Development of an Ordinal NMA Model Allowing for Testing of the Proportional Odds Assumption

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Tim Disher, PhD, RN | Loon | Halifax, NS, Canada

INTRODUCTION

The NICE TSDs provide standardized code for probit ordinal network meta-analysis (NMA) models when outcomes are ordinal. However, these models present challenges in interpretation: (1) The treatment effect scale is unfamiliar to clinicians; (2) Assessing the proportional odds assumption is difficult with current models; and (3) NICE TSD models borrow information from the control arm cumulative probabilities across trials

OBJECTIVES

We describe simple modifications to existing TSD code to allow for:

1. Treatment effects on the log odds instead of probit scale;
2. Formal hypothesis testing of the violation of the proportional odds assumption;
3. Use of fixed study intercepts to avoid sharing between study information in the reference arm.

METHOD

We combine a separation strategy for modelling between study heterogeneity in treatment effects at different thresholds with a logit link version of the NICE TSD 2 multivariate ordered probit link code to allow for separate treatment effects for each threshold under assessment. Results were validated via comparison to a simulated dataset that either follows or violates the proportional odds assumption.

Moving from probit to logit link

Treatment effects on the probit scale are interpreted as SMDs on the latent scale which is a non-standard summary of treatment effects on binary endpoints in medical research. The model is therefore modified as follows:

```
p[i,k,C[i,j]] <- 1 - phi(theta[i,k,j-1])
```

```
p[i,k,C[i,j]] <- 1 - ilogit(theta[i,k,j-1])
```

Specifying the between-studies model

The within-study correlation in outcomes is captured through the existing multinomial likelihood. For simplicity and flexibility, we use a separation strategy that allows parameterization in terms of a correlation matrix and standard error matrix. This ensures positive semi-definiteness while allowing for flexibly informative priors on between study heterogeneity and correlations.

Diagonal Matrix

```
sigma_c[1, 1] <- sd[1]
sigma_c[1, 2] <- 0
sigma_c[2, 1] <- 0
sigma_c[2, 2] <- sd[2]
```

Correlation Matrix

```
Rho[1, 1] <- 1.0
Rho[1, 2] ~ dunif(-1, 01)
Rho[2, 1] <- Rho[1, 2]
Rho[2, 2] <- 1.0
```

```
Sigma <- sigma_c %*% Rho %*% sigma_c
```

Comparison of estimates

We tested the ability of the model to correctly identify deviations from proportional odds in a simulated meta-analysis. Treatment effects on 2 thresholds were specified as odds ratios of 5 and 3, with between study heterogeneity standard deviation of 0.3 and 0.1. Ten trials with N = 2000 were simulated to allow for evaluation under ideal conditions.

Simulation with decreasing treatment effects on higher thresholds was required to avoid situations where cumulative ordering was violated (i.e., higher probabilities for the second threshold).

Inclusion Criteria	Proportional Odds Model	Non-proportional Odds Model
DIC	2137	355
OR vs Placebo	3.22	OR1 = 4.7 OR2 = 3.0
SD	0.12	SD1 = 0.3 SD2 = 0.1
Total residual deviance (on 40 data points)	1833	37

Conclusions

The specified model correctly identifies violation of proportional odds and allows exploration of whether the assumption influences subsequent decision making but may not be appropriate for economic modelling since predictions in a new populations can violate ordering rules. In practice this scenario may highlight possible violations of the transitivity assumption. Future research will evaluate whether adaptive constraints on treatment effects similar to those used in the NICE TSD 2 binomial identity and log link models can address ordering violation in simulation exercises.

References

Dias, S., Welton, N. J., Sutton, A. J., & Ades, A. E. (2011). NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials.

tim@loonbio.com