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Background

Network meta-analysis (NMA) can be hindered by patient **heterogeneity across trials** or a **lack of head-to-head trials**

Simulated treatment comparisons (STC) are often used to **adjust for observed heterogeneity** across trials to facilitate indirect comparisons when individual patient data (IPD) is not available for all trials

Adjusting for heterogeneity using STC requires the estimation of an outcome model, however, it is **common practice for STC analyses to ignore uncertainty introduced by this adjustment**

Failure to propagate the error from STC adjustments **can lead to confidence intervals or credible intervals that are too narrow**

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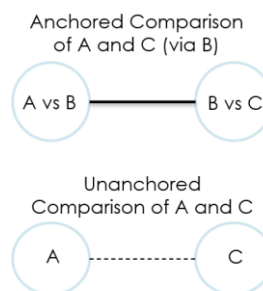
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Overview

In this presentation we

- Outline a method for propagating the error from the STC adjustment
- Demonstrate its efficacy via simulation

We focus on **parametric survival** application with an unanchored treatment comparison between two single-arm studies where **IPD is available for one study, and digitized Kaplan-Meier curve and summary statistics for the other**



Our approach differs somewhat from a typical STC:

- As recommended by NICE, we opt to compute relative treatment effects on the link scale (log scale) rather than the outcome scale
- After we estimate our outcome regression model using the available IPD, we implement the adjustment for heterogeneity directly in our model for estimating the treatment effects rather than simulating adjusted outcome values for one of the two trials

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Simulation Setup

We simulated data for two single-arm studies (N=300) with age and overall survival. Both datasets will be binned with **IPD retained for study 1 only**.

The age in study 1, X_1 , and age in study 2, X_2 , are drawn according to

$$\begin{aligned} X_1 &\sim \text{Unif}[55, 75] \text{ and} \\ X_2 &\sim \text{Unif}[50, 70]. \end{aligned}$$

We draw survival times Y_1 in study 1 and Y_2 in study 2 according to

$$\begin{aligned} Y_1 &\sim \text{Exp}(\lambda_1) \text{ and} \\ Y_2 &\sim \text{Exp}(\lambda_2) \end{aligned}$$

where the event rate parameters λ_1 and λ_2 depend on a common intercept, μ , the study 2 relative treatment effect, d_{12} , as well as the patient's age by the following formulas:

$$\begin{aligned} \ln(\lambda_1) &= \mu + \beta X_1 \\ \ln(\lambda_2) &= \mu + \beta X_2 + d_{12} \end{aligned}$$

For simplicity, we assume that there is no censoring.

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Simulation Parameters

For our simulation we use parameter values $\mu = -6$, $d_{12} = -0.3$, and $\beta = 0.05$

This means that the hazard ratio for treatment 2 relative to treatment 1 is 0.74 for patients of the same age

Additionally, age has a large impact on the hazard rate—a patient not receiving the treatment will have the same hazard rate as a patient that is 6 years older and on the treatment

Since patients in study 2 are on average 5 years younger, we will overestimate the relative treatment effect for treatment 2 if we do not adjust for the age difference between the two trials

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Methods – The Adjustment Term

We first note that for study 1 the log hazard rate for study 1 at the mean age, \bar{X}_1 , is

$$\begin{aligned}\ln \lambda_1(t; \bar{X}_1) &= \mu + \bar{X}_1\beta \\ &= \mu'\end{aligned}$$

Similarly, for study 2 at the mean age, \bar{X}_2 , we get

$$\begin{aligned}\ln \lambda_2(t; \bar{X}_2) &= \mu + \bar{X}_2\beta + d_{12} \\ &= (\mu + \bar{X}_1\beta) + d_{12} + (\bar{X}_2 - \bar{X}_1)\beta \\ &= \mu' + d_{12} + (\bar{X}_2 - \bar{X}_1)\beta \\ &= \mu' + d_{12} + \zeta\end{aligned}$$

Where $\mu' = \mu + \bar{X}_1\beta$ and $\zeta = (\bar{X}_2 - \bar{X}_1)\beta$

This means that once we adjust for ζ the difference in the log hazard rate between studies 2 and 1 is, on average, equal to the relative treatment effect d_{12} .

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Methods – The Adjustment Term and its Variance

We estimate the adjustment term, $\hat{\zeta}$, and its variance, $\hat{\sigma}_{\hat{\zeta}}^2$, using an exponential survival model estimated on the Study 1 IPD and the mean age difference between studies 2 and 1

In order to account for the uncertainty in the estimates of ζ when we estimate the relative treatment effect, d_{12} , we use the approximation $\zeta \sim N(\hat{\zeta}, \hat{\sigma}_{\hat{\zeta}}^2)$ as a prior in our Bayesian model

The imposition of this prior for ζ rather than treating it as fixed at $\zeta = \hat{\zeta}$ is the key to the error propagation.

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Sample Binned Data

Binned Study 1 and 2 Data

n1	r1	t1	dt1	n2	r2	t2	dt2
300	66	4	4	300	41	4	4
234	50	8	4	259	33	8	4
184	35	12	4	226	28	12	4
149	31	16	4	198	27	16	4
118	28	20	4	171	18	20	4
90	22	24	4	153	20	24	4
...

Where n1 and n2 are the numbers at risk in studies 1 and 2, respectively, r1 and r2 are the number of events, t1 and t2 are the bin end times, and dt1 and dt2 are the bin time lengths

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Methods – Estimating the Treatment Effect

We use a standard approach for modelling binned digitized Kaplan-Meier data which treats the hazard as approximately constant when modelling the number at risk, n_{ki} , and number of events, r_{ki} , within each study k and bin i :

$$\begin{aligned}
 r_{ki} &\sim \text{Binom}(n_{ki}, p_{ki}) \\
 p_{ki} &= 1 - \exp(-h_{ki} \cdot dt_{ki}) \\
 \ln(h_{ki}) &= \mu' + (d_{12} + \zeta) \cdot 1\{k = 2\}
 \end{aligned}$$

With the following priors:

$$\begin{aligned}
 \zeta &\sim N(\hat{\zeta}, \hat{\sigma}_{\zeta}^2) \\
 \mu' &\sim N(0, 100^2) \\
 d_{12} &\sim N(0, 100^2)
 \end{aligned}$$

The model without error propagation can be viewed as a special case where the adjustment term, ζ , is fixed at $\zeta = \hat{\zeta}$ (i.e. the prior has variance zero).

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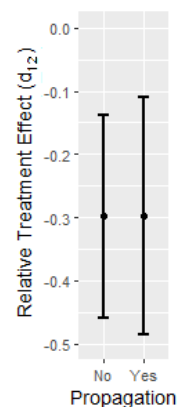
Simulation Results

We simulated 10,000 datasets and, for each dataset, ran our “with propagation” and “without propagation” Bayesian model using Stan (6 chains with 1,000 iterations and burn-in length of 500). Convergence was assessed for a handful of individual runs.

Results of STC with and without Error Propagation

Error Propagation (Yes / No)		No	Yes
Relative treatment effect	2.5th Percentile*	-0.46	-0.49
(d_{12}) posterior	Mean*	-0.30	-0.30
	97.5th Percentile*	-0.14	-0.11
95% CrIs capturing the true relative treatment effect		86.8%	92.0%

*Averaged over 10,000 simulations



- The remaining shortfall after propagating the error may be due to measurement error introduced by the binning procedure or due to limitations of using sample means rather than the full IPD as the basis for the heterogeneity adjustment
- Exact coverage and CrI widths will vary depending on the scenario. Additionally, smaller IPD sample sizes could lead to a larger discrepancy between the “with propagation” and “without propagation” CrIs

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Limitations

The method still requires that all effect modifiers be accounted for in the anchored case, and all effect modifiers **and** all prognostic variables in the unanchored case

The method relies on differences in mean covariate values to perform the adjustment, rather than the complete IPD, which means the relative **treatment effect estimates may be subject to ecological bias**

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Next Steps

Additional simulation scenarios will need to be studied

Extension to more flexible survival models is needed

Sensitivity to ecological bias will need to be explored further

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