Network meta-analyses in national clinical guidelines: a description and quality assessment

Heather Stegenga, Gabriel Rogers, Prashanth Kandaswamy, Dylan Jones

Internal clinical guidelines programme
Centre for clinical practice
National Institute for Health and Clinical Excellence (NICE)
United Kingdom
Background

- A number of treatment options
- How to decide?

- Often gaps in the literature between treatments of interest
- Rarely one trial comparing all possible treatments for a decision problem
- Decisions made implicitly?

Value of network meta-analysis is making decisions more explicit that are otherwise made implicitly
Indirect treatment comparison (ITC)

No head-to-head trials of A vs B

Treatment effect A vs B (indirect) = treatment effect C vs A (direct) – treatment effect C vs B (direct)  

Plus, add the variances of treatment effect.
Indirect treatment comparison (ITC)

Key feature: disconnected network
Mixed/multiple treatment comparison (MTC) or multiple-treatment meta-analysis (MTM)

Head-to-head trial(s) between A vs B (direct estimate)

Pool indirect and direct estimates to get more precise estimate of treatment effect
Mixed/multiple treatment comparison (MTC) or multiple-treatment meta-analysis (MTM)

Important!
Need to check difference (or consistency) between indirect and direct estimates

Inconsistency = imbalance in effect modifiers in indirect and direct studies
Why combine direct and indirect?

• Helpful if there is some reason that we might not be confident in the results of the head-to-head study/studies:
  – Results are not precise
  – Low study quality
  – Manufacturer supported
  – Study sizes
  – Small number of trials (ie. only 1 head-to-head trial)

• Level of consistency/inconsistency across the network (between direct and indirect treatment effects) can be informative and provide coherence throughout the whole network of treatments
A developing methodology = different terminology

- Multiple treatment comparison (MTC)
- Indirect treatment comparison (ITC)
- Multiple treatment meta-analysis (MTM)
- Mixed treatment comparison (MTC)
- Network meta-analysis
For the purposes of this project, mixed/multiple treatment comparisons AND indirect treatment comparisons are both considered network meta-analyses (NMA).
NICE Decision support unit checklist – 4 main areas

A. Definition of decision problem

B. Method of analysis

C. Issues specific to the network synthesis

D. Embedding the synthesis into a probabilistic cost-effectiveness model
Our objective

• To describe and quality assess the NMAs used in NICE clinical guidelines

• Adapted version of checklist – added some descriptive variables to provide some points of comparison

*Inclusion criteria:* published up to January 2012

*Exclusion criteria:* in development (including those in the public domain which have been out for public consultation)
NICE clinical guidelines

Total 145 published guidelines

8% (11) with NMA
- 7 de novo
- 3 from published study
- 1 with both
Number of networks per guideline

<table>
<thead>
<tr>
<th>Condition</th>
<th>Networks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer (CCancer)</td>
<td>5</td>
</tr>
<tr>
<td>NocEnur</td>
<td>3</td>
</tr>
<tr>
<td>BO</td>
<td>1</td>
</tr>
<tr>
<td>VTE</td>
<td>15</td>
</tr>
<tr>
<td>T2 Diab (Update)</td>
<td>3</td>
</tr>
<tr>
<td>Schiz</td>
<td>2</td>
</tr>
<tr>
<td>BCancer</td>
<td>2</td>
</tr>
<tr>
<td>Epileps</td>
<td>6</td>
</tr>
<tr>
<td>Depress</td>
<td>2</td>
</tr>
<tr>
<td>SCC</td>
<td>1</td>
</tr>
<tr>
<td>T2 Diab</td>
<td>3</td>
</tr>
</tbody>
</table>

National Institute for Health and Clinical Excellence
Type of interventions

- **55%** pharmacological
- **27%** various (including pharmacological)
- **18%** endoscopic (including radiotherapy, etc) or surgical procedures
Use in economic model

- Used in economic model
- Unclear
Methodology

- Bayesian
- Bucher's adjusted indirect comparison
- "Adjusted indirect comparison"
- Comparison of point estimates
- Unknown
Re: methods
## Complexity of networks

<table>
<thead>
<tr>
<th></th>
<th>Average (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions in decision space</td>
<td>8.4 (2-19)</td>
</tr>
<tr>
<td>Additional interventions in network (for indirect comparisons)</td>
<td>2.2 (1-5)</td>
</tr>
<tr>
<td>Number of connected loops (MTC)</td>
<td>6.2 (1-14)</td>
</tr>
<tr>
<td>Interventions with only one link</td>
<td>29% (0-55%)</td>
</tr>
<tr>
<td>Number of trials</td>
<td>41 (2-128)</td>
</tr>
<tr>
<td>Trials in head-to-head comparison (MTC) (vs indirect)</td>
<td>78% (50-100%)</td>
</tr>
<tr>
<td>Links with only one trial</td>
<td>47% (0-100)</td>
</tr>
</tbody>
</table>
Presentation of NMA

- Diagram/picture of the network:
  - All but 1 guidelines with de novo NMA
    (1 without was an ITC)
Re: presentation

- 3 of the 8 guidelines with de novo networks, including the 2 most recent

- Use with caution: doesn’t take into account uncertainty around treatment effect

Colorectal cancer (CG131)
Only one guideline used a rankogram

Rankograms which take into account the probability of being best, second best, etc are ideal

---

Table 84 Rankings of each antidepressant in terms of efficacy and cost effectiveness

<table>
<thead>
<tr>
<th>Efficacy (Response)*</th>
<th>Cost effectiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MODERATE depression</td>
</tr>
<tr>
<td>1) Mirtazapine</td>
<td>1) Mirtazapine</td>
</tr>
<tr>
<td>2) Escitalopram</td>
<td>2) Sertraline</td>
</tr>
<tr>
<td>3) Venlafaxine</td>
<td>3) Escitalopram</td>
</tr>
<tr>
<td>4) Sertraline</td>
<td>4) Citalopram</td>
</tr>
<tr>
<td>5) Citalopram</td>
<td>5) Venlafaxine</td>
</tr>
<tr>
<td>6) Paroxetine</td>
<td>6) Paroxetine</td>
</tr>
<tr>
<td>7) Fluoxetine</td>
<td>7) Fluoxetine</td>
</tr>
<tr>
<td>8) Duloxetine</td>
<td>8) Fluvoxamine</td>
</tr>
<tr>
<td>9) Fluvoxamine</td>
<td>9) Duloxetine</td>
</tr>
<tr>
<td>10) Reboxetine</td>
<td>10) Reboxetine</td>
</tr>
</tbody>
</table>

* Adapted from Cipriani et al. (2009); ranked according to ORs versus fluoxetine as reference compound

---

Depression (update) (CG90)
Inconsistency (MTC)

• Recommended methods:
  – Repeat indirect methods for each ‘loop’
  – Develop a model of inconsistency and compare this with the standard network inconsistency

• Some guidelines said they checked for inconsistency but it was often not clear how

• Of the 122 possible inconsistencies across the networks, there were only 2 reported inconsistencies (2 different guidelines).

• There was very little discussion about inconsistencies in many of the guidelines. Does that mean that few were found?
Overall difficulties encountered

- Considerable variation of where details found
- Some variation expected, i.e., different developers, different topic areas and, importantly, developing methodology
- Methods were not reported or were unclear
- Checklist is new (available in early 2012) and is an attempt to improve methods and reporting
Discussion

- Value of network meta-analysis is being explicit about decisions otherwise made implicitly
- Value of being explicit is lost when description is lost
- Inability to assess the adequacy of decisions made from the results of the NMA

**Recommendations:**
- Fully describe methods used
- Present networks in diagram
- Use rankograms
- Report and discuss inconsistency across networks
Further information

• All guidelines available from www.nice.org.uk
• NICE Decision support unit: http://www.nicedsu.org.uk/

My contact details:
Heather.stegenga@nice.org.uk
Disclosure of Interests (last 3 years)

Heather Stegenga

I certify that, to the best of my knowledge, no aspect of my current personal or professional situation might reasonably be expected to affect significantly my views on the subject on which I am presenting.