Challenges of Evaluating the Efficacy of Tumour Agnostic Drugs: Bayesian Hierarchical Modelling as a Potential Way Forward?

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Disclosure

- Advisor at Inka Health, an HEOR analytics consulting company
- No conflicts of interest related to this presentation
- Opinions expressed are my own

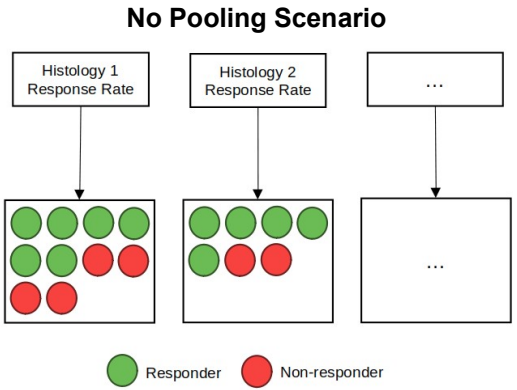
Background

- For drugs targeting rare mutations/biomarkers can be very **difficult to recruit enough patients** for a well-powered randomized controlled trial (RCT)
  - Potential solution: **increase enrolment by including multiple tumour histologies** with a common targetable mutation/biomarker (“basket trial” approach)

- But response or survival outcomes may vary across tumour histologies
  - Can we pool together different histologies in our analysis or are we back to the problem of small sample sizes?

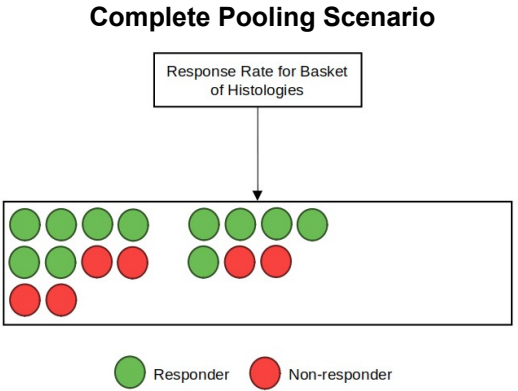
Should We Avoid Pooling?

- Could estimate response rate separately for each histology
- Pros:
  - Does not assume response is the same across histologies
  - Yields unbiased estimates of histology-specific response rates
- Con: back to square one with small histology-specific sample sizes limiting precision/power



Or Should We Pool?

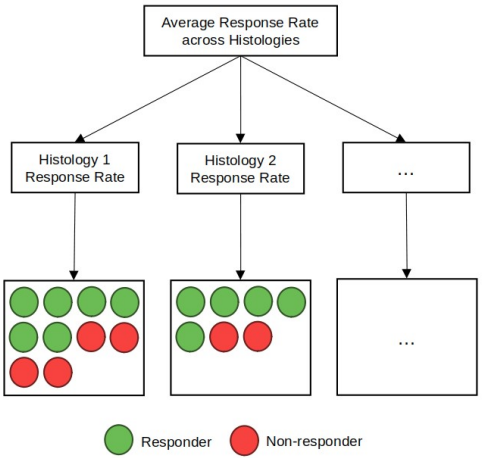
- Could estimate response rate for the overall basket trial
- Improves power/precision of estimates due to larger sample size from enrolling multiple tumour types
- But what if treatment outcomes differ by tumour histology?
  - Estimated response rate won't be informative for response prospects in specific histologies of interest
  - Argument for analyzing histologies separately



Can We Find a Middle-ground?

- **Bayesian hierarchical models (BHM)** allow for **partial pooling**--a middle-ground between the extremes of complete pooling and no pooling
- Allows response rates to differ across histologies but assumes they are related (“exchangeability assumption”)
- Amount of partial pooling (or “borrowing”) across histologies depends on degree of heterogeneity in responses across histologies
- See Murphy et al. (2020) for a more detailed overview[1]

Bayesian Hierarchical Model

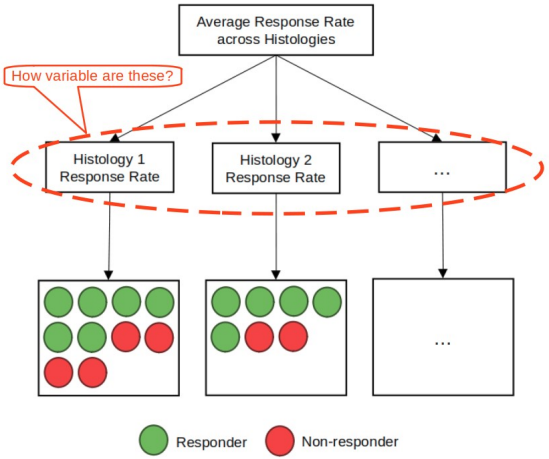


[1] Murphy P, Glynn D, Dias S, Hodgson R, Claxton L, Beresford L, Cooper K, Tappenden P, Ennis K, Grosso A, Wright K. Modelling approaches for histology-independent cancer drugs to inform NICE appraisals: a systematic review and decision-framework. Health technology assessment. 2022.

Determining the Amount of Partial Pooling

- Heterogeneity parameter is estimated based on the trial data
- High heterogeneity → little borrowing
- Low heterogeneity → more borrowing

Bayesian Hierarchical Model



Choosing Priors

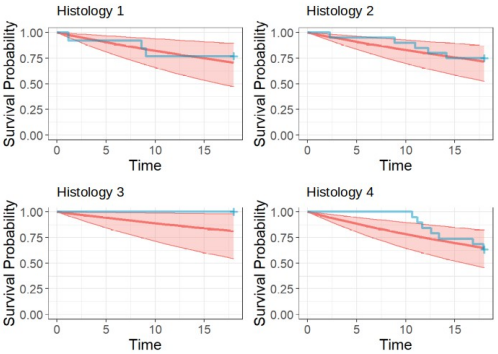
- A major advantage of Bayesian methods is the ability to incorporate external information by means of priors
- Take care in choosing priors for data-scarce settings like basket trials
  - Clinically plausible weak priors preferable to implausibly-vague priors
- Results can be particularly sensitive to choice of prior for heterogeneity parameter
  - Consider priors that are not overly informative and allow for both high-and-low heterogeneity scenarios (e.g. see Gelman[2])
  - Potential to use external data sources to inform priors--e.g. real-world data (RWD) on outcomes by histology for an appropriate standard of care?
  - Limited precedents for basket trials--active area for research

[2] Gelman A. Prior distributions for variance parameters in hierarchical models. Bayesian analysis. 2006.

What About Survival Endpoints?

- BHM approach can be extended to survival endpoints
- However, assumption of exchangeability may be more tenuous
- Survival data immaturity also a challenge (limited follow-up and few events)
- NICE indicated receptiveness to use of BHMs for survival endpoints (in addition to binary response endpoints) in their technology appraisal of larotrectinib for NTRK-fusion-positve solid tumours[3]

Survival BHM Demonstration for Simulated Data for 4 (out of 12) Tumour Histologies



[3] NICE. Larotrectinib for treating NTRK fusion positive solid tumours: technology appraisal guidance. 2020.

Indirect Treatment Comparisons

- Particularly challenging for basket trials
  - Generally only single-arm trial available
  - Potentially very heterogeneous populations across trials/real-world data sources necessitates care in performing comparisons
  - Limited sample sizes create further challenge for adjusting for potential confounders when performing comparisons
- Conventional population-adjusted indirect comparisons (PAIC) or synthetic control arm (SCA) methods may be challenging to successfully implement in basket trial settings
  - Although PAIC methods have been used to compare two basket trials[4]
  - Comparisons against standard of care (SoC) have been performed using RWD[5]
  - BHM models have also been extended to ITC applications[6,7]

[4] Garcia-Foncillas et al. Indirect treatment comparison of larotrectinib versus entrectinib in treating patients with TRK gene fusion cancers. Cancers. 2022.
[5] Chen et al. Tackling Challenges in Assessing the Economic Value of Tumor-Agnostic Therapies: A Cost-Effectiveness Analysis of Pembrolizumab as a Case Study. Value in Health. 2024.
[6] Mackay et al. MSR46 A Bayesian Hierarchical Modelling Approach for Indirect Comparison of Response Outcomes in Histology-Independent Therapies [Abstract]. Value in Health. 2022.
[7] Mackay et al. MSR73 Bayesian hierarchical models for indirect treatment comparisons of histology-independent therapies for survival outcomes [Abstract]. Value in Health. 2023.

Challenges with Application of BHMs

- Care is needed in choosing priors--particularly for the heterogeneity parameter
- Plausibility of exchangeability assumption still needs careful consideration
  - Parametric assumption may be a useful approximation but clinical input needed
  - Model variants such as EXNEX can partially relax this assumption[8]
- Limited data still a challenge
  - Few histologies
  - Few patients per histology
  - Immature survival data
- Unique challenges for indirect treatment comparisons and estimation of long-term patient outcomes for economic analyses

[8] Neuenschwander B, Wandel S, Roychoudhury S, Bailey S. Robust exchangeability designs for early phase clinical trials with multiple strata. Pharmaceutical statistics. 2016.

Concluding Remarks

- Basket trials present a way forward in addressing challenge of recruiting enough patients to assess efficacy of new tumour-agnostic drugs
- Bayesian hierarchical models provide a middle-ground between no-pooling and complete pooling extremes to better manage trade-offs between precision and bias
- Indirect treatment comparisons and survival extrapolation are particularly challenging in basket trial settings but methodological approaches exist and continue to be developed to address these difficulties

Thank You!

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