Bayesian Dynamic Borrowing to Enhance Evidence for New Therapies

A practical approach to leverage the totality of evidence to reduce uncertainty in efficacy outcomes

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SUPPLEMENTARY MATERIALS

META-REGRESSION AND RELATED INPUTS

Following Kappos et al 2025[26] an unweighted linear model was fitted to nine historical trials (Table S1) to obtain a predicted effect on the log hazard ratio (HR) scale:

$$\hat{y} = -0.4173 + 0.5425 * \theta_T + 0.3377 * P$$

where θ_T is an estimate of the log HR for CDP-T25FWT and P is an indicator variable such that P=1 if the new trial population has PPMS or non-active secondary progressive MS, and P=0 otherwise.

An inverse weighted variance linear model was also considered; however, its predictive performance in cross-validation was inferior to that of the unweighted linear model.

The residual SE from the model was $\sigma_R = 0.1156$ and

$$Var(\hat{y}) = \begin{pmatrix} 1 & \theta_T & P \end{pmatrix} \begin{pmatrix} 0.0135 & 0.0267 & -0.0093 \\ 0.0267 & 0.0793 & -0.0145 \\ -0.0093 & -0.0145 & 0.0093 \end{pmatrix} \begin{pmatrix} 1 \\ \theta_T \\ P \end{pmatrix} + Var(\hat{\theta}_T)(0.0793 + 0.5425^2)$$

where $\hat{\theta}_T$ is the TE estimator for the intermediate outcome and $Var(\hat{\theta}_T)$ is its variance. $Var(\hat{\theta}_T)$ captures (1) the variance of the TE estimator on the intermediate outcome; (2) the covariance between the estimators of the TE on the intermediate and final outcome, which in this case is 0.5425; and (3) the variance of the estimator of the covariance, which in this case is 0.0793.

TABLE S1. Historical trials reporting treatment effects on CDP-T25FWT and CDP-EDSS

Study name	Phase	Design	Population phenotype	Treatments	N (total) (active treatment/ comparator)	TE (95% CI) CDP-EDSS TE (95% CI) CDP-T25FWT	Source:
AFFIRM [NCT00027300]	3	Multicentre, randomised, double-blind, parallel group, placebo controlled	RRMS	Natalizumab, placebo	942 (627/315)	0.46 (0.31-068) 0.69 (0.45-1.05)	Dong et al 2014
ASCEND [NCT01416181]	3b	Multicentre, randomised, double-blind, placebo-controlled	SPMS	Natalizumab, placebo	889 (440/449)	1.06 (0.74-1.53) 0.98 (0.74-1.3)	Kapoor et al 2018
EXPAND [NCT01665144]	3	Multicentre, randomised, double-blind, parallel group, placebo controlled	SPMS	Siponimod, placebo	1652 (1105/546)	0.79 (0.65-0.95) 0.94 (0.8-1.1)	Kappos et al 2018
INFORMS [NCT00731692]	3	Multicentre, randomised, double-blind, parallel group, placebo controlled	PPMS	Fingolimod, placebo	970 cohort 1: (147/133) cohort 2: (336/354)	0.88 (0.72-1.08) 0.94 90.78-1.14)	Lublin et al 2016
OLYMPUS [NCT00087529]	3	Multicentre, randomised, double-blind, parallel group, placebo controlled	PPMS	Rituximab, placebo	439 (292/147)	0.77 (0.55-1.09) 0.67 (0.5-0.9)	Hawker et al 2009
OPERA I [NCT01247324]	3	Multicentre, randomised, double-blind, double-dummy, parallel-group plus long-term extension	RMS	Ocrelizumab, interferon-β-1a SC	821 (410/411)	0.57 (0.37-0.90) 0.62 (0.42-0.91)	Roche database
OPERA II [NCT01412333]	3	Multicentre, randomised, double-blind, double-dummy, parallel-group plus long-term extension	RMS	Ocrelizumab, interferon-β-1a SC	835 (417/418)	0.63 (0.42-0.92) 0.85 (0.6-1.22)	Roche database
ORATORIO [NCT01194570]	3	Multicentre, randomised, parallel-group, double-blind, placebo-controlled plus long-term extension	PPMS	Ocrelizumab, placebo	732 (488/244)	0.76 (0.59-0.98) 0.75 (0.61-0.92)	Roche database
PROMISE [NA]	NA	Multicentre, randomised, double-blind, placebo-controlled	PPMS	Glatiramer acetate, placebo	943 (627/316)	0.87 (0.71-1.07) 0.91 90.81-1.01)	Wolinsky et al 2007

Note: CDP confirmed disability progression, EDSS Expanded Disability Status Scale, PPMS primary progressive multiple sclerosis, RMS relapsing MS, RRMS relapsing-remitting MS, SC subcutaneous, SPMS secondary progressive multiple sclerosis, T25FWT Timed 25-Foot Walk Test. Source: Kapp

NEW TRIALS AND RELATED ASSUMPTIONS ON TEs

FIGURE S1. cCDP Definition and Components

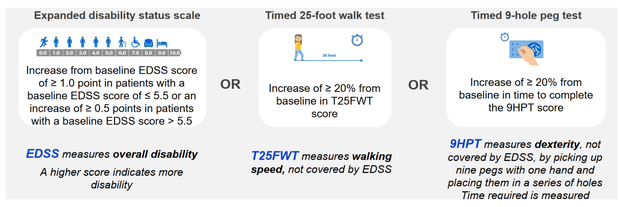

TABLE S2. Assumed TEs on Components of cCDP in Hypothetical New Trials in MS

Trial Setting	Outcome	TE (HR (95% CI)
RMS	CDP-EDSS	0.60 (0.36-1.00)
	CDP-T25FWT	0.80 (0.64-1.00)
PPMS	CDP-EDSS	0.70 (0.49-1.00)
	CDP-T25FWT	0.60 (0.45-0.80)

BDB AND RELATED ASSUMPTIONS AND CALCULATIONS

The variance of the sceptical prior SP is specified to be $\sigma_S^2 = 1$ as this implies a 16% chance of HR < $exp\,(-1) = 0.37$ for CDP-EDSS. For illustrative purposes, we also set $\Upsilon = 1$.

BDB TE estimate and corresponding 95% credible interval (CrI) are obtained as follows:

$$log\ HR\ estimate\ = \frac{\sigma_P^2}{\sigma_P^2 + \sigma_E^2}\theta_E + \frac{\sigma_E^2}{\sigma_P^2 + \sigma_E^2}\hat{y}\ exp\left(-\frac{|\theta_E - \hat{y}|}{\sigma_E}\right)$$

$$95\%\ credible\ interval\ =\ log\ HR\ estimate\ \pm z_{0.975}\sqrt{\frac{\sigma_P^2\,\sigma_E^2}{\sigma_P^2 + \sigma_E^2}},$$

$$\sigma_P^2 = \left\{1 - exp\left(-\frac{|\theta_E - \hat{y}|}{\sigma_E}\right)\right\}^2 + exp\left(-\frac{2|\theta_E - \hat{y}|}{\sigma_E}\right)(Var(\hat{y}) + 0.1156^2),$$

Where $z_{1-a/2}$ is the $100(1 - \alpha/2)th$ quantile of a standard normal distribution.

LEAVE-ONE-OUT CROSS VALIDATION

TABLE S3. Treatment effect estimates on CDP-EDSS from fitting a Cox model to only the new trial data, meta-regression, and BDB

Trial	New trial		Meta-regression		BDB	
	Estimate (95% CI)	SE	Estimate	Prediction error	Estimate (95% CrI)	SD of posterior distribution
AFFIRM	0.46 (0.31-0.68)	0.200	0.58	0.163	0.48 (0.32-0.67)	0.193
ASCEND	1.06 (0.74-1.53)	0.185	0.86	0.134	1.05 (0.75-1.50)	0.179
EXPAND	0.79 (0.65-0.95)	0.097	0.92	0.137	0.79 (0.65-0.95)	0.096
INFORMS	0.88 (0.72-1.08)	0.103	0.90	0.156	0.89 (0.73-1.06)	0.093
OLYMPUS	0.77 (0.55-1.09)	0.174	0.71	0.214	0.78 (0.56-1.05)	0.158
OPERA I	0.57 (0.37-0.90)	0.227	0.46	0.209	0.59 (0.38-0.86)	0.212
OPERA II	0.63 (0.42-0.92)	0.200	0.58	0.205	0.64 (0.45-0.89)	0.177
ORATORIO	0.76 (0.59-0.98)	0.129	0.80	0.159	0.77 (0.60-0.96)	0.122
PROMISE	0.87 (0.71-1.07)	0.105	0.88	0.145	0.88 (0.73-1.03)	0.088

Note: BDB Bayesian dynamic borrowing, CDP-EDSS confirmed disability progression Expanded Disability Status Scale, CI confidence interval, CrI credible interval, SD standard deviation, SE standard error.

TABLE S4. The number of CDP-EDSS events in the New Trial and gained by BDB.

Trial	Trial randomization ratio	Variance	Estimated events, n	BDB variance	Estimated events with BDB-derived variance, n	Events gained by applying BDB, n
AFFIRM	2:1	0.040	113	0.037	121	8
ASCEND	1:1	0.034	117	0.032	125	8
EXPAND	2:1	0.009	478	0.009	488	10
INFORMS	1:1	0.011	377	0.009	462	85
OLYMPUS	2:1	0.030	149	0.025	180	32
OPERA I	1:1	0.052	78	0.045	89	11
OPERA II	1:1	0.040	100	0.031	128	28
ORATORIO	2:1	0.017	270	0.015	302	32
PROMISE	2:1	0.011	408	0.008	581	173

Note: BDB Bayesian dynamic borrowing, CDP-EDSS confirmed disability progression Expanded Disability Status Scale.