WS I: Conducting & Interpreting Indirect Treatment Comparisons and Network Meta-Analysis: Learning the Basics

Conducted by members of the ISPOR Indirect Treatment Comparisons Task Force

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Agenda
- Background
- Concepts
- Example
- Reporting and interpreting results
- Q & A

Indirect Treatment Comparisons and Network Meta-Analysis: Background

Joe Cappelleri

Frequent Scenario
- New drugs are often compared with placebo or standard care, but not against each other, in trials aimed to contribute (as expeditiously as possible) toward obtaining approval for drug licensing
- Commercial incentive to compare the new treatment with an active control may be wanting
- Such commercial impetus may be lacking because it is not practical -- drugs are still investigational and there are constraints due to small sample sizes and short durations of follow-up

Acknowledged Value of Indirect Treatment Comparisons
- Available treatments tend to increase over time
  - For example, a large number of different (old and new) drugs are available for the treatment of depressive and other mental disorders
  - How to make sense of it all?
- Clinical, patients, and health-policy makers often need to determine which treatments are “best”
  - Make sense of a complex set of treatments
  - Primary: comparison between active treatments
  - Secondary: pure effect of drug (vs. placebo)
  - Select the best choice(s) of treatment
Value of Indirect Treatment Comparisons

- When there is no or insufficient evidence from direct comparison trials, it may be possible, in theory, to use results of different trials to estimate the relative efficacy of different treatments.

- Many interventions have not been directly compared in randomized controlled trials (RCTs).

- Over the period 1971-2002, 254 trials included over 100 different chemotherapy regimens for advanced non-small-cell lung cancer but direct evidence from at least 1000 individuals is available on only two regimens (Lancet 2006; 368:1470-1472).

Value of Indirect Treatment Comparisons

- Offers the opportunity to compare what may not have been otherwise compared—
  - Different therapeutic classes
  - Different drugs within the same class
  - Different doses of the same drug

General Principles: From Theory to Practice

- Guidelines are useful to support the appropriate use of certain methods like network meta-analysis.

- Application of indirect comparisons should be based on the scientific merits of the network meta-analysis — not on their results per se.

General Principles

- Well-conducted RCTs provide the most valid estimates of the relative efficacy of competing health-care interventions.

- Advocate their development and use whenever possible, with replication.

- Well-conducted observational studies also have merit.

General Principles

- Ensure that the use of network meta-analysis adheres to certain standards and assumptions that can be tested or evaluated.

- Doing so will make this method more credible.
Indirect Treatment Comparisons and Network Meta-Analysis: The Concepts

Jeroen P. Jansen

Anchored ITC (or 'adjusted' ITC)

Mixed Treatment Comparison

Network meta-analysis

Closed loops in network: combination of direct and indirect evidence

Networks of evidence

Definition

Frequentist framework

Bayesian framework

(Probabilistic interpretation of uncertainty and ranking of interventions)

Step wise approach (multiple sequential meta-analyses, followed by indirect comparison of pooled pairwise results)

Simultaneous evidence synthesis of all pairwise comparisons across the range of interventions

Network meta-analysis

Treatment*covariate interactions in meta-regression models to improve similarity / consistency assumptions and explain heterogeneity

Models without covariates

Analysis & synthesis methods

Frequentist framework

Bayesian framework

(Probabilistic interpretation of uncertainty and ranking of interventions)

Is an indirect comparison biased?

RCT 1

Tx A 61%  RR=2.5  Placebo 24%  Follow-up 24 weeks

RCT 2

Tx B 63%  RR=2.1  Placebo 30%  Follow-up 24 weeks

RCT 3

Tx B 42%  RR=2.1  Placebo 20%  Follow-up 30 weeks

Anchored indirect comparison

RR=2.5 / 2.1 = 1.2

No bias, because differences in study characteristics across trials do not influence the RR

Is an indirect comparison biased?

RCT 1

Tx A 61%  RR=2.5  Placebo 24%  Follow-up 24 weeks

RCT 2

Tx B 63%  RR=2.1  Placebo 30%  Follow-up 24 weeks

RCT 3

Tx B 50%  RR=2.5  Placebo 20%  Follow-up 36 weeks

Bias in anchored indirect comparison of trial 1 with trial 3, because there are differences in study follow-up across trials that do influence the RR
Mixed Treatment Comparisons

Indirect comparison: 2-step approach

1a) Meta-analysis of AC trials

1b) Meta-analysis of AB trials

Indirect estimate

Direct estimate

Simultaneous evidence synthesis & indirect comparison with regression model

k-1 basic parameters: $d_{AB}$, $d_{AC}$, $d_{AD}$

(Priors needed for these in Bayesian model)

Remaining contrasts are functional parameters,

$\begin{align*}
    d_{BC} &= d_{AC} - d_{AB} \\
    d_{CD} &= d_{AD} - d_{AC} \\
    &\vdots \\
    d_{BD} &= d_{AD} - d_{AB}
\end{align*}$

A total of $k(k-1)/2$ contrasts

1 AB study

$$
    \eta_k = \begin{cases} 
        \mu & k = A \\
        \mu + d & k = B
    \end{cases}
$$

Fixed effects meta-analysis

$$
    \eta_{jk} = \begin{cases}
        \mu_j & k = A \\
        \mu_j + d & k = B
    \end{cases}
$$
Fixed effects network meta-analysis model

\[ \eta_{jk} = \begin{cases} 
\mu_j + \delta_{jk} & \text{if } k = b \\
\mu_j + d_{jk} - d_{ab} & \text{if } k' \text{ after } b 
\end{cases} \]

\[ d_{ab} = 0 \]

Random effects network meta-analysis

\[ \eta_{jk} = \begin{cases} 
\mu_j + \delta_{jk} & \text{if } k = b \\
\mu_j + \delta_j & \text{if } k = A 
\end{cases} \]

\[ \delta_j \sim N(\mu_j, \sigma^2) \]

Bayes Theorem

Frequentist output:
Point estimate (with 95%CI)

"No significant difference between Tx A and Tx B"

Bayesian output:

Probability distribution

"75% Probability that Tx B is better than Tx A"

Difference between frequentist and Bayesian output

Adapted from Hollenbeak, ISPOR 2004
Indirect Treatment Comparisons and Network Meta-Analysis: Example

Neil Hawkins

Drug Eluting Stents for Coronary Artery Disease

- Comparators
  - Bare Metal Stent (A)
  - Paclitaxel Eluting Stent (B)
  - Sirolimus Eluting Stent (C)

- Binary Endpoint
  - Target lesion revasculariation

- 17,609 subjects in 37 studies

Network of trial evidence

Direct comparisons form a network of evidence

Odds Ratio of C versus B
OR_{BC} = 0.72 (0.61 to 0.87)

Odds Ratio of C versus A
OR_{AC} = 0.25 (0.18 to 0.35)

Odds Ratio of B versus A
OR_{AB} = 0.43 (0.31 to 0.58)

Network meta-analysis

- Treatment effects (log hazard ratios) are estimated for each treatment (B and C) compared to A: \( \beta_B, \beta_C \)

- Values are estimated to best fit the observed trial data:
  - Log transf. Odds Ratio of C vs B: \( \ln OR_{BC} = \beta_C - \beta_B \)
  - Log transf. Odds Ratio of C vs A: \( \ln OR_{AC} = \beta_C \)

- May be estimated using Bayesian or Maximum Likelihood techniques

Results of pairwise comparisons

<table>
<thead>
<tr>
<th>Stent</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td></td>
<td>2.66 (2.03 to 3.46)</td>
<td>4.1 (3.2 to 5.24)</td>
</tr>
<tr>
<td>B</td>
<td>0.38 (0.29 to 0.49)</td>
<td>-</td>
<td>1.56 (1.22 to 1.96)</td>
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<tr>
<td>C</td>
<td>0.25 (0.19 to 0.31)</td>
<td>0.35 (0.51 to 0.82)</td>
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</tbody>
</table>
Adjusted comparison: Bucher et al. method

- OR_{AC} and OR_{BC} are available from pairwise meta-analyses

- Estimate odds ratios of treatment C vs. B (OR_{BC})
  \[ OR_{BC} = \frac{OR_{AC}}{OR_{AB}} \]

- Taking logs:
  \[ \ln(OR_{BC}) = \ln(OR_{AC}) - \ln(OR_{AB}) \]

- Allows the Standard Error (SE) to be Calculated on the Log scale:
  \[ SE(\ln(OR_{BC})) = \sqrt{SE(\ln(OR_{AC}))^2 + SE(\ln(OR_{AB}))^2} \]


C vs B – adjusted indirect comparison

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparator</th>
<th>Odds Ratio (95% CI)</th>
<th>Log Odds Ratio (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>A</td>
<td>0.25 (0.18 to 0.35)</td>
<td>1.39 (0.17)</td>
</tr>
<tr>
<td>B</td>
<td>A</td>
<td>0.41 (0.31 to 0.53)</td>
<td>0.84 (0.16)</td>
</tr>
<tr>
<td>C</td>
<td>B</td>
<td>0.58 (0.37 to 0.92)</td>
<td>0.54 (0.23)</td>
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</table>

Consistency

- C vs B: Odds Ratio (95% CI)
  - Direct: 0.72 (0.61 to 0.87)
  - Indirect: 0.58 (0.37 to 0.92)
  - Combined: 0.65 (0.51 to 0.82)

Outline

- Assessing the internal and external validity of ITC/MTC
- Reporting ITC/MTC results
- Interpreting ITC/MTC results
- Decision-making in the absence of RCTs
- Conclusion

Indirect Treatment Comparisons and Network Meta-Analysis: Reporting and interpreting results

Rachael Fleurence
Assessing the internal and external validity of an ITC & network meta-analysis

- **Internal Validity**
  - Appropriate identification of studies
  - Quality of included studies
  - Confounding bias violating similarity and consistency assumptions

- **External Validity**
  - External validity of included trials

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**Reporting ITC/MTC results**

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<td>Table/list of studies with information regarding study design and patient characteristics (e.g. sample size, attrition)</td>
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Interpreting ITC/MTC results

- Do the findings apply to the decision problem at hand?
- Which treatment is most effective in the population of interest?
- What should we do with multiple endpoints?
- What about safety, patient preferences and costs?

Decision Making in the absence of RCTs

- ITC/MTC are a good option in the absence of head to head pragmatic randomized trials
- ITC/MTC remain a form of observational evidence
- Should we use comparative observational data?
- Decisions will benefit from explicit and transparent assessments

Indirect Treatment Comparisons and Network Meta-Analysis: Conclusions

- Network meta-analysis (ITC/MTC) are an extension of traditional pairwise meta-analysis
- ITC can provide complementary evidence to direct evidence
- Both direct and indirect evidence contribute to total body of evidence. The results from indirect evidence in combination with the direct evidence in a MTC, may strengthen the assessment between treatments directly evaluated

Conclusion

- Similarity and consistency assumption need to hold; Risk of residual confounding bias remains
- Researchers must continue to conduct RCTs with head-to-head comparisons of different treatments
- Applications of this method are likely to grow particularly in light of CER

Indirect Treatment Comparisons and Network Meta-Analysis: Questions & Answers
WHAT CAN GO WRONG?
Risperidone and Haloperidol for Schizophrenia
(Outcome: Not Clinically Improved)

Informal indirect comparison:
Odds ratio of haloperidol vs. placebo suggested a greater treatment effect than the odds ratio of risperidone vs. placebo, despite the overlapping confidence intervals.

Adjusted indirect comparison: Favors haloperidol over risperidone.

Direct comparison: Favors risperidone over haloperidol.

Combination of direct and indirect: Validity doubtful given their inconsistent evidence.

Source: Song. What is indirect comparison. Part of the “What is…?” series. February 2009.

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Risperidone and Haloperidol for Schizophrenia: What Happened?

- Similarity assumption violated
- Consistency assumption violated for combining direct and indirect estimates
- Inconsistent results between them may give invalid and misleading results
  - Example: risperidone versus haloperidol for schizophrenia (large I-square = 85%)
- When results are inconsistent, it is important to investigate possible causes of discrepancy
  - Chance, invalid indirect comparison, invalid head-to-head comparison, clinically meaningfully heterogeneity across trials

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Risperidone and Haloperidol for Schizophrenia: What Happened?

- Patient characteristics, dose of drug, and treatment duration were similar between the two sets of placebo-controlled trials.
- But clinical improvement was defined differently:
  - Placebo-controlled trials of risperidone: 20% or more greater reduction in total score on the Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale
  - Placebo-controlled trials of haloperidol: rated by clinicians using the Clinical Global Impression or other scales