Statistics in Health Technology Assessment: Issues and challenges

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Once a product is approved to be used, what is the next step?

Once a product is approved, what is next?

Get reimbursed.

- Each country has its own regulation
- Each country has its own standard of care

Some of issues we face are:

- Mixed treatment comparison
- Cross-over
- Real world data

Network meta-analysis or Mixed treatment comparison

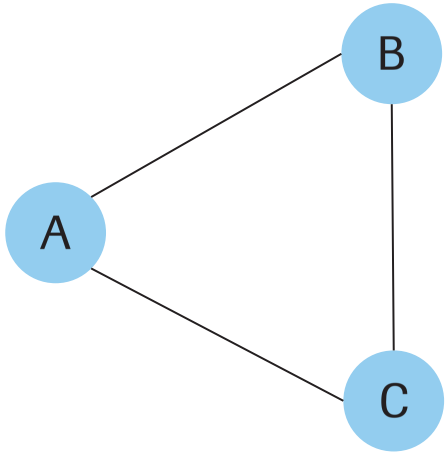
Background of indirect treatment comparisons

- A: New product
- B: Product used in country X
- C: Product used in country Y

Compare the outcomes of the products using head to head studies

The ideal situation is:

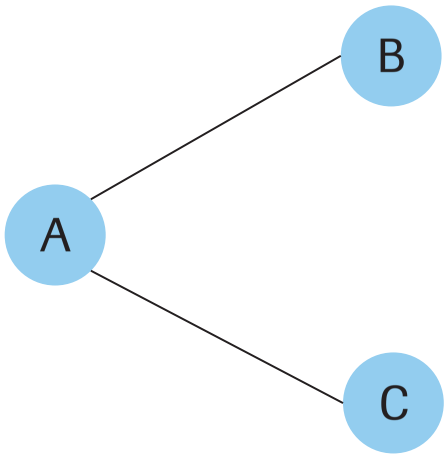
The three products have been compared in one or more clinical trials



The line indicates that there is one or more studies that estimates the comparison directly

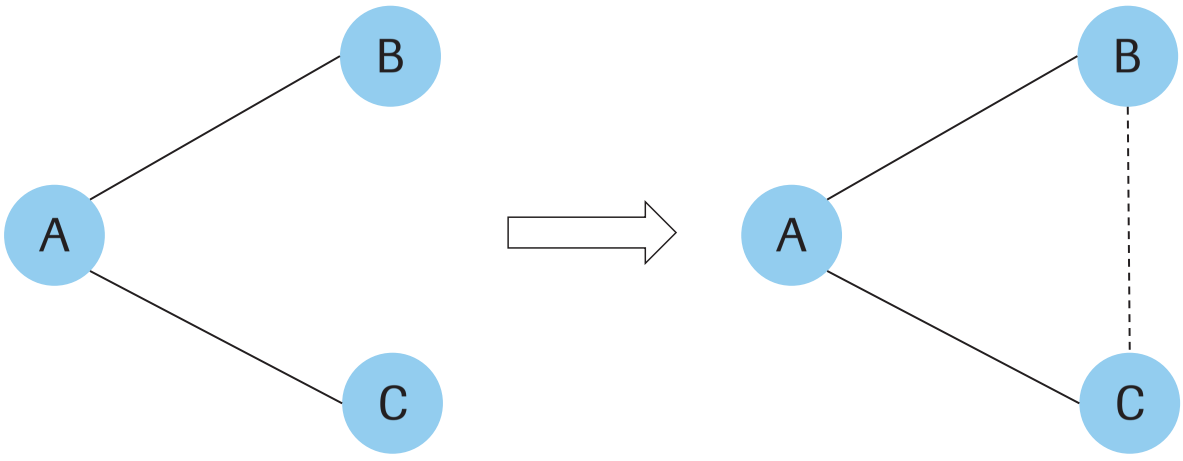
The real life situation may be:

- Not all the comparators can be included in one clinical trial
- There are time and money constraints



The real life situation may be:

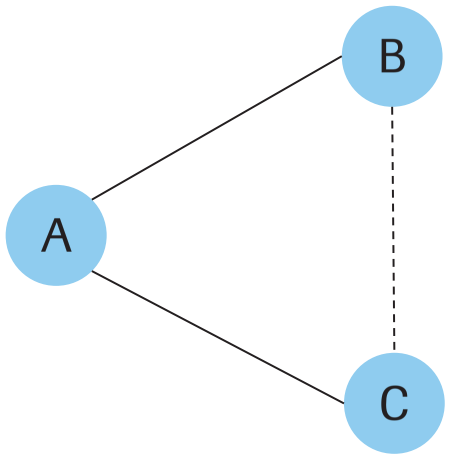
- There is evidence to compare A-B and A-C (Direct)
- The comparison B-C is indirect



Mixed treatment comparison

Real life situation

- The differences in relative treatment effect are: $\delta_{AB}, \delta_{AC}, \delta_{BC}$



Mixed treatment comparison

Named network meta-analysis when more than 2 studies in network

Considerations about network meta-analysis

- Assumptions
- Analysis methods
- Extensions and
- Precautions

Assumptions (1)

Transitivity assumption

One can learn about the comparison A and B via C.

This assumption can be evaluated conceptually and epidemiologically, however it can not be formally tested.

Assumptions (1)

Are the key trials in the network sufficiently similar to obtain meaningful results of the indirect and the mixed treatment comparisons?

If not then the estimates of the indirect treatment comparison may be biased.

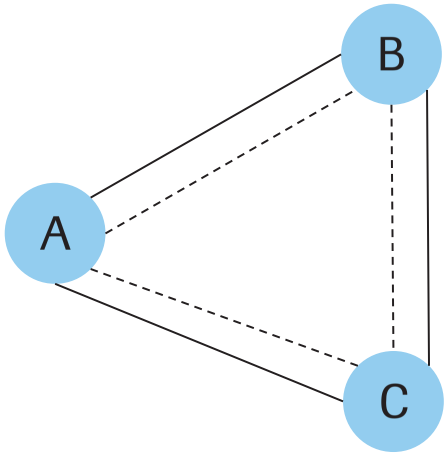
Effect modifiers may be:

- Patients characteristics
- Outcomes definitions or measurements
- Protocol requirements
- Length of follow up

Assumptions (2)

Consistency assumption

Is the direct evidence consistent with the indirect evidence?



$$\delta_{BC} = \delta_{AC} - \delta_{AB}$$

$$\delta_{AB} = \delta_{CB} - \delta_{CA}$$

$$\delta_{AC} = \delta_{BA} - \delta_{BC}$$

How to analyse it?

- Simultaneous evidence synthesis
- Models without covariates
- Meta-regression
- Frequentist framework
- Bayesian framework

Use relative effect measurements to preserve randomization

Extending the network meta-analysis

- Network meta-regression to adjust for factors that can vary across comparisons.
- The issue of bias revisited when comparing multiple interventions.
- Multivariate versions of the models.
- Extending the current tools.

MTC must be used with caution

"network meta-analysis must be designed rigorously and conducted carefully"

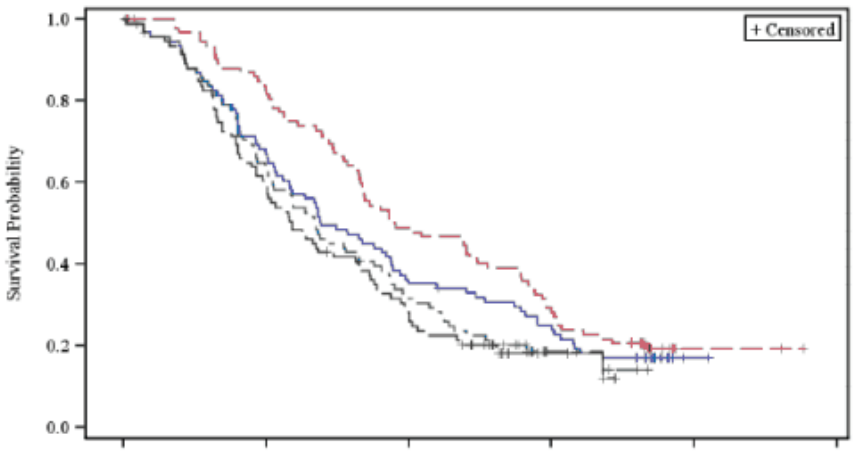
Li, T., Puhan M. A. et al. "Network meta-analysis-highly attractive but more methodological research is needed." *BMC medicine* 9.1 (2011): 79.

Cross-over or treatment switching

Some real life situation in oncology

- The objectives of the trial may be progression free survival and overall survival
- Patient is randomized to the control group
- After disease progression, the patient is permitted to switch treatments or cross over to receive the new innovative treatment, which confounds the assessment of OS

An example



Control group

Control group cross-over adjustment method 1

Control group cross-over adjustment method 2

Can we know the truth (the differences in the survival curves) despite of the crossover?

We cannot estimate the survival differences based on the actual data unless we make assumptions

Key message

Simple methods have several issues and therefore are not recommended

- ITT analysis underestimates the treatment effect
- PP leads to selection bias, if the excluded differ in prognosis from those retained in the analysis.
- Cox model with treatment as time-varying covariate. Can break the randomization balance and it is prone to selection bias.

Some of the sophisticated methods are

- Law and Kaldor (1996)
- Loeys and Goetghebeur (2003)

} Adjusted hazard ratio methods

- Robins and Tsiatis (1991)
- Branson and Whitehead (2002)
- Walker et al. (2004)

} Accelerated failure time models methods

Comparison of the methods

Morden, J. P., Lambert P. C. et al. (2011) include a simulation study to compare the six methods previously mentioned.

Latimer N. R. et al. (2013) compares more complex methods and proposes a new one to deal with treatment switching.

On a specific study

- The situation (clinical trial data) must be careful evaluated.
- Sensitivity analyses must be performed.

Real-world data

What is Real-World Data?

Based on the ISPOR Real-World Data Task Force

"…data used for decision making that are not collected in conventional randomized controlled trials (RCTs)"

Garrison, L. P., Neumann P. J. et al. "Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report" *Value in Health* (2007): 10(5) 326-335.

Why do we need Real-World Data?

We need real-world evidence (costs and benefits of treatment) to assess the value of medical treatment.

The evidence is crucial for payers to decide about coverage and physicians to decide about treatment options.

Types of outcomes

- Clinical outcomes
- Economic outcomes
- Patient reported outcomes/quality of life

Limitations

- Potential bias and confounding due to the nature of the data
- Methodological rigor
- Resources

Sources of outcomes

- Supplements to traditional registration RCT
- Large simple trials
- Registries
- Administrative data
- Health surveys
- Electronic health records

Recent initiatives

Innovative Medicine Initiative: GetReal

- Includes four work-packages
- Partners from academic, pharmaceutical industry, and regulatory or HTA.

Summary

- Network meta-analyses
- Cross-over
- Real-world data

Selected References

Jansen, J. P., Fleurence, R., et al.. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices, part 1. *Value in Healt*h, 14(4), 417-428.

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Morden, J. P., Lambert P. C. et al. Assessing methods for dealing with treatment switching in randomised controlled trials. *BMC Medical Research Methodology* (2011) 11:4.

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Mullins, C. D., Montgomery R., and Tunis S. Uncertainty in assessing value of oncology treatments. *The Oncologist* 15.Supplement 1 (2010): 58-64.

Doing now what patients need next