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Industry views on the place of meta-analyses in the clinical development

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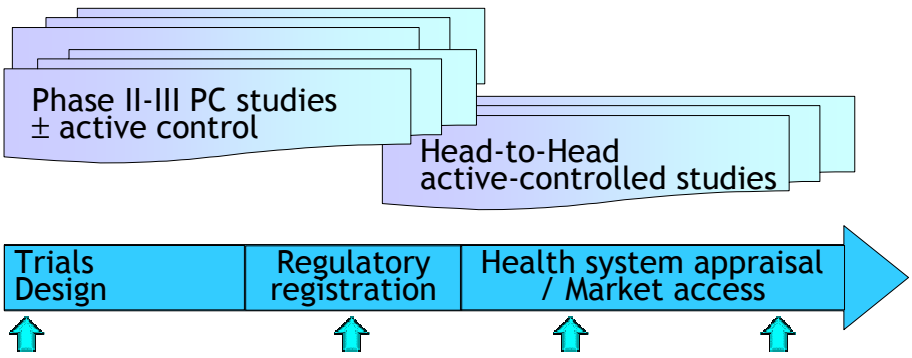
Use of Meta-analyses during the clinical development - Overview



Areas where placebo-controlled trials are recommended

Meta-analyses during the clinical development

- Different Aims and settings, meaning differences in terms of:
  - Criteria for inclusion of studies
  - Endpoint(s) studied
  - Databases & identifications of the studies
    - Sponsor database, Bibliographic data, Regulatory authority, etc.
  - Statistical methods
    - Standard Meta-analysis of the direct evidence, Indirect Comparison, Mixed treatment comparison, Network Meta-analysis (or Multiple-treatments Meta-analysis)

Outlines

Use of meta-analyses during the clinical development for

- Future trial Designs
- Applications for the Marketing Authorisation
- Post-marketing Authorization purposes

Future trial Designs
&
Meta-Analyses on competitors

Future trial design

- First discussions on study protocols and a development plan
  - Bibliographic data on competitor(s)
    ⇒ Sample size calculations
    ⇒ The choice of Non-Inferiority margin
  - Aim of meta-analysis: Interpreting competitor treatment effects from several trials
  - Meta-analyses are sometimes already published
  - Standard meta-analysis based on summary results could also be carried out

Future trial design

- Meta-analyses can provide
  - For sample size, in case of no previous sponsor experience
    - an estimate of the effect size
  - For the choice of non-inferiority margin, in case of no widely accepted non-inferiority margin
    - an estimate of the established treatment effect over placebo and the associated CI

Future trial design

- Limits in quantifying those estimates
  - Differences in terms of Population, Endpoint,…
  - Effect over placebo may possibly be overestimated

    e.g. Publication bias or placebo responses improved over time
  - Heterogeneity of the competitor treatment effect

  ⇒To be taken into account when dealing with the sample size calculations or for the choice of Non-inferiority margin
  - Discrepancies of published meta-analysis results

    e.g. Kirsch et al. (2008) vs Fountoulakis and Moller (2010)

Applications for the Marketing Authorisation (MA)

&

Standard Meta-analyses relying on sponsor studies

Summary of Clinical Efficacy vs Placebo for Applications for MA

- In the majority of cases: No claim based on meta-analysis
- Individual Placebo-controlled studies powered to satisfy their objective
- Similar objectives, design, target population and evaluation criteria

Summary of Clinical Efficacy vs Placebo for Applications for MA

- Aim of meta-analysis:
  - To summarise the overall efficacy results
    ⇒ Estimate the overall treatment effect from all PC studies while improving precision
    and taking into account fluctuation of the treatment effect across studies
  - To study secondary endpoints or particular (pre-specified) subgroups while increasing power
    e.g. particular subgroup in the indication as more severely ill

Summary of Clinical Efficacy vs Placebo for Applications for MA

- Meta-analysis proposed by the applicant
  - Protocol defines rules regarding which trials are to be combined and in what way
  - Pre-planned within a development plan
- Or required by *Rapporteurs* during the appraisal

Summary of Clinical Efficacy vs Placebo for Applications for MA

- Main discussions are often on the criteria for the selection of studies

  Study population, study duration, dosage (e.g. sub-therapeutic doses), etc.

- → Importance of the well-defined objective for each Meta-Analysis

  e.g. Treatment effect of claimed therapeutic doses for the indication population on the primary endpoint

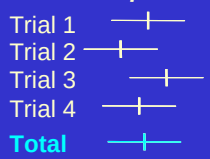
Summary of Clinical Efficacy vs Placebo for Applications for MA

- Statistical methods
  - Applications relying on the exhaustive Sponsor database & individual data
    - Allow homogeneity in terms of methods (e.g. ITT, handling of missing data, adjustment factors)
  - Standard methods ⇒ Estimation
    - Methods account for variations of treatment effect across trial / Random-effects models are usually used
  - Robustness analyses

Summary of Clinical Efficacy vs Placebo for Applications for MA

A versus placebo

Trial 1
Trial 2
Trial 3
Trial 4
Total



Standard Meta-analysis of the direct evidence

Fixed-effects meta-analysis

$$\hat{\theta} = \frac{\sum w_i y_i}{\sum w_i}$$

$$\text{var}(\hat{\theta}) = \frac{1}{\sum w_i}$$

where $w_i = 1/\text{v}_i$

Random-effects meta-analysis

$$\hat{\mu} = \frac{\sum w_i^* y_i}{\sum w_i^*}$$

$$\text{var}(\hat{\mu}) = \frac{1}{\sum w_i^*}$$

where $w_i^* = 1/(\text{v}_i + \hat{\tau}^2)$

and τ the among-study variance

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Summary of Clinical Efficacy vs Placebo for Applications for MA

- Mixed result studies are included
  - Positive and negative studies
  - Three-arm studies having no assay sensitivity
  - Studies with or without active comparator arm

    e.g. Placebo response rates may be influenced by the number of active treatment arms (M. Sinyor et al., 2010)

  $\Rightarrow$ Induce heterogeneity

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Summary of Clinical Efficacy vs Placebo for Applications for MA

- Heterogeneity
  - Homogeneity test is used, in addition to a visual inspection of Plots
  - Extensive in case of numerous meta-analyses
  - In case of “qualitative” interaction
    - Acceptance of an overall meta-analytic estimation is still open to discussion
    - If possible analysis on subsets of trials that are homogeneous for important features

Clinical Efficacy vs established drugs for Applications for MA

- Placebo-controlled studies including an active control
  - Information to position a new product compared to established drugs through direct comparisons
  - low power for comparison vs active comparator
  - Similar objectives, design, target population and evaluation criteria
  - Meta-analysis could be used to estimate the overall treatment effect vs an active comparator (or class) from those PC studies, while improving power

Clinical Efficacy vs established drugs for Applications for MA

- Active-controlled studies (with or without placebo arm)
  - Usually limited
  - To date we are used to considering individual study(ies) in itself
  - The question of whether to "pool" these studies or not could be considered
    - Between themselves or with three-arm studies
    - Even if the target population could be the same, objectives and primary evaluation criterion (e.g. safety) could be different

Summary of Clinical Safety for Applications for the MA

- Mainly naïve Pooling of data rather than meta-analysis due to large numbers of variables
  - Based on all phase II-III studies whatever the indications
- For some pre-specified risks linked to the therapeutic class (e.g. Suicide for Major Depressive Episode) or to the product
  - ⇒ Meta-analytical approach is planned to obtain a reliable estimate
- For some rare events, identified from naïve Pooling (not pre-specified risk)
  - ⇒ Meta-analytical approach is applied to confirm that the difference observed is not biased (due to heterogeneous study factors as population, follow-up, etc.)

Summary of Clinical Safety for Applications for the MA

- Tendency to have:
  - Regular safety updates based on cumulative safety database
  - More systematic meta-analyses approach to quantify the product effect

Post-marketing Authorization purposes

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Standard Meta-analysis of the direct evidence, Indirect comparison, MTC, Network Meta-analysis

Post- Marketing Authorization

- Comparison to competitors needed
- Comparative Effectiveness Research
- Closer to the effect that could be expected in clinical practice

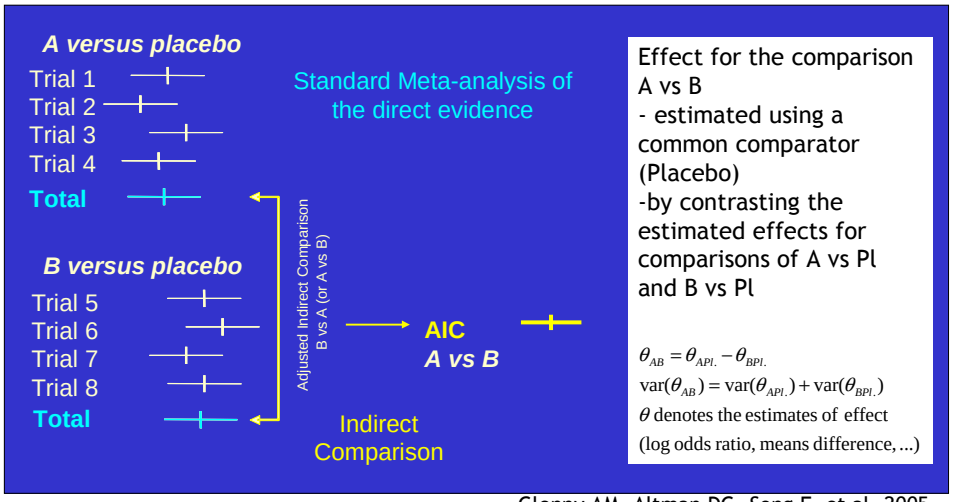
  E.g. National reimbursement/pricing, Health Technology assessments…

⇒ Head-to-head comparisons predominantly performed after the approval

Post- Marketing Authorization

- Meta-analysis may also be helpful
- Beyond Standard Meta-analysis of the direct evidence,
- Indirect comparison, Mixed treatment comparison, Network Meta-analysis are options

Indirect Comparison



Effect for the comparison A vs B
- estimated using a common comparator (Placebo)
-by contrasting the estimated effects for comparisons of A vs Pl and B vs Pl

$\theta_{AB} = \theta_{APl.} - \theta_{BPl.}$

$\text{var}(\theta_{AB}) = \text{var}(\theta_{APl.}) + \text{var}(\theta_{BPl.})$

θ denotes the estimates of effect (log odds ratio, means difference, ...)

Glenny AM, Altman DG, Song F, et al, 2005

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Indirect Comparison

- Preserves the randomisation of study groups in the trials
- Issues with Indirect Comparisons
  - Differences between the two sets of studies
    - Conditions, Time, Patient population,
    - Primary efficacy evaluation, etc.
  - Constancy of the effect of the common comparator

    e.g. Placebo response improving with Time in Depression

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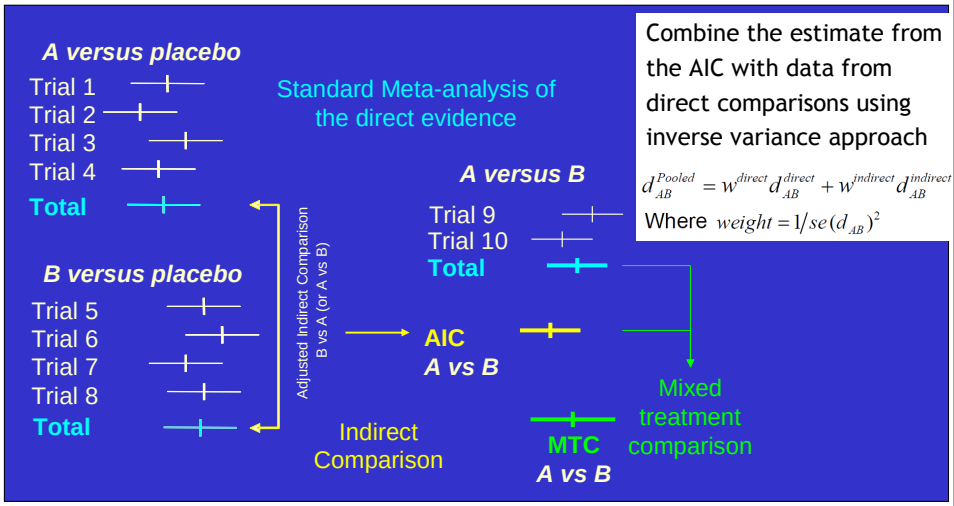
Indirect Comparison

- Up to now, Indirect Comparisons have mainly been used when there is no direct evidence
- Individual comparative studies are preferred, as one considers that most reliable information comes from direct comparison (same time, population, evaluation, etc.)
- However, some papers showed that adjusted IC could be in accordance with the direct comparisons results
- And even some approaches combine both indirect and direct estimates

Mixed treatment comparison

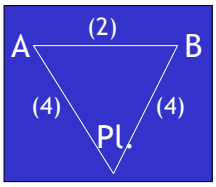
- To compare two active compounds
- Combine both the indirect estimate and the direct estimate
- Precision increased

Mixed treatment comparison



Network Meta-Analysis

- To summarize available clinical trials evidence of several treatments (or classes of treatments)
- Combines both indirect estimate and direct estimate
- To Provide estimates of the relative effects of each treatment compared with every other treatment



Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis – A. Cipriani et al. (2009)

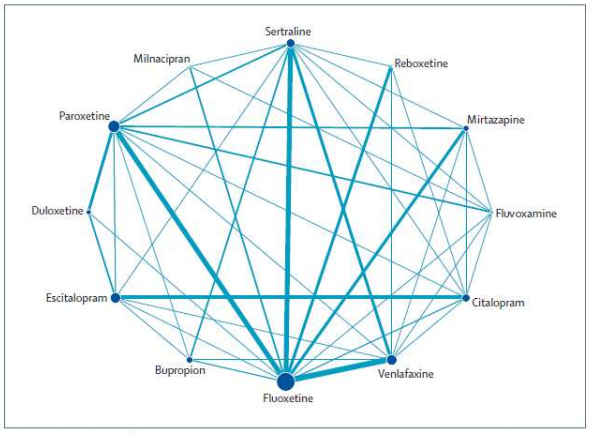


Figure 2: **Network of eligible comparisons for the multiple-treatment meta-analysis for efficacy (response rate)**
The width of the lines is proportional to the number of trials comparing each pair of treatments, and the size of each node is proportional to the number of randomised participants (sample size). The network of eligible comparisons for acceptability (dropout rate) analysis is similar.

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Network Meta-Analysis

- Interest
  - To position several treatments
  - Whether or not they have been directly compared in trials
- Limits
  - Recent
  - Approach very much debated
  - Technical difficulties

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Network Meta-Analysis

- Most of the criticisms is also valid for Indirect comparisons, MTC or standard MA on Head-to-Head trials but are increased due to the number of treatments involved

e.g.

- Bibliographic search
- Studies and data selection
  - The question of whether to include the placebo in the network or not has been asked
  - Treatments: Drugs or class of treatments, unused drugs, different forms, add-on, monotherapy,…
  - Doses: sub-therapeutic doses, multiple doses, forced titration,…

Network Meta-Analysis

- Statistical methods

Several methods, mainly Bayesian methods

- Overall Estimates
  - Simultaneous inference on all K(K-1)/2 comparisons
  - The estimate A vs B depends on every other pairwise comparisons of the network
  - The weight of direct and indirect comparisons => inverse variance weighting
  - Large number of drugs and few studies leading to difficulties to estimate or obtain interpretable results (wide CI)

Network Meta-Analysis

- Overall Estimates
  - Overall pair-wise Estimates (e.g. OR, effect size) calculated

  but also
  - Calculate the probability that each treatment is the most effective

    =>To rank the treatments
  - However these probabilities could sometimes be viewed as very similar

Network Meta-Analysis and Inconsistency

- Using evidence in this way makes assumptions
- Assumption of consistency between direct and indirect evidence
- Two different sources of "Heterogeneity"
  - Heterogeneity between trials making the same comparison
  - Inconsistency between different types of comparisons, i.e.
    - Through a direct and an indirect comparison
    - Through 2 different indirect comparisons

Network Meta-Analysis and Inconsistency

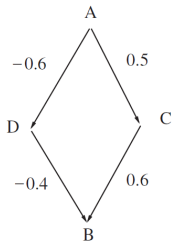


Figure 2. An incoherent network of comparisons.

Figure 2 (T. Lumley,2002) demonstrates this problem for two different Indirect Comparisons. The right path suggests that A is better than B, but the left path suggests that A is worse.

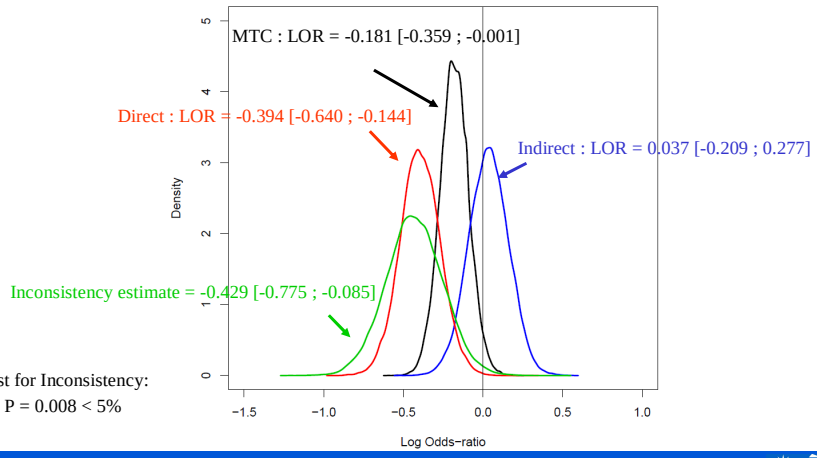
Network Meta-Analysis and Inconsistency

- Papers, and several published in 2010, propose methods to identify potential inconsistencies
- Node-splitting method (Dias et al., 2010), separates evidence on a particular comparison into “direct” and “indirect”
  - Check consistency of direct and indirect evidence
  - Illustrate how the direct and indirect evidence combine to produce the posterior MTC estimates
- Computationally intensive (by pairwise comparison)
- E.g., if we applied Node-splitting to Cipriani et al. data network, we can detect an inconsistency for the citalopram-escitalopram comparison

Example : Cipriani et al. (2009)

Citalopram versus Escitalopram Comparison

Posterior densities of the mean log-odds ratio (LOR) calculated using the full MTC model (black), and direct and indirect evidence only (red and blue respectively)



Test for Inconsistency:
P = 0.008 < 5%

Network Meta-Analysis and Inconsistency

- Facing with inconsistency on a particular comparison does not automatically tell us which evidence is “wrong”
- As in standard meta-analysis where heterogeneity is large, it seems important to look for possible causes of variation

IC, MTC, Network Meta-Analysis Questions raised

- Who should perform that? Independent third party preferable?
- To be updated regularly?
- Access to clinical trials results
  - Full raw dataset available ⇒ Sponsor Database
  - Competitors
    - Bibliographic search: Publication bias, Incomplete results,…
    - EPAR now available (or similar information for other regions)
    - Not available for old references
    - Clinical trials included in the application (not after)
    - Clinical Trial Registry & future

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Conclusion

- Meta-analyses are more and more often used in the clinical development for different purposes
- Crucial problem for meta-analysis in general: the identification of all relevant studies
- Meta-analysis on direct comparisons are well-known and standard
- For the other type of meta-analyses, controversy remains
  - Are indirect estimates biased?
  - Should direct and indirect evidence be combined?
  - Can conclusions be drawn?

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