

A comparison of different borrowing approaches in a trial evaluating therapy in HIV-infected children

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Outline

- Background of the trial
 - ODYSSEY trial of first-line/second-line antiretroviral therapy for HIV-infected children
 - Analysis: ‘borrowing of information’
- Re-analysis methods
- Re-analysis results
- Discussion

Background - ODYSSEY

- Randomised trial of dolutegravir (DTG)-based antiretroviral therapy (ART) vs. standard of care (SoC) in children with HIV infection
- Children recruited were starting first-line ART or switching to second-line ART
- Trial includes 707 children aged (4 weeks-18 years], weighing $\geq 14\text{kg}$, and 85 children weighing $\geq 3\text{kg}$ and $< 14\text{kg}$
- Non-inferiority trial
- Primary outcome: treatment failure by 96 weeks

Problem: Children weighing $< 14\text{kg}$ were recruited 12 months later and needed to be analysed separately¹.

Borrowing of information between subgroups

Aim:

To estimate the treatment effect comparing DTG-based ART to SoC in children weighing $<14\text{kg}$ (the target subgroup)

- A standalone analysis would be underpowered
- The treatment effects in both subgroups were likely to be similar
- Investigators decided to borrow information from the children weighing $\geq 14\text{kg}$ using Bayesian analysis, with the aim of increasing power and precision.

Question: How much information did we need to borrow from the $\geq 14\text{kg}$ subgroup?

The Bayesian model

θ_1 and θ_0 are the difference in clinical/virological failure rates in the target subgroup and borrowed subgroup.

Data from the target subgroup provided an estimate of θ_1 :

$$y_1 \sim N(\theta_1, \sigma_1^2)$$

Data from the borrowed subgroup provided an estimate of θ_0 :

$$y_0 \sim N(\theta_0, \sigma_0^2)$$

We used a vague normal prior for θ_0 and a bias parameter $\delta \sim N(0, \sigma_\delta^2)$ to describe the difference between treatment differences

The commensurability parameter σ_δ determined the degree of borrowing between the subgroups – could be informed by elicitation or estimated

→ Different approaches for the analysis

Publications on ODYSSEY trial^{1,2}



Once-daily dolutegravir-based antiretroviral therapy in infants and children living with HIV from age 4 weeks: results from the below 14 kg cohort in the randomised ODYSSEY trial



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Turner et al.
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RESEARCH ARTICLE

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Borrowing information across patient subgroups in clinical trials, with application to a paediatric trial



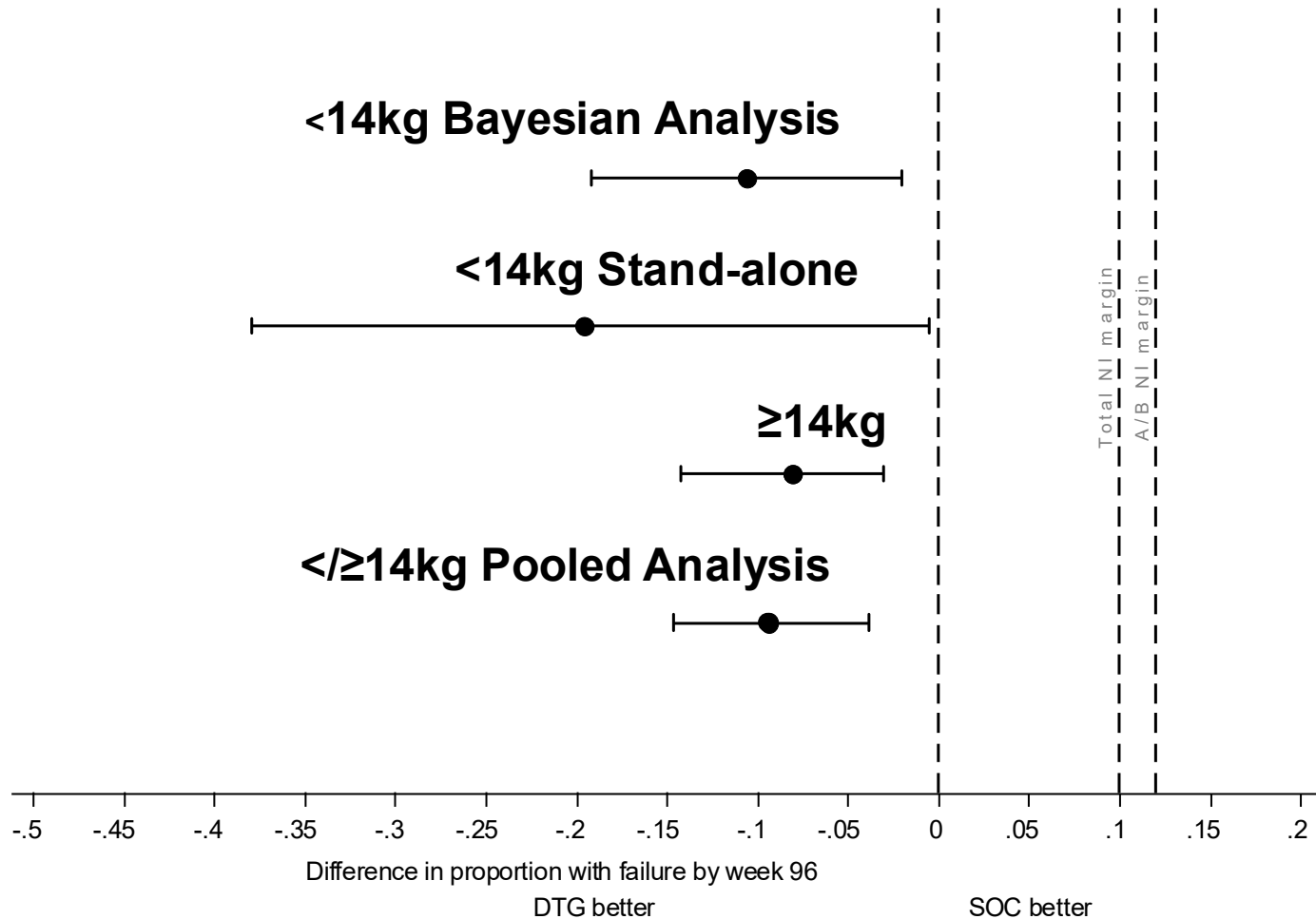
Rebecca M. Turner^{1*}, Anna Turkova¹, Cecilia L. Moore¹, Alasdair Bamford^{1,2,3}, Moherndran Archary^{4,5}, Linda N. Barlow-Mosha⁶, Mark F. Cotton⁷, Tim R. Cressey^{8,9}, Elizabeth Kaudha¹⁰, Abbas Lugemwa¹¹, Hermione Lyall¹², Hilda A. Mujuru¹³, Veronica Mulenga¹⁴, Victor Musiime^{10,15}, Pablo Rojo¹⁶, Gareth Tudor-Williams¹⁷, Steven B. Welch¹⁸, Diana M. Gibb¹, Deborah Ford^{1†}, Ian R. White^{1†} and the ODYSSEY Trial Team

Elicitation-based commensurate predictive prior approach

To estimate θ_1 , we followed a two-stage analysis:

- 1) Analyse the borrowed subgroup
- 2) Derive the marginal prior for θ_1 , i.e. a commensurate predictive prior for θ_1
- 3) Use the prior to analyse the target subgroup
 - Relative weight given to the data from the borrowed subgroup was a function of σ_δ
 - Individually elicited opinion from 13 paediatrics HIV clinicians on the weighting
 - Elicitations were done before trial results were known
 - σ_δ was fixed (based on the elicitations)

Original results from a Bayesian analysis



- A Bayesian analysis was the primary analysis of the <14kg subgroup, in which data from the ≥14kg subgroup contributed 78% of the weight
- The Bayesian approach allowed us to estimate the treatment effect with increased precision and confirmed the superior efficacy of DTG-based ART vs. SoC

Amuge et al., 2022

Re-analysis of the ODYSSEY trial

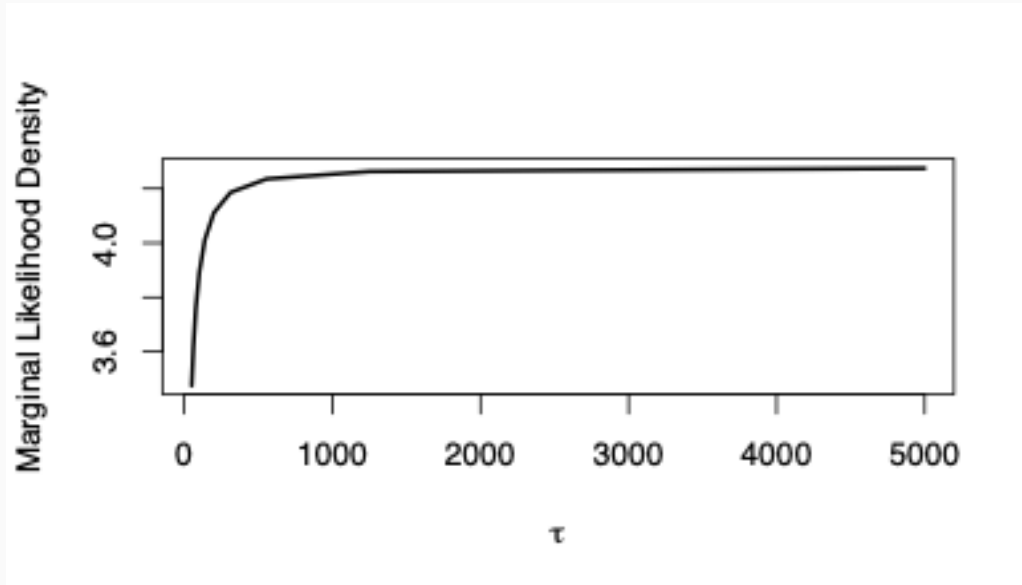
We propose several alternative methods for implementing Bayesian borrowing across subgroups and classify them into:

- Commensurate predictive prior (CPP) approaches
- Meta-analytic (MA) approaches
- Power prior (PP) approaches

Aim:

To explore how these proposed approaches could differ in estimation results and potentially in conclusions, and to further explore any practical implications

Empirical Bayes-Commensurate Predictive Prior



Unrestricted maximisation

- EB estimation of σ_δ :
 - 1) Compute the marginal likelihood of the data conditional on the precision parameter $\tau = \sigma_\delta^{-2}$.
 - 2) Determine the marginal maximum likelihood estimate (MMLE) for τ .

$$\hat{\tau} = \arg \max_{\tau > 0} [m(y_0, \sigma_0^2, y_1, \sigma_1^2 | \tau)]$$

- EB-CPP assumes no uncertainty for σ_δ
- Appropriate prior specifications are required

Relaxing σ_δ - Bayesian dynamic borrowing

Elicitation-based SAS-CPP

- A spike-and-slab prior is used for the precision parameter τ
- A local uniform distribution for the slab component $\rightarrow w$ (0.5 or based on the pairwise Hellinger distance⁴)
 - Point mass concentrated at the spike (based on elicitation)

Elicitation-based robust CPP (rCPP)

- A normal mixture prior is used for θ_1
- Informative component (based on elicitation) assumes similar treatment effects $\rightarrow w$ (0.5, empirical Bayes³, tipping point⁴)
 - Robust component assumes independence of the target treatment effect
 - Location at the null; dispersion scaled for a unit-information prior

More/less borrowing when the target subgroup data are **consistent/inconsistent** with the borrowed subgroup data

Meta-analytic approaches

Elicitation-based MA

$$\theta_1, \theta_0 \sim N(\mu, \eta^2)$$

- The between-subgroup heterogeneity parameter η^2 controls the degree of borrowing
- An informative prior for η would be required, e.g. based on elicitation

$$2\eta^2 = \sigma_\delta^2$$

→ **Some equivalence** between methods: elicitation-based MA and CPP; empirical Bayes MA (EB-MA) and EB-CPP

Elicitation-based robust MA (rMA)

$$\theta_1, \theta_0 \sim w_k N(\mu, \eta^2) + (1 - w_k) N(m_k, \sigma_k^2)$$

- An informative prior for η would be required, e.g. based on elicitation
- BDB: a robust extension to the elicitation-based MA

Power prior approaches

Elicitation-based PP

- The power parameter α controls the degree of borrowing
- Power prior for θ_1 is equivalent to inflating the marginal prior variance, $N\left(y_0, \frac{\sigma_0^2}{\alpha}\right)$
- No need to estimate the between-subgroup heterogeneity

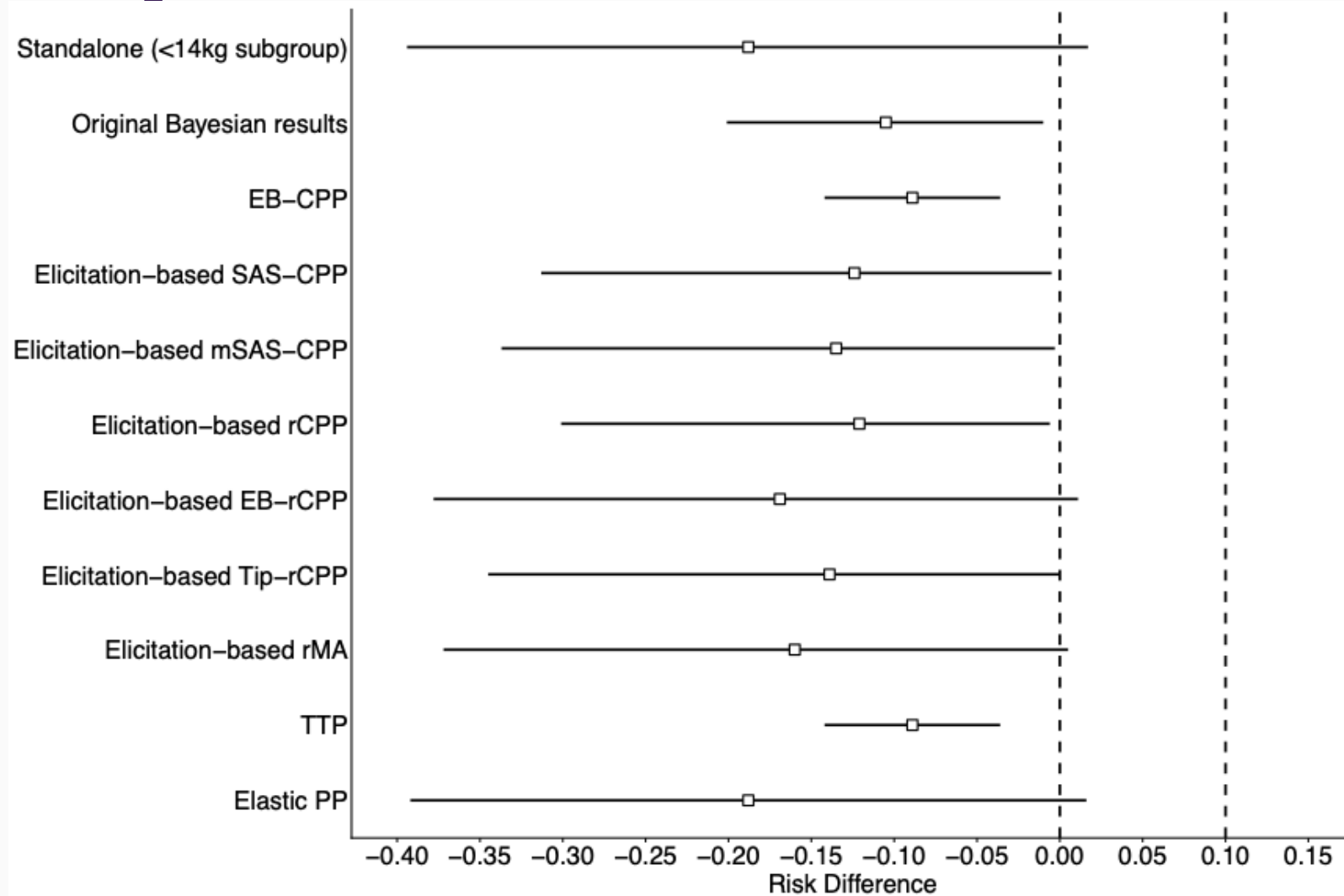
$$\alpha = \frac{\sigma_0^2}{\sigma_0^2 + \sigma_\delta^2}$$

→ **Some equivalence** between methods: elicitation-based PP and CPP; Empirical Bayes-PP (EB-PP) and EB-CPP

Elastic PP

- BDB: α determined via simulation-based calibration considering frequentist operating characteristics⁵

Re-analysis results



Forest plot including mean estimates with 95% intervals; TTP is test-then-pool⁶, which is the most basic dynamic borrowing approach; EB-MA, EB-PP, elicitation-based MA and PP approaches are not shown due to the equivalence.

Discussion

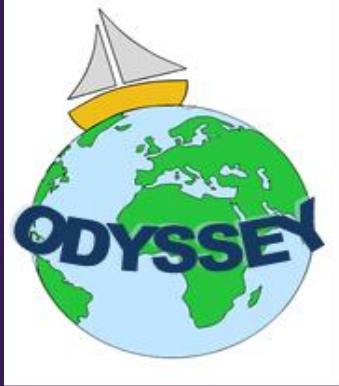
- Compared several methods for informing the degree of borrowing, with parameters determined using elicitation, empirical Bayes estimation, or considering the operating characteristics of a planned Bayesian analysis
- Borrowing of information facilitated treatment effect estimation in a small subgroup of patients, i.e. precision and power gains compared to a standalone analysis → beneficial for basket trials, e.g. paediatrics, oncology
- Filled the knowledge gap in dynamic borrowing of information within the same trial rather than just external historical control data
- Demonstrated an equivalence across various elicitation-based/EB-based approaches → use readily available R package for meta-analyses
- Instead of purely relying on elicitations, we recommend exploring EB approaches for easy implementation, and BDB approaches for robustness against a prior-data conflict

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