SUPPLEMENTARY MATERIAL
TO
COST-EFFECTIVENESS OF TERIFLUNOMIDE COMPARED TO INTERFERON BETA-1b FOR RELAPSING MULTIPLE SCLEROSIS PATIENTS IN CHINA

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Conflict of Interest:

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Given that limited literature is available regarding treatment patterns and healthcare resource use in RMS patients in China, a KOL survey was conducted to obtain input for the models. A total of 11 KOLs in various regions of China who specialize in MS management were identified for the survey. KOLs had to meet the following inclusion criteria to participate in the survey: (1) attending neurologist or higher level (e.g., assistant director physician, director physician), (2) have at least 10 years of experience managing MS patients, and (3) currently manage more than 15 MS patients a year.

The survey covered questions on the resource use associated with RMS treatment and management during remission and relapse by disease severity based on the EDSS score, as well as resource use associated with the management of AEs.

Supplementary Table 1. Resource use in relapse phase as identified using the physician survey

	Mean	SD	25th Percentile	75th Percentile	Unit cost	Source
Methylprednisolone (IV x 9 days and oral x 30 days)	1				¥2,124	Based on physician survey input: IV: 1000 mg x 3 days + 500 mg x 3 days + 240 mg x 3 days then switch to oral 120 mg x 30 days Unit cost inputs derived from https://www.yaozh.com ¥120 per 500 mg IV, ¥73 per 250 mg IV, ¥39 per 125 mg; ¥27 per 120 mg oral
Neurology outpatient visits	1.3	1.1	0.7	2.1	¥248 per visit	CHIRA[1] inflated to 2018
Emergency room visits	0.4	0.4	0.1	0.5	¥1,054 per visit	Inflated to 2018 from Shanlian Hu et al 2014[2]
Routine test	0.68	1.0	1.0	2.5	¥1,202	Average cost for blood count, liver function test, urinalysis, and MRI from Supplementary Table 2
Hospitalization in internal neurology unit						
Hospitalization length of stay	16	6	11	17	¥1,054 per day	Inflated to 2018 from Shanlian Hu et al 2014[2]

Supplementary Table 2.Resource use and indirect cost inputs by EDSS category as identified using the physician survey

	EDSS 0-3.5	EDSS 4-6	EDSS 7-9	Unit cost	Reference
	Mean (IQR)	Mean (IQR)	Mean (IQR)		
Neurology hospitalization visits	0.5 (0-0.88)	1.15 (0-2.63)	1.25 (0-2.63)		
Hospitalization length of stay	5.3 (0-12)	25.75 (0-37.88)	35.68 (0-64.63)	¥1,054 per day	Inflated to 2018 from Shanlian Hu et al 2014[2]
Neurology Outpatient visits	6.95 (3-9.5)	7.5 (3.63-9.63)	7.75 (3.5-10.5)	¥248 per visit	CHIRA[1] inflated to 2018
Emergency room visits	0.43 (0-1)	1 (0.5-1)	1.57 (0.5-2)	¥1,054 per visit	Inflated to 2018 from Shanlian Hu et al 2014[2]
Routine tests					
MRI (brain)	1.22 (0.5-1)	1.67 (0.5-2.5)	1.22 (0-2.5)	¥576	CHIRA[1] inflated to 2018
MRI (spinal cord)	1.22 (0.5-1)	1.67 (0.5-2.5)	1.22 (0-2.5)	¥576	CHIRA[1] inflated to 2018
Blood Count	2 (1.5-2)	2.67 (2-4)	2.11 (1.5-2.5)	¥8	CHIRA[1] inflated to 2018
Urinalysis	2 (1.5-2)	2.33 (2-2.5)	2.00 (1-2.5)	¥9	CHIRA[1] inflated to 2018
Hepatic function	1.39 (0-2)	1.67 (0-2.5)	0.94 (0-2)	¥34	CHIRA[1] inflated to 2018
Renal function	1.39 (0-2)	1.67 (0-2.5)	0.94 (0-2)	¥21	CHIRA[1] inflated to 2018
Cane	1.3% (0-0)	42.8% (20-61)	16.3% (0-36.3)	¥45	Taobao-top selling www.taobao.com
Wheelchair	0% (0-0)	4.4% (0-6)	66.9% (57.5-80)	¥345	Taobao-top selling www.taobao.com
Loss of productivity					
% Employed	55%	20%	0%	¥25,974	2017 China Economic Annual Report: Income House and Consumption. National Bureau of Statistics of China www.stats.gov.cn Average annual salary assuming 250 work days per year
Number of days missed from work per year for medical care (including hospital LOS)	9	30	0		
% Unemployed due to MS	20%	70%	90%		
% Retired not due to MS	25%	10%	10%		
Informal care					
Care needed %	14.4% (10-20)	64.4% (64-71)	90% (80-100)	¥200	Cost of social workers visit per day[3]
Days	85.8 (26.4-131.2)	255.7 (198.5-317.1)	347.1 (345-365)		

Supplementary Table 3. Direct and indirect cost of managing RMS by EDDS stage

		Mean (Interquartile range) RMS management cost by EDSS score									
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Direct medical cost	Mean	¥0	¥2,019	¥9,736	¥17,453	¥25,169	¥32,886	¥39,187	¥45,015	¥50,844	¥56,672
	IQR	(¥0-¥0)	(¥1,253-¥2,263)	(¥1,440-¥27,264)	(¥1,627-¥52,265)	(¥1,814-¥77,266)	(¥2,001-¥102,267)	(¥1,930-¥129,152)	(¥1,773-¥156,665)	(¥1,616-¥184,178)	(¥1,459-¥211,691)
Loss of productivity	Mean	¥457	¥3,950	¥7,443	¥10,936	¥14,429	¥17,922	¥20,044	¥21,710	¥23,377	¥25,043
Informal care cost	Mean	¥0	¥0	¥6,533	¥14,656	¥22,780	¥30,903	¥40,992	¥51,735	¥62,478	¥73,221
Cost of managing relapse											
Leading to hospitalization	Mean	¥16,865									
	IQR	(¥11,595 - ¥17,919)									
Not leading to hospitalization	Mean	¥3,685									
	IQR	(¥2,643 - ¥5,006)									

RMS: Relapsing Multiple Sclerosis; EDSS: Expanded Disability Status Scale;

Note: In this table, unit cost in China was based on the China Health Insurance Research Association (CHIRA) database, resource use estimates were obtained from the Chinese key opinion leaders survey.

Direct medical care costs include: inpatient admissions, day admissions, consultations with specialists (neurologist or general practitioner), investigations/tests (MRI [brain], MRI [spine], blood and various tests)

Loss of productivity: short-term absence and reduced working time/income, early retirement

Informal care costs: social workers visits

Monitoring costs were based on resource consumption (in the first year and subsequent years that patients receive treatment) and unit costs for resources. As teriflunomide was not approved in China at the time when the KOL survey was conducted, resource use was initially obtained from the Chinese KOLs for interferon beta-1b but then estimated and validated by KOLs for teriflunomide using teriflunomide's Chinese package insert. Unit costs associated with the monitoring resources are based on published sources in China (***Supplementary Table 3*** and ***Supplementary Table 4***)

Supplementary Table 4. Resource Use for Monitoring as identified in the physician survey

Treatment		Number of Laboratory Tests / Visits		Source
	Monitoring Requirements	**First Year of Treatment**	**Subsequent Years While on Treatment**	
Teriflunomide 14 mg	Office visit	5	3.5	Assume the same as Interferon beta-1b
	Full blood count	4.5	3.3	Assume the same as Interferon beta-1b
	Liver function test	7.5	3	Teriflunomide Chinese PI for the first 6 months and assume the same as Interferon beta-1b afterword
	Renal function test	4.5	3	Assume the same as Interferon beta-1b
	Urinalysis	4	2.8	Assume the same as Interferon beta-1b
	MRI (brain)	2	1.5	Assume the same as Interferon beta-1b
Interferon beta-1b 250 mcg	Office visit	5	3.5	Chinese KOL input
	Full blood count	4.5	3.3	Chinese KOL input
	Liver function test	4.5	3	Chinese KOL input
	Renal function test	4.5	3	Chinese KOL input
	Urinalysis	4	2.8	Chinese KOL input
	MRI (brain)	2	1.5	Chinese KOL input

Abbreviations: MRI = magnetic resonance imaging

Supplementary Table 5. Unit Costs Associated with Monitoring Resources

Monitoring Requirement	Unit Cost (¥) 2018	Source
Office visit (routine medical check- up)	¥7	CHIRA[1] inflated to 2018
Full blood count	¥8	CHIRA[1] inflated to 2018
Liver function test	¥34	CHIRA[1] inflated to 2018
Renal function test	¥21	CHIRA[1] inflated to 2018
Urinalysis with urine cell counts	¥9	CHIRA[1] inflated to 2018
MRI scan (to detect PML)	¥576	CHIRA[1] inflated to 2018

Abbreviations: MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy
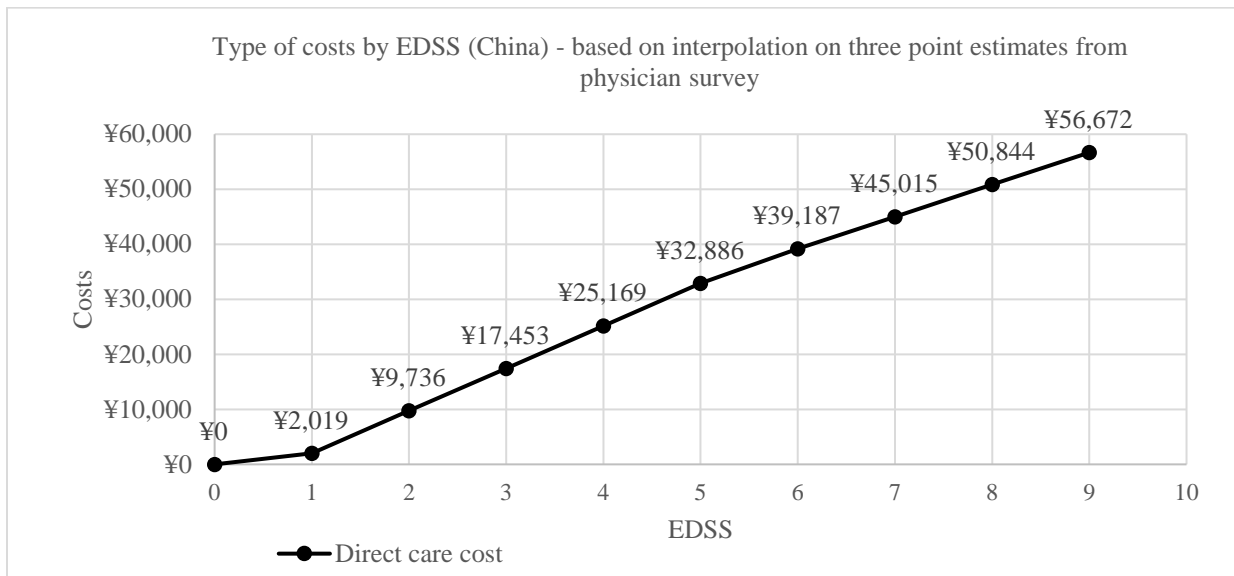Source: Survey Report on the Use of Drugs, Medical Equipment and Treatments about patients with Basic Medical Insurance in 2016" developed by China Health Insurance Research Association

The approach to convert the three-group EDSS estimates from the survey to the individual EDSS stages required for the model is outlined below. A previous study from a US perspective[4] calculated the costs for each EDSS health state using linear interpolation from the values estimated from a survey of 1909 US patients using EDSS values of <4, 4–6, and >6.

A justification for using such an approach is further provided by another analysis[5] in which data from the Sonya Slifka database was explored and due to the absence of robust evidence on the relationship between the EDSS and the costs of care in the US, a straight line relationship was assumed between EDSS progression and the associated costs of care. The lack of a linear relationship between costs across all EDSS stages could be due to very small sample size of patients contributing in EDSS stages between 5 and 7.5. However, this non-linearity could be addressed by assuming two independently linear portions going from EDSS 0-5 and from 5-9.

After using linear interpolation on the point estimates for mild, moderate, and severe EDDS categories from the physician survey, **Supplementary Figure 1** presents medical costs per each individual EDDS state in China.

Supplementary Figure 1. Direct EDSS costs based on interpolation of point estimates for direct costs for mild, moderate, and severe MS disease - from Chinese physician survey

Type of costs by EDSS (China) - based on interpolation on three point estimates from physician survey

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