optional part of usual care may not solve this problem, even if offered by one's own providers (or care coordinator) as opposed to research staff. This is not that different from offering other services to help patients, such as health coaches, where it is paramount to minimize the stigma associated with accepting help.

Logistical issues were prominent barriers, and some could be resolved by "productizing" this intervention. For example, ensuring software compatibility of pillbox software and the EHR, having multiple pharmacists trained in programming the software and dispensing medication trays, and taking advantage of economies of scale would likely help a great deal. There would also need to be a more concerted effort to facilitate early communication between prescribing clinicians and pharmacists, especially around early provision of discharge prescriptions. Nevertheless, it is likely that implementing this intervention would always take longer than not implementing it, and so the costs and benefits would need to be more clearly defined to make the case for using it. Moreover, some logistical issues are harder to correct, such as the tension between time constraints to set up a pillbox and the rush and unpredictability of hospital discharge, and the restricted hours of most hospital-based ambulatory pharmacies, which make evening and weekend discharges challenging. Also, more work would need to be done to encourage patients, caregivers, and PCPs (or their staff) to use the adherence reports.

Some issues would require more systemic change. For example, could insurance companies agree to a waiver of early refills and a reduction in copayments to 90-day levels in exchange for using the intervention? They may find that the improvements in medication adherence and disease control, possibly leading to reduced health care utilization, are worth it. Another question is whether there is a sustainable business model for pharmacies to do the extra work, and if not, who pays for it. The business case might be clearest for self-insured integrated delivery systems, where investments in time and resources may be practical in exchange for reduced downstream costs like hospital readmissions.

Lastly, some issues require iterative technological improvements, including signal strength, pillbox connectivity, thresholds for detecting pill removal, and improving portability. We should also acknowledge that some patients may not be ideal candidates for this intervention, including those with many medications outside the pillbox or with frequently changing regimens. Patients who travel frequently were also resistant to using the pillbox. Patients who were not technically savvy or with mild cognitive impairment were resistant to using the pillbox despite the fact that they may be the ones to

benefit the most, especially with assistance from a caregiver. There may also be a point at which cognitive impairment is too severe for this intervention to work.

Several technologies to improve medication organization and adherence are beginning to emerge, each with its own advantages and disadvantages. The smart pillbox used in this study, with pharmacist-provided prefilled medication trays, is particularly good at reducing medication discrepancies, especially if the regimen is reviewed with the EHR prior to each new shipment. However, it has disadvantages in terms of portability and issues with frequently changing regimens (and as noted above, restrictions in terms of repackaging medications). Issues with having a pharmacist fill the medication trays were particularly challenging at the time of hospital discharge and might be less in a routine ambulatory setting. We should note that the TowerView product is no longer available. However, other similar products are still available, such as Maya by MedMinder. The product allows for both pre-filled trays filled by a pharmacist, similar to TowerView's product (with similar advantages in terms of reducing discrepancies but also the same logistical challenges at the time of discharge), and manually filled trays (which is easier logistically but is only as accurate as the person filling the pill box).

Other options include blister-packaging of medications by community pharmacies, which lack any technology to encourage or detect adherence but can minimize discrepancies and simplify medication-taking, as long as pharmacies have the correct information. Changes to medication regimens between refills remain a challenge. PillPack involves individually wrapped medication pouches for each dose, mailed to the patient's home, which are more portable than a smart pillbox but less accommodating to medication changes and do not promote or detect medication adherence. At the high-tech end of the spectrum are automatic medication dispensing machines such as MedaCube. Each medication is placed in a container in the top of the device, and each dose of medications is dispensed out the bottom at the appropriate time. It provides alerts if doses are not retrieved at the right time. Most importantly, the machine can be remotely programmed by a prescriber (e.g., to double the dose of a diuretic for a week), which works as long as sufficient medication is in the machine. The device itself is not portable, but in theory one or more doses of medications could be taken "to go." **Table 5** summarizes the advantages and disadvantages of various medication adherence technologies. In general, most of these technologies are not well-studied,[16] although MedaCube is being evaluated by our team as part of a comprehensive post-discharge "rehab at home" program. To our knowledge, none of these other technologies have been studied in the transitional care setting.

This study was obviously limited by problems with enrollment and delivery of the intervention. Nevertheless, the results on outcomes were encouraging. Moreover, the lessons learned about the challenges of delivering this intervention and what it would take to implement related types of technology in the transitional care setting were extremely valuable.

In conclusion, a smart pillbox has the potential to decrease medication discrepancies and improve medication adherence and disease control. Otherwise ideal candidates for this intervention may resist this electronic intervention for a variety of reasons. On the other hand, some patients may not be ideal candidates, including those with frequent travel or because of the nature of their medication regimens. The obstacles to implementing this intervention were striking, and it remains an open question of whether the logical challenges of using this in the transitional care setting are outweighed by the potential advantages of making this intervention (or related interventions) an optional part of usual care during a high-risk period for medication safety.

Tables

Table 1. Outcome Measures

Outcome	Timing	Data Sources and Measurement Process	Form of Analytic Variable
Primary Outcomes			
Medication Discrepancies	Monthly for the 6 months after discharge	Differences between medications dispensed each month (from pillbox trays or bottles) based on SureScripts data, and the documented medication regimen in the Epic EHR on the same day	Number of discrepancies per patient (mean per month)
Medication Adherence	6 months after discharge	Prescription fill data from SureScripts. Calculation of Proportion of Days Covered (PDC) and Daily Polypharmacy Possession Ratio (DPPR)	Proportion of patients with PDC > 80%. Proportion of patients with DPPR > 80%.
Implementation – intervention arm only			
Proportion of regimen in pill trays	Biweekly for the 6 months after discharge	Medication dispense data from BWH pharmacy and TowerView pharmacy (medication trays only) compared with medication regimen data from Epic EHR	Mean proportion of regimen in pill trays, averaged over all dispense episodes
Biweekly delivery of trays	Biweekly for the 6 months after discharge	Medication dispense data from BWH pharmacy and TowerView pharmacy. Presence or absence of delivery for each two-week period	Proportion of two-week periods for which delivery was made
Use of adherence reports by patients	Cumulative during the 6 months after discharge	Log of times patients go into online adherence reports	Number of times accessed per patient
Use of adherence reports by caregivers	Cumulative during the 6 months after discharge	Log of times caregivers go into online adherence reports (will be given access by patients)	Number of times accessed by caregivers, per patient
Use of adherence reports by providers (Partners only)	Cumulative during the 6 months after discharge	Log of times providers use Epic link to access reports	Number of times accessed by providers, per patient
Actions taken by providers	Cumulative during the 6 months after discharge	Documentation from ambulatory notes in Epic that any action taken in response to adherence data when baseline adherence (PDC) is < 80%	Proportion of eligible patients where action taken by providers

Outcome	Timing	Data Sources and Measurement Process	Form of Analytic Variable
Other Patient Outcomes: Disease Control*			
Blood Pressure Control (in patients on antihypertensive medications)	Last two values during 6-month post-discharge study period compared with last two values prior to admission	Blood pressure data from Epic EHR	If BP at goal at baseline: maintenance of goal. If BP not at all goal at baseline: decrease in systolic and diastolic BP to reach achievement of goal
LDL Cholesterol Control (in patients on statins)	Last value during 6-month post-discharge study period compared with last value prior to admission	LDL cholesterol data from Epic EHR	If LDL at goal at baseline: maintenance of goal. If LDL not at all goal at baseline: decrease in LDL to reach achievement of goal
Diabetes Control (in patients on diabetes medications)	Last value during 6-month post-discharge study period compared with last value prior to admission	A1c data from Epic EHR	If A1c at goal at baseline: maintenance of goal. If A1c not at all goal at baseline: decrease in A1c to reach achievement of goal
Measurement – intervention arm only			
14-day adherence	Proportion of doses opened on schedule from pillbox during any 14-day period	Data calculated automatically from TowerView adherence reports.	Descriptive statistics: mean (SD), median (IQR), range, proportion > 80% adherence. Intra-patient variation

Table 2. Barriers to Implementation and Potential Solutions

Barriers During Patient Enrollment	**Potential Solutions**
Patient denial of previous problems with adherence	Scripts to reduce stigma of accepting the intervention; engagement of patient's caregivers and providers
Perceived portability issues with pillbox	Educate patient that pills may be removed early in the day
Too many medications dispensed outside of the pillbox	Text reminders for non-pillbox medications; patient education re: using pillbox under different situations
Potential for copayments to increase	Emphasize that the benefits of the intervention may be worth the copay increase
Resistance to participating in research studies	Highlight potential benefits to patients and general public
Barriers at Discharge	**Potential Solutions**
Turn-around time: pharmacy often receives prescriptions for patient <2 hours before anticipated discharge	Encourage clinicians to provide prescriptions as early as possible; facilitate early communication between pharmacist and clinician
Time required to dispense initial medications and enter information into pillbox application	Develop pillbox software interface compatible with hospital EHR system
Outpatient pharmacy closed on weekends	Developed protocol for patients discharged over the weekend to return on Monday to receive pillbox
Lack of insurance coverage for early prescription refills	Plan to engage insurance companies to allow for early refills
Barriers Post Discharge	**Potential Solutions**
Difficulty reaching patients to confirm refills	Attempt to reach through multiple methods in addition to phone calls
Difficulty obtaining prescription refills from providers, esp. if multiple prescribers per patient	Procedures for obtaining refills from each practice and documenting usual prescriber for each medication
Pillbox connectivity: poor signal in some locations	Planned pillbox enhancements; optimizing location of the pillbox within the home
Pillbox threshold for detecting removal of small pills	Group medications for each dose if possible; planned pillbox enhancements to detect one small pill

Table 3. Effect of Intervention on Medication Adherence

	Overall	Usual care	Smart pillbox	Unadjusted p-value	Adj. Comparison (95% CI)	Adjusted p-value*
PDC, mean (std dev)	0.65 (0.29)	0.61 (0.30)	0.70 (0.28)	0.076	0.11 (0.01-0.21)[a]	0.038
% patients with PDC > 0.80	37.5%	30.5%	45.7%	0.055	2.56 (1.10-5.96)[b]	0.030

*Adjusted for patient age, sex, marital status, insurance, Morisky score, presence and relationship of caregiver, health literacy using s-TOFHLA
PDC: proportion of days covered

[a]Adjusted mean difference
[b]Adjusted odds ratio

Table 4a. Disease Control: Proportion Reaching Target

Metric	Overall	Usual care only	Smart pillbox	Unadjusted p-value	Adjusted Odds Ratio (95% CI)	Adjusted p-value*
Systolic BP[a]	71.77%	68.42%	77.08%	0.2984	2.38 (0.70-8.11)	0.1650
Diastolic BP[b]	83.87%	77.63%	93.75%	0.0258	7.69 (1.32-44.67)	0.0231
LDL cholesterol[c]	91.18%	94.12%	88.24%	0.5528	<0.001 (<0.001, >999.99)	0.8961
HbA1c[d]	70.21%	71.43%	68.42%	0.8250	0.13 (0.01-1.48)	0.0993

*Adjusted for pre-intervention value, patient age, sex, marital status, insurance, Morisky score, presence and relationship of caregiver, health literacy using s-TOFHLA
[a] Maintain systolic blood pressure goal of $\leq$ 130 mmHg or decrease to that goal if not at goal at baseline
[b] Maintain diastolic blood pressure goal of $\leq$ 80 mmHg or decrease to that goal if not at goal at baseline
[c] Maintain low density lipoprotein (LDL) cholesterol goal of $\leq$ 130 mg/dL or decrease to that goal if not at goal at baseline
[d] Maintain glycated hemoglobin (HbA1c) goal of $\leq$ 6.5% or decrease to that goal if not at goal at baseline
CI: Confidence Interval

Table 4b. Disease Control: Continuous Measures Pre- vs. Post-Intervention

Time Period	Metric	Overall	Usual care	Smart pillbox	Unadjusted p-value	Adjusted difference-in-difference (95% CI)	Adjusted p-value*
Pre	Systolic BP	133 (20)	134 (19)	133 (22)	0.0878	-13.88 (-22.09, -5.66)	0.0011
Post	Systolic BP	127 (19)	129 (18)	123 (20)			
Pre	Diastolic BP	72 (12)	72 (12)	72 (12)	0.0253	-9.31 (-14.86, -3.75)	0.0012
Post	Diastolic BP	70 (14)	73 (14)	67 (13)			
Pre	LDL cholesterol	87 (54)	85 (51)	89 (59)	0.0666	-5.01 (-67.72, 57.70)	0.8671
Post	LDL cholesterol	87 (58)	110 (69)	65 (36)			
Pre	HbA1c	8.3 (2.1)	8.4 (2.2)	8.2 (1.9)	0.5259	-0.13 (-1.22, 0.96)	0.8069
Post	HbA1c	7.8 (2.1)	7.8 (2.0)	7.9 (2.4)			

*Adjusted for pre-intervention value, patient age, sex, marital status, insurance, Morisky score, presence and relationship of caregiver, health literacy using s-TOFHLA

Table 5. Advantages and Disadvantages of Medication Dispensing Technologies

Feature	Simple Pillbox	Smart Pillbox	Blister Packaging	PillPack	MedaCube
Option to be filled by a pharmacist	Not usually	Yes	Yes	Yes	No (but less necessary, easy to fill)
Reminds patients to take medications	No	Yes	No	No	Yes
Detects non-adherence	No	Yes	No	No	Yes
Provides alerts and adherence reports to caregivers and providers	No	Yes	No	No	Yes
Allows pharmacies to dispense medications as they normally would (e.g., 30 or 90-day supplies in pill bottles)	Yes	Only if manually filled	No	No, uses its own pharmacy	Yes
Flexible to changes in medication regimens between refills	Yes, but requires knowledge-able person to make changes	Difficult to do	Difficult to do	Difficult to do	Yes, changes can be programmed remotely
Easy to take medications with you (portable)	Depending on design, can take one dose or one day's supply	Depending on design, can take one dose or one day's supply	Can't usually separate doses, but packaging usually light	Yes	Can pre-dispense doses, requires extra container
Cost	Minimal	$$	$	$	$$$

Figures

Figure 1. Smart Pillbox

Figure 2. Medication Adherence Reports

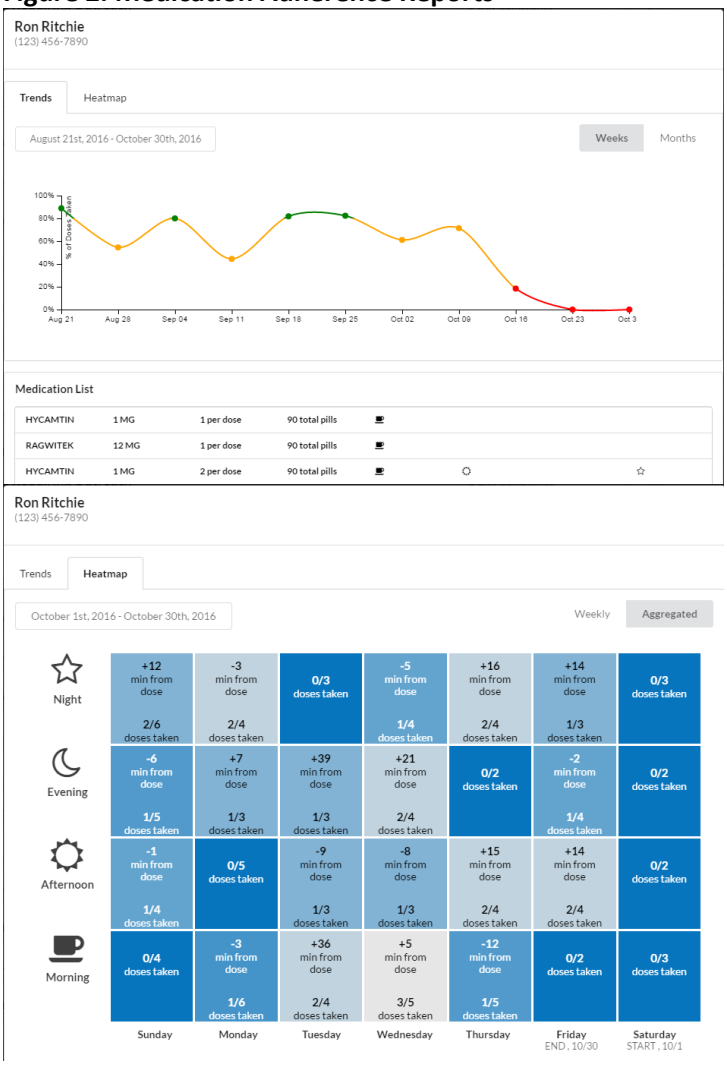
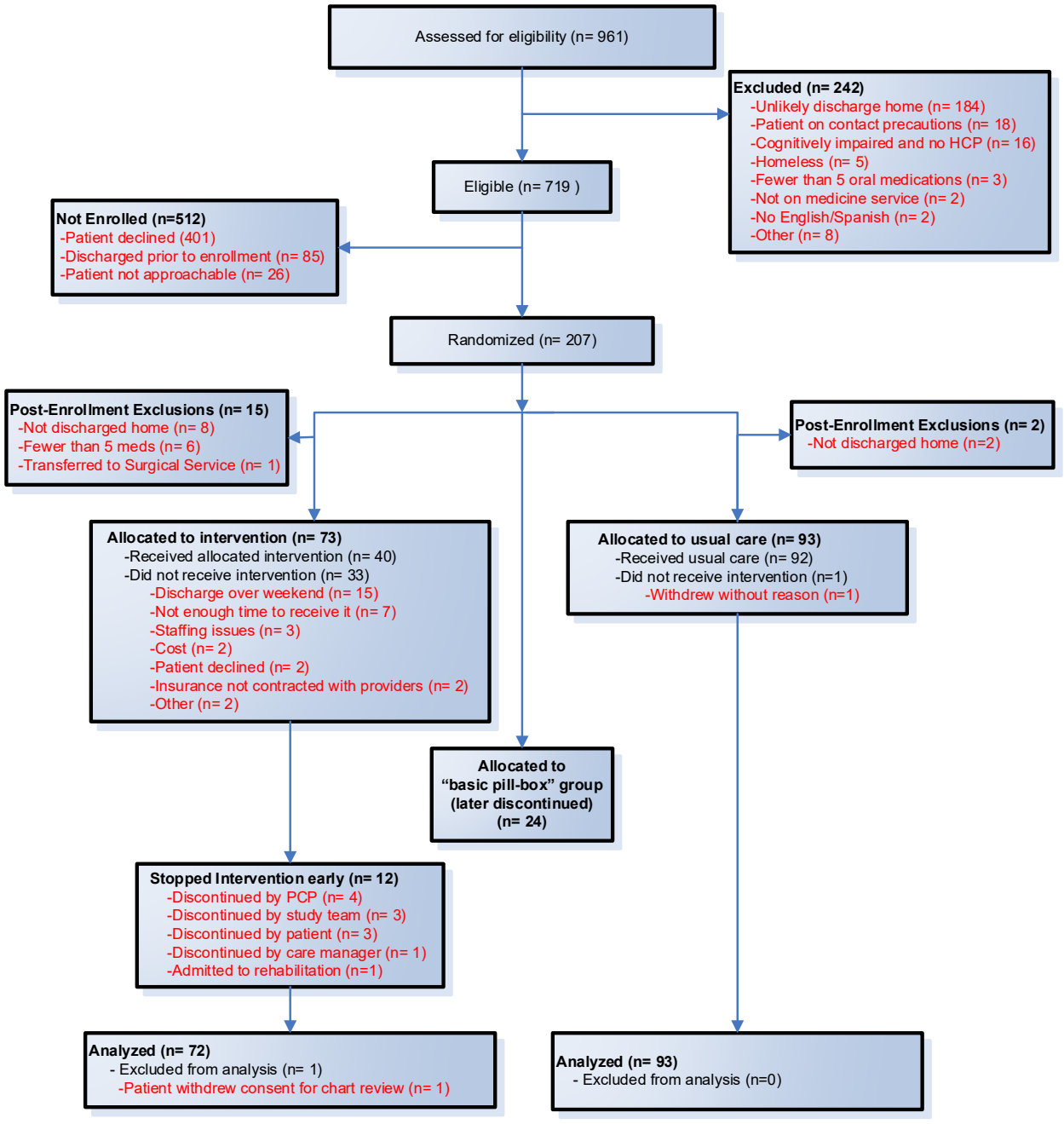


Figure 3. Flow Diagram



List of Publications and Products

Abstracts:

1. **Schnipper JL**, DeCastro RS, Reyes Nieva H, Chabria A, Shannon EM, Jain R, Ganesan H, Cerciello E. An electronic pillbox to improve medication safety during care transitions. Society of Hospital Medicine Annual Meeting, Las Vegas, NV, 2017.
2. **Schnipper J**, Cruz Garcia J, Reyes H, Chabria A, Shannon E, Czado K, Jain R, Ganesan H, Cerciello E, Dave J. Barriers and facilitators to implementing an electronic pillbox intervention during care transitions. Society of Hospital Medicine Annual Meeting, Orlando, FL, 2018.

Presentations:

1. "Smart Pillbox" Transitions Study / Webinar
   AHRQ National Web Conference on the Role of Health IT to Improve Medication Management, 2018.

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