A critical review of methods for the assessment of interactions in individual patient data meta-analysis

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Objectives & methods

• Individual patient data (IPD) meta-analysis (MA)
  ▪ Treatment, outcome and covariate known for each patient
    ⇒ Treatment-covariate interactions
    ⇒ Targeted treatment

• Research questions
  ▪ How should treatment-covariate effects be analysed?
  ▪ How should such analyses be presented?

• Methods & objectives
  ▪ Literature search for existing approaches
  ▪ Critical appraisal of identified approaches
  ▪ Apply these approaches to existing IPD datasets
  ▪ Develop guidance
Post-op RT vs surgery alone in non-small-cell lung cancer

Outcome is overall survival (time-to-event)

Question: does trt effect differ by disease stage group?

For simplicity, interaction measured using a linear slope fitted across subgroups
Distribution of disease stage

Trial 1

Trial 2

Trial 3

Trial 4

No. of patients

No. of patients

No. of patients

No. of patients

Stage I | Stage II | Stage III
---|---|---
71 | 13 | 14
82 | 6 | 16

Stage I | Stage II | Stage III
---|---|---
92 | 91 | 52

Stage I | Stage II | Stage III
---|---|---
107 | 54 | 113
103 | 54 | 108

Treatnent | Control
---|---

ISCB Conference 2009, Prague

David Fisher (26th August 2009)
Within-trial (WT) effect

- Measures how disease stage affects treatment outcome for individual pts within an “average” trial
- Can be visualised as “average” slope
- Patients are randomised to trt arms within disease stage subgroups, all subject to the same trial protocol
**Across-trial effect**

- **Across-trial (AT) effect**
  - Measures how the “average” disease stage in a trial affects treatment outcome
  - Not randomised, and subject to “ecological bias”
  - Difference in “average” between trials may not be representative of differences between individuals

![Graph showing distribution of patients by stage and treatment group across two trials.](image)
Why use across-trial information?

- WT info tells us how treatment effect differs between patients with different values of a covariate: – true interaction
- AT info might help when combined with WT if WT has low power and AT has greater power
  - Analogous with case for non-randomised studies (cohort/case-control) – providing extra evidence where RCT evidence is low
  - If analysis is exploratory, may wish to maximise power if risk of bias is considered acceptable
1. Pooling of **Within-Trial covariate Interactions (WTI)**

- “Two-step” pooling of within-trial covariate interactions
  - Step 1: Fit regression model with interaction term separately within each trial $i$: 
    \[
g(y_{ij}) = \alpha_i + \beta_i x_{ij} + \gamma_i z_{ij} + \delta_i x_{ij} z_{ij}
\]
  - Step 2: Combine interaction coeffs $\delta_i$ using inverse-variance MA

\[
\hat{\delta}_w = \frac{\sum_i w_i \hat{\delta}_i}{\sum_i w_i}
\]
\[
se(\hat{\delta}_w) = 1/\sqrt{\sum_i w_i}
\]

$W = \text{“within-trials”}$
Critique of WTI

- Within-trials effect only, so randomisation is retained
- Solid, simple approach for continuous and ordered categorical covariates (e.g. disease stage)

**BUT:**
- Trials with data in only one subgroup cannot be included
- Unordered covariates cannot be analysed
2. Across Covariate Subgroup effect (ACS)

Step 1: Split data into disease stage subgroups

Step 2: Carry out standard IPD MA for treatment effect $\hat{\beta}_k$ within each subgroup $k$

Step 3: Fit a trend line to the treatment estimates $\hat{\beta}_k$ to obtain estimate of interaction $\delta$:

$$\hat{\beta}_k = \beta_0 + \delta + \epsilon_k, \quad \epsilon_k \sim N(0, \sigma(\hat{\beta}_k)^y)$$
Critique of ACS

• Relatively simple
• Very commonly used (e.g. cancer)
• BUT:
  ▪ Randomisation structure is broken
  ▪ Within-trial correlations across covariate subgroups are unaccounted for
  ▪ Mixture of within- and across-trials info, which cannot be separated: “black box”
    ⇒ no way to assess ecological bias
3. Combining **Within- & Across-trials effects (CWA)**

**Pooled within-trials effect (WTI)**

Step 1: Separately estimate within-trials effect $\delta_W$ using **WTI**, and across-trials effect $\delta_A$ using meta-regression (MR) on trial-level disease stage means.

Step 2: Combine the two estimates in a further meta-analysis:

$$\hat{\delta} = \frac{w_W \hat{\delta}_W + w_A \hat{\delta}_A}{w_W + w_A}, \quad se(\hat{\delta}) = \frac{1}{\sqrt{w_W + w_A}}$$

where $w_W = 1/se(\hat{\delta}_W)^2$ and $w_A = 1/se(\hat{\delta}_A)^2$
Critique of CWA

- Relatively simple
- Can increase power over WTI in certain circumstances
- Allows WT & AT to be combined: pros & cons of this discussed later
- Transparency and user control
  - Each effect derived independently and combined manually by the analyst
- More open to bias and/or bad judgment?
  - Analyst could downweight unfavourable results
4. **Mixed-Effects Models (MEM)**

- “One-step” mixed-effects model
  - Uses all available data in a single interaction model:
    \[ g(y_{ij}) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta x_{ij} z_{ij} \]
  - Interaction term \( \delta x_{ij} z_{ij} \) can also be parameterised so as to separate within- and across-trial effects:
    \[ g(y_{ij}) = \alpha_i + \beta x_{ij} + \gamma z_{ij} + \delta_w x_{ij} (z_{ij} - \bar{z}_i) + \delta_A x_{ij} \bar{z}_i \]
    where \( \bar{z}_i \) is the covariate mean value in trial \( i \); 
    \( \delta_w = \) within-trial effect; \( \delta_A = \) across-trial effect. 
    Difference \( \delta_A - \delta_w \) is a quantification of ecological bias.

Reference: Simmonds (2005)
• Arguably ‘gold standard’ since other models are special cases
• Well-established in other study areas e.g. multi-centre trials
• Flexible & maximises power
  ▪ Allows simultaneous estimation of multiple parameters, allowing non-linear interactions etc.
  ▪ Can be parameterised to isolate WT & AT
• BUT:
  ▪ Currently issues with random-effects with time-to-event data
  ▪ Complex and computationally intensive; greater expertise & care required
• Allows WT & AT to be combined: pros & cons of this discussed later
Using across-trials information

- Use of AT is controversial
  - Many analysts will never want to use it
  - Including it in the wrong circumstances risks ecological bias
  - Might be used if analysis is hypothesis generating, & more power is desired at the risk of increased bias

- In the event that AT info is under consideration, it is important to decide a priori:
  - Whether to consider it, with reasons
  - How to include it, with specific criteria

- Examples of criteria:
  - Estimates could differ by less than a pre-specified amount
  - Variance of the across-trial estimate could be increased by a factor before combining (CWA)
Examples

**Treatment effect by covariate subgroup (1)**

<table>
<thead>
<tr>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>Subgroup 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTI (WT only)</td>
<td>MEM (WT only)</td>
<td>Meta-regression (AT only)</td>
</tr>
<tr>
<td>CWA (combined WT &amp; AT)</td>
<td>MEM (combined WT &amp; AT)</td>
<td>“Across covariate subgroup”</td>
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</tbody>
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Interaction method:

Using AT will introduce bias

**Treatment effect by covariate subgroup (2)**

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Interaction method:

AT might be included to increase power
Guidance

Proposed strategy:

1. Make an *a priori* decision whether or not to consider using across-trials info, together with criteria for inclusion
   - Most analysts will decide not to
2. **WTI** is recommended in many situations, especially if complex stats are unnecessary
3. If across-trials info is to be considered, fit a meta-regression and test results against the pre-specified criteria; if criteria are met, use **CWA**
4. For those with suitable expertise and resources, **MEM** is a powerful and versatile alternative, and can include or exclude across-trials info as desired
5. **ACS** is not recommended for patient-level covariates and should be avoided.
Děkuji!

Thankyou!