ECONOMIC EVALUATION OF LONG ACTING ANTIPSYCHOTIC INJECTION IN SCHIZOPHRENIA

Mr. Osot Nerapusee

A Dissertation Submitted in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy Program in Social and Administrative Pharmacy
Department of Social and Administrative Pharmacy
Faculty of Pharmaceutical Sciences
Chulalongkorn University
Academic Year 2013

การประเมินความคุ้มค่าทางเศรษฐศาสตร์ของยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นในผู้ป่วยจิตเภท

นายโอสถ เนระพูสี

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรดุษฎีบัณฑิต
สาขาวิชาเภสัชศาสตร์สังคมและบริหาร ภาควิชาเภสัชศาสตร์สังคมและบริหาร
คณะเภสัชศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2556

Thesis Title	ECONOMIC EVALUATION OF LONG ACTING ANTIPSYCHOTIC INJECTION IN SCHIZOPHRENIA
By	Mr. Osot Nerapusee
Field of Study	Social and Administrative Pharmacy
Thesis Advisor	Assistant Professor Rungpetch Sakulbumrungsil, Ph.D.
Thesis Co-Advisor	Pudtan Phanthunane, Ph.D.

Accepted by the Faculty of Pharmaceutical Sciences, Chulalongkorn University in Partial Fulfillment of the Requirements for the Doctoral Degree

.....Dean of the Faculty of Pharmaceutical Sciences
(Assistant Professor Rungpetch Sakulbumrungsil, Ph.D.)

THESIS COMMITTEE

.....Chairman
(Associate Professor Sathitpong Thanaviriyakul)

.....Thesis Advisor
(Assistant Professor Rungpetch Sakulbumrungsil, Ph.D.)

.....Thesis Co-Advisor
(Pudtan Phanthunane, Ph.D.)

.....Examiner
(Associate Professor Vithaya Kulsomboon, Ph.D.)

.....Examiner
(Assistant Professor Tanattha Kittisopee, Ph.D.)

.....External Examiner
(Associate Professor Thienchai Ngamthipwatthana, M.D.)

โอสถ เนระพูสี : การประเมินความคุ้มค่าทางเศรษฐศาสตร์ของยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นในผู้ป่วยจิตเภท. (ECONOMIC EVALUATION OF LONG ACTING ANTIPSYCHOTIC INJECTION IN SCHIZOPHRENIA) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ. ภญ. ดร. รุ่งเพ็ชร สกุลบำรุงศิลป์, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: อ. ดร. พุดตาน พันธุเณร, 112 หน้า.

ยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นเป็นยาที่มีการแนะนำให้ใช้ในการรักษาผู้ป่วยจิตเภทที่ไม่ให้ความร่วมมือในการรับประทานยา ปัจจุบันยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นรุ่นที่ 1 จำนาวน 4 รายการถูกบรรจุอยู่ในบัญชียาหลักแห่งชาติได้แก่ Haloperidol dec, Flupentixol dec, Flupenazine dec . และ Zuclopentixol dec แต่ยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นรุ่นที่ 2 จำนวน 2 รายการยังไม่ได้ถูกบรรจุไว้ได้แก่ Paliperidone LAI และ Risperidone LAI. การประเมินความคุ้มค่าทางเศรษฐศาสตร์ของยาทั้งหมดในกลุ่มนี้ อาจจะมีส่วนสนับสนุนการตัดสินใจของแพทย์ในการเลือกใช้ยาอย่างเหมาะสมในเวชปฏิบัติและอาจมีส่วนสนับสนุนการพิจารณาการบรรจุยากลุ่มใหม่ในชุดสิทธิประโยชน์การรักษาพยาบาลของผู้ป่วยต่อไป การศึกษานี้มีวัตถุประสงค์เพื่อต้องการประเมินความคุ้มค่าทางเศรษฐศาสตร์ของยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นจำนวน 6 รายการที่มีอยู่ในประเทศไทยสำหรับการรักษาผู้ป่วยจิตเภทที่ไม่ให้ความร่วมมือในการรับประทานยา การประเมินความคุ้มค่าประสิทธิผลของยารักษาโรคจิตชนิดฉีดออกฤทธิ์เนิ่นจะใช้วิธีการวิเคราะห์แบบต้นทุนอรรถประโยชน์(cost utility analysis)และอาศัยแบบจำลอง Markov ภายใต้มุมมองทางสังคม แบบจำลองมีการดัดแปลงมาจากงานของ NICE ผลลัพธ์เป้าหมาย 3 รายการในการวิเคราะห์ถูกกำหนดให้มีลักษณะเลือกเอาอย่างใดอย่างหนึ่ง (mutually exclusive outcomes) ได้แก่ จำนวนผู้ป่วยที่เกิดการกลับเป็นซ้ำ (relapse) จำนวนผู้ป่วยที่หยุดใช้ยาเนื่องจากอาการข้างเคียง และจำนวนผู้ป่วยที่หยุดใช้ยาเนื่องจากเหตุผลอื่นๆ ความน่าจะเป็นของการเปลี่ยนสถานะของผลลัพธ์เป้าหมาย 3 รายการคำนวณมาจากงานทบทวนวรรณกรรมอย่างเป็นระบบ และงานศึกษาวิเคราะห์อภิมาณแบบ mixed treatment comparison meta-analysis with completing risk models โดยวิธีการวิเคราะห์ทางคณิตศาสตร์แบบ Bayesian นอกจากนี้ข้อมูลด้านต้นทุนราคาในแบบจำลองจะถูกนำมาจากงานตีพิมพ์ที่สืบค้นได้และคำนวณให้เป็นมูลค่าในปีที่ทำการวิเคราะห์คือปี 2557 การวิเคราะห์จะคำนวณหาผลลัพธ์แบบค่าเฉลี่ย(deterministic analysis) และแบบความน่าจะเป็น (probabilistic analysis) โดยจะครอบคลุมระยะเวลา 2 แบบคือแบบ 10 ปีและแบบตลอดชีวิต ผลลัพธ์ที่ได้นำเสนอในรูปแสดงระนาบต้นทุนประสิทธิผล (cost effective analysis plane) และระดับความคุ้มค่าที่ยอมรับได้ (cost effectiveness acceptability curve) การประเมินจะกระทำตามคู่มือการประเมินเทคโนโลยีด้านสุขภาพสำหรับประเทศไทย (HITAP guideline) และการวิเคราะห์ดังกล่าวนี้ใช้โปรแกรม TreeAgePro 2014 ผลการวิเคราะห์ด้วยค่าเฉลี่ย(deterministic analysis) ในยา 6 รายการพบว่า Haloperidol dec มีความคุ้มค่าทางเศรษฐศาสตร์ในการเป็นยาลำดับแรกในการรักษาผู้ป่วยจิตเภทที่ไม่ให้ความร่วมมือในการรับประทานยา สำหรับยา Flupenazine dec., Flupentixol dec. Paliperidone LAI และ Risperidone LAI มีความคุ้มค่าทางเศรษฐศาสตร์เพื่อใช้ทดแทน ในกรณีที่ไม่สามารถจัดหา haloperidol dec. ได้ ซึ่งมีค่า ICER ดังนี้ 808,580, 3,995,921, 5,052,900, และ32,712,811 บาท/QALY แต่ทั้งนี้ค่า ICERs ของยาทั้ง 4 ตัวสูงเกินกว่าระดับความเต็มใจที่จะจ่าย อย่างไรก็ตาม ไม่พบความคุ้มค่าทางเศรษฐศาสตร์ของยา Zulcopentixol dec เนื่องจากพบค่า ICER ติดลบเท่ากับ 627,116 บาท/QALY ส่วนการวิเคราะห์แบบความน่าจะเป็น (Probabilistic analysis) พบว่า Haloperidol dec ยังมีความคุ้มค่าทางเศรษฐศาสตร์ในการเป็นยาลำดับแรกในการรักษาผู้ป่วยจิตเภทที่ไม่ให้ความร่วมมือในการรับประทานยาเช่นกัน นอกจากนี้พบว่าโอกาสที่ยา Paliperidone LAI และ Risperidone LAI อาจจะมีความคุ้มค่ามากกว่ายา Haloperidol dec นั้น ก็ต่อเมื่อ ระดับความเต็มใจที่จะจ่ายมีค่าสูงที่ระดับ 3,000,000 บาท/QALY ผลการวิเคราะห์ที่ได้ไม่แตกต่างกันในการวิเคราะห์แบบระยะเวลา 10 ปีและแบบตลอดชีวิต โดยสรุป Haloperidol dec มีความคุ้มค่าทางเศรษฐศาสตร์ในการเป็นยาลำดับแรกในการรักษาผู้ป่วยจิตเภทที่ไม่ให้ความร่วมมือในการรับประทานยาทั้งการวิเคราะห์ข้อมูลด้วยค่าเฉลี่ย(deterministic analysis) และแบบความน่าจะเป็น (probabilistic analysis) ทั้งนี้เพื่อลดความไม่แน่นอนในแบบจำลองทางเศรษฐศาสตร์ การวิจัยในอนาคตควรมีการศึกษาครอบคลุมอาการข้างเคียงของยากลุ่มนี้ด้านระบบประสาทและเมตาบอลิซึม รวมทั้งการพิจารณาค่าอรรถประโยชน์ของผู้ป่วยที่มีการกลับเป็นซ้ำหลายครั้ง และอาจรวมถึงลักษณะของผู้ป่วยที่มีปัจจัยเสี่ยงแตกต่างกัน

ภาควิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อนิสิต	.....
สาขาวิชา	เภสัชศาสตร์สังคมและบริหาร	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก	.....
ปีการศึกษา	2556	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม	.....

5177108433 : MAJOR SOCIAL AND ADMINISTRATIVE PHARMACY
KEYWORDS: ECONOMIC EVALUATION / SCHIZOPHRENIA / MIXED TREATMENT COMPARISON / LONG ACTING INJECTION / ANTIPSYCHOTICS

OSOT NERAPUSEE: ECONOMIC EVALUATION OF LONG ACTING ANTIPSYCHOTIC INJECTION IN SCHIZOPHRENIA. ADVISOR: ASST. PROF. RUNGPETCH SAKULBUMRUNGSIL, Ph.D., CO-ADVISOR: PUDTAN PHANTHUNANE, Ph.D., 112 pp.

Long acting injection anti-psychotics (LAIs) are suggested in management of schizophrenia with oral medication non-adherence. Four of first generation LAIs; Haloperidol dec, Flupentixol dec, Flupenazine dec . and Zuclopentixol dec., are listed in national list of essential medicine but two of newer second generation LAIs.; Paliperidone LAI, and Risperidone LAI. Economic evaluation evidence of these medications may not only guide healthcare profession to choose LAIs for their patients appropriately but also support healthcare policy makers to consider any newer interventions for future health benefit scheme. This research aims to assess cost effectiveness of six LAIs registered in Thailand for schizophrenia with oral medication non-adherence. A cohort Markov modelling for cost utility analysis of six LAIs is conducted under societal perspective. Model structure is modified from NICE economic model for schizophrenia. Three mutually exclusive outcomes include number of subjects with relapse, discontinuation with intolerable side effect, and due to other reasons are considered. The transitional probability of these outcomes are retrieved from systematic review and mixed treatment comparison meta-analysis with completing risk models. Bayesian framework is applied for meta-analysis work. Other published cost data accessed where available are adjusted to present values of the current analysis year 2014. Deterministic analysis and probabilistic sensitivity analysis are applied for two time horizons; 10 year and lifetime, and presented in the cost effective analysis plane and the cost effectiveness acceptability curve respectively. This economic evaluation will follow HITAP guideline. Markov economic modelling is conducted in TreeAgePro 2014 software. Result of the deterministic analysis, Haloperidol dec. is the most cost effective among 6 LAIs for first line treatment of schizophrenia with oral non-adherence. Flupenazine dec., Flupentixol dec. Paliperidone LAI. and Risperidone LAI. might be next alternatives if Haloperidol dec is not available, with ICER of 808,580, 3,995,921, 5,052,900, and 32,712,811 baht per QALY gained. However these ICERs exceed the willingness to pay threshold. However, Zuclopentixol dec is not cost effective option because ICER is -627,116 baht/QALY. Probabilistic analysis also suggests Haloperidol dec has highest probability of being cost effective, with wide range of willingness to pay threshold, among the other LAIs for the first line treatment of schizophrenia with oral non-adherence. Higher probability of being more cost effective of Paliperidone LAI and Risperidone LAI than Haloperidol dec may be seen when WTP threshold increases up to 3,000,000 baht/QALY. Analysis results of both time horizons remain the same. In conclusion, Haloperidol dec is the most cost effective LAIs for the first line treatment in schizophrenia with oral non adherence under deterministic and probabilistic analysis. Future researches to address uncertainty of economic models may include long term neurological and metabolic side effects, utility of repeated relapses and variation of patient intrinsic factors.

Department:	Social and Administrative Pharmacy	Student's Signature .....
Field of Study:	Social and Administrative Pharmacy	Advisor's Signature .....
Academic Year:	2013	Co-Advisor's Signature .....

ACKNOWLEDGEMENTS

I am indebted to many people for the suggestions I have received during my Ph.D. program. Without GREAT supports from these people, I could not reach this step. I wish to THANKS :

Asst Prof Rungpetch Sakulbumrungsil Ph. D. Chulalongkorn University

Assoc Prof. Sathitpong Thanaviriyakul Chulalongkorn University

Pudtan Phanthunane Ph. D. Naresuan University

Assoc.Prof. Vithaya Kulsomboon Ph. D. Chulalongkorn University

Asst Prof. Tanattha Kittisopee Ph. D. Chulalongkorn University

Assoc.Prof Thienchai Ngamthipwatthana M.D. Siriraj Hospital

Anusorn Thanataveerat MPH. Columbia Mailman School of Public Health, Columbia University, USA.

Chanadda Chinthammit MS., Pharmaceutical Economics, Policy, and Outcomes department , University of Arizona , USA.
Prof Daniel C Malone Ph.D., Pharmaceutical Economics, Policy, and Outcomes department, University of Arizona, USA.

Chavalit Romyen B. Sc. Pharm, Chiang Mai University

Maneeporn Pangjunhom Pharm D. Chiang Mai University

Adawan Methasate Ph. D.

All faculty member of Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand

Finally, THANKS to my family member and working colleagues during the years of my educational program.

CONTENTS

Page

Page

Page

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER 1
INTRODUCTION

This chapter will describe overview of Schizophrenia disease include prevalence, clinical treatment goal and treatment options, and economic burden. Rationales of study, research questions, study objectives and expected contributions are included in this chapter.

1.1 Disease and prevalence overview

Schizophrenia is a term to describe major psychiatric disorder include individual's perception, thoughts, affect and behavior. Schizophrenia is chronic psychiatric disease which includes hallucinations, delusions, thought disorder, disorganized speech, grossly disorganized behavior, reduced motivation, and reduced social functioning (1).The symptoms and behaviour associated with schizophrenia may have a distressing impact on family and their social life. After an acute episode, there are often problems including social exclusion, few chances to return to work, and develop relationships.

Worldwide, schizophrenia was estimated to be top ten illness causing disability (2).
A systematic review study of prevalence showed the median lifetime prevalence was 3.3 per 1,000 (3).

Thailand National survey in 2003, prevalence of psychotic disorders among persons with age of 15-59 years was 1.2 % (4). Mental disorders in Thailand report 2004 showed prevalence in schizophrenia were 0.47 % for men and 0.38 %for women while incidence were 0.021 % for men and 0.015% for women(5). Year of lives with disability for schizophrenia was ranked as the 3rd in women and 5th in men(5).
Recently, a Thailand prevalence study by Phanthunane presented the prevalence of schizophrenia with ages of 15-59 years was 8.8 per 1,000 with a male-to-female ratio of 1.1-to-1 (6).

1.2 Diagnosis

Two major standard criteria were widely used for schizophrenia diagnosis; Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (2, 7).

Both ICD-10 and DSM-IV are similar on the symptom clusters of schizophrenia. Three main domains are considered , including: psychotic symptoms, such as certain types of auditory

hallucinations (hearing voices), delusions (paranoia and telepathy) and thought disorder (incomprehensible speech); negative symptoms, such as poor self-care, reduced motivation, reduced ability to experience pleasure, alogia (reduced production of thought), affective blunting (lack of emotional expression) and reduced social functioning; and the rarer symptom of catatonia. ICD-10 requires that at least one such diagnostic symptom from one of the three domains which clearly present for 1 month. ICD-10 also accepts the diagnosis if two of these symptoms present less clearly for 1 month. Prominent mood symptoms, such as depression or mania are not made in diagnosis. There is similarity between DSM-IV and ICD-10 that diagnostic symptoms need to present for at least 1 month. However DSM-IV also required that symptom should be persisting for at least 6 months.

1.3 Treatment goal and options

The Ultimate goal in the treatment of schizophrenia is to enable subjects to lead maximally productive and personally meaningful lives. As of lacking of definitive cure treatment, healthcare providers should have plan to include treatment interventions directed towards decreasing manifestations of the illness, rehabilitative services directed towards enhancing adaptive skills, and social support mobilization aimed at optimizing function and quality of life(8)

Tandon provided a conceptual framework for maximizing the effectiveness of treatments and other services towards promoting recovery of persons with schizophrenia. Pharmacological, psychological, and social strategies that decrease the burden of the disease of schizophrenia on affected individuals and their families while adding the least possible burden of treatment are demonstrated in figure 1.1 and table 1.1. (source : Tandon RT. page 349 -350, 2006 (8))

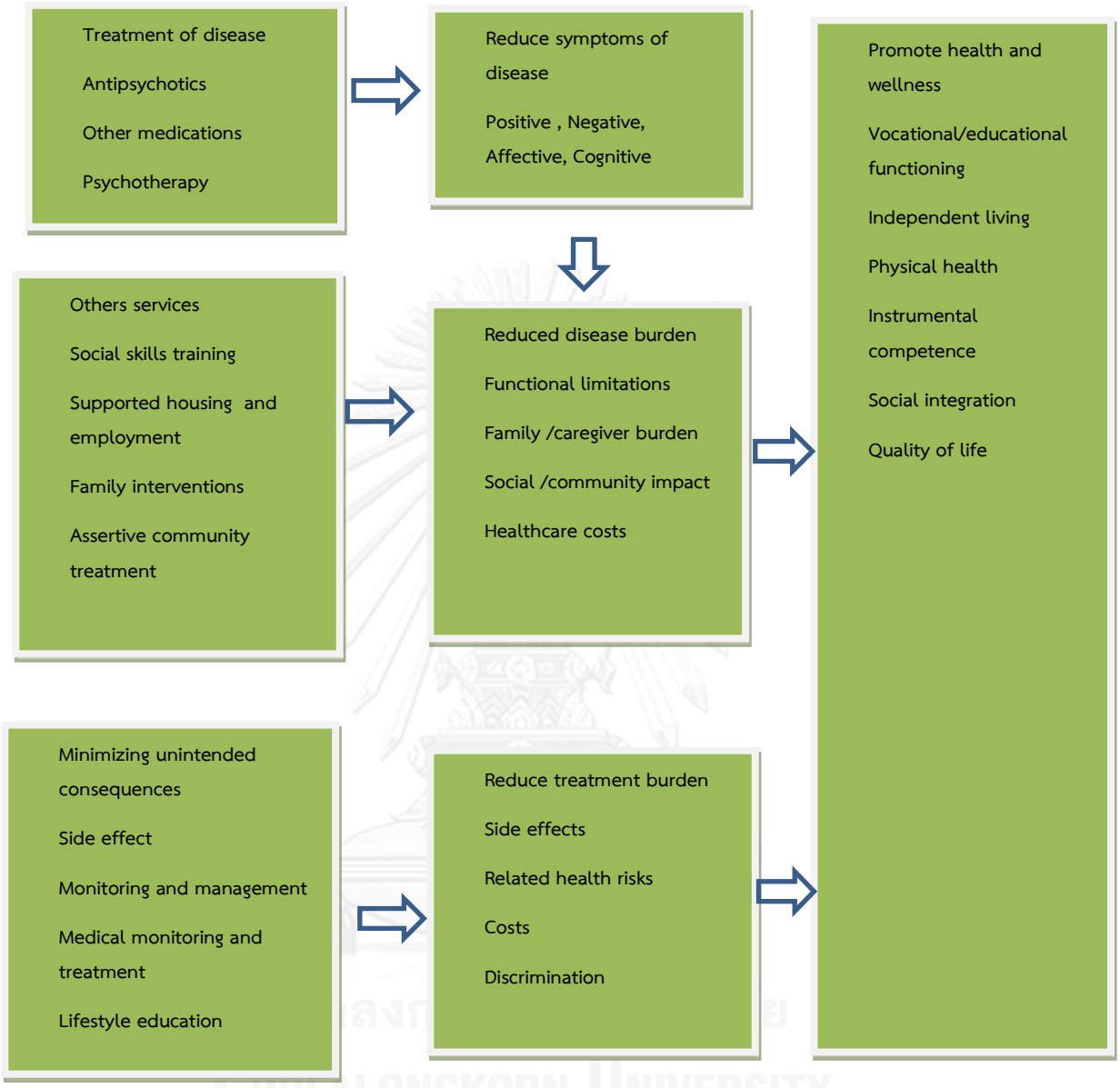


Figure 1.1 Optimizing subject outcomes; How treatment and other services can impact the four domains of effectiveness

Table 1.1 Outcome domains of clinical effectiveness

Disease symptoms	Treatment burden	Disease burden	Health and welfare
• Positive and negative symptoms • Aggressiveness and hostility • Mood and anxiety • Cognition	• Motor side effects(i.e. EPS, Parkinsonism, tardive dyskinesia) • Metabolic endocrinological side effects i.e. weight gain, dyslipidemia, glucose dysregulation) • Others (sexual side effects , dizziness, sedation) • Medical health risks	• Impact on interpersonal, educational and vocational functioning • Impact on family functions • Impact on finances • Impact on caregivers • Impact on extended social network • Healthcare costs/resource utilization	• Social reintegration • Quality of life and personal satisfaction • Independent living • Vocational /educational functioning • Physical health

Currently, a curative treatment for schizophrenia has not reached. However antipsychotic medication becomes the mainstay of treatment to delay the occurrence and reduce the severity of symptoms(1).

1.3.1 Pharmacological treatment

To date, antipsychotic medication is the primary treatment for schizophrenia in both hospital and community setting. Efficacy of antipsychotics in management of acute psychotic episodes and relapse prevention were discussed and established(9).

Conventional or typical antipsychotic agents (so called first-generation antipsychotics or FGAs) are associated various side effects including sedation, weight gain, sexual dysfunction and movement disorders; extra pyramidal side effects(EPS), parkinsonism, akathisia, dystonia, and tardive dyskinesia. Twenty percent of subjects who use FGAs reported having tardive dyskinesia(10).

Newer or atypical antipsychotic agents (so called second-generation antipsychotics or SGAs) were introduced to overcome the limited use of prior group. They had less movement disorder side effect but more on weight gain and metabolic syndromes which might increase risk of type 2 diabetes and cardiovascular disease(11). In addition, raising level of serum prolactin was another concern among subjects with antipsychotics (12).

1.3.2 Non- pharmacological treatment

Non-pharmacological treatment included cognitive behavioural therapy (CBT) for subjects and family intervention program (FI) for care givers were recommended to start either during the acute phase or later, including in insubject settings (1).

Care givers and friends were important factors in the process of assessment and engagement and in the long-term successful treatments.

Evidences also suggested that delayed access to mental health services in early schizophrenia was associated with less recovery, and increased risk of relapse and poorer long-term outcome(13).

1.4 Clinical Practice Guideline

1.4.1NICE guideline #82 for schizophrenia 2009

Oral antipsychotic medication is suggested for subject with newly diagnosed schizophrenia (1).

For promoting recovery phase, it is suggested for subjects to keep a long-term maintenance medication unless contraindication.

According to NICE guideline, consider offering LAIs antipsychotic medication to subjects:

- who prefer such treatment after an acute episode
- where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication.

When starting LAIs antipsychotic medication:

- consider subjects' preferences and attitudes towards the mode of administration and administration process
- always discuss and provide benefit and risk information of the drug regimen
- start a small test dose based on product information.

For subjects with schizophrenia whose illness has not responded adequately to pharmacological or non-pharmacological intervention treatment:

- Offer clozapine to subjects whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second-generation antipsychotic.

1.4.2Thai guideline for schizophrenia treatment 2001

Conventional antipsychotic medication is suggested to use as 1st line drug in subjects with schizophrenia(14). When subjects fail, it is suggested to switch to 1) conventional antipsychotic medication with different chemical structure 2) second generation antipsychotic medication. Clozapine or electroconvulsive therapies are options in the resistance cases.

LAIs is suggested to use in schizophrenic subjects who are oral non-adherence as of non EPS causes.

1.5 Treatment non-adherence

Adherence (or compliance with)to medication regimen means as the extent to which subjects take medications as prescribed by their health care providers(15). The word of Adherence is preferred more because compliance's suggest that subject is passively action rather than collaboration between providers and subjects.

Under controlled study conditions , up to 25% of subjects were classified as noncompliant within 7-10 days. When subjects were monitored longer , at least 50% of subjects became partially complaint or noncompliant within 1 year, and 75% within 2 years of discharge as presented in figure 1.2 (source : Keith SJ page 1310 , 2003 (16))

Most of subjects responded well to oral antipsychotic medication but discontinuation rate within 1.5 years was high up to 74% (17).

Rates of adherence among schizophrenic subjects are range of 40-50 % (18). In systematic review work during 1975-1996 of Cramer's ,schizophrenic psubjects receiving antipsychotics took an average of 58 percent of the recommended amount of the medications, with a range from 24 to 90 percent(19).

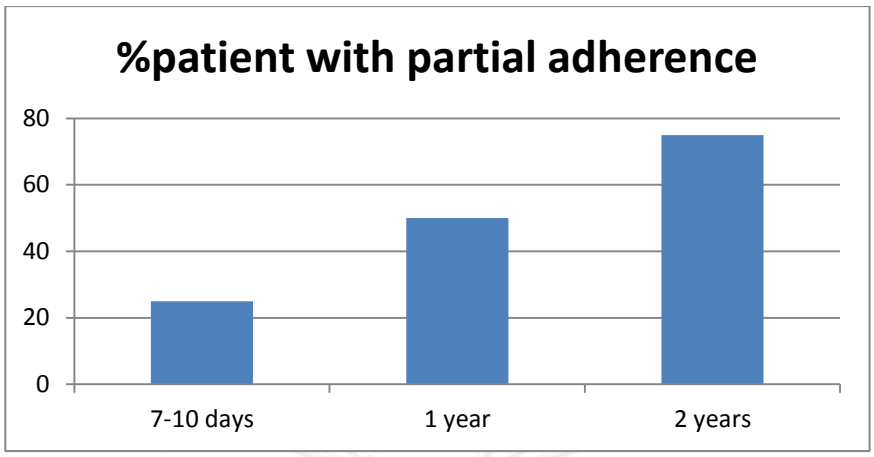


Figure 1.2 Time course of antipsychotic medication compliance

Predictors of poor adherence are discussed widely; including psychological problems, cognitive impairment, asymptomatic diseases, inadequate follow-up or discharge planning, side effects, lacking of belief of efficacy, lack of insight into the illness, poor provider-subject relationship, barriers to care or medications, missed appointments, treatment complexity, and cost of medication (15).

Due to the many factors contributing to poor adherence to medication, a multifactorial approach is needed, and a single approach may not be effective (20). Some simple strategies for optimizing a subject's ability was suggested in table 1.2 (source : Osterberge page 493 , 2005 (15).)

Table 1.2 Strategies for improving adherences to medication regimen

1. Identify poor adherence
    a) Look for markers of nonadherences; missed appointments (“no-shows”),
    b) lack of response to medication, missed refills
    c) Ask about barriers to adherence without being confrontational
2. Emphasize the value of the regimen and the effect of adherence
3. Elicit subject’s feelings about his or her ability to follow the regimen, and if necessary, design supports to promote adherence
4. Provide simple, clear instructions and simplify the regimen as much as possible
5. Encourage the use of a medication-taking system
6. Listen to the subject, and customize the regimen in accordance with the subject’s wishes
7. Obtain the help from family members, friends, and community services when needed
8. Reinforce desirable behavior and results when appropriate
9. Consider more “forgiving” medications when adherence appears unlikely†
    a) Medications with long half-lives
    b) Depot (extended-release) medications
    c) Transdermal medications

1.6 Economic burden

Schizophrenia was ranked as the ninth leading cause of disability among all diseases worldwide In 1990 by the World health Organization (WHO) (2). In Thailand 1999, schizophrenia was the 8th and 9th leading cause of Years Lived with Disability (YLD) in men and women, respectively, with 5% contribution for all causes. If Disability –Adjusted Life Years (DALYs) was measured, schizophrenia would be the 3rd rank in mental health disorder(21).

In Thailand 2008, the disease burden in disability-adjusted life years in men and women were 70,000 (95% CI: 64,000, 77, 000) and 75,000 (95% CI: 69,000, 83,000) respectively (6).

Cost of schizophrenia in US 2002 was reported of US$ 62.7 billion. More than half of this cost was from productivity losses (unemployment, reduced work productivity, and premature mortality) (22).

Cost of treatment for Thai schizophrenia in 2007 under social security system healthcare scheme was 436-903 million Baht with 5-99 Baht per individual (23). While the annual cost of schizophrenia in Phanthunane’s study 2008 was 87,000 Baht (95% CI: 83,000, 92,000) per

person or 31 billion Baht for the whole population. Two third of total economic burden were from indirect cost including unemployment , absenteeism, and presenteeism of subjects and care givers.

1.7 Rationales of study

Thai government try to encourage all key stakeholders including healthcare providers to use cost-effectiveness evidences for choosing the appropriate interventions in clinical practices. As of limited health resources, Thai government allocated only 3% of health expenditure to mental health in 2008. With budget constraint, the policy makers need to prioritize the resource among various interventions. Without systematic analysis in form of full economic evaluation, it is very difficult for all stakeholders to decide whether alternative interventions are more efficient. Economic evaluation study will be on a one of good tools to support their decision.

Recently, cost-effectiveness of oral antipsychotics and family intervention in Thai schizophrenia was evaluated. Generic risperidone tablet and family intervention was proposed as first line treatment and clozapine was for 1st line failure cases (24).

Long acting injection anti-psychotics (LAIs) are suggested in management of schizophrenia with oral medication non-adherence. Four of first generation LAIs; Haloperidol dec, Flupentixol dec, Flupenazine dec . and Zuclopentixol dec., are listed in national list of essential medicine except two of newer second generation LAIs.; Paliperidone LAI, and Risperidone LAI. Economic evaluation evidence of these medications may not only guide healthcare profession to choose LAIs for their patients appropriately but also support healthcare policy makers to consider any newer interventions for future health benefit scheme.

As there are various LAIs introduced and there is no economic evaluation of LAIs in schizophrenia with oral medication non-adherence in Thailand available yet. As above reasons, there is clearly medical need for LAIs in clinical setting. Therefore our economic evaluation study of LAIs for subjects with oral non-adherence in Thailand will be one of evidences to support the ongoing healthcare system's need.

1.8 Research questions

Are LAIs cost effective in schizophrenia with oral medication non-adherence in Thailand?

1.9 Objectives

To estimate cost-effectiveness of all available LAIs for subjects with schizophrenic who are oral medication non-adherence

1.10 Expected Contributions

- This will be a scientific evidence to support policy decision makers on cost effectiveness of treatment alternatives for schizophrenia to be considered for reimbursement under the health benefit scheme
- This will encourage the use of cost effectiveness studies for price setting of new medication as well as establishing the practice guideline among pharmaceutical industry

CHAPTER 2
LITERATURE REVIEW

This chapter will cover all published literatures related to economic modelling and its guideline, prior economic evaluation of schizophrenia in Thailand, all treatment guidelines for schizophrenia, and our target interventions.

2.1 Economic Modeling

Cost effectiveness analysis could be done alongside a randomized clinical study but it has a number of limitations of all simultaneously required data collection. As a result, economic evaluation for decision making usually is suggested to make on evidence from range of sources (25).

Decision analytic modeling had theoretical foundations in statistical decision concept and combined with expected utility theory. Expected utility theory of von Neumann-Morgenstern's explained individual's decision under uncertainty condition (26).

Decision analytical modeling should cover a framework for decision-making under uncertainty factors. The modeling need to have these key parts including 1) model structure ; reflect the disease or treatment pattern, 2) evidence; good source of input data 3) evaluation; combine and analyze all input data with appropriate decision rule , 4) uncertainty and variability ; able to assess all uncertainty of model structure and input parameters , 5) future research ; able to identify priorities for future research under the current uncertainty parameters (25).

A key stage to develop of decision model is a process of choosing on the structure. Drummond M.F. suggested the checklist for model structure considerations;(25)

1Do event occur only once or several times over the study period ?
2 Is there a series of completing event risks?
3What is the durability of effectiveness of particular intervention?Do probabilities of events change over time or are they constant regardless of time?
4Are all essential events included and is a double counting of events avoided?
5In case of chronic disease, does model allow for both cost and health outcome to be included?

However, most decision models in economic evaluation demonstrate their structure model schematically. There are four model structures predominating in the economic evaluation, decision tree model, cohort Markov model, micro-simulation Markov model, and discrete event simulation model (DES). All advantages and limitations of model structures are discussed to support our study selection(25, 27).

2.1.1 Decision tree model

Decision tree model is generally considered to be the most simplistic structure for decision model in economic evaluation. Number of parameters to be incorporated is small. Data collection time and model building time is relatively short. There are some limitations including time independent model, and non-repeated event.

Glazer and Ereshefsky proposed the decision analysis model through decision tree model presented in Figure 2.1 (source: Heeg page 636, 2008 (27)) to suggest that switching to the depot route in a subject with a history of relapse and re-hospitalization may reduce total direct treatment costs by approximately $650 to $2600/year compared with an oral atypical agent and approximately $460 to $1150/year compared with a conventional oral antipsychotics over the first year.(28)

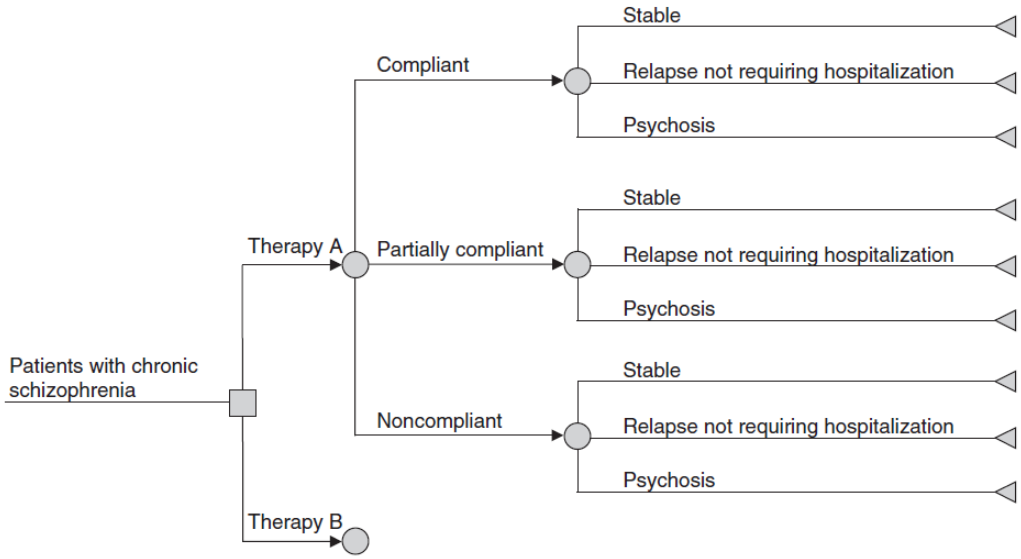


Figure 2.1 Decision tree with time horizon 1 year

2.1.2Cohort Markov model

Cohort Markov model are based on a series of “state” with a given point in time. Time dependent event and repeated events in chronic disease will meet model qualification.

Markov model enables researcher to reflect reality more closely. Main limitations of cohort Markov model are no memory feature and fixed time to events.

NICE used cohort Markov model to evaluate the cost effectiveness of pharmacological interventions for people with schizophrenia in UK. 2009 (1). See figure2.2 (source: NICE page 182, 2009 (1)). Zotepine oral atypical antipsychotic medication was the most cost-effectiveness for relapse prevention in subjects with schizophrenia in remission. As of high uncertainty and probabilistic analysis of input data, no oral antipsychotic medication could be clearly cost-effective compared with the other options in this analysis set; with probability of each option being cost-effective ranged from 5% (hololperidol) to 27-30% (zotepine) regardless of willingness to pay threshold and time horizon of model (10 years and lifetime).(1)

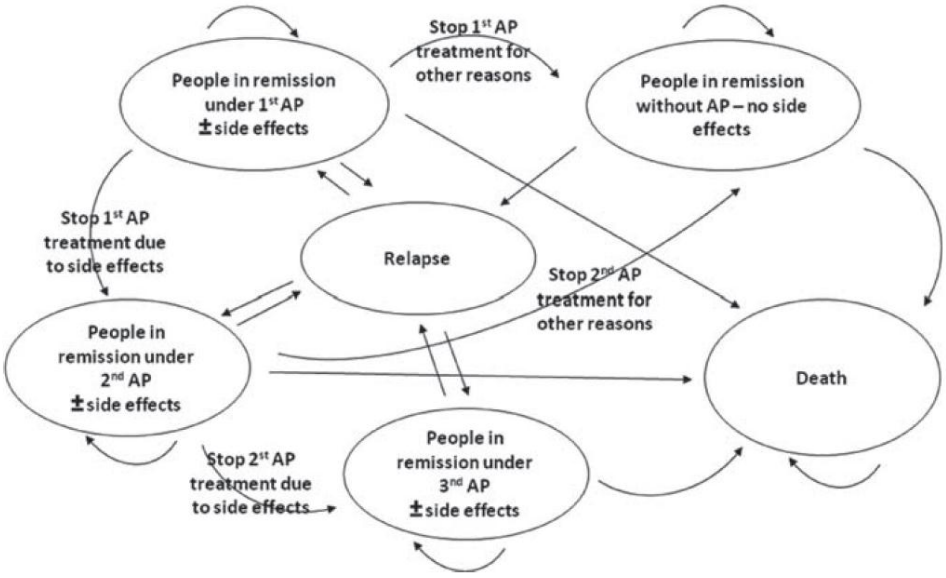


Figure 2.2 Schematic diagram of economic model structure

2.1.3 Micro-simulation Markov model (individual subject simulation Markov model)

When individual subjects factor (subject heterogeneity) need to be incorporated into evaluation, micro-simulation Markov model will be good tool for this purpose. Major limitations include long simulation time

Vera-Llonch applied micro-simulation Markov model to compare expected outcomes and costs in subjects with chronic schizophrenia or schizoaffective disorders who are treated with risperidone versus olanzapine (29). Model included factors of interest s; the incidence of relapse and selected side effects (i.e. EPS), prolactin-related disorders and diabetes, weight gain. At the end of 1 year , the estimated percentage of subjects remaining on initial therapy was higher for risperidone than olanzapine (76.9% vs. 45.6%, respectively). Expected mean total costs of care per month of therapy were $2163 for risperidone and $2316 for olanzapine. It was concluded that olanzapine may result in greater increases in body weight, higher rates of therapy discontinuation, and higher costs of medical-care services than risperidone. (29)

2.1.4 Discrete event simulation model (DES)

However, all three decision models above do not meet requirement of interaction between subjects. DES offer much more flexible design which is close to real life situation. It takes all possible disease conditions and also environment factors into model consideration. Key elements of DES over prior models are flexible time to event and interaction between subjects. DES property has corrected all defects which found in all prior models. However input data collection, simulation time and model building time are major constraints. Comparison diagram between cohort Markov model, micro-simulation Markov model and Discrete Event Simulation model is presented in figure 2.3 (source: Heeg page 637,2008 (27))

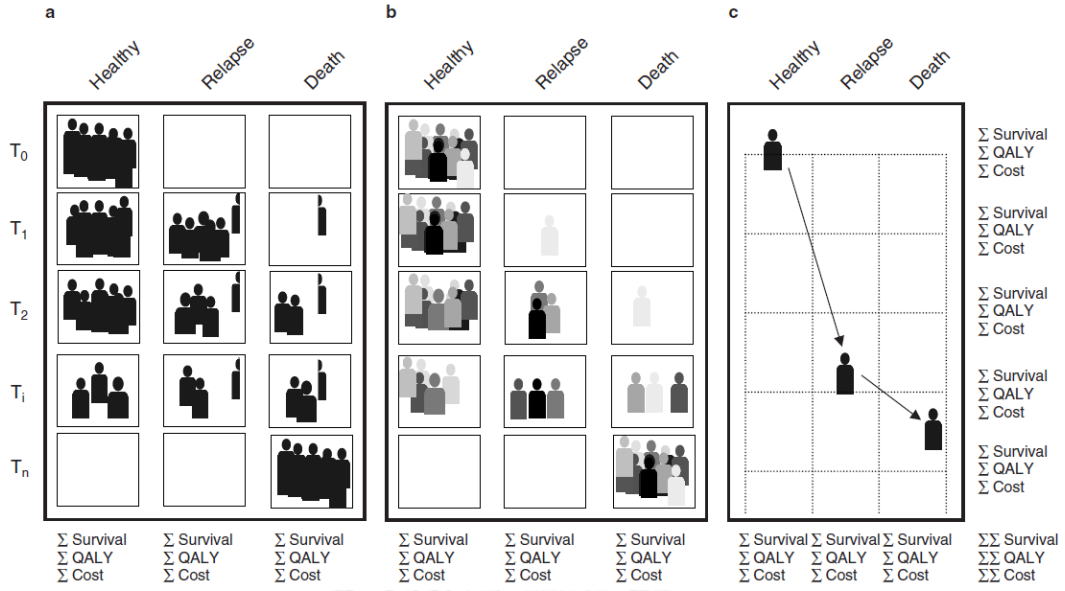


Figure 2.3 Cohort Markov model , micro-simulation Markov model and Discrete Event Simulation model diagram

Heeg used DES modeling to analyze the potential benefit of improving compliance with antipsychotic in non first episode schizophrenia in UK (30). Two major groups of variables were included. Time independent variables included sex, age, severity, harm risk, social environment factors and side effect. Time dependent variables included psychotic episodes, doctor appointment, treatment options, compliance, symptom, lack of self care, healthcare setting selection. All items are demonstrated in figure 2.4 (source: Heeg page 640, 2008 (27)) Time horizon limited to 5 years. Outcome was costs, psychotic episodes and symptoms. Univariate and multivariate sensitivity analysis were performed. With a payer perspective, direct medical costs were used (year 2002), with 6% discount rate in cost and 1.5% discount rate for outcome. Based on 2000 cases simulation in @RISK /Excel software, 20% compliance increase would save £ 16,147 and avoid 0.55 psychotic episodes per subject over 5 years. Key finding is to confirm that better compliance increases the time between relapses, decreases the symptom score, and reduces the requirement for treatment in an intensive subject care setting, leading to cost savings.

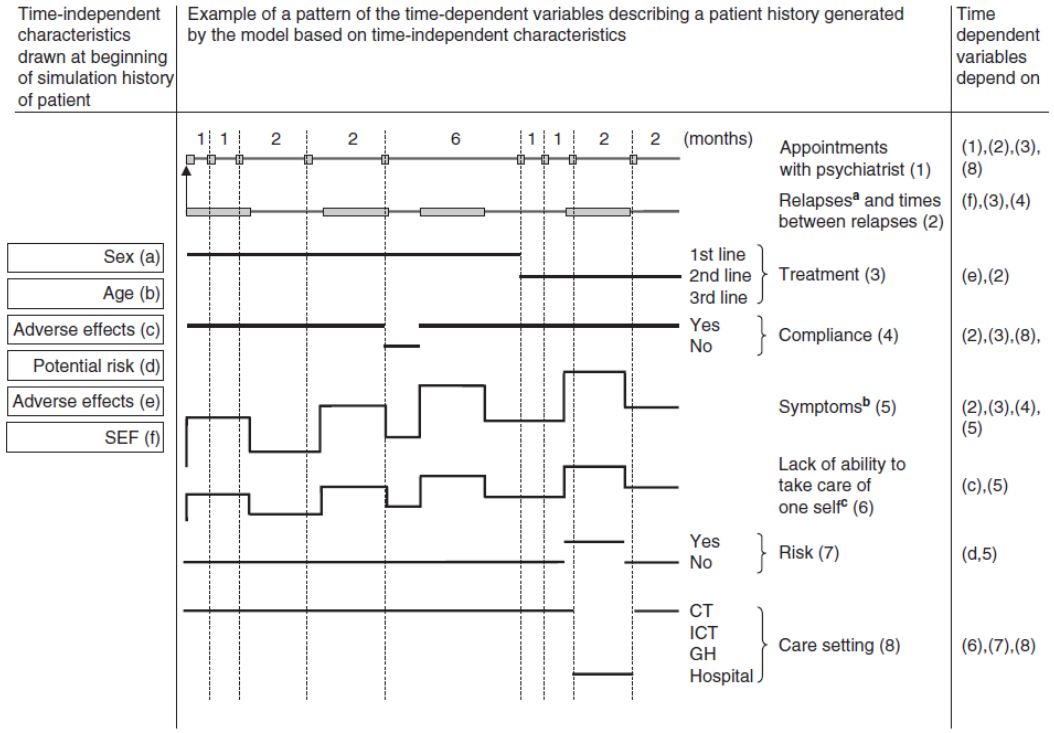


Figure 2.4 Example of subject history from time of entering model during relapse at visit to psychiatrist for DES model

Recommendation on the good economic modeling practice was discussed by Buxton including 1 keep model as simple as possible in order to help understanding by decision makers , 2 provide transparent result in order to be ready for review , 3 declare the input data sources clearly between controlled RCT and opinion expert , 4 test the model robustness through sensitivity analysis , and 5 validate the result with prior studies (31).

As no single perfect model could fit for all approach, choosing any model for economic evaluation should be weighed between model simplicity and realistic. With our model review above, we decide to use cohort Markov model in our modeling with the following reasons.

a) Schizophrenia is chronic disease with repeated symptoms
b) Timing is involved in our consideration
c) Markov model provide more realistic for disease pattern than decision tree model
d) NICE 2009 use Cohort Markov model

e) We don't plan to involve the completing risk (queuing system) in our approach so it is not necessary to use DES model.

f) Micro simulation Markov model maybe better than cohort Markov model in term of subject with variability factors but it might be too complicated for researcher to collect all data input for this model.

2.2 Guideline for economic evaluation

A guideline for economic evaluation of healthcare interventions was introduced in Thailand 2008 by Health Intervention and Technology Assessment Program (HITAP) under Ministry of Public Health (32).

2.2.1. Scope of study

a) Perspective of study should be societal perspective. If other perspective is undertaken, justification is needed.

b) Target population should be clearly described.

c) Full description of the intervention or program of interest should be included.

d) There are detailed enough that the readers fully understand how the intervention or program are used and are capable of imitating the same intervention.

2.2.2. Comparators

a) If the aim of study is to replace the most commonly used intervention with the intervention of interest, the comparator should be the most widely used one.

b) It should be clearly specified in the context of the analysis

c) If the aim of study is to replace the standard therapy, the comparator should be the most effective alternative.

d) In some circumstances where do-nothing is current practice or standard of care, no treatment can be a viable alternative.

2.2.3. Type of economic analysis

a) Cost minimization analysis (CMA) and cost benefit analysis (CBA) are not recommended.

b) Cost utility analysis (CUA) is recommended when data and resources are available or when possible since it provided more complete picture of the compared alternatives.

c) However, cost effectiveness analysis (CEA) is more appropriate in case only intermediate outcomes of the compared alternatives are available.

2.2.4. Measurement of cost

a) Economic or opportunity cost is first priority used in economic evaluation.

b) Major perspective should be societal perspective.

c) Costs to be included are depended on study perspective.

d) Reference unit cost (i.e. reimbursement rate of public health facilities used for the CSMBS), setting specific unit cost, and national standard cost menu are recommended.

e) It is not recommended to use expert opinion to directly identify these costs since it often leads to systematic bias in data.

f) The source of cost data used should be identified and stated ranking based on those proposed by Cooper et al (33).

   (1) Rank 1: Prospective data collection or analysis of reliable administrative data for specific study

   (2) Rank 2: Recently published results of prospective data collection or recent analysis of reliable administrative data – same jurisdiction

   (3) Rank 3: Unsourced data from previous economic evaluation – same jurisdiction

   (4) Rank 4: Recently published results of prospective data collection or recent analysis of reliable administrative data – different jurisdiction

   (5) Rank 5: Unsourced data from previous economic evaluation – different jurisdiction

   (6) Rank 6: Expert opinion

g) Micro-costing approach is preferred for direct cost calculation.

h) Human capital approach is recommended for indirect cost calculation.

i) Healthcare specific inflation rate from the Bureau of Trade and Economic Indices should be taken as a conversion rate.

2.2.5. Measurement of health outcome; efficacy/effectiveness

a) Clinical effectiveness should be used rather than clinical efficacy derived under highly controlled circumstance.

b) Outcome measures should include the final intended effects of the proposed health technology.

c) The use of surrogate indicators should be avoided.

d) Researchers must make the presentation of the data transparent and explain the rationale for the source of data used in the study.

e) The inclusion of the grey literature such as research reports, master dissertations or Ph.D. theses is also considered to be very important in the Thai context.

f) Use of modeling is acceptable, but ttransparency in a model is very important.

g) Evidence available in a higher hierarchy based on the level of clinical evidence should be selected. See table 2.1 (source : Canadian task force ,1979 (34))

2.2.6. Measurement of health outcome; utility

a) If a researcher collects a primary data of utility, Euro QoL -5 dimension(EQ-5D) is the most recommended utility method (Thai algorithm version is preferred when available).
b) Other direct and indirect utility methods such as Visual analog scale (VAS), standard gamble(SG), time trade off (TTO), human utility index(HUI) and quality of well being (QWB)can also be used but should be justified.
c) If a researcher uses a secondary data, a systematic approach including meta-analysis to combine utilities taken from different studies should be employed.
d) Expert opinion, WTP, mapping VAS to TTO and SG, and deriving utilities from SF-36 are not recommended.
e) Disease-specific measures should be used contemporarily with utility measures.
f) A perspective of utility measurement depends on the objectives of the study.
g) Meta-analysis or systematic review is strongly recommended as a source of effectiveness data to be used in cost-effectiveness analysis.
h) If meta-analysis is not available, a potential for performing meta-analysis should be explored.

2.2.7. Medical statistic

a) The first best is the primary data obtained from an original study in which the observations are
    i) at the non-aggregate level
    ii) contain a time-to-event variable
    iii) subject specific characteristics in addition to the health outcome variable.
b) If the variable of time to event is not readily available, a multivariate analysis for binary outcome such as logistic regression or probit is the model of choice.

2.2.8. Time handling

a) Time horizon should be long enough to capture the full costs and effects of the intervention.
b) If a time horizon > 1 year, the opportunity costs of investments and their health consequences should be taken into account through discounting.
c) Discounting cost and outcome should be done using the same rate.
d) The appropriate discount rate for cost and outcome at base case is 3% and 0-6% for performing sensitivity analysis

2.2.9. Uncertainty handling

a) Probabilistic modelling and univariate sensitivity analysis should be used.
b) The results of each alternative analysis should be presented separately and in a probabilistic format.
c) Clear reporting of input parameters, model assumptions, and methods used in the modelling exercise is particularly important.

2.2.10.Final report

a) Defining the scope of the study
b) Selection of comparator(s)
c) Defining the type of economic evaluation
d) Measurement of costs
e) Measurement of clinical effects
f) Handling time in the economic evaluation studies
g) Handling uncertainty and sensitivity analysis
h) Presentation of the cost-effectiveness results
i) Discussion, limitation, and impact on healthcare, expenditure, and equity
j) Disclosure of funding and author's interest
k) Clearly state all key elements
l) Parameter and model assumptions
m) Transitional probabilistic used in the model
n) Source of cost and effectiveness data
o) Breakdown of costs and effects
p) Base-cases estimates and probabilistic distribution
q) ICER and Cost-effectiveness acceptability curve
r) Discussion should cover
    i) Limitations of the study
    ii) Comparing results to relevant results from other studies
    iii) Potential impact on healthcare expenditure
    iv) Equity alongside policy recommendations

Table 2.1 Clinical study evidence level

Rate	Study design
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias.
2++	High-quality systematic reviews of case control or cohort studies. High-quality case control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal.
2+	Well-conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal.
3	Non-analytic studies: for example, case reports, case series.
4	Expert opinion

2.3 Prior studies of economic evaluation in Thailand

2.3.1. Phanthunane 's study 2011

This study aimed to policy maker to identify the optimal cost effective treatment of drug and non-drug interventions for schizophrenia in Thailand (24). See figure 2.5 (source : Phanthunane page 2 ,2011 (24))

A Markov model is applied to evaluate the cost effectiveness of typical antipsychotics, generic risperidone, olanzapine, clozapine, and family interventions. Health outcomes were quantified by disability adjusted life years (DALY). Direct and indirect costs were included. Uncertainty by Monte Carlo Simulation was applied.

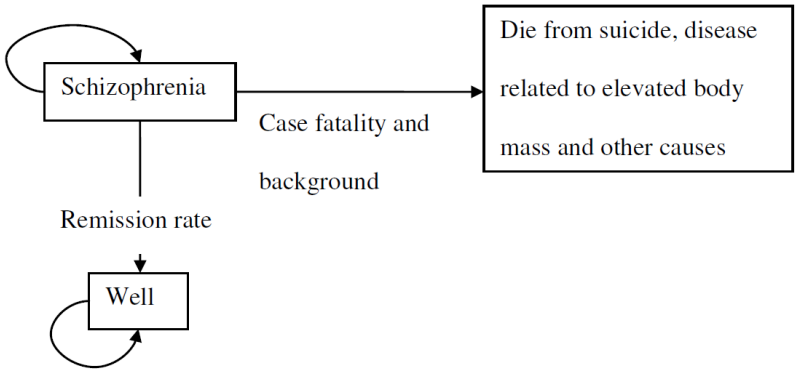


Figure 2.5 Health state diagram

Combining family intervention with risperidone had incremental cost –effectiveness ratio of 1,900 baht/DALY with a 100% probability of less than one GDP threshold (110,000 baht). See figure 2.6 (source : Phanthunane page 6, 2011 (24)). However providing clozapine instead of risperidone to most severe one-third of subjects had ICER of 320,000 baht/DALY with a 51% probability under three GDP thresholds.

Price sensitivity of generic risperidone was also calculated. Up to a cost of 19 baht (95% uncertainty interval 15-25 baht) replacing typical antipsychotics by risperidone was able to be considered a cost effective intervention within one GDP threshold.

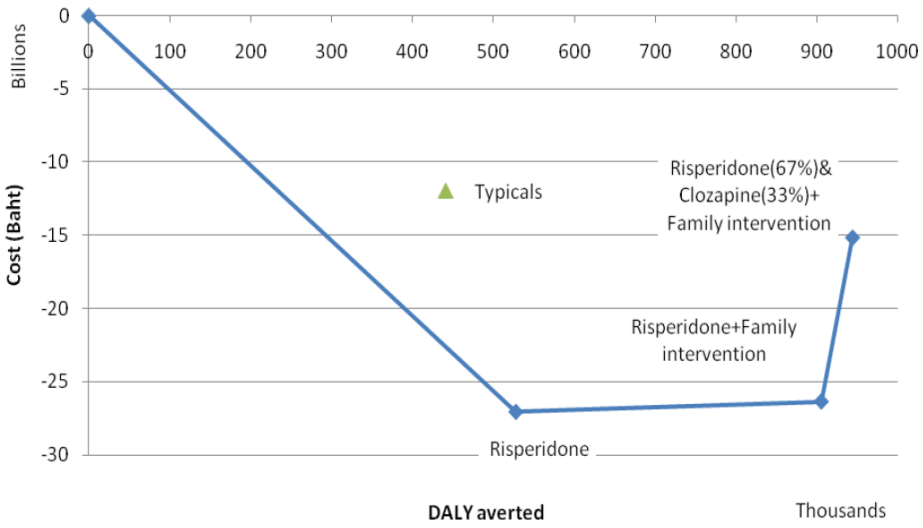


Figure 2.6 Ideal mix of schizophrenia interventions based on their cost-effectiveness ratio in Thailand

At the end, it was suggested that combination of generic risperidone at cost less of 10 baht / 2mg tablet as the first line treatment , with family interventions , consisting of 10 weekly 2 hour sessions during the first year and 2 booster sessions every year after that , as adjunctive treatment. If subjects failed the first line treatment combination, it was suggested to use clozapine as the third option with compulsory condition of continuously blood testing.

Target of subjects in this study is different from our dissertation. They focus on general cases include severe cases. However severe cases have different meaning from the non-adherence group. Dosage form of clozapine and risperidone are oral tablets but my intervention is a long acting injection. In the other words, long acting injection should be proposed as an alternative choice for subjects with oral medication non-adherence.

2.3.2. **Kongsakon** ‘s study 2005

This study aimed to compare the annual cost of treatment schizophrenia with atypical antipsychotics; olanzapine, risperidone, quetiapine, and ziprasidone and one typical antipsychotic; haloperidol in Thailand (35).

Medication cost, hospitalization cost, relapse cost, unemployment cost, and suicidal related cost were analyzed. The final report showed the ranking of annual cost from the cheapest to the most expensive; haloperidol 86,004 baht, olanzapine 103,225 baht, risperidone 104,564 baht, ziprasidone 118,314 baht, and quetiapine 146,526 baht .This study is designed to compare only the cost between oral medications. Study design did not meet full economic evaluation criteria which required comparing both cost and health outcome of two or more alternative interventions.

2.4 Treatment guidelines

2.4.1.NICE guideline #82 for schizophrenia, 2009

NICE guideline 2009 for subject with newly diagnosed schizophrenia, suggest oral antipsychotic medication as the first line drug. Benefits and side-effect profile of each medication should be provided and discussed with subjects. The choice of drug should be made by subjects and doctors (1).

Initiate regular combined antipsychotic medication is not recommended, except for short periods (for example, when changing medication)

For promoting recovery, NICE suggest to not use targeted, intermittent dosage maintenance approach routinely. However, consider them for only subjects who are unwilling to accept a continuous maintenance regimen or if there is another contraindication to maintenance therapy, such as side-effect.

According to NICE guideline, consider offering LAIs antipsychotic medication to subjects:

a) who prefer such treatment after an acute episode
b) where avoiding covert non-adherence (either intentional or unintentional) to antipsychotic medication is a clinical priority within the treatment plan.

When starting LAIs antipsychotic medication:

a) consider subjects' preferences and attitudes towards the mode of administration (regular intramuscular injections) and administration process (for example, home visits and location of clinics)
b) always provide benefit and risk information of the drug regimen
c) start a small test dose as set out in product information.

For subjects with schizophrenia whose illness has not responded adequately to pharmacological or non-pharmacological intervention treatment:

a) review the diagnosis
b) establish that there has been adherence to antipsychotic medication, prescribed at an adequate dose and for the correct duration
c) review engagement with and use of non-pharmacological treatments including cognitive behavioural therapy or family intervention.
d) consider other causes of non-response, such as comorbid substance misuse (including alcohol), the concurrent use of other prescribed medication or physical illness.
e) Offer clozapine to subjects whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs. At least one of the drugs should be a non-clozapine second-generation antipsychotic.

NICE 2009 have not discussed how to manage subjects who fail to LAIs and also has not mentioned about electroconvulsive therapy (ETC) in the treatment plan.

2.4.2.American Psychiatric Association guideline, 2004

American Psychiatric Association has set different treatment goals based on different phase of disease (36).

A. Acute Phase: Goal of treatment (1-2 months)

• Prevent harm

• Control disturbed behavior

• Reduce the severity of psychosis and associated symptoms (e.g. agitation, aggression, negative symptoms, affective symptoms)

• Determine and address the factors that led to the occurrence of the acute episode

• Effect a rapid return to the best level of functioning

• Develop an alliance with the subject and family

• Formulate short- and long-term treatment plans

• Connect the subject with appropriate aftercare in the community

B. Stabilization phase: Goal of treatment (2-6 months)

• Minimize stress on the subject and provide support to minimize the likelihood of relapse.

• Enhance the subject's adaptation to life in the community.

• Facilitate continued reduction in symptoms and consolidation of remission, and promote the process of recovery.

C. Stable phase: Goal of treatment (thereafter stabilization phase)

• Ensure that symptom remission or control is sustained.

• Maintain or improve the subject's level of functioning and quality of life.

• Effectively treat increases in symptoms or relapses.

• Continue to monitor for adverse treatment effects

APA suggests using LAI in group of repeated non-adherence to pharmacological therapy. Use of electroconvulsive therapy (ECT) in combination with antipsychotic medications may be considered for subjects with schizophrenia or schizoaffective disorder with severe psychotic symptoms that have not responded to treatment with antipsychotic agents.

2.4.3.Thai national formulary 2010

Thai national formulary 2010 in the Central nervous system volume 1 suggests LAIs should be prescribed to subjects who are unable to take oral medication (37). Convention LAIs may have more EPS side effect than oral form, but there is less EPS side effect when using atypical LAIs i.e. Risperidone. However Risperidone LAI is not listed in national list of essential drug (NLED) 2010.

Currently, only four LAIs are listed in NLED 2010; Fluphenazine decanoate, Haloperidol decanoate, Flupentixol decanoate, and Zuclopenthixol decanoate.

2.4.4.Guidelines for LAI treatment in schizophrenia 1998

There have been discussed how to manage subjects who failed to respond to LAIs in this guideline (38). According to results of controlled trials involving depot medication indicated that around 15% of subjects may relapse within one year. Therefore non-adherence factors could be ruled out in this group as causative factor and other causes could be taken with appropriate attention; reduction of environment stress, substance abuse, comorbid condition etc. These subjects might be switched to a different class of drug, though there were limited evidences.

2.4.5.Thai guideline for schizophrenia 2001

The working group of Royal College of Psychiatry of Thailand and Mental Health, Ministry of Public Health, Thailand introduced a guideline for schizophrenia treatment in Thailand 2001 (14). Three phases of disease including acute, stabilization, and stable phases were identified.

If there is poor response in acute phase non 1st episode schizophrenia subjects after 4-6 weeks trial of either FGA or SGA medication, this has been suggested to switch to either other FGA or SGA with different chemical structure or clozapine or ECT alone or combination.

However a result of meta-analysis by the working group to compare efficacy and subject discontinuation between FGA and SGA medication has stated that SGA has not better efficacy than FGA but subject discontinuation is higher in group of FGA.

2.4.6.World Health Organization guideline 2009

WHO suggest using LAIs when treatment adherence is a major problem in the long-term therapy (39). Other non-pharmacological interventions to increase adherence (subject

education, family psycho-education, specific psychotherapeutic interventions) may additional be implemented.

2.5 Medication

LAI not only provide more stable serum concentrations but also correct non-adherence medication issue. Based on pharmacological action, SGA should have better potency as they act on both two main receptors; dopamine and serotonin. But clinical outcome of some effectiveness large scale study has demonstrated indifferently. (17)

However SGA may have advantage over FGA in term of fewer side effects and better functioning. All side effects are described in table 2.2 (source: APA guideline page30, 2004 (36))

Currently, four first generation LAIs; Fluphenazine decanote (FLUD), Flupentixol decanoate (FPD), Haloperidol decanoate (HAL), and Zuclopenthixol decanoate (ZPD), are already listed in national list of essential medicine (NLEM) of Thailand. But two of second generation LAIs; Paliperidone palmiate (PLAI), and Risperidone (RLAI), are not listed yet.

Table 2.2 Selected side effects of common used antipsychotic medication

medication	EPS/tardive dyskinesia	Prolactin elevation	Weight gain	Glucose intolerance	Lipid abnormalities	QTc prolongation	sedation	Hypotension	Anticholinergic side effects
Thioridazine	+	++	+	+?	+?	+++	++	++	++
Perphenazine	++	++	+	+	+?	0	+	+	0
Haloperidol	+++	+++	+	+	0	0	++	0	0
Clozapine	0	0	+++	+++	+++	0	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	0
Olanzapine	0	0	+++	+++	+++	0	+	+	++
Quetiapine	0	0	++	++	++	0	++	++	0
Ziprasidone	0	+	0	0	0	++	0	0	0
Aripiprazone	0	0	0	0	0	0	+	0	0

Defined daily dose of all LAIs are provide by WHO (40). Thai national formulary 2010 also provides dose and frequency of LAIs administration (41). All details are shown in table 2.3.

Table 2.3 Dosage regimen of LAIs

LAIs			DDD-WHO*	dose guide**	Dose for 28 days
1	Fluphenazine dec	FLUD	1 mg	start 12.5 mg then 7 days start 12.5-100 mg q 7-28 days	14 mg q 14 days
2	Flupentixol dec	FPD	4 mg	start 20 mg then 7 days start 20-40 mg q 14-28 days	56 mg q 14 days
3	Haloperidol dec	HAL	3.3 mg	start 50 mg q 28 days and max at 300 mg q 28 days	92.4 mg q 28days
4	Zuclopentixol dec	ZPD	15 mg	start 100 mg then 7 days start 200-600 mg q 7-28 days	210 mg q 14 days
5	Paliperiodne LAI	PLAI	2.5 mg	start 150 mg then 7 days start 100 mg and then start 25-150 mg q 28 days	70 mg q 28 days
6	Risperidone LAI	RLAI	2.7 mg	start 25 mg then 14 days start 25-50 mg q 14 days	37.8 mg q 14 days

*http://www.whocc.no/atc_ddd_index/?code=N05A cited 15 Apr 2014

**Thai national formulary 2010, Central Nervous system Volume 1, 4.2.2 antipsychotic depot injection page 49-52

CHAPTER 3
METHODOLOGY

This chapter will describe study design scope, economic model structure, systematic review and mixed treatment comparison meta-analysis work, effectiveness and cost data input and analysis steps.

3.1 Study design scope

As cost effectiveness studies of long acting injection antipsychotics (LAI) in the treatment of schizophrenia in Thailand is not available. So our study objective is to evaluate cost – effectiveness of LAI in schizophrenia with oral non adherence under Thailand setting.

In 2008, Health Intervention and Technology Assessment Program (HITAP) under Ministry of Public Health, Thailand introduced a guideline for economic evaluation of all interventions in Thailand(1) . So our economic modeling will be applied and comply with this guideline.

Intervention comparison will include only marketed long acting injection antipsychotic in Thailand, 2011.

A number of available studies on pharmacological treatment of schizophrenia will be reviewed and applied. Up-to-date information on cost and clinical outcomes will be incorporated in the model. However all input data of publication from Thai source will be used as priority if available.

As schizophrenia is a chronic disease and subjects need long-term maintenance treatment, Markov model with one year cycle is chosen for this analysis. Time horizon of model will be assessed over 99 years to cover total period of whole cohort is expected to survive.

According to HITAP guideline (32) , societal perspective and discount rate at 3% for both cost and benefit will be used.

One way sensitivity analysis will be tested for pricing of atypical long acting anti psychotics. Probabilistic sensitivity analysis using Monte Carlo simulation is undertaken for parameter uncertainty analysis.

3.2 Interventions assessed

We evaluate options of maintenance treatment offered for subjects with schizophrenia who are non-adherence with prior oral antipsychotics. This group of patients has not fit with oral dosage form any longer.

Only marketed LAIs in Thailand, 2013 are chosen to evaluate. Consequently Fluphenazine decanote (FLUD), Flupentixol decanoate (FPD), Haloperidol decanoate (HAL) , Zuclopenthixol decanoate (ZPD), Paliperidone palmiate (PLAI), and RisperidoneCONSTA (RLAI) will be assessed.

3.3 Model structure and assumption

Markov model will be created using TreeAge Pro 2014. Model is simulated in yearly cycles. Each LAI will be initiated in subjects with schizophrenia who are oral non-adherence (1st LAI).

The starting age of population in model is 25 years old as this is the mean age at onset of schizophrenia.

Within each year, subject may either remain in remission, or experience a relapse, or stop medication as of intolerable side effect, or stop medication for any reasons (except relapse or intolerable side effect) , or die.

Subjects who stop the 1st LAI as of intolerable side effect will be switched to 2nd LAI .

Subjects who stop the 1st LAI as of other reasons will be move to no treatment and wait until they develop relapse. All of subjects with relapse under no medication will be treated and move to 2nd LAI (100%)

Subject with relapse during the remission state will stop current LAI and then are treated for acute episode. Then subject of this state will either return to previous LAI (50% of them) or switch to 2nd LAI (the rest 50%).

Subjects who start 2nd LAI will experience the same as described above.

Subjects who stop 2nd LAI either as of intolerable side effect or relapse (50% of them) will be switched to 3rd line treatment. No further medication switches are provided after this stage. It means subjects are assumed not to stop medication as of intolerable side effect or for other reasons, and all of them will return to 3rd line option after relapse treatment.

However we assume that intolerable side effect will occur in the first year of use each LAI. But discontinuation of LAI for other reasons or relapse is assumed to occur every year at the same rate.

Cost and QALYs will be estimated at the middle of each cycle. Time horizon of model will be examined until age of 100 years of study population. An overview model is demonstrated in figure 3.1. Model with more detail flow is clarified in figure 3.2.

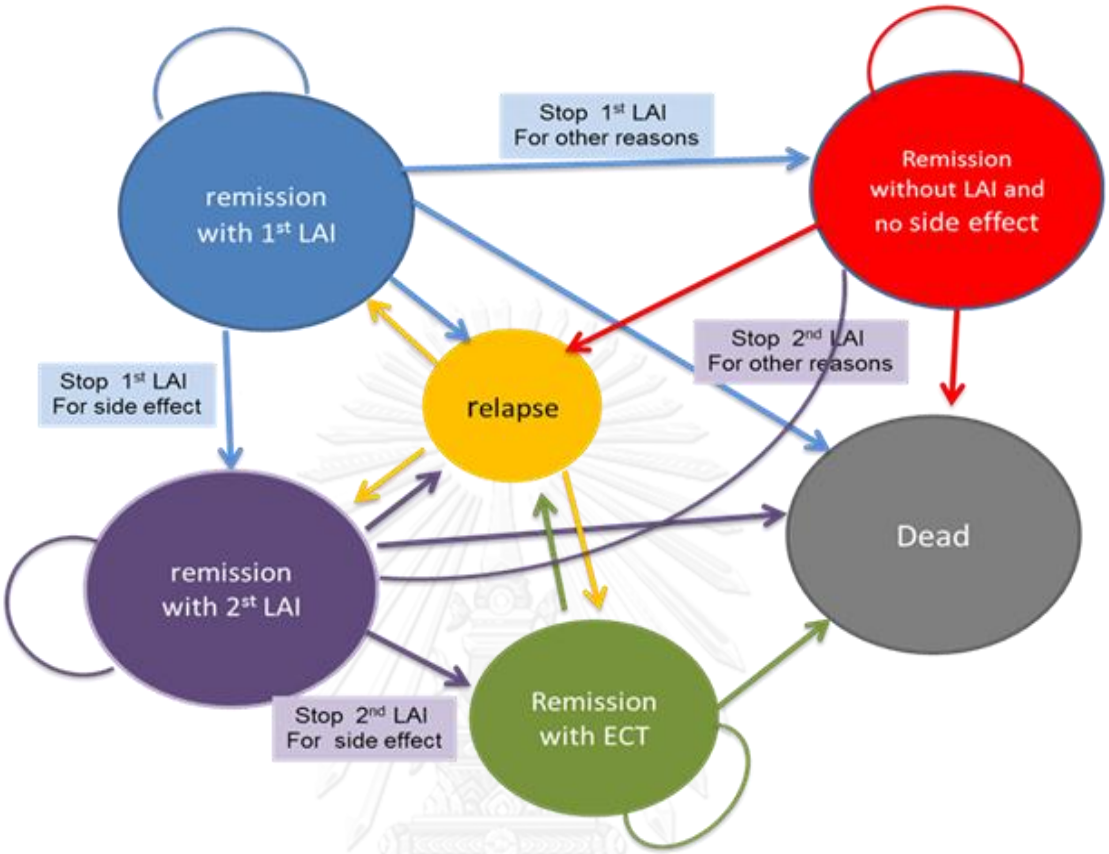


Figure 3.1 Overview of Markov model diagram version 1

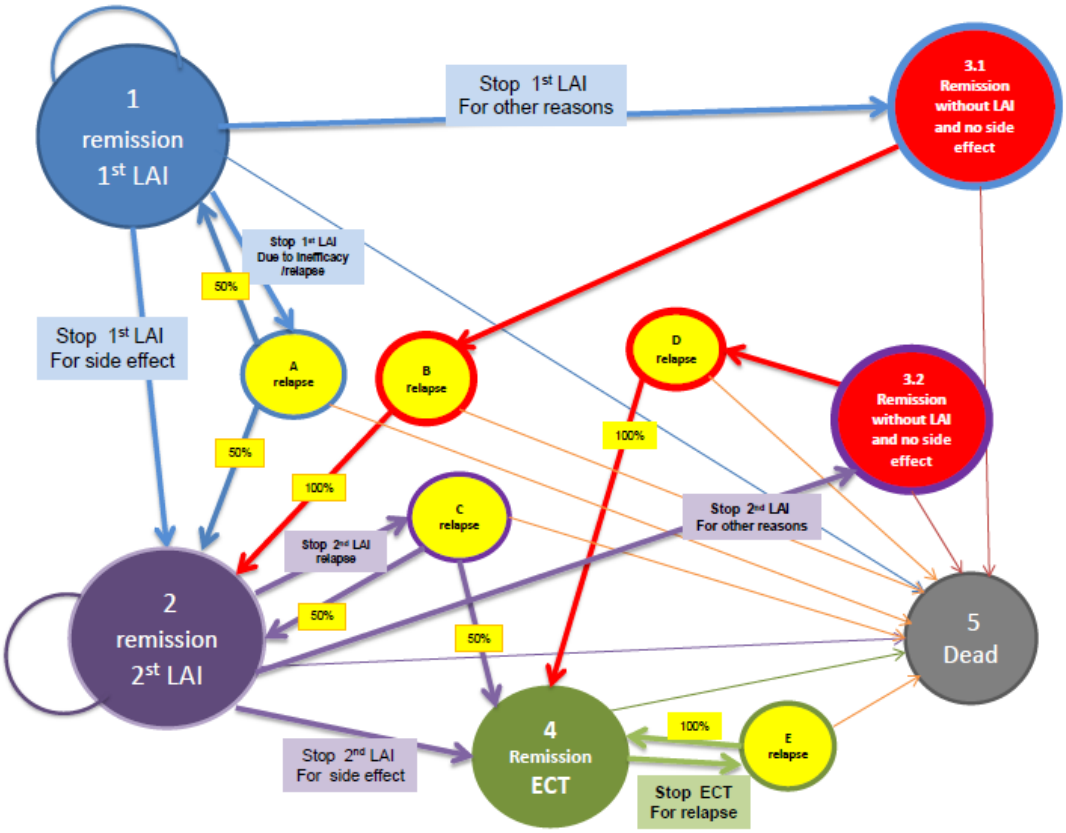


Figure 3.2 Overview of Markov model diagram with more detail version 2

Treatment guideline in Thailand suggest to use LAI in subject who are oral non-adherence but there is no suggestion to choose one of available LAIs (42).

Our study objective is to compare all available LAIs options in Thai subjects who are in oral non adherence group.

The 1st line of treatment in our model will be any of 6 LAIs. Haloperidol decanoate is chosen for the 2nd line of treatment if subjects are switched from any 1st line of LAIs. Except 2nd line of LAIs after Haloperidol decanoate , the 2nd line treatment will be Zuclopenthixol decanoate . The 3rd line of treatment will be the electroconvulsive therapy (ECT).

Aim of adding 3 lines of treatment in model is not to guide the specific steps of treatment. We plan to evaluate the relative cost effectiveness between the 1st line LAI only. But our aim of adding drug switching in the model is to evaluate the impact of lack of effectiveness in relapse prevention (presented by subjects with relapse), intolerance (presented by subjects with discontinuation due to intolerable side effects) , and unacceptability (presented by discontinuation rates as of other reasons) of the 1st line LAI on future costs and health outcomes. Our proposed model provides more realistic situation of disease management. Our model follows economic evaluation of oral anti-psychotic in UK which proposed by NICE (1). All 6 LAIs are demonstrated in table 3.1

Table 3.1 Treatment step proposed in our model for 6 LAIs.

1st line of treatment	2nd line of treatment	3rd line of treatment
Fluphenazine decanoate	Haloperidol decanoate	Electro convulsive therapy
Haloperidol decanoate	Zuclopenthixol decanoate	Electro convulsive therapy
Flupentixol decanoate	Haloperidol decanoate	Electro convulsive therapy
Zuclopenthixol decanoate	Haloperidol decanoate	Electro convulsive therapy
Risperidone consta LAI	Haloperidol decanoate	Electro convulsive therapy
Paliperiodne plamitate LAI	Haloperidol decanoate	Electro convulsive therapy

3.4 Economic evaluation type and perspective of assessment

We apply cost utility analysis (CUA) for our economic evaluation. Perspective of this evaluation will be taken under societal view(32). This means both direct and indirect cost will be included into analysis. Costs consist of medication costs, inpatients and outpatient care costs, cost of treating side effects, cost of care givers, opportunity cost of subjects, and travelling cost. Quality Adjusted Life Year (QALY) will be measured for health outcome.

3.5 Overview of method employed for evidence synthesis

All health outcome parameter will be generated from all available systematic review and meta-analysis studies. If this is not up-to-date or unavailable, we need to conduct our systematic review and meta-analysis for specific inputs. As mixed treatment comparison (MTC) meta-analysis is a generalization of standard pair wise meta-analysis to combine all direct and indirect comparison studies(43). MTC technique is employed to our study.

3.6 Relapse and discontinuation data input

Completing risk outcomes in relapse prevention with antipsychotics in subjects with schizophrenia were applied in health economic evaluation by NICE guidelines on core interventions in the treatment and management of schizophrenia 2009 (1, 44). Completing risk meta-analysis permitted studies with different follow up times, multiple outcomes and multiple treatments in one analysis setting (44). Three of key input data of a) relapse, b) discontinuation due to intolerable side effect, and c) discontinuation due to other reasons need to be collected from a systematic review of LAI studies. Most studies include these outcomes which are mutually exclusive in the final publication report. Sum of three outcomes mostly refer to sum of treatment failure. This means that within the study time frame, any subjects who do not remain under treatment and in treatment success outcome are at risk of one of these three outcomes. A few studies may report subjects with relapse within the study time frame, without information of their study remaining status after relapse and could be double counted if they discontinued treatment due to intolerable side effect or other reasons before study ends. Therefore three outcomes will be assumed and treated as mutually exclusive (completing risk) in our model.

Overview of systematic review and meta-analysis method is described in the following section to generate transitional probabilities of three major outcomes.

3.7 Systematic review and meta-analysis method of three outcomes; relapse, discontinuation due to intolerable and other reasons

Systematic review and mixed treatment comparison meta-analysis (MTC) is currently common alternative method to compare multiple products in the one setting (43, 45, 46).

Meta-analysis with completing risk outcomes in relapse prevention with antipsychotics in subjects with schizophrenia are applied in our work. This method supports to analyze all studies with different follow up times, multiple outcomes and multiple treatments in one analysis setting to generate 52 week transitional probability of three outcomes for our next economic evaluation part(44).

The primary objective of this study phase is to compare three completing outcomes of multiple LAIs antipsychotics available in Thailand for subjects with schizophrenia by using MTC approach. Three completing outcomes are relapses, discontinuation due to intolerable adverse events, and discontinuation due to other reasons. Systematic review of randomized controlled trials is applied. The outcome of this study is planned to support our economic evaluation of LAIs at the next stage.

Method

Search strategy

We conduct a search strategy using MEDLINE/PubMed and Cochrane library (last search: November 2013), for RCTs of LAIs antipsychotics in schizophrenia. Search terms included terms of 1) antipsychotics; 2) schizophrenia; 3) randomized controlled trials; 4) long acting injection (depot). The hand search was also used if there were relevant references. Search limited to only English full publication.

Search term

("antipsychotic agents"[Pharmacological Action] OR "antipsychotic agents"[MeSH Terms] OR ("antipsychotic"[All Fields] AND "agents"[All Fields]) OR "antipsychotic agents"[All Fields] OR "antipsychotic"[All Fields]) AND ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields]) AND ("injections"[MeSH Terms] OR "injections"[All Fields] OR "injection"[All Fields])

Inclusion criteria

RCTs, head to head comparison of any of 6 LAIs and placebo for treatment of schizophrenia were included. Subjects had to be > 18 years old and have diagnoses of schizophrenia. We included studies with 24 weeks study duration or longer and provided information of

symptom control outcome, discontinuation, relapse or re-hospitalization. We excluded LAIs which were not registered in Thailand before November 2013.

Data extraction and Outcomes

At least two staffs conducted a review and data extraction. Any disagreement was discussed. The primary binary outcome was all-cause discontinuation including, 1 relapse (defined as relapse or discontinuation due to inefficacy), 2 discontinuation due to intolerable adverse events , and 3 discontinuation due to other reasons (such as non-adherence). These outcomes were completing risks meaning that within the study time frame , any subjects who were not under treatment and in remission(which would be success case) was at risk of either one of three outcomes .

Of 1,245 articles (PubMed: 1180, Cochrane: 65), 304 RCTs were reviewed. Reasons for articles excluded were non-injection dosage form = 44, non-RCT = 67, product unavailability in Thailand = 82, no- efficacy & safety outcome = 31, non-accessible to full publication = 8, publication duplication = 3, short study duration = 7, and other reasons = 58. Finally 17 studies were selected for data extraction and analysis. Study selection flow of our systematic review process was shown in Figure 3.3

Total subject in our meta-analysis was 1,904. The number of subjects per study ranged from 19-747 (median: 54). Mean of study duration was 52.29 weeks (range 24-96 weeks). Median scores of study quality assessment were 4 (range 2-5). Summary of key data extraction is shown in Table 3.2

The number of studies per medication were placebo(PBO) = 6, FLUD = 11 ,FPD =4 , HAL= 8 , ZPD=2 , PLAI=2 and RLAI =1. Network diagram is demonstrated of which pairs of treatments are directly compared. A diagram is shown in Figure 3.4

Data analysis

Intent-to-treat (ITT) population where subjects who dropped out since arm assignment was included in our analysis. Study quality score (JADAD) was applied to assess including randomization technique, allocation concealment, blinding method and subject withdrawal description (47).

Statistical analysis

Mixed treatment completing risks logistic regression model under Bayesian framework is applied for multinomial distribution of data. Bayesian statistic framework is applied to our analysis because it combines prior probability distribution and a distribution of pooled effect

based on the observed data to generate a posterior probability distribution of pooled effect. This method is chosen because it provides useful outputs including probability of which treatments is the best , rank ordering of treatments ,and confidence intervals (45).

This model is calculated by Markov Chain Monte Carlo simulation (MCMC) in WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, England). WinBUGS codes are provided in appendix A. The first 60,000 iterations were discarded and 300,000 further iterations were run with every 30^{th} simulation was retained. The results are presented including 52-week probabilities with standard deviations (SDs). Sensitivity analysis are also conducted including two chains of initial values for Markov chain Monte Carlo simulation, goodness of fit test of model using residual deviance (resdev) and the deviance information criteria (DIC) tool comparing between random effects model and fixed effects model. Assumption of fixed effects model is to estimate the same true treatment effect for all studies and differences between studies are solely due to sampling error. But assumption of random effects model is to consider the variation in true treatment effect of all studies plus sampling error.(45) Random effects model emphasis the heterogeneity but fixed effects model does not. None of models is ideal. When heterogeneity is not explained by covariates in meta regression analysis, random effects model should be applied(48).

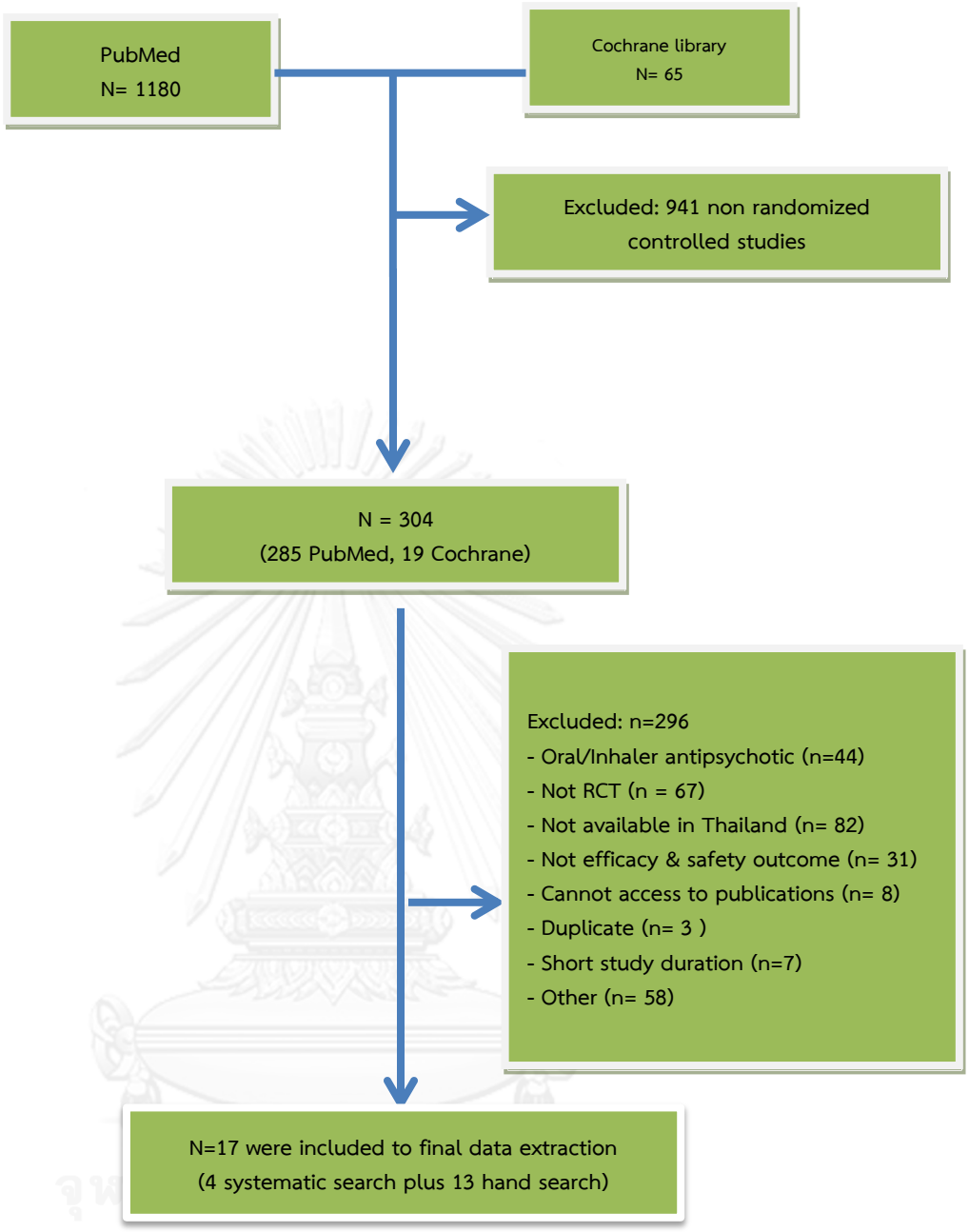


Figure 3.3 Systematic review and study selection flow

Table3.2 Summary of data extraction in our systematic review on LAI antipsychotic for schizophrenia

author	study ID	week	total subject	JADAD score	Medication and dose	total number of subjects per arm	Number of subjects who have discontinuation			no discontinuation
							relapse	adverse event	other reasons	
Hirsch SR 1973 (49)	1	60	81	2	Placebo	40	25	0	3	12
					Fluphenazine dec ≥ 25 mg q 4 weeks	41	3	0	4	34
Odejide OA 1982 (50)	2	48	53	4	Placebo	27	15	0	8	4
					Fluphenazine dec 50 mg q 4-8 weeks	26	5	0	9	12
Sampath G 1992 (51)	3	48	16	3	Placebo	12	9	0	0	3
					Fluphenazine dec 17-95 mg q 2 weeks	4	4	0	0	0
Eberhard G1986 (52)	4	48	32	3	Flupenthixol dec 10-120 mg q 4 weeks	16	3	0	3	10
					Haloperidol dec 25-300 mg	16	3	0	3	10
Chouinard G 1985 (53, 54)	5	32	72	5	Fluphenazine dec 2.5-300 mg q 2-4 weeks	36	0	0	0	36
					Haloperidol dec 15-900 mg	36	1	0	1	34
Cookson JC 1986 (55)	6	48	19	5	Fluphenazine dec 12.5-37.5 mg	10	0	2	0	8
					Haloperidol dec 50-100 mg q 2-6 weeks	9	2	0	0	7
Jolley AG 1986 (56, 57)	7	96	54	4	Placebo	27	3	0	9	15
					Fluphenazine dec 25 mg q 4 weeks	27	12	0	15	0
Kissling W 1985 (58)	8	24	54	4	Haloperidol dec 80 mg q 4 weeks	32	1	0	9	22
					Fluphenazine dec 20 mg q 2 weeks	22	1	5	7	9
McKane JP 1987 (59)	9	60	38	4	Haloperidol dec 120 mg q 4 weeks	19	10	0	8	1
					Fluphenazine dec 105 mg q 4 weeks	19	10	1	6	2
Sharma SK 1991 (60)	10	48	59	4	Haloperidol dec ≥ 25 mg q 4 weeks	30	10	4	6	10
					Fluphenazine dec ≥ 25 mg q 4 weeks	29	6	3	3	17
Fleischhacker W 2012 (61)	11	53	747	4	Risperidone LAI 25- 50 mg q 2 weeks	368	76	23	0	269
					Paliperidone palmitate 25- 100 mg q 4 weeks	379	99	25	0	255
Hough D 2010 (62)	12	24	408	5	Placebo	203	97	2	26	78
					Paliperidone palmitate 25- 100 mg q 4 weeks	205	36	3	27	139
Pinto R 1979 (63)	13	72	64	4	Flupenthixol dec 36.6 mg three times weekly	31	0	0	0	31
					Fluphenazine dec 25 mg three times weekly	33	0	1	7	25
Wisted B 1983 (64)	14	96	32	4	Flupenthixol dec27 mg q 3weeks	17	0	0	8	9
					Fluphenazine dec 31 mg q 3 weeks	15	0	0	6	9

author	study ID	week	total subject	JADAD score	Medication and dose	total number of subjects per arm	Number of subjects who have discontinuation			no discontinuation
							relapse	adverse event	other reasons	
Wisted B 1991 (65)	15	36	64	3	Zuclopenthixol dec 100-600 mg q 4 weeks	36	4	1	2	29
					Haloperidol dec 39-200 mg q 4 weeks	28	7	1	0	20
Eklund K 1991 (66)	16	48	43	3	Placebo	23	16	0	0	7
					Haloperidol dec 60 mg q 4 weeks	20	2	2	1	15
Dencker SJ 1980 (67)	17	48	60	2	Zuclopenthixol dec 50-600 mg q 4 weeks	30	3	0	0	27
					Flupentixol palmitate 25-300 mg q 4 weeks	30	4	0	3	23

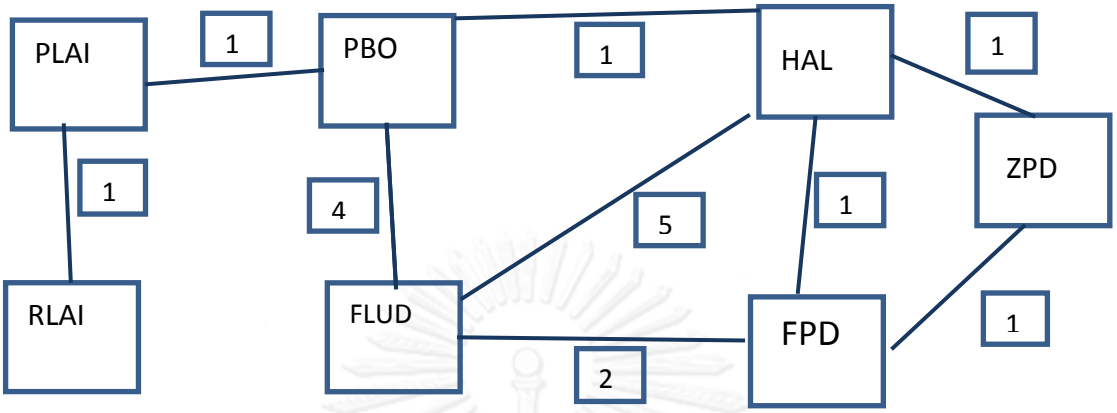


Figure 3.4 Network diagram. The connecting lines means which pairs of treatment is directly compared in randomized trials; number on lines means number of trials

A summary of 52 week probability of three outcomes are presented in table 3.3 and Appendix B. In the random effects model, subjects with schizophrenia under RLAI have the least 52 week probability of relapse outcome (mean $\pm$ SD, 0.263 $\pm$ 0.321) and follow with PLAI (0.297 $\pm$ 0.314). Excluding PBO, subjects under ZPD have the least 52 week probability of discontinuation due to intolerable adverse event (0.074$\pm$ 0.159) and discontinuation due to other reasons (0.262 $\pm$ 0.295) respectively.

In the fixed effects model, subjects with schizophrenia under PLAI have the least 52 week probability of relapse outcome (mean $\pm$ SD, 0.205 $\pm$ 0.198) and the least 52 week probability of discontinuation due other reasons (0.186 $\pm$ 0.235). However subjects under ZPD have the least 52 week probability of discontinuation due to intolerable adverse event (0.073$\pm$ 0.134). Goodness of fit model is tested. Total residual deviation is more preferable to random effects model than fixed effects model (112.56 VS.568.46). DIC parameter is also more preferable to random effects model than fixed effects model (5,323.85 VS. 36,115.70).

With this, 52 week probability of relapse, discontinuation due to intolerable adverse event and discontinuation due to other reasons under random effects model will be referred in our economic evaluation. Our meta-analysis work is being submitted to medical peer reviewed journal for further publication.

Table 3.3 A 52 week Probability of three outcomes for 6 LAIs; random effects model and fixed effects model

Outcomes	Random effects model	Fixed effects model
1 Relapse	Probability 52 weeks (SD)	Probability 52 weeks (SD)
PBO	0.4921 (0.263)	0.491(0.263)
FLUD	0.360 (0.312)	0.214 (0.200)
FPD	0.365 (0.329)	0.492 (0.334)
HAL	0.406 (0.330)	0.214 (0.207)
ZPD	0.326 (0.328)	0.371 (0.289)
PLAI	0.297 (0.314)	0.205 (0.198)
RLAI	0.263 (0.321)	0.331 (0.269)
2 Discontinuation due to adverse event	Probability 52 weeks (SD)	Probability 52 weeks (SD)
PBO	0.065 (0.113)	0.066(0.114)
FLUD	0.109 (0.180)	0.213 (0.256)
FPD	0.089 (0.164)	0.123 (0.187)
HAL	0.074 (0.147)	0.141 (0.204)
ZPD	0.074 (0.159)	0.073 (0.134)
PLAI	0.129 (0.213)	0.420 (0.377)
RLAI	0.123 (0.218)	0.092 (0.161)
3 Discontinuation due to other reasons	Probability 52 weeks (SD)	Probability 52 weeks (SD)
PBO	0.254(0.246)	0.251(0.247)
FLUD	0.321 (0.299)	0.405 (0.300)
FPD	0.313 (0.304)	0.227 (0.263)
HAL	0.313 (0.302)	0.504 (0.317)
ZPD	0.262 (0.295)	0.209 (0.249)
PLAI	0.266 (0.286)	0.186 (0.235)
RLAI	0.311 (0.346)	0.297 (0.300)
Goodness-of-fit	Mean (SD)	Mean(SD)
Resdev1	9.59 (42.68)	172.70 (120.50)
Resdev2	44.33 (24.40)	-60.64(92.70)
Resdev3	58.64 (36.27)	456.40 (423.70)
Total Resdev	112.56	568.46
DIC	5,323.85	36,115.70

3.8 Probability of relapse under no treatment group

Subjects who discontinuing treatment due to other reasons and entering to no treatment group were assumed to stop treatment immediately, and were on the risk of relapse at 50% over the first 7 months (68). With this, the first year probability of relapse in no treatment group will be 0.6062 (1)

The annual probability of relapse for no treatment for the following years is assumed to be equal to placebo effect (0.4921) which is retrieved from our current meta-analysis work. See more detail in table 3.4.

3.9 Probability of relapse under ECT

Annual probability of relapse in subject under ECT is taken from data on relapse in Cochrane review by Tharyan P.(69). See more detail in table 3.4.

3.10 Probability of relapse under 2nd line of treatment

Annual probability of 2nd line of treatment with HAL and ZPD are assumed to equal to probability of HAL and ZPD in 1st line of treatment (0.406 and 0.326 respectively). See more detail in table 3.4.

3.11 Side effects

We assume Extra Pyramidal Syndrome (EPS) as major side effect for all LAIs. The annual probability EPS of all 6 LAIs are generated from data on EPS in Cochrane reviews (70-75) . We follow the NICE model that annual probability EPS of the following years of all LAIs is assumed to 10% (1). All EPS probability is shown in table 3.4. Tardive dyskinesia is not included in our EPS data because it has lasting effects. Cost of EPS treatment and decreased quality of life of subjects with EPS need to be included in the economic model. Omission of tardive dyskinesia and other side effects is noted as a limitation of our economic analysis.

Table 3.4 Annual transitional probability of key data input

Items	Distribution	Parameter description	Mean	SE	Alpha	Beta	Reference
pRLnotreat1	beta	annual prob of relapse under no treatment for 1st year	0.6062	0.5740	1.12	0.54	Viguera et al 1997
pRLnotreat2	beta	annual prob of relapse under no treatment on the following years	0.4921	0.2631	3.50	0.14	Osot N et al MTC TBD.
pRLFlud	beta	annual prob of relapse fluphenazine dec	0.3600	0.3117	1.33	0.27	Osot N et al MTC TBD.
pRLFPD	beta	annual prob of relapse flupentixol dec	0.3653	0.3288	1.23	0.30	Osot N et al MTC TBD.
pRLHAL	beta	annual prob of relapse haloperidol dec	0.4057	0.3296	1.52	0.27	Osot N et al MTC TBD.
pRLZPD	beta	annual prob of relapse zuclopentixol dec	0.3263	0.3276	0.99	0.33	Osot N et al MTC TBD.
pRLPLAI	beta	annual prob of relapse paliperidone LAI	0.2970	0.3137	0.90	0.33	Osot N et al MTC TBD.
pRLRLAI	beta	annual prob of relapse risperidone LAI	0.2632	0.3207	0.67	0.39	Osot N et al MTC TBD.
pAEFLUD	beta	annual prob ofAE discontinuation fluphenazine dec for 1st year	0.1087	0.1800	0.36	0.30	Osot N et al MTC TBD.
pAEFPD	beta	annual prob of AE discontinuation flupentixol dec for 1st year	0.0889	0.1636	0.30	0.30	Osot N et al MTC TBD.
pAEHAL	beta	annual prob of AE discontinuation haloperidol dec for 1st year	0.0743	0.1470	0.26	0.29	Osot N et al MTC TBD.
pAEZPD	beta	annual prob of AE discontinuation zuclopentixol dec for 1st year	0.0743	0.1591	0.22	0.34	Osot N et al MTC TBD.
pAEPLAI	beta	annual prob of AE discontinuation paliperidone LAI for 1st year	0.1287	0.2130	0.37	0.35	Osot N et al MTC TBD.
pAERLAI	beta	annual prob of AE discontinuation risperidone LAI for 1st year	0.1229	0.2182	0.32	0.39	Osot N et al MTC TBD.
pOFLUD	beta	annual prob of other reason discontinuation fluphenazine dec	0.3209	0.2990	1.15	0.28	Osot N et al MTC TBD.
pOFPD	beta	annual prob of other reason discontinuation flupentixol dec	0.3128	0.3035	1.06	0.29	Osot N et al MTC TBD.
pOHAL	beta	annual prob of other reason discontinuation haloperidol dec	0.3133	0.3020	1.08	0.29	Osot N et al MTC TBD.
pOZPD	beta	annual prob of other reason discontinuation zuclopentixol dec	0.2617	0.2947	0.79	0.33	Osot N et al MTC TBD.
pOPLAI	beta	annual prob of other reason discontinuation paliperidone LAI	0.2661	0.2859	0.87	0.31	Osot N et al MTC TBD.
pORLAI	beta	annual prob of other reason discontinuation risperidone LAI	0.3113	0.3458	0.81	0.38	Osot N et al MTC TBD.
pComFLUD	beta	prob of EPS fluphenazine dec at 1st year	0.5221	0.0316	130	119	David A 2005
pComFPD	beta	prob of EPS flupentixol dec at 1st year	0.4891	0.0518	45	47	Quraishi SN 2000
pComHAL	beta	prob of EPS haloperidol dec at 1st year	0.5887	0.0440	73	51	Quraishi SN 2000
pComZPD	beta	prob of EPS zuclopentixol dec at 1st year	0.6536	0.0383	100	53	Coutinho E 2000
pComPLAI	beta	prob of EPS paliperidone LAI at 1st year	0.1586	0.0096	230	1220	Nussbaum AM 2012
pComRLAI	beta	prob of EPS risperidone LAI at 1st year	0.0728	0.0149	22	280	Hosalli P 2003
pComALL	beta	prob of EPS all medications for the following years	0.1000				GDG expert opinion NICE 2009 page 221
pRLECT	beta	annual prob of relapse ECT	0.1071	0.0335	9	75	Tharyan P 2005

3.12 Mortality

As of lacking of data of risk of death among LAIs, risk of death will be assumed to be independent of individual LAIs. However mortality rate of subjects with schizophrenia was higher than general population(76). A 2.6 standard mortality ratio of schizophrenia, age adjusted mortality rate of subjects with age 25 years and above would be calculated for probability of death (76, 77). See more detail in table 3.5.

Table 3.5 Probability of Mortality

Mortality rate 2011*				SMR 2.6**	Probability of dying with adjust SMR and age
Age (year)	Male	Female	Total		
25-29	0.00242	0.00088	0.00166	0.00432	0.00431
30-34	0.00312	0.00126	0.00219	0.00569	0.00568
35-39	0.00399	0.00162	0.00278	0.00723	0.00720
40-44	0.00507	0.00216	0.00355	0.00923	0.00919
45-49	0.00658	0.00302	0.00471	0.01225	0.01217
50-54	0.00895	0.00446	0.00659	0.01713	0.01699
55-59	0.01256	0.00691	0.00962	0.02501	0.02470
60-64	0.01847	0.01133	0.01475	0.03835	0.03762
65-69	0.02758	0.01754	0.02224	0.05782	0.05618
70-74	0.04473	0.03122	0.03725	0.09685	0.09231
75-79	0.06261	0.04508	0.05264	0.13686	0.12791
80-84	0.08450	0.06846	0.07516	0.19542	0.17751
85-89	0.11906	0.10567	0.11090	0.28834	0.25049
90-94	0.17517	0.16577	0.16898	0.43935	0.35554
95-99	0.26907	0.26428	0.26562	0.69061	0.49873
100+	0.43153	0.42819	0.42892	1.11519	0.67215

*WHO life table Thailand 2011

**MaGrath et al. 2008

3.13 Utility data and estimation of QALY

Systematic review on the studies reporting utility values for schizophrenia found that health state utility values generated with EQ-5D were not readily available in schizophrenia field (78). Researcher also suggested a condition-specific preference-based tool may be more suitable than a generic measurement for cost utility analysis in schizophrenia(78). As a result of this systematic review study, the utility scores of Lenert study was finally chosen to support NICE economic model on schizophrenia (79). The reasons to choose this study included: data covered board range of health states of all levels of symptoms; PANSS was used to generate health states; study method was described appropriately; valuation was made among general public by Standard Gamble method; and health state with side effect was also addressed. PANSS might be not an ideal tool for utility measurement because clinicians perform rating instead of patients. However this was acceptable because of two reasons: subjects with schizophrenia might lack of insight to perform this rating ; PANSS utility tool had better precision and power than (patient-rated) SF-36 in any changes of schizophrenia symptom (80). With the expert opinion, subjects with several relapses are considered to have worse utility than subjects who have less relapses. Utility penalty are prepared to support this suggestion. Details of utility scores are shown in table 3.7 and utility penalty are presented in Appendix C.

3.14 Cost data

Our economic evaluation was assessed under societal perspective therefore both direct medical cost, direct non-medical cost, and indirect costs were included.

Costs associated with medication were calculated by combining healthcare utilization use cost. Costs of relapse and remission states consist of relevant medication costs, outpatient visit cost, inpatient (hospitalization) cost, medication cost of treating acute symptoms (relapse state only), travelling cost, and cost of subject and care giver ‘s income loss.

Medication cost is referred to purchasing price of general hospital in Thailand which is posted at DMSIC website, Ministry of Public Health 2014 (81). Price were adjusted with reimbursement price guideline of civil service medical benefit scheme (CSMBS). Defined daily dose (DDD) by WHO and dose administration in Thai national formulary guidebook 2010 were used as reference source for our dose calculation for costing (40, 41). See more details in table 3.6.

Example; DDD of Fluphenazine parenteral route is 1 mg/day and dose administration is taken every 2 week. Therefore standardized dose would be 14 mg /14 days. Product was available in from DMSIC-MOPH website was 25 mg/ml @36 baht and 50 mg/2ml @54 baht. These

DMSIC prices were re-adjusted with CSMBS price reimbursement guideline before further analysis. Finally, 25mg/ml injection was chosen for our analysis because it was the lowest available dose. Unused product per injection was discarded for this case. A 26 of 25 mg Fluphenazine injections were assumed to use for 52 weeks. Therefore overall cost of Fluphenazine per 52 weeks would be 936 baht.

All detail of dose administration and total drug cost per 52 weeks are shown in table 3.6 & 3.7 Cost of OPD per visit with adjusted consumer price index in 2014 was 702.79 $\pm$ 351.39 baht and cost of IPD excluding medication cost was 30,682.65 $\pm$ 15,341.32 baht (82). Number of OPD visit per year for remission cases were 4 times per year (23).

All relapse cases were assumed to require hospital admission for 4 weeks per one admission(83). Direct medical care cost and related parameter are shown in table 3.7 . Cost of LAIs for 48 weeks was prepared if subjects need to be treated relapse during the year. Cost of LAIs for 48 weeks was calculated with 0.92308 of cost for LAIs for 52 weeks.

Direct non-medical care cost include traveling cost, meal cost for patients and care givers were sourced from HITAP costing guideline 2010. Indirect cost was calculated when patients and care givers need to visit the hospitals. Indirect cost including work loss cost of patients and care givers were referred to minimal pay per day for employee by ministry of labor's announcement 2014.

If those cost data was not reported in the current year of 2014, all cost would be adjusted based on Consumer Price Index (CPI) of Bank of Thailand report. (Appendix D)

ECT was provided three times weekly for 4 weeks. Subjects were required to stay in the hospitals to receive the full course of ECT (84). Treatment of EPS side effect was Benhexol 15 mg tablet three times a day for 60 days. Total cost of Benhexol was 180 baht. Medication cost of relapse treatment was referred to medication cost for schizophrenia in IPD.(83) . Other additional cost is shown in table 3.7. Cost and utility per health state are formulated for analysis and presented in the table 3.8 and 3.9.

Table 3.6 Dose administration and drug cost per 52 weeks

Drug			dose	cost /injection (baht)	number of injection per 52 weeks	cost per 52 weeks (baht)
1	Fluphenazine dec	FLUD	14 mg q 14 days	25 mg/ml @36, 50 mg/2ml @54	25mg x26	936
2	Flupentixol dec	FPD	56 mg q 14 days	20mg/ml@110, 40m/ml@220	20mgx3x26	8,580
3	Haloperidol dec	HAL	92.4 mg q 28days	50mg/ml@ 67-77 , 100mg/2ml @ 147	100mgx13	1,911
4	Zuclopentixol dec	ZPD	210 mg q 14 days	100mg/2 ml@257	100mgx2x26	13,364
5	Paliperiodne LAI	PLAI	70 mg q 28 days	75-100 mg/ml @8106 , 150 mg/ml @10383	75 mg x 13	105,378
6	Risperidone LAI	RLAI	37.8 mg q 14 days	25 mg /ml @5299 37.5 mg/ml @7888	37.5 mg x 26	205,088

Table 3.7 Cost data input

Items	Distribution	Parameter description	Mean	SE	Alpha	Beta	Reference
Direct medical care costs							
cOPD	gamma	cost of OPD per visit	702.79	351.39	4.00	175.70	Puapanprasert B 2005
cIPD	gamma	cost of IPD per relapse admission	30,682.65	15,341.32	4.00	7,670.66	Puapanprasert B 2005
dIPD		duration of hospital days if admission required	30				Puapanprasert B 2003
Cost of Medication							
cFlud	gamma	annual cost of fluphenazine dec	936	842.40	1.23	758.16	DDD & DMSIC & CSMBS reimbursement
cFPD	gamma	annual cost of flupentixol dec	8,580	7,722	1.23	6,949.80	DDD & DMSIC & CSMBS reimbursement
cHAL	gamma	annual cost of haloperidol dec	1,911	1,719.90	1.23	1,547.91	DDD & DMSIC & CSMBS reimbursement
cZPD	gamma	annual cost of zuclopentixol dec	13,364	12,027.60	1.23	10,824.84	DDD & DMSIC & CSMBS reimbursement
cPLAI	gamma	annual cost of paliperidone LAI	105,378	94,840.20	1.23	85,356.18	DDD & DMSIC & CSMBS reimbursement
cRLAI	gamma	annual cost of risperidone LAI	205,088	18,4579.20	1.23	166,121.28	DDD & DMSIC & CSMBS reimbursement
cEct	gamma	cost of ECT (12ECT times within 4 weeks IPD)	12,000	10800	1.23	9,720.00	Kongsakon R 2000 & Cost at Somdetchaopraya hospital 2014
cBenhx	gamma	cost of benhexol 15 mg	180	162	1.23	145.80	Kongsakon R 2000 & Cost at Somdetchaopraya hospital 2014
cRelapse	gamma	cost of relapse treatment (medication)	725.95	835.34	0.76	961.21	Puapanprasert B 2003
Direct non-medical care cost							
cPatient OPD travel	gamma	cost of OPD travel / round trip	295.02	386.92	0.58	507.44	HITAP costing guideline 2010
cPatient OPD meals	gamma	cost of OPD1 day meal	54.34	92.90	0.34	158.83	HITAP costing guideline 2010
cPatient IPD travel	gamma	cost of IPD travel / round trip	295.02	368.92	0.64	461.33	HITAP costing guideline 2010
cPatient IPD meals	gamma	cost of IPD 30 days meals	1,630.13	2,787.00	0.34	4,764.88	HITAP costing guideline 2010
Indirect non-medical cost							
cWorkloss	gamma	cost of patient & family work loss /day	450.00	225.00	4.00	112.50	Ministry of labor 2014
Utility parameters							
uRemission	beta	utility for remission	0.80	0.08	19.25	4.84	Lenert 2004
uRelapse	beta	utility for relapse	0.67	0.07	32.33	15.92	Lenert 2004
uEPS		utility adjusted for remission with EPS	-0.10				NICE experts

Table 3.8 Cost calculation per health state

health state	direct medical cost	direct non- medical cost	indirect cost
remission with 1line LAI_1st year	cLAIs1st52 + cOPD*4 + (cBenhz*PcomLAIs1st)	(cPatOPDtravel+cPatOPD meal)*4	cworkloss*4
remission with 1line LAI_nextyear	cLAIs1st52 + cOPD*4 + (cBenhz*Pcom_nextyear)	(cPatOPDtravel+cPatOPD meal)*4	cworkloss*4
relapse A	(0.5*cLAIs1st48) + (0.5*cLAIs2nd48)+cOPD*4 + (0.5*cBenhz*PcomLAI1st) + (0.5*cBenhz*PcomLAI2nd) +cRxRL+cIPD	(cPatOPDtravel+cPatOPD meal)*4+ cPatIPDtravel+cPatIPDmeal	cworkloss*30+cw orkloss*4
remission with 2line LAI_1styear	cLAIs2nd52 + cOPD*4 + (cBenhz*PcomLAIs2nd)	(cPatOPDtravel+cPatOPD meal)*4	cworkloss*4
remission with 2line LAI_nextyear	cLAIs2nd52 + cOPD*4 + (cBenhz*Pcom_nextyear)	(cPatOPDtravel+cPatOPD meal)*4	cworkloss*4
relapse C	(0.5*cLAIs2nd48) + (0.5*cECT)+cOPD*2 + (0.5*cBenhz*PcomLAI2nd) +cRxRL+ cIPD*1.5	(cPatOPDtravel+cPatOPD meal)*2+(cPatIPDtravel+cPatIP Dmeal)*1.5	cworkloss*60+cw orkloss*4
remission w/oLAIs1st	0	0	0
remission w/oLAIs2nd	0	0	0
relapse B	cLAIs2nd48+cOPD*4 +cBenhz*PcomLAI2nd +cRxRL+cIPD	(cPatOPDtravel+cPatOPD meal)*4+ cPatIPDtravel+cPatIPDmeal	cworkloss*30+cw orkloss*4
relapse D	cECT+cRxRL+cIPD*2	(cPatIPDtravel+cPatIPDmeal)*2	cworkloss*60
relapse E	cECT+cRxRL+cIPD*2	)cPatIPDtravel+cPatIPDmeal)*2	cworkloss*60
remisison with ECT	cECT+cIPD	cPatIPDtravel+cPatIPDmeal	cworkloss*30

Table 3.9 Utility calculation per health state

health state	utility of each state
remission with 1line LAI	uRemission*(1-pComLAI1st)+pComLAI1st*uRemission*0.9
relapse A	uRelapse
remission with 2line LAI	uRemission*(1-pComLAI2nd)+pComLAI2nd*uRemission*0.9
relapse C	uRelapse
remission w/oLAIs1st	uRemission
remission w/oLAIs2nd	uRemission
relapse B	uRelapse
relapse D	uRelapse
relapse E	uRelapse
remission with ECT	uRemission

3.15 Data analysis and presentation of results

Our Markov model was prepared in TreeAgePro 2014 which shown with more detail in Appendix E. Analysis plan were arranged as follows.

3.15.1 Deterministic sensitivity analysis

Deterministic analysis which input data was point estimation was presented as a mean total costs and QALYs associated with each medication. Relative cost effectiveness among medications was compared using incremental analysis which ranked from the most to the least effective. Incremental Cost Effectiveness Ratios (ICERs) was presented for all pairs of consecutive options. ICERs supported to consider whether additional benefit was worth the additional cost when selecting one treatment option over another.

$$ICER = \frac{COST\ A - COST\ B}{QALY\ A - QALY\ B}$$

Results of deterministic analysis were presented in form of Cost Effectiveness Acceptability Plane. The Cost Effectiveness Plane demonstrated between incremental cost (Baht) and incremental effectiveness (QALYs). This graph supported to choose the product of choice in sequential way.

One way sensitivity analysis was performed to some key data inputs include price of LAIs. Outcome of one way sensitivity analysis were presented in Tornado diagram

3.15.2 Probabilistic Sensitivity Analysis

When input data was expressed as probability distribution, probabilistic analysis was calculated and presented. When we repeated 1,000 iterations in Monte Carlo Simulation, program will randomly select each data input with its probability distribution range. This approach provided more accurate estimation of ICERs (averaging results from 1,000 iterations), with a concept of the non-linearity economic model structure (32, 85). Normally lowest ICER was chosen under technical efficiency. However both deterministic sensitivity analysis and Probability analysis were methods to manage the uncertainty of all input data(32). Results of Probabilistic analysis was presented in form of Cost Effectiveness Acceptability Curve (CEACs). The CEACs curve l demonstrated between the probabilities of each intervention being the most cost-effective and different thresholds of willingness-to-pay per (WTP) unit of effectiveness. Allocative efficiency will be measured via WTP threshold. As HITAP guideline suggested to use three times of gross domestic product (GDP) per capita as the maximum threshold of WTP in Thailand. Therefore 522,957 Baht (based on 2014 Thai GDP) was referred to our maximum level of WTP threshold .(32)

3.15.3 Different time horizons sub-analysis

The guideline economic analysis suggested that time horizon should be long enough to cover the end result of effectiveness. Patients with schizophrenia need long-term treatment in case of remission period. Development of new intervention is ongoing therefore any new interventions might be introduced in this field within the next 10-20 years. With this, we proposed to examine the results whether there are any different of LAIs cost effectiveness between 10 years vs lifetime horizon. Our data were analyzed in two scenarios (table 3.10).

Table 3.10 Two scenarios analysis

Scenario	Staring age (years)	Time horizon (years)	Perspective
1	25	75	societal
2	25	10	societal

CHAPTER 4
RESULTS

This chapter will cover main analysis results of Markov economic modelling including two analysis scenarios (10 years and lifetime horizon). One way sensitivity analysis and probabilistic sensitivity analysis are also included.

4.1 Markov output ; age of 25 years , time horizon of 75 years , societal perspective

4.1.1 Deterministic analysis

Overall ratio of cost /effectiveness of 6 LAIs are not much different with range of 80,450-95,579 baht/QALY. Comparing to next product, the incremental cost are range of 6,830-109,479 baht and incremental effectiveness are range of 0.0024 - 0.0217 QALY.
When we compare ICER under deterministic analysis, Haloperidol dec is the most cost effective option among 6 LAIs. Fluphenazine dec, Flupentixol dec, Paliperidone LAI and Risperidone LAI may be considered to be chosen for the next choices after Haloperiodol dec with ICER of 808,580, 3,995,921, 5,052,900, and 32,712,811 baht/QALY, respectively. However ICERs of these products exceed the maximum WTP threshold of 530,000 baht. Zuclopentixol dec is not cost effective under deterministic analysis because it has negative ICER of 627,116 baht/QALY. Mean cost, QALY and ICER of all 6 LAIs are presented in table 4.1. Deterministic cost effective plane of all 6 LAIs is shown in figure 4.1.

Table 4.1 Cost effectiveness deterministic result (age of 25 years , time horizon of 75 years , societal perspective)

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER	C/E	remark
Excluding dominated							
Haloperidol	1,144,779		14.2298			80,450	
Fluphenazine	1,157,242	12,462	14.2452	0.0154	808,580	81,238	
Flupentixol	1,166,672	9,430	14.2475	0.0024	3,995,921	81,886	
Paliperidone	1,276,151	109,479	14.2692	0.0217	5,052,900	89,434	
Risperidone	1,364,089	87,938	14.2719	0.0027	32,712,811	95,579	
All							
Haloperidol	1,144,779	-	14.2298	-	-	80,450	undominated
Fluphenazine	1,157,242	12,462	14.2452	0.0154	808,580	81,238	undominated
Flupentixol	1,166,672	9,430	14.2475	0.0024	3,995,921	81,886	undominated
Zuclopenthixol	1,173,502	6,830	14.2366	(0.0109)	(627,116)	82,428	abs. dominated
Paliperidone	1,276,151	109,479	14.2692	0.0217	5,052,900	89,434	undominated
Risperidone	1,364,089	87,938	14.2719	0.0027	32,712,811	95,579	undominated
All referencing common baseline							
Haloperidol	1,144,779		14.2298			80,450	
Fluphenazine	1,157,242	12,462	14.2452	0.0154	808,580	81,238	
Flupentixol	1,166,672	21,893	14.2475	0.0178	1,231,822	81,886	
Zuclopenthixol	1,173,502	28,723	14.2366	0.0069	4,174,202	82,428	
Paliperidone	1,276,151	131,372	14.2692	0.0394	3,330,983	89,434	
Risperidone	1,364,089	219,310	14.2719	0.0421	5,205,868	95,579	
All by Increasing effectiveness							
Haloperidol	1,144,779		14.2298			80,450	
Zuclopenthixol	1,173,502		14.2366			82,428	
Fluphenazine	1,157,242		14.2452			81,238	
Flupentixol	1,166,672		14.2475			81,886	
Paliperidone	1,276,151		14.2692			89,434	
Risperidone	1,364,089		14.2719			95,579	

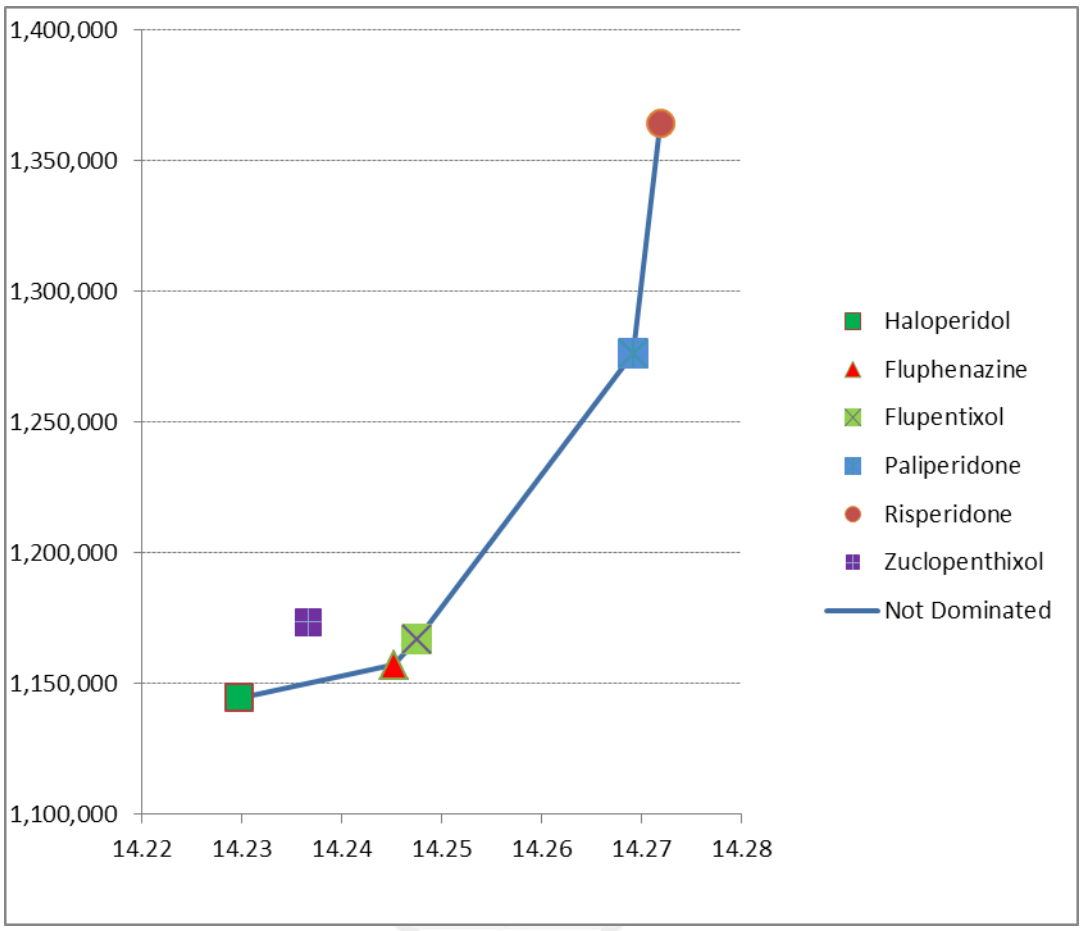


Figure 4.1 Cost effective plane –deterministic analysis (age of 25 years, time horizon of 75 years, societal perspective)

4.1.2 Probabilistic analysis

Result of probabilistic analysis of Monte Carlo simulation 1,000 iterations are presented in cost effective acceptability curve figure 4.2 and scatter plot figure 4.3. Result show Haloperidol dec has higher probability (31-46%) of being better cost-effective option among all LAI within WTP threshold of 1,000,000 baht. New LAIs include Paliperidone LAI and Risperidone LAI has higher probability of being more cost effective than Haloperidol dec when WTP threshold is increased to 3,000,000 baht. Additional Markov outputs are presented in Appendix F.

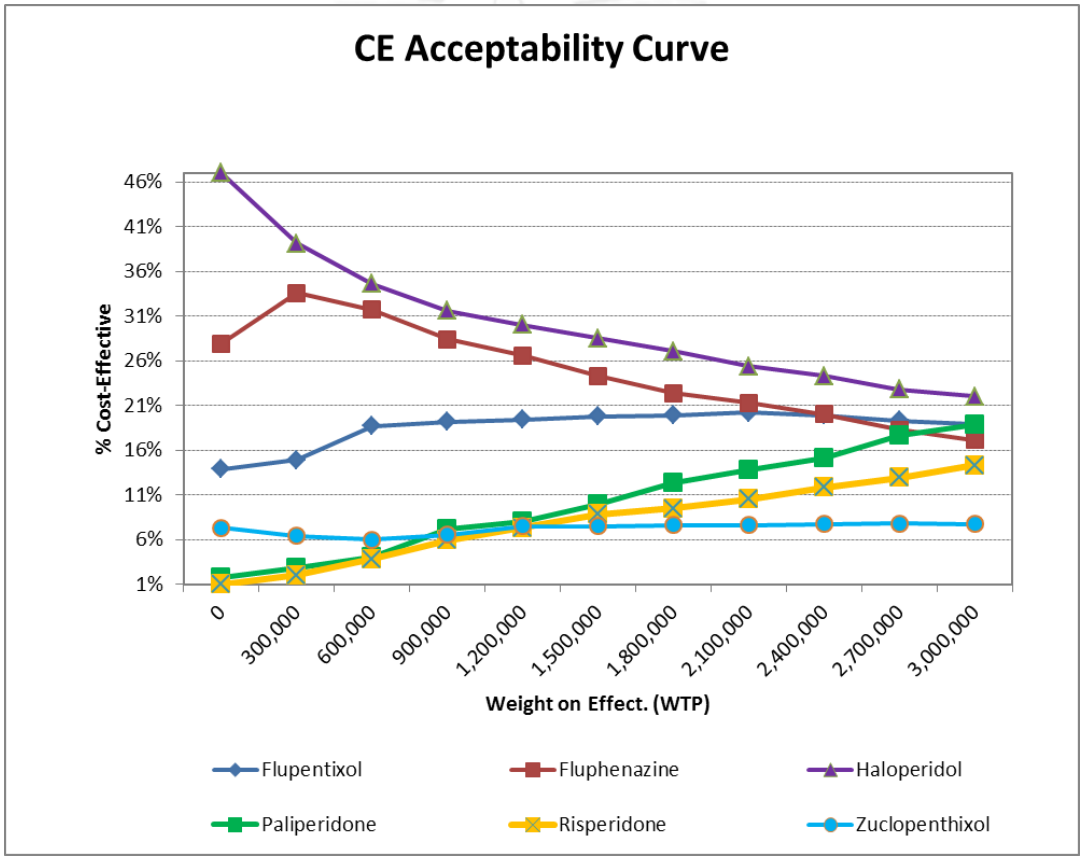


Figure 4.2 Cost effective acceptability curve (age of 25 years, time horizon of 75 years, societal perspective)

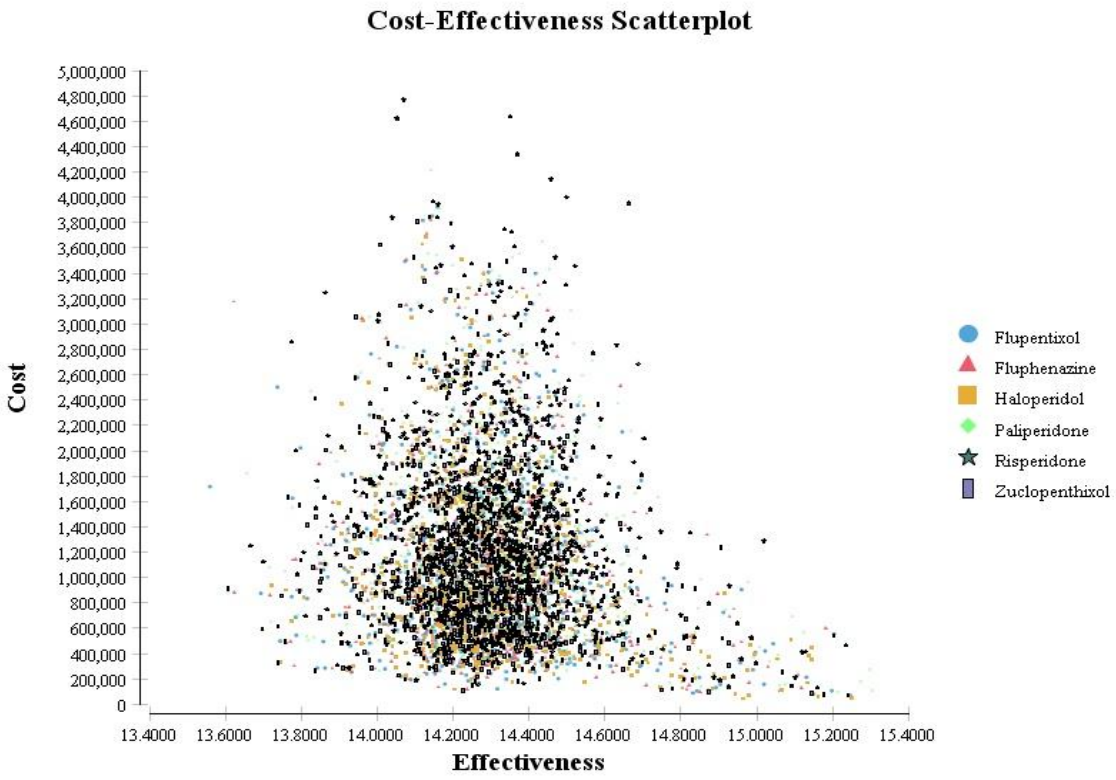


Figure 4.3 Scatter plot of Monte Carlo simulation 1,000 iteration of cost and effectiveness of all LAIs (age of 25 years, time horizon of 75 years, societal perspective)

4.1.3 Tornado sensitivity analysis

One way sensitivity analysis is presented in Tornado diagram figure 4.4. Three parameters that have high impact on the final net benefit include discounting rate for outcome, discounting rate for cost, and age at starting point. Higher discounting rate of outcome and higher age decrease the final net benefit but higher discounting rate of cost reverses final benefit. All 6 LAIs are consistent in correlation's direction among key parameters include probability of relapse, probability of revert to prior treatment, probability of discontinuation due to other reasons. We observe higher of probability of discontinuation due to other reasons and higher probability of revert to prior treatment will generate higher net benefit outcome. Figure 4.5 present association between these parameters and final net benefit.

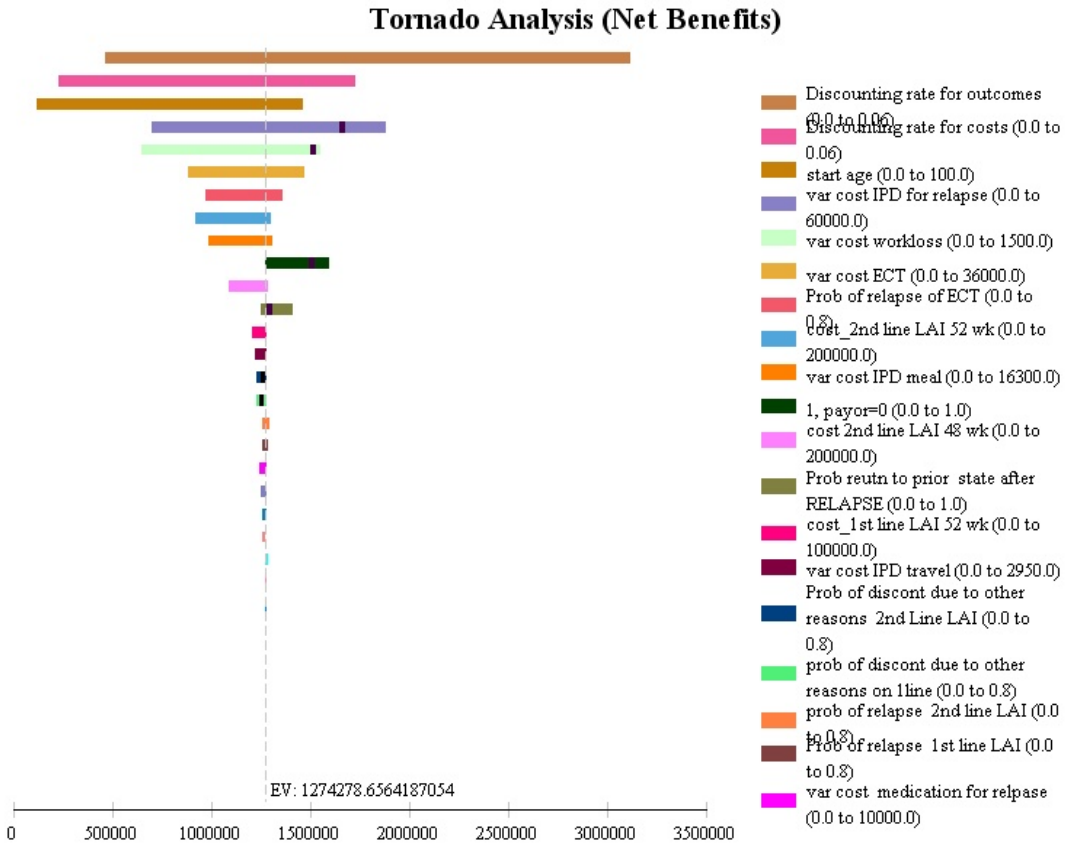


Figure 4.4 Tornado diagram (age of 25 years, time horizon of 75 years, societal perspective)

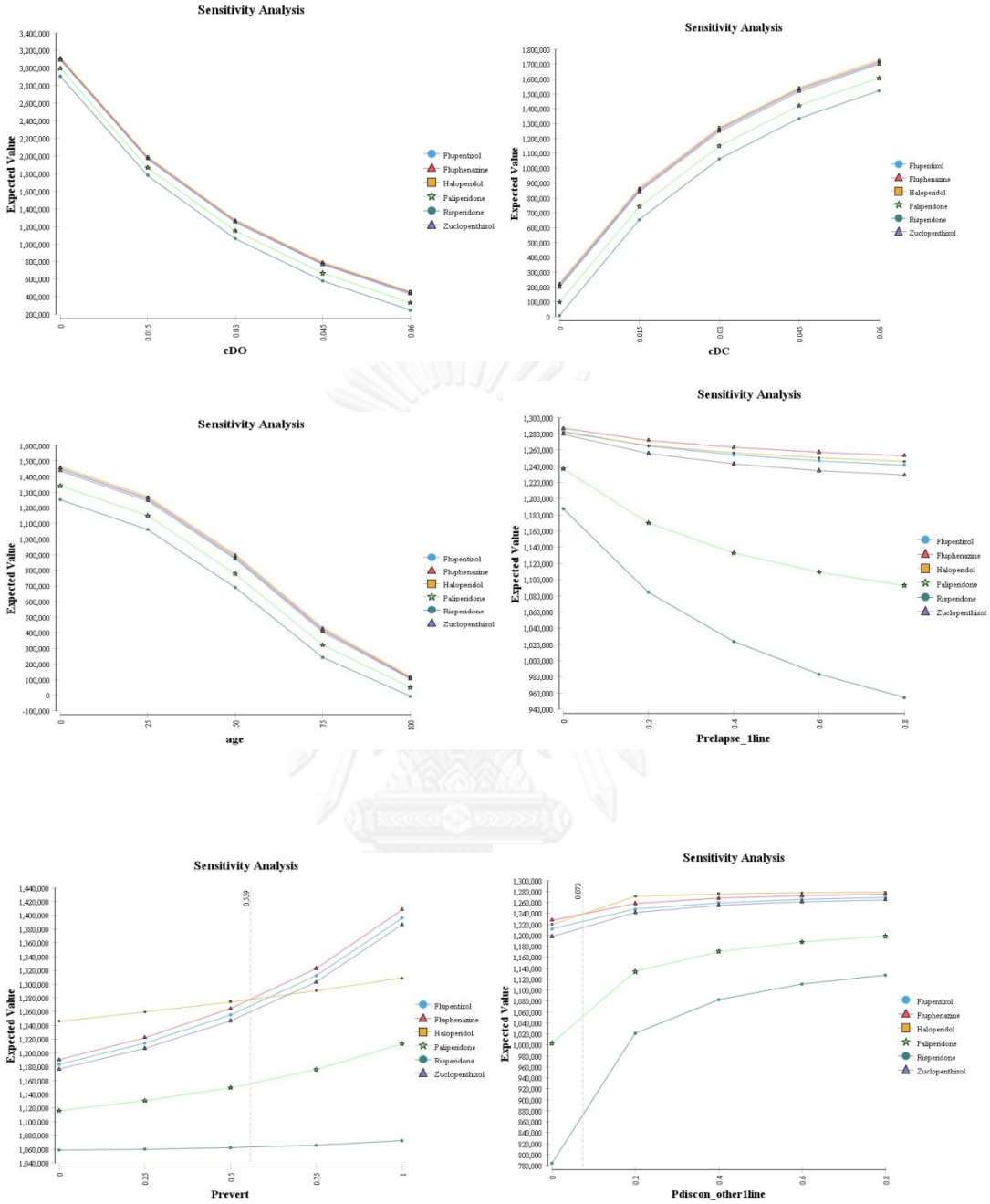


Figure 4.5 One way sensitivity analysis of three parameters on final net benefit(age of 25 years, time horizon of 75 years, societal perspective)

4.1.4 Price sensitivity analysis for Paliperidone LAI

Monte Carlo Simulation of cost effectiveness comparison is arranged between Paliperidone LAI and Haloperidol dec. Incremental cost effectiveness between two LAIs are analyzed at WTP threshold range. Probability of current pricing of Paliperidone LAI being more cost effectiveness than Haloperidol dec at WTP threshold of 170,000 and 530,000 baht are 14.4% and 20.4% respectively. More detail is presented in table 4.2 and figure 4.6

Table 4.2 Simulation report between Paliperidone LAI vs Haloperidol dec at WTP threshold of 170,000 and 530,000 baht(age of 25 years, time horizon of 75 years, societal perspective)

COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	124	0.124
C2	I	IE>0	IC>0	ICER<170000.0	20	0.02
C3	III	IE<0	IC<0	ICER>170000.0	14	0.014
C4	I	IE>0	IC>0	ICER>170000.0	642	0.642
C5	III	IE<0	IC<0	ICER<170000.0	1	0.001
C6	II	IE<0	IC>0	Inferior	199	0.199
Indiff	origin	IE=0	IC=0	0/0	0	0
COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	124	0.124
C2	I	IE>0	IC>0	ICER<530000.0	80	0.080
C3	III	IE<0	IC<0	ICER>530000.0	10	0.010
C4	I	IE>0	IC>0	ICER>530000.0	582	0.582
C5	III	IE<0	IC<0	ICER<530000.0	5	0.005
C6	II	IE<0	IC>0	Inferior	199	0.199
Indiff	origin	IE=0	IC=0	0/0	0	0.000

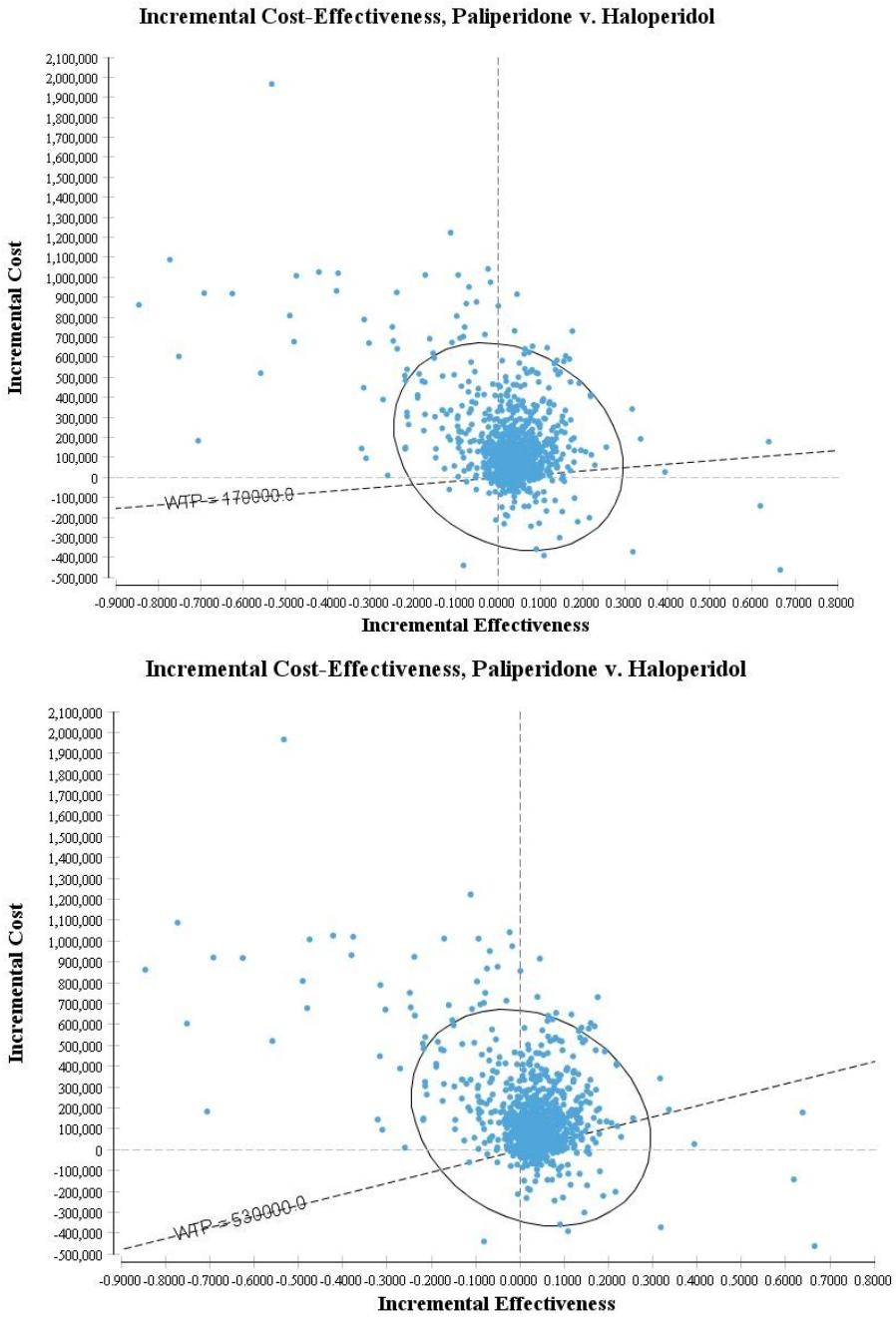


Figure 4.6 Scatter plot of ICER between Paliperidone LAI and Haloperidol dec with WTP threshold of 170,000 and 530,000 baht (age of 25 years, time horizon of 75 years, societal perspective)

One way price sensitivity of Paliperidone LAI was also tested. If we need to replace Haloperidol dec with Paliperidone LAI as first line drug , annual cost of Paliperidone LAI should be 20,000 baht with WTP threshold at 530,000 baht. Detail is shown in table 4.3

Table 4.3 One way price sensitivity of Paliperidone LAI

VARIABLE	STRATEGY	COST	EFF	CE	INCRCOST	INCREFF	INCRCE
-	Paliperidone	1,156,102	14.2692	81,021	11,322	0.0394	287,084
2,000	Paliperidone	1,158,380	14.2692	81,180	1,138	0.0240	47,380
4,000	Paliperidone	1,160,658	14.2692	81,340	3,417	0.0240	142,211
6,000	Paliperidone	1,162,937	14.2692	81,500	5,695	0.0240	237,041
8,000	Paliperidone	1,165,215	14.2692	81,660	7,974	0.0240	331,872
10,000	Paliperidone	1,167,494	14.2692	81,819	822	0.0217	37,926
12,000	Paliperidone	1,169,772	14.2692	81,979	3,100	0.0217	143,086
14,000	Paliperidone	1,172,051	14.2692	82,139	5,379	0.0217	248,246
16,000	Paliperidone	1,174,329	14.2692	82,298	7,657	0.0217	353,406
18,000	Paliperidone	1,176,608	14.2692	82,458	9,936	0.0217	458,566
20,000	Paliperidone	1,178,886	14.2692	82,618	12,214	0.0217	563,726
22,000	Paliperidone	1,181,164	14.2692	82,777	14,492	0.0217	668,886
24,000	Paliperidone	1,183,443	14.2692	82,937	16,771	0.0217	774,046
26,000	Paliperidone	1,185,721	14.2692	83,097	19,049	0.0217	879,206
28,000	Paliperidone	1,188,000	14.2692	83,256	21,328	0.0217	984,366
30,000	Paliperidone	1,190,278	14.2692	83,416	23,606	0.0217	1,089,526

4.2 Markov output ; age of 25 years , time horizon of 10 years , societal perspective

4.2.1.Deterministic analysis

It is similar to 75 year time horizon analysis. Overall ratio of cost /effectiveness of 6 LAIs are not much different with range of 53,378 – 91,536 baht/QALY. Comparing to next product, the incremental cost are range of 9,474- 109,338 baht and incremental effectiveness are range of 0.0023 - 0.0217 QALY.

When we compare ICER under deterministic analysis, Haloperidol dec is the most cost effective option among 6 LAIs. Fluphenazine dec, Flupentixol dec, Paliperidone LAI and Risperidone LAI may be considered to be chosen for the next choices after Haloperiodol dec with ICER of 1,069,311, 4,093,540, 5,038,489and 29,595,880 baht/QALY, respectively. However ICERs of these products exceed the maximum WTP threshold of 530,000 baht. Zuclopentixol dec is not cost effective under deterministic analysis because it has negative ICER of 630,447 baht/QALY. Mean cost, QALY and ICER of all 6 LAIs are presented in table 4.4. Deterministic cost effective plane of all 6 LAIs is shown in figure 4.7

Table 4.4 Cost effectiveness deterministic result (age of 25 years , time horizon of 10 years , societal perspective)

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	ICER	C/E	remark
Excluding dominated							
Haloperidol	304,306		5.7010			53,378	
Fluphenazine	319,145	14,840	5.7148	0.0139	1,069,311	55,845	
Flupentixol	328,619	9,474	5.7172	0.0023	4,093,540	57,479	
Paliperidone	437,957	109,338	5.7389	0.0217	5,038,489	76,314	
Risperidone	525,584	87,626	5.7418	0.0030	29,595,880	91,536	
All							
Haloperidol	304,306	-	5.7010	-	-	53,378	undominated
Fluphenazine	319,145	14,840	5.7148	0.0139	1,069,311	55,845	undominated
Flupentixol	328,619	9,474	5.7172	0.0023	4,093,540	57,479	undominated
Zuclopenthixol	335,526	6,907	5.7062	(0.0110)	(630,447)	58,800	abs. dominated
Paliperidone	437,957	109,338	5.7389	0.0217	5,038,489	76,314	undominated
Risperidone	525,584	87,626	5.7418	0.0030	29,595,880	91,536	undominated
All referencing common baseline							
Haloperidol	304,306		5.7010			53,378	
Fluphenazine	319,145	14,840	5.7148	0.0139	1,069,311	55,845	
Flupentixol	328,619	24,313	5.7172	0.0162	1,501,555	57,479	
Zuclopenthixol	335,526	31,220	5.7062	0.0052	5,963,087	58,800	
Paliperidone	437,957	133,652	5.7389	0.0379	3,527,115	76,314	
Risperidone	525,584	221,278	5.7418	0.0409	5,416,397	91,536	
All by Increasing effectiveness							
Haloperidol	304,306		5.7010			53,378	
Zuclopenthixol	335,526		5.7062			58,800	
Fluphenazine	319,145		5.7148			55,845	
Flupentixol	328,619		5.7172			57,479	
Paliperidone	437,957		5.7389			76,314	
Risperidone	525,584		5.7418			91,536	

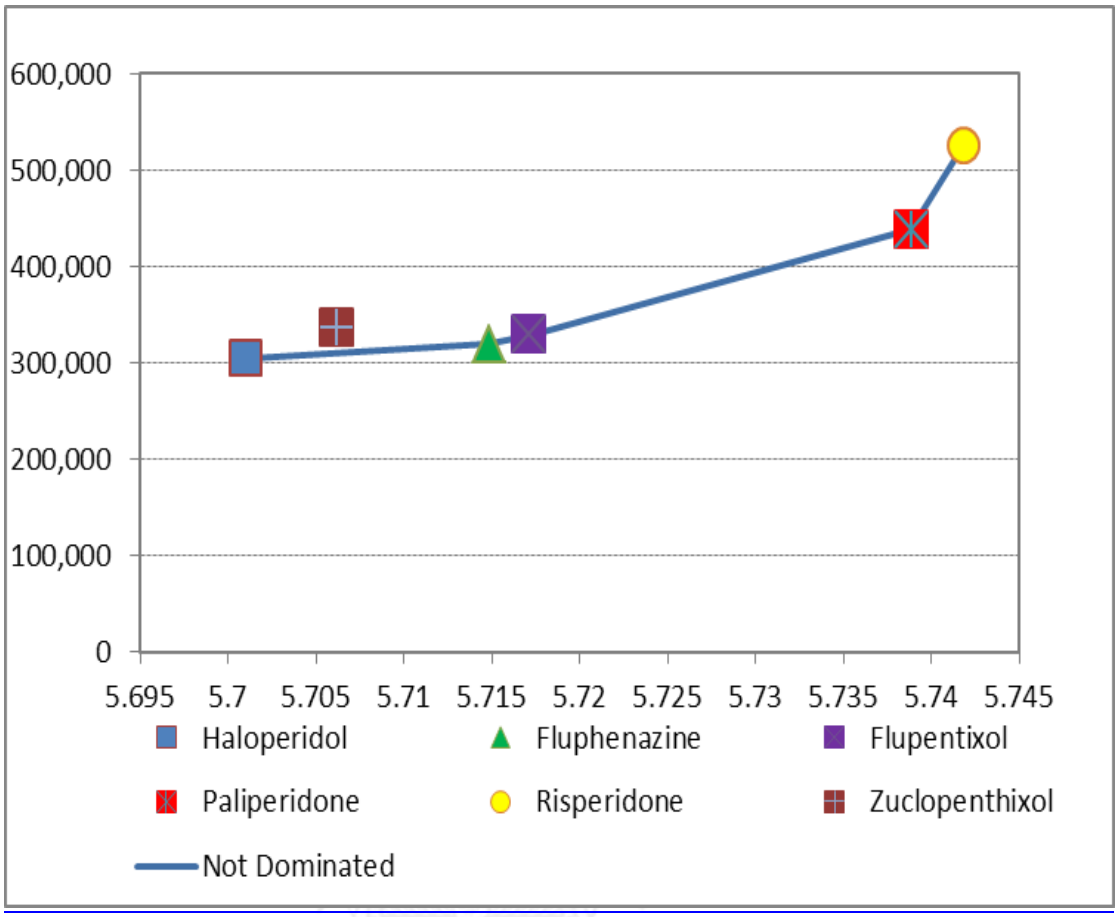


Figure 4.7 Cost effective plane –deterministic analysis (age of 25 year time horizon of 10 years, societal perspective)

4.2.2.Probabilistic analysis

Result of probabilistic analysis of Monte Carlo simulation 1,000 iterations are presented in cost effective acceptability curve figure 4.8 and scatter plot figure 4.9. Result show Haloperidol dec has higher probability (32-46%) of being better cost-effective option among all LAI within WTP threshold of 1,000,000 baht. New LAIs include Paliperidone LAI has higher probability of being more cost effective than Haloperidol dec when WTP threshold is increased to 3,000,000 baht.

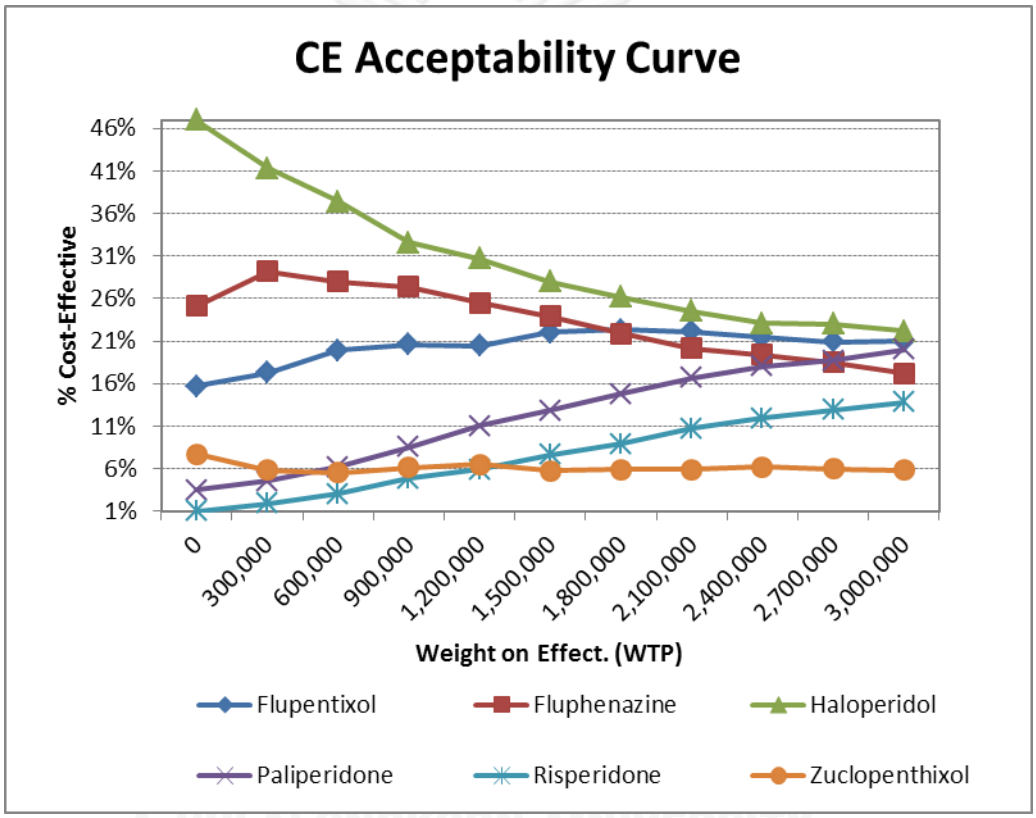


Figure 4.8 Cost effective acceptability curve (age of 25 years, time horizon of 10 years, societal perspective)

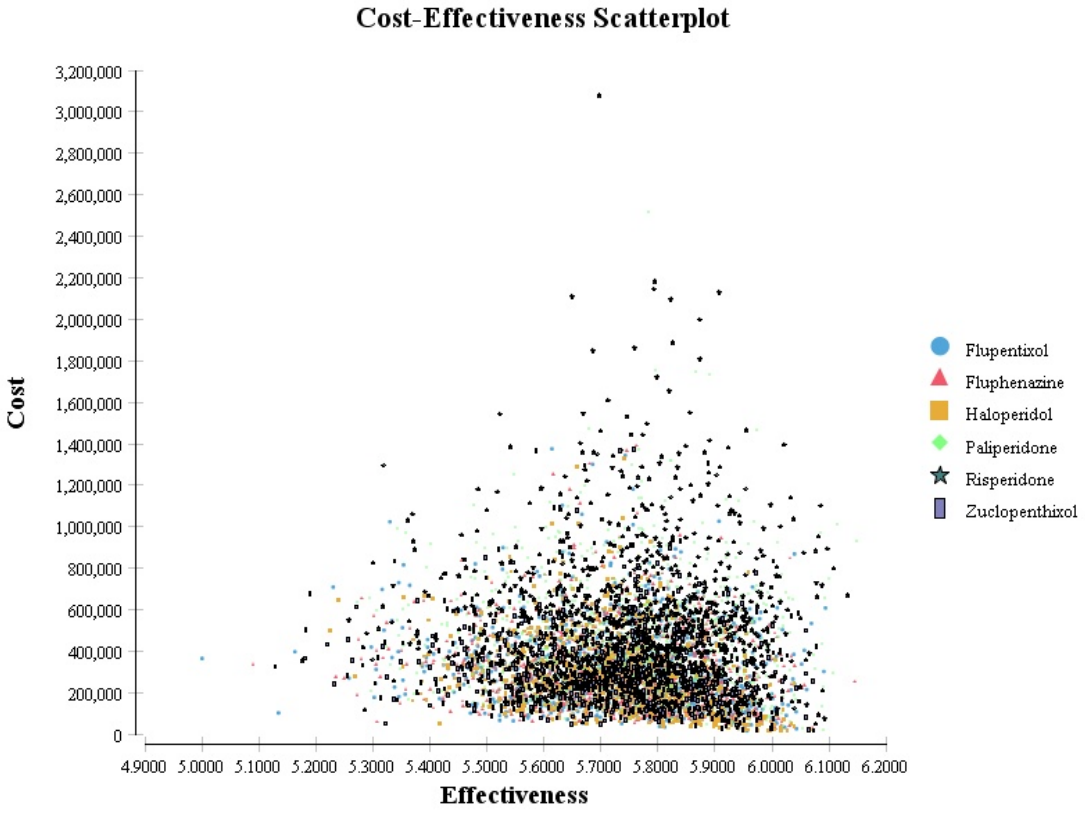


Figure 4.9 Scatter plot of Monte Carlo simulation 1000 iteration of cost and effectiveness of all LAIs (age of 25 years, time horizon of 10 years, societal perspective)

4.2.3. Tornado sensitivity analysis

One way sensitivity analysis is presented in Tornado diagram figure 4.10. Three parameters that have higher impact on the final net benefit include age at starting point, cost of 2nd line LAIs and cost of IPD. These parameters are slightly different from 75 year time horizon in term of impact size and ranking.

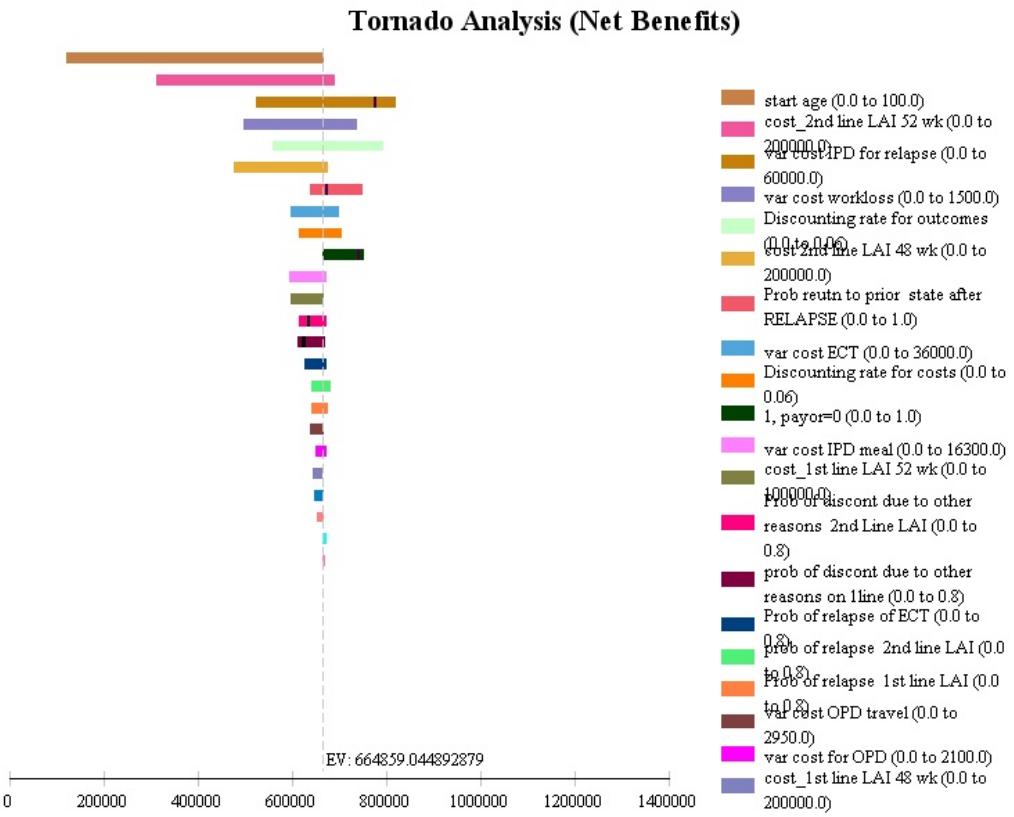


Figure 4.10 Tornado diagram (age of 25 years, time horizon of 10 years, societal perspective)

4.2.4.Price sensitivity analysis for Paliperidone LAI

Monte Carlo Simulation of cost effectiveness comparison is arranged between Paliperidone LAI and Haloperidol dec. Incremental cost effectiveness between two LAIs are analyzed at WTP threshold range. Probability of current pricing of Paliperidone LAI being more cost effectiveness than Haloperidol dec at WTP threshold of 170,000 and 530,000 baht are 11.5% and 16.9% respectively. More detail is presented in table 4.5 and figure 4.11

Table 4.5 Simulation report between Paliperidone LAI vs Haloperidol dec at WTP threshold of 170,000 and 530,000 baht (age of 25 years, time horizon of 10 years, societal perspective)

COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	95	0.095
C2	I	IE>0	IC>0	ICER<170000.0	20	0.020
C3	III	IE<0	IC<0	ICER>170000.0	21	0.021
C4	I	IE>0	IC>0	ICER>170000.0	658	0.658
C5	III	IE<0	IC<0	ICER<170000.0	0	0.000
C6	II	IE<0	IC>0	Inferior	206	0.206
Indiff	origin	IE=0	IC=0	0/0	0	0.000
COMPONENT	QUADRANT	INCREFF	INCRCOST	INCRCE	FREQUENCY	PROPORTION
C1	IV	IE>0	IC<0	Superior	95	0.095
C2	I	IE>0	IC>0	ICER<530000.0	74	0.074
C3	III	IE<0	IC<0	ICER>530000.0	17	0.017
C4	I	IE>0	IC>0	ICER>530000.0	604	0.604
C5	III	IE<0	IC<0	ICER<530000.0	4	0.004
C6	II	IE<0	IC>0	Inferior	206	0.206
Indiff	origin	IE=0	IC=0	0/0	0	0

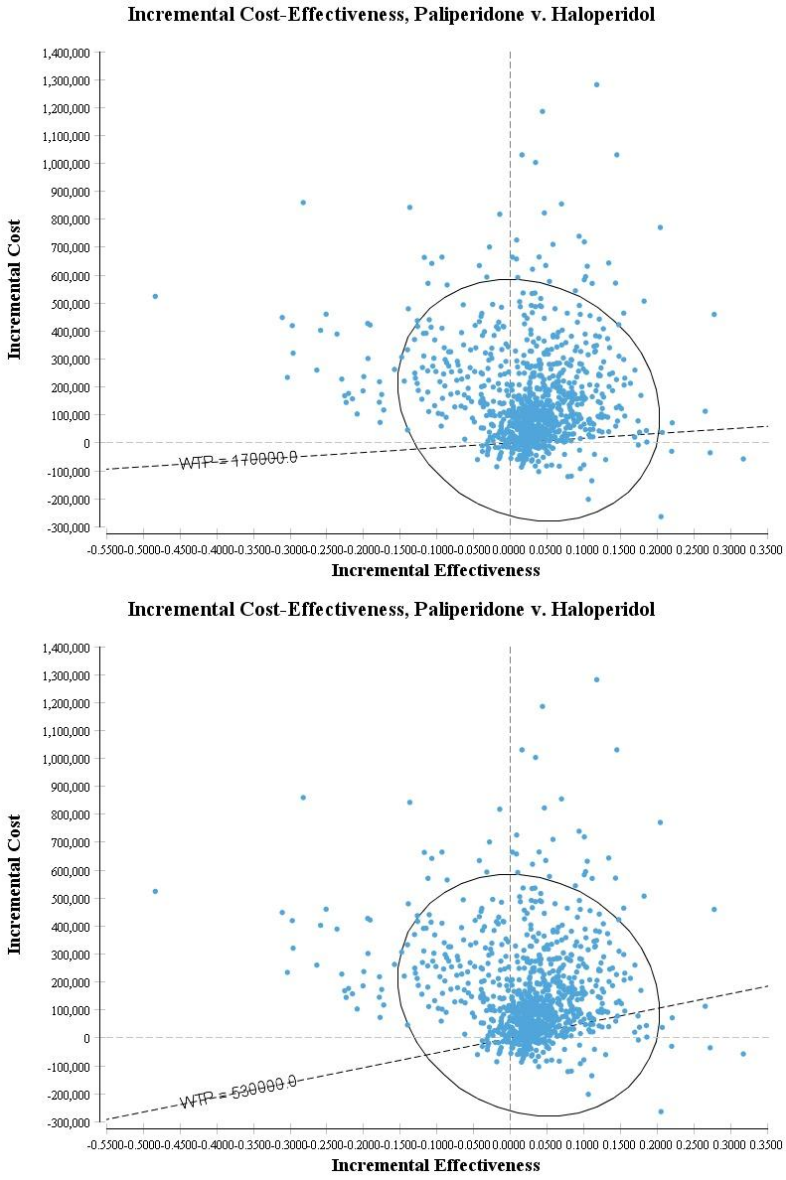


Figure 4.11 Scatter plot of ICER between Paliperidone LAI and Haloperidol dec with WTP threshold of 170,000 and 530,000 baht(age of 25 years, time horizon of 10 years, societal perspective)

CHAPTER 5
DISCUSSION AND CONCLUSION

This chapter will discuss our economic evaluation findings, study limitations, policy recommendation, final conclusion and suggestion for future researches.

5.1 Discussion

Our research study has two composites which are different from the other studies in this field. Firstly, this is the first economic evaluation study of LAIs for subjects with schizophrenia. Our study includes only LAIs (four of first generation LAIs and two second generation LAIs). Our Markov economic evaluation model follow NICE economic model which applied for oral antipsychotic drugs for the maintenance treatment of schizophrenia. We aim to assess which LAIs could be the first line treatment of schizophrenia with oral non-adherence. Secondly, Data input of three target outcomes; number of relapses, discontinuation due to intolerable side effects and other reasons are treated as completing risks model. These input data are generated from systematic review and mixed treatment comparison with completing risk model. The mixed treatment meta-analysis with completing risk model enables us to compare multiple interventions and multiple outcomes in one setting. Prior systemic review and meta-analysis works of antipsychotic drugs in schizophrenia mostly compares either pairwise treatments or multiple treatments per single outcome (86-88). Our meta-analysis is conducted under Bayesian framework to generate the probability of each outcome for 52 weeks for probabilistic decision model. Bayesian approach has advantages to fit with complex models that would be difficult to fit with frequentist (classical) approach

Result of our economic evaluation under deterministic framework show Haloperidol dec is the most cost effective LAIs for subjects with schizophrenia who are oral non-adherence. Haloperidol dec dominated all other LAIs under deterministic analysis both 10 year and over a life time horizon. The other four LAIs include Flupenazine dec , Flupentixol dec , Paliperidone LAI and Risperidone LAI might be the next choice if Haloperidol dec is not available. However ICERs of these alternatives exceed the maximum WTP threshold of 530,000 baht/QALY gained.

In probabilistic analysis with1,000 iteration of Monte Carlo simulations, Haloperidol dec demonstrates the highest probability of being the cost effective among the other LAIs with a

wide range up to 3,000,000 baht WTP threshold. This result is similar to both 10 year and over a lifetime horizon. However Paliperidone LAI and Risperidone LAI have higher probability of being cost effective than Haloperidol dec when WTP threshold exceed to 3,000,000 baht per QALY gained. As a result of deterministic and probabilistic analysis, Haloperidol dec is the most cost effective and should be a choice for 1st line treatment of schizophrenia that is oral non-adherence.

One way price sensitivity of Paliperidone LAI show if we need to replace Haloperdiol dec with Paliperidone LAI , Price of Paliperdione LAI need to reduce significantly. Our additional sub-analysis show the higher cost of hospital admission of relapse cases, higher indirect cost and higher non-medical direct cost will increase probability of Paliperidone LAI to be more cost effectiveness.

There are a few economic evaluation works of LAIs with different decision models available (89-93). Those outcomes were measured with different effectiveness unit, different economic analysis method, shorter time horizon and different comparators. Moreover transitional probability used in our model are generated from systematic and mixed treatment meta-analysis with completing risk model. So the result of our analysis is quite unique and may not compare directly with others.

NICE economic evaluation group has introduced this assessment model of oral antipsychotic drugs for relapse prevention in schizophrenia(1). We apply this model to our current work but we assess LAIs instead of oral antipsychotic drugs. Result of NICE U.K. work show Zotepine, Olanzapine and Paliperidone oral dosage form have better cost effective than Haloperidol oral dosage form. We accept the price gap among those comparators, all direct and indirect cost in NICE U.K. setting is much higher than ours.

Various uncertainty related to economic evaluation model are managed. HITAP standard guideline on economic evaluation is followed to minimize methodology uncertainty. We also apply probabilistic sensitivity analysis (PSA) to minimize parameters uncertainty.

5.2 Study limitation

Some limitations need to be considered. Double counting between subjects with relapse and subjects with discontinuation due to inefficacy might be seen. One of the major

drawbacks of our economic analysis was definition of clinical terms that used in our systematic review and meta-analysis works. Relapse definition was varied across 17 studies. PANSS score with more rigid criteria was used to quantify the clinical outcome in newer studies while clinical judgment was used in the older studies. Patient flow was not clarified clearly in the many studies, especially the older studies. This is another factor that should be aware when interpreting the economic result.

Our economic evaluation also assessed two different time horizon (10 years and 75 years – life time) to support our decision. Results of two time horizon are similar. Schizophrenia is characterized with phase of relapse alternating with phase of remission over a lifetime. One limitation on this approach was extrapolation of short term clinical data over a lifetime. Because there is no available long term data, only studies with duration of 24 - 96 weeks are included. The 52 week probability of three major outcomes ; relapse , discontinuation due to intolerable side effect and discontinuation due to other reasons, are generated based on these study and applied at the same rate to every year cycle over time horizon. With this assumption, overall effectiveness of LAIs may be overestimated because smaller effect size of antipsychotic in longer trials was seen in the prior evidence (86).

Our economic model is designed to fit with the real life situation by adding major adverse event ; EPS , into our economic assessment. The EPS adverse event will increase cost and decrease utility for any subjects who have experience of this adverse event. Nevertheless, our model omitted many other important adverse events include tardive dyskinesia, increase of prolactin hormone level, sexual dysfunction, weight gain, glucose intolerance as well as cardiovascular dysfunction. Lacking of incorporating these adverse events may affect the final cost effectiveness results. Especially, lacking of tardive dyskinesia, which has lasting effects and cause significant impairment on quality of life, might favor first generation LAIs unintentionally.

As described earlier, our model is similar to NICE model. But there is no information of utility of patients who have several relapses. Based on expert opinion, subjects with several relapses have worse quality of life and difficulty to treat as well. In order to support this concept, model is needed to add utility penalty every cycle.

As EQ-5D is non-specific generic utility tool which HITAP prefer to use in health economic evaluation. However we applied utility modified from PANSS score from Lenert study instead because this tool is more sensitive to schizophrenia than EQ-5D and this has been used in

NICE economic evaluation for schizophrenia as well. However future research on the appropriate utility tool for this particular group will help to standardize to compare QALY across diseases appropriately.

Building up the economic model is known to require many assumptions and some expert opinions include mutually exclusive condition of three main outcomes (subjects with relapse , discontinuation due to intolerable side effects and discontinuation due to other reasons) , number of cost data (cost of opportunity loss, cost of relapse management, cost of OPD visit per year for remission case etc) , number of side effect events during the therapy , duration per Markov simulation time , etc. When apply our result in general setting, user need to understand our study conditions well. Some environment and patient condition may not be addressed in our setting.

5.3 Policy recommendation

Our current work supports Haloperidol dec, which already listed in the national list of essential medicine (NLEM), to be the first line treatment of schizophrenia with oral non-adherence. This finding confirms the current list of LAIs in NLEM. If we consider the second generation LAIs; Paliperidone LAI to replace Haloperidol dec. as the first line option, all related costs including direct and indirect cost need to be revised. Instead of replacement strategy, we may consider the special subgroup of patients who fit with the second generation LAIs.

5.4 Conclusion

Our cohort Markov modelling for cost utility analysis of six LAIs is conducted under societal perspective. Model structure is modified from NICE economic model for schizophrenia. Three mutually exclusive outcomes include number of subjects with relapse, discontinuation with intolerable side effect, and due to other reasons are considered. The transitional probability of these outcomes are retrieved from systematic review and mixed treatment comparison meta-analysis with completing risk models. Bayesian framework is applied for meta-analysis work. Other published cost data accessed where available are adjusted to present values of the current analysis year 2014. This economic evaluation follow HITAP guideline. Markov economic modelling is conducted in TreeAgePro 2014 software. Result of the deterministic analysis confirms Haloperidol dec. is the most cost effective among 6 LAIs for first line

treatment of schizophrenia with oral non-adherence. Flupenazine dec., Flupentixol dec. Paliperidone LAI and Risperidone LAI. might be next alternatives if Haloperidol dec is not available, with ICER of 808,580, 3,995,921, 5,052,900, and 32,712,811 baht per QALY gained. However these ICERs exceed the willingness to pay threshold. However, Zuclopentixol dec is not cost effective option because ICER is -627,116 baht/QALY. Probabilistic analysis also suggests Haloperidol dec has highest probability of being cost effective, with wide range of the willingness to pay threshold, among the 6 LAIs for the first line treatment of schizophrenia with oral non-adherence. Higher probability of being more cost effective of Paliperidone LAI and Risperidone LAI than Haloperidol dec may be seen when WTP threshold increases up to 3,000,000 baht/QALY. Analysis results of both time horizons remain the same. In conclusion, Haloperidol dec is the most cost effective LAIs for the first line treatment in schizophrenia with oral non adherence under deterministic and probabilistic analysis.

5.5 Future researches

Potential researches are required in this field. Clinical data input on relapse prevention on individual selected study under systematic review and meta- analysis work need to be accessed and better clarified, to enable the comprehensive economic evaluation result. The new research may include more long term neurological and metabolic side effects to address uncertainty of economic results. New Markov economic model with micro-simulation may address patient intrinsic factors to meet the real life situation. Moreover future research on generic utility tool (EQ5D) calibrated with PANSS is required.

REFERENCES

1. NICE. Schizophrenia :core interventions in the treatment and management of schizophrenia in primary and secondary care (update). National Institue for Health and Clinical Excellence 2009; 82:1-399.
2. WHO. World Health Organization International Classification of Diseases(10th edition). Geneva ;WHO 1990.
3. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. PLoS Med. 2005;2(5):e141.
4. Siriwanarangsun. Prevalence of medical disorders in Thailand : A national survey 2003. Journal of mental Health of Thailand 2004;12(3):177-88.
5. Years of Lives with disability from Mentaal disorder, Thailand International Health Policy Program , Minitry of Public Health , Thailand 2004:21 pp.
6. Phanthunane P, Vos T, Whiteford H, Bertram M, Udomratn P. Schizophrenia in Thailand: prevalence and burden of disease. Popul Health Metr. 2010;8:24.
7. American Psychiatirc Association Dignostic and Staistical Manual of Mental Disorders (DSM-IV). APA. 1994;4th edn(Washhington):DC.
8. Tandon R, Targum SD, Nasrallah HA, Ross R. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. Journal of psychiatric practice. 2006;12(6):348-63.
9. Janicak PGD, John M.; Preskorn, Sheldon H.; Ayd, Frank J., Jr. , . Principles and practice of psychopharmacotherapy. Williams & Wilkins Co 1993; xxiii,:592pp.
10. Kane JM, Woerner M, Lieberman J. Tardive dyskinesia: prevalence, incidence, and risk factors. Psychopharmacology Suppl. 1985;2:72-8.
11. Suvisaari JM, Saarni SI, Perala J, Suvisaari JV, Harkanen T, Lonnqvist J, et al. Metabolic syndrome among persons with schizophrenia and other psychotic disorders in a general population survey. The Journal of clinical psychiatry. 2007;68(7):1045-55.
12. Meaney AM, O'Keane V. Bone mineral density changes over a year in young females with schizophrenia: relationship to medication and endocrine variables. Schizophrenia research. 2007;93(1-3):136-43.
13. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? Psychological medicine. 2003;33(1):97-110.
14. Disyavanish C. SM, Karnjanathanalers N.,Theeramoke v.,Kongsakon R.Kittiratanapaibool P., Raktrakool R., Pratumsri V. Thai schizophrenia Treatment guideline Beyond Enterprise 2001:67-90.

15. Osterberg L, Blaschke T. Adherence to medication. The New England journal of medicine. 2005;353(5):487-97.
16. Keith SJ, Kane JM. Partial compliance and patient consequences in schizophrenia: our patients can do better. The Journal of clinical psychiatry. 2003;64(11):1308-15.
17. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. The New England journal of medicine. 2005;353(12):1209-23.
18. Lacro JP, Dunn LB, Dolder CR, Leckband SG, Jeste DV. Prevalence of and risk factors for medication nonadherence in patients with schizophrenia: a comprehensive review of recent literature. The Journal of clinical psychiatry. 2002;63(10):892-909.
19. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatric services. 1998;49(2):196-201.
20. Cramer JA. Optimizing long-term patient compliance. Neurology. 1995;45(2 Suppl 1):S25-8.
21. Bundhamchareon K TYVT, Begg S. Burden of disease and injuries in Thailand ; priority setting for policy. Ministry of Public Health. 2002;Nonthaburi.
22. Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. The Journal of clinical psychiatry. 2005;66(9):1122-9.
23. Kongsakon R KB. Cost analysis of treatment for schizophrenic patients in social security scheme, Thailand ASEAN Journal of Psychiatry. 2007;8 :(2):118-23.
24. Phanthunane P, Vos T, Whiteford H, Bertram M. Cost-effectiveness of pharmacological and psychosocial interventions for schizophrenia. Cost Eff Resour Alloc. 2011;9:6.
25. Drummond M.F. SMJ, Torrance G.W. , O'Brien B.J. Stoddart G.L. Economomic evaluation using decision analystic modelling , chapter 6. Methods for the economic Evaluation of Health Care Programmes. 2005:277-309.
26. von Neumann J. MO. Theory of Games and Economic Behavior (Commemorative Edition) Princeton, NJ, Princeton University Press;. 1944.
27. Heeg B.M.S. DJ, Buskens E., Caleo S., Charro F.D. Modelling Approaches;The Case of Schizophrenia PharmacoEconomics. 2008;26(8):633-48.
28. Glazer WM, Ereshefsky L. A pharmacoeconomic model of outpatient antipsychotic therapy in "revolving door" schizophrenic patients. The Journal of clinical psychiatry. 1996;57(8):337-45.
29. Vera-Llonch M, Delea TE, Richardson E, Rupnow M, Grogg A, Oster G. Outcomes and costs of risperidone versus olanzapine in patients with chronic schizophrenia or

schizoaffective disorders: a Markov model. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2004;7(5):569-84.

30. Heeg B, Buskens E, Knapp M, van Aalst G, Dries PJ, de Haan L, et al. Modelling the treated course of schizophrenia: development of a discrete event simulation model. PharmacoEconomics. 2005;23 Suppl 1:17-33.
31. Buxton MJ, Drummond MF, Van Hout BA, Prince RL, Sheldon TA, Szucs T, et al. Modelling in economic evaluation: an unavoidable fact of life. Health Econ. 1997;6(3):217-27.
32. Teerawattananon Y, Chaikledkaew U. Thai health technology assessment guideline development. Journal of the Medical Association of Thailand 2008;91 Suppl 2:S11-5.
33. Cooper N, Coyle D, Abrams K, Mugford M, Sutton A. Use of evidence in decision models: an appraisal of health technology assessments in the UK since 1997. J Health Serv Res Policy. 2005;10(4):245-50.
34. The periodic health examination. Canadian Task Force on the Periodic Health Examination. Can Med Assoc J. 1979;121(9):1193-254.
35. Kongsakon R, Leelahanaj T, Price N, Birinyi-Strachan L, Davey P. Cost analysis of the treatment of schizophrenia in Thailand: a simulation model comparing olanzapine, risperidone, quetiapine, ziprasidone and haloperidol. Journal of the Medical Association of Thailand = Chotmaihet thangphaet. 2005;88(9):1267-77.
36. Lehman AF. JAL, L. B. Dixon,T. H. McGlashan, A. L. Miller,O. Perkins, J Kreyenbuhl. Practice guideline for the treatment of patients with schizophrenia American Psychiatric Association. 2004(Second Edition):154 pp.
37. Central nervous system, Thai national formulary 2010;1:234pp.
38. Kane JM, Aguglia E, Altamura AC, Ayuso Gutierrez JL, Brunello N, Fleischhacker WW, et al. Guidelines for depot antipsychotic treatment in schizophrenia. European Neuropsychopharmacology Consensus Conference in Siena, Italy. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 1998;8(1):55-66.
39. WHO. Pharmacological treatment of mental disorders in primary health care. World Health Organization. 2009.
40. WHO. ATC/DDD index WHO colaborating center for drug statistics methodology. 2014.
41. Thai National Formulary, Central nervous system Bangkok: TFDA. MOPH; 2010.vol 1, 234 p.
42. Clinical Practice Guideline, Thai schizophrenia Treatment guideline. 2000:1-27.

43. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Statistics in medicine. 2004;23(20):3105-24.
44. Ades AE, Mavranezouli I, Dias S, Welton NJ, Whittington C, Kendall T. Network meta-analysis with competing risk outcomes. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2010;13(8):976-83.
45. Jansen JP, Crawford B, Bergman G, Stam W. Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2008;11(5):956-64.
46. Leucht S, Cipriani A, Spineli L, Mavridis D, Örey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. The Lancet.382(9896):951-62.
47. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Controlled clinical trials. 1996;17(1):1-12.
48. Sutton AJ AK, Jones DR, Sheldon TA, Song F Methods for Meta-anlysis in medical research. . London: Wiley; 2000.
49. Hirsch SR, Gaind R, Rohde PD, Stevens BC, Wing JK. Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. Report to the Medical Research Council Committee on Clinical Trials in Psychiatry. British medical journal. 1973;1(5854):633-7.
50. Odejide OA, Aderounmu AF. Double-blind placebo substitution: withdrawal of fluphenazine decanoate in schizophrenic patients. The Journal of clinical psychiatry. 1982;43(5):195-6.
51. Sampath G, Shah A, Krska J, Soni SD. Neuroleptic discontinuation in the very stable schizophrenic patient: Relapse rates and serum neuroleptic levels. Human Psychopharmacology: Clinical and Experimental. 1992;7(4):255-64.
52. Eberhard G, Hellbom E. Haloperidol decanoate and flupenthixol decanoate in schizophrenia. A long-term double-blind cross-over comparison. Acta psychiatrica Scandinavica. 1986;74(3):255-62.
53. Chouinard G, Annable L, Campbell W. A randomized clinical trial of haloperidol decanoate and fluphenazine decanoate in the outpatient treatment of schizophrenia. Journal of clinical psychopharmacology. 1989;9(4):247-53.
54. Chouinard G, Annable L, Campbell W, Boisvert D, Bradwejn J. A Double–Blind Controlled Clinical Trial of Haloperidol Decanoate and Fluphenazine Decanoate in

the Maintenance Treatment of Schizophrenia. Psychiatry the State of the Art: Springer; 1985. p. 759-61.

55. Cookson JC, Kennedy NM, Gribbon D. Weight gain and prolactin levels in patients on long-term antipsychotic medication: a double-blind comparative trial of haloperidol decanoate and fluphenazine decanoate. International clinical psychopharmacology. 1986;1 Suppl 1:41-51.
56. Jolley AG, Hirsch SR, Morrison E, McRink A, Wilson L. Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical and social outcome at two years. Bmj. 1990;301(6756):837-42.
57. Jolley AG, Hirsch SR, McRink A, Manchanda R. Trial of brief intermittent neuroleptic prophylaxis for selected schizophrenic outpatients: clinical outcome at one year. Bmj. 1989;298(6679):985-90.
58. Kissling W, Moller HJ, Walter K, Wittmann B, Krueger R, Trenk D. Double-blind comparison of haloperidol decanoate and fluphenazine decanoate effectiveness, side-effects, dosage and serum levels during a six months' treatment for relapse prevention. Pharmacopsychiatry. 1985;18(3):240-5.
59. McKane JP, Robinson AD, Wiles DH, McCreadie RG, Stirling GS. Haloperidol decanoate v. fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. The British journal of psychiatry : the journal of mental science. 1987;151:333-6.
60. Sharma SK JS. A comparison of fluphenazine decanoate and haloperidol decanoate in chronic schizophrenia. . British Journal of Clinical Research 1991(2):177-86.
61. Fleischhacker WW, Gopal S, Lane R, Gassmann-Mayer C, Lim P, Hough D, et al. A randomized trial of paliperidone palmitate and risperidone long-acting injectable in schizophrenia. The International Journal of Neuropsychopharmacology. 2012;15(01):107-18.
62. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophrenia research. 2010;116(2-3):107-17.
63. Pinto R, Bannerjee A, Ghosh N. A double-blind comparison of flupenthixol decanoate and fluphenazine decanoate in the treatment of chronic schizophrenia. Acta psychiatrica Scandinavica. 1979;60(4):313-22.
64. Wistedt B, Ranta J. Comparative double-blind study of flupenthixol decanoate and fluphenazine decanoate in the treatment of patients relapsing in a schizophrenic symptomatology. Acta psychiatrica Scandinavica. 1983;67(6):378-88.

65. Wistedt B, Koskinen T, Thelander S, Nerdrum T, Pedersen V, Mølbjerg C. Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia: a double-blind multicentre study. Acta psychiatrica Scandinavica. 1991;84(1):14-21.
66. Eklund K, Forsman A. Minimal effective dose and relapse--double-blind trial: haloperidol decanoate vs. placebo. Clinical neuropharmacology. 1991;14 Suppl 2:S7-12; discussion S-5.
67. Dencker SJ, Lepp M, Malm U. Clopenthixol and flupenthixol depot preparations in outpatient schizophrenics. I. A one year double-blind study of clopenthixol decanoate and flupenthixol palmitate. Acta psychiatrica Scandinavica Supplementum. 1980;279:10-28.
68. Viguera AC, Baldessarini RJ, Hegarty JD, van Kammen DP, Tohen M. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. Archives of general psychiatry. 1997;54(1):49-55.
69. Tharyan P, Adams CE. Electroconvulsive therapy for schizophrenia. The Cochrane database of systematic reviews. 2005(2):Cd000076.
70. David A, Adams CE, Eisenbruch M, Quraishi S, Rathbone J. Depot fluphenazine decanoate and enanthate for schizophrenia. The Cochrane database of systematic reviews. 2005(1):CD000307.
71. Quraishi S, David A. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. The Cochrane database of systematic reviews. 2000(2):CD001470.
72. Quraishi S, David A. Depot haloperidol decanoate for schizophrenia. The Cochrane database of systematic reviews. 2000(2):CD001361.
73. Coutinho E, Fenton M, Quraishi S. Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. The Cochrane database of systematic reviews. 2000(2):Cd001164.
74. Nussbaum AM, Stroup TS. Paliperidone palmitate for schizophrenia. The Cochrane database of systematic reviews. 2012;6:CD008296.
75. Hosalli P, Davis JM. Depot risperidone for schizophrenia. The Cochrane database of systematic reviews. 2003(4):CD004161.
76. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. Epidemiol Rev. 2008;30:67-76.
77. WHO. Life expectancy by country ;Thailand -life table 2014 [April 2014]. Available from: http://apps.who.int/gho/data/view.main.61640
78. Mavranezouli I. A review and critique of studies reporting utility values for schizophrenia-related health states. PharmacoEconomics. 2010;28(12):1109-21.

79. Lenert LA, Sturley AP, Rapaport MH, Chavez S, Mohr PE, Rupnow M. Public preferences for health states with schizophrenia and a mapping function to estimate utilities from positive and negative symptom scale scores. Schizophrenia research. 2004;71(1):155-65.
80. Lenert LA, Rupnow MF, Elnitsky C. Application of a disease-specific mapping function to estimate utility gains with effective treatment of schizophrenia. Health and quality of life outcomes. 2005;3:57.
81. DMSIC. purchasing price references for general hospitals in Thailand Ministry of Public Health. 2014.
82. Unit cost of health service in department of mental health, Ministry of Public Health. Nonthaburi Thailand Department of mental health , Ministry of Public Health 2005.
83. Puapanprasert B. Sanichwankul K PS. Cost of psychiatry care by casemix approach, Suanprung psychiatry hospital. Nonthaburi , Thailand Health System Research Institue 2003.
84. Kongsakon R RS. Olanzapine versus Haloperidol in the treatment of refractory schizophrenia : a cost effectiveness analysis. J Psychiatr Assoc Thailand 2000;45(1):71-85.
85. Claxton K, Sculpher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ. 2005;14(4):339-47.
86. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Salanti G, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012;379(9831):2063-71.
87. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet. 2013;382(9896):951-62.
88. Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, et al. Long-acting injectable vs oral antipsychotics for relapse prevention in schizophrenia: a meta-analysis of randomized trials. Schizophrenia bulletin. 2014;40(1):192-213.
89. Laux G, Heeg B, van Hout BA, Mehnert A. Costs and effects of long-acting risperidone compared with oral atypical and conventional depot formulations in Germany. PharmacoEconomics. 2005;23 Suppl 1:49-61.
90. Achilla E, McCrone P. The cost effectiveness of long-acting/extended-release antipsychotics for the treatment of schizophrenia: a systematic review of economic evaluations. Applied health economics and health policy. 2013;11(2):95-106.

91. Yang YK, Tarn YH, Wang TY, Liu CY, Laio YC, Chou YH, et al. Pharmacoeconomic evaluation of schizophrenia in Taiwan: model comparison of long-acting risperidone versus olanzapine versus depot haloperidol based on estimated costs. Psychiatry and clinical neurosciences. 2005;59(4):385-94.
92. Einarson TR, Zilbershtein R, Skoupa J, Vesela S, Garg M, Hemels ME. Economic and clinical comparison of atypical depot antipsychotic drugs for treatment of chronic schizophrenia in the Czech Republic. Journal of medical economics. 2013;16(9):1089-95.
93. Einarson TR, Geitona M, Chaidemenos A, Karpouza V, Mougiakos T, Paterakis P, et al. Pharmacoeconomic analysis of paliperidone palmitate for treating schizophrenia in Greece. Annals of general psychiatry. 2012;11(1):18.

APPENDIX

Appendix A

WinBUGS codes used for mixed treatment comparison with completing risks

A. Random effect model

```
model{
# code for treatment effects relative to placebo (treatment 1)
for(i in 1:34){ # LOOP OVER ARMS
                    r[i,1:4] ~ dmulti(p[i,1:4],n[i]) # likelihood
                    slam[i] <- sum(lam[,i]) # sum of the 3 hazard rates
          for (m in 1:3) { # LOOP OVER 3 ENDPOINTS
                              p[i,m] <- lam[m,i] * (1-exp(-slam[i]*w[i]/52)) / slam[i] # cumulative
                    pr(failed) at each end point
                              log(lam[m,i]) <- theta[m,i] # log rates for each arm, each end point
                              theta[m,i] <- mu[m,s[i]] + delta[m,i]*(1-equals(t[i],b[i])) # baseline &
                    treatment effects
                              delta[m,i] ~ dnorm(md[m,i],pr[m])#random outcome- & trial-specific
                    relative effect
                              md[m,i] <- d[m,t[i]] - d[m,b[i]] # mean of the random effect
                              rhat[m,i] <- p[i,m]*n[i]
                              dev[m,i] <- -2*r[i,m]*log(rhat[m,i]/r[i,m])
                            } # END LOOP OVER 3 ENDPOINTS
                    p[i,4] <- 1- sum(p[i,1:3]) # pr(no failure)
                } # END LOOP OVER ARMS

for (m in 1:3) { resdev[m] <- sum(dev[m,])}

totresdev <- sum(resdev[])

for (m in 1:3) {d[m,1] <- 0
          for (k in 2:7) {d[m,k] ~ dnorm(0,0.001) # priors for treatment effects
                              log(hazr[m,k]) <- d[m,k] # hazard ratios
       }
          for (j in 1:17) {mu[m,j] ~ dnorm(0,0.001) } # priors for baselines
                    }
for (m in 1:3) {pr[m] <- pow(sd[m],-2)
                              sd[m] ~ dunif(0,5)
                    }

# code for predicted effects at 52 weeks, on a probability scale. baseline risks in mub[1:3,7]#
for (m in 1:3) {d.new[m,1] <- 0
                    A[m] ~ dnorm(meanA[m],precA[m])
          for (k in 2:7) {d.new[m,k] ~ dnorm(d[m,k],pr[m])}
          for (k in 1:7) {theta52[m,k] <- A[m] + d.new[m,k]
                              log(lam52[m,k]) <- theta52[m,k]
                               p52[m,k] <- lam52[m,k] * (1-exp(-slam52[k])) / slam52[k]
                               }
                     }
for (k in 1:7) {slam52[k] <- sum(lam52[1:3,k])
                    p52[4,k] <- 1-sum(p52[1:3,k])
           for (m in 1:4){rank52[m,k] <- rank(p52[m,],k) } #Smallest is best (i.e. rank 1) except
           outcome#4 prefer larger rank number
```

```
            for (m in 1:3){ best[m,k] <- equals(rank52[m,k],1)} #Record whether best (rank=1 for
outcomes m = 1,2,3)
                best[4,k] <- equals(rank52[4,k],7) #Record whether best (rank = 8 for outcome m = 4)
                 }

#All pairwise log hazard ratios and hazard ratios
for (m in 1:3){
 for (c in 1:(NT-1)){
 for (k in (c+1):NT){
 lhr[m,c,k] <- d[m,k] - d[m,c]
 log(hr[m,c,k]) <- lhr[m,c,k]
    }
   }
                 }
}

# initial values 1
list(d=structure(.Data=c(NA,1,3,0,0,0,0,
                         NA,1,2,3, 0,5,0,
                         NA,0,0,3, -1,0,0),.Dim=c(3,7)),
    sd=c(1,1,1),
    mu=structure(.Data=c(0,0,0,-1,0, 0,0,0,0,0, 2,3,4,0,0, 7,0,
                          0,0,3,0,0, 0,2,0,1,0, 0,2,0,-1,0, 0,0,
                          0,0,.5,0,0, 0,0,0,0,0, 0,-5,0,0,0, 0,0),.Dim=c(3,17)),
        delta = structure(.Data=c(0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0,
0,0,0,0,
                          0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,
                         0,0,0,0,2, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0, 0,0,0,0,0,
0,0,0,0),.Dim=c(3,34)),
    A=c(1,1,1),
   d.new=structure(.Data=c(NA,0,0,-3, 0,0,0,
                           NA,0,0,0, 0,2,0,
                           NA,0,0.5,0, 0,0,0),.Dim=c(3,7))
)


# initial values 2
list(d=structure(.Data=c(NA,-1,-1,-1, -1,-1,-1,
                         NA,-1,-1,-1, -1,-1,-1,
                         NA,-1,-1,-1, -1,-1,-1),.Dim=c(3,7)),
 sd=c(2,2,2),
    mu=structure(.Data=c(-1,-1,-1,-1,-1, -1,-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,
                          -1,-1,-1,-1,-1, -1,-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,
                          -1,-1,-1,-1,-1, -1,-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1),.Dim=c(3,17)),
        delta = structure(.Data=c(-1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-
1, -1,-1,-1,-1,-1, -1,-1,-1,-1,
                         -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-
1,-1, -1,-1,-1,-1,
                          -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,-
1,-1,-1, -1,-1,-1,-1),       .Dim=c(3,34)),
     A=c(0,0,0),
   d.new=structure(.Data=c(NA,-1,-1,-1,-1,-1,-1,
                           NA,-1,-1,-1,-1,-1,-1,
                           NA,-1,-1,-1,-1,-1,-1),.Dim=c(3,7)),

)
```

B. Fixed effect model

```
model{
# code for treatment effects relative to placebo (treatment 1)
for(i in 1:34){ # LOOP OVER ARMS
                    r[i,1:4] ~ dmulti(p[i,1:4],n[i]) # likelihood
                    slam[i] <- sum(lam[,i]) # sum of the 3 hazard rates
          for (m in 1:3) { # LOOP OVER 3 ENDPOINTS
                              p[i,m] <- lam[m,i] * (1-exp(-slam[i]*w[i]/52)) / slam[i] # cumulative
                    pr(failed) at each end point
                              log(lam[m,i]) <- theta[m,i] # log rates for each arm, each end point
                              theta[m,i] <- mu[m,s[i]] + d[m,t[i]]-d[m,b[i]] # baseline & treatment effects
                              rhat[m,i] <- p[i,m]*n[i]
                              dev[m,i] <- -2*r[i,m]*log(rhat[m,i]/r[i,m])
                            } # END LOOP OVER 3 ENDPOINTS
                    p[i,4] <- 1- sum(p[i,1:3]) # pr(no failure)
                } # END LOOP OVER ARMS

for (m in 1:3) { resdev[m] <- sum(dev[m,])}

totresdev <- sum(resdev[])


for (m in 1:3) {d[m,1] <- 0
          for (k in 2:7) {d[m,k] ~ dnorm(0,0.001) # priors for treatment effects
                              log(hazr[m,k]) <- d[m,k] # hazard ratios
                              }
                    sd[m] ~ dunif(0,5)
                    pr[m] <- pow(sd[m],-2)
          for (j in 1:17) {mu[m,j] ~ dnorm(0,0.001) } # priors for baselines
                    }
# code for predicted effects at 52 weeks, on a probability scale. baseline risks in mub[1:3,7]
for (m in 1:3) {
                    A[m] ~ dnorm(meanA[m],precA[m])
          for (k in 1:7) {theta52[m,k] <- A[m] + d[m,k]
                              log(lam52[m,k]) <- theta52[m,k]
                              p52[m,k] <- lam52[m,k] * (1-exp(-slam52[k])) / slam52[k]
                              }
                    }

for (k in 1:7) {slam52[k] <- sum(lam52[1:3,k])
                    p52[4,k] <- 1-sum(p52[1:3,k])
          for (m in 1:4){rank52[m,k] <- rank(p52[m,],k) #Smallest is best (i.e. rank 1)}
          for (m in 1:3){ best[m,k] <- equals(rank52[m,k],1)} #Record whether best (rank=1 for
outcomes m = 1,2,3)
                    best[4,k] <- equals(rank52[4,k],7) #Record whether best (rank = 8 for outcome m = 4)
                    }

#All pairwise log hazard ratios and hazard ratios
for (m in 1:3){
 for (c in 1:(NT-1)){
  for (k in (c+1):NT){
    lhr[m,c,k] <- d[m,k] - d[m,c]
    log(hr[m,c,k]) <- lhr[m,c,k]
     }
                                  }
```

```
                    }
}

# initial values 1
list(d=structure(.Data=c(NA,1,3,0,0,0,0,
                         NA,1,2,3, 0,5,0,
                         NA,0,0,3, -1,0,0),.Dim=c(3,7)),
    sd=c(1,1,1),
    mu=structure(.Data=c(0,0,0,-1,0, 0,0,0,0,0, 2,3,4,0,0, 7,0,
                          0,0,3,0,0, 0,2,0,1,0, 0,2,0,-1,0, 0,0,
                          0,0,.5,0,0, 0,0,0,0,0, 0,-5,0,0,0, 0,0),.Dim=c(3,17)),

    A=c(1,1,1),

)


# initial values 2
list(d=structure(.Data=c(NA,-1,-1,-1, -1,-1,-1,
                         NA,-1,-1,-1, -1,-1,-1,
                         NA,-1,-1,-1, -1,-1,-1),.Dim=c(3,7)),
 sd=c(0.5,0.5,0.5),
    mu=structure(.Data=c(-1,-1,1,-1,-1, -1,-1,-1,-1,-1, 1,-1,-1,-1,-1, -1,-1,
                          -1,-1,-1,-1,2, -1,-1,-1,-1,-1, -1,-1,-1,-1,-1, -1,-1,
                          -1,-1,-1,-1,-1, -1,-1,2,-1,1, 1,-1,-1,-1,-1, -1,-1),.Dim=c(3,17)),

     A=c(0,0,0),


)
```

Appendix B

Mixed treatment meta-analysis outputs

Table B.1 WinBUGS random effect output

Winbug Random 17 studies outcome completing risk model								
node	mean	sd	MC	2.50%	median	97.50%	start	sample
best[1,1]	0.002	0.046	3.32E-04	0	0	0	60001	20000
best[1,2]	0.097	0.296	0.002235	0	0	1	60001	20000
best[1,3]	0.115	0.319	0.002101	0	0	1	60001	20000
best[1,4]	0.072	0.259	0.00215	0	0	1	60001	20000
best[1,5]	0.183	0.386	0.002993	0	0	1	60001	20000
best[1,6]	0.184	0.387	0.003097	0	0	1	60001	20000
best[1,7]	0.347	0.476	0.004471	0	0	1	60001	20000
best[2,1]	0.048	0.213	0.001875	0	0	1	60001	20000
best[2,2]	0.057	0.232	0.001721	0	0	1	60001	20000
best[2,3]	0.136	0.343	0.003655	0	0	1	60001	20000
best[2,4]	0.156	0.362	0.003479	0	0	1	60001	20000
best[2,5]	0.314	0.464	0.005332	0	0	1	60001	20000
best[2,6]	0.095	0.293	0.002278	0	0	1	60001	20000
best[2,7]	0.196	0.397	0.003494	0	0	1	60001	20000
best[3,1]	0.051	0.219	0.001812	0	0	1	60001	20000
best[3,2]	0.068	0.251	0.001744	0	0	1	60001	20000
best[3,3]	0.097	0.296	0.002532	0	0	1	60001	20000
best[3,4]	0.092	0.289	0.002681	0	0	1	60001	20000
best[3,5]	0.237	0.425	0.003673	0	0	1	60001	20000
best[3,6]	0.150	0.357	0.002813	0	0	1	60001	20000
best[3,7]	0.305	0.461	0.004913	0	0	1	60001	20000
best[4,1]	0.029	0.168	0.001201	0	0	1	60001	20000
best[4,2]	0.067	0.249	0.001873	0	0	1	60001	20000
best[4,3]	0.091	0.288	0.002886	0	0	1	60001	20000
best[4,4]	0.066	0.248	0.001838	0	0	1	60001	20000
best[4,5]	0.296	0.457	0.003775	0	0	1	60001	20000
best[4,6]	0.200	0.400	0.003527	0	0	1	60001	20000
best[4,7]	0.251	0.434	0.003965	0	0	1	60001	20000
d[1,2]	-0.5963	0.6847	0.01396	-2.014	-0.5748	0.7307	60001	20000
d[1,3]	-0.6388	1.169	0.0209	-3.081	-0.6068	1.592	60001	20000
d[1,4]	-0.3778	0.8771	0.02499	-2.186	-0.3497	1.282	60001	20000
d[1,5]	-1.167	1.414	0.02365	-4.055	-1.153	1.6	60001	20000
d[1,6]	-1.25	1.374	0.009617	-4.003	-1.254	1.524	60001	20000
d[1,7]	-1.527	1.931	0.01446	-5.445	-1.522	2.412	60001	20000
d[2,2]	0.4327	0.6899	0.01104	-0.9431	0.4285	1.859	60001	20000
d[2,3]	0.01697	1.021	0.02054	-2.183	0.1141	1.954	60001	20000
d[2,4]	-0.0823	0.717	0.009199	-1.563	-0.0732	1.432	60001	20000
d[2,5]	-0.7211	1.378	0.01931	-3.519	-0.6909	1.952	60001	20000
d[2,6]	0.2463	1.264	0.01678	-2.242	0.2201	2.807	60001	20000
d[2,7]	0.1606	1.494	0.01792	-2.772	0.1401	3.149	60001	20000
d[3,2]	0.3215	0.4453	0.006016	-0.5372	0.3061	1.249	60001	20000
d[3,3]	0.2406	0.6783	0.01044	-1.185	0.2471	1.634	60001	20000
d[3,4]	0.3139	0.5557	0.008036	-0.734	0.2527	1.547	60001	20000
d[3,5]	-0.3968	1.094	0.01083	-2.59	-0.3838	1.78	60001	20000
d[3,6]	-0.2186	0.7501	0.005459	-1.761	-0.2283	1.348	60001	20000
d[3,7]	-0.2098	2.084	0.02639	-4.391	-0.2066	3.993	60001	20000
d.new[1,2]	-0.5914	1.512	0.0178	-3.713	-0.5647	2.392	60001	20000
d.new[1,3]	-0.6467	1.806	0.02316	-4.295	-0.6185	2.892	60001	20000
d.new[1,4]	-0.3671	1.612	0.02625	-3.711	-0.3383	2.841	60001	20000
d.new[1,5]	-1.165	1.959	0.02549	-5.157	-1.146	2.674	60001	20000

d.new[1,6]	-1.255	1.949	0.01386	-5.178	-1.26	2.666	60001	20000
d.new[1,7]	-1.528	2.358	0.01681	-6.267	-1.547	3.245	60001	20000
d.new[2,2]	0.4352	1.012	0.01184	-1.645	0.4386	2.538	60001	20000
d.new[2,3]	0.01897	1.261	0.02172	-2.697	0.1281	2.469	60001	20000
d.new[2,4]	-0.07912	1.024	0.0101	-2.234	-0.0695	2.071	60001	20000
d.new[2,5]	-0.732	1.569	0.02033	-3.918	-0.7085	2.344	60001	20000
d.new[2,6]	0.2404	1.463	0.01771	-2.632	0.2096	3.163	60001	20000
d.new[2,7]	0.1589	1.658	0.01843	-3.107	0.1359	3.52	60001	20000
d.new[3,2]	0.3246	0.8235	0.008006	-1.385	0.3061	2.011	60001	20000
d.new[3,3]	0.2373	0.9804	0.01198	-1.87	0.2417	2.233	60001	20000
d.new[3,4]	0.3181	0.8915	0.009244	-1.458	0.2434	2.216	60001	20000
d.new[3,5]	-0.4024	1.303	0.01218	-3.02	-0.396	2.24	60001	20000
d.new[3,6]	-0.2203	1.019	0.007426	-2.316	-0.2241	1.921	60001	20000
d.new[3,7]	-0.2166	2.195	0.0267	-4.657	-0.2123	4.218	60001	20000
hr[1,1,2]	0.6979	0.6411	0.008237	0.134	0.563	2.076	60001	20000
hr[1,1,3]	1.103	4.544	0.03283	0.046	0.545	4.915	60001	20000
hr[1,1,4]	1.006	1.313	0.02103	0.112	0.705	3.604	60001	20000
hr[1,1,5]	1.128	16.13	0.1129	0.017	0.316	4.951	60001	20000
hr[1,1,6]	1.217	18.13	0.1255	0.018	0.285	4.591	60001	20000
hr[1,1,7]	8.102	323.3	2.256	0.004	0.218	11.160	60001	20000
hr[1,2,3]	1.578	2.754	0.02233	0.1304	0.9731	6.49	60001	20000
hr[1,2,4]	1.53	1.322	0.01629	0.3439	1.256	4.24	60001	20000
hr[1,2,5]	1.47	9.249	0.06265	0.04491	0.5693	7.046	60001	20000
hr[1,2,6]	4.775	157.3	1.111	0.02529	0.5077	12.46	60001	20000
hr[1,2,7]	38.29	2241	15.77	0.006373	0.3876	25.55	60001	20000
hr[1,3,4]	2.18	6.103	0.04176	0.1839	1.31	8.81	60001	20000
hr[1,3,5]	1.355	6.326	0.0454	0.05608	0.5838	6.433	60001	20000
hr[1,3,6]	17.41	993.6	7.001	0.01455	0.525	22.11	60001	20000
hr[1,3,7]	84.12	4985	35.18	0.004479	0.4003	38.5	60001	20000
hr[1,4,5]	1.108	8.344	0.06027	0.0454	0.4538	4.872	60001	20000
hr[1,4,6]	5.85	321.1	2.268	0.01646	0.4047	12.04	60001	20000
hr[1,4,7]	37.77	2218	15.6	0.004639	0.3092	23.25	60001	20000
hr[1,5,6]	33.17	1454	10.27	0.01966	0.8988	55.22	60001	20000
hr[1,5,7]	276.6	16850	118.3	0.006142	0.6715	86.83	60001	20000
hr[1,6,7]	2.908	45.97	0.3219	0.04881	0.7556	11.9	60001	20000
hr[2,1,2]	1.977	1.81	0.02738	0.389	1.535	6.416	60001	20000
hr[2,1,3]	1.683	2.575	0.02361	0.113	1.121	7.055	60001	20000
hr[2,1,4]	1.224	1.515	0.0198	0.210	0.929	4.185	60001	20000
hr[2,1,5]	1.328	5.311	0.04634	0.030	0.501	7.046	60001	20000
hr[2,1,6]	3.304	27.43	0.2162	0.106	1.246	16.550	60001	20000
hr[2,1,7]	5.469	63.86	0.4706	0.063	1.150	23.320	60001	20000
hr[2,2,3]	0.89	0.9267	0.01191	0.1085	0.769	2.776	60001	20000
hr[2,2,4]	0.684	0.4211	0.006933	0.2127	0.5989	1.653	60001	20000
hr[2,2,5]	0.7469	5.82	0.04203	0.0224	0.324	3.53	60001	20000
hr[2,2,6]	3.122	50.41	0.357	0.04825	0.8194	15.51	60001	20000
hr[2,2,7]	6.279	243	1.713	0.02991	0.7541	20.57	60001	20000
hr[2,3,4]	1.4	2.445	0.04523	0.188	0.8356	6.009	60001	20000
hr[2,3,5]	1.13	3.738	0.03392	0.03921	0.4775	5.789	60001	20000
hr[2,3,6]	15.14	1197	8.485	0.05546	1.199	37.31	60001	20000
hr[2,3,7]	60.65	6912	48.97	0.03569	1.111	48.66	60001	20000
hr[2,4,5]	1.137	4.068	0.03354	0.04299	0.5408	5.396	60001	20000
hr[2,4,6]	6.069	143.5	1.017	0.07902	1.357	26.17	60001	20000
hr[2,4,7]	12.92	643.6	4.545	0.04837	1.262	36.13	60001	20000
hr[2,5,6]	30.72	1175	8.347	0.06918	2.565	112.7	60001	20000
hr[2,5,7]	83.8	6597	46.73	0.04486	2.354	140.3	60001	20000
hr[2,6,7]	1.448	9.903	0.06837	0.1764	0.908	5.048	60001	20000
hr[3,1,2]	1.532	0.914	0.01357	0.584	1.358	3.486	60001	20000
hr[3,1,3]	1.623	1.927	0.01563	0.306	1.280	5.123	60001	20000
hr[3,1,4]	1.661	5.192	0.0438	0.480	1.287	4.699	60001	20000
hr[3,1,5]	1.299	3.567	0.02941	0.075	0.681	5.932	60001	20000
hr[3,1,6]	1.800	93.470	0.663	0.172	0.796	3.848	60001	20000

hr[3,1,7]	21.100	1414.000	10.02	0.012	0.813	54.220	60001	20000
hr[3,2,3]	1.069	0.7044	0.01179	0.2798	0.9647	2.648	60001	20000
hr[3,2,4]	1.084	0.5783	0.006038	0.453	0.9757	2.29	60001	20000
hr[3,2,5]	0.8487	1.927	0.01465	0.06109	0.4962	3.563	60001	20000
hr[3,2,6]	1.362	58.44	0.4143	0.09859	0.5886	3.49	60001	20000
hr[3,2,7]	16.14	892	6.309	0.007995	0.5929	42.71	60001	20000
hr[3,3,4]	1.313	1.217	0.02726	0.3545	1.028	3.851	60001	20000
hr[3,3,5]	0.8843	2.379	0.02235	0.07315	0.5359	3.579	60001	20000
hr[3,3,6]	1.422	18.02	0.133	0.08	0.6248	5.314	60001	20000
hr[3,3,7]	21.53	1087	7.677	0.008073	0.6359	55.66	60001	20000
hr[3,4,5]	0.8318	2.154	0.01624	0.06255	0.5049	3.428	60001	20000
hr[3,4,6]	1.099	11.45	0.08501	0.08286	0.6156	3.782	60001	20000
hr[3,4,7]	12.77	331	2.366	0.007445	0.5993	44.87	60001	20000
hr[3,5,6]	5.749	236.9	1.695	0.08103	1.194	16.66	60001	20000
hr[3,5,7]	78.18	3912	27.49	0.01018	1.207	139.6	60001	20000
hr[3,6,7]	9.111	74.22	0.7635	0.02057	1.032	50.35	60001	20000
p52[1,1]	0.4921	0.2631	0.00188	0.06387	0.4748	0.9619	60001	20000
p52[1,2]	0.36	0.3117	0.003269	0.005106	0.2652	0.9785	60001	20000
p52[1,3]	0.3653	0.3288	0.003062	0.003416	0.255	0.9883	60001	20000
p52[1,4]	0.4057	0.3296	0.004756	0.005511	0.3234	0.989	60001	20000
p52[1,5]	0.3263	0.3276	0.003468	0.001783	0.1894	0.992	60001	20000
p52[1,6]	0.297	0.3137	0.002156	0.001509	0.1615	0.986	60001	20000
p52[1,7]	0.2632	0.3207	0.002425	2.80E-04	0.1033	0.9923	60001	20000
p52[2,1]	0.065	0.113	7.45E-04	7.66E-04	0.0229	0.4119	60001	20000
p52[2,2]	0.1087	0.18	0.001484	4.12E-04	0.0327	0.709	60001	20000
p52[2,3]	0.08894	0.1636	0.001222	1.66E-04	0.0212	0.6417	60001	20000
p52[2,4]	0.07429	0.147	0.001257	2.00E-04	0.0176	0.5754	60001	20000
p52[2,5]	0.07433	0.1591	0.001418	7.99E-05	0.0126	0.6396	60001	20000
p52[2,6]	0.1287	0.213	0.00181	2.48E-04	0.033	0.8429	60001	20000
p52[2,7]	0.1229	0.2182	0.001935	8.22E-05	0.0255	0.8802	60001	20000
p52[3,1]	0.254	0.246	0.001832	0.007364	0.1622	0.8763	60001	20000
p52[3,2]	0.3209	0.299	0.002662	0.004629	0.2131	0.9678	60001	20000
p52[3,3]	0.3128	0.3035	0.00212	0.003006	0.1977	0.9738	60001	20000
p52[3,4]	0.3133	0.302	0.003159	0.003344	0.1978	0.9724	60001	20000
p52[3,5]	0.2617	0.2947	0.002392	0.001393	0.129	0.9747	60001	20000
p52[3,6]	0.2661	0.2859	0.001944	0.002183	0.1461	0.9661	60001	20000
p52[3,7]	0.3113	0.3458	0.003493	3.88E-04	0.1393	0.9959	60001	20000
p52[4,1]	0.1887	0.1914	0.001344	8.45E-06	0.1238	0.6507	60001	20000
p52[4,2]	0.2104	0.241	0.001781	1.44E-14	0.108	0.789	60001	20000
p52[4,3]	0.233	0.2636	0.003066	0.000	0.118	0.836	60001	20000
p52[4,4]	0.2068	0.2455	0.002121	0.000	0.094	0.796	60001	20000
p52[4,5]	0.3376	0.3079	0.002887	1.11E-16	0.273	0.920	60001	20000
p52[4,6]	0.3082	0.2912	0.002233	1.11E-16	0.232	0.891	60001	20000
p52[4,7]	0.3026	0.3182	0.002583	0	0.179	0.927	60001	20000
rank52[1,1]	5.4	1.277	0.01463	3	6	7	60001	20000
rank52[1,2]	4.0	1.828	0.01483	1	4	7	60001	20000
rank52[1,3]	4.0	1.934	0.01388	1	4	7	60001	20000
rank52[1,4]	4.4	1.877	0.02538	1	5	7	60001	20000
rank52[1,5]	3.7	2.021	0.01847	1	3	7	60001	20000
rank52[1,6]	3.5	1.963	0.02018	1	3	7	60001	20000
rank52[1,7]	3.0	2.11	0.02144	1	2	7	60001	20000
rank52[2,1]	4.0	1.483	0.01861	1	4	7	60001	20000
rank52[2,2]	4.7	1.807	0.0185	1	5	7	60001	20000
rank52[2,3]	3.9	1.97	0.02717	1	4	7	60001	20000
rank52[2,4]	3.5	1.815	0.0243	1	3	7	60001	20000
rank52[2,5]	3.2	2.08	0.02669	1	3	7	60001	20000
rank52[2,6]	4.6	2.043	0.02357	1	5	7	60001	20000
rank52[2,7]	4.1	2.25	0.02569	1	4	7	60001	20000
rank52[3,1]	3.7	1.41	0.0124	1	4	6	60001	20000
rank52[3,2]	4.5	1.827	0.01467	1	5	7	60001	20000
rank52[3,3]	4.4	1.944	0.02084	1	5	7	60001	20000

rank52[3,4]	4.3	1.91	0.02481	1	5	7	60001	20000
rank52[3,5]	3.5	2.092	0.01955	1	3	7	60001	20000
rank52[3,6]	3.7	1.943	0.01565	1	4	7	60001	20000
rank52[3,7]	3.8	2.474	0.02899	1	3	7	60001	20000
rank52[4,1]	3.8	1.478	0.01158	1	4	7	60001	20000
rank52[4,2]	3.6	1.797	0.01458	1	3	7	60001	20000
rank52[4,3]	3.7	1.934	0.02341	1	4	7	60001	20000
rank52[4,4]	3.5	1.861	0.01516	1	3	7	60001	20000
rank52[4,5]	4.8	2.077	0.01731	1	5	7	60001	20000
rank52[4,6]	4.6	1.99	0.02053	1	5	7	60001	20000
rank52[4,7]	4.2	2.333	0.02208	1	4	7	60001	20000
resdev[1]	9.587	42.68	1.57	-72.1	8.879	94.71	60001	20000
resdev[2]	44.33	24.4	0.9806	-2.072	44.31	91.67	60001	20000
resdev[3]	58.64	36.27	1.841	-9.421	59.61	126.1	60001	20000

Table B.2 WinBUGS Fixed effect output

Winbug Fix 17 studies outcome completing risk model								
node	mean	sd	MC	2.50%	median	97.50%	start	sample
best[1,1]	0.000	0.000	5.00E-13	0	0	0	60001	20000
best[1,2]	0.061	0.240	0.002785	0	0	1	60001	20000
best[1,3]	0.049	0.217	0.003836	0	0	1	60001	20000
best[1,4]	0.227	0.419	0.01413	0	0	1	60001	20000
best[1,5]	0.193	0.395	0.01401	0	0	1	60001	20000
best[1,6]	0.257	0.437	0.01643	0	0	1	60001	20000
best[1,7]	0.212	0.409	0.01532	0	0	1	60001	20000
best[2,1]	0.528	0.499	0.02641	0	1	1	60001	20000
best[2,2]	0.001	0.037	2.81E-04	0	0	0	60001	20000
best[2,3]	0.120	0.325	0.003659	0	0	1	60001	20000
best[2,4]	0.045	0.208	0.003582	0	0	1	60001	20000
best[2,5]	0.204	0.403	0.01352	0	0	1	60001	20000
best[2,6]	0.021	0.145	0.002024	0	0	0	60001	20000
best[2,7]	0.080	0.271	0.006438	0	0	1	60001	20000
best[3,1]	0.116	0.320	0.008556	0	0	1	60001	20000
best[3,2]	0.002	0.039	2.99E-04	0	0	0	60001	20000
best[3,3]	0.190	0.393	0.01184	0	0	1	60001	20000
best[3,4]	0.002	0.042	3.16E-04	0	0	0	60001	20000
best[3,5]	0.182	0.386	0.007906	0	0	1	60001	20000
best[3,6]	0.332	0.471	0.01703	0	0	1	60001	20000
best[3,7]	0.177	0.382	0.01293	0	0	1	60001	20000
best[4,1]	0.007	0.081	5.65E-04	0	0	0	60001	20000
best[4,2]	0.074	0.262	0.005395	0	0	1	60001	20000
best[4,3]	0.027	0.163	0.002238	0	0	1	60001	20000
best[4,4]	0.004	0.062	5.02E-04	0	0	0	60001	20000
best[4,5]	0.646	0.478	0.01012	0	1	1	60001	20000
best[4,6]	0.056	0.230	0.004377	0	0	1	60001	20000
best[4,7]	0.187	0.390	0.009025	0	0	1	60001	20000
d[1,2]	-0.9015	0.2195	0.003095	-1.346	-0.8943	-0.4863	60001	20000
d[1,3]	1.657	2.845	0.1993	-2.084	3.094	5.112	60001	20000
d[1,4]	-0.4635	0.5297	0.03434	-1.456	0.01888	0.01888	60001	20000
d[1,5]	-0.8414	0.9558	0.06121	-2.683	0.01793	0.01793	60001	20000
d[1,6]	-0.625	0.6521	0.04528	-1.588	0.0119	0.0119	60001	20000
d[1,7]	-0.7827	0.7717	0.05339	-1.949	-0.03177	-0.03177	60001	20000
d[2,2]	1.545	1.232	0.07868	-0.6135	1.823	3.311	60001	20000
d[2,3]	2.358	2.728	0.1847	-1.922	3.084	6.017	60001	20000
d[2,4]	1.429	1.63	0.1102	-1.291	2.977	2.977	60001	20000
d[2,5]	-0.4176	1.001	0.03187	-2.94	0.008635	1.229	60001	20000
d[2,6]	2.592	2.472	0.1689	-1.394	4.958	4.958	60001	20000
d[2,7]	0.09629	0.748	0.01624	-1.556	0.05971	1.906	60001	20000
d[3,2]	0.9118	0.5753	0.03636	-0.06721	0.9547	1.828	60001	20000
d[3,3]	1.441	1.343	0.09122	-0.6032	1.672	3.281	60001	20000
d[3,4]	1.702	1.297	0.09003	-0.2247	2.969	2.969	60001	20000
d[3,5]	-0.7117	0.6778	0.01895	-1.926	-0.9693	0.9614	60001	20000
d[3,6]	-0.1138	0.2224	0.007638	-0.6767	-0.00784	0.2352	60001	20000
d[3,7]	-0.0789	1.291	0.01299	-3.116	0.05052	2.793	60001	20000
hr[1,1,2]	0.4157	0.09077	0.001197	0.260	0.409	0.615	60001	20000
hr[1,1,3]	46.76	53.77	3.304	0.124	22.070	166.100	60001	20000
hr[1,1,4]	0.7132	0.3189	0.02175	0.233	1.019	1.019	60001	20000
hr[1,1,5]	0.6176	0.4123	0.02848	0.068	1.018	1.018	60001	20000
hr[1,1,6]	0.6503	0.3639	0.0257	0.204	1.012	1.012	60001	20000

hr[1,1,7]	0.5957	0.3752	0.02651	0.142	0.969	0.969	60001	20000
hr[1,2,3]	109	121.1	7.693	0.3322	64.71	363.1	60001	20000
hr[1,2,4]	1.749	0.8274	0.05136	0.6416	1.66	3.38	60001	20000
hr[1,2,5]	1.507	1.05	0.06834	0.1786	1.584	3.378	60001	20000
hr[1,2,6]	1.605	0.9332	0.06033	0.4392	1.509	3.357	60001	20000
hr[1,2,7]	1.466	0.9555	0.06275	0.317	1.375	3.213	60001	20000
hr[1,3,4]	0.703	0.8792	0.04926	0.006138	0.135	2.792	60001	20000
hr[1,3,5]	0.341	0.4318	0.02344	0.006132	0.04613	1.416	60001	20000
hr[1,3,6]	0.5417	0.7325	0.03792	0.006096	0.08705	2.403	60001	20000
hr[1,3,7]	0.4196	0.5786	0.02923	0.005835	0.05851	1.891	60001	20000
hr[1,4,5]	0.7673	0.3088	0.01655	0.1999	0.999	1.082	60001	20000
hr[1,4,6]	0.8862	0.2346	0.007817	0.3973	0.993	1.331	60001	20000
hr[1,4,7]	0.7758	0.2478	0.01252	0.2867	0.9506	1.064	60001	20000
hr[1,5,6]	1.442	1.057	0.03314	0.5571	0.994	4.333	60001	20000
hr[1,5,7]	1.205	0.811	0.01943	0.4121	0.9515	3.395	60001	20000
hr[1,6,7]	0.8642	0.1256	0.006649	0.5915	0.9573	0.9838	60001	20000
hr[2,1,2]	8.641	8.18	0.478	0.541	6.188	27.410	60001	20000
hr[2,1,3]	87.33	127.4	6.151	0.146	21.850	410.400	60001	20000
hr[2,1,4]	10.39	9.269	0.6569	0.275	19.640	19.640	60001	20000
hr[2,1,5]	0.9821	1.267	0.01028	0.053	1.009	3.418	60001	20000
hr[2,1,6]	72.23	70.11	4.98	0.248	142.300	142.300	60001	20000
hr[2,1,7]	1.56	2.49	0.05688	0.211	1.062	6.726	60001	20000
hr[2,2,3]	6.028	7.273	0.3813	0.1343	3.536	23.33	60001	20000
hr[2,2,4]	1.066	0.6664	0.0319	0.2888	0.8935	2.713	60001	20000
hr[2,2,5]	0.2954	0.6085	0.01599	0.0311	0.1037	1.699	60001	20000
hr[2,2,6]	6.337	6.249	0.3311	0.1181	5.363	20.1	60001	20000
hr[2,2,7]	0.8516	2.442	0.06471	0.03737	0.1329	5.703	60001	20000
hr[2,3,4]	0.8676	1.342	0.05072	0.04789	0.341	4.329	60001	20000
hr[2,3,5]	0.5335	1.494	0.03904	0.00246	0.02772	3.476	60001	20000
hr[2,3,6]	2.932	12.22	0.1674	0.1563	1.167	16.85	60001	20000
hr[2,3,7]	2.184	10.32	0.1849	0.002589	0.03413	15.79	60001	20000
hr[2,4,5]	0.4556	1.031	0.02946	0.05136	0.05136	2.738	60001	20000
hr[2,4,6]	5.181	5.144	0.1615	0.1914	7.246	10.64	60001	20000
hr[2,4,7]	1.494	4.585	0.1208	0.05406	0.05406	10.36	60001	20000
hr[2,5,6]	76.35	72.11	4.61	0.2104	141.1	141.1	60001	20000
hr[2,5,7]	6.045	30.92	0.4644	0.1803	1.052	39.58	60001	20000
hr[2,6,7]	0.4791	0.5116	0.03355	0.00746	0.3186	1.468	60001	20000
hr[3,1,2]	2.914	1.584	0.09677	0.935	2.598	6.224	60001	20000
hr[3,1,3]	8.706	8.397	0.527	0.547	5.321	26.610	60001	20000
hr[3,1,4]	10.57	8.911	0.6323	0.799	19.470	19.470	60001	20000
hr[3,1,5]	0.6524	0.72	0.01994	0.146	0.379	2.615	60001	20000
hr[3,1,6]	0.9131	0.1843	0.005724	0.508	0.992	1.265	60001	20000
hr[3,1,7]	26.14	3035	21.54	0.044	1.052	16.330	60001	20000
hr[3,2,3]	2.315	1.649	0.1052	0.4398	1.976	5.658	60001	20000
hr[3,2,4]	2.957	2.072	0.1338	0.6492	2.371	7.003	60001	20000
hr[3,2,5]	0.3444	0.467	0.01796	0.05885	0.1289	1.607	60001	20000
hr[3,2,6]	0.4142	0.2442	0.01199	0.1587	0.3255	1.045	60001	20000
hr[3,2,7]	14.61	1634	11.62	0.02821	0.2793	10.98	60001	20000
hr[3,3,4]	1.391	0.5401	0.005269	0.6243	1.294	2.721	60001	20000
hr[3,3,5]	0.3829	0.589	0.02554	0.01425	0.05698	1.965	60001	20000
hr[3,3,6]	0.4298	0.486	0.02583	0.03728	0.1595	1.643	60001	20000
hr[3,3,7]	19.32	2167	15.4	0.03011	0.09931	14.24	60001	20000
hr[3,4,5]	0.2966	0.4689	0.01985	0.01949	0.01949	1.543	60001	20000
hr[3,4,6]	0.317	0.3394	0.01898	0.05097	0.08306	1.152	60001	20000
hr[3,4,7]	26.78	3400	24.13	0.0269	0.05403	11.29	60001	20000
hr[3,5,6]	2.316	2.413	0.02837	0.2881	2.616	6.009	60001	20000

hr[3,5,7]	90.13	11440	81.11	0.05113	2.773	34.91	60001	20000
hr[3,6,7]	54.3	6862	48.68	0.05651	1.06	19.71	60001	20000
p52[1,1]	0.4914	0.2634	0.001848	0.06322	0.4736	0.9602	60001	20000
p52[1,2]	0.214	0.200	0.003896	0.007782	0.1488	0.7543	60001	20000
p52[1,3]	0.492	0.334	0.01689	0.02087	0.4695	0.9849	60001	20000
p52[1,4]	0.214	0.207	0.00422	0.006207	0.143	0.7657	60001	20000
p52[1,5]	0.371	0.289	0.0127	0.01514	0.303	0.9578	60001	20000
p52[1,6]	0.205	0.198	0.002674	0.004937	0.1396	0.7436	60001	20000
p52[1,7]	0.331	0.269	0.01064	0.009187	0.2579	0.9274	60001	20000
p52[2,1]	0.066	0.114	7.39E-04	7.33E-04	0.02303	0.4264	60001	20000
p52[2,2]	0.213	0.256	0.007364	0.001746	0.09702	0.8996	60001	20000
p52[2,3]	0.123	0.187	0.003079	7.15E-04	0.0402	0.7302	60001	20000
p52[2,4]	0.141	0.204	0.004838	8.70E-04	0.04958	0.7728	60001	20000
p52[2,5]	0.073	0.134	9.64E-04	3.79E-04	0.02103	0.5121	60001	20000
p52[2,6]	0.420	0.377	0.02117	0.001659	0.3182	0.9898	60001	20000
p52[2,7]	0.092	0.161	0.002215	5.94E-04	0.02845	0.6359	60001	20000
p52[3,1]	0.251	0.247	0.001874	0.00769	0.1584	0.878	60001	20000
p52[3,2]	0.405	0.300	0.003418	0.016	0.3419	0.9658	60001	20000
p52[3,3]	0.227	0.263	0.008567	0.002221	0.111	0.9256	60001	20000
p52[3,4]	0.504	0.317	0.008752	0.02375	0.498	0.9824	60001	20000
p52[3,5]	0.209	0.249	0.005574	0.003803	0.09964	0.9275	60001	20000
p52[3,6]	0.186	0.235	0.006962	0.001131	0.08233	0.8648	60001	20000
p52[3,7]	0.297	0.300	0.003576	0.003756	0.176	0.9778	60001	20000
p52[4,1]	0.191	0.193	0.001325	6.37E-06	0.1298	0.655	60001	20000
p52[4,2]	0.169	0.205	0.006271	4.13E-14	0.07538	0.6922	60001	20000
p52[4,3]	0.159	0.239	0.01135	-2.22E-16	9.07E-09	0.7608	60001	20000
p52[4,4]	0.141	0.211	0.009217	0	0.01147	0.7038	60001	20000
p52[4,5]	0.348	0.268	0.007709	1.63E-04	0.3134	0.8662	60001	20000
p52[4,6]	0.189	0.249	0.01216	0	0.0344	0.7757	60001	20000
p52[4,7]	0.280	0.259	0.006451	5.30E-09	0.2107	0.8326	60001	20000
rank52[1,1]	6.0	0.9708	0.06654	5	6	7	60001	20000
rank52[1,2]	3.2	1.459	0.07425	1	3	6	60001	20000
rank52[1,3]	5.3	1.981	0.1025	1	6	7	60001	20000
rank52[1,4]	3.1	1.669	0.0865	1	3	6	60001	20000
rank52[1,5]	4.3	2.172	0.1284	1	6	7	60001	20000
rank52[1,6]	2.9	1.515	0.066	1	3	6	60001	20000
rank52[1,7]	3.2	1.42	0.0622	1	4	6	60001	20000
rank52[2,1]	2.3	1.658	0.08308	1	1	6	60001	20000
rank52[2,2]	5.6	1.034	0.02051	3	6	7	60001	20000
rank52[2,3]	3.9	1.645	0.02644	1	4	7	60001	20000
rank52[2,4]	4.0	1.327	0.04101	1	4	6	60001	20000
rank52[2,5]	2.8	1.564	0.01555	1	3	7	60001	20000
rank52[2,6]	6.0	1.688	0.07703	2	7	7	60001	20000
rank52[2,7]	3.5	1.844	0.0681	1	3	7	60001	20000
rank52[3,1]	3.3	1.2	0.0567	1	4	5	60001	20000
rank52[3,2]	5.5	1.015	0.02097	3	6	7	60001	20000
rank52[3,3]	3.2	1.821	0.09446	1	3	7	60001	20000
rank52[3,4]	6.3	1.155	0.05205	3	7	7	60001	20000
rank52[3,5]	2.9	1.594	0.02849	1	3	7	60001	20000
rank52[3,6]	2.4	1.416	0.05454	1	2	6	60001	20000
rank52[3,7]	4.4	1.972	0.04855	1	5	7	60001	20000
rank52[4,1]	3.8	1.977	0.1133	1	5	6	60001	20000
rank52[4,2]	3.6	1.378	0.05069	1	4	7	60001	20000
rank52[4,3]	2.7	1.881	0.1018	1	2	7	60001	20000
rank52[4,4]	2.9	1.102	0.02538	1	3	6	60001	20000
rank52[4,5]	6.2	1.319	0.0267	2	7	7	60001	20000

rank52[4,6]	3.8	1.654	0.08449	1	4	7	60001	20000
rank52[4,7]	5.1	1.75	0.03445	1	5	7	60001	20000
resdev[1]	172.7	120.5	8.286	-4.731	212.6	326.5	60001	20000
resdev[2]	-60.64	92.7	6.472	-173.1	-39.33	65.12	60001	20000
resdev[3]	456.4	423.7	30.07	-7.885	809.6	914.1	60001	20000

Appendix C

Utility scores

utility penalty table											
uRelapseA		uRelapseC		uRelapseE		Remission A		RemissionC		RemissionE	
Index	Value 1	Index	Value 1	Index	Value 1	Index	Value 1	Index	Value 1	Index	Value 1
1	0.67	1	0.62	1	0.57	1	0.75	1	0.75	1	0.64
2	0.6	2	0.55	2	0.5	2	0.7	2	0.7	2	0.6
3	0.55	3	0.5	3	0.45	3	0.65	3	0.65	3	0.55
4	0.5	4	0.45	4	0.4	4	0.6	4	0.6	4	0.5
5	0.45	5	0.4	5	0.35	5	0.55	5	0.55	5	0.45
6	0.4	6	0.35	6	0.3	6	0.5	6	0.5	6	0.4
7	0.35	7	0.3	7	0.25	7	0.45	7	0.45	7	0.35
8	0.3	8	0.25	8	0.2	8	0.4	8	0.4	8	0.3
9	0.25	9	0.2	9	0.15	9	0.35	9	0.35	9	0.25
10	0.2	10	0.15	10	0.1	10	0.3	10	0.3	10	0.2
11	0.15	11	0.1	11	0.1	11	0.25	11	0.25	11	0.15
12	0.1	12	0.1	12	0.1	12	0.2	12	0.2	12	0.1
13	0.1	13	0.1	13	0.1	13	0.15	13	0.15	13	0.1
14	0.1	14	0.1	14	0.1	14	0.1	14	0.1	14	0.1
15	0.1	15	0.1	15	0.1	15	0.1	15	0.1	15	0.1
16	0.1	16	0.1	16	0.1	16	0.1	16	0.1	16	0.1
17	0.1	17	0.1	17	0.1	17	0.1	17	0.1	17	0.1
18	0.1	18	0.1	18	0.1	18	0.1	18	0.1	18	0.1
19	0.1	19	0.1	19	0.1	19	0.1	19	0.1	19	0.1
20	0.1	20	0.1	20	0.1	20	0.1	20	0.1	20	0.1
21	0.1	21	0.1	21	0.1	21	0.1	21	0.1	21	0.1
22	0.1	22	0.1	22	0.1	22	0.1	22	0.1	22	0.1
23	0.1	23	0.1	23	0.1	23	0.1	23	0.1	23	0.1
24	0.1	24	0.1	24	0.1	24	0.1	24	0.1	24	0.1
25	0.1	25	0.1	25	0.1	25	0.1	25	0.1	25	0.1
26	0.1	26	0.1	26	0.1	26	0.1	26	0.1	26	0.1
27	0.1	27	0.1	27	0.1	27	0.1	27	0.1	27	0.1
28	0.1	28	0.1	28	0.1	28	0.1	28	0.1	28	0.1
29	0.1	29	0.1	29	0.1	29	0.1	29	0.1	29	0.1
30	0.1	30	0.1	30	0.1	30	0.1	30	0.1	30	0.1

Appendix D

Consumer price index

BE (ปีพ.ศ.)	AD (ปีค.ศ.)	CPI (All commodities)	CPI (Medical care)
2543	2000	74.51	88.69
2544	2001	75.71	90.77
2545	2002	76.24	91.90
2546	2003	77.62	93.11
2547	2004	79.76	95.29
2548	2005	83.39	96.87
2549	2006	87.26	97.92
2550	2007	89.21	98.39
2551	2008	94.08	98.92
2552	2009	93.28	99.31
2553	2010	96.33	99.41
2554	2011	100.00	100.00
2555	2012	103.02	100.96
2556	2013	105.27	101.94
2557	2014	107.74	102.71

Source: Ministry of Commerce

Ref: Report of Consumer Price Index of Thailand Year 2003-2013 (BASE YEAR 2011): Bureau of Trade and Economic Indices, Ministry of Commerce. Available from: http://www.indexpr.moc.go.th/price_present/TableIndexG_region.asp?table_name=cpig_index_country&province_code=&type_code=g&check_f=i&year_base=2554&nyear=2546

Appendix E

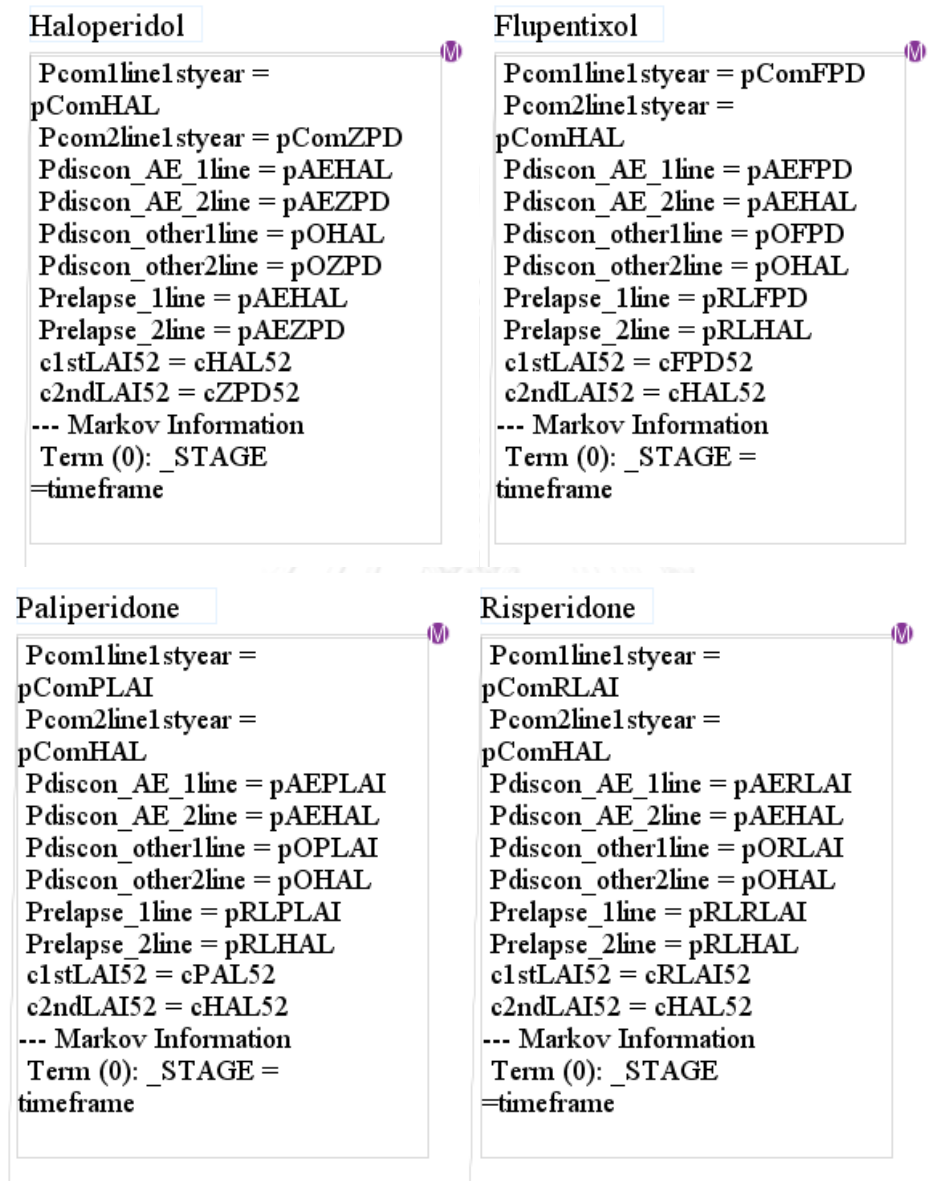
Markov model in TreeAge Pro 2014

E.1 Master node

Starting node

```
Pcomall_nextyear = 0.1
Prelapse_ECT = pRLECT
Prelapse_noRX1 =
pRLnotreat1
Prelapse_noRX2 =
pRLnotreat2
Prevert = 0.5
age = 25
c1stLAI48 =
0.92308*c1stLAI52
c2ndLAI48 =
0.92308*c2ndLAI52
cDC = 0.03
cDO = 0.03
c_Benhx = CBenhx
c_ECT = cECT
c_IPD = cIPD
c_IPDmeal = cIPDmeal
c_IPDtravel = cIPDtravel
c_OPD = cOPD
c_OPDmeal = cOPDmeal
c_OPDtravel = cOPDtravel
c_RxRL = cRXRL
c_Workloss = cWorkloss
perspective = 1
timeframe = 75
uEPS = 0.9*uRemission
--- Tracker Defaults
ECT_first = 0.0
First_noncomply = 0.0
RelapseC = 0.0
RelaseE = 0.0
TRL_notx_yr = 0.0
first_LAI = 0.0
non_comly_second = 0.0
relapseA = 0.0
second_LAI = 0.0
```

E.2 node for 6 LAIs



Zuclopenthixol

Pcom1line1styear = pComZPD
Pcom2line1styear = pComHAL
Pdiscon_AE_1line = pAEZPD
Pdiscon_AE_2line = pAEHAL
Pdiscon_other1line = pOZPD
Pdiscon_other2line = pOHAL
Prelapse_1line = pRLZPD
Prelapse_2line = pRLHAL
c1stLAI52 = cZPD52
c2ndLAI52 = cHAL52
--- Markov Information
Term (0): _STAGE =timeframe

Fluphenazine

Pcom1line1styear = pComFLUD
Pcom2line1styear = pComHAL
Pdiscon_AE_1line = pAEFLUD
Pdiscon_AE_2line = pAEHAL
Pdiscon_other1line = pOFLUD
Pdiscon_other2line = pOHAL
Prelapse_1line = pRLFLUD
Prelapse_2line = pRLHAL
c1stLAI52 = cFLUD52
c2ndLAI52 = cHAL52
--- Markov Information
Term (0): _STAGE = timeframe

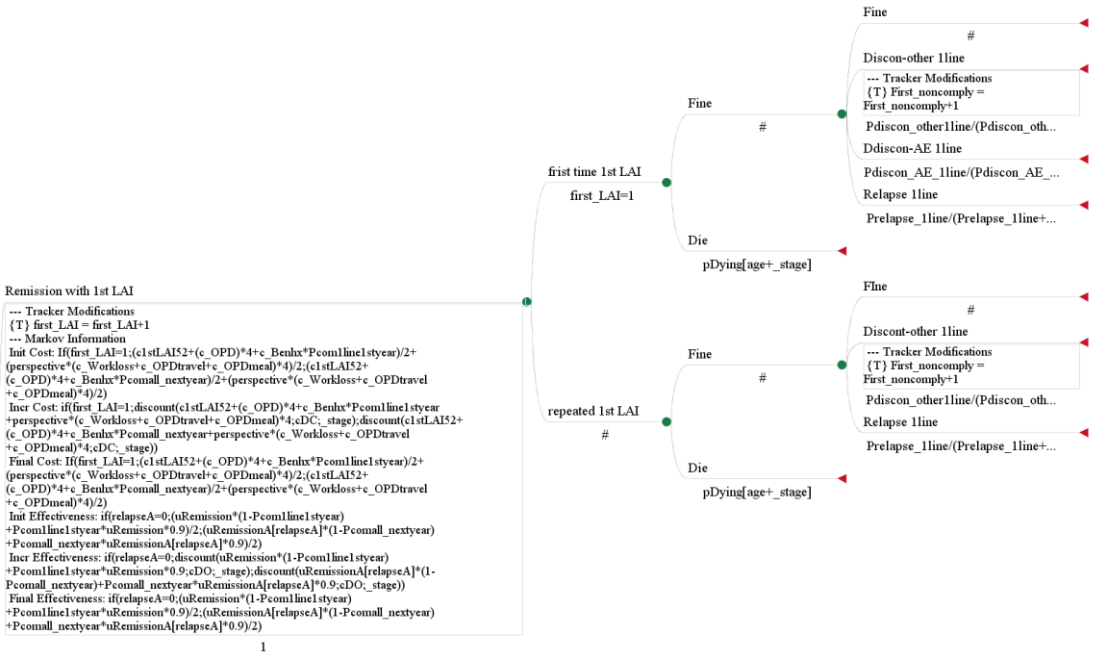
1

E.3 remission node with 1st LAI

Remission with 1st LAI

--- Tracker Modifications
{T} first_LAI = first_LAI+1
--- Markov Information
Init Cost: If(first_LAI=1;(c1stLAI52+(c_OPD)*4+c_Benhx*Pcom1line1styear)/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2;(c1stLAI52+(c_OPD)*4+c_Benhx*Pcomall_nextyear)/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2)
Incr Cost: if(first_LAI=1;discount(c1stLAI52+(c_OPD)*4+c_Benhx*Pcom1line1styear+perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4;cDC;_stage);discount(c1stLAI52+(c_OPD)*4+c_Benhx*Pcomall_nextyear+perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4;cDC;_stage))
Final Cost: If(first_LAI=1;(c1stLAI52+(c_OPD)*4+c_Benhx*Pcom1line1styear)/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2;(c1stLAI52+(c_OPD)*4+c_Benhx*Pcomall_nextyear)/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2)
Init Effectiveness: if(relapseA=0;(uRemission*(1-Pcom1line1styear)+Pcom1line1styear*uRemission*0.9)/2;(uRemissionA[relapseA]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionA[relapseA]*0.9)/2)
Incr Effectiveness: if(relapseA=0;discount(uRemission*(1-Pcom1line1styear)+Pcom1line1styear*uRemission*0.9;cDO;_stage);discount(uRemissionA[relapseA]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionA[relapseA]*0.9;cDO;_stage))
Final Effectiveness: if(relapseA=0;(uRemission*(1-Pcom1line1styear)+Pcom1line1styear*uRemission*0.9)/2;(uRemissionA[relapseA]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionA[relapseA]*0.9)/2)

1

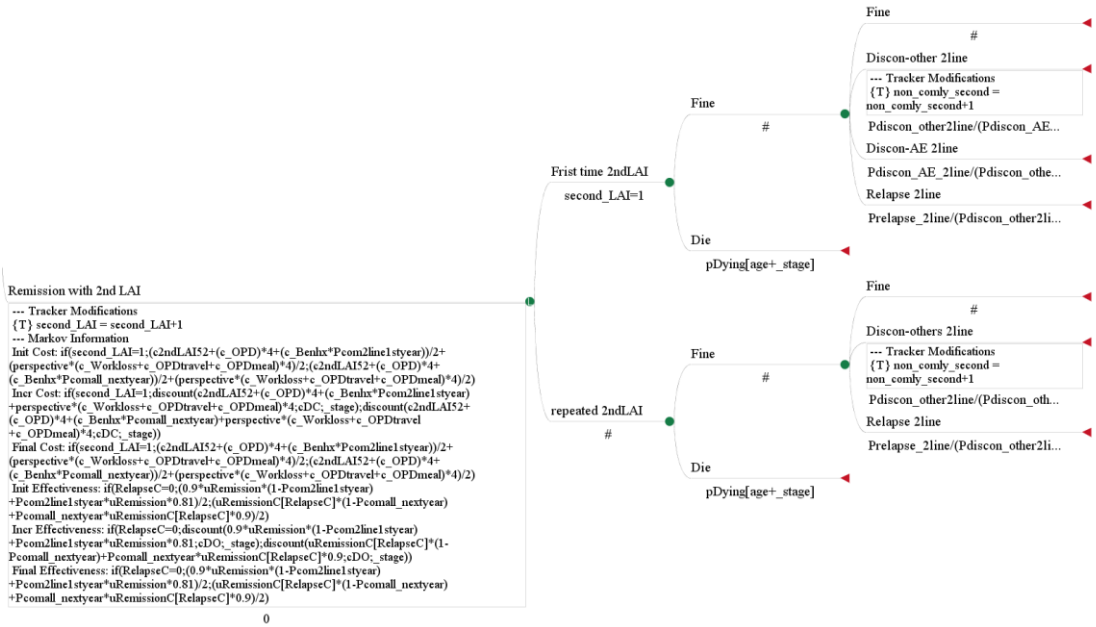


E.4 remission node with 2nd LAI

Remission with 2nd LAI

--- Tracker Modifications
{T} second_LAI = second_LAI+1
--- Markov Information
Init Cost: if(second_LAI=1;(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcom2line1styear))/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2;(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcomall_nextyear))/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2)
Incr Cost: if(second_LAI=1;discount(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcom2line1styear)+perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4;cDC;_stage);discount(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcomall_nextyear)+perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4;cDC;_stage))
Final Cost: if(second_LAI=1;(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcom2line1styear))/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2;(c2ndLAI52+(c_OPD)*4+(c_Benhx*Pcomall_nextyear))/2+(perspective*(c_Workloss+c_OPDtravel+c_OPDmeal)*4)/2)
Init Effectiveness: if(RelapseC=0;(0.9*uRemission*(1-Pcom2line1styear)+Pcom2line1styear*uRemission*0.81)/2;(uRemissionC[RelapseC]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionC[RelapseC]*0.9)/2)
Incr Effectiveness: if(RelapseC=0;discount(0.9*uRemission*(1-Pcom2line1styear)+Pcom2line1styear*uRemission*0.81;cDO;_stage);discount(uRemissionC[RelapseC]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionC[RelapseC]*0.9;cDO;_stage))
Final Effectiveness: if(RelapseC=0;(0.9*uRemission*(1-Pcom2line1styear)+Pcom2line1styear*uRemission*0.81)/2;(uRemissionC[RelapseC]*(1-Pcomall_nextyear)+Pcomall_nextyear*uRemissionC[RelapseC]*0.9)/2)

0



E.5 node with ECT remission , no LAI & SE remission 1&2

Remission with ECT

```
--- Tracker Modifications
{T} ECT_first = ECT_first+1
--- Markov Information
Init Cost: (c_ECT+c_IPD+perspective*(c_Workloss*30+c_IPDmeal+c_IPDtravel))/2
Incr Cost: discount(c_ECT+c_IPD+perspective*(c_Workloss*30+c_IPDmeal
+c_IPDtravel);cDC;_stage)
Final Cost: (c_ECT+c_IPD+perspective*(c_Workloss*30+c_IPDmeal+c_IPDtravel))/2
Init Effectiveness: uRemissionE[RelaseE]/2
Incr Effectiveness: discount(uRemissionE[RelaseE];cDO;_stage)
Final Effectiveness: uRemissionE[RelaseE]/2
```

0

Remission without LAI and no SE 1

```
--- Markov Information
Init Effectiveness: uRemissionC[relapseA]/2
Incr Effectiveness: discount(uRemissionC[relapseA];cDO;_stage)
Final Effectiveness: uRemissionC[relapseA]/2
```

0

Remission without LAI and no SE 2

```
--- Markov Information
Init Effectiveness: uRemissionE[RelapseC]/2
Incr Effectiveness: discount(uRemissionE[RelapseC];cDO;_stage)
Final Effectiveness: uRemissionE[RelapseC]/2
```

0

E.6 node with Relapse A-E

Relapse A

--- Tracker Modifications
{T} relapseA = relapseA+1
--- Markov Information
Init Cost: if(first_LAI=1;
(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*(Pcom1line1styear
+Pcom2line1styear)+c_RxRL+c_IPD+perspective*(c_Workloss*34+(c_OPDtravel
+c_OPDmeal)*4+c_IPDmeal+c_IPDtravel))/2;
(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*(Pcomall_nextyear)+c_RxRL+c_IPD
+perspective*(c_Workloss*34+(c_OPDtravel+c_OPDmeal)*4+c_IPDmeal+c_IPDtravel))/2)
Incr Cost:
if(first_LAI=1;discount(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*(Pcom1line1styear
+Pcom2line1styear)+c_RxRL+c_IPD+perspective*(c_Workloss*34+(c_OPDtravel
+c_OPDmeal)*4+c_IPDmeal
+c_IPDtravel);cDC;_stage);discount(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*Pcomall_ne
+c_RxRL+c_IPD+perspective*(c_Workloss*34+(c_OPDtravel+c_OPDmeal)*4+c_IPDmeal
+c_IPDtravel);cDC;_stage))
Final Cost: if(first_LAI=1;
(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*(Pcom1line1styear
+Pcom2line1styear)+c_RxRL+c_IPD+perspective*(c_Workloss*34+(c_OPDtravel
+c_OPDmeal)*4+c_IPDmeal+c_IPDtravel))/2;
(0.5*(c1stLAI48+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*(Pcomall_nextyear)+c_RxRL+c_IPD
+perspective*(c_Workloss*34+(c_OPDtravel+c_OPDmeal)*4+c_IPDmeal+c_IPDtravel))/2)
Init Effectiveness: (uRelapseA[relapseA])/2
Incr Effectiveness: discount(uRelapseA[relapseA];cDO;_stage)
Final Effectiveness: (uRelapseA[relapseA])/2

0

Realpse C

```
--- Tracker Modifications
{T} RelapseC = RelapseC+1
--- Markov Information
Init Cost: if(second_LAI=1 ; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2)
Incr Cost: if(second_LAI=1;discount(0.5*(c_ECT
+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5);cDC;_stage);discount(0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5);cDC;_stage))
Final Cost: if(second_LAI=1 ; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2)
Init Effectiveness: (uRelapseC[RelapseC])/2
Incr Effectiveness: discount(uRelapseC[RelapseC];cDO;_stage)
Final Effectiveness: (uRelapseC[RelapseC])/2
```

0

Realpse C

--- Tracker Modifications
{T} RelapseC = RelapseC+1
--- Markov Information
Init Cost: if(second_LAI=1 ; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2)
Incr Cost: if(second_LAI=1;discount(0.5*(c_ECT
+c2ndLAI48)+c_OPD*4+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5);cDC;_stage);discount(0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5);cDC;_stage))
Final Cost: if(second_LAI=1 ; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcom2line1styear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2; (0.5*(c_ECT
+c2ndLAI48)+c_OPD*2+0.5*c_Benhx*Pcomall_nextyear+c_RxRL+1.5*c_IPD
+perspective*(c_Workloss*64+(c_OPDtravel+c_OPDmeal)*2+(c_IPDmeal
+c_IPDtravel)*1.5))/2)
Init Effectiveness: (uRelapseC[RelapseC])/2
Incr Effectiveness: discount(uRelapseC[RelapseC];cDO;_stage)
Final Effectiveness: (uRelapseC[RelapseC])/2

0

Relapse B

```
--- Markov Information
Init Cost: (c2ndLAI48+c_RxRL+c_OPD*4+c_Benhx*Pcom2line1styear+c_IPD
+perspective*(c_Workloss*34+(c_OPDmeal+c_OPDtravel)*4+c_IPDmeal+c_IPDtravel))/2
Incr Cost: discount(c2ndLAI48+c_RxRL+c_OPD*4+c_Benhx*Pcom2line1styear+c_IPD
+perspective*(c_Workloss*34+(c_OPDmeal+c_OPDtravel)*4+c_IPDmeal
+c_IPDtravel);cDC;_stage)
Final Cost: (c2ndLAI48+c_RxRL+c_OPD*4+c_Benhx*Pcom2line1styear+c_IPD
+perspective*(c_Workloss*34+(c_OPDmeal+c_OPDtravel)*4+c_IPDmeal+c_IPDtravel))/2
Init Effectiveness: uRelapseA[relapseA]/2
Incr Effectiveness: discount(uRelapseA[relapseA];cDO;_stage)
Final Effectiveness: uRelapseA[relapseA]/2
```

0

Relapse D

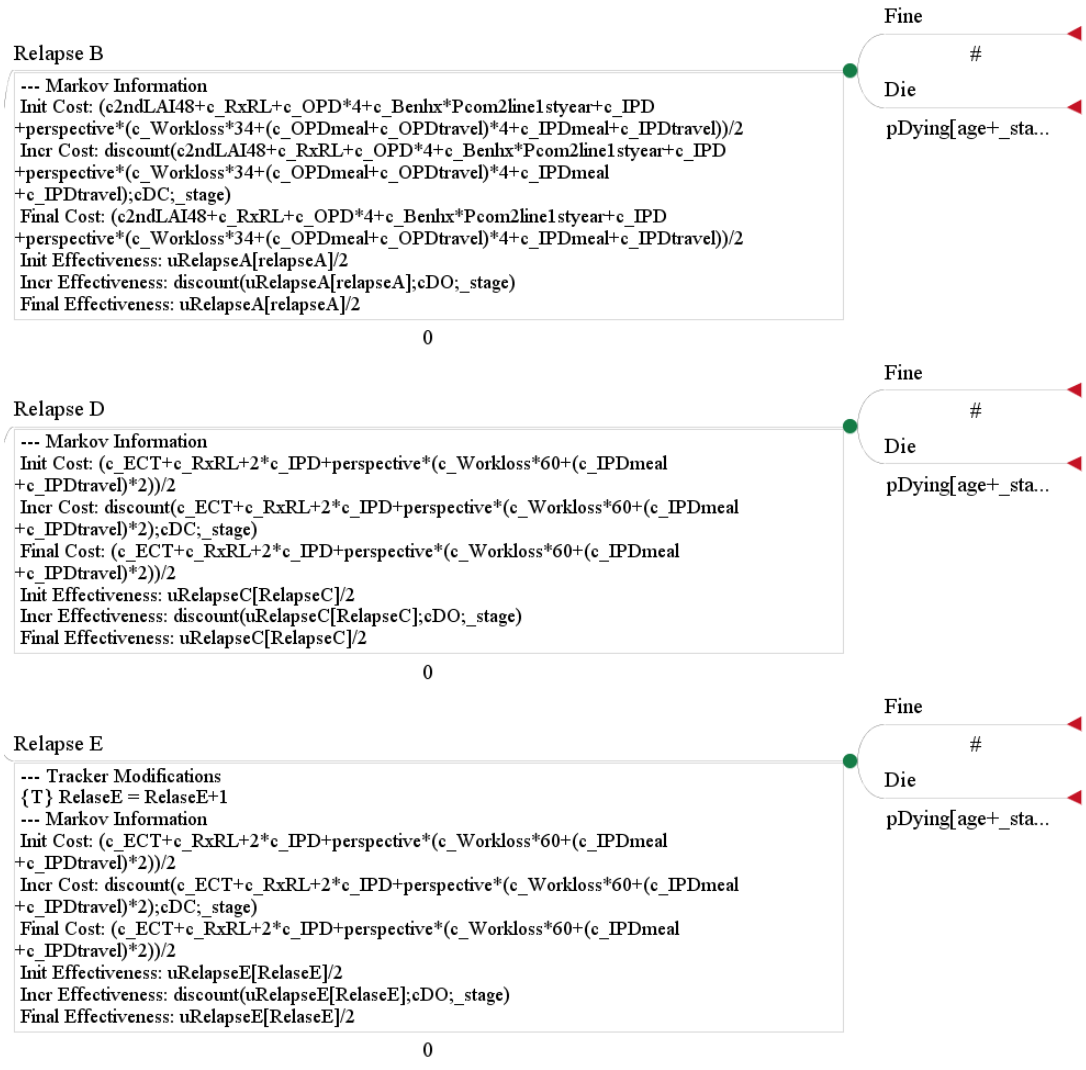
```
--- Markov Information
Init Cost: (c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2))/2
Incr Cost: discount(c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2);cDC;_stage)
Final Cost: (c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2))/2
Init Effectiveness: uRelapseC[RelapseC]/2
Incr Effectiveness: discount(uRelapseC[RelapseC];cDO;_stage)
Final Effectiveness: uRelapseC[RelapseC]/2
```

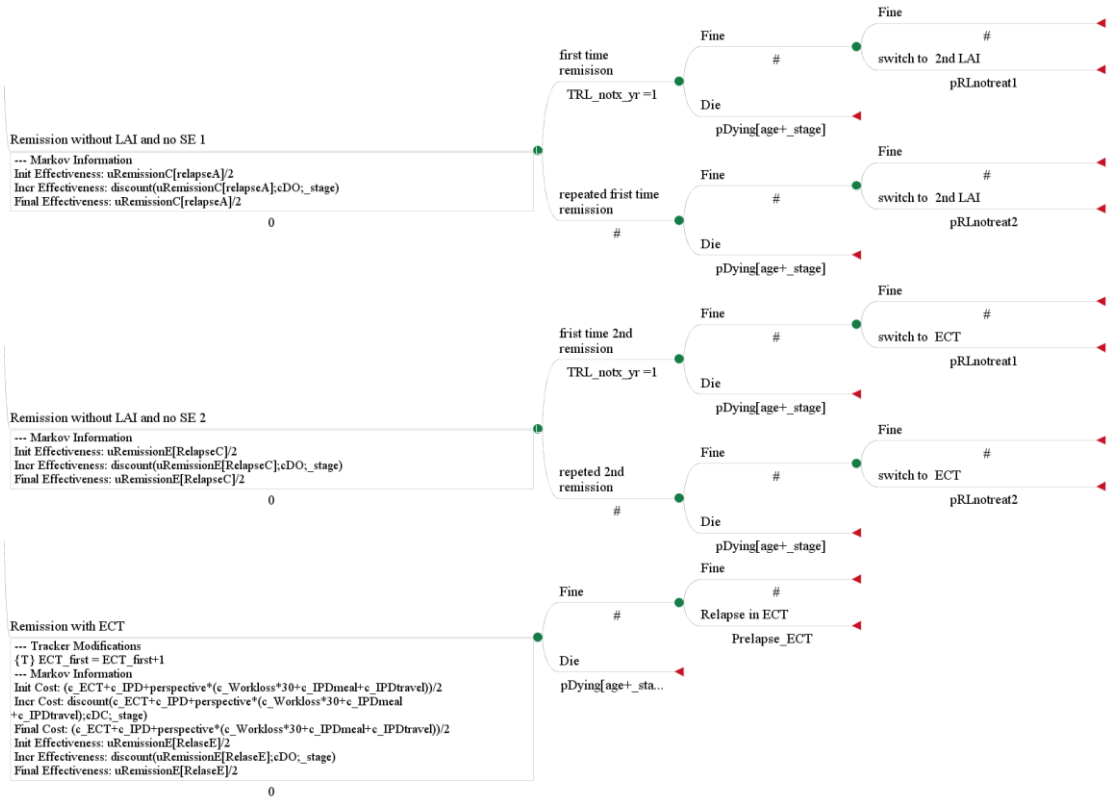
0

Relapse E

```
--- Tracker Modifications
{T} RelaseE = RelaseE+1
--- Markov Information
Init Cost: (c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2))/2
Incr Cost: discount(c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2);cDC;_stage)
Final Cost: (c_ECT+c_RxRL+2*c_IPD+perspective*(c_Workloss*60+(c_IPDmeal
+c_IPDtravel)*2))/2
Init Effectiveness: uRelapseE[RelaseE]/2
Incr Effectiveness: discount(uRelapseE[RelaseE];cDO;_stage)
Final Effectiveness: uRelapseE[RelaseE]/2
```

0





Appendix F

Additional Markov outputs

Table F.1 Statistic PSA parameters (age of 25 years for 75 year time horizon, societal perspective)

STATISTIC	Haloperidol			Flupentixol			Paliperidone		
	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB
Mean	1,079,376	14.29	(1,079,376)	1,125,856	14.29	(1,125,856)	1,247,949	14.30	(1,247,949)
Std Deviation	619,125	0.20	619,125	637,271	0.20	637,271	650,985	0.19	650,985
Minimum	15,011	13.68	(4,124,882)	22,256	13.68	(4,176,727)	74,942	13.60	(4,248,794)
2.5%	219,133	13.96	(2,530,086)	256,707	13.93	(2,631,322)	346,508	13.93	(2,892,210)
10%	423,839	14.07	(1,913,385)	451,317	14.05	(1,988,234)	565,387	14.06	(2,110,169)
Median	944,520	14.27	(946,477)	987,609	14.29	(988,597)	1,122,708	14.31	(1,122,845)
90%	1,901,993	14.49	(425,063)	1,987,745	14.50	(452,000)	2,095,816	14.53	(565,880)
97.5%	2,530,086	14.82	(219,133)	2,631,322	14.69	(256,707)	2,892,210	14.70	(346,508)
Maximum	4,124,882	15.38	(15,011)	4,176,727	15.38	(22,256)	4,248,794	15.20	(74,942)
Sum (n*Mean)	1,079,375,701	14,285.31	(1,079,375,701)	1,125,855,961	14,287.39	(1,125,855,961)	1,247,948,508	14,304.73	(1,247,948,508)
Size (n)	1,000	1,000.00	1,000	1,000	1,000.00	1,000	1,000	1,000.00	1,000
Variance	383,316,248,120	0.04	383,316,248,120	406,114,559,820	0.04	406,114,559,820	423,780,960,152	0.04	423,780,960,152
Variance/Size	383,316,248	0.00	383,316,248	406,114,560	0.00	406,114,560	423,780,960	0.00	423,780,960
SQRT[Variance/Size]	19,578	0.01	19,578	20,152	0.01	20,152	20,586	0.01	20,586
STATISTIC	Haloperidol			Flupentixol			Paliperidone		
	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB
Mean	1,357,998	14.31	(1,357,998)	1,129,145	14.27	(1,129,145)	1,114,516	14.28	(1,114,516)
Std Deviation	702,605	0.20	702,605	631,121	0.20	631,121	633,690	0.20	633,690
Minimum	40,213	13.59	(5,454,745)	64,786	13.51	(4,120,336)	19,239	13.60	(4,149,277)
2.5%	397,729	13.95	(3,119,492)	273,924	13.90	(2,689,804)	252,666	13.92	(2,627,117)
10%	607,850	14.07	(2,276,831)	450,952	14.03	(1,982,095)	448,788	14.05	(1,991,113)
Median	1,225,691	14.31	(1,225,891)	1,003,920	14.28	(1,004,352)	976,142	14.28	(976,268)
90%	2,266,695	14.54	(610,557)	1,972,475	14.48	(452,108)	1,979,448	14.50	(449,047)
97.5%	3,119,492	14.72	(397,729)	2,689,804	14.68	(273,924)	2,627,117	14.71	(252,666)
Maximum	5,454,745	15.40	(40,213)	4,120,336	15.31	(64,786)	4,149,277	15.39	(19,239)
Sum (n*Mean)	1,357,997,796	14,312.62	(1,357,997,796)	1,129,145,431	14,273.87	(1,129,145,431)	1,114,516,197	14,284.09	(1,114,516,197)
Size (n)	1,000	1,000.00	1,000	1,000	1,000.00	1,000	1,000	1,000.00	1,000
Variance	493,653,539,386	0.04	493,653,539,386	398,314,092,449	0.04	398,314,092,449	401,563,304,063	0.04	401,563,304,063
Variance/Size	493,653,539	0.00	493,653,539	398,314,092	0.00	398,314,092	401,563,304	0.00	401,563,304
SQRT[Variance/Size]	22,218	0.01	22,218	19,958	0.01	19,958	20,039	0.01	20,039

Table F.2 Statistic PSA parameters (age of 25 years for 10 year time horizon, societal perspective)

STATISTIC	Haloperidol			Flupentixol			Paliperidone		
	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB
Mean	284,028	5.72	(284,028)	314,588	5.73	(314,588)	438,530	5.75	(438,530)
Std Deviation	180,663	0.14	180,663	185,572	0.16	185,572	250,826	0.16	250,826
Minimum	9,483	5.26	(1,188,370)	31,013	5.16	(1,313,557)	40,029	5.20	(1,887,726)
2.5%	52,210	5.42	(744,618)	77,353	5.36	(769,393)	104,594	5.39	(1,067,587)
10%	92,946	5.54	(537,728)	121,376	5.51	(563,703)	170,559	5.53	(766,051)
Median	242,619	5.73	(243,018)	273,887	5.75	(274,003)	384,927	5.77	(386,105)
90%	534,483	5.90	(93,097)	563,381	5.92	(121,711)	763,177	5.93	(170,609)
97.5%	744,618	5.98	(52,210)	769,393	6.00	(77,353)	1,067,587	6.02	(104,594)
Maximum	1,188,370	6.07	(9,483)	1,313,557	6.13	(31,013)	1,887,726	6.08	(40,029)
Sum (n*Mean)	284,027,821	5,722.35	(284,027,821)	314,588,279	5,728.22	(314,588,279)	438,530,050	5,749.88	(438,530,050)
Size (n)	1,000	1,000.00	1,000	1,000	1,000.00	1,000	1,000	1,000.00	1,000
Variance	32,639,134,385	0.02	32,639,134,385	34,436,792,924	0.02	34,436,792,924	62,913,723,253	0.02	62,913,723,253
Variance/Size	32,639,134	0.00	32,639,134	34,436,793	0.00	34,436,793	62,913,723	0.00	62,913,723
SQRT[Variance/Size]	5,713	0.00	5,713	5,868	0.00	5,868	7,932	0.00	7,932
STATISTIC	Risperidone			Zuclopenthixol			Fluphenazine		
	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB	Cost	Effectiveness	NMB
Mean	549,174	5.76	(549,174)	323,032	5.71	(323,032)	306,212	5.73	(306,212)
Std Deviation	361,022	0.16	361,022	185,995	0.16	185,995	185,830	0.16	185,830
Minimum	54,367	5.12	(3,157,886)	14,796	5.12	(1,306,432)	21,203	5.14	(1,263,009)
2.5%	121,667	5.41	(1,442,759)	66,291	5.35	(745,423)	66,548	5.37	(759,293)
10%	206,217	5.54	(981,681)	124,120	5.49	(567,712)	111,847	5.51	(552,657)
Median	470,032	5.77	(471,029)	288,363	5.73	(288,689)	262,187	5.74	(263,174)
90%	981,218	5.95	(206,746)	566,870	5.90	(124,141)	551,759	5.91	(111,864)
97.5%	1,442,759	6.03	(121,667)	745,423	5.99	(66,291)	759,293	6.00	(66,548)
Maximum	3,157,886	6.13	(54,367)	1,306,432	6.05	(14,796)	1,263,009	6.06	(21,203)
Sum (n*Mean)	549,174,248	5,756.98	(549,174,248)	323,031,862	5,714.28	(323,031,862)	306,211,530	5,726.07	(306,211,530)
Size (n)	1,000	1,000.00	1,000	1,000	1,000.00	1,000	1,000	1,000.00	1,000
Variance	130,337,169,746	0.02	130,337,169,746	34,594,140,248	0.03	34,594,140,248	34,532,703,333	0.02	34,532,703,333
Variance/Size	130,337,170	0.00	130,337,170	34,594,140	0.00	34,594,140	34,532,703	0.00	34,532,703
SQRT[Variance/Size]	11,417	0.00	11,417	5,882	0.01	5,882	5,876	0.00	5,876

VITA

Osot Nerapusee was born in 1963, Bangkok, Thailand. He graduated in B. Sc. Pharm, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand 1987, M.B.A. Thammasat University, Thailand 1999, and Ph.D. candidate, Social and Administrative Pharmacy, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Thailand during 2008-2013