Indirect Comparisons in Economic Evaluations: Experience from the Common Drug Review

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Presentation Outline

Background on indirect comparisons

Description of the study
  • Objective
  • Methods
  • Results

Summary

Discussion
In the absence of head-to-head active comparator trials, manufacturers often use indirect comparisons in their economic evaluations submitted to the Common Drug Review.

Situations in which indirect comparisons may be required:

- Only placebo-controlled trials are available, no head-to-head trial of the drug submitted with standard treatment.
- Placebo-controlled trials would be unethical, but a comparison between the drug submitted versus no treatment is relevant.
- Comparator trials are versus previous standard of care.
If the comparison of interest is A versus C:
Types of Indirect Comparisons

Unadjusted / Naïve

• Randomization linking treatment groups is broken
• Not recommended

Adjusted / Common reference-based

• Two (or more) interventions are compared through their relative effect versus a common comparator
• Strength of randomization is partially maintained
• Measure of the effect size and confidence interval for the comparison of A versus C is calculated
• Preferred methods
Statistical methods to perform adjusted indirect comparisons

Bucher method

- Only one common comparator

![Diagram showing Bucher method with A, B, and C nodes and arrows indicating pooled effect estimates of A versus B, B versus C, and an indirect comparison between A and C.](image)
Statistical methods to perform adjusted indirect comparisons (cont’d)

Lumley Network Meta-analysis

- An indirect comparison between two treatments of interest can be obtained through more than one common comparator
- Indirect comparisons within indirect comparisons
Mixed Treatment Comparisons

- Allows combination of both direct and indirect evidence
- Allows simultaneously indirect comparisons among several comparators

Diagram:
- A
- B
- C
- D
Limitations of Indirect Comparisons

The validity of the adjusted indirect comparisons depends on the internal validity and similarity of the included trials.

Factors that may cause heterogeneity of treatment effects:

- Differences in patients’ baseline risk
- Differences in the length of follow-up
- Differences in the measurement of outcomes

The validity of indirect comparisons is influenced by the consistency of the relative efficacy of interventions across different trials.

Loss of power, resulting in wider confidence interval than direct comparisons.
A Good Indirect Comparison would ideally be:

- Appropriately calculated for the comparative treatment effect and its 95% confidence interval (adjusted)
- Based on a large number of good quality RCTs
- Based on similar RCTs
Study Objectives

To review economic evaluations that used indirect comparisons to inform clinical inputs, reviewed by CDR in 2007 or 2008

To critically assess the methods employed for indirect comparisons in these economic evaluations
Methods

All pharmacoeconomic reviews completed (presented at a CEDAC meeting) in 2007 or 2008 were reviewed to identify submissions based on indirect comparisons

- Total number of 2007 submissions: 27
- Total number of 2008 submissions: 28

Submissions were assessed using a standard data extraction sheet
Methods (cont’d)

Data extraction sheet

• General submission information
• Information on individual indirect comparison
• If the indirect comparison was adjusted
  ▪ Number of comparators, number of trials
  ▪ Statistical method
  ▪ Sensitivity analyses
## Results

<table>
<thead>
<tr>
<th></th>
<th>2007 n (%)</th>
<th>2008 n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of economic submissions</strong></td>
<td>27</td>
<td>28</td>
<td>55</td>
</tr>
<tr>
<td>- Based on assumption of equivalent efficacy</td>
<td>5 (19)</td>
<td>2 (7)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>- Based on at least 1 indirect comparison</td>
<td>8 (30)</td>
<td>10 (36)</td>
<td>18 (33)</td>
</tr>
</tbody>
</table>
## Results (cont’d)

<table>
<thead>
<tr>
<th>Description</th>
<th>Total n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submissions with ≥ 1 indirect comparison</td>
<td>18</td>
</tr>
<tr>
<td>Number of indirect comparisons per submission</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10/18 (56)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>8/18 (44)</td>
</tr>
<tr>
<td>Total number of individual indirect comparisons performed</td>
<td>37</td>
</tr>
</tbody>
</table>
## Results (cont’d)

<table>
<thead>
<tr>
<th>Information on individual indirect comparisons</th>
<th>Total n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Justification provided to conduct an indirect comparison</td>
<td>37/37 (100)</td>
</tr>
<tr>
<td>Conducted by</td>
<td></td>
</tr>
<tr>
<td>Manufacturer or manufacturer-funded</td>
<td>32/37 (86)</td>
</tr>
<tr>
<td>Update of a comparison performed by an independent group (e.g. NICE)</td>
<td>5/37 (14)</td>
</tr>
<tr>
<td>Type</td>
<td></td>
</tr>
<tr>
<td>Naïve/Unadjusted</td>
<td>25/37 (68)</td>
</tr>
<tr>
<td>Adjusted</td>
<td>12/37 (32)</td>
</tr>
</tbody>
</table>
### Results (cont’d)

<table>
<thead>
<tr>
<th>Adjusted indirect comparisons</th>
<th>Total N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of comparators</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11/12 (92)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Number of trials used</td>
<td></td>
</tr>
<tr>
<td>1 study per intervention</td>
<td>3/12 (25)</td>
</tr>
<tr>
<td>≥ 1 meta-analysis for one of the interventions compared</td>
<td>9/12 (75)</td>
</tr>
<tr>
<td>Description of how the trials were selected</td>
<td>10/12 (83)</td>
</tr>
<tr>
<td>Factors of heterogeneity of treatment effects discussed</td>
<td>6/12 (50)</td>
</tr>
<tr>
<td>Event rates in the common reference group compared</td>
<td>0/12 (0)</td>
</tr>
</tbody>
</table>
### Results (cont’d)

<table>
<thead>
<tr>
<th>Adjusted indirect comparisons</th>
<th>Total N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mathematical model used</td>
<td></td>
</tr>
<tr>
<td>Bucher</td>
<td>9/12 (75)</td>
</tr>
<tr>
<td>Mixed treatment comparison</td>
<td>1/12 (8)</td>
</tr>
<tr>
<td>Not specified</td>
<td>2/12 (17)</td>
</tr>
<tr>
<td>Methodology described in detail</td>
<td>7/12 (58)</td>
</tr>
<tr>
<td>Calculation of the indirect comparison reported</td>
<td>7/12 (58)</td>
</tr>
<tr>
<td>Stated method actually used</td>
<td>7/12 (58)</td>
</tr>
<tr>
<td>Sensitivity analyses performed</td>
<td>4/12 (33)</td>
</tr>
</tbody>
</table>
Summary

The reason for using an indirect comparison was always provided.

The indirect comparisons were usually performed or funded by the manufacturer.

Most of the indirect comparisons were naïve/unadjusted (68%).

For the adjusted indirect comparisons:

• The Bucher method was the most commonly used.
• Factors that may cause heterogeneity across trials / event rates in the common reference group were often not discussed.
• Sensitivity analyses were rarely performed.
Guidance for Manufacturers

Ensure transparency of methods

- Justification for indirect comparison
- Identification and selection of clinical trial and/or meta analyses
- Provide clear description of methods
- Present the characteristics of the included trials that may cause heterogeneity
- Provide details on how heterogeneity among trials is handled
Guidance for Manufacturers (cont’d)

Ideally use adjusted methods
- Give details on the method used, provide estimates

Consider sensitivity analyses
- Assess the impact of the selection of trials
- Use different statistical methods
Reference Papers on Indirect Comparisons

• 2009 CADTH report: Indirect Evidence: Indirect Treatment Comparisons in Meta-Analysis (available at http://www.cadth.ca/media/pdf/H0462_itc_tr_e.pdf)

• Indirect comparison software application (Bucher method) (freely available at http://www.cadth.ca/index.php/en/itc-user-guide)


Questions