Robust Bayesian Sequential Borrowing:

Adaptive borrowing for multi trial programs

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Small downstream populations need a safer way to use earlier evidence

- **Clinical constraint:** Later studies can be small because recruitment is difficult and practical or ethical limits may apply.
- **Potential efficiency:** Earlier populations can inform later studies when treatment effects and populations are sufficiently comparable.
- **Partial exchangeability:** Populations are not always equally comparable; relevance may weaken with biological and clinical distance.
- **Regulatory:** Preference for methods that reflects potential heterogeneous exchangeability in FDAs draft guidance [3]
- **Statistical risk:** Ignoring earlier evidence loses precision, while unrestricted pooling can inflate false-positive risk under heterogeneity.
- **Research need:** A borrowing strategy that reflects population order and remains robust when effects differ.

Proximity create a natural evidence order



- **Ordered setting:** Multi-population programmes may follow a natural sequence, for example, adults → adolescents → children.
- **Adjacent relevance:** Neighbouring populations are more plausibly exchangeable than populations separated by several steps.
- **Direction matters:** Evidence order should constrain which earlier studies can inform each later study.

Evidence should move through supported adjacent links and not bypass an intermediate population.

Sequential, adjacent-only borrowing

- **No borrowing:** Protects against cross-population bias, but can be inefficient when later studies are small.
- **Full pooling:** Can be precise under homogeneity, but may inflate false positives when treatment effects differ.
- **Robust multi-source models:** MAP and EXNEX approaches can discount conflict, but generally treat historical sources symmetrically[1,2].
- **Solution:** A unified framework should encode sequence and adjacency, adapt borrowing to compatibility, and support prospective calibration.

RBSB identifies explicit sequential, adjacent-only borrowing as a largely unexplored design problem.



Objective: combine ordered borrowing with protection against conflict

- **Prespecify the programme:** Define the population order, admissible adjacent links, and initial borrowing weights.
- **Adapt borrowing to compatibility:** Combine eligible earlier evidence with a unit-information component and update each adjacent link from predictive evidence.
- **Evaluate prospectively:** Assess Type I error, power, assurance, and sensitivity to the calibration choices at study and programme levels.

RBSB aims to improve efficiency under agreement while attenuating borrowing when adjacent data conflict.

RBSB combines a robust mixture prior with path-dependent weights

ROBUST PRIOR FOR STUDY J + 1

$$\pi(\mu_{j+1} \mid \theta_{1:j}) = w_{j+1} \sum_{S \in P1:j} W_S \, N(\mu_S, s_S) + (1 - w_{j+1}) \, N(\mu_0, s_0)$$

$P_1{:}_j$ contains contiguous paths only; evidence cannot skip an intermediate population.

Definitions: s_i is the standard error of $\hat{\mu}_i$. m_{inf} and m_{vag} are marginal predictive densities under the informative and vague components. w_j^* is posterior support for borrowing across link j.

POSTERIOR BORROWING WEIGHT

$$w_j^* = w_j \, m_{inf}(\theta_j) \, / \, m_{mix}(\theta_j)$$

$$m_{mix}(\theta_j) = w_j \, m_{inf}(\theta_j) + (1 - w_j) \, m_{vag}(\theta_j)$$

$\mathbf{m_{mix}(\theta_j)}$ is the marginal predictive density of θ_j under the robust mixture prior. Thus w_j^* is the posterior mixture weight on the informative component.

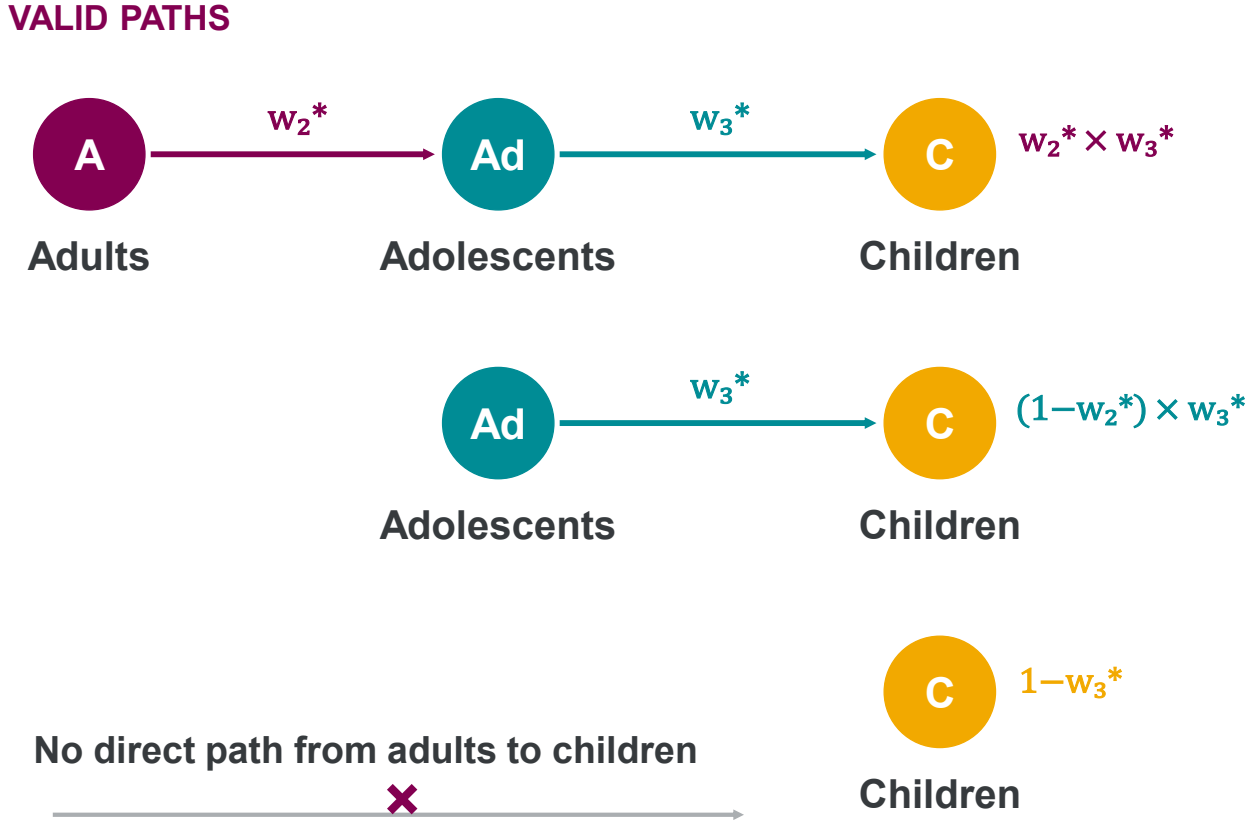
RECURSIVE PATH WEIGHT

$$W_{s,\,i:j} = (1 - w_i^*) \prod w_\ell^*$$

Product index: $\ell = i + 1, \ldots, j$ Boundary: $w_1^* := 0$

The path segment runs from population i through j. Each supported link contributes one factor to the product, so longer paths receive less weight.

Path weights make distant borrowing conditional on every link



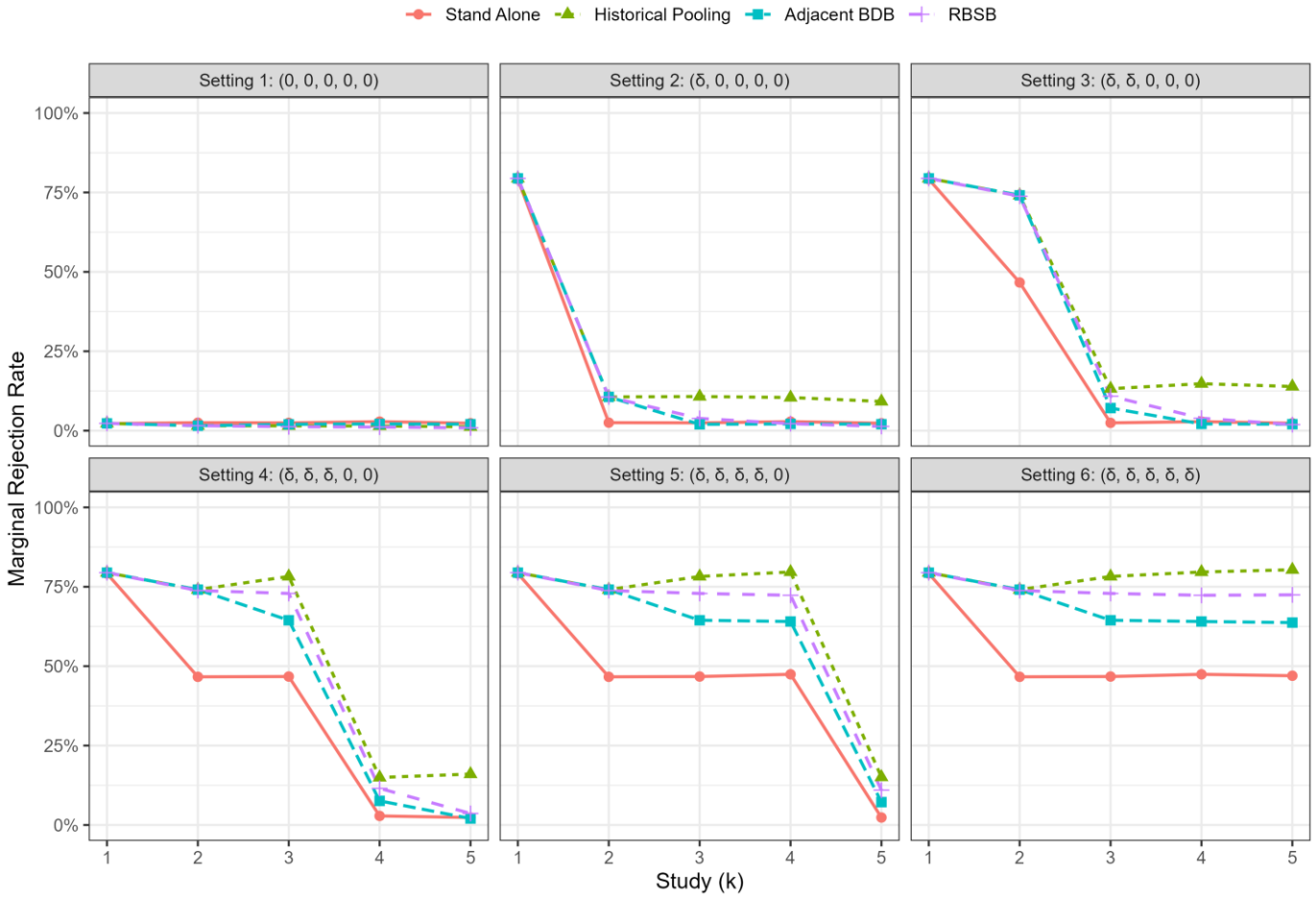
- **Link weight:** w_j^* is posterior support for borrowing across adjacent link j.
- **Full path:** Adults → adolescents → children; weight $w_2^* \times w_3^*$.
- **Adjacent path:** Adolescents → children; weight $(1-w_2^*) \times w_3^*$.
- **Local path:** Children only; weight $1-w_3^*$.

Adult evidence cannot bypass adolescents; each additional link can only reduce its contribution.

Simulation design evaluates efficiency and robustness across nine trajectories

Design element	Specification
Models compared	Standalone · full pooling · adjacent-only borrowing · RBSB
Effect trajectories	Nine settings: global null, aligned effects, abrupt conflict, and attenuation.
Study sequence	Five ordered studies: $n_1 = 160$; n_2–$n_5 = 60$.
Simulation volume	10,000 simulation replicates per setting.
Calibration	Non-null treatment effect $\delta = 0.5$; initial link weight $w = 0.5$.
Decision rule	Success if $Pr(\mu_j > 0 \mid data) > 0.975$.
Reported metrics	Marginal, conditional, and joint rejection rates · bias · effective sample size percentage (ESS%).

Selected scenarios illustrate the efficiency–robustness trade-off



ALIGNED EFFECTS, SETTING 6

Study 5 power: RBSB 73.0%; adjacent-only borrowing 64.5%; full pooling 80.8%.

EARLY EFFECT FOLLOWED BY NULL, SETTING 2

Study 5 Type I error: RBSB 1.6%; full pooling 11.3%.

INTERPRETATION

In these selected settings, RBSB retains part of the power gain under alignment and limits late-stage false positives under conflict.

SCOPE

Two representative settings are highlighted; all nine trajectories used 10,000 replicates.

In the illustrative START analysis, 75% of posterior weight follows the full path

Observed and posterior hazard ratios by age group

Population	N	Observed HR (95% CI)	Posterior HR (95% CrI)	ESS%
Adults (18–66)	3,970	0.54 (0.40, 0.74)	0.54 (0.40, 0.74)	0.6%
Adolescents (11–17)	1,221	0.56 (0.30, 1.04)	0.55 (0.39, 0.79)	74.3%
Children (5–10)	1,974	0.60 (0.40, 0.90)	0.57 (0.44, 0.77)	57.3%

HR = hazard ratio; CI = confidence interval; CrI = credible interval; ESS% = effective sample size percentage.
Illustrative sequential reordering of concurrently studied strata; w = 0.5 was not prospectively elicited. Source: [1] §5.

Posterior path weights

75% All age groups

13% Adolescents and children

12% **Children only**

Compatible subgroup estimates place most posterior weight on the full adjacent path.

Conclusions depend on the ordering and calibration assumptions

- **Methodological contribution:** RBSB restricts borrowing to contiguous paths and attenuates each path using adjacent predictive evidence.
- **Evaluated simulation evidence:** RBSB retained efficiency under aligned effects and reduced false-positive inflation relative to full pooling under conflict.
- **Scope of interpretation:** Results apply to the evaluated simulation settings; the START analysis is an illustrative reordering of concurrent strata.
- **Required specification:** The programme order, prior weights, unit-information scale, and decision thresholds must be set and calibrated prospectively.
- **Limitations:** The Normal approximation and selection effects in conditional programme metrics require assessment.

Link to preprint

References

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- [3] U.S. Food and Drug Administration. Use of Bayesian Methodology in Clinical Trials for Drug and Biological Products. FDA guidance.