Meta-regression Analyses Controlling for Baseline Relapse Rate: Clinical Efficacy and Safety of Disease-modifying Therapies for Multiple Sclerosis

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METHODS SUMMARY

Meta-regressions allow one to investigate whether study characteristics are related to absolute or relative treatment effects. In the present investigation, we test whether baseline prior relapse rate (i.e., the rate of relapses over the 12 months prior to study entry) is related to the relative treatment effects versus placebo for the annualized relapse rate (ARR) ratio, sustained accumulation of disability at 3 months (SAD3), or discontinuations, in the all-years, 80% relapsing-remitting multiple sclerosis (RRMS) subset of multiple sclerosis (MS) studies. In statistical terms, the heart of the model is changing the simple specification of the log-effect (where that effect can be a hazard ratio, a rate ratio, or an odds ratio):

$$\text{Log(treatment effect)} = \theta$$

to a specification that allows the log-effect for placebo-controlled studies to vary based on a mean-centered regressor, in this case, prior relapse rate over the last year:

$$\text{Log(treatment effect)} = \theta + \gamma^{*}[\text{Prior Relapse Rate[i]-Prior Relapse Rate (mean)}].$$

Some studies did not have data on the 1-year prior relapse rate but did have data on the relapse rate over the previous 2 years. Analysis of the subset of studies with data on both the 1-year and 2-year rates found a relatively consistent relationship between the two; we estimated that the 2-year rate is, on average, 1.49 times higher than the 1-year rate (see Table 2). This ratio was used to impute 1-year rates from studies with 2-year data. Sensitivity analyses were conducted to examine the effect if the 2-year rates were exactly twice the 1-year rates.

Studies with missing data at both 1 year and 2 years could still be included in the analysis if they were not placebo-controlled, as the meta-regression assumed that any effect of prior relapse rate was limited to the relationship to placebo. A more complex model would be possible (i.e., one in which each treatment was affected differently by prior relapse rate) if there were more studies; however, the dataset was too sparse to power such a model.

Studies that were placebo-controlled and did not have a 1-year or 2-year rate were dropped from analyses. Fortunately, only a few studies were lost: Jacobs (1996; Avonex®); Kappos (2008; BG-12 [dimethyl fumarate]); Vollmer (2011; Avonex® and laquinimod); Hauser (2008; rituximab); and Polman (2005; laquinimod). No comparators were dropped from analyses due to the loss of these studies. Further details are shown in Table 3. A sample of WinBUGs code is shown for SAD3 in Appendix A.

RESULTS

Annualized Relapse Rate

Initial analyses using the “All-Years, 80%+ RRMS” inclusion criteria found homogeneous results for ARR ratios, with a sqrt(tau) of 0.038. This was lower than the estimate found in the base-case results (0.061, post-2000, 80%+ RRMS), suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies did nothing to increase statistical heterogeneity.

A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in ARR ratios. As noted above, the meta-regression investigates whether there is an interaction effect between active treatment efficacy and placebo efficacy.

The estimate of gamma (the relationship between the prior relapse rate and the log-ARR ratios for active treatment vs. placebo) was estimated at 0.056 [-0.351, 0.262]. This is both substantively and statistically non-significant (in a Bayesian sense). The result is not surprising when one considers the study effects that are driving the estimate – studies have similar ratios, even as their prior relapse rate varies.

For instance, consider the fingolimod trials and glatiramer acetate (GA) trials, which drive the meta-regression, as these are the trials for which there is the most variation in prior relapse rate within treatment comparison:

Table 1. Example ARR Ratios and Prior Relapse Rates (for Fingolimod and GA Trials)

	Fingolimod	**Placebo**	**ARR Ratio**	**Prior Relapse Rate**
FREEDOM	0.18	0.4	0.45	1.47
Kappos (2006)	0.35	0.77	0.45	1.27
	GA	**Placebo**	**ARR Ratio**	**Prior Relapse Rate**
Comi (2001)	0.81	1.21	0.67	1.78
Johnson (1995)	0.59	0.84	0.7	1.95
CONFIRM (2012)	0.29	0.4	0.73	1.38

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate

The ratios are extremely stable even as the prior relapse rate (and placebo response rate) varies. This is in part why the estimate of random-effects variation was so low in the original (non meta-regression) mixed treatment comparison (MTC) analyses.

Table 4 shows that point estimates of the rate ratios for treatments relative to placebo (and thus, to each other) change very little after the effect of prior relapse rate is accounted for by the meta-regression analyses.

The sensitivity analysis in which 2-year rates were assumed to be twice the 1-year rates (if 1-year rates were missing) found a similarly insignificant estimate (frequentist-equivalent *p*-value >0.30) for the effect of prior relapse rate on the relapse rate ratio.

Three-month Sustained Accumulation of Disability

Initial analyses using the “All-Years, 80%+ RRMS” inclusion criteria found relatively homogeneous results for SAD3 hazard ratios, with a sqrt(tau) of 0.069. This was the same as the estimate found in the base-case results (0.069, post-2000, 80%+ RRMS), suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies did nothing to increase statistical heterogeneity. A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in SAD3 hazard ratios.

The estimate of gamma (the relationship between the log-hazard ratio (HR) and treatment efficacy vs. placebo) was estimated at -0.50 [-1.10, 0.08]. This is statistically marginally significant (the frequentist p-value with this confidence interval would be 0.08; the Bayesian interpretation would be that if our model assumptions are true, there is a 95.8% chance that the effect of prior relapse rate is a negative one [i.e., the higher the baseline relapse rate, the greater the advantage for most active treatments versus placebo]) and is substantively of moderate importance. For example, consider the PRISMS study, which found an HR of Rebif vs. placebo of 0.65, with a prior relapse rate of 2.01 relapses per year. The predicted HR for this study with a prior relapse rate of 1.51 relapses per year (common of newer studies) would be exp[ln(0.65)+0.5*0.50)] = 0.83, or a reduction in efficacy relative to placebo of over 50%.

Investigation of the studies driving this estimate found 3 studies with substantively higher-than-average prior relapse rates (Bornstein, 1987, GA vs. placebo, 2.58; IFNB study group, IFNB-250 vs. placebo, 2.30; PRISMS, Rebif vs. placebo, 2.01). All 3 studies found higher active treatment vs. placebo rates than the other direct evidence (in the case of Bornstein, the other GA vs. placebo studies found weaker GA effects) or indirect evidence (the indirect evidence for IFNB 250 vs. placebo and for Rebif vs. placebo suggested a weaker relationship than found in the IFNB study and PRISMS, respectively).

A sensitivity analysis was conducted to determine if the Bornstein study was the primary driver of the effect. As it has the highest prior relapse rate and is the only study for which there is direct evidence contradicting it, it might be reasoned that this study alone is the reason for the almost significant effect. However, the size of the effect diminished only slightly after dropping the Bornstein study (from -0.50 to -0.42), suggesting that other studies also are contributing to the effect of baseline relapse rate on the estimate of treatment effect for the SAD3 outcome.

Table 4 shows that point estimates of the HRs for treatments relative to placebo (and thus, to each other) change slightly after the effect of prior relapse rate is accounted for.

The sensitivity analysis in which 2-year rates were assumed to be twice the 1-year rates (if 1-year rates were missing) found a weakly converging and poorly estimated non-significant estimate of -1.28, with a frequentist-equivalent *p*-value of 0.15, and a 92.6% chance that there is a positive association between prior relapse rate and the relative odds of disability progression.

Treatment Discontinuations

The “All-Years” inclusion criteria were applied, and the analysis found relatively homogeneous results for the odds ratios for discontinuations, with a sqrt(tau) of 0.09. This was higher than the estimate found in the base-case results (post-2000, 80%+ RRMS) of 0.070, suggesting that the greater clinical heterogeneity present after the inclusion of the pre-2000 studies may be responsible for an increase in statistical heterogeneity. A meta-regression was conducted to investigate whether prior relapse rate would explain significant variation in odds ratios for discontinuations.

The estimate of gamma (the relationship between the log-HR ratio and treatment efficacy vs. placebo) was estimated at 0.60 [-0.03, 1.25]. The model showed convergence for this parameter but not as strongly as for the other models, likely due to the sparser data network; fewer studies reported discontinuations, and in many studies there were very few events, meaning that some multicollinearity can occur between treatments given and the predictor of interest. The estimate of 0.60 is marginally

statistically significant (the frequentist p-value with this confidence interval would be 0.06; the Bayesian interpretation would be that if our model assumptions are true, there is a 96.9% chance that the effect of prior relapse rate is a positive one, i.e., the higher the rate, the smaller the advantage or greater the disadvantage for most active treatments vs. placebo).

The point estimate itself is substantively of moderate importance. For example, consider the PRISMS study, which found an odds ratio (OR) of Rebif vs. placebo of 1.15, with a prior relapse rate of 2.01 relapses per year. The OR>1 means that there were a higher proportion of events found on Rebif than on placebo. The predicted OR for this study with a prior relapse rate of 1.51 relapses per year would be exp[ln(1.15)-0.5*0.60)] = 0.85; more discontinuations would be expected on placebo than on Rebif.

Investigation of what studies might be driving this estimate found that the effect was driven by many studies. In general, newer studies (such as CONFIRM and FREEDOMS) had low prior relapse rates as well as more extreme ORs that were in favor of treatment (i.e., noticeably fewer events on treatment than on placebo). Because discontinuations come from a variety of sources (lack of efficacy, safety, etc.), it is difficult to tell whether the effect of prior relapse rate is the primary cause of the difference (if one truly exists) or whether it is acting as a proxy for another variable, such as differences in study protocols in newer studies.

The sensitivity analysis in which 2-year rates were assumed to be twice the 1-year rates (if 1-year rates were missing) found a weakly converging and poorly estimated non-significant estimate of 1.16, with a frequentist-equivalent p-value of 0.20, and a 90% chance that there is a positive association between prior relapse rate and the relative odds of discontinuing treatment.

DISCUSSION/SUMMARY

Meta-regressions were conducted for 3 of the key outcomes for the health-economic model, investigating whether prior relapse rate was related to the relative treatment effects versus placebo for the ARR ratio, SAD3, or discontinuations. No effect was found for prior relapse rate on ARR ratios, but a marginally significantly negative effect was found for SAD3, and a marginally significant positive effect was found for discontinuations. It is unknown whether the effects are due to prior relapse rate itself or differences in study protocols/methods between older studies (which tend to have higher prior relapse rates) and newer studies. Point estimates change slightly for SAD3 and discontinuations when prior relapse rate is accounted for, primarily due to the adjustment for prior relapse rate, but in part because placebo-controlled studies with missing data on prior relapse rate were dropped from analyses.

Table 2. Comparison of 1-year and 2-year Prior Relapse Rate Across Trials

Author, Year	Trial Name	Treatment	Prior Relapse Rate, 1-year	Prior Relapse Rate, 2-year	Calculated 2-year to 1-year Ratio
Comi, 2012	ALLEGRO	Laquinimod	1.2	1.9	1.58
Comi, 2012	ALLEGRO	Placebo	1.3	1.9	1.46
Comi, 2011	FORTE	GA 20 mg	1.5	2	1.33
Comi, 2011	FORTE	GA 40 mg	1.4	2	1.43
Kappos, 2010	FREEDOMS	Fingolimod 1.25 mg	1.5	2.1	1.40
Kappos, 2010	FREEDOMS	Fingolimod 0.5 mg	1.5	2.1	1.40
Kappos, 2010	FREEDOMS	Placebo	1.4	2.2	1.57
Calabresi, 2012	FREEDOMS II	Fingolimod 1.25 mg	1.5	2.3	1.53
Calabresi, 2012	FREEDOMS II	Fingolimod 0.5 mg	1.4	2.2	1.57
Calabresi, 2012	FREEDOMS II	Placebo	1.5	2.2	1.47
Kappos, 2006	FTY720 D2201 Study	Fingolimod 1.25 mg	1.3	1.9	1.46
Kappos, 2006	FTY720 D2201 Study	Fingolimod 5 mg	1.3	1.9	1.46
Kappos, 2006	FTY720 D2201 Study	Placebo	1.2	1.8	1.50
Saida, 2012	Japanese Phase II	Placebo	1.7	2.8	1.65
Saida, 2012	Japanese Phase II	Fingolimod 0.5 mg	1.4	2.2	1.57
Saida, 2012	Japanese Phase II	Fingolimod 1.25 mg	1.5	2.3	1.53
O'Connor, 2011	TEMSO	Placebo	1.4	2.2	1.57
O'Connor, 2011	TEMSO	Teriflunomide 7 mg	1.4	2.3	1.64
O'Connor, 2011	TEMSO	Teriflunomide 14 mg	1.3	2.2	1.69
Vermersch, 2012	TENERE	IFNβ-1a 44 µg	1.3	1.7	1.31
Vermersch, 2012	TENERE	Teriflunomide 7 mg	1.4	1.7	1.21
Vermersch, 2012	TENERE	Teriflunomide 14 mg	1.2	1.7	1.42
Kappos, 2012	TOWER	Placebo	1.4	2.1	1.50
Kappos, 2012	TOWER	Teriflunomide 7 mg	1.4	2.1	1.50

Author, Year	Trial Name	Treatment	Prior Relapse Rate, 1-year	Prior Relapse Rate, 2-year	Calculated 2-year to 1-year Ratio
Kappos, 2012	TOWER	Teriflunomide 14 mg	1.4	2.1	1.50
Cohen, 2010	TRANSFORMS	Fingolimod 1.25	1.5	2.2	1.47
Cohen, 2010	TRANSFORMS	Fingolimod 0.5 mg	1.5	2.3	1.53
Cohen, 2010	TRANSFORMS	IFNβ-1a 30 µg	1.5	2.3	1.53

Abbreviations: GA = Glatiramer acetate; IFNβ-1a = Interferon beta-1a; mg = milligram; µg = microgram

Table 3. Prior Relapse Rates Among Analyzed Trials (All Years with 80% RRMS)

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	Discontinuation Analysis
AFFIRM	Natalizumab	1.53			Yes	Yes	Yes
AFFIRM	Placebo	1.5			Yes	Yes	Yes
ALLEGRO	Laquinimod	1.2	1.9		Yes	Yes	Yes
ALLEGRO	Placebo	1.3	1.9		Yes	Yes	Yes
BECOME	GA 20 mg	NR			Yes	--	Yes
BECOME	Interferon β-1b 250 ug	NR			Yes	--	Yes
BEYOND	Interferon β-1b 500 ug	1.6			Yes	Yes	Yes
BEYOND	Interferon β-1b 250 ug	1.6			Yes	Yes	Yes
BEYOND	GA 20 mg	1.6			Yes	Yes	Yes
BG-12 Phase Iib Study	BG-12 120mg qd	NR			Excluded	--	Excluded
BG-12 Phase Iib Study	BG-12 120 tid	NR			Excluded	--	Excluded
BG-12 Phase Iib Study	BG-12 240mg tid	NR			Excluded	--	Excluded
Bornstein 1987	GA 20 mg	2.58*	3.8		--	Yes	--
Bornstein 1987	Placebo	2.58*	3.9		--	Yes	--
BRAVO	Laquinimod 0.6 mg	NR			Excluded	--	--
BRAVO	Interferon β-1a 30 ug	NR			Excluded	--	--
BRAVO	Placebo	NR			Excluded	--	--
CAMMS223	Interferon β-1a 44 ug	NR			Yes	Yes	Yes
CAMMS223	Alemtuzumab 12 mg	NR			Yes	Yes	Yes

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	Discontinuation Analysis
CAMMS223	Alemtuzumab 24 mg	NR			Yes	Yes	Yes
CARE MS I	Interferon β-1a 44 ug	1.8			Yes	Yes	Yes
CARE MS I	Alemtuzumab 12 mg	1.8			Yes	Yes	Yes
CARE-MS II	Interferon β-1a 44 ug	1.5			Yes	Yes	Yes
CARE-MS II	Alemtuzumab 12 mg	1.7			Yes	Yes	Yes
CARE-MS II	Alemtuzumab 24 mg	1.6			Yes	Yes	Yes
CombiRx	Interferon β-1a 30 ug	1.7		2.6	Yes	--	--
CombiRx	GA 20 mg	1.6		2.4	Yes	--	--
CONFIRM	Placebo	1.4			Yes	Yes	Yes
CONFIRM	BG-12 240 mg bid	1.3			Yes	Yes	Yes
CONFIRM	BG-12 240 tid	1.4			Yes	Yes	Yes
CONFIRM	GA 20 mg	1.4			Yes	Yes	Yes
Copolymer 1 Multiple Sclerosis Study Group	GA 20 mg	1.95*	2.9		Yes	Yes	Yes
Copolymer 1 Multiple Sclerosis Study Group	Placebo	1.95*	2.9		Yes	Yes	Yes
DEFINE	placebo	1.3			Yes	Yes	Yes
DEFINE	BG-12 240 mg bid	1.3			Yes	Yes	Yes
DEFINE	BG-12 240 mg tid	1.3			Yes	Yes	Yes
Dose Comparison 9006 Study Group	GA 20 mg	1.5			Yes	--	Yes
Dose Comparison 9006 Study Group	GA 40 mg	1.5			Yes	--	Yes

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	Discontinuation Analysis
European/Canadian Glatiramer Acetate Study	GA	1.78*	2.8		Yes	--	Yes
European/Canadian Glatiramer Acetate Study	Placebo	1.78*	2.5		Yes	--	Yes
EVIDENCE	Interferon β-1a 44 ug	1.74*	2.6		Yes	Yes	Yes
EVIDENCE	Interferon β-1a 30 ug	1.74*	2.6		Yes	Yes	Yes
FORTE Study Group	GA 20 mg	1.5	2		Yes	--	Yes
FORTE Study Group	GA 40 mg	1.4	2		Yes	--	Yes
FREEDOMS	Fingolimod 1.25 mg	1.5	2.1		Yes	Yes	Yes
FREEDOMS	Fingolimod 0.5 mg	1.5	2.1		Yes	Yes	Yes
FREEDOMS	Placebo	1.4	2.2		Yes	Yes	Yes
FREEDOMS II	Fingolimod 1.25 mg	1.5	2.3		Yes	Yes	--
FREEDOMS II	Fingolimod 0.5 mg	1.4	2.2		Yes	Yes	--
FREEDOMS II	Placebo	1.5	2.2		Yes	Yes	--
FTY720 D2201 Study Group	Fingolimod 1.25 mg	1.3	1.9		Yes	--	Yes
FTY720 D2201 Study Group	Fingolimod 5 mg	1.3	1.9		Yes	--	Yes
FTY720 D2201 Study Group	Placebo	1.2	1.8		Yes	--	Yes
HERMES	Rituximab 1000 mg	NR			Excluded	--	Excluded
HERMES	Placebo	NR			Excluded	--	Excluded
IFNB MS Study Group	Interferon β-1b 1.6 MIU	2.3*	3.3		Yes	Yes	Yes
IFNB MS Study Group	Interferon β-1b 8 MIU	2.3*	3.4		Yes	Yes	Yes

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	Discontinuation Analysis
IFNB MS Study Group	Placebo	2.3*	3.6		Yes	Yes	Yes
Japanese Phase II study	Placebo	1.7	2.8		Yes	--	Yes
Japanese Phase II study	Fingolimod 0.5 mg	1.4	2.2		Yes	--	Yes
Japanese Phase II study	Fingolimod 1.25 mg	1.5	2.3		Yes	--	Yes
LAQ/5062	Laquinimod 0.3 mg	1.46			Yes	--	Yes
LAQ/5062	Laquinimod 0.6 mg	1.51			Yes	--	Yes
LAQ/5062	Placebo	1.37			Yes	--	Yes
Laquinimod in Relapsing MS	Laquinimod 0.3 mg	NR			--	--	Excluded
Laquinimod in Relapsing MS	Laquinimod 0.1 mg	NR			--	--	Excluded
Laquinimod in Relapsing MS	Placebo	NR			--	--	Excluded
MSCRG	Interferon β-1a 30 ug	NR			Excluded	--	Excluded
MSCRG	Placebo	NR			Excluded	--	Excluded
PRISMS	Interferon β-1a 22 ug	2.01*	3		--	Yes	Yes
PRISMS	Interferon β-1a 44 ug	2.01*	3		--	Yes	Yes
PRISMS	Placebo	2.01*	3		--	Yes	Yes
REGARD	Interferon β-1a 44 ug	1.33*	Unclear		Yes	--	Yes
REGARD	GA 20 mg	1.33*	Unclear		Yes	--	Yes
SELECT	Daclizumab HYP 300 mg	1.3			Yes	Yes	Yes
SELECT	Daclizumab HYP 150 mg	1.4			Yes	Yes	Yes

Trial Name	Treatment	1-year rate	2-year rate	3-year rate	ARR Analysis	SAD3 Analysis	Discontinuation Analysis
SELECT	Placebo	1.3			Yes	Yes	Yes
TEMSO	Placebo	1.4	2.2		Yes	Yes	Yes
TEMSO	Teriflunomide 7 mg	1.4	2.3		Yes	Yes	Yes
TEMSO	Teriflunomide 14 mg	1.3	2.2		Yes	Yes	Yes
TENERE	IFNβ-1a 44 µg	1.3	1.7		Yes	Yes	Yes
TENERE	Teriflunomide 7 mg	1.4	1.7		Yes	Yes	Yes
TENERE	Teriflunomide 14 mg	1.2	1.7		Yes	Yes	Yes
Teri in MS	Placebo	1.47			Yes	--	Yes
Teri in MS	Teriflunomide 7 mg	1.47			Yes	--	Yes
Teri in MS	Teriflunomide 14 mg	1.47			Yes	--	Yes
TOWER	Placebo	1.4	2.1		Yes	Yes	Yes
TOWER	Teriflunomide 7 mg	1.4	2.1		Yes	Yes	Yes
TOWER	Teriflunomide 14 mg	1.4	2.1		Yes	Yes	Yes
TRANSFORMS	Fingolimod 1.25	1.5	2.2		Yes	Yes	Yes
TRANSFORMS	Fingolimod 0.5 mg	1.5	2.3		Yes	Yes	Yes
TRANSFORMS	IFNβ-1a 30 µg	1.5	2.3		Yes	Yes	Yes

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate; IFN = Interferon; pbo = placebo; SAD = Sustained accumulation of disability; µg = microgram

Note: Prior relapse rate is only important for placebo-controlled trials. Active controlled trials with missing data were still included in the analysis. Grayed out trials are those placebo-controlled trials not reporting prior relapse rate or reporting only the median prior relapse rate.

*Indicates 1-year imputation from 2-year rate.

Table 4. Summary of MTC, Meta-regression, and Literature Results

Comparison	Base Case – Post-2000, 80% RRMS (MTC)	All Years with 80% RRMS	All Years with 80% RRMS Controlling for Relapse (Meta-regression)	Direct Evidence	Trial Name	Author, Year
ARR						
GA vs. pbo	0.64 [0.53, 0.76]	[redacted]	[redacted]	0.72 [0.61, 0.87] 0.7 [0.57, 0.86] 0.67 [0.48, 0.93]	CONFIRM Copolymer 1 MS Study* European/Canadian GA Study*	Fox, 2012 Johnson, 1995 Comi, 2001
Rebif 44 µg vs. pbo	0.62 [0.51, 0.76]	[redacted]	[redacted]	--	--	--
Rebif 22 µg vs. pbo	--	[redacted]	[redacted]	--	--	--
Avonex vs. pbo	0.78 [0.67, 0.91]	[redacted]	[redacted]	0.73 [0.62, 0.86] 0.82 [0.68, 0.98]	BRAVO MSCRG*	Vollmer, 2012 Jacobs, 1996
Betaferon vs. pbo	0.68 [0.52, 0.88]	[redacted]	[redacted]	0.66 [0.56, 0.79]	IFNB MS Study*	Duquette, 1993
Teriflunomide 14 vs. pbo	0.67 [0.57, 0.77]	[redacted]	[redacted]	0.68 [0.36, 1.27] 0.69 [0.58, 0.81] 0.64 [0.53, 0.77]	O'Connor, 2006 TEMSO TOWER	O'Connor, 2006 O'Connor, 2011 Kappos, 2012
SAD3						
GA vs. pbo	0.93 [0.59, 1.45]	[redacted]	[redacted]	0.93 [0.63, 1.37] 0.32 [0.09, 1.09] 0.86 [0.51, 1.45]	CONFIRM Bornstein, 1987* Copolymer 1 MS Study*	Fox, 2012 Bornstein, 1987 Johnson, 1995
Rebif 44 µg vs. pbo	0.79 [0.51, 1.24]	[redacted]	[redacted]	0.65 [0.45, 0.94]	PRISMS*	Ebers, 1998
Rebif 22 µg vs. pbo	--	[redacted]	[redacted]	0.75 [0.53, 1.08]	PRISMS*	Ebers, 1998
Avonex vs. pbo	0.91 [0.61, 1.33]	[redacted]	[redacted]	--	--	--
Betaferon vs. pbo	1.21 [0.68, 2.16]	[redacted]	[redacted]	0.68 [0.4, 1.17]	IFNB MS Study*	Duquette, 1993
Teriflunomide 14 vs. pbo	0.71 [0.53, 0.92]	[redacted]	[redacted]	0.7 [0.51, 0.96] 0.68 [0.47, 1]	TEMSO TOWER	O'Connor, 2011 Kappos, 2012

Comparison	Base Case – Post-2000, 80% RRMS (MTC)	All Years with 80% RRMS	All Years with 80% RRMS Controlling for Relapse (Meta-regression)	Direct Evidence	Trial Name	Author, Year
Discontinuation						
GA vs. pbo	[redacted]	[redacted]	[redacted]	0.59 [0.43, 0.81]	CONFIRM	Fox, 2012
				1.15 [0.57, 2.33]	Copolymer 1 MS Study*	Johnson, 1995
				1.01 [0.34, 2.97]	European/Canadian GA Study*	Comi, 2001
Rebif 44 µg vs. pbo	[redacted]	[redacted]	[redacted]	1.15 [0.58, 2.29]	PRISMS*	Ebers, 1998
Rebif 22 µg vs. pbo	[redacted]	[redacted]	[redacted]	0.68 [0.39, 1.17]	PRISMS*	Ebers, 1998
Avonex vs. pbo	[redacted]	[redacted]	[redacted]	1.45 [0.61, 3.45]	MSCRG*	Jacobs, 1996
Betaferon vs. pbo	[redacted]	[redacted]	[redacted]	1.04 [0.55, 1.97]	IFNB MS Study*	Duquette, 1993
Teriflunomide 14 vs. pbo	[redacted]	[redacted]	[redacted]	3.8 [1.15, 12.58]	O'Connor 2006	O'Connor, 2006
				0.9 [0.65, 1.25]	TEMSO	O'Connor, 2011
				1.07 [0.79, 1.45]	TOWER	Kappos, 2012

Abbreviations: ARR = Annualized relapse rate; GA = Glatiramer acetate; ICER = Incremental cost-effectiveness ratio; MTC = Mixed treatment comparison; pbo = placebo; RRMS = Relapsing remitting multiple sclerosis; SAD = Sustained accumulation of disability; µg = microgram

*Study enrolled patients prior to 2000.

** Correct values. Those in Table AA2.7 in Additional Appendix 2 of STA submission wrong (misread off Table AA2.9.) although correct values entered in HE model

APPENDIX A. WINBUGS CODE FOR META-REGRESSION ANALYSES

Below is the model code for the SAD3 meta-regression analyses; the code for the Discontinuations meta-regression is essentially the same, modeling placebo-controlled studies as having effects equal to a grand mean, modified by gamma01, the slope for the effect of (a mean-centered) prior relapse rate.

```
model {

for (i in 1:N) {
prec.Prog3HR[i] <- 1/(Prog3HR.se[i]*Prog3HR.se[i])
Prog3HR[i]~dnorm(theta[i],prec.Prog3HR[i])
theta[i] <- delta[i] + gamma01*(PriorRR[i]-PriorRR.bar)*step(1.1-nb[i])
                delta[i] ~ dnorm(md[i],prec)
                md[i] <-  dd[ntreat[i]] - dd[nb[i]]

        }

gamma01~dnorm(0.0,0.0001)

PriorRR.bar<-1.64076923076923

tau<-1/prec
tau.sqrt<-sqrt(tau)


# Prior for between-study precision/sd
prec <- 1/(sd*sd)
sd ~ dunif(0,1)

#Give priors for differences
            dd[1]<-0
            for (k in 2:19){dd[k] ~ dnorm(0,0.0001) }


#All pairwise comparisons
for (c in 1:19-1){
            for (k in (c+1):19){
                        logHR[c,k] <- dd[k] - dd[c]
                        logHRprob[c,k] <- step(logHR[c,k])
                        HR[c,k] <- exp(logHR[c,k])
                        }
            }

gamma01better<-step(gamma01)
```