Impact on patients' COmpliance with Medication using Pre-packed blisters for Long term medical therapY (I-COMPLY study).

Background:

Patients with chronic medical conditions are commonly required to adhere to pharmacological treatment regimens consisting of multiple daily medications to be taken at different frequencies. Several studies have reported that multiple daily drug regimens and complexity of the treatment contribute to poor patients' adherence to the treatment (1 - 4). Studies indicate that improving the patients' adherence to the treatment of chronic conditions like hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure etc. may reduce the risk of development and progression of cardiovascular diseases and lower the health care costs (4, 5). We hypothesize that providing the patients with medications in blisters containing all the pills to be taken at a given time could reduce the complexity of the treatment and improve patients' adherence to treatment.

Aim:

1. To compare the 2 month medication adherence between patients receiving medications in pre-packed blisters and patients receiving medications in pill bottles and/or strips.

Inclusion Criteria:

1. Patients aged 18 or older.

2. Patients who follow up with their Primary Care Physicians (PCP) at the Stephanie Tubbs Jones Family Health Center (STJ FHC) and have seen their PCP at least 2 times in the last 1 year.

3. Patients with chronic medical conditions taking at least 4 different scheduled medications daily.

4. Patients with Medicaid insurance (covers prescriptions to be filed at Exact Care pharmacy).

Exclusion Criteria:

1. Planned hospital admission for any intervention or surgery during the study period (4 months). Patients with emergency/unplanned hospital stays after being enrolled in the study will not be excluded from the study.

2. Patients already receiving medications in pre-packed blisters.

3. Patients from nursing homes, assisted care livings or patients with home health relying on somebody else to administer the medications. (This will be asked to the patient during the initial phone encounter made to assess eligibility and willingness of the patient to participate in the study).

4. Patients following with PCPs that refuse to have their patients enrolled in the study.

Sample size adjustment:

A total of 100 (50 per group) patients will be enrolled. With this sample size, the study has a power of 85% to detect an effect size of 0.6 between the two groups (two-sided type I error=0.05). With a 10% dropout rate, the power will be 80%.

Methods:

Identifying the Patients:

All the PCP's at STJ FHC will receive an email explaining the study and asking for permission to enroll their patients in the study. We will request our clinical operations analyst from the Administration department of STJ FHC to provide us medical record numbers of patients whose PCP's have agreed to participate in the study. From this list we will select patients who are on at least 4 scheduled medications and who have a follow up appointment scheduled with the PCP in the next 6 months. From this list we will randomly select 200 patients meeting all the inclusion criteria's. A total of 200 patients will be selected to account for patients who do not wish to participate in the study. Eligible patients will then be approached via telephone by one of the study investigators to assess their willingness to participate in the study. A telephone encounter will be created in the patient's electronic records (EPIC) for all the patients willing to participate in the study.

Enrollment:

Patients who are willing to participate in the study will be requested to come 30 minutes earlier for their subsequent office visit with their PCP. They will be asked to bring all their pills, bottles, etc. for all the medications they are currently taking.

During the subsequent office visit patients willing to participate in the study will be consented by the care coordinators/study investigators. At that time, the patients' PCP will be informed about the patients' inclusion in the study as well as the patients' randomization group. The PCP will be informed in person as well as via a secure password protected e-mail. A separate encounter will be created in the EMR (EPIC) to document the patients' enrollment in the study.

All prescription orders will be placed in EPIC by patients' own PCPs. For the patients randomized to the study group the care coordinators/study investigators will change in EPIC the patients' preferred

pharmacy to Exact Care pharmacy. Thus, patients in the study group will have all prescriptions e-scripted to Exact Care pharmacy. Patients randomized to the control group, will continue to receive their medications in the same way they were receiving them before being enrolled in the study. Once we have 100 patients enrolled in the study we will stop recruiting more patients.

Randomization:

Patients will be randomized into two groups: the study group, assigned to receive the medications in pre-packed blisters and the control group, assigned to receive the medications in the standard pill bottles and/or strips. We will consider two strata, 4-5 pills/day and 6+ pills/day.

Given the relatively small sample size, a block scheme with a block size of 4 will be used to randomly assign patients to one of the two groups. The block randomization has the advantage of reducing bias and achieving balance in the allocation of participants to the two groups. This would increase the probability that each group will contain patients with similar baseline characteristics.

Study Groups:

The patients in the study group will receive the medications in blisters (figure 1) packed according to the frequency and time at which the pills are prescribed. Exact Care pharmacy will pack all medications (except for medications taken on an "as needed" (PRN) basis or medications that need constant dose changes eg. Warfarin) into blisters as described below. Insulin and other injectable medications will not be included in the blisters, but will count towards the total number of drugs the patient is taking and will be provided to the patient by Exact Care Pharmacy.

Figure 1: Exact Care medication blisters.

Patients in the control group will continue to receive the medications the same way they were getting them before being enrolled in this study. They will receive instructions about the time and frequency of medication administration from their physicians and nurses. Prescriptions for these medications will be either sent electronically to the pharmacies or will be printed, according to

patients' preference. Patients will pick up the medications in bottles or strips from the pharmacies they choose.

Packaging of blisters by Exact Care Pharmacy:

Patients in the study group will have their prescriptions e-scripted to Exact Care pharmacy by the patients' PCP. The patients in the study group will receive 1 thirty day prescription and 3 refills. After receiving the e-scripts, Exact Care pharmacy will do the following:

1. Assess what medications need to be refilled for the current prescription period. Once Exact Care receives medication prescriptions it will try to fill the medications for the patient and will charge Medicaid for the prescriptions. At this point, Medicaid will inform Exact Care if the patient already has medications left from any previous prescriptions and the earliest date the individual medications can be refilled (this information between Medicaid and Exact Care occurs electronically and within a coupe fo seconds to minutes). Exact Care will then adjust for all the medications the patient has left from previous prescriptions and send pill bottles for all the medications the patient needs refilled for the current prescription period. Patients with Medicaid insurance receive only 30 day supply of their medications. Hence at any point during the current prescription period the patients will not need more the 30 days of medication refill for any of their medications.

Following graph (figure 2) explains the way medications will be filled for the first prescription period. The patient depicted in figure 1 is on 4 medications. During enrollment (beginning of the graph on the left) he has 10 days supply of medication 1, 20 days supply of medication 2, 15 days supply of medication 3 and 8 days supply of medication 4 from previous prescriptions. As soon as Exact Care receives prescriptions for the patient it will try to fill the medications and charge Medicaid for the prescriptions. At this point Medicaid will inform Exact Care how many days of medication supply does the patient already have from the previous prescription and when is the earliest date individual medication can to be refilled. Since our patient has medication 2 to last for 20 days which is more than other remaining medications, Exact Care will fill other medications to last the patient till the end of the 20^{th} day. Hence Exact Care will send the patient pill bottles containing 10 days supply of medication 1, 5 days supply of medication 3 and 12 days supply of medication 4 on the day the patient needs refills. Thus at the end of 20 days the patient will need refills for all 4 medications.

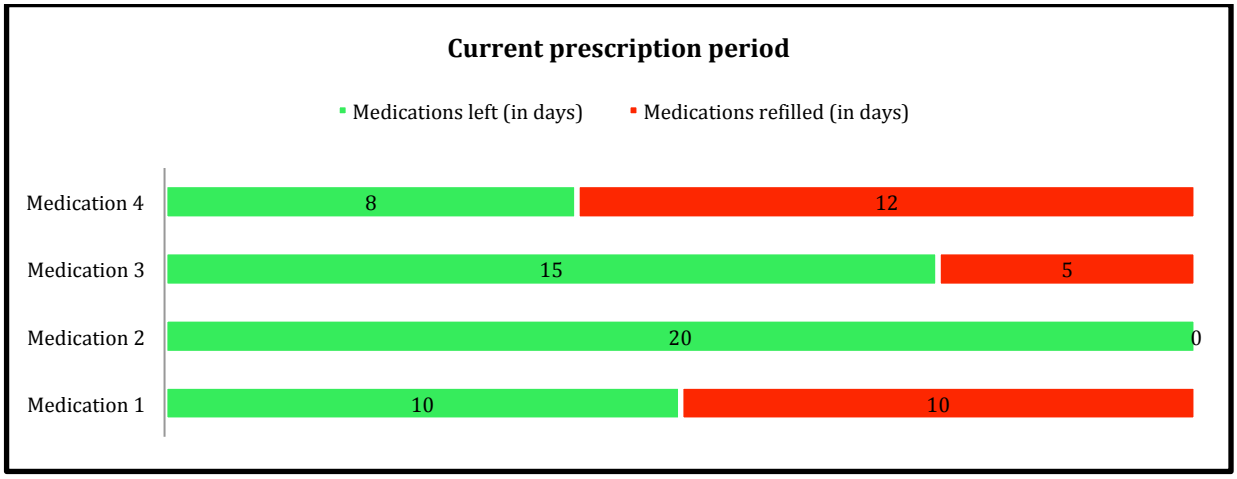


Figure 2

2. For the next refilling period Exact care will prepare the blisters containing pills based on the frequency at which the pills are to be taken. The blisters will then be packed into boxes which will be delivered to the patients' house within 24-48 hours.

As stated above, on the 20th day the above patient will need refills for all his medications. Hence on the 20th day Exact Care will pack blisters containing all 4 medications based on the frequency at which the pills are to be taken for the subsequent refilling period. This has been depicted in figure 3.

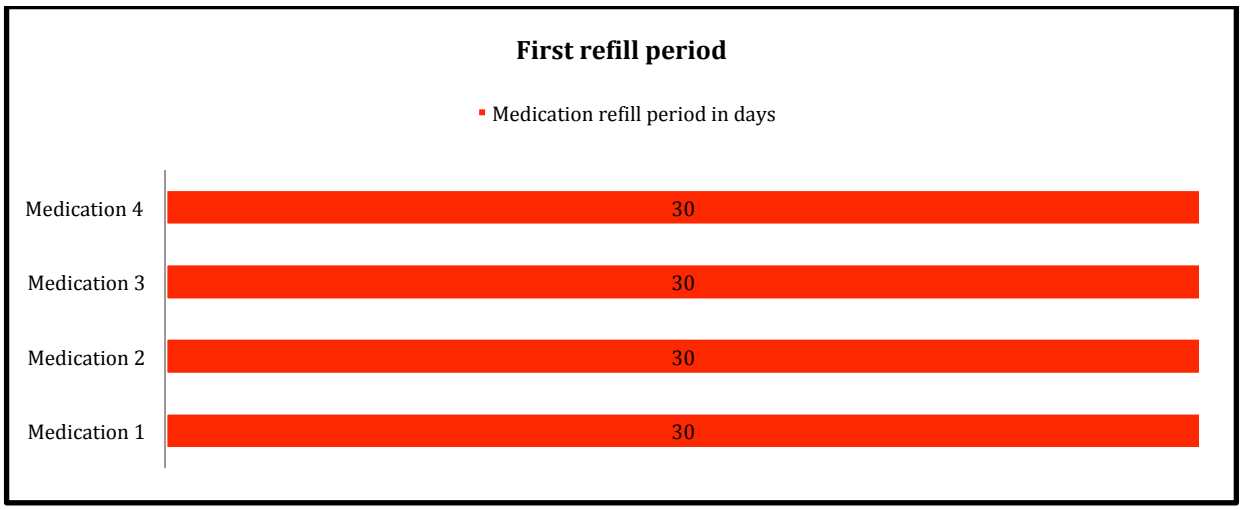


Figure 3

Each blister will contain pills to be taken at a given time. For instance all pills to be taken in the morning will be packed in one blister and all the pills to be taken in the evening will be packed in another blister. This will allow the patient to open a blister and take all the pills at once, eliminating the need for the patient to sort the medications. The blisters will include printed instructions about the content and the time of medication administration. Prescriptions for PRN medications, medications requiring constant dose changes or injectable medications like insulin will be filled by Exact care pharmacy. These medications will not be included in the blister packaging. PRN

medications and medications requiring frequent dose change will be supplied in separate pill bottles to allow the patient to take those medications as and when required. The blisters will be delivered to the patients' home by Exact Care pharmacy in 24-48 hours.

During the study period Exact Care will be electronically notified about any changes made to the patient's active treatment regimen. If a new medication is added to the existing regimen, Exact Care pharmacy will mail a new pill bottle to the patient's home and the patient will take the medication as directed by his/her physician in addition to the medications from the blister for that filling period. When new blisters are packed for the next refilling period the additional medication from the previous filling period will be included in the new blister. If a medication is removed from the patient's treatment regimen then the patient will be advised to manually remove that medication from the blister for that filling period. Every pill in the blister will have a code imprinted on it (figure 1). The blister pack will mention what code represents which medication. This way the patient will be able to identify the medication that is not supposed to be taken. For the next medication-filling period Exact Care will pack new blisters with the deleted medication removed. Thus any change to the treatment regimen during the study period will be incorporated in the blisters when they are freshly packed during the next filling period.

Intervention:

On the day of patient's office visit with his/her PCP:

A. The care coordinator will:

1. Obtain patients' consent to participate in the study prior to seeing the PCP.

2. Allot the patients to either the study or the control group based on the block randomization.

3. Inform the patients' PCP about the patients' inclusion in the study as well as the patients' randomization group in person and via secure e-mail.

4. Create a separate encounter in the patients' electronic chart (EPIC) to document the patients' involvement in the study and the study arm the patient was assigned to.

5. Change the pharmacy of the patients assigned to the study group to Exact Care pharmacy in (EPIC).

B. During this same visit the pharmacist will:

1. Count all remaining medications from all previous prescriptions that the patient is actively taking at the time of enrollment.

2. Schedule an appointment for patients from both the groups with the phramacist, 3 months +/- 15 days from that visit.

Patients from the study group will receive 1 thirty-day prescription with 3 refills for all the medications they need. For the first prescription period, Exact Care will adjust and send the patient only those medications that need to be refilled by the patient, as mentioned above. Although the patients will be studied for medication adherence only for a 2-month period they will receive refill prescriptions for a 3-month period. This will ensure that the patients do not run out of medication blisters before their pharmacist visit at the end of 2 months (study period). Patients from the control group will continue to receive their medication prescriptions as decided by the patients with their PCP.

At the end of 3 months +/- 15 days the patients from both the groups will return to the office for the pharmacist's appointment. Patients will be contacted via telephone by the care coordinator/pharmacist before the pharmacist's appointment to request them to bring with them all remaining medications from the prescriptions given to them during the study period. This telephone call will be documented in EPIC as a telephone encounter by the care coordinator/pharmacist.

During the pharmacist's appointment the following will be performed:

1. All remaining medications from the prior prescriptions for patients in both the groups will be counted to assess the patients' adherence to the treatment.

2. For patients in the control group the pharmacist will call their pharmacies to assess if they had refilled their medications in a timely fashion.

3. Give the patients from both groups feedback forms to fill (assessing ease of use of their pharmacy).

During the study period there will be no intentional contact between the study team and the patient. If the patient decides to withdraw from the study, he/she may do so at any time. The patient will have no limitations to contact his/her PCP if and when the patient feels necessary. For any questions regarding the study protocol or exact care pharmacy (for patients in the study group), the patients will be given phone number (216-767-4242) which they can call during regular working hours (8 am to 5 pm) on weekdays.

Outcome:

At the end of the study the patients will be assessed for medication adherence. The patients in the study group will be given 1 prescription for thirty days and 3 refills:

- The 1st thirty day prescription period will be the adjusting period during which patients in the study group will get refills in such a way that the patients will need all the medications to be refilled at the same time for the 1st refill period (figure 2).

- The first and second refill period will be the study period, during which the adherence to medication will be assessed.

- The third refill period will ensure that the patients in the study group do not run out of their medications before their pharmacist appointment.

For the patients in the control group the patients and the PCP will decide how the medications will be prescribed to the patients. It should be noted that all our patients are covered by Medicaid insurance and will not receive more than 30 days of medication supply at any time. Patients in the control group will be studied for adherence for the 2 - 3 months immediately after enrollment. The follow up appointment in 3 months +/- 15 days will ensure that the patients in the control group have completed the study period of 2 months.

Adherence will be determined by counting the pills the patients have left at the end of the study period from prescriptions given to the patient at the beginning and during the study period.

The primary outcome of this study will be to assess the difference in the mean percentages of missed pills between the study and the control group.

The secondary outcome will be to assess the difference in the mean percentages of missed pills based on the indication for the pills or the pill type/category (eg. Hypertension pills, diabetes mellitus pills, fibromyalgia pills etc.).

Statistical Analysis:

Baseline patient characteristics will be summarized as means and standard deviations, median and inter-quartile ranges or frequencies and percentages appropriately for the two groups. Continuous characteristics will be compared using t-test or Wilcoxon rank sum test, and categorical characteristics will be compared using Chi-squared test.

We will compute the number and percentages of missed pills for each subject and summarize them by group. The primary analysis will compare the mean percentage of missed pill between the two groups using t-test. The analysis will follow the intention-to-treat principle. Linear regression models will used to adjust the results for patient characteristics that differ significantly (two-sided p-value <0.05) between the two groups. All analyses will be conducted using R (cran.r-project.org) and statistical significance will be considered with a two-sided p-value <0.05.

Patient confidentiality:

A master list (excel spread sheet) with information about patients will be created. Each patient will be assigned a unique ID in the database. The data will be saved on a password protected Excel spread sheet and stored on a secure Cleveland Clinic Server. Only the pharmacist and the care coordinator will have access to the patient identity information. For the purpose of analysis, the data will be deidentified prior to sharing with the other investigators and statisticians. The excel spread sheet will include the following patient information:

- Age
- Sex: M/F
- Race
- Smoking and alcohol history
- Comorbid conditions:

- Hypertension (using ICD 9 codes)
- Diabetes Mellitus (using ICD 9 codes)
- Dyslipidemia (using ICD 9 codes)
- Myocardial infarction, heart attack, NSTEMI, unstable angina, STEMI (using ICD 9 codes)
- History of angioplasty/ PCI.
- CHF OR congestive heart failure OR heart failure (using ICD 9 codes)
- CKD or Chronic kidney disease (using ICD 9 codes)
- History of Stroke/TIA (using ICD 9 codes)
- Other comorbidities

- Medications:
  - Medications prior to baseline clinic visit
  - New medication added to the treatment regimen during the study period
  - Medications removed from the treatment regimen during study period
  - Medication list at the end of clinic visit.

A folder will be created for each patient, including all the documents exchanged between the patient and the study team including a copy of the protocol, consent form, data collection sheet, and feedback form. A study log will be created containing all documents created for the study or relevant to the study including the Curriculum Vitae of the study participants. These folders will be kept securely locked in the administrative office of the nurse conducting the study at STJ FHC.

Role of Exact Care pharmacy:

The Exact Care pharmacy will serve the function of a pharmacy, packing and delivering the medications as mentioned above. It will not have access to patients' health information. The Exact Care pharmacy will not receive any compensation. Exact care pharmacy does not charge the patient or the patients insurance any extra charge for packaging the blisters or mailing the medications to the patients' home.

Reason to choose Medicaid:

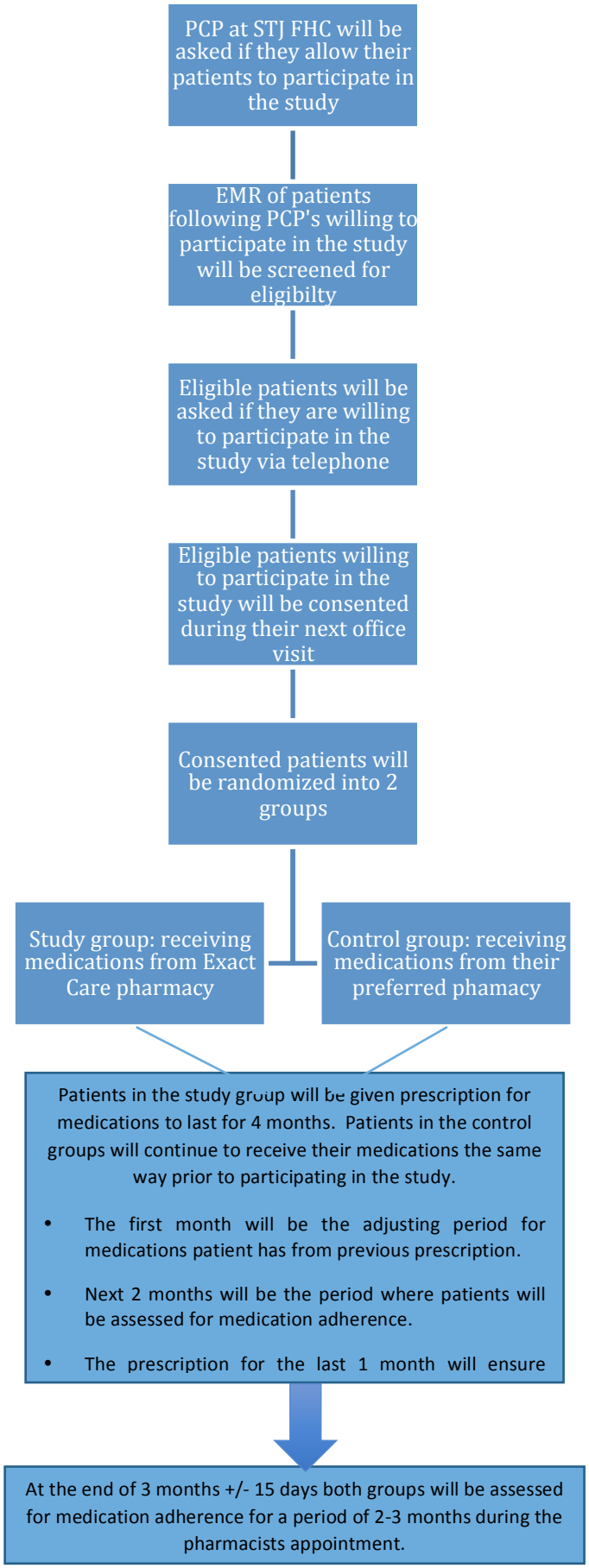
1. Majority of the patients following PCP's at STJ FHC have Medicaid as their insurance.

2. Medicaid covers 100% of the patients' medications cost.

3. Medicaid approves Exact Care pharmacy to fill medications for the patient.

4. It does not allow to fill more then 30 days prescription at a given time. Hence for every refilling period the patient will need refills for all his medications which is necessary for the study.

Schematic overview of Study Design:



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