

Supplementary Appendix

To calibrate the *default model*, first we selected the maximum age-specific parameter for decreases in ARR to match the calibration targets by age (29% per 5 years; Supplementary Table S1-S2). Next, we fit to the calibration targets by disability status (Table 2 and Supplementary Table S1) by examining model output for the ARR weighted by person-years per EDSS *score* category. We then repeated these steps to develop the best-fit parameter sets, which produced model output matching all of the calibration targets (Table 2) as closely as possible. Primarily, we examined model results for ages 30-74, because the model simulation began at age 30, and given censoring at older ages in the observed sample from which we derived calibration targets. Additionally, we considered age 30 through the full life expectancy (~~Supplementary Table S2~~).

For the *secondary model*, first we fit to the calibration targets by disability status (Table 2 and Supplementary Table S3). We then estimated the additional age-related decrease needed to match the ARR targets by age, and again repeated these steps iteratively to determine the final model parameters.

Supplementary Table S1. Calibration results for *default model* simulation of adults with relapsing-onset MS, ages 30 to 74.

	EDSS 0-2.5	EDSS <u>3.0</u> -5.5	EDSS 6- <u>6.0</u> -7.5	EDSS 8- <u>8.0</u> -9.5
Calibration targets (Table 2) for ARR by EDSS <u>category</u>	N/A	0.19	0.12	0.04
	Maximum age-related decrease (29%/5y) in ARR, no decrease by EDSS			
Weighted ARR by p-y <u>at</u> EDSS <u>category states</u>	0.27	0.18	0.11	0.08
	Final age-related decrease (28%/5y) in ARR, 66% decrease in ARR at EDSS <u>scores</u> states 8-8.0 -9.5 relative to 0-5.5			
Weighted ARR by p-y <u>at</u> EDSS <u>category states</u>	0.28	0.19	0.12	0.04

Key: ARR= annualized relapse rate; EDSS= Expanded Disability Status Scale; N/A= not applicable; p-y= person-years. Calibration targets for ARR by EDSS score categories are bolded.

Supplementary Table S2. Additional calibration results for *default model* simulation of adults with relapsing-onset MS, ages 30 to life expectancy.

	EDSS 0-2.5	EDSS 3.0 -5.5	EDSS 6- 6.0 -7.5	EDSS 8- 8.0 -9.5
Calibration targets (Table 2) for ARR by EDSS <u>category</u>	N/A	0.19	0.12	0.04
	Maximum age-related decrease (29%/5y) in ARR, with no decrease by EDSS			
Weighted ARR by p-y <u>at</u> EDSS <u>category states</u>	0.26	0.17	0.09	0.06
	Final age-related decrease (28%/5y) in ARR, 66% decrease in ARR at EDSS <u>scores</u> states 8-8.0 -9.5 relative to 0-5.5			
Weighted ARR by p-y <u>at</u> EDSS <u>category states</u>	0.26	0.17	0.10	0.03

Key: ARR= annualized relapse rate; EDSS= Expanded Disability Status Scale; N/A= not applicable; p-y= person-years. Calibration targets for ARR by EDSS score categories are bolded.

Supplementary Table S3. Calibration results for *secondary model* simulation of adults with relapsing-onset MS, ages 30 to 74.

	EDSS 0-2.5	EDSS 3.0-5.5	EDSS 6- 6.0-7.5	EDSS 8- 8.0-9.5
Calibration targets (Table 2) for ARR by EDSS <u>category</u>	N/A	0.19	0.12	0.04
	No age-related decrease in ARR, maximum decrease in ARR by EDSS of 37% at EDSS <u>scores states</u> 6.0-7.5 and 80% at 8.0-9.5 relative to 0-5.5			
	EDSS 0-2.5	EDSS 3.0-5.5	EDSS 6- 6.0-7.5	EDSS 8- 8.0-9.5
Weighted ARR by p-y <u>at</u> in EDSS <u>category states</u>	0.51	0.51	0.14	0.04
	Intermediate age-related decrease (24%/5y) in ARR, decreases in ARR of 37% at EDSS <u>scores states</u> 6-6.0-7.5 and 80% at 8-8.0-9.5 relative to 0-5.5			
Weighted ARR by p-y <u>at</u> in EDSS <u>category states</u>	0.30	0.22	0.09	0.02
	Final age-related decrease (27%/5y), 6% decrease in ARR at EDSS <u>scores states</u> 6-6.0-7.5 and 71% in 8-8.0-9.5 relative to 0-5.5			
Weighted ARR by p-y <u>at</u> in EDSS <u>category states</u>	0.28	0.20	0.12	0.03

Key: ARR= annualized relapse rate; EDSS= Expanded Disability Status Scale; N/A= not applicable; p-y= person-years. Calibration targets for ARR by EDSS score categories are bolded.

Supplementary Table S4. Age-related decrease in ARR per 5 years among simulated cohorts of adults with relapsing-onset MS: sensitivity analysis of the rate of disability progression.^a

Initial ARR during the 5 years following MS symptom onset	<i>Default model, reduced relapses by age and at EDSS scores states 8-8.0-9.5</i>	<i>Secondary model, reduced relapses by age and at EDSS scores states 6-6.0-9.5</i>	<i>Replication model, reduced relapses by age and no relapses at EDSS scores states 6-6.0-9.5</i>
<u>0.33^a</u>	<u>22%^e</u> (21-22%)	<u>21%</u> (20-21%)	<u>14%</u> (10-15%)
0.51 ^b	28% (28-28%)	27% (26-27%)	21% (17-22%)
0.33	22% (21-22%)	21% (20-21%)	14% (10-15%)
0.60 ^c	30% (30-30%)	29% (29-30%)	23% (20-24%)
1.00 ^d	37% (35-37%)	36% (35-36%)	30% (27-31%)

AbbreviationsKey: ARR= annualized relapse rate; EDSS= Expanded Disability Status Scale.

^a Estimate from a previously published study including a cohort of MS patients aged 30-<40 at onset,⁶ and near the lower end of the range of ARR reported in placebo arms of clinical studies.^{22,23}

^b Analyses of a cohort of MS patients from the British Columbian MS database (1980-2009).

^c Estimate from previously published studies using MS Markov models.^{12,13}

^d Near the higher end of the range of ARR reported in placebo arms of clinical studies.^{22,23}

^{ea}. Median time to sustained EDSS 6 = 30.8 years (analyses of a cohort of MS patients from the British Columbian MS database), with a range of 23 to 36 years (observations from MS natural history studies; sensitivity analysis results reported in parentheses below main results).¹⁴