THE IMPACT OF PHARMACY BENEFIT DESIGN CHANGES ON MEDICATION ADHERENCE AND GENERIC DRUG UTILIZATION AMONG COMMERCIALLY INSURED CONTINUOUSLY ENROLLED PATIENTS WITH CHRONIC DISEASES

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Abstract

While it is crucial for health plans to be protected against rising prescription drug costs, increasing cost sharing too much may mean that beneficiaries can not afford medication and non-compliance will become an issue.

The objective of the study was to investigate the impact of pharmacy benefit design (PBD) changes on adherence to chronic medications and generic utilization. The study samples were three cohorts of commercially insured continuously enrolled patients with pharmacy claims of diabetes, hypertension, and hyperlipidemia between Oct. 1, 2010 and Jun. 30, 2013. Pre and post quasi-experimental design with control group was applied. To understand the impact comprehensively, PBD changes were examined in two steps: Step 1—Any changes in PBD; Step 2—Changes in cost sharing strategies only. Medication adherence was measured in proportion of days covered (PDC) by at least one medication of the target disease. PDC was also dichotomized as PDC>=80% and PDC<80%. Generic utilization was measured as the generic dispensing rate (GDR) for all medications took during the study period.

Two statistical models were fit: General Linear Regression model for the continuously measured variables of PDC and GDR; and Logistic Regression for dichotomized PDC. Control variables were classified into three categories based on Andersen's behavioral model: predisposing characteristics, enabling resources, and need factors, including beneficiaries' demographic and socioeconomic information, medication conditions, and a proxy health risk estimate using Prospective Risk Score.

The study sample was made up of 445,983 patients, of whom 45,850 were

identified with benefit changes and 400,133 were not. In the experimental group, 8,049 beneficiaries had claims for diabetes, 36,712 beneficiaries had claims for hypertension, and 20,704 beneficiaries had claims for hyperlipidemia. The final control groups were randomly selected and were three times the number of those in the experimental group for each disease respectively. Mean pre-PDC is significantly higher than post-PDC, and mean pre-GDR is significantly lower than post-GDR for both groups. All models indicated no significant association between adherence and PBD changes. There were, however, significant associations between GDR and PBD changes in two cohorts. Beneficiaries with PBD changes had 0.007($p=0.0002$) higher post-GDR in the diabetes cohort; beneficiaries with PBD changes had 0.004 ($p<0.001$) higher post-GDR in the hypertension cohort. Neither cost-sharing strategy had a significant impact on PDC within studied pharmacy benefit designs. Generic dispensing rate was also not significant associated with most of the cost sharing strategies except the copayment decrease of generics. For beneficiaries with a decrease in the amount of copayment for generic products, the mean post-GDR was 0.017 ($p=0.0003$) lower than beneficiaries without copayment changes in the diabetes cohort, although not significant in the hypertension and hyperlipidemia cohorts.

Within the studied pharmacy benefit designs, design changes did not seem to affect medication adherence, but did positively affect generic drug utilization.

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Chapter 1 Introduction

1.1 Background

Annual prescription drug spending in the US is $374 billion in 2014 (Kaiser, May 2014). The increasing rate is 13% from 2013 to 2014. The large amount of prescription drug spending has been recognized as the most rapidly growing component of healthcare costs and has become the focus of policy attention(Huskamp, Deverka, Landrum, Epstein, & McGuigan, 2007; K. V. Nair, RJ., 2004). Pharmacy benefit management strategies were developed to contain greatly rising prescription drug spending without affecting health care quality.

Pharmacy benefit management companies (PBMs) are specialized managed care organizations (MCOs) focused specifically on management of prescription drug services. PBMs manage pharmaceutical benefits for managed care organizations, other medical providers or employers who interested in optimizing the clinical and economic performance of their pharmacy benefit. Their activities include benefit plan design, the creation and administration of retail and mail service networks, claims processing and managed prescription drug care services such as drug utilization review, formulary management, generic dispensing, prior authorization and disease and health management. A number of different measures have been used to report on these activities undertaken on behalf of PBMs clients, to ensure appropriate and cost-conscious used of prescription drugs.

Through the design of pharmacy benefit structures, PBMs have strongly influenced the delivery of pharmaceutical services. The cost per prescription and the number of prescriptions utilized are two central components to control total prescription drug costs. To achieve unit cost control and utilization management, pharmacy benefit design involves beneficiaries paying a copayment or coinsurance whenever they obtain prescriptions. The cost sharing mechanism was first introduced in mid-1980s to financially reward beneficiaries for using generic substitution and formulary drugs (Navarro, 2009). These cost sharing strategies not only reduce prescription cost paid by the health plan but also can affect prescription utilization. Most savings are derived from brand-to-generic conversion; some are attributed to reduce brand-name drug utilization. Encouraging the use of less costly substitutions, such as generic substitutions, can reduce pharmacy program costs by 10 percent to 15 percent (Navarro, 2009). Additionally, switches from non-preferred brands (usually a third tier) to preferred brands (usually a second tier) also contribute to the reduction in prescription drug spending. Switches arise when the copayment differential between these two tiers increases (Zhang et al., 2007).

By spreading the financial risk to beneficiaries, pharmacy benefit design attempts to increase appropriate drug use and at the same time minimize pharmacy benefit costs to the extent possible (Crown et al., 2004). Previous researchers have consistently found that higher cost sharing is associated with reduced prescription drug spending (Fairman, Motheral, & Henderson, 2003; Gilman & Kautter, 2008; B. Motheral & Fairman, 2001; B. Motheral & Sheth, 2003). Specifically, Gilman and Kautter found that a 10% increase in copayment levels would be associated with a 1.3% reduction in gross drug spending.

The efforts to control prescription utilization have significantly slowed the growth of overall prescription drug spending (CMS, accessed 2013 May 27).

While it is crucial for health plans to be protected against rising prescription drug costs, increasing cost sharing too much may mean that beneficiaries can not afford medication and non-compliance will become an issue, especially for vulnerable populations. Heisler et al found cost-related medication restriction could be a mechanism for worse health outcomes among low-income and other vulnerable populations due to the reduction in medications(Heisler et al., 2004).

Today, pharmacy benefit managers are still in a stage of finding the perfect balance between cost sharing and access to medications. Pharmacy benefit designs are modified or even completely changed during the process of pursuing this balance. There are extensive variations in pharmacy benefit design changes. Many health plans increase prescription cost sharing across all tiers to lower the burden of prescription cost. Some health plans change from tiered copayment to coinsurance to share with beneficiaries the financial burden of brand-name drugs. In addition, the fast development of emergent high deductible health plans is making pharmacy benefit designs and their managements more complex. The changes that health plan managers make to pharmacy benefit designs as they struggle to manage plan expenditures brings forward the question "Do pharmacy benefit design changes affect patient utilization of, and adherence to, prescribed medications?"

Raising the level of cost sharing has been demonstrated to be associated with non-adherence and have adverse impacts on health care utilization among patients with chronic diseases in a 2005 review (Gibson, Ozminkowski, & Goetzel, 2005). The

copayment differentials in the reviewed studies are smaller than the copayment differentials in place today. As copayment differentials rise, non-adherence could be a critical issue. On the other hand, a 2011 study noted that switching to a high deductible health plan did not change medication availability or reduce usage of essential medications for chronic diseases(Reiss et al., 2011). These relatively early studies and the inconsistency of findings between traditional cost-sharing strategies and the relatively new strategy of high deductible health plans suggests that new investigation of the impact of pharmacy benefit design changes on plan management and patient adherence to therapy should be reinvestigated.

This study, involving varying levels of cost sharing structures, investigates whether cost sharing changes made in pharmacy benefit designs during a contract renewal period affect medication adherence among commercially insured, continuously enrolled patients with chronic diseases. Proportion of days covered (PDC) applied in the study is a commonly used measure of adherence(Choudhry et al., 2014).

This study also estimates whether these changes increase the efficiency of formulary management. Generic dispensing rate (GDR) is one of the standard performance benchmarks monitored by PBMs to evaluate the effectiveness of pharmacy benefit design policies and procedures. Each one percent increase in GDR has been associated with a drop of 2.5 percent in gross pharmacy expenditures (Liberman & Roebuck, 2010).

1.2 Objective and specific aims

The overall objective of this study is to investigate the impact of pharmacy benefit design changes on medication adherence and generic drug utilization among commercially insured continuously enrolled patients with three common chronic diseases. For this study, pharmacy benefit design changes include only the combination changes in copayment, coinsurance with or without a minimum / maximum out-of-pocket per prescription claim, cumulative annual out-of-pocket maximum, annual deductible. Other elements of pharmacy benefit design, such as pharmacy network limitations and utilization management programs designed to ensure appropriate medication use, are not included in the study.

Medication adherence is calculated using proportion of days covered (PDC). Generic drug utilization is analyzed using generic dispensing rate (GDR). Chronic diseases affect health and quality of life. It is also a major driver of health care costs because patients typically require lifelong medication therapy to induce and maintain remission. As the most common chronic disease, hypertension, diabetes, and hyperlipidemia are included in the study.

In keeping with the overall objective, this study has two specific aims:

Aim 1: To investigate the impact of pharmacy benefit design changes on adherence to prescription drugs for chronic diseases.

Hypothesis 1a: Changes in pharmacy benefit design (copayment; coinsurance with or without a minimum / maximum out-of-pocket per prescription claim; cumulative annual out-of-pocket maximum; annual deductible) are associated

with changes in adherence to medication therapy for hypertension, diabetes, and hyperlipidemia (i.e. PDC) after controlling for other characteristics.

Hypothesis 1b: As the amount of copayment and/or coinsurance increases, adherence to medication therapy for hypertension, diabetes, and hyperlipidemia (i.e. PDC) decreases after controlling for other characteristics.

Aim 2: To investigate the impact of pharmacy benefit design changes on generic drug utilization for chronic diseases.

Hypothesis 2a: Changes in pharmacy benefit design (copayment; coinsurance with or without a minimum / maximum out-of-pocket per prescription claim; cumulative annual out-of-pocket maximum; annual deductible) are associated with changes in generic use of medication therapy for hypertension, diabetes, and hyperlipidemia (i.e. GDR) after controlling for other characteristics.

Hypothesis 2b: As the amount of copayment and/or coinsurance increases, generic use of medication therapy for hypertension, diabetes, and hyperlipidemia (i.e. GDR) increases after controlling for other characteristics.

1.3 Key terms and definitions

Table 1 provides key terms and definitions used in this study.

Table 1 Study key terms and definitions

Study key terms	Definitions
Pharmacy benefit management companies (PBMs)	Organizations that manage pharmaceutical benefits for managed care organizations, other medical providers or employers who interested in optimizing the clinical and economic performance of their pharmacy benefit. PBM activities include some or all of the following: benefit plan design, creation/administration of retail and mail service networks, claims processing and managed prescription drug care services such as drug utilization review, formulary management, generic dispensing, prior authorization and disease and health management.
Prior authorization	An administrative tool normally used by health plans or PBMs that requires prescribers to receive pre-approval for prescribing certain drugs to qualify those drugs for coverage under the terms of the pharmacy benefit plan.
Utilization management	Managing the use of medical services to ensure that a patient receives necessary, appropriate, high-quality care in a cost-effective manner. As it applies to a pharmacy benefit, utilization management is any of a number of measures used to ensure appropriate medication utilization, including quantity limitations, step therapy, prior authorization and/or additional steps as deemed appropriate by the health plan's Pharmacy and Therapeutics Committee.

Mandatory generic substitution	A pharmacy benefit management tool that mandates the use of a generic equivalent drug product whenever one is available. Prescribers must justify the use of a brand-name product over the use of its generic equivalent.
Pharmacy benefit design	The coverage elements included in a health insurance policy under which prescription drugs and services will be paid by beneficiaries and health plan providers. A sound pharmacy benefit design balances patient care outcomes, costs, quality, risk management, and provision of the services that beneficiaries expect.
Tiered copayment benefits	A pharmacy benefit design that financially rewards patients for using generic and preferred drugs by requiring the patient to pay progressively higher copayments for preferred brand-name and non-preferred brand-name drugs.
Prescription cost sharing	Some portion of prescription drug cost paid by the insurer party, often being seen in the form of tier copayment, coinsurance, individual/family deductibles, and maximum individual/family out of pocket limits.
Preferred brand drug	A brand name drug for which the managed care organization (MCO) has determined to be a valuable, cost-effective treatment option.
Non-preferred	A brand name drug for which the managed care organization

brand drug	(MCO) has determined offers less value and cost-effectiveness than preferred brand drugs. In multiple tiered pharmacy benefit plans, such drugs are typically placed on the third tier.
Deductible	A limit up to which the beneficiary pays the full cost of the drug. Copayments and coinsurance are in place after the deductible amount being reached.
Copayment	A fixed amount of payment per prescription that the beneficiary pays, i.e. $10.
Coinsurance	A percentage of the contracted price for the medication in quantity dispensed that the beneficiary pays, i.e. 10%.
Out-of-pocket cost	A limit that is set as a fixed dollars amount after which the insurer pays 100%. It is the sum of the amount paid through deductible, copayment and coinsurance. Copayments and coinsurance are in place prior to the limit being reached.
Full drug insurance	The beneficiary dos not pay any out-of-pocket expenditure at the time the prescription is dispensed.
Medication adherence	Refill compliance or adequacy of medication coverage for the beneficiary.
Proportion of days covered (PDC)	The ratio of the number of "usable" days supplied from all refills to the total number of calendar days following (and including) medication initiation during a determined period of time (e.g., 12 months).

PDC threshold	The level of PDC above which the medication has a reasonable likelihood of achieving most of the potential clinical benefit (80%for diabetes and cardiovascular drugs).
Medication possession ratio (MPR)	The sum of the days supply for all claims during a defined period of time (e.g., 12 months) divided by the number of days elapsed during the period.
Generic utilization	The number of generic prescription claims for the insurance plan beneficiary during a period of time (e.g., 1 months).
Generic dispensing rate (GDR) or generic fill rate (GFR)	The total number of retail generic prescription claims dispensed divided by the total number of retail prescription claims for the beneficiary during a determined period of time (e.g., 12 months).
Prospective Risk Score	The member's predicted "health risk" (i.e. the likelihood of exceeding predefined cost thresholds) for the 12 months directly following the claims experience period. The process involves three phases: 1) National Drug Codes (NDCs) recorded on pharmacy claims are assigned to unique Drug Class Codes (DCCs); 2) Individual's number of unique DCCs are mapped to 105 initial Optum Symmetry Pharmacy Risk Groups (PRG) to combine DCCs of similar clinical and risk characteristics; 3) Further Pharmacy Risk Groups (153 total) reflected

	comorbidities are defined based on member age and the combination of initial Pharmacy Risk Groups observed; 4) Array markers for each member to create a clinical risk profile; 5) The sum of the pre-determined weights assigned to these risk markers provides the overall risk scores for the individual.
Optum Symmetry Pharmacy Risk Groups	A pharmacy-based assessment that uses prescription data and proprietary classification systems to estimate a member's future resource use and expenditure. See appendix 1 for a list of pharmacy risk groups.
Generic Product Identifier (GPI)	Medi-Span's Generic Product Identifier (GPI) categorizes drug products by a hierarchical therapeutic classification scheme for use in computerized therapeutic drug monitoring applications (such as duplicate therapy and drug dosing), market research, and reporting applications.
Drug formulary	A continually updated list of medications and related products supported by current evidence-based medicine, judgment of physicians, pharmacists and other experts in the diagnosis, treatment of disease and preservation of health to encourage the use of the safe, effective and most affordable medications.
Open formulary	The payer generally provides coverage for all formulary and non-formulary drugs. The payers include the health plan, the employer, or PBMs acting on behalf of the health plan or

	employer.
Closed formulary	The payer does not reimburse non-formulary drugs. Formulary exception policies allow patients and physicians reimbursement and access to non-formulary medications where medically appropriate.
Treatment termination date	The last observed fill date plus the number of days for which the medication was dispensed.

1.4 Study design and limitations

As proposed, this is a retrospective observational cohort study. The study used pharmacy claims data from a large pharmacy benefits management company located in Minnesota. To explore the hypotheses discussed above, logistic regression and generalized linear modeling were utilized.

There are a number of major limitations. Firstly, limitations related to claims data must be acknowledged beforehand:

(1) Coding errors or inaccurate entries may exist.

(2) Pharmacy claims may not completely represent patients' medication coverage.

(3) Patients' consumption compliance cannot be evaluated through claims data. Pharmacy claims represent the acquisition of a prescribed medication only.

(4) The measurements of generic drug utilization and medication adherence may not be accurate because some sources of supply that are not recorded in

claims, such as out-of-plan use of pharmacy services and over-the-counter (OTC) medications.

(5) Socioeconomic information was not provided in the claims data. Data related to income, educational level, and races/ethnicity were estimated from 2010 census data by ZIP code of residence.

Secondly, as this study is a quasi-experimental design observational study, it is subject to the concern regarding internal validity. Therefore, this study only examines the association, instead of causal relationship, between pharmacy benefit design changes and generic drug utilization and medication adherence.

Thirdly, this study primary focuses on examining behaviors driven by the change of benefit design on cost sharing. Patients may choose to forgo a drug or change an established drug regimen for other reasons; among these are side effects, low curative effects, perceptions about the similarity of lower-tier substitutes and providers' opinions of discontinuing or altering established drug therapies, and other changes in benefit designs. Above factors all provide some insights into the evaluation of generic drug utilization and medication adherence. However, data to measure these other possible reasons are not available.

Various predisposing, enabling, and need factors used in the statistic analysis were limited. Variables such as belief constructs (patient perception), prescriber characteristics (specialty), and local area characteristics (region) were not incorporated due to limitations of the data source. The analysis might be subject to unobserved confounding.

Finally, since the data is restricted to populations from employer-sponsored, commercially insured health plans from 2011 to 2012, the results can not be generalized to other settings or years, such as Medicare, Medicaid, or other public plans.

1.5 Significance of the study

The intent of a pharmacy benefit plan is to encourage efficient use of prescription drugs, abate inefficient use, and avoid undermining health outcomes. The introduction of cost sharing structures intends to promote greater patient engagement. Even though a pharmacy benefit design helps to control prescription drug expenditures, it also causes concerns on the adverse effects of inadequate treatment in the process of medication use. The way that pharmacy benefit plans are structured and implemented can affect patient behavior and health outcomes. The type of cost sharing structures that is available to beneficiaries varies widely. It is important to find the right mixes of cost sharing characteristics to ensure positive plan management and patient care in today's healthcare system. Cost sharing for chronic diseases matters more from a clinical and economic point of view.

Compared to previous studies, this study was based on large samples using "real-world" pharmacy claims data. "Real-word" data has higher validity to be generalized to real-world clinical practice than data from clinical trials, where individuals are monitored closely. The study also employed pre- and post-experimental design with control group, not commonly adopted in literatures studying benefit design changes.

The study examined both medication adherence (measured by PDC) and generic drug utilization (measured by GDR) for chronic diseases. PDC is the pharmacy quality alliance (PQA) recommended metric for estimation of medication adherence for patients using chronic medications. Centers for Medicare and Medicaid Services (CMS) Star Ratings is a plan ratings that indicates the quality of Medicare plans on a scale of 1 to 5 stars with 5 stars being the highest rating. The overall star rating is determined through numerous performance measures across several domains of performance. PDC of chronic diseases is one measure for Star Ratings. Generic utilization is also an important performance measure of benefit plans. It is highly associated with prescription expenditures. Understanding the association between medication adherence and benefit design changes, generic utilization and benefit plan changes are important knowledge need. The results can provide guidance for PBMs and other MCOs to refine the structure of pharmacy benefits.

Chapter 2 Literature review

Studies selected for the literature review were based on electronic searches of OVID Medline, International Pharmaceutical Abstracts, and Google Scholar. Key words or phrases were pharmacy benefit, benefit design, utilization, adherence, compliance, generic fill rate, generic dispensing rate/ratio, deductible, copayment, coinsurance, tier formulary and cost sharing. Key words were searched in various combinations. Additional studies were identified from the reference lists of selected publications.

Abstracts were reviewed for relevance to the study aims. Full articles regarding the impact of pharmacy benefit design on medication adherence or generic utilization were identified for further review and evaluation. Publications selected were published in English within the period 1990 to 2015. The populations studied were from the United States or Canada. Additional criteria included the underlying disease or condition (with an emphasis on diabetes, hypertension, and hyperlipidemia), pharmacy benefit plans (tiered copayment and coinsurance, deductible, maximum out-of-pocket limits), and study measures (PDC and GDR) used.

To review the impact of pharmacy benefit design changes on medication adherence and generic unitization, this literature review covers three aspects: the elements of pharmacy benefit design, the impact of pharmacy benefit design on medication adherence, and the impact of pharmacy benefit design on generic utilization.

2.1 Elements of pharmacy benefit design

Today in the US, more than 90% of covered workers have prescription drug coverage as part of their health insurances (Kaiser, May 2014). Almost all of them face the requirement to share drug costs through some form of prescription cost sharing. Prescription cost sharing is put into place to encourage consideration of prescription costs prior to the purchase of the medications by the beneficiaries(Choudhry et al., 2014).

The essential structure of the pharmacy benefit design among US health care plans is the multi-tiered formulary. Multi-tiered formularies classify drugs into two or more tiers with different level of cost sharing based on safety, clinical effectiveness, acquisition cost, and the availability of comparable medications (Mullins, Palumbo, & Saba, 2007). The first-tier drugs are usually generics; the second-tier drugs are typically preferred brands; the third-tier drugs are generally non-preferred brands; the forth-tier drugs are life style drugs or specialty drugs. Cost sharing increases with each tier level (first tier has lowest copayment and fourth tier the highest).

Most multi-tiered formularies refer to formulary-based medications; non-formulary medications are usually placed at the highest cost sharing level. More than three out of four covered workers are in plans with three or more cost-sharing tiers for prescription drugs. For these workers copayments, rather than coinsurance, continue to be a more common form of cost sharing(Kaiser, May 2014).

Multi-tiered formulary structures are categorized into several types including: flat-dollar tier (e.g., flat-dollar 3-tier, flat-dollar 2-tier), flat coinsurance, tiered coinsurance, and a mix of tiered copayment and coinsurance. Some designs also apply family/individual deductible amounts and family/individual maximum/minimum out of pocket limits other than tiered copayment and coinsurance. These represent various forms of cost sharing as discussed below.

2.1.1 Copayment structure

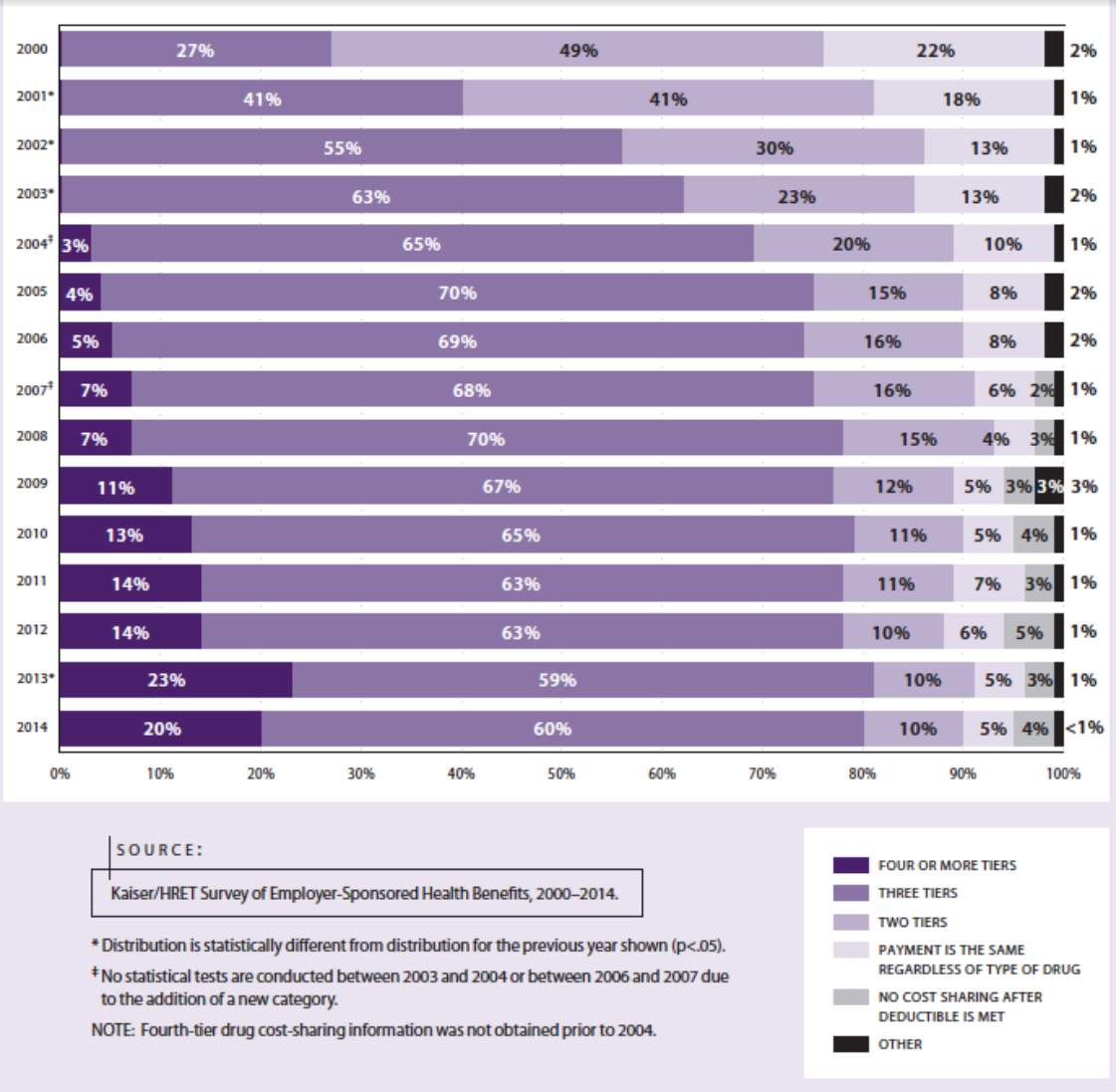
There are wide variations in the design of multi-tiered formulary. The flat-dollar, two-tier plan is the simplest one. The formulary list (i.e. the drugs that have been approved for coverage by the insurer) is divided into two tiers—the first tier being the generic version of approved drugs, and the second tier being the brand name version of approved drugs. A copayment dollar value is assigned to each of the two tiers and is usually higher for the second tier. The copayment differentials between first and second tiers, however, generally not provide an adequate incentive for patients to use generic substitutions. Therefore, two-tier plans have been rapidly declining and being replaced by plans with more tiers.

In a three-tier formulary, brand drugs are divided into preferred brands and non-preferred brands (Frank, 2001). The three-tier formulary structure has been the most commonly used.

In a four-tier formulary, brand drugs are usually further differentiated by higher cost sharing for specialty drugs and expensive biologics (Roebuck & Liberman, 2009). A growing number of specialty drugs have been introduced to the market (See Figure 1). The application of higher tier plans enables beneficiaries to have access to newer or more expensive drugs at a cost-sharing burden.

In three or more tier plans, the average copayments for non-preferred drugs have increased significantly, while remaining constant for generic drugs. For covered beneficiaries in plans with three, four, or more tiers of cost sharing, the average

copayments are $11 for first-tier drugs, $31 for second-tier drugs, $53 for third-tier drugs, and $83 for fourth-tier drugs (see Table 2). For covered employees with two tiers of prescription cost sharing, the average copayments are $11 for generics and $30 for preferred drugs (see Table 3).



*Source: Kaiser/HRET survey of employer-sponsored health benefits, 2000-2014.

Figure 1 Distribution of covered workers facing difference cost sharing formulas for prescription drug benefits, 2000-2014

Table 2 Among covered workers with three, four, or more tiers of prescription cost sharing, average copayments and average coinsurance by drug type, 2000-2014

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Average Copayments															
First-Tier Drugs, Often Called Generic	$8	$8	$9	$9*	$10*	$10	$11*	$11	$10	$10	$11	$10	$10	$10	$11*
Second-Tier Drugs, Often Called Preferred	$15	$16*	$18*	$20*	$22*	$23*	$25*	$25	$26	$27	$28*	$29	$29	$29	$31
Third-Tier Drugs, Often Called Nonpreferred	$29	$28	$32*	$35*	$38*	$40*	$43*	$43	$46*	$46	$49*	$49	$51	$52	$53
Fourth-Tier Drugs	^	^	^	^	$59	$74	$59	$71*	$75	$85	$89	$91	$79	$80	$83
Average Coinsurance															
First-Tier Drugs, Often Called Generic	18%	18%	18%	18%	18%	19%	19%	21%	21%	20%	17%	18%	20%*	16%*	19%
Second-Tier Drugs, Often Called Preferred	NSD	23%	24%	23%	25%	27%	26%	26%	25%	26%	25%	25%	26%	25%	24%
Third-Tier Drugs, Often Called Nonpreferred	28%	33%	40%	34%*	34%	38%	38%	40%	38%	37%	38%	39%	39%	38%	37%
Fourth-Tier Drugs	^	^	^	^	30%	43%*	42%	36%	28%	31%	36%	29%	32%	32%	29%

SOURCE:

Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 2000–2014.

* Estimate is statistically different from estimate for the previous year shown (p<.05).

^ Fourth-tier drug copayment or coinsurance information was not obtained prior to 2004.

NSD: Not Sufficient Data.

*Source: Kaiser/HRET survey of employer-sponsored health benefits, 2000-2014.

Table 3 Among covered workers with two tiers of prescription cost sharing, average copayments and average coinsurance, by drug type, 2000-2014.

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Average Copayments															
First-Tier Drugs, Often Called Generic	$7	$8*	$9*	$9	$10	$10	$11	$10	$11	$10	$10	$11	$11	$11	$11
Second-Tier Drugs, Often Called Preferred	$14	$15*	$18*	$20*	$22*	$22	$23	$23	$24	$26	$28	$28	$29	$31	$30
Average Coinsurance															
First-Tier Drugs, Often Called Generic	19%	17%	20%	21%	17%	16%	22%	21%	19%	NSD	NSD	NSD	NSD	NSD	NSD
Second-Tier Drugs, Often Called Preferred	28%	25%	25%	28%	25%	24%	27%	28%	32%	28%	27%	30%	27%	30%	27%

SOURCE:

Kaiser/HRET Survey of Employer-Sponsored Health Benefits, 2000–2014.

* Estimate is statistically different from estimate for the previous year shown (p<.05).

NSD: Not Sufficient Data.

*Source: Kaiser/HRET survey of employer-sponsored health benefits, 2000-2014.

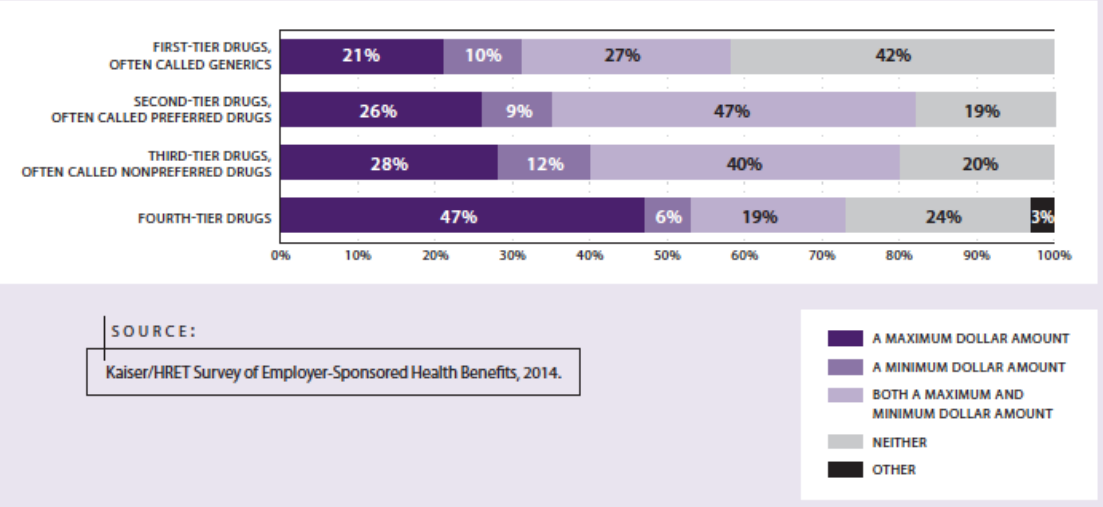
2.1.2 Coinsurance structure

While multi-tiered, flat-fee copayment benefit designs have been widely employed among US health insurers, coinsurance benefit design is becoming increasing popular(Klepser, Huether, Handke, & Williams, 2007). However, copayments are still more common than coinsurance for beneficiaries in plans with two tiers (see Figure 2). Coinsurance structure (the amount of cost sharing that is incurred by the beneficiaries) is directly related to drug price—the more expensive the drug, the more of the cost the beneficiaries bear. Coinsurance stabilizes the cost-share mix between beneficiaries and insurers.

To ensure beneficiaries against high dollar expenditures with expensive medications, some designs introduce a maximum beneficiary out-of-pocket limit per

prescription with the coinsurance benefit. If a specialty drug that might cost $1000, the maximum out-of-pocket limit might limit the financial burden to a maximum of $250 rather than $300 with a coinsurance of 30%. Minimum coinsurance out-of-pocket limits per prescription can also be defined within the coinsurance structure, which sets the lowest amount of money that the beneficiary must pay per prescription. For generic drugs, 21% of beneficiaries have only a maximum dollar amount attached to the coinsurance rate, 10% have only a minimum dollar amount, 27% have both, and 42% have neither (Kaiser, May 2014).

Coinsurance structure can also divide drugs into different tiers as copayment structure does. For covered beneficiaries in plans with three, four, or more tiers of cost sharing, the average coinsurance is 19% for first-tier drugs (generally generic drugs), 24% for second-tier drugs, 37% for third-tier drugs, and 29% for a fourth-tier of specialty drugs (see Table 2). These estimates are all smaller than the estimated coinsurance rate in 2012. The smaller percentage assigned to fourth-tier drugs (generally expensive specialty drugs) still results in high out-of-pocket expenditures that will exceed third-tier drugs at the higher coinsurance rate. Ten percent of covered workers are in a plan that has two tiers for prescription drug cost sharing. The average coinsurance rate for the second tier is 27%.



*Source: Kaiser/HRET survey of employer-sponsored health benefits, 2000-2014.

Figure 2 Distributions of coinsurance structures for covered workers facing a coinsurance for prescription drugs, by drug tier, 2014

2.1.3 Deductible and OOP costs

Deductible is the fixed dollar amount paid by beneficiaries before insurance benefits pay out. Deductible amount usually refers to an individual limit but for some benefit plans, a family deductible limit may also be applied. In either case, the deductible amount must be reached within a contract year before other health insurance benefits are applied.

OOP cost is a fixed dollar amount after which the insurer pays 100% of all incurred costs. It is the sum of the amount paid by the beneficiary through the deductible amount, copayment/coinsurance amount, and the cost for any services not covered by insurance, which are in place prior to the limit being reached. OOP costs include individual OOP costs and family OOP costs if they are specified. Once the individual

OOP cost amount is met, all other costs for that individual will be reimbursed. If a family OOP cost limit is part of the benefit plan, once it is met, the cost to all family members will be fully reimbursed thereafter.

2.1.4 Other structures

There are several other mechanisms to motivate patient behaviors other than cost sharing, including a defined physician provider network, a defined pharmacy provider network, a drug formulary, a mandatory generic substitution program, dispense-as-written (DAW) financial penalty, maximum allowable benefit (MAB), mail delivery and so on(Roebuck & Liberman, 2009). MAB caps the total amount paid by insurers for prescription drugs either annually or lifetime. Mail delivery encourages beneficiaries to order prescriptions for chronic conditions by mail and receive a lower OOP cost per medication day supplied.

2.2 Changes of pharmacy benefit management

The essential pharmacy benefit design components have not changed significantly since they were introduced in the mid 1980s. However, the aggressiveness and effectiveness by which pharmacy benefits are managed has changed. As health insurers and self-insured employers attempt to reduce the financial burden associated with the

growing use of prescription drugs, beneficiaries are increasingly faced with higher cost sharing benefits at the time of their annual enrollment period.

Plans can choose to remain with the same cost sharing structures but make dollar amount changes to individual components. There can be increases or decreases in the copayment amount or coinsurance within formulary tiers, increases or decreases in deductible amount (individual or family), or increases or decreases OOP cost (individual or family) at contract renewal.

Other component changes can also impact cost sharing. Typical changes include the transition from copayment to coinsurance, or from coinsurance to copayment, the transition from either single copayment or single coinsurance to a mix of copayment and coinsurance, and the transition from copayment to a high deductible plan. There can also be structural changes to the drug benefit such as changes to the formulary tiers. While today, benefit plans tend to change from a low number of tiers to a higher number of tiers.

2.3 Medication adherence to chronic diseases

The importance of medication adherence in the management of chronic diseases has been demonstrated by several research studies. Non-adherence can cause adverse impacts on health outcomes, such as a higher danger of readmission, which may results in more consumption of medical utilizations(Dunbar-Jacob & Mortimer-Stephens, 2001). In contrast, higher adherence to drug therapy is associated with lower costs and better health outcomes(Sokol, McGuigan, Verbrugge, & Epstein, 2005). Sokol et al found that

increased drug utilization for diabetes and hyperlipidemia could provide a net economic return when it was driven by improved adherence.

In the process of recommending drug therapy, physicians prescribe the treatment regimen without necessarily having concern about drug costs or formulary coverage (Shrank et al., 2005). Beneficiaries are left to inquire about lower cost substitutes under their prevailing insurance and make decisions about filling the prescription, switching to a lower cost drug, or abandoning the treatment based on their perceptions of affordability. Prescription drug coverage is, therefore, an important factor determining patient preference for drug therapy and adherence to the prescribed drug (D'Souza, Smith, Miller, Doyle, & Ariely, 2008).

Additionally, adherence to medication is influenced by many other factors. Included among them are: satisfaction with the current prescription (effectiveness, experienced side effects), continued availability, provider's opinion, the disease being treated, knowledge of and perceptions about lower-tier substitutes, geography, socioeconomic status, gender, and age. Age, sex, and socioeconomic status are frequently examined factors(Couto et al., 2014; Doshi, Zhu, Lee, Kimmel, & Volpp, 2009). Couto found younger age beneficiaries, lower income beneficiaries, and females were less adherent to chronic medications for hypertension, diabetes, and hyperlipidemia.

To fully explain medication adherence, many more studies of varying quality have focused on insurance design factors such as copayment, coinsurance, deductible, and max OOP limits(Choudhry et al., 2014; Doshi et al., 2009; Gibson et al., 2005; Gibson et al., 2010; Goldman et al., 2004; Landsman, Yu, Liu, Teutsch, & Berger, 2005;

Mann et al., 2014; Pilote, Beck, Richard, & Eisenberg, 2002). The next section discusses these financial factors in more detail.

2.4 Insurance design factors influent medication adherence

2.4.1 Copayment and coinsurance

The association between cost sharing and adherence is non-linear. Factors such as the absolute size of copayments in absolute terms, the size of the copayment changes, the time horizon examined, and assignment of drugs to tiers all have been identified in the literature as affecting the strength of association. Also, the impact of cost sharing on adherence appears to be different for new users and existing users; new users who lack experience with prescription drugs might be more sensitive to cost sharing changes(Goldman, Joyce, & Zheng, 2007; Solomon, Goldman, Joyce, & Escarce, 2009).

After reviewing related literature published before 2013, Mann concluded that small cost sharing (up to 25% cost sharing) did not impact medication adherence significantly, while large cost sharing (i.e., 95% cost sharing) had a substantial impact (Mann et al., 2014). Landsman's study predicted that doubling copayments in a typical 2-tier plan was associated with significant reductions in use, especially among therapies for diabetes, but the impact on medication adherence appeared to be small (Landsman et al., 2005).

Some researchers have found that increased cost sharing or the addition of tiers (which would affect cost sharing) would reduce prescription use (Joyce, Escarce,

Solomon, & Goldman, 2002; B. Motheral & Fairman, 2001). Some studies have found an inverse association between copayment and medication adherence to drug therapy of chronic diseases(Atella & Kopinska, 2014; Gibson et al., 2005; Goldman et al., 2004; Lesen, Andersson Sundell, Carlsten, Mardby, & Jonsson, 2014; Simoens & Sinnaeve, 2014). Zhang found that a 10-dollar greater cost share was associated with 31.9 percent greater odds of being non-persistent (PDC was used to measure persistence) among members newly initiating ACEI or ARB therapy(Zhang et al., 2007). Happe found that there was strong evidence of a negative correlation between formulary restrictions (including step therapy, cost sharing, prior authorization, preferred drug lists, and quantity limits) and medication adherence outcomes (Happe, Clark, Holliday, & Young, 2014). Doshi and colleagues demonstrated that increasing copayment by $5 resulted in up to 40% lower adjusted odds of adherence in a high-risk group of US veterans(Doshi et al., 2009).

Additionally, Choudhry found that value based insurance design plans (which have linked copay levels to the clinical value of the product or service) that provide more generous coverage (e.g., 100% coverage) were associated with higher rates of medication adherence (Choudhry et al., 2014). Other researchers have reported that greater OOP cost was associated with lower adherence(Aarnio et al., 2014; Suehs et al., 2014). To some extent, full reimbursement may be more cost-effective than copayment program when considering the impact of medication adherence.

Some plans may have a hybrid design—fixed copayment design with a subsequent addition of coinsurance or switch completely from one design to the other. Scheneeweiss found a small decrease in adherence to statin when plans change from full

coverage to the mix design of cost sharing(Schneeweiss, Patrick, Maclure, Dormuth, & Glynn, 2007). Klepser studied plans that changed from 3-tier copayment to 4-tier coinsurance and found no significant reduction in overall drug utilization (Klepser et al., 2007).

2.4.2 Deductibles

In a literature review, the use of deductible (up to $350 per year) did not have substantial association with medication adherence (Mann et al., 2014). This study however referenced literature with lower deductible designs than exist today. In the current healthcare system, the deductible designs may go up to $10,000 or more in some high deductible health plans (see Table 15). The impact of high deductible design on medication adherence was uncertain. There may be a threshold effect of deductible amount; because the deductible may be too high to afford, beneficiaries may either not initiate or discontinue drug therapy before reaching the threshold.

2.4.3 Maximum out-of-pocket limits

The impact of maximum out-of-pocket expenditure on medication adherence is uncertain(Doshi et al., 2009; Pilote et al., 2002). Doshi found that US Veteran's Administration beneficiaries without a maximum out-of-pocket expenditure had a slight decline in adherence compared to those with a maximum out-of-pocket expenditure

($840 US per year). In a Canadian study, Pilote and his colleagues, however, found no apparent change in adherence when plans changed from copayment to coinsurance with varying levels of annual maximum out-of-pocket expenditure (ranging from $250 to $ 750 CDN).

2.5 Generic utilization of chronic drugs

The use of generic drugs could result in significant cost saving(Duru et al., 2014). Increase the use of generics by 10% can reduce Medicare costs by about $1 billion annually("Zero copayment for generic statins could save billions," 2013). Facing the increasing financial burden of prescription drugs, generic substitution is an essential option to save cost, especially for chronic diseases (Goldman et al., 2004).

Both supply-side and demand-side factors have impacts on generic utilization. Financial incentives for community pharmacy networks (high dispensing fees for generics) have been the dominant supply-side drivers, while aggressive benefit designs, step therapy, and prior authorization have been the dominant demand-side drivers(Liberman & Roebuck, 2010). The premise of cost sharing strategy of benefit design is that by shifting the burden of cost onto beneficiaries, they will be more judicious in consuming prescriptions. With the application of tiered cost sharing, beneficiaries may have preference of generics.

The use of generic is an important cost sharing strategy. It has been defined with a measure, the generic dispensing rate (GDR), which is now considered an important

measure of formulary management efficiency. The generic dispensing rate is the proportion of all prescriptions filled as generic. PBMs generally report that a 1% increase in GDR will save 1% to 2% of total pharmacy expenditures(Roebuck & Liberman, 2009).

Gibson's review identified studies of three-tier plans and found that different levels of cost sharing structure impacted GDR variously (Gibson et al., 2005). Five out of seven studies reported an increase in GDR when cost sharing increases or generic-only policy applied, while the other two studies found no significant association between GDR and cost sharing changes. Specifically, Nair et al found an increase in GDR by 6-8% whether there were tier changes or not(K. V. Nair et al., 2003). Motheral and Henderson found an increase from $10 to $15 for brand copays was associated with an increase in GDR(B. R. Motheral & Henderson, 1999). Thomas et al found more aggressive cost-sharing requirements combined with other management strategies were associated with an increase in GDR(Thomas, Wallack, Lee, & Ritter, 2002). Christian-Herman et al found a generic-only benefit was associated with an increase in GDR(Christian-Herman, Emons, & George, 2004). Kamal and Briesacher found two tier plans with generic and brand differentials of $10 was relative to higher GDR compared to flat-copayment plans(Kamal-Bahl & Briesacher, 2004).

However, these studies cited did not specifically address the relationship between percentage changes in cost sharing and GDR. Gilman et al did examine copayment changes and found that a 10% increase in copayment was associated with a 0.7 percentage points increase in GDR(Gilman & Kautter, 2007). Smaller copayment differentials provide fewer incentives for patients to switch to a formulary alternative. That is, with small increase in copayment, use of prescriptions was relatively inelastic

(Landsman et al., 2005). On the other hand, if the cost sharing change was too high, patients tended to discontinue the use of medications (Huskamp et al., 2007).

Beneficiaries with higher generic cost sharing had lower generic use; larger cost sharing difference between brands and generics were significantly associated with greater generic use of chronic drugs(Roebuck & Liberman, 2009; Tang, Gellad, Men, & Donohue, 2014; Zimmerman, 2012). Higher brand cost sharing design appears to attenuate increases in drug spending by decreasing the consumption of brands and steering beneficiaries to generics. Also, reductions in cost sharing of generics would motivate beneficiaries to use generics(Clark et al., 2014; Lieberman, Polinski, Choudhry, Avorn, & Fischer, 2014). For example, low or zero copayment is the greatest influencer of generic statin utilization.

Plan cost sharing changes usually go alone with tier changes. The findings of the impact of tier changes on generic use were inconsistent. A few studies found the association of more formulary tiers (>= 3 tiers) with increased generic utilization(Gilman & Kautter, 2008; Huskamp et al., 2003; Landon et al., 2007; Mager & Cox, 2007). Mager found 3-tier design had GDRs that were two percentage points higher than 2-tier structures. Gilman et al found GDRs were 4.3 percentage points higher for 3-tiers compared to 1-tier plans. It is expected to have a reduction in the use of brand name drugs as well as non-formulary drugs, and a raise in generic utilization. Nair, however, found no significant difference in GDRs when plan changed from 2-tier to 3-tier, comparing to plans stay in the same tier design (K. V. Nair et al., 2003). Motheral et al also reported no significant change in GDRs following the implementation of an aggressive benefit change(B. Motheral & Fairman, 2001).

Other than cost sharing structure, factors such as brand loyalty also affect generic utilization. Gibson found that almost all of the studies demonstrated that a third tier resulted in a reduction in pharmacy utilization, but the price elasticity varied for different medication classes(Gibson et al., 2005). For example, beneficiaries are more loyal to therapy classes related to symptomatic diseases, and, therefore, less sensitive to patient cost sharing. Gender and disease status were also demonstrated to be associated with generic utilization(K. V. Nair et al., 2003). Nair et al found that the GDR for women were 6.2% greater than men. Beneficiaries with arthritics were more likely to use generic medications, while beneficiaries with diabetics and hypertensive were less likely to do so.

2.6 Summary

The literature that has been summarized, points out that socio-demographic factors combined with the design of prescription drug insurance benefit can influence medication adherence and the efficiency with which prescription drugs are managed. Only a few studies utilize strong research designs like a pre-post intervention design with a comparator group. For the studies that do use a pre-post intervention design with a comparator group, the comparator group does not always represent a carefully matched control group nor is the statistical analysis rigorous. For example, in Nair's study, both comparator and intervention groups experienced an increase in copayment amounts, which were not measured, during the study calendar year(K. V. Nair et al., 2003).

Motheral and Fairman's study is one of the earliest efforts to examine the utility of benefit design in influencing prescription utilization (B. R. Motheral & Henderson, 1999). However, the copayment differentials (from a $10 to $15 copayment for brand names) in that study and other studies about this topic are normally smaller than current cost sharing arrangements. As cost sharing continues to rise, beneficiaries may be more sensitive to the cost of prescription drugs. Hence, previous research may not be relevant when considering the impact of a more aggressive benefit design structure. Also, the types of plans that were examined in previous research are very limited. Few studies have examined the changes seen in larger cost sharing arrangements in a commercial insurance population.

The study that is the subject of this dissertation focuses primarily on prescription drug benefits and the impact that changes to these benefits has on subsequent medication adherence and generic drug utilization. Chapter three presents the underlying conceptual framework for this research.

Chapter 3 Conceptual framework

The conceptual framework of this study is based on the economic theories of demand for health insurance and the Andersen's behavioral model of health services utilization. The economic theories of demand are used to predict the relationship between benefit design changes and medication adherence, and to predict the relationship between benefit design changes and generic utilization. We use the Andersen's behavioral model to order and array predictors.

3.1 The economic theories of demand for health insurance

Bernoulli originally proposed the theory of demand for health insurance in his seminar paper in 1738(Nyman, 2003). Bernoulli suggested that the insured was risk adverse and his/her demand for health insurance was due to the need of maximizing individual's expected utility. Neumann and Morgenstern advanced the theory by developing a practical method for measuring utility as a function of income. In 1963, Arrow argued that government should intervene and expand health insurance coverage based on the conventional expected utility theory. Shortly after that, Pauly brought up the theory of moral hazard that was associated with health insurance. Moral hazard was defined as any change in behavior that was due to becoming insured. It represented a movement along the consumer's demand curve.

Pauly thought of moral hazard as a welfare loss to society. Figure 3 illustrates Pauly's argument (Nyman, 2003). D represents the demand for medical care (M). When

the customer is uninsured, the price of medical care equals to the marginal cost. The amount of medical care consumed is Mu. If the customers are insured with full coverage, the price becomes 0. The amount of medical care consumed raises to Mi. The amount of Mi-Mu is the additional medical care consumed by the customer because of being insured. Thus, the cost of moral hazard is the marginal price times the quantity, which equals to abMiMu; while the value of the moral hazard is the area under the demand curve, which equals to aMiMu. The moral hazard welfare loss is the cost minus the value, which equals to abMi. Therefore, if the insurer raises the coinsurance rate from 0 to c, the customer's price becomes cP. The movement along the demand curve reduces moral hazard by Mi-Mc. The welfare loss is reduced from abMi to acd.

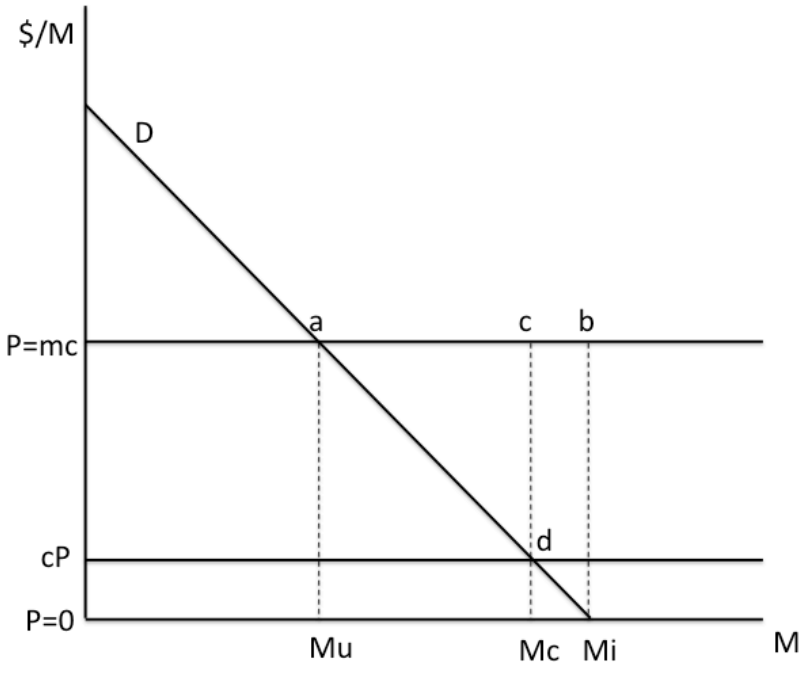


Figure 3 Moral hazard welfare loss.

Pauly's article was the most influential article in the health economics literature and directed policies at containing health care costs. It prompted the policy of raising the level of cost sharing on demand-side and the policy of imposing managed care on supply-side (Nyman, 2003). Feldstein's study sustained Pauly's view of moral hazard. Feldstein found that the welfare loss from moral hazard exceeded the gain from risk avoidance and suggested raising the coinsurance rate to 66%. The rate is a lot higher than current coinsurance rate applied in health insurance design. The result of RAND Health Insurance Experiment (HIE), the most costly and famous experiment, was also concordance with Pauly's theory (Manning et al., 1987; Newhouse et al., 1987). RAND HIE concluded that cost sharing contributed to a reduction of 31% health care expenditures without affecting health outcomes.

Prescriptions are normal goods with positive income elasticity. The economic theories applied in health care also fit in the pharmaceutical industry, where employers and insurers continue to use cost-sharing strategies. Following health economics theory, the demand for prescription drugs will decrease as the price increases (Folland, Goodman, & Stano, 2013). Economists assume that rational customers will consume an optimal amount of products subject to their income constraints. Based on this economic principle, raising the price will result in a reduction in consumption of higher costly products and increasing cheaper substitutions.

Figure 4 shows the effect of cost sharing on beneficiary's purchase decision(Nicholson, 2005). Beneficiary's decision of continuing using drugs is assumed to be a rational trade-off between drugs and other goods. The isoquant curve U1 shows all the combinations of other goods Y and prescription drugs M that can produce U1

output. When the demand line Dp1, where the cost-sharing amount of prescription drugs is p1, tangent to the isoquant curve U1, the input combination of (M1, Y1) minimizes cost to get the same output. Suppose the prescription cost-sharing increase to p2 (p2>p1) and the prices of other goods stay the same, the new isoquant curve will change to U2 (U1>U2). Thus, the new optimal combination becomes (M2, Y2) to maximum utility under budget constraint. An increase in the cost sharing of prescription drugs will lower beneficiary's quantity demand.

Two different effects come into play in the consequence of the movement between M1 and M2, when the patient cost sharing changes. On one hand, to stay on the same isoquant curve U1, beneficiaries have to substitute other goods for prescription drugs, called the substitution effect. It causes a downward movement from M1 to Mb. On the other hand, income effect will induce a reduction in the beneficiary's purchasing power. It causes a downward movement of indifference curve, which means the change from U1 to U2. Mb-M2 is the income effect showed in the figure(Nicholson & Snyder, 2012).

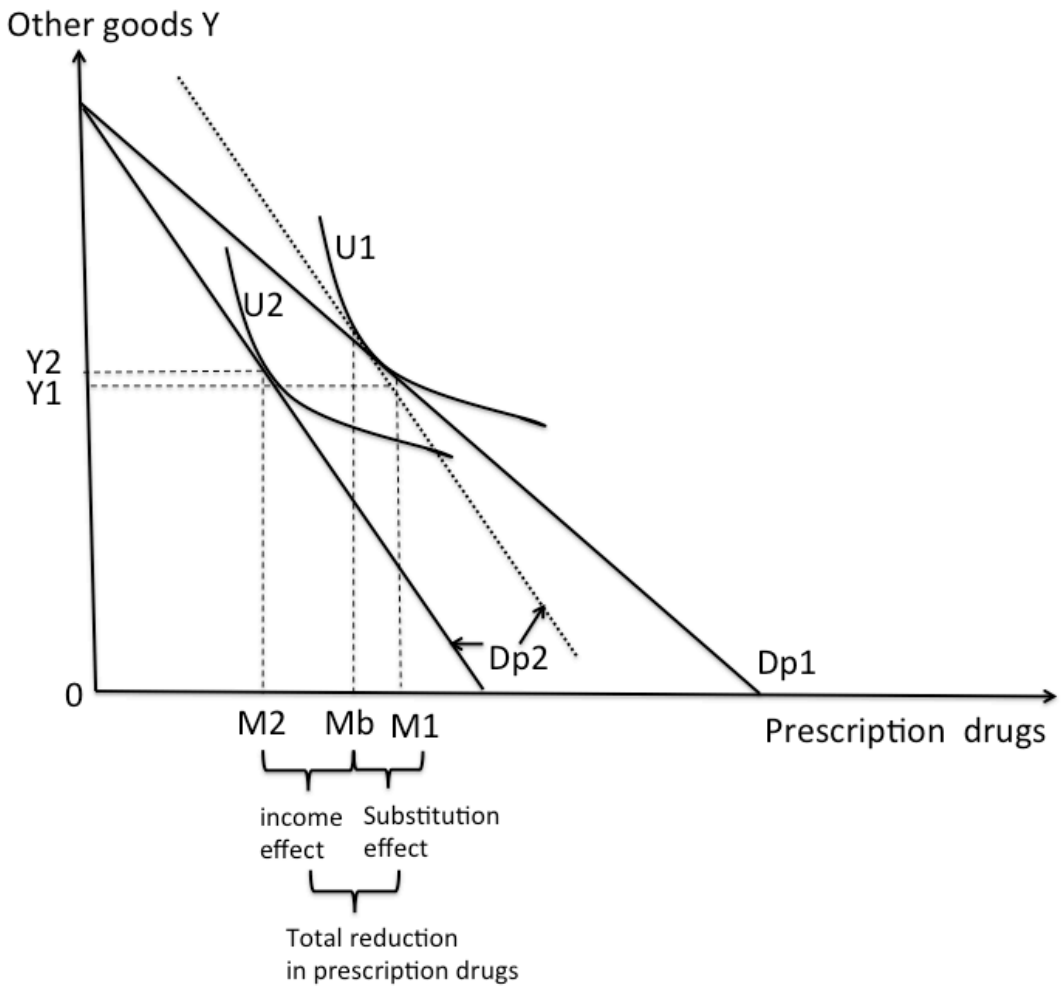


Figure 4 The effect of cost sharing on prescription drug consumption

According to the above economic theories of demand, we can generally expect that:(1) In order to reduce moral hazard, beneficiaries are forced to face an increasing patient cost-sharing; (2) beneficiaries who face a higher cost-sharing will have a reduction in pharmacy utilization. Here we include the income effect and substitute effect to predict beneficiary's pharmacy utilization. Beneficiary may substitute expensive brand drugs with cheaper generics. All the assumptions above consider the effects of other parties, such as physicians and pharmacists, are held equal across all customers.

Cost sharing strategies help limit the consumption of unnecessary drug therapy that may otherwise result from generous benefits. Today, patient cost sharing within pharmacy benefit design have risen considerably, especially for brand name drugs. The challenge is to identify the level of patient cost sharing so that patients will have sufficient access to prescription drugs without increasing welfare loss.

3.2 Andersen's behavioral model of health services utilization

There is a set of determinants that are in traction with health behavior, including personal determinants, family determinants, social determinants, institutional and cultural determinants, disease groups, and structured communities.

Andersen displayed and tested those factors in a study published in 1968. The original model ordered and arrayed three main predictors and two indicators of health care utilization, and built up the causal pathways between them(Gochman, 1997). The three predictors are predisposing characteristics, enabling resources, and need factor. They have been widely used to display complex causal models of health care-seeking behaviors (see Figure 5).

Predisposing characteristics are factors that describe the propensity of individuals to seek care, which may exist before illness, including demographics (age and gender), social structure (education, occupation, ethnicity and social network), and health beliefs (attitudes, values, and knowledge about health and health services). Enabling resources describe the resources must be present for use to take place, including community (source of care, travel and waiting time) and personal resources (income and health insurance

benefits). Need factors represent either a subjective acknowledgement of need or professional judgment, which, therefore, is categorized into two components—perceived need (individual or provider judgments of the presence of illness) and evaluated needs (judgments of the severity of conditions)(Aday et al., 1993).

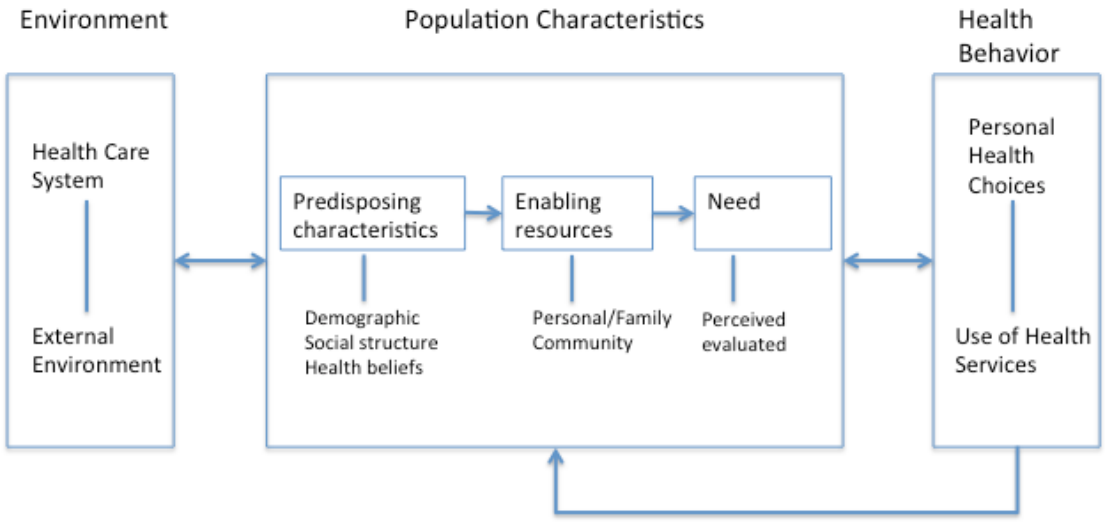


Figure 5 The initial behavioral model of health service use(R. M. Andersen, 1995)

The original Andersen model purported that health services utilization is dependent on individuals' predisposition to use health services, their ability to access services and their need for health care. The model also suggested that need for care factors were the strongest predictors followed by enabling resources and predisposing characteristics. Each component was conceived as independent contribution to predict utilization. The model promoted the government to develop policy for equitable access (R. M. Andersen, 1995). This behavioral model was a concise yet comprehensive model generated from sociology, economic, psychology, and medical literatures. Critiques of

the model included the validity of measuring concepts, interactions of predictor variables, need for additional variables (Gochman, 1997).

A revised framework, named Andersen and Newman Utilization framework in the late 1970s, was more responsive to societal and policy changes as well as the increasing complexity of health care service delivery(R. Andersen & Newman, 1973). Shortly thereafter, Aday and Andersen Access Framework was developed specifically to evaluate the performance of governmental and private programs in enhancing health care access(Aday & Andersen, 1974).

Both Andersen's original and revised behavioral model of health services utilization has been adapted to address patients' health behaviors, and to predict and explain their utilization of health service, including prescription drugs (Bhattacharya, Chatterjee, Carnahan, & Aparasu, 2011; Blalock et al., 2005; Kamble, Chen, Sherer, & Aparasu, 2008; Mehta, Nagar, & Aparasu, 2009; Smith, Boyd, & Kirking, 1999). It is normally used as conceptual framework and characterized by three distinct categories to predict factors associated with pharmacy utilization.

The purpose of Andersen's model is to discover conditions that either facilitate or impede utilization. In this study, we aim at determining whether the additional variables add additional prediction to medication adherence while adjusting for the three predictors. Meanwhile, the same factors within Andersen's model are also hypothesized to be associated with the decision to use generic substitution when facing a higher cost sharing of prescription drugs.

Chapter 4 Methods

This retrospective cohort study analyzed enrollment and pharmacy claims data maintained by a pharmacy benefit management (PBM) company. Supplements included public files (e.g., 2010 census data). This chapter introduces the data source, cohort design, and statistical models.

4.1 Database and cohort design

4.1.1 Database description

The dataset used in this study was obtained from Prime Therapeutics, LLC. (Prime), a PBM company owned by 11 Blue Cross and Blue Shield Plans in Florida, Illinois, Kansas, Minnesota, Montana, Nebraska, New Mexico, North Dakota, Oklahoma, Texas and Wyoming. Prime has benefit management responsibility for approximately 14.7 million lives. All claims and eligibility files are maintained in a health insurance portability and accountability act (HIPPA) compliant secure data warehouse. The study documents were submitted to the Institutional Review Board (IRB) at the University of Minnesota; approval was received on March 25, 2013 (see Appendix 2).

This study utilized personal-level pharmacy claims data based on a unique patient identifier. All of the enrollees included in the database belonged to employer-sponsored health insurance plans. Pharmacy claims and eligibility data were extracted and aggregated at the patient-level to create a dataset of PBM clients during the period.

At the time of data extraction, the following exclusions were applied:

(1) Persons lacking complete data enrolled in Medicaid, Medicare Part B, and Medicare Part D supplement;

(2) Persons enrolled in Medicare Part D plans;

(3) Persons enrolled in North Carolina (no benefit data available);

(3) Persons enrolled in plans with uncommon benefit designs such as 3-Tier Non Formulary Benefit Design.

The final dataset included records of more than 10,000,000 beneficiaries and their related retail prescription information from Oct. 1, 2010 until Jun. 30, 2013. The dataset included three portions: Pharmacy Claims File, Member Information File, and Benefits Information File.

Pharmacy claims file included: CAG (De-identified carried ID, Account ID and Group ID), De-identified Member ID, Date of Birth, Sex, Zip Code, Date of Service, Filled Year, Days Supply Weighted Claim Count, Days Supply, Generic Product Identifier (GPI) Number, Product Service ID (NDC), Client Claim Cost, Client Member Pay, Client Plan Pay, Plan Drug Status, Formulary Status, Generic Flag, Deliver Channel, and Drug Category.

Member information file included: CAG, De-identified Member ID, Sex, Date of Birth, Zip Code, Prospective Risk and Monthly Enrollment Status.

Benefits Information file included: CAG, Mandatory Mail, Mandatory Generic, Individual & Family Deductible Amount, Individual & Family Yearly Out-of-pocket

Maximum Limit, Copayment or Coinsurance of generics, Copayment or Coinsurance of preferred brands, Copayment or Coinsurance of non-preferred brands, Minimum Coinsurance Amount of each tier, Maximum Coinsurance Amount of each tier, and Formulary Tiers Field.

All three files contained a CAG identifier or a re-identified Member ID to link with each other.

4.1.2 Study time frame

This study established a 12-month pre- and post-implementation period based on the date when a new benefit plan was launched. The study design allowed beneficiaries to enter the study cohort up to 15 months prior to the earliest index date, but considered only 12 months of pre-implementation data.

The time frame of the study is from October 1, 2010 to June 30, 2013 (33 months). Figure 6 below shows the time frame based on the defined study periods.

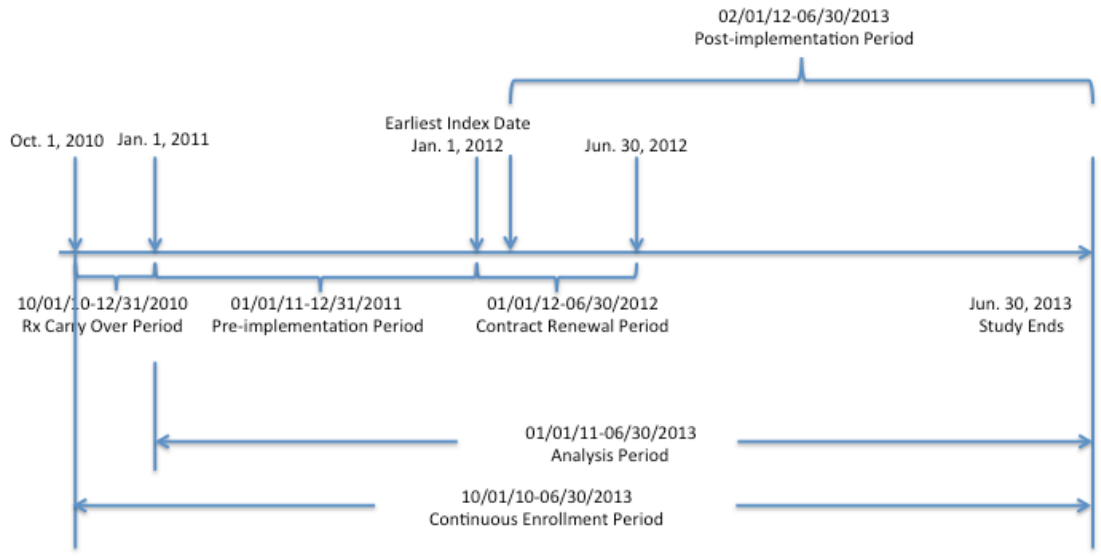


Figure 6 Study time framework

Time intervals of the time frame are defined below:

Rx carry over period (10/1/2010-12/31/2010) is a 3-month period of time utilized to account for the overlapping pharmacy claims (e.g., an early refill) and to ensure the most accurate PDC calculation during the pre-implementation period. Overlapping pharmacy claims are accessed for PDC calculation based on the assumption that the prior supply is taken fully before the new supply is initiated.

Pre-implementation period (1/1/2011-12/31/2011) is a 12-month period of time, in which the variables such as historical PDC and GDR are determined. Pre-implementation period is utilized to ratify provider determinants.

Contract renewal period/Identification period (1/1/2012-6/30/2012) is a 6-month period of time, in which pharmacy benefit plan changes were determined. The first 6 months was included to observe benefit plan changes, because the largest number of contract renewals generally happens at the beginning of the calendar year.

The index date is the first day of the month when apparent contract renewal occurred. The earliest possible index date for the study was Jan. 1, 2011. The exact implementation date for each employer was not revealed in order to protect the employers' anonymity and for small employers the anonymity of individual employees.

Post-implementation period (2/1/2012-06/30/2013) is a 12-month period of time after the month of the index date, in which the primary variables of interest, PDC and GDR, were determined. As an example, if contract renewal occurred on Jan.1, 2012, the period 2/1/2012-1/31/2013 is the post-implementation period; contract renewal on Jun. 1, 2012 has a post-implementation period of 7/1/2012- 6/30/2013.

Analysis period (1/1/2011-6/30/2013) is a 30-month period of time that includes both pre- and post-period. Beneficiaries in the study period were tracked from the date they fill their first eligible prescription and measured yearly PDC of both pre-implementation period and post-implementation period.

4.1.3 Identification of subjects

Inclusion criteria: To be included in the analytic sample, beneficiaries were required:

1) To be continuously enrolled for all 33 months of the study (Oct. 1, 2010 — Jun. 30, 2013);
2) To have benefit information included in the benefit file;

3) To have a zip code number included in the enrollment file that could be matched to 2010 census data;
4) To be 18 years of age or older at the beginning of the study period; and
5) To have retail prescriptions for diabetes, hypertension, or hyperlipidemia in the pre-implementation period, with the diagnosis determined using Medispan Generic Product Identifier (GPI) numbers included in the pharmacy claims file (see Table 4).

Three criteria were applied when selecting the primary medications of interest under study:

(1) The medications need to be identified as Centers for Medicare and Medicaid Services (CMS) adherence categories in Star Rating.
(2) The medications are limited to medications designated as chronic therapy in the Prime data file;
(3) The population of the users must be of a sufficient size to make inferences about the population at large.

Medication classes using the GPI code were used to assign beneficiaries to one or more of the three disease states. The same beneficiary could be assigned to all three-disease groups if his/her claim history had medications representing all three diseases.

Table 4 GPI codes for medications treating diabetes, hypertension, and hyperlipidemia

Oral Antidiabetes Agents	
Therapeutic Class	**GPI***
Amylin Analogs, Incretin Mimetic Agents	2715, 2717
Sulfonylureas	2720, 279970, 279978
Amino Acid Derivatives, Meglitinide Analogues, Alpha-Glucosidase Inhibitors	2723, 2728, 279950, 2750
Biguanides	2725, 279925, 279950, 279960, 279970, 279980, 279990
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors	2755, 279925, 279930, 279940
Dopamine Receptor Agonists	2757
Thiazolidinediones	2760, 279940, 279978, 279980
Sodium-Glucose Co-transporter 2 (SGLT2) Inhibitors	2770, 279960
Antihypertensive Agents	
Therapeutic Class	**GPI**
ACE Inhibitors, Angiotensin II Receptor Blockers (ARBs), Renin Inhibitors	3610, 3615, 3617, 369915, 369918, 369930, 369940, 369945, 369960, 369965, 369967
Beta Blockers	33100005, 33100007, 33100010, 33100025, 33100030, 33100040, 33100050, 3320, 3330, 369920
Calcium Channel Blockers	34, 409925, 369915, 369930, 369945
Diuretics (includes Spironolactone and Eplerenone, Acetazolamide)	3710, 3720, 3750, 3760, 379900, 369910, 369918, 369920, 369940, 369945, 369950, 369955, 369960, 369990, 3625
Miscellaneous: Vasodilators (Hydralazine, minoxidil, Nitroprusside, Fenoldopam), Clonidine, Guanfacine, Methyldopa, Alpha blockers, Phenoxybenzamine, Phentolamine, Metyrosine, Diazoxide, Mecamylamine, Metyrosine, Tolazoline	3620, 3630, 3640, 3660, 369910, 369950, 369955, 369990
Antihyperlipidemia Agents (i.e., Statins)	
Therapeutic Class	**GPI**
HMG CoA Reductase Inhibitors	3940, 399940, 409925

* GPI is a 14-character hierarchical drug classification system that consists of seven couplets including drug group, drug class, drug sub-class, drug name, drug name extension, dosage form, and strength. Products with the same GPI code are pharmaceutically equivalent.

The requirement of continuous enrollment ensures that results are not biased by differential attrition of participants and nonparticipants. The requirement of age is to make sure that the beneficiaries have the ability of making independent decision about their medications, so that their voluntary medication taking behavior can be evaluated precisely. To examine PDC changes, beneficiaries must have at least one pharmacy claim designated as chronic therapy for those three diseases and remain on the medication for at least 28 days in the pre-observation period. The requirements of at least 28 days supply is to avoid including beneficiaries who cannot tolerate the drug or for whom the drug is not effective with a small initial supply. The requirement of matching with 2010 census data enables the collection of some demographics data such as education, income, and race.

Exclusion criteria: Beneficiaries were excluded:

1) If they obtained any medications through mail-order pharmacies
2) If they had missing data in demographics or benefit information;
3) If their benefit plan changes and contract renewal occurred outside contract renewal period (1/1/2012- 6/30/2012);
4) If the information in the benefit file is not consistent with the claim adjudication identified in the prescription claims file;
5) If enrolled in CAGs with fewer than 15 beneficiaries.

4.1.4 Construction of study cohorts

Once all subjects were identified, they were classified into three-disease cohorts (Diabetes cohort, Hypertension cohort, and Hyperlipidemia cohort) if beneficiaries with claims generally used to treat these conditions.

For each disease cohort, they were further classified into two groups—beneficiaries who experienced a change in benefit design during the study period (the experimental group) and who did not experience a benefit design change (the concurrent control group). Pre and post quasi-experimental design with control group was used to assess interventions applied at the individual level. This design was chosen to avoid the impact of regression to the mean and maturation effects.

The experimental group was defined as beneficiaries who obtained prescription drugs prior to and following a contract renewal that included one or more changes to their pharmacy benefits.

In the experimental group, the study assumed the contract renewal happened between Jan.1, 2012 and Jun. 30, 2012. Beneficiaries with contract renewals that included benefit changes occurring outside the period were excluded. Since the benefit file did not provide plan renewal date, the renewal dates of all subjects were estimated based on the pharmacy claims file. For beneficiaries with benefit changes, the amount paid by beneficiaries for prescription fills would be different from the amount paid for fills of prescriptions before contract renewal (or the index date). To determine this, beneficiaries were sorted into CAGs and their claims histories were reviewed to determine the cost share differences paid prior to Jan. 1, 2012 and the period from Jan. 1, 2012 to Dec. 31, 2012. Once a cost share difference was noted for any claims by any beneficiary, all beneficiaries in the CAG were assigned to the experimental group. The

index date was determined to be the earliest date in the period from Jan. 1, 2012 and Dec. 31, 2012 when a change was identified. This assignment was considered the best option to determine the index date, because individual beneficiaries do not experience benefit design changes alone; all beneficiaries in the CAGs experience the same benefit design changes. However, this method of determining the index date requires availability of a sufficient number of adjudicated claims. In some instances, an index date could not be identified and the decision was made to exclude these CAGs.

The control group was defined as beneficiaries who obtained prescription drugs prior to and following a contract renewal that did not include evidence of a change in pharmacy benefits using the same method of index date determination described above. A random selection of three beneficiaries without benefit design changes was made using matching criteria of sex for each beneficiary in the experimental group. Prior to data analysis, the balance between the experimental and control group was verified to ensure validity of comparison.

4.2 Outcome measures

4.2.1 Measure of medication adherence

As a dependent variable, medication adherence was measured for a 12-month period of time beginning the first month following index date (i.e., the estimated contract renewal date).

Medication adherence can be measured directly or indirectly. Direct measurement includes direct measures of the drug and its metabolites in biological fluid and direct observation of drug taking behavior. Direct measurement is rarely used because of the complexity of obtaining biological samples or observing patients and the high associated costs of these methods. Indirect measures include medication monitoring (e.g., pill counts), self-report measures, and prescription claims data. Both medication monitoring and self-report measures require extra labor and, therefore, high associated costs for data collection; self-report measures carry concern about bias. This leaves claims data as a likely data source.

The use of prescription claims data is the most common approach to study refill adherence. While there are several measurement metrics to study adherence based on claims data(Christian-Herman et al., 2004; D'Souza et al., 2008; Gibson et al., 2010), medication possession ratio (MPR) and proportion of days covered (PDC) are the two recommended measures(Karve et al., 2008). MPR is defined as the sum of the days supply for all claims during a defined period of time (e.g., 12 months) divided by the number of days elapsed during the period. PDC is defined as the ratio of the number of "usable" days supplied from all refills to the total number of days following (and including) medication initiation during a determined period of time (e.g., 12 months). The rule for interpreting adherence is the same for both measures—beneficiaries with a MPR or PDC of at least 80% are considered medication adherent. Above 80% is usually considered to be the range when the medication has a likelihood of achieving the most clinical benefit.

It should be noted that MPR has been criticized for overestimating adherence since MPR is the simple summation of days of supply. In contrast, when calculating the numerator for the PDC, the researcher should create vectors to reflect the dates that are encompassed by each medication fill. The denominator for the PDC is the number of days between the first prescription claim during the analysis period and the end of the analysis period. This is considered a more accurate reflection of adherence. Additionally, more variations in MPR calculations exist than PDC. MPR is not operationally defined as consistently as PDC. The differences between those two methods are more substantial for beneficiaries taking multiple drugs within a broad class (e.g., all oral anti-diabetics) as it is in this study(Martin et al., 2009). Therefore, PDC is the preferred methodology to measure medication adherence.

In this study, medications filled to treat the target conditions (i.e., diabetes, hypertension, and hyperlipidemia) are included to calculate PDC. The method of PDC calculation as specified by the Pharmacy Quality Alliance (PQA) is shown in table 5. Interval based method with "at least one" definition was applied. Because of the limited penetration of electronic prescribing, it may be politically and practically most reasonable to use a measure that is sensitive to non-adherence(Choudhry et al., 2009).

PDC can be measured as a continuous variable, but more frequently it is reported as a categorical variable. The most common categorization is dichotomous: a PDC of 80% or above is considered as medication adherence, and a PDC of less than 80% is considered to be not adherent (Simpson & Mendys, 2010).

Table 5 PQA measure specifications of PDC

Steps	Calculation Method
1	Determine the beneficiary's measurement period, defined as the index prescription date (e.g., first fill of medication) to the end of the measurement period (e.g., Dec. 31, 2011).
2	Within the measurement period, count the days when the beneficiary is covered by at least one drug in the class (e.g., oral anti-diabetics) based on the prescription fill date and days of supply. If prescription fills for the same drug overlap, then adjust the prescription start date to be the day after the previous fill has ended. No adjustment is needed if beneficiaries are taking multiple drugs within a broad class.
3	Divide the number of covered days found in Step 2 by the number of days found in Step 1. Multiply this number by 100 to obtain the PDC (as a percentage) for each beneficiary.

An example of the PDC calculation for all oral anti-diabetes agents is shown in figure 7. For the purpose of this example, the study pre-period is calendar year 2011. As the start date of the measurement period is January 1, 2011, any prescription fills prior to that date are excluded, even though the impact of such a fill may extend into the measurement period. Thus, the 30-day supply filled on December 20, 2010 is excluded. The "at least 1" method is used in the calculation — days covered by at least one drug in the broad class during the analysis period are counted and used as the numerator. Therefore, in this example, there are 123 days covered by the prescription fills in the pre-period. The denominator is calculated as the number of days between the first fill of the medication (i.e., Jun.28, 2011) during the measurement period and the end of the pre-period (i.e., Jan.1, 2011 — Dec. 31, 2011), which is 187 days. The index date is the first day of the month when the beneficiary's contract renewed. The example assumed the index date was Jan.1, 2011. Thus, the post-period starts Feb.1 and lasts for a 12-month period (i.e., Feb.1, 2012 — Jan. 31, 2013) and the PDC for the post period is calculated.

In summary, for this example, PDC for the pre- and post-period are 65.78% and 49.02%, respectively.

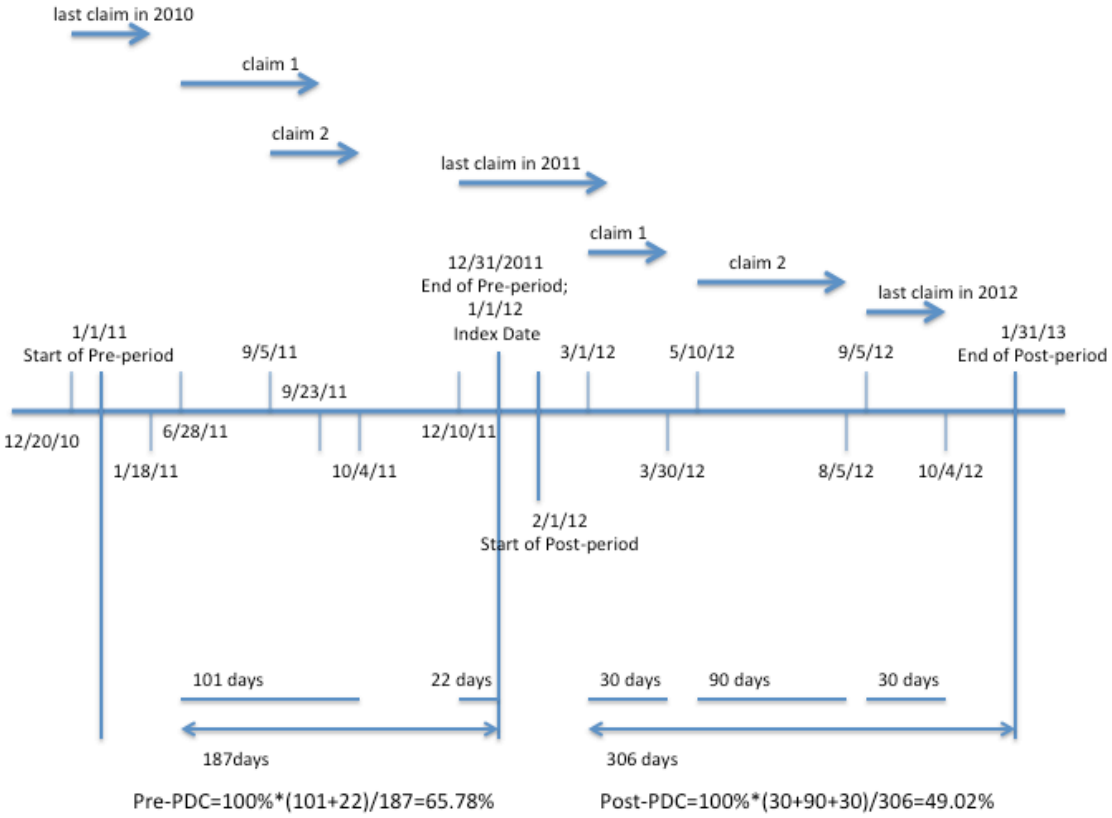


Figure 7 Prescription fill pattern and PDC calculation illustration

4.2.2 Measure of generic utilization

CMS has suggested that monitoring utilization of generic drugs would help to control drug costs and promote access to affordable prescription drugs. The generic dispensing rate (GDR) measure has been one of the most frequently reported utilization

metrics adopted as an indicator of pharmacy benefit performance, and has become a key performance metric for CMS and managed care organizations.

The GDR performance metric is derived by dividing the total number of generic prescriptions by the total number of prescriptions dispensed per beneficiary in a given period. This metric takes into account all dispensed drugs regardless of whether they have a generic equivalent or not. All drug fills were adjusted to a supply weighted claim count (1 weighted claim count equals to a 30-day equivalent prescription). The method of GDR calculation in this study is showed in table 6.

Table 6 GDR measures

Steps	Calculation Method
1	Determined the beneficiary's measurement period; pre-period was defined as a calendar year before the index date (e.g., Jan. 1, 2011 — Dec. 31, 2011); post-period was defined as a calendar year after the month of index date (e.g., Feb.1, 2012 — Jan. 31, 2013).
2	Within the measurement period (e.g., pre-period), sum the supply weighted claim count of each generic claim for each beneficiary.
3	Within the measurement period (e.g., pre-period), sum the supply weighted claim count of each claim for each beneficiary.
4	Divide the number found in Step 2 by the number in Step 3. Multiply this number by 100 to obtain the GDR for each beneficiary.

4.3 Measure of predictors

Hypothesis 1 proposes to identify whether any benefit changes would have affected medication adherence or generic utilization. A dummy indicator was thus designed to assess benefit design changes.

Hypothesis 2 proposes to identify factors among cost sharing strategies that were associated with study outcomes. A series of categorical variables were created to indicate the changes in cost sharing strategies.

4.3.1 Benefit design changes

A dummy indicator was used to allow tracking of beneficiaries who were in experimental group, experiencing one or more benefits changed during the process of contract renewal. Beneficiaries who had any changes in benefits during allowable contract renewal period were selected into the experimental group.

4.3.2 Changes in cost sharing strategies

A series of categorical variables were created to indicate the changes in cost sharing strategies among all tiers, including the indicators of copayment and coinsurance. Further explanations of those variables are as follow:

1) Three categorical variables indicated the change trends of copayment for generics, preferred brands, and non-preferred brands respectively;
2) Three categorical variables indicated the change trends of coinsurance for generics, preferred brands, and non-preferred brands respectively.

4.4 Measure of control variables

Using Andersen's behavioral model of health services utilization, the control variables in this study were classified into three categories: predisposing characteristics, enabling resources, and need factors.

4.4.1 Predisposing characteristics

Age: Age was identified at the beginning of the pre-intervention period (i.e., Jan. 1, 2011) from the member information file. It was calculated as an integer from the date of birth until Jan.1, 2011.

Sex: Sex (male/female) was also identified from member information file.

Education: Because beneficiaries' educational level was not available from the dataset, education was identified from the Census 2010 Data based on the beneficiary's zip code of residence.

Race: Because beneficiaries' race information was not available in the dataset, race was identified from the Census 2010 Data based on the beneficiary's zip code of residence.

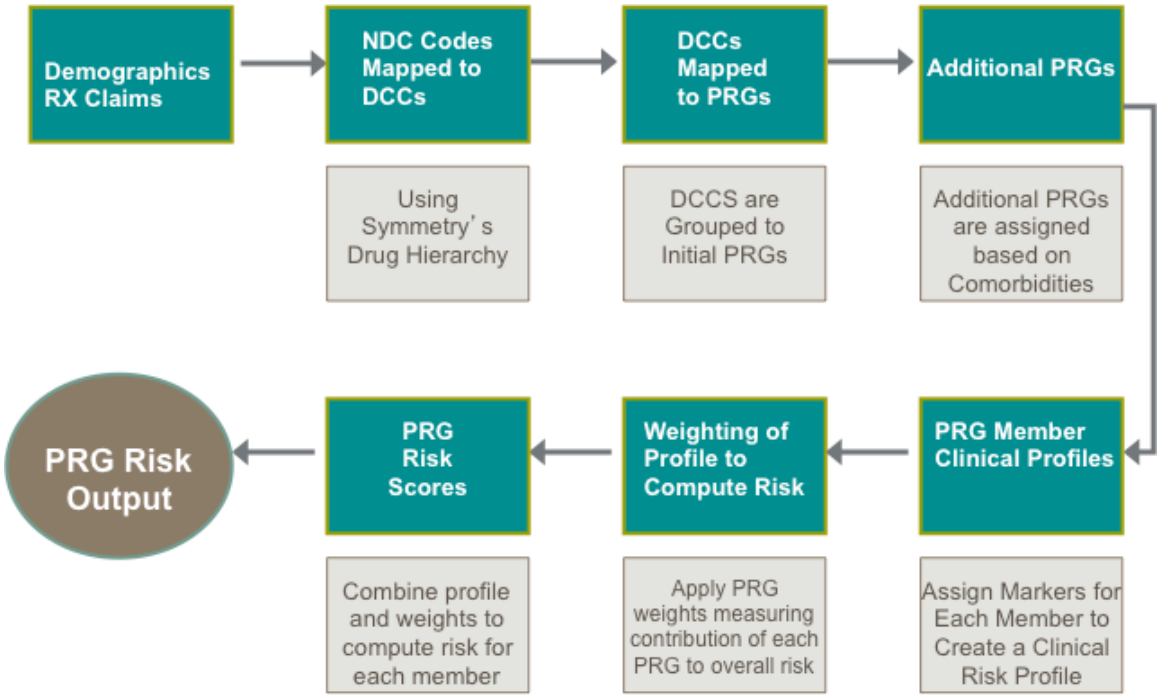
4.4.2 Enabling resources

Household income: As beneficiaries' income information was not available from the dataset, median household income from the 2010 U.S. Census was identified based on the beneficiary's zip code of residence.

4.4.3 Need factors

Prospective Risk Score was provided by Prime to assess a beneficiary's "health risk". The calculation of prospective risk score is based on Optum Symmetry Pharmacy Risk Groups® (PRG). The PRG should be considered as a proxy for severity of illness. It is determined using proprietary algorithms based on filled prescription claims data during the year prior to the index date, and predicts future resource use and expenditure and thus allows for risk adjustment in the absence of medical claims data. A relative risk score of 1.0 indicates average risk, above 1.0 indicates higher than average risk, and below 1.0 indicates lower than average risk. It has been used to illuminate the effect of disease severity on episode costs because of its established predictive ability and industry acceptance(Liliedahl, Finch, Axene, & Goertz, 2010).

The illustration below (Figure 8) provides an overview of the PRG process to calculate prospective risk score. The PRG risk output is named as the prospective risk score in this study.



*From: INGENIX symmetry pharmacy risk groups concepts guide version 7.6

Figure 8 Pharmacy risk score calculation process

Number of medications is defined as the total number of unique medications taken by the beneficiary in the pre-intervention period. Because the number of pharmacy visits that beneficiaries make to pick up prescriptions (the extent of prescribing and filling complexity) was association with adherence(Choudhry et al., 2011), number of medications was included as a control variable in this study. For analysis purpose, the variable was calculated based on Product Service ID in the claims file and categorized into four levels.

Table 7 shows the definitions and measures for each study variable.

Table 7 Definitions and measures of dependent and independent variables

Dependent Variables	**Measurement**	**Operationalization**
Adherence	PDC: The ratio of the number of days with at least one retail refill to the total number of calendar days following (and including) medication initiation during a determined period of time (i.e., pre- and post-period).	0: PDC<80%; 1: PDC>=80%; Dichotomous; Or 0—100%; Continuous
Generic utilization	GDR: The total number of retail generic prescription claims dispensed divided by the total number of retail prescription claims for the beneficiary during a determined period of time (i.e., pre- and post-period).	0—100%; Continuous

Predictor Variables	**Definition**	**Measure**	**Operationalization**
Benefit design changes	One or more benefits (e.g., deductible, copayment, coinsurance, OOP limits, mandatory mail, or mandatory generic) changed during contract renewal.	A categorical indicator is used to allow tracking of beneficiaries who were in the experimental group.	1: Experimental Group; 0: Control Group; Dichotomous
Copayment	The amount paid by the beneficiary at the counter, including copays for generics, preferred brands, and non-preferred brands.	A categorical variable indicate the change trend of copayment for generics, preferred brands, and non-preferred brands.	Categorical: -1: Decrease; 0: No changes; 1: Increase
Coinsurance	The percentage amount paid by the beneficiary at the counter, including coinsurance for generics, preferred brands, and non-preferred brands.	A categorical variable indicate the change trend of coinsurance for generics, preferred brands, and non-preferred brands.	Categorical: -1: Decrease; 0: No changes; 1: Increase

Control Variables	**Definition**	**Measure**	**Operationalization**
Age	The age of the beneficiary on Jan. 1, 2011.	An integer calculated from the date of birth until Jan. 1, 2011	Continuous
Sex	The gender of the beneficiary according to the enrollment file.	Male/Female	1: Male; 0: Female; Dichotomous

Education	The percentage of residents that obtained bachelor's degree or above in the individual's home zip code area.	Percentage of adults >= 25 years of age with >=college education; Census 2010 data based on individual's home zip codes.	0—100%; Continuous
Race	The percentage of residents those were white in the individual's home zip code area.	Percentage of individuals self-reporting white; Census 2010 data based on individual's home zip codes.	0—100%; Continuous
Income	Median household income in the individual's home zips code area.	A categorical variable indicated whether the median household income was above $50,000 or not; Census 2010 data based on individual's home zip codes.	0: Median Income<$50,000; 1: Median Income>$50,000; Dichotomous
Number of medications	Total number of different medications in the pre-intervention period (i.e., 12 months).	A categorical variable indicated the level of medications consumed.	Categorical: 0: 1-5; 1: 6-10 2: 10-15; 3: >=16
Prospective Risk Score	It is the member's pharmacy risk group for the 12 months (i.e., 2012) directly following the claims experience period (i.e., 2011).	A continuous variable with higher numbers indicating higher risk.	Continuous (Range: 0.0324-74.8423)

4.5 Statistical analysis

All statistical analyses were conducted using SAS Version 9.2 (SAS Institute Inc., Cary, NC, USA). The significance level was set at 0.001(2-tailed), a more rigorous

significance level to take into account of the large sample size identified (Lin, Lucas, & Shmueli, 2013).

4.5.1 Descriptive analysis

Descriptive statistics were used to summarize patient demographics, as well as the measures of medication adherence and generic utilization. Numbers, percentages, and odds ratio were provided for dichotomous or categorical variables. Means, range, standard deviations (S.D.), minimum values, 25% percentiles, medians, 75% percentiles, and maximum values were calculated for continuous variables.

Two-group tests were applied to make comparisons of changes (e.g., Post-PDC minus Pre-PDC) in the outcomes in the experimental and control group. Student's t tests were used for continuous outcomes (PDC and GDR) and Chi-square tests were used for count outcomes (e.g., number of adherent beneficiaries). These two-group tests offer simplicity and straightforward interpretability of the results, but do not adjust for confounders without multiple levels of stratification. Additionally, two-group tests detect changes in adherence levels but not changes in trends.

4.5.2 Regression

Multi-variate techniques were employed to examine the difference in PDC and GDR between the two identified groups taking into account of confounding variables. Both general linear regression and logistic regression were conducted.

Some researchers use simple ordinary least square regression with a Gaussian distributional assumption because of the simplicity of this technique. Some critics point out that the use of linear regression violates both normality and homoscedasticity assumptions, and therefore, should conduct Tobit, NLS (nonlinear least squares), Fractional Logit models, Beta regression, or Simplex regression to handle proportional outcomes like those in this study. However, assumptions of these alternative regression techniques could still be violated since they too carry assumptions of normality or homoscedasticity.

The two-limit Tobit model is one of the most recommended models when handling proportion outcomes. A fundamental argument against its censoring assumption is that values out of [0, 1] is not a result of the censorship but due to the fact that they are not defined. Tobit model is also based on normal distribution and subject to homoscedasticity.

A Logit model (e.g., a logistic function of GDR/(1 − GDR)), Beta regression, and Simplex regression are generally used with the open interval of (0, 1). But in this study, a sufficient number of beneficiaries might have PDC or GDR equaled to 1, which makes it more complex to use any of these other regression techniques.

When counting numbers of binary outcomes of a Bernoulli distributed random process, it might be appropriate to model proportion with the assumption of binomial error structure, such as logistic regression. However, when using the proportion to

standardize and relativize continuous data, there is not unanimous consensus on either the distributional assumption or the modeling practice. Therefore, in this study, general linear regression modeling is the most robust model and was conducted to estimate medication adherence and generic utilization. To estimate the effect of policy changes, dummy indicators were used to allow tracking of beneficiaries who were in control group. Those indicators are the primary variables of interest.

To address this controversy a multiple logistic regression with categorized PDC was also conducted. Logistic regression model was conducted to quantify the relationship between medication adherence and benefit changes, allowing for statistical control of known confounders.

Data on income, education, and race were obtained by linking beneficiaries' ZIP codes of residence with 2010 Census data from the US Census Bureau. The census data specified the median income, percentage of bachelor degree, and percentage of white among the geographic population associated with each ZIP code. In the study, income was dichotomized as being more or less than $50,000.

4.5.2.1 General linear model (GLM)

GLM were used for continuous normally distributed outcomes, such as PDC and GDR. GLM included a constant term, a binary indicator for exposure (such as having or not having benefit design changes), and adjusted variables for beneficiary's age, sex, race, income, education, number of prescriptions, and comorbidity burden (using

prospective risk score) as of the date of their cohort entry. Parameter estimates were presented. 95% confidence intervals (CI) and associated P-values were reported as well.

4.5.2.2 Logistic regression

When logistic regression was conducted, PDC was defined as a dichotomous variable (e.g., PDC >= 80%). The logistic regression model also included predictor variables ─ beneficiary's age, sex, race, income, education and prospective risk as of the date of their cohort entry as defined previously.

Only variables with a p-value of less than 0.001 were considered significant. Statistically significant variables were presented and reported as adjusted odds ratio (ORs); 95% confidence intervals (CI) and associated P-values were also reported as well.

4.6 Ethical considerations

A limited data set was received after all direct individual identifiers were removed from the data according to the requirements of HIPAA. It is impossible to identify an individual through the information provided by the dataset used in this study. The study was approved by University of Minnesota's Institutional Review Board (See Appendix 2).

Chapter 5 Results

This chapter presents the results of statistical analysis. Study subjects and their general characteristics, descriptive statistics of variables, and results of the three statistical models.

5.1 Data extraction and cohort construction

5.1.1 Data extraction

Figure 9 shows the beneficiary selection flowchart leading to the definitions of the three-study cohorts (diabetes, hypertension, and hyperlipidemia). There were more than 10,000,000 records of beneficiaries in the member file. Among them, 3,074,370 eligible beneficiaries continuously enrolled from Oct. 1, 2010 to Dec. 31, 2013. Among these continuously enrolled beneficiaries, 96,013 beneficiaries had no benefit records or zip code information; 737,825 beneficiaries were less than 18 years of age on Jan.1, 2011; 33,009 beneficiaries' demographic data could not be matched to 2010 census data. Thus, leaving 2,207883 beneficiaries.

Among the remaining 2,207883 beneficiaries, there were a total of 79,430,151 prescription records during the observation period. Among those fill records, 24,684,755 claims were prescribed for the chronic diseases diabetes, hypertension and hyperlipidemia. 73.73% (18,200,665) of the claims were retail orders. As a result,

577,725 beneficiaries with pharmacy claims indicative of the three diseases were identified.

One final exclusion criterion was applied at this stage. In order to study adherence as proposed in this study, PDC in 2011 could not be 0; therefore, beneficiaries were required to have at least one prescription claim for a drug indicative of the study diseases in 2011. The number of qualified beneficiaries was thus reduced to 450,899; 77,511 beneficiaries had prescription claims for diabetes drugs, 360,768 beneficiaries had prescription claims for hypertension drugs, and 206,258 beneficiaries had prescription claims for hyperlipidemia drugs.

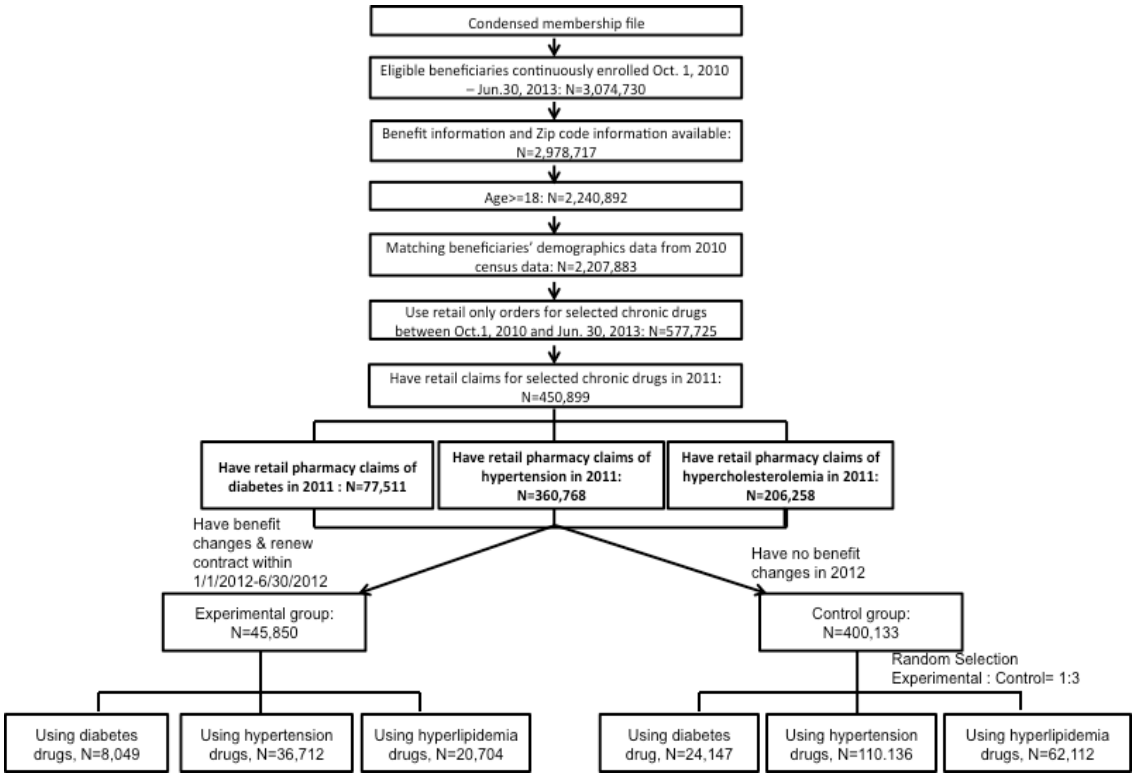


Figure 9 The beneficiary flowchart

Contract renewal dates were estimated as described in Chapter 4 (Methods). From 2011 to 2012, there were 7,483 different types of benefit plan changes. Beneficiaries with benefit plan changes but a contract renewal date that occurred outside of the specified study period were excluded. Some beneficiaries identified with benefit changes had claims records with amounts paid after the contract renewal date that were inconsistent with the amount paid before the contract renewal and were excluded from the final sample. In addition, about 5% of beneficiaries identified with benefit changes were excluded because the cost sharing benefits included in the benefit information file were inconsistent with the dollar amounts included in their prescription claim files.

5.1.2 Cohort construction

Table 8 summarizes beneficiaries' medication claims for the drug therapy classes of interest in the pre-period. Beneficiaries with anti-hypertension agents accounted for the largest proportion (46.14%); beneficiaries taking both anti-diabetes agents and anti-hyperlipidemia (statins) agents accounted for the smallest proportion (1.52%). Beneficiaries were enrolled into a disease cohort as long as their prescription claims history included claims for drugs that treated the disease (i.e., a beneficiary could be assigned to more than one disease cohort depending on his/her prescription claims history). For example, 4.95% of the subjects taking both anti-diabetic agents and anti-hypertensive agents were enrolled into both the diabetes and hypertension cohorts.

Table 8 Beneficiaries' medications taken in the pre-period

Drugs taken by beneficiaries	Number of Beneficiaries	Percent
Anti-diabetes agents	14,013	3.14
Anti-hypertension agents	205,762	46.14
Anti-hyperlipidemia agents	68,372	15.33
Anti-diabetes agents & Anti-hypertension agents	22,065	4.95
Anti-diabetes agents & Anti-hyperlipidemia agents	6,772	1.52
Anti-hypertension agents & Anti-hyperlipidemia agents	95,204	21.35
Anti-diabetes agents & Anti-hypertension agents & Anti-hyperlipidemia agents	33,795	7.58

Figure 10 shows the selected beneficiaries with plan changes and contract renewal within the first six months of 2012. A total of 45,850 beneficiaries met the criteria and were enrolled into the experimental groups. Beneficiaries (400,133) without benefit changes were about 9 times more than the experimental group. Therefore, the final control groups were randomly selected and were three times the number of those in the experimental group for each disease cohort respectively.

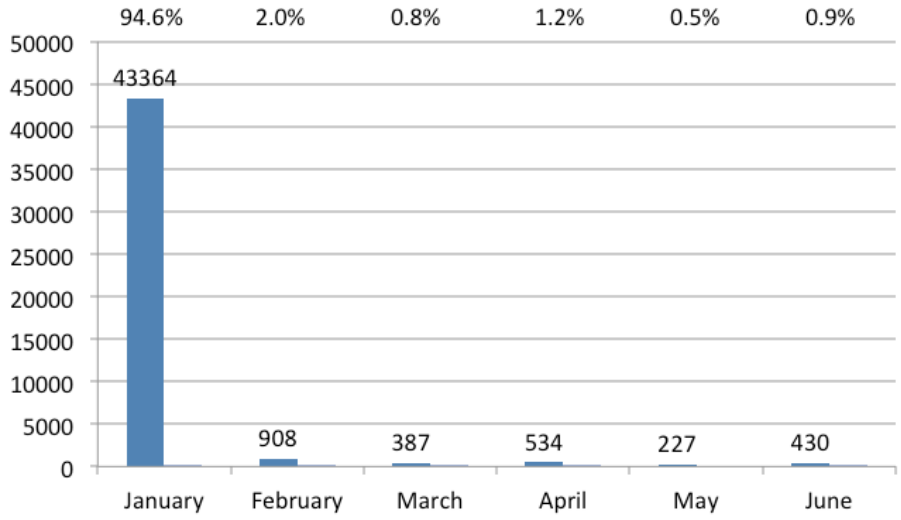


Figure 10 Number of beneficiaries with plan changes occurring in the first 6 months of 2012

For the experimental group, beneficiaries' tier structures are shown in table 9. More beneficiaries were in plans with one tier in pre-intervention period compared to pre-intervention period. One possible explanation for this finding is that more and more beneficiaries have chosen to enroll in high deductible health plans.

Table 9 Tier changes of the selected population in experimental group

Tier structure	**Pre-Period**		**Post-Period**	
	Frequency	Percent%	Frequency	Percent%
1	4,677	10.20	4,815	10.50
2	5,118	11.60	5,342	11.65
3	36,055	78.63	35,683	77.82

The number of beneficiaries and their retail copayment designs in 2011 and 2012 are shown in table 10. A zero dollar copayment most likely indicates that a beneficiary's prescription drug benefits design included a coinsurance design for prescription drugs. It might also indicate no copayment needed for those drugs (about 10%). For generic drugs, the most common copayment designs in 2011 were $5, $8, $10, $15, $20 and $25, while the most commonly occurring copayment designs in 2012 were $4, $5, $7.5, $10, $15, and $20. For preferred brand name drugs, the most common copayment designs in 2011 were $20, $25, $30, $35, and $40, while the most commonly occurring in 2012 were $20, $30, $35, $40, and $50. For non-preferred brand name drugs, the most common copayment designs in 2011 were $20, $35, $40, $45, $50, and $60, while the most commonly occurring in 2012 were $20, $50, and $60.

Table 10 Beneficiaries and their retail copayment designs in pre- and post-period

Copayment design for generic drugs (Tier 1)$	**Frequency in Pre-period**	**Frequency in Post-period**
0	11,160	14,569
2	14	0
3	3	52
4	4	1033
4.5	0	1
5	5995	4033
5.5	1	0
6	36	0
7	50	10
7.5	11	969
8	1047	122
9	99	6
10	18119	12521
11	6	5
12	19	15
12.5	6	0
13	1	0
14	190	0
15	6916	10684
18	35	0
20	1086	1750
25	1042	57
30	10	23
Copayment design for preferred brand drugs (Tier 2)$	**Frequency in 2011**	**Frequency in 2012**
0	12948	14594
3	0	1
4.5	0	1
5	1	0
5.5	1	0
7	1	0
7.5	2	0
8	6	0
9	5	0
10	310	8
11	213	0
12	43	210

15	497	108
20	4792	3066
24	2	9
25	10965	1585
26	2	2
29	1	3
30	8848	11927
35	3901	5557
36	35	0
40	2043	6039
45	21	239
50	1164	2422
60	48	79
75	1	0
Copayment design for non-preferred brand drugs (Tier 3)$	**Frequency in 2011**	**Frequency in 2012**
0	13434	15112
4.5	0	1
5.5	1	0
8	1	1
9	3	0
10	12	2
11	210	0
12	19	210
15	29	39
20	2200	2050
22	29	0
24	0	7
25	116	13
26	3	0
30	506	81
35	2043	610
40	3945	979
45	3937	1616
48	2	2
50	12750	8254
55	1697	918
57	35	0

The coinsurance designs and frequency of each design from 2011to 2012 are shown in table 11. A zero percent coinsurance most likely indicates that a beneficiary's

prescription benefits design included a copayment for prescription drugs or that no coinsurance payment was needed for associated drugs (less than 5%). For generic drugs, the most common coinsurance designs in 2011 were 10%, 15%, 20%, 25%, and 30%, while the most common ones in 2012 were 10%, 15%, 20%, and 30%. For preferred brand name drugs, the most common coinsurance designs in both 2011 and 2012 were 10%, 20%, 25%, 30%, and 50%. For non-preferred brand name drugs, the most common coinsurance designs in 2011 were 10%, 20%, 25%, 35%, 40%, and 50%, while the most common ones in 2012 were 20%, 30%, 35%, and 50%.

Table 11 beneficiaries and their retail coinsurance designs in 2011 and 2012

Coinsurance design for generic drugs (Tier 1)%	**Frequency in 2011**	**Frequency in 2012**
0	36069	35885
5	5	0
10	2458	2110
15	1567	2888
20	3494	3839
25	1188	239
30	657	586
40	3	6
50	277	251
100	132	46
Coinsurance design for preferred brand drugs (Tier 2)%	**Frequency in 2011**	**Frequency in 2012**
0	33995	33601
10	1728	1856
15	8	42
20	2233	2872
25	4179	2382
30	1234	2923
35	1537	1498
40	48	85
50	553	528
60	196	10

100	139	53
Coinsurance design for non-preferred brand drugs (Tier 3)%	**Frequency in 2011**	**Frequency in 2012**
0	33521	34464
10	1705	515
15	8	42
20	2024	2378
25	1132	462
30	722	1331
35	1584	1399
40	1012	595
45	124	959
50	3646	3406
55	1	0
60	232	246
100	139	53

A total of 8164 CAGs with benefit changes were included in this study. Among them, 4393 CAGs changed mainly in the amount of copayment or percentage of coinsurance (type 1); 1116 CAGs changed from high deductible health plan with no cost sharing to benefit plans with cost sharing structures (type 2); 1450 CAGs changed from benefit plans with cost sharing structures to high deductible health plan with no cost sharing (type 3); and 1205 CAGs kept high deductible benefit designs with no cost sharing but changed the family or individual deductible amount (type 4).

Table 12-15 shows the cost sharing changes and deductible amount changes for the four types. For type 1 (see Table 12), the average copayment of generics slightly increased from $12.1 to $12.6; the average coinsurance of generics slightly decreased from 26.4% to 23.7%; the average copayment of preferred brands increased from $30.1 to $35.4; the average coinsurance of preferred brands decreased from 30.1% to 27.2%;

the average copayment of non-preferred brands increased from $48.7 to $56.6; the average coinsurance of non-preferred brands decreased from 42.7% to 36.3%.

Table 12 Copayment and coinsurance changes of CAGs in type 1 from 2011 to 2012

	Minimum		Median		Maximum		Mean ± S.D.	
	2011	2012	2011	2012	2011	2012	2011	2012
Copayment of generics ($)	0	0	10	10	30	30	12.1±4.6	12.6 ±4.8
Coinsurance of generics (%)	0	0	25	20	100	100	26.4 ±15.8	23.7 ±14.6
Copayment of preferred brands ($)	5	3	30	35	75	70	30.1±8.8	35.4 ±7.6
Coinsurance of preferred brands(%)	10	10	25	25	100	100	30.1±15.5	27.2 ±15.7
Copayment of non-preferred brands ($)	5	4.5	50	60	105	110	48.7±12.8	56.6 ±12.0
Coinsurance of non-preferred brands(%)	10	10	50	30	100	100	42.7 ±15.9	36.3 ±18.8

For type 2 (see Table 13), some high deductible health plans with no cost sharing strategies changed to deductible health plans with cost sharing strategies. The average family deductible amount decreased from $6242.7 to $3337.1; the average individual deductible amount decreased from $3119.6 to $1298.2; the average copayment of generics became $11.0; the average coinsurance of generics became 19.9%; the average copayment of preferred brands became $35.4; the average coinsurance of preferred brands became 25.9%; the average copayment of non-preferred brands became $55.4; the average coinsurance of non-preferred brands became 35.9%.

Table 13 Copayment, coinsurance and deductible changes of CAGs in type 2 from 2011 to 2012

	Minimum		Median		Maximum		Mean ± S.D.	
	2011	2012	2011	2012	2011	2012	2011	2012
Family deductibles ($)	2400	60	6000	3000	11900	20000	6242.7 ±1818.5	3337.1 ±2424.8
Individual deductibles ($)	1200	25	3000	1200	5950	10000	3119.6 ±909.7	1298.2 ±1307.0
Copayment of generics ($)		0		10		20		11.0±3.8
Coinsurance of generics (%)		0		20		100		19.9±15.0
Copayment of preferred brands ($)		15		35		60		35.4±8.7
Coinsurance of preferred brands(%)		10		20		100		25.9±16.3
Copayment of non-preferred brands ($)		15		50		100		55.4±15.1
Coinsurance of non-preferred brands(%)		10		30		100		35.9±20.0

For type 3 (see Table 14), some deductible health plans with cost sharing strategies changed to high deductible health plans with no cost sharing strategies. The average family deductible amount increased from $3259.1 to $7328.4; the average individual deductible amount increased from $1204.3 to $3699.6; the average copayment of generics was $11.0 in 2011; the average coinsurance of generics was 22.7% in 2011; the average copayment of preferred brands was $31.5 in 2011; the average coinsurance of preferred brands was 26.7% in 2011; the average copayment of non-preferred brands was $51.5 in 2011; the average coinsurance of non-preferred brands was 33.2% in 2011.

Table 14 Copayment, coinsurance and deductible changes of CAGs in type 3 from 2011 to 2012

	Minimum		Median		Maximum		Mean ± S.D.	
	2011	2012	2011	2012	2011	2012	2011	2012
Family deductibles ($)	60	1000	3000	6000	40000	22500	3259.1±2603.4	7328.4±2223.3

Individual deductibles ($)	25	500	1000	3000	20000	10000	1204.3±1330.1	3699.6±1196.8
Copayment of generics ($)	0		10		30		11.0±4.4	
Coinsurance of generics (%)	0		20		100		22.7±20.2	
Copayment of preferred brands ($)	5		30		60		31.5±8.8	
Coinsurance of preferred brands(%)	10		20		100		26.7±18.3	
Copayment of non-preferred brands ($)	10		50		100		51.5±14.2	
Coinsurance of non-preferred brands(%)	10		20		100		33.2±21.0	

For type 4 (see Table 15), some high deductible health plans with no cost sharing strategies changed family or individual deductible amount. The average family deductible amount decreased from $7574.4 to $6611.6; the average individual deductible amount decreased from $3841.1 to $3311.7.

Table 15 Deductible changes of CAGs in type 4 from 2011 to 2012

	Minimum		Median		Maximum		Mean ± S.D.	
	2011	2012	2011	2012	2011	2012	2011	2012
Family deductibles ($)	2400	2000	7000	6000	22500	12000	7574.4±2245.3	6611.6±2140.8
Individual deductibles ($)	1200	250	3500	3000	7500	10000	3841.1±1138.2	3311.7±1196.3

5.2 Descriptive statistics of study variables

5.2.1 Descriptive statistics of dependent variables

Two dependent variables were identified for this study—medication adherence (measured as PDC) and generic utilization (measured as GDR) in the post-intervention period following contract renewal. This section presents the descriptive statistics for these two variables.

5.2.1.1 Medication adherence

Medication adherence was measured as Proportion of Days Covered (PDC), which was defined as the percentage of the number of days in the measurement period covered by at least one prescription claim for a drug treating the disease. In this study, the measurement period was a 12-month period of time beginning the first month after the month of the beneficiary's index date. This definition follows the recommendations of PQA as identified in Chapter 4 (Methods).

Table 16 presents the information concerning PDC during the 12 months after the index date (identified as "post-PDC" for the table). In each cohort, PDC was calculated at the disease level (i.e., for diabetes, all oral diabetes drugs were included; for hypertension, all hypertension drugs were included; for hyperlipidemia, all statin agents were included) for both the control and experimental groups. On average, regardless of disease cohort beneficiaries acquired medications to cover approximately 80% of the 12 months of treatment. The PDCs of the experimental groups in all three cohorts were lower than the PDCs of the control groups. These differences, however, are not statistically significant. Based on the common definition of medication adherence (PDC>=80%), more than 60% of the beneficiaries were classified with adequate adherence in all three cohorts.

Table 16 Descriptive statistics of medication adherence (measured as PDC) in post-intervention period

Post-PDC	Diabetes		Hypertension		Hyperlipidemia	
	Control	Exper	Control	Exper	Control	Exper
Mean ± S.D.	79.4±21.7%	78.8±22.1%	84.3±19.4%	83.8±19.5%	79.6±20.3%	79.5±20.4%
Minimum	8.3%	8.3%	1.7%	3.4%	4.6%	8.9%
25% Quartile	67.5%	66.2%	78.3%	77.6%	70.0%	70.1%
Median	88.3%	87.8%	92.8%	92.2%	87.7%	87.5%
75% Quartile	96.2%	96.2%	97.4%	97.2%	94.8%	94.8%
Maximum	100%	100%	100%	100%	100%	100%
PDC>=80 %, n (%)	11,869 (63.0%)	3,904 (62.0%)	66,385 (73.3%)	21,723 (72.4%)	30,697 (63.9%)	10,211 (63.7%)

5.2.1.2 Generic utilization

Generic utilization was measured as the generic dispensing rate (GDR), which was defined as the percent of prescriptions in the measurement period dispensed using generic products for each beneficiary. In this study, the measurement period was 12 months after a beneficiary's index date. This definition is the most common definition used among pharmacy benefit managers and other managed care organizations as identified in Chapter 4 (Methods).

Table 17 presents the information concerning GDR. In each cohort, GDR was calculated at the individual level for both the control and experimental groups. The mean GDR was greater than 75% for all three cohorts. There are only small differences in the GDR between the experimental groups and control groups within each disease cohort. These differences are not statistically significant.

Table 17 Descriptive statistics of generic utilization (measured as GDR) in post-intervention period

Post-GDR	Diabetes		Hypertension		Hyperlipidemia	
	Control	Exper	Control	Exper	Control	Exper
Mean ± S.D.	75.1±21.8%	75.1±21.5%	80.2±22.8%	80.1±22.8%	76.7±24.3%	76.7±23.9%
Minimum	0%	0%	0%	0%	0%	0%
25% Quartile	61.3%	61.3%	67.6%	67.1%	62.7%	62.5%
Median	78.5%	78.0%	88.2%	88.0%	82.8%	82.4%
75% Quartile	94.43%	94.3%	100%	100%	100%	100%
Maximum	100%	100%	100%	100%	100%	100%

5.2.2 Descriptive statistics of benefit design changes

Benefit design changes that alter a beneficiary's cost-share, and thereby influent a beneficiary's adherence to prescribed medication and his/her decision to use generic alternatives to brand name medications is the primary focus of this study. This study has two measurement periods for these variables, the 12-month period prior to the index date and the 12-month period after the index date. Benefit designs and the related cost-sharing strategies for these two periods were identified for the experimental group in each of the three cohorts. This section provides information about the benefit design changes experienced by the experimental group.

5.2.2.1 Benefit design changes of the experimental group

Tables 18, 19, and 20 present the benefit designs of the experimental group in the pre- and post-intervention period for the diabetes, hypertension, and hyperlipidemia cohorts, respectively.

For all three cohorts, the vast majority of beneficiaries (more than 99%) did not have a mandatory mail requirement or a mandatory generic substitution requirement in either the pre- or post-intervention periods. A large number of beneficiaries did not have a deductible design (around 60%) or a maximum OOP limitation (around 80%). A large percent of beneficiaries had a copayment design (around 75% had a copayment design for generics).

The pharmacy benefit design of coinsurance only was uncommon. There were, however, a large number of beneficiaries having a mix of coinsurance and copayment designs. Beneficiaries with a copayment plus coinsurance design usually had a fixed copayment for generic products and a coinsurance design for brand products. For example, 25.8% of the beneficiaries had a coinsurance design for non-preferred brand name drugs while 76% of beneficiaries had a copayment design for generics in the pre-period. Compared to the pre-period, fewer beneficiaries had a design of minimum coinsurance amount while more had a design of maximum coinsurance amount in the post-period.

Overall, the benefit design changes from pre-intervention period to post-intervention period were very similar among all three cohorts. Differences in benefit designs between the pre-period and post-period were tested using Chi-square. In general, significant differences were noted in the proportion of beneficiaries with mandatory generic, deductibles, copayments and coinsurance levels. There are some differences

between disease cohorts however. The significant changes that are noted are due to large sample size and may not represent meaningful differences. For example, in the hypertension cohort (Table 16), the proportion of beneficiaries with mandatory mail design decreased from 0.3% in the pre-period to 0.2% in the post-period. The absolute difference is only 0.1%.

Table 18 Beneficiaries with benefit design changes in the pre- and post-intervention period in diabetes cohort

Benefit designs	Pre-period	Post-period	P-value
Mandatory mail			
Yes	23(0.3%)	6(0.07%)	0.0016
No	8,026(99.7%)	8,043(99.93%)	
Mandatory Generic			
Yes	5(0.06%)	52(0.6%)	<0.0001*
No	8,044(99.94%)	7,997(99.4%)	
Deductible			
Medical & Pharmacy Deductible	683(8.5%)	929(11.5%)	<0.0001*
Pharmacy Only Deductible	1,882(23.4%)	1,875(23.3%)	
No deductible	5,484(68.1%)	5,245(65.2%)	
Maximum OOP limitation			
Medical & Pharmacy OOP	990(12.3%)	927(11.5%)	0.0970
Pharmacy Only OOP	388(4.8%)	434(5.4%)	
No OOP	6,671(82.9%)	6,688(83.1%)	
1-tier Copayment			
Yes	6117(76.0%)	5503(68.4%)	<0.0001*
No	1932(24.0%)	2546(31.6%)	
2-tier Copayment			
Yes	5867(72.9%)	5620(69.8%)	<0.0001*
No	2182(27.1 %)	2429(30.2%)	
3-tier Copayment			
Yes	5813(72.2%)	5566(69.1%)	<0.0001*
No	2236(27.8%)	2483(30.9%)	

1-tier Coinsurance			
Yes	1734(21.5%)	1724(21.4%)	0.8478
No	6315(78.5 %)	6325(78.6 %)	
1-tier Minimum Coinsurance			
Yes	814(10.1%)	770(9.6%)	0.2443
No	7235(89.9%)	7279(90.4%)	
1-tier Maximum Coinsurance			
Yes	349(4.3%)	684(8.5%)	<0.0001*
No	7700(95.7%)	7365(91.5%)	
2-tier Coinsurance			
Yes	2028(25.2%)	2117(26.3%)	0.1087
No	6021(74.8%)	5932(73.7%)	
2-tier Minimum Coinsurance			
Yes	1023(12.7%)	853(10.6%)	<0.0001*
No	7026(87.3%)	7196(89.4%)	
2-tier Maximum Coinsurance			
Yes	628(7.8%)	1287(16.0%)	<0.0001*
No	7421(92.2%)	6762(84.0%)	
3-tier Coinsurance			
Yes	2081(25.8%)	1961(24.4%)	0.0292
No	5968(74.2%)	6088(75.6%)	
3-tier Minimum Coinsurance			
Yes	1064(13.2%)	884(11.0%)	<0.0001*
No	6985(86.8%)	7165(89.0%)	
3-tier Maximum Coinsurance			
Yes	659(8.2%)	1332(16.5%)	<0.0001*
No	7,390(91.8%)	6,717(83.5%)	

Table 19 Beneficiaries with benefit design changes in the pre- and post-intervention period in hypertension cohort

Benefit designs	Pre-period	Post-period	P-value
Mandatory mail			
Yes	121(0.3%)	55(0.2%)	<0.0001*
No	36,591(99.7%)	36,657(99.8%)	
Mandatory Generic			
Yes	38(0.1%)	265(0.7%)	<0.0001*

No	36,674(99.9%)	36,447(99.3%)	
Deductible			
Medical & Pharmacy Deductible	3,715(10.1%)	5,202(14.2%)	<0.0001*
Pharmacy Only Deductible	8,573(23.4%)	8,487(23.1%)	
No deductible	24,424(66.5%)	23,023(62.7%)	
Maximum OOP limitation			
Medical & Pharmacy OOP	4,585(12.5%)	5,001 (13.6%)	<0.0001*
Pharmacy Only OOP	1,988(5.4%)	2,157(5.9%)	
No OOP	30,139(82.1%)	29,554(80.5%)	
1-tier Copayment			
Yes	27900(76.0%)	25091(68.3%)	<0.0001*
No	8812(24.0%)	11621(31.7%)	
2-tier Copayment			
Yes	26577(72.4%)	25317(69.0%)	<0.0001*
No	10135(27.6%)	11395(31.0%)	
3-tier Copayment			
Yes	26200(71.4%)	24916(67.9%)	<0.0001*
No	10512(28.6%)	11796(32.1%)	
1-tier Coinsurance			
Yes	7761(21.1%)	7867(21.4%)	0.3392
No	28951(78.9%)	28845(78.6%)	
1-tier Minimum Coinsurance			
Yes	3119(8.5%)	2912(7.9%)	0.0054
No	33593(91.5%)	33800(92.1%)	
1-tier Maximum Coinsurance			
Yes	1665(4.5%)	2815(7.7%)	<0.0001*
No	35047(95.5%)	33897(92.3%)	
2-tier Coinsurance			
Yes	9308(25.4%)	9602(26.2%)	0.0131
No	27404(74.6%)	27110(73.8%)	
2-tier Minimum Coinsurance			
Yes	4149(11.3%)	3302(9.0%)	<0.0001*
No	32563(88.7%)	33410(91.0%)	
2-tier Maximum Coinsurance			

Yes	3055(8.3%)	5205(14.2%)	<0.0001*
No	33657(91.7%)	31507(85.8%)	
3-tier Coinsurance			
Yes	9678(26.4%)	8946(24.4%)	<0.0001*
No	27034(73.6%)	27766(75.6%)	
3-tier Minimum Coinsurance			
Yes	4441(12.1%)	3559(9.7%)	<0.0001*
No	32271(87.9%)	33153(90.3%)	
3-tier Maximum Coinsurance			
Yes	3287(8.9%)	5563(15.1%)	<0.0001*
No	33425(91.1%)	31149(84.9%)	

Table 20 Beneficiaries with benefit design changes in the pre- and post-intervention period in hyperlipidemia cohort

Benefit designs	Pre-period	Post-period	P-value
Mandatory mail			
Yes	35(0.2%)	24 (0.1%)	0.1518
No	20,669(99.8%)	20,680(99.9%)	
Mandatory Generic			
Yes	18(0.1%)	145 (0.7%)	<0.0001*
No	20,686(99.9%)	20,559(99.3%)	
Deductible			
Medical & Pharmacy Deductible	2,280(11.0%)	3,096(15.0%)	<0.0001*
Pharmacy Only Deductible	4,607(22.3%)	4,523(21.8%)	
No deductible	13,817(66.7%)	13,085(63.2%)	
Maximum OOP limitation			
Medical & Pharmacy OOP	2,754(13.3%)	2,973(14.4%)	0.0002*
Pharmacy Only OOP	1,220(5.9%)	1,334 (6.4%)	
No OOP	16,730(80.8%)	16,397(79.2%)	
1-tier Copayment			
Yes	15528(75.0%)	14086(68.0%)	<0.0001*
No	5176(25.0%)	6618(32.0%)	
2-tier Copayment			
Yes	14671(70.9%)	13970(67.5%)	<0.0001*

No	6033(29.1%)	6734(32.5%)	
3-tier Copayment			
Yes	14467(69.9%)	13749(66.4%)	<0.0001*
No	6237(30.1%)	6955(33.6%)	
1-tier Coinsurance			
Yes	4510(21.8%)	4590(22.2%)	0.3424
No	16194(78.2%)	16114(77.8%)	
1-tier Minimum Coinsurance			
Yes	1706(8.2%)	1603(7.7%)	0.0619
No	18998(91.8%)	19101(92.3%)	
1-tier Maximum Coinsurance			
Yes	988(4.8%)	1645(7.9%)	<0.0001*
No	19716(95.2%)	19059(92.1%)	
2-tier Coinsurance			
Yes	5502(26.6%)	5663(27.3%)	0.0746
No	15202(73.4%)	15041(72.7%)	
2-tier Minimum Coinsurance			
Yes	2360(11.4%)	1926(9.3%)	<0.0001*
No	18344(88.6%)	18778(90.7%)	
2-tier Maximum Coinsurance			
Yes	1883(9.1%)	3066(14.8%)	<0.0001*
No	18821(90.9%)	17638(85.2%)	
3-tier Coinsurance			
Yes	5698(27.5%)	5215(25.2%)	<0.0001*
No	15006(72.5%)	15489(74.8%)	
3-tier Minimum Coinsurance			
Yes	2520(12.2%)	2073(10.0%)	<0.0001*
No	18184(87.8%)	18631(90.0%)	
3-tier Maximum Coinsurance			
Yes	2017(9.7%)	3261(15.7%)	<0.0001*
No	18687(90.3%)	17443(84.3%)	

5.2.2.2 Cost sharing design changes of the experimental group

Table 21 summarizes beneficiaries' cost sharing changes among the three study cohorts. None of the changes in cost sharing designs had significant differences at the p-value of 0.001:

1) 1-tier copayment: A large percent of beneficiaries (around 44%) stayed at the same copayment design for generic drugs. Some beneficiaries (around 31%) had an increase in generics copayment while a smaller amount of beneficiaries (around 25%) had a decrease in copayment design for generics.

2) 2-tier copayment: More than a half of the beneficiaries (around 51%) changed to a design with higher copayment for preferred brand name drugs. Only a minority of the beneficiaries (around 7%) had a decrease in the amount of copayment.

3) 3-tier copayment: Just as with the 2-tier copayment, a large percent of the beneficiaries (around 42%) changed to a design with higher copayment for non-preferred brand name drugs. Only a minority of the beneficiaries (around 7%) had a decrease in the amount of copayment.

4) 1-tier coinsurance: A small number of beneficiaries (around 5%) underwent a decrease in coinsurance rate compared to those (around 4%) who underwent an increase in the coinsurance rate for generic drugs.

5) 2-tier coinsurance: The number of beneficiaries with an increase in the percent of coinsurance was twice the number of beneficiaries with a decrease in percent of coinsurance of preferred brands.

6) 3-tier coinsurance: The number of beneficiaries with an increasing copayment design was similar to the number of beneficiaries with a decreasing copayment design of non-preferred brands.

Table 21 Changes in cost sharing strategies in the experimental group

Design	Diabetes Cohort	Hypertension Cohort	Hyperlipidemia Cohort	P-value
1-tier Copayment				
Decrease	2000(24.9%)	9057(24.7%)	4888(23.6%)	0.0049
No changes	3525(43.8%)	16018(43.6%)	9344(45.1%)	
Increase	2524(31.3%)	11637(31.7%)	6472(31.3%)	
2-tier Copayment				
Decrease	562(7.0%)	2665(7.3%)	1414(6.8%)	0.0781
No changes	3378(42.0%)	15234(41.5%)	8815(42.6%)	
Increase	4109(51.0%)	18813(51.2%)	10475(50.6%)	
3-tier Copayment				
Decrease	612(7.6%)	2802(7.6%)	1473(7.1%)	0.1097
No changes	4078(50.7%)	18662(50.8%)	10457(50.5%)	
Increase	3359(41.7%)	15248(41.5%)	8774(42.4%)	
1-tier Coinsurance				
Decrease	382(4.8%)	1853(5.0%)	1055(5.1%)	0.0026
No changes	7370(91.5%)	33289(90.7%)	18680(90.2%)	
Increase	297(3.7%)	1570(4.3%)	969(4.7%)	
2-tier Coinsurance				
Decrease	268(3.3%)	1342(3.7%)	777(3.8%)	0.2094
No changes	7241(90.0%)	32858(89.5%)	18446(89.1%)	
Increase	540(6.7%)	2512(6.8%)	1481(7.1%)	
3-tier Coinsurance				
Decrease	514(6.4%)	2556(7.0%)	1524(7.4%)	0.0112
No changes	6979(86.7%)	31503(81.8%)	17630(85.1%)	
Increase	556(6.9%)	2653(7.2%)	1550(7.5%)	

5.2.3 Descriptive statistics of control variables

Control variables were identified based on Andersen's behavioral model of health services utilization. They were classified into three categories as described in Chapter 4 (Methods). Age, sex, comorbidity (measured as prospective risk score), number of medications, pre-PDC, and pre-GDR were measured at the individual level. Race,

education and income information were not available at the individual level and were measured using 2010 census data at the 5-digit ZIP code level reported in the member enrollment file.

Tables 22, 23, and 24 show the descriptive statistics of control variables in the diabetes, hypertension, and hyperlipidemia cohorts, respectively. The distributions of control variables were similar for all three-disease cohorts.

For all disease cohorts, age, income, and number of medications were significantly different ($p < 0.001$) between the control and experimental groups. Beneficiaries in the control groups were slightly older than those in the experimental groups. These differences, while statistically significant, were judged not to be particularly meaningful being differences of 1 year (diabetes cohort) or less (hypertension and hyperlipidemia cohorts).

Slightly more than half of the beneficiaries were female in the diabetes and hypertension cohorts; more than half of the beneficiaries were male in hyperlipidemia cohort. These differences are not statistically significant, however.

The zip code level data is also shown in Table 22, 23, and 24. Using the diabetes cohort as an example, in the five-digit zip code areas where the study subjects in the control group lived, 25.2% of zip code residents who were 25 years of age or older had a college degree or higher; 76.2% reported their race as white; 46.8% had a median household income more than $50,000. Beneficiaries in the experimental group with diabetes may have higher incomes since in general they live in zip code areas where 51.2% of residents had a median household income more than $50,000.

The variable "number of medications" measured the number of unique medications taken by each beneficiary during the pre-period. A large percent of beneficiaries (around 40%) took six to ten unique medications. On average, beneficiaries in the diabetes cohort took more unique prescription drugs during the pre-period (see Table 25).

There were not significant differences in pre-PDC and pre-GDR between the control group and experimental group for any disease cohort. A large percent of beneficiaries (more than 60%) had high medication adherence in the pre-intervention period among all three cohorts. Except for the hypertension cohort, less than half of the beneficiaries had a high percentage of generic use.

Table 22 Descriptive statistics of control variables in diabetes cohort

Control Variables	Control group	Experimental group	P-value
Age, (mean ± S.D.)	51.8±11.1	50.8±10.6	<0.0001*
Sex, n (%)			
Female	12,325(51.0%)	4,108(51.0%)	1.000
Male	11,822(49.0%)	3,941(49.0%)	
Race (% White), (mean ± S.D.)	76.2±21.0%	75.9±18.8%	0.9604
Education (% Bachelor's Degree or above), (mean ± S.D.)	25.2±14.7%	26.8±15.0%	0.7965
Median income, n (%)			
$0 - $50,000	12,845(53.2%)	3,926(48.8%)	<0.0001*
> $50,000	11,302(46.8%)	4,123(51.2%)	
Comorbidity (Prospective Risk Score), (mean ± S.D.)	4.5±3.0	4.5±2.9	0.9953
Number of medications,			

n (%)			
1-5	5,991(24.8%)	1,829(22.7%)	<0.0001*
6-10	10,124 (41.9 %)	3,343(41.5%)	
11-15	5,261 (21.8%)	1,840(22.9%)	
>=16	2,771(11.5%)	1,035(12.9%)	
Pre-GDR, (mean ± S.D.)	71.7±22.8%	70.8±22.8%	0.2447
Pre-PDC, (mean ± S.D.)	80.6±20.4%	80.3±20.6%	0.9573
Pre-PDC >= 80%, n(%)	12,115 (64.3%)	4,046(64.3%)	0.9742

Table 23 Descriptive statistics of control variables in hypertension cohort

Control Variables	Control group	Experimental group	P-value
Age, (mean ± S.D.)	51.7±11.1	50.5±10.6	<0.0001*
Sex, n (%)			
Female	57795(52.5%)	19265(52.5%)	1.000
Male	52341(47.5%)	17447(47.5%)	
Race (% White), (mean ± S.D.)	78.3±20.2%	77.8±18.4%	0.9319
Education (% Bachelor's Degree or above), (mean ± S.D.)	27.4±15.9%	29.0±16.0%	0.8015
Median income, n (%)			
$0 - $50,000	54181(50.9%)	16716(45.5%)	<0.0001*
> $50,000	52341(49.1%)	19996(54.5%)	
Comorbidity (Prospective Risk Score), (mean ± S.D.)	3.3±2.9	3.3±3.0	0.5517
Number of medications			
1-5	45475(41.3%)	14804(40.3%)	<0.0001*
6-10	40536(36.8%)	13564(37.0%)	
11-15	16565(15.0%)	5582(15.2%)	
>=16	7560(6.9%)	2754(7.5%)	
Pre-GDR, (mean ± S.D.)	77.0±24.4%	76.4±24.6%	0.9201
Pre-PDC, (mean ± S.D.)	84.7±18.5%	84.3±18.8%	0.9377
Pre-PDC >= 80%,	66,742 (73.7%)	21,877(72.9%)	0.8579

n(%)			

Table 24 Descriptive statistics of control variables in hyperlipidemia cohort

Control Variables	Control group	Experimental group	P-value
Age, (mean ± S.D.)	54.1±9.4	53.2±9.0	<0.0001*
Sex, n (%)			
Female	26090(42.0%)	8737(42.2%)	0.6229
Male	36022(58.0%)	11967(57.8%)	
Race (% White), (mean ± S.D.)	79.7±18.5%	79.1±17.0%	0.9165
Education (% Bachelor's Degree or above), (mean ± S.D.)	28.9±16.7%	30.5±16.7%	0.8044
Median income, n (%)			
$0 - $50,000	28559(46.0%)	8611(41.6%)	<0.0001*
> $50,000	33553(54.0%)	12093(58.4%)	
Comorbidity (Prospective Risk Score), (mean ± S.D.)	3.7±2.8	3.7±2.8	0.4006
Number of medications			
1-5	25080(40.4%)	8156(39.4%)	0.0012
6-10	23219(37.4%)	7695(37.2%)	
11-15	9391(15.1%)	3239(15.7%)	
>=16	4422(7.1%)	1610(7.8%)	
Pre-GDR, (mean ± S.D.)	70.1±26.9%	69.7±26.7%	0.9508
Pre-PDC, (mean ± S.D.)	80.6±19.0%	80.5±19.2%	0.9857
Pre-PDC >= 80%, n(%)	31,277 (65.1%)	10,443(65.1%)	0.9535

Table 25 Descriptive characteristics of number of medications among the three-disease cohorts

Number of medications	Diabetes		Hypertension		Hyperlipidemia	
	Control	Exper	Control	Exper	Control	Exper
Mean ± S.D.	9.5±5.2	9.9±5.2	7.7±4.9	7.8±5.0	7.7±4.9	7.8±5.0

Minimum	1	1	1	1	1	1
25% Quartile	6	6	4	4	4	4
Median	9	9	7	7	7	7
75% Quartile	12	13	10	10	10	10
Maximum	138	57	89	45	138	57

5.3 Preliminary analysis of PDC and GDR

A preliminary analysis was conducted to determine the general relationship between pre- and post-PDC and pre- and post-GDR. Experimental and control within group differences were tested for each disease cohort.

The results of the Z-tests show a general pattern that is similar across disease cohorts. Mean pre-PDC is significantly higher than post-PDC, and mean pre-GDR is significantly lower than post-GDR for both control and experimental groups (see Table 26).

Table 26 Results of Z-test

Tests	Diabetes		Hypertension		Hyperlipidemia	
	Control	Exper	Control	Exper	Control	Exper
Z-test (post-PDC – pre-PDC)						
Mean	-1.16%	-1.47%	-0.39%	-0.43%	-1.05%	-1.00%
P-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
Z-test (post-GDR – pre-GDR)						
Mean	3.53%	4.49%	3.43%	3.89%	6.69%	7.03%
P-value	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*

5.4 Results of regression analyses

For these analyses, the dependent variables are PDC and GDR in the post-intervention period. Results from two regression analysis methods are presented. For general linear models, post-PDC and post-GDR are analyzed as continuous variables. For logistic regression models, PDC is categorized as a dichotomous variable (i.e., 1:PDC>=80%, 0:PDC<80). A model was constructed for each dependent variable for each disease cohort. For the analysis of PDC, some beneficiaries were excluded because PDC values of 0 were found after the establishment of the contract renewal date.

The regression analyses were completed in two steps. In the first step, the impact of ***any*** benefit plan changes on PDC and GDR were estimated—a total of 6 models for PDC and 3 models for GDR. In the second step, the impacts of the cost sharing strategies of copayment and coinsurance specifically were estimated in the experimental group—a total of 6 models for PDC and 3 models for GDR as well.

Each model included the same set of predictor variables—the predictor variable of primary interest being group (experimental or control) in step 1. In step 2, the variable of primary interest was cost sharing strategies in the experimental group. Other variables believed to have an influence on PDC and/or GDR were identified from literature or based on availability in the claims files and included in the models. The one exception was the non-inclusion of "number of medications" in the GDR models. This was because the total number of prescription claims is also the denominator of the outcome variable GDR.

5.4.1 Step1—Regression analyses in the comparison groups

5.4.1.1 Medication adherence

Table 27 summarizes the results from general linear regression (GLM) and multiple logistic regressions. The results of general linear regressions and multiple logistic regressions share similarity in all three-disease cohorts.

1) PDC in Diabetes

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the mean of post-PDC between the control group and the experimental group is not significantly different from 0 (PE=0.002; p=0.3506). PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-diabetes agents.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the odds of being adherent in the post period is not significantly different between the control group and the experimental group (OR=1.041; p =0.2572).) PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract

renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-diabetes agents.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, race, and number of unique medications. After controlling for other factors, post-PDC will increase by 0.575 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.002($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.02($p<0.001$) for male beneficiaries; post-PDC will increase by 0.044 ($p<0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area; compared to beneficiaries who took the number of unique medications above 15, beneficiaries who took the number of unique medications between 1 to 5 medications in pre-period will increase post-PDC by 0.001 ($p<0.001$); beneficiaries who took the number of unique medications between 6 to 10 medications in pre-period will increase post-PDC by 0.002 ($p<0.001$).

Other significant variables in logistic regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, race, and number of unique medications. After controlling for all other factors, beneficiaries who were adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 780% (OR=8.8, 95% CI=[8.281, 9.351], $p<0.001$) compared to beneficiaries who were not adherent in pre-intervention period; the odds of adherence will increase by 2.8% (OR=1.028, 95%CI=[1.025, 1.031], $p<0.001$) with a one-year increase of age and by 79.2% (OR=1.792, 95%CI=[1.546, 2.077], $p<0.001$) with every unit increase in the percentage of population reporting white only in the

beneficiary's five-digit zip code area. Male beneficiary will increase the odds of adherence by 28.3% (OR=1.283, 95%CI=[1.207, 1.364], p<0.001). The larger number of unique medications (>15 medications) taken in the pre-intervention period was associated with increased medication adherence in the post-intervention period (p<0.001). If every thing else is held constant, compared to beneficiaries who took the number of unique medications above 15, beneficiaries who took the number of unique medications under 6 (1-5 medications in pre-period) the odds of adherence will decrease by 24.8%((1-0.752)*100%); beneficiaries who took the number of unique medications between 6 to 10, the odds of adherence will decrease by 8.6%((1-0.914)*100%); beneficiaries who took the number of unique medications between 11 to 15, the odds of adherence will decrease by 3.1%((1-0.969)*100%).

2) PDC in hypertension

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the mean of post-PDC between the control group and the experimental group is not significantly different from 0 (PE=0; p=0.958). PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-hypertension agents.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the odds of being adherent in the post period is not significantly different between the control group and the experimental group (OR=1.001; p =0.967). PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-hypertension agents.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, race, and prospective risk scores. After controlling for other factors, post-PDC will increase by 0.572 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.002($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.006($p<0.001$) for male beneficiaries; post-PDC will increase by 0.038 ($p<0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area; post-PDC will increase by 0.002 for every unit increase in prospective risk score.

Other significant variables in logistic regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, race, and prospective risk scores. After controlling for other factors, beneficiaries who were adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 998% (OR=10.98, 95% CI=[10.66, 11.33]) compared to beneficiaries who were not adherent in pre-intervention period; the odds of adherence will increase by 2.9% (OR=1.029, 95%CI=[1.028, 1.031] $p<0.001$) with a one-year

increase of age, and by 83.5% (OR=1.835, 95%CI=[1.703, 1.978] p<0.001) with 1% increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area. Male beneficiary will increase the odds of adherence by 11.4% (OR=1.114, 95%CI=[1.081, 1.149]). The odds of adherence will increase by 2.8% (OR=1.028, 95%CI=[1.021, 1.035]) with a unit increase in Prospective Risk Score.

3) PDC in hyperlipidemia

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the mean of post-PDC between the control group and the experimental group is not significantly different from 0 (PE=-0.001; p=0.355). PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-hyperlipidemia agents.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the odds of being adherent in the post period is not significantly different between the control group and the experimental group (OR=0.992; p =0.702). PDC in the post-period was not significantly different between beneficiaries in the control group (no benefit changes at contract renewal) and those in the experimental group (having at least one change in benefit design at contract

renewal). The conclusion is that benefit design changes were not significantly associated with adherence to anti-hyperlipidemia agents.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, education level, income, and race. After controlling for other factors, post-PDC will increase by 0.550 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.002($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.010($p<0.001$) for male beneficiaries; post-PDC will increase by 0.028 ($p<0.001$) for every unit increase in the percentage of population graduated from college or above in the beneficiary's five zip code area; post-PDC will increase by 0.054 ($p<0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area.

Other significant variables in logistic regression: There are other variables significant in predicting adherence including pre-PDC, age, sex, education level, income, and race. After controlling for other factors, beneficiaries who were adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 709.4% (OR=8. 094, 95% CI=[7.797, 8.402]) compared to beneficiaries who were not adherent in pre-intervention period; the odds of adherence will increase by 2.5% (OR=1.025, 95%CI=[1.022, 1.027] $p<0.001$) with a one-year increase of age, and by 117.3% (OR=2.173, 95%CI=[1.957, 2.414] $p<0.001$) with 1% increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area. Male beneficiary will increase the odds of adherence by 14.5% (OR=1.145, 95%CI=[1.102, 1.189]). The odds of adherence will increase by 7.6%

(OR=1.076, 95%CI=[1.029, 1.125]) if beneficiaries live in an area with median household income above $50,000.

Table 27 Results of regression analyses for PDC in step 1

Variables	General linear regression				Multiple Logistic Regression			
	PE[#]	95% CI		P-value	OR	95% CI		P-value
Diabetes [1,2]								
Benefit Change: Control vs. Experimental	0.002	0.003	0.008	0.3506	1.041	0.971	1.116	0.2572
Pre-PDC	0.575	0.563	0.585	<0.001*	8.800	8.281	9.351	<0.001*
Age	0.002	0.002	0.002	<0.001*	1.028	1.025	1.031	<0.001*
Prospective Risk Score	0.001	-0.001	0.001	0.3739	0.998	0.985	1.011	0.7930
Male vs. Female	0.020	0.015	0.024	<0.001*	1.283	1.207	1.364	<0.001*
% of pop. With >= college degree	0.016	-0.001	0.034	0.0674	1.353	1.060	1.726	0.0152
Income >=$50,000 vs. Income < $50,000	-0.001	-0.006	0.004	0.6859	1.005	0.934	1.080	0.9027
% of pop. Self-reporting White	0.044	0.033	0.055	<0.001*	1.792	1.546	2.077	<0.001*
1-5 medications in pre-period vs. >15 medications	-0.010	-0.019	-.001	0.0021	0.752	0.662	0.854	<0.001*
6-10 medications in pre-period vs. >15 medications	0.001	-0.007	0.009	<0.001*	0.914	0.817	1.021	<0.001*
11-15 medications in pre-period vs. >15 medications	0.002	-0.006	0.010	<0.001*	0.969	0.866	1.084	<0.001*
Hypertension [3,4]								
Benefit Change: Control vs. Experimental	0.000	-0.002	0.002	0.958	1.001	0.967	1.036	0.967
Pre-PDC	0.572	0.567	0.577	<0.001*	10.98	10.66	11.33	<0.001*
Age	0.002	0.002	0.002	<0.001*	1.029	1.028	1.031	<0.001*
Prospective Risk Score	0.002	0.002	0.002	<0.001*	1.028	1.021	1.035	<0.001*
Male vs. Female	0.006	0.005	0.008	<0.001*	1.114	1.081	1.149	<0.001*
% of pop. With >= college degree	0.004	-0.002	0.011	0.209	1.115	0.995	1.249	0.062
Income >=$50,000 vs. Income < $50,000	0.002	0.000	0.004	0.082	1.027	0.990	1.065	0.154
% of pop. Self-reporting White	0.038	0.033	0.042	<0.001*	1.835	1.703	1.978	<0.001*

1-5 medications in pre-period vs. >15 medications	0.002	-0.003	0.006	0.471	1.005	0.934	1.081	0.129
6-10 medications in pre-period vs. >15 medications	0.005	0.002	0.009	0.007	1.063	0.992	1.139	0.019
11-15 medications in pre-period vs. >15 medications	0.005	0.001	0.009	0.022	1.050	0.977	1.128	0.245
Hyperlipidemia [5,6]								
Benefit Change: Control vs. Experimental	-0.001	-0.005	0.002	0.355	0.992	0.950	1.035	0.702
Pre-PDC	0.550	0.543	0.557	<0.001*	8.094	7.797	8.402	<0.001*
Age	0.002	0.002	0.002	<0.001*	1.025	1.022	1.027	<0.001*
Prospective Risk Score	0.000	0.000	0.001	0.558	0.998	0.989	1.006	0.563
Male vs. Female	0.010	0.007	0.013	<0.001*	1.145	1.102	1.189	<0.001*
% of pop. With >= college degree	0.028	0.019	0.037	<0.001*	1.400	1.228	1.596	<0.001*
Income >=$50,000 vs. Income < $50,000	0.006	0.002	0.009	0.001*	1.076	1.029	1.125	0.001*
% of pop. Self-reporting White	0.054	0.046	0.061	<0.001*	2.173	1.957	2.414	<0.001*
1-5 medications in pre-period vs. >15 medications	0.001	-0.006	0.007	0.875	0.985	0.901	1.076	0.244
6-10 medications in pre-period vs. >15 medications	0.002	-0.004	0.008	0.491	1.013	0.933	1.101	0.732
11-15 medications in pre-period vs. >15 medications	0.003	-0.003	0.009	0.277	1.033	0.948	1.125	0.238

PE=Parameter Estimate

*Denotes being statistically significant.

1. $\chi^2(11)=1185.98$,p-value<0.0001, $R^2=0.3306$
2. LR $\chi^2(11)=6947$, p-value<0.0001, Pseudo $R^2=0.3426$
3. $\chi^2(11)=24042.3$,p-value<0.0001, $R^2=0.3432$
4. LR $\chi^2(11)=11866.56$,p-value<0.0001, Pseudo $R^2=0.3375$
5. $\chi^2(11)=2410.85$,p-value<0.0001, $R^2=0.2935$
6. LR $\chi^2(11)=31692.95$,p-value<0.0001, Pseudo $R^2=0.2914$

4) Summary

The findings among all the models regarding the association between benefit design changes and PDC are consistent. All models indicated no significant association between adherence and benefit design changes.

Four control variables are significant across all three-disease cohorts including pre-PDC, age, sex, and race. Number of unique medications taken is only associated with medication adherence to anti-diabetes agents; prospective risk score is only associated with adherence to anti-hypertension agents; Median household income and percent of population graduated from college or above in the beneficiary's zip code area are only associated with anti-hyperlipidemia agents.

5.4.1.2 Generic utilization

Table 28 summarizes the results from general linear regression (GLM) of generic dispensing rate in the post period. The results of GLM indicate similarity in all three-disease cohorts.

1) GDR in diabetes

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of benefit changes for generic dispensing rate is -0.007 (p=0.0002), suggests that with all other variables held constant, mean post-GDR in the control group was 0.007 lower than the experimental group.

Benefit design changes are significantly associated with an increase in generic utilization of anti-diabetes agents.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.684 ($p<0.001$); for every unit increase in Prospective Risk Score, generic dispensing rate in the post period will decrease by 0.004($p<0.001$).

2) GDR in hypertension

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of benefit change for generic dispensing rate is -0.004 ($p<0.001$), suggests that with all other variables held constant, mean post-GDR in the control group is 0.004 lower than the experimental group. Benefit design changes are significantly associated with an increase in generic utilization of anti-diabetes agents.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR, age, education, income, and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.700 ($p<0.001$); when age of the beneficiary increases by one year, post-GDR will increase but with limited amount (close to 0, $p<0.001$); for every unit increase in Prospective Risk Score, generic dispensing rate in the post period will decrease by 0.003($p<0.001$); beneficiaries with median household income equal to or

higher than 50,000 dollars in the individual's zip code area will increase post-GDR by 0.005 ($p<0.001$).

3) GDR in hyperlipidemia

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of benefit change for generic dispensing rate is -0.003 ($p=0.028$), suggests that with all other variables held constant, mean post-GDR in the control group is 0.003 lower, but not significant, than the experimental group.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR, age, race, income, and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.638 ($p<0.001$); when age of the beneficiary increases by one year, post-GDR will increase by 0.001 ($p<0.001$); for every unit increase in Prospective Risk Score, generic dispensing rate in the post period will decrease by 0.005($p<0.001$); beneficiaries with median household income equal to or higher than 50,000 dollars in the individual's zip code area will increase post-GDR by 0.006 ($p<0.001$) compared to beneficiaries with median household income lower than 50,000 dollars in the individual's zip code area; for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area, post-GDR will increase 0.014 ($p<0.001$).

Table 28 Results of regression models of GDR in step 1

Variables	Parameter Estimates	95% Confidence Intervals		p-value
Diabetes[1]				
Control vs. Experimental	-0.007	-0.011	-0.003	0.0002*
Pre-GDR	0.684	0.677	0.692	<0.001*
Age	0.000	0.000	0.001	0.002
Prospective Risk Score	-0.004	-0.005	-0.003	<0.001*
Male vs. Female	-0.001	-0.004	0.003	0.656
% of pop. With >= college degree	-0.013	-0.027	0.0001	0.005
Income >=$50,000 vs. Income < $50,000	0.002	-0.002	0.006	0.328
% of pop. Self-reporting White	0.004	-0.005	0.012	0.430
Hypertension [2]				
Benefit Change: Control vs. Experimental	-0.004	-0.005	-0.002	<0.001*
Pre-GDR	0.700	0.697	0.703	<0.001*
Age	0.000	0.000	0.000	<0.001*
Prospective Risk Score	-0.003	-0.003	-0.003	<0.001*
Male vs. Female	0.000	-0.002	0.001	0.857
% of pop. With >= college degree	-0.015	-0.021	-0.009	<0.001*
Income >=$50,000 vs. Income < $50,000	0.005	0.004	0.007	<0.001*
% of pop. Self-reporting White	0.006	0.002	0.010	0.002
Hyperlipidemia[3]				
Benefit Change: Control vs. Experimental	-0.003	-0.006	0.000	0.028
Pre-GDR	0.638	0.634	0.642	<0.001*
Age	0.001	0.000	0.001	<0.001*
Prospective Risk Score	-0.005	-0.006	-0.005	<0.001*
Male vs. Female	0.002	0.000	0.004	0.092

% of pop. With >= college degree	-0.002	-0.010	0.007	0.664
Income >=$50,000 vs. Income < $50,000	0.006	0.003	0.009	<0.001*
% of pop. Self-reporting White	0.014	0.007	0.021	<0.001*

*Denotes being statistically significant.
1. $\chi^2(8)$=,p-value<0.0001, R^2 =0.5226
2. $\chi^2(8)$=,p-value<0.0001, R^2 =0.5737
3. $\chi^2(8)$=,p-value<0.0001, R^2 =0.5054

4) Summary

The findings among all the models regarding the association between benefit design changes and generic dispensing rate are not consistent across three diseases cohorts. There are significant associations between generic utilization of anti-diabetes and anti-hypertension agents and benefit design changes, but not a significant association between benefit design changes and generic utilization of anti-hyperlipidemia agents in the post-intervention period.

Two control variables are significant across all three-disease cohorts including pre-GDR and prospective risk score. Age is also significant across all three-disease cohorts at the level of 0.005. Percentage of population graduated from college or above in the zip code area is only significantly associated with generic use of anti-hypertension agents. Median household income is associated with generic use of anti-hypertension and anti-hyperlipidemia agents. Percentage of self reported white only in the zip code area is only associated with generic use of anti-hyperlipidemia agents. Sex is the only variable that is not significantly associated with any use of generic drug.

5.4.2 Step 2—Results of regression in the experimental group

The dependent variables are PDC and GDR (proportion outcome) in the post-intervention period of the experimental group for general linear models, categorized PDC of the experimental group (i.e., 1:PDC>=80%, 0:PDC<80%) in the post period for multiple logistic regressions. An independent model was constructed for each dependent variable. Each model included the same set of independent variables and control variables, except that control variable "number of medications" was dropped when predicting GDR. Beneficiaries with a pre-PDC or post-PDC equaled 0 were excluded from the model.

5.4.2.1 Medication adherence

Table 29 summarizes the results from general linear regression (GLM) and multiple logistic regressions in the experimental group. The results of general linear regressions and multiple logistic regressions share similarity in all three-disease cohorts.

1) PDC in diabetes

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing

strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents.

Other significant variables in linear regression: three control variables are significant in both models in predicting adherence, including pre-PDC, race, and age. After controlling for other factors, post-PDC will increase by 0.577 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.003($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.043 ($p=0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area.

Other significant variables in logistic regression: two control variables are significant in both models in predicting adherence, including pre-PDC and age. After controlling for other factors, beneficiaries who are adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 795.4% (OR=8.954, 95% CI=[7.923, 10.120]) compared to beneficiaries who are not adherent in pre-intervention period; the odds of adherence will increase by 3.1% (OR=1.031, 95%CI=[1.025, 1.038], $p<0.001$) with a one-year increase of age.

2) PDC in hypertension

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents.

Other significant variables in linear regression: four control variables are significant in both models in predicting adherence, including pre-PDC, prospective risk score, race, and age. After controlling for other factors, post-PDC will increase by 0.566 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.002($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.003 ($p<0.001$) for every unit increase in prospective risk score; post-PDC will increase by 0.030 ($p<0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area.

Other significant variables in logistic regression: four control variables are significant in both models in predicting adherence, including pre-PDC, prospective risk score, race, and age. After controlling for other factors, beneficiaries who are adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 949.0% (OR=10.49, 95% CI=[9.867, 11.15] p<0.001) compared to beneficiaries who are not adherent in pre-intervention period; the odds of adherence will increase by 3.0% (OR=1.030, 95%CI=[1.027, 1.034], p<0.001) with a one-year increase of age; by 83.6% (OR=1.836, 95%CI=[1.559, 2.161] p<0.001) with one unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area; by 3.9% (OR=1.039, 95%CI=[1.025, 1.053] p<0.001) with an unit increase in Prospective Risk Score.

3) PDC in Hyperlipidemia

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents. However, the coefficient of the 1-tier copayment increase (copayment for generic drugs) is 0.012 (p=0.002) indicated a 0.012 higher, but not significant, in the mean of post-PDC between beneficiaries with

copayment decrease and beneficiaries with no changes in copayment of generics when controlling for other factors.

Logistic regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, none of the cost sharing parameters is significant. Post-GDR is not significantly different between beneficiaries with one of the cost-sharing strategies increase (or decrease) and beneficiaries with no changes in that cost sharing strategies. The conclusion is that changes of cost sharing strategies are not significantly associated with adherence to anti-diabetes agents.

Other significant variables in linear regression: four control variables are significant in both models in predicting adherence, including pre-PDC, sex, race, and age. After controlling for other factors, post-PDC will increase by 0.548 ($p<0.001$) for every unit increase in pre-PDC; post-PDC will increase by 0.002($p<0.001$) for every one-year increase of age; post-PDC will increase by 0.014($p<0.001$) male beneficiaries; post-PDC will increase by 0.038 for every unit increase in the percentage of population graduated from college or higher degree; post-PDC will increase by 0.046 ($p<0.001$) for every unit increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area.

Other significant variables in logistic regression: four control variables are significant in both models in predicting adherence, including pre-PDC, sex, race, and age. After controlling for other factors, beneficiaries who are adherent to medications in the pre-intervention period will increase the odds of adherence in the post-intervention period by 728.8.0% (OR=8.288, 95% CI=[7.686, 8.936] $p<0.001$) compared to beneficiaries who are not adherent in pre-intervention period; the odds of adherence will increase by

2.6% (OR=1.026, 95%CI=[1.022, 1.031], p<0.001) with a one-year increase of age; by 104.9% (OR=2.049, 95%CI=[1.629, 2.578] p<0.001) with 1% increase in the percentage of population reporting white only in the beneficiary's five-digit zip code area; by 22.8% (OR=1.228, 95%CI=[1.137, 1.327], p<0.001) with male beneficiaries.

Table 29 Results of regression models of PDC in step 2

Variables	General linear regression				Multiple Logistic Regression			
	PE[#]	95% CI		P-value	Odds Ratio	95% CI		P-value
Diabetes [1,2]								
Pre-PDC	0.577	0.555	0.600	<0.001 *	8.954	7.923	10.12	<0.001 *
Age	0.003	0.002	0.003	<0.001 *	1.031	1.025	1.038	<0.001 *
Prospective Risk Score	0.002	0.000	0.004	0.067	1.016	0.989	1.044	0.252
Male vs. Female	0.010	0.001	0.020	0.024	1.182	1.045	1.338	0.008
% of pop. With >= college degree	0.018	-0.017	0.053	0.313	1.268	0.785	2.050	0.332
Income >=$50,000 vs. Income < $50,000	-0.003	-0.014	0.008	0.640	0.948	0.817	1.100	0.481
% of pop. Self-reporting White	0.043	0.018	0.067	0.001*	1.674	1.206	2.325	0.002
1-5 medications in pre-period vs. >15 medications	0.014	-0.004	0.033	0.130	0.922	0.716	1.188	0.094
6-10 medications in pre-period vs. >15 medications	0.018	0.002	0.034	0.028	1.049	0.844	1.303	0.720
11-15 medications in pre-period vs. >15 medications	0.020	0.005	0.036	0.011	1.166	0.939	1.448	0.030
1-tier copayment decrease vs. no changes	0.008	-0.004	0.020	0.201	1.027	0.873	1.209	0.724
1-tier copayment increase vs. no changes	0.002	-0.010	0.014	0.763	1.000	0.845	1.183	0.862
1-tier coinsurance decrease vs. no changes	0.006	-0.035	0.046	0.782	1.164	0.671	2.017	0.992
1-tier coinsurance increase vs. no changes	0.018	-0.018	0.055	0.327	1.348	0.827	2.196	0.288
2-tier copayment	-0.008	-0.054	0.038	0.735	0.704	0.371	1.334	0.220

decrease vs. no changes								
2-tier copayment increase vs. no changes	0.005	-0.010	0.019	0.517	1.102	0.907	1.339	0.138
2-tier coinsurance decrease vs. no changes	-0.052	-0.101	-0.002	0.042	0.608	0.310	1.190	0.115
2-tier coinsurance increase vs. no changes	0.054	-0.067	0.175	0.384	2.036	0.304	13.62	0.314
3-tier copayment decrease vs. no changes	0.002	-0.042	0.046	0.926	1.227	0.663	2.271	0.414
3-tier copayment increase vs. no changes	-0.004	-0.017	0.008	0.505	0.901	0.757	1.072	0.238
3-tier coinsurance decrease vs. no changes	0.029	0.003	0.054	0.030	1.207	0.842	1.730	0.197
3-tier coinsurance increase vs. no changes	-0.062	-0.180	0.056	0.304	0.412	0.064	2.638	0.298
Hypertension [3,4]								
Pre-PDC	0.566	0.556	0.575	<0.001 *	10.49	9.867	11.15	<0.001 *
Age	0.002	0.002	0.002	<0.001 *	1.030	1.027	1.034	<0.001 *
Prospective Risk Score	0.003	0.002	0.003	<0.001 *	1.039	1.025	1.053	<0.001 *
Male vs. Female	0.004	0.000	0.007	0.057	1.076	1.012	1.144	0.019
% of pop. With >= college degree	0.019	0.005	0.032	0.007	1.164	0.928	1.460	0.190
Income >=$50,000 vs. Income < $50,000	0.002	-0.002	0.007	0.306	1.019	0.946	1.097	0.623
% of pop. Self-reporting White	0.030	0.019	0.040	<0.001 *	1.836	1.559	2.161	<0.001 *
1-5 medications in pre-period vs. >15 medications	0.004	-0.004	0.012	0.357	1.168	1.013	1.346	0.176
6-10 medications in pre-period vs. >15 medications	0.006	-0.002	0.014	0.147	1.162	1.017	1.328	0.166
11-15 medications in pre-period vs. >15 medications	0.005	-0.003	0.013	0.205	1.157	1.007	1.328	0.333
1-tier copayment decrease vs. no changes	0.006	0.001	0.011	0.020	1.100	1.014	1.194	0.351
1-tier copayment increase vs. no changes	0.006	0.001	0.011	0.013	1.128	1.038	1.225	0.059
1-tier coinsurance	0.004	-0.011	0.019	0.584	1.128	0.873	1.458	0.789

decrease vs. no changes								
1-tier coinsurance increase vs. no changes	0.004	-0.010	0.018	0.564	1.200	0.948	1.517	0.229
2-tier copayment decrease vs. no changes	0.014	-0.005	0.032	0.144	1.222	0.893	1.673	0.139
2-tier copayment increase vs. no changes	-0.006	-0.012	-0.001	0.031	0.932	0.848	1.024	0.057
2-tier coinsurance decrease vs. no changes	-0.018	-0.036	0.000	0.052	0.771	0.571	1.041	0.044
2-tier coinsurance increase vs. no changes	0.046	0.008	0.083	0.017	1.325	0.701	2.505	0.196
3-tier copayment decrease vs. no changes	-0.005	-0.023	0.013	0.602	0.971	0.713	1.323	0.772
3-tier copayment increase vs. no changes	0.004	-0.001	0.009	0.149	1.034	0.951	1.124	0.584
3-tier coinsurance decrease vs. no changes	0.005	-0.005	0.015	0.336	1.012	0.856	1.196	0.369
3-tier coinsurance increase vs. no changes	-0.042	-0.078	-0.006	0.022	0.754	0.409	1.393	0.355
Hyperlipidemia [5,6]								
Pre-PDC	0.548	0.534	0.562	<0.001 *	8.288	7.686	8.936	<0.001 *
Age	0.002	0.002	0.002	<0.001 *	1.026	1.022	1.031	<0.001 *
Prospective Risk Score	0.000	-0.001	0.002	0.504	0.996	0.980	1.013	0.671
Male vs. Female	0.014	0.009	0.020	<0.001 *	1.228	1.137	1.327	<0.001 *
% of pop. With >= college degree	0.038	0.019	0.056	<0.001 *	1.622	1.244	2.116	<0.001 *
Income >=$50,000 vs. Income < $50,000	0.003	-0.004	0.010	0.398	1.088	0.991	1.194	0.077
% of pop. Self-reporting White	0.046	0.029	0.063	<0.001 *	2.049	1.629	2.578	<0.001 *
1-5 medications in pre-period vs. >15 medications	0.007	-0.005	0.020	0.256	0.958	0.803	1.143	0.331
6-10 medications in pre-period vs. >15 medications	0.005	-0.007	0.016	0.422	0.971	0.824	1.143	0.450
11-15 medications in pre-period vs. >15 medications	0.010	-0.002	0.022	0.113	1.056	0.893	1.249	0.152

1-tier copayment decrease vs. no changes	0.012	0.004	0.019	0.002	1.120	1.010	1.242	0.150
1-tier copayment increase vs. no changes	0.009	0.002	0.016	0.017	1.092	0.987	1.207	0.509
1-tier coinsurance decrease vs. no changes	0.007	-0.016	0.029	0.549	1.070	0.780	1.467	0.991
1-tier coinsurance increase vs. no changes	0.013	-0.007	0.033	0.214	1.147	0.862	1.527	0.383
2-tier copayment decrease vs. no changes	-0.028	-0.054	-0.002	0.034	0.826	0.575	1.187	0.320
2-tier copayment increase vs. no changes	-0.004	-0.012	0.005	0.384	0.986	0.878	1.106	0.443
2-tier coinsurance decrease vs. no changes	-0.023	-0.049	0.003	0.086	0.880	0.609	1.271	0.185
2-tier coinsurance increase vs. no changes	0.008	-0.049	0.065	0.784	1.509	0.672	3.391	0.242
3-tier copayment decrease vs. no changes	0.025	-0.001	0.051	0.060	1.262	0.878	1.815	0.153
3-tier copayment increase vs. no changes	-0.004	-0.011	0.004	0.351	0.938	0.845	1.041	0.082
3-tier coinsurance decrease vs. no changes	-0.001	-0.015	0.013	0.921	0.954	0.784	1.161	0.211
3-tier coinsurance increase vs. no changes	-0.025	-0.080	0.030	0.376	0.530	0.242	1.158	0.125

#PE=parameter estimate

*Denotes being statistically significant.

1. $\chi^2(22)$=,p-value<0.0001, R^2 = 0. 3490
2. LR $\chi^2(22)$=,p-value<0.0001, Pseudo R^2 = 0.3370
3. $\chi^2(22)$=,p-value<0.0001, R^2 = 0. 3436
4. LR $\chi^2(22)$=,p-value<0.0001, Pseudo R^2 = 0.3335
5. $\chi^2(22)$=,p-value<0.0001, R^2 = 0. 2979
6. LR $\chi^2(22)$=,p-value<0.0001, Pseudo R^2 = 0.2985

4) Summary

The findings among all the models regarding the association between cost sharing strategy changes and medication adherence are consistent across all three cohorts. They all indicated no significant association between adherence and cost sharing changes within experimental group.

Three control variables are significant across all three-disease cohorts including pre-PDC, age, and race. Prospective risk score is only associated with adherence to anti-hypertension agents; Sex and percentage of population graduated from college or above in the zip code area are only associated with anti-hyperlipidemia agents.

5.4.2.2 Generic utilization

Table 30 summarizes the results from general linear regression (GLM) of generic dispensing rate in the post period in the experimental group. The results of GLM indicate similarity in all three-disease cohorts.

1) GDR in diabetes

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of 1-tier copayment change for generic dispensing rate is -0.017 ($p<0.001$), suggests that mean post-GDR for beneficiaries with 1-tier decrease is 0.017 lower than beneficiaries without 1-tier copayment changes. The result indicates that a decrease in generic copayment does not necessarily increase generic utilization.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.668 ($p<0.001$); for every unit increase in Prospective Risk Score, generic dispensing rate in the post period will decrease by 0.005($p<0.001$).

2) GDR in hypertension

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of 1-tier coinsurance increase is 0.017 ($p=0.006$), suggests that mean post-GDR for beneficiaries with 1-tier coinsurance increase is 0.017 lower, but not significant, than beneficiaries without 1-tier coinsurance changes.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR, age, and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.687 ($p<0.001$); when age of the beneficiary increases by one year, post-GDR will increase but with limited amount (close to 0, $p<0.001$); for every unit increase in prospective risk score, generic dispensing rate in the post period will decrease by 0.003($p<0.001$).

3) GDR in hyperlipidemia

Linear regression: after controlling for beneficiaries' predisposing characteristics, enabling resources, and need factors, the coefficient of 1-tier copayment decrease for generic dispensing rate is -0.009 (p=0.006), suggests that mean post-GDR for beneficiaries with 1-tier decrease is 0.009 lower, but not significant, than beneficiaries without 1-tier copayment changes. The result indicates that a decrease in generic copayment does not necessary increase generic utilization.

Other significant variables in linear regression: There are other variables significant in predicting adherence including pre-GDR, age, and prospective risk score. After controlling for other factors, for every unit increase in pre-GDR, post-GDR will increase by 0.625 (p<0.001); when age of the beneficiary increases by one year, post-GDR will increase but with limited amount (close to 0, p<0.001); for every unit increase in prospective risk score, generic dispensing rate in the post period will decrease by 0.006(p<0.0001).

Table 30 Results of regression models of GDR in step 2

Variables	Parameter Estimates	95% Confidence Intervals		P-value
	Diabetes [1]			
Pre-GDR	0.668	0.653	0.683	<0.001*
Age	0.000	0.000	0.001	0.006
Prospective Risk Score	-0.005	-0.006	-0.004	<0.001*
Male vs. Female	-0.008	-0.015	-0.002	0.014
% of pop. With >= college degree	0.006	-0.020	0.032	0.652
Income >=$50,000 vs. Income < $50,000	0.000	-0.008	0.008	0.955
% of pop. Self-reporting White	0.008	-0.010	0.027	0.375
1-tier copayment decrease vs. no changes	-0.017	-0.026	-0.008	<0.001*
1-tier copayment increase vs. no changes	-0.006	-0.015	0.003	0.184

1-tier coinsurance decrease vs. no changes	-0.022	-0.053	0.009	0.167
1-tier coinsurance increase vs. no changes	0.015	-0.012	0.042	0.281
2-tier copayment decrease vs. no changes	0.021	-0.015	0.057	0.250
2-tier copayment increase vs. no changes	0.002	-0.009	0.012	0.776
2-tier coinsurance decrease vs. no changes	0.045	0.007	0.083	0.021
2-tier coinsurance increase vs. no changes	-0.066	-0.155	0.023	0.144
3-tier copayment decrease vs. no changes	-0.020	-0.055	0.015	0.271
3-tier copayment increase vs. no changes	-0.002	-0.012	0.007	0.606
3-tier coinsurance decrease vs. no changes	-0.019	-0.039	0.001	0.068
3-tier coinsurance increase vs. no changes	0.069	-0.017	0.155	0.115
Hypertension [2]				
Pre-GDR	0.687	0.681	0.694	<0.001*
Age	0.000	0.000	0.000	<0.001*
Prospective Risk Score	-0.003	-0.004	-0.003	<0.001*
Male vs. Female	-0.003	-0.006	0.001	0.101
% of pop. With >= college degree	-0.016	-0.028	-0.005	0.006
Income < $50,000 vs. Income >=$50,000	0.002	-0.002	0.006	0.312
% of pop. Self-reporting White	0.005	-0.004	0.014	0.295
1-tier copayment decrease vs. no changes	-0.003	-0.007	0.001	0.172
1-tier copayment increase vs. no changes	-0.001	-0.005	0.003	0.604
1-tier coinsurance decrease vs. no changes	0.000	-0.014	0.013	0.943
1-tier coinsurance increase vs. no changes	0.017	0.005	0.029	0.006
2-tier copayment decrease vs. no changes	-0.005	-0.021	0.011	0.531
2-tier copayment increase vs. no changes	0.003	-0.001	0.008	0.164
2-tier coinsurance decrease vs. no changes	0.011	-0.004	0.027	0.157
2-tier coinsurance increase	-0.011	-0.041	0.020	0.492

vs. no changes				
3-tier copayment decrease vs. no changes	0.013	-0.003	0.028	0.105
3-tier copayment increase vs. no changes	-0.002	-0.006	0.002	0.406
3-tier coinsurance decrease vs. no changes	-0.004	-0.013	0.005	0.379
3-tier coinsurance increase vs. no changes	0.008	-0.021	0.037	0.592
Hyperlipidemia [3]				
Pre-GDR	0.625	0.616	0.634	<0.001*
Age	0.000	0.000	0.001	0.001*
Prospective Risk Score	-0.006	-0.007	-0.005	<0.001*
Male vs. Female	-0.001	-0.006	0.003	0.541
% of pop. With >= college degree	0.000	-0.017	0.016	0.970
Income >=$50,000 vs. Income < $50,000	0.002	-0.004	0.008	0.446
% of pop. Self-reporting White	-0.001	-0.015	0.013	0.908
1-tier copayment decrease vs. no changes	-0.009	-0.016	-0.003	0.006
1-tier copayment increase vs. no changes	-0.002	-0.008	0.005	0.596
1-tier coinsurance decrease vs. no changes	-0.010	-0.030	0.010	0.339
1-tier coinsurance increase vs. no changes	0.014	-0.004	0.031	0.124
2-tier copayment decrease vs. no changes	-0.018	-0.042	0.005	0.130
2-tier copayment increase vs. no changes	0.002	-0.005	0.010	0.544
2-tier coinsurance decrease vs. no changes	0.027	0.003	0.050	0.025
2-tier coinsurance increase vs. no changes	0.045	-0.002	0.091	0.059
3-tier copayment decrease vs. no changes	0.021	-0.002	0.045	0.072
3-tier copayment increase vs. no changes	-0.003	-0.010	0.003	0.306
3-tier coinsurance decrease vs. no changes	-0.008	-0.021	0.005	0.206
3-tier coinsurance increase vs. no changes	-0.034	-0.078	0.011	0.136

*Denotes being statistically significant.

1. $\chi^2(19) =$,p-value<0.0001, $R^2 = 0.5179$

2. $\chi^2(19)$=,p-value<0.0001, R^2 = 0.5668
3. $\chi^2(19)$=,p-value<0.0001, R^2 = 0.4979

4) Summary

The findings among all the models regarding the association between cost sharing strategies and generic utilization are not consistent across three diseases cohorts. There are significant associations between generic utilization of anti-diabetes and 1-tier copayment increase, but not significant findings in the other cohorts. The finding from diabetes cohort indicates that a decrease in generic copayment does not necessary increase generic utilization.

Two control variables are significant across all three-disease cohorts including pre-GDR and prospective risk score. Age is significant in the hypertension and hyperlipidemia cohorts.

Chapter 6 Discussion

This study adopted a pre- and post-quasi experimental design with control group, and used claims data from a large PBM company located in Minnesota. There were two objectives for this study. The first was to investigate the impact of any pharmacy benefit design changes on adherence with chronic medications. The second objective was to examine the impact of any pharmacy benefit design changes on generic utilization. The two objectives were examined in three disease cohorts: diabetes, hypertension and hyperlipidemia. To understand the impact comprehensively, pharmacy benefit design changes were examined in two steps: (1) step 1—Any changes in pharmacy benefit design, including changes in copayment, coinsurance, deductibles, maximum out-of-pocket limitations, maximum coinsurance amount, minimum coinsurance amount; (2) step 2—Changes in two cost sharing strategies (an increase or decrease in copayment and coinsurance) only.

The two objectives represent two important underlying concepts in the management of pharmacy services. On one hand, adherence is a patient-oriented outcome and an important element in medication management, particularly when the drug therapy is directed at chronic diseases like diabetes, hypertension and hyperlipidemia. The importance has been emphasized in the Centers for Disease Prevention and Management (CMS) Star Ratings. On the other hand, generic drug utilization, as measured by GDR, is an important formulary management metric. The use of generic medications represents an important and useful strategy in reducing overall pharmacy costs for managed care

organizations. Responsible benefit management balances the need for plan cost savings with patient management.

Medication adherence was measured in proportion of days covered (PDC) by at least one medication used to treat the target disease. PDC was also dichotomized as PDC>=80% and PDC<80%. Generic utilization was measured as the generic dispensing rate (GDR) for all medications the individual took during the study period (i.e., the 12 month period of time following the estimated contract renewal).

Two statistical models were fit in accordance with the two outcome measures: (1) General linear regression model for the continuously measured variables of PDC and GDR; and (2) Logistic regression for PDC measured as a dichotomous variable (1=adherence: PDC>=80%; 0=non-adherence: PDC<80%). The control variables were classified into three categories based on Andersen's behavioral model of health services use: predisposing characteristics, enabling resources, and need factors. These control variables included beneficiaries' demographic and socioeconomic information, medication conditions, and a proxy health risk estimate using Prospective Risk Score.

In this chapter, the first section summarizes and discusses the study findings. The second section discusses the strengths of the study. The third section presents additional limitations of the study beyond those identified in Chapter 1 (Introduction) as inherent in the use of claims data. The fourth section discusses the implications of the study. Finally, the fifth section provides recommendations for future research.

6.1 Summary of study results

The study sample was made up of 445,983 patients, of whom 45,850 were identified with benefit changes and 400,133 were identified with no benefit changes at contract renewal.

Over 60% of the beneficiaries in 12-month measurements were classified as adherent (PDC>=80%). The mean post-PDC and post-GDR for each group within each cohort are shown in Table 31. Mean PDC and GDR in the post period varied across the three disease cohorts. PDC and GDR in the hypertension cohort were generally higher than those in the diabetes and hyperlipidemia cohorts. The diabetes and hyperlipidemia cohort had similar PDC and GDR. In addition, to understand the preliminary relationship between pre- and post-PDC and pre- and post-GDR, Z-tests were conducted and showed that mean pre-PDC was significantly higher than post-PDC, and mean pre-GDR was significantly lower than post-GDR across both groups in all three study cohorts.

Table 31 Mean PDC and GDR in each disease cohort

Outcome	Diabetes		Hypertension		Hyperlipidemia	
	Control	Exper	Control	Exper	Control	Exper
Post-PDC Mean ± S.D.	79.4±21.7%	78.8±22.1%	84.3±19.4%	83.8±19.5%	79.6±20.3%	79.5±20.4%
Post-GDR Mean ± S.D.	75.1±21.8%	75.1±21.5%	80.2±22.8%	80.1±22.8%	76.7±24.3%	76.7±23.9%

To understand the influence of benefit design changes on medication adherence and generic utilization, two-step statistical analyses were completed.

1) Step one

Step one examined whether or not ***any*** benefit design changes at contract renewal resulted in changes in PDC or GDR. The findings among all the models regarding the associations between the benefit design changes that occurred and PDC were consistent. All models indicated no significant associations between adherence and benefit design changes.

There were, however, significant associations between GDR and benefit design changes in the diabetes and hypertension cohort. The experimental group had 0.007($p=0.0002$) higher post-GDR compared to the control group in the diabetes cohort; beneficiaries in the experimental group had 0.004 ($p<0.001$) higher post-GDR compared to the control group in the hypertension cohort. The different findings among the three study cohorts could be driven by different levels of elasticity. Elasticity for primarily chronic symptomatic treatments could be lower than those for primarily acute symptomatic treatments(Landsman et al., 2005). Therefore, beneficiaries may have been less sensitive to copayment changes among treatments that are perceived as less urgent conditions such as hyperlipidemia, which until a crisis episode may not be "visible" to beneficiaries.

There were some slight differences in results between linear models and logistic models attributable, in part, to two underlying requirements of logistic regression. First, logistic regression has a log transformation of the outcome variable. Second, logistic regression requires a categorical variable; therefore, PDC was dichotomized at 80% as the measure of adherence, as is commonly done when studying PDC. It is important to note, however, that although this is the common practice, there is little clinical evidence to support that PDC>=80% is clinically important.

2) Step two

Statistical analysis in step two examined the influence of cost sharing changes on post-PDC and post-GDR of which two components were studied, tiered copayment and coinsurance designs. This selection was based on two reasons. First, these cost sharing strategies are the most common prescription benefit designs. Second, cost sharing has the most visibility to beneficiaries, since at the time of acquiring a prescription, a beneficiary faces an immediate financial responsibility—they must either pay the calculated amount of their coinsurance rate (a percentage of the total amount of the prescription charge) or pay the copayment amount of the tier to which the specific drug dispensed is assigned in the formulary.

In the analysis of step two, neither cost-sharing strategy had a significant impact on PDC. This finding is consistent with a few previously published studies. Motheral et al found no differences in continuation rates when copayment increased in both hypertension cohort and hyperlipidemia cohort(B. Motheral & Fairman, 2001). Nair et al found no significance increase in formulary compliance rate among beneficiaries who stayed in the same tier design but experienced some benefit changes (i.e., 2-tier to another 2-tier or 3-tier to another 3-tier structure). Huskamp et al found a switch from brands to generics when a more aggressive copayment design was implemented, but not to stop taking a giving classes of medications altogether(Huskamp et al., 2003). Fariman et al found chronic medication therapy continuation rates did not differ significantly at

any other time point for anti-hypertension, or anti-hyperlipidemia agents when plan design changed from 2-tier to 3-tier.

There are two possible reasons for the study's finding that changes in the studied cost-sharing strategies did not impact PDC. Firstly, the copayment differences between pre and post period were not large. The average copayment changes were within $10; the average coinsurance changes were also smaller than 10% as shown in tables 12-15. It may take a larger copayment differential to affect medication adherence. The second reason of non-significance may be related to the social economic status of the study sample. Tamblyn et al found that increased cost sharing for prescription drugs in elderly persons and welfare recipients was followed by reductions in use of essential drugs and a higher rate of serious adverse events associated with these reductions(Tamblyn et al., 2001). Stuart and Zacker also found that even modest copayment requirements could reduce the likelihood that Medicaid recipients filled any prescriptions(Stuart & Zacker, 1999). Unlike those studies, this study included beneficiaries who were commercially insured employees with possible higher income level and health status. Thus, the findings could be different.

Studies that have reported associations between cost sharing and adherence (usually reporting on non-adherence) were also generally studies of individuals newly initiating on prescription medications(Gleason, Starner, Gunderson, Schafer, & Sarran, 2009). Goldman et al found that doubling co-payments was associated with reductions in the use of eight therapeutic classes, but patients diagnosed as having a chronic illness and receiving ongoing care were less responsive to copayment changes(Goldman et al., 2004). In contrast to studies of individuals newly initiated on medications, this study

included individuals established on prescription medications for the treatment of chronic illnesses. Beneficiaries who initiated therapy in the post period (the 12-months following the estimated contract renewal date) were excluded. The differences found between adherence and the effect of cost sharing when taking into account the time of initiation of prescription drug therapy is important. Underlying cost sharing strategies may be less influential on decision making once beneficiaries have initiated therapy.

Results from the second dependent variable, generic dispensing rate, also showed no significance with most of the cost sharing strategies. One exception was noted in the diabetes cohort. For beneficiaries with a decrease in the amount of copayment for Tier 1 (generic products) the mean post-GDR was 0.017 ($p=0.0003$) lower than beneficiaries without copayment changes in the diabetes cohort; changes in post-GDR were not significant in the hypertension and hyperlipidemia cohorts.. The inconsistency of this finding can also be found in literature. A review of published literature would indicate that a reduction in generic cost sharing should motivate beneficiaries to use generics (Clark et al., 2014). While a majority of studies reported in literature have demonstrated that a higher generic cost sharing was associated with lower generic use (Roebuck & Liberman, 2009; Tang et al., 2014; Zimmerman, 2012). There are also studies that have reported an increase in GDR with or without benefit changes. Nair et al found an increase in GDR by 6—8% with or without benefit changes(K. V. Nair, RJ., 2004) and Landsman et al found different generic use rates among different therapeutic classes when benefit changes(Goldman et al., 2004).

Overall, this study found that mean post-PDC was lower than pre-PDC, a suggestion that adherence generally decreased over the time period identified for this study (1/1/2011 to 6/30/2013), while GDR generally increased over the same time period, The regression results suggest, however, that the benefit design changes that occurred for beneficiaries during this time period did not appear to have a significant influence on adherence as measured by PDC, but were associated with an increase in generic utilization using GDR as the metric.

Non-adherence with chronic therapy has serious clinical implications, such as reduced control over disease parameters, increased risk of disease sequelae, and impaired quality of life. The decrease in PDC over time identified in the preliminary analysis needs to be carefully monitored in the future, particularly given the strong emphasis being placed on adherence in these three therapeutic groups in the CMS Star Ratings.

The finding is, therefore, relatively important. ***The decrease in PDC is not associated with benefit design changes, while the increase in GDR is associated with benefit design changes within the studied pharmacy benefit designs.***

While this study did not find significant associations between benefit design changes and PDC or between the specific cost sharing strategies of copayment and coinsurance and PDC or GDR, there were other variables that were significant in predicting post-PDC and post-GDR (see Table 28). It was anticipated that both post-PDC and post-GDR would be significantly associated with pre-PDC and pre-GDR, respectively and statistical analysis supported this relationship. In general, prior

adherence is significantly associated with future adherence and the use of generic medications is significantly associated with the future use of generically equivalent medications.

Age and race were consistently associated with post-PDC in step one and step two across all three-disease cohorts. Older beneficiaries and a higher percentage of self-reported white beneficiaries appear to have significantly higher post-PDC controlling for other factors. Findings in the literature are consistent with the findings in this study. Couto, et al found younger age beneficiaries, lower income beneficiaries, and females were less adherent to chronic medications for hypertension, diabetes, and hyperlipidemia(Couto et al., 2014). Benner et al. demonstrated that black and other nonwhite races were less adherent to statin therapy(Benner et al., 2002). This study's findings regarding the influence of race, income, education on medication adherence and generic utilization should be interpreted cautiously since the inclusion of these measures were based on the percentage of the population in a five-digit zip code area, taken from the 2010 US census. These measurements are subject to error, as they do not reflect the actual individual information.

The association between demographic and socioeconomic characteristics and GDR is not commonly found in literature. Nair et al, as one of the only studies to report on this relationship, found that the GDR for women was 6.2% greater than men(K. V. Nair et al., 2003). This study, in contrast, did not find a significant association between sex and GDR. Prospective Risk Score, however, was inversely associated with GDR in most of the models' findings, meaning that as risk score increases, GDR decreases.

The findings of these significant variables were not consistent across the study's disease cohorts. Considerably more variables were found to be significantly associated with PDC or GDR in the hypertension cohort. One possible explanation is a methodological one—the hypertension cohort had a substantially larger sample size. Other explanations may be found in the large body of literature reporting on the contribution of sociodemographic factors to differences (literature frequently uses the term disparities) in many aspects of health care including access to prescription drugs, use of generic medications and adherence to prescribed therapies.

Table 32 Other significant variables in predicting post-PDC and post-GDR

Disease cohorts	Step1: PDC		Step2: PDC		Step1: GDR		Step2: GDR	
	Variables	P-value	Variables	P-value	Variables	P-value	Variables	P-value
Diabetes	Pre-PDC	<0.001	Pre-PDC	<0.001	Pre-GDR	<0.001	Pre-GDR	<0.001
	Age	<0.001	Age	<0.001				
	Sex	<0.001						
	Race	<0.001	Race	<0.001				
	# of medications	<0.001						
					Prospective risk score	<0.001	Prospective risk score	<0.001
Hypertension	Pre-PDC	<0.001	Pre-PDC	<0.001	Pre-GDR	<0.001	Pre-GDR	<0.001
	Age	<0.001	Age	<0.001	Age	<0.001	Age	<0.001
	Prospective risk score	<0.001	Prospective risk score	<0.001	Prospective risk score	<0.001	Prospective risk score	<0.001
	Race	<0.001	Race	<0.001				
					Education	<0.001		
					Income	<0.001		
Hyperlipidemia	Pre-PDC	<0.001	Pre-PDC	<0.001	Pre-GDR	<0.001	Pre-GDR	<0.001
	Age	<0.001	Age	<0.001	Age	<0.001	Age	0.001
	Sex	<0.001	Sex	<0.001				
	Education	<0.001	Education	<0.001				
	Income	0.001						
	Race	<0.001	Race	<0.001				
							Prospecti	<0.001

							ve risk score	

It is important to note that the general linear models had small but fair R^2 values, indicating that these models had explanatory power in explaining medication adherence and generic utilization. The R^2 of the regressions were between 20% and 40%, indicating that the study models explain around 20-40% of the dependent variables, while the baseline variable (pre-PDC and pre-GDR) accounted for a relative large percentage of R^2. A small R^2 may be caused by the lack of availability of variables that have been identified as important in other literature—variables such as health beliefs, and attitudes toward the need for and use of prescription drugs. For logistic regressions, since Pseudo R square is inadequate to check the goodness of fit, Hosmer and Lemeshow goodness-of-fit tests were conducted. All models had a p-value above 0.05, indicating that the models built fit the set of observations.

In the study, the significant level was adjusted from 0.05 to 0.001. As sample size increases, the chance of finding a significant difference will increase as well. Therefore, the decision was made to use a more strict decision rule to determine significance.

6.2 Strength of the study

This study has several strengths compared to existing studies. First of all, this study thoroughly examined the impact of benefit design changes on medication adherence and generic utilization after controlling for variables that potentially affect the

two outcomes as well, including demographic information, socioeconomic status, estimated health status, and medication history.

Secondly, this study examined the impact of medication adherence and generic utilization in three disease cohorts: diabetes, hypertension and hyperlipidemia. By providing a more comprehensive comparison of the similarities and differences across the three diseases, this study has more generalizability in terms of study populations. In addition, this study had significantly large sample size and included commercially enrolled beneficiaries from more than 12 states. Compared to previous studies, our study is based on large samples using "real-world" pharmacy claims data. "Real-word" data has higher validity to be generalized to real-world clinical practice than data from clinical trials, patient registries, or studies initiated in clinics where individuals are monitored more closely.

Thirdly, the study design was a pre- and post quasi-experimental design with control group. Other studies with significant findings were commonly lacked of control groups or adjusting baseline (pre-PDC and pre-GDR). A study design that includes a control group allows adjustment for baseline trends and will, therefore, more accurately predict the relationship between benefit design changes and medication adherence and generic utilization.

Fourthly, PDC was conducted based on disease level and allowed for examination of adherence to multiple concurrent medications. GDR was calculated based on individual level and provided a more comprehensive assessment of individuals' generic drug use. Additionally, PDC was measured as both continuous variable and categorical variable with general linear regression and logistic regression, respectively.

Quantifying adherence at both continuous and categorical levels provides a possibility to systematically and thoroughly examined the findings and increases the accuracy of measure adherence.

6.3 Study limitations

Despite the above noted strengths of the study, there are some limitations of this study that need to be noted. These limitations are related to data source, study design, generalizability, and variable measurement.

The data sources for this study were beneficiaries' pharmacy claims data supplemented with administrative data files (including a benefit information file and a member information file), and 2010 census data. The original purpose of claims data collected by PBM is to obtain reimbursement for health services, not for health research. Fields related to reimbursement are generally accurate, but coding errors or inaccurate entries in some other fields may occur. For example, during the process of estimating plan change date, the study found some claims payment by beneficiaries were not consistent with the cost sharing design in the benefit file. The other example is the accuracy of the days supply used to calculate PDC. There were some claims that shared the same daily dosage and quantity dispensed, but had quite different records of the days supply. However, given the extremely large sample size, minor inaccuracy in coding may not make a difference in computing the results.

Additionally, patients' consumption compliance cannot be evaluated through

claims data. Pharmacy claims represent the acquisition of a prescribed medication only. Claims records can only indicate beneficiaries' medication acquisition behaviors (filling the prescriptions) instead of medication consumption behaviors (actually taking the medications). But the PDC calculated based on pharmacy record has been showed a good correlation with actual drug levels and has been widely used in adherence studies (Doshi et al., 2009; Steiner, Koepsell, Fihn, & Inui, 1988). Pharmacy claims data are also believed to be more objective in measuring compliance since self-reports might overestimate medication use (Wang et al., 2004). Additionally, pharmacy claims may not completely represent patients' medication coverage. The measurements of generic drug utilization and medication adherence may not be accurate because some sources of supply are not recorded in claims, such as out-of-plan use of pharmacy services and over-the-counter (OTC) medications.

The three diseases cohorts included in this study were created using pharmacy claims only. Medical claims were not available to determine if ICD-9-CM codes suggesting diagnoses of diabetes, hypertension or hyperlipidemia were present. Some beneficiaries without hypertension disease might also fill claims for hypertension drugs and used them to treat other diseases. Classifying disease cohorts based solely on prescription claims could, therefore, overestimate the number of beneficiaries with hypertension .

Another limitation is the generalizability of this study. The subjects of this study were employer-sponsored, commercially enrolled beneficiaries with a mean age of about 53 years. Therefore, the results of the study may not be generalized to other settings, such as Medicare, Medicaid, or other public plans. Also, the setting of changes of benefit plan

designs was between Jan. 1, 2012 and Jun.30, 2012. The benefit design could be quite different at different time settings. It may not be generalizable to other years.

The third limitation is that this study is an observational study. The internal validity of an observational study is always questionable. This study can only examine the association between pharmacy benefit design changes and generic drug utilization and medication adherence. Any interpretation of these findings as indicative of causality is inappropriate. This study primarily focuses on examining behaviors driven by the change of benefit design on cost sharing. Patients may choose to forgo a drug or change an established drug regimen for other reasons, among these are side effects, low curative effects, perceptions about the similarity of lower-tier substitutes and providers' opinions of discontinuing or altering established drug therapies, and other changes in benefit designs. Above factors all provide some insights into the evaluation of generic drug utilization and medication adherence. Such factors are likely to influence beneficiaries' treatment decisions but are difficult to capture in recorded data. Therefore, the analysis might be subject to unobserved confounding without measuring those factors.

In addition, the observational period in this study is only 12 months, which may not be long enough to comprehensively capture the beneficiaries' behavior changes in response to benefit design changes. The study found that decrease copayment of generic drugs did not necessary increase the generic dispending rate. It is possible that beneficiaries had not been aware of the copayment decrease or had not have the opportunity to fill more generic prescriptions within the study period.

The fourth limitation is the measurement of PDC and GDR. In the study, PDC was computed at disease level, which makes it possible to have multiple claims at the

same period of time. When calculating how many days were covered by at least one drug, it is assumed those drug were taken concurrently. Therefore, any early fills were not adjusted to a new start date when prior fills ran out. As a result, it may underestimate adherence if these drugs were not required concurrently. GDR was measured as the total number of retail generic prescription claims dispensed divided by the total number of retail prescription claims for the beneficiary during a 12-months period of time. However, there are some brands that do not have generic substitutions. Without considering this factor, GDR might be underestimated.

In addition, because this study excluded beneficiaries who received prescription drugs by mail order, both PDC and GDR were underestimated. There are also other sources for acquiring prescription medications, such as prescriptions paid by cash and free samples from physicians that were not taken into account in the claims count to calculate GDR and PDC in this study.

The fifth limitation is the adoption of 2010 Census data. Socioeconomic information was not provided in the claims data file. Data related to income, educational level, and races/ethnicity were estimated from 2010 census data by ZIP code of residence. Because of the lack of alternatives with claims data analyses, census data were commonly adopted in health services research. But they might not be the ideal proxies of individual-level information. Inference related to these three variables should be made cautiously when analyzing results from regression models.

Finally, the sixth limitation is the study model. Despite the inclusion of important covariates and the leveraged use of census data, the potential endogeneity of pharmacy benefit design remains. Additionally, copayments across tiers may be correlated, thereby

increasing the possibility of multicollinearity in multivariate models.

6.4 Implications for plan management

Benefit designs that increase cost savings without consideration of patient outcomes and the opposite, benefit designs that increase patient outcomes without consideration of the implications for costs, are not desirable. The ideal—improved patient outcomes and decreased health care costs—may not be achievable but the potential for increased cost savings and neutral impact on a patient outcome like medication adherence may be possible.

Many studies argue that higher cost sharing is associated with lower adherence, and adherence to chronic medications generally results in lower rates of office visits and hospitalizations; lower levels of cost sharing may thus translate to better health outcomes(Gibson et al., 2010). Medical plans, employers, and policy makers should consider implementation of interventions targeted to improve and maintain higher levels of medication adherence. In this study, overall the post-PDC was lower than pre-PDC across both the study and control groups in all three-disease cohorts studied, indicating that for the study time period there was an overall decrease in medication adherence. Study findings indicated that this reduction in PDC was not associated with the benefit design changes that occurred in this study population; other factors may be the reason that actually causes the reduction in adherence.

The mean adherence in the post-intervention period (measured in PDC) is 79.2%, 84.1% and 79.6% for diabetes, hypertension and hyperlipidemia, respectively. These

findings were based on a 12-month observation period. The mean adherence level may likely be lower if PDC is measured for a longer period of time. Therefore, continued monitoring of PDC is important, with more efforts focused on initiatives to improve patients' adherence to chronic medications that take into account of elements beyond benefit designs.

The study results indicated that changes in benefit design of the magnitude found in the study population were not significantly associated with medication adherence, but were significantly associated with generic utilization. This finding has several implications for policy-making regarding benefit designs for chronic diseases. Because of bioequivalence, a generic drug is much more cost-effective compared to its respective brand name product. Considering the burden of health care expenditures, increasing the generic dispensing rate is an important strategy. Among this commercially enrolled group of beneficiaries, the changes that occurred in the pharmacy benefit design are actually going in the right direction (i.e., increasing GDR)—a positive outcome for plan management efforts.

It is important to note, however, that this study found no significant adverse effect of small benefit design changes (less than $10 for copayment and 10% for coinsurance). Larger benefit design changes could be detrimental. In some respects it may be better to improve the efficiency of health care delivery and the appropriate use of prescription medications rather than attempting to control drug costs through health insurance strategies of increasing cost-sharing to beneficiaries (Steinwachs, 2002).

6.5 Recommendations for future research

Chronic disease, such as diabetes, hypertension, and hyperlipidemia, can dramatically affect beneficiary's quality of life. Medication adherence to chronic medications is extremely important. Our study did not find a significant association between medication adherence and benefit plan changes that occurred in the contract renewal period for this study population. Medication adherence in the post period, however, decreased significantly according to the results of Z-test. Medication adherence may not be related to benefit changes, but due to unavailability of data, some factors such as beneficiaries' social structure, health beliefs, and perceived needs were not included in the study. These may be important factors leading to reductions in medication adherence and would contribute to a better understanding of the decrease in PDC noted. Future research may investigate these factors more thoroughly. It may be necessary to take a step back and consider whether the real problem is pharmacy benefit design.

In addition, this study used beneficiaries' five-digit zip code level information matching from 2010 census data to present individual level information including race, income, and education. Aggregate proxies are very likely to introduce measurement errors. Future studies are recommended to use actual individual level information to examine their effects on medication adherence.

It was noted that there was an overall reduction in adherence during the time frame of this study. Because of the importance of adherence to clinical outcomes, and the CMS emphasis being placed on adherence for the three therapeutic disease areas included in this study, additional attention to this reduction is warranted. Further studies need to be

performed to determine the potential reasons for the reduction in adherence from 2011 to 2012 and the potential for adherence to continue to decline.

Beneficiaries enrolled in Medicaid and Medicare programs were not included in this study. Medicaid beneficiaries are typically financially disadvantaged and have different socioeconomic characteristics. Therefore, health seeking and medication adherence behaviors of beneficiaries enrolled in Medicaid or Medicare could be quite different from commercially enrolled beneficiaries. Future research could include those patients and compare whether the effect of benefit design changes is different. Also, this study examined the impact of benefit plan changes on medication adherence and generic utilization in three chronic disease cohorts. Further research could examine how the impact of benefit changes may vary across other chronic conditions.

The study explored the impact of benefit design changes on adherence up to 12-months following a change in prescription drug benefits. As discussed in the limitation section, a 12-month follow up time may not be long enough to detect any difference in adherence and generic drug use caused by benefit plan changes. A longer follow up period should be conducted, which may identify differences in adherence and that may be more reflective of the long term use of medications used in the treatment of chronic diseases.

This study examined in greater depth the two most common prescription benefit designs that may be targeted for annual contract changes--tiered co-payment and co-insurance. Other design strategies, such as deductible amounts with or without minimum/maximum limits, also have financial implications for a beneficiary and can be

modified during contract renewal periods. The impact of these benefit design changes on PDC and GDR would be of interest.

Additionally, regarding the measurement of PDC and GDR, a fruitful area of research would be to adopt multiple measurements and compare the effects to help develop more reliable and valid adherence measurement. For example, future research should consider a more specific definition of GDR—one that takes into the account of the availability of generic substitution when calculating GDR.

Finally, this study did not find any significant associations between cost sharing strategies and adherence. One reason could be that the changes within copayment or coinsurance were relatively small. Future studies to determine the impact of large changes in cost sharing are recommended.

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Appendices

Appendix 1 A list of Pharmacy Risk Groups

In the table below, Array Position is the position of the PRG ID in the Risk Record's PRG Array, with the first array element being number one. In any given Symmetry release, the order of the PRG IDs may or may not correspond with the order of the PRG Array positions (For example, a release may include a new ID with a low number positioned at the end of the array.) Combination Pharmacy Risk Markers are prefaced with an asterisk (*).

PRG ID	Description	Array Position
01.01	Amebicides & antifungal antibiotics	1
01.02	Aminoglycosides excluding cystic fibrosis agents	2
01.03	Other arthritis agents	3
01.04	Antituberculosis agents	4
01.05	Cephalosporins, macrolides, other selected anti-infective agents	5
01.06	HIV antiviral agents	6
01.07	Leprostatic agents used in chemotherapy/major illness	7
01.08	Miscellaneous antibiotics, not elsewhere classified	8
01.09	Non-HIV antiviral agents, not elsewhere classified	9
01.10	Quinolones	10
01.11	Higher cost anti-infectives, not elsewhere classified	11
01.12	Higher cost arthritis agents	12
01.40	Cephalosporins, macrolides, other selected anti-infective agents, infant	13
01.81*	Multiple selected anti-infective agents, I	14
01.82*	Multiple selected anti-infective agents, II	15
02.01	Antineoplastics, I (nitrogen mustards, nitrosoureas, anthracycline antibiotics)	16
02.02	Antineoplastics, II (androgens/anti-androgens for chemotherapeutic use)	17
02.03	Antineoplastics, III (antimetabolites & selected chemotherapy & related agents)	18
02.04	Antineoplastics, IV (gonadotropin-releasing hormones for chemotherapy)	19
02.05	Antineoplastics, V (miscellaneous antineoplastics, not elsewhere classified)	20
02.06	Antineoplastics, VI (hepatitis agents)	21
02.07	Antineoplastics, VII (agents to treat breast cancer, I)	22

02.08	Antineoplastics, VII (agents to treat breast cancer, II)	23
02.09	Antineoplastics, V (miscellaneous antineoplastics, not elsewhere classified, II)	24
02.81*	Higher risk antineoplastics & CNS agents, not elsewhere classified	25
02.82*	Antineoplastics & hormone therapy	26
03.01	Antihemophilic agents	27
03.02	Anticoagulants, antiplatelets, coumarin, heparins, glycosaminoglycans	28
03.03	Folic acid or folinic acid products	29
03.04	Hematopoietic agents	30
03.05	Iron & iron combinations	31
03.06	Hemostatics & thrombolytic enzymes	32
03.07	Vitamin B-12 & K products	33
03.81*	Iron & calcium channel antagonists	34
04.01	Beta adrenergic antagonists, alpha1-adrenergic antagonists	35
04.02	Carvedilol, nitrates & nitrites, digoxin	36
04.03	Antihypertensive agents	37
04.04	Anti-arrhythmic agents	38
04.05	Other cardiovascular agents, not elsewhere classified	39
04.06	Calcium channel antagonists	40
04.07	Vasodilating agents	41
04.08	Vasopressors used in shock, midodrine HCL	42
04.81*	Higher risk CAD, anti-infectives/antibiotics comorbidity	43
04.82*	Higher risk CAD, CNS comorbidity	44
04.83*	Higher risk CAD, GI comorbidity	45
04.84*	Higher risk CAD, insulin comorbidity	46
04.85*	Higher risk CAD, respiratory comorbidity	47
04.86*	Moderate/lower risk CAD/hypertension, GI comorbidity	48
04.87*	Moderate/lower risk CAD/hypertension, insulin comorbidity	49
04.88*	Moderate/lower risk CAD/hypertension, respiratory comorbidity	50
04.89*	Loop & higher risk diuretics comorbidity	51
05.01	Migraine agents & selected salicylates	52
05.02	Agents to treat Alzheimer's disease	53
05.03	Agents to treat multiple sclerosis	54
05.04	Agents to treat ALS	55
05.05	Agents to treat Parkinson's disease	56
05.06	Amphetamines & miscellaneous CNS stimulants, not elsewhere classified	57
05.07	Anorexiants	58
05.08	Anti-emetic agents used in treatment of cancer	59

05.09	Anti-emetic agents, not elsewhere classified, adult	60
05.10	Antipsychotic & antimanic agents	61
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Appendix 2 University of Minnesota Institutional Review Board Approval

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To: suxxx191@umn.edu
Cc: dobrovca@umn.edu
IRB Review Not Required

March 26, 2013 12:07 AM

TO : carls007@umn.edu, suxxx191@umn.edu,

PI: Weiping Su

IRB HSC: 1303E29986

Title:
Effect of prescription tier copayments and coinsurance benefits on abandonment of medication therapy and the generic fill rate as a proxy for patient purchase decisions

From: Institutional Review Board (IRB) The IRB determined your planned activities described in this application do not meet the regulatory definition of research with human subjects and do not fall under the IRB's purview for one or both of the following reasons:

1) The proposed activities are a) not a systematic investigation and/or b) not designed to develop or contribute to generalizable knowledge [45CFR46.102(d)].

Quality assurance activities and evaluation projects designed for self-improvement or program evaluation, not meant to contribute to "generalizable" knowledge, do not meet the threshold of research with human subjects.

Although IRB review may not be required for case studies, you still may have HIPAA obligations. Please contact the Privacy Office at 612-624-7447 for their requirements.

and/or

2) You will not obtain private identifiable information from living individuals [45 CFR 46.102(f)].

Interviews of individuals where questions focus on things not people (eg. questions about policies) do not require IRB review.

You will be analyzing aggregate data that cannot be linked to a living individual.

The above referenced IRB Human Subjects Code (HSC) will be inactivated in the database and you will have no further obligations for this project. Please do not hesitate to contact the IRB office at 612-626-5654 if you have any questions. Thank you for allowing the IRB to make the determination about whether or not review is required.

HRPP Staff