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Estimating Interactions and Subgroup-Specific Treatment Effects in Meta-Analysis Without Aggregation Bias: A Within-Trial Framework

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Disclosures

- Peter Godolphin: No disclosures

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Treatment-covariate interactions

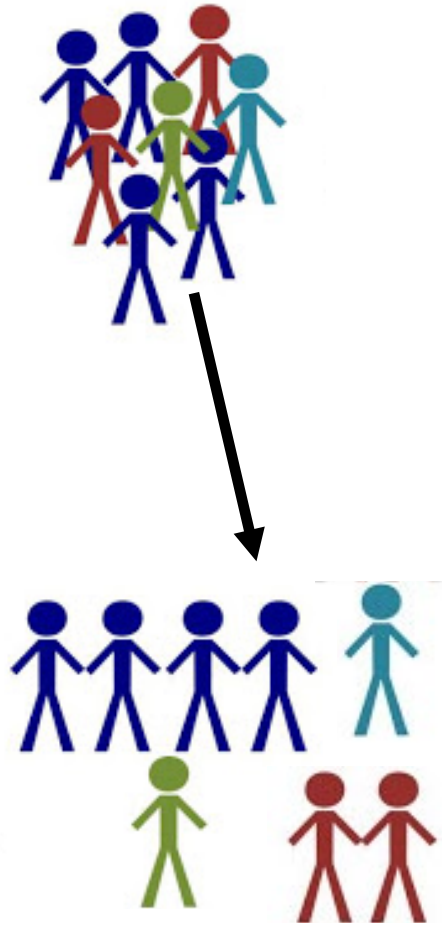
Primary aim of RCTs is to estimate *overall* effect of treatment vs control

But may also be interest in whether treatment effect *varies* based on patient characteristics ("interaction")

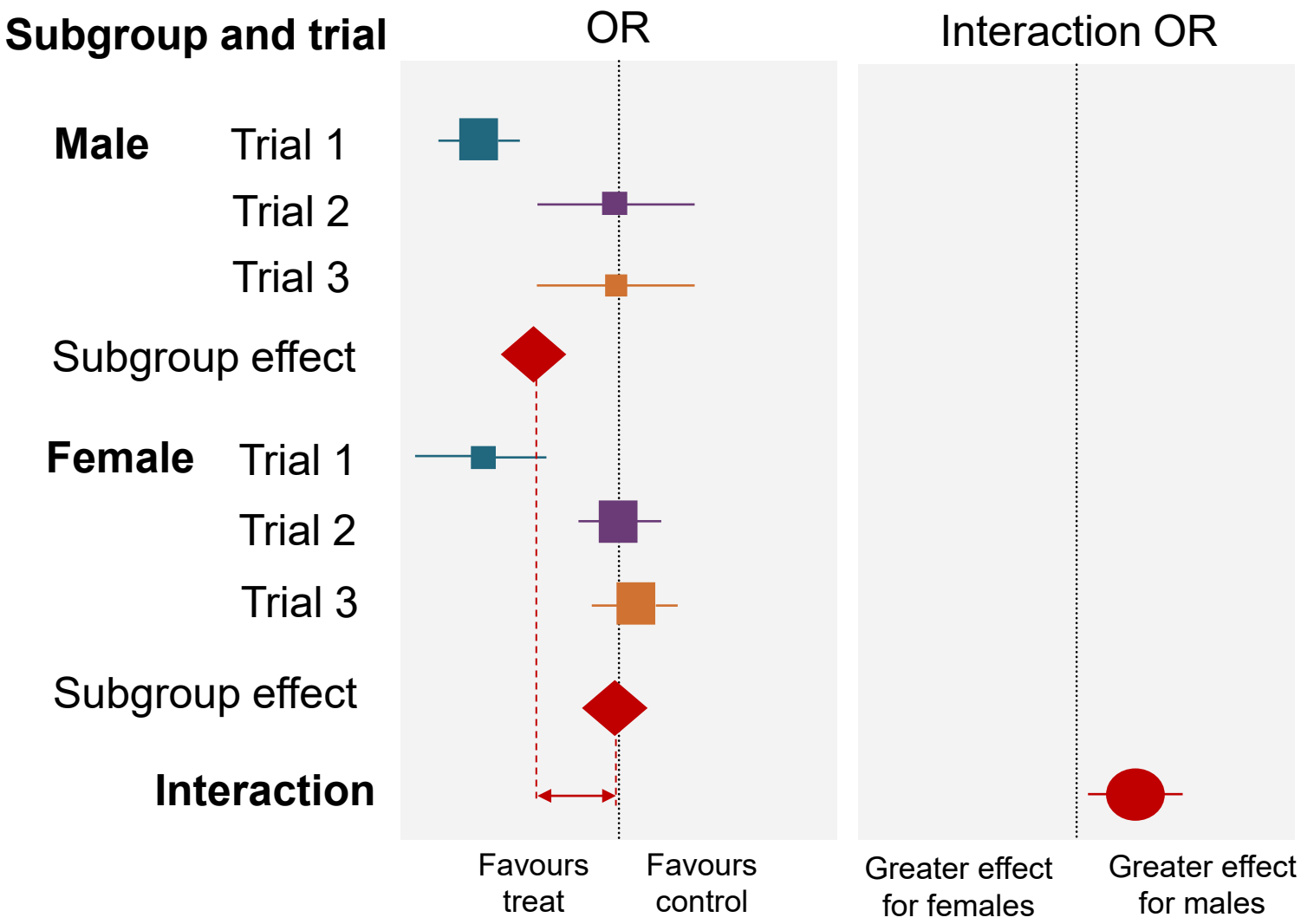
Estimating interactions

Single RCT will usually *lack power* to detect a true interaction effect

Hence, may wish to use *meta-analysis* to help identify interactions



“Traditional” approach to treatment covariate-interactions (across- and within-trial)



ELSEVIER

Journal of Clinical Epidemiology 64 (2011) 949–967

Journal of Clinical Epidemiology

A critical review of methods for the assessment of patient-level interactions in individual participant data meta-analysis of randomized trials, and guidance for practitioners

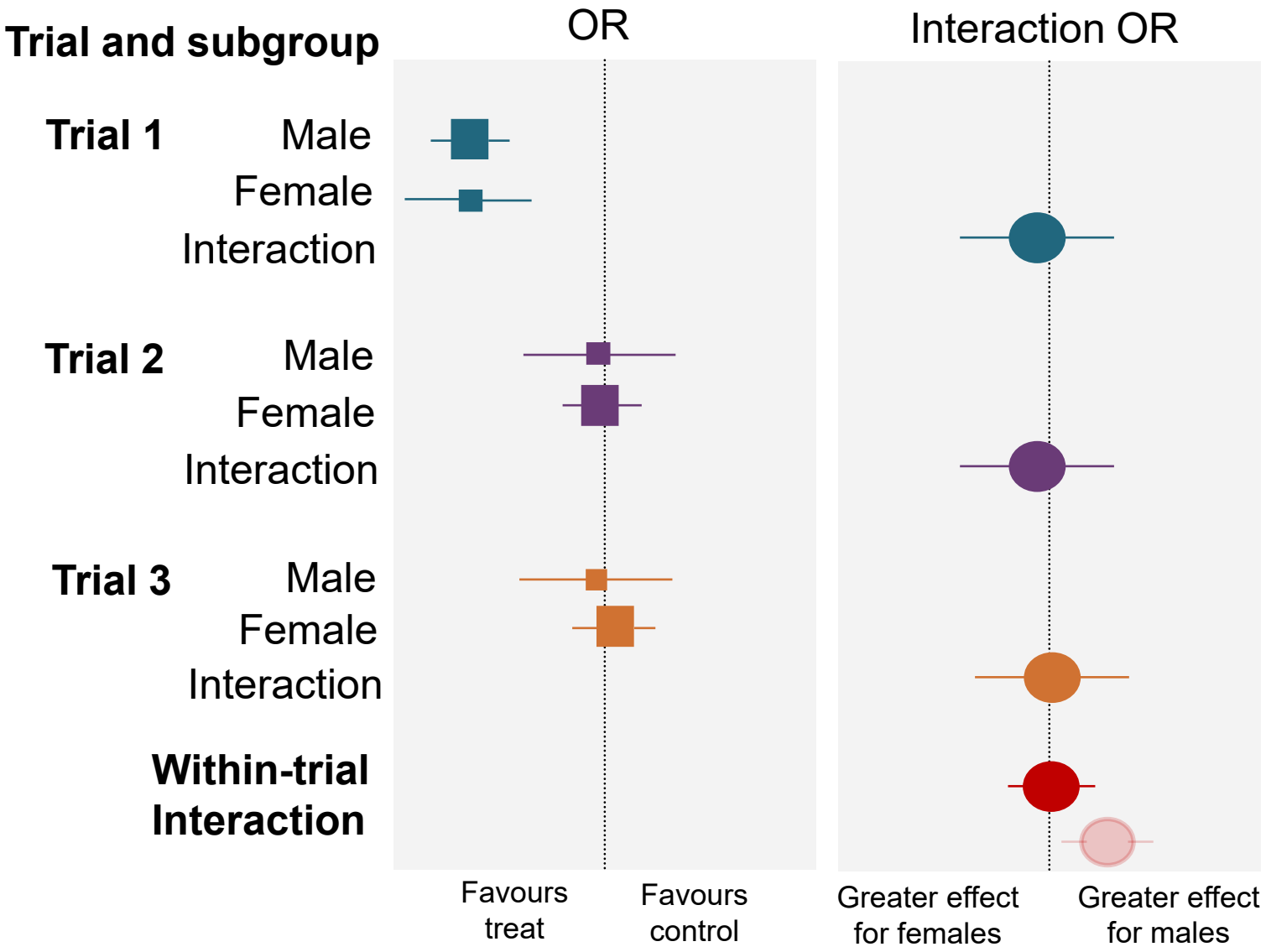
D.J. Fisher*, A.J. Copas, J.F. Tierney, M.K.B. Parmar

Medical Research Council Clinical Trials Unit, London NW1 2DA, UK

Accepted 24 November 2010

BUT… this approach is at risk of aggregation bias

Within-trial approach to treatment-covariate interactions



RESEARCH METHODS AND REPORTING

Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach?

David J Fisher,[1] James R Carpenter,[1,2] Tim P Morris,[1] Suzanne C Freeman,[1] Jayne F Tierney[1]

BUT… this approach does not give a subgroup effect. And current methods limited to binary subgroups

Within-trial framework: Aims

Reliably test for interactions between treatment and any categorical covariate

Estimate subgroup effects that are compatible with within-trial interactions

Ensure methodology is easy to use

Within-trial framework: Subgroup effects

- Meta-analysis with n trials $(i = 1, \ldots, n)$
- Covariate with k subgroups $(j = 1, \ldots, k)$ Sex, $k=2$
- $\hat{\beta}_{ji}$ = observed trt. effect in subgroup j of trial i $\hat{\beta}_{11}$ is effect for males in trial 1; $\hat{\beta}_{21}$ is effect for females in trial 1
- $\widehat{\boldsymbol{\beta}}_i$ = *vector* of effects $\hat{\beta}_{ji}$ for trial i
- Standard MV-MA model:

$$\widehat{\boldsymbol{\beta}}_1 = \begin{bmatrix} \hat{\beta}_{11} \\ \hat{\beta}_{21} \end{bmatrix} \quad \widehat{\boldsymbol{\beta}}_2 = \begin{bmatrix} \hat{\beta}_{12} \\ \hat{\beta}_{22} \end{bmatrix} \quad \widehat{\boldsymbol{\beta}}_n = \begin{bmatrix} \hat{\beta}_{1n} \\ \hat{\beta}_{2n} \end{bmatrix}$$

$$\widehat{\boldsymbol{\beta}}_i \sim MVN\left(\boldsymbol{\beta}, \boldsymbol{S}_i + \boldsymbol{\Sigma}_\beta\right)$$

Subgroup effects in each trial

Pooled subgroup effects

Covariance matrix

Between-trial heterogeneity matrix

Within-trial framework: Interactions

- $\hat{\boldsymbol{\gamma}}_i = \begin{bmatrix} \hat{\gamma}_{2i} \\ \vdots \\ \hat{\gamma}_{ki} \end{bmatrix} = \begin{bmatrix} \hat{\beta}_{2i} - \hat{\beta}_{1i} \\ \vdots \\ \hat{\beta}_{ki} - \hat{\beta}_{1i} \end{bmatrix}$

k=2, so: $\hat{\boldsymbol{\gamma}}_i = \hat{\gamma}_{2i} = \hat{\beta}_{2i} - \hat{\beta}_{1i}$

In each trial i, the within-trial interaction is:

[effect for females] – [effect for males]

- Standard MV-MA model:

$$\hat{\boldsymbol{\gamma}}_i \sim MVN\left(\boldsymbol{\gamma}, \boldsymbol{V}_i + \boldsymbol{\Sigma}_\gamma\right)$$

Interactions within each trial

Pooled interaction effect(s)

Covariance matrix

Between-trial heterogeneity matrix

Within-trial framework: Compatibility

- We wish to link the model for the subgroup effects ($\boldsymbol{\beta}$) with the model for the interactions ($\boldsymbol{\gamma}$)
- Define a **compatibility** relationship:

$$\boldsymbol{\beta} = \begin{bmatrix} \beta_1 \\ \beta_2 \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_1 + \gamma_2 \end{bmatrix}$$

Subgroup effect for females is effect for males + interaction

"Floating" subgroup effects

$$\boldsymbol{\beta} = \beta_1 \mathbf{1} + \begin{bmatrix} 0 \\ \boldsymbol{\gamma} \end{bmatrix}$$

Pooled effect in reference subgroup

Pooled within-trial interaction(s)

Vector of 1's, length *k*

- Relationship ensures that:

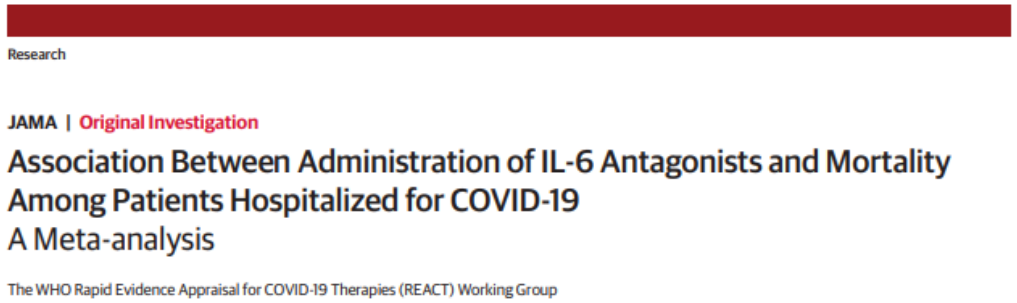
  [difference between subgroup effects] = [within-trial interaction]

Within-trials framework: Step-by-step

- **Step 1:** Estimate the within-trial interaction $\boldsymbol{\gamma}$ and variance
- **Step 2:** Estimate "floating" subgroup effects ($\boldsymbol{\beta}$) compatible with $\boldsymbol{\gamma}$
- **Step 3:** Correct the "naïve" variance of $\boldsymbol{\beta}$ to account for the error in $\boldsymbol{\gamma}$.

Example 1: Corticosteroid use in IL6 MA

- Setting: Patients hospitalised with COVID-19
- Studies: 15 RCTs
- Treatment: Tocilizumab
- Subgroup: Corticosteroid use at randomisation (Yes, No)
- Outcome: 28-day mortality (OR)

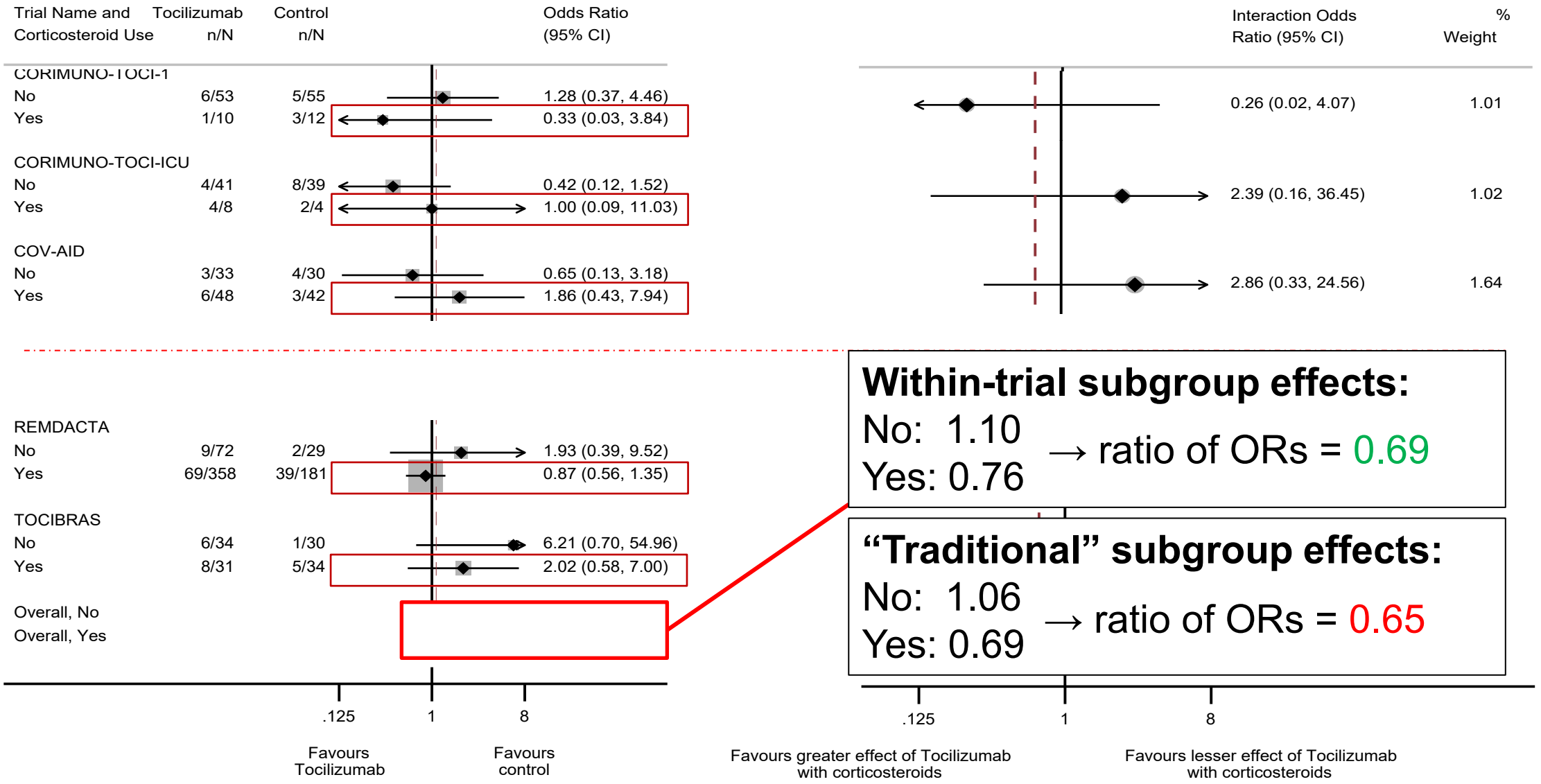

Research

JAMA | Original Investigation

Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Example 1: Corticosteroid use in IL6 MA



Within-trial subgroup effects:

No: 1.10
Yes: 0.76
→ ratio of ORs = 0.69

"Traditional" subgroup effects:

No: 1.06
Yes: 0.69
→ ratio of ORs = 0.65

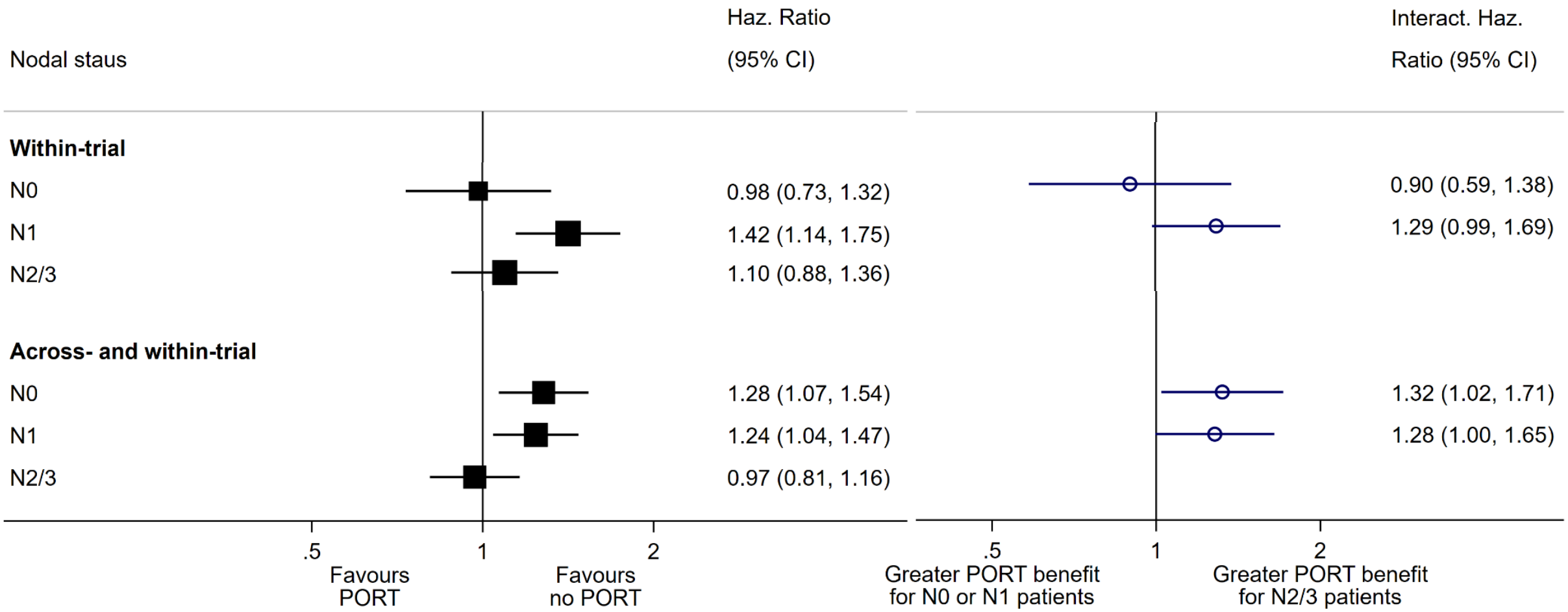
Example 2: Nodal status in PORT MA

- Setting: Patients with non-small cell lung cancer
- Studies: 11 RCTs
- Treatment: Post operative radiotherapy (PORT)
- Subgroup: Nodal status (N0, N1, N2/3)
- Outcome: Overall survival (HR)

Postoperative radiotherapy for non-small cell lung cancer (Review)

Burdett S, Rydzewska L, Tierney J, Fisher D, Parmar MKB, Arriagada R, Pignon JP, Le Pechoux C, on behalf of the PORT Meta-analysis Trialists Group

Example 2: Nodal status in PORT MA



Summary, future work, and conclusion

Properties of the method

- Designed for use with summary data or two-stage IPD
- Account for multiple sources of heterogeneity (subgroup effects and interactions) via random-effects

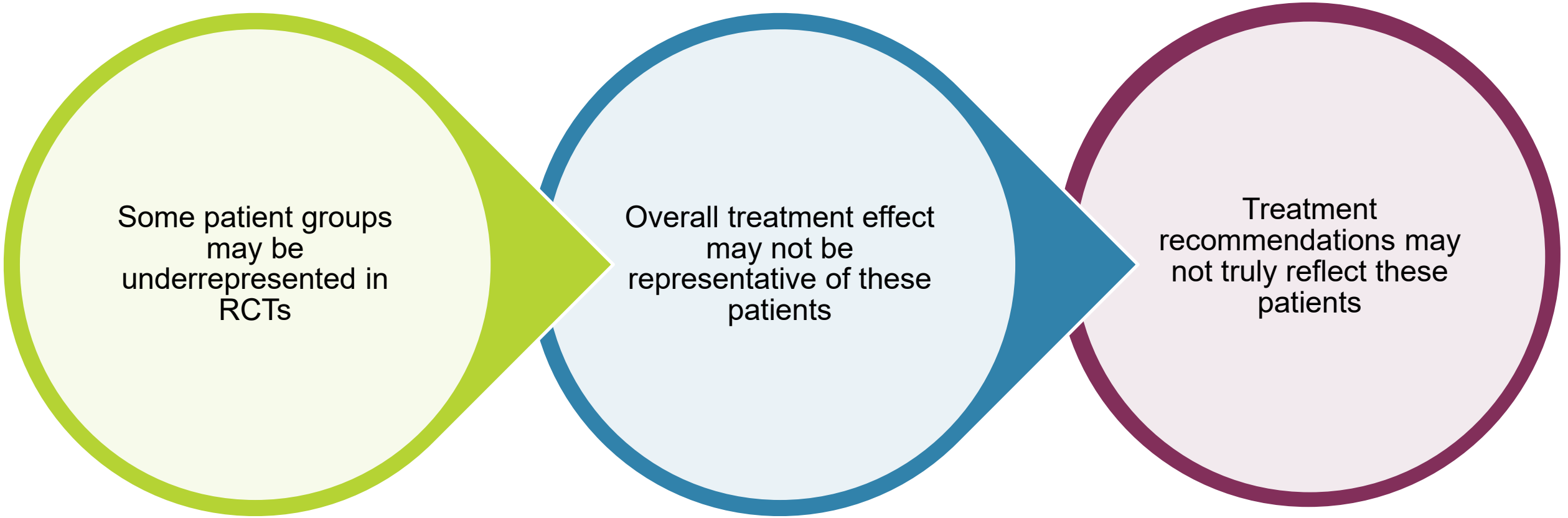
What's next?

- Paper under revision in Research Synthesis Methods
- Stata code available via GitHub (https://github.com/ucl/metafloat)
- Working on extension to IPD

Conclusion

- We present a complete meta-analytic framework for reliable estimation of how well treatments work for different groups of patients

How would you utilize equity, diversity, and inclusion in your methodology?



Meta-analysis using our within-trial framework may be the only way to get an appropriate estimate of the effect of treatment for these patient groups

Disclosures

- Peter Godolphin: No disclosures

References

@petegodolphin

Fisher D, et al. (Journal of Clinical Epidemiology, 2011), *A critical review of methods for the assessment of patient-level interactions in individual patient data (IPD) meta-analysis of randomised trials, and guidance for practitioners*

Fisher D, et al. (BMJ, 2017) *Meta-analytical methods to identify who benefits most from treatments: daft, deluded, or deft approach?*

Shankar-Hari M, et al. (JAMA, 2021) *Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis*

Burdett S, et al. (Cochrane Database of Systematic Reviews, 2016) *Postoperative radiotherapy for non-small cell lung cancer*

Incorporating heterogeneity into the framework

- Fully common effects: set $\boldsymbol{\Sigma}_{\gamma}$ and $\boldsymbol{\Sigma}_{\beta}$ to zero
- Partial random-effects model: Common-effect for the interactions ($\boldsymbol{\Sigma}_{\gamma} = 0$), random effects on the subgroup estimates
- Fully random-effects (common heterogeneity): Interactions and subgroups have (different) common heterogeneity parameters. Exchangeable structures for both $\boldsymbol{\Sigma}_{\gamma}$ and $\boldsymbol{\Sigma}_{\beta}$
- Fully random-effects (unstructured): Allow unstructured heterogeneity covariances

Within-trials framework: the idea (k-level covariate)

- **Using a k-subgroup covariate $\boldsymbol{\beta_i} = \left[\beta_{1i}, \beta_{2i}, \ldots, \beta_{ki}\right]^T$, k > 2**
- **Step 1:** Estimate the within-trial interaction ($\boldsymbol{\gamma}$)
  - Here $\boldsymbol{\gamma} = \left[\gamma_2, \gamma_3, \ldots, \gamma_k\right]^T$
  - Work out the within-trial interactions (k-1 contrasts) for each study *i:*

    $\hat{\boldsymbol{\gamma}}_i = \left[\hat{\beta}_{2i} - \hat{\beta}_{1i}, \ldots, \hat{\beta}_{ki} - \hat{\beta}_{1i}\right]^T$
  - Pool $\hat{\boldsymbol{\gamma}}_i$ to estimate $\boldsymbol{\gamma}$ in a MV-MA model

Within-trials framework: the idea (k-level covariate)

- **Step 2:** Estimate floating subgroup-specific treatment effects ($\boldsymbol{\beta}$)
  - Subtract $\boldsymbol{\gamma}$ from the non-reference subgroup values ($\hat{\beta}_{2i}$ ... $\hat{\beta}_{ki}$)
  - We then pool $\begin{bmatrix} \hat{\beta}_{1i} \\ \hat{\beta}_{2i} - \gamma_2 \\ \vdots \\ \hat{\beta}_{ki} - \gamma_k \end{bmatrix}$ in a MV-MA model to estimate θ
  - Finally, we reverse our previous operations which scaled the non-reference subgroup: $\widehat{\boldsymbol{\beta}} = \begin{bmatrix} \hat{\beta}_1 \\ \hat{\beta}_2 \\ \vdots \\ \hat{\beta}_k \end{bmatrix} = \hat{\theta}\mathbf{1} + \begin{bmatrix} 0 \\ \widehat{\boldsymbol{\gamma}} \end{bmatrix} = \begin{bmatrix} \hat{\theta} + 0 \\ \hat{\theta} + \hat{\gamma}_2 \\ \vdots \\ \hat{\theta} + \hat{\gamma}_k \end{bmatrix}$

Example 2: Nodal status in PORT MA