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Using Bayesian Evidence Synthesis Methods to Incorporate Real-World Evidence in Surrogate Endpoint Evaluation

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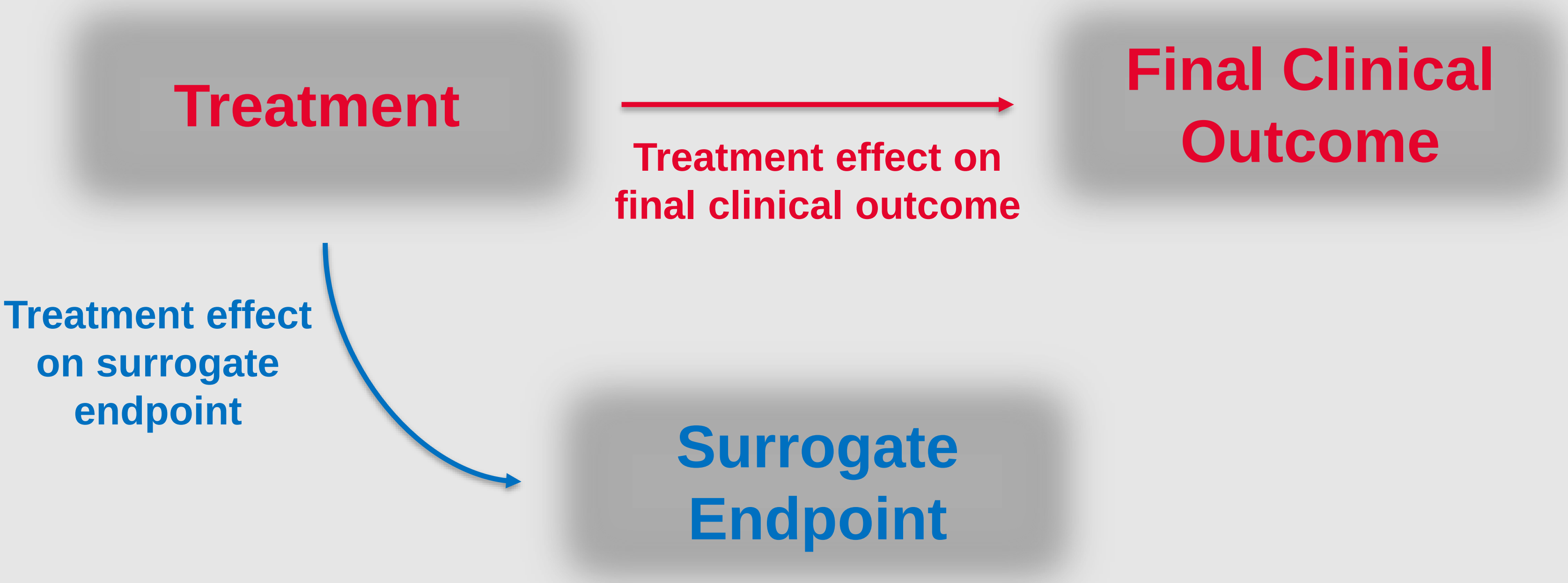
What are surrogate endpoints?

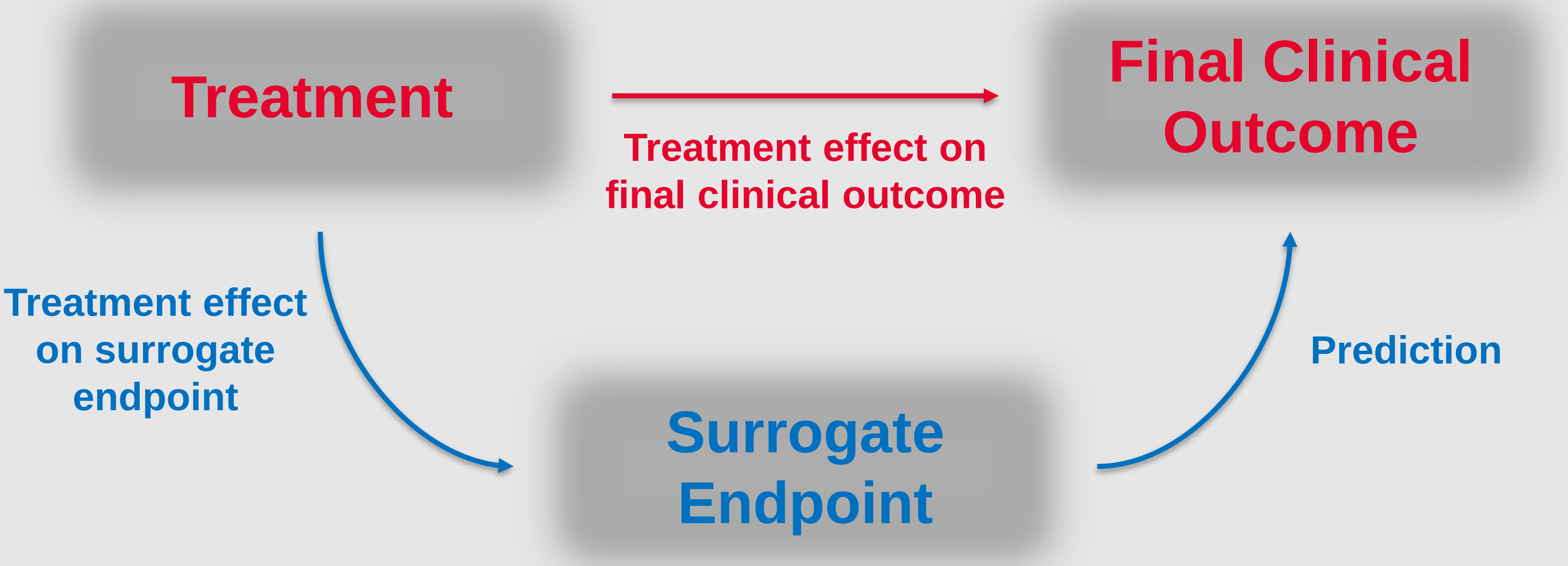
Treatment → **Final Clinical Outcome**

Treatment effect on final clinical outcome

What are surrogate endpoints?



What are surrogate endpoints?



Surrogate Endpoint Validation

Validation

- Trial-level
- Individual-level
- Biological Plausibility

Surrogate endpoints should be **validated**.

Trial-level **validation traditionally uses RCT data** making it hard to obtain sufficient numbers of trials for validation.

Alan et al, *Statistics in Medicine*, 2003

Real-World Evidence

There has been **increased use of real-world evidence (RWE)** at all stages of drug development.

- Increase evidence base
- Increase follow-up
- More generalisable

Objective

To investigate approaches for including **comparative RWE** and **single-arm RWE** alongside RCT data in surrogate endpoint evaluation, **accounting for potential differences** in treatment effects between sources of data, to **improve surrogate endpoint validation and prediction** of treatment effects on final outcomes.

Case Study: Metastatic Colorectal Cancer

Data

- 7 RCTs
- 4 comparative RWE studies
  - Comparative RWE studies only included if analysis **adjusted** for covariates
- 16 single-arm RWE studies on control arm
- 8 single-arm RWE studies on treatment arm

Matching single-arm RWE

Single-arm RWE studies were **matched using aggregate covariate data** according to the method proposed by Schmitz et al:

$$\Delta_{total}[j,k] = \frac{\sum_{i=1}^{n} w_i \cdot \Delta_i[j,k]}{\sum_{i=1}^{n} w_i}$$

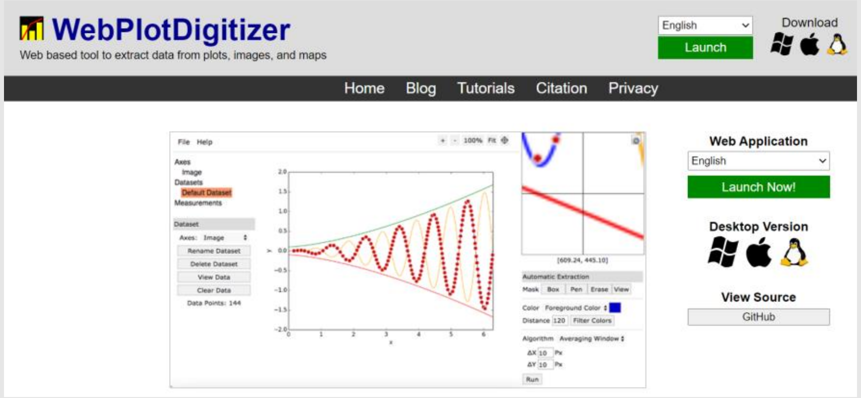
- $\Delta_{tot}[j,k]$ - distance measure
- w_i - weight assigned to covariate (from Goey et al consensus statement)
- $\Delta_i[j,k]$ – normalised difference between studies j and k in covariate i

Schmitz et al, *BMC Medical Research Methodology*, 2018.

Goey et al, *European Journal of Cancer*, 2018.

Obtaining Treatment Effects for Single-Arm RWE

- Kaplan-Meier curves **digitized to obtain reconstructed IPD**.
- **Reconstructed IPD** analysed using the **Cox model** to obtain logHRs for progression free survival and overall survival and corresponding standard errors.



Wei et al, *The Stata Journal*, 2017.

Methods: Bivariate Random-Effects Meta-Analysis

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} \\ \delta_{2i} \end{pmatrix}, \Sigma_i = \begin{pmatrix} \sigma_{1i}^2 & \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} \\ \sigma_{1i}\sigma_{2i}\rho_{wi}^{12} & \sigma_{2i}^2 \end{pmatrix} \right)$$

$$\begin{cases} \delta_{1i} \sim N(\eta_1, \psi_1^2) \\ \delta_{2i} | \delta_{1i} \sim N(\eta_{2i}, \psi_2^2) \\ \eta_{2i} = \lambda_0 + \lambda_1 \delta_{1i} \end{cases}$$

Bujkiewicz et al, *Statistics in Medicine*, 2013.

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Bujkiewicz et al, *Statistics in Medicine*, 2013.

Methods: Bivariate Random-Effects Meta-Analysis

A **perfect surrogate relationship** occurs when

$\lambda_0 = 0$

$\lambda_1 \neq 0$

$\psi_2^2 = 0$

Between-study correlation (ρ) and R^2 can also be derived.

Daniels & Hughes, *Statistics in Medicine*, 1997.

Methods: Bias Adjustment

Within-study model for comparative RWE:

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} + \alpha_{1i} \\ \delta_{2i} + \alpha_{2i} \end{pmatrix}, \Sigma_i\right)$$

$$\alpha_{1i} \sim N(\alpha_1, \sigma^2_{\alpha_1})$$

$$\alpha_{2i} \sim N(\alpha_2, \sigma^2_{\alpha_2})$$

Within-study model for matched single arm RWE:

$$\begin{pmatrix} Y_{1i} \\ Y_{2i} \end{pmatrix} \sim N\left(\begin{pmatrix} \delta_{1i} + \beta_{1i} \\ \delta_{2i} + \beta_{2i} \end{pmatrix}, \Sigma_i\right)$$

$$\beta_{1i} \sim N(\beta_1, \sigma^2_{\beta_1})$$

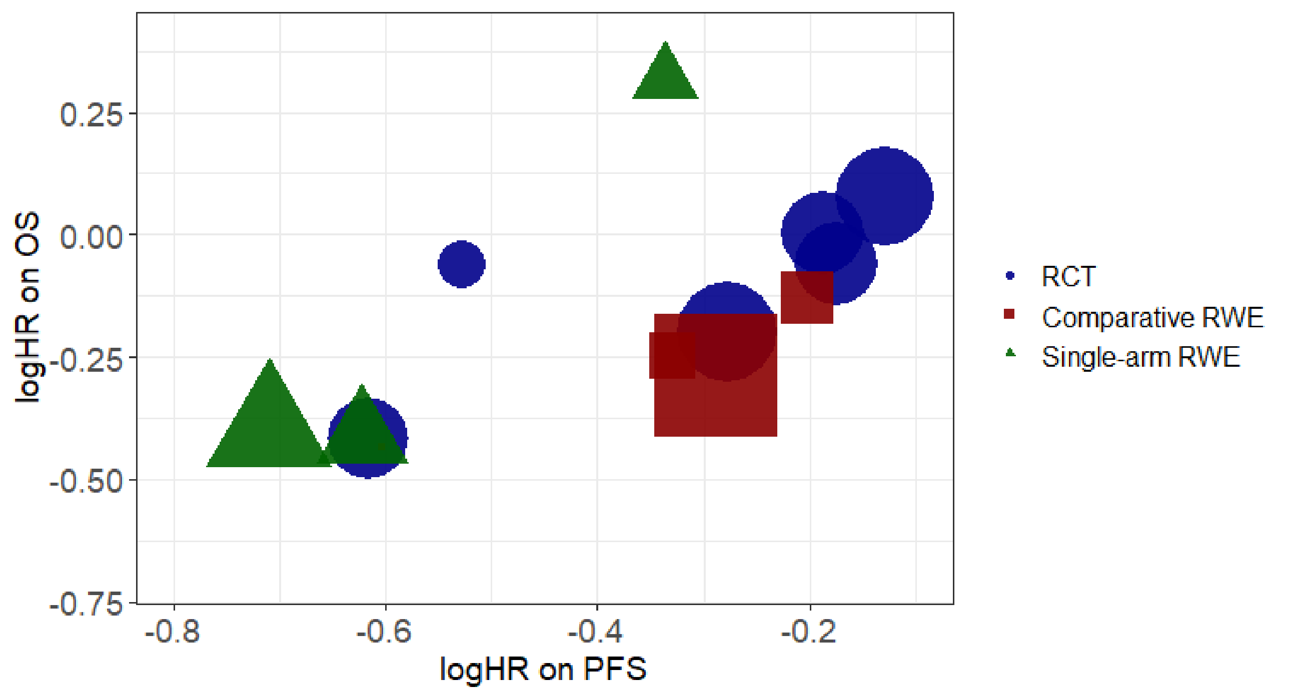
$$\beta_{2i} \sim N(\beta_2, \sigma^2_{\beta_2})$$

Methods: Cross Validation

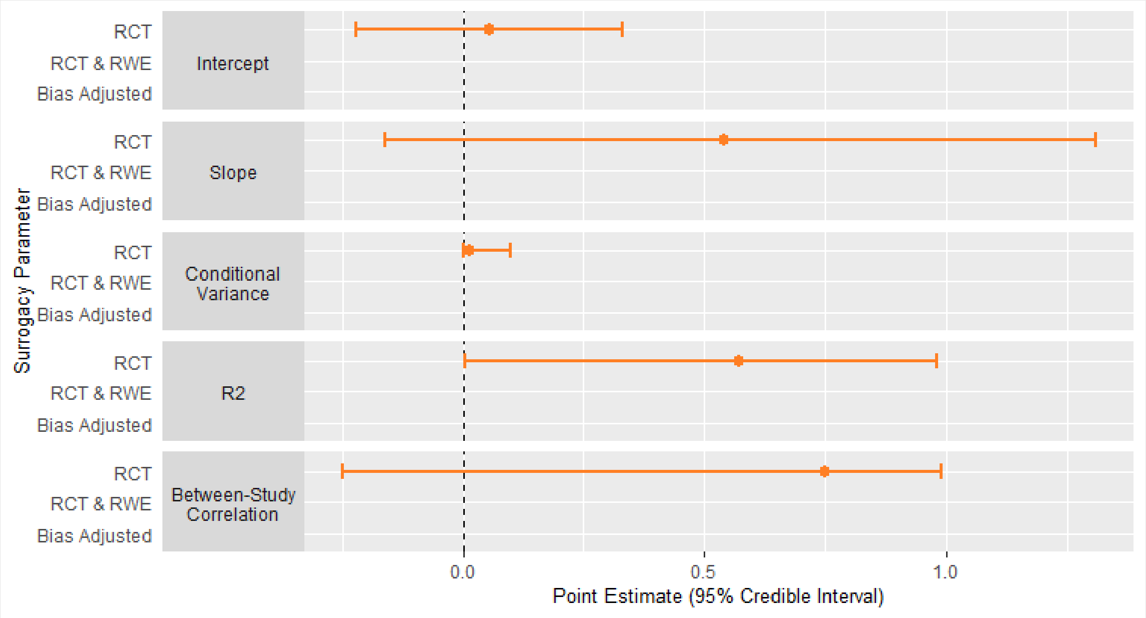
- Cross validation was conducted on the bivariate random-effects meta-analysis with and without bias adjustment.
- "**take-one-out" cross-validation** was conducted.
- Treatment effect on the final outcome was predicted from the treatment effect on the surrogate endpoint.

Bujkiewicz et al, NICE DSU TSD20, 2019.

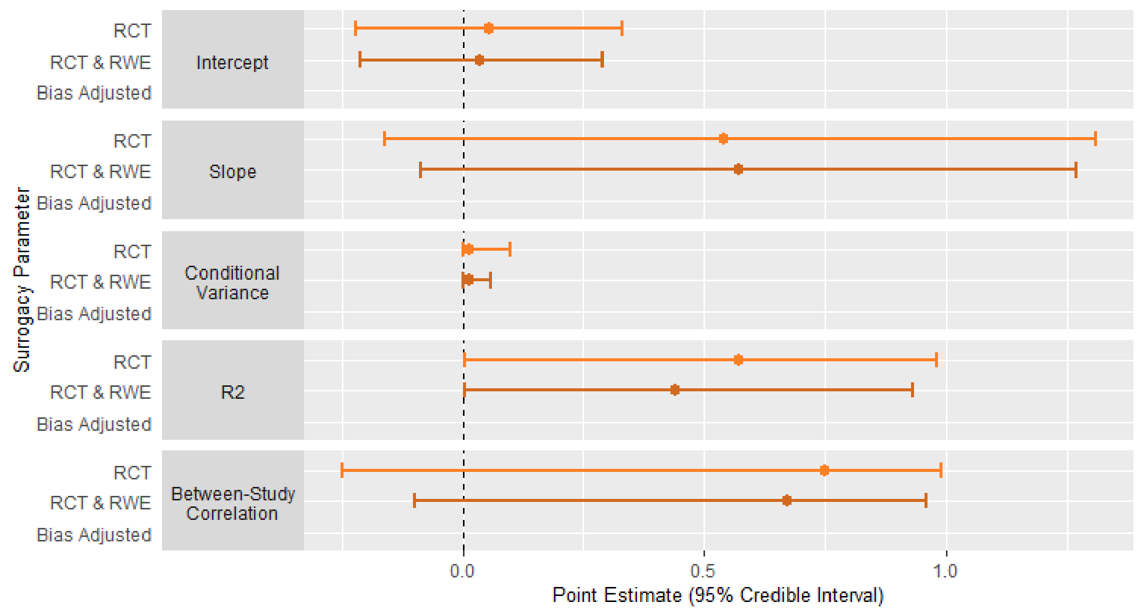
Results: Summary of Data



Results: Bivariate Random-Effects Meta-Analysis



Results: Bivariate Random-Effects Meta-Analysis



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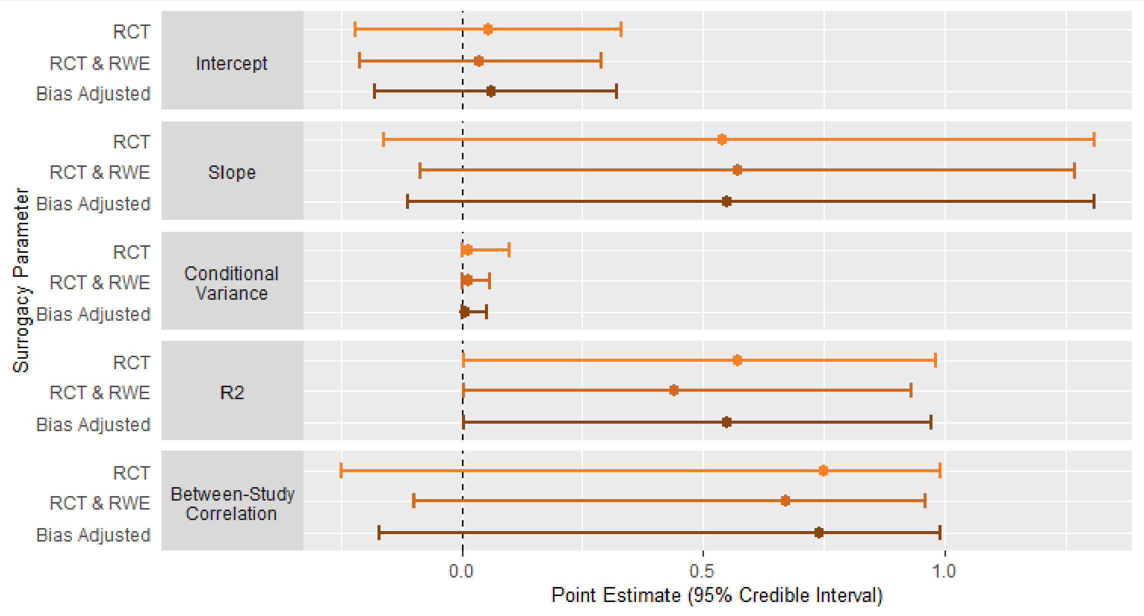
Results: Bivariate Random-Effects Meta-Analysis



Results: Cross Validation

	RCTs	RCTs & RWE	Bias Adjusted
Absolute discrepancy, median (range)	0.16 (0.017, 0.26)	0.16 (0.017, 0.51)	0.17 (0.020, 0.43)
Ratio of width of 95% predicted interval to width of observed 95% confidence interval, median (range)	2.74 (1.61, 3.30)	1.90 (1.18, 2.78)	1.79 (1.19, 3.67)

Discussion

- When **trial data are limited validation of surrogate endpoints may fail.**
- Treatments **might not receive conditional marketing authorization**.
- May still **fail at the HTA stage.**
- Provided an approach for using **RWE to strengthen the evidence base for surrogate endpoint evaluation**.

Limitations

- Inclusion of matched single arm RWE studies **relied on extracting and digitizing Kaplan-Meier curves** from published articles.
- Matching of single arm trials was based on **study level covariates.**
- All **sources of evidence contributed the same weight** to the model.

Conclusions

- Addition of **RWE can improve precision of estimation of surrogacy parameters.**
- Addition of **RWE can improve precision of prediction of final outcomes** from outcomes observed on surrogate endpoints.
- To fully investigate, **a simulation study should be conducted.**

Acknowledgements

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