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1. Remarks on TA and NH's presentations

2. Some general remarks on statistical issues in MCMA

Bias in meta-analysis: target parameter

Target population:



- Population of treatment centers
- In each center a population of patients fulfilling in/exclusion criteria
- (True) relative treatment effect in each center, may differ across centers
- The target parameter δ of the meta-analysis is the mean of the relative treatment effects

Target population

- is seldom made-explicit
- depends on perspective: individual doctor, health policy maker, clinical researcher,...

Bias

- Single Comparison Meta-Analysis (SCMA) being unbiased depends on target population one has in mind
- In particular, in a MCMA the target population can be different than in a SCMA

SCMA can be biased if

- Individual studies are biased (not internally valid)
- The studies are selected on a hidden relative treatment effect modifier (“UREM”)

Bias in a single comparison meta-analysis (SCMA) comparing A to B

Standard SCMA model:

Relative effect $\delta_{AB} = d_{AB} + e_{AB}$ (E e_{AB} = 0)

An SCMA is biased if hidden selection on unrecognized effect modifier X (“UREM”)

$$\delta_{AB} = d_{AB} + \eta_{AB}X + e_{AB} \quad (\text{with } EX=0, \text{ var}(X) = 1)$$

$$\text{MSE} = (\eta_{AB}^2 + \text{var}(e_{AB}))/N$$

- The absolute error in a SCMA is never zero, even if the trials are infinitely large. (TA)
- What’s the value of one big trial? (TA & NH)

Consequence: Plea for doing many low-powered trials??

Bias in MCMA: Indirect versus direct evidence

The role of (unidentified) effect modifiers



TA: Making explicit models (thought experiments) may help to get insight.

Suppose X is a UREM (mean 0 and var=1)

Mean outcome per treatment

$$\begin{aligned} \mu_A + \eta_A X + e_A \\ \mu_B + \eta_B X + e_B \\ \mu_C + \eta_C X + e_C \end{aligned}$$

Relative effects

$$\begin{aligned} \bar{\delta}_{AB} &= d_{AC} - d_{BC} + (\eta_{AC} - \eta_{BC})X + e_{AB} \\ \bar{\delta}_{AC} &= d_{AC} + \eta_{AC}X + e_{AC} \\ \bar{\delta}_{BC} &= d_{BC} + \eta_{BC}X + e_{BC} \end{aligned}$$

- If average X overall zero and X not correlated with the type of comparison then no bias (direct or indirect). (treatments are Missing at Random (MAR))
- MSEs might be different

Indirect AB:	$\eta_{AC}^2 + \eta_{BC}^2 + 2\sigma^2$
Direct AB:	$\eta_{AC}^2 + \eta_{BC}^2 - 2\eta_{AC}\eta_{BC} + \sigma^2$
- Mostly in practice the direct estimate has smaller variance, more so by the within trial sampling variability.

It is possible that indirect estimate might have smaller MSE than the direct!

TA looks at a plausible particular case:

X acts equally on A and B, but not on C

$$\begin{aligned}\mu_A \\ \mu_B + \eta X \\ \mu_C + \eta X\end{aligned}$$

$$\begin{aligned}\bar{\delta}_{AB} &= d_{AC} - d_{BC} + \eta X \\ \bar{\delta}_{AC} &= d_{AC} + \eta X \\ \bar{\delta}_{BC} &= d_{BC}\end{aligned}$$



3rd comparator similar

$$\begin{aligned}\text{Direct AB:} & \quad \text{MSE} = \eta^2 \\ \text{Indirect AB:} & \quad \text{MSE} = \eta^2\end{aligned}$$

3rd comparator different

$$\begin{aligned}\text{Direct BC:} & \quad \text{MSE} = 0 \\ \text{Indirect BC:} & \quad \text{MSE} = 2\eta^2\end{aligned}$$

Conclusion of “direct and indirect comparisons qualitatively and quantitatively similar” justified?

TA and NH give several plausible scenarios and examples where a UREM is associated with the type of comparison.



Then, $\bar{X} \neq 0$ for one or more comparisons.

$$\begin{aligned}E\delta_{AB} &= d_{AC} - d_{BC} + (\eta_{AC} - \eta_{BC})\bar{X}_{AB} \\E\delta_{AC} &= d_{AC} + \eta_{AC}\bar{X}_{AC} \\E\delta_{BC} &= d_{BC} + \eta_{BC}\bar{X}_{BC}\end{aligned}$$

- Direct comparison might be unbiased, but indirect biased, and vice versa.
- Bias in indirect comparison might cancel out or be enforced.
- Indirect evidence can only be biased if at least one of the direct comparisons is biased.
- Inconsistency between direct and indirect estimates: Sign that there is something wrong, but it doesn't mean necessarily that direct evidence is to be trusted more.

Should we use indirect evidence? Conclusion

TA and NH: Indirect evidence should be used



- The information is there, ignoring it would be a waste and unethical
- Most arguments against it apply to single comparison meta-analysis too
- Indirect evidence can be less biased than direct evidence
- Inconsistency of direct and indirect evidence means that there is something wrong with the head-to-head comparisons too

- So we should do multiple comparisons meta-analyses.
- Formal methods of indirect comparisons are invaluable (NH)

However, given that the use of indirect evidence is accepted, there can be many analytical problems.

Remark from the point of view of experimental design

- A MCMA is an **incomplete block design**
- Trial = block, mostly with only 2 treatments
- We assume treatments Missing At Random, but this is often questionable
- We would like to have more complete blocks: multiple treatment RCTs
- If the block*treatment interaction is substantial, we would like to have many blocks
- So from experimental point of view: Given a total number of patients, we would like to have many complete blocks

Consequence:

Should we advise doing many small multiple treatment RCT's?

Statistical issues in MCMA



1. Simple case

- no multiple treatment trials
- per pair of treatments number of trials is either zero or large enough for a standard meta-analysis method

Carry out the standard frequentist or Bayesian methods and combine the results.

2. More complicated case: Multivariate meta-analysis model

- much more assumptions needed than in single comparison MA

Multivariate model

Treatments $t = 0, \dots, T$; trial $i = 1, \dots, N$

Dichotomous outcome per patient: Y_{it} = no. of events for treatment t in trial i .

- **Within trial model:** independent binomial distributions per treatment arm

$$Y_{it} \sim \text{Bin}(\text{expit}(\mu_{it}), n_{it})$$

- **Between trials model:** $\mu_i \sim \text{MVN}(\mu, \Sigma_\mu)$

Alternatively, define $\Delta_{it} = \mu_{it} - \mu_{i0}$ ($t=1, \dots, T$) ($T=0$ reference treatment)

$$\Delta_i \sim \text{MVN}(\Delta, \Sigma_\Delta)$$

- Extension with covariates: $\mu = X\beta$ or $\Delta = X\beta$
- Each study has missing treatments: MAR assumption

Statistical issues



1. Estimation of (co)variance parameters

- Typically there are many (co)variance parameters.
For some or many comparisons only a few or even none head-to-head trials available.
- Several (co)variance parameters are not estimable
- Simplifying assumptions on the covariance matrix needed
 - standard assumption: (non)homogeneous compound symmetry with $\rho=0.5$
 - how robust results against misspecification?
 - exploring richer structures (flexible lower dimensional structures)
 - insight could be gained by sorting out which (functions of) (co)variance parameters are estimable
 - algorithm for which are the estimable functions of the covariance parameters (v. Houwelingen, pers. com.)

2. Role of the baseline

- Bayesian approach:
 $\Delta_i \sim \text{MVN}(\Delta, \Sigma_\Delta)$ and independent vague priors on the baseline parameters μ_{i0}
 (Correct? See Senn & Van Houwelingen, Stat Med 1999)
- Model the baseline too: $\mu_i \sim \text{MVN}(\mu, \Sigma_\mu)$
 - gain of precision
 - only valid under MAR
 - possible bias because of using between trial information
 - $\mu_A + \eta X + e_A$
 - $\mu_B + \eta X + e_B$
 - $\mu_C + \eta X + e_C$

If type of comparison (AB, AC, or BC) is related to X , then bias introduced.
- Condition on total no. of events in trial and replace the binomial by (multivariate) non-central hypergeometric distribution.
 Leads to random effects conditional logistic regression.

3. Consistency checks

- Direct and indirect evidence should be consistent
- Several testing methods available
- Not often used in practice?

4. Software:

Bayesian:

Is dominant method in the literature

WinBUGS

Difficult and error sensitive for non-statisticians

Difficult to figure out what authors have exactly done (in medical articles)

Frequentist:

- Not much available
- I have done some analyses with random effects conditional logistic regression in SAS Proc NLMIXED
- Need for user friendly (frequentist) programs