

Cost-Effectiveness of Teriflunomide and Fingolimod in The First-Line Treatment of Relapsing-Remitting Multiple sclerosis—The Chinese Health System Perspective

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Abstract

Objective The aim of this study is to evaluate the cost-effectiveness of teriflunomide and fingolimod in relapsing-remitting patients in the first-line treatment from the perspective of the Chinese health system perspective.

Methods A Markov model was developed to evaluate the cost effectiveness of disease-modifying drugs (DMDs) from the Chinese health system perspective. Cost input includes medication, follow-up, nursing, recurrence treatment and adverse reaction management. Treatment effects, including monthly confirmed disability worsening and annualized relapse rate. The output result was ICER and the threshold of willingness to pay (WTP) was three times per capita GDP. One-way sensitivity analysis and probability sensitivity analysis are carried out to test the stability of the model results.

Results In the context of medical insurance with Chinese characteristics. The total cost of treatment with teriflunomide was ¥423,816.61, and the total cost of treatment with fingolimod was ¥656,055.95. The cumulative QALYs of teriflunomide was 5.14, and the cumulative QALYs of fingolimod was 5.25. The ICER value of Fingolimod and Liflunomide is ¥2139444.61/QALY, which is higher than WTP, so teriflunomide has a dominant advantage. Sensitivity analysis proves that the model was stable.

Conclusion From the perspective of Chinese health system perspective, teriflunomide is the more cost-effective of the two interventions.

1 Introduction

Multiple sclerosis (MS) is a chronic, progressive, and degenerative disease of the central nervous system, which is characterized by diffuse demyelination of nerve fibers in the brain and spinal cord^[1]. MS is usually diagnosed at 30–40 years old, and the average age of onset is 30 years old. The incidence of MS is 2–3 times that of men. The main types of MS are relapsing-remitting (RRMS), secondary progressive (SPMS) and primary progressive (PPMS), among which relapsing-remitting type is the most common, accounting for about 85% of all types of patients^[2–3]. MS lacks typical clinical symptoms. Common clinical manifestations involve motor, sensory, visual and autonomic nervous systems, mainly manifested as visual impairment, pain, difficulty walking, cognitive impairment and fatigue^[4]. Once MS is diagnosed, the disease will continue to progress until the patient gets on a wheelchair or even dies.

For the treatment of MS, monoclonal antibodies, oral low-dose hormones, and traditional immunosuppressive agents were used in the early stage of treatment in the world. However, due to the poor therapeutic effect and no delay in disease progression, disease modification therapy (DMT) is currently recommended internationally^[5–6]. Disease correction treatment can delay or even prevent the damage to the central nervous system caused by the disease, thereby significantly reducing the damage to the limb function caused by the disease, and greatly reducing the number of disease recurrences.

Internationally used drugs for the first-line treatment of MS include fingolimod, teriflunomide, glatiramer acetate and dimethyl fumarate, etc. However, currently, only two drugs are on the market in China, of which teriflunomide is The first oral DMT drug marketed in China was approved by the National Medical Products Administration (NMPA) in July 2018 and included in medical insurance. Teriflunomide in China's phase III clinical (TOWER) study, daily oral administration of 14 mg teriflunomide can effectively reduce the annual recurrence rate of MS by 71.2%^[7]. Fingolimod, as the second oral DMT drug, was approved for marketing by NMPA in July 2019 and will be officially included in medical insurance in 2021. Fingolimod, as a potent oral DMT drug, can significantly reduce the annual recurrence rate of MS and slow down the progression of the disease in a phase III clinical study^[8-9].

The aim of this study is to evaluate the cost-effectiveness of long-term use of teriflunomide and fingolimod from the perspective of the Chinese health system perspective, so as to analyze and guide patients to choose drugs based on their own economic status.

2 Methods

In this study, the Markov model was established to simulate the cost-effectiveness analysis of the two regimens of fingolimod and teriflunomide in the treatment of RRMS patients. The research data comes from the phase III clinical trials and real-world studies of teriflunomide and fingolimod, as well as the collection and investigation of medical resources of Sir Run Run shaw Hospital of Zhejiang Province.

2.1 Model Overview

The model's disability progression is determined by the extended disability status (EDSS) score, which ranges from 0 to 10 points (0 points are defined as normal, 10 points are deaths, during which the larger the score, the more severe the disability)^[10], according to Five Markov states are established for EDSS scoring: EDSS 0-2, 2.5-3.5, 4-6.5, 7-9.5 and death (Fig. 1). The corresponding different states are: unaffected life, mild activity restriction, severe Restriction of movement, loss of mobility in bed, and death. The five state classifications are based on the average actual illness time (7.97 years) of the patients in Sir Run Run Shaw Hospital in Zhejiang Province, combined with the severity of MS disease for the corresponding length of illness in the literature^[11]. The population included in the study meets the diagnostic criteria established by McDonald criteria (2017)^[12]. MS is a chronic progressive disease. Once it occurs, it will continue to progress. According to the characteristics of the disease, the cycle period is set to 1 month to simulate the survival of patients in the next 10 years.

2.2 Transition probability

By searching web of science, Elsevier and other databases, I found an article about the natural transition probability under different EDSS scoring states of MS, and the baseline transition probability of this study can be obtained by calculating the classification^[13]. After calculating the baseline metastasis probability, it is necessary to obtain the hazard ratio^[7] and the relative annualized relapse rates of the different

regimens of teriflunomide and fingolimod for the treatment of MS. The relevant data can be obtained. Obtained through the phase III clinical trial of teriflunomide TOWER^[7] and the phase III clinical trial of Fingolimod FREEDOMS^[14]. The final transition probability can be obtained by multiplying the baseline transition probability of each state and the progress risk ratio. The probability of each state progressing to death comes from the relevant literature. Because the mortality of MS has a strong positive correlation with the clinical severity, and the severity of the disease continues to increase with the time of illness, each state is defined by the patient's medical history. The mortality rate^[15-16]. The probability of recurrence is derived from the baseline recurrence rate^[17-19] and the relative decline in the annual recurrence rate of real-world research centers^[20].(Table 1)

Table 1
Estimates of multiple sclerosis metastatic probability data

Variable	Probability estimates	one-way sensitivity analysis		source
Probability of each state transition (month)				
EDSS 0-2	0.06275	NA	NA	[13]
EDSS 2.5-3.5	0.09280	NA	NA	[13]
EDSS 4-6.5	0.03921	NA	NA	[13]
Probability of each state progressing to death (month)				
EDSS 0-2	0.000400	NA	NA	[15-16]
EDSS 2.5-3.5	0.002023	NA	NA	[15-16]
EDSS 4-6.5	0.002459	NA	NA	[15-16]
EDSS 7-9.5	0.004073	NA	NA	[15-16]
Hazard ratio (HR)				
Fingolimod vs placebo	0.62	NA	NA	[14]
Teriflunomide vs placebo	0.68	NA	NA	[7]
Baseline monthly recurrence rate	0.0755	NA	NA	[17-19]
Fingolimod vs Teriflunomide	0.11:0.31	NA	NA	[20]

2.3 Utility

The baseline data of each state of the utility value is derived from the data published by the British MS risk sharing plan^[21], and then based on the cases obtained by the Run Run Shaw Hospital in Zhejiang Province, the relevant utility value is calculated mainly based on the recurrence in the case and the hospitalization caused by the recurrence. The annual utility value of hospitalization due to recurrence decreased to 0.302, and the annual utility value of hospitalization not caused by recurrence decreased to 0.091^[22]. The duration of recurrence was observed from the case data of Sir Run Run Shaw Hospital. It lasted about two weeks, and the recurrence caused hospitalization. The probability is 82%, and the probability that recurrence does not lead to hospitalization is about 18%. At the same time, adverse reactions will also lead to a decrease in the annual utility value^[23].(Table 2)

Table 2
Estimated utility of multiple sclerosis

	Utilities estimates	one-way sensitivity analysis	
EDSS 0-2	0.954	1	0.943
EDSS 2.5-3.5	0.899	0.985	0.87
EDSS 4-6.5	0.821	0.93	0.81
EDSS 7-9.5	0.491	0.745	0.245

2.4 Cost

The cost acquisition method is a face-to-face consultation with a neurologist in the hospital to obtain the drug costs required for disease treatment (including the drug costs for intervention methods and the cost of emergency treatment in the case of an acute disease), diagnosis costs, and inspection costs, Hospitalization expenses and nursing expenses, and other indirect costs are not considered for the time being. Both drugs have entered the medical insurance, so the drug prices are marked with medical insurance. The medication cost of teriflunomide is ¥4061/month, and fingolimod is ¥6840/month. The cost of adverse reactions is calculated based on the incidence of grade 3/4 adverse reactions and treatment costs. The follow-up cost is based on the frequency of follow-up once every 3 months. Calculated with the cost of each follow-up, patients with EDSS scores of 7-9.5 have severe disability. Patients with mobility impairments will increase the cost of additional care according to the doctor's recommendation. The cost of MS patients' recurrence is divided into recurrence hospitalization and recurrence non-hospitalization, according to recurrence hospitalization. Calculate the cost of recurrence based on the proportion of non-hospitalization and the corresponding cost, as well as the probability of recurrence per cycle. Finally, it is calculated that when the EDSS of teriflunomide is 0-6.5, the cost is ¥4683.23/month, and when the EDSS is 7-9.5, the cost is ¥5463.23/month; when the EDSS of Fingolimod is 0-6.5, the cost is ¥7415.23 /month, and when the EDSS is 7-9.5, the cost is ¥8195.23/month.(Table 3)

Table 3
Direct medical costs for multiple sclerosis

	teriflunomide	one-way sensitivity analysis		Fingolimod	one-way sensitivity analysis	
Drug price (month)	4061	3654.90	4467.10	6840	6156	7524
Adverse events cost (month)	119.08	107.17	130.99	127.20	144.48	139.92
Follow-up fee (month)	422	379.80	464.20	422	379.80	464.20
Nursing expenses (month)	780	702	858	780	702	858
Relapse leading to hospitalization	3515.03	3163.53	3866.53	3515.03	3163.53	3866.53
Relapse not leading to hospitalization	1518.45	1366.61	1670.30	1518.45	1366.61	1670.30

2.5 State entry distribution

The distribution of MS patients entering each state comes from the actual patient situation in the hospital. The proportion of patients whose initial state is EDSS 0–2 points is about 75%, and the proportion of patients whose EDSS 2.5–3.5 points is about 16.67%. The proportion of patients with EDSS 4-6.5 points is about 8.33%.

2.6 Discounted value

In order to compare the indicators of this study more accurately, the cost and health utility value of this study are discounted using the discounted value in pharmacoeconomics, starting from the second year at a discounted value of 5% per year^[24].

2.7 Adverse Events

The increase in annual cost and the decrease in utility value associated with each plan's adverse reactions are estimated based on the percentage of different types of adverse reactions, the percentage of serious adverse reactions, the cost of serious adverse reactions, and the duration of each type of adverse event. The adverse reactions of the two treatment options mainly consider the more serious grade 3/4 adverse reactions, and the incidence of related adverse reactions is $\geq 5\%$. Assuming that in the next 10-year simulation, the incidence of adverse reactions does not change, multiply the utility of each adverse reaction by the duration of the adverse reaction to obtain the utility value drop within one year. The incidence rate of grade 3/4 adverse reactions, the annual cost and annual utility value decline of different types of adverse reactions used in this study are derived from related publicly published literature^[23,25–26].(Table 4)

Table 4
Cost of multiple sclerosis adverse events

Treatment	AEs	Annual probability	Annual Loss in QALYs from AEs	Monthly cost
Teriflunomide	nausea	7.40%	0.00013	¥11.08
	Increased neutrophil count	13.70%	0	¥38.58
	Hair loss	6.70%	0	¥4.25
	Increased lymphocyte count	6.80%	0	¥38.58
	ALT/AST Increased	7.80%	0	¥13.08
	Diarrhea	7.30%	0.0003	¥12.92
				0.00043
Fingolimod	Upper respiratory tract infection	17.30%	NA	NA
	Headache	13.30%	NA	NA
	Hypertension	11.00%	NA	NA
	Decreased lymphocyte count	10.70%	NA	NA
				0.0048
AEs Adverse Events,ALT alanine aminotransferase,AST aspartate aminotransferase				

2.8 Sensitivity analysis

In order to evaluate the impact of parameter uncertainty on cost-benefit estimates, a one-way probability sensitivity analysis was performed to assess whether two different treatment options are stable. The upper and lower limits of the treatment cost of different intervention options are ($\pm 10\%$). The upper and lower limits of the utility value are set to 25th and 75th in different states according to the situation in the relevant literature^[21], and the upper and lower limits of the discount rate are set to 8% and 3%, so as to perform a one-way sensitivity analysis to evaluate all model parameters Uncertainty. The parameter order of the tornado graph is sorted from top to bottom starting with the most sensitive parameter. Probabilistic sensitivity analysis uses second-order Monte Carlo simulation (1000 times).

3 Results

The results of ten years of running simulations of teriflunomide and fingolimod through TreeAge show that the total cost of treatment with teriflunomide is ¥423,816.61, the total cost of using fingolimod is ¥656,176.25, teriflunomide and The QALYs accumulated by fingolimod are 5.14 and 5.25, respectively. In contrast, fingolimod has better health benefits, but requires more costs. The ICER value of teriflunomide and fingolimod is ¥2139444.61/QALY. Assuming that the WTP of the Chinese population is about three times the per capita GDP is ¥216743.04/QALY, the ICER value is much greater than that of WTP, so fingolimod is compared to Teriflunomide is not cost effective.

In the one-way sensitivity analysis, the utility value, cost and discount value with an EDSS score of 7-9.5 points have the greatest impact on the cost difference, and the utility value of the adverse reaction has the least impact (Fig. 2). All parameters have stable effects on the model. The cost-effectiveness acceptance curve shows that when the WTP is higher than ¥2,139444.61/QALY, the acceptability of fingolimod is higher, and when the WTP is lower than ¥2,139444.61/QALY, the acceptability of teriflunomide is higher. When it is assumed that the WTP of the Chinese population is three times the per capita GDP of about ¥216743.04/QALY, the acceptability of teriflunomide has a clear advantage (Fig. 3). The points in the probability sensitivity analysis are randomly generated 1000 times according to the upper and lower limits of cost and effect, and the results show that all points are higher than the WTP value. Therefore, compared with fingolimod, teriflunomide is a more cost-effective intervention (Fig. 4).

4 Discussion

In this study, based on the disease characteristics of relapsing-remitting multiple sclerosis and the EDSS score, a Markov model was established to evaluate the cost-effectiveness of two different treatment options of teriflunomide and fingolimod. The results show that the cost of teriflunomide is ¥423,816.61 and the effect is 5.14 QALYs; the cost of fingolimod is ¥656,176.25 and the effect is 5.25 QALYs, and teriflunomide is a more cost-effective solution. As far as we know, this study is the first pharmacoeconomic evaluation of multiple sclerosis based on China's medical and social conditions. Most previous studies are based on the perspective of American society^[27-28]. The two selected in this study This intervention plan is currently the only two listed oral DMT drugs in China, and the two are in a competitive relationship, and the two drugs have recently been included in the China Medical Insurance Reimbursement List.

In previous studies, Xinke Zhang et al^[27]. analyzed the cost-effectiveness of fingolimod, teriflunomide, dimethyl fumarate, and IFN-β1a as first-line treatment for RRMS patients from the perspective of American society. The results show that dimethyl fumarate is the most cost-effective intervention, and the cost-effectiveness between fingolimod and teriflunomide is compared. The ICER value is calculated to be \$3201672/QALY, and teriflunomide is more effective. It is cost-effective and more consistent with the results obtained in this article. At the same time, this study also set up a drug withdrawal mechanism and second-line treatment with natalizumab after drug withdrawal, so that the results are closer to the real situation. Yan Xu et al^[23]. conducted a cost-effect analysis of teriflunomide and IFN-β1a from the perspective of Chinese medical care, and found that teriflunomide has a lower cost and a higher effect,

compared to IFN β -1a. With absolute advantages, this study is the first cost-effectiveness analysis conducted from the Chinese subgroup clinical III trial population.

The main factors affecting the results of this study are cost, utility value, transition probability, discount rate and other factors. Considering these aspects, the study has certain limitations. From a cost point of view, the prices of the two drugs are the prices after reimbursement by China Medical Insurance. According to the recommended dosage of each box of drugs, they are converted into the price of drugs used in each cycle. Follow-up expenses, diagnosis expenses, recurrence-related expenses and nursing expenses are all from the survey data of the Department of Neurology, Hospital, Zhejiang Province. They are obtained through face-to-face interviews with 3 doctors. However, the cost of adverse reactions cannot be obtained through inquiry and case inquiry, because it is extremely large. In most cases, patients' treatment of more serious adverse reactions is based on rest and withdrawal, which is difficult to measure in monetary terms. Therefore, the cost of adverse reactions in this study comes from other literature and has some errors with other cost data in this study. In addition, the medical insurance reimbursement situation in China is different, and different medical insurance policies have different reimbursement ratios. The medical insurance reimbursement ratio used in this study is the case where the most reimbursement methods are used in the investigation of Sir Run Run Shaw Hospital in Zhejiang Province, that is, the calculation of the medical insurance reimbursement ratio for ordinary employees in Zhejiang Province. The corresponding price. The cost adopts direct medical cost, because indirect factors such as labor loss caused by MS and hidden costs are not considered because they cannot be accurately obtained. The initial utility value of the disease comes from relevant literature, because the cohort population in the literature is mainly European countries, but this study is based on the Chinese population for pharmacoeconomic evaluation, there is currently no MS utility value study based on the Chinese population, so there are some deviations in the effect. Regarding the probability of each state progressing to death, many previous studies mostly used natural mortality^[29-30], but with the progression of the disease, the mortality rate of MS has increased significantly. Therefore, this study is based on the duration of illness and the EDSS score are more accurate in the probability of progression to death derived from the relevant literature^[15-16].

The Markov model established in this study was established in a relatively ideal state. If the actual conditions of the two related programs are considered, the discontinuation and withdrawal of treatment due to severe AEs should be considered, and due to MS disease. With continuous progress, most patients with an EDSS score of 7-9.5 will progress from RRMS to SPMS. At this time, it is necessary to consider changing the disease medication from first-line oral DMT drugs to second-line drugs, such as natalizumab^[31]. The limitation of this research model is that it cannot stop the drug or switch to a different treatment mode according to the different conditions of each patient during the actual medication process, and restart the treatment after using other treatment methods. Teriflunomide and fingolimod are the only two oral DMT drugs currently on the market in China for the treatment of MS. Europe and the United States believe that dimethyl fumarate is the most cost-effective treatment option,

but they have not yet It is marketed in China, so future research should include dimethyl fumarate or other newer DMT drugs.

5 Conclusion

From the perspective of the Chinese health system, our analysis shows that teriflunomide and fingolimod are a more cost-effective intervention in relapsing-remitting multiple sclerosis. This study can provide reference opinions for clinical decision makers in the treatment of multiple sclerosis in China.

Declarations

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The research has been approved in writing by the patient's guardian. Availability of data and material: Not applicable. All data generated or analysed during this study are included in this published article. The authors declare that they have no competing interests. This study was supported in part by grants from Zhejiang Provincial Federation of Social Sciences Project. Zhichao Hu and Zuojun Dong were responsible for compiling the manuscript, Jingwen Wng and Xiaoying Zhou wrote Forms 1-4, and all authors undertook the review work of the article. We appreciated Wenyu Li for providing the data for the manuscript.

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Authors' contributions

Zhichao Hu and Zuojun Dong were responsible for compiling the manuscript, Jingwen Wng and Xiaoying Zhou wrote Forms 1-4, and all authors undertook the review work of the article.

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The authors claim that none of the material in the paper has been published or is under consideration for publication elsewhere.

Availability of data and materials

All data generated or analysed during this study are included in this published article.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of People's Government of Zhejiang Province. Obtained the consent of all patients and guardians.

Consent for publication

All authors agree to publish.

Competing interests

The authors have declared that no competing interests exist.

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Figures

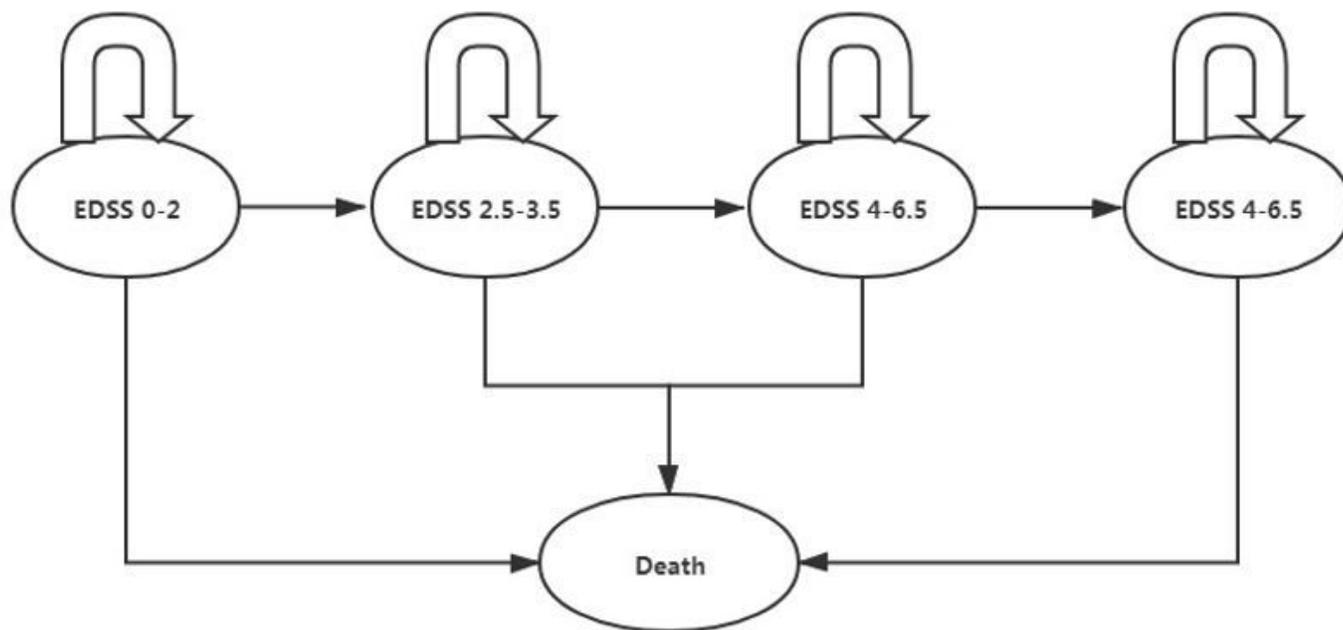


Figure 1

Multiple sclerosis Markov state transition diagram

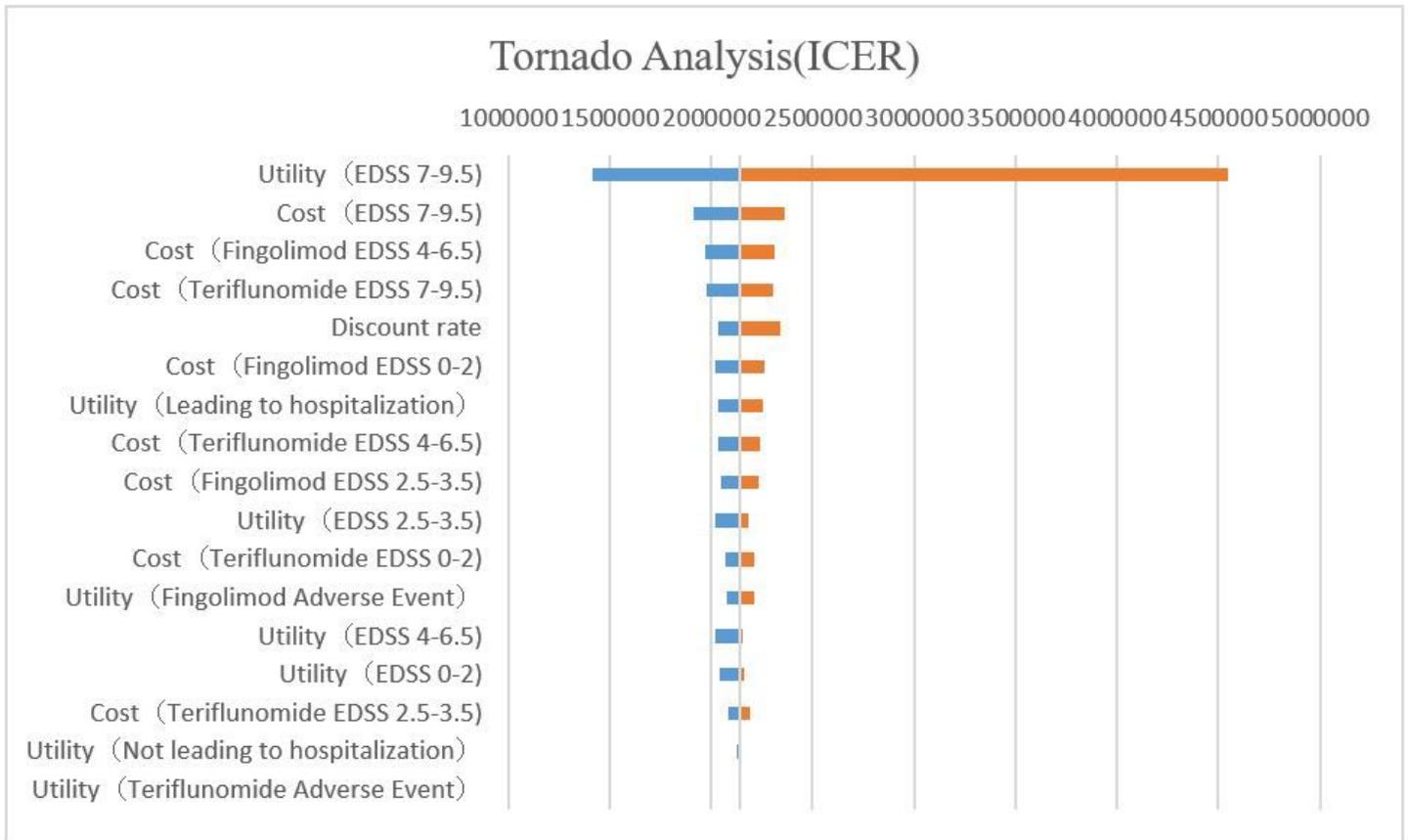


Figure 2

Tornado diagram of univariate analyse

Incremental Cost-Effectiveness, fengemode v. telifuan

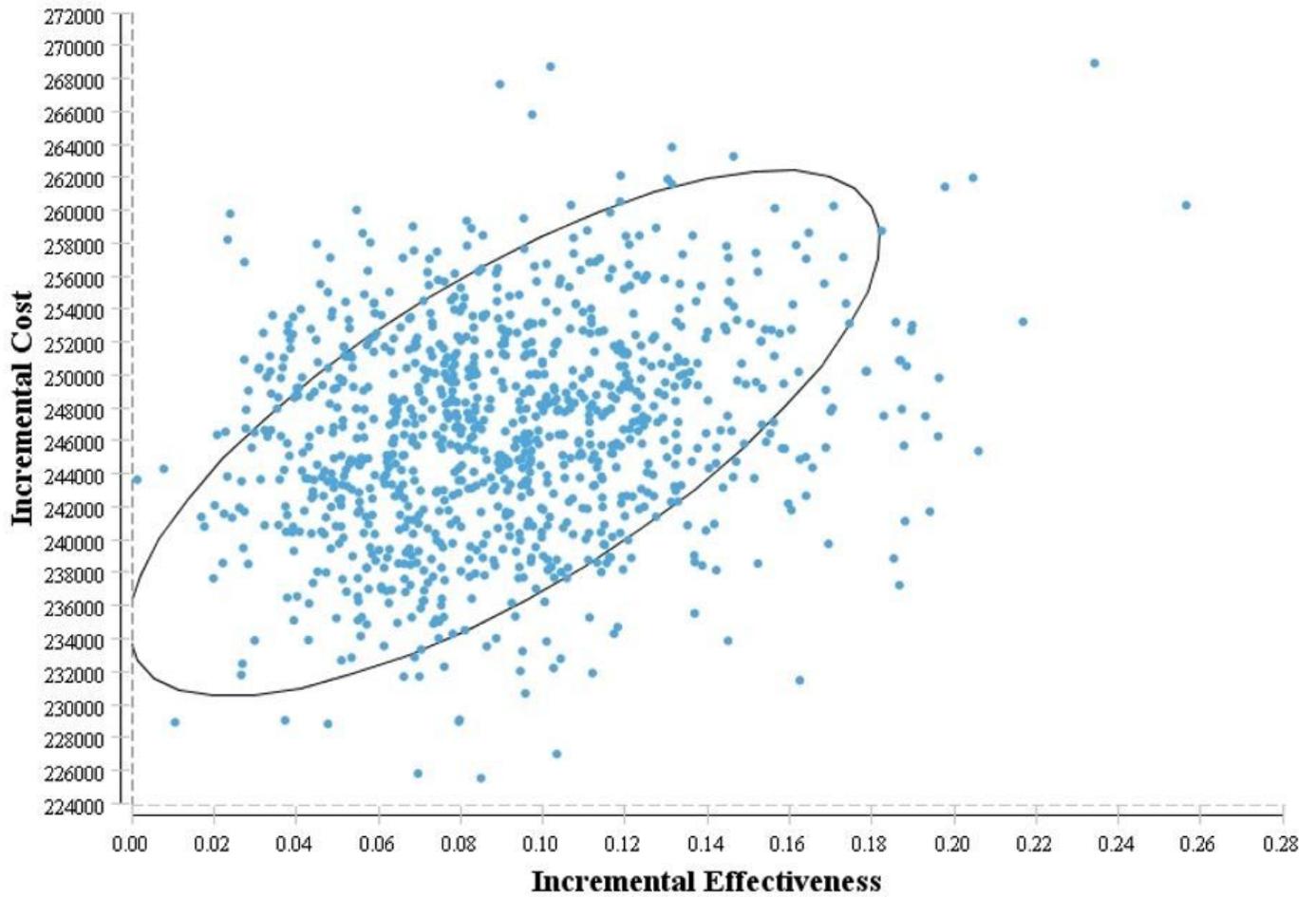


Figure 3

probabilistic incremental cost-effectiveness ratio (ICER) estimates based on 1000 iterations for the pooled relapsing multiple sclerosis (RMS) population.

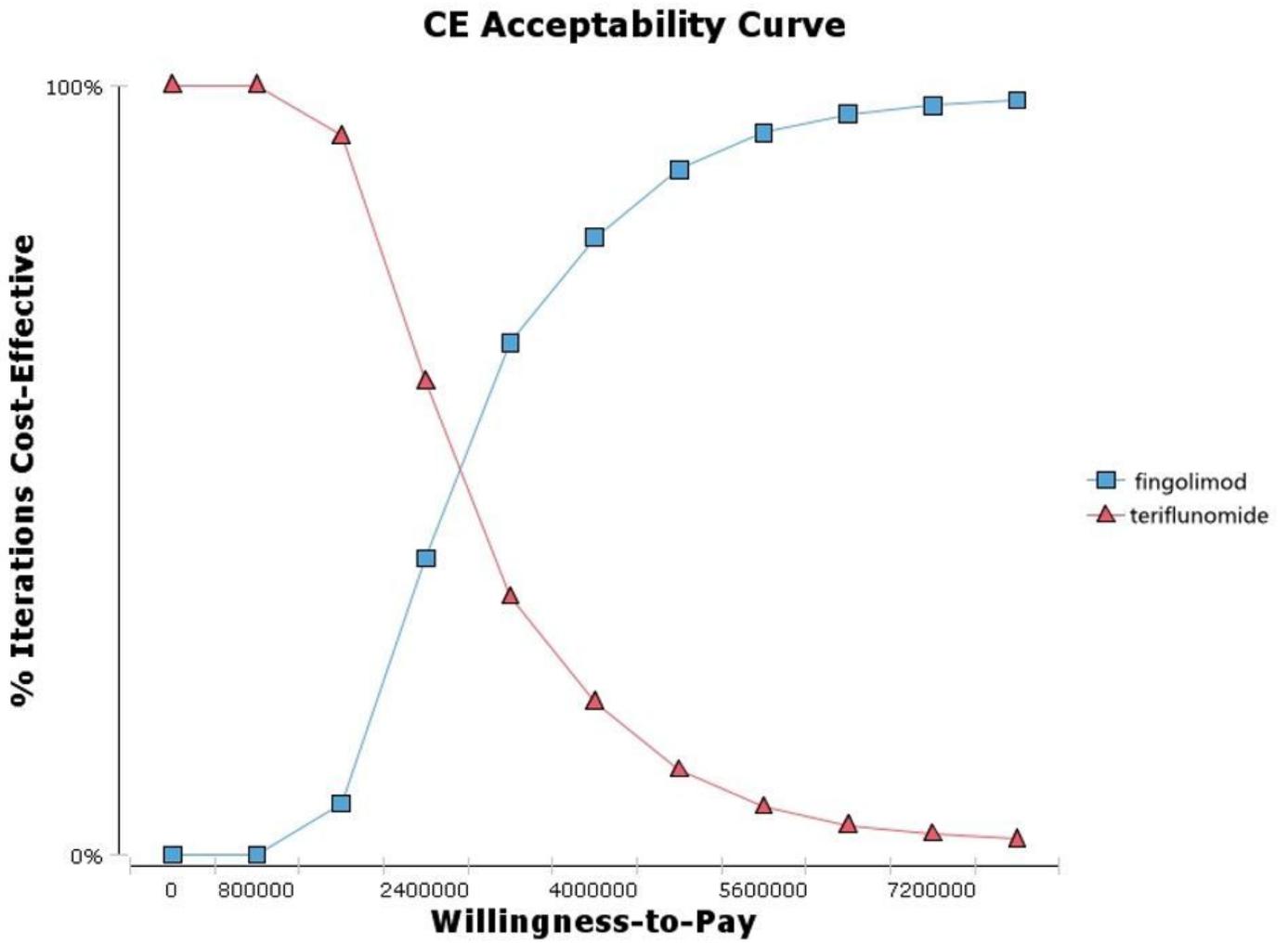


Figure 4

cost effectiveness acceptability curve for the pooled RMS population