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Meta-analyses with subgroups of patients: From subgroup-first to trial-first and stopping in between

Frank Weber
Institute for Quality and Efficiency in Health Care, Department of Medical Biometry

Introduction

- Major methodological principles for subgroups of *patients* (not trials) [1]:
  - *Subgroup-first* (current IQWiG standard): subgroup-specific meta-analyses → contrast pooled treatment effects
  - *Trial-first* (goes back at least to [2]; recent work by [3]): within-trial contrasts (of subgroup-specific treatment effects) → meta-analysis
- Trial-first method by [3] focuses on avoiding aggregation bias (can occur especially in case of no or small subgroup differences and heterogeneous treatment effects within subgroups, paired with „unfortunate“ imbalance of subgroups across trials); might come with reduced ability to discover true subgroup differences
- Mixture of subgroup-first and trial-first approaches occurs in [3], but not further investigated there; goes back (in restricted form) at least to [4]
- Ultimate objective (later): Identify method for meta-analyses with subgroups of patients most appropriate for IQWiG; desirable properties (in particular):
  - Invariance of subgroup-specific treatment effect estimates to choice of reference subgroup
  - Suitability for both, frequentist and Bayesian framework
- Objective here: Identify relationships between (and [dis-]advantages of) candidate methods

Methods

- Following [3]: Multivariate meta-analysis (dimensions: subgroups and/or their contrasts) is natural model for patient subgroups → Write underlying models from all approaches as such
- Notation and assumptions (unlisted quantities: estimated by „∧“ variants):
  - n trials (index: i) with k subgroups *each*
  - $\widehat{\boldsymbol{\beta}}_i = \left(\hat{\beta}_{i1}, \ldots, \hat{\beta}_{ik}\right)^T \in \mathbb{R}^k$: subgroup-specific treatment effect estimates
  - $\widehat{\boldsymbol{S}}_i = \mathrm{diag}\left[\widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right), \ldots, \widehat{\mathrm{Var}}\left(\hat{\beta}_{ik}\right)\right] \in \mathbb{R}^{k \times k}$: subgroup-specific sampling variance estimates
  - $\boldsymbol{I}_{k-1}$: $(k-1) \times (k-1)$ identity matrix
  - $\boldsymbol{M} = [-\mathbf{1}_{k-1} \quad \boldsymbol{I}_{k-1}] \in \mathbb{R}^{(k-1) \times k}$: contrast matrix (reference subgroup: 1)
  - $\widehat{\boldsymbol{\gamma}}_i = \boldsymbol{M}\widehat{\boldsymbol{\beta}}_i \in \mathbb{R}^{k-1}$: within-trial contrast estimates
  - $\boldsymbol{J}_{k-1}$: $(k-1) \times (k-1)$ matrix of ones
  - $\widehat{\boldsymbol{V}}_i = \boldsymbol{M}\widehat{\boldsymbol{S}}_i\boldsymbol{M}^T = \widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right)\boldsymbol{J}_{k-1} + \mathrm{diag}\left[\widehat{\mathrm{Var}}\left(\hat{\beta}_{i2}\right), \ldots, \widehat{\mathrm{Var}}\left(\hat{\beta}_{ik}\right)\right] \in \mathbb{R}^{(k-1) \times (k-1)}$: contrast-specific sampling variance estimates

Results and discussion

- Underlying models and their relationships depicted in Figure 1
- Trial-first approach of [3] not easily (if at all) transferable to Bayesian framework
- At IQWiG: Usually (more or less) homogeneous treatment effects within subgroups → Strict avoidance of aggregation bias not necessary → Mixture of subgroup-first and trial-first approaches conceptually suitable, fulfills desirable properties from above
- Simulation study needed to compare performance of the methods (data-dependent model selection would have to be included as well)

Conclusion

- Mixture of subgroup-first and trial-first approaches: theoretically sensible compromise → candidate method for IQWiG analyses; to be investigated further

References

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Subgroup-first: single model with diagonal-structure across-trial covariance matrix

$\widehat{\boldsymbol{\beta}}_i \sim \mathrm{N}_k\left(\boldsymbol{\beta}, \widehat{\boldsymbol{S}}_i + \boldsymbol{\Sigma}_\beta\right)$ with $\boldsymbol{\Sigma}_\beta$ diagonal

→ No use of within-trial contrasts

Allow for non-zero covariance in $\boldsymbol{\Sigma}_\beta$, thereby making use of the within-trial contrasts

Mixture of *subgroup-first* and *trial-first*: single model; here: unstructured across-trial covariance matrix ★

$\widehat{\boldsymbol{\beta}}_i \sim \mathrm{N}_k\left(\boldsymbol{\beta}, \widehat{\boldsymbol{S}}_i + \boldsymbol{\Sigma}_\beta\right)$ with $\boldsymbol{\Sigma}_\beta$ unstructured

Contrast-based reparameterization:

$\left(\hat{\beta}_{i1}, \widehat{\boldsymbol{\gamma}}_i^T\right)^T \sim \mathrm{N}_k\left((\beta_1, \boldsymbol{\gamma}^T)^T, \widehat{\boldsymbol{H}}_i + \boldsymbol{\Sigma}_H\right)$ with

$\boldsymbol{\Sigma}_H$ unstructured (top-left: $[\boldsymbol{\Sigma}_\beta]_{1,1}$; bottom-right: $\boldsymbol{\Sigma}_\gamma$)

and $\widehat{\boldsymbol{H}}_i = \begin{bmatrix} \widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) & -\widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) \\ -\widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) & \widehat{\boldsymbol{V}}_i \end{bmatrix}$

→ Combines steps (1) and (2) from the trial-first approach of [3]
→ Within-trial contrasts not treated in isolation

Trial-first: stepwise procedure [3]; here: unstructured across-trial covariance matrix ★

(1) $\widehat{\boldsymbol{\gamma}}_i \sim \mathrm{N}_{k-1}\left(\boldsymbol{\gamma}, \widehat{\boldsymbol{V}}_i + \boldsymbol{\Sigma}_\gamma\right)$ with $\boldsymbol{\Sigma}_\gamma$ unstructured

(2) $\left(\hat{\beta}_{i1}, \widehat{\boldsymbol{\gamma}}_i^T\right)^T \sim \mathrm{N}_k\left((\beta_1, \widehat{\boldsymbol{\gamma}}^T)^T, \widehat{\boldsymbol{H}}_i + \widetilde{\boldsymbol{\Sigma}}_H\right)$ with $\widehat{\boldsymbol{\gamma}}$ fixed (from (1)), $\widetilde{\boldsymbol{\Sigma}}_H$ unstructured but constrained (bottom-right: $\widehat{\boldsymbol{\Sigma}}_\gamma$ fixed [from (1)]), and $\widehat{\boldsymbol{H}}_i = \begin{bmatrix} \widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) & -\widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) \\ -\widehat{\mathrm{Var}}\left(\hat{\beta}_{i1}\right) & \widehat{\boldsymbol{V}}_i \end{bmatrix}$

(3) „inflation“ of the estimated covariance matrix of the *floating estimates* $\widehat{\boldsymbol{\beta}} = \left(\hat{\beta}_1, \hat{\beta}_1 \cdot \mathbf{1}_{k-1}^T + \widehat{\boldsymbol{\gamma}}^T\right)^T$

Treat within-trial contrasts in isolation

★ Possible simplification: Adapt structure in across-trial covariance matrix (without restriction to covariance of zero) to data at hand; e.g., compound symmetry structure if favored by model comparison based on predictive performance

Figure 1: Methods for meta-analyses with subgroups of patients, extended from [3].

Contact: frank.weber@iqwig.de