A Bayesian Hierarchical Modelling Approach for Indirect Comparison of Response Outcomes in Histology-Independent Therapies

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Background

- Challenges exist in assessing efficacy of targeted therapies for rare mutations in oncology due to difficulty of recruiting enough patients into clinical trials
- Basket trials have been used to assess histology-independent therapies (HITs) to address this issue
- Underlying assumption: mutation-positive patients have potential to respond to therapy **regardless** of cancer type/histology
- Growing interest in use of Bayesian hierarchical models (BHM) to model heterogeneity across tumour types in basket trials [1,2]
- FDA approved cancer treatment based on common biomarker rather than tumour site for the first time in May 2017 [1]
- 1st marketing authorization granted in 2019 in Europe [1]
- HITs may be used among populations for which treatment options are limited or lacking
- NICE indicated receptiveness to BHMs in the technical appraisal for larotrectinib in NTRK-fusion positive solid tumours (TA630) [2]
- BHM allows for analysis of pooled overall response rates accounting for heterogeneity across different tumour types as well as histology-specific inferences [1,2,3]

Objectives

1. Develop new methods to facilitate **indirect comparisons of HITs** given data limitations and need to assess comparative efficacy of novel therapies for rare indications. HITs evaluated in basket trials present a particular challenge for indirect comparison methods due to potential prognostic importance of tumour type and very limited sample sizes to facilitate standard adjustment methods such as matching.
2. Extend previously established BHM approach [3] to allow for comparison of response outcomes between two basket trials, relying on aggregate-level data
3. Assess performance of our proposed method via simulation vs. indirect comparisons of simple pooled overall response rates which do not account for heterogeneity in response across tumour types

Methods

- The proposed BHM model allows for indirect treatment comparisons for a binary response endpoint between two HITs investigated in basket trial settings.
- The model relies on the following key assumptions:
  i. The relative treatment effect is constant across histologies (which can be relaxed with an exchangeable treatment effect assumption)
  ii. Histology-specific response outcomes satisfy a conditional exchangeability requirement
  iii. Patient characteristics within each histology do not systematically differ between included trials
  iv. There is overlap in the types of histologies included in each trial
- We assess the performance of the method on 500 simulated datasets
- On each dataset we estimate the model using 10,000 MCMC iterations and 4 chains with implementation via Stan[4]. We assess convergence via the $\hat{R}$ statistic[5] ($\hat{R} < 1.1$).
- Our model specification assumes that response y_i for patients $i = 1, \ldots, n_C + n_T$ with individual patient histologies $k(i) \in \{1, \ldots, K\}$ follows:

$$y_i \sim \text{Bernoulli}(p_i)$$
$$\text{logit}(p_i) = \mu + \delta z_i + \beta_{k(i)}$$
$$\beta_k \sim N(0, \sigma^2)$$

- where μ is an intercept term, δ is the relative treatment effect, $z_i \in \{0,1\}$ is a treatment indicator, β_k is the random effect for the tumour site k, and n_T and n_C are the number of patients in the basket trials for the treatment of interest and comparator treatment, respectively.
- We use the following diffuse priors as a default:

$$\mu \sim N(0, 100^2)$$
$$\delta \sim N(0, 100^2)$$
$$\sigma \sim \text{Unif}(0, 100)$$

- We demonstrate the method using simulated response data with 100 patients in the basket trials for the treatment of interest ($n_T = 100$) and comparator ($n_C = 100$) and differing distributions across $K = 12$ prognostically important histologies in each trial.

$$y_i \sim \text{Bernoulli}\left(\text{logit}^{-1}(\mu + \delta z_i + X\beta)\right)$$
$$\beta \sim N(\mathbf{0}, \sigma^2 I_K)$$

- Where $X_{(n_C+n_T)\times K}$ is a dummy/one-hot encoded matrix indicating each patient i's histology assignment. Probability of assignment to histology $k \in \{1, \ldots, K\}$ is decreasing in k for the treatment of interest's basket trial and increasing in k for the comparator treatment's basket trial. The components of $\beta_{K\times 1}$ are sorted so that prognostic importance is increasing in k.
- And the following simulation parameters were used:

$$n_C = n_T = 100, K = 12$$
$$\mu = -0.4, \delta = 1, \sigma = 0.7$$

Results

- Among the 500 simulated datasets, the 95% credible interval (CrI) captured the true treatment effect 91.6% of the time versus 59.4% for the simple pooled estimate. However, MCMC convergence was not achieved for 1.2% of cases.
- Figure 1 illustrates the performance of the BHM compared to simple pooled estimates for 20 simulated datasets.
  - The BHM point estimates (posterior means) are generally closer to the true treatment effect (dotted line) and the BHM 95% CrIs more often capture the true effect
- Figure 2 shows the distribution of the treatment effect posterior mean estimates for the 500 simulated datasets.
  - Use of the BHM was able to reduce bias compared to the simple pooled estimates of the treatment effect
  - Although the BHM still tended to underestimate the true treatment effect.

Figure 1. Comparison of BHM vs. Simple Pooled Treatment Effect Estimates and 95% Credible Intervals (CrI) for a Subset of 20 Simulated Datasets

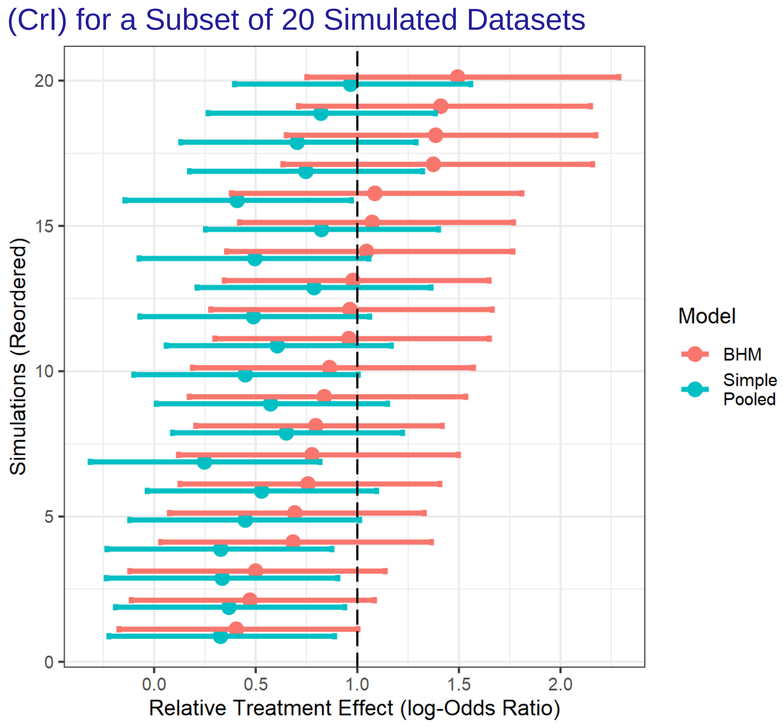
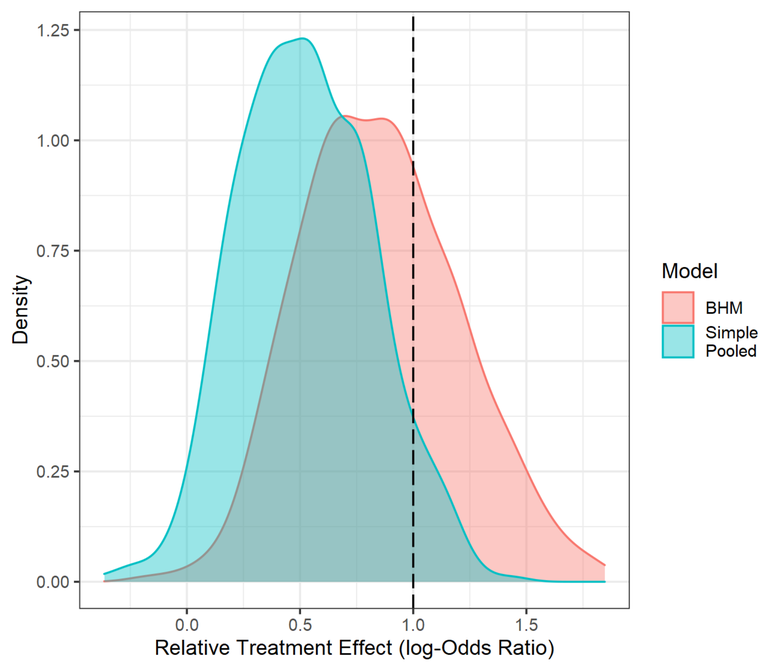


Figure 2. Distribution of Posterior Mean Treatment Effect Estimates for the BHM vs. Simple Pooled Approach



Conclusions

- In the presence of response heterogeneity across histologies, the proposed BHM model was able to reduce bias in indirect comparisons for HITs relative to simple pooled comparisons.
- When paired with careful selection of priors and sensitivity analysis, the method may facilitate more balanced comparisons of HITs between basket trials.
- The proposed method could open the door to more reliable indirect treatment comparisons for treatments targeted at rare mutations, particularly where external control arm or naïve indirect treatment comparison approaches may be infeasible or tenuous.

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BHM: Bayesian hierarchical model; HIT: histology-independent therapy; MCMC: Markov chain Monte Carlo; FDA: U.S. Food and Drug Administration; NICE: U.K. National Institute for Health and Care Excellence; NTRK: neurotrophic tyrosine receptor kinase; CrI: credible interval

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