IMPACT OF MAXIMUM PRESCRIPTION LENGTH SUPPLY POLICY ON PATIENT MEDICATION ADHERENCE, HEALTH AND ECONOMIC OUTCOMES

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A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy in Social and Administrative Pharmacy
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ผลกระทบของนโยบายการกำหนดระยะเวลาสูงสุดในการจ่ายยาต่อความร่วมมือในการใช้ยาของผู้ป่วย ผลลัพธ์ทางสุขภาพและผลลัพธ์ทางเศรษฐศาสตร์

ร.อ.อินทร จารุจำรัส

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
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Field of Study	Social and Administrative Pharmacy
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โรงพยาบาลพระมงกุฎเกล้าฯ มีนโยบายในการเพิ่มจำนวนวันในการจ่ายยาจาก 30 วันเป็น 90 วัน เพื่อเพิ่มความร่วมมือในการใช้ยาของผู้ป่วย การวิจัยนี้มีวัตถุประสงค์เพื่อประเมินผลลัพธ์ของนโยบาย ต่อความร่วมมือในการใช้ยาของผู้ป่วย ผลลัพธ์ด้านคลินิกได้แก่การตรวจค่าเฉลี่ยระดับน้ำตาลในเลือด (HbA1c level) และระดับไขมันคอเลสเตอรอลในเลือด ผลลัพธ์ทางด้านเศรษฐศาสตร์ได้แก่ ต้นทุนสุขภาพรวม ต้นทุนการเข้ารับรักษาในโรงพยาบาล และต้นทุนมูลค่ายาในผู้ป่วยเบาหวานและไขมันในเลือดผิดปกติของโรงพยาบาลพระมงกุฎเกล้า การศึกษานี้เป็นการวิจัยกึ่งทดลอง โดยวิเคราะห์จากฐานข้อมูลโรงพยาบาลตั้งแต่ปี พ.ศ.2557- 2560 ใช้การวิเคราะห์ข้อมูลโดยใช้คะแนนโพรเพนซิตี้ (propensity score matching) และการวิเคราะห์แบบ difference-in-difference เพื่อเปรียบเทียบผลก่อนและหลังนโยบายประกาศใช้ในผู้ป่วยกลุ่มสิทธิ์ประกันสุขภาพถ้วนหน้า นอกจากนี้ยังใช้การวิเคราะห์ถดถอยพหุคูณเชิงเส้นและโลจิสติกส์ในการศึกษาความสัมพันธ์ระหว่างตัวแปรทำนายและตัวแปรที่สนใจ

ผลการวิจัยพบว่ากลุ่มผู้ป่วยเบาหวานที่ได้รับผลจากนโยบายมีความร่วมมือในการใช้ยาเพิ่มขึ้น 5% และกลุ่มผู้ป่วยไขมันผิดปกติมีความร่วมมือในการใช้ยาเพิ่มขึ้น 4% อย่างมีนัยสำคัญทางสถิติ นอกจากนี้ยังพบว่ากลุ่มผู้ป่วยเบาหวานสามารถลดค่าเฉลี่ยระดับน้ำตาลในเลือดได้ 0.08% เช่นเดียวกับกลุ่มผู้ป่วยไขมันผิดปกติในเลือดสามารถลดค่าเฉลี่ยระดับคอเลสเตอรอลในเลือดได้ 2.83 mg/dL สำหรับผลการวิเคราะห์ถดถอยเชิงพหุคูณแสดงให้เห็นว่าผู้ป่วยเบาหวานที่มีความร่วมมือในการใช้ยาเพิ่มขึ้น 10% จะสามารถลดค่าเฉลี่ยระดับน้ำตาลในเลือดได้ 0.015% ส่วนผู้ป่วยไขมันผิดปกติในเลือดจะสามารถลดระดับไขมันคอเลสเตอรอลในเลือดได้ 1 mg/dL สำหรับความร่วมมือในการใช้ยาที่เพิ่มขึ้น 10% นอกจากนี้ผลลัพธ์ทางเศรษฐศาสตร์ยังชี้ให้เห็นว่าผู้ป่วยที่มีความร่วมมือในการใช้ยาที่เพิ่มขึ้นเมื่อเปรียบเทียบกับกลุ่มผู้ป่วยที่มีความร่วมมือในการใช้ยาที่น้อยกว่าแม้ว่าจะมีต้นทุนมูลค่ายาที่สูงกว่าแต่เมื่อวิเคราะห์ถึงต้นทุนสุขภาพรวมแล้วพบว่ากลุ่มผู้ป่วยที่มีความร่วมมือในการใช้ยาที่เพิ่มขึ้นจะสามารถประหยัดต้นทุนสุขภาพรวมได้มากกว่าเนื่องจากผู้ป่วยกลุ่มนี้จะมีต้นทุนการเข้ารับการรักษาในโรงพยาบาล และต้นทุนเวลาที่น้อยกว่า กล่าวโดยสรุป ยังมีปัจจัยหลายประการที่ส่งผลต่อความร่วมมือในการใช้ยาของผู้ป่วยรวมไปถึงจำนวนวันของการจ่ายยา การศึกษานี้แสดงให้เห็นว่าการเพิ่มจำนวนวันจ่ายยาสามารถเพิ่มความร่วมมือในการใช้ยาให้กับผู้ป่วยได้ สามารถลดค่าเฉลี่ยระดับน้ำตาลในเลือดและระดับไขมันคอเลสเตอรอลในเลือดได้ รวมไปถึงยังสามารถลดต้นทุนสุขภาพรวมของผู้ป่วยเบาหวานชนิดที่ 2 และผู้ป่วยไขมันผิดปกติในเลือดได้

สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต .....
ปีการศึกษา	2563	ลายมือชื่อ อ.ที่ปรึกษาหลัก .....

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KEYWORD: adherence medication possession ratio antihyperglycemic medications lipid-lowering medications difference-in-difference method propensity score

Inthorn Jarujumrus : IMPACT OF MAXIMUM PRESCRIPTION LENGTH SUPPLY POLICY ON PATIENT MEDICATION ADHERENCE, HEALTH AND ECONOMIC OUTCOMES. Advisor: Asst. Prof. SUTHIRA TAYCHAKHOONAVUDH, Ph.D.

In February 2016, Phramongkutklao hospital has implemented Extended Dispensing Policy (EDP), which increasing prescription length from 30-day to 90-day, with the purpose to increase adherence of patient to their medication prescribed. The objectives of this study were to determine the effects of the increasing in maximum prescription refill length from 30-day to 90-day on medication adherence, clinical outcomes such as HbA1c level and cholesterol level, economic outcomes including total healthcare costs, hospitalization costs, and total medication costs among diabetes and dyslipidemia patients in the Phramongkutklao hospital. This study is a quasi-experiment, pre-post, using a retrospective database from a hospital between 2014 to 2017. A difference-in-difference method with propensity score matching was applied to examine the change in medication adherence before and after the EDP implemented among the Universal Coverage insured patients. Multiple logistic and linear regression was performed to determine the association between predictors and interesting outcomes. For DM patients, the DID of MPR enhanced by 5% ($P < 0.001$). Likewise, the DID of dyslipidemia patients showed a significant increase of 4% ($P < 0.001$). In addition, the difference-in-difference of HbA1c in the intervention group over control group was lessened by 0.08% while reduction in cholesterol level by 2.83 mg/dL statistically significant ($p < 0.001$). Moreover, the results from regression revealed that for each 10% improvement in medication adherence was related with the significant reduction in HbA1c by 0.015% ($p < 0.001$), and cholesterol level by 1 mg/dl ($p = 0.001$). Furthermore, results from economic outcomes indicates that despite higher total medication costs, patients with greater medication adherence contributes significant saving due to reductions in time costs and hospitalization costs. There are several factors that affect medication adherence, particularly prescription length. Increasing prescription length from 30-day to 90-day, improved medication adherence, reduced in cholesterol and HbA1c level, and minimize total healthcare costs in dyslipidemia and type-2 diabetes patients.

Field of Study:	Social and Administrative Pharmacy	Student's Signature .....
Academic Year:	2020	Advisor's Signature .....

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ACEIs	Angiotensin Converting Enzyme Inhibitors	**HDL**	High-Density Lipoprotein
AIDs	Acquired Immunodeficiency syndrome	**HITAP**	Health Intervention and Technology Assessment Program
AOR	Adjusted Odd Ratio	**HTA**	Health Technology Assessment
ARBs	Angiotensin II Receptor Blockers	**ICD-10**	International Classification of Diseases, 10th Revision
ART	Antiretroviral therapy	**IPD**	In-Patient Department
BBs	Beta-blockers	**LDL**	Low-Density Lipoprotein
CCI	Charlson Comorbidity Index	**MEMS**	Medication Event Monitoring System
CHF	Congestive Heart Failure	**MI**	Myocardial Infarction
CI	Confidence Interval	**MPR**	Medication Possession Ratio
CMA	Continuous Multiple Interval Measure of Medication Acquisition	**NCD**	Non-Communicable Diseases
CMG	Continuous Measure of Medication Gaps	**NLED**	National List of Essential Medicine
CSA	Continuous Single Interval Measure of Medication Acquisition	**OPD**	Out-Patient Department
CSG	Continuous Single Interval Measure of Medication Gaps	**PDC**	Proportion of Day Covered
CSMBS	Civil Servant Monetary Benefit Scheme	**PSM**	Propensity Score Matching
CVA	Cerebrovascular Accident	**PVD**	Peripheral Vascular Disease
CVD	Cardiovascular Disease	**SD**	Standard Deviation
DID	Differences in Difference	**SGLT-2**	Sodium Glucose co-transporter 2
DM	Diabetes Mellitus	**SS**	Social Security
DPP-4	Dipeptidyl Peptidase-4	**TZDs**	Thiazolidinediones
EDP	Extended Dispensing Policy	**THB**	Thai Baht
FPG	Fasting Plasma Glucose	**UC**	Universal Coverage
GDP	Gross Domestic Product	**UHOSNET**	University Hospital Network
GLP-1	Glucagon-Like Peptide-1	**US**	United States
GNP	Gross National Product	**USD**	United States Dollar
HbA1c	Glycosylated hemoglobin	**W/O**	Without

CHAPTER 1

INTRODUCTION

1.1 Background and rationale of the study

Over the last decades, expenditure on healthcare, especially pharmaceuticals spending had been increasing globally and at the faster pace than ever[1, 2]. Most of European countries have encountered the growth of healthcare costs which are higher than the growth rate of gross national product (GNP)[3]. The US has also been facing the surging of healthcare expenditure more than 10% increased from 2014, which was greater than growth rate in 2013 (only 2.9%)[4], to a result of three trillion US dollars in 2015 which was proportionate about 18% of the gross domestic product (GDP)[2]. In the next decades, it was estimated that worldwide healthcare spending will be moved up more than 200% from 2013 to 2040 and per capita health spending is projected to increase mostly in higher-middle-income countries by three percent annually [5]. For the total health care spending in the US, pharmaceutical costs also accounted for 10% and their growth rate was increased more than 10% from 2013 to 2014[4].

The situation is the same in Thailand, both drug expenditure and healthcare expenditure had increased at the similar pace (7-8 percent per year) which is also higher than the growth rate of the country's GDP (5-6 percent per year)[6, 7].

Policy makers worldwide have launched a range of approaches to contain these climbing costs, such as escalating the amount of patients cost sharing, setting more restrictive formulary, switching from innovative brands to lower price generic brands, requiring prior authorizations for prescribing expensive medications, employing reference pricing and cutting down the length of prescription refill[3, 8-11]. These cost-regulation approaches have demonstrated to be effective in containing healthcare costs[12], however, they generally have unexpected spill over impact on patients which are increase the hospitalization or admission, increase mortality including decrease patient's medication adherence[12, 13].

Commonly, treatment for chronic conditions required a continuous long extent of time or even life-long therapy and follow-up. Adherence to medication therapy regimens of each patient is an essential aspect of patient care impacting the effectiveness of the medication[14, 15]. Nonadherence to medication contributes to unfavorable both economic and clinical outcomes[16, 17], increasing of comorbidities and mortality rate, and also generate avoidable healthcare spending[14]. Accordingly, adherence to prescription drug issue is increasing emphasis among healthcare providers, policymakers and also other stakeholders in healthcare system[18]. Despite increasing interest in medication adherence, patients' nonadherence rate is considerably progress. Many studies in the US and other developed countries indicated that proportion of patients' adherence range from 60 to 100% with the average of 70% while in the developing countries revealed the lower rate of adherence [15, 19-21].

Adherence to medication is a sophisticated management and is affected by a lot of factors[14, 22-24]. There are numerous literatures that described factors related with medication adherence. For example, patient-level factors that influenced adherence are gender, age, level of education, ethnicity, and socio-economic status of each patient[25-27]. For therapy-related factors associating medication adherence are relationships between physician and patient, regimen complexity, side effects of the medication[28]. Also, the healthcare system-related factors affecting adherence are patient cost-sharing size, limitation of time to communicate with healthcare providers, inadequate excellence of services, types of medication allow for reimbursement and restriction of day supply of medication prescribed[14, 24, 29-31].

One approach that policy makers use to control costs is restraining the number of medications dispensed for treating chronic diseases. Restricted to one-month medication supply has been currently enforced to nearly 90% of states in the US Medicaid program[32]. Although the adoption of restriction prescription length policy has been increasing, little information is available about the effect of prescription length on medication adherence[11].

In 2016, Phramongkutklao hospital has implemented Extended Dispensing Policy (EDP) with the purpose to improve patient's convenience and increase patient's

adherence to medication prescribed while controlling hospital's budget. Before the policy was put into action, patients under the Universal Coverage (UC) scheme and the Social Security (SS) scheme; were prescribed with one-month and two-month supply, respectively. The maximum length of prescription for patients under the Civil Servant Medical Benefit Scheme (CSMBS), however, were longer with three months of medication supply. After the implementation of the regulations, all patients with stable chronic diseases can acquire up to three months of medication prescribed despite their health benefits.

In this study, the revision of policy is estimated to reduced patient expenditures, minimize wastage while improved patient' adherence to the medication. Based on the literature, increasing prescription length for patients with chronic diseases from 30-day to 90-day may promote medication adherence while containing overall cost[17, 33, 34]. However, there is still lack of studies which investigated the impact of increased prescription length on both clinical and economic outcomes.

1.2 Objectives of study

1. To determine the effects of the increasing in maximum prescription refill length from 30-day to 90-day on medication adherence among chronic disease patients in the Phramongkutklao hospital.
2. To assess the clinical and economic outcomes of increasing prescription refill length from 30-day to 90-day among chronic disease patients in the Phramongkutklao hospital
3. To investigate consequences of policy change from key informant perspectives.

1.3 Conceptual framework

In this study, the general aspects of medication adherence and the factors associated with medication adherence were constructed to illustrate each research question.

This study concentrates on medication adherence of the patients with chronic diseases and applied general aspects of medication adherence[14] to construct the framework in the analysis. For this aspect, the authors explained that medication adherence is greatly complicated and individualize, involving with various factors. However, the researchers should concern both the treatment and the outcome factors of medication adherence as shown in Figure 1.

Figure 1 General Aspects of Medication Adherence

According to the review literature that there are a lot of determinants influencing medication adherence. All of these factors were categorized into three main groups which are patient-related factors, physician-related factors and healthcare system related factors[14, 28, 35].

Age and gender were found to have a strong association with medication adherence[26-28] while other factors, for example, marital status and ethnicity are still inconclusive[28]. Then, only age and gender will be recruited to the patient-related factor. Additionally, complexity of therapy[36], route of administration[37], adverse events of the medication[38, 39], duration of treatment period[40], and comorbidities[41] were correlated with medication adherence. However, patient's medication adherence was measured only in oral dosage form of same interested group of medications with the constant period of study. Then route of administration, adverse events of medication, duration of treatment period factors were omitted due to the patients had the same route of administration. Additionally, this study mainly focused on the effect of increased prescription length which was not directly related with adverse events of medication also patient recruited in this study were used the same medication in both pre- and post-period, then the adverse effects of medications in this study were not different and were not affected with the interested outcome. Moreover, all of patients

were included to the study with a fixed period of two years, so the duration of treatment was not different and was controlled by the same period of time. The remaining included factors are complexity of therapy and comorbidities which classified into disease/therapy-related factors. For the complexity of therapy defined as the number of medications prescribed while comorbidities factor was determined as the number of diseases and uncontrolled of diseases. Lastly, health system-related factor was comprised of types of insurance coverage, policies, and prescription length which the latter is our main interesting variable as shown in Figure 2.

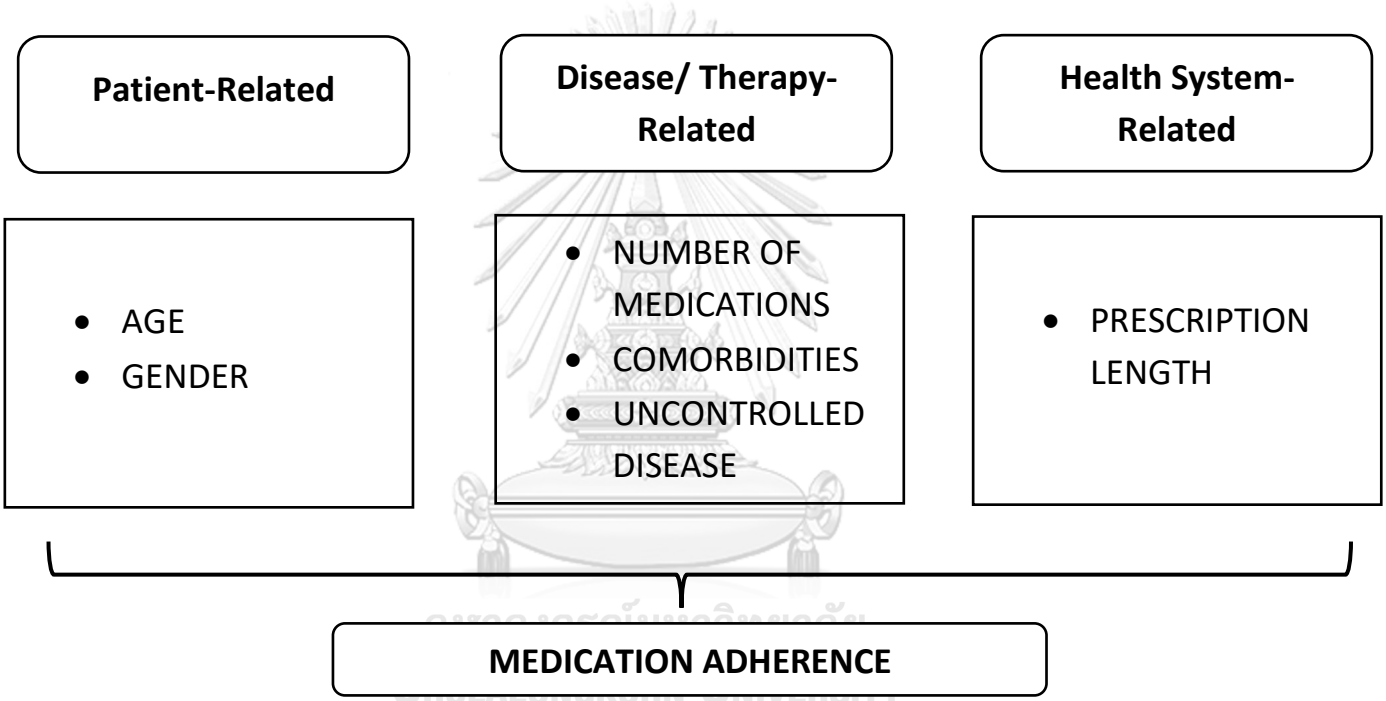

Figure 2 Factors associated with medication adherence

Both of general aspects model and factors related with medication adherence model were incorporated to construct a conceptual framework (Figure 3). In this model, patient's medication adherence will be affected by three major factors which are patient-, disease/therapy-, and health system-related factors. Then medication adherence of patient will impact to their clinical outcome and economic outcomes in the long run.

According to the first objective, medication adherence of each individual patient was measured in the study period by using medication possession ratio (MPR) method. The next step is to determine the effects of the increasing in maximum prescription refill length from 30-day to 90-day among chronic disease patients in the Phramongkutklao hospital.

For the second objective, both clinical and economic outcome of patients were evaluated. In term of clinical outcome, $HbA1_c$ and cholesterol level of each patient were analyzed. At the same time, we will assess economic outcome by calculating total healthcare costs, hospitalization costs and costs of medication per patient and compared between patients who received medication supply for thirty day and ninety day.

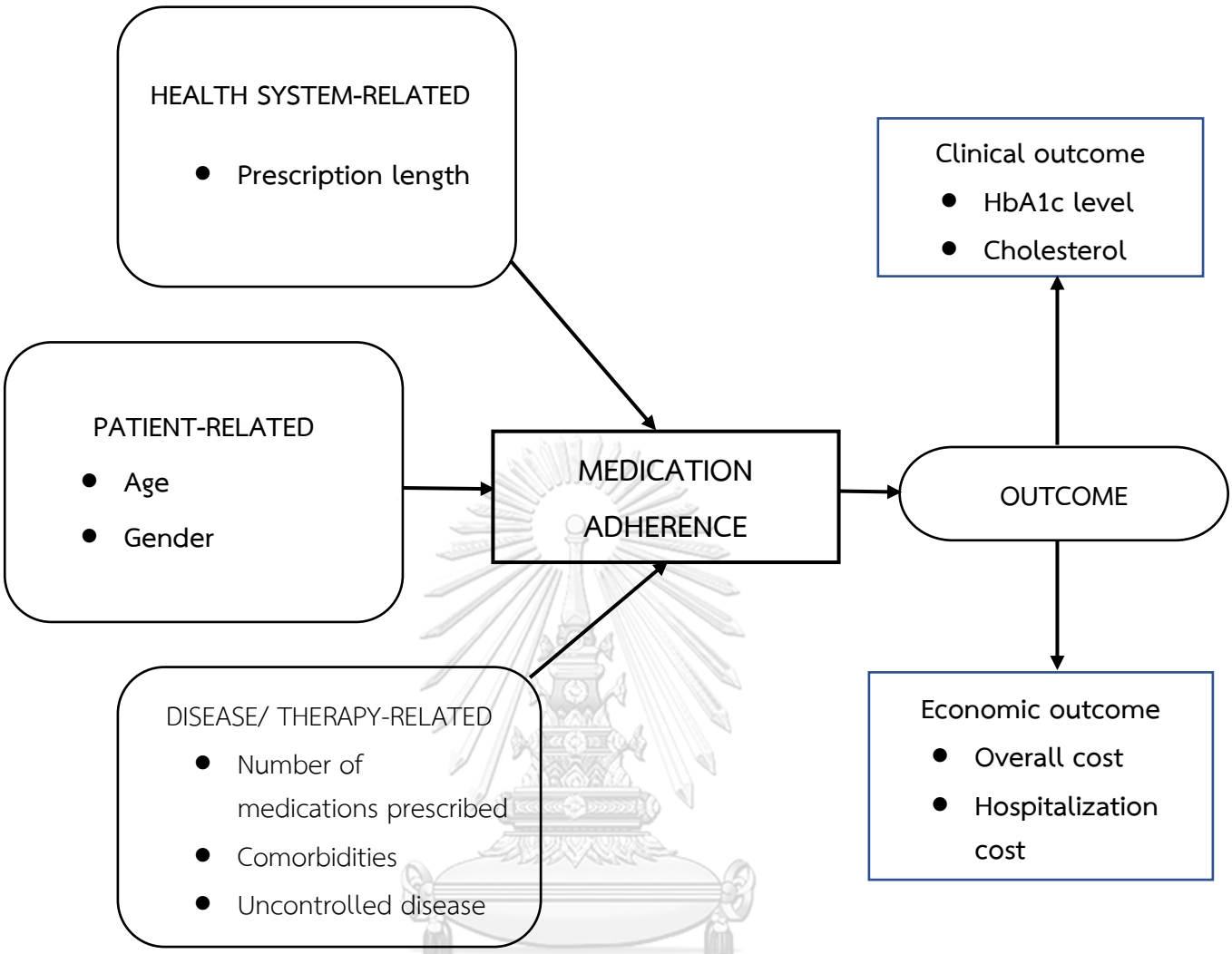

Figure 3 Conceptual Framework

1.4 Significances of the study

This study enhances the current literature in many approaches. While a few literatures have already conducted to assess the impact of prescription length on medication adherence, almost all of them are cross-sectional designs in which endogeneity is an issue[22, 26]. This study, however, is a natural experiment with control group comparing pre- and post-policy implementation. Second, the impact of prescription length on both clinical and economic impacts were estimated. Lastly, the

dominant of previous literature was conducted in the US healthcare context[17, 24, 31, 42], however, there is still limited evidence investigating the effects of duration of prescription supply on medication adherence in the low-to-middle income countries, especially in Thailand. Finding from this study will provide suggestions for hospital administrators the appropriate prescription length that maximize patient's medication adherence and patient's health outcomes while minimizing health care costs.

CHAPTER 2

LITERATURE REVIEW

This chapter illustrated a synopsis of the literatures related to the factor affecting both clinical and economic outcomes in this study. The details of the discussion were mentioned as the following:

- Medication adherence
- Factor affecting medication adherence
- Adherence measurement

2.1 Medication adherence

In the past, the most frequently used definition of medication compliance term is patient's behaviors correspond with healthcare providers' recommendations in agreement of taking prescribed medication comply with dosing regimen, interval, and continuous of medication utilization. Usually, other related term which has been used interchangeably with compliance is adherence. However, their meanings are rather disparate: adherence infers the accepting and willingness of patients to the recommendations while compliance indicates that patients have to follow to physician's advices only[14, 28]. Recently, various studies introduced the term "concordance" which represent similar concept with compliance and adherence[43, 44]. Though, this recent term focusing on the patient to the center of care, set up them as a decision-maker in the procedure and establishes physicians-patients reconciliation and understanding[28].

Regularly, the therapeutic interventions of diseases incorporate the long-lasting utilize of medications. Even if these treatments are potent in alleviating illness, their entire advantages are frequently not recognized due to nearly a half of patients do not consume their medicines as physicians prescribed[14]. Accordingly, the successful

treatment can be established only if patients act in accordance with the healthcare providers recommended.

Medication adherence is influenced by several variables including clinical and societal variables[14, 28]. In accordance with the World Health Organization (WHO)[45], these multifactorial causes of non-adherence were organized into five series of factors: socioeconomic factors, healthcare system-associated factors, disease condition-related factors, therapy-related factors and patient-related factors.

2.2 Factors affecting medication adherence

2.2.1 Patient-related factors

An extraordinary group of patients may be more likely to nonadherence due to their necessity for additional assistance or informational intervention[35]. Research have found that several demographic characteristics including age, gender, race, educational level, and marital status impact medication adherence.

2.2.1.1 Age

Considerable studies revealed that age of patients correlate with medication-adherence[25-27]. A systematic review of Jing J. et al.[28] presented an interaction between age and nonadherence, which the effect of age can be classified into three main groups: the adolescent group (age < 40 years old), the middle-aged group (age range from 40 to 54 years), and the elderly group (age above 55 years old).

Young patients experience many individual and personal problem situations. Juveniles who are suffering problems about their family, society, or their emotion themselves may challenge to adhere to medications[35]. The results from the numerous literatures are still not in one direction. Many of studies proposed that patient with younger age will have lower adherence compared with elderly[27, 31, 33, 46, 47]. According to a panel data analysis from Korea, patients in this study were categorized by age into four groups: under 45 years, from 45 to 64 years, from 65 to 74 years, and more than

74 years. The results revealed that patients who increased age in every age group were more probably to take their antihypertensive medication consistently[27]. In the US, administrative data claims were also examined and the results represented that type 2 diabetes mellitus patients who adhere to liraglutide were positively associated with age over 50 years[33]. These conclusions are persistent with results from another systematic review[28].

Although, several articles indicate that patients with older age mostly adhere to the medication prescribed, elderly patients tend to take medication incorrectly compare to younger patients due to their physical constraints[35].

2.2.1.2 Gender

The systematic review of 22 research demonstrate that gender of patient corresponded with medication adherence, but the conclusion are inconsistent[28]. Some literature described that female patients will have higher adherence than male, significantly[27, 48, 49] while a few study proposed in another way[50]. In study of Noah MI. et al., exhibited both directions of results which different in group of medication. Women patients who take beta-blockers (BBs) medications had higher adherence to men significantly. While there was a tendency that women adhere more than men in the group of patients taking Angiotensin Converting Enzyme Inhibitors/ Angiotensin II Receptor Blockers (ACEI/ARB), whereas men had high adherence than women in statins taking group[51]. Furthermore, some research concluded that they could not identify a correlation between gender and adherence[22, 52]. This result is emphasized by additional systematic review on patients' adherence to medications which concluded that gender was not detected to affect adherence[29]. Then, gender may not be a reliable predictor for medication adherence due to the uncertain conclusions.

2.2.1.3 Ethnicity

The investigation of this factor affecting non-adherence has been studies broadly in the European countries, US and Asia Pacific region[53-55]. In some studies, white

patients were more likely to have better adherence than others[54, 56], while Hispanics, African-Americans, Native Americans, Asians and other ethnic minority were determined to have relatively low adherence[53]. Nevertheless, a systematic review proposed a reasonable clarification for this factor that may be because of the language obstacle and the problem of socioeconomic status of patient in each region studied[28]. Consequently, ethnicity might not be a suitable predictor of medication nonadherence due to this factor has many confounding variables.

2.2.1.4 Marital status

There were some literatures that detected positively impact of marital status with medication adherence[57, 58]. However, Chunhua noted that there was no association among marital status and medication adherence of antihypertensive medications[50]. This result was correspond with a systematic review of Xiang CT. et al., reporting that in all twenty-five studies of schizophrenia adult patients, marital status was found no correlation with medication adherence[59]. This variation may be due to the latter studies explored the consequence of marital status in chronic diseases (hypertension, schizophrenia) which were unlike to those assessed in the earlier research, with the effect being obscured by the factors that correlated with disease.

2.2.1.5 Educational level

Various studies identified that patients who have higher educational level were more prone to have higher medication adherence than those with lower status[27, 50], while a few studies explained no correlation between both factors[60]. Supposedly, patients who have higher level of education should have more awareness about the illness and medication, for this reason they are more adherent.

2.2.2 Disease condition factors

Utilizing medication over an extended time period for treating many chronic diseases and frequently adherence to therapy regimens decreases substantially with

time. This generally occurs when patient have fluctuation or lack of symptoms, for example, hypertension and asthma may have an unfavorable adherence. It is necessary for healthcare providers to elicit patient understanding the diseases and progression if they are not treated.

2.2.2.1 Comorbidities

According to the recent study of Michael which aimed to evaluate adherence of patient with multiple sclerosis to disease-modifying drug[41]. The results revealed that patients who have depression at the beginning of the study were more likely to have lower adherence[41]. Additionally, the study of Hyekyung which proposed to explore factors impacting medication adherence in elderly patients in Korea. The results explained that elderly patients who have additional health problems were associated with decreased medication adherence[60].

2.2.3 Therapy-related factors

2.2.3.1 Therapy intricacy

Study has showed that number of prescription drugs taking does not associate with medication adherence[60], but the frequency of drug administration does[36]. The proportion of adherence declined as the amount of pill increased. This can be explained by study of Yoshitsugu Obi, et al. which adherence was evaluated by indirect method (self-reporting questionnaire). The result showed that patients taking single daily dose were significantly correlated with greater adherence with odd ratio of 0.40[61]. In addition, a meta-regression analysis concluded that patients who take cardiovascular disease drugs once-daily dose seem to be more adherent than patients taking medications twice-daily dose, significantly (83.1% and 74.2%, respectively)[62]. In this way, facilitating the frequency of medication taking could promote adherence, substantially.

2.2.3.2 Route of administration

To make patients adhere to their medications, healthcare providers should consider a convenient route of administration for them. Study in allergen immunotherapy which allowed patients to choose their way to administer medications compared adherence between subcutaneous injection and sublingual. The authors confirmed that considering favorable treatment of patients could raise their adherence to allergen immunotherapy[63]. Additionally, this result was supported by the systematic review on subcutaneous injection administration which found that way of medication delivery correspond to patient choice may improves medication adherence[37].

2.2.3.3 Adverse events of the medication

Patients are less likely to comply with therapy plan when the adverse event is frequent[35]. Numerous literatures studying about adverse events aspect demonstrated that side effects influence patient's adherence[38, 39, 64]. In a Cameroon study, the authors analyzed that patients who experience side effects of antiretroviral therapy (ART) medication were corresponded with non-adherence to medication[38]. Similarly, a study performed in the US demonstrated that schizophrenia patients who encounter with side effect of antipsychotic drug were remarkably and significantly correlated with inferior adherence[39].

2.2.3.4 Continuance of treatment period

Commonly, treating patients with acute diseases, for example, diarrhea, common cold is related with greater adherence than patients with chronic diseases. Extend period of therapy may lessen patient's adherence[40]. According to the study of Tayebeh et al**.,** glaucoma patient who have the disease for longer period of time would increase the rate of non-adherence to medication[40].

Nevertheless, the systematic review illustrated that they found some studies reported contrary result which longer period of the disease demonstrated in

satisfactory adherence[28]. This result may imply that adherence of patient is enhanced due to perception of patient about opposing the illness is decreased then they complied to the therapy after experiencing from the illness for a long time.

2.2.4 Socioeconomic factors

2.2.4.1 Cost of treatment and Income of the patient

Cost is one of an essential concern in patient's medication adherence particularly for patient with chronic condition since the duration of therapy could be lifelong[65]. If one patient has high earnings or covered by medical insurance, the cost of therapy may not impact patients' compliance as much as in patients who have lower income or do not have insurance coverage. A several literatures established that patients who did not covered by health insurance, or who obtain inadequate salary were more probably to be nonadherent to therapy[13, 29, 32, 66, 67]. Data from the US National Survey of households found that almost 10% of Americans could not purchase and refill their medications within twelve months[65]. However, in other systematic review, economic status was not significantly associated with adherence level[25]. This disagreement in findings regarding cost of treatment and patient's income may owing to different countries have different healthcare systems. For that reason, providers of health services should be concern about financial situation of patient and encourage them to utilize medication resource more efficiently.

2.2.4.2 Social support

The result from recent studies in adult type-2 diabetes mellitus patients and hypertension patients demonstrated that social assistance and support from members of the family, colleague or even medical professional team can promote patients adhere to their medications[68-70]. This factor encouraged patients in diminishing unfavorable attitudes to therapy, having consideration and perceiving to the treatment[68, 70].

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2.2.5 Healthcare system factors

The fundamental factor verified that linking to medication adherence include accessibility of patient and availability of healthcare system[28], shortage of accessibility to healthcare services, extended waiting time for outpatient department (OPD) visit, barriers for patient to fill their prescriptions[30] and undesirable experiences with healthcare services all contributed to unfavorable adherence[28].

2.2.5.1 Relationship between healthcare providers and patients

The relationship between providers-patient is one of the most important factor influencing adherence. A friendly relationship which presents reinforcement and assistance from healthcare provider, has a positive influence on medication adherence. While the absence of conversation involving advantages, guidance for medication use, side effects, and adverse effects of drugs, can also devote to medication nonadherence, particularly in elderly patients with cognition problem[22, 60].

2.2.5.2 Prescription length

Continuation of therapy for chronic diseases treatment is generally recommended as an approach of strengthening therapy response and lessening the risk of recurrence. The numerous literatures indicated that increasing length of prescription were related with higher medication adherence. From the study of Liberman reported that there has been considerable increment in dispensing prescriptions for ninety day and this tendency is expected to continue for insurance providers in the US[71]. Furthermore, the retrospective study of Michael et al. which conducted by using pharmacy claim database in the US, displayed that patients who received medication in four groups: antihypertensive, statins, oral hypoglycemic and selective serotonin reuptake inhibitors with 90-day prescription were adhere to their medication compared with those who refill with 30-day supply. Also, patients prescribed with 90-day supply had better persistency, reduced wastage and produce more saving[34]. Likewise, literature conducted by Ivers et al. described that elderly patients whom prescribed lipid-

lowering agents or statins with longer length of prescription for secondary prevention of coronary artery disease at hospital discharged appears to enhance the trend of long-period medication adherence[51]. Similarly with recent study of Thomas et al which demonstrated that extending prescription length of statins medication from thirty day to sixty day or ninety day were correlated with increasing medication adherence of patients, promote health outcomes and contribute to more saving of healthcare resources[72]. However, excessive medication supply may converse the adherence outcome. According to the study of Chen which concluded that both oversupply and undersupply compared with applicable supply of medication were correlated with lower clinical outcomes including [73].

2.3 Factors affected by medication adherence

There were many factors affected by medication adherence or medication nonadherence. Factors was categorized into two main groups by using outcomes which were clinical outcomes and economic outcomes.

2.3.1 Clinical outcomes

Clinical outcomes in this study including HbA1c level and total cholesterol level were described below.

2.3.1.1 HbA1c level

There were many studies reported the relationship between medication adherence and glycemic control. Ho et al. proposed that for each 25% increment in medication adherence was related with a reduction of HbA1c level by 0.05% significantly[74]. Additionally, Schectman et al. reported that patients who had 10% more adhere to their medication would reduce HbA1c level by 0.16%[75].

Lower level of medication adherence was also correlated with increased in HbA1c level. The study of Pladevall et al. demonstrated that diabetes patients who had non adhere to metformin medication by 10% increment, HbA1c level raised by 0.14%[76]. Furthermore, the study conducted by Lin et al. illustrated that diabetes patients who had lower adherence than 40% or non-adherence was associated with an elevated in HbA1c level by 0.38%[77]. Additionally, the results from Parris et al. supported that non adherent had a lower reduction in HbA1c level when compared with adherent by 0.06%[78].

2.3.1.2 Cholesterol level

Cholesterol level which comprised of many types of plasma lipoproteins, for instance, high-density lipoproteins (HDL); low-density lipoproteins (LDL); very-low density lipoproteins (VLDL) was widely used in clinical practice due to its association with cardiovascular diseases[79]. Many of studies were examined the relationship between cholesterol level and medication adherence. Parris et al. found that patients with dyslipidemia and diabetes mellitus who attained the target of LDL cholesterol level would have a higher medication adherence than patients who did not achieve[78]. Additionally, the study conducted by Chi et al. to evaluate the association between low-density lipoprotein (LDL) target achievement and statin medication adherence in coronary artery disease patients[80]. They displayed that adherence patients were more probably to achieve at goal of LDL-cholesterol level than nonadherent. Further, study of Batal et al. which evaluated the relationship between medication adherence and total cholesterol level reported that patients who were adhere to their statin medication (adherence ≥ 80%) were predictive of lower total cholesterol level about 18 mg/dL[31]. Specifically, Vodonos et al. also studied the association between medication adherence of statin and LDL cholesterol level by stratified statin users into three groups through their dose of therapy, including low, moderate, and high intensity. They reported that patients with higher adherence were correlated with lower LDL cholesterol level: for every 10% increasing in medication adherence contribute to reducing of LDL cholesterol by 3.5, 5.8, and 7.1 mg/dL, respectively. However, when

they adjusted for other variables to analyze the adherence effect, the result revealed that only adherence patients with high intensity statin were associated with reduce in LDL cholesterol level[81].

2.3.2 Economic outcomes

Economic outcomes including total healthcare costs, hospitalization costs and total medication costs, were reviewed in this chapter.

2.3.2.1 Total healthcare cost

Frequently, patients who had low level of medication adherence were related with a higher rate of healthcare services using, therefore with greater expenditures[82, 83]. The study of relationship between medication adherence and healthcare cost in osteoporosis patients in Korea was performed by Cho et al.[84]. They noticed that patients with greater medication adherence could cut down osteoporosis-associated healthcare cost by reducing cost of hospitalization through preventing fracture of bones. Martin et al. also supported this direction of association by their literature review. They conducted a review of association between healthcare cost and medication adherence or persistence in type-2 diabetes mellitus patients. The results of this study demonstrated that patients with better medication adherence were correlated with decreased healthcare cost[85]. Similarly, the results from systematic review proved that nonadherence patients across 14 groups of diseases were associated with larger total healthcare cost with the annual healthcare costs ranged from $949 to $44,190 USD per patient depended on their conditions[86]. The main reason was caused by the reduction of unpredictable expenses associated with emergency visit or hospitalization. Patients with better medication adherence, for example, type-2 diabetes mellitus indicated that they can managed their disease progression, which decreased the complication risks and the additional demand for healthcare services[85].

2.3.2.2 Hospitalization cost

The study using administrative database from Netherland which evaluated the impact of antihypertensive medication discontinuation on the risk of stroke and myocardial infarction detected that patients who were non persistence to their antihypertensive medication had more risk of hospital admission for myocardial infarction by fifteen percent[87]. Additionally, Aubert et al. explained that comparing with adherence patients, nonadherent had more 8 admission per 100 patients, resulting to an increment of healthcare cost per year by $ 868 USD[88]. Furthermore, the study of association between level of medication adherence and healthcare costs in Canada revealed that patients who were non adhere to their statin medication (< 80% adherence) had 7% more likely to be admitted to the hospital by resulting of coronary artery disease compared with those who were adhere to their medication[89]. They also predicted that nonadherence patients who were admitted to the hospital was associated with an increment of hospitalization costs by $1,032 USD significantly[89].

For diabetes patients, result from the study of Hong and Kang reported that patients newly diagnosed with type-2 diabetes who were non adhere to their medication developed the risk of hospitalization by twenty six percent[82].

2.3.2.3 Total medication cost

Medication or pharmacy cost is one of the most factor that affected with medication adherence[28]. The National Health Interview Survey of US from 2013-2017 was analyzed by Khera et al. to examine the factors that affected medication nonadherence[90]. They found that about 13% of patients with cardiovascular disease suffered from cost of medications. Almost nine percent of these patients consumed their medication lesser than dose recommended in the prescription and more than ten percent decided to discontinue their prescription refills to control costs. Moreover, patients who had problems with medication cost compared with patient without problems had almost eleven-fold more likelihood of asking cheap cost medications and about nine-fold higher tendency of employing non-medication therapy. A literature review conducted in type-2 diabetes mellitus patients found that patients

with higher medication adherence were more likely to have a higher pharmacy cost. However, the pharmacy rising cost was balanced by significant saving of other expense, for example, hospitalization cost, emergency visit cost[85].

2.4 Adherence measurement

As discussed above, medication adherence is meaningful to both healthcare providers and researchers. Inaccurate assessment of patients' adherence to their medications can contribute to various complexity which are likely catastrophic and vulnerability in both groups. On the contrary, precise evaluates of medication adherence can be used as a tool to monitor patients' outcome and to evaluate intervention aiming at improving medication adherence.

There are various measurements developed to measure medication adherence. The accuracy, predictability, and sensitivity of this measurement is still needed to be verified[91]. The selection of an approach to track adherence of medication should rely on the objectives that how adherence would be applied and used. Nowadays, none of these methods is accepted as a standard of excellence and the integration of approaches is suggested[92].

Most subjective assessment tools involve healthcare professional or patient on the assessment of the patient's drug-consuming behavior. The most typical tools used to estimate medication adherence level are healthcare provider evaluations and self-report[93]. However, the classical weakness of these methods is that patients are likely to understate non-adhere to medication to hide dissatisfaction from medical professionals[94].

Objective assessment comprise of pill counts, analysis of secondary database, using electronic medication event monitoring system and biological markers and are expected to perform an enhancement over subjective assessment[93]. Therefore, objective assessments should be operated to confirm and compare with the results from subjective ones. However, the results from a meta analyses explained that multi subjective assessment procedure may have greater sensitivity than applying an

individual objective assessments, but not accuracy[95]. In conclusion, subjective and objective assessments have both benefits and drawbacks and should be employed in consolidation.

2.4.1 Direct assessment

Medication adherence assessment tools can also be classified as direct and indirect measurement[96, 97]. Direct assessments involve measuring level of the medication or their metabolite concentration in blood stream or urine and then calculate the presence biologic indicator provided with the medication therapy and continuous examination behavior of patients.

Although direct adherence assessment is perceived to be the most precise and could be performed as a tangible documentation to confirm that patient has ingested the medication, there are many disadvantages respecting their practice[97]. In addition, direct assessments are costly and difficult to accomplish since many multidisciplinary healthcare teams are needed to control the process and perform the evaluations.

2.4.2 Assessment containing secondary database analysis

This type of information supports assessment adherence of medication to different types of refill adherence calculates. Refill patterns of how patients refilling their medication correlate with their medication-consuming behavior. These evaluations have a main assumption that the medication is ingested completely as prescribed[91].

Refill adherence can be mainly classified into 3 categories:

1) Dichotomous variable in which patients are classified into adherent or non-adherent depended on criteria in each setting.
2) Continuous variable which was estimated from the date that patients refill their first prescription to the last prescription in electronic database record, for instance, Proportion of Days Covered (PDC)

3) Length of gaps between prescription filled, for example, Continuous Measure of Medication Gaps (CMG), Continuous Measure of Medication Acquisition (CMA)[91].

Evaluating administrative prescription records needs an integrated computerized system[98]. This method supports an evaluation in case of a large population and this approach is generally accepted in healthcare system research. Furthermore, this method is capable to appraise adherence of multidrug and to define risk of patients failure to treatment[18].

2.4.2.1 Medication Possession Ratio (MPR)

This method measures adherence of patients by calculating the number of days of medication provided over the follow-up period where the follow-up period is fixed period[99, 100]. The deviation of denominator causes MPR complicated to perform an evaluation on a large-scale population. Therefore, suitable correlation would be essential to accommodate for long-term adherence values[101]. In addition, this method has some limitations that should be discussed. This approach does not analyze the gaps between each refill period and lack of constant treatment with multiple prescriptions[102]. Subsequently, overrated medication adherence is found during employing this approach.

2.4.2.2 Continuous Multiple Interval Measure of Medication Acquisition (CMA)

CMA value is obtained as the accumulated days of medication provide over an interval divided by the total day of follow-up period in the study. The CMA contributes the value of adherence of the whole study period. Some studies propose that MPR and CMA maintain interchangeable adherence assessing power[101].

2.4.2.3 Continuous, Single Interval Measure of Medication Gaps (CSG)

This approach analyzes time duration between patients do not expose to medication. It is computed by the sum of days that patients do not receive any medications over the sum of total days in the study interval. Unlike MPR, the CSG approach is more applicable for calculation short-term medication usage, for instance, the patients who prescribed with one prescription[103].

2.4.2.4 Continuous, Single Interval Measure of Medication Acquisition (CSA)

For the CSA value is measured using total of days that retrieved medication over the total day of the follow-up period in the study[104]. Comparable to CSG, CSA may causes bias when patient prescribed more than one prescription[103].

2.4.3 Assessment containing Electronic devices

2.4.3.1 Medication Events Monitoring System (MEMS)

Despite miscellaneous approaches had been invented for a long time, the fundamental concept of this process is that when the drug is taken out from the container, a microchip installed will store the date and time period, presuming that the patient has ingested that medication at the specific time[55, 92, 105].

This objective approach is greatly precise in various studies[105]. It helps determine if the nonadherence is intermittent or persistent or uncommon medication consuming behavior and it can determine the amount of regularly doses at any point of time on partial adherence condition. Due to these advantageous characteristics cause this method more applicable than other adherence measurement, such as self-report or using biochemical markers[105]. Moreover, the trend of misleading is smaller than performing pill count due to the patient has to open the container at the same point of time in case that they want to throw the medication away to assure that the constant adherence behavior is

recorded[18, 59]. Therefore, this method usually applied as a benchmark for verifying other adherence measurement methods.

2.4.4 Assessment containing healthcare provider evaluation and self-report

2.4.4.1 Self-report

Many literatures suppose that these methods, which are subjective measure, have the least predictable among all methods. However, their small expense, straightforwardness, and actual time response have led to their acceptance in clinical settings[106-109]. They can be conducted as a construction interrogate, online survey, self-questionnaires, and so forth. Moreover, according to their adaptability these surveys are easy to find individual worries and afterwards adjust suitable intervention[110]. Definitely, these disadvantages of this method should be concerned. Negativism in questions, blaming patients with the reason of not completely take their medication, may contribute to bias. Patient's emotional condition can also affect to the answer[111]. Consequently, the objective approaches can forecast adherence to medication of patient and are more frequently operated in clinical

2.4.4.2 Pill count

This approach is objective, and indirect assess the amount of medication that have been consumed during two clinical appointments. The amount would be analyzed with the total amount of medications prescribed to patients to determine the adherence ratio[112, 113]. The straightforward and low cost of this technique lead to its recognition and most common used procedure for evaluating patient adherence to antiretroviral therapy. However, considerable drawbacks have been established[113-116].

Firstly, this approach is unworkable in determining for the medication that used only for alleviate symptoms. Additionally, underestimation of medication adherence usually appears, because this procedure directly applies the prescribed period as the

denominator of the comparison without concerning the probability of having medication oversupply. Particularly for patients who have chronic illnesses, when they refill their prescriptions it is typical for them to refill before exhaust supply[94]. Furthermore, the cutoff point to separate patient who are adherence and patient who are nonadherence is inconsistent which can contribute to variation on verifying and comparing medication adherence of patient between studies [91].

CHAPTER 3

METHODOLOGY

This chapter demonstrated the approaches used in the study. There are seven topics comprising study design, data source, study population, definition of terms used, inclusion and exclusion criteria, study variable, and statistical analysis.

3.1 Study design

This study is an observational quasi-experiment pre-post control using a retrospective cohort from the hospital database.

3.2 Data source

Database will be obtained from Phramongkutklao hospital, a quarternary care, one of the members of the University Hospital Network (UHOSNET) and one of the largest military hospitals in Thailand. The database system used in the hospital are called Phramongkutklao Hospital Management System (PMKHMS).

The electronic medical database contains three main necessary information including:

1) Demographic characteristic of patients (gender, age, types of health coverage, hospital number)
2) Clinical information database containing disease diagnostic data by using International Classification of Diseases, Tenth Revision [ICD-10], visiting date, laboratory data, medical service.
3) Prescription details or database of pharmacy department including medication code, list of medication, dosing regimen, quantity of medication per each prescription and number of medications remaining from last to recent visit). All of doctor prescriptions were verified and dispensed by

pharmacists applying standardized procedures and any modifications in the prescriptions were recorded in the database.

The sampling framework for this study contained the whole population of patients in Phramongkutklao hospital, which is more than 50,000 of patients registered in each year.

This study got approval from the Institutional Review Board of the Royal Thai Army Medical Department (IRB-RTA) to achieve the Phramongkutklao Hospital administrative database used in this study. Data were regularly collected as an administrative claims database and were de-identified before recruit to the analysis.

3.3 Study population

In this study, I focused on chronic non-communicable diseases (NCDs) based on the definition from World Health Organization (WHO), which are the leading causes of mortality worldwide[117] also in Thai population in every recent year[118]. Moreover, this study aimed an attention on the cardiovascular disease (CVD) which is the second predominant cause of global death from NCDs next to cancer, especially ischemic heart disease and stroke[119]. Additionally, both of two diseases are correlated with alteration of lipid and glucose metabolism and primarily caused by dyslipidemia and diabetes mellitus (DM)[120, 121]. Accordingly, we decided dyslipidemia and diabetes mellitus to represent for NCDs.

This study determined patients diagnosed with diabetes mellitus and dyslipidemia by using the International Classification of Diseases, Tenth Revisions, 2016 (ICD-10) codes. For patients with type-2 diabetes mellitus, codes E10 - E14 were searched and then exclude insulin-dependent diabetes mellitus or type 1 DM: E10 and malnutrition-related diabetes mellitus: E12. The remaining codes are E11, E13, E14 which are non-insulin-dependent diabetes mellitus, other specific diabetes mellitus and unspecified diabetes mellitus, respectively[122]. Patients with dyslipidemia in this study were determined by using ICD-10 code E78, disorders of lipoprotein metabolism

and other lipidemias. The summary of ICD-10 codes for the conditions was listed in Table 1.

Table 1 Code of ICD-10 and criteria for identifying patients with designated chronic diseases

Condition	ICD-10 codes*
Diabetes mellitus	E11.X, E13.X, E14.X
Disorders of lipoprotein metabolism and other lipidemias	E78.X
*For "X" illustrate that all valid values were incorporated	

In February 2016, Phramongkutklao hospital implemented a new prescription length policy. Before 2016, beneficiaries under the universal coverage (UC) scheme were prescribed with the maximum of one-month supply while beneficiaries under the Civil Servant Medical Benefit Scheme (CSMBS) were prescribed with the maximum of three-month supply. The new policy allows beneficiaries in every health insurance scheme to receive their medication with the maximum three-month supply as this is thought to enhance the efficiency of the hospital. The overall changes were summarized in table 2.

Table 2 Length of prescription before and since 2016 in the Phramongkutklao hospital

Types of insurance	Before 2016	Since 2016
	Length of maximum prescription	Length of maximum prescription
Universal Coverage (UC)	30-day	90-day
Civil Servant Medical Benefit Scheme (CSMBS)	90-day	90-day

3.4 Definition of terms used in the study

Index date: determined as the date which the prescription of an interesting medication was prescribed during the study period.

Stable regimen: defined as patients that were prescribed with the same generic medication and the same strength.

This study had 4 major periods which are: (1) identification period, (2) pre-implementation period, (3) post-implementation period, and (4) follow-up period. We extracted the data of all patients from PMKHMS database who had been diagnosed with the purposed diseases from the first period to the last period. Six months of identification period were used to verify that patients were prescribing a medication for dyslipidemia and/ or type 2 diabetes mellitus treatment with the stable regimen. Since the Extended Dispensing Policy (EDP) was implemented on February 1st, 2016, then the study consisting of twelve months pre-implementation period before implementing EDP and twelve months post-period following with extended six months period after the end of study period which designated as follow-up period. The overall study period run from February 1st, 2015 through January 31st, 2017 as illustrated in Figure 4.

3.5 Inclusion and exclusion criteria

3.5.1 Inclusion criteria

3.5.1.1 Objective 1:

This study aimed to assess the impact of the policy which was implemented on February 1st, 2016, so data of patients were incorporated in the study if they satisfied these following criteria:

1) Patients with age at least 18 years old on the index date to exclude all pediatric patients.

2) Patients had at least one prescription (in any of the seven antihyperglycemic agent classes of interest (sulfonylureas, non-sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, SGLT-2 inhibitors or statins medication class) refilled during the study period from February 1st, 2015 to January 31st, 2016 and had at least one prescription refilled from February 1st, 2016 to February 1st, 2017. Patients also had to have at least another one prescription for related medications after the study period in six months to assure sufficient follow-up (figure 4). For the study period, defined as an interval since February 1st, 2015 through February 1st, 2017.

3) Patients had to be on a stable regimen for statins and/or antihyperglycemic agents for 180 days (six months) prior to their index date of first[72] (figure 4).

3.5.1.2 Objective 2:

1) We use patients from our analysis in objective 1. For patients with type 2 DM were required at least one lab test result of HbA_{1C} during the pre-period and at least another one lab HbA1C result after the post-period. Additionally, patients with dyslipidemia were required their serum cholesterol level at least one test during the pre-period and at least one lab of cholesterol test in the post-period.

3.5.2 Exclusion criteria

1) Patients who received their insulin prescriptions or glucagon-like peptide-1 receptor agonists (GLP-1 receptor agonists) for treatment diabetes mellitus in any of the time during the study period will be excluded. Due to inadequacy of data about insulin dosing and GLP-1 receptor agonists which are both injectable drug for individual in the secondary claim database (e.g., commonly patients treated with insulin were adjust doses frequently or using sliding scale regimen), researcher was incapable to examine the amount of daily doses for injectable medication utilization accurately[15, 75, 123]. Additionally, patients with type 1 diabetes mellitus also excluded from this study because they had to handle with insulin as the fundamental therapy.

Patients who satisfied the inclusion criteria were observed from the index date to the final dispensation date of any interesting drug class. For example, in the figure 4 a patient obtained the first medication from March 1st to May 29th, 2015. The second prescription refill was filled from June 1st to September 29th, 2015. Then, the last prescription refill started from October 1st to December 30th, 2015. Therefore, patient was followed up from March 1st to December 29th, 2016 for any generic name of interesting medication. In the situation of patient having more than one medication within the same therapeutic class for different numbers of days during a refill, we applied method of Karen LT. et al.[124] which used the average value of class-specific calculation. For example, if patient received two classes of antihyperglycemic medication, each medication will be calculated for medication adherence. Then average the value of all medication adherence.

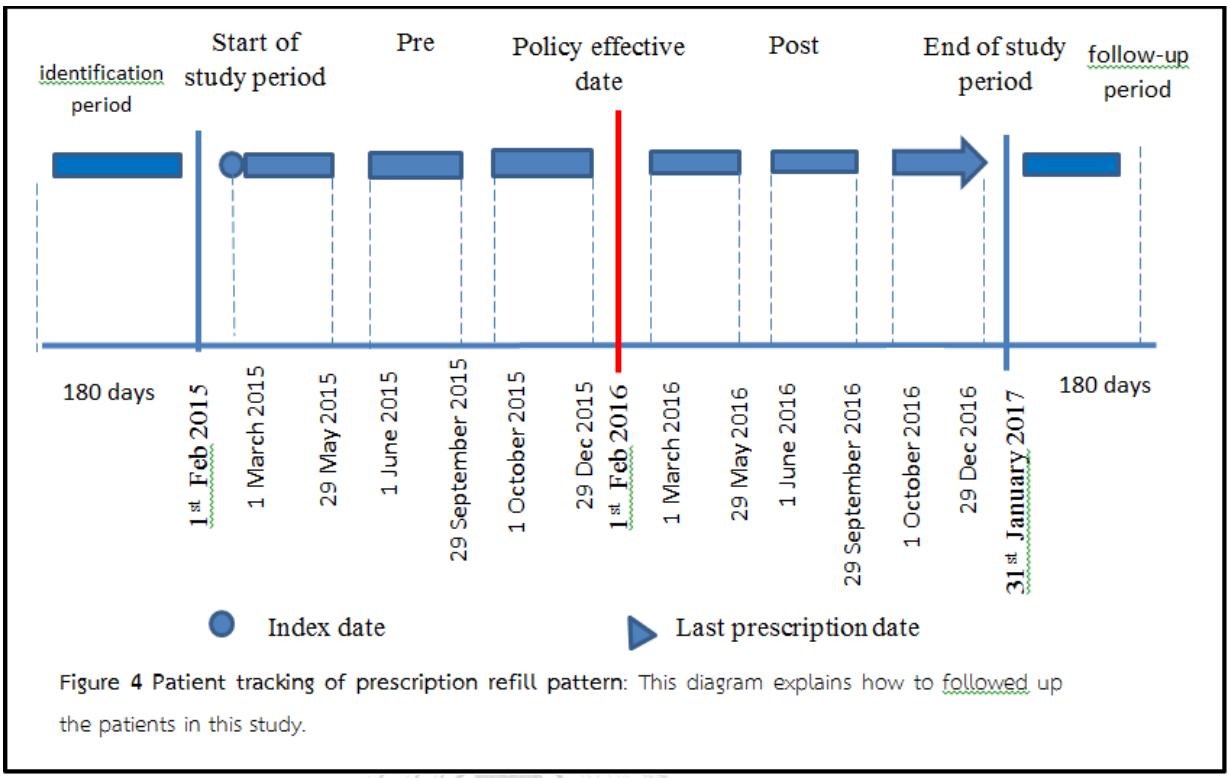

Figure 4 Patient tracking of prescription refill pattern in study period

3.6 Study variables

3.6.1 Objective 1: To determine the effects of the increasing in maximum prescription refill length from 30-day to 90-day among chronic disease patients in Phramongkutklao hospital.

➢ **Outcome of interest**

For patients with chronic disease, the essential component for favorable treatment outcome such as lower risk of complications, minimize risk of hospitalization and fatality as well as contain healthcare expenditure is an adherence to medication[17, 46, 72, 124]. Thus, medication adherence of patients is picked as an outcome of interest.

In this study, we calculate medication adherence measurement for each of 8 medication classes: by using the Medication Possession Ratio (MPR)

➢ *Medication Possession Ratio (MPR)*

We used the medication possession ratio (MPR) as a proxy to verify medication adherence. The MPR calculation is the most popular method, in which the total days of each medication therapy class provided to patients divided by total day that patient follow-up in the study[9, 17, 31, 34]. As a result, MPR value run from 0 to 1. The MPR assessment of individual is computed from the pharmacy administrative database, by operating the following formula:

$$MPR = \frac{\text{Total days of medication provided}}{\text{Total days of follow} - \text{up}}$$

This formula was applied with the assumption that all daily statins and antihyperglycemic medications were all took by the patients. Although, one notable drawbacks of using claim database to estimate medication adherence is the weakness to approve that refill prescription associate with medication used. However, literature have revealed a high correlation between medication adherence calculated from secondary database and pill counts, indicating that the portion which patients replenish their medication prescriptions is generally dependable with the portion at which patients consume their medications[125, 126].

Every adherence ratio was assessed for two patient cases: one who recruited during the year prior to the implementation of the maximum prescription length supply policy (set as a baseline) and another one who entered during the year after the implementation (set as an intervention). The baseline year started from February 1st, 2015 through January 31st, 2016 (365 days), and the intervention year started from February 1st, 2016 through January 31st, 2017 (366 days).

According to the recent clinical practice guidelines, statins are the most cost-effective medications and most generally used to the treatment of dyslipidemia[127, 128]. Furthermore, seven medication classes of antihyperglycemic medication which used in this study are systematically recommend in current national practice guidelines and are generally used in diabetes mellitus evaluation study[129-131]. Therefore, we selected

statins to represents for treatment patients with dyslipidemia and seven medication classes of antihyperglycemic medication (sulfonylureas, non-sulfonylureas, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium glucose co-transporter subtype 2 inhibitors) for treatment patient with diabetes mellitus.

The medication in this study were identified by using their specific medication code in the hospital. For statins and oral antihyperglycemic medication list available in Phramongkutklao hospital including generic name, strength, dosage form, and code were described in table as follow:

Table 3 Medication classes in the study; their generic name, strength, and codes

Diseases condition	Medication therapy classes	Generic name of medications	Code of medications
Diabetes Mellitus	Sulfonylureas	Glibenclamide 5 mg tablet	GLI103N
		Glipizide 5 mg tablet	GLI101N
		Glimepiride 2 mg tablet	AMA102N
		Glimepiride 3 mg tablet	AMA103N
		Gliclazide 30 mg tablet	GLI106N
		Gliclazide 60 mg MR tablet	DIA110N
		Gliclazide 80 mg tablet	GLI107N
	Non-sulfonylureas	Repaglinide 1 mg tablet	NOV102N
		Repaglinide 2 mg tablet	NOV103N
	Biguanides	Metformin 500 mg tablet	MET101E
		Metformin 850 mg tablet	MET105E

Diseases condition	Medication therapy classes	Generic name of medications	Code of medications
		Metformin 1,000 mg XR tablet	GLU107E
	Thiazolidinediones	Pioglitazone 15 mg tablet	PIO102E
		Pioglitazone 30 mg tablet	PIO101E
		Pioglitazone 45 mg tablet	ACT108N
	Alpha-glucosidase inhibitors	Acarbose 100 mg tablet	GLU104N
		Voglibose 0.2 mg tablet	BAS101N
	Dipeptidyl Peptidase-4 inhibitors (DPP-4 inhibitors)	Sitagliptin 100 mg tablet	JAN101N
		Vildagliptin 50 mg tablet	GAL101N
		Saxagliptin 5 mg tablet	ONG100N
		Linagliptin 5 mg tablet	TRA109N
	Sodium Glucose Co-transporter subtype 2 inhibitors (SGLT-2 inhibitors)	Empagliflozin 10 mg tablet	JAR101N
		Dapagliflozin 10 mg tablet	FOR101N

Diseases condition	Medication therapy classes	Generic name of medications	Code of medications
Dyslipidemia	Statins	Simvastatin 10 mg tablet	SIM103E
		Simvastatin 20 mg tablet	SIM101E
		Simvastatin 40 mg tablet	SIM102E
		Rosuvastatin 10 mg tablet	ROS103N
		Rosuvastatin 20 mg tablet	ROS104N
		Pitavastatin 1 mg tablet	LIV102N
		Mevalotin 20 mg tablet	MEV103N
		Mevalotin 40 mg tablet	MEV104N
		Atorvastatin 20 mg tablet	ATO102N
		Atorvastain 40 mg tablet	ATO103N
		Atorvastatin 80 mg tablet	LIP110N
		Fluvastain 80 mg XL tablet	LES103N

Firstly, to calculate MPR value clearly, days of medication dispensed at least one class of interesting medication along follow-up period were summed. As the initiation date of the assessment period is March 1st, 2015 (Figure 2), any prescription fills preceding to this date are not included to the calculation, although the effect of prescription fill may expand into the assessment period. Accordingly, the prior supply is not included to the calculation. Also, the prescription refill which falls outside of the study interval was truncated. As demonstrated in Figure 5, the patient retrieved a 90-day prescription refill on December 29th, 2015. The medication will be depleted by March 28th, 2016; however, the evaluation for pre-implementation period terminates

on February 1st, 2016. Therefore, the 90-day supply of medication was reduced to 34-day supply.

Next, verified overall follow-up period by subtract the index date with the end of follow-up date in each year, or finished at the first time of death, or patient who did not receive any interesting medication for a duration of at least 90 days (or a gap or therapy) were considered as discontinuation of therapy[33, 100]. Furthermore, if the patients were admitted to the hospital, number of the days with medication prescribed were considered as days with each medication available.

Then, divide the total number of medications dispensed from step 1 by the number of days calculated in step 2 to retrieve the MPR for individual patient.

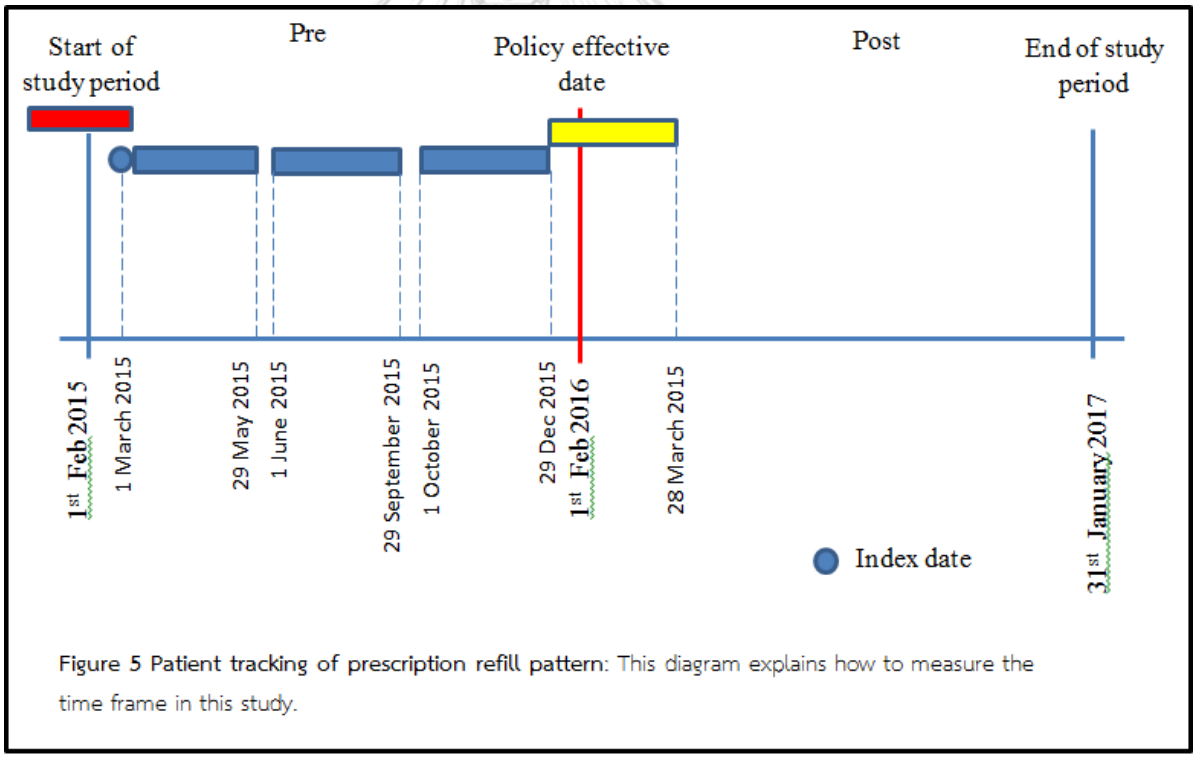

Figure 5 Patient tracking of prescription refill pattern: This diagram explains how to measure the time frame in this study.

Figure 5 Patient tracking of prescription refill pattern in transition period

For each therapeutic class of medication listed above were calculated a medication possession ratio for individual patient for each of the two years investigations. For instance, if a total of patient prescribed a whole medication supplied of 275 days in a follow-up period and if the patient's first dispensed of the drug is on day 22 on the year, so the follow-up period is 345 days (365-22 = 343). Therefore, this patient would have a medication possession ratio of 0.80 (obtained from 275 days of medication supplied divided by 343 days of follow-up).

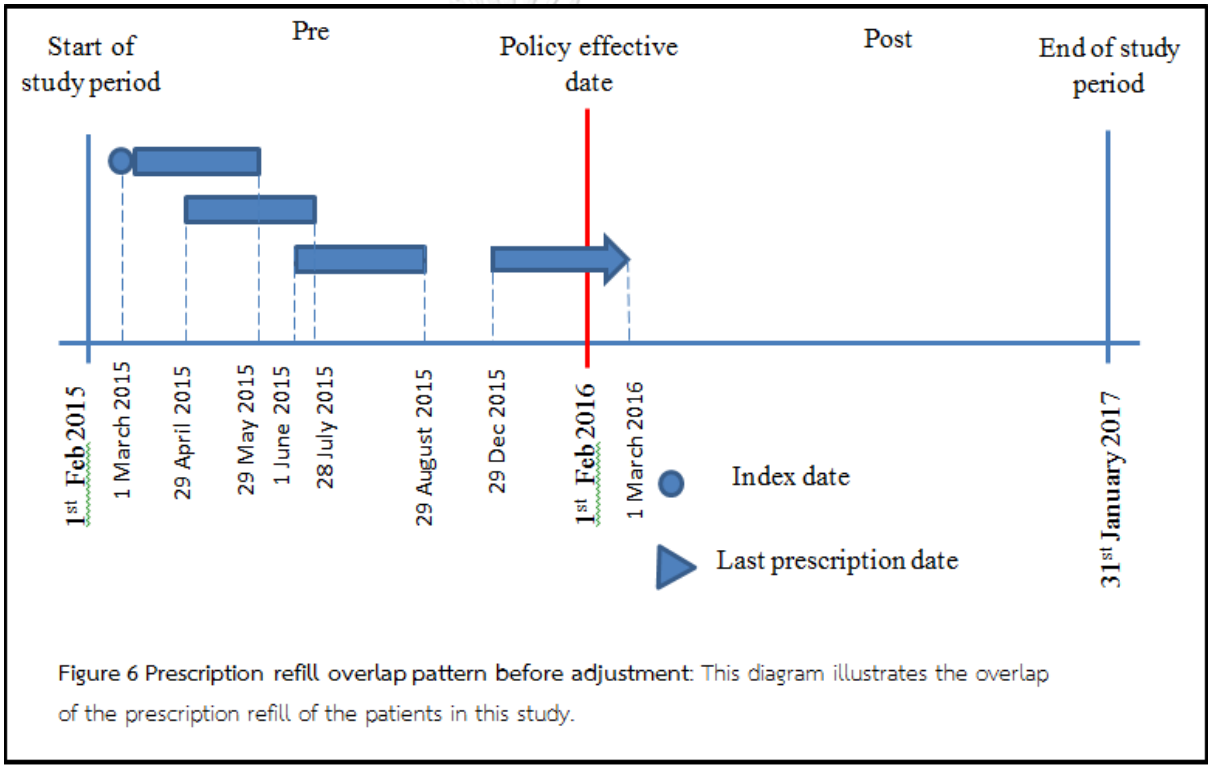

Figure 6 Prescription refill overlap pattern before adjustment: This diagram illustrates the overlap of the prescription refill of the patients in this study.

Figure 6 Prescription refill overlap pattern before adjustment

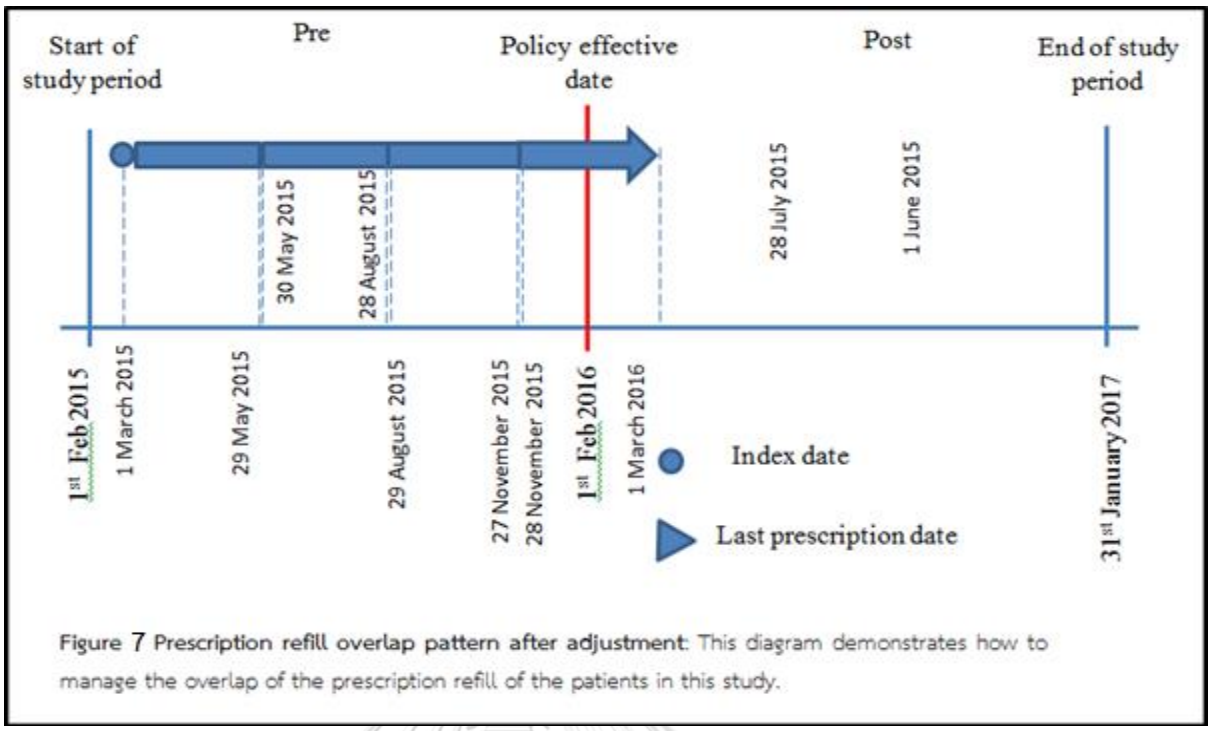

Figure 7 Prescription refill overlap pattern after adjustment

On account of pharmacy claims database, patients adhere to medications about 80% of the period is correlated with enhanced control of hypercholesterolemia[132], diabetes mellitus[133], and cut down mortality rate in patients with heart disease[132, 133]. Accordingly, this cut-off point has widely been classified as adherent in many research[46, 73, 99, 100]. Thus, the MPR was acknowledged agreeable if the computed value is ≥ 0.8 while a calculated MPR below than 0.8 demonstrates as undersupply of medication and was considered nonadherence to medication[17, 99, 134]. Whereas the value of MPR larger than 1.2 was truncated to 1.2[124].

3.6.2 Objective 2: To assess the clinical and economic outcomes of increasing prescription refill length from 30-day to 90-day among chronic disease patients in the Phramongkutklao hospital

- **Outcome of interest**

For the objective 2.1, we applied clinical outcome of patient as a proxy for assess health impacts. We decided HbA1c level and cholesterol level as a marker for diabetes mellitus and dyslipidemia patients, respectively.

For the objective 2.2, we calculated three types of cost to use as a proxy for assess economic impacts which are total healthcare costs, hospitalization costs, and total medication costs.

- **Independent variables, clinical variables and covariates**

In this study, numerous confounding variables will be adjusted using the regression model analysis including patient demographics, diseases-related and healthcare system-related factors. For patient characteristics, we adjusted for three demographic variables which are age, gender and health insurance of patient.

1. Demographic variables/ patient-related variables

In this group of variables containing of sociodemographic of patients which are age, gender, health insurance coverage.

1.1 Patient age was considered as continuous variable and determined when patient received prescription at the first time in the database linked to their date of birth.

1.2 Gender was managed as nominal scale which are male and female. We assigned value “0” for female patient while a value “1” was allocated.

2. Therapy- and diseases-related variables

This group of variables including the complexity of medication therapy which combines the number of medications, comorbidities, and uncontrolled of chronic diseases.

2.1 The number of concurrent medications prescribed at index date

This variable was reported as number of medication and then separated into two categories as follow:

Table 4 Classification of number of concurrent medications

Number of concurrent medications	Classified groups
Only one medication	1 medication
More than one medication	>1 medication

2.2 Comorbidities

For the medical comorbidity status were screened to be chronic conditions by using the definition of the World Health Organization's definition of chronic conditions[135]. The chronic diseases were described using ICD-10 codes from patients' database. To adjust for the existence of other illnesses, the Charlson Comorbidity Index score was evaluated for each year[136].

Table 5 List of comorbidities and score of each condition

Comorbidities	Weighted score
Myocardial infarction	1
Congestive Heart Failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic Pulmonary disease	1
Mild Liver disease	1
Rheumatic disease	1
Peptic Ulcer disease	1
Diabetes without chronic complication	1
Diabetes with end organ damage	2
Hemiplegia/ paraplegia	2
Renal disease	2
Any malignancy/ lymphoma/ leukemia	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS/ HIV	6

2.3 Uncontrolled of chronic diseases

Data from the literature review reported that uncontrolled of chronic diseases, such as dyslipidemia, hypertension, and diabetes mellitus were associated with nonadherence to medication. Therefore, improper control of chronic diseases was measured by "if the patient was admitted to the hospital or had visit an emergency department for disease-associated situations". I used patients' history of having hospitalization to the hospital. This variable was ranged from 0 to 1 all along 12-month period which 0 value represented patient has no history of hospital admission in the period of this study while value of 1 displayed that each patient has at least one hospital admission in the study period.

3. Healthcare system-related variables

3.1 Time variable (Time dummy variable)

We also incorporate time dummy variables to adjust for the time of changing policy during 2015 to 2017. For the time-period before the policy has been implemented in 2015, we assigned "pre variable" and given value "0" for this variable. While the time-period after the policy implemented in 2016, a "post variable" with value "1" was allocated. Scores were determined separately for each variable.

3.2 Intervention variable (Intervention dummy variable)

For changes in length of prescription supply, we identify a treatment group (UC insured) and a control group (CSMBS insured). We assigned this variable with "1" if patient were UC insured and "0" if patient were CSMBS insured.

Table 6 Summary table of the study variables

Variables	Unit of analysis	Data source	Definition
Objective 1: Outcome variable			
Medication Possession Ratio (MPR)	Patient	Phramongkutklao database claims (PMK database)	Total days of each medication therapy class provided to patients divided by total day that patients were followed-up in the study
Patient-related variables			
Age	Patient	PMK database	Date of birth at the index date
Gender	Patient	PMK database	Male/ Female
Disease/ Therapy-related variables			
No. of medications	Patient	PMK database	number of medication that patients were prescribed at that time
Comorbidities	Patient	PMK database	Calculated by using Charlson Comorbidity Index
Uncontrolled of chronic diseases	Patient	PMK database	History of admit to the hospital
Healthcare system-related variables			
Time variable	Dummy variable	Phramongkutklao database claims	Time of changing policy during 2015 to 2017. Assign value “0” for the time period before the policy has been implemented in 2015 and assigned value “1” for period after the policy implemented in 2016
Intervention variable	Dummy variable	Phramongkutklao database claims	Assigned 1 if UC insured, 0 if CSMBS insured

3.7 Statistical analysis

3.7.1 Objective 1: To determine the effects of the increasing in maximum prescription refill length from 30-day to 90-day among chronic disease patients in the Phramongkutklao hospital.

The baseline characteristics of the patient will be reported as frequency counts (N) and percentages (%). Age of patient was described as means and standard deviations (Mean ± S.D.) while gender was expressed as frequencies of male and female. Furthermore, these baseline attributes were analyzed by employing the chi-square test for categorical variables and the t-test for continuous variables.

Multivariable logistic regression was performed to determine the relationship between prescription length, and medication adherence by adjusting for patient baseline characteristics and diseases-related variables (age, gender, Charlson Comorbidities Score, concurrent medications used, uncontrolled diseases). A model will be analysed separately for patients with dyslipidemia and diabetes mellitus. The magnitude of the correlation between interesting variable is displayed as an adjusted odds ratio (aOR) with confidence intervals (CI) with percentage of ninety-five were examined and *p* values were examined to be statistically significant when value were lower than 0.05

According to the study design, which was a natural experiment, a difference-in-differences method was applied. Generally, this is an approach to measure treatment effects from the changing of the policy by adjusting for confounding factors which time is the major difference and used to appraise the impact before and after a policy implemented. We identify a treatment (patients in the UC) and a control (patients in the CSMBS) group, as well as a post-period (post-2016, after implement the policy) and a pre-period (pre-2016, before implement the policy). The main equation for evaluating the impact of policy implemented is as follow.

$$logit(\Pr(y = 1|time, intervention)) = \beta_0 + \beta_1 time_{ti} + \beta\ intervention_{ti} + \beta_3 time \cdot intervention_{ti} + \varepsilon$$

y = Adherence to the medication which "1" value represent for adhere to medication while "0" represent for non-adhere to medication.

$_t$ = this subscription indicated time period before policy implemented and after policy implemented.

$_i$ = this subscription indicated each patient from 1 to n.

$time_{ti}$ = dummy variable of time period. If the time during 2015-2016 (before policy implemented) a "0" value was given and if the time period since 2016-2017 (after policy implemented) a "1" value was given.

$intervention_{ti}$ = dummy variable of group of patients that affected by the policy. For the patients in the UC which were affected by the policy (intervention group) was given value of "1" while the patients in the CSMBS which were not affected by the policy (control group) was given value of "0".

$time.intervention_{ti}$ = impact of the policy on the medication adherence that change over time

With two groups represented by intervention variable (1 = intervention group and 0 = control group) and two periods displayed by time variable (0= before and 1= after policy implemented), the accepted trend corresponds to a simple model of intervention and control outcome. In order to demonstrate that the estimate of β will build up the DiD estimate, each value of time and intervention variable were put in the equation:

For the control group in pre-period:

$$logit(\Pr(y = 0|time, intervention)) = \beta_0 + \beta_1(0)_{ti} + \beta\ (0)_{ti} + \beta_3(0)\cdot(0)_{ti}\varepsilon$$

$$logit(\Pr(y = 0|time, intervention)) = \beta_0$$

For the control group in post-period

$$logit(\Pr(y = 0|time, intervention)) = \beta_0 + \beta_1(1)_{ti} + \beta\ (0)_{ti} + \beta_3(1)\cdot(0)_{ti} + \varepsilon$$

$$logit(\Pr(y = 0|time, intervention)) = \beta_0 + \beta_1$$

For the intervention group in pre-period

$$logit(\Pr(y = 1|time, intervention)) = \beta_0 + \beta_1(0)_{ti} + \beta\ (1)_{ti} + \beta_3(0)\cdot(1)_{ti} + \varepsilon$$

$$logit(\Pr(y = 1|time, intervention)) = \beta_0 + \beta$$

For the intervention group in post-period

$$logit(\Pr(y = 1|time, intervention)) = \beta_0 + \beta_1(1)_{ti} + \beta\ (1)_{ti} + \beta_3(1)\cdot(1)_{ti} + \varepsilon$$

$$logit(\Pr(y = 1|time, intervention)) = \beta_0 + \beta_1 + \beta + \beta_3$$

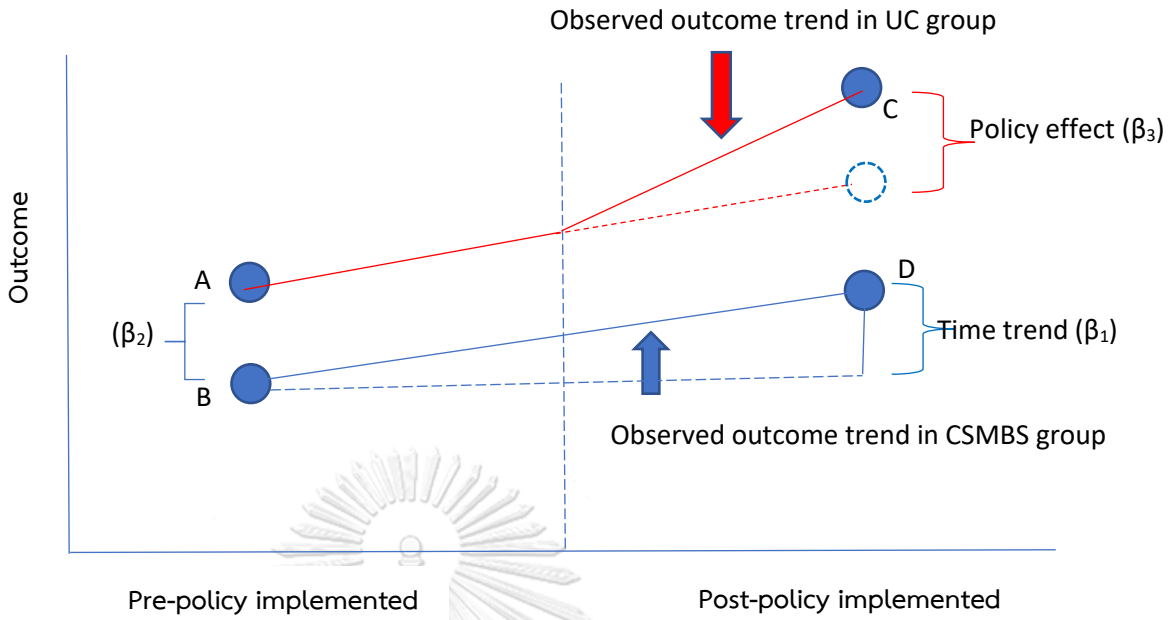

Figure 8 Difference-in-Differences estimation

We examined the impact of the policy separately for type-2 diabetes and dyslipidemia patient by using multiple logistic regression analysis. It was possible that some patients were prescribed with both classes of medications. In this situation, patient's medication adherence was investigated for both analyses.

3.7.2 Objective 2: To assess the clinical and economic outcomes of increasing prescription refill length from 30-day to 90-day among chronic disease patients in Phramongkutklao hospital

In this objective, we separated the analysis into two sections which were clinical and economic outcomes.

3.7.2.1 Objective 2.1: Clinical outcomes of increasing prescription refill length from 30-day to 90-day

For this objective, two outcomes of measurement are the HbA_{1C} and cholesterol level of the diabetes mellitus and dyslipidemia patients, respectively. In this study, these outcomes will be continuous variables. These variables were obtained for any patient at baseline of the study in pre-period and post-period. During study period, many HbA1c outcomes were investigated. We demonstrated the HbA1c levels as individual patient's average HbA1c levels per 1-year study period which are pre-period and post-period. In the same way, if > 1 value of lipid profile, including serum total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides, were documented, the average of all values was applied. Glycemic control and other metabolic parameters alter from baseline until the end of study period were measured in term of difference in mean.

The predictor variable is the medication adherence which the value run from 0 to 1. We will adjust the model with patient characteristics and diseases-related variables (age, gender, Charlson Comorbidities Score, concurrent medications used, history of admit to the hospital).

A stepwise multiple linear regression was performed to determine the association between medication adherence and clinical outcomes. The model will be analyzed separately for patients with dyslipidemia and type-2 diabetes mellitus.

For type-2 diabetes mellitus patients

Multiple regression models:

$$Y = \beta_0 + \beta_1 MPR_{ti} + \beta_2 Age_{ti} + \beta_3 Gen_{ti} + \beta_4 Med_{ti} + \beta_5 Class_{ti} + \beta_6 Comorbid_{ti} + \beta_7 Charlson_{ti} + \varepsilon$$

Y = interested health outcome which is HbA_{1c} level

$_t$ = this subscription indicated time period before policy implemented and after policy implemented.

$_i$ = this subscription indicated each patient from 1 to n.

MPR = medication adherence of patient measured by using MPR value which range from 0 to 1

Age = age of patients

Gen = gender of patients

Med = number of medications prescribed at the index date

Class = Class of medications prescribed

Comorbid = comorbidities of patients

Charlson = Charlson comorbidity index of patients

ε = error terms

For dyslipidemia patients

Multiple regression models:

$$Y = \beta_0 + \beta_1 MPR_{ti} + \beta_2 Age_{ti} + \beta_3 Gen_{ti} + \beta_4 Med_{ti} + \beta_5 Class_{ti} + \beta_6 Comorbid_{ti} + \varepsilon$$

Y = interested health outcome which is Cholesterol level

$_t$ = this subscription indicated time period before policy implemented and after policy implemented.

$_i$ = this subscription indicated each patient from 1 to n.

MPR = medication adherence of patient measured by using MPR value which range from 0 to 1

Age = age of patients

Gen = gender of patients

Med = number of medications prescribed at the index date

Class = Class of medications prescribed

Comorbid = comorbidities of patients

ε = error terms

3.7.2.2 Objective 2.2: Economic outcome of increasing prescription refill length from 30-day to 90-day

To evaluate the effect of increasing prescription refill length on healthcare expenses of patients with stable chronic diseases, we use patient-level data from the objective 1 to calculate cost.

Study perspective

The cost analysis was operated from the societal perspective.

Costs calculation

This study conducted on societal perspective which affect to the cost calculated in this perspective. We consider all cost including direct medical cost, direct non-medical cost, and indirect cost for societal perspective. We introduce the costs to healthcare provider sector as well as the costs to patients and their family or caretakers.

Direct medical costs included medication costs, cost of laboratory tests (a follow-up test of lipids profile, fasting plasma glucose, HbA1c level, urine albumin, and creatinine ratio), cost of physician fee, cost of pharmaceuticals, cost of ambulatory visit, also cost of hospitalization. We gathered the cost of medications from the Drug and Medical Supply Information Center (DMSIC), Ministry of Public Health.[137] Additional unit costs were collected from secondary sources like the Health Intervention and Technology Assessment program (HITAP), Ministry of Public Health.[138] With the intention to determine the actual prescription medication costs, the number of pharmacy visits were multiplied by cost of pharmaceuticals, also frequency of doctor visits were multiplied by cost of physician fee.

Direct non-medical cost was comprised time cost, transportation cost, meal cost and personal care cost. Personal caregiver cost was considered applying the opportunity cost approach which evaluates the cost of informal caregiver earnings lost owing to concentrating time on providing personal care.[139] We assumed that one elderly patient (age ≥ 60 years old) need one caregiver along the time in the hospital

and therefore personal care cost was expressed by calculating the average hourly wage rate with the total hours the caregivers was expected to spending time on patients.

Indirect cost was calculated by using human-capital procedure which contained the cost of absenteeism. We obtained minimum wage rate in Bangkok, which Phramongkutklao hospital is located, from Ministry of Labour[140] then multiplied by total time of patients spent, since they went out from their home to the hospital, through healthcare process until came home, which was specified to six hours by average[138] and divided by total working hours per day, which generally not exceed eight hours or maximum of eight hours per day.

Also for cost estimated, costing data from Thailand database and literature were accessed then adjusted to 2015 values by applying with net present value approach using discounted rate at 3%[141]. For comparing money value between Thai baht (THB) to United States dollar (USD), we use exchange rate from Bank of Thailand with rate about $1 ≈ 31.227 THB.[142]

Table 7 Medication and healthcare services costs

Parameter	Cost	Adjusted cost*		Reference
		Pre-period	Post-period	
Cost				
Direct medical costs				
→Medication cost				Drug Medical Supply and Information Center (DMSIC), Ministry of Public Health[137]
Statins				
Simvastatin 10 mg tablet	0.5	0.44	0.46	
Simvastatin 20 mg tablet	0.75	0.67	0.69	
Simvastatin 40 mg tablet	1.35	1.20	1.24	
Rosuvastatin 10 mg tablet	17.2	15.28	15.74	
Rosuvastatin 20 mg tablet	21.4	19.01	19.58	
Pitavastatin 1 mg tablet	15	13.33	13.73	
Pravastatin 20 mg tablet	20.72	18.41	18.96	
Pravastatin 40 mg tablet	33.17	29.47	30.36	
Atorvastatin 20 mg tablet	15.15	13.46	13.86	
Atorvastain 40 mg tablet	25	22.21	22.88	
Atorvastatin 80 mg tablet	50	44.42	45.76	
Fluvastain 80 mg XL tablet	21.77	19.34	19.92	

Parameter	Cost	Adjusted cost*		Reference
		Pre-period	Post-period	
Sulfonylurea				
Glibenclamide 5 mg tablet	0.25	0.22	0.23	
Glipizide 5 mg tablet	0.23	0.20	0.21	
Glimepiride 2 mg tablet	3.75	3.33	3.43	
Glimepiride 3 mg tablet	5.14	4.57	4.70	
Gliclazide 30 mg tablet	2.15	1.91	1.97	
Gliclazide 60 mg MR tablet	10.7	9.51	9.79	
Gliclazide 80 mg tablet	0.88	0.78	0.81	
Nonsulfonylurea				
Repaglinide 1 mg tablet	7.01	6.23	6.42	
Repaglinide 2 mg tablet	7.01	6.23	6.42	
Biguanides				
Metformin 500 mg tablet	0.4	0.36	0.37	
Metformin 850 mg tablet	0.6	0.53	0.55	
Metformin 1,000 mg XR tablet	7.13	6.33	6.52	

Parameter	Cost	Adjusted cost*		Reference
		Pre-period	Post-period	
Thiazolidinediones				
Pioglitazone 15 mg tablet	0.95	0.84	0.87	
Pioglitazone 30 mg tablet	1.83	1.63	1.67	
Pioglitazone 45 mg tablet	2.85	2.53	2.61	
Alpha-glucosidase inhibitors				
Acarbose 100 mg tablet	5.43	4.82	4.97	
Voglibose 0.2 mg tablet	3.43	3.05	3.14	
Dipeptidylpeptidase-4 inhibitors				
Sitagliptin 100 mg tablet	32.68	29.04	29.91	
Vildagliptin 50 mg tablet	19.60	17.41	17.94	
Saxagliptin 5 mg tablet	32.50	28.88	29.74	
Linagliptin 5 mg tablet	37.72	33.51	34.52	
SGLT-2 inhibitors				
Empagliflozin 10 mg tablet	44.94	39.93	41.13	
Dapagliflozin 10 mg tablet	44.94	39.93	41.13	

Parameter	Cost	Adjusted cost*		Reference
		Pre-period	Post-period	
→Treatment cost				
Physician fee (OPD)	67	80.0	82.40	Standard cost lists for Health Technology Assessment (HTA)[138]
Pharmacist fee	67.94	81.12	83.56	
Hospitalization cost	1,215	1,450.77	1,494.30	
→Lab test cost				
Lab test for lipids profiles	270	322.39	332.07	
Lab test for fasting plasma glucose	54	64.48	66.41	
Lab test for HbA1c	202	241.20	248.43	
Lab test for urine albumin	364	434.64	447.67	
Lab test for creatinine ratio	67	80	82.4	
Direct non-medical costs				
→Transportation cost (per person per visit)	142.55	170.21	175.32	
→Meal cost (per person per visit)	52.51	62.70	64.58	

Parameter	Cost	Adjusted cost*		Reference
		Pre-period	Post-period	
→Caregiver cost (per person per year; additional for patient ≥ 60 years old)	443.31	447.05	460.47	
Indirect cost				
→Productivity loss cost	248.25	214.14	220.57	

*Cost adjusted by applying net value approach using discounted rate at 3%

Median costs and differences among direct-, indirect- and total costs between 30-day supply and 90-day supply group were analyzed. To examine healthcare costs, we operated multiple linear regression model[33] and then adjusting for major covariates including age, gender, Charlson Comorbidities Score, concurrent medications used, uncontrolled diseases. Additionally, total healthcare cost, hospitalization cost, and total medication cost were separately analyzed in each model.

Multiple linear regression models:

$$Y = \beta_0 + \beta_1 MPR_{ti} + \beta_2 Age_{ti} + \beta_3 Gen_{ti} + \beta_4 Med_{ti} + \beta_5 HbA1c_{ti} + \beta_6 Admit_{ti} + \beta_7 Class_{ti} + \beta_8 Comorbid_{ti} + \beta_9 Charlson_{ti} + \varepsilon$$

Y = healthcare cost which were total healthcare cost, hospitalization cost, and total medication cost

MPR = medication adherence of patient measured by using MPR value which range from 0 to 1

Age = age of patients

Gen = gender of patients

Med = number of medications prescribed at the index date

HbA1c = lab test of HbA1c of each patient

Admit = History of admit to the hospital

Class = Class of medications prescribed

Comorbid = comorbidities of patients

Charlson = uncontrolled diseases of patients

ε = error terms

3.7.3 Objective 3: Overall impacts of policy change from key informant perspectives

In this objective, we performed descriptive exploratory design to attain valuable data and examine consequences from different perspective within the context of policy change in Phramongkutklao hospital.

Design, setting, and participants

A purposive sampling was used to choose pharmacist members, and patients based on their information and role in policy revision and implementation of increasing prescription length in Phramongkutklao hospital. The pharmacist members election was depended on their workplace in different departments in the hospital where pharmacy services were provided. There were four main departments of pharmacists including outpatient department, inpatient department, logistics department, and pharmaceutical production department. Both male and female pharmacists in each department were selected in the interview. For the patients were selected based on their impacts from policy implemented. To assure diversity of interviewees, both male and female from hospital units were selected to join in each interview.

Participants were all interviewed at least three months after the policy was implemented (between May 2016 and January 2017) to make sure that every participant especially patient-participant was already affected from the policy implemented.

Interview instrument and data collection

One-on-one in-depth interviews were semi-structured with open-ended questions created to obtain respondents' perspectives about the policy revision. The tool for pharmacist interviewees containing of three parts: Part I- demographic data, Part II-present roles of professional in Phramongkutklao hospital, and Part III- opinion about impact of the policy implementation. Also, for the patient interviewees tool consisting of two parts: Part I-demographic data, Part II-opinion about impact of the policy implementation. The key research questions in opinion part for this study were,

‘Was there a difference in way of life after the policy was implemented? Second, what advantages did you gain from this new policy? Third, what problems were caused by the new policy? The interview run until reaching a point of data saturation which was perceived to be met when no new ideas presented. Data were documented in electronic forms and transcribed data were rectified with the audio files.

CHAPTER 4

RESULTS

The purpose of this study was to evaluate impacts of changing policies which increasing in maximum prescription refill length from 30-day to 90-day on medication adherence among chronic disease patients in the Phramongkutklao hospital and assess the effects on clinical and economic outcomes. Additionally, the opinions from key informant perspectives were also investigated.

This chapter presented the results including number of patients enrolled in each objective, patients' demographic data, descriptive data of variables with inferential statistical analysis.

4.1 Baseline characteristics and clinical status

A total of 130,300 patients in the PMKHMS data during the study period of August 1, 2014 through July 31, 2017 were applied in this study. Of these, there were 16,144 patients satisfied the inclusion criteria and were recruited into the study.

The most of descriptive characteristic demonstrated differences among the intervention and the control group. Patients in the control group were older than the patients in the intervention group (65.6 vs. 63.8, $P<0.01$) and less likely to have a history of hospitalization to the hospital (24.1% vs. 43.4%, $P<0.01$). Gender, class of medication prescribed, and Charlson Comorbidity Index (CCI) was also statistically different between two groups ($P<0.01$). However, the number of medications prescribed at the index date show no significant differences among-group ($P>0.05$).

Table 8 Baseline characteristic of patients

Baseline characteristic	Intervention (N = 1,163)	Control (N = 14,981)	*P*-value
Age (years) mean ± SD	63.8 ± 13.5	65.6 ± 12.3	< 0.01
Age group, n (%)			< 0.01
18-25 yr	18 (1.6)	11 (0.1)	
26-50 yr	152 (13.1)	1,492 (10.0)	
51-75 yr	749 (64.4)	9,846 (65.7)	
>76 yr	244 (20.9)	3,632 (24.2)	
Gender, N (%)			< 0.01
Female	695 (59.7)	7,295 (48.7)	
Male	469 (40.3)	7,693 (51.3)	
Number of medications per prescription at index date Group, n (%)			0.147
Only 1 medication	455 (39.1)	5,540 (63.0)	
More than one medication	708 (60.9)	9,441 (37.0)	
History of admission to the hospital, n (%)			
Yes	505 (43.4)	3,618 (24.1)	< 0.01
No	658 (56.6)	11,363 (75.9)	

Baseline characteristic	Intervention (N = 1,163)	Control (N = 14,981)	*P*-value
Morbidities, n (%)			
Acute MI	51 (4.4)	334 (2.2)	< 0.01
CHF	69 (5.9)	388 (2.6)	< 0.01
Peripheral vascular disease	15 (1.3)	93 (0.6)	< 0.05
Cerebrovascular disease	144 (12.4)	1,403 (9.4)	< 0.01
Dementia	12 (1.0)	327 (2.2)	< 0.01
Chronic Pulmonary disease	46 (3.9)	555 (3.7)	>0.05
Rheumatic disease	57 (4.9)	247 (1.6)	< 0.01
Peptic ulcer disease	3 (0.3)	96 (0.6)	> 0.05
Mild Liver disease	45 (3.9)	548 (3.7)	> 0.05
Diabetic without complication	465 (39.8)	4,845 (32.3)	< 0.01
Diabetic with chronic complication	115 (9.9)	1,180 (7.9)	< 0.05
Hemiplegia or Paraplegia	2 (0.2)	26 (0.2)	< 0.01
Renal disease	187 (16.1)	1,720 (11.5)	< 0.01
Cancer	27 (2.3)	193 (1.3)	< 0.01
Moderate to severe liver disease	1 (0.1)	6 (0.04)	>0.05
Metastasis solid tumor	3 (0.3)	20 (0.1)	>0.05
AIDs	5 (0.4)	60 (0.4)	>0.05

Baseline characteristic	Intervention (N = 1,163)	Control (N = 14,981)	*P*-value
Charlson's Comorbidity index, Mean (SD)	1.3 ± 1.3	0.9 ± 1.2	<0.01
Group, n (%)			
0	329 (28.3)	6,395 (42.7)	
1	443 (38.1)	5,192 (34.7)	
2	391 (33.6)	3,394 (22.6)	
Baseline medication used, n (%)			
Sulfonylureas	270 (14.6)	2,998 (12.4)	< 0.05
Non-sulfonylureas	1 (0.1)	53 (0.2)	0.183
Biguanides	389 (21.1)	4,369 (18.0)	< 0.05
TZDs	68 (3.7)	1,216 (5.0)	< 0.01
Alpha-Glucosidase inhibitors	16 (0.9)	530 (2.2)	< 0.01
DPP-4 inhibitors	12 (0.7)	779 (3.2)	< 0.01
SGLT-2 inhibitors	1 (0.1)	55 (0.2)	> 0.05
Statins	1,089 (59.0)	14,269 (58.8)	> 0.05

To stabilize these significantly imbalanced baseline characteristics, a propensity score matching (PSM) analysis was applied. After adjusting, the final population contained a total of 2,046 patients, with 1,023 patients in the intervention and control group equally. All demographic variable containing age, gender, history of hospital admission, comorbidities and medication prescribed were not significantly different between the two groups (Table 9).

Table 9 Baseline characteristic of patients with propensity score matched

Baseline characteristic	Propensity score matched		
	Intervention (N = 1,023)	Control (N = 1,023)	*P*-value
Age (years) mean ± SD	64.2 ± 12.8	64.8 ± 12.2	0.3083
Age group, n (%)			0.4604
18-25 yr	9 (0.9)	2 (0.2)	
26-50 yr	127 (12.4)	119 (11.6)	
51-75 yr	672 (65.7)	683 (66.8)	
>76 yr	215 (21.0)	219 (21.4)	
Gender, N (%)			0.112
Female	609 (59.5)	645 (63.0)	
Male	414 (40.5)	378 (37.0)	
Number of medications per prescription at index date	2.2 ± 1.4	2.3 ± 1.3	0.2987
Group, n (%)			
Only 1 medication	384 (37.5)	351 (34.3)	0.140
More than one medication	639 (62.5)	672 (65.7)	
History of admission to the hospital, n (%)			
Yes	409 (40.0)	389 (38.0)	0.389

Baseline characteristic	Propensity score matched		
	Intervention (N = 1,023)	Control (N = 1,023)	*P*-value
No	614 (60.0)	634 (62.0)	
Morbidities, n (%)			
Acute MI	37 (3.6)	32 (3.1)	0.625
CHF	52 (5.1)	46 (4.5)	0.605
Peripheral vascular disease	13 (1.3)	6 (0.6)	0.165
Cerebrovascular disease	126 (12.3)	130 (12.7)	0.841
Dementia	8 (0.8)	10 (1.0)	0.814
Chronic Pulmonary disease	42 (4.1)	34 (3.3)	0.413
Rheumatic disease	36 (3.5)	32 (3.1)	0.712
Peptic ulcer disease	3 (0.3)	2 (0.2)	1.000
Mild Liver disease	43 (4.2)	32 (3.1)	0.239
Diabetic without complication	405 (39.6)	430 (42.0)	0.280
Diabetic with chronic complication	96 (9.4)	116 (11.3)	0.168
Hemiplegia or Paraplegia	2 (0.2)	1 (0.1)	1.000
Renal disease	156 (15.2)	150 (14.7)	0.757
Cancer	20 (2.0)	25 (2.4)	0.547
Moderate to severe liver disease	0 (0.0)	0 (0.0)	-
Metastasis solid tumor	3 (0.3)	1 (0.1)	0.625

Baseline characteristic	Propensity score matched		
	Intervention (N = 1,023)	Control (N = 1,023)	*P*-value
AIDs	2 (0.2)	0 (0.0)	0.500
Charlson's Comorbidity index, Mean (SD)	1.21 ± 1.21	1.20 ± 1.20	0.7252
Group, n (%)			
0	301 (29.4)	315 (30.8)	0.7794
1	408 (39.9)	390 (38.1)	
2	314 (30.7)	318 (31.1)	
Baseline medication used, n (%)			
Sulfonylureas	237 (23.2)	266 (26.0)	0.150
Non-sulfonylureas	0 (0.0)	1 (0.1)	1.000
Biguanides	348 (34.0)	383 (37.4)	0.117
TZDs	63 (6.2)	60 (5.9)	0.853
Alpha-Glucosidase inhibitors	15 (1.5)	7 (0.7)	0.132
DPP-4 inhibitors	4 (0.4)	5 (0.5)	1.000
SGLT-2 inhibitors	1 (0.1)	0 (0.0)	1.000
Statins	964 (94.2)	978 (95.6)	0.190

4.2 Results from objective 1

4.2.1 Change in medication adherence

Table 10 represents the change in MPR in 1-year before and after EDP implemented for patients in control and intervention groups. The pre-post differences in the mean adherence (MPR) for both the antihyperglycemic agents and lipid-lowering agents were significantly increased across intervention and control groups (P <0.001). For antihyperglycemic agents, the MPR for the intervention group enhanced by 14% (P <0.001), compared with an increment of 9% in the control group (P <0.001). Likewise, the average adherence of lipid-lowering agents in the intervention group showed a significant increased by 22% (P <0.001), also the control group presented a rise of 18% (P <0.001) in the post-period.

Table 10 Change in MPR between intervention and control groups before and after matching with propensity score.

Measure	Unmatched		Propensity score matched	
Type-2 diabetes patients				
	Intervention	**Control**	**Intervention**	**Control**
No. of patients (n)	470	5,463	400	400
MPR (mean ± SD)				
Pre-period	0.47 ± 0.27	0.53 ± 0.27	0.46 ± 0.26	0.49 ± 0.24
Post-period	0.58 ± 0.30	0.59 ± 0.28	0.60 ± 0.30	0.58 ± 0.28
Difference in mean (Post-Pre)	+ 0.11	+0.06	+ 0.14	+ 0.09
P value	< 0.001	< 0.001	< 0.001	< 0.001
Difference in Difference	+ 0.05		+ 0.05	
P value	< 0.001		< 0.001	
Adherence group (%, MPR ≥ 0.8)				
Pre-period	13.2 %	17.8 %	11.2 %	10.5 %
Post-period	26.0%	24.4 %	28.0 %	21.8 %
Difference in %	+ 12.8 %	+ 6.6 %	+ 16.8 %	+ 11.3 %
P value	< 0.001	< 0.001	< 0.001	< 0.001

Measure	Unmatched		Propensity score matched	
Dyslipidemia patients				
	Intervention	**Control**	**Intervention**	**Control**
Total (n)	1,099	14,396	934	934
MPR (mean ± SD)				
Pre-period	0.46 ± 0.30	0.55 ± 0.32	0.44 ± 0.27	0.48 ± 0.28
Post-period	0.64 ± 0.32	0.68 ± 0.32	0.66 ± 0.32	0.66 ± 0.32
Difference in mean (Post-Pre)	+ 0.18	+ 0.13	+ 0.22	+ 0.18
P value	< 0.001	< 0.001	< 0.001	< 0.001
Difference in Difference	+ 0.05		+ 0.04	
P value	< 0.001		< 0.001	
Adherence group (%, MPR ≥ 0.8)				
Pre-period	17.8 %	25.5 %	13.9 %	15.3 %
Post-period	36.6 %	41.0 %	38.3 %	38.4 %
Difference in %	+ 18.8 %	+ 15.5 %	+ 24.4 %	+ 23.1 %
P value	< 0.001	< 0.001	< 0.001	< 0.001

Before adjusted with the PSM, the changes in the proportion of type-2 diabetes patients who attained at least 0.8 of the MPR exhibited similar directions between intervention and control groups. The proportion of adherent patients increased from 13.2% to 26% for intervention group and increased from 17.8 % to 24.4 % for the control group (P <0.001). In addition, the percentage of adherent dyslipidemia patients in the intervention group demonstrated a significant rise of 18.8 % (P < 0.001), and the control group also showed an increase of 15.5 % (P <0.001). After propensity score matching, the tendencies of pre-post changes of adherent patients (MPR ≥ 0.8) also increased in both control and intervention group for type-2 diabetes patients. For the dyslipidemia patients, the intervention group reported a markedly increase of 24.4 % (P <0.001), while the control group reveal an increase of 23.1% statistically significant (P <0.001).

4.2.2 Policy impact on medication adherence

With the objective to identify the effect of EDP on adherence, we performed a multivariate logistic regression, adjusting for patient demographic and other potential predictors that are likely affect medication adherence. After the policy was implemented, a raise in medication adherence was detected. Patients in the intervention group who were insured by the UC were almost 2 times higher in medication adherence than the patients control group who were insured by the CSMBS (P <0.001; 95% CI: 1.78-1.99). There was a trend in age effect. Both groups of the patients aged 51-75 and those aged older than 75 years compared with patients 26-50 years of age, were 1.04 and 1.16 times more adherent to medication, respectively. Gender was an important predictor of adherence: women were less likely to be adherent to their medication than men (P <0.001). Patients who had a history of hospitalization during study period, were 16% less likely to be adherent than those who had no history of hospitalization (aOR = 0.84; 95 % CI, 0.83-0.86; P <0.001). Total number of medications prescribed was strongly correlated with patient medication adherence. For those who had only one medication prescribed at the index date, compared with patients who were prescribed with more than one medication, were more likely than three times to be adherent to their medications. There was no statistically significant effect in adherence to class of medication prescribed, with the exemption of the alpha-glucosidase inhibitor group. Most of the comorbidities had an association with medication adherence significantly, except for diabetes patients without complication. Moreover, the Charlson Comorbidity Index (CCI) score showed

positive effect with adherence of medication. Patients with score 1 of CCI, compared with patients with no score of CCI, had a 18% greater probability of being adherent to medication (aOR = 1.18; 95% CI, 1.15-1.21; *P* <0.001)

Table 11 Logistic regression results for evaluation the EDP impact on medication adherence (MPR ≥ 0.8)

Variables	Adjusted odds ratio	95 % CI	*P* value
time (β_1)	1.73	1.71-1.76	< 0.001
Intervention (β_2)	0.47	0.45-0.49	< 0.001
time x intervention (β_3)	1.88	1.78-1.99	< 0.001
Age in group (years)			
18-25	Reference		
26-50	0.58	0.45-0.74	< 0.001
51-75	0.88	0.69-1.12	0.305
>75	0.97	0.76-1.24	0.803
Gender			
Female	Reference		
Male	1.12	1.11-1.14	< 0.001
Number of medications prescribed at the index date			
>1	Reference		
1	2.83	2.78-2.88	< 0.001
Have a history of admitted to the hospital	0.84	0.83-0.86	< 0.001

Variables	Adjusted odds ratio	95 % CI	*P* value
Class of medications			
Sulfonylurea	0.19	0.19-0.20	< 0.001
Non-sulfonylurea	0.15	0.12-0.19	< 0.001
Metformin	0.51	0.05-5.59	< 0.001
Thiazolidinediones	0.22	0.21-0.23	< 0.001
Alpha-glucosidase inhibitors	0.39	0.37-0.42	< 0.001
DPP-4 inhibitors	0.38	0.37-0.40	< 0.001
SGLT-2 inhibitors	0.41	0.33-0.50	< 0.001
Statins	0.79	0.75-0.83	< 0.001
Comorbidities			
Acute myocardial infarction	1.10	1.05-1.15	< 0.001
Congestive heart failure	0.88	0.84-0.92	< 0.001
Cerebrovascular disease	0.88	0.85-0.90	< 0.001
Dementia	1.35	1.28-1.42	< 0.001
Chronic pulmonary disease	0.82	0.78-0.85	< 0.001
Peptic ulcer Disease	1.16	1.05-1.27	0.003
Mild liver disease	0.84	0.81-0.88	< 0.001
Diabetes without chronic complication	1.38	1.34-1.43	< 0.001
Diabetes with chronic complication	1.62	1.58-1.66	< 0.001

Variables	Adjusted odds ratio	95 % CI	*P* value
Hemiplegia	0.70	0.59-0.83	< 0.001
Cancer	0.68	0.63-0.74	< 0.001
Solid tumor	1.39	1.10-1.77	0.005
AIDs	1.41	1.24-1.60	< 0.001
Charlson Comorbidity Index score			
0	Reference		
1	1.18	1.15-1.21	< 0.001
>2	1.23	1.19-1.26	< 0.001
R^2 = 0.22			

4.3 Results from objective 2

4.3.1 Objective 2.1 – To assess clinical outcomes of increasing prescription refill length from 30-day to 90-day

In this objective, clinical outcomes of measurement are the HbA_{1C} and cholesterol level of the diabetes mellitus and dyslipidemia patients, respectively.

4.3.1.1 Glycemic control and other parameters

The changes in clinical parameters related with glycemic control from pre-period to post-period are displayed in Table 12. After propensity score matching, this analysis included 390 intervention and 390 matched controlled patients (Table 12). Reductions in mean of HbA1c during the study period were statistically significant (p < 0.001) for both intervention and control group, however, patient in intervention group

exhibited better glycemic control and showed greater reduction than control group ($p < 0.001$). For the intervention arm, HbA1c level decreased by 0.32% compared with a reduction of 0.24% in the control arm (p<0.001). The difference-in-difference of HbA1c in the intervention group over control group was lessened by 0.08% statistically significant ($p < 0.001$).

Table 12 Change in HbA1c level between intervention and control groups in pre- and post-period both unmatched and propensity scored-matched patients

	Unmatched		Propensity matched	
	Intervention (n =421)	Control (n=6,340)	Intervention (n= 390)	Control (n=390)
HbA_{1C} (mean ± SD) (%)				
Pre-period	7.14 ± 1.61	6.76 ± 1.30	7.10 ± 1.47	7.13 ± 1.52
Post-period	6.91 ± 1.53	6.59 ± 1.31	6.78 ± 1.18	6.89± 1.44
Difference in mean (pre-post)	-0.23	-0.17	-0.32	-0.24
P value	< 0.001	< 0.001	< 0.001	< 0.001
Difference in Difference	-0.06		-0.08	
P value	< 0.001		< 0.001	

In the multivariate analysis, which adjusted HbA1c outcome with medication adherence (MPR), patient demographic, class of medication and comorbidity, the results demonstrate that for each 10% improvement in medication adherence was related with the HbA1c mean reduction by 0.15%, significantly ($p = 0.001$). Patients, who were prescribed with only one medication at index date, were more probably to

have 0.13% lower HbA1c level compared with more than one medication (p = 0.002) (Table 13). Within class of medications, all class of medication excepted non-sulfonylurea exhibit relationship with HbA1c level (p < 0.001). Patients who were prescribed with sulfonylurea, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, and DPP-4 inhibitors, were more likely to have a higher level of HbA1c 0.267%, 0.283%, 0.698%, 0.888% and 0.94%, respectively (p < 0.001). While patients, who took a novel class of antidiabetic medication, sodium-glucose cotransporter 2 (SGLT-2) inhibitors, demonstrated strongly associated with lower HbA1c level (0.827%, p < 0.001). Patients with older age were more apparently to have 0.02% lower level of HbA1c (p < 0.001). Female were more likely to have higher level of HbA1c compared with male (p < 0.001). Additionally, comorbidity conditions and Charlson comorbidity Index score also have impacts on HbA1c level. The mean of HbA1c was 0.389% higher for each 1-point increment in Charlson comorbidity score index (p < 0.05).

Table 13 Multivariate predictors of HbA1c level

Independent variable	Parameters estimate	*P*-value
MPR	-0.149	0.001
Age	-0.02	< 0.001
Charlson Comorbidity Score	0.389	0.03
Sex (female = 0)	-0.157	< 0.001
Number of medications at index date		
> 1	reference	
1	-0.132	0.002
Class of medications		

Independent variable	Parameters estimate	*P*-value
Sulfonylureas	0.267	< 0.001
Non-sulfonylureas	-0.010	0.960
Biguanides	0.283	< 0.001
Thiazolidinediones	0.698	< 0.001
Alpha-glucosidase inhibitors	0.888	< 0.001
DPP-4 inhibitors	0.94	< 0.001
SGLT-2 inhibitors	-0.827	< 0.001
Comorbidities		
Acute myocardial infarction	-0.649	0.001
Congestive heart failure	-0.387	0.036
Peripheral vascular disease	-0.511	0.036
Cerebrovascular disease	-0.751	< 0.001
Chronic pulmonary disease	-0.583	0.003
Rheumatic heart disease	-0.157	0.433
Peptic ulcer disease	-0.156	< 0.001
Mild liver disease	-0.56	0.003
Diabetes without chronic complication	-0.008	0.964
Diabetes with chronic complications	0.127	0.477
Renal disease	-0.381	0.034
Cancer	-0.686	< 0.001

Independent variable	Parameters estimate	*P*-value
Solid tumor	-0.272	0.140
F (26, 12685) = 187.06, $p < 0.001$	R^2 = 0.277, Adjusted R^2 = 0.275, 95% CI	

4.3.1.2 Cholesterol level and other predictors

After propensity score matching, this analysis included 595 intervention and 595 matched controlled patients (Table 14). At the time of initiation of study period, cholesterol level was determined as the mean cholesterol level during the study period. In adjusted findings, a reduction in mean cholesterol level was detected for both the intervention and control groups after the policy was implemented. Intervention group enrollees reduced cholesterol level by 9.48 mg/dL ($p < 0.001$) and 6.65 mg/dL ($p < 0.001$) for the control group, respectively. The mean cholesterol level difference over time among the intervention group and control group was also significantly improved by 2.83 mg/dL ($p < 0.001$)

Table 14 Change in cholesterol level between intervention and control groups in pre- and post-period both unmatched and propensity scored-matched patients

	Unmatched		Propensity matched	
	Intervention (n= 625)	Control (n=9,410)	Intervention (n=595)	Control (n=595)
Cholesterol (mean ± SD) (mg/dL)				
Pre-period	184.55 ± 41.84	178.83 ± 39.55	187.36 ± 38.21	183.52 ± 40.23

	Unmatched		Propensity matched	
	Intervention (n= 625)	**Control (n=9,410)**	**Intervention (n=595)**	**Control (n=595)**
Post-period	176.17 ± 40.29	175.10 ± 37.67	177.88 ± 38.32	176.87 ± 37.49
Difference in mean (pre-post)	-8.38	-3.73	-9.48	-6.65
P value	< 0.001	< 0.001	< 0.001	<0.001
Difference in Difference	-4.65		-2.83	
P value	< 0.001		< 0.001	

Multiple linear regression analyses of dyslipidemia patients, an adherence to their medications (as measured by medication possession ration; MPR) was the potent predictor of cholesterol level after controlling for their age, gender, number of medications at index date, total number of medications prescribed, and other clinical predictors. The mean cholesterol level was 1 mg/dL lower for each 10% improvement in medication adherence ($p < 0.001$). Male patients were more likely to have 10 mg/dL lower level of cholesterol compared with female patients ($p < 0.001$). Older patients were more probably to have lower cholesterol level, for each 10 years increment of age; the mean cholesterol level was 3 mg/dL lower, p< 0.001). By total number of medications prescribed, the increase in number of medications prescribed was associated with higher level of cholesterol (for each medication addition; the mean cholesterol value was 7.66 mg/dL higher, p <0.001). In addition, number of medications at the index date was correlated with cholesterol level. Patients with more than 1 medication at the index date were more supposedly to have a 3.34 mg/dL higher level of cholesterol compared with patients with only one medication at the index date ($p < 0.05$). There was a significant correlation between cholesterol level

and class of medications in this model. More than two-thirds of medication in class was inversely associated with cholesterol levels; included sulfonylureas, biguanides, DPP-4 inhibitors, SGLT-2 inhibitors, and statins (cholesterol level reduced by 17.73 mg/dL, 15.04 mg/dL, 15.53 mg/dL, 18.98 mg/dL, and 8.22 mg/dL, $p < 0.001$, respectively). Comorbidities significantly related with cholesterol level were acute myocardial infarction, congestive heart failure, cerebrovascular disease, mild liver disease, diabetes without chronic complication, renal disease, and cancer (p <0.001). (Table 15).

Table 15 Multivariate predictors of cholesterol level

Independent variable	Parameters estimate	*P*-value
MPR	-10.06	< 0.001
Age	-0.31	< 0.001
Sex (female = 0)	-10.17	< 0.001
Number of medications at index date		
> 1	reference	
1	-3.34	< 0.05
Total number of medications prescribed	7.66	< 0.001
Class of medications		
Sulfonylureas	-17.73	< 0.001
Non-sulfonylureas	-4.22	0.975
Biguanides	-15.04	< 0.001
Thiazolidinediones	1.91	0.211

Independent variable	Parameters estimate	*P*-value
Alpha-glucosidase inhibitors	2.12	0.376
DPP-4 inhibitors	-15.53	< 0.001
SGLT-2 inhibitors	-18.98	< 0.01
Statins	-8.22	< 0.001
Comorbidities		
Acute myocardial infarction	4.20	< 0.05
Congestive heart failure	-15.62	< 0.001
Peripheral vascular disease	-3.12	0.414
Cerebrovascular disease	-11.81	< 0.001
Dementia	1.45	0.792
Chronic pulmonary disease	0.49	0.838
Rheumatic heart disease	0.23	0.937
Mild liver disease	9.73	< 0.001
Diabetes without chronic complications	-5.29	< 0.001
Diabetes with chronic complications	-2.17	0.072
Renal disease	-3.53	< 0.001
Cancer	23.63	< 0.001
F (26, 9254) = 56.71, p <0.001 R^2 = 0.137, Adjusted R^2 = 0.135, 95% CI		

4.3.2 Objective 2.2- To assess economic outcome of increasing prescription refill length from 30-day to 90-day.

4.3.2.1 Economic outcomes in diabetic mellitus patients

Based on the multiple linear regression model, exhibited in Table 16, both HbA1c level and fasting plasma glucose were significantly correlated with total healthcare expenses from societal perspective. Each 1% increment of HbA1c was associated with addition of 251.83 THB ($p < 0.001$), also increase 1 mg/dL of fasting plasma glucose was related with addition of 3.49 THB ($p < 0.001$). Adherence to medications, as measured by MPR, was also an important predictor for total healthcare expenses, hospitalization expenses and total medication expenses. An improvement of medication with 10% was related with a reduction of total healthcare costs, hospitalization costs and total medication costs by 75.68, and 439.54 THB ($p = 0.002$, < 0.001, respectively). However, patients with higher adherence had significantly higher total medication costs than patients with lower adherence (231.69 THB increase per 10% adherence addition, p <0.001). Elder patients were more probably to have higher healthcare expense compared with younger patients ($p < 0.001$). Male patients were more likely to spend 294.98 THB more for total healthcare expenses and 1,148.21 THB for total medication costs than female patients ($p = 0.007$, < 0.001, respectively). Patients who have more than one medication prescribed at the index date were correlated with higher healthcare expenses and medication expenses compared with patients who have only one medication ($p < 0.001$). Moreover, the total number of medications prescribed were associated with all types of the expenses. Total healthcare expenses, hospitalization expenses, and total medication expenses were 2,342.60, 83.76, and 1,509.87 THB higher in every increment in number of medications prescribed ($p < 0.001$). Compared with patients who have history of admission to the hospital, patients who have no history of admission had lower levels of healthcare expenses (13,116.5 THB reduction, $p < 0.001$) and hospitalization expenses (12,055.22 THB reduction, $p < 0.001$). Concerning the association among the class of medications, all type of costs decreased when patients were prescribed with sulfonylureas, biguanides, and thiazolidinediones ($p < 0.001$). In contrast, all type of costs raised when patients were prescribed with alpha-glucosidase inhibitors, DPP-4 inhibitors, and SGLT-

2 inhibitors ($p < 0.001$). For patients who were prescribed with non-sulfonylureas, and statins were significantly associated only with reduced hospitalization expenses ($p = 0.002$, $p < 0.001$, respectively). When the patient gained one score higher on Charlson comorbidity index (indicating more severity of comorbidity) total healthcare expenses raised with 2,208.52 THB, hospitalization expenses increased with 1,405 THB, and total medication expenses increased with 147.59 THB ($p < 0.001$). Acute myocardial infarction and peripheral vascular disease were discovered to be considerably correlated with all type of costs ($p < 0.001$). More particularly, total healthcare costs, hospitalization costs, and total medication costs raised respectively by 5,232.65 THB, 1,695.76 THB, and 2,156.75 THB when patients were diagnosed with acute myocardial infarction ($p < 0.001$) and increased subsequently with 10,257.01 THB, 6,155.64 THB, and 6,546.76 THB if patients were diagnosed with peripheral vascular disease ($p < 0.001$).

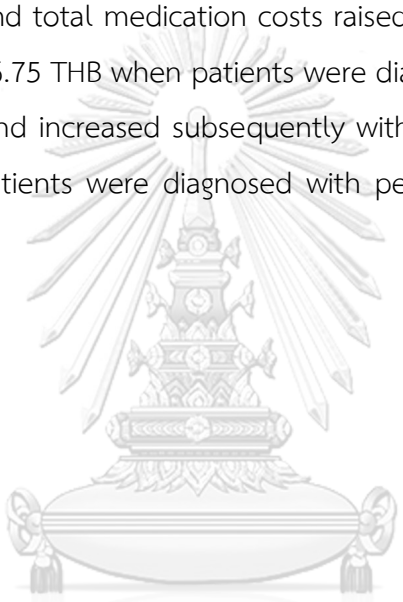

Table 16 The effects of oral antidiabetic medication adherence on healthcare expenses

Variables	Parameters estimate					
	Total healthcare costs (THB)*	**P-value**	**Hospitalization costs (THB)****	**P-value**	**Total medical costs (THB)*****	**P-value**
MPR	-756.79	0.002	-4,395.41	< 0.001	2,316.92	< 0.001
Age	153.83	< 0.001	-3.51	0.392	20.27	< 0.001
Gender						
Male	294.98	0.007	-357.60	0.026	1,148.21	< 0.001
Number of medications at index date						
Only 1 medication	-1,049.52	< 0.001	480.12	0.028	-1,098.51	< 0.001
Total number of medications prescribed	2,342.60	< 0.001	83.76	< 0.001	1,509.87	< 0.001
HbA1c level (%)	251.83	< 0.001	-212.84	< 0.001	257.42	< 0.001
Fasting plasma glucose (mg/dL)	3.49	0.009	11.80	< 0.001	-7.39	< 0.001
History of admission to hospital	13,116.5	< 0.001	12,055.22	< 0.001	-309.53	< 0.001

Variables	Parameters estimate					
	Total healthcare costs (THB)*	P-value	Hospitalization costs (THB)**	P-value	Total medical costs (THB)***	P-value
Class of medications						
Sulfonylureas	-2,281.31	< 0.001	-1,319.32	< 0.001	-713.27	< 0.001
Non-sulfonylureas	-1,947.17	< 0.001	-1,277.58	0.002	-438.09	0.077
Biguanides	-1,942.45	< 0.001	-507.80	< 0.001	-809.47	< 0.001
Thiazolidinediones	-2,324.00	< 0.001	-1,379.33	< 0.001	-467.49	< 0.001
α-glucosidase inhibitors	3,548.68	< 0.001	-925.96	< 0.001	4,701.51	< 0.001
DPP-4 inhibitors	11,894.02	< 0.001	-580.41	< 0.001	12,779.82	< 0.001
SGLT-2 inhibitors	7,566.23	< 0.001	-908.98	0.002	6,913.83	< 0.001
Statins	-72.29	0.772	-1,312.41	< 0.001	1,982.28	< 0.001
Charlson comorbidity score index	2,208.52	< 0.001	1,405.00	< 0.001	147.59	< 0.001
Comorbidity conditions						
Acute MI	5,232.65	< 0.001	1,695.76	< 0.001	2,156.75	< 0.001
CHF	3,617.09	< 0.001	3,124.10	< 0.001	-399.41	0.022
PVD	10,257.01	< 0.001	6,155.64	< 0.001	6,546.76	< 0.001
DM w/o complications	-1,997.63	< 0.001	-173.98	0.164	-1,605.99	< 0.001

* For predictors model of total healthcare cost

F (21, 72527) = 2281.24, $p < 0.001$ $R^2 = 0.398$, Adjusted $R^2 = 0.397$, 95% CI

** For predictors model of hospitalization cost

F (21, 72527) = 1003.18, $p < 0.001$ $R^2 = 0.225$, Adjusted $R^2 = 0.224$, 95% CI

*** For predictors model of total medication cost

F (21, 72527) = 3643.90, $p <0.001$ $R^2 = 0.513$, Adjusted $R^2 = 0.513$, 95% CI

4.3.2.2 Economic outcomes in dyslipidemia patients

Among the patients with dyslipidemia, when compared with lower adherence to medications patients, total healthcare costs and total medication costs tended to be higher for patients with greater medication adherence ($p < 0.001$) (Table 17). However, the costs for hospitalization were lower for patients with higher adherence to medication ($p < 0.001$). Additionally, all type of costs was higher for male patients ($p < 0.001$) and lower for patients with only one medication prescribed at the index date ($p < 0.001$; for both total healthcare costs and total medication costs, $p = 0.006$; for hospitalization costs). Female patients were more likely to spend 560.05. THB less for total healthcare expenses, 255.07 THB for hospitalization costs, and 651.81 THB for total medication costs than male patients ($p < 0.001$). Moreover, the total number of medications prescribed were associated with total healthcare expenses, and total medication expenses. Every addition in number of medications was associated with increment of 2,166.03 THB and 1,408.23 THB in total healthcare expenses and total medication expenses, respectively ($p < 0.001$). Younger patients were more seemingly to have lower total healthcare costs and hospitalization costs compared with elder patients ($p < 0.001$). Patients with history of admission to the hospital were associated with an increase of total healthcare costs, hospitalization costs, and total medication costs by 15,075.54 THB, 13,211.95 THB, and 635.82 THB, respectively ($p < 0.001$). Total healthcare costs, hospitalization costs, and total medication costs was associated with lipid profiles. One point additional on the cholesterol level, was correlated with a total healthcare costs increment of 56.09 THB ($p < 0.001$), hospitalization costs increase of

48.55 THB ($p < 0.001$), and total medication costs addition of 11.01 THB ($p < 0.002$). In contrast, high-density lipoprotein (HDL) cholesterol level was negatively associated with all type of costs whereby an increase of 1 mg/dL of HDL level was related with a reduction of total healthcare costs, hospitalization costs, and total medication costs by 71.15 THB, 53.61 THB, and 17.95 THB, respectively ($p < 0.001$). Similar results were examined in the low-density lipoprotein (LDL) cholesterol level; patient with 1 mg/dL higher on LDL level tended to have lower total healthcare expenses ($p < 0.001$), hospitalization expenses ($p <0.001$), and total medication expenses ($p = 0.001$). Another metabolic parameter, triglyceride level, found no relations with total healthcare costs ($p = 0.054$), however, there was an association with hospitalization costs ($p = 0.031$), and total medication costs ($p < 0.001$). Concerning the association among the class of medications, all type of costs decreased when patients were prescribed with biguanides ($p < 0.001$). For patients who were prescribed with statins were significantly associated only with reduced hospitalization expenses ($p = 0.001$). When the patient gained one score higher on Charlson comorbidity index (indicating more severity of comorbidity) total healthcare expenses raised with 1,293.19 THB, hospitalization expenses increased with 1,013.8 THB, and total medication expenses reduced by 604.61 THB ($p < 0.001$). Congestive heart failure, peripheral vascular disease, and cerebrovascular disease were discovered to be considerably correlated with all type of costs ($p < 0.01$). More particularly, total healthcare costs, hospitalization costs, and total medication costs raised respectively by 4,681.88 THB, 3,229.11 THB, and 1,539.41 THB when patients were diagnosed with congestive heart failure ($p < 0.001$). Similarly, total healthcare costs, hospitalization costs, and total medication costs increased respectively by 3,911.73 THB, 2,212.47 THB, and 1,657.10 THB when patients were diagnosed with cerebrovascular disease ($p < 0.001$) and reduced subsequently with 2,809.16 THB, 1,431.34 THB, and 682.48 THB if patients were diagnosed with peripheral vascular disease ($p < 0.001$, $p = 0.005$, and $p = 0.008$, respectively).

Table 17 The effects of oral lipid-lowerings medication adherence on healthcare expenses

Variables	Parameters estimate					
	Total healthcare cost (THB)*	P-value	Hospitalization cost (THB)**	P-value	Total medical cost (THB)***	P-value
MPR	1,811.92	< 0.001	-2,956.82	< 0.001	3,290.78	< 0.001
Age	137.53	< 0.001	22.59	< 0.001	-18.73	< 0.001
Gender						
Male	560.05	< 0.001	255.07	0.01	651.81	< 0.001
Number of medications at index date						
Only 1 medication	-2,156.33	< 0.001	-452.13	0.006	-1176.75	< 0.001
Total number of medications prescribed	2,166.03	< 0.001	-	N/A	1,408.23	< 0.001
Triglyceride (mg/dL)	-2.55	0.054	-2.47	0.031	126.92	< 0.001
Cholesterol (mg/dL)	56.09	< 0.001	48.55	< 0.001	11.01	0.002
HDL cholesterol (mg/dL)	-71.15	< 0.001	-53.61	< 0.001	-17.95	< 0.001
LDL cholesterol (mg/dL)	-61.01	< 0.001	-50.35	< 0.001	-12.14	0.001
History of admission to hospital	15,075.54	< 0.001	13,211.95	< 0.001	635.82	< 0.001
Class of medications						
Sulfonylureas	-837.67	< 0.001	-781.38	< 0.001	126.92	0.043

Variables	Parameters estimate					
	Total healthcare cost (THB)*	P-value	Hospitalization cost (THB)**	P-value	Total medical cost (THB)***	P-value
Non-sulfonylureas	-	N/A	-	N/A	-	N/A
Biguanides	-3,817.47	< 0.001	-1,696.32	< 0.001	-1,490.13	< 0.001
Thiazolidinediones	-	N/A	-	N/A	-	N/A
α-glucosidase inhibitors	3,359.57	< 0.001	-859.43	< 0.001	4,420.86	< 0.001
DPP-4 inhibitors	13,396.17	< 0.001	-	N/A	12,290.98	< 0.001
SGLT-2 inhibitors	7,863.91	< 0.001	-	N/A	4,610.58	< 0.001
Statins	1,122.41	< 0.001	-780.67	0.001	2,612.32	< 0.001
Charlson comorbidity score index	1,293.19	< 0.001	1,013.8	< 0.001	-604.61	< 0.001
Comorbidity conditions						
Acute MI	2,418.85	< 0.001	-	N/A	2,462.54	< 0.001
CHF	4,681.88	< 0.001	3,229.11	< 0.001	1,539.41	< 0.001
PVD	-2,809.16	< 0.001	-1,431.34	0.005	-682.48	0.008
CVA	3,911.73	< 0.001	2,212.47	< 0.001	1,657.10	< 0.001
Mild liver disease	1,792.73	< 0.001	-	N/A	1,690.60	< 0.001
Moderate to severe liver disease	12,137.88	849.59	13,640.97	< 0.001	-	N/A

* For predictors model of total healthcare cost

F (23, 90991) = 1995.81, p < 0.001 R^2 = 0.335, Adjusted R^2 = 0.335, 95% CI

** For predictors model of hospitalization cost

F (18, 90996) = 1179.66, $p < 0.001$ R^2 = 0.189, Adjusted R^2 = 0.189, 95% CI

*** For predictors model of total medication cost

F (22, 90992) = 2816.07, p <0.001 R^2 = 0.405, Adjusted R^2 = 0.405, 95% CI

4.3.2.3 Subgroup analysis of dyslipidemia patients

After including only medications in national list of essential drugs or NLED, subgroup analysis indicated that the direction of association between medication adherence and all types of cost was changed. Dyslipidemia patients with higher adherence to medications tended to reduce total healthcare costs and hospitalization costs by 501.33 THB (p = 0.04) and 3,397.55 THB ($p < 0.001$), respectively (Table 18).

Table 18 Subgroup analysis of dyslipidemia patients who prescribed with medications in national list of essential drugs

Variables	Parameters estimate					
	Total healthcare cost (THB)*	**P-value**	**Hospitalization cost (THB)****	**P-value**	**Total medical cost (THB)*****	**P-value**
MPR	-501.33	0.04	-3,397.55	< 0.001	1,351.90	< 0.001
Age	158.22	< 0.001	33.66	< 0.001	-6.09	0.01
Gender						
Male	296.02	0.015	215.71	0.04	594.99	< 0.001
Number of medications at index date	-1,991.23	< 0.001	-	N/A	-1,433.89	< 0.001
Total number of medications prescribed	2,202.00	< 0.001	80.62	0.039	1,340.43	< 0.001
Triglyceride (mg/dL)	-	< 0.001	-4.69	< 0.001	-1.89	0.002
Cholesterol (mg/dL)	38.32	< 0.001	55.19	< 0.001	9.82	0.008
HDL cholesterol (mg/dL)	-63.91	< 0.001	-67.43	< 0.001	18.26	< 0.001
LDL cholesterol (mg/dL)	-37.36	< 0.001	-49.82	< 0.001	-11.26	0.002
History of admission to hospital	14,486.58	< 0.001	12,849.71	< 0.001	490.48	< 0.001
Class of medications						
Sulfonylureas	-1,030.05	< 0.001	-883.92	< 0.001	-	N/A
Non-sulfonylureas	-	N/A	-	N/A	-	N/A

Variables	Parameters estimate					
	Total healthcare cost (THB)*	P-value	Hospitalization cost (THB)**	P-value	Total medical cost (THB)***	P-value
Biguanides	-2,569.71	< 0.001	-1,343.92	< 0.001	-585.37	< 0.001
Thiazolidinediones	-	N/A	-	N/A	-	N/A
α-glucosidase inhibitors	2,397.41	< 0.001	-1,249.79	< 0.001	4,062.44	< 0.001
DPP-4 inhibitors	12,681.37	< 0.001	-	N/A	11,319.78	< 0.001
SGLT-2 inhibitors	7,952.23	< 0.001	-	N/A	4,985.87	< 0.001
Statins	-553.38	0.044	-1,151.47	< 0.001	1,510.94	< 0.001
Charlson comorbidity score index	1,451.87	< 0.001	929.20	< 0.001	-366.18	< 0.001
Comorbidity conditions						
Acute MI	3,371.36	< 0.001	-	N/A	2,427.57	< 0.001
CHF	3,800.47	< 0.001	2,516.60	< 0.001	1,560.20	< 0.001
PVD	-4,473.56	< 0.001	-2,201.82	< 0.001	-2,244.89	< 0.001
CVA	3,252,75	< 0.001	2,516.60	< 0.001	1,762.02	< 0.001
Mild liver disease	1,660.01	< 0.001	876.08	< 0.001	1,067.46	< 0.001
Moderate to severe liver disease	13,225.52	< 0.001	14,600.67	< 0.001	-	N/A

* For predictors model of total healthcare cost

F (22, 62695) = 1671.61, p < 0.001 R^2 = 0.369, Adjusted R^2 = 0.369, 95% CI

** For predictors model of hospitalization cost

F (19, 62673) = 926.32, $p < 0.001$ R^2 = 0.219, Adjusted R^2 = 0.219, 95% CI

*** For predictors model of total medication cost

F (21, 62671) = 2239.20, p <0.001 R^2 = 0.428, Adjusted R^2 = 0.428, 95% CI

4.4 Results from objective 3: Overall impacts of policy change from key informant perspectives

Participants

A total of 11 participant interviews with a balanced sex distribution (males n = 5, females n = 6) were conducted. Of these participants, three were patient with the UC, which included two women. Eight pharmacist-participants from four departments were interviewed with equally 4 males and 4 females.

Question 1: Was there a difference in way of life after the policy was implemented?

Patient's perspective

The Extended Dispensing Policy (EDP) propose to increase maximum prescription length of the patients under the Universal Coverage (UC) scheme from thirty days to ninety days. Patient-participants expressed a difference in terms of feeling:

"I was happy about the new dispensing policy and I did not have to come here in every month. It wasted my time. I thought that this service should have been established for a long time ago." (Patient (1), female)

"I can have more medicine than the previous visit. I felt that the government give me a good thing." (Patient (2), male)

“If this was the new policy, 90 days, then I had to be brightened of what I had got. I disliked answering pharmacist questions in every time I refill my additional medications and I thought pharmacists might be boring to ask me a question too. Then this was quite a good opportunity to everyone” (Patient (3), female)

Pharmacist’s perspective

In perspective of pharmacist, they expressed in term of working:

“This policy had relief my workload for the first check of pharmacist. I had to calculate the medicines that patients would have in a month and then the rest of them would be cut and transcribed to the other prescription for the next refill but now I do not have to deal with it.” (OPD-Pharmacist (1), male)

“I had no worry about forgetting to give a prescription to patient for their next refill and pay less attention about the quantity of medication that patient should have when I dispensed.” (OPD-Pharmacist (2), female)

“I never heard about this policy and I think this new policy doesn’t involve in my routine job.” (IPD-Pharmacist (1), male)

“Generally, patients who were admitted to the hospital would be dispensed by the one-day or three-day system which automatically generated by the computer system. I am not sure that this policy would affect to inpatient dispensing system.” (IPD-Pharmacist (2), female)

“My main job was related with producing pharmaceutical product and I thought this policy was not change my job description.” (Pharmaceutical production pharmacist (1), male)

“I thought that the policy may have an indirect effect to some of pharmaceutical production, for example, tar shampoo or calamine lotion. If patients can have more medications from one bottle to a maximum of three bottle, then the production line would be affected with this policy.” (Pharmaceutical production pharmacist (2), female)

"I had to push all of my assistants to work more. I had heard this policy before then I prepared to purchase more to prevent the consequences." (Logistics pharmacist (1), male)

"I always have to deal with the new regulation or policy and this policy would affect with my stock." (Logistics pharmacist (2), female)

Question 2: What advantage did you gain from this new policy?

Patient's perspective

Most of patient-participants suggested that the EDP had some advantages for them which were considered individual:

"I can spare my time to do other things, because I have to do my own job. If I had to come to the hospital every month, then I loss my job and money." (Patient (1), female)

"When I went back home in other province, I can have enough medicine to use along the time. No need to buy additional medicine from pharmacies or clinics in other place, they sometimes have no medicine like the one received from this hospital." (Patient (2), male)

"I felt more comfortable to come to this hospital because I had less argument with the pharmacists. I do not have to wait for my medicines for a long time, and I can save my taxi service fee that costs me more than two hundred baht per one trip." (Patient (3), female)

Pharmacist's perspective

Other aspects of pharmacists appeared that the policy had an advantage for some departments.

"In the rush hour period, I noticed that there were no patients in the UC scheme come to refill their prescription. I thought that the congestion of this period

was relieved and make me less stress. However, total patients in full-time period were not significant difference" (OPD-Pharmacist (1), male)

"I felt that I had less prescription to dispensed, especially I the morning shift that I had to work. Before the policy was implemented, patients always come back to the hospital in every month, generally in the morning that causes my morning shift full of patients." (OPD-Pharmacist (2), female)

"I thought that I had no advantage from this policy. No matter what the policy changed, I still focus on the IPD dispensed system." (IPD-Pharmacist (1), male)

"In the IPD system which use system separately from the OPD system, then I guessed that I gain no advantage from the policy changed. (IPD-Pharmacist (2), female)

"I can't imagine how this new policy implemented would be benefit for me." (Pharmaceutical production pharmacist (1), male)

"The advantage of this policy for me was that the more pharmaceutical dispensed, the higher rate of production performed. Then I can reduce the problem about the expiration of the material because of the increasing of turnover rate of production." (Pharmaceutical production pharmacist (2), female)

"There were some of us that thought about the advantage of this policy. While I had to deal with the new Government Procurement and Supplies Management Act, I had to concern about the lack of medicine." (Logistics pharmacist (1), male)

"I don't think that this policy would be beneficial for me." (Logistics pharmacist (2), female)

Question 3: What problems were caused by the new policy?

Patient's perspective

Some of patient-participants expressed concern induced by increases in medication dispensed, and benefits.

"I concerned that the hospital may charges my money back for the additional medicines." (Patient (1), female)

"I thought this policy is good for me and expect that I still have the maximum through the time. I hope that the policy would not have the problems." (Patient (2), male)

"This policy causes no problem to me and to every patient. I felt that if patients can come to the hospital in less frequency, I will wait for medicine in shorter time." (Patient (3), female)

Pharmacist's perspective

Pharmacist noted they had a difficulty from the new policy implemented, particularly pharmacists who worked in logistics department. They explained about how this policy caused them problems.

"At first, I had to explained to every UC patient about the new change and this took me more time for dispensing in each case." (OPD-Pharmacist (1), male)

"To make patients understand what is changed and why, was the most difficult things at the time of dispensing." (OPD-Pharmacist (2), female)

"I concerned about the problem of medicine supply. Due to the higher rate of medicine consumption in the hospital that might cause the issues for me" (IPD-Pharmacist (1), male)

"One problem that I found from this policy was the lack of medicines. When OPD sometimes had shortness of medicines, they had to borrow some medicines from IPD and that may cause problem in managing stock." (IPD-Pharmacist (2), female)

“I thought that there was no problem about the policy in the production process.” (Pharmaceutical production pharmacist (1), male)

“The problem was that I had to expect the rate of production of each item to supply enough medicines to all patients.” (Pharmaceutical production pharmacist (2), female)

“I thought I had got into big trouble. I had to buy the medications in higher amount while limiting in budget. I had to work within the laws, for example, Regulation of the Office of the Prime Minister B.E.2535 (thereafter changed to be the Government Procurement and Supplies Management Act B.E.2560), Regulation of the Ministry of Finance on Government Procurement and Supplies Management B.E.2560. However, when I can forecast the rate of medication use in the first six to twelve months after the policy was implemented, this trouble was managed. Moreover, the budget used to purchase the medication was expanded due to the Government Procurement and Supplies Management Act B.E.2560.” (Logistics pharmacist (1), male)

“This new policy caused me a problem that requisition rate of each outpatient department was three times inflated and the amount of medicine withdrawal would be triple increased.” (Logistics pharmacist (2), female)

Summary in patients’ perspective

In patients’ perspective, they represented that they had more convenience and felt more comfortable to come to hospital. They had to visit to hospital four times per year compare with twelve times per year before the policy was implemented. They can save more money from reduced travel time to hospital via transportation cost. In addition, they can save money from opportunity loss cost due to absent from their jobs. Each time patients come to hospital they always feel uncomfortable, so they feel more relaxed because they did not have to come to hospital every month.

Summary in pharmacists’ perspective

Pharmacists who worked in outpatient department feel that they work less than time-period that policy not implemented especially pharmacist in morning shift

(7.00 a.m. to 8 a.m.) and pharmacist who worked in morning time-period (5.00 a.m. to 10 a.m.). However, these differences were not much significant due to patients affected by the policy were distributed in vary time-period. While pharmacists who worked in inpatient department felt that their work did not affected by the policy because the policy was focused on patients in outpatient department. Additionally, pharmacists who worked in pharmaceutical production department expressed that the policy would not directly affect to their work. In the early period of implemented, one of them had to forecast rate of production to supply enough stock in the hospital, while rest of them explained that he had no problem from this policy. In contrast, pharmacists who worked in logistics department feel that they had to face with purchasing and inventory managing problems. According to the policy that prescription length was increased from 30-day to maximum 90-day, the amount of medication prescribed would be triple increased. This situation firstly influenced inventory department due to requisition rate of each outpatient department was three times inflated. Then procurement department was affected by the policy since they had to purchase high amount of the medications while limiting budget. Pharmacists who worked in procurement department seem stressed because they had to work within the laws, for example, Regulation of the Office of the Prime Minister B.E.2535 (thereafter changed to be the Government Procurement and Supplies Management Act B.E.2560), Regulation of the Ministry of Finance on Government Procurement and Supplies Management B.E.2560. However, this difficulty occurred only in the first six to twelve months after the policy was implemented due to the pharmacists can estimate rate of medication used. Moreover, the budget used to purchase the medication was expanded due to the Government Procurement and Supplies Management Act B.E.2560.

CHAPTER 5

DISCUSSION AND CONCLUSION

This chapter represents the discussion, limitations of the study, conclusion, recommendation for policy makers, and for future research.

5.1 Discussion

5.1.1 Objective 1:

Based on our information, this was the first quasi-experimental, pre-post analysis to investigate the impact of the new policy implemented on medication adherence using administrative claims database in the quaternary care hospital in Thailand. The remarkable finding of this study was the EDP, a new policy to improve patient adherence contributing privileges to patients, especially who were insured under the UC, was correlated with better medication adherence in dyslipidemia and type-2 diabetes patients. Moreover, the policy substantially increase number of adherent patients, which was related with decreasing health care costs and risk of hospitalization.[18, 143-145] These findings from the study suggest that increasing the prescription length from 30-day to maximum of 90-day reinforced patients to concentrate on their affiliation hospitals, which produced a continuity of care in each hospital, also healthcare professionals to have more time for taking care of their patients routinely.

Our results of enhancement in adherence to medication were similar to previously published that assessed the effect of increasing day supply.[31, 34, 72] They determining the impact of prescription size in patients who refilled statins therapy for sixty days compared with those who refilled medication in thirty days, reported that extended number of day prescribed was associated with higher adherence.[31] Furthermore, the retrospective study displayed that patients who received medication in four groups: antihypertensive, statins, oral hypoglycemic and selective serotonin

reuptake inhibitors with 90-day prescription compared with those who refilled with 30-day supply, were more seemingly adherent to their medication.[34] Similarly, the study that extending prescription length of statins medication from thirty day to sixty day or ninety day were correlated with increasing medication adherence of patients.[72]

We noticed that the baseline adherence rate of study population was also inadequate with only 11.2 % and 13.9 % of the patients were identified adherent to antihyperglycemic agents and lipid-lowering agent through 1-year study period in the intervention group. This is mainly due to the limited prescription day supply up to 30-day before the policy was implemented, however, the proportion of adherent patient raised to 28.0% and 38.3% after the policy was enacted. This finding was comparable to the overall adherence rate (42.4%) among patients who prescribed with antihyperglycemic medication.[146] Furthermore, the rate of adherence this study was relevant to other studies that conducted on medical and pharmacy claims database.[41, 143, 147]

Additionally, this study designed to examine patient-, therapy-, disease- and healthcare system-related factors on medication adherence. We found that several patient characteristics had significant effect on adherence, specifically older age, male sex, class of medication prescribed, number of medications prescribed at the index date, have a history of hospitalization, and the presence of comorbidities.

There was a non-significant tendency between age of patient to medication adherence. Patients aged 26-50 years were less apparently to adhere to their medication compared to those with younger group (18-25 years) significantly. While the older groups were more supposedly to be adherent, whereas this trend did not achieve significant results. However, these findings were comparable to a previous systematic review that investigated the effect of patient age on medication adherence. They demonstrated that there was an inverted U-shaped association between age of patients and medication adherence.[148] Moreover, a recent study has reported that dyslipidemia patients aged ≤ 54 years compared with the older patients were less possibly to be adherent.[149] Furthermore, another study has revealed that statin users who older than 74 years were more prone to be non-adherent.[150] Additionally, a male

sex in this study exhibited the relationship with medication adherence. The results from systematic review demonstrated that patient sex corresponded with medication adherence, but the conclusion were inconsistent[28]. Some literature described that female patients will have higher adherence than male, significantly[27, 48, 49] while a few study proposed in another way[50].

For the therapy-related factors, this study discovered that number of medications prescribed at the index date and different medication classes had effect on the adherence. Patients who prescribed with only one medication had 2.83 times more likelihood of having a medication adherence than those who were prescribed more than one medication which is corresponding to the study of Yoshitsugu et al. Their results from self-reporting medication adherence revealed that patients taking single daily dose were significantly correlated with greater adherence[61]. In contrast, some study has showed that number of prescription medication does not associate with medication adherence[60], but the frequency of drug administration does.[36] However, a meta-regression analysis concluded that patients who take cardiovascular disease drugs once-daily dose seem to be more adherent than patients taking medications twice-daily dose, significantly.[62] In this way, facilitating the frequency of medication taking could promote adherence, substantially**.** Additionally, this study discovered that all medication classes, especially Alpha-Glucosidase Inhibitors; SGLT-2 inhibitors; Metformin; and Statins, had exceptionally influence on lower medication adherence (OR = 0.36, 0.49, 0.50, 0.75; $P < 0.001$, respectively). Because of their unique mechanism of action, for instance, Alpha-Glucosidase inhibitors which prevent digestion and delay absorption of carbohydrate through the intestine, patients may experience the side effects of the medication, such as flatulence, nausea and diarrhea[151, 152]. Furthermore, the remarkable glycosuric effect of SGLT-2 inhibitors will promote the excretion of glucose via urine, therefore frequent urination, dry mouth, and infections of urinary tract would be occurred to the patients.[153, 154] Moreover, patients may also suffered from common adverse effects of metformin, which are abdominal bloating, vomiting, loss of appetite, and metallic taste[155]; and statins, which are myalgia, myositis, abdominal and joint pain.[156] Our findings are similar to the report

of Bubalo et al., which confirmed that patients are less likely to comply with therapy plan when the adverse event is frequent[35].

In consideration of the correlation between disease-related factors and medication adherence, we found that comorbidities had a meaningful association with medication adherence. Patients who had been diagnosed with a congestive heart failure, cerebrovascular disease, chronic pulmonary disease, mild liver disease, hemiplegia and cancer were less likely to be adherent, while other diseases were more possibly to be adherent. Nonetheless, these contrary results were also demonstrated by previous studies with some of these research publishing a higher adherence level as the number of comorbid conditions.[157, 158], while others mentioned lower medication adherence with complex comorbid conditions.[159, 160] Numerous explanations could express these conflicting findings. Due to increasing number of comorbidity condition, patients may need complicated medical care procedures. Equally, medical care complexity raises, patients' perception to the care plan may reduce, which contribute to decreased medication adherence.[161] Moreover, the complicated treatment was highly associated with the accumulating number of medication, which may lead to omission to take them as prescribed and reduced adherence.[61, 62] Furthermore, utilizing medication for a long period of time for treating many chronic diseases, adherence to therapy regimens decreases substantially with time.[40] This generally occurs when patient have fluctuation or lack of symptoms, for example, hypertension and asthma may have an unfavorable adherence. Also, consideration discussed for a higher rate of adherence in patients with multiple comorbid conditions involve that after experiencing from the illness for a long time, patients' belief of opposing the illness is decreased and they were more likely to comply to the treatment[26].

5.1.2 Objective 2:

Administrative health claims information contributes an extraordinary facility to observe patients for many years and pay attention to their medication prescriptions. Even though literature indicates that patient with chronic conditions especially type 2 diabetes, dyslipidemia could have better control of their glycemic level or lipid profiles if they adhere to their medications[15, 16, 20, 31, 33]. However, a broad aspect of factors can influence medication adherence, various approaches are used to manage modifiable factors related medication adherence. The Extended Dispensing Policy (EDP), which increased prescription length from 30-day to 90-day, with the intention improve patient's convenience and increase patient's adherence to medication prescribed.

As far as we know, this study is the first observational study with purposes to determine the clinical and economic outcomes of medication adherence affected by the EDP during two consecutive years in patients with type-2 diabetes mellitus and patients with dyslipidemia in Thailand. The major findings of this study propose that the EDP, a new policy adding appropriate advantages to both group of patients, who were diagnosed with type-2 diabetes mellitus and dyslipidemia, was correlated with better metabolic parameters, for example, HbA1c, fasting plasma glucose, cholesterol level, triglyceride level, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol. Additionally, the new policy significantly minimized total healthcare cost and hospitalization cost in both group of patients.

The association between medication adherence and clinical outcomes in this study, particularly both HbA1c level, fasting plasma glucose (FPG), and lipid profiles are similar direction to preceding studies[15, 16, 75, 162]. Andrew et al[15] described that patients who do not adhere to oral glucose-lowering medications would have lower HbA1c decrease compared with adherence patients. Iloh et al[16] explained that patients who adhere to their treatment were associated with plasma glucose controlled. Additionally, if patient adherence level to antidiabetic medication increased by 10%, level of HbA1c reduced by 0.16% as reported by Schectman[75]. Moreover, So-yeon et al[162] concluded that adherent patients not only associated with better HbA1c level but also reduced fasting plasma glucose. For patients with

dyslipidemia, increased length of statins from 30-day to 60-day at each prescription refill leads to better medication adherence and improved effectiveness of medication[31]. Another study that investigated the effects of expanding prescription length of statin from 30-day to 60-day and from 30-day to 90-day contributed to improvement in cholesterol level[72].

Relationship among medication adherence and decreased healthcare costs have been described. Sokol et al[163] proved that disease-related costs were more apparently lower at high level of medication adherence in diabetes mellitus and hypercholesterolemia patients, contribute to a reduction in total healthcare cost. In addition, Roebuck et al[17] also supported that improved medication adherence was constantly associated with higher saving in total healthcare costs in four chronic diseases, including congestive heart failure, hypertension, diabetes, and dyslipidemia. Moreover, Gaziano et al[72] demonstrated that increasing prescription length to improve medication adherence have established a decrease in cardiovascular burden and an improvement in personal cost saving. The present study results are consistent with these findings. Total healthcare costs, hospitalization costs and total medication costs were associated with medication adherence to antidiabetics. By 10 percent of medication adherence increase was related to lower total healthcare costs and hospitalization costs while total medication costs were diversely inflated. It is possible that due to the higher costs of the medications especially medications not listed in the National List of Essential Medicine-NLEM, which are often expensive. Further the number of medications prescribed may depended on how adequately their blood sugar level was managed, also may increase if they cannot maintain blood sugar in the optimum value. Consistent with Espoti et al[164], they found that diabetes patients who have higher level of HbA1c were related with higher diabetes-related health care costs including medication costs. For dyslipidemia patients, the direction of association between total healthcare costs and medication adherence were different from patients with diabetes. This can be explained that due to cost of medications for treating dyslipidemia was expensive, then only medications listed in the NLEM were analyzed. The analysis of subgroup displayed that the higher of medication adherence were associated with lower total healthcare cost. The most noticeable findings in

current study were that medication adherence in both diabetes and dyslipidemia patients were associated with reduced total healthcare costs, hospitalization costs while increased total medication costs. A study conducted by Buysman et al[33] explained conflicting results, with higher medication adherence level in liraglutide a higher in total healthcare costs due to higher cost of liraglutide. Moreover, increased medication adherence to oral antidiabetic agents led to increased medication-related costs while overall healthcare costs and hospitalization costs were not affected[162]. While, Roebuck et al[17] determined that in spite of higher pharmacy expenditures including medication costs, medication adherence contributes meaningful medical saving, by reason of reductions in cost of hospitalization. Furthermore, Gaziano et al[72] discussed that the majority of the total healthcare saving caused by the reduction of transportation costs , decreased time costs, and shortened pharmacist time visit.

Other parameters, for example, class of medications, history of admission to the hospital, and Charlson Comorbidity Index were affected economic outcomes.

The examination of subgroups exposed two additional essential findings: first, medication costs especially medications that not listed in the National List of Essential Medicine (NLEM) which generally have expensive cost had an impact on total healthcare costs. Second, we could confirm that the advantage of medication adherence persisted with the reduced of total healthcare costs, since dyslipidemia patients prescribed with medications in NLEM revealed a decreased total healthcare costs as well as a reduced hospitalization costs with an increased in medication adherence.

5.2 Study limitations

This study has some limitations that should be mentioned. First, this study used an administrative pharmacy claims from PMK hospital database and might not be surrogate of all database utilized in Thailand. These results from impact of the policy changes should be generalize to other hospital with appropriate consideration.

Second, this database is mainly operated for reimbursement, several predictors which indicated to have an association with adherence (e.g., education level[27], race and ethnicity[53-55], socioeconomic status[50], adverse event of medications[35, 39],

relationship between healthcare providers and patients[22], and social support[68, 70]) were not available in the database.

Third, due to the nature of a retrospective study which was not a randomized analysis, therefore, the results could be affected by selection bias and unobserved differences. To handle these problems, the propensity score matching was performed to control for bias introduced by sample selection and difference-in-difference strategy was used to adjust for unobservable differences.

In addition, this study used the MPR as a proxy measure of medication adherence which based on administrative prescription refills, but in real world patients might not exactly use the medications as prescribed by their healthcare providers. However, previous literature demonstrated that adherence calculated from administrative data have a high association with other approaches to assess medication adherence, namely self-reported[165, 166], pill counts[167], and direct measure of serum drug concentration[168], indicating that the amount of medications refilled is constant with the amount at which patients consume them.

Finally, we were unable to address any medications that patients had acquired from other pharmacies or hospitals which may cause an underestimation of medication adherence.

5.3 Policy recommendations

Improving access to fundamental medicines while balancing pharmacy utilization is a major concern of policy makers. They must counterbalance the possible expense of increasing length of prescription against the desirable benefit of increased medication adherence. However, the expansion in 90-day prescriptions at hospital pharmacy in Thailand is seemingly to suspend because of a lack of adequate information.

The results from this study demonstrates the conceivable advantages to the patient by increasing longer length of prescription, contributing better convenience to

patient, improved controlling of blood sugar level and lipid profiles, and overall health advantages by reason of improved adherence to medication.

5.4 Conclusion and future research

In summary, this study indicated that the EDP, a policy for increasing prescription length from 30-day to 90-day, could make a substantial contribution in promoting adherence to medication of the patients with dyslipidemia and type-2 diabetes. However, there are several variables that affect patient's adherence to their medication, some of which are: patient-, therapy-related variables. Determining clearly changeable variable correlated to both patient and therapy would be beneficial to healthcare providers, patients, and national health services. Further research should establish appropriate efforts to examine these influencing variables accurately. These findings can be advantageous to policy makers to decide new policies for the hospital.

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APPENDIX

APPENDIX A

Stata commands

```
/* USING FILE FINAL DATE CHANGED */

. use "C:\Users\DELL\Desktop\thesis\_raw_append new\1+2+3+4+5+6_new.dta", clear


/*Add eventdate which is Stata Internal Form*/

. gen eventdate= date( d_date, "DMY")


/*Change format of eventdate to Human Readable Form*/

. format eventdate %td


/* GENERATE DAY OF WEEK; WHICH SUNDAY = 0, MONDAY = 1,etc.*/

. gen dayofweek = dow( eventdate)


/* TURN DAY OF WEEK WHICH ARE NUMBER TO NAME OF THE DAY */

. forv i=0/6 {

        local w: word `=`i'+1' of `c(Weekdays)'

        local wd "`wd' `i' `w'"

}

label def dow `wd'

label val dayofweek dow
```

l dayofweek dayofweek in 1/20

/* CHECK THE DISTRIBUTION OF THE DAY OF WEEK */

. tab dayofweek

/* CREATE YEAR VARIABLE */

. generate year = year(eventdate)

/* GENERATE NUMBER OF VISIT IN EACH DATE */

. g n=1

. bysort hn year eventdate: gen visit = sum(n)

** This will summing the number of visit of patient in eventdate but not year **

/* GENERATE NUMBER OF VISIT IN EACH YEAR */

. bysort hn year (eventdate): gen yvisit = sum(n)

** This latter will summing the number of visit in every patient in each year**

/* GENERATE TOTAL VISIT OF PATIENT IN EACH YEAR */

. bysort hn year (eventdate): egen totalvisit = max(yvisit)

/* GENERATE NUMBER OF VISIT PER YEAR PER PATIENT */

. bysort year hn: gen hn_count=_N

```
/* GENERATE NUMBER OF MEDICATIONS PER VISIT DATE PER YER PER PATIENT */

. by hn year eventdate, sort: gen num_med = _N

/* GENERATE SUM OF MEDICATIONS PER VISIT DATE OF PATIENTS */

. bysort hn eventdate : gen cumfreq = _N if _n == 1


/* GENERATE VARIABLE FOR GENDER WITH NUMERIC VALUE AND LABEL */

. gen sex2=0

. replace sex2=1 if sex=="M"

. replace sex2=2 if sex=="F"

. label define sex2 1 "M" 2 "F"


/*CHANGE VALUE OF  MEDICINE CODE FROM CRE101N AND CRE102N TO ROS103N AND
ROS104N*/

. replace code = "ROS103N" if code =="CRE101N"

. replace code = "ROS104N" if code =="CRE102N"


/*CATEGORIZE MEDICATION TO EACH GROUP OF THEIR MECHANISM */

*Sulfonylurea*

. generate sulfonylurea = 1

. replace sulfonylurea = 0
```

. replace sulfonylurea = 1 if code =="GLI103N" | code == "GLI101N" | code == "AMA102N" | code == "AMA103N" | code == "GLI106N" | code == "GLI107N" | code == "DIA110N"

Non-sulfonylurea

. gen non_sulfonylurea = 1

. replace non_sulfonylurea = 0

. replace non_sulfonylurea =1 if code =="NOV102N" | code =="NOV103N"

Biguanides

. gen biguanide = 1

. replace biguanide=0

. replace biguanide = 1 if code =="MET101E" | code == "MET105E" | code =="GLU107E"

Thiazolidinediones

. g thiazolidine = 1

. replace thiazolidine=0

. replace thiazolidine = 1 if code =="PIO102E" | code == "PIO101E" | code =="ACT108N"

Alpha-glucosidase inhibitors

. g alphaglucosidase = 1

. replace alphaglucosidase=0

. replace alphaglucosidase = 1 if code =="GLU104N" | code == "BAS101N"

Dipeptidyl-peptidase 4 inhibitors (DPP-4 inhibitors)

. g dpp4 = 1

. replace dpp4=0

. replace dpp4 = 1 if code =="JAN101N" | code == "GAL101N" | code == "ONG100N" | code == "TRA109N"

*Sodium-Glucose Cotransporter-2 inhibitors (SGLT2-inhibitors) *

. g sglt2 = 1

. replace sglt2=0

. replace sglt2=1 if code =="JAR101N" | code =="FOR101N"

* Statins*

. g statin =1

. replace statin=0

. replace statin=1 if code =="SIM101E" | code =="SIM102E" | code =="SIM103E" | code =="ROS103N" | code =="ROS104N" | code =="LIV102N" | code =="MEV103N" | code =="MEV104N" | code =="ATO102N" | code =="ATO103N" | code =="LIP110N" | code == "LES103N"

/********** CLASS OF MEDICATIONS **********/

. label define drug_class 1 "Anti-Diabetic" 2 "Lipid Lowering"

```
/** NUMBER OF CODE SHOULD NOT MORE THAN 9 CODES ********/

/* ANTIDIABETIC MEDICATIONS */

.gen byte drug_class:drug_class = 1 if inlist( code , "GLI103N", "GLI101N", "AMA102N", "AMA103N", "GLI106N","GLI107N","DIA110N","NOV102N","NOV103N")

.replace drug_class = 1 if inlist( code ,"MET101E","MET105E","GLU107E","PIO102E", "PIO101E", "ACT108N", "GLU104N","BAS101N","JAN101N")

.replace drug_class = 1 if inlist( code ,"GAL101N","ONG100N","TRA109N","JAR101N","FOR101N")

/* LIPID-LOWERING  MEDICATIONS*/

.replace drug_class = 2 if inlist (code,"SIM101E" ,"SIM102E", "SIM103E", "ROS103N", "ROS104N", "LIV102N","MEV103N","MEV104N","ATO102N")

replace drug_class = 2 if inlist(code,"ATO103N","LIP110N","LES103N")


/** SEPARATE GROUP OF DISEASES BY UISNG GROUP OF MEDICATIONS **/

/* GROUP OF PATIENTS WITH DM AND DYSLIPID */

** USING FILE GROUP OF MEDICATION.DTA **


. preserve

. keep if drug_class==1| drug_class==2


** THEN SAVE INTO FILE NAME DM+DYS.DTA **

. restore
```

```
/* GROUP OF PATIENTS WITH DM */

. preserve

. keep if drug_class==1

** THEN SAVE INTO FILE NAME DM.DTA **

. restore


/* MERGE FILE USING DM+DYS AND DM FILE WITH 1:1 MERGE*/

. use C:\Users\DELL\Desktop\thesis\work_files\Disease\DM+DYS.dta


. merge 1:1 hn using "C:\Users\DELL\Desktop\thesis\work_files\Disease\DM.dta"

** YOU WILL GET MERGED FILE OF PATIENT WITH DM (MAY BE WITH SOME DYSLIPID) **


/* MERGE FILE USING DM+DYS AND DYS FILE WITH 1:1 MERGE*/

. use "C:\Users\DELL\Desktop\thesis\work_files\Disease\DM+DYS.dta", clear

. merge 1:1 hn using "C:\Users\DELL\Desktop\thesis\work_files\Disease\DYS.dta"

** YOU WILL GET MERGED FILE OF PATIENT WITH DYSLIPID (MAY BE WITH SOME DM)
**


** KEEP ONLY MEDICATIONS INTERESTED **

. keep if drug_class==1|drug_class==2


** GENERATE VARIABLE FOR LABEL
```

```
. gen label1=substr(label,1,14)


** GENERATE VARIABLE FOR DRUG-TAKING TIME **

. gen morning =0

. gen lunch =0

. gen dinner =0

. gen bedtime =0


** CHANGE VALUE FOR EACH TIME **

. replace lunch =1 if substr(label1,1,3)=="0-1"

. replace dinner =0.5 if substr(label1,1,7)=="0-1-0.5"

. replace morning = 0.25 if label1=="0.25TBBIDAC"

. replace dinner = 0.25 if label1=="0.25TBBIDAC"

. replace morning=1 if substr(label1,1,2)=="1-"

. replace morning=0 if substr(label1,1,4)=="1-TB"

. replace morning=1 if substr(label1,1,5)=="1-TBX"

. replace morning=0 if label1== "1-2TBX1PCD"


/* GENERATE DDD FOR EACH MEDICATION */

. gen DDD =0

. replace DDD=2 if code=="AMA102N"
```

```
. replace DDD=10 if code=="GLI101N"

. replace DDD=2000 if code=="MET101E"| code=="MET105E"

. replace DDD=300 if code=="GLU104N"

. replace DDD=30 if code=="SIM101E"| code=="SIM102E"| code=="SIM103E"

. replace DDD=60 if code=="DIA110N"| code=="GLI106N"| code=="GLI107N"

. replace DDD=20 if code=="LIP110N"| code=="ATO102N"| code=="ATO103N"

. replace DDD=4 if code=="NOV102N"| code=="NOV103N"

. replace DDD=30 if code=="PIO101E"| code=="PIO102E"

. replace DDD=10 if code=="ROS103N"| code=="ROS104N"

. replace DDD=5 if code=="TRA109N"

. replace DDD=100 if code=="GAL101N"

. replace DDD=2 if code=="AMA103N"

. replace DDD=100 if code=="JAN101N"

. replace DDD=17.5 if code=="JAR101N"

. replace DDD=2 if code=="LIV102N"

. replace DDD=30 if code=="MEV104N"

. replace DDD=0.6 if code=="BAS101N"

. replace DDD=10 if code=="GLI103N"

. replace DDD=60 if code=="LES103N"

. gen strength=0

. replace strength=2 if code=="AMA102N"
```

```
. replace strength=5 if code=="GLI101N"

. replace strength=500 if code=="MET101E"

. replace strength=850 if code=="MET105E"

. replace strength=100 if code=="GLU104N"

. replace strength=20 if code=="SIM101E"

. replace strength=10 if code=="SIM103E"

. replace strength=60 if code=="DIA110N"

. replace strength=80 if code=="LIP110N"

. replace strength=1 if code=="NOV102N"

. replace strength=15 if code=="PIO102E"

. replace strength=30 if code=="GLI106N"

. replace strength=80 if code=="LES103N"

. replace strength=40 if code=="SIM102E"

. replace strength=20 if code=="ATO102N"

. replace strength=2 if code=="NOV103N"

. replace strength=40 if code=="ATO103N"

. replace strength=30 if code=="PIO101E"

. replace strength=10 if code=="ROS103N"

. replace strength=80 if code=="GLI107N"


. replace strength=5 if code=="TRA109N"

. replace strength=50 if code=="GAL101N"
```

. replace strength=3 if code=="AMA103N"

. replace strength=100 if code=="JAN101N"

. replace strength=10 if code=="JAR101N"

. replace strength=2 if code=="LIV102N"

. replace strength=40 if code=="MEV104N"

. replace strength=0.2 if code=="BAS101N"

. replace strength=5 if code=="GLI103N"

. replace strength=20 if code=="ROS104N"

. gen dose = DDD/strength

. gen tbpday_DDD=dose

. replace dinner = 1 if code =="LIV102N"

. replace dinner = 1 if code =="LES103N"

. replace morning =1 if code =="JAR101N"

. replace morning =0.5 if code =="JAN101N"

. replace dinner = 1 if code =="AMA103N"

. replace morning=0.5 if code=="GAL101N" & hn=="12460/44"

. replace morning=1 if code=="GAL101N" & hn=="18834/43"

. replace dinner=1 if code=="GAL101N" & hn=="18834/43"

. replace dinner=1 if code=="GAL101N" & hn=="28632/42"

. save "C:\Users\DELL\Desktop\thesis\work_files\label missing1 with assume.dta", replace

/*MERGE FILE USING DM AND DYS FILE WITH 1:! MERGE TO GET SOME INTERSECT POINT*/

. use "C:\Users\DELL\Desktop\thesis\work_files\Disease\DM.dta", clear

. merge 1:1 hn using "C:\Users\DELL\Desktop\thesis\work_files\Disease\DYS.dta"

** YOU WILL GET MERGED FILE OF PATIENT WITH DM AND DYSLIPID **

. keep if _merge==3

. drop _merge

** THEN SAVE FILE INTO DM+DYS ACTUAL.DTA **

/* GROUP OF PATIENTS WITH DYSLIPIDEMIA */

. preserve

. keep if drug_class==2

/* GENERATE GROUP TO CATEGORIZE CREDIT OF PATIENT*/

. gen c1=0

/* ASSIGN GROUP 1 FOR INTERVENTION GROUP (UC GROUP) */

. replace c1=1 if credit_id1==10| credit_id1==11| credit_id1==45 |credit_id1==62| credit_id1==67| credit_id1==68| credit_id1==74| credit_id1==113| credit_id1==115| credit_id1==78| credit_id1==81| credit_id1==103| credit_id1==19| credit_id1==98

```
/* ASSIGN GROUP 2 FOR INTERVENTION GROUP ( SSS GROUP)  */

. replace c1=2 if credit_id1==3| credit_id1==8| credit_id1==42| credit_id1==44| credit_id1==73| credit_id1==88


/* ASSIGN GROUP 3 FOR CONTROL GROUP (CSMBS GROUP)   */

. replace c1=3 if credit_id1==39| credit_id1==52| credit_id1==75| credit_id1==76| credit_id1==105| credit_id1==106| credit_id1==110| credit_id1==121| credit_id1==122


/* ASSIGN GROUP 4 FOR OUT OF POCKET GROUP (OP GROUP) */

. replace c1=4 if credit_id1==53


/* GROUP 0 ARE OTHER GROUP  */

/* GENERATE SUFFIX FOR CREDIT OF PATIENTS (J VARIABLE) */

. bys hn: gen n=_n


/* RESHAPE FROM LONG TO WIDE */

. reshape wide credit_id, i(hn) j(n)


/****************** PATIENTS WITH 2 CREDITS******************/
```

. use "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit start.dta"

. gen group=0

. replace group=1 if credit_id1==10| credit_id1==11| credit_id1==45|credit_id1==62 | credit_id1==67| credit_id1==68| credit_id1==74| credit_id1==113|credit_id1==115| credit_id1==78| credit_id1==81| credit_id1==103| credit_id1==19| credit_id1==98

. replace group=2 if credit_id1==3| credit_id1==8| credit_id1==42| credit_id1==44| credit_id1==73| credit_id1==88

. replace group=3 if credit_id1==39| credit_id1==52| credit_id1==75| credit_id1==76| credit_id1==105| credit_id1==106| credit_id1==110| credit_id1==121| credit_id1==122

. replace group=4 if credit_id1==53

. rename group pre

. gen group=0

. replace group=1 if credit_id2==10| credit_id2==11| credit_id2==45 |credit_id2==62| credit_id2==67| credit_id2==68| credit_id2==74| credit_id2==113| credit_id2==115| credit_id2==78| credit_id2==81| credit_id2==103| credit_id2==19| credit_id2==98

. replace group=2 if credit_id2==3| credit_id2==8| credit_id2==42| credit_id2==44| credit_id2==73| credit_id2==88

. replace group=3 if credit_id2==39|credit_id2==52| credit_id2==75| credit_id2==76| credit_id2==105| credit_id2==106| credit_id2==110| credit_id2==121| credit_id2==122

. replace group=4 if credit_id2==53

. rename group post

. preserve

. keep if pre==post

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with same credit group.dta"

. restore

. preserve

. keep if pre==1

. keep if post==4

. gen group=0

. replace group=1

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 1.dta"

. preserve

. keep if pre==2

. keep if post==4

. gen group=0

. replace group =2

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 2.dta"

. restore

. preserve

. keep if pre==3

. keep if post==4

. gen group=0

. replace group=3

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 3.dta"

. restore

. preserve

. keep if pre==4

. keep if post==1

. gen group=0

. replace group=1

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 4.1.dta"

. restore

. preserve

. keep if pre==4

. keep if post==2

. gen group=0

. replace group=2

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 4.2.dta"

. restore

. preserve

. keep if pre==4

. keep if post==3

. gen group=0

. replace group=3

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape two credit with diff credit group 4.3.dta"

. restore

. preserve

. keep if pre==0

/******************** PATIENTS WITH 3 CREDITS **********************/

. use "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape three credit.dta"

. gen c1=0

. replace c1=1 if credit_id1==10| credit_id1==11| credit_id1==45| credit_id1==62| credit_id1==67| credit_id1==68| credit_id1==74| credit_id1==113| credit_id1==115| credit_id1==78| credit_id1==81| credit_id1==103| credit_id1==19| credit_id1==98

. replace c1=2 if credit_id1==3| credit_id1==8| credit_id1==42| credit_id1==44| credit_id1==73| credit_id1==88

. replace c1=3 if credit_id1==39| credit_id1==52| credit_id1==75| credit_id1==76| credit_id1==105| credit_id1==106| credit_id1==110|credit_id1==121|credit_id1==122

. replace c1=4 if credit_id1==53

. preserve

. gen c2=0

.replace c2=1 if credit_id2==10| credit_id2==11| credit_id2==45| credit_id2==62| credit_id2==67| credit_id2==68| credit_id2==74| credit_id2==113| credit_id2==115| credit_id2==78| credit_id2==81| credit_id2==103| credit_id2==19| credit_id2==98

. replace c2=2 if credit_id2==3| credit_id2==8| credit_id2==42| credit_id2==44| credit_id2==73| credit_id2==88

.replace c2=3 if credit_id2 ==39| credit_id2 ==52| credit_id2 ==75| credit_id2 ==76| credit_id2==105| credit_id2==106|credit_id2==110| credit_id2==121| credit_id2==122

. replace c2=4 if credit_id1==53

. gen c3=0

.replace c3=1 if credit_id3==10| credit_id3==11| credit_id3==45| credit_id3==62| credit_id3==67| credit_id3==68| credit_id3==74 | credit_id3==113| credit_id3==115| credit_id3==78| credit_id3==81| credit_id3==103| credit_id3==19| credit_id3==98

. replace c3=2 if credit_id3==3| credit_id3==8| credit_id3==42| credit_id3==44| credit_id3==73| credit_id3==88

. replace c3=3 if credit_id3==39| credit_id3==52| credit_id3==75| credit_id3==76| credit_id3==105| credit_id3==106| credit_id3==110| credit_id3==121| credit_id3==122

. replace c3=4 if credit_id3==53

. replace c2=4 if credit_id2==53

. replace c3=4 if credit_id3==53

. gen c2=0

.replace c2=1 if credit_id2==10| credit_id2==11| credit_id2==45| credit_id2==62| credit_id2==67| credit_id2==68| credit_id2==74| credit_id2==113| credit_id2==115| credit_id2==78| credit_id2==81| credit_id2==103| credit_id2==19| credit_id2==98

. replace c2=2 if credit_id2==3| credit_id2==8| credit_id2==42| credit_id2==44| credit_id2==73| credit_id2==88

.replace c2=3 if credit_id2==39| credit_id2==52| credit_id2==75| credit_id2==76| credit_id2==105| credit_id2==106| credit_id2==110| credit_id2==121| credit_id2==122

. replace c2=4 if credit_id2==53

. gen c3=0

.replace c3=1 if credit_id3==10| credit_id3==11| credit_id3==45| credit_id3==62| credit_id3==67| credit_id3==68| credit_id3==74| credit_id3==113| credit_id3==115| credit_id3==78| credit_id3==81| credit_id3==103| credit_id3==19| credit_id3==98

. replace c3=2 if credit_id3==3| credit_id3==8| credit_id3==42| credit_id3==44| credit_id3==73| credit_id3==88

.replace c3=3 if credit_id3==39| credit_id3==52| credit_id3==75| credit_id3==76| credit_id3==105| credit_id3==106| credit_id3==110| credit_id3==121| credit_id3==122

. replace c3=4 if credit_id3==53

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape three credit start.dta"

/****************** PATIENTS WITH 4 CREDITS ******************/

. use "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape four credit.dta"

gen c1=0

.replace c1=1 if credit_id1==10| credit_id1==11| credit_id1==45| credit_id1==62| credit_id1==67| credit_id1==68| credit_id1==74| credit_id1==113| credit_id1==115| credit_id1==78| credit_id1==81| credit_id1==103| credit_id1==19| credit_id1==98

. replace c1=2 if credit_id1==3| credit_id1==8| credit_id1==42| credit_id1==44| credit_id1==73| credit_id1==88

.replace c1=3 if credit_id1==39| credit_id1==52| credit_id1==75| credit_id1==76| credit_id1==105| credit_id1==106| credit_id1==110|credit_id1==121| credit_id1==122

. replace c1=4 if credit_id1==53

. gen c2=0

. replace c2=1 if credit_id2==10| credit_id2==11| credit_id2==45| credit_id2==62| credit_id2==67| credit_id2==68| credit_id2==74| credit_id2==113| credit_id2==115| credit_id2==78| credit_id2==81| credit_id2==103| credit_id2==19| credit_id2==98

. replace c2=2 if credit_id2==3| credit_id2==8| credit_id2==42| credit_id2==44| credit_id2==73| credit_id2==88

.replace c2=3 if credit_id2==39| credit_id2==52| credit_id2==75| credit_id2==76| credit_id2==105| credit_id2==106| credit_id2==110| credit_id2==121| credit_id2==122

. replace c2=4 if credit_id2==53

. gen c3=0

.replace c3=1 if credit_id3==10| credit_id3==11|credit_id3==45| credit_id3==62| credit_id3==67| credit_id3==68| credit_id3==74| credit_id3==113| credit_id3==115| credit_id3==78| credit_id3==81| credit_id3==103| credit_id3==19| credit_id3==98

. replace c3=2 if credit_id3==3| credit_id3==8| credit_id3==42| credit_id3==44| credit_id3==73| credit_id3==88

.replace c3=3 if credit_id3==39| credit_id3==52| credit_id3==75| credit_id3==76| credit_id3==105| credit_id3==106| credit_id3==110| credit_id3==121| credit_id3==122

. replace c3=4 if credit_id3==53

. gen c4=0

.replace c4=1 if credit_id4==10| credit_id4==11| credit_id4==45| credit_id4==62| credit_id4==67| credit_id4==68| credit_id4==74| credit_id4==113| credit_id4==115| credit_id4==78| credit_id4==81| credit_id4==103| credit_id4==19| credit_id4==98

. replace c4=2 if credit_id4==3| credit_id4==8| credit_id4==42| credit_id4==44| credit_id4==73| credit_id4==88

.replace c4=3 if credit_id4==39| credit_id4==52| credit_id4==75| credit_id4==76| credit_id4==105| credit_id4==106| credit_id4==110|credit_id4==121| credit_id4==122

. replace c4=4 if credit_id4==53

/****************** PATIENTS WITH 5 CREDITS *********************/

. use "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape five credit.dta"

. gen c1=0

.replace c1=1 if credit_id1==10| credit_id1==11| credit_id1==45| credit_id1==62| credit_id1==67| credit_id1==68| credit_id1==74| credit_id1==113| credit_id1==115| credit_id1==78| credit_id1==81| credit_id1==103| credit_id1==19| credit_id1==98

. replace c1=2 if credit_id1==3| credit_id1==8| credit_id1==42| credit_id1==44| credit_id1==73| credit_id1==88

.replace c1=3 if credit_id1==39| credit_id1==52| credit_id1==75| credit_id1==76| credit_id1==105| credit_id1==106| credit_id1==110| credit_id1==121| credit_id1==122

. replace c1=4 if credit_id1==53

. gen c2=0

.replace c2=1 if credit_id2==10| credit_id2==11| credit_id2==45| credit_id2==62| credit_id2==67| credit_id2==68| credit_id2==74| credit_id2==113| credit_id2==115| credit_id2==78| credit_id2==81| credit_id2==103| credit_id2==19| credit_id2==98

. replace c2=2 if credit_id2==3| credit_id2==8| credit_id2==42| credit_id2==44| credit_id2==73| credit_id2==88

.replace c2=3 if credit_id2==39| credit_id2==52| credit_id2==75| credit_id2==76| credit_id2==105| credit_id2==106| credit_id2==110| credit_id2==121| credit_id2==122

.replace c2=3 if credit_id2==39| credit_id2==52| credit_id2==75| credit_id2==76| credit_id2==105| credit_id2==106| credit_id2==110| credit_id2==121| credit_id2==122

. replace c2=4 if credit_id1==53

. gen c3=0

.replace c3=1 if credit_id3==10| credit_id3==11| credit_id3==45| credit_id3==62| credit_id3==67| credit_id3==68| credit_id3==74| credit_id3==113| credit_id3==115| credit_id3==78| credit_id3==81| credit_id3==103| credit_id3==19| credit_id3==98

. replace c3=2 if credit_id3==3|credit_id3==8|c redit_id3==42| credit_id3==44| credit_id3==73| credit_id3==88

.replace c3=3 if credit_id3==39| credit_id3==52| credit_id3==75| credit_id3==76| credit_id3==105| credit_id3==106| credit_id3==110| credit_id3==121| credit_id3==122

. replace c3=4 if credit_id3==53

. replace c2=0 if credit_id1==53

. replace c2=4 if credit_id2==53

. gen c4=0

.replace c4=1 if credit_id4==10| credit_id4==11| credit_id4==45| credit_id4==62| credit_id4==67| credit_id4==68| credit_id4==74| credit_id4==113| credit_id4==115| credit_id4==78| credit_id4==81| credit_id4==103| credit_id4==19| credit_id4==98

.replace c4=2 if credit_id4==3| credit_id4==8| credit_id4==42| credit_id4==44| credit_id4==73|credit_id4==88

.replace c4=3 if credit_id4==39| credit_id4==52| credit_id4==75| credit_id4==76| credit_id4==105| credit_id4==106| credit_id4==110| credit_id4==121| credit_id4==122

. replace c4=4 if credit_id4==53

. gen c5=0

.replace c5=1 if credit_id5==10|credit_id5==11| credit_id5==45| credit_id5==62| credit_id5==67| credit_id5==68| credit_id5==74| credit_id5==113| credit_id5==115| credit_id5==78| credit_id5==81| credit_id5==103| credit_id5==19| credit_id5==98

.replace c5=2 if credit_id5==3| credit_id5==8| credit_id5==42| credit_id5==44| credit_id5==73|credit_id5==88

.replace c5=3 if credit_id5==39| credit_id5==52| credit_id5==75| credit_id5==76| credit_id5==105| credit_id5==106| credit_id5==110| credit_id5==121| credit_id5==122

. replace c5=4 if credit_id5==53

/****************** PATIENTS WITH 6 CREDITS ******************/

. use "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape six credit with group.dta"

```
. gen c1=0

. gen c2=0

. gen c3=0

. g c4=0

. g c5=0

. g c6=0

. replace c1 = 1 in 1

. replace c1 = 1 in 2

. replace c1 = 1 in 3

. replace c1 = 1 in 4

. replace c1 = 1 in 5

. replace c1 = 4 in 6

. replace c2 = 4 in 1

. replace c2 = 3 in 2

. replace c2 = 1 in 3

. replace c2 = 4 in 4

. replace c2 = 1 in 5

. replace c2 = 1 in 6

. replace c2 = 0 in 6

. replace c3 = 4 in 2

. replace c3 = 1 in 5
```

. replace c3 = 1 in 6

. replace c4 = 1 in 1

. replace c4 = 1 in 2

. replace c4 = 4 in 3

. replace c4 = 1 in 4

. replace c4 = 1 in 6

. replace c5 = 3 in 1

. replace c5 = 1 in 2

. replace c5 = 1 in 4

. replace c5 = 3 in 5

. replace c5 = 1 in 6

. replace c6 = 1 in 1

. replace c6 = 1 in 2

. replace c6 = 1 in 3

. replace c6 = 1 in 4

. replace c6 = 4 in 5

. replace c6 = 1 in 6

. replace group = 5 in 1

. save "C:\Users\DELL\Desktop\thesis\work_files\Credit of patients\reshape six credit with group.dta", replace

********** AGE OF PATIENTS **********

```
/* CHECK MISSING DATA */

* From this step you will find the missing data of patient age *

. egen nmis =rmiss2(patient_age)

. tab nmis

* Generate first date of prescription *

. sort hn eventdate

. by hn: egen first_date = min(eventdate)

. format first_date %td

* Generate year of first date *

. gen yoffdate = year(first_date)

* Generate new variable for patient age *

. gen new_age=0

. replace new_age=patient_age if eventdate==first_date

* To limit range of time into pre-period *

. drop if td(01feb2015)<=eventdate & eventdate<td(01feb2016)

* Select only patient who meets criteria, have an index prescription *

. keep if new_age>0

* To calculate patient age *

. sum new_age
```

```
/* CORRECT THE MISSING VALUE */


* In this dataset, there are 7 patients which their age are missing. Five patient

* cannot track or guess their age, so the decision is to drop these patients*


drop if nmis==1


/* CATEGORIZE GROUP OF CREDIT */

/* GROUP OF CONTROL GROUP (CSMBS) */

keep if credit_id == 52 | credit_id== 110 | credit_id==75 | credit_id==76 |
credit_id==100


/* GROUP OF SSS*/

keep if credit_id == 3 | credit_id== 8


/* GROUP OF UC */

keep if credit_id == 10 | credit_id== 11 | credit_id==98




/* OTHER GROUP*/
```

```
drop if credit_id == 52 | credit_id== 110 | credit_id==75 | credit_id==76 | credit_id==100
| credit_id==3 | credit_id==8 | credit_id==10| credit_id==11| credit_id==98


********** STEP OF CALCULATING MPR VALUE **********

/*************************** PRE-PRERIOD ***********************************/

********** STEP 1 : DEFINE PRE-PERIOD & IDENTIFICATION-PERIOD **********

. gen pre=0

. replace pre=1 if td(01feb2015)<=eventdate & eventdate<td(01feb2016)

. gen iden_period=0

. replace iden_period=1 if eventdate<td(01feb2015)


********** STEP 2 : SORT THE DATA **********

. sort hn eventdate


***** STEP 3: GENERATE NEW VARIABLE FOR CALCULATING DAYSUPPLY FOR PRE-PERIOD
***

. gen daysupply_pre = daysupply if pre==1

. by hn: gen ttldsup_pre = sum(daysupply_pre) if pre==1

. by hn: egen totdaysup_pre = max(ttldsup_pre) if pre==1


********** STEP 4: GENERATE NEW VARIABLE FOR DAY BETWEEN FILL DATE **********
```

```
. by hn: gen btwday_pre = eventdate - eventdate[_n-1] if pre==1

********** STEP 5: GENERATE INDEX DATE FOR PRE-PERIOD **********

. by hn: egen index_pre = min(eventdate) if pre==1

. format index_pre %td

********** STEP 6: ADDING DAYS TO DATE **********

. by hn: gen t1_pre = index_pre + daysupply_pre

. format t1 %td

. by hn: egen tot1_pre = max(index_pre + daysupply_pre) if pre==1

. format tot1_pre %td

. by hn: gen t2_pre = eventdate + daysupply_pre

. format t2 %td

. by hn: egen tot2_pre = max(eventdate + daysupply_pre) if pre==1

. format tot2_pre %td

********** STEP 7: GENERATE DURATION **********

. by hn: gen duration_pre = max(tot1_pre, tot2_pre) - index_pre

********** STEP 8: CALCULATE TOTAL NUMBER OF FILLS **********

. by hn: egen numfill_pre = count(eventdate) if pre==1
```

********** STEP 9: CALCULATE THE NUMBER OF REFILL IN ASCENDING ORDER **********

. by hn: gen n1_pre = _n

* not add if pre==1 because it will cause a missing number *

********** STEP 10: CALCULATE THE MPR IF THE DURATION IS 365 **********

. by hn: gen compdiff_pre = duration_pre - 365

. by hn: gen dsuptrnc_pre = totdaysup_pre - compdiff_pre

. by hn: gen mpr_pre = dsuptrnc_pre/365

********** STEP 11: IF DURATION IS LESS THAN 365 **********

. by hn: replace mpr_pre = totdaysup_pre/365 if duration_pre<=365

********** STEP 12: CALCULATE THE MPR WITH A MAX MPR=1 **********

. by hn: gen mpr_adj_pre = min(mpr_pre, 1.0) if pre==1

****** STEP 13: CALCULATE THE MPR WITH A DURATION THAT HAS A MAX OF 365 ********

. by hn: gen duration2_pre = max(duration_pre, 365)

/********** POST-PRERIOD **********/

********** STEP 1 : DEFINE POST-PERIOD & FOLLOW-UP-PERIOD **********

```
. gen post=0

. replace post=1 if eventdate>=td(01feb2016) & eventdate<=td(31jan2017)


. gen fu_period=0

. replace fu_period=1 if eventdate>td(31jan2017)


********** STEP 2 : SORT THE DATA **********

. sort hn eventdate


*****STEP 3: GENERATE NEW VARIABLE FOR CALCULATING DAYSUPPLY FOR POST-PERIOD ***

. gen daysupply_post=daysupply if post==1

. by hn: gen ttldsup_post = sum(daysupply_post) if post==1

. by hn: egen totdaysup_post = max(ttldsup_post) if post==1
```



```
********** STEP 4: GENERATE NEW VARIABLE FOR DAY BETWEEN FILL DATE **********

. by hn: gen btwday_post = eventdate - eventdate[_n-1] if post==1


********** STEP 5: GENERATE INDEX DATE FOR POST-PERIOD **********

. by hn: egen index_post = min(eventdate) if post==1

. format index_post %td
```

```
************************** STEP 6: ADDING DAYS TO DATE **************************

. by hn: gen t1_post = index_post + daysupply_post

. format t1_post %td

. by hn: egen tot1_post = max(index_post + daysupply_post) if post==1

. format tot1_post %td

. by hn: gen t2_post = eventdate + daysupply_post

. format t2_post %td

. by hn: egen tot2_post = max(eventdate + daysupply_post) if post==1

. format tot2_post %td


********************** STEP 7: GENERATE DURATION ******************************

. by hn: gen duration_post = max(tot1_post, tot2_post) - index_post


******************** STEP 8: CALCULATE TOTAL NUMBER OF FILLS ********************

. by hn: egen numfill_post = count(eventdate) if post==1


********** STEP 9: CALCULATE THE NUMBER OF REFILL IN ASCENDING ORDER ************

. by hn: gen n1_post = _n

* not add if post==1 because it will cause a missing number *


************** STEP 10: CALCULATE THE MPR IF THE DURATION IS 365 ***************
```

. by hn: gen compdiff_post = duration_post - 365

. by hn: gen dsuptrnc_post = totdaysup_post - compdiff_post

. by hn: gen mpr_post = dsuptrnc_post/365

********** STEP 11: IF DURATION IS LESS THAN 365 **********

. by hn: replace mpr_post = totdaysup_post/365 if duration_post<= 365

********** STEP 12: CALCULATE THE MPR WITH A MAX MPR=1 **********

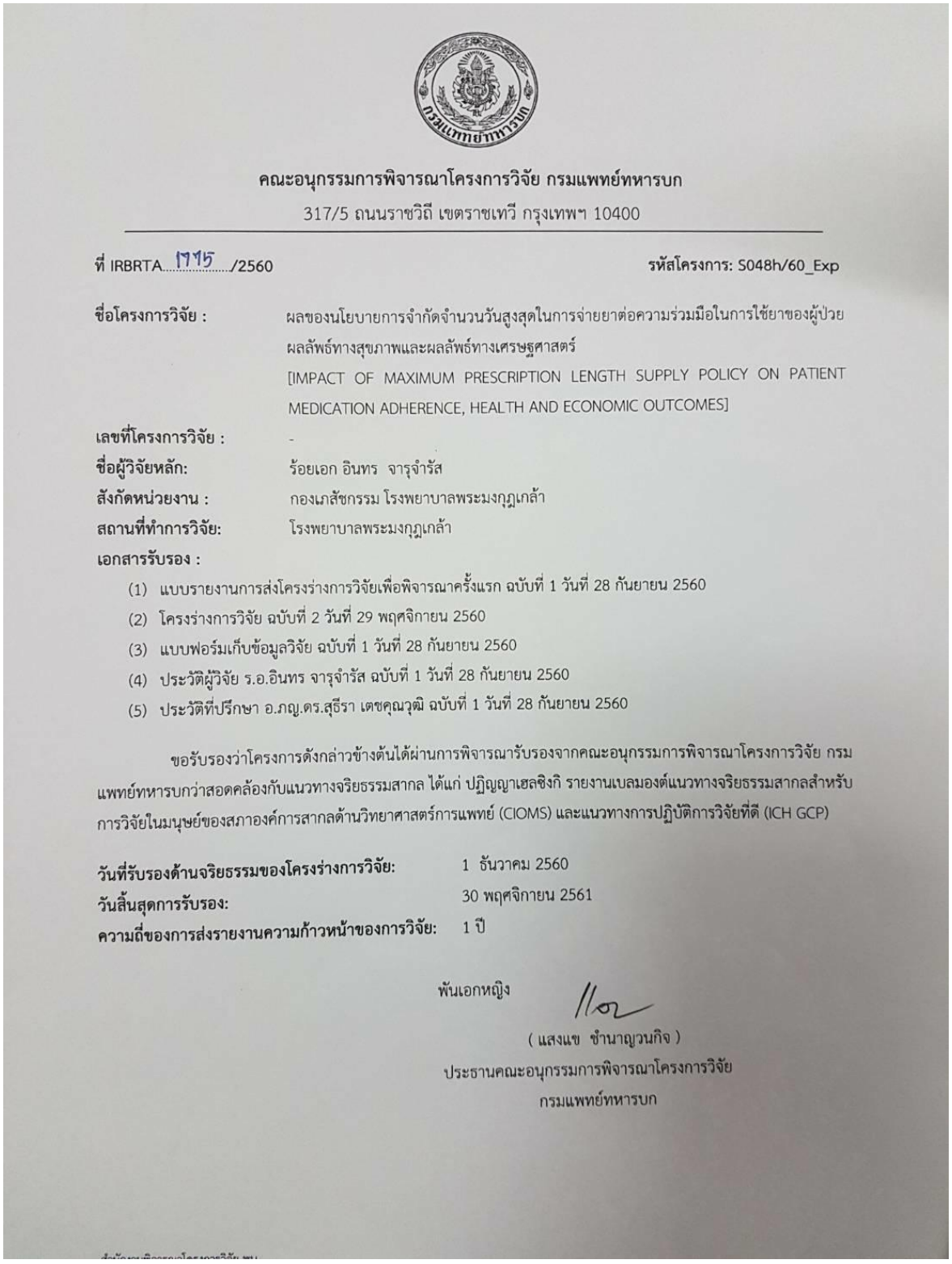
. by hn: gen mpr_adj_post = min(mpr_post, 1.0) if post==1

********** STEP 13: CALCULATE THE MPR WITH A DURATION THAT HAS A MAX OF 365 ********

. by hn: gen duration2_post = max(duration_post, 365)

APPENDIX B

The Certificate of IRB Approval



คณะอนุกรรมการพิจารณาโครงการวิจัย กรมแพทย์ทหารบก

317/5 ถนนราชวิถี เขตราชเทวี กรุงเทพฯ 10400

ที่ IRBRTA 1715 /2560 **รหัสโครงการ: S048h/60_Exp**

ชื่อโครงการวิจัย : ผลของนโยบายการจำกัดจำนวนวันสูงสุดในการจ่ายยาต่อความร่วมมือในการใช้ยาของผู้ป่วย ผลลัพธ์ทางสุขภาพและผลลัพธ์ทางเศรษฐศาสตร์
[IMPACT OF MAXIMUM PRESCRIPTION LENGTH SUPPLY POLICY ON PATIENT MEDICATION ADHERENCE, HEALTH AND ECONOMIC OUTCOMES]

เลขที่โครงการวิจัย : -

ชื่อผู้วิจัยหลัก: ร้อยเอก อินทร จารุจำรัส

สังกัดหน่วยงาน : กองเภสัชกรรม โรงพยาบาลพระมงกุฎเกล้า

สถานที่ทำการวิจัย: โรงพยาบาลพระมงกุฎเกล้า

เอกสารรับรอง :

(1) แบบรายงานการส่งโครงร่างการวิจัยเพื่อพิจารณาครั้งแรก ฉบับที่ 1 วันที่ 28 กันยายน 2560
(2) โครงร่างการวิจัย ฉบับที่ 2 วันที่ 29 พฤศจิกายน 2560
(3) แบบฟอร์มเก็บข้อมูลวิจัย ฉบับที่ 1 วันที่ 28 กันยายน 2560
(4) ประวัติผู้วิจัย ร.อ.อินทร จารุจำรัส ฉบับที่ 1 วันที่ 28 กันยายน 2560
(5) ประวัติที่ปรึกษา อ.ภญ.ดร.สุธีรา เตชคุณวุฒิ ฉบับที่ 1 วันที่ 28 กันยายน 2560

ขอรับรองว่าโครงการดังกล่าวข้างต้นได้ผ่านการพิจารณารับรองจากคณะอนุกรรมการพิจารณาโครงการวิจัย กรมแพทย์ทหารบกว่าสอดคล้องกับแนวทางจริยธรรมสากล ได้แก่ ปฏิญญาเฮลซิงกิ รายงานเบลมองต์แนวทางจริยธรรมสากลสำหรับการวิจัยในมนุษย์ขององค์การสากลด้านวิทยาศาสตร์การแพทย์ (CIOMS) และแนวทางการปฏิบัติการวิจัยที่ดี (ICH GCP)

วันที่รับรองด้านจริยธรรมของโครงร่างการวิจัย: 1 ธันวาคม 2560
วันสิ้นสุดการรับรอง: 30 พฤศจิกายน 2561
ความถี่ของการส่งรายงานความก้าวหน้าของการวิจัย: 1 ปี

พันเอกหญิง
(แสงแข ชำนาญวนกิจ)
ประธานคณะอนุกรรมการพิจารณาโครงการวิจัย
กรมแพทย์ทหารบก

RL 01_2560

คณะอนุกรรมการพิจารณาโครงการวิจัย กรมแพทย์ทหารบก
ชั้น 5 อาคารพระมงกุฎเกล้าเวชวิทยา วิทยาลัยแพทยศาสตร์พระมงกุฎเกล้า
317/5ถนน ราชวิถี เขตราชเทวี กรุงเทพฯ 10400 โทรศัพท์, (662) 763-4297, (662) 763-4270โทรสาร (662) 354-9011
www.irbrta.pmk.ac.th, www.amed.go.th/rtamed/irbrta/ E-mail; irbrta@yahoo.com, irbrta@amed.go.th

ที่ IRBRTA 1775 /2560 6 ธันวาคม 2560

เรื่อง ขอชี้แจงการดำเนินการต่างๆ เกี่ยวกับโครงร่างการวิจัยที่ได้รับการรับรอง

เรียน ร้อยเอก อินทร จารุจำรัส

ตามที่ท่านได้ส่งโครงร่างการวิจัยและเอกสารที่เกี่ยวข้อง เพื่อพิจารณาระเบียบวิธีวิจัยและจริยธรรม ฉบับที่ 2 วันที่ 29 พฤศจิกายน 2560 (รหัส S048h/60_Exp) เรื่อง "ผลของนโยบายการจำกัดจำนวนวันสูงสุดในการจ่ายยาต่อความร่วมมือในการใช้ยาของผู้ป่วย ผลลัพธ์ทางสุขภาพและผลลัพธ์ทางเศรษฐศาสตร์" [IMPACT OF MAXIMUM PRESCRIPTION LENGTH SUPPLY POLICY ON PATIENT MEDICATION ADHERENCE, HEALTH AND ECONOMIC OUTCOMES] นั้น คณะอนุกรรมการฯได้พิจารณารับรองโครงร่างการวิจัย เมื่อ 1 ธันวาคม 2560 ระยะเวลาการรับรอง 1 ปี นับตั้งแต่วันที่ได้รับการรับรองโครงการวิจัย และความถี่ในการส่งรายงานความก้าวหน้าทุก 1 ปี ผู้วิจัยกรุณาส่งรายงานความก้าวหน้างานวิจัย ภายใน 1 เดือน ก่อนหมดอายุการรับรอง เพื่อพิจารณาการรับรองต่อเนื่องคณะอนุกรรมการฯขอชี้แจงเกี่ยวกับการส่งรายงานต่างๆ มายังคณะอนุกรรมการฯ ดังนี้

(1) แบบรายงานส่วนแก้ไขเพิ่มเติมโครงร่างการวิจัย (Amendment) (RF 02_2560) เมื่อมีการแก้ไขเพิ่มเติมโครงร่างการวิจัย ผู้วิจัยต้องส่งโครงร่างการวิจัยที่มีการแก้ไขเพิ่มเติม เพื่อแจ้งให้คณะอนุกรรมการฯ พิจารณารับรองก่อนดำเนินการตามที่ได้แก้ไขเพิ่มเติม (ยกเว้นในกรณีที่การแก้ไขเพิ่มเติมนั้นกระทำเพื่อความปลอดภัยของอาสาสมัคร)

(2) รายงานความก้าวหน้าของการวิจัย (Progress report) (RF 03_2560) ผู้วิจัยต้องส่งรายงานความก้าวหน้าของการวิจัยตามระยะเวลาที่คณะอนุกรรมการฯ กำหนดและอย่างน้อย 30 วัน ก่อนหมดอายุการรับรอง ในกรณีที่การวิจัยยังไม่สิ้นสุด ผู้วิจัยต้องส่งจดหมายขอต่ออายุการรับรองโครงร่างการวิจัย

(3) รายงานเหตุการณ์ไม่พึงประสงค์ (RF 04_1_2560 หรือ RF 04_2_2560) เมื่อมีเหตุการณ์ไม่พึงประสงค์ชนิดร้ายแรงให้รายงานตามข้อกำหนดของ ICH GCP

(4) รายงานไม่ปฏิบัติตามข้อกำหนด (RF 05_2560) เมื่อมีการเบี่ยงเบนหรือไม่ปฏิบัติตามโครงร่างการวิจัยที่ได้รับการรับรอง

(5) รายงานสรุปผลการวิจัย (Final report) (RF 06_2560) และบทคัดย่อภาษาไทยและ/หรือภาษาอังกฤษเมื่อการวิจัยสิ้นสุดแล้ว

หมายเหตุ สามารถ Download แบบรายงานต่างๆ ได้ที่ http://www.irbrta.pmk.ac.th

จึงเรียนมาเพื่อทราบ

ขอแสดงความนับถือ

พันเอกหญิง

(แสงแข ชำนาญวนกิจ)

ประธานคณะอนุกรรมการพิจารณาโครงการวิจัย

กรมแพทย์ทหารบก

VITA

NAME	อินทร จารุจำรัส
DATE OF BIRTH	4 มีนาคม 2528
PLACE OF BIRTH	กรุงเทพฯ
INSTITUTIONS ATTENDED	ปริญญาตรี เภสัชศาสตรบัณฑิต จุฬาลงกรณ์มหาวิทยาลัย ปริญญาโท เภสัชศาสตรมหาบัณฑิต มหาวิทยาลัยนเรศวร
HOME ADDRESS	66/12 หมู่ 9 ซอยเพชรเกษม 33/8 แขวงบางหว้า เขตภาษีเจริญ กรุงเทพฯ 10160