

2015

The economic impact of a pharmacy-based hybrid medication adherence model in patients with metabolic syndrome

Kevin Edward Omerza
University of Toledo

Follow this and additional works at: <http://utdr.utoledo.edu/theses-dissertations>

Recommended Citation

Omerza, Kevin Edward, "The economic impact of a pharmacy-based hybrid medication adherence model in patients with metabolic syndrome" (2015). *Theses and Dissertations*. 1831.
<http://utdr.utoledo.edu/theses-dissertations/1831>

This Thesis is brought to you for free and open access by The University of Toledo Digital Repository. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of The University of Toledo Digital Repository. For more information, please see the repository's [About page](#).

A Thesis

entitled

The Economic Impact of a Pharmacy-Based Hybrid Medication Adherence Model in
Patients with Metabolic Syndrome

by

Kevin Omerza

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the
Master of Science Degree in Pharmaceutical Sciences

Dr. Sharrel Pinto, Committee Chair

Mr. Robert Bechtol, Committee Member

Dr. Aliaksandr Amialchuk, Committee Member

Dr. Patricia Komuniecki, Dean
College of Graduate Studies

The University of Toledo

May 2015

Copyright 2015, Kevin Edward Omerza

This document is copyrighted material. Under copyright law, no parts of this document may be reproduced without the expressed permission of the author.

An Abstract of
The Economic Impact of a Hybrid Medication Adherence Intervention in Patients with
Metabolic Syndrome

by

Kevin Omerza

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the
Master of Science Degree in Pharmaceutical Sciences

The University of Toledo

May 2015

Background: Individual pharmacy-based interventions have improved outcomes, but have not solved the \$290 billion problem of medication non-adherence. Combinations of interventions have a potential to more heavily impact medication adherence, and associated healthcare costs.

Objectives: To 1) Describe the implementation, and initial experiences, of a hybrid model of pharmacy care for patients with metabolic syndrome, 2) Study the impact of a hybrid model of pharmacy care on economic outcomes when compared to other community pharmacy models of care in patients with metabolic syndrome. 3) To study the impact of a hybrid model of pharmacy care on adherence to medications targeted by the CMS Five-Star Quality Rating System in patients with metabolic syndrome.

Methods: This is an exploratory pilot of a large, prospective, randomized control study. The hybrid model utilizes an appointment based model to provide adherence blister packaging, Medication Therapy Management (MTM) and refill synchronization. A second group receives adherence packaging and refill synchronization, a third group MTM alone, and a control group receives none of the aforementioned services. Contact

between the researcher and participant occurs every three months, alternating between face-to-face and telephonic. All four groups are compared for healthcare cost and utilization, as well as adherence to medications identified by the Centers for Medicare and Medicaid Services (CMS) STAR measures.

Participants were recruited from a local endocrinology practice within an Integrated Delivery Network (IDN), and included adults within a certain health plan selected from a Diabetes Center. Patients were required to have; diabetes, hypertension and hyperlipidemia, and at least one medication for each disease state.

Cost data was obtained via medical and prescription claims. Medication adherence was calculated from the claims data as the proportion of days covered (PDC). Baseline consists of data for the six months prior to enrollment. This is compared, via trend analysis, with data for six months post-enrollment.

Results: Initial economic outcomes showed promising trends in all of the intervention groups. Overall, the hybrid model of care did not experience a change in total costs. This is due to a decrease in medical costs and a concurrent increase in prescription costs.

Discussion: Literature suggests that the trends experienced may lead to prevention of avoidable medical costs and long-term overall savings. Initial trends in medication adherence suggest that the hybrid model of care may have an impact on CMS STAR ratings. This may have policy implications as insurers plan to maximize their STAR ratings. Further study, including the continuation and expansion of the current study, is required to provide evidence to support the provision of the hybrid model of care.

I dedicate this thesis to my parents, grandparents, as well as the rest of my family for all of their love, support, and inspiration throughout my educational journey.

Acknowledgements

I would like to acknowledge Dr. Sharrel Pinto for her support and guidance throughout my undergraduate and graduate studies at the University of Toledo. She has provided opportunities and challenges, and helped me to grow through experiences. I am thankful for the support of Professor Robert Bechtol for his guidance, inspiration, and countless discussions. I am also grateful to Dr. Aliaksandr Amialchuk for his time, assistance and advice on this project. I would be remiss if I did not also mention the thoughts and insight of Dr. Varun Vaidya and Dr. Monica Holiday-Goodman.

I would also like to thank Joseph and Judith Conda for their support and generosity, which helped to propel me through my experiences in research and practice.

I would like to acknowledge my fellow graduate, and undergraduate, students within the HOSS division. This includes Tessa Hastings, Andrew Brinkerhoff, Alex Born, Feyikemi Osundina and Matt Jordan within PCOR, as well as Keyuri Adhikari, Vamshi Ruthwik Anupindi, Drishti Shah and Duy Le. It has been a pleasure to get to know them individually through courses, projects, late nights and conferences.

I would like to thank my family and friends (including persons already mentioned). This thesis would not have been possible without their love and constant support, especially during the periods of sleepless nights and stressful days. Lastly, I would like to express my gratitude towards my parents for supporting me in every possible way through my educational endeavors.

Table of Contents

Abstract.....	iii
Acknowledgements.....	vi
Table of Contents.....	vii
List of Tables.....	xi
List of Figures.....	xii
List of Abbreviations.....	xiii
1. Introduction.....	1
1.1 Background.....	1
1.2 Problem Statement.....	5
1.3 Goal.....	5
1.4 Objectives.....	6
2. Literature Review.....	7
2.1 Medication Adherence.....	7
2.2 Economic Impact of Medication Adherence.....	9
2.3 Metabolic Syndrome.....	14
2.4 Cost of Metabolic Syndrome.....	17
2.5 Factors Affecting Medication Adherence.....	20
2.6 Measurement of Medication Adherence.....	27
2.7 The Role of the Pharmacist.....	32

2.8 Interventions to Improve Medication Adherence.....	34
2.8.1 Medication Therapy Management (MTM).....	35
2.8.2 Appointment Based Model.....	40
2.8.3 Adherence Packaging.....	41
2.8.4 Refill Synchronization.....	43
2.8.5 Multi-component Interventions.....	45
3. Methods.....	47
3.1 Design.....	47
3.1.1 IRB Approval.....	49
3.2 Implementation of the Hybrid Model.....	50
3.3 Study Sample.....	55
3.3.1 Population.....	55
3.3.2 Sample size.....	55
3.3.3 Inclusion.....	56
3.3.4 Exclusion.....	56
3.4 Process Regarding Practice.....	57
3.4.1 Groups.....	57
3.4.2 Setting.....	57
3.4.3 Protocol.....	58
3.5 Process Regarding Research.....	62
3.5.1 Identification.....	62
3.5.2 Recruitment.....	63
3.5.3 Enrollment.....	64

3.5.4 Randomization.....	65
3.5.5 Research Personnel.....	65
3.5.6 Data Collection.....	66
3.5.7 Data Coding.....	66
3.5.8 Data Analysis.....	67
4. Results.....	69
4.1 Study Enrollment.....	69
4.2 Study Groups.....	72
4.3 Baseline Characteristics.....	72
4.4 Economic Analysis.....	75
4.4.1 Data.....	75
4.4.2 Total Cost.....	77
4.4.3 Inpatient Cost and Utilization.....	77
4.4.4 Outpatient Cost and Utilization.....	79
4.4.5 Emergency Room Cost and Utilization.....	81
4.4.6 Prescription Cost and Utilization.....	82
4.5 Adherence.....	84
5. Discussion.....	87
5.1 Implementation and Experiences.....	87
5.2 Economic Outcomes.....	89
5.3 Adherence Outcomes.....	93
5.4 Limitations.....	95
5.5 Conclusions.....	96

5.6 Implications and Future Research	97
References	101
A. Study Timeline	126
B. Operational Definitions	127
C. Visit Algorithms	128
D. Outcomes Table	133
E. Screening Tool	134
F. Intake Form	135
G. CMR	137
H. PMR	140
I. Telephonic Follow-Up	142
J. Database and Data Dictionaries	144

List of Tables

2-1	Thresholds for 5-Star Ratings	13
2-2	Risk Factors for Metabolic Syndrome	14
2-3	Dimensions of Medication Adherence.....	21
3-1	Randomization Groups	57
4-1	Breakdown of Participants by Study Group	72
4-2	Baseline Demographic Characteristics	73
4-3	Baseline Clinical Markers.....	74
4-4	Baseline Service Utilization.....	74
4-5	Number of Patients with Data Each Month: All Participants	75
4-6	Number of Patients with Data Each Month: Six Month Participants	76
4-7	Participants Missing Prescription Data.....	76
4-8	Adherence to Medications Included in CMS Star Ratings	85
4-9	Thresholds for 5-Star Ratings	85
4-10	STAR Measure Adherence Ratings	86

List of Figures

2-1	MPR and PDC Equations.....	30
3-1	Theoretical Framework.....	49
4-1	Flow Diagram for Physician and Pharmacist Letters	70
4-2	Flow Diagram of Direct Calls.....	71
4-3	Total Costs	77
4-4	Inpatient Costs	78
4-5	Inpatient Utilization	79
4-6	Outpatient Costs.....	79
4-7	Outpatient Utilization.....	80
4-8	Emergency Room Costs.....	81
4-9	Emergency Room Utilization	82
4-10	Prescription Costs	83
4-11	Prescription Fills	83

List of Abbreviations

ANOVA	Analysis Of Variance (A statistical Test)
CMR.....	Comprehensive Medication Review
CMS	Center for Medicare and Medicaid Services
ECA.....	Estimated Cost Avoidance
EDCC.....	Endocrine and Diabetes Care Center
HMO	Health Maintenance Organization
IRB.....	Institutional Review Board
JNC-VII.....	Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: Seventh Report
MAP	Medication Action Plan
MPR	Medication Possession Ratio (An adherence measure)
MTM.....	Medication Therapy Management
MTR.....	Medication Therapy Review (Similar to CMR above)
NCEP	National Cholesterol Education Program
OTC.....	Over-The-Counter (Medication)
PCMH	Patient Centered Medical Home
PDC.....	Proportion of Days Covered (An adherence measure)
PI.....	Principle Investigator
PMPM.....	Per Member Per Month
PMR	Personal Medication Record
RA.....	Research Assistant
RAAS.....	Renin-Angiotensin-Aldosterone System
ROI.....	Return on Investment
SAS	Statistical Analysis System
SPSS.....	Statistical Package for Social Sciences

Chapter 1

Introduction

This chapter provides a brief introduction to important concepts of this study. Background information, a need for the study and study objectives are presented.

1.1 Background

A lack of adherence to medications is a problem which leads to billions of dollars annually in otherwise avoidable costs. Adherence is the extent to which patients take medications as prescribed by their health care providers, with a lack of adherence termed as medication non-adherence.¹ Taking medications as prescribed at least 80% of the time has been shown to improve health and reduce hospitalizations.² Non-adherence to medications contributes to an estimated \$290 billion dollars in avoidable costs through emergency room visits and hospitalizations which could be prevented through control of patients' disease states.³

Medication non-adherence can be attributed to multiple causes. Some causes are due to the patient, such as concerns about medications or side effects⁴, increased age⁴⁻¹¹, lower economic status^{6,1112} and race.^{6,7} A lack of knowledge regarding disease or treatment can also lead to lower adherence, as the patient does not understand how or

why to take their medications.¹²⁻¹⁴ Patients can forget to take their medication, or they can forget the instructions, leading to missing a dose.¹⁵⁻¹⁹ Patients who have more contact with a healthcare provider have been associated with higher adherence.^{8,10,20} There are a number of therapy related risk factors for non-adherence such as increased regimen complexity, increased length of therapy and medication side effects.^{6,7,9-11,21,22} Condition factors, such as a lack of symptoms in diseases such as diabetes, hyperlipidemia and hypertension, may lead to lower adherence, due to a lack of perceived benefit.^{5,23,24}

In addition to non-adherence to medications, the increase of long-term chronic disease presents a risk of increased costs and utilization of healthcare. Studies have shown that improved adherence, especially adherence levels higher than 80%, can decrease overall healthcare costs in patients with diabetes,²⁵⁻²⁸ hypertension,²⁹⁻³¹ and hyperlipidemia.²⁹⁻³¹ Improving adherence to diabetes alone could provide a savings of \$8.3 billion annually.³² Metabolic syndrome is a group of chronic risk factors, which increases the risk for a myriad of disease states such as heart disease and stroke.³³ A study of long-term costs among a group of Medicare beneficiaries found that metabolic syndrome increased healthcare costs by 20% over 10 years.³⁴ The direct costs of care for metabolic syndrome increases costs to the healthcare system. The costs of metabolic syndrome are of great concern due to the fact that many costly health issues can be avoidable with medications and lifestyle modifications.^{35,36}

Recent reforms in healthcare reimbursement focus on improving quality, while decreasing the cost of care, and reflect the importance of medication adherence. The Center for Medicare and Medicaid Services (CMS) has implemented the Five-Star Quality Rating System to measure the quality of care provided by health and prescription

drug plans. Three of the measures within this system target medication adherence in diabetes, hypertension and hyperlipidemia respectively, and are given a greater weight when determining a plan's overall score.³⁷ These ratings can have serious implications on enrollment, reimbursement and contracts for health plans. Plans may receive bonus payments for exceeding, or penalties for failing to meet, predetermined thresholds. Due to the potential cost savings and reimbursement implications of improved adherence, targeted interventions by healthcare professionals are economically attractive.³⁸

Interventions to improve adherence are as varied as the causes of non-adherence. Various healthcare practitioners have tried strategies aimed at the causes of non-adherence.³⁹ This includes behavioral and educational interventions.⁴⁰ Behavioral interventions include the timing, packaging and reminder strategies for medications and educational interventions include providing oral and written information to individuals or groups. Unfortunately, studies assessing the economic outcomes of such interventions are scarce in the literature. In the studies which assess economic outcomes, the majority of interventions are provided by pharmacists. Pharmacists can play a key role in providing adherence interventions, as they are accessible to patients,⁴¹ and have an extensive knowledge of medications.⁴² Pharmacists have provided interventions such as pillboxes, unit-of-use packaging, calendars, written or telephone refill reminders, dosage-schedule changes, counseling, education and medication therapy management (MTM).⁴⁰ Medication therapy management (MTM), specialized adherence packaging, and refill synchronization are three interventions which are becoming more common. MTM is a means to educate the patient regarding their disease state and medications.⁴³ MTM has been shown to improve adherence and reduce overall health care costs. MTM programs

have been found to greatly decrease healthcare costs through improved disease control, and avoiding unnecessary healthcare utilization.⁴⁴⁻⁴⁷ Due to this improved disease state control, the savings have been shown to range from \$1.29 to \$12.10 for each dollar spent to provide the service.⁴⁸⁻⁵¹ Patients and providers have additionally noted the benefits of MTM programs on healthcare quality and satisfaction.^{47,52,48,53} Adherence packaging involves dispensing medications in specialized packaging which is designed and organized to promote remembrance of medication dosage times.⁵⁴⁻⁵⁷ Patients have found that this makes medications easier and safer to take.⁵⁸⁻⁶² MTM can be provided within an Appointment Based Model (ABM). An ABM involves scheduling MTM visits in advance. This allows both the pharmacist and the patient to prepare for the visit. Providing MTM within an Appointment Based Model can help to make MTM sessions more efficient and effective.⁶³ Adherence packaging has been shown to improve adherence and prevent discontinuation.⁵⁴⁻⁵⁷ Refill synchronization is a strategy in which the refill times of all medications are scheduled to occur at the same time, making it easier for patients to obtain their medications.⁶⁴⁻⁶⁶ This can reduce regimen complexity,⁶⁴ and limit the burden on the patient through decreased visits to obtain medications.^{65,67,68} This decreased burden led to patients having medications more consistently and an improvement in adherence.⁶⁴

Pharmacy-based interventions have often been studied alone and have been known to be effective in improving adherence, but it has been shown that combining interventions has a greater effect.⁶⁹ A handful of studies have attempted combinations of interventions.^{70,71} While these studies did show an improvement in adherence, they did not assess if the results were due to the combinations of interventions or due to the

individual interventions they contained. Further studies are needed to determine the effect of combining multiple interventions.

The changing healthcare landscape, including the Affordable Care Act, provides a focus on decreasing healthcare costs and improving collaboration of healthcare professionals.⁷² In recent years, MTM has become more integrated into Medicare, with all Medicare Part D sponsors required to offer MTM coverage.⁷³ This increased coverage has led to an increase in MTM provision, allowing more patients to benefit from the outcomes.⁷⁴ Outside of the increasing provision of reimbursement for MTM, provision of pharmacy services are not often covered by health care payers. Reimbursement can incentivize, as well as allow the ability to provide, the provision of pharmacy services. This, in turn, can improve the overall quality of care provided, leading to long term economic implications for payers. In order to incentivize this coverage, evidence of the economic impact of these services must be shown.

1.2 Problem Statement

The impact of a hybrid model of care, which combines multiple interventions needs to be studied to assess the impact on adherence, costs and healthcare utilization.

1.3 Goal

To provide evidence of the economic value of a hybrid model of care consisting of adherence packaging, refill synchronization and MTM within an appointment based model.

1.4 Objectives

1. To describe the implementation, and initial experiences, of a hybrid model of care for patients with metabolic syndrome.
2. To study the impact of a hybrid model of care on economic outcomes when compared to other community pharmacy models of care in patients with metabolic syndrome.
3. To study the impact of a hybrid model of care on adherence to medications targeted by the CMS Five-Star Quality Rating System in patients with metabolic syndrome.

Chapter 2

Literature Review

This chapter provides a brief insight into major concepts of this study. A review of the literature has been conducted focusing on the impact of medication adherence, metabolic syndrome, the financial burden of both and strategies to improve adherence.

2.1 Medication Adherence

Adherence to a medication regimen is generally defined as the extent to which patients take medications as prescribed by their health care providers.¹ Medication adherence involves active, voluntary, and collaborative involvement of the patient in treatment of disease.⁷⁵ This requires that the patient is educated enough to make an informed decision. The patient must understand the nature of the medical problem, be committed to addressing it, and believe the prescribed medication is an effective means of treating the problem. The term “adherence” is preferred by many health care providers over the term "compliance", as “compliance” suggests that the patient is passively following the doctor's orders.⁷⁶ Both terms can be found in the literature, and are often used interchangeably. A third term, persistence, is also frequently used. Persistence refers to the behavior of taking the full course of therapy for the prescribed duration.⁷⁷ For

chronic conditions, persistence equates to the continuation of a medication, but also can be used as a measure of the time elapsed since the initiation of a medication which can be helpful in therapeutic decisions.

A lack of adherence can be subdivided into primary and secondary non-adherence. Primary non-adherence refers to a patient failing to pick up the first fill of a prescription in a timely manner.⁷⁸ Data to measure primary non-adherence can be obtained via matching medical records to prescription claims or via patient survey. The necessity of matching prescribing records with pharmacy claims or surveying patients has led to a lack of data on primary non-adherence, although electronic prescribing is providing an easier means of collecting data.⁷⁸ Estimates of primary non-adherence after hospital discharge have been found to be 17% for blood pressure medications⁷⁹ and 24% among hospital patients⁸⁰. Chronic medications tend to have higher rates of primary non-adherence.⁸¹ A survey of patients not picking up a cholesterol medication, found that the most common reasons were concerns regarding the medication, including side effects, and a decision to try lifestyle modification instead.⁸² Knowledge of, and interventions to prevent, primary non-adherence can help to improve the number of patients who pick-up a medication.⁸³ This information could potentially also then be used to help patients to continue picking up their medications.

By contrast, secondary non-adherence is related to inability to take a medication as prescribed and not obtaining refills in a timely manner, or not obtaining them at all.¹ This data can be obtained via a number of different techniques, such as pill counts, direct observation of the patient, biochemical analysis of patient's blood, patient self-report, and electronic medication monitors. Unfortunately, these techniques can be resource intensive

and in the case of self-report rely on patient honesty. To overcome these limitations, pharmacy claims databases can be analyzed to assess secondary medication adherence. Due to the myriad of options, and relative ease of measuring secondary medication adherence, it is more often reported in the literature.⁷⁸ A common goal for medication adherence, at which patients are considered adherent, is having medications 80% of days. In a study of over 700,000 patients, it was found that 72.3% of high blood pressure, 65.4% of diabetic 54.6% of high cholesterol patients were adherent.⁸⁴ Additionally having more chronic diseases resulted in lower adherence.⁸⁴ The rates of medication adherence are not ideal, and this has a significant impact on healthcare costs.⁸⁵

2.2 Economic Impact of Medication Adherence

The association between medication non-adherence and healthcare cost and utilization has been studied for decades. The New England Healthcare Institute noted that non-adherence, in addition to suboptimal prescribing, drug administration, and diagnosis, results in avoidable health care spending of approximately \$290 billion each year.³ It has been projected that improving adherence to diabetes alone could provide a savings of \$8.3 billion annually through decreased hospitalizations and emergency department visits.³² Medication non-adherence produces a significant burden on the American healthcare system.

Medication non-adherence affects many different components of overall healthcare cost. A study conducted by Sokol et al studied the effect of increased adherence of healthcare costs. They analyzed adherence and cost claims through database review. Patients with hyperlipidemia and diabetes had significant reductions in medical

costs with adherence levels >80%. A significant decrease in hospitalization risk can help to explain this reduction in cost. As a result of improved adherence, the costs of medications increased. This increase in medication cost was more than offset by the decrease in medical costs, resulting in a decrease in overall healthcare costs. Hypertension was also associated with a decrease in hospitalization risk, however this did not result in a significant decrease in medical costs as hypertension has a lower risk of complications.⁸⁵ An analysis by Roebuck et al. also found that medical cost savings offset prescription cost increases. Cost-benefit ratios were found to be 1:10.1 for hypertension, 1:6.7 for diabetes and 1:3.1 for hypertension. Increased adherence was also associated with a decrease in hospitalizations and emergency department visits.⁸⁶ Interventions to improve medication adherence can lead to an increase in prescription costs, but can lead to a decrease in overall healthcare costs.

The overall healthcare costs of medication non-adherence seen in the literature are most commonly reported for diabetes medications. A database analysis by Shenolikar and Balkrishnan studied the association of adherence and healthcare utilization for the first year of a diabetic prescription. An increase in the medication possession ratio by 10% was found to be significantly associated with a 6.9% decrease in likelihood of hospitalizations and a 5.1% decrease in likelihood of emergency department visits.²⁵ Similarly, Balkrishnan et al. found that a 10% increase in the medication possession ratio was associated with an 8.6% to 28.9% decrease in annual costs.⁸⁷ It is important to note that the association of costs and adherence is not perfectly linear. Because of this, a decrease in healthcare costs may not be seen until adherence exceeds 20-39%, although greater savings are found with higher levels of adherence.²⁶ While adherence can

decrease overall healthcare utilization, outpatient visits can increase. A study conducted by Egede et al. found that adherent patients, >80% refill adherence, experienced 37% higher pharmacy costs and 7% higher outpatient costs. This was more than offset, however, by a 41% decrease in hospitalization costs. It was estimated that an annual savings of \$661 million annually could be saved if all patients were >60% up to \$1.16 billion if all patients were to have “perfect”, or 100%, adherence.⁸⁸ Adherence to medications not directly indicated for diabetes can provide economic benefit in diabetic patients. For example, studies have assessed adherence to lipid lowering medications^{27,28} and antihypertensive²⁸ medications, and shown associations between improved adherence and decrease healthcare utilization and costs in patients with diabetes.

Although not as prevalent, studies have also assessed the economic effects of adherence in patients with hypertension and hyperlipidemia. The associations are similar to those in diabetic patients, with slightly lower decreases in healthcare costs. Adherence in hypertensive patients has been associated with decreased hospitalizations, as well as healthcare costs.^{29,30} Additionally, a decrease in disease related emergency department visits can also be seen.³⁰ In hyperlipidemia patients, adherence has similarly been associated with a decrease in hospitalizations and a decrease in healthcare costs, excluding the cost of medications.³¹ Due to the potential cost savings of increased adherence, interventions by healthcare professionals can be economically attractive if designed to minimize cost.³⁸ A large portion of the increase in healthcare costs has been driven by chronic disease, especially those which are poorly controlled. Diabetes, hypertension and hyperlipidemia are three of the most common chronic disease states, and are all associated with metabolic syndrome.

Medication adherence has recently taken on an increased economic significance through healthcare reforms. In addition to medication adherence lowering the cost of care, it is now being tied directly to reimbursement via the Five-Star Quality Rating System through the Center for Medicare and Medicaid Services (CMS).³⁷ This system measures the quality of care provided by Medicare Advantage and Medicare Part D plans on a scale of one to five stars, with one being poor, three being average and five being excellent plan performance. These star ratings are used by CMS, as well as publicly reported on the CMS website. Plans are measured across multiple domains including customer service, member experience and clinical measures. Part D plans are rated on 13 measures, while Advantage plans are rated on 44, of which three are measures of medication adherence.³⁷

These three measures of medication adherence include adherence to statins for hyperlipidemia, renin-angiotensin-aldosterone system inhibitors (RAAS-I) for hypertension, and six classes of oral diabetes medications. Adherence is reported as the percent of members who have greater than 80% adherence measured by Proportion of Days Covered (PDC). Medication adherence is a clinically-relevant measure, and accounts for a significant portion of the overall score due to being assigned a weight 3 times higher than that of most other measures. When measuring adherence for the star ratings, the measures look at the percentage of patients within a plan who are adherent. Star rating thresholds are adjusted annually based upon performance. The 2015 adherence thresholds for five star ratings are shown in Table 2-1.

Table 2-1 Thresholds for 5-Star Ratings³⁷

Stars	Medicare Advantage Plans					Medicare Part D Plans				
	1	2	3	4	5	1	2	3	4	5
Diabetes	<69	69-73	73-77	77-81	>81	<74	74-79	79-82	82-85	>85
RAAS-I	<72	72-76	76-81	81-85	>85	72	72-76	76-81	81-84	>84
Statin	<59	59-68	68-76	76-83	>83	<62	62-69	69-75	75-78	>78

**These numbers represent the percentage of plan beneficiaries who are adherent to their medications*

There are many implications of the overall star ratings. Plans that earn a rating of four or five stars are eligible to receive a quality bonus payment of 4% and 5% of their total reimbursement respectively. In addition, a high rating can have enrollment implications. Star ratings are publicly reported and visible when members are selecting their plans. This allows members to compare the quality of the plan, as well as the cost when making their decision. Plans that receive a five star rating will be accompanied by a high performing icon, making it easy for members to identify the top performing plans. For the 2015 enrollment year, there were 11 Medicare Advantage and three Part D plans that achieved this status. Plans that achieve a five star rating also have the advantage of being able to enroll members during a special enrollment period extending from December 8th to November 30th of the following year.

While strong performance on quality measures is rewarded, poor performance has consequences. Plans that fail to achieve average performance, a rating of at least three stars, will be associated with a low-performing icon making it easier for members to identify plans with poor performance. For the 2015 enrollment year, seven total plans received a low-performing icon.⁸⁹ In addition to enrollment implications, plans that fail to achieve average performance for three consecutive years may be removed from Medicare. For 2015, CMS chose not to remove any poor performing plans, as all poor

performers were showing signs of improvement. CMS maintains this authority for future years. Due to the increased focus on the quality and cost of care, as well as reimbursement and enrollment implications, there is an incentive for plans to improve adherence. The star ratings measure adherence to medications for diabetes, hypertension and hyperlipidemia, which are all associated with metabolic syndrome.

2.3 Metabolic Syndrome

Metabolic syndrome is the name for a group of risk factors which increase the risk of heart disease, stroke as well as a myriad of other disease states. The five risk factors involved are; an elevated waist circumference, elevated blood pressure, elevated triglycerides, low high density lipoprotein-C and an elevated fasting blood sugar. The definitive criteria for each of these components are listed in Table 2-2. In order to be diagnosed with metabolic syndrome, at least three of the risk factors must be present.

Table 2-2 Risk Factors of Metabolic Syndrome

Risk Factor	Term	Criteria
Elevated waist circumference	Abdominal obesity	>40 in (102cm) in men or >35 in (88cm) in women ⁹⁰
Elevated Blood Pressure	Hypertension	Systolic BP \geq 130mmHG, diastolic BP \geq 85mmHG, or on antihypertensive therapy ³³
Elevated Triglycerides	Hyperlipidemia	Triglycerides \geq 150 mg/dL or medications for elevated triglycerides ³³
Low HDL-C	Dyslipidemia	HDL-C<40 mg/dL in men or <50 mg/dL in women or medications for low HDL-C ³³
Elevated fasting blood sugar	Hyperglycemia	\geq 100 mg/dL or medication for elevated glucose ³³

Metabolic syndrome is a prevalent risk factor in the United States. A study conducted by Alberti et al. was designed to assess the prevalence of metabolic syndrome, the individual risk factors and their change over time from 1999 to 2010.³³ Data was obtained through National Health and Nutrition Examination Surveys. Overall, it was found that the prevalence of metabolic syndrome in the United States declined from 25.5% to 22.9%. The risk factors, however, were variable. Hypertension decreased from 32.3% to 24% and hyperlipidemia decreased from 33.5% to 24.3%. These decreases were found to have coincided with an increased in recognition and treatment with medications. The decreases in two risk factors were partially offset by a rise in abdominal obesity from 45.4% to 56.1% and a rise in elevated blood sugar from 12.9% to 16%.⁹¹

Metabolic syndrome is associated with an increased risk of morbidity and mortality. Metabolic syndrome can lead to plaque build-up in arteries, as well as alter heart muscle, leading to heart disease, heart attack and stroke.^{92,93} An analysis of the NHANES II data conducted by Malik et al. supported this increased risk.⁹⁴ Metabolic syndrome was associated with an almost two fold increased risk of death due to coronary heart disease and cardiovascular disease, and a 1.5 increased risk of death due to any cause. The risk of cardiac death was much higher in patients with metabolic syndrome, when compared to having only 1-2 of the risk factors. Even those with one or two of the metabolic risk factors are at an almost two-fold-greater risk of cardiac death. This increased risk of death highlights the importance of adequate control of all risk factors.⁹⁴

In persons with metabolic syndrome, up to 80% of coronary heart disease events, such as heart attack and stroke, may be preventable from optimal control of triglycerides,

cholesterol, and blood pressure.³⁶ These components of metabolic syndrome have become targets for lifestyle modification, medications, and surgical interventions.⁹⁵

Lifestyle modification seeks to control the levels of cholesterol, blood sugar and blood pressure, and is a first-line therapy for metabolic syndrome.⁹⁶ Common lifestyle modifications include body weight control, specialized diets, regular physical exercise, smoking cessation, and decreased alcohol intake.⁹⁶ Lifestyle modification has been shown to be a cost-effective method for controlling disease progression.⁹⁷ Treatment guidelines have lifestyle modification as initial therapy in combination with medications, with the exception of mild elevated cholesterol in which it is the sole initial treatment.^{96,98,99} Lifestyle modification is continued throughout treatment, and its contribution to treatment cannot be overemphasized.⁹⁸

While lifestyle modification has been found to be a cost-effective treatment, it is often insufficient to control metabolic syndrome, necessitating the need for medication therapy. There are a large number of effective medications to control the risk factors of metabolic syndrome. Elevated blood pressure treatment includes multiple classes which focus on promoting removing fluids from the body, altering the blood vessels, or slowing the heart rate.⁹⁸ Medications for cholesterol are aimed at preventing cholesterol from the diet from being absorbed and helping the body to process cholesterol.⁹⁶ Diabetes consists of elevated blood sugar is divided into two types. Type I diabetes involves the inability of the body to produce insulin, which is required by the body to breakdown sugar. Treatment for Type I is limited to insulin replacement through injection of insulin products.⁹⁹ Type II diabetes occurs when the body is not capable of breaking down sugar with insulin. There are various mechanisms for type II therapy, including decreasing the

amount of sugar absorbed, increasing the production of insulin and increasing the effectiveness of insulin.⁹⁹ For each disease state, one medication is started initially, and if is not effective, an additional medication with a different mechanism of action is added.^{96,98,99} Medications, in combination with lifestyle modification, are considered to be cost-effective when utilized to control disease. These treatments prevent costly disease progression and higher cost treatments such as surgery, with non-adherence leading to increased healthcare costs.⁹⁷

2.4 Cost of Metabolic Syndrome

Chronic diseases are expensive to treat. In the United States, over 50% of the population has at least one chronic disease, with 4.9% of Americans having four or more chronic diseases.¹⁰⁰ Patients with multiple chronic conditions can have a large impact on the cost of healthcare. The Veteran's Affairs administration devotes >90% of its resources to patients with multiple chronic conditions.¹⁰¹ In 2010, 14% of Medicare beneficiaries had six or more chronic diseases, and accounted for a disproportionate 46% of total Medicare expenditures.¹⁰² Additionally, access for those with multiple chronic conditions is set to improve under the Affordable Care Act, increasing the burden on insurers.¹⁰⁰

Diabetes, hypertension and hyperlipidemia are three chronic disease states which lead to the increase in healthcare costs. In insured patients, most of this cost is born by the insurer. A study of the Veteran's Affairs health system analyzed costs of patients with multiple disease states. VA patients with three or more medications accounted for 32-35% of patients, and 65-67% of all healthcare costs. Among those with three or more disease

states, diabetes, hypertension, and hyperlipidemia was the most common combination, present in 24% to 29% of patients. Metabolic syndrome leads to median annual health care costs of \$7,000 per person, however, poor control can lead to far greater costs. Combinations of chronic diseases including conditions such as chronic heart failure, ischemic heart disease, renal failure, and stroke can lead to median annual costs upwards of \$50,000 per person in individuals under the age of 65.¹⁰¹ The common triad of diabetes, hypertension, and hyperlipidemia is a burden on health systems outside of the Veteran's Affairs health system as well. A study conducted by Boudreau et al utilized data from three integrated delivery networks to compare healthcare utilization and costs of treatment for those with, and those without, metabolic syndrome. Patients with metabolic syndrome incurred an additional \$2,000 in healthcare costs annually. This was driven by greater utilization of outpatient and inpatient services, as well as greater need for medications. A majority of this increase in cost and utilization was attributed to diabetes treatment.¹⁰³ Given that the prevalence of metabolic syndrome has been found to be as high as 35% of the United States.¹⁰⁴ This presents a large cost to healthcare payers.

Metabolic syndrome increases current healthcare costs, and can elevate future healthcare costs as well. A study conducted by Nichols and Moler looked at treatment costs for over 50,000 patients with components of metabolic syndrome in a large health maintenance organization.¹⁰⁵ Patients with metabolic syndrome accrued over \$4,500 in annual costs for treatment. Each component of metabolic syndrome contributed to outpatient visit and medication costs. Beyond treatment costs, which included medications and outpatient care, 4.1% of patients required a hospitalization related to cardiovascular disease. Hospitalizations related to cardiovascular disease, which is

associated with poor control of the components of metabolic syndrome, incurred costs which were significantly higher. These hospitalizations produced additional costs of \$11,000 to \$14,000 annually per patient. The cost associated with a hospitalization far exceeded the costs of maintenance treatments such as medications and outpatient visits.¹⁰⁵ As cardiovascular disease, and resulting hospitalizations, is largely preventable through control of metabolic syndrome,³⁶ it is important to develop effective strategies to control metabolic syndrome, and allocate resources accordingly.

The increased cost and utilization due to metabolic syndrome occurs in both working age and elderly populations. An analysis of employee data of a large US employer found that those with metabolic syndrome had annual treatment costs of \$4,603 compared with \$1,859 with no risk factors of metabolic syndrome. Both medical and pharmaceutical costs increased, with medical costs averaging \$259 higher for those with metabolic syndrome.¹⁰⁶ When short-term disability costs are included, employees with metabolic syndrome have costs 3.66 fold higher than employees without metabolic syndrome.¹⁰⁷ Higher healthcare costs also translate from the working age population to the elderly population. A study by Curtis et al. found that Medicare costs were also higher in patients with metabolic syndrome when compared to those without. Patients with metabolic syndrome incurred, on average, an increase of 50% in total healthcare costs over a 10 year period, with a significant amount due to preventable complications and disease progression.³⁴ Additionally, metabolic syndrome is becoming more prevalent in adolescents which provides a longer potential duration of disease, and a greater chance of progression to more costly conditions.¹⁰⁸ As an increasing portion of the United States has risk factors included in metabolic syndrome, it is important to control these risk

factors and prevent their progression. While medications can be a cost-effective means of controlling healthcare costs for diabetes,⁹⁷ hypertension,¹⁰⁹ and hyperlipidemia¹¹⁰ through preventing complications, they only have an optimal effect when taken regularly.¹⁰⁹ In order to design effective interventions aimed at improving adherence and reducing healthcare costs, especially among those with chronic diseases, an understanding of the factors contributing to medication non-adherence is required.

2.5 Factors Affecting Medication Adherence

Medication adherence can range from absolute adherence to perfect adherence, although 80% adherence is shown to be a threshold to achieve adequate effects from medications. When patients are non-adherent, they are often in the area termed “partial non-adherence” referring to taking some, but not all, of the prescribed doses.¹¹¹ This can manifest as regular or irregular non-adherence. Regular non-adherence occurs when missed or mistimed doses happen consistently, whereas irregular non-adherence occurs when patients experience periods of non-adherence deemed “drug holidays”.¹¹² The most common forms of non-adherence are not taking doses or delays in administration, with occasional events of overconsumption.¹¹³ Reasons for non-adherence vary widely, as patients have many factors influencing the taking of medications. As 80% adherence is often necessary to achieve the benefits of medication therapies, the barriers of adherence need to be identified in each patient to help in selecting appropriate interventions.

There are a number of barriers to medication adherence. The World Health Organization has divided factors affecting adherence into five dimensions.¹¹⁴ These dimensions include patient related factors, therapy related factors, condition related

factors, social and economic factors, and health system related factors. The five dimensions of medication adherence are described in Table 2-3.

Patient-related problems have often been studied in relation to medication adherence. The common belief that patients are solely responsible for taking their treatment is misleading, as other factors also affect adherence to treatment.¹¹⁴ Patient related factors include both physical and psychological factors.

Table 2-3: Five Dimensions of Medication Adherence

Dimensions of Non-adherence	Examples
Patient	Physical: Visual, Hearing, Cognitive, and Swallowing Impairment; Age; Race Psychological: Knowledge and Perceived Risk of Disease; Perceived Benefit, Adverse Effects, Fear of Dependence of Medications; Confidence in Ability to Follow Treatment; Motivation; Forgetfulness
Therapy	Complexity of Regimen; Duration of Therapy; Side Effects; Lack of Benefit
Condition	Chronic Disease; Lack and Severity of Symptoms; Mental Disorders; Comorbidities
Social and Economic	Low Health Literacy; Lack of Social Support; economic status; Lack of Health Insurance
Health-system	Provider–Patient Relationship; Lack of Access to Healthcare; Continuity of Care

Physical impairments can impact medication adherence. Visual impairment can make taking medications more difficult, such as making it difficult to read labels or be able to distinguish between different pills, resulting in lower adherence.¹¹⁵ Utilizing larger and higher contrast printing can help to alleviate this issue of visual impairment.¹¹⁶

Hearing impairment can also cause difficulty in taking medications, as it can be difficult for patients to comprehend instructions from a physician.^{117,118} It is important to ensure patient understanding of instructions, as well as provide patient-appropriate written materials to aid in medication adherence.¹¹⁶ Cognitive impairment can lead to difficulty understanding directions, requires scheduling medication administration into the daily routine, and leads to uncooperative patients.¹¹⁹ Patients with a cognitive impairment should have caregivers to assist with medical care.¹¹⁶ An additional impairment affecting adherence is a difficulty in swallowing.¹²⁰ Health care professionals should ensure the ability of the patient to swallow prior to prescribing solid dosage forms.¹¹⁶ If the patient is unable to swallow, it may be more appropriate to select an alternative dosage form such as a liquid or injection. In addition to physical impairment, patient demographics can also contribute to medication non-adherence.

Demographics can have an impact on medication adherence. Patient age can have an effect on medication adherence, with older patients having higher adherence rates to lipid medications,⁵⁻⁹ antihypertensive medications,^{5-7,9-11} and oral diabetes medications.^{5-7,9} In addition to age, patient race has also been identified as a factor, with Caucasians reported as having higher rates of adherence.^{6,7} This can be due to disparities in access healthcare, as well as patient beliefs.⁶

Also affecting adherence are patient beliefs and perceptions regarding disease states and medications. Patient perceptions regarding their disease state, such as severity and risks, can have a large effect on medication adherence.²³ Chronic diseases without symptoms, such as hypertension, tend to have low adherence, illustrating the need for patients to be educated on the risks of not receiving treatment.²⁴ Medication perceptions

include concerns of side effects, perceived benefit of a medication, and fear of dependence on medications.⁵ A study performed by Phatak and Thomas used the Beliefs about Medications Questionnaire and Morisky Medication Adherence Scale to assess the association of various medication beliefs on medication adherence. The three negative medication beliefs listed above accounted for 22.4% of the non-adherence of patients.⁴ Potential side effects, and other perceived harmful effects, are associated with lower adherence levels, as patients may perceive the side effects to outweigh the benefits of the treatment.¹²¹ A belief that the medication will not provide an improvement in health has also been associated with lower adherence, as the medication may cause harm.¹²² In many patients, the fear of becoming dependent on, or addicted to, prescription medications has been shown to influence adherence.^{17,123} These same beliefs lead to a decrease in adherence through increasing the risk of forgetting to take medications and forgetting to refill medications.¹⁸ These perceptions are often due to misconceptions, and highlight the importance of educating patients on disease states and medications.

It is also important to note that patient beliefs about themselves can affect adherence. Patients who have low self-efficacy, who do not feel that they are capable of taking their medications, are 4.3 times more likely to be non-adherent.⁵ It is important to include the patient in medical decisions to give them the perceived ability to control their disease in order to improve their self-efficacy. A lack of motivation to adhere to medication has also been implicated in non-adherence.¹²⁴ This lack of motivation stems from the disease and medication perceptions listed above, once more highlighting the importance of patient education.¹²⁵ When medications are prescribed, patients must be educated and provided with the support they require to adhere to medication therapies.

Many times, non-adherence is due to forgetfulness on the part of the patient. Patients can forget to take their medication, or they can forget the instructions, leading to missing a dose.¹⁵ Forgetting a dose has been found to be the most common reasons for non-adherence to medications.¹⁶⁻¹⁹ Common interventions can include reminder strategies, timing medications into the daily routine, and specialized packaging.¹²⁶ Forgetting instructions can also lead to non-adherence through not understanding when and how often to take medications.¹²⁷ Patient forgetfulness regarding instructions can be occur even within the first 30 days, illustrating the need to reassess understanding at each visit, as well as provide written instruction.¹²⁷

There are a number of therapy related risk factors for non-adherence. The complexity of a medication regimen for a disease can affect the extent of medication adherence. As such, medications dosed once daily tend to have higher adherence levels than those dosed multiple times daily.^{10,11,21} Another contributor to complexity is the number of medications in a regimen. A medication regimen involving more medications results in improved adherence as medications can serve as reminders to take other medications^{6,7,9,22}. One exception to this is the use of fixed-dose combination pills. A study by Melikian et al. found that patients who are switched from multiple pills to a combination pill have higher adherence. Patients who are initiated on a fixed-dose product also had higher adherence compared to patients initiated on separate medications.¹²⁸ In patients on multiple medications, low adherence levels can be misleading. In a study by Grant et al. of patients on multiple medications, it was found that 71% of patients who were deemed non-adherent were perfectly adherent to all but one medication. This can be important to consider when determining a medication

regimen, including number of medications and number of daily doses. In addition to the complexity of therapy, increasing the length of therapy leads to lower adherence.⁷ This is especially important for chronic medication, which a patient will take for life. There are many therapy factors which can affect adherence, which should be taken into account when designing a medication regimen.

Similar to patient perceptions, side effects and a lack of a benefit can lead to non-adherence. Side effects are a common reason for non-adherence as well as discontinuation of medications.^{5,122} Additionally, a medication which does not provide a benefit which can be seen by the patient, as is the case in diseases without symptoms, is at high risk of non-adherence.^{5,24} This once again illustrates the importance of educating patients on the importance of medication therapy.

The disease itself can provide risk factors for non-adherence. Just as long-term treatment can reduce adherence, long-term diseases can as well.¹¹⁴ This corresponds with a lack of disease symptoms contributing to non-adherence.^{5,24} In addition to the disease state being treated, patients with multiple comorbidities have been found to have higher adherence rates when compared with patients with only one disease state.^{6,9,11,129} This is due to the fact that medications for one disease can serve as reminders to take medications for other diseases.^{6,7,9,22} Education regarding the conditions of a patient can help to alleviate some of the risk factors of medication non-adherence.

The socioeconomic status of the patient includes many criteria, including low health literacy, a lack of social support, lower economic status and a lack of healthcare insurance. Health literacy is the ability of the patient to understand the information needed to appropriately manage their disease.¹² Low health literacy jeopardizes the

ability of patients to take their medications safely and effectively, leading to a decrease in medication adherence.^{13,14} Interventions should seek to provide health information at a level similar to the health literacy of the patient.¹³⁰ Social support from medical workers and family can also impact adherence, with lower support being associated with lower adherence.^{131,132} It remains to be seen, however, if interventions aimed to improve social support will lead to increased adherence.¹³³ These social aspects can lead to reduced adherence, although there is not a large amount of data to support interventions targeting these risk factors to improve adherence.

In addition to patient social factors, economic factors also have been shown to affect medication adherence. The economic status of a patient is associated with adherence. Patients with higher incomes have higher adherence levels,⁶ while those with lower incomes and those receiving social assistance have lower adherence levels.¹¹ In addition to economic status, increased insurance coverage is also associated with better adherence.¹²¹ The impacts of these economic factors on adherence highlight the economic disparities in healthcare, as well as the importance of access to care.

Medication adherence is not solely the responsibility of the patient, and the healthcare system can significantly affect adherence levels. The fractured provision of healthcare has contributed to non-adherence, including the relationship of the patient and healthcare provider, a lack of access to care, low continuity of care and the costs of medications. Patients who have more contact with a healthcare provider have been associated with higher adherence by a number of studies.^{8,10,20}

Access to, and continuity of, care has been associated with medication adherence. A lack of access to care, including medical care and pharmaceutical care, leads to a

decrease in medication adherence.¹³⁴ This lack of access is targeted by interventions ranging from monetary assistance to community clinics.^{135,136} Continuity of care is often seen by patients to mean that they have a consistent primary care physician.¹³⁷ Increased continuity of care can lead to more confidence and a better relationship with the physician.¹³⁸ A lack of continuity of care has been associated with lower medication adherence.^{139,140} Patients who have more than one prescriber,^{8,11} and who utilize more than one pharmacy^{19,22} have lower adherence levels to antihypertensive therapy. Medication adherence can be impacted by both the relationship with the provider as well as continuity of care.

Medication cost is also a barrier to medication adherence. Higher medication costs¹²⁹ and higher copayments¹⁴¹ are associated with lower adherence. One study found that each \$5 increase in cost to the patient resulted in a 15% decrease in the odds of being adherent.¹⁴² Cost is a significant barrier to adherence, and many programs are available to help reduce the cost to the patient, with many programs showing promising results.^{143,144} Medication cost is a barrier to medication adherence, which includes the cost of the medication as well as patient copays. It is of paramount importance that factors impacting medication adherence can be identified and targeted for intervention to improve medication adherence.

2.6 Measurement of Medication Adherence

The methods utilized to measure medication adherence can be direct measures and indirect measures. Within each subtype, there are a number of available methods. It

is important to note that they all have their strengths and weaknesses, and that there is not a true “gold standard” of measuring medication adherence.¹⁴⁵

Direct measures involve the healthcare professional directly assessing adherence. This can be done through obtaining serum concentrations of the drug, administering the medication to the patient or observing the administration of the medication. These methods provide a more reliable measure of adherence when compared to indirect measures, but are not without their faults. The main limitation is the resources required to use these techniques.¹⁴⁵ They require healthcare professional time, lab services or both. In addition, the measurement of serum levels only measures the adherence of the past few doses, and may not provide a clear picture of the medication adherence throughout the time interval between measurements. Due to the limited time period measured through serum levels, they are subject to distortion through “white coat adherence”.¹⁴⁶ White coat adherence is a behavior pattern in which patient adherence increases in the days approaching an appointment. This can lead to an overestimation of the overall adherence of the patient.

Indirect measures of adherence involve assessing adherence through means other than direct observation or measurement. This can include asking the patient about their adherence, asking the patient to keep a medication diary, performing pill counts, using electronic medication monitors, and analyzing rates of prescription refills. Questioning the patient or caregiver, or having them maintain patient diaries are methods which are relatively easy to use, and therefore can be helpful in busy environments or situations with limited time.¹⁴⁷ While they can be relatively accurate, especially amongst patients who claim to be non-adherent,¹⁴⁷ patient responses can be intentionally or unintentionally

inaccurate.¹⁴⁸ This can result in the health care provider's overestimating the adherence of the patient. Pill counts can involve the patient bringing their medications to be counted, and having the counts compared to the quantity they should have remaining. This quantity is based off of the total days supply and the days since the last refill. While this measure is simple to perform, it only provides the number of medications taken, not when they were taken.¹⁴⁹ Pill counts are also susceptible to distortion by the patient through "pill dumping", taking extra doses periodically, and require the patient to bring in the pill bottle.¹⁴⁹ Electronic medication monitors are a newer method of measuring adherence. This involves a pill container with a microchip in the cap which records when the bottle is opened. This data can then be viewed by the healthcare professional to assess adherence. This provides a continuous monitoring of medication administration, as it also provides time information on when the dose is taken. This information can be very useful to assess adherence but has limitations. The microchip in the cap adds cost to the prescription. In addition, the patient must use the container to store their medications and cannot transfer them into a pillbox with their other medications.¹⁵⁰ It also requires that only one dose is removed from the container at a time, and assumes that the dose is administered at the time of opening, which may not always be accurate.¹⁴⁹ There has also been an analysis of combination of electronic medication monitors, pill count and patient self-report in HIV patients. The resulting composite adherence score was found to correlate better with viral load, but the authors acknowledged that this method would be burdensome to use in clinical practice.¹⁵¹ A common method widely used is the calculation of refill adherence from claims databases.

Prescription claims can be analyzed to assess if patients have the medications they are to take. Utilizing prescription claims is an economical and timely way to obtain adherence information.¹⁵² Analyzing refill adherence is becoming easier with the increased availability of prescription claims information.² Once the refill information is obtained, there are a number of different statistical equations which can be applied.¹⁵³ The most commonly used equations are the medication possession ratio (MPR) and proportion of days covered (PDC).² Equations of MPR and PDC are shown in Figure 2-1.

$\text{MPR} = \frac{\text{Total Rx Days Supply}}{\text{Length of Index Period}}$
$\text{PDC} = \frac{\text{Length of Index Period} - \text{Days without Supply}}{\text{Length of Index Period}}$

Figure 2-1: MPR and PDC Equations

Both MPR and PDC require the determination of an index date, which is the date of an initial fill, or the date of the first fill in the period to be measured. The MPR is obtained by taking the total number of days supplied in the index period and dividing them by the number of days, excluding days hospitalized. The PDC is obtained by taking the total days of medication supplied and divide by the number of days in the index period. For example, if a patient was followed for 100 days, and during this time they were without medication for 20 days, their adherence would be $\frac{100-20}{100} = 80\%$. There is a cap placed so that it cannot exceed 100%, and since it only counts days in which all medications are available, it prevents the double counting of days possible through the MPR method.¹⁵³ PDC is the preferred method of measuring adherence, according to the

Pharmacy Quality Alliance,¹⁵⁴ and is included in a checklist for adherence studies. Pharmacy Quality Alliance is a consensus-based, multi-stakeholder organization committed to improving health care quality and patient safety through the appropriate use of medications. This is due to the fact that PDC is more consistently defined in the literature, and provides a more conservative estimate of medication adherence.¹⁵⁵ PDC does not over count due to switches between drugs or due to duplication of drugs to treat a disease.

Refill adherence rates are often analyzed in a dichotomous manner, with a cutoff point below which patients are considered to be non-adherent. Acceptable rates of adherence vary by disease state and the outcome which is being assessed.¹⁵⁶ An adherence rate of 80% has been found to be adequate for antihypertensive medications to control blood pressure.¹⁵⁷ Another study found that non-adherent diabetic patients, defined as adherence rates below 80%, had a higher risk of hospitalization in the following year, with hypertension and hyperlipidemia showing insignificant results at the same adherence level.¹⁵⁸ A study conducted by Karve et al. attempted to find the optimal “cut-point” of adherence among five disease states to reduce the risk of hospitalizations. This was obtained through an analysis of the Arkansas Medicaid database, and identifying adherence levels which corresponded to the highest possible sensitivity and specificity. The optimal “cut-points” regarding all-cause hospitalizations found were 80% for schizophrenia, 89% for diabetes, 82% for hypertension, 81% for hyperlipidemia and 63% for congestive heart failure. This supports the commonly used 80% level to be used in schizophrenia, hypertension and hyperlipidemia. The data also suggests that a higher level is needed for diabetes medications and a lower level can be used for CHF.²

Limitations of analyzing refill adherence include a lack of information regarding when or if doses are taken.¹⁵⁶ Additionally, analyzing refill adherence requires that the prescriptions be filled through the same prescription claims database.¹⁵⁶ The identification of medication non-adherence is the first step toward improvement. In order to improve adherence, the barriers to adherence must be identified and corrected.

2.7 The Role of the Pharmacist

There are a number of issues confronting the healthcare system in the United States. This includes an increase in the prevalence of chronic diseases, the increase of patients with multiple chronic diseases, as well as their associated healthcare costs and utilization.¹⁵⁹ In addition, there is also a projected shortage of physicians, requiring more non-physician clinical personnel.¹⁶⁰ The pharmacist has the ability to participate in clinical care as a result of the expansion and development of the role of the pharmacist.¹⁶¹

In 1990, Hepler and Strand called for an expansion of the role of pharmacy to take on more clinical services.¹⁶² They proposed the provision of pharmaceutical care as a means to accomplish this. Pharmaceutical care is defined as the “responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient’s quality of life.”¹⁶² These outcomes include curing disease, alleviating symptoms, slowing disease progression and preventing disease. This has served as a guide for the profession of pharmacy. Since 1990, the role of a pharmacist has greatly expanded, due in part to the relative accessibility of a pharmacist compared with other healthcare professionals.⁴¹ In addition, the education of a pharmacist has evolved through the implementation of increased education of medications through the PharmD degree. With this increase in

specialized education, pharmacists are seen as the “medication experts”. This has allowed the profession to embrace the concept of pharmaceutical care.

A pharmacist’s expertise with prescription drugs enables him or her to perform a number of clinical services. The introduction of central-fill services allows for a larger portion of a pharmacist’s time to work directly with patients.⁶⁶ This puts pharmacists in a logical environment to provide services such as MTM, advanced patient counseling, adherence assessment, disease screening and immunizations. Additionally, due to medication filling, patients often interact with a pharmacist more often than a physician.⁴¹ Political support has also contributed through a mandate for MTM provision in the Medicare part D plan.⁷³ The Affordable Care Act, which is changing the landscape of healthcare, provides an opportunity to expand clinical responsibilities, but pharmacists must rise to accept them.⁷² The Affordable Care Act shift from the traditional fee-for-service model to the pay-for-performance model has led to an increased focus on health outcomes. In order to continue the expansion of pharmacy services, pharmacists must continue to provide evidence of the value through improvements in outcomes and decreases in costs.

The clinical services which pharmacists provide have led to overall savings in healthcare costs. An MTM program in Connecticut assessed pharmacist resolution of drug therapy problems. MTM provided to 88 patients resulted in an estimated annual saving of \$1,123 per patient on medication claims and \$472 per patient on medical, hospital, and emergency department expenses. This savings was greater than the cost of the pharmacist time.¹⁶³ Pharmacists are able to provide clinical interventions, which affect medication adherence and impact economic as well as clinical outcomes.

2.8 Interventions to Improve Medication Adherence

The interventions studied to improve medication non-adherence are as varied as the risk factors associated with non-adherence. Interventions are commonly provided by a number of healthcare professionals, including pharmacists, physicians and nurses.¹⁶⁴ Interventions are often divided into behavioral and educational. Behavioral interventions include tools or actions that change a patient's skill level or normal routine, such as pillboxes, unit-of-use packaging, calendars, written or telephone refill reminders, and dosage-schedule changes.⁴⁰ Educational interventions are those which teach the patient about the medication or disease, such as counseling, providing informational resources, reinforcement and group sessions.^{40,165} Interventions are delivered via many methods, such as telephone contacts/counseling, special packaging, handouts, home visits, computer-/video-/audio-based education programs, medication timing devices, and group and individual sessions.¹⁶⁴ Interventions are most commonly delivered in clinic and pharmacy settings.¹⁶⁴ The most effective interventions tend to be complex and include combinations of educational and behavioral interventions.¹⁶⁵ Many interventions to improve adherence have been used, yet no intervention has been shown to be vastly superior due to the variability of non-adherence risk factors among patients.⁴⁰

While these interventions are found in the literature, and may improve medication adherence, there is little to no data regarding economic outcomes for many interventions.¹⁰² This is partially due to the limited time period of most studies, leading to a focus on surrogate endpoints such as adherence and clinical outcomes.¹⁰⁴ While many interventions have been shown to improve medication adherence, very few have noted a

corresponding reduction in healthcare costs. An intervention by community health workers reduced the odds of being readmitted to the hospital within 30 days of being discharged.¹⁰⁸ Another program included telephonic case management by nurses for patients discharged with heart failure.¹⁰⁹ It was noted that this telephonic program reduced heart failure hospitalizations by 47.8% and heart failure costs by 45.5% at six months compared with control patients.¹⁰⁹ While overall, there is limited economic evidence supporting adherence interventions among health care professionals, there is a growing body of economic evidence supporting such interventions provided by pharmacists.

A specialized knowledge in medications, as well as accessibility greater than physicians and nurses, allow for pharmacists to provide effective interventions for medication adherence.⁴¹ Medication Therapy Management (MTM) is an education-focused intervention, which has been shown to improve adherence and healthcare costs.¹⁶³ As intervention models which combine educational and behavioral interventions tend to be more effective,¹⁶⁵ models which combine MTM with a behavioral intervention need to be assessed. Adherence packaging is a behavioral intervention, as is refill synchronization.⁴⁰ A model combining MTM, adherence packaging, refill synchronization as well as an appointment based model should prove to be more effective than MTM alone.

2.8.1 Medication Therapy Management (MTM)

Medication Therapy Management consists of a group of services provided by a healthcare professional. It consists of five core elements, including; (1) a medication

therapy review (MTR) to identify drug-related problems; (2) development of a personal medication record (PMR) which lists information regarding a patient and all medications they are taking; (3) A medication action plan (MAP) which provides expectations of duties and outcomes of the patient and healthcare provider; (4) performance of interventions or referrals to correct drug-related problems, which may require coordination with other healthcare professionals; and (5) documentation of the service, and follow-up with the patient and other healthcare providers.⁴³ In recent years, MTM has become more integrated into Medicare. All Medicare Part D sponsors are required to offer MTM to patients to optimize medication use. MTM improves adherence through promoting patient understanding of medications, improving medication adherence and preventing/controlling adverse drug events.⁷³ A longitudinal analysis was completed regarding the provision of MTM services in Minnesota.⁷⁴ This analysis found annual increases in MTM provision, with an increase in the number of sessions provided and the compensation received by pharmacists. There has yet to be a similar analysis using nation-wide data in the United States. This is due to the evidence provided in the literature regarding MTM. There have been both retrospective and prospective studies assessing the impact of MTM on economics and adherence. Retrospective studies have assessed the healthcare cost reductions through Estimated Cost Avoidance and through cost data.

Estimated Cost Avoidance (ECA) is a method utilized to assess the economic affect of an adherence intervention, commonly MTM. ECA is used as it is reported for reimbursement for services, and it does not require claims data making it easier to obtain. The use of ECA involves the assignment of a severity level to the interventions made by

a pharmacist, with higher levels indicating interventions involving life-threatening issues. The ECA level is then assigned a dollar value which is derived annually from average healthcare utilization costs in the United States. Not all interventions receive a monetary ECA value, the probability that an ECA will be greater than \$0 was found to be 0.35.¹⁶⁶ ECA is a method to assess the healthcare cost savings provided by MTM services.

Retrospective analyses utilizing ECA have found improved economic outcomes through the provision of MTM. Studies often report a return on investment (ROI) comparing the economic benefits of the program to the economic costs to provide it. For example, a 10 year analysis conducted by Olivera, Brummel and Miller found an ROI of \$1.29 for each dollar spent to provide MTM, through an estimated average savings of \$86 per encounter.⁴⁸ A smaller six month analysis of 63 patients found a decrease in pharmacy, medical and total costs resulting in an ROI of \$1.67 per dollar spent.⁴⁹ Barnett et al. conducted an analysis of seven years of data, and found an average ECA of \$93.78, with an average pharmacy reimbursement of \$8.44.⁵⁰ This would represent an ROI to the payer of almost \$11.10 per dollar spent. An additional finding reported in this study was a shift in the type of interventions from education and monitoring to prescriber consultations regarding cost-efficacy. During the same period, a shift was also noted from claims involving acute therapies to chronic therapies and a corresponding increase in older patients. These shifts provided increasingly higher ECA levels, while pharmacy reimbursement remained relatively low.

Retrospective analyses have also found overall cost savings utilizing actual cost data. The Asheville Project is an ongoing healthcare program designed to treat diabetes, but has expanded to also include asthma, hypertension, hyperlipidemia and depression.

This program was one of the first to elevate the role of pharmacists to provide MTM services. A review conducted by Bunting, Smith and Sutherland assessed the six-year economic outcomes of the program for patients with hypertension and hyperlipidemia. The financial cohort included 620 participants, and assessed the healthcare costs three years prior to enrollment and six years post enrollment. Participants were included even if they did not have full economic data available for the time period, resulting in 1,189 patient years prior to and 1,268 patients years following enrollment. The per person per year medical costs related to the disease states decreased from \$1,362 to \$734. Medication costs during the same period increased by 290%, though the overall savings exceeded this by 12.6%. Additionally, a comparison was made between what the costs were projected to have been without MTM and what the realized costs were through the six years studied, resulting in a \$928,926 reduction in disease related medical costs.⁴⁴ An analysis conducted of asthma participants in the same program also assessed indirect costs. Due to a decrease in hospitalizations and emergency visits, the direct savings averaged \$725 annually per patient. Indirect savings, calculated by absenteeism and presenteeism hour's data provided by employees via a survey, was estimated to be \$1,230 annually per patient.⁴⁵

Prospective analyses have also been conducted of various MTM programs. A 2002 study of heart and lung patients in a health maintenance organization (HMO) assessed the effects of MTM on healthcare utilization, number of medications and costs. After an initial visit, follow-up sessions were encouraged at each medication fill, but this data was not collected. The study findings were not similar to previous studies, as the number of medications and clinic visits increased as a result of MTM services. The

researchers hypothesized that the increases may illustrate patients becoming more involved in their healthcare, and suggested further research is required. Healthcare costs and hospital visits were not different compared to patients not receiving MTM, and the researchers suggest longer-term studies to realize these cost benefits.⁴⁶

Two subsequent studies have also assessed economic outcomes of MTM by comparing claims data for the year prior to MTM to the year of the intervention. A study by Isetts et al., consisting of an initial visit and at least one follow-up MTM session, found an annual savings of \$700,837. The cost of providing MTM services was \$49,490, resulting in an ROI of \$12.1 for each dollar spent.⁵¹ A study conducted by Pinto et al. assessed diabetes patients receiving an initial visit, as well as follow-ups at three, six, and nine months. The employer realized a total savings of \$179,047.80 with decreases in inpatient and emergency room costs. Office visit costs were found to increase despite a decrease in utilization. The impact on adherence was also assessed through the use of a patient survey, and found a slight decrease at six months with an overall improvement at twelve months.⁴⁷ These prospective studies show that the provision of MTM services with follow-up visits provide an overall healthcare cost savings.

MTM services have received the support of patients. Patients regarded MTM in a positive view, especially the personalized medication information and increase communication among their healthcare professionals.⁵² The qualification of a pharmacist to provide MTM was questioned, suggesting the need to educate the public on the education and ability of pharmacists.⁵² When asked if MTM improved their overall health and wellbeing, 95.3% of patients agreed or strongly agreed.⁴⁸ Another survey looked at patient experiences with the pharmacist, the pharmacy staff, the pharmacy and overall

satisfaction, with all improving from baseline.⁴⁷ Patients are supportive of MTM services, but may require information regarding the abilities of pharmacists.

The studies above involved various models of MTM programs. These programs ranged from single MTM visits to multi-year studies, with multiple visits per year. Seeing the patient longitudinally may help to build a relationship between patient and pharmacist, which may help to improve the effectiveness of resulting interventions. Additionally, if appointments are made in advance, the pharmacist may be able to better prepare and provide a more efficient MTM visit.

2.8.2 Appointment Based Model

In order for MTM to be effective, scheduled appointments allow the pharmacist time to prepare for the visit. This provides a one-on-one interaction which can be used to review and discuss the medication regimen and overall health of the patient. This one-on-one interaction provides a means in which to individualize the experience to better help the patient. Holdford and Inocencio found that the appointments were helpful to proactively manage the medication needs of the patient, and allowed for the promotion of MTM and immunizations where appropriate.⁶⁴ The predictability also allowed more time for the pharmacist to review medications and prepare for the patient. The use of an appointment based model is currently limited, as appointment based models represent a significant resource burden in the form of pharmacist time. Also, many pharmacies may not offer a service, such as refill synchronization, which would bring patients to the pharmacy at a predictable interval.⁶⁴ Further research is required regarding the use of

appointment based models to assess the effect of the individual components, the relationship to other interventions and the effect of appointment adherence.

2.8.3 Adherence Packaging

Adherence packaging involves a specialized packaging that can help to organize medications by time. This can help to simplify the taking of medication, as well as serve to remind the patient when to take their dose. Additionally, this organization can help identify which doses have been taken, and which have yet to be taken. This can consist of self-filled options, such as pill boxes, or prefilled options, such as calendar or blister packaging. Pillboxes have been highly recommended to patients to help organize their medication regimens, although there is very little evidence to show there is a positive effect. Pill boxes also have the additional risk of being incorrectly filled by the patient. A mistake in the filling process can lead to adverse events.⁵⁸ In addition, due to the preparation of multiple doses at one time, a single mistake can lead to an entire week of improper medication administration.⁵⁹ Blister packaging is designed to alleviate these errors, as they are prefilled by pharmacy staff.

Prefilled adherence packaging has been used since the 1960s for oral contraceptive medications. These packages often include a calendar feature, allowing for easy identification of when doses are to be taken. Adherence packaging has been associated with an increase refill adherence and a decrease in the likelihood of medication discontinuation.⁵⁴ In addition to improving adherence levels, adherence packaging has also been associated with a higher likelihood of achieving an adherence level above 80%.⁵⁷ A randomized controlled trial conducted by Schneider, Murphy and

Pedersen compared blister packaging to traditional pill vials. The patients who used the blister packaging had a 13.7% higher rate of on time refills, as well as a higher medication possession ratio.⁵⁶ Prefilled adherence packaging has a positive impact on medication adherence.

The above studies have shown blister packaging to be associated with higher adherence levels than traditional pill vials. A pair of studies by Huang et al. compared adherence outcomes between pillboxes and vials as well as blister packaging and pillboxes. The first study compared pillboxes to traditional vials. When compared to vials, pillboxes were not shown to have a significant effect on adherence. This finding could potentially be due to an abnormally high adherence rate amongst the users of traditional vials. The second study compared blister packaging with pill boxes. Blister packaging was associated with a marginally higher adherence rate. In addition, patients using blister packaging had significantly fewer problems taking medications as well as a lower frequency of forgetting to take medications.⁵⁵ This shows that, in addition to potential advantages in safety, blister packaging may also provide higher levels of adherence when compared with pillboxes.

Patients are aware of the impact adherence packaging can have on their medication adherence. A prospective study and survey conducted by Jansen, Andersen and Bruning assessed patient perceptions of blister package service. Out of the patients surveyed, 79% found the packaging easy to use, and 46% felt that it made it easier to remember to take tablets. As a result of experiences, 61% of responders signified that they would continue to use the packaging if offered.⁶⁰ Combining adherence packages has also provided a perceived benefit. Patients who were offered a combination package

including adherence packages of calcium and vitamin D supplementation found it easier to use than two separate packages. Responders also stated that this made it easier to remember to take medications. In addition to perceptions, patients had a higher knowledge of the correct medication instructions assessed by a series of medication related questions.⁶¹ While patients are aware of the impact that adherence packaging has, there may be physical barriers preventing effective use.

The patient can have an impact on the use and effect of adherence packaging. The abilities of patients to open packaging can play a large role. Elderly patients have been found to have difficulty opening pillboxes as well as the pill vials which are commonly dispensed. A study of 604 elderly patients found that 32% were unable to open a vial with a snap lip, 14% unable to open a vial with a screw-on lid, while only 10% were unable to open a blister package.⁶² A study by Adams queried patients as to difficulties which can be seen with blister packages that contain multiple different medications. The packaging was reviewed by a number of elderly patients. The patients found that the text was of sufficient size to read, although some of the plastic areas provided glare which could complicate reading.¹⁶⁷ Blister packaging can have positive effects on adherence, and provide additional benefits in being easier to open than pill vials.

2.8.4 Refill Synchronization

In order for a blister package to be filled with all of a patient's medications, refills must be synchronized to occur at the same time. This can reduce regimen complexity, as well as increase accessibility for patients with transportation issues.⁶⁴ To synchronize medications, the pharmacist first identifies an "anchor medication". This will help

determine the first synchronization date around which other medications will be scheduled. In order to align the refills, a pill count can be used to determine how much of each medication is required to supply the patient until the first synchronization date.⁶⁴

Without refill synchronization, patients with more than one medication can have multiple trips to a pharmacy each month to obtain all of their medications. A survey of 50 Medicaid patients found that 52% of patients were forced to visit a pharmacy more than once a month, and that contribute to 46% of patients to miss a day or more of therapy.⁶⁵ This becomes a burden to the patient and caregiver.⁶⁷ A study conducted by Choudry et al. found that patients taking lipid lowering statins or antihypertensive angiotensin medications made an average of five visits to a pharmacy over a three month period. In addition, 10% visited a pharmacy more than 11 times in the same period. Patients making more trips to the pharmacy had adherence levels that were 8.4% lower than those who had refill synchronization.⁶⁸ Holdford and Inocencio conducted a refill synchronization study targeting six chronic medications. Patients receiving refill synchronization services were 3.4 to 6.1 times more likely to be adherent than patients without synchronization, depending upon the drug class. Patients without synchronization were 52% to 73% more likely to stop taking chronic medications over the course of a year.⁶⁴

Refill synchronization can be an effective intervention to improve medication adherence. The predictability of dispenses can also allow for easier implementation of a central-fill pharmacy model.⁶⁶ This involves the filling of chronic medications at one location and transporting them to the dispensing locations. Refill synchronization does have one major limitation. In order to be synchronized, all of a patient's medications must be filled at the same pharmacy. In 2009, 43.2% of patients in a national survey were

identified as users of multiple pharmacies, ranging from 2 to 17 different pharmacies.¹⁶⁸ This negatively impacts adherence levels, as each additional pharmacy used can decrease adherence by 1.6%.⁶⁸ This must be addressed if refill synchronization is to be more effective on a larger scale.

2.8.5 Multi-component Interventions

As no intervention is a “one size fits all” approach to adherence, pharmacy has experimented with combining interventions. The FAME study⁷⁰ evaluated a combined intervention using adherence packaging, refill synchronization and pharmacist counseling, similar to telephonic MTM in elderly veteran patients. The adherence packaging utilized was arranged similar to a pillbox with four blisters each day associated with different dosing times. Refill synchronization was achieved through discarding the remaining medications of a patient and starting the package with new prescriptions. Each blister was capable of holding all of the medications to be administered at a given dosing time. The results found that medication adherence improved at six months and was associated with improved systolic blood pressure and LDL levels.⁷⁰ In order for combination interventions to be sustainable, however, it needs to show an improvement in long-term effects, such as hospitalizations and healthcare costs.

Long-term endpoints have also been assessed with combination therapy. A prospective study conducted by Zillich et al.⁷¹ assessed the influence of telephonic MTM, adherence packaging and medication synchronization. The outcomes studied included adherence, all-cause as well as ambulatory related hospitalizations and emergency visits. The proportion of patients who were compliant to medications was more than twice that

of the control group receiving traditional therapy, as was the proportion of patients who were persistent. This difference in adherence, however, did not translate into cost and utilization endpoints. All-cause hospitalizations decreased slightly, with all other utilization endpoints not achieving a statistical significance.⁷¹ The study by Zillich et al. experienced a large amount of attrition. Of 1007 intervention patients enrolled, 332 patients never received a telephonic MTM call and only 371 patients received at least 3 MTM calls as well as at least 6 months of the adherence packaging. As the study was conducted as-an-intention to treat analysis, attrition may have contributed to the lack of significant results. Future studies must attempt to minimize attrition, as well as persist for longer than six months to better detect long-term differences in utilization and cost outcomes.

Summary

Medication non-adherence is a significant problem. This leads to significant costs, and additional burden on the health care system in the United States. Non-adherence can be due to multiple factors, and is prevalent among chronic diseases. Metabolic syndrome is a combination of three such chronic diseases which, when not controlled, can lead to serious implications on patient health and cost of care. Pharmacists are well positioned to help with the problem of non-adherence. They have successfully provided multiple interventions, including refill synchronization, adherence packaging and MTM within an appointment based model. Combinations of interventions have been known to be more effective than single interventions. More evidence is needed to support a model of care combining MTM within an ABM with adherence packaging.

Chapter 3

Methods

This chapter explains the methodology used in this study. This is a prospective longitudinal study, using a randomized control trial model. This is to determine the impact of a hybrid model of care consisting of adherence packaging, MTM services, medication refill synchronization and an appointment based model in patients with metabolic syndrome. The methodology will be discussed under the following sections:

- Design
- Implementation
- Study Sample
- Process objectives regarding practice
- Process objectives regarding research

3.1 Design

The current study is an exploratory pilot analysis of a large, multi-center, prospective longitudinal study, using a randomized control trial model. The purpose of the overall study, entitled “Study to Measure the Impact of Pharmacists and Packaging on Medication Non-Adherence” (STOMPP), is to assess the impact of a hybrid model of

care on medication adherence as well as economic, clinical, and humanistic outcomes of patients with metabolic syndrome. This pilot analysis will assess the economic outcomes under study, including healthcare costs and utilization, as well as report medication adherence relevant to the CMS Five-Star Quality Rating System. The STOMPP study is to be conducted for two years, with enrollment underway since August 2014 (see Appendix A). The study will involve two distinct phases. Phase I involves an assessment of the population including identification, recruitment and enrollment of eligible participants. Phase II involves the provision of the pharmaceutical intervention(s) according to the study group in which the participant is enrolled. For this pilot analysis, data has been collected, coded and analyzed at the six month time point for an initial group of enrollees.

This analysis attempts to address the problem of medication non-adherence through the provision of multiple pharmacy services as a hybrid model of care. The theoretical framework of the study (Figure 3-1) is derived from that of the Andersen Behavioral Model¹⁶⁹ and the Information Motivation Behavioral Model.¹⁷⁰ Based upon the factors identified in the literature, it is hypothesized that the hybrid model of care will affect economic outcomes through multiple paths. This includes an improvement in knowledge of disease states and medications provided by MTM, as well as behavioral skills regarding timing and taking of medications provided by MTM and the adherence packaging. Additionally, the hybrid model of care may assist through enabling factors such as improved organization provided by the adherence packaging, and improved access to medications through synchronization of refills. In addition, the number of medications and doses could potentially be consolidated through MTM services. All of

these factors should affect medication adherence which, as shown in the literature, could lead to an overall decrease in health care costs and utilization, although medication costs may increase. In addition, certain predisposing factors may exist within the patient, which have been shown to affect medication adherence, but are not affected by the adherence interventions within the hybrid model of care. Operational definitions of terms within the theoretical framework may be found in Appendix B.

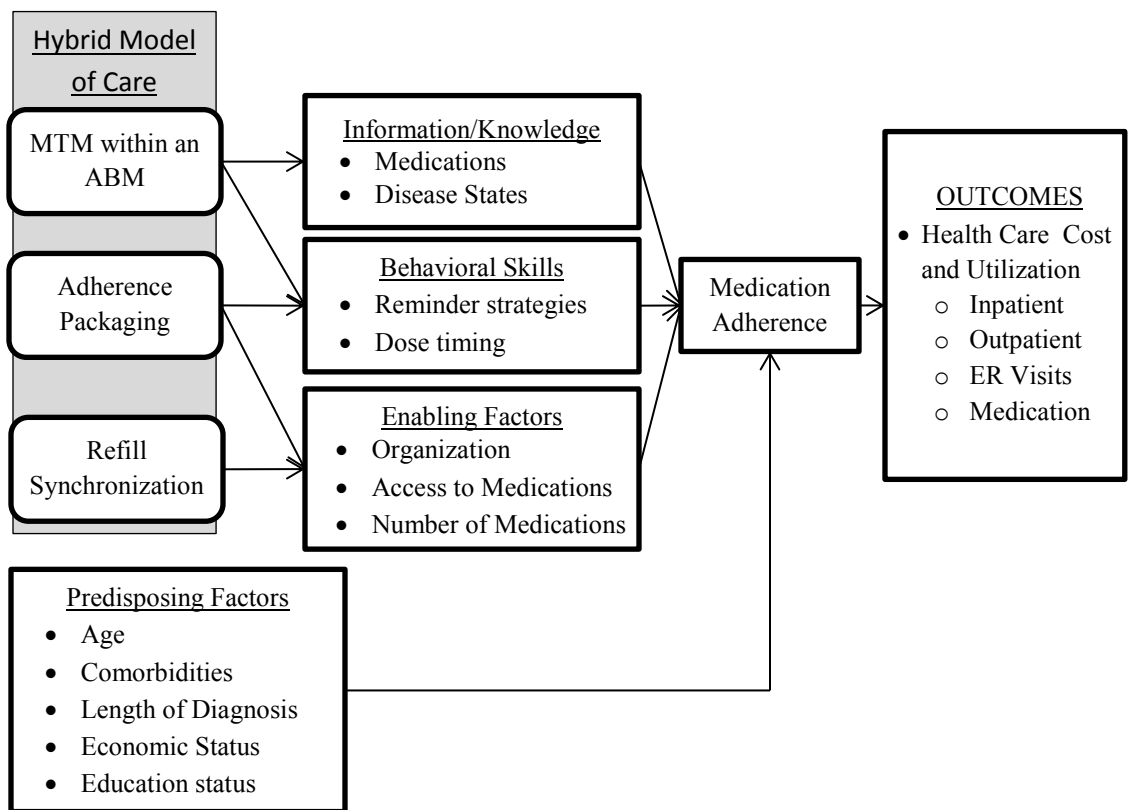


Figure 3-1: Theoretical Framework

3.1.1 IRB Approval

The overall study has received approval by the Biomedical Institutional Review Board (IRB) at the University of Toledo. Participants were provided the biomedical informed consent form for review and signature prior to being enrolled in the study.

3.2 Implementation of the Hybrid Model

This study examines the provision of the hybrid model of care at a single study site. This implementation occurred through the collaboration within ProMedica, an Integrated Delivery Network (IDN). This IDN provides more than 4.4 million patient encounters annually through 13 hospitals, four ambulatory surgery centers, as well as more than 300 other facilities. These facilities provide care to 27 counties in Northwest Ohio and Southeast Michigan. Among these facilities are the Endocrine and Diabetes Care Center (EDCC) and The Pharmacy Counter pharmacy chain which provide components of the hybrid model of care under study. This IDN also includes a locally owned health insurance company providing commercial, Medicare and Medicaid plans. Collaboration among these entities within the IDN is made possible through a shared electronic health record, integrated electronic systems and open lines of communication among providers. This collaboration is most evident within the EDCC.

The EDCC is a multi-disciplinary group practice within the IDN, similar to a Patient-Centered Medical Home practice. This practice consists of endocrinologists, nurse practitioners, nurses, diabetes educators and pharmacists who work together to provide care to the patient. The endocrinologists and nurse practitioners see patients who were referred through primary care providers, such as a primary care practice which is housed in the same facility. This facility, known as the Diabetes Center for Excellence, houses multiple groups practices. It also includes a pharmacy, as well as multiple rooms for counseling and group education sessions. The endocrinologists and nurse practitioners, with the assistance of nurses and administrative staff, diagnose and provide targeted care for endocrine disorders, including diabetes, hypertension and

hyperlipidemia. Through collaborative agreements, they refer patients to other health professionals for more specific management, including diabetes educators and pharmacists.

The diabetes educators provide individual and group education promoting lifestyle management, diet and exercise. A clinical pharmacist in the facility provides MTM services to patients. An additional pharmacist staffs a location of The Pharmacy Counter which is housed within the same facility. This provides a convenient location for patients to obtain their medications, as well as durable medical equipment. The provision of these services by a multi-disciplinary team in the same facility not only provides convenience for patients, but also improves the ability for communication and collaboration amongst healthcare professionals.

The Pharmacy Counter includes a number of locations in addition to the location within the facility of the EDCC. There are four retail locations distributed throughout the greater Toledo area, including the one adjacent to the EDCC. This allows for convenient pick-up of medications by patients. For further convenience, the main retail location also coordinates mail and delivery services for medications and medical supplies. In addition to the 4 retail locations, there are also two specialized locations which focus on central-fill and adherence pharmacy services respectively. The central fill location utilizes automation and minimal staff to efficiently supply medication refills for patients. Combined with the retail locations, then central fill location provides medications to patients who receive medications in pill bottles. The adherence pharmacy focuses on improving medication adherence, and supplies the adherence packaging utilized in the hybrid model of care.

The adherence pharmacy is an innovative pharmacy facility within The Pharmacy Counter. This pharmacy currently services a population of 900 patients with adherence packaging. This pharmacy is designed around the provision of adherence packaging. The layout of the pharmacy includes pharmacist workspace, medication stock area, space for automation for filling the packaging and workspace for technicians to coordinate filling and delivery. The pharmacy also includes two counseling rooms which can be used to educate new adherence patients as well as provide MTM services. The adherence pharmacy is staffed by four pharmacists, consisting of a pharmacy manager, two clinical pharmacists and a staff pharmacist. Additionally, three technicians as well as one to two pharmacy students help to staff the pharmacy. The pharmacists provide MTM services, develop comprehensive medication lists, synchronize refills, contact patients prior to each filling, and check packages prior to dispensing. This contact is to address any concerns the patient may have, as well as to verify if any changes have been made to the patients' medication regimen which may impact filling the adherence packaging. The pharmacy students assist in these tasks, especially in the process of transferring prescriptions, synchronizing refills and contacting patients. Pharmacy technicians work to fill the packaging with the help of specialized automation. This automation allows for the staff to fill monthly supplies for 40 patients every day consisting of 160 weekly adherence packages. Technicians ensure that the prescription data is linked to the software for the automation, as well as ensure that the needed medications are available within the machine. Technicians also apply labels to the packaging designating which days of the week each row of the packaging is for. Once the packaging is checked by the pharmacist, the technicians coordinate delivery of the medications to a patients' residence

or to another pharmacy counter location from which the patient will pick it up. This provides a convenient means for the patient to obtain medications, and allows the pharmacy staff to focus on preparing and verifying the packages.

In order to provide the hybrid model of pharmacy-based care, pharmacy staff must communicate as well as collaborate with other health care providers. This begins with the identification and referral of patients. In the setting of our study, this process was conducted by members of the research team with access to the electronic health records of the endocrinology practice. Patients who were not part of the study could also potentially receive the hybrid model of care. This includes patients who were not eligible for study enrollment, as well as patients who began receiving the services before the study was implemented. Through collaboration within the EDCC, patients are referred from their endocrinologist to receive MTM from the clinical pharmacist. In addition, patients may be introduced to the adherence packaging by the pharmacist, or by the endocrinologist directly.

If a patient is to receive the hybrid model of care, they receive the services in a set order. The patients received MTM services first upon referral to the pharmacist, prior to beginning the process to set-up adherence packaging. This is due to the fact that medication regimens may change as a result of the MTM. Ensuring that these changes are made prior to the adherence packaging may help to prevent unnecessary changes to the packages in the future. During the MTM session, a comprehensive medication list is generated for the patient, including the pharmacy they were filled at, as well as the last date they were dispensed. This list can then be shared with the adherence pharmacy for inclusion in the packaging.

If a patient is interested in receiving the adherence packaging, they are provided with the contact information for the adherence pharmacy. They will receive some information regarding the packing and the filling process and, if interested, they can agree to obtain their medications in this manner. Additionally, if the patient is not part of an MTM program, they may receive MTM services at the adherence pharmacy prior to filling the adherence packaging.

The initiation process for the adherence packaging takes approximately two to three weeks. The first step is securing transfers of prescriptions from outside pharmacies if needed. This can be completed by pharmacists or pharmacy students. Once prescriptions are obtained, the pharmacist works to set a fill date which minimizes medication waste. The pharmacist also works with physicians to obtain additional refills or new prescriptions as needed in order to complete this initial fill. In the event that a patients' supply of some medications may not get them to this fill date, the pharmacy provides these medications to the patient. The packages are filled for a month supply, consisting of four weekly adherence packages. The adherence packages are filled four to five days in advance of when the patient requires the medications. This provides time for the medications to be delivered or for the patient to pick them up without causing a gap in medication supply. For future fills, the patient is contacted one week prior to filling the packages. This allows time to address any changes in therapy as well as provide time to receive refill authorizations or new prescriptions which may be necessary.

The provision of the hybrid model of care requires significant communication and collaboration. Communication with the patient through MTM sessions and timely phone calls from the adherence pharmacy is necessary to ensure that pharmacists are up to date

regarding the medication therapy. Communication between pharmacists can also help in this regard. Collaboration with other health care professionals is also key. This can allow for access to clinical information which can help in the provision of effective MTM. Additionally, collaboration can help in implementing changes in care identified by the pharmacist, which can also be included in collaborative practice agreements. Finally, there must be pharmacy structure in place in order to provide and integrate pharmacy services with adherence packaging services. With communication, collaboration and pharmacy infrastructure in place, the hybrid model of care may be effectively implemented to improve patient care.

3.3 Study Sample

3.3.1 Population

The population under study consists of patients with metabolic syndrome, including diabetes, hypertension, and hyperlipidemia. This pilot analysis focuses on participants from a single site, the ProMedica Endocrine and Diabetes Care Center in Toledo, Ohio. Participants are insured through Paramount insurance, an affiliate of ProMedica. For the pilot analysis, data was obtained through agreements with Paramount, ProMedica and the staff at the Endocrine and Diabetes Care Center.

3.3.2 Sample size

Due to the exploratory nature of this study, the sample size was limited to 38 participants.

3.3.3 Inclusion

Candidates were required to have health insurance through a participating insurance. For this pilot analysis, the only participating insurance is Paramount insurance. Inclusion criteria also required diagnosis and treatment for type II diabetes, hypertension, and hyperlipidemia; at least one medication prescribed for each of the three disease states listed above for a minimum of one year; a minimum of five (5) prescribed oral medications for a minimum of one year; the ability to self-administer medications as prescribed; and the ability to speak and understand English. Potential candidates were required to provide informed consent. Additionally, as half of the participants in the study would be receiving MTM services, adequate transportation was also required.

Participants were required to have their prescriptions filled at a participating pharmacy, which may have required them to switch from their current pharmacy. A connected, in-service, phone number was also required to be reached for enrollment purposes, reminders and telephonic visits. For this pilot analysis, The Pharmacy Counter is the only participating pharmacy.

3.3.4 Exclusion

Patients were excluded from the study if they were diagnosed with a terminal illness and given less than three years to live; are pregnant or suspected of being pregnant; are planning to leave the area or employer within three years; and/or being enrolled or having involvement with a current MTM program.

3.4 Process Regarding Practice

3.4.1 Groups

This study consisted of four groups. The first group (PB) served as a control group, and did not receive any of the adherence interventions. The second group (PB+MTM) received MTM utilizing an appointment-based model. The third group (BP) received adherence packaging and refill synchronization. The fourth group (BP+MTM) received the hybrid model of care, consisting of adherence packaging, MTM, refill synchronization and an appointment-based model. Services provided to each group are depicted in Table 3-1. All participants were provided the option of having medications delivered to their place of residence.

Table 3-1: Randomization Groups

Intervention	Group 1 (PB) (Control)	Group 2 (PB+MTM) (Experimental)	Group 3 (BP) (Experimental)	Group 4 (BP+MTM) (Hybrid Model)
Pill Bottles	X	X		
Blister Packaging			X	X
Refill Synchronization			X	X
MTM		X		X

3.4.2 Setting

This study focused on a single site of a large multi-center study. Participants from this site receive clinical care from an endocrinologist in the Endocrine and Diabetes Care Center (EDCC).

Multiple locations are used for the provision of pharmacy services. The participating pharmacy is The Pharmacy Counter, a pharmacy chain in Toledo, Ohio. This chain has multiple locations, including a location within the Endocrine and Diabetes Care Center. This allows participants to conveniently retrieve prescriptions. There are three additional retail locations throughout the greater Toledo area. There are also two additional specialized locations, a central-fill pharmacy and an adherence pharmacy. The central fill pharmacy performs central fill and delivery operations, while the adherence pharmacy performs services related to adherence packaging.

3.4.3 Protocol

Groups not receiving MTM

Two study groups do not receive MTM services. Of these two groups, group 1 (PB) was dispensed medications in pill bottles and group 3 (BP) was dispensed medications in adherence packaging. These two groups followed a similar path. See the visit algorithm in Appendix C. Appendix D provides a table with outcomes collected at each visit.

The baseline visit occurred at the Endocrine and Diabetes Care Center within one to two weeks after enrollment and randomization. A research team member conducted the visit utilizing a standardized written guide. Once informed consent was reviewed and signed, enrollment information was obtained from the participant and the participant's electronic health record and recorded on an intake form (see appendix F). Three surveys were administered to the participant, including a quality of life survey, a work

productivity survey and a disease knowledge questionnaire. A brief adherence survey was administered at this enrollment visit. The research assistant recorded information from their medication vials and recorded a count of their medications for use as an adherence measure while the participant completed the surveys. At the end of the enrollment visit, the participant was informed that they would receive a phone call in three months to schedule a brief telephonic visit. A research team member facilitated prescription transfers to a participating pharmacy. For participants in a group receiving blister packaging, the staff at the adherence pharmacy synchronized medication refills.

Participants in the non-MTM groups did not receive additional pharmacy services beyond standard counseling. Standard counseling included information about what the drug is used for, common side effects and any special instructions that the participant should be made aware of while on the medication. Participants had the opportunity to contact the pharmacy if they had any questions between visits. If a pharmacist judges a medication issue to jeopardize the safety of the participant, they may intervene and interventions were documented.

A visit at three months was conducted over the telephone with a member of the research team. The purpose of this follow-up interaction was to 1) Assess participant adherence via a self pill-count and 2) Refer any questions or problems, which arose to a pharmacist. A guide for information to be collected and calculated via the telephonic visits can be found in Appendix I. One to two days prior to each interaction (baseline and telephonic visits) participants received a reminder phone call.

At six months, participants were asked to come in to the Endocrine and Diabetes Care Center. At this visit, the knowledge and adherence questionnaires were re-

administered and a pill count was performed. Clinical markers from the electronic health record were collected to update the intake form.

Groups Receiving MTM

Groups 2 and 4 both received MTM services. The difference between these groups was that group 2 (PB+MTM) included participants receiving medications dispensed in pill bottles, while group 4 (BP+MTM) received medications dispensed in adherence packaging. Appendix D provides a table with outcomes collected at each visit.

For the proposed study, the MTM visit algorithm was developed after consulting published literature and current American Diabetes Association standards of care, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure—Complete Report (JNC-VII), and the National Cholesterol Education Program (NCEP) guidelines from the National Heart, Lung, and Blood Institute. Appendix C contains the visit algorithm for the groups receiving MTM. The algorithm was developed in consultation with a panel of practicing clinical pharmacists so as to adequately service all participants.

An enrollment process, similar to that used for groups not receiving MTM, was used for groups receiving MTM. Following enrollment, the initial MTM visit occurred within one month of the baseline visit and was no more than one hour in length. At this visit the pharmacist discussed the participants' disease state(s), therapy and management, and establishes personal goals for therapy. Prior to the first MTM visit, the pharmacist assessed the participants' demographic and lifestyle information, clinical markers, and

social history collected from the intake form. A comprehensive medication review (CMR) was conducted with each participant (see Appendix G). A CMR is a systematic process of collecting medication and therapy-related information about participants to identify and prevent drug related problems. Topics covered within the CMR include, but are not limited to, discussing with the participant how their medications work, what to expect when taking their medications, potential adverse drug events, and potential ways to make their medications work better for them (i.e. timing of dose, taking it with/without food). Additionally, the pharmacist assessed if current medication therapy goals are being met, and worked with the participant to establish future goals, discussed the importance of medication adherence, as well as any other topics the pharmacist saw fit to discuss.

Each participant received a personalized medication record (PMR) (see Appendix H) and medication action plan (MAP) at the end of this MTM visit either in person or via mail. A PMR is a comprehensive and portable record of a participant's medications. Medications included in this list were prescription medications, non-prescription medications, which are also known as over-the-counter (OTC), herbal/supplements, and vitamins/minerals. A MAP is a patient-centered document containing a plan that outlines tasks for the patient and pharmacist to perform over a given period of time. The MAP contains short-term and long-term goals and is developed by the pharmacist in conjunction with the patient. Participants are required to meet with the pharmacists for a follow-up visit every six months, but more frequent visits may be scheduled at the discretion of the pharmacist.

A member of the research team conducted a telephonic study visit at three months. The purpose of this follow-up interaction was to 1) Assess participant adherence

via a self-pill count and 2) Refer any questions or problems that arose to a pharmacist. A guide for information to be collected and calculated via the telephonic visits can be found in Appendix I.

A follow-up at six months was conducted face-to-face with a pharmacist. The purpose of this visit was to counsel participants about their medication regimen, disease states, and address any problems or concerns participants may have. Knowledge topics may have been re-visited on a case-by-case basis depending upon the pharmacist's assessment. Participants' medication action plans (MAP) were reassessed and goals adjusted. Upon arriving for the MTM visit, but prior to seeing the pharmacist, the participant saw a member of the research team who re-administered the knowledge survey, adherence survey and conducted a pill count. Participants received a reminder call 1-2 days before the visit.

3.5 Process Regarding Research

The process for Phase 1, including identification, recruitment, enrollment and randomization of participants is provided in Appendix C.

3.5.1 Identification

Potential participants were identified through a retrospective and ongoing review of patients at the Endocrine and Diabetes Care Center. This identified patients who met the inclusion criteria of disease states, number of medications and age. Once patients were assessed, they were contacted for recruitment.

3.5.2 Recruitment

Multiple recruitment strategies were used to contact patients. The initial method involved sending invitation letters to all potentially eligible patients identified at the Endocrine and Diabetes Care Center (EDCC). The letter was printed on the letterhead of the EDCC, and included the signatures of the patients' EDCC physician, as well as the principle investigator of the study. The letter, from the perspective of the physician, suggested that the patient participate in the study. The invitation letter included a phone number to call if the patient is willing to participate. This phone number would prompt the patient to leave a voice message with their name, phone number and a good time to reach them. The voice messages were then retrieved from an online system, and calls were returned by a research team member within 48 hours. Patients who did not respond to the initial letter within six weeks received a similar second invitation, and the same process was followed.

Patients who did not respond within six weeks of the first two mailings, and were identified as already utilizing The Pharmacy Counter were selected to receive a third invitation. This invitation was on the letterhead of The Pharmacy Counter, and bore the signature of the Director of Pharmacy Operations of the pharmacy. This letter followed a similar process as the other invitation letters, as it prompted the patient to call and leave a message. A member of the research team would return the call within 48 hours and begin the enrollment process.

Four months after the initial invitation was sent, a list of patients who had not responded to any of the invitations was generated. The patients on this list received a direct phone call inviting them to participate. If the call was not answered, a standardized

voicemail was left. Patients received up to four direct invitation calls from a research team member at least one week apart. Patients who did not answer and did not respond to voicemail messages were not pursued any further.

In addition to the direct calls, another recruitment tool was used around the same time. Postcards were printed as a means of study recruitment. These postcards were given to the physician group at the Endocrine and Diabetes Care Center as well as The Pharmacy Counter. The research team put flags and notes in the electronic records of both groups which noted that the patient was eligible for participation in the study. This note would also prompt them to provide the patient with a postcard. Postcards were printed with the logos of the participating pharmacy, the Endocrine and Diabetes Care Center and the University of Toledo. The postcards listed the three disease states of metabolic syndrome and prompted the patient to call the study phone number, provided on the card, if the patient met these criteria and was interested in participating. Postcards were delivered to the office staff at the Endocrine and Diabetes Care Center and the Director of Pharmacy Operations of The Pharmacy Counter for distribution to their staff.

3.5.3 Enrollment

Interested patients called the phone number provided on the invitation letters, or the voicemail messages in the cases of patient who were called. This phone number is set to go straight to a voice mail box. The patient was instructed to leave a message stating their name, as well as instructions on the best way to contact them. A member of the research team then uses this information to contact the candidate. During this call, the patient is asked a series of questions using a screening tool (See Appendix E) to ensure

that inclusion criteria is met and their participation in the study is appropriate. If a patient is eligible and agrees to participate, an enrollment visit is scheduled at the Endocrine and Diabetes Care Center.

3.5.4 Randomization

Patients are randomized into their respective study groups using covariate adaptive randomization. This randomization strategy takes specific covariates and confounding variables, as well as previous assignments of participants into account during randomization. This strategy uses the method of minimization to assess the variation of sample size among several covariates.¹⁷¹ Covariates/confounding variables used in the randomization process include number of medications, length of diagnosis, number of co-morbidities, and type of insurance (commercial, Medicare or Medicaid). This information is gathered from the screening tool (Appendix E).

3.5.5 Research Personnel

The study was conducted with a Principle investigator (PI), as well as seven additional research team members. Research team members were delegated to individual tasks, but were cross-trained to assist in multiple areas of the study. All research team members participated in the recruitment phase through calling potential participants, and scheduling of enrollment visits. For consistency, only one research team member conducted randomization. This same team member also conducted the telephonic follow-ups at the three-month time point. The other research team members were also trained in these procedures. These research team members were responsible for conducting the

face-to-face visits with study participants at the Endocrine and Diabetes Care Center. All members of the research team met regularly to discuss the progress of the study as well as any difficulties which were identified.

Prior to the study, the PI and members of the research team met with pharmacy personnel to provide information regarding the protocol and forms being used. Additionally, the procedures of the MTM sessions were reviewed to ensure sessions were conducted in a consistent manner from one pharmacist to another.

3.5.6 Data Collection

Appendix D contains a table with the outcomes included in this study, the measures used, the sources of data, and the data collection time-points.

Economic outcomes, consisting of cost and utilization data, were collected through medical and prescription insurance claims data. Data was obtained for the six months prior to the study to determine a baseline cost and utilization for each participant similar to previous studies.^{47,51} Adherence levels used in the third objective were calculated as the Proportion of Days Covered (PDC), using prescription claims data. Baseline characteristics collected at the enrollment visit were entered and kept in a central database.

3.5.7 Data Coding

A database, representing the economic outcomes and adherence measures was created in Microsoft Excel (see Appendix J). In order to protect participant confidentiality, patient identifiers were replaced with a study ID number. This number

was assigned upon randomization into the study. This assigned number is the study ID number used when entering data from the intake forms, and cleaning the economic data. This two-digit number was created for the purposes of the study. This is a consecutive number representing the order in which the participant enrolled. For example, the fifteenth participant consented and enrolled was numbered: 1 5. Following study ID number assignment, associated data was entered into the databases.

3.5.8 Data Analysis

To address the first objective, the provision of the hybrid model was described. Participant baseline characteristics were summarized and tested for uniformity across study groups/arms utilizing an ANOVA test. This analysis was conducted utilizing the Statistical Package for Social Sciences (SPSS) version 21. The significance level is established at 0.5%.

The second study objective was to examine the effect of the hybrid model on healthcare costs and utilization when compared to other community practice models for patients with metabolic syndrome. This was done utilizing a trend analysis comparing cost and utilization six months prior to enrollment with cost and utilization in the six months after enrollment.

The third study objective examined the effect of the hybrid model on adherence to medications included in the quality measures for the Center for Medicare and Medicaid Services (CMS). To assess this objective, the Proportion of Days Covered (PDC) was calculated for each of the medications included in the quality measure. The PDC calculation was conducted utilizing the Statistical Analysis System (SAS) version

9.3 The percentage of participants who were adherent (PDC >80%) to selected therapies is calculated for each study group six months prior to enrollment and six months after enrollment for each of the three quality measures.

Chapter 4

Results

This chapter presents the results of the analyses performed on the data obtained for the study. They are presented as follows:

- Study enrollment.
- Description of the demographic characteristics of participants.
- Trend analyses and frequency distributions performed to answer the research questions of this study.

4.1 Study Enrollment

Review of electronic medical records of the patient population at the Endocrine and Diabetes Care Center began in July 2014. Based upon diagnoses in their medical records, 424 potential participants were identified.

The initial group of 424 potential participants was sent an initial invitation letter, inviting them to leave a voicemail with the research team if they are interested in participation. Of the 424 mailers, a total of 98 potential participants responded. Of these, a total of 27 participants were enrolled into the study. A total of 306 potential participants

did not respond to the initial mailing. A second invitation letter was mailed to 222 potential participants, including non-respondents to the initial mailing. Of this group, 20 patients responded, but there were no enrollments from this group.

A third mailing targeted potential participants within the Endocrine and Diabetes Care Center who were already using a participating pharmacy. These letters, addressed from the Director of Pharmacy Operations of The Pharmacy Counter, were sent to 115 potential participants. This provided an additional four enrollments, leading to a total of 31 patients enrolled through invitation letters. Figure 4-1 summarizes the results of the invitation letter recruitment.

Initially 424 patients were identified. Further study of the electronic records, as well as new enrollees into the Endocrine and Diabetes Care Center provided additional patients receiving subsequent letters. These additional patients provided for a total of 451 patients who received an invitation letter for recruitment purposes.

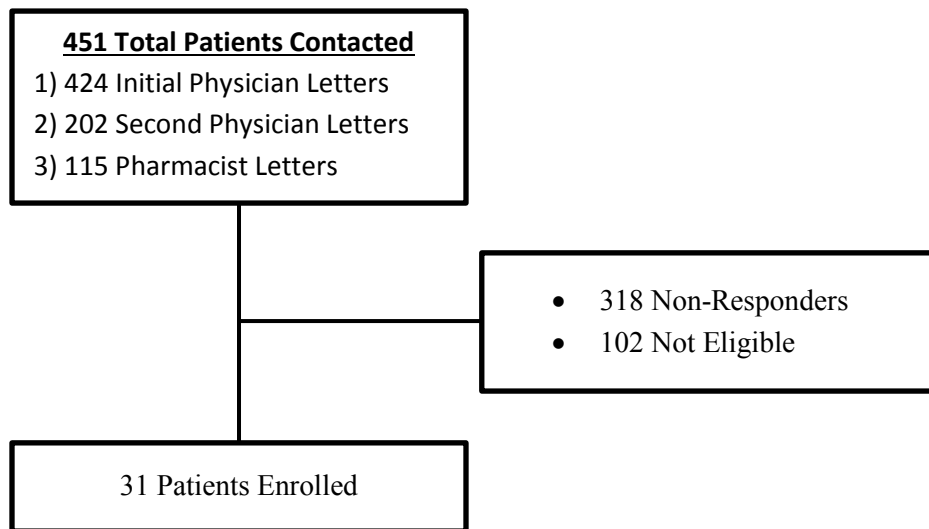


Figure 4-1: Flow Diagram for Physician and Pharmacist Letters

After the invitation letters, two additional recruitment efforts were initiated. This included directly calling patients who had not responded to the invitation letters and postcards distributed by physicians and pharmacists.

Two hundred and five non-responding patients were called directly by the research team. This resulted in 111 patient contacts, leading to 12 enrollments. Of the other patients contacted, 14 were placed on a waiting list as they were not ready to commit to the study and 85 patients were deemed to not meet study criteria. A total of 95 patients were unable to be contacted. This was often due to out-of-service phone numbers or patients not returning voice-mail messages left by the research team. Figure 4-2 summarizes the results of the direct call recruitment.

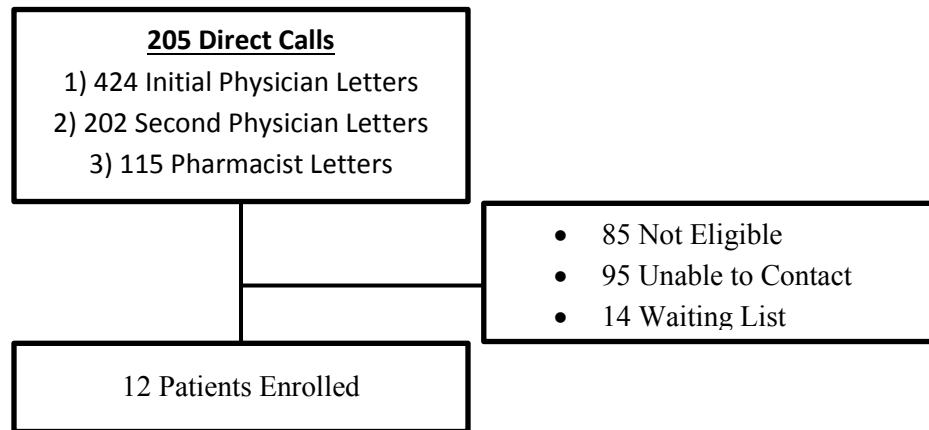


Figure 4-2: Flow Diagram of Direct Calls

A total of 260 post cards were printed for distribution. Of these, 140 were given to staff at the Endocrine and Diabetes Care Center and dispersed among the 20 exam rooms. The other 120 were given to the Director of Pharmacy Operations of the pharmacy to be dispersed amongst the pharmacy locations. Physicians and pharmacists were instructed to provide a postcard to potential participants, which had been flagged in their electronic

systems. These post cards did not directly result in any phone calls from potential participants or any enrollments.

As a result of the recruitment methods utilized, a total of 43 participants were enrolled in the study. Of these 43 participants, 38 participants had more than one month of economic data available, and were included in the analysis. Of the participants not included in the analysis, two had dropped out prior to one month of enrollment and three were recently enrolled with less than one month of data at the time of analysis.

4.2 Study Groups

The breakdown of participants by study group is provided in Table 4-1. This table provides a breakdown for all study participants who had been enrolled, the group of 38 participants who were included in the analysis and the 28 participants who had been in the study for six months.

Table 4-1: Breakdown of Participants by Study Group

Group	Enrolled	Analyzed	6 Months of Data Available
1 (PB) ^a	11	9	5
2 (PB+MTM) ^b	12	12	8
3 (BP) ^c	9	7	7
4 (BP+MTM) ^d	11	10	9
Total	43	38	28

^a3 patients dropped out of group 1, data available for 1 patient for analysis

^b1 patient dropped out of group 2, but had 2 months of data available for analysis

^c2 patients had less than one month of data and were not included in analyses.

Additionally, 1 patient dropped out but had 6 months of data available for analysis.

^d1 patient had less than one month of data and was not included in analyses

4.3 Baseline Characteristics

Patient baseline characteristics are provided in Tables 4-2, 4-3 and 4-4. Table 4-2 provides background characteristics of study participants. Overall, 37% of the population

was male, with an average age was 61 years old. The study population has a long length of diagnosis, with a majority of participants with a length of diagnosis of nine years or greater. Participants were on an average of 10 medications at baseline. Education and income varied slightly, but no significant differences existed between groups.

Table 4-2: Baseline Demographic Characteristics

Measure	Group 1 (PB)	Group 2 (PB+MTM)	Group 3 (BP)	Group 4 (BP+MTM)	Sig
Age (Mean (SD))	61.8 (8.3)	58.5 (10.1)	60.4 (10.0)	62.4 (8.2)	0.765
Gender (Male)	5 (55.6%)	4 (36.4%)	2 (28.6%)	3 (27.3%)	0.602
Education					0.063
Some High School	0 (0%)	1 (9.1%)	0 (0%)	1 (12.5%)	
Completed High School	0 (0%)	1 (9.1%)	1 (16.7%)	1 (12.5%)	
Some College	3 (37.5%)	6 (54.5%)	2 (33.3%)	3 (37.5%)	
Associates Degree	0 (0%)	2 (18.2%)	3 (50%)	1 (12.5%)	
Bachelor's Degree	3 (37.5%)	1 (9.1%)	0 (0%)	2 (25%)	
Graduate Degree	2 (25%)	0 (0%)	0 (0%)	0 (%)	
Income					0.145
<\$30,000	2 (28.6%)	5 (45.5%)	4 (66.8%)	5 (55.6%)	
\$30,000-\$50,000	0 (0%)	3 (27.3%)	0 (0%)	2 (22.2%)	
\$50,000-\$75,000	2 (28.6%)	1 (9.1%)	1 (16.6%)	2 (22.2%)	
\$75,000-\$100,000	0 (0%)	0 (0%)	1 (16.6%)	0 (0%)	
>\$100,000	3 (42.8%)	2 (18.1%)	0 (0%)	0 (0%)	
Total Medications (Mean (SD))	10.8 (4.1)	8.4 (2.5)	9.1 (2.9)	11.5 (4.5)	0.214
Charlson Comorbidity Index					0.552
0-1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
2-3	7 (77.8%)	8 (72.7%)	4 (57.1%)	6 (54.6%)	
4-5	2 (22.2%)	2 (18.2%)	3 (42.9%)	3 (27.3%)	
>6	0 (0%)	1 (9.1%)	0 (0%)	2 (18.2%)	
Length of Diagnosis					0.939
<2 years	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
2-9 years	1 (11.1%)	1 (9.1%)	1 (14.3%)	2 (18.2%)	
>9 years	8 (88.9%)	10 (90.9%)	6 (85.7%)	9 (81.8%)	
Smoking Status	0 (0%)	2 (18.2%)	0 (0%)	0 (0%)	0.168

Participants in the study had an average Body Mass Index (BMI) of 37.6, signifying obesity. This corresponds with a diagnosis of metabolic syndrome, as obesity

is a risk factor for all three diseases within metabolic syndrome. Other than obesity, most participants within each study were at or near goals for diabetes, hypertension and hyperlipidemia. Baseline clinical markers are provided in Table 4-3.

Table 4-3: Baseline Clinical Markers

Measure (Mean (SD))	Group 1 (PB)	Group 2 (PB+MTM)	Group 3 (BP)	Group 4 (BP+MTM)	Sig
Height (in)	69.4 (4.6)	67.0 (4.3)	65.5 (5.1)	65.3 (2.8)	0.137
Range	(59.92 - 74)	(59 - 73.5)	(60 - 74.8)	(61.5 - 71.1)	
Weight (lbs)	246.8 (40.0)	235.5 (38.6)	233.0 (30.5)	235.4 (59.3)	0.918
Range	(182 - 296.6)	(174.5 - 326.7)	(177.4 - 245.4)	(164.6 - 392.2)	
BMI	36.0 (4.6)	36.8 (5.3)	39.1 (9.1)	38.6 (7.8)	0.722
Range	(30.7 - 42.5)	(29 - 47)	(25.5 - 49.1)	(26.8 - 57.9)	
HgA1c	7.8 (1.2)	7.7 (1.9)	8.1 (1.2)	8.0 (1.6)	0.924
Range	(6.6 - 10.2)	(5 - 12.4)	(6.9 - 10.1)	(5.5 - 10.3)	
LDL	66.1 (34.3)	72.8 (18.6)	105.6 (41.7)	79.7 (30.4)	0.266
Range	(57 - 104)	(55 - 92.2)	(69.2 - 176.0)	(36 - 119)	
BP Systolic	131.1 (23.0)	121.5 (3.8)	122.6 (5.1)	124.1 (11.3)	0.398
Range	(104 - 186)	(116 - 126)	(114 - 130)	(110 - 142)	
BP Diastolic	75.1 (7.7)	78.9 (5.8)	73.7 (10.5)	72.3 (7.2)	0.234
Range	(60 - 84)	(68 - 84)	(60 - 90)	(62 - 82)	

Study participants received many preventative services which are recommended through diabetes guidelines. These include flu shots, as well as visits with dentists and ophthalmologists. However, most patients were not visiting their podiatrists at baseline. Utilization of these services is provided in Table 4-4.

Table 4-4: Baseline Service Utilization

Measure (n (%))	Group 1 (PB)	Group 2 (PB+MTM)	Group 3 (BP)	Group 4 (BP+MTM)	Sig
Yearly Flu Shot	8 (88.9%)	11 (100%)	4 (57.1%)	9 (81.8%)	0.109
Podiatrist Visit	3 (33.3%)	4 (36.4%)	3 (42.9%)	4 (36.4%)	0.986
Dentist Visit	8 (88.9%)	9 (81.8%)	6 (85.7%)	8 (72.7%)	0.827
Ophthalmologist Visit	9 (100%)	9 (81.8%)	7 (100%)	10 (90.9%)	0.419

4.4 Economic Analysis

This section describes the cost and utilization of healthcare services by the patient population.

4.4.1 Data

Medical and prescription claims data was obtained for study participants in March 2015. Some patients did not have medical and prescription claims data for the entire analysis period. Economic data were analyzed twice, once for all patients enrolled at least one month in the study, and another group including only those patient enrolled for six months. The number of participants with data available during each month of the analysis period, from 6 months prior to enrollment through 6 months post-enrollment is provided in Table 4-5.

Table 4-5: Number of Patients with Data Each Month: All Participants

Group	Pre-Enrollment						Post-Enrollment					
	6	5	4	3	2	1	1	2	3	4	5	6
1 (PB)	9	9	9	9	9	9	9	8	5	5	5	5
2 (PB+MTM)	11	11	12	12	12	12	12	12	8	8	8	8
3 (BP)	7	7	7	7	7	7	7	7	7	7	7	7
4 (BP+MTM)	9	9	9	10	10	10	10	10	9	9	9	9

An additional analysis was completed with patients enrolled for six months. The number of participants with data available during each month of the analysis period for the group of patients enrolled for six months is provided in Table 4-6. There were two patients who did not have claims data available for the entire 6 months prior to enrollment, one each in the hybrid model group and the MTM with pill bottles groups respectively. There were also multiple patients who were not enrolled for 6 months at the time of analysis. These patients were analyzed based upon the length of enrollment. To account for the varying number of patients per group as well as length of enrollment

among participants, costs and utilization were analyzed on a Per-Member-Per-Month (PMPM) basis.

Table 4-6: Number of Patients with Data Each Month: 6 Month Participants

Group	Pre-Enrollment						Post-Enrollment					
	6	5	4	3	2	1	1	2	3	4	5	6
1 (PB)	5	5	5	5	5	5	5	5	5	5	5	5
2 (PB+MTM)	7	7	8	8	8	8	8	8	8	8	8	8
3 (BP)	7	7	7	7	7	7	7	7	7	7	7	7
4 (BP+MTM)	8	8	8	9	9	9	9	9	9	9	9	9

Additionally, prescription data was missing for five participants. The baseline characteristics are provided in Table 4-7. These patients were similar to the overall characteristics of their respective study groups. These participants were near the mean age, had similar comorbidity scores and length of diagnosis, as well as the number of medications fell within the standard deviation of their study group. These five patients without available prescription claims data were similar to other patients in their study group in regards to baseline characteristics.

Table 4-7: Participants Missing Prescription Data

Excluded Patient	1	2	3	4	5
Group	4	4	3	1	2
Gender	Male	Female	Female	Female	Male
Age	59	57	60	61	59
Education	Associate Degree	Some College	N/A	Graduate Degree	Associates Degree
Income	\$50,000-\$75,000	\$30,000-\$50,000	N/A	N/A	>\$100,000
Charlson Comorbidity Index	4-5	4-5	4-5	2-3	2-3
Total Medications	12	7	8	8	7
Length of Diagnosis	>9 Years	>9 Years	>9 Years	>9 Years	2-9 Years

4.4.2 Total Cost

Total costs showed varying trends among the study groups. Total costs decreased in groups not receiving MTM services, and increased in group 2 (PB+MTM). The only difference which carried over when analyzing all patients was the decrease seen in group 3 (BP) patients. This was driven by decreases in inpatient, outpatient and ER costs. When analyzing all patients, groups 1 (PB), 2 (PB+MTM) and 4 (BP+MTM) did not show a change in the total costs per member per month. Figure 4-3 shows the total costs experienced during the analysis period.

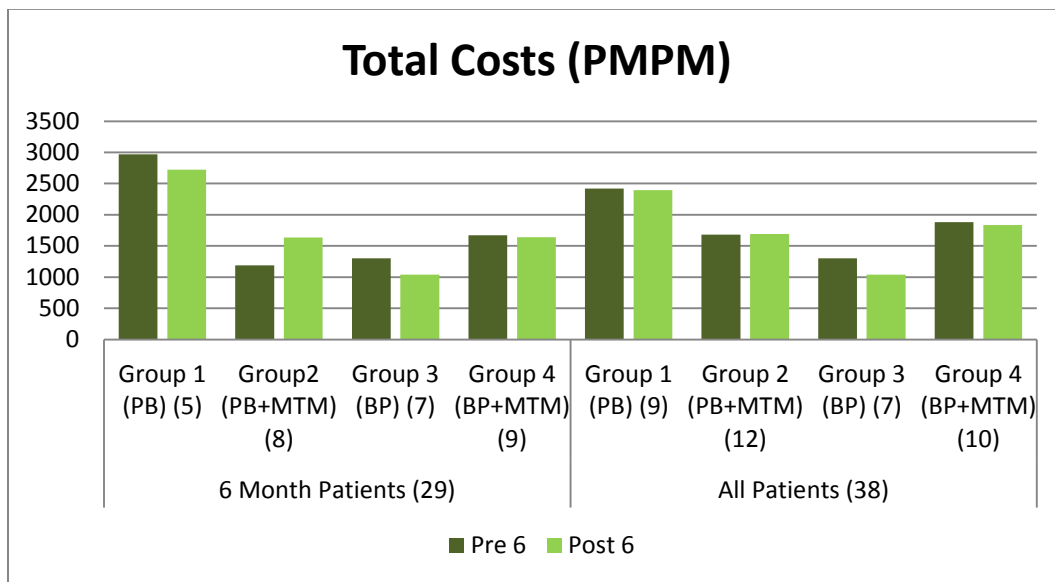


Figure 4-3: Total Costs

4.4.3 Inpatient Cost and Utilization

During the analysis period, there were a total of 11 inpatient visits. These visits all occurred within the patients who were enrolled for at least six months in the study. There was a large increase noted in group 1 (PB+MTM). While each half of the study period included one inpatient hospitalization for group 1, the visit in the six months prior to

enrollment was only charged as \$150. Group 3 experienced a decrease in inpatient costs. This was due a more expensive hospitalization post-enrollment. A comparison of inpatient costs is shown in Figure 4-4.

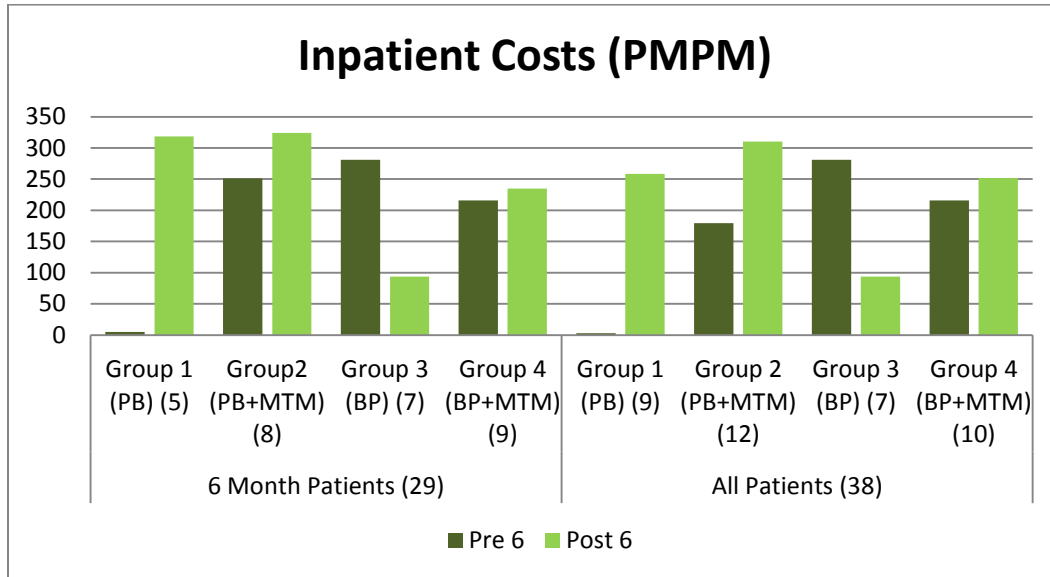


Figure 4-4: Inpatient Costs

Per-member-per-month utilization stayed relatively stable through the analysis period. The only group which experienced a difference was the group receiving MTM services, which saw one hospitalization during the six months post enrollment compared with two in the six months prior to enrollment. When comparing with the costs, this decrease in utilization was more than offset by the larger cost of the hospitalization, leading to an increase in PMPM inpatient costs during the analysis period. A comparison of inpatient utilization is shown in Figure 4-5.

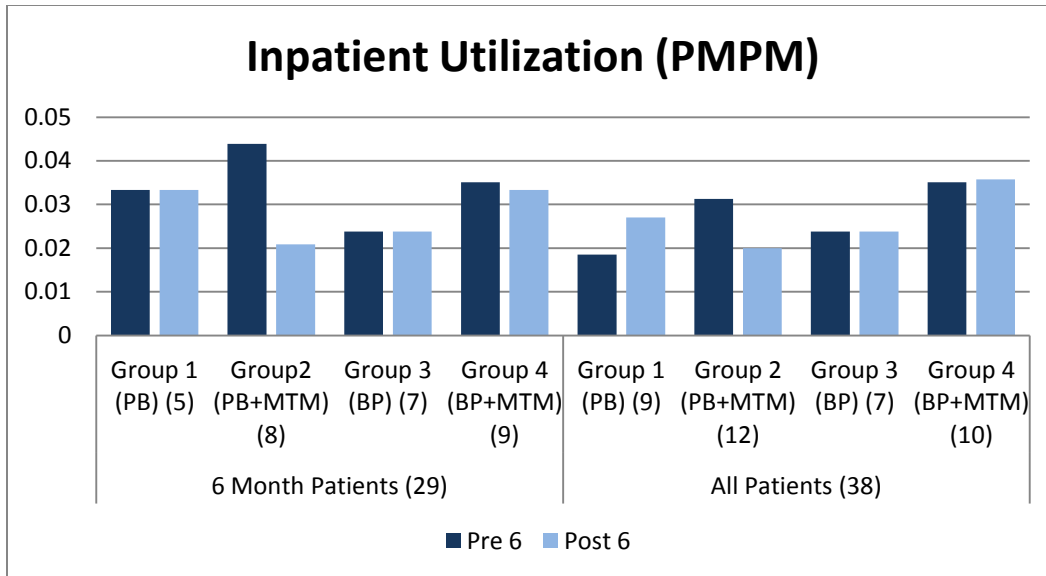


Figure 4-5: Inpatient Utilization

4.4.4 Outpatient Cost and Utilization

All study groups experienced a decrease in PMPM outpatient costs (Figure 4-6). For both of the groups receiving MTM services (groups two and four), the savings are more pronounced when including all patients. This suggests that the patients who have not yet been enrolled for six months are seeing a larger difference in outpatient costs.

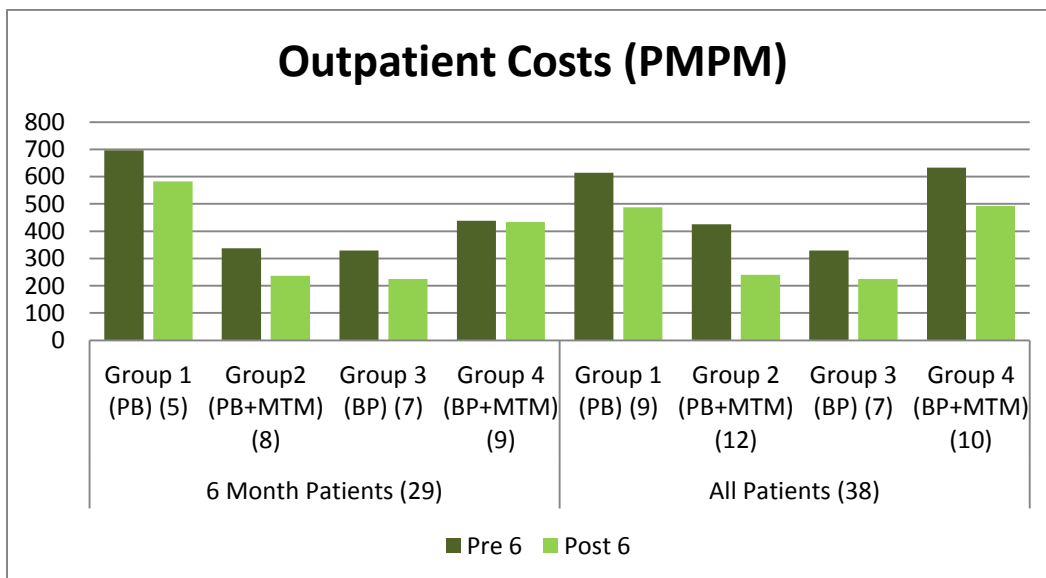


Figure 4-6: Outpatient Costs

Trends in outpatient utilization varied widely amongst the study groups. The groups who received MTM services (groups two and four) experienced a slight increase in outpatient utilization during study enrollment. This may be partially explained by the fact that the MTM services received are included in the medical claims. While utilization slightly increased due to MTM, outpatient costs decreased overall suggesting fewer and less-intensive outpatient visits, including optometrist visits. Outpatient utilization rose in group one, receiving medications in pill bottles with no MTM. This is partially the result of an increase in the frequency of physician office visits. An increase in the frequency of physician office visits may suggest poorer disease control. There was a decrease in more costly outpatient visits and procedures, which offset the increase in the less-expensive physician office visits. Figure 4-7 depicts the changes in outpatient utilization during the analysis period.

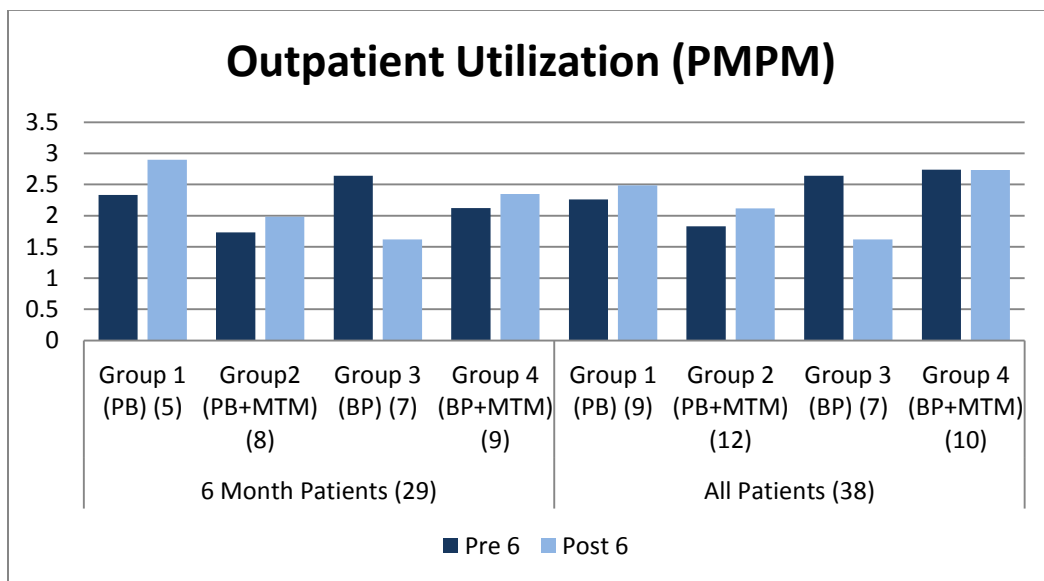


Figure 4-7: Outpatient Utilization

4.4.5 Emergency Room Cost and Utilization

Emergency room costs decreased for all study groups during the analysis period, when compared per-member-per-month. All groups except for group three, who received blister packaging services only, experienced a large decrease in per-member-per-month costs. Figure 4-8 shows ER costs.

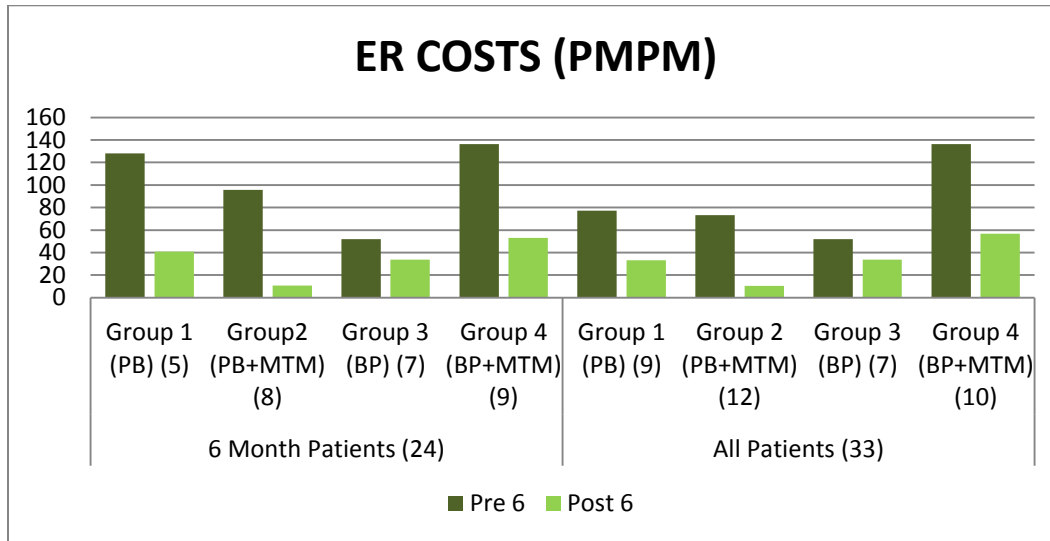


Figure 4-8: Emergency Room Costs

Emergency room utilization showed favorable trends for groups receiving MTM services, groups experiencing a decrease in utilization. This may help to explain the decrease experienced in healthcare costs. ER utilization in groups not receiving MTM remained stable through the analysis period. While utilization did not change, the decrease in costs suggests a decrease in the severity of the ER visits. Figure 4-9 depicts the ER utilization during the analysis period.

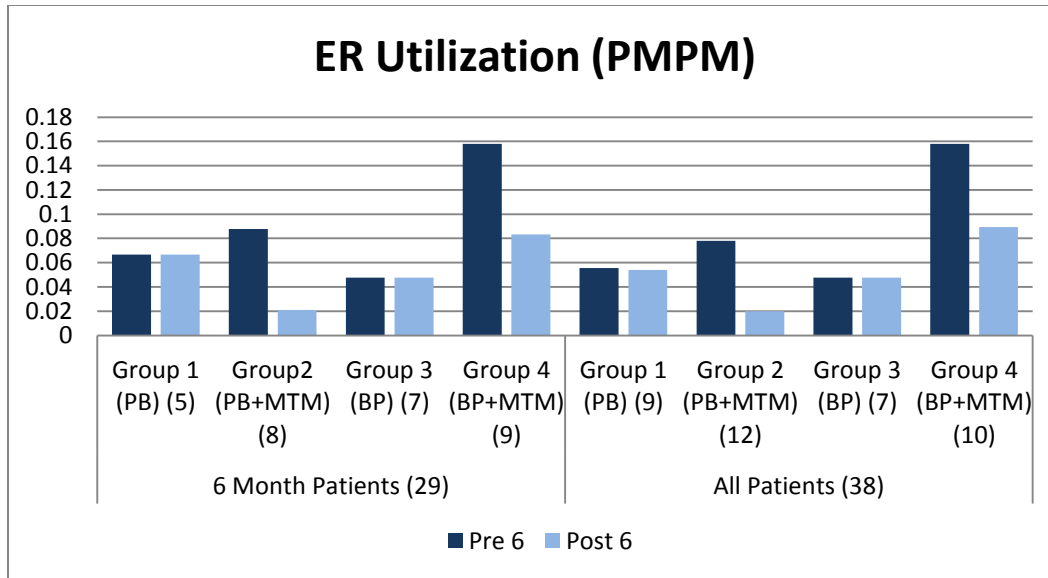


Figure 4-9: Emergency Room Utilization

4.4.6 Prescription Cost and Utilization

Prescription costs included all medications for which a prescription claim was available for analysis. A total of five participants (one patient in groups one, two and three as well as two patients in group four) did not have prescription claims data available. Due to this, prescription costs and utilization was only taken as a per-member-per-month average based upon participants who had prescription claims data available.

Prescription costs decreased in the control group, but increased in every intervention group. A difference is evident for group two patients when looking at all patients compared with only those with six months of enrollment. This increase in costs is driven by three patients who had costly medications added to their medication regimens. Two of these medications were for the treatment of diabetes. This change in therapy was not necessarily an escalation, but to therapies dosed once daily. Figure 4-10 shows prescription costs during the analysis period.

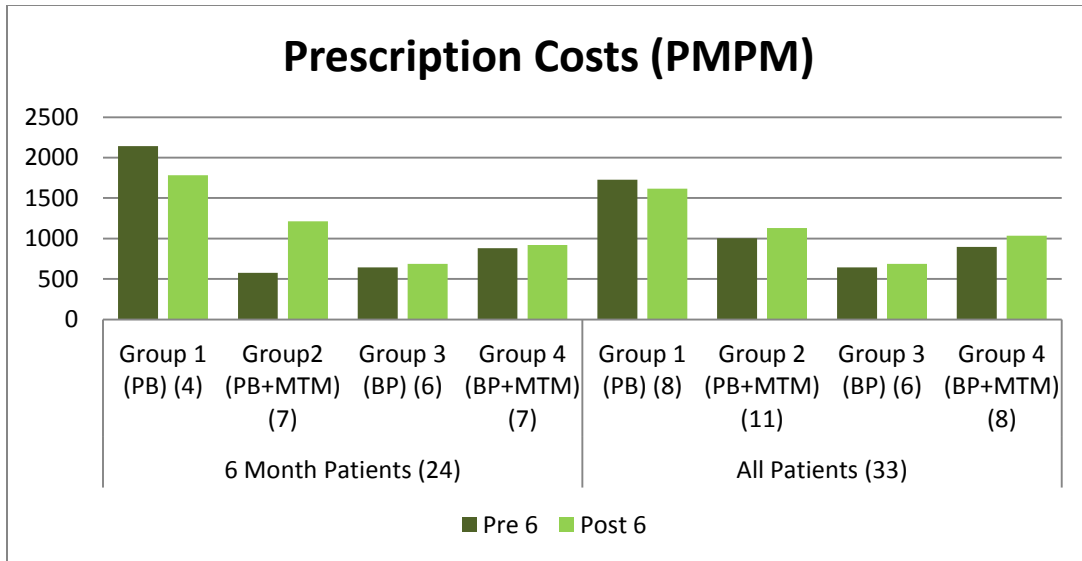


Figure 4-10: Prescription Costs

Most study groups experienced an increase in prescription fills. Group 1 (PB) noticed only a slight increase in prescription fills. For group 3 (BP), this increase was driven more by patients who were enrolled for six months. Group 2 (PB+MTM) saw a decrease in fills overall. This may be due to the timing of 90 day prescription refills. Figure 4-11 shows prescription fill data.

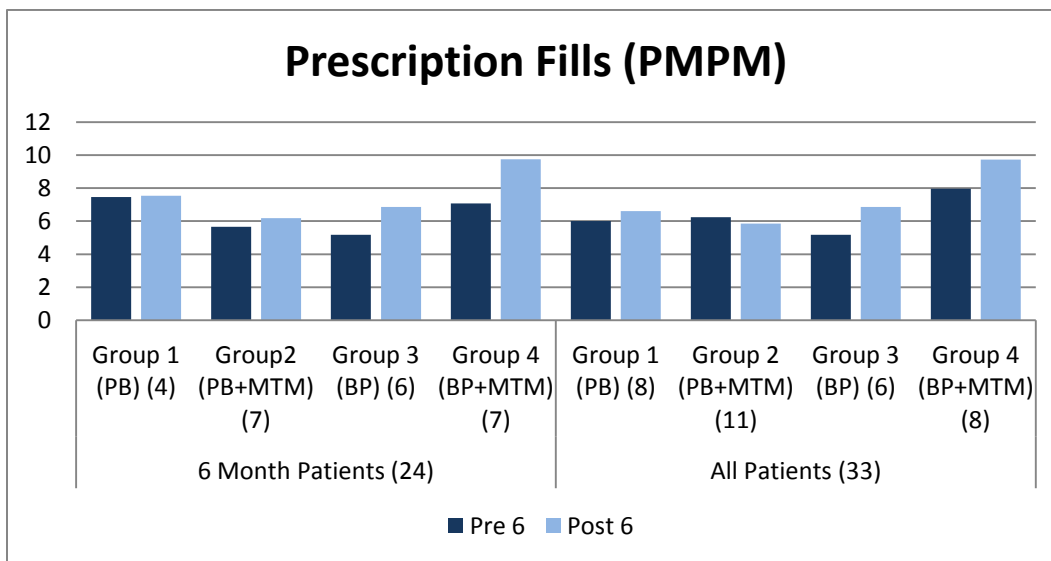


Figure 4-11: Prescription Fills

4.5 Adherence

Medication adherence was measured as a percentage of patients who were adherent to medications measured by the 2015 CMS STAR criteria. For diabetes this included biguanides, sulfonylureas, thiazolidinediones, and DiPeptidyl Peptidase-IV Inhibitors, incretin mimetics, and meglitinides. This does not include insulins or the newer sodium-glucose-transfer protein inhibitors. For hypertension this included medications which inhibit the renin-angiotensin-aldosterone system, and did not include diuretics which most patients are on. Hyperlipidemia included only statins, and no other cholesterol-lowering therapies. This analysis includes only patients who have been enrolled for six months. It is important to note that five patients were excluded from this analysis for lack of prescription claims data as discussed in the section on prescription costs and utilization. Additionally, one additional participant in group four was excluded. Though this participant was enrolled for six months, only three months of data was available. The participant was adherent for the first three months for all three measures after being non-adherent in the six months prior to the study. Despite this initial adherence, the lack of data prevents a proper analysis of this patient.

All study groups showed an improvement in adherence for all three of the CMS adherence measures. Intervention groups showed a greater percentage of patients achieving adherence (PDC>80%) during the study period when compared to the control group (group 1), except for statin therapy. Control group patients receiving statin therapy were non-adherent prior to enrollment, and became adherence during the study period. During the same time, patients in group 2 (PB+MTM) did not all become adherent. The number of patients in each group who were adherent to the medications of interest are

presented in Table 4-8. White columns represent adherence prior to enrollment while shaded columns represent adherence to medications during six months of enrollment.

Table 4-8: Adherence to Medications Included in CMS Star Ratings

Group	Diabetes 6 Months Pre		Diabetes 6 Months Post		RAAS Inhibitors 6 Months Pre		RAAS Inhibitors 6 Months Post		Statins 6 Months Pre		Statins 6 Months Post	
	N	%	N	%	N	%	N	%	N	%	N	%
1	1/3	33.3	2/3	66.6	1/3	33.3	2/3	66.6	0/3	0.0	3/3	100
2	5/7	71.4	6/7	85.7	2/7	28.5	6/7	85.7	3/8	37.5	5/8	62.5
3	2/6	33.3	6/6	100	1/5	20.0	4/5	80.0	1/5	20.0	5/5	100
4*	3/6	50.0	6/6	100	0/5	0.0	4/5	80.0	2/5	40.0	5/5	100

**One patient in group 4 only had 3 months of claims data post-enrollment and, though adherent during these 3 months, had a PDC of <80% for the 6 month period.*

In order to assess the impact of the hybrid model of care on the STAR measures, the adherence data must be converted. This conversion looks at the number of adherent patients (>80% PDC) at each time point. This percentage is then compared with criteria thresholds published each year by CMS. The 2015 criteria, which were provided in Table 2-1 are repeated here in Table 4-9.

Table 4-9 Thresholds for 5-Star Ratings³⁷

Stars	Medicare Advantage Plans					Medicare Part D Plans				
	1	2	3	4	5	1	2	3	4	5
Diabetes	<69	69-73	73-77	77-81	>81	<74	74-79	79-82	82-85	>85
RAAS-I	<72	72-76	76-81	81-85	>85	<72	72-76	76-81	81-84	>84
Statin	<59	59-68	68-76	76-83	>83	<62	62-69	69-75	75-78	>78

STAR measures were provided based on the criteria for both Medicare Advantage as well as Medicare Part D plans. Due to the likeness between the criteria, this resulted in the same STAR ratings, except in the case of diabetes medications at baseline. All patients receiving an intervention improved to four or five star levels, with the exception of statins in the group receiving only MTM services which still experienced an increase to a two star level. STAR measure adherence categories and the corresponding star ratings of the study population is shown in Table 4-10.

Table 4-10: STAR Measure Adherence Ratings

Group	Diabetes		RAAS Inhibitors		Statins	
	Pre	Post	Pre	Post	Pre	Post
1	1	1	1	1	1	5
2	1-2*	5	1	5	1	2
3	1	5	1	4	1	5
4	1	5	1	4	1	5

**This would be 2 stars for a Medicare Advantage Plan or 1 Star for a Part D Plan*

Chapter 5

Discussion

This chapter provides a thorough discussion of the findings presented in the previous chapter. The discussion is divided into the following headings:

- Implementation and Experiences
- Economic Outcomes
- Medication Adherence
- Limitations
- Conclusions
- Implications for Future Research

5.1 Implementation and Experiences

This study is an exploratory pilot of a large, prospective, multi-center study. A large amount of collaboration is required for such a study to take place. This exploratory pilot analysis benefitted from the fact that the physicians, pharmacy and payer were all within the same integrated delivery network (IDN). The physicians were familiar, and had a working relationship with, a clinical pharmacist who provided MTM services, as

well as with The Pharmacy Counter. The physicians were open to pharmacy interventions and recommendations, including adherence packaging. A strong working relationship, and collaboration between physicians and pharmacists is crucial to providing effective pharmacy services, including MTM.⁷¹

Collaboration with physicians provided access to a population of potential participants. Agreement with the physician group and associated integrated delivery network, provided access to electronic health records for the purposes of identifying patients, as well as accessing predetermined clinical values for the study. The collaboration with physicians was instrumental in effectively identifying and reaching out to potential program participants.

In addition to effective collaboration, the pharmacy staff involved was experienced in providing the pharmacy services utilized in the study. The clinical pharmacist who conducted the MTM sessions for study participants was experienced in provision of MTM using an appointment-based model. A meeting was held with research team members and the pharmacist to provide education on the study protocol, as well as address any questions or concerns which the pharmacist may have. An open line of communication was kept with the pharmacist, including notifying them when a patient was enrolled who was to receive MTM services.

Pharmacy staff experienced with adherence packaging is also essential for provision of the hybrid model. The Pharmacy Counter also had a location devoted to adherence pharmacy services, with an emphasis on blister packaging. The pharmacists and staff at this location were familiar with blister packaging services, as well as medication synchronization. Additionally, this pharmacy included automation which

aided in the filling of blister packages. This allows for the filling of 40 blister packages per hour with a minimal staff. Open lines of communication were also kept with the adherence pharmacy, including advanced warning when sending information on a newly enrolled patient. This collaboration aided in transitioning patients to receive blister packaging services. Collaboration and communication among professionals is key in the effective and timely implementation of the hybrid model.

5.2 Economic Outcomes

Pilot economic trend analyses were conducted on each of the study groups for all patients as well as only those patients who had been enrolled for six months in the study. Analyses were completed for inpatient, outpatient, emergency room and prescription costs and utilization. Total cost was also analyzed. In order to account for varying numbers of patients, as well as months for which data was available, per study group, costs and utilization were analyzed on a per-member-per-month (PMPM) basis. While most groups did not experience a large change in total cost. However, initial trends within the various costs and utilization measured may predict future health care costs.

Patients in the pill bottle group experienced a slight decrease in PMPM healthcare costs. This decrease was driven by decreases in outpatient, prescription, and emergency room costs. During this same period, outpatient utilization increased, while emergency room visits and prescription fills did not change. The increase in outpatient service utilization included more frequent physician follow-ups, suggesting a disease which is less well controlled. There were two inpatient admissions, one in the pre-enrollment period and one in the post-enrollment period. The pre-enrollment admission was very

brief and was only for imaging tied to diabetes and hyperlipidemia. The admission in the post enrollment period included a coronary catheterization tied to the diagnosis codes for hyperlipidemia and hypertension. While there was a short-term savings in ER and outpatient costs, the more frequent physician office visits and minimal increase in prescription fills may lead to long term increases in inpatient costs and utilization. This long-term trend has been noted in diabetic patients.⁸⁸ While total costs have decreased for participants in the control group in this short term analysis, underlying economic trends suggest the trend in total cost may be misleading.

Participants in the group receiving only MTM through the appointment based model experienced economic trends supporting long-term savings. This group experienced three inpatient admissions, all from the same patient. This included a hernia repair and admission for ischemic heart disease and a urinary tract infection prior to enrollment, as well as a more costly admission for atrial fibrillation and tachycardia post enrollment. This group experienced an increase in outpatient utilization with the addition of the MTM visits with the clinical pharmacist. Overall outpatient costs were lower, due to less costly preventative care visits and MTM sessions. Emergency room costs and utilization both decreased in the group receiving MTM services. Prescription utilization remained mostly unchanged, although adherence improved. This is partially due to an increase in 90 day prescriptions, which limit the number of fills required. This may also be attributed to the education on the importance of adherence during the MTM sessions. Prescription costs remained stable over all of the patients. The patients enrolled for six months experienced an increase in prescription costs due to the addition of Januvia, Invokana and Aggrenox in the post enrollment period, which were all much more

expensive than therapies in the six months prior to enrollment. With all of these costs, there was no change in costs when taking all enrolled patients into account. There was a slight increase in total costs for those enrolled for 6 months due to the increase in prescription costs.

Similar economic trends in MTM programs have been shown in the literature. In a study looking at one year before and after enrollment, similar trends in pharmacy costs as well as emergency room and outpatient utilization.¹⁷² This study found a savings in total costs at the one year time point due to an additional decrease in inpatient costs and utilization. Of note in our MTM population is that of the three inpatient visits, only the pre-enrollment admission for ischemic heart disease can be attributed to metabolic syndrome. Another study looking at one year data for an employer sponsored MTM program found total cost savings driven by decreases in inpatient and emergency room cost and utilization.⁴⁷ A long-term study looking at up to seven years of economic outcomes in a diabetes MTM program found an overall decrease in total health care costs.⁴⁵ This total cost savings was driven by a large decrease in medical insurance claims, while prescription claims increased through the study period. The economic trends of MTM programs decreasing medical costs, while increasing prescription costs, similar to our group, lead to an overall savings in long-term health care costs.

The group receiving adherence packaging, along with refill synchronization, experienced a savings in total cost. In this group, medical costs for inpatient, outpatient and emergency room visits all decreased. Utilization remained stable, or in the case of emergency room visits, also decreased. This decrease in medical costs and utilization was accompanied by an increase in prescription costs and utilization. If the relationship

between initial trends and long term costs is similar to that seen with MTM, these trends suggest a similar long-term saving in total health care costs.⁴⁵ There is a gap in the literature regarding the effect of adherence packaging on economic outcomes.¹⁷³ Adherence packaging has been shown to promote adherence and lower blood pressure in patients with hypertension.⁵⁶ These surrogate endpoints may lead to better disease control and overall decreases in medical costs and utilization as a result of increased prescription utilization.

The hybrid model of care, group four, experienced little change in total cost. This is due to costs in some areas offsetting savings in other areas. One area of increase is in inpatient costs. There were two patients who experienced inpatient visits, and they had one admission pre and post enrollment each. For one patient, the pre enrollment admission was for heart and respiratory failure, while the post enrollment admission was for diastolic heart failure. The second patient was admitted for dizziness, linked to various diagnosis codes for diabetes, while the post enrollment admission was related to ischemic heart disease and kidney failure. There was a slight increase in the number of outpatient visits, especially in the group enrolled six months due to the addition of MTM visits. This was associated with a decrease in outpatient costs due to less costly MTM and wellness visits. Emergency room cost and utilization decreased during the enrollment period. These outpatient and emergency room savings were largely offset by a large increase in prescription costs and utilization in addition to the increased inpatient cost.

While this shift in costs from emergency room, outpatient and hospital costs to prescription costs is a pattern consistent with the other intervention groups within this study, it differs from the only available literature. In a retrospective analysis of a program

providing specialized packaging and telephonic MTM, conducted by Zillich et al. inpatient and emergency room costs remained consistent, while outpatient, prescription and total costs increased.⁷¹ This represents a similar trend in replacing inpatient and emergency room costs with preventative outpatient and prescription costs. However, the prescription costs rose to a larger extent than in our study, while emergency room and outpatient costs did not decrease in turn.

Overall, this exploratory pilot analysis noted a slight change in total costs in the intervention groups. While total costs did not change, some interesting trends in the analyzed costs have begun to emerge. In contrast to the control group, the groups receiving a pharmacy-based intervention led to an increase in prescription costs, which was mostly offset by decreases in medical costs. In the adherence packaging group, a great decrease in medical costs led to an overall lower total cost per patient per month. While short-term savings are not readily apparent, economic trends suggest long-term economic savings through improved medication utilization.

5.3 Adherence Outcomes

In this study, groups receiving pharmacy-based interventions have experienced improvements in medication adherence. The adherence measures in this study assess the same medications as the Centers for Medicare and Medicaid Services (CMS) STAR measures. Increases in adherence correlated to four or five stars based upon the 2015 CMS criteria. The exception was statin adherence in the MTM study group. While adherence levels did improve, not all patients achieved a PDC >80%. This STAR rating is higher than that attained in a previous study of care managers providing targeted phone

calls along with a pharmacy managing prescription refills.¹⁷⁴ Overall, pharmacy-based interventions provided improvements in STAR measure ratings compared to baseline.

In an effort to promote quality and reduce costs, the CMS has implemented a STAR rating system. Using this system, CMS defines objectives to improve the quality of care. Performance measures are then developed by CMS to assess insurance plans' ability to meet these objectives. This system provides STAR ratings of one to five stars to assess progress towards on the measures. Three measures target medication adherence to diabetes medications, RAAS inhibitors for hypertension and statins for hyperlipidemia.³⁷ These measures are weighted three times higher than other measures, carrying serious implications for Medicare insurance plans.

STAR ratings have serious implications on Medicare insurance plans. These implications range from bonus payments for achieving four or five star ratings to the potential to being dropped from Medicare for performing below three stars. Due to these implications, and the fact that the adherence measures are weighted when calculating overall STAR rating, plans are taking an increased interest in medication adherence. This includes evaluating the performance of pharmacies.¹⁷⁵

Pharmacies, and pharmacists, have the ability to impact medication adherence. Insurance plans are beginning to recognize the impact that quality pharmacies can have on medication adherence and, by extension, STAR ratings. Some plans are developing preferred pharmacy networks, and admitting only those pharmacies which have shown they can provide benefit in the form of STAR ratings. There is also the knowledge that medication adherence can be improved through the provision of pharmacy services. These services can include MTM and adherence packaging, among other interventions.¹⁷⁵

These services, especially MTM, are expected to play a key role in care due to the implications of STAR ratings.¹⁷⁵

5.4 Limitations

As this was an exploratory pilot, the small sample size and short time horizon may not capture the full economic effects of the hybrid model in this population. Nevertheless, some of the trends seen in this study seem encouraging. Additionally, among the small population, five patients (about 13% of the population) did not have prescription data available for analysis. Despite these limitations, it is still possible to identify some initial economic trends within the study groups. The short time horizon also does not allow for the assessment of sustained improvements in medication adherence.

A second limitation of the study is the fact that the patient population, despite having metabolic syndrome, were near their clinical goals. At baseline, most participants were at or near goal for diabetes, hypertension and hyperlipidemia. The population within this study showed similarities and differences with available MS demographics. An analysis of 98,091 patients with metabolic syndrome among 3 insurers was conducted by Boudreau et al.¹⁰³ The patients in the current study had a similar age to that seen by Boudreau. Looking at clinical markets, the patients in the current study had lower blood pressures and LDLs that that seen by Boudreau, which did not report A1c levels. Another key difference was the BMI which for Boudreau was 33kg/m² compared to the average of 37.6kg/m² in the current study. These differences may potentially be due to the fact that the patient population in the current study was recruited from an endocrine specialty

practice. This may provide the study population with better monitoring and disease state control, though patients may still need assistance with diet and exercise as evidenced by the elevated BMI. This limits the generalizability of study findings. Though generalizability is limited, it may be logical to hypothesize that patients who are poorly controlled at baseline may experience a greater impact on economic outcomes as a result of the hybrid model of care.

A third limitation is the change seen in the control group. This is particularly true for medication adherence. The number of patients who were adherent to therapy improved in the control group among all three adherence measures, achieving five star status for statin medications. This can make it difficult to potentially associate an improvement in adherence to the interventions. The improvement in adherence of the control group suggest that participation in a research study and being monitored periodically may have contributed to the increase in medication adherence.

5.5 Conclusions

Overall, pharmacy-based interventions to promote medication adherence, including the hybrid model of care, demonstrate interesting economic and adherence trends. The intervention groups experienced a shifting of health care costs from medical costs to prescription costs. This provided a short-term savings in the group receiving blister packaging. The two groups receiving MTM services, including the hybrid model of care, did not experience short term savings in overall health care costs, but still experienced the shift in costs. This shift in costs to medications may allow for greater

savings in the long-term through avoiding inpatient, emergency room and unnecessary outpatient utilization.

With an increased emphasis on quality of care in addition to cost, medication adherence is becoming more significant. The inclusion in the STAR measures by which insurance plans is already beginning to show implications through the use of preferred pharmacy networks based on both cost and quality instead of cost alone. This study suggests that pharmacy-based interventions, including the hybrid model of care, can impact the medication adherence of insurance plan beneficiaries. This may have implications on pharmacy contracts, as well as reimbursement for pharmacy provided services.

Our study provides a pilot exploratory analysis of the economic impact of the provision of a hybrid model of care, including MTM and adherence packaging. Initial trends suggest long-term economic implications, as well as short-term adherence implications related to the CMS STAR measures. Further study is warranted to further evaluate the economic implications of the hybrid model of care.

5.6 Implications and Future Research

The implementation of quality-based reimbursement for health care plans under Medicare brings greater importance to medication adherence. Pharmacists are in a position to aid with these adherence measures due to their accessibility and medication knowledge. Due to medication adherence receiving a greater weight when calculating the overall STAR measures, this is becoming an increasing focus of health plans due to the impact on reimbursement. If health plans fail to achieve adherence, it can carry

significant implications for reimbursement. Health plans are beginning to realize the impact of pharmacies on these measures, and are holding pharmacies accountable through the provision of preferred pharmacy networks. This aligns the goals of the pharmacy and the health plan to be improving medication adherence as well as controlling costs.

Findings from this study suggest implications of pharmacy provided services. Short term trends suggest the potential for long-term cost savings. While the current study suggests that the hybrid model of care will have long-term economic benefits, it does not appear to be superior to the individual interventions in this exploratory analysis. It may take time for any economic superiority of the hybrid model over individual interventions to become evident. Additionally, clinical and humanistic outcomes will need to be taken into effect Literature has shown that pharmacy provided interventions can have a positive impact on medication adherence, with combinations of services providing a greater impact. This improvement in adherence is supported by the change in STAR measures seen in this study. As health plans look to create preferred pharmacy networks in an effort to improve their STAR quality measures, they should seek out pharmacies which offer, or have the capacity to offer, adherence interventions. Pharmacies which can offer combinations of services, including behavioral and educational interventions, may provide the greatest benefit.

In turn, pharmacies should provide and measure their adherence-promoting services. This can allow for assessment of the appropriateness of the intervention in the patient population. In this pilot analysis of a population of patients with metabolic syndrome, the hybrid model of care provided short term economic and adherence

improvements comparable to that of MTM or adherence packaging services provided individually. Such studies can be helpful to pharmacies by providing new and innovative interventions, especially when implementation is described. Pharmacies would benefit through the investigation and provision of such combinations, although the optimal combination may vary based upon population and disease state. Additionally, pharmacies can use the data collected to illustrate the value of the services provided. This can aid in contract negotiations with health plans, and potential reimbursement for these cognitive services, and extra revenue for the pharmacy. This is not only important in negotiations with Medicare plans, but as health plans are becoming aware of the long-term economic impact of improved adherence, these measures are likely to be included in Medicaid and commercial plans as well. Pharmacies should begin providing adherence interventions, because if they do not start showing value today, they may not be around tomorrow.

Further study may help to determine the optimal provision of a hybrid model of care. The effects of pharmacy-based interventions may vary based upon patient population and target disease states. Different combinations of pharmacy-provided services, or additional services, may offer varying impact on adherence and economic outcomes. Different hybrid models should be tailored to the target patient population, or to the individual patient.

Additionally, the cost of the provision of any proposed hybrid model of care must also be considered before widespread implementation is considered. If the cost of providing an intervention is greater than the benefit experienced through reimbursement and economic savings, it will not be in the best interest for the pharmacy to provide, or the health plan to reimburse, such a service. The costs of provision of the hybrid model of

care are not provided within this analysis. Future research should assess the costs of providing these interventions together to see if such services can be sustainable. MTM services are reimbursable through Medicare Part D plans, and can potentially justify the presence of a pharmacist devoted to MTM services. Adherence packaging services may serve to obtain new prescriptions through patient interest and physician referral. As the adherence packaging replaces all of the pill vials, there will be a break-even point for the number of medications at which the cost of the adherence packaging becomes cheaper than multiple pill vials. This break- even point will vary by pharmacy, due to differences in the use of automation as well as differences in the cost of labor and materials. This is why it is important to consider the implications of pharmacy services when selecting which ones to implement. It may also be beneficial to implement services individually. For example, since reimbursement for MTM services is directly available for Medicare Part D plans, this may provide a more reliable source of reimbursement. Regularly monitoring outcomes of pharmacy services, including preliminary trends can help identify if interventions are having an impact, as well as identifying areas for improvement.

Further study is currently underway through the continued study of this patient population, as well as expansion to other populations. This will provide a larger number of patients and a longer time horizon. This, in turn, may allow for the capture of more economic data as well as improve the generalizability of this hybrid model of care to other populations. Additionally, the costs of providing the hybrid model should be investigated due to their implications on the ability for the hybrid model to be implemented in practice.

References

1. Osterberg L, Blaschke T. Adherence to medication. *The New England journal of medicine*. Aug 4 2005;353(5):487-497.
2. Karve S, Cleves MA, Helm M, Hudson TJ, West DS, Martin BC. Good and poor adherence: optimal cut-point for adherence measures using administrative claims data. *Current medical research and opinion*. Sep 2009;25(9):2303-2310.
3. New England Healthcare Institute. Thinking outside the pill-box: a system-wide approach to improving patient medication adherence for chronic disease.
Accessed at
www.nehi.net/publications/44/thinking_outside_the_pillbox_a_systemwide_approach_to_improving_patient_medication_adherence_for_chronic_disease,
December 26, 2013.
4. Phatak HM, Thomas J, 3rd. Relationships between beliefs about medications and nonadherence to prescribed chronic medications. *The Annals of pharmacotherapy*. Oct 2006;40(10):1737-1742.
5. Gatti ME, Jacobson KL, Gazmararian JA, Schmotzer B, Kripalani S. Relationships between beliefs about medications and adherence. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Apr 1 2009;66(7):657-664.

6. Rolnick SJ, Pawloski PA, Hedblom BD, Asche SE, Bruzek RJ. Patient characteristics associated with medication adherence. *Clinical medicine & research*. Jun 2013;11(2):54-65.
7. Schectman JM, Bovbjerg VE, Voss JD. Predictors of medication-refill adherence in an indigent rural population. *Medical care*. Dec 2002;40(12):1294-1300.
8. Wiegand P, McCombs JS, Wang JJ. Factors of hyperlipidemia medication adherence in a nationwide health plan. *The American journal of managed care*. Apr 2012;18(4):193-199.
9. Billups SJ, Malone DC, Carter BL. The relationship between drug therapy noncompliance and patient characteristics, health-related quality of life, and health care costs. *Pharmacotherapy*. Aug 2000;20(8):941-949.
10. Bailey JE, Lee MD, Somes GW, Graham RL. Risk factors for antihypertensive medication refill failure by patients under Medicaid managed care. *Clinical therapeutics*. Nov-Dec 1996;18(6):1252-1262.
11. Perreault S, Lamarre D, Blais L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. *The Annals of pharmacotherapy*. Sep 2005;39(9):1401-1408.
12. Loke YK, Hinz I, Wang X, Salter C. Systematic review of consistency between adherence to cardiovascular or diabetes medication and health literacy in older adults. *The Annals of pharmacotherapy*. Jun 2012;46(6):863-872.
13. McNaughton CD, Jacobson TA, Kripalani S. Low literacy is associated with uncontrolled blood pressure in primary care patients with hypertension and heart disease. *Patient education and counseling*. Aug 2014;96(2):165-170.

14. Gerber BS, Cho YI, Arozullah AM, Lee SY. Racial differences in medication adherence: A cross-sectional study of Medicare enrollees. *The American journal of geriatric pharmacotherapy*. Apr 2010;8(2):136-145.
15. Martin LR, Williams SL, Haskard KB, Dimatteo MR. The challenge of patient adherence. *Therapeutics and clinical risk management*. Sep 2005;1(3):189-199.
16. Nair KV, Belletti DA, Doyle JJ, et al. Understanding barriers to medication adherence in the hypertensive population by evaluating responses to a telephone survey. *Patient preference and adherence*. 2011;5:195-206.
17. Marshall IJ, Wolfe CD, McKeivitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. *BMJ (Clinical research ed.)*. 2012;345:e3953.
18. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? *BMC health services research*. 2012;12:98.
19. Karakurt P, Kasikci M. Factors affecting medication adherence in patients with hypertension. *Journal of vascular nursing : official publication of the Society for Peripheral Vascular Nursing*. Dec 2012;30(4):118-126.
20. Chapman RH, Petrilla AA, Benner JS, Schwartz JS, Tang SS. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. *Drugs & aging*. 2008;25(10):885-892.
21. Coleman CI, Limone B, Sobieraj DM, et al. Dosing frequency and medication adherence in chronic disease. *Journal of managed care pharmacy : JMCP*. Sep 2012;18(7):527-539.

22. Shalansky SJ, Levy AR. Effect of number of medications on cardiovascular therapy adherence. *The Annals of pharmacotherapy*. Oct 2002;36(10):1532-1539.
23. Kucukarslan SN. A review of published studies of patients' illness perceptions and medication adherence: lessons learned and future directions. *Research in social & administrative pharmacy : RSAP*. Sep-Oct 2012;8(5):371-382.
24. Miller NH. Compliance with treatment regimens in chronic asymptomatic diseases. *The American journal of medicine*. Feb 17 1997;102(2A):43-49.
25. Shenolikar RA, Balkrishnan R. Oral antidiabetes medication adherence and health care utilization among Medicaid-enrolled type 2 diabetic patients beginning monotherapy. *Diabetes care*. Feb 2008;31(2):e5.
26. Hepke KL, Martus MT, Share DA. Costs and utilization associated with pharmaceutical adherence in a diabetic population. *The American journal of managed care*. Feb 2004;10(2 Pt 2):144-151.
27. Wu J, Seiber E, Lacombe VA, Nahata MC, Balkrishnan R. Medical utilization and costs associated with statin adherence in Medicaid enrollees with type 2 diabetes. *The Annals of pharmacotherapy*. Mar 2011;45(3):342-349.
28. Stuart B, Davidoff A, Lopert R, Shaffer T, Samantha Shoemaker J, Lloyd J. Does medication adherence lower Medicare spending among beneficiaries with diabetes? *Health services research*. Aug 2011;46(4):1180-1199.
29. Dragomir A, Cote R, Roy L, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. *Medical care*. May 2010;48(5):418-425.

30. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. *The American journal of managed care*. Aug 2010;16(8):568-576.
31. Aubert RE, Yao J, Xia F, Garavaglia SB. Is there a relationship between early statin compliance and a reduction in healthcare utilization? *The American journal of managed care*. Jun 2010;16(6):459-466.
32. Jha AK, Aubert RE, Yao J, Teagarden JR, Epstein RS. Greater adherence to diabetes drugs is linked to less hospital use and could save nearly \$5 billion annually. *Health affairs (Project Hope)*. Aug 2012;31(8):1836-1846.
33. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. Oct 20 2009;120(16):1640-1645.
34. Curtis LH, Hammill BG, Bethel MA, Anstrom KJ, Gottdiener JS, Schulman KA. Costs of the metabolic syndrome in elderly individuals: findings from the Cardiovascular Health Study. *Diabetes care*. Oct 2007;30(10):2553-2558.
35. Lerman I. Adherence to treatment: the key for avoiding long-term complications of diabetes. *Archives of medical research*. May-Jun 2005;36(3):300-306.
36. Wong ND, Pio JR, Franklin SS, L'Italien GJ, Kamath TV, Williams GR. Preventing coronary events by optimal control of blood pressure and lipids in

- patients with the metabolic syndrome. *The American journal of cardiology*. Jun 15 2003;91(12):1421-1426.
37. Otani K, Waterman B, Faulkner KM, Boslaugh S, Burroughs TE, Dunagan WC. Patient satisfaction: focusing on "excellent". *Journal of healthcare management / American College of Healthcare Executives*. Mar-Apr 2009;54(2):93-102; discussion 102-103.
38. Cherry SB, Benner JS, Hussein MA, Tang SS, Nichol MB. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jun 2009;12(4):489-497.
39. Banning M. A review of interventions used to improve adherence to medication in older people. *International journal of nursing studies*. Nov 2009;46(11):1505-1515.
40. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Apr 1 2003;60(7):657-665.
41. Tsuyuki RT, Johnson JA, Teo KK, et al. A randomized trial of the effect of community pharmacist intervention on cholesterol risk management: the Study of Cardiovascular Risk Intervention by Pharmacists (SCRIP). *Archives of internal medicine*. May 27 2002;162(10):1149-1155.

42. U.S. Census Bureau AF. "Geographic Identifiers: 2010 Demographic Profile Data (G001): Toledo, OH Metro Area". Retrieved April 7, 2013.
43. American Pharmacists Association and the National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model (version 2.0). *Journal of the American Pharmacists Association : JAPhA*. May-Jun 2008;48(3):341-353.
44. Bunting BA, Smith BH, Sutherland SE. The Asheville Project: clinical and economic outcomes of a community-based long-term medication therapy management program for hypertension and dyslipidemia. *Journal of the American Pharmacists Association : JAPhA*. Jan-Feb 2008;48(1):23-31.
45. Bunting BA, Cranor CW. The Asheville Project: long-term clinical, humanistic, and economic outcomes of a community-based medication therapy management program for asthma. *Journal of the American Pharmacists Association : JAPhA*. Mar-Apr 2006;46(2):133-147.
46. Fischer LR, Defor TA, Cooper S, et al. Pharmaceutical care and health care utilization in an HMO. *Effective clinical practice : ECP*. Mar-Apr 2002;5(2):49-57.
47. Pinto SL, Kumar J, Partha G, Bechtol RA. Improving the economic and humanistic outcomes for diabetic patients: making a case for employer-sponsored medication therapy management. *ClinicoEconomics and outcomes research : CEOR*. 2013;5:153-159.

48. Ramalho de Oliveira D, Brummel AR, Miller DB. Medication therapy management: 10 years of experience in a large integrated health care system. *Journal of managed care pharmacy : JMCP*. Apr 2010;16(3):185-195.
49. Wittayanukorn S, Westrick SC, Hansen RA, et al. Evaluation of medication therapy management services for patients with cardiovascular disease in a self-insured employer health plan. *Journal of managed care pharmacy : JMCP*. Jun 2013;19(5):385-395.
50. Barnett MJ, Frank J, Wehring H, et al. Analysis of pharmacist-provided medication therapy management (MTM) services in community pharmacies over 7 years. *Journal of managed care pharmacy : JMCP*. Jan-Feb 2009;15(1):18-31.
51. Isetts BJ, Schondelmeyer SW, Artz MB, et al. Clinical and economic outcomes of medication therapy management services: the Minnesota experience. *Journal of the American Pharmacists Association : JAPhA*. Mar-Apr 2008;48(2):203-211; 203 p following 211.
52. Garcia GM, Snyder ME, McGrath SH, Smith RB, McGivney MS. Generating demand for pharmacist-provided medication therapy management: identifying patient-preferred marketing strategies. *Journal of the American Pharmacists Association : JAPhA*. Sep-Oct 2009;49(5):611-616.
53. Alkhateeb FM, Unni E, Latif D, Shawaqfeh MS, Al-Rousan RM. Physician attitudes toward collaborative agreements with pharmacists and their expectations of community pharmacists' responsibilities in West Virginia. *Journal of the American Pharmacists Association : JAPhA*. Nov-Dec 2009;49(6):797-800.

54. Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. *Patient preference and adherence*. 2012;6:499-507.
55. Huang HY, Maguire MG, Miller ER, 3rd, Appel LJ. Impact of pill organizers and blister packs on adherence to pill taking in two vitamin supplementation trials. *American journal of epidemiology*. Oct 15 2000;152(8):780-787.
56. Schneider PJ, Murphy JE, Pedersen CA. Impact of medication packaging on adherence and treatment outcomes in older ambulatory patients. *Journal of the American Pharmacists Association : JAPhA*. Jan-Feb 2008;48(1):58-63.
57. Zedler BK, Joyce A, Murrelle L, Kakad P, Harpe SE. A pharmacoepidemiologic analysis of the impact of calendar packaging on adherence to self-administered medications for long-term use. *Clinical therapeutics*. May 2011;33(5):581-597.
58. Levings B, Szep S, Helps SC. Towards the safer use of dosettes. *Journal of quality in clinical practice*. Mar 1999;19(1):69-72.
59. Field TS, Mazor KM, Briesacher B, Debellis KR, Gurwitz JH. Adverse drug events resulting from patient errors in older adults. *Journal of the American Geriatrics Society*. Feb 2007;55(2):271-276.
60. Jansen A, Andersen KF, Bruning H. Evaluation of a compliance device in a subgroup of adult patients receiving specific immunotherapy with grass allergen tablets (GRAZAX) in a randomized, open-label, controlled study: an a priori subgroup analysis. *Clinical therapeutics*. Feb 2009;31(2):321-327.
61. Ringe JD, Fardellone P, Kruse HP, Amling M, van der Geest SA, Moller G. Value of a new fixed-combination pack of bisphosphonate, calcium and vitamin

- D in the therapy of osteoporosis: results of two quantitative patient research studies. *Drugs & aging*. 2009;26(3):241-253.
62. Beckman A, Bernsten C, Parker MG, Thorslund M, Fastbom J. The difficulty of opening medicine containers in old age: a population-based study. *Pharmacy world & science : PWS*. Oct 2005;27(5):393-398.
63. Chalker JC, Wagner AK, Tomson G, Johnson K, Wahlstrom R, Ross-Degnan D. Appointment systems are essential for improving chronic disease care in resource-poor settings: learning from experiences with HIV patients in Africa. *International health*. Sep 2013;5(3):163-165.
64. Holdford DA, Inocencio TJ. Adherence and persistence associated with an appointment-based medication synchronization program. *Journal of the American Pharmacists Association : JAPhA*. Nov-Dec 2013;53(6):576-583.
65. Ross A, Jami H, Young HA, Katz R. Sync and swim: the impact of medication consolidation on adherence in medicaid patients. *Journal of primary care & community health*. Oct 1 2013;4(4):240-244.
66. Traynor K. Synchronized prescription fills improve patients' medication adherence. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Jul 15 2013;70(14):1190-1191.
67. Wilson PM, Kataria N, McNeilly E. Patient and carer experience of obtaining regular prescribed medication for chronic disease in the English National Health Service: a qualitative study. *BMC health services research*. May 24 2013;13(1):192.

68. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. *Archives of internal medicine*. May 9 2011;171(9):814-822.
69. Haynes RB, McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. *The Cochrane database of systematic reviews*. 2002(2):CD000011.
70. Lee JK, Grace KA, Taylor AJ. Effect of a pharmacy care program on medication adherence and persistence, blood pressure, and low-density lipoprotein cholesterol: a randomized controlled trial. *JAMA : the journal of the American Medical Association*. Dec 6 2006;296(21):2563-2571.
71. Zillich AJ, Jaynes HA, Snyder ME, et al. Evaluation of specialized medication packaging combined with medication therapy management: adherence, outcomes, and costs among Medicaid patients. *Medical care*. Jun 2012;50(6):485-493.
72. Matzke GR. Health care reform 2011: opportunities for pharmacists. *The Annals of pharmacotherapy*. Apr 2012;46(4):S27-32.
73. Centers for Medicare and Medicaid Services Department of Health and Human Services. Medicare prescription drug benefit. Final rule. *Federal register*. Jan 28 2005;70(18):4193-4585.
74. Larson S, Drake S, Anderson L, Larson T. Adoption of medication therapy management programs in Minnesota: 2006-11. *Journal of the American Pharmacists Association : JAPhA*. May-Jun 2013;53(3):254-260.
75. Meichenbaum D TD. *Facilitating Treatment Adherence: A Practitioner's Guidebook*. New York: Plenum Press; 1987.

76. Haynes RB TD, Sackett DL. *Compliance in health care*. Baltimore, Md.: Johns Hopkins University Press; 1979.
77. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jan-Feb 2008;11(1):44-47.
78. Joyce GF. Understanding primary nonadherence. *American Journal of Pharmacy Benefits*. 2010;2(2):109-110.
79. Shah NR, Hirsch AG, Zacker C, et al. Predictors of first-fill adherence for patients with hypertension. *American journal of hypertension*. Apr 2009;22(4):392-396.
80. Fallis BA, Dhalla IA, Klemensberg J, Bell CM. Primary medication non-adherence after discharge from a general internal medicine service. *PloS one*. 2013;8(5):e61735.
81. Shin J, McCombs JS, Sanchez RJ, Udall M, Deminski MC, Cheetham TC. Primary nonadherence to medications in an integrated healthcare setting. *The American journal of managed care*. Aug 2012;18(8):426-434.
82. Harrison TN, Derosé SF, Cheetham TC, et al. Primary nonadherence to statin therapy: patients' perceptions. *The American journal of managed care*. Apr 2013;19(4):e133-139.
83. Storm A, Andersen SE, Benfeldt E, Serup J. One in 3 prescriptions are never redeemed: primary nonadherence in an outpatient clinic. *Journal of the American Academy of Dermatology*. Jul 2008;59(1):27-33.

84. Briesacher BA, Andrade SE, Fouayzi H, Chan KA. Comparison of drug adherence rates among patients with seven different medical conditions. *Pharmacotherapy*. Apr 2008;28(4):437-443.
85. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. *Medical care*. Jun 2005;43(6):521-530.
86. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. *Health affairs (Project Hope)*. Jan 2011;30(1):91-99.
87. Balkrishnan R, Rajagopalan R, Camacho FT, Huston SA, Murray FT, Anderson RT. Predictors of medication adherence and associated health care costs in an older population with type 2 diabetes mellitus: a longitudinal cohort study. *Clinical therapeutics*. Nov 2003;25(11):2958-2971.
88. Egede LE, Gebregziabher M, Dismuke CE, et al. Medication nonadherence in diabetes: longitudinal effects on costs and potential cost savings from improvement. *Diabetes care*. Dec 2012;35(12):2533-2539.
89. King JT, Jr., Tsevat J, Lave JR, Roberts MS. Willingness to pay for a quality-adjusted life year: implications for societal health care resource allocation. *Medical decision making : an international journal of the Society for Medical Decision Making*. Nov-Dec 2005;25(6):667-677.
90. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High

- Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA : the journal of the American Medical Association*. May 16 2001;285(19):2486-2497.
91. Beltran-Sanchez H, Harhay MO, Harhay MM, McElligott S. Prevalence and trends of metabolic syndrome in the adult U.S. population, 1999-2010. *Journal of the American College of Cardiology*. Aug 20 2013;62(8):697-703.
 92. Reaven GM. Non-insulin-dependent diabetes mellitus, abnormal lipoprotein metabolism, and atherosclerosis. *Metabolism: clinical and experimental*. Feb 1987;36(2 Suppl 1):1-8.
 93. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. Apr 2001;37(4):1053-1059.
 94. Malik S, Wong ND, Franklin SS, et al. Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation*. Sep 7 2004;110(10):1245-1250.
 95. Eckel RH, Alberti KG, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet*. Jan 16 2010;375(9710):181-183.
 96. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. Dec 17 2002;106(25):3143-3421.
 97. Li R, Zhang P, Barker LE, Chowdhury FM, Zhang X. Cost-effectiveness of interventions to prevent and control diabetes mellitus: a systematic review. *Diabetes care*. Aug 2010;33(8):1872-1894.

98. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA : the journal of the American Medical Association*. Feb 5 2014;311(5):507-520.
99. Standards of medical care in diabetes--2014. *Diabetes care*. Jan 2014;37 Suppl 1:S14-80.
100. Clemans-Cope L, Long SK, Coughlin TA, Yemane A, Resnick D. The expansion of Medicaid coverage under the ACA: implications for health care access, use, and spending for vulnerable low-income adults. *Inquiry : a journal of medical care organization, provision and financing*. May 2013;50(2):135-149.
101. Yoon J, Zulman D, Scott JY, Maciejewski ML. Costs associated with multimorbidity among VA patients. *Medical care*. Mar 2014;52 Suppl 3:S31-36.
102. Centers for Medicare and Medicaid Services. Chronic Conditions among Medicare Beneficiaries, Chartbook, 2012 Edition. Baltimore, ME. 2012.
103. Boudreau DM, Malone DC, Raebel MA, et al. Health care utilization and costs by metabolic syndrome risk factors. *Metabolic syndrome and related disorders*. Aug 2009;7(4):305-314.
104. Ford ES, Li C, Zhao G. Prevalence and correlates of metabolic syndrome based on a harmonious definition among adults in the US. *Journal of diabetes*. Sep 2010;2(3):180-193.
105. Nichols GA, Moler EJ. Metabolic syndrome components are associated with future medical costs independent of cardiovascular hospitalization and incident diabetes. *Metabolic syndrome and related disorders*. Apr 2011;9(2):127-133.

106. Birnbaum HG, Mattson ME, Kashima S, Williamson TE. Prevalence rates and costs of metabolic syndrome and associated risk factors using employees' integrated laboratory data and health care claims. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine*. Jan 2011;53(1):27-33.
107. Schultz AB, Edington DW. Analysis of the association between metabolic syndrome and disease in a workplace population over time. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Mar-Apr 2010;13(2):258-264.
108. Eisenmann JC, Welk GJ, Wickel EE, Blair SN. Stability of variables associated with the metabolic syndrome from adolescence to adulthood: the Aerobics Center Longitudinal Study. *American journal of human biology : the official journal of the Human Biology Council*. Nov-Dec 2004;16(6):690-696.
109. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. *American journal of hypertension*. Nov 2006;19(11):1190-1196.
110. Huser MA, Evans TS, Berger V. Medication adherence trends with statins. *Advances in therapy*. Mar-Apr 2005;22(2):163-171.
111. Burnier M. Long-term compliance with antihypertensive therapy: another facet of chronotherapeutics in hypertension. *Blood pressure monitoring*. 2000;5 Suppl 1:S31-34.
112. Cramer JA. Microelectronic systems for monitoring and enhancing patient compliance with medication regimens. *Drugs*. Mar 1995;49(3):321-327.

113. Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. *Diabetes care*. Oct 1997;20(10):1512-1517.
114. Sabaté E, Network GAI, Organization WH. Adherence to long-term therapies: evidence for action/[edited by Eduardo Sabaté]. 2003.
115. Ammassari A, Trotta MP, Murri R, et al. Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature. *Journal of acquired immune deficiency syndromes (1999)*. Dec 15 2002;31 Suppl 3:S123-127.
116. Foundation ASoAaASoCP. Adult Meducation:Improving Medication Adherence in Older Adults. 2006. Accessed July, 2014.
117. Cardenas-Valladolid J, Martin-Madrazo C, Salinero-Fort MA, Carrillo de-Santa Pau E, Abanades-Herranz JC, de Burgos-Lunar C. Prevalence of adherence to treatment in homebound elderly people in primary health care: a descriptive, cross-sectional, multicentre study. *Drugs & aging*. Aug 1 2010;27(8):641-651.
118. Park JH, Park JH, Lee SY, Kim SY, Shin Y, Kim SY. Disparities in antihypertensive medication adherence in persons with disabilities and without disabilities: results of a Korean population-based study. *Archives of physical medicine and rehabilitation*. Aug 2008;89(8):1460-1467.
119. Campbell NL, Boustani MA, Skopelja EN, Gao S, Unverzagt FW, Murray MD. Medication adherence in older adults with cognitive impairment: a systematic evidence-based review. *The American journal of geriatric pharmacotherapy*. Jun 2012;10(3):165-177.

120. Schiele JT, Quinzler R, Klimm HD, Pruszydlo MG, Haefeli WE. Difficulties swallowing solid oral dosage forms in a general practice population: prevalence, causes, and relationship to dosage forms. *European journal of clinical pharmacology*. Apr 2013;69(4):937-948.
121. Gregoire JP, Moisan J, Guibert R, et al. Determinants of discontinuation of new courses of antihypertensive medications. *Journal of clinical epidemiology*. Jul 2002;55(7):728-735.
122. Grant RW, Devita NG, Singer DE, Meigs JB. Polypharmacy and medication adherence in patients with type 2 diabetes. *Diabetes care*. May 2003;26(5):1408-1412.
123. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. *Journal of human hypertension*. Sep 2004;18(9):607-613.
124. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Therapeutics and clinical risk management*. Feb 2008;4(1):269-286.
125. Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. *Circulation*. Mar 30 2010;121(12):1455-1458.
126. Fenerty SD, West C, Davis SA, Kaplan SG, Feldman SR. The effect of reminder systems on patients' adherence to treatment. *Patient preference and adherence*. 2012;6:127-135.

127. Cline CM, Bjorck-Linne AK, Israelsson BY, Willenheimer RB, Erhardt LR. Non-compliance and knowledge of prescribed medication in elderly patients with heart failure. *European journal of heart failure*. Jun 1999;1(2):145-149.
128. Melikian C, White TJ, Vanderplas A, Dezii CM, Chang E. Adherence to oral antidiabetic therapy in a managed care organization: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. *Clinical therapeutics*. Mar 2002;24(3):460-467.
129. Bailey GR, Barner JC, Weems JK, et al. Assessing barriers to medication adherence in underserved patients with diabetes in Texas. *The Diabetes educator*. Mar-Apr 2012;38(2):271-279.
130. Negarandeh R, Mahmoodi H, Noktehdan H, Heshmat R, Shakibazadeh E. Teach back and pictorial image educational strategies on knowledge about diabetes and medication/dietary adherence among low health literate patients with type 2 diabetes. *Primary care diabetes*. Jul 2013;7(2):111-118.
131. Carrieri MP, Leport C, Protopopescu C, et al. Factors associated with nonadherence to highly active antiretroviral therapy: a 5-year follow-up analysis with correction for the bias induced by missing data in the treatment maintenance phase. *Journal of acquired immune deficiency syndromes (1999)*. Apr 1 2006;41(4):477-485.
132. Martini M, D'Elia S, Paoletti F, et al. Adherence to HIV treatment: results from a 1-year follow-up study. *HIV medicine*. Jan 2002;3(1):62-64.
133. Zwikker HE, van den Bemt BJ, Vriezekolk JE, van den Ende CH, van Dulmen S. Psychosocial predictors of non-adherence to chronic medication: systematic

- review of longitudinal studies. *Patient preference and adherence*. 2014;8:519-563.
- 134.** Kronish IM, Diefenbach MA, Edmondson DE, Phillips LA, Fei K, Horowitz CR. Key barriers to medication adherence in survivors of strokes and transient ischemic attacks. *Journal of general internal medicine*. May 2013;28(5):675-682.
- 135.** Russo HE, Kirsh WD. Population-based medication adherence programmes: a window of opportunities. *World hospitals and health services : the official journal of the International Hospital Federation*. 2013;49(3):14-17.
- 136.** Tajouri TH, Driver SL, Holmes DR, Jr. 'Take as directed'--strategies to improve adherence to cardiac medication. *Nature reviews. Cardiology*. May 2014;11(5):304-307.
- 137.** Schers H, Webster S, van den Hoogen H, Avery A, Grol R, van den Bosch W. Continuity of care in general practice: a survey of patients' views. *The British journal of general practice : the journal of the Royal College of General Practitioners*. Jun 2002;52(479):459-462.
- 138.** Schers H, van den Hoogen H, Bor H, Grol R, van den Bosch W. Familiarity with a GP and patients' evaluations of care. A cross-sectional study. *Family practice*. Feb 2005;22(1):15-19.
- 139.** Chen CC, Tseng CH, Cheng SH. Continuity of care, medication adherence, and health care outcomes among patients with newly diagnosed type 2 diabetes: a longitudinal analysis. *Medical care*. Mar 2013;51(3):231-237.

140. Uijen AA, Bosch M, van den Bosch WJ, Bor H, Wensing M, Schers HJ. Heart failure patients' experiences with continuity of care and its relation to medication adherence: a cross-sectional study. *BMC family practice*. 2012;13:86.
141. Barron J, Wahl P, Fisher M, Plauschinat C. Effect of prescription copayments on adherence and treatment failure with oral antidiabetic medications. *P & T : a peer-reviewed journal for formulary management*. Sep 2008;33(9):532-553.
142. Hunt J, Rozenfeld Y, Shenolikar R. Effect of patient medication cost share on adherence and glycemic control. *Managed care (Langhorne, Pa.)*. Jul 2009;18(7):47-53.
143. Shaw CR. Reducing the burden of medication costs to improve medication adherence. *The Nurse practitioner*. Jul 13 2014;39(7):43-47.
144. Laba TL, Bleasel J, Brien JA, et al. Strategies to improve adherence to medications for cardiovascular diseases in socioeconomically disadvantaged populations: a systematic review. *International journal of cardiology*. Sep 10 2013;167(6):2430-2440.
145. Alcoba M, Cuevas MJ, Perez-Simon MR, et al. Assessment of adherence to triple antiretroviral treatment including indinavir: role of the determination of plasma levels of indinavir. *Journal of acquired immune deficiency syndromes (1999)*. Jun 1 2003;33(2):253-258.
146. Modi AC, Ingerski LM, Rausch JR, Glauser TA, Drotar D. White coat adherence over the first year of therapy in pediatric epilepsy. *The Journal of pediatrics*. Oct 2012;161(4):695-699 e691.

147. Haynes RB, Taylor DW, Sackett DL, Gibson ES, Bernholz CD, Mukherjee J. Can simple clinical measurements detect patient noncompliance? *Hypertension*. Nov-Dec 1980;2(6):757-764.
148. Patel M, Perrin K, Pritchard A, et al. Accuracy of patient self-report as a measure of inhaled asthma medication use. *Respirology (Carlton, Vic.)*. Apr 2013;18(3):546-552.
149. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. *JAMA : the journal of the American Medical Association*. Jun 9 1989;261(22):3273-3277.
150. Murray MD, Young J, Hoke S, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. *Annals of internal medicine*. May 15 2007;146(10):714-725.
151. Liu H, Golin CE, Miller LG, et al. A comparison study of multiple measures of adherence to HIV protease inhibitors. *Annals of internal medicine*. May 15 2001;134(10):968-977.
152. Fairman K, Matheral B. Evaluating medication adherence: which measure is right for your program? *strategies*. 2000;2:4.
153. Hess LM, Raebel MA, Conner DA, Malone DC. Measurement of adherence in pharmacy administrative databases: a proposal for standard definitions and preferred measures. *The Annals of pharmacotherapy*. Jul-Aug 2006;40(7-8):1280-1288.
154. Nau DP, Director CS, Alliance PQ. Proportion of days covered (PDC) as a preferred method of measuring medication adherence. 2012.

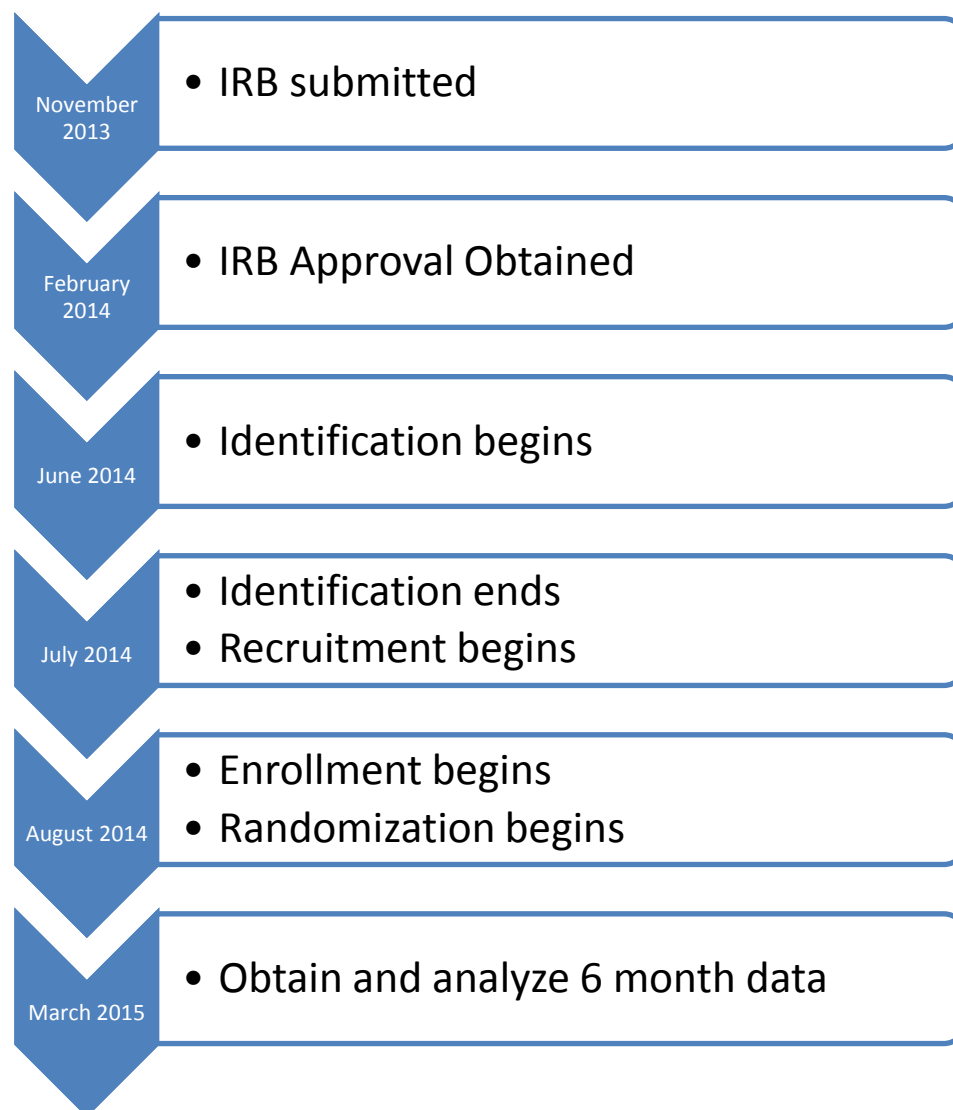
- 155.** Martin BC, Wiley-Exley EK, Richards S, Domino ME, Carey TS, Sleath BL. Contrasting measures of adherence with simple drug use, medication switching, and therapeutic duplication. *The Annals of pharmacotherapy*. Jan 2009;43(1):36-44.
- 156.** Steiner JF, Prochazka AV. The assessment of refill compliance using pharmacy records: methods, validity, and applications. *Journal of clinical epidemiology*. Jan 1997;50(1):105-116.
- 157.** Steiner JF, Earnest MA. The language of medication-taking. *Annals of internal medicine*. Jun 6 2000;132(11):926-930.
- 158.** Lau DT, Nau DP. Oral antihyperglycemic medication nonadherence and subsequent hospitalization among individuals with type 2 diabetes. *Diabetes care*. Sep 2004;27(9):2149-2153.
- 159.** Vogeli C, Shields AE, Lee TA, et al. Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. *Journal of general internal medicine*. Dec 2007;22 Suppl 3:391-395.
- 160.** Chen PG, Mehrotra A, Auerbach DI. Do We Really Need More Physicians? Responses to Predicted Primary Care Physician Shortages. *Medical care*. Dec 3 2013.
- 161.** Berdine HJ, Skomo ML. Development and integration of pharmacist clinical services into the patient-centered medical home. *Journal of the American Pharmacists Association : JAPhA*. Sep-Oct 2012;52(5):661-667.
- 162.** Hepler CD, Strand LM. Opportunities and responsibilities in pharmaceutical care. *American journal of hospital pharmacy*. Mar 1990;47(3):533-543.

- 163.** Smith M, Giuliano MR, Starkowski MP. In Connecticut: improving patient medication management in primary care. *Health affairs (Project Hope)*. Apr 2011;30(4):646-654.
- 164.** Gwadry-Sridhar FH, Manias E, Lal L, et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research*. Jul-Aug 2013;16(5):863-871.
- 165.** McDonald HP, Garg AX, Haynes RB. Interventions to enhance patient adherence to medication prescriptions: scientific review. *JAMA : the journal of the American Medical Association*. Dec 11 2002;288(22):2868-2879.
- 166.** Branham AR, Katz AJ, Moose JS, Ferreri SP, Farley JF, Marciniak MW. Retrospective analysis of estimated cost avoidance following pharmacist-provided medication therapy management services. *Journal of pharmacy practice*. Aug 2013;26(4):420-427.
- 167.** Adams R, May H, Swift L, Bhattacharya D. Do older patients find multi-compartment medication devices easy to use and which are the easiest? *Age and ageing*. Nov 2013;42(6):715-720.
- 168.** Look KA, Mott DA. Multiple pharmacy use and types of pharmacies used to obtain prescriptions. *Journal of the American Pharmacists Association : JAPhA*. Nov-Dec 2013;53(6):601-610.
- 169.** Andersen RM. Revisiting the behavioral model and access to medical care: does it matter? *Journal of health and social behavior*. Mar 1995;36(1):1-10.

170. Fisher JD, Fisher WA. Changing AIDS-risk behavior. *Psychological bulletin*. May 1992;111(3):455-474.
171. Kang M, Ragan BG, Park JH. Issues in outcomes research: an overview of randomization techniques for clinical trials. *Journal of athletic training*. Apr-Jun 2008;43(2):215-221.
172. Moore JM, Shartle D, Faudskar L, Matlin OS, Brennan TA. Impact of a patient-centered pharmacy program and intervention in a high-risk group. *Journal of managed care pharmacy : JMCP*. Apr 2013;19(3):228-236.
173. Cohen MR. The Institute of Medicine report, preventing medication errors: another good day. *American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists*. Jul 15 2007;64(14 Suppl 9):S1-2.
174. Ward BW, Schiller JS. Prevalence of Multiple Chronic Conditions Among US Adults: Estimates From the National Health Interview Survey, 2010. *Preventing chronic disease*. 2013;10:E65.
175. Rotter T, Kugler J, Koch R, et al. A systematic review and meta-analysis of the effects of clinical pathways on length of stay, hospital costs and patient outcomes. *BMC health services research*. 2008;8(1):265.

Appendix A

Study Timeline



Appendix B

Operational Definitions

For the purposes of this study, select terminology has been defined as follows:

Information/ Knowledge	This is the knowledge which patients have regarding their medications and disease state which help them to safely and effectively adhere to therapy
Behavioral Skills	A set of learned abilities which help a patient to adhere to their medication therapy
Reminder Strategies	Using alarms, phone calls, smart phone applications, emails text messages or letters designed to remind a patient to take or pick-up their medications
Dose Timing	A strategy of synchronizing the time a patient is to take their medications with activities within their daily routine. This is to promote remembrance for taking doses
Enabling Factors	Aspects of care which help a patient to adhere to therapy
Organization	Having medications organized by dosage time to facilitate remembrance of doses and simplify medication taking behavior
Access to Medications	The ease at which patients can obtain their needed medications. Improved access can occur through fewer monthly pick-ups through medication synchronization or delivery of medications to a patient's residence
Number of medications	The number of medications which a patient takes. This can be reduced through consolidation of a patient's medication list, as well as removal of unnecessary medications
Predisposing Factors	Characteristics of a patient which may affect their adherence, but are not themselves affected by adherence interventions
Medication Adherence	The extent to which a patient is able to take their medications as prescribed by their physician
Health Care Cost	The cost of care incurred by the insurer during the study period
Health Care Utilization	The number of unique visits, or the number of fills in the case of prescriptions, a patient received during the study period

Appendix C

Visit Algorithms

Phase I

Identification

June 2014-July 2014

- Review of Endocrine and Diabetes Care Center patients for inclusion criteria for metabolic syndrome

Recruitment

August 2014-February 2015

- Contact eligible patients via signed letters from endocrinologist.
- Contact non-responders with second mailing via signed letters.
- Contact non-responders who already utilize a participating pharmacy via a signed letter from the Director of Pharmacy Operations of the pharmacy.
- Patients who still have not responded receive a phone-call from a research team member

Enrollment

August 2014-February 2015

- Interested potential participants contact the study phone number
- Research team representative will contact the candidate and utilize the screening tool to verify inclusion criteria and obtain covariates
- Schedule Enrollment Visit

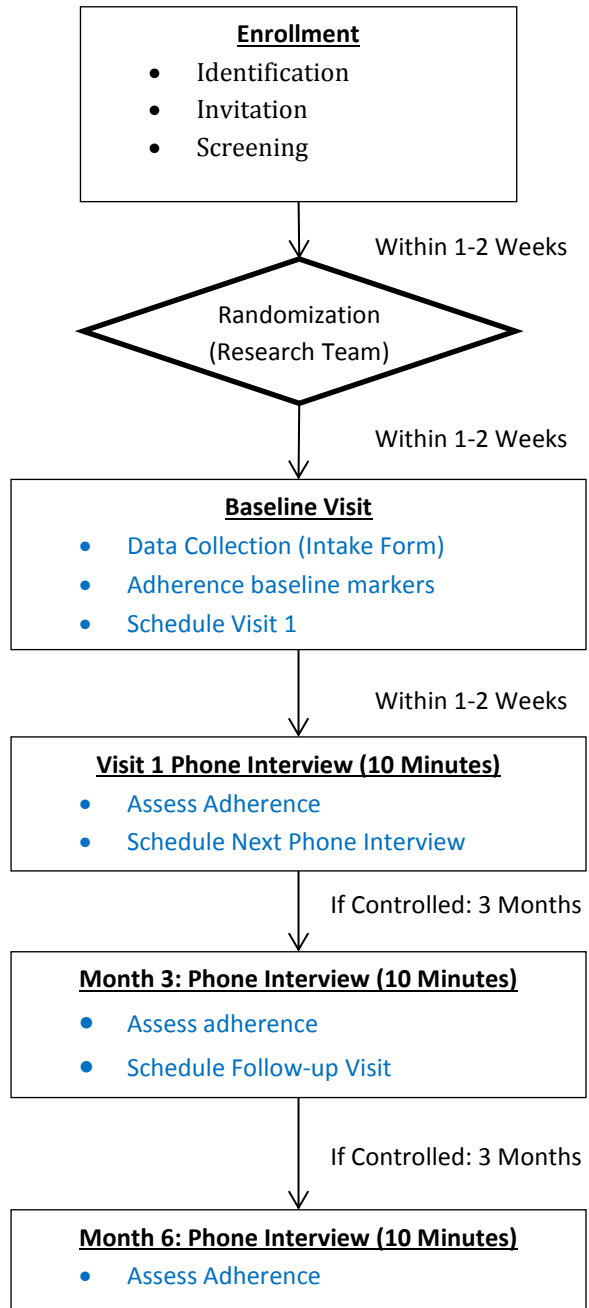
Randomization

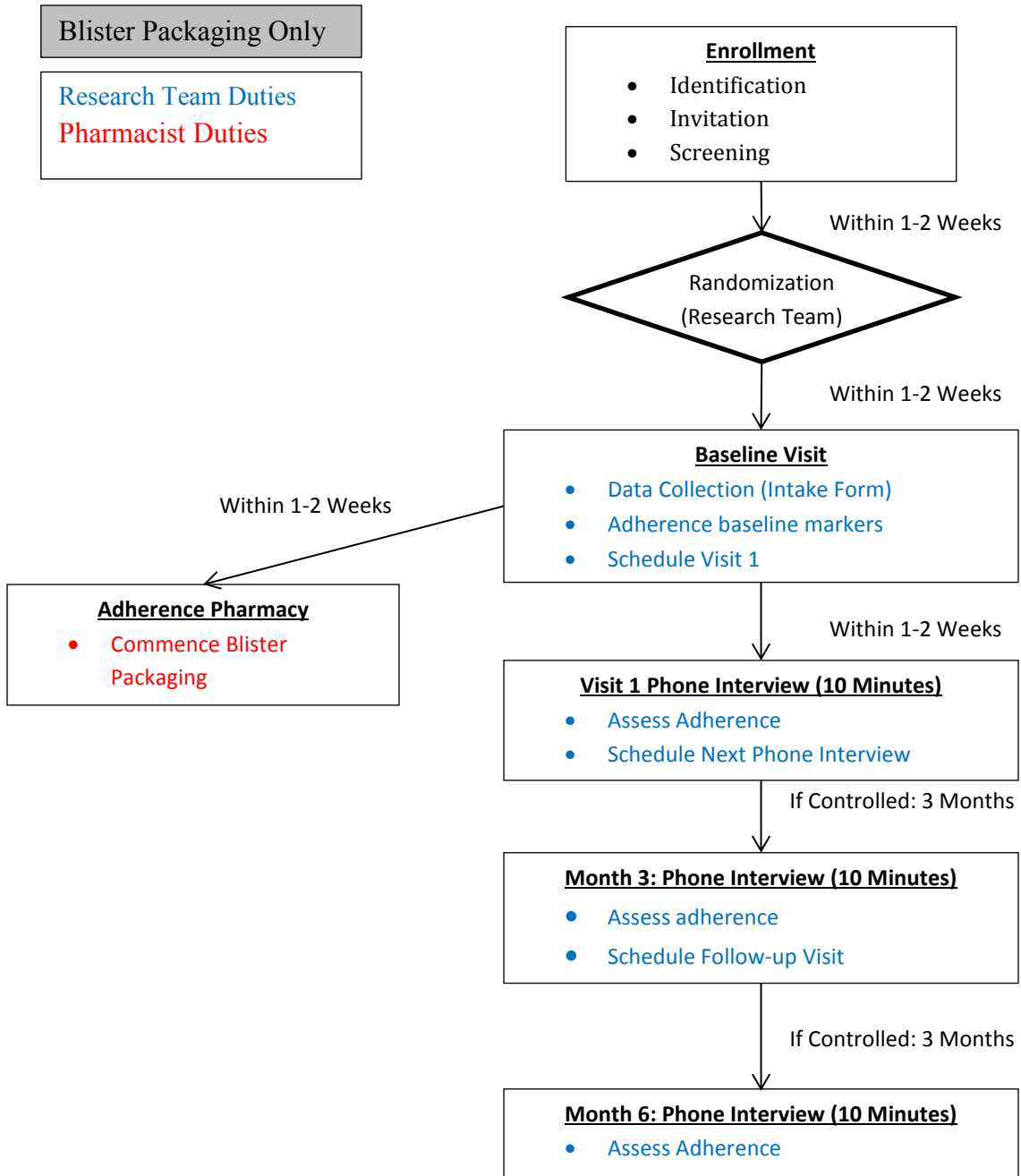
August 2014-February 2015

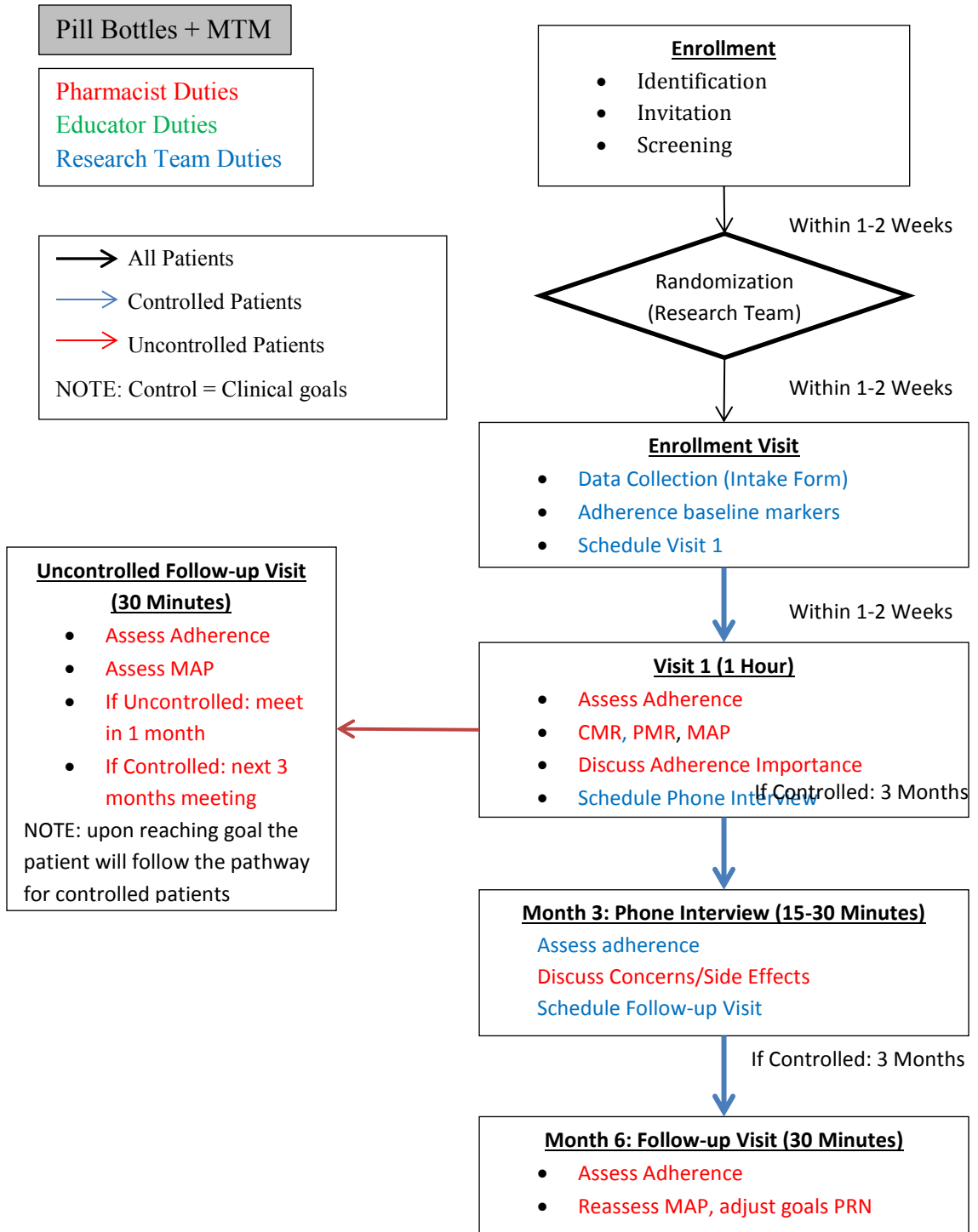
- Covariate adaptive randomization into four groups
- Assign study ID number
- Contact participant to schedule baseline visit

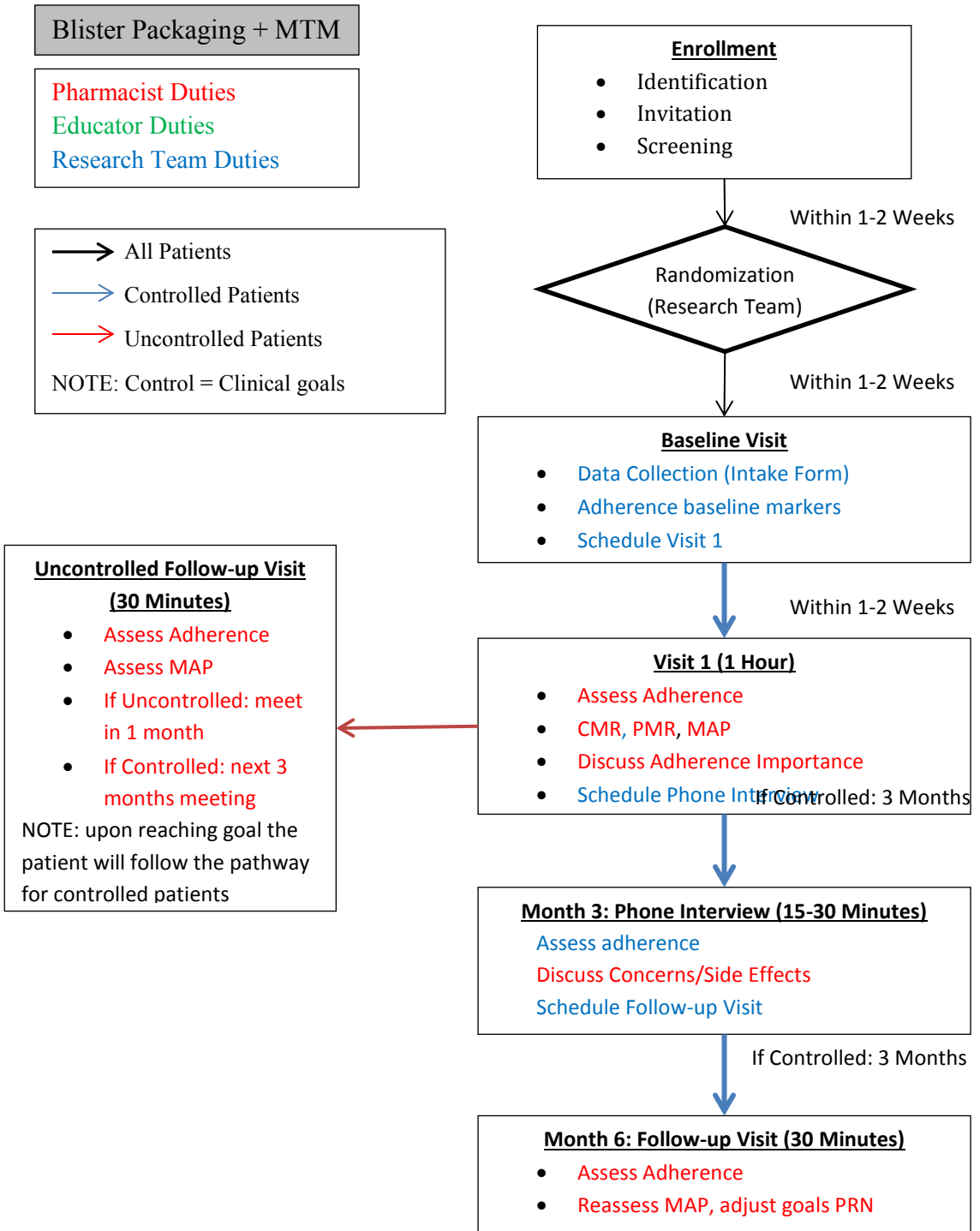
Control Group (Pill Bottles)

Research Team Duties









Appendix D

Outcomes Table

Outcome	Measure	Collection	Baseline	6 months
ADHERENCE	PDC	Research Team – Claim info	X	X
ECONOMIC	Total Cost	Research Team – claim info	X	X
	Number and cost of physician office visits	Research Team – claim info	X	X
	Number and cost of ER/ED visits	Research Team – claim info	X	X
	Number and cost of hospitalizations	Research Team – claim info	X	X
	Number and cost of Prescriptions	Research Team – claim info	X	X
Patient Characteristics	Age, Number of Medications, Smoking Status, Number of Co-morbidities, Length of Diagnosis	Research Team—collected during enrollment using screening tool	X	

Appendix E

Screening Tool

Subject Name: Phone Number: Date:

Inclusion Criteria			Exclusion Criteria		
In order to participate, all answers to the following questions must be YES .			In order to participate, all answers to the following questions must be NO .		
1. Do you speak and understand English?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	1. Do you have type I diabetes?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
2. Are you 18 years of age or older?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	2. Have you been diagnosed with a terminal illness and given less than three years to live?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
3. Are you currently diagnosed with type II diabetes, hypertension, and hyperlipidemia?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	3. Are you pregnant/expect to become pregnant?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
4. Are you currently prescribed at least one medication for each of these conditions?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	4. Are you planning to leave your employer or the area in the next three years?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
5. Are you currently prescribed a minimum of five medications?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	5. Are you currently enrolled in a MTM study?	YES <input type="checkbox"/>	NO <input type="checkbox"/>
6. Can you self-administer your medications as prescribed by your doctor?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	Background Information		
7. Do you/are you willing to fill prescriptions at a participating pharmacy?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	Gender: <input type="text"/>	Age: <input type="text"/>	
8. Do you have adequate transportation to attend counseling sessions at a participating pharmacy?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	Smoker <input type="checkbox"/>	Non-Smoker <input type="checkbox"/>	
9. Are you willing and able to have lab work done as requested and have results delivered by you or have your physician fax them to the participating pharmacy?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	When were you diagnosed with type II diabetes, hypertension, and hyperlipidemia?		<input type="text"/>
10. Do you have a connected, in-service phone number to be reached at for telephonic reminders and follow-ups?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	How many medications are you currently taking (include vitamins/supplements/ etc.)?		<input type="text"/>
11. Do you have Paramount health insurance or is your employer a member of the FrontPath Health Coalition?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	How many diseases (other than type II diabetes, hypertension, and hyperlipidemia) do you have?		<input type="text"/>
12. Are you willing and able to provide informed consent to participate in the study?	YES <input type="checkbox"/>	NO <input type="checkbox"/>	Are you currently receiving blister packs?	YES <input type="checkbox"/> NO <input type="checkbox"/>	
			Does your pharmacy automatically refill your prescriptions for you?	YES <input type="checkbox"/> NO <input type="checkbox"/>	
			Does your pharmacy coordinate with your doctor to make sure all of your prescriptions are ready to be picked up at one time without your involvement?	YES <input type="checkbox"/> NO <input type="checkbox"/>	

Appendix F

Intake Form

Page 1

Intake Form for Adherence Study

Name Mo Fr Date of Birth Age I.D. Number

Address Primary Language Insurance

City State Zip Marital Status

Phone(Home) Phone(Cell) Phone(Work) Email Address

Emergency Contact/Caregiver Relationship Phone

Highest Education Completed: Some high school High school Diploma/GED Some college Associates Degree Bachelor's Degree Graduate Degree

Yearly Income: <\$30,000 \$30,000-\$50,000 \$50,000-\$75,000 \$75,000-\$100,000 >\$100,000

Primary Care Physician Phone Fax

Endocrinologist Phone Fax

Cardiologist Phone Fax

Preferred Pharmacy Phone Fax

Other Pharmacy Phone Fax

Disease States

(Report approximate duration in months/years)

<input type="checkbox"/> Asthma/COPD	<input type="checkbox"/> Diabetes	<input type="checkbox"/> Hyperlipidemia	<input type="checkbox"/> Migraine Headaches	<input type="checkbox"/> Thyroid Disorder
<input type="checkbox"/> CVD	<input type="checkbox"/> GERD/PUD	<input type="checkbox"/> Hypertension	<input type="checkbox"/> OA/RA	<input type="checkbox"/> Other
<input type="checkbox"/> Depression	<input type="checkbox"/> Heart Failure	<input type="checkbox"/> Mental Health	<input type="checkbox"/> Osteoporosis	<input type="checkbox"/> Other

Surgical History

Allergy History

Procedure and Approximate Date	Allergy	Reaction
1. <input type="text"/>	1. <input type="text"/>	<input type="text"/>
2. <input type="text"/>	2. <input type="text"/>	<input type="text"/>
3. <input type="text"/>	3. <input type="text"/>	<input type="text"/>
4. <input type="text"/>	4. <input type="text"/>	<input type="text"/>

Page 2

Family History

Substance/Activity	Average per day	Condition	Family Member(s)
Diabetes Mellitus		Cancer	
Hypertension		Other (Please Specify)	
Hyperlipidemia		Other (Please Specify)	
Obesity		Other (Please Specify)	

Social History

Time-points	Baseline	6 months	12 months	18 months	24 months
Date					
Alcohol Consumption (#drinks/day)					
Caffeine Consumption (#cups/day)					
Nicotine Use (#packs/day)					
Exercise (#hours/day)					
Diet: Breakfast					
Diet: Lunch					
Diet: Dinner					

Page 3

Intake Values

Time-points	Baseline	6 months	12 months	18 months	24 months
Date					
Height					
Weight					
BMI					
LDL					
A1c					
BP					
Number of hypoglycemic episodes in past 6 months					
Flu Shot (yearly)					
Podiatrist (Approx Date)					
Dentist (Approx Date)					
Ophthalmologist (Approx Date)					

Appendix G

Comprehensive Medication Review (CMR)

Page 1.

Comprehensive Medication Review (CMR) Form for Adherence Study

Prescription Medications: *Baseline Visit Question:* What Rx are you currently on? *Follow-up Visit Question:* Are there any new Rx medications?

No	Name/ Strength	Name of the Prescriber	Indication	How did your doc tell you to take it? (Route, ToD, Duration)	How do YOU take it? <input checked="" type="checkbox"/> if same as Rx Details if not	Is it Work- ing?	How do you know?	Problems	Missed doses per week?	What do you do if you miss a dose?
1.	Metformin	Schwartz	Diabetes	BID with food	<input type="checkbox"/>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	A1c at goal	Diarrhea	2	Take next day
2.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
3.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
4.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
5.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
6.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
7.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
8.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
9.					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
10					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				

Page 2.

Prescription Medications: Baseline Visit Question: What Rx are you currently on? **Follow-up Visit Question:** Are there any new Rx medications?

No	Name/ Strength	Name of the Prescriber	Indication	How did your doc tell you to take it? (Route, ToD, Duration)	How do YOU take it? <input type="checkbox"/> if same as Rx Details if not	Is it Work- ing?	How do you know?	Problems	Missed doses per week?	What do you do if you miss a dose?
11					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
12					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
13					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
14					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
15					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
16					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
17					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
18					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
19					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				
20					<input type="checkbox"/>	<input type="checkbox"/> Yes <input type="checkbox"/> No				

NOTE: If medication is dc, delete from here and insert under recently dc medication list.

Page 3.

Adherence Assessment

Baseline: Ask all 3 adherence questions. **Follow-up:** Ask all 3 questions for previously listed meds and asked the missed dose question for the remaining meds OR the meds that reflected non-adherence.

Name /medication # listed above	What do you do if you miss a dose?	Reason for missing dose	RPh Intervention	↓ AT FOLLOW-UP			Adherence to intervention at next visit
				Adherence to intervention at next visit	Reason for Failure	2 nd RPh Intervention	
Metformin	Take next day	forget	Take to work	<input type="checkbox"/> Success <input type="checkbox"/> Failure	Forgets morning dose	Ask doc to switch to ER	<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure
				<input type="checkbox"/> Success <input type="checkbox"/> Failure			<input type="checkbox"/> Success <input type="checkbox"/> Failure

Page 4.

OTC/Vitamins/Minerals/Herbals/Dietary Supplements

Baseline Visit Question: What are you currently on? *Follow-up Visit Question:* Are there any new medications?

Name/Strength	Qty/How Often	Indication/Reason	Concerns

Recently Changed/Discontinued Medications

Have you take any other prescription medications in the last 3-6 months that you aren't currently taking right now?

Name/Strength	Indication	Directions	Duration of Therapy	Reason for Discontinuing

Other Patient Concerns

WORK ON MAP: Now I want to discuss a document of responsibilities that I will create following this session. This document contains short-term and long-term goals that you and I will be held accountable for...to help us keep you healthy!.....(Go to MAP) Establish at baseline...review /edit at 6mo time-points

Follow-Up	Date and Time: <input type="text"/>	How (Contact Information) <input type="text"/>	Why (Reason) <input type="text"/>
------------------	-------------------------------------	--	-----------------------------------

Here is my business Card with pharmacy phone number. You can call here with any questions.

Page 5.

Drug Therapy Problems

Problem	Drug/Cause	Action	Patient Consultation	Prescriber Consultation
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change
			<input type="checkbox"/> Patient Accepts Change <input type="checkbox"/> Patient Rejects Change	<input type="checkbox"/> Prescriber Accepts Change <input type="checkbox"/> Prescriber Rejects Change

Personal Medication Record Form

Name: _____ Address: _____ Phone: (____) - ____ - ____

Always carry your medication record with you. Show it to all your doctors, pharmacists and other healthcare providers.

Emergency Contact Information			
Name:	Relationship:	Phone:	
Primary Care Physician			
Name		Phone:	
Specialist			
Specialty:	Name:	Phone:	
Specialty:	Name:	Phone:	
Specialty:	Name:	Phone:	
Specialty:	Name:	Phone:	
Primary Pharmacy/Pharmacist			
Name		Phone:	
Allergy Information			
Allergy		Reaction	
Medication Reactions			
Medication		Reaction	
Notes:			
When you are prescribed a new medication, ask your doctor or pharmacist:			
What am I taking?			
What is it for?			
When do I take it?			
Are there any side effects?			
Are there any special instructions?			
What do I do if I miss a dose?			
This Medication Record is complete and accurate to the best of my knowledge:			
Patient's Signature:	Healthcare Provider's Signature:	Date Created:	
		Last Reviewed:	

Appendix I

Telephonic Follow-up

Page 1.

<p>For each medication the patient is taking, the following data will be collected from the participant:</p> <ul style="list-style-type: none"> • The most recent dispense date • The number of pills dispensed • The number of pills remaining • The number they are required to take each day (and if they have taken any yet that day) <p>From this data, the following will be calculated:</p> <ul style="list-style-type: none"> • Elapsed days since last fill = Current date-Dispense date • Self Pill Count = (# dispensed - #remaining) / (Elapsed days * # prescribed per day) • A separate self pill count will be calculated for each medication 							
Call Date	Med	Disp Date	Elapsed Days since last fill	# Dispensed at last fill	# remaining at count	# To take per Day	Self Pill Count
9/4/14	Metformin	8/4/14	31	180	125	2	0.89

Self Pill Count Interpretation

*High Adherence = 0.80-1.0

*Intermediate Adherence = 0.60-0.79

*Low Adherence = <0.60

Medication Adherence Assessment for Telephonic Follow-up

Subject Name:

Name of Recorder:

Date:

1. Are you facing any problems with taking your medication?

No

YES (If YES, Document the problems)

2. Are you able to get your medication on time?

Yes

NO (If NO, Document the reasons)

3. In the past two weeks about how many times did you forget to take your medication?

4. Do you have any questions for your pharmacist?

No

YES (If YES, schedule a time when the pharmacist can call them back)

Appendix J

Databases and Data Dictionaries

Economic

ID	Group	IPC_0	IPU_0	IPC_1	IPU_1	OPC_0	OPU_0	OPC_1	OPU_1	RXC_0
1	4	0	0	0	0	2287.66	20	1697.6	17	1243
2	3	150.09	1	0	0	10511.51	22	4498.19	29	7818.05

ID – Patient identification number assigned by study personnel

Group – Study group number (1=PB only, 2=PB+MTM, 3=BP only, 4=BP+MTM)

IPC_0 – Inpatient costs in 6 months prior to enrollment

IPU_0 – Inpatient utilization in 6 months prior to enrollment

IPC_1 – Inpatient costs in 6 months post enrollment

IPU_1 – Inpatient utilization in 6 months post enrollment

OPC_0 – Outpatient costs in 6 months prior to enrollment

OPU_0 – Outpatient utilization in 6 months prior to enrollment

OPC_1 – Outpatient costs in 6 months post enrollment

OPU_1 – Outpatient utilization in 6 months post enrollment

ERC_0	ERU_0	ERC_1	ERU_1	RXC_0	RXU_0	RXC_1	RXU_1	TC_0	TC_1	difference
652.65	1	0	0	1243	12	1342	13	4183.31	3039.6	-1143.71
2795.83	1	754.98	1	7818.05	20	8924.7	25	21275.48	14177.87	-7097.61

ERC_0 – Emergency room costs in 6 months prior to enrollment

ERU_0 – Emergency room utilization in the 6 months prior to enrollment

ERC_1 – Emergency room costs in the 6 months post enrollment

ERU_1 – Emergency room utilization in the 6 months post enrollment

RXC_0 – Total prescription costs in the 6 months prior to enrollment

RXU_0 – Total prescription utilization in the 6 months prior to enrollment

RXC_1 – Total prescription fills in the 6 months post enrollment

RXU_1 – Total prescription fills in the 6 months post enrollment

TC_0 – Total costs in the 6 months prior to enrollment

TC_1 – Total costs in the 6 months post enrollment

Difference – Difference in total cost between 6 months prior to and 6 months post enrollment

Adherence

ID	group	prediab	postdiab	prehtn	posthtn	prehld	posthld
1	1			0	1	0	1
2	3						

ID – Patient identification number assigned by study personnel

Group – Study group to which patient is enrolled

Prediab – Diabetes adherence in the 6 months pre-enrollment

Postdiab – Diabetes adherence in the 6 months post-enrollment

Prehtn – RAAS adherence in the 6 months pre-enrollment

Posthtn – RAAS adherence in the 6 months post-enrollment

Prehld – Statin adherence in the 6 months pre-enrollment

Posthld – Statin adherence in the 6 months post-enrollment

In the database, “1” denotes adherence (PDC>80%), “0” denotes non-adherence (PDC<80%), and a blank cell denotes that the patient does not have a prescription claim for a medication which is measured in that therapeutic area of the STAR ratings.