

TITLE: Bayesian Hierarchical Modelling Approaches to Indirect Treatment Comparisons between Single-arm Basket Trials: An Application to NTRK-fusion Solid Tumours

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ABSTRACT:

Background:

As new cancer drugs are developed targeting rarer mutations, single-arm basket trials which enrol mutation-positive patients with multiple tumour histologies are seeing increased use to address challenges of patient recruitment. Partial pooling via Bayesian hierarchical models (BHM) has been proposed as a middle-ground between two extremes of analyzing each histology separately and pooling them all together (ignoring potential heterogeneity in response across histologies). However, there remains a need for indirect treatment comparison methods (ITC) to compare treatments trialled in separate basket trials for the purpose of health technology assessment.

Methods:

We outline two BHM approaches to performing ITCs between treatments trialled in single-arm basket trials and apply them to a comparison of two drugs targeting NTRK-fusion solid tumours: larotrectinib and entrectinib. These methods allow for estimation of the odds ratio (OR) of response for larotrectinib vs. entrectinib while accounting for differences in the composition of tumour histologies in both basket trials. Both models assume histologies are exchangeable, with one model assuming a constant relative treatment effect and the other allowing for heterogeneity in relative treatment effects across histologies.

Results:

Under both models we find some evidence of superior response for larotrectinib: the posterior probability that the OR for response exceeds 1 is greater than 80% for all included tumour types, however, evidence falls short of conventional thresholds (97.5% for a two-sided test). We focus our discussion on the assumptions underlying each model, comparison of prior and posterior distributions for key parameters, and quantifying cross-histology heterogeneity under the models.

Conclusion:

BHM-based ITC approaches present a potential way forward to assess the relative benefits of therapies trialled in basket trial settings for health technology assessment.