Can models for surrogate endpoint evaluation be used to predict generic measures from disease specific measures of health related quality of life HRQoL based on summary data?

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Aims

We aimed to explore the use of meta-analytic models for surrogate endpoint evaluation to obtain estimates of generic measures of HRQoL from disease specific measures. Applied to systematic reviews of treatments for ankylosing spondylitis (AS) and non-radiographic axial Spondyloarthritis (nr-axSpA).

Background

In a Health Technology Assessment (HTA), evidence synthesis is often employed when trials do not provide head-to-head evidence on the relative treatment effects along a pathway. AS, nr-axSpA a group of inflammatory rheumatologic diseases, have no cure and a detrimental effect on the QoL captured by;

•Bath Ankylosing Spondylitis Disease Activity Index (BASDAI),

•Bath Ankylosing Spondylitis Functional Index (BASFI),

•The Short Form 36 Physical Functioning component (SF36-PCS) and, the Mental Health component (SF36-MCS).

Data extracted from 25 randomised control trials (RCTs) of Tumour necrosis factor-alpha (TNF-alpha) inhibitors reported in two systematic reviews MTA 383 and STA407, described in table 1.

Table 1 List of Studies and outcomes extracted

No.	Trial	Year	Treatment	BASDAI	BASFI	SF36 - PCS	SF36 - MCS
3	Huang	2014	ADA	•	•	•	•
4	Lambert	2007	ADA	-	-	-	-
5	ABILITY-1	2013	ADA	•	•	•	•
6	ATLAS	2006	ADA	•	-	•	•
7	RAPID-axSpA	2014	CERT	•	•	•	•
8	Barkham	2010	ETA	•	•	-	-
9	Davis	2003	ETA	•	•	-	-
10	Dougados	2011	ETA	•	•	-	-
...	...	...	...	...	...	...	...
...	...	...	...	...	...	...	...
25	Measure 2	2015	SEC	•	•	•	-

• reported, – not reported, Adalimumab ADA, Certolizumab pegol CER, Etanercept ETA, Golimumab GOL, Infliximab INF, Secukinumab SEC

Our objective was to use the bivariate surrogate endpoints models described in Technical Support Document 20 to jointly model the possible combinations of disease specific and generic HRQoL outcomes assuming surrogacy in in the absence of individual patient data (IPD).

- Short-list correlated disease specific and generic HRQoL outcomes.
- Cross validate the surrogate endpoint models for the short-listed outcomes.
- Map from disease specific to generic HRQoL outcomes.
- Compare the results of the surrogate endpoints models.
- Compare the pooled results of bivariate surrogate endpoint and univariate models.

Methods

Prospective surrogate endpoints (BASFI, BASDAI) and target outcomes (SF-36) were jointly modelled and cross-validated with bivariate random meta-analysis (BRMA) models; Daniels-Hughes (D&H) and product normal formulation (PNF). It is assumed the true underlying treatment effects on the reported endpoints of each study are normally distributed, correlated (investigated with meta-regression) and study-specific or exchangeable.

The BRMA D&H model (1) utilises treatment effects on the surrogate endpoint Y_{1i} and target outcome Y_{2i} to estimate the underlying true effects δ_{1i} and δ_{2i}, standard deviations σ_{1i} and σ_{2i} correlation ρ_{wi}, between them in each study i. The underlying true effect on the surrogate δ_{1i} is assumed to have a study specific (fixed effects) linear relationship to the true effect on the target δ_{2i}.

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{MVN}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix}\right) \quad (1)$$

$$\delta_{2i} \mid \delta_{1i} \sim N(\lambda_0 + \lambda_1\delta_{1i}, \psi^2)$$

The BRMA PNF (2) is a random effects model which assumes exchangeability of the underlying true effect on the surrogate $\delta_{1i} \sim N(\eta_1, \psi_1^2)$ with a linear relationship between the studies (3).

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim \text{N}\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i\right), \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi} \\ \sigma_{1i}\sigma_{2i}\rho_{wi} & \sigma_{2i}^2 \end{pmatrix} \quad (2)$$

$$\begin{cases} \delta_{1i} \sim N(\eta_1, \psi_1^2) \\ \delta_{2i} \mid \delta_{1i} \sim N(\eta_{2i}, \psi_2^2) \\ \eta_{2i} = \lambda_0 + \lambda_1\delta_{1i}. \end{cases} \quad (3)$$

In the absence of IPD and external sources of information , correlation is investigated using a range of values between ±1 $\rho_w \sim Unif(-1,1)$, the models' parameters are given vague priors $\delta_{1i} \sim N(0,1000), \lambda_0 \sim N(0.0,1000), \lambda_1 \sim N(0.0,1000), \psi_2 \sim N(0,100)I(0,), \eta_1 \sim N(0,1000), \lambda_0 \sim N(0,1000)$.

Missing standard errors σ_{ji} are estimated by extension of the exchangeability assumption to the population variances $var_{ji} = {\sigma_{ji}}^2 N_i$. These are assumed to come from the distribution $var_{ji} \sim N(0, h_j)I(0,), h_j \sim \Gamma(1.0,0.01)$. For studies with unbalanced treatment arms $var_{ji} = {\sigma_{ji}}^2/\left(\frac{1}{N_{Ai}} + \frac{1}{NB_i}\right)$.

Results

The frequentist pairwise meta-analysis indicated that random effects models reduce the between study heterogeneity. The pairwise meta-regression (figures 1, 2) show the correlated disease specific and generic HRQoL outcomes in.

Figure 1 Pairwise meta regression bubble plots of the differences in treatment scores for SF36-PCS vs BASDAI

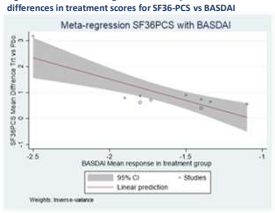
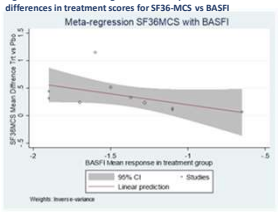


Figure 2 Pairwise meta regression bubble plots of the differences in treatment scores for SF36-MCS vs BASFI



Jointly modelling correlated HRQoL outcomes increased the number of studies when pooling the estimates jointly vs in comparison to when pooled separately as seen in (figures 3, 4).

Figure 3 Network Plots for the Separate BASDAI, SF36-PCS and combined BASDAI/SF3F-PCS Networks

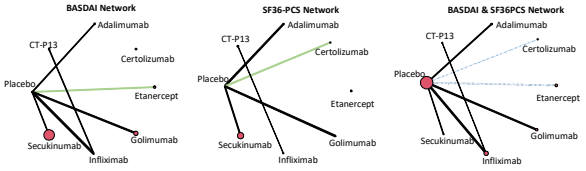
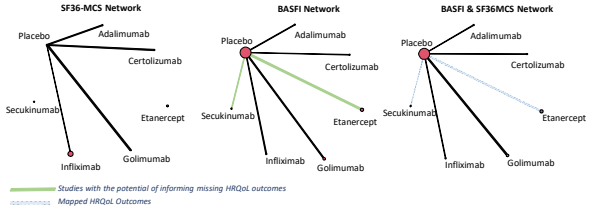
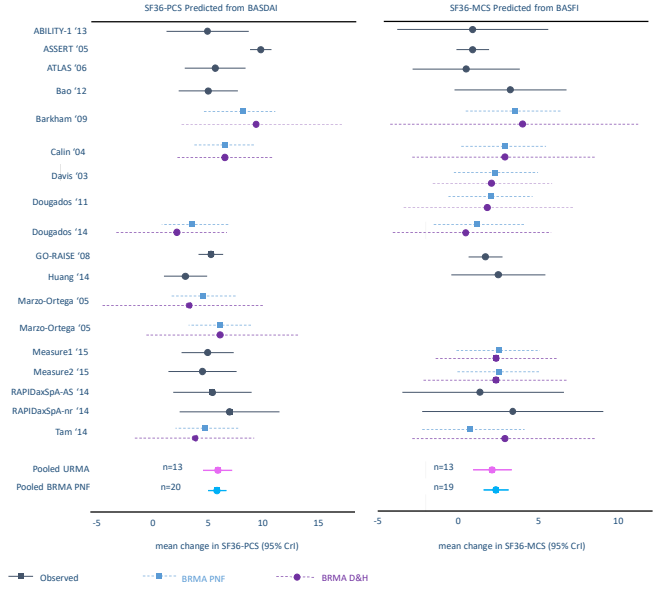


Figure 4 Network Plots for the Separate BASFI, SF36-MCS and combined BASFI/SF3F-MCS Networks



Cross validation confirmed the models' prediction intervals to contain the observed estimates for at least 90% of included studies. The pooled estimates from BRMA PNF were more precise than the estimates from D&H. The BRMA PNF reduces uncertainty by 36% on SF36-MCS, and 38% on SF36-PCS when compared to a Univariate Meta Analysis URMA model. The results presented in the forest plot figure 5.

Figure 5 Forest Plot showing the observed outcomes, the predicted outcomes for the individual studies and the pooled outcomes for all the studies in their respective networks



Conclusion

BRMA PNF model is the authors' choice for jointly modelling and mapping between the surrogate (disease specific) and target (generic) measures of HRQoL. This method made more data available and increased precision of the pooled estimates.

Further research is required to investigating the impact of the methods presented here on the uncertainty in cost-effectiveness for this class of treatments. This may be achieved by undertaking a probabilistic economic decision model .

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References