Cost-Effectiveness Analysis of Adaptive Monitoring Strategies for Depression Treatment

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Abstract

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Depression is a significant challenge for the American medical care system and affects as high as 10% of the adult population in the U.S. There are many challenges in treating depression. People are reluctant to reveal their symptoms and seek care because many see mental health problem as a personal weakness. Meanwhile, a lack of effective monitoring and treatment interventions may slow down the recovery progress. This study performs a cost-effectiveness analysis (CEA) of adaptive depression monitoring and care strategies. A Markov decision-analytic model is developed to compare the projected cost and benefit of the adaptive monitoring strategies and the status quo in depression care. Quality-adjusted life-years (QALY) is used as a measurement of patients' long-term health benefit. We run the baseline analysis applying three different monitoring schedules and sensitivity analysis on major parameters including treatment effect and Markov transition matrices. Results of our CEA study suggest adopting adaptive monitoring strategy can be potentially cost-effective for major depression care and is therefore worthy of further observational research.

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I will always keep these valuable memories with me and keep moving forward on the road ahead.

DEDICATION

This thesis is dedicated to my parents Baoquan Yang and Shuyun Wang for all their supports and understanding.

Chapter 1. INTRODUCTION

Depression is a significant challenge for the American medical care system. In primary care settings, prevalence estimates of major depressive disorder range from 5% to 13% in all adults, with lower estimates in those older than 55 years (6% to 9%) [5]. There are many difficulties in treating depression. People are reluctant to reveal their symptoms and seek care for they see it as a personal weakness. Meanwhile, lack of effective monitoring and treatment interventions also slow down the recovery progress. In this chapter, current depression diagnostics and major treatments for depression will be reviewed. The second section will be a literature review on depression related cost-effectiveness analysis models. Although many cost-effectiveness analyses (CEA) have been done on different treatment strategies as well as some on screening methods, few CEA on adaptive monitoring strategy has been conducted.

1.1 DEPRESSION DIAGNOSTICS

Major depression (or clinical depression), as a medical condition, may lead to significant, long-lasting symptoms and affect a person's ability to perform routine tasks. Patients' suffering from depression is often related to factors including changes in brain function, genetics and life stresses etc. [1]. Depression is commonly detected in patients with other chronic diseases as well as in postpartum and pregnant women. It not only affects individuals but also harms families, business and society. From US Preventive Services Task Force (USPSTF), depression is among the leading causes of disability in people 15 years and older [2]. Depression is very often to be found with other co-occurring medical conditions. In patients with cardiac disease, hypertension, stroke, obesity and epilepsy, there is higher prevalence of major depressive disorder than in the general population [4]. As a mental illness that requires not only general medical resources but also specialty mental health treatment, depression is difficult to detect and the treatment usually costs significant resources.

Depression diagnosis is a complicated process including physical test and other necessary depressive symptoms checks. Widely used assessments of depression severity include the Patient Health Questionnaire (PHQ), Hopkins Symptom Checklist (HSCL-20) and Hamilton Rating

Scale-Depression (HRSD). PHQ-9 is a 3-page self-administered version of the primary care evaluation of mental disorder (PRIME-MD) that has been validated in two important studies where 8 primary care clinics and 3,000 patients were included [3]. In this study, we use PHQ-9 as patients' depression severity assessment. There are 9 items on the PHQ depression scale, consisting comparable sensitivity and specificity, while it's only half the length of many other depression measures. As shown in Table 1.1, PHQ-9 score ranges from 0 to 27 indicating 5 different depression severity from healthy to severe depression.

PHQ-9 SCORES	DEPRESSION SEVERITY
1 - 4	None
5 - 9	Mild
10 - 14	Moderate
15 - 19	Moderately Severe
20 - 27	Severe

Table 1.1 PHQ-9 scores and matching depression severity

1.2 Depression Treatment

In primary care settings, most commonly recommended treatments for depressive disorders are antidepressants medication and psychotherapy. For the selection of first-line medication, a lot of studies has been done trying to find the treatment with the greatest benefit and lowest risk. Selective serotonin reuptake inhibitor (SSRI) antidepressants are widely used in medication for patients with depression [6]. However, existing antidepressant treatments are not often effective. Evidence shows that as many as 40% of depressed patients meet treatment failures after first-line treatment [7]. Patients' responses also vary a lot with different treatment. Although switching treatment can usually bring more benefits for patients, evidence has shown that nearly one-half patients make no follow-up visits, which makes it hard for them to benefit from second-line treatment.

Besides medications, Shulberg et al. [8] found out that systematic and guideline-based depression treatment had improved outcomes than usual primary care in either clinical or functional outcomes. Simon et al. [9] proposed a stepped collaborative care program for depressed primary care patients, which turned out to bring significant increase in treatment effectiveness and moderate increase in costs. They also evaluated the cost-effectiveness of collaborative depression care management considering patients' willingness-to-pay and quality-adjusted life year (QALY) gained. In our study, a collaborative depression management program is being considered as the

second-line treatment for patients with major depressive disorders, which will be introduced in detail in the following chapters.

1.3 SCREENING AND MONITORING

Besides medication and psychotherapy, screening and monitoring are two important methods to identify patients with depression symptoms and make necessary follow-ups to ensure patients to have on-time treatment adjustment or switching.

In 2016, USPSTF has recommended screening for depression in the general adult population with the use of PHQ-9 that typically take less than 5 minutes to complete. It also underscores the necessity for screening to be linked with adequate systems in place to ensure accurate diagnosis, effective treatment and appropriate follow-ups [2]. Many studies have been done to evaluate the cost-effectiveness of screening. In CEA study by Valenstein et al. [10], the cost-effectiveness of annual screening for depression in primary care patients is as high as $192,444/QALY. Although annual and periodic screening for depression may cost more than patients' willingness to pay (WTP), one-time screening is cost-effective. Elizabeth et al. [11] conducted a systematic review on screening for depression in adult patients. More than 100 studies were included with the conclusion that depression screening without crucial professional medical care supports are not likely to achieve substantial outcomes. It also underscores the importance of close monitoring of adult patients who are under on-going antidepressant treatment.

For the best of our knowledge, almost no CEA on adaptive monitoring for major depression patients has been conducted. For patients with different depression severity trajectories, monitoring frequency may also vary from person to person. The main idea is by adopting adaptive monitoring strategy, we want to catch patients at the right time, as much as possible, to make treatment adjustment for their best interest.

1.4 OBJECTIVE AND COST EFFECTIVENESS ANALYSIS

Due the limitation of healthcare resources, resource allocative efficiency is important to be considered when conducting new interventions to patients in medical field. CEA is an effective way to provide insights for policymakers in order to make informed decisions. A CEA would

require that explicit probabilities be assigned to events for all pathways as well as treatment cost and outcomes [10].

In this study, Firstly, a Markov decision-analytic model will be developed to simulate patients' depression progression, treatment and monitoring status on patients' group level for life-time. Then, we will conduct an explicit CEA incorporating different treatment cost, patients' QALY to evaluate the proposed adaptive monitoring strategy for patients who are currently under depression treatment and are willing to be monitored for long term.

Chapter 2. METHODS

This chapter will discuss methodologies including Markov model development, data sources and parameter settings. A Markov decision-analytic model will be developed to simulate the long-term effect on health outcomes and costs, as an evaluation for the adaptive depression monitoring strategy. Two monitoring strategies will be evaluated: the current status quo and the adaptive monitoring strategy. According to patients' specific depression trajectory pattern, they will be assigned varied monitoring interventions. Then depending on treatment responses, patients may have different subsequent treatment interventions.

2.1 MARKOV DECISION-ANALYTIC MODEL

2.1.1 *Model Schematics*

A model schematic is presented to illustrate how Markov decision-analytic model is developed as Figure 2.1. There are two monitoring strategies: status quo and adaptive strategy. Patients under status quo are following a fixed monitor frequency while patients under adaptive strategy will be assigned to an adaptive monitoring frequency. Patients are assumed to be in one of the five subgroups according to their trajectory patterns.

The Markov node is where cohort begins entering the Markov process. Patients start from an initial depression state. At each cycle, patients will either take monitoring or skip monitoring depending on their own monitoring schedule. If they are monitored, certain intervention (action) will be taken based on patients' specific situations. Then all patients progress to the next state

according to a transition matrix differs by treatment status. Cycle length in the model is set to be two weeks.

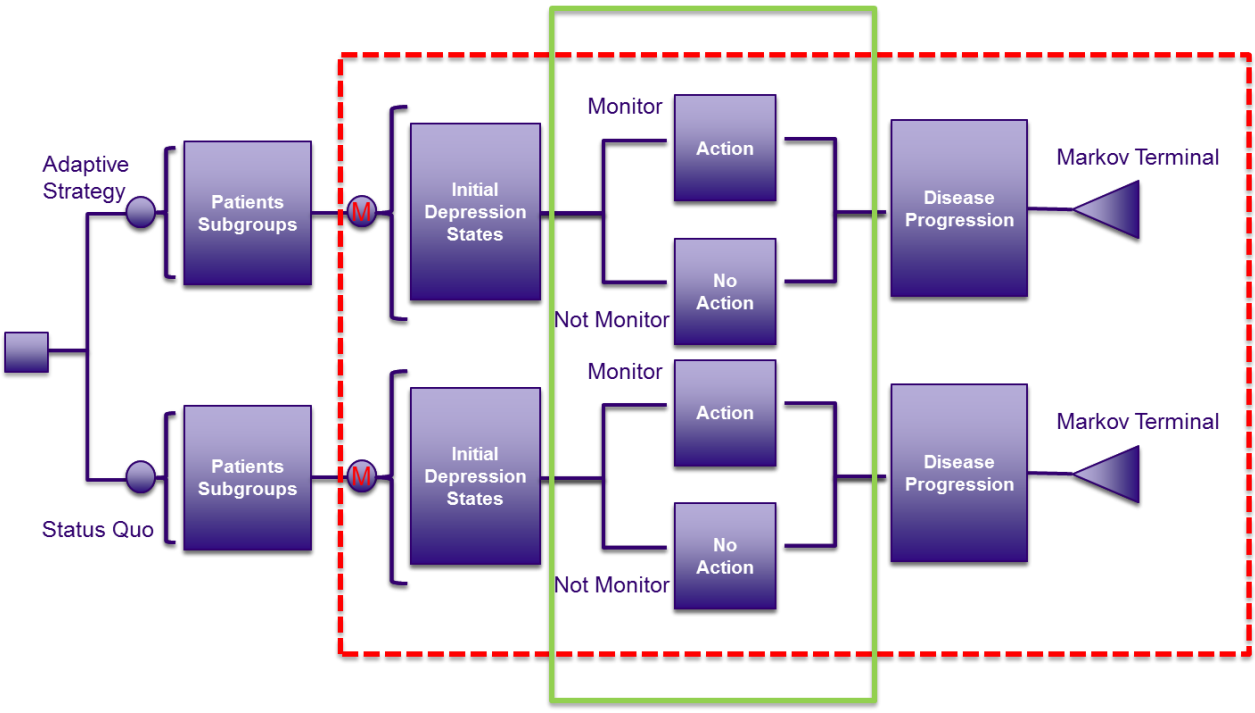

Figure 2.1 Markov decision-analytic model schematics

(: Decision node; : Logic node; M : Markov node; In red square is the Markov decision process and in green square is the intervention part.)

2.1.2 *Interventions and Markov States*

If patients are being monitored in the current cycle, three options are provided when patients come to the intervention process. 1) Patient will stay in the current treatment and keep being monitored. This is for patients whose treatment works well but still need necessary follow-ups. 2) Patient will be switched to a second-line treatment and keep being monitored. This is for patients who meet treatment failure and need to be switched to a second-line treatment. 3) Patient will be dropped out of monitoring and stay with the current treatment. This is for patients with positive treatment response and close to remission. As mentioned in the previous chapter, when dealing with treatment failures, physicians usually augment the current medication or switch patients to a second-line treatment. In this study, a second-line treatment is applied when patients meet treatment failure. Figure 2.2 is a demonstration of how patients will evolve from mild depression to the next cycle.

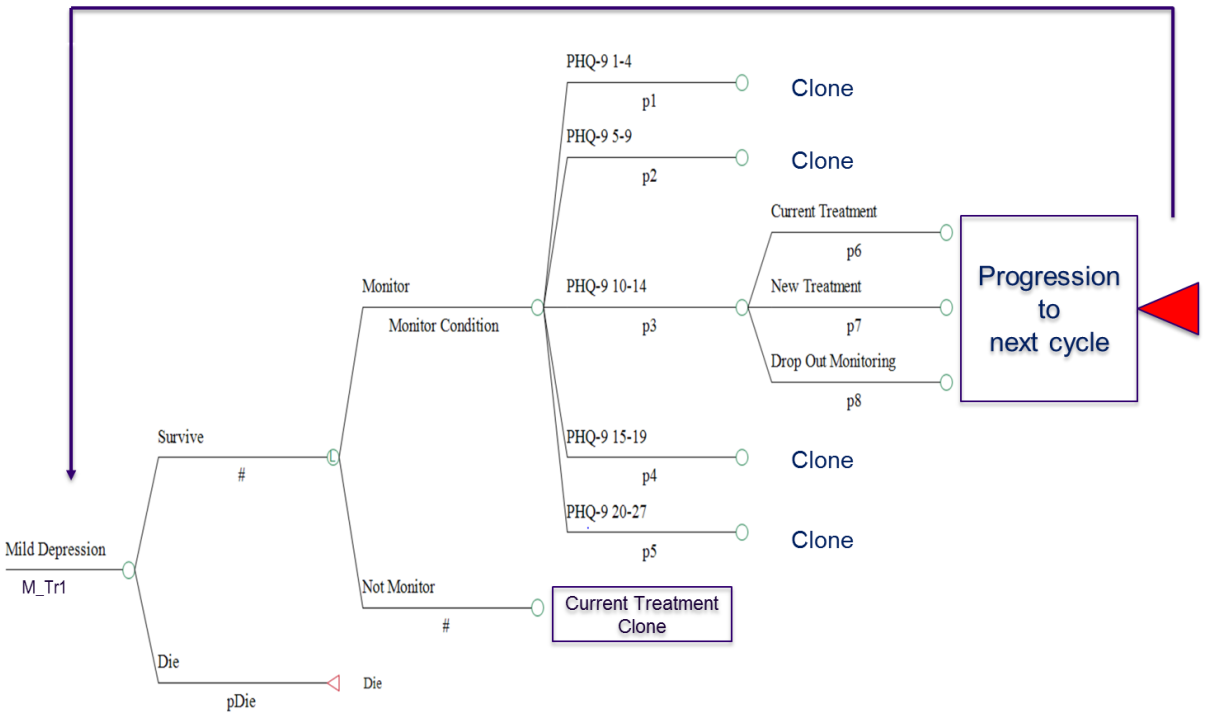

Figure 2.2 Demonstration of Markov state progression

Based on depression severity measured from PHQ-9 scores, patients are diagnosed into five depression states; Healthy, Mild Depression, Moderate Depression, Moderately Severe Depression and Severe Depression. For monitoring status, patients are either being monitored or dropped out of monitoring. For treatment status, patients are either in first-line treatment or second-line treatment. To sum up, there are in total 20 Markov states being applied to the model as shown in Table 2.1.

Healthy_M_Tr1	Mild_M_Tr1	Mod_M_Tr1	ModSevere_M_Tr1	Severe_M_Tr1
Healthy_M_Tr2	Mild_M_Tr2	Mod_M_Tr2	ModSevere_M_Tr2	Severe_M_Tr2
Healthy_NM_Tr1	Mild_NM_Tr1	Mod_NM_Tr1	ModSevere_NM_Tr1	Severe_NM_Tr1
Healthy_NM_Tr2	Mild_NM_Tr2	Mod_NM_Tr2	ModSevere_NM_Tr2	Severe_NM_Tr2

Table 2.1 Markov states

(M: Monitoring; NM: No monitoring; Tr1: First-line treatment; Tr2: Second-line treatment.)

2.2 COHORTS INFORMATION AND DEPRESSION PROGRESSION PATTERN

The Markov decision-analytic input data is from Electronic Health Record (EHR) where patients take the PHQ-9 questionnaire. The database contains above 6000 patients with ongoing antidepressant medications, of which 70% are female and 30% are male. We assume these patients represent progression on first-line treatment.

From the EHR data, patients' depression has varied progression trajectories. Lin et al. [34] classified patients into five subgroups based on their PHQ-9 scores progression patterns using K-means clustering method. The five subgroups are: Stable Low Group, patients PHQ-9 scores always stay under 5; Increasing Group, patients are getting worse as time goes by; Decreasing Group, patients PHQ-9 scores are getting smaller over time; Fluctuating Group, patients with unstable progression; Stable High Group, PHQ-9 scores stay high meaning there are no improvement over time.

As shown in Figure 2.3, the x-axis shows the number of biweeks as depression progresses (patients are being monitored every two weeks). Y-axis shows patients' PHQ-9 scores.

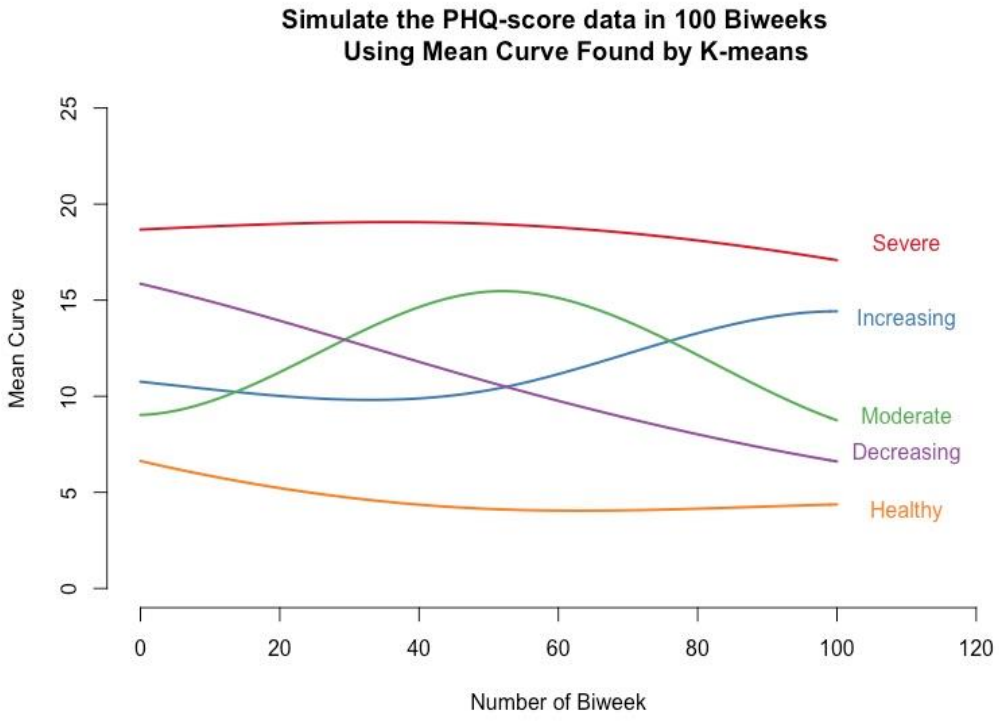

Figure 2.3 Patients subgroup patterns from Lin et al. [34]

Based on EHR data, Jiaqi et al. [33] has derived Markov transition matrices for each of the five subgroup patients using counting method. These matrices are applied to the Markov decision-analytic model as transition matrices for patients under first-line treatment (Table 2.3 – 2.7).

Table 2.2 shows the initial states distribution of depression states in each of the five subgroups in the Markov decision-analytic model.

Subgroup	*H*	*Mi*	*Mo*	*MS*	*S*
Increasing	9.53%	33.45%	42.38%	12.09%	2.55%
Decreasing	0.23%	3.84%	41.07%	40.47%	14.39%
Stable Low	38.08%	41.73%	16.99%	3.03%	0.17%
Stable High	0.32%	2.74%	16.25%	40.39%	40.31%
Fluctuating	20.78%	37.48%	32.65%	8.16%	0.93%

(Note: H, healthy state; Mi, mild depression state; Mo, moderate depression state; MS, moderately severe depression state; S, severe depression state.)

Table 2.2 Patients' initial states distribution by subgroups

Increasing	H	Mi	Mo	MS	S
H	0.9489	0.0511	0	0	0
Mi	0.0033	0.9692	0.0275	0	0
Mo	0	0.0078	0.9801	0.0121	0
MS	0	0	0.0205	0.9696	0.0099
S	0	0	0	0.0302	0.9698

Table 2.3 Markov transition matrix (UC Treatment) – Increasing Group [33]

Decreasing	H	Mi	Mo	MS	S
H	0.9900	0.0100	0	0	0
Mi	0.0201	0.9755	0.0044	0	0
Mo	0	0.0373	0.9610	0.0017	0
MS	0	0.0001	0.0796	0.9192	0.0010
S	0	0	0	0.1578	0.8422

Table 2.4 Markov transition matrix (UC Treatment) – Decreasing Group [33]

Stable Low	H	Mi	Mo	MS	S

H	0.9917	0.0083	0	0	0
Mi	0.0173	0.9799	0.0028	0	0
Mo	0	0.0737	0.9242	0.0021	0
MS	0	0	0.1186	0.8753	0.0061
S	0	0	0	0.0556	0.9444

Table 2.5 Markov transition matrix (UC Treatment) – Stable Low Group [33]

Stable High	H	Mi	Mo	MS	S
H	0.8333	0.1667	0	0	0
Mi	0.0085	0.9232	0.0683	0	0
Mo	0	0.0059	0.9681	0.0260	0
MS	0	0	0.0119	0.9803	0.0078
S	0	0	0	0.0218	0.9782

Table 2.6 Markov transition matrix (UC Treatment) – Stable High Group [33]

Fluctuating	H	Mi	Mo	MS	S
H	0.9603	0.0397	0	0	0
Mi	0.0076	0.9717	0.0208	0	0
Mo	0	0.0139	0.9768	0.0093	0
MS	0	0	0.0245	0.9722	0.0032
S	0	0	0	0.0467	0.9533

Table 2.7 Markov transition matrix (UC Treatment) – Fluctuating Group [33]

2.3 STATUS QUO AND ADAPTIVE MONITORING STRATEGY

To simulate the monitoring status quo in healthcare setting for major depression treatment, we set up two type of monitor schedules in the model. In status quo 1(SQ1), patients are being monitored every 6 months. In 2013, Group Health Cooperative suggested a minimum of three patient follow-ups be made after diagnosis [36]. Based on this follow-up frequency suggestion, we set the patients in status quo 2 (SQ2) to be monitored at 4^{th} week, 8^{th} week and 6^{th} month after diagnosis.

The basic principle of the adaptive monitoring strategy is to take patients' disease progression into consideration so that patients in Increasing Group, Stable High Group and Fluctuating Group get relatively higher monitoring frequency compared to the other two groups. Shang et al. [35] developed a personalized depression prediction model and subgroup-specific

monitoring schedules based on three monitoring rules. Under each monitoring rule, patients are assigned to different monitoring frequencies depending on the subgroup they belong to.

Table 2.3 shows the monitoring schedule for SQ1 and three monitoring rules on subgroup level in month unit. For example, number 6 means patient will be monitored every 6 months and 0.5 means they are being monitored every half month. All patients in SQ1 and 3 rules in adaptive monitoring will be monitored from age of 31 until age of 70. Patients in SQ2 will only be monitored for 3 times (4^{th} week, 8^{th} week and 6^{th} month), after diagnosis or each time when they start a new treatment.

Figure 2.4 is a flow chart demonstrating adaptive monitoring Rule 3. Three monitor scheduling rules are [35]:

1. Patients come back in 2 months if score < 10, 1 month if 10<score<15, 2 weeks if score >15;
2. Patients come back in 6 months if score < 10, 4 months if 10<score<15, 4 weeks if score >15;
3. Patients come back in 12 months if score < 10, 6 months if 10<score<15, 2 months if score >15;

Subgroups	*SQ1*	*Rule1*	*Rule2*	*Rule3*
Increasing	6.0	1.0	3.5	7.0
Decreasing	6.0	1.0	4.0	6.5
Stable Low	6.0	2.0	5.5	11.0
Stable High	6.0	0.5	1.5	3.0
Fluctuating	6.0	1.0	4.0	7.0

Table 2.8 Monitoring schedules for SQ1 and adaptive strategy [35]

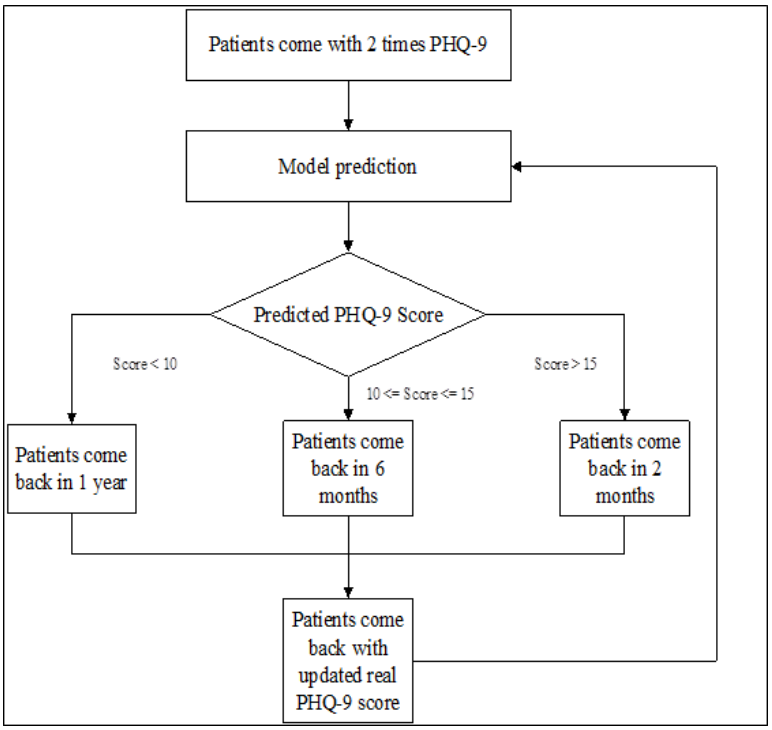

Figure 2.4 Flow chart of monitoring scheduling system based on depression prediction model from Shang et al. [35]

2.4 INTERVENTIONS

2.4.1 *Switch Patients to Second-Line Treatment*

In Markov decision-analytic model, two treatment options are applied. Simon et al. [12] conducted an observational research, where they focused on evaluating the impact of a systematic primary care-based depression treatment program. They compared the treatment effect of Usual Care (UC) and Depression Management Program (DMP) in primary care settings and concluded that a systematic primary care-based treatment program can decrease depression severity and improve general health status compared with usual care.

From our EHR data, although there is no detail information about patients' specific treatments, most of them are taking antidepressant medication, which is considered as Usual Care. When treating patients with major depression, about 40% patients won't respond to the first-line treatment [7]. When failure happens, the most common method is to either do augmentation of current medication treatment or switch to a second-line treatment. Studies have shown that there is no strong evidence showing one strategy is superior to the other. Therefore, to simplify, we

assume when entering the Markov model, all patients are under usual care (UC) treatment. When there is no response in UC, patients may be switched to the second-line treatment, which is similar to the Depression Management Program (DMP).

Different from traditional treatment, DMP consists of patient education materials, physician education programs, telephone-based treatment coordination, and antidepressant pharmacotherapy initiated and managed by patients' primary care physicians [13]. A group of 1465 patients were included in the study [12] and 407 patients met eligibility criteria. 218 patients were involved in the DMP group and 189 in the UC group.

Since we already assumed transition matrices for the UC group, how could we estimate the transition matrices for second-line treatment (DMP)? In Simon's study [13], patients' depression severity is being assessed by the Hamilton Depression Rating Scale (HDRS). HDRS is a multiple item questionnaire used to provide an indication of depression severity and HDRS results are converted to depression free days (DFD). DFD is a commonly used outcome measurement for depression treatment. Since we are using PHQ-9 scores as outcome of measurement, conversion between these two measurements is another issue to solve. Next, we will first calculate the patients' switch treatment probability and then walk through the process of deriving the Markov transition matrices for DMP treatment estimated from to Simon's study [13].

Probability of being Switched to the Second-Line Treatment

As mentioned before, the probability of first-line treatment (e.g. antidepressant) failure is 40% during an 8 weeks monitoring period [7]. In our Markov decision-analytic model, the cycle-length is set to be 2 weeks. We converted the 40% to a biweekly probability with rate-probability formulas:

$$r = \frac{-\ln(1-p)}{t} \tag{2.1}$$

$$p = 1 - \exp(-rt) \tag{2.2}$$

The probability of first-line treatment failure biweekly is 0.092 with the above calculations. When patients meet treatment failure, they are supposed to be switched to a second-line treatment. Therefore, in our model, we use this probability as the switch treatment probability for patients in Stable High, Increasing and Fluctuating subgroups.

Treatment Effect Derived from Literature

In Simon's study [12], depression severity is assessed by HRDS and then converted to depression free days (DFD) to evaluate treatment effect. Depression-free days were first brought up in Lave's study using HRDS assessment scores [14]. If patients have a HRSD score of 7 or lower, they are assumed to have a full DFD. If patients have HRDS score of 22 or higher, assumption will be made that they lack a DFD. Between 7 and 22, DFD is calculated by linear interpolation.

Similarly, PHQ-9 scores, as another measurement of depression severity, could also be converted to DFDs. Vannoy et al. [15] demonstrated one way to generate the conversion. Cutoff point was chosen with DFD being 1 if PHQ-9 score is smaller than 5, which is considered the healthy state. With PHQ-9 scores bigger than 14, patients will have 0 DFD. And middle values are determined by linear interpolation. Table 2.9 shows the conversion between PHQ-9 scores to DFD with the same criteria of five depression states defined in the Markov decision-analytic model. The connection between PHQ-9 score and HRSD score is established.

PHQ-9 scores	*DFD Scale*
1-4	1
5-9	0.67
10-14	0.33
15-19	0
20-27	0

Table 2.9 Scale of PHQ-9 scores to DFD

Figure 2.5 shows patients' scores on HDRS during the 12-month study [12]. The base-line treatment is Usual Care while the other treatment is DMP. Patients are being monitored five times in one year. If we conduct linear interpolation in the middle where there are no monitoring results, total average DFD in one year could be derived for both groups of patients. Then the ratio of two treatments effects (UC and DMP) is calculated in the following:

$$\frac{DFD_{UC}}{DFD_{DMP}} = \frac{181.9}{229.3} = 0.7933 \tag{2.3}$$

Recall the goal is to figure out how to apply treatment effect into the model and modify UC transition matrix so that we could come up with a new transition matrix for DMP treatment.

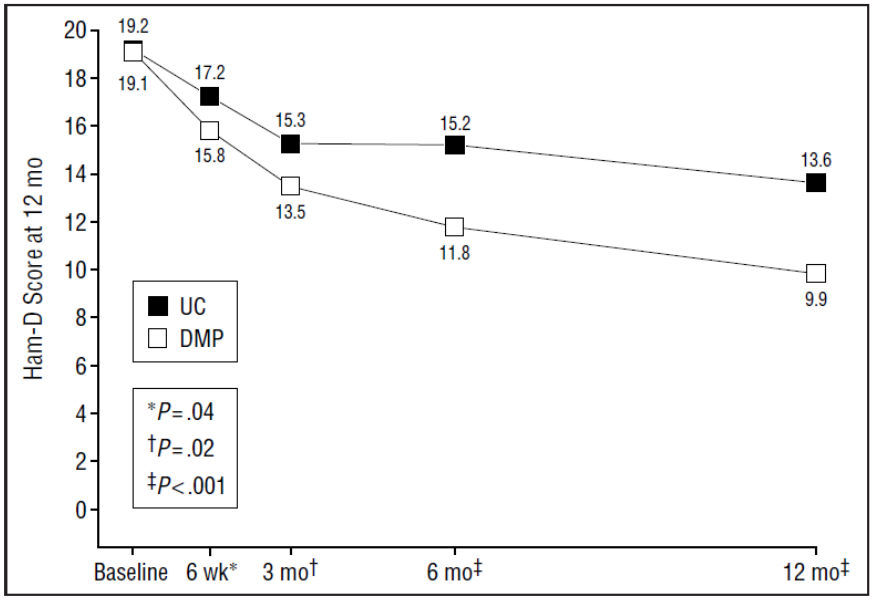

Figure 2.5 Patients' scores on HDRS during 12-month study [12]

Markov Stationary Distribution

For any irreducible ergodic Markov chain, $\lim_{n\to\infty} p_{ij}^{(n)}$ exists and is independent of i. Furthermore,

$$\lim_{n\to\infty} p_{ij}^{(n)} = \pi_j > 0, \tag{2.4}$$

where the π_j uniquely satisfy the following **steady-state equations** [16]

$$\pi_j = \sum_{i=0}^{M} \pi_i p_{ij}, \quad for\ j = 0,1 \ldots M, \quad (\bar{\pi} = \bar{\pi} * \mathbf{P}, \ \mathbf{P} \text{ is transition matrix})$$

$$\sum_{j=0}^{M} \pi_j = 1. \tag{2.5}$$

Current Markov transition matrices can be proved irreducible and ergodic. When Markov chain comes to steady states, $\boldsymbol{\pi}$ is taken as the stationary distribution of all Markov states. Since transition matrix of UC treatment is fixed, its stationary distribution is unique. Table 2.10 presents the calculated steady-state distribution for patients under first-line treatment. π_j represents steady-state probability for its indicated j depression states (5 depression states in total).

UC Stationary	**Increasing**	**Decreasing**	**Low**	**High**	**Fluctuating**

$\pi 1$	0.0089	0.6437	0.6684	0.0011	0.0581
$\pi 2$	0.1357	0.3183	0.3193	0.0215	0.3047
$\pi 3$	0.4794	0.0373	0.0121	0.2469	0.4540
$\pi 4$	0.2830	0.0008	0.0002	0.5384	0.1713
$\pi 5$	0.0929	0.0000	0.0000	0.1921	0.0119

(Note: π_i is the steady – state distribution of the ith state, with i=1,2,3,4,5 indicating the five depression states respectively)

Table 2.10 Steady-state distribution of 5 subgroups patients under UC treatment

With the concept of steady-state probability, a reasonable assumption can be made that, if a different treatment has been applied to the same group of patients, we would result in a different steady-state distribution. According to Figure 2.5, since it already has been observed that DMP has better treatment effect compared to UC, if we apply DMP to the same groups of patients in our Markov decision-analytic model, there will be an improved steady-state probability distribution. As more patients will be pushed to a relative healthier depression state, the probability in healthier states will become larger with probability in more severe depression states becoming smaller, compared with UC treatment.

It is already established that each depression state has its range regarding PHQ-9 scores. PHQ-9 scores could be converted to DFD from certain scale. Therefore, a weighted average DFD for UC could be calculated using current Markov steady-state distributions and its matching scaled DFD. In conclusion, treatment effect ratio between UC and DMP can be represented in another way:

$$\frac{DFD_{UC}}{DFD_{DMP}} = \frac{\sum \pi_i S(PHQ9_i)}{\sum \pi_i' S(PHQ9_i)} = 0.7933 \quad (2.6)$$

($S(PHQ9_i)$ represents scale of PHQ9 scores to DFD in i depression state.)

Here, the weighted average DFD from DMP treatment could be calculated, which is the sum product of $\boldsymbol{\pi}$ and PHQ-9 scales. Next step will be calculating each π_i' for the new treatment. Figure 2.6 shows the demographics and other characteristics of patients in Simon et. al.'s study. All patients started with average HRSD scores around 19. Patients under UC ended with average HRSD scores of 13.6 and DMP with 9.9. Based on the depression severity it indicated, DMP has pushed more people from Mild and Moderate to Healthy and Mild states.

Demographic and Patient Characteristics*

	DMP (n = 218)	UC (n = 189)	P†
Age, y, mean (95% CI)	45.6 (44.0-47.1)	45.4 (43.9-46.9)	.89
Female, % (95% CI)	76.6 (70.9-82.4)	78.3 (71.7-84.9)	.69
White, % (95% CI)	87.6 (82.4-92.8)	77.3 (70.5-84.0)	.02
Married, % (95% CI)	71.1 (64.6-77.6)	65.6 (58.8-72.5)	.25
Years of education, mean (95% CI)	13.6 (13.4-13.9)	13.8 (13.4-14.1)	.52
Depression status, % (95% CI)			
Current	64.7 (59.4-70.0)	63.5 (56.4-70.6)	.79
Partial remission	35.3 (30.0-40.6)	36.5 (29.4-43.6)	.79
SF-20 subscales, mean (95% CI)			
Ham-D	19.1 (18.7-19.6)	19.2 (18.7-19.7)	.75
MHI-5	47.4 (44,7-50.0)	48.5 (45.7-51.4)	.56
GHP	37.4 (34.2-40.6)	38.6 (34.8-42.4)	.64
PF	54.6 (50.2-58.9)	50.4 (45.6-55.1)	.20
Patient seeing mental health provider (last 2 y), % (95% CI)	33.9 (27.8-40.1)	34.4 (27.2-41.6)	.93
Inadequate trial of antidepressant (last 90 d), % (95% CI)	24.3 (18.5-30.1)	13.8 (7.7-19.8)	.01

Figure 2.6 Demographic and patient characteristics [12]

With that in mind, and due to the constraints we have so far, assumptions are made that: π_1, π_2 increase while π_3, π_4, π_5 decrease the same percentatge:

$$\Delta\pi_1 = \Delta\pi_2, \Delta\pi_3 = \Delta\pi_4 = \Delta\pi_5 \tag{2.7}$$

$\boldsymbol{\pi}'$ is then calculated as shown in Table 2.11. Noted that we only apply new treatment to subgroup where patients are actually getting worse with the first-line treatment. Therefore, patients in Decreasing and Stable Low subgroups will stay in the original treatment meaning that their Markov transition matrices stay the same. Only patients in Increasing, Stable High and Fluctuating subgroups will be switched to new Markov transition matrices.

DMP Stationary	Increasing	Decreasing	Low	High	Fluctuating
$\pi 1$	0.0153	0.6437	0.6684	0.0027	0.0874
$\pi 2$	0.2344	0.3183	0.3193	0.0525	0.4578
$\pi 3$	0.4205	0.0373	0.0121	0.2386	0.3241
$\pi 4$	0.2482	0.0008	0.0002	0.5205	0.1223
$\pi 5$	0.0815	0.0000	0.0000	0.1857	0.0085

Table 2.11 Steady-state distribution of 5 subgroups patients under DMP treatment

New Markov Transition Matrices Calculation

With the new Markov steady-states distribution, next step is to back track new Markov transition matrices under DMP treatment. Transition matrix for each subgroup is 5-by-5, which means there are too many degree of freedoms if we don't add additional constraints. Similar to the assumption we made before, DMP treatment mainly improve patients in Mild and Moderate states to healthier states:

$$P_{22} \uparrow, P_{23} \downarrow, P_{32} \uparrow, P_{33} \downarrow$$

(Note: P_{ij} represents transition probability from depression state i to depression state j. 1, Healthy; 2, Mild; 3, Moderate; 4, Moderately Severe; 5, Severe)

Also, the constraint that the transition probability from certain depression state to other states should sum up to 1:

$$\begin{cases} \sum_{j=1}^{5} p_{ij} = 1 \\ \pi_j = \sum_{i=0}^{M} \pi_j p_{ij} \end{cases}$$

$$i, j = 1,2,3,4,5 \qquad (2.8)$$

Table 2.12 - Table 2.14 are the calculated Markov transition matrices from the above method. Results that are marked with yellow are real changes due to treatment effects. There are limitations of this calculation methodology, which will be discussed in Conclusion.

Increasing	H	Mi	Mo	MS	S
H	0.9489	0.0511	0	0	0
Mi	0.0033	0.9759	0.0207	0	0
Mo	0	0.0115	0.9763	0.0121	0
MS	0	0	0.0205	0.9696	0.0099
S	0	0	0	0.0302	0.9698

Table 2.12 Markov transition matrix under DMP treatment (Increasing Group)

Stable High	H	Mi	Mo	MS	S
H	0.8333	0.1667	0	0	0
Mi	0.0085	0.9442	0.0473	0	0
Mo	0	0.0107	0.9634	0.0260	0
MS	0	0	0.0119	0.9803	0.0078
S	0	0	0	0.0218	0.9782

Table 2.13 Markov transition matrix under DMP treatment (Stable High Group)

Fluctuating	H	Mi	Mo	MS	S
H	0.9603	0.0397	0	0	0
Mi	0.0076	0.9772	0.0152	0	0
Mo	0	0.0218	0.9689	0.0093	0
MS	0	0	0.0245	0.9722	0.0032
S	0	0	0	0.0467	0.9533

Table 2.14 Markov transition matrix under DMP treatment (Fluctuating Group)

2.4.2 *Drop patients out of monitoring*

In the previous section, we discussed how to deal with patients with deteriorating depression disease. There are also patients who are getting better and or becoming stable in relative healthy states. If patients are in Decreasing and Stable Low subgroups and if their depression states are either Healthy or Mild, we modeled a 10% yearly rate of dropping out of monitoring to save cost and medical resources. This annual dropping out probability is converted into biweekly probability before applied to the Markov decision-analytic model. This number will be explored more in later Sensitivity Analysis section.

After patients are dropped out of monitoring, they are assumed to still keep the current treatment strategy and progressing under the same Markov transition matrices.

2.4.3 *Keep current treatment and progression*

For patients with ongoing treatment who are neither switched to a second-line treatment nor dropped out of monitoring, they are suggested to keep being monitored and stay with the current treatment for further follow-ups. In our model, the probability of this intervention will be

calculated as (1-*pSwitch-pStopMonitoring*), *pSwitch* is the probability of switching patients to DMP while *pStopMonitoring* is the probability of dropping patients out of monitoring in the current Markov cycle.

2.5 MORTALITY AND HAZARD RATIO

In this Markov decision-analytic model, when entering the model, patients' average age is 31 years old. The proposed plan is to monitor patients for life-time. Notice that there are 20 Markov transition states in total and an additional dead state that is an absorbing state. As shown in Figure 2.2, when cohort starts evolve at the beginning of each cycle, they will hit a probability node controlled by *pDie*, which is the probability of dying at the current cycle. *pDie* is calculated from the U.S. Life Table and an estimated major depression mortality hazard ratio from literature.

The death rate of ordinary cohort at each age can be obtained from [31]. The probability of dying each cycle (biweekly) is calculated as follow using the rate-probability formula:

$$p = 1 - \exp(-rt) \tag{2.9}$$

$$(r: death\ rate\ per\ unit\ time; t: time;)$$

Literature review has been conducted to explore the mortality hazard ratio for major depression. Major depression hazard ratio can be affected by many factors, Zheng et al. [19] focused on investigating risk among white people in the U.S. Other co-occurring medical conditions can also have an impact. For example, patients with depression and cardiac diseases usually have higher risk of dying compared with patients suffering only from major depressive symptoms. In this paper, since we only consider patients' depressive disorders, impact from other co-occurring diseases should be accounted. Cuijpers et al. [22] conducted meta-analysis aiming to compare excess mortality in major depression with that in subthreshold depression. 18,705 participants were included, of whom 2,881 died during follow-up. Results showed that the relative risk of dying in major depression compared with participants without depression was 1.58 (%95 CI 1.31-1.89, P<0.001).

The 1.58 hazard ratio is used in this study to account for the higher risk of death for major depression. Although some research do observe a difference between male and female depression mortality [18], evidence is not convincing enough to support it.

2.6 REWARDS IN MARKOV DECISION-ANALYTIC MODEL

There are three types of rewards being evaluated in the model. Treatment effectiveness is calculated using quality-adjusted life year (QALY). Two types of treatment cost are included as Markov state cost. Monitoring cost is input as Markov transition cost when patients are being monitored. We discounted future cost using an annual discount rate of 3%.

We combined several important studies for depression states utilities. In Revicki et al.'s study [32], seventy patients with major depressive disorder or dysthymia completed at least 8 weeks of antidepressant treatment. Participants' depression severity was being assessed by HRSD and they took standard gamble interviews to obtain utilities for different depression-related states, varying depression severities. The mean of utility number for severe depression is 0.30, 0.63 for moderate depression and 0.73 for mild depression. Since we also have moderately severe depression in our model, utility for moderately severe depression is calculated through linear interpolation. Utilities for the five depression states are shown in Table 2.15.

Depression States	uHealthy	uMild	uMod	uModSevere	uSevere
Utility	0.900	0.730	0.630	0.465	0.300

Table 2.15 Utilities for depression states

2.7 COST OF TREATMENTS AND MONITORING

Cost of two treatments UC and DMP, cost of one-time monitoring are all obtained from Simon et al. [9] shown in Table 2.16.

Name	**Base case**	**Min**	**Max**
Cost of Monitoring	135	132	138
Cost of UC Treatment	3909	3123	4695
Cost of DMP Treatment	5549	4313	6784

Table 2.16 Cost of treatments and one-time monitoring

2.8 OTHER PARAMETER INPUT TABLE

Other input parameters, including initial trajectory subgroup distributions, initial depression states distributions are listed in Appendix.

Chapter 3. RESULTS AND DISCUSSIONS

In this chapter, results of cost-effectiveness analysis will be presented. Important outcomes including incremental cost-effectiveness ratios (ICERs), discounted total cost and QALYs, since those are the most important factors decision makers would care about in order to make informed decisions. Sensitivity analysis on all influential factors are carried out to interpret the results in-depth.

3.1 SCENARIO ANALYSIS ON MONITORING SCHEDULES

We input the three adaptive monitoring schedules from Table 2.8 into our model, and run cost-effectiveness analysis for patients starting from age 31 until age 100. The results are shown in Table 3.1.

SCHEDUEL	STRATEGY	COST	EFF	INCRCOST	INCREEFF	ICER
Rule 1	SQ2	146,484	17.3034			
	SQ1	180,236	17.4381	33,752	0.1346	250,697
	ADP	232,666	17.4745	52,429	0.0364	1,438,841
Rule 2	SQ2	146,484	17.3034			
	SQ1	180,236	17.4381	33,752	0.1346	250,697
	ADP	193,647	17.4575	13,411	0.0194	689,676
Rule 3	SQ2	146,484	17.3034			
	SQ1	180,236	17.4381	33,752	0.1346	250,697
	ADP	179,816	17.4398	33,332	0.1364	244,447

(Note: SQ, Status Quo; ADP, Adaptive monitor schedules)

Table 3.1 CEA results for three monitoring schedules

From the above results, we can tell that ADP in Rule 3 is cost-saving against SQ1. To better understand the cost-effectiveness among the four monitor schedules and check if there is extended dominance, we recalculated the ICER with the ranking based on cost shown in Table 3.2. We can tell that both Rule 1 and Rule 2 are not cost-effective against either SQ1 or SQ2 if we set the threshold of ICER to be $100,000/QALY. Rule 3 is cost-effective against SQ1 but not SQ2.

SCHEDULE	***COST***	***EFF***	***ICER***
SQ2	146,484	17.3034	
ADP RULE 3	179,816	17.4398	244,447
SQ1	180,236	17.4381	DOMINATED

ADP RULE 2	193,647	17.4575	780,421
ADP RULE 1	232,666	17.4745	2,296,131

Table 3.2 ICER analysis on 5 monitor schedules

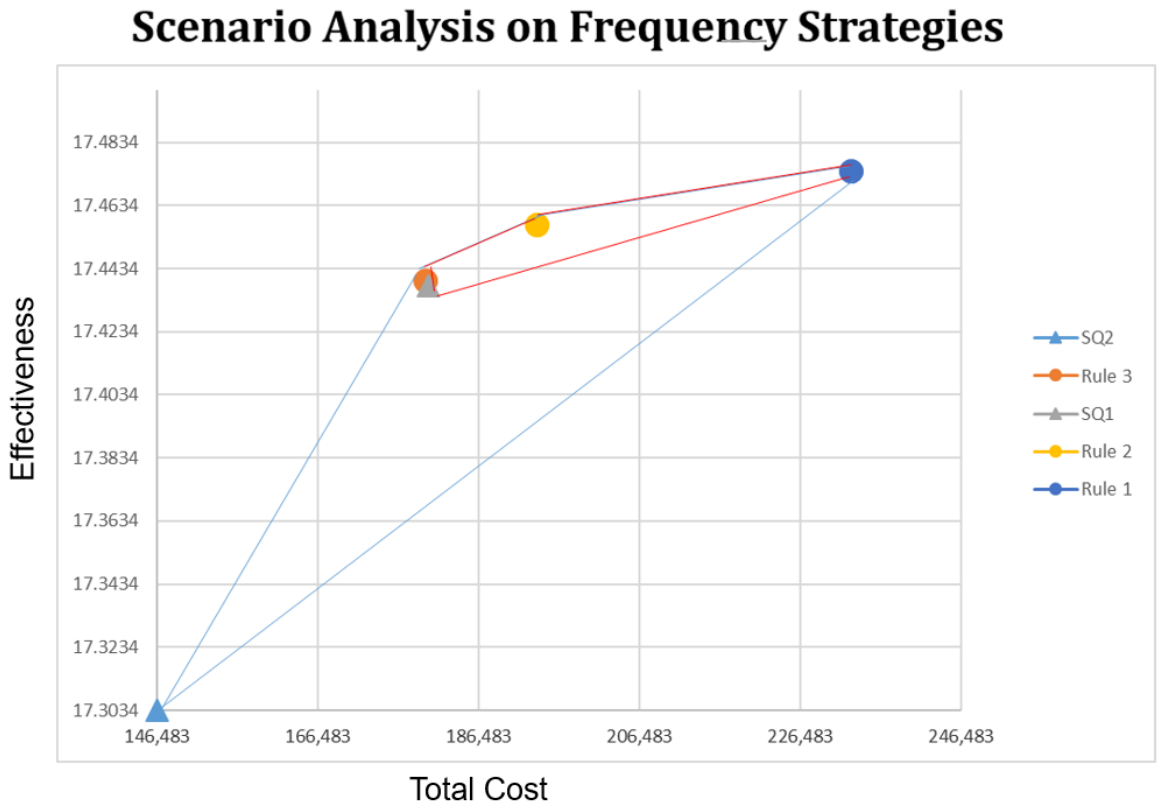

Figure 3.1 Scenario analysis on monitor schedules

Recall the three monitor schedules we talked about in Section 2.3, Rule 1 is the most frequent and Rule 3 is less frequent compared with the other two. Adaptive Strategy (ADP) in Rule 1 gained most effectiveness at the highest cost. ADP in rule 3 is the only dominant (against SQ1) strategy we have so far, which is cost-saving and gained more effectiveness than SQ1. Explanation for this result can be, Rule 3 applies less frequent monitoring frequency on subgroups with lower severity while applying relative more frequent monitoring frequency on subgroups with severe depression states. This is the goal of adaptive monitoring strategy; catching patients at the most appropriate time while controlling the cost of monitoring. However, compared to SQ2, no rule is considered to be cost-effective. Because in SQ2, patients are only monitored for less than 6 times throughout the whole process, which definitely costs a lot less than ADP. Meanwhile, ADP Rules

do not gain as much effectiveness under the current treatment strategy. As Rule 3 is the best monitor strategy we have so far, we will use Rule 3 as our base-case scenario for further analysis.

From scenario analysis on monitoring schedules, we find that it is important to achieve a balance on monitor frequency, neither too frequent nor too sparse. Too frequent will cause unnecessary resource use while too sparse might result in disease deterioration. While this paper is not focusing on developing the best adaptive monitoring frequency, there should be more future explorations focusing on finding the optimal monitoring rules.

3.2 SENSITIVITY ANALYSIS (SA)

3.2.1 *Tornado Analysis on Interventions*

First a sensitivity analysis is conducted on the following six parameters shown in Table 3.2. These six parameters are related with the intervention process. Willingness-to-pay is set to $50,000/QALY. A Tornado Analysis is conducted in TreeAge, outcome is measured using Net Monetary Benefit (NMB), which is calculated as:

$$NMB = E \times WTP - C \tag{3.1}$$

Note: E, total effectiveness gained; C, total cost.

Variable Name	***Description***	***Base Case***	***Min***	***Max***
pStopMonitoring	Probability of drop out monitoring	0.004	0.001	0.007
pSwitch	Probability of switch treatment (biweekly)	0.092	0.0138	0.1702
pTr_DMP	DMP treatment cost	5399	4314	6485
pTr_UC	UC treatment cost	7665	5957	9371
cMonitor	Monitor cost (one time)	186	149	229
HR	Hazard Ratio	1.58	1.10	1.80

Table 3.3 SA on intervention related parameters

Figure 3.2 presents the Tornado diagram. With all one-way SA we conducted, NMB is positive meaning patients are gaining benefit with the parameter ranges applied. Of these six parameters, DMP treatment cost and mortality hazard ratio play relatively bigger impacts on the NMB outcomes.

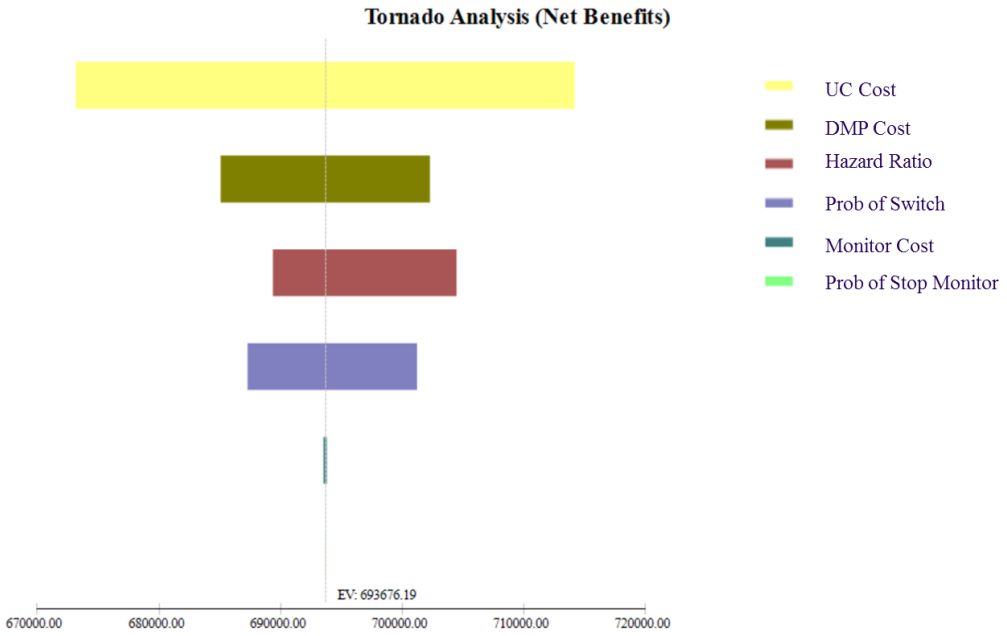

Figure 3.2 Tornado diagram of intervention related parameters

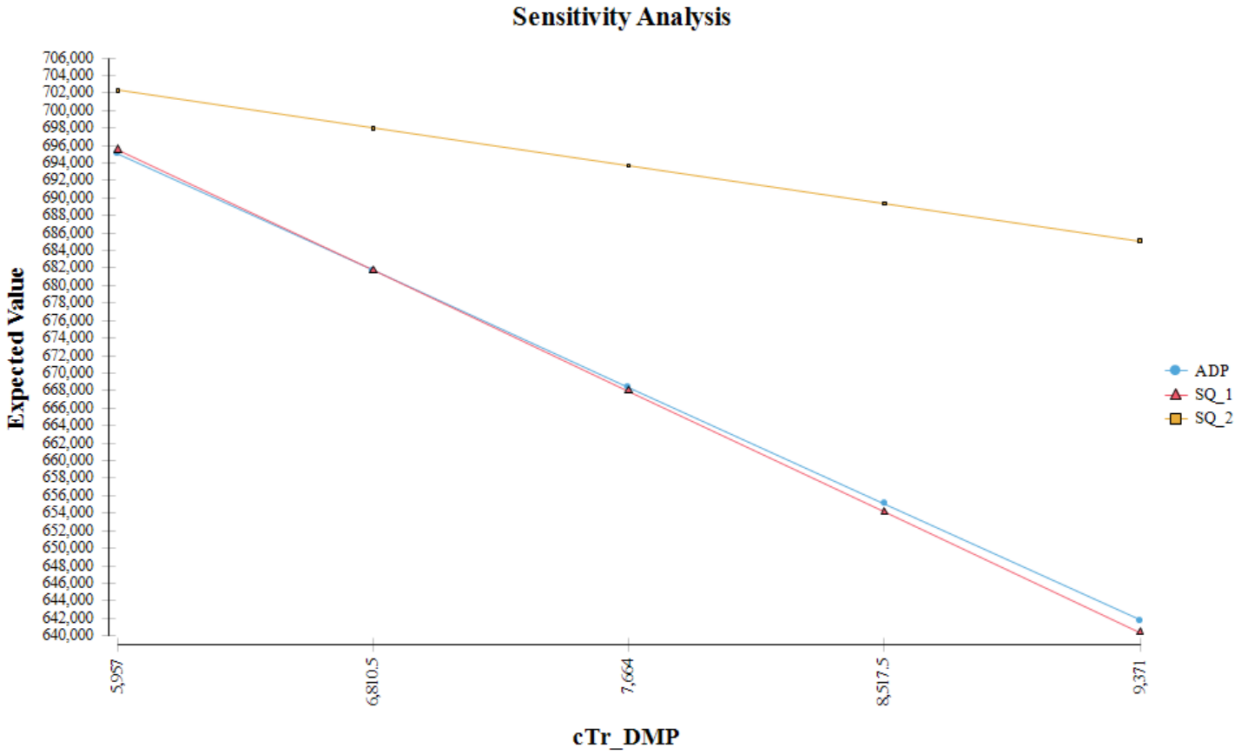

Figure 3.3 SA on DMP treatment cost

It’s reasonable to see that as the cost of second-line treatment becomes higher, NMB is going down.

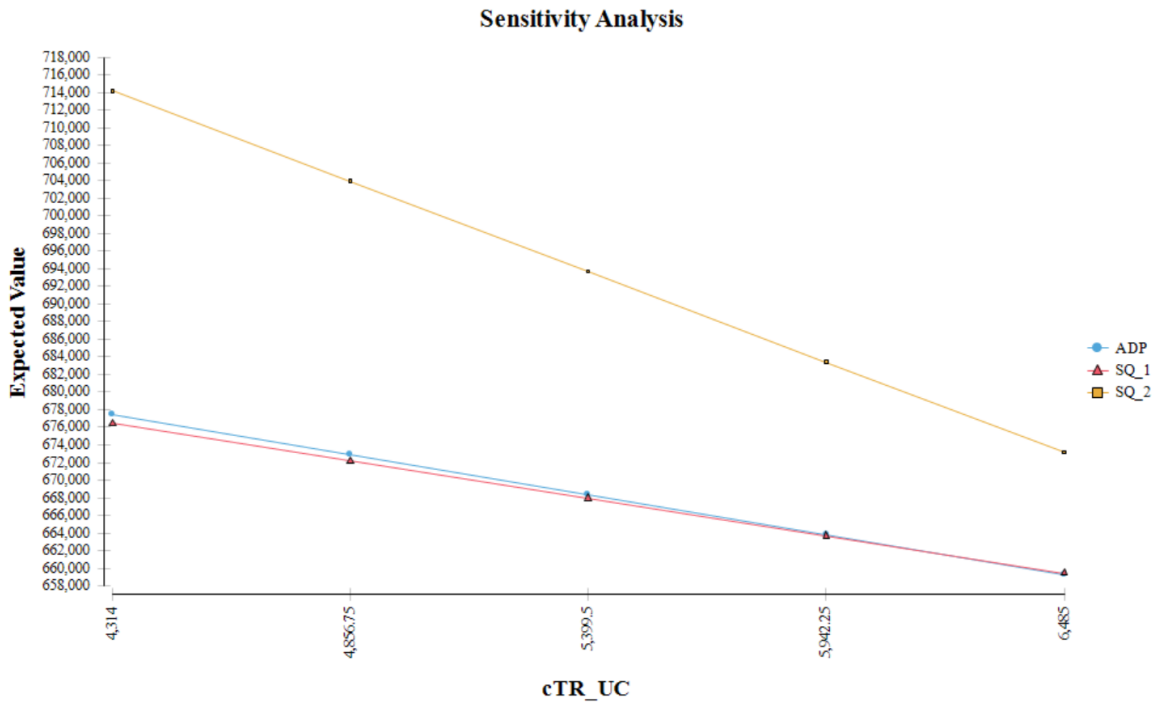

Figure 3.4 SA on UC treatment cost

The cost for first-line treatment also has a linear relation with NMB. As treatment cost gets higher, patients are getting less NMB.

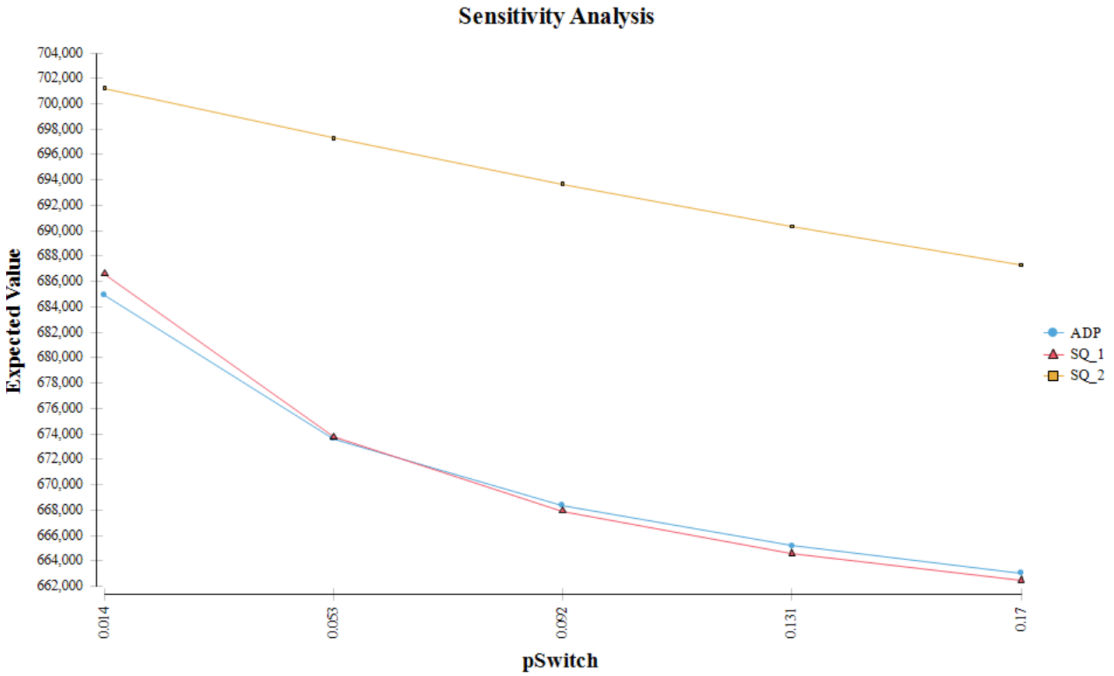

Figure 3.5 SA on switching to second-line treatment

The probability of switching treatment is derived from failure rate of first-line depression treatment. In this model, since DMP has gained better treatment effect than UC [9], we assume second line treatment is more effective. But in reality, this might not be the case. Although studies show the treatment response rate is higher than first line treatment, more exploration on this switching treatment probability is needed. As we increase the probability of switching treatment, patients will have a larger change being switched to a second-line treatment thus costing more money without gaining effectiveness as much. This explains why NMB decreases.

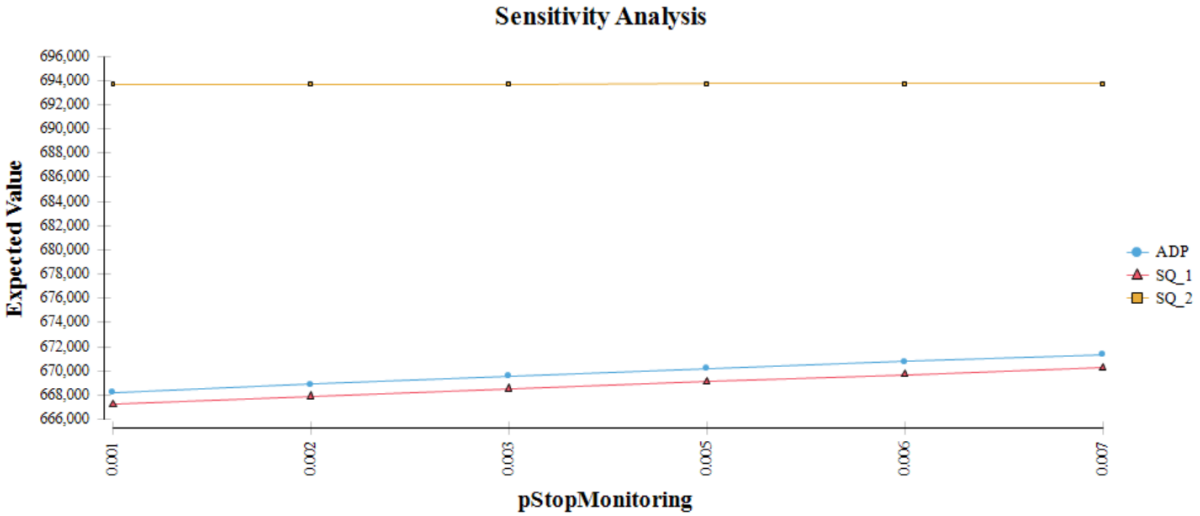

Figure 3.6 SA on dropping patients out of monitoring

The probability of dropping patients out of monitoring presents appropriately linear relation with NMB. It's reasonable since as we only drop patients out of monitoring from Decreasing and Stable Low Groups, patients in these two groups are not given chance to be transited to the second-line treatment. It is assumed that stop monitoring does not affect their treatment effect thus they are saving monitoring cost.

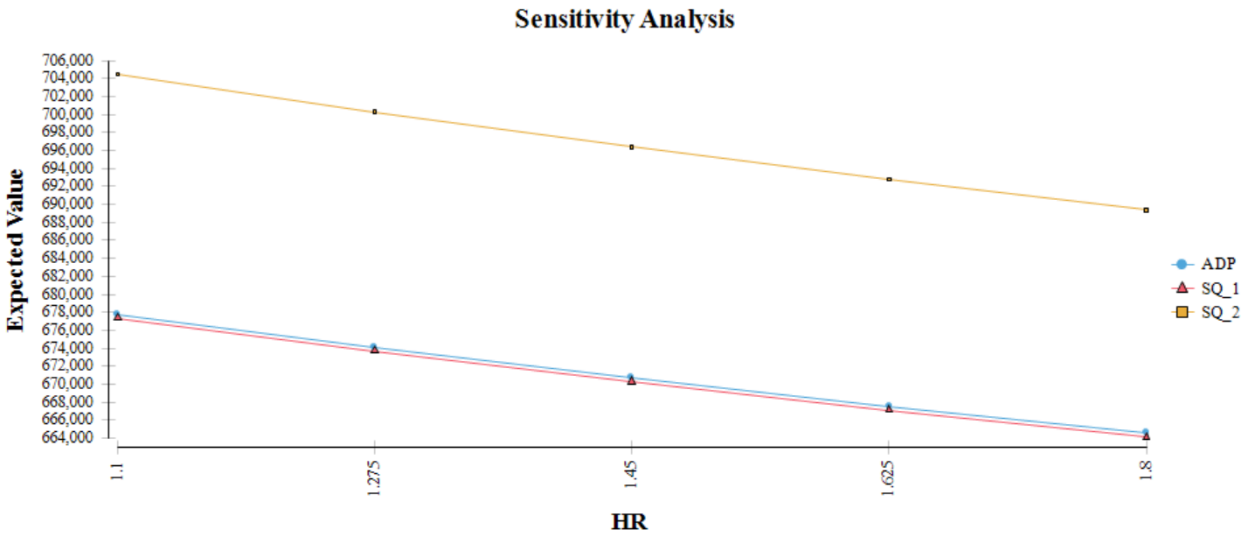

Figure 3.7 SA on hazard ratio

3.2.2 *Tornado Analysis on Utilities*

Table 3.3 shows the range of utility parameters we run for sensitivity analysis. Basically we increase and decrease them by 10% as Min and Max based on its base-case value. Figure 3.3 shows the sensitivity analysis results.

Variable Name	Description	Base Case	Min	Max
uHealthy	Utility of State Healthy	0.9000	0.810	0.990
uMild	Utility of State Mild	0.7300	0.657	0.803
uMod	Utility of State Moderate	0.6300	0.567	0.693
uModSevere	Utility of State Moderately Severe	0.4650	0.419	0.512
uSevere	Utility of State Severe	0.3000	0.270	0.330

Table 3.4 SA on utilities

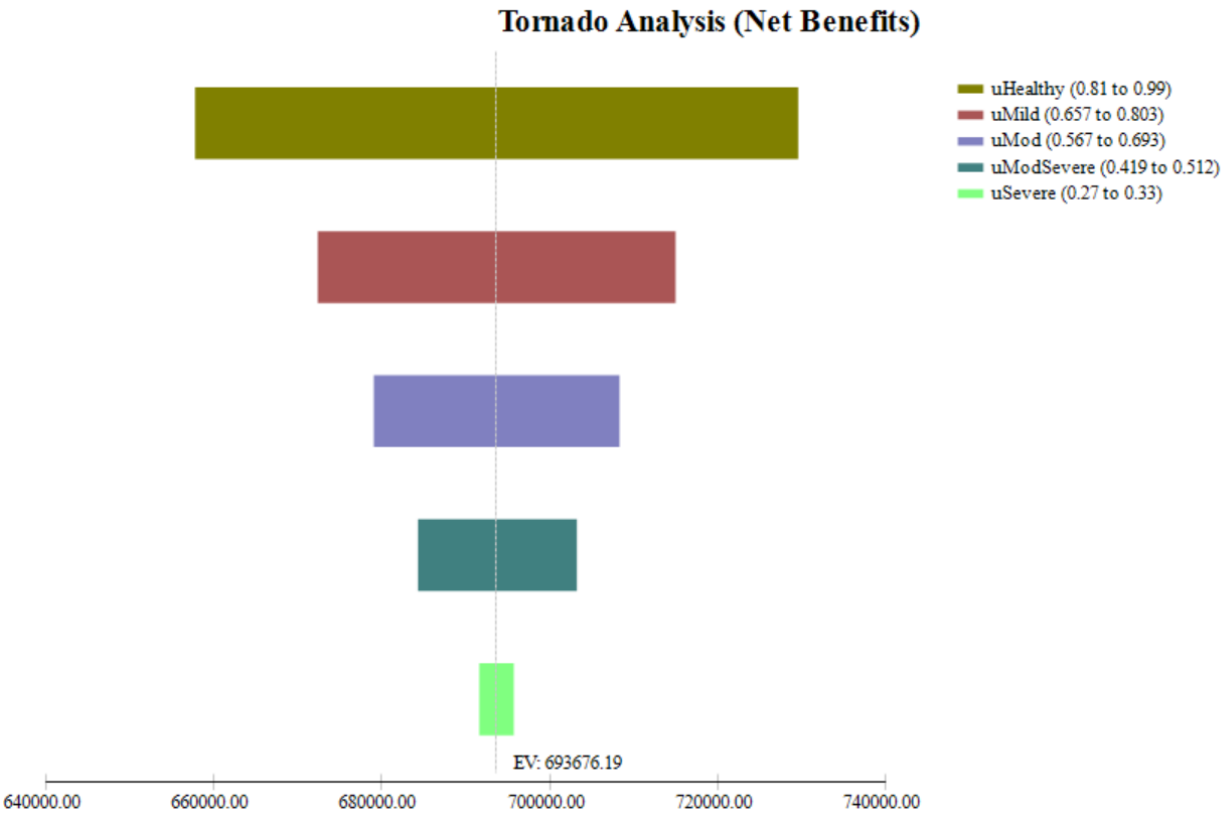

Figure 3.8 Tornado analysis on utilities

3.2.3 *SA on Treatment Effect*

As transition matrix for second-line treatment is derived from the treatment effect ratio between UC and DMP in literature, it would be really interesting to see will the CEA results become better if treatment effect increases?

Recall the base case treatment effect ratio is calculated as 0.7933 in Section 2.4.1. If we increase second-line treatment to be twice as effective as first-line treatment, effectiveness ratio becomes 0.5. Then we repeat the same process developed in Section 2.4.1.

First, Markov steady-state distribution is calculated as in Table 3.4. Note that Decreasing Group and Stable Low Group stay with same distribution because we assume first-line treatment works well on patients from these two groups and they will stay with the original treatment. Next, with the same assumptions and calculation method, we estimated new Markov transition matrices for second-line treatment. Table 3.5 – Table 3.7 are calculated Markov transition matrices for each group.

DMP Stationary	Increasing	Decreasing	Low	High	Fluctuating
$\pi 1$	0.0254	0.6437	0.6684	0.0052	0.1329
$\pi 2$	0.3880	0.3183	0.3193	0.1008	0.6964
$\pi 3$	0.3288	0.0373	0.0121	0.2258	0.1216
$\pi 4$	0.1941	0.0008	0.0002	0.4925	0.0459
$\pi 5$	0.0637	0.0000	0.0000	0.1757	0.0032

Table 3.5 SA on treatment effect – Steady State Distribution

Increasing	H	Mi	Mo	MS	S
H	0.9489	0.0511	0	0	0
Mi	0.0033	0.9849	0.0118	0	0
Mo	0	0.0139	0.9740	0.0121	0
MS	0	0	0.0205	0.9696	0.0099
S	0	0	0	0.0302	0.9698

Table 3.6 Markov transition matrix (SA on treatment effect) – Increasing Group

Stable High	H	Mi	Mo	MS	S
H	0.8333	0.1667	0	0	0
Mi	0.0085	0.9762	0.0153	0	0
Mo	0	0.0068	0.9672	0.0260	0
MS	0	0	0.0119	0.9803	0.0078
S	0	0	0	0.0218	0.9782

Table 3.7 Markov transition matrix (SA on treatment effect) – Stable High Group

Fluctuating	H	Mi	Mo	MS	S
H	0.9603	0.0397	0	0	0
Mi	0.0076	0.9880	0.0045	0	0
Mo	0	0.0257	0.9651	0.0093	0
MS	0	0	0.0245	0.9722	0.0032

S	0	0	0	0.0467	0.9533

Table 3.8 Markov transition matrix (SA on treatment effect) – Fluctuating Group

Then we apply these new transition matrices into the Markov decision-analytic model and run three scenarios of different monitoring schedules. Table 3.9 presents the cost-effectiveness analysis results after we change the treatment effect ratio to 0.5.

SCHEDUEL	STRATEGY	COST	EFF	INCRCOST	INCREEFF	ICER
RULE 1	SQ2	146,622	17.3809			
	SQ1	*180,816*	*17.7152*	*34,193*	*0.3343*	*102,284*
	ADP	233,358	17.8075	52,543	0.0923	569,367
RULE 2	*SQ2*	*146,622*	*17.3809*			
	SQ1	180,816	17.7152	34,193	0.3343	102,284
	ADP	*194,262*	*17.7636*	*13,447*	*0.0484*	*277,933*
RULE 3	SQ2	146,622	17.3809			
	SQ1	*180,816*	*17.7152*	*34,193*	*0.3343*	*102,284*
	ADP	180,396	17.7188	*33,774*	*0.3379*	*99,949*

Table 3.9 CEA results for 3 monitoring schedules after increasing effectiveness for second-line treatment

Compared with results in Table 3.1, all three monitoring schedules gain more effectiveness and the ICER for Rule 1 and Rule 2 decreases significantly. The result indicates that the more effective second-line treatment is, patients gain more benefits from this adaptive monitoring strategy, but the gain is not large enough to make Rule 1 and 2 cost-effective at a WTP of $100,000/QALY.

3.2.4 *SA on Markov Transitions*

Recall that the dataset for our base case in the model is from EHR which contains 6000 patients' record. In this dataset, all patients have more than four observations but they may be sparse and irregular. To test the robustness of our Markov decision-analytic model, we choose subjects in the original dataset that have more than six observations and more regular monitor frequency within 20 bi-week time window as a new dataset. Figure 3.9 presents the new subgroups trajectories by k-means clustering. Here, we also observe five subgroups by Increasing, Decreasing, Mild,

Moderate, Severe Group. The subgroups distributions and initial depression state distributions for this new dataset are shown in Table 3.10 [34].

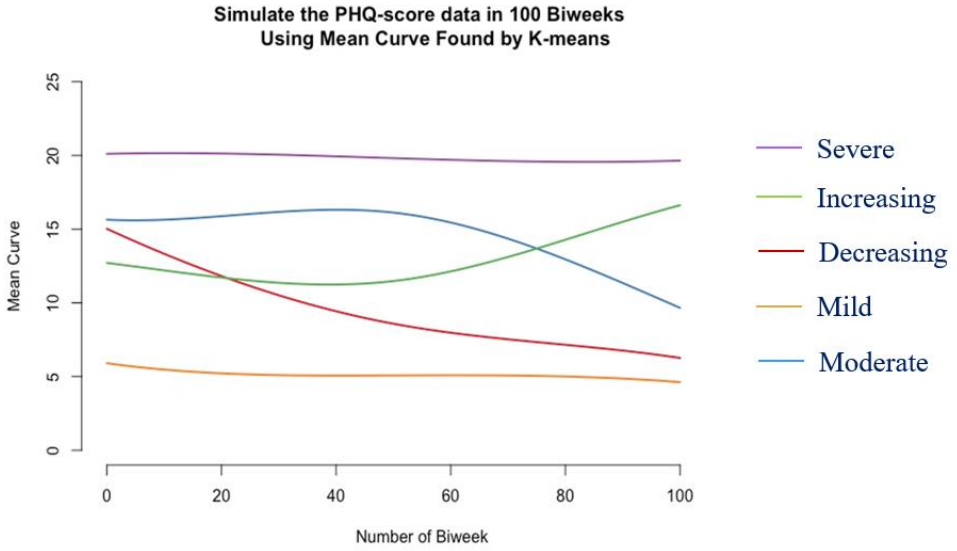

Figure 3.9 Subgroups trajectories by K-means clustering (610 dataset) [34]

	Healthy	**Mild**	**Mod**	**ModSevere**	**Severe**	**Subgroup Distribution**
Increase	0.149	0.241	0.274	0.204	0.131	0.170
Decrease	0.440	0.335	0.167	0.049	0.008	0.213
Mild	0.131	0.200	0.253	0.226	0.190	0.220
Moderate	0.013	0.047	0.164	0.322	0.454	0.213
Severe	0.177	0.273	0.294	0.160	0.097	0.184

Table 3.10 Initial distribution by subgroups (610 dataset) [34]

With the same process, we calculated Markov transition matrices for second-line treatment. From the trajectory pattern of each subgroup, we decide to only provide the switching treatment option for Increase Group, Moderate Group and Severe Group. Mild and Healthy Groups will stay in the first-line treatment, which seems to be working well on them. All Markov transition matrices will be listed in Appendix. Next, we use the same process and run scenario analysis for all three monitoring schedules. The results are shown in Table 3.11. Rule 3 remains to be the most cost saving strategy. We also put all four strategies together and compared their ICER. Table 3.12 shows the organized summary for all four strategies. If we evaluate ICER with the ranking of cost

in ascending order, we come up with the same conclusion that Rule 3 is still most cost-effective, while Rule 1 and Rule 2 are not.

SCHEDUEL	*STRATEGY*	*COST*	*EFF*	*INCRCOST*	*INCREEFF*	*ICER*
Rule 1	SQ2	146,019	16.7575			
	SQ1	182,952	16.9939	36,933	0.2364	156,209
	ADP	235,156	17.0666	52,204	0.0727	718,195
Rule 2	SQ2	146,019	16.7575			
	SQ1	182,952	16.9939	36,933	0.2364	156,209
	ADP	196,384	17.0444	13,432	0.0505	266,087
Rule 3	SQ2	146,019	16.7575			
	SQ1	182,952	16.9939	36,933	0.2364	156,209
	ADP	182,667	17.0161	36,648	0.2586	141,702

Table 3.11 Scenario analysis for three monitoring schedules (610 dataset)

SCHEDULE	**COST**	**EFF**	**ICER**
SQ2	146,019	16.7575	
ADP RULE 3	182,667	17.0161	141,702
SQ1	182,952	16.9939	DOMINATED
ADP RULE 2	196,384	17.0444	484,923
ADP RULE 1	235,156	17.0666	1,745,963

Table 3.12 ICER analysis on 5 monitor schedules (610 dataset)

To summarize, the results on 610 dataset conform with our base case results using 6000 dataset, which indicates the robustness of our conclusion as well as the methodologies being applied.

Chapter 4. CONCLUSIONS

This dissertation is focusing on exploring cost-effective monitoring strategies for patients under major depressive disorders. A comprehensive Markov decision-analytic model on the group level is developed to evaluate adaptive monitoring strategies. The whole process has incorporated characteristics of Markov transitions, different treatment effects and cohort depression trajectories.

As depression affects more and more people all over the world, effective depression treatment and monitoring is becoming extremely important. A systematic treatment does not only

consist of medication treatment, but also requiring consistent follow-ups and appropriate monitoring strategy. As few study has been done on the cost-effectiveness of monitoring strategy, our work shows the potential benefit of developing adaptive monitoring strategy for patients with specific depression progression characteristics. Chapter 1 introduces background of this study, including depression diagnostics procedure and treatment methods, where monitoring plays a crucial role in tracking patients' disease state and capture patients on time for treatment adjustment.

Chapter 2 provides the overall schematics of the Markov decision-analytic model and goes through the process in details about how the intervention steps are conducted. We assume that monitoring itself does not bring any benefit to patients. The intervention we take based on the monitoring results really matters. Adaptive monitoring frequency is decided based on patients' progression characteristics. So far in primary care settings, patients under depression treatment are either monitored on a frequency based on doctors' experience, or take depression assessments out of their own will. The fact is that the majority of patients just seek care one or two times and never come back.

Chapter 3 presents preliminary results adopting different monitor schedules and conducts explicit sensitivity analysis on important parameters. A WTP threshold of $50,000/QALY is used to calculate the net monetary benefit. From SA on monitoring frequency we can tell that applying a suitable monitoring schedule is very important but difficult. Monitor too frequently would commit unnecessary resources while monitor not frequently enough would result in missed treatment opportunities and gaining less benefit. SA on treatment effect shows the importance of adjustment for second-line treatment.

We filled in the blank in healthcare decision making for CEA on major depression monitoring strategy. The major contribution of this study is that we use DFDs as treatment outcome measurement and connect treatment effect with Markov steady-state distribution then apply it to improved Markov transition matrices. Our results showed that there is potential that adopting adaptive monitoring strategy can be cost-saving and beneficial for patients under depression treatment. The prediction of patients' disease trajectory and the precision of catching patients at the right time with adaptive monitoring strategy play very crucial rule. From the results analysis, if we set ICER of $100,000/QALY as threshold for the tested monitor schedules, only the one with improved treatment effect (ICER $99,949/QALY) can be considered as cost-effective against SQ2 and SQ1. This suggests that the efficiency of treatment adjustment has significant impact to the

strategy outcome too. At the same time, this study provides a motivation for designing further observational study in primary care settings on adaptive monitoring strategy.

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APPENDIX A: Chapter 2 Supplemental Material

DESCRIPTION	BASE CASE
Initial probability of Healthy state	
Increasing Group	0.0953
Decreasing Group	0.0023
Stable Low Group	0.3808
Stable High Group	0.0032
Fluctuating Group	0.2078
Initial probability of Mild state	
Increasing Group	0.3345
Decreasing Group	0.0384
Stable Low Group	0.4173
Stable High Group	0.0274
Fluctuating Group	0.3748
Initial probability of Moderate state	
Increasing Group	0.4238
Decreasing Group	0.4107
Stable Low Group	0.1699
Stable High Group	0.1625
Fluctuating Group	0.3265
Initial probability of ModSevere state	
Increasing Group	0.1209
Decreasing Group	0.4047
Stable Low Group	0.0303
Stable High Group	0.4039
Fluctuating Group	0.0816
Initial probability of Severe state	
Increasing Group	0.0255
Decreasing Group	0.1439
Stable Low Group	0.0017
Stable High Group	0.4031
Fluctuating Group	0.0093

Table 4.1 Input cohort distribution in Markov Decision-Analytic Model

APPENDIX B: CHAPTER 3 SUPPLEMENTAL MATERIAL

UC_Increase	H	Mi	Mo	MS	S
H	0.7622	0.2280	0.0097	0	0
Mi	0.0990	0.6811	0.2198	0	0
Mo	0	0.1311	0.7012	0.1676	0
MS	0	0.0074	0.2009	0.5980	0.1935
S	0	0	0.0107	0.2299	0.7593

Table 4.2 Markov Transition Matrix under UC Treatment for Increase Group (610 dataset) [34]

DMP_Increase	H	Mi	Mo	MS	S
H	0.7622	0.2280	0	0	0
Mi	0.0990	0.7716	0.1294	0	0
Mo	0.0000	0.1311	0.7012	0.1677	0
MS	0	0.0074	0.2010	0.5980	0.1935
S	0	0	0.0107	0.2299	0.7594

Table 4.3 Markov Transition Matrix under DMP Treatment for Increase Group (610 dataset)

UC_Decrease	H	Mi	Mo	MS	S
H	0.8739	0.1261	0	0	0
Mi	0.1238	0.8000	0.0763	0	0
Mo	0.0012	0.1759	0.7650	0.0579	0
MS	0	0.0054	0.3703	0.5865	0.0378
S	0	0	0.0222	0.3822	0.5956

Table 4.4 Markov Transition Matrix under UC Treatment for Increase Group (610 dataset) [34]

UC_Mild	H	Mi	Mo	MS	S
H	0.9178	0.0822	0	0	0
Mi	0.0996	0.8346	0.0658	0	0
Mo	0	0.1778	0.7474	0.0747	0
MS	0	0	0.2143	0.7679	0.0179
S	0	0	0	0.3333	0.6667

Table 4.5 Markov Transition Matrix under UC Treatment for Mild Group (610 dataset) [34]

UC_Moderate	H	Mi	Mo	MS	S
H	0.7429	0.2163	0	0	0

Mi	0.1653	0.6454	0.1892	0	0
Mo	0	0.1860	0.6566	0.1573	0
MS	0	0.0090	0.1970	0.6806	0.1134
S	0	0	0.0023	0.1896	0.8081

Table 4.6 Markov Transition Matrix under UC Treatment for Moderate Group (610 dataset) [34]

DMP_Moderate	H	Mi	Mo	MS	S
H	0.7429	0.2163	0	0	0
Mi	0.1653	0.7462	0.0884	0	0
Mo	0	0.1810	0.6617	0.1573	0
MS	0	0.0090	0.1970	0.6806	0.1134
S	0	0	0.0023	0.1896	0.8081

Table 4.7 Markov Transition Matrix under DMP Treatment for Moderate Group (610 dataset)

UC_Severe	H	Mi	Mo	MS	S
H	0.3333	0.6111	0	0	0
Mi	0.0143	0.6143	0.3714	0	0
Mo	0	0.0408	0.7461	0.2132	0
MS	0	0	0.0711	0.8092	0.1197
S	0	0	0	0.0962	0.9038

Table 4.8 Markov Transition Matrix under UC Treatment for Severe Group (610 dataset)

DMP_Severe	H	Mi	Mo	MS	S
H	0.3333	0.6111	0	0	0
Mi	0.0143	0.8239	0.1618	0	0
Mo	0	0.0396	0.7472	0.2132	0
MS	0	0	0.0711	0.8092	0.1197
S	0	0	0	0.0962	0.9038

Table 4.9 Markov Transition Matrix under DMP Treatment for Severe Group (610 dataset)