Population-adjusted treatment comparisons in Health Technology Assessment

An overview of approaches and perspectives

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Session Overview

- David Phillippo: Overview and recommendations from the NICE Decision Support Unit
- Mark Belger: Providing an Industry Perspective
- Ahmed Elsada: The NICE perspective
- Audience/Panel: Questions / Discussion

Population-adjusted treatment comparisons
Overview and recommendations from the NICE Decision Support Unit

David M Phillippo, *University of Bristol*

NICE DSU TECHNICAL SUPPORT DOCUMENT 18: METHODS FOR POPULATION-ADJUSTED INDIRECT COMPARISONS IN SUBMISSIONS TO NICE

REPORT BY THE DECISION SUPPORT UNIT

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Available from www.nicedsu.org.uk

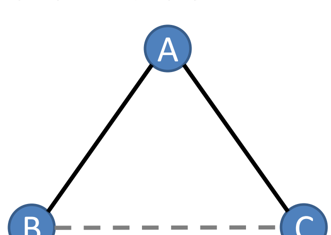
Outline

- Background
  - Standard indirect comparisons
  - Population adjustment
- MAIC and STC
- Assumptions and properties
- Recommendations

Background: Indirect Comparisons

Wish to compare two treatments B and C

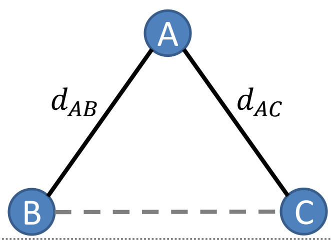
- Not studied in the same trial
- Instead, each compared with a common comparator A through AB and AC trials.



Background: Indirect Comparisons

Standard indirect comparisons:

- $d_{BC} = d_{AC} - d_{AB}$
- Biased if there are imbalances in effect modifiers *(EMs)* between AB and AC; $d_{AB(AB)} \neq d_{AB(AC)}$



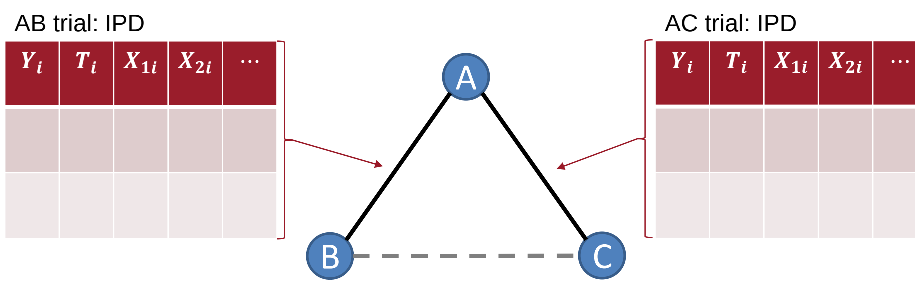
Background: Population Adjustment

- Standard indirect comparisons assume constancy of relative effects
- Population adjustment methods seek to adjust for imbalance in EMs
  - Relaxed constancy assumption
  - Create a fair comparison in a specific target population

Background

Ideal scenario: full individual patient data (IPD)

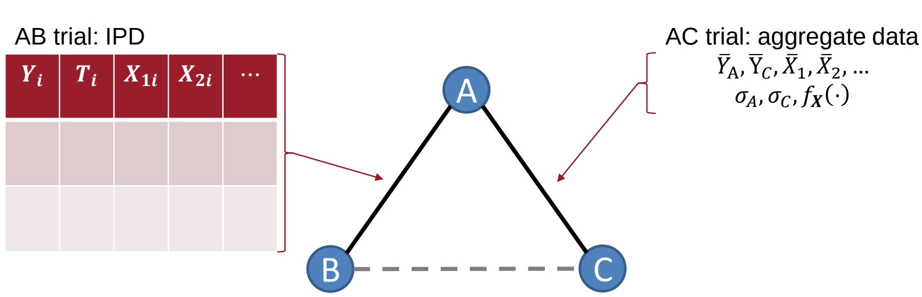
- "Gold standard" – IPD meta-regression



Background

Common scenario: limited IPD

- Several recent methods make use of mixed data



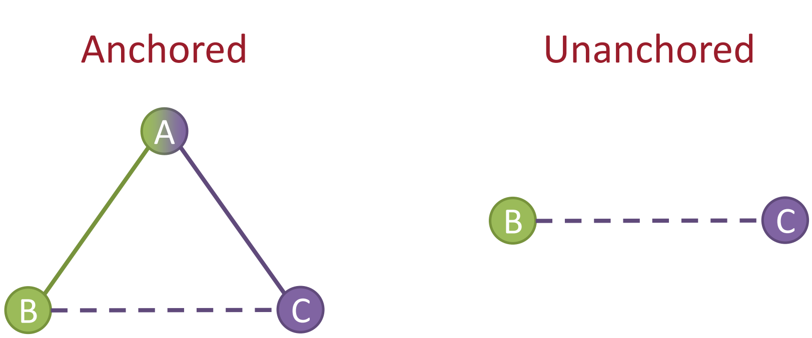
Population adjustment: MAIC and STC

Matching-Adjusted Indirect Comparison	Simulated Treatment Comparison
• Population reweighting method	• Outcome regression method
• Weight AB individuals to balance covariate distribution with AC trial	• Fit regression model in AB trial
• Estimate outcomes on A and B in AC trial using weights	• Estimate outcomes on A and B in AC trial using regression model
• Check distribution of weights, effective sample size	• Standard model checking, AIC/DIC, examine residuals…

- AB and AC population must have sufficient overlap
  - Compare covariate distributions, inclusion/exclusion criteria
- Not the only approaches, but at present the most popular

Population adjustment

Two possible forms of indirect comparison



Population adjustment

Two possible forms of indirect comparison

Anchored

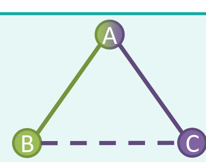
$$\hat{\Delta}_{BC(AC)} = g\left(\bar{Y}_{C(AC)}\right) - g\left(\bar{Y}_{A(AC)}\right) - \left(g\left(\hat{Y}_{B(AC)}\right) - g\left(\hat{Y}_{A(AC)}\right)\right)$$

Unanchored

$$\hat{\Delta}_{BC(C)} = g\left(\bar{Y}_{C(C)}\right) - g\left(\hat{Y}_{B(C)}\right)$$

- Comparison is on a given transformed scale
- The latter requires much stronger assumptions, but doesn't need a common comparator arm

Assumptions and properties: constancy

	Anchored 		Unanchored 
Form of comparison	Standard indirect comparison	Anchored population-adjusted indirect comparison	Unanchored population-adjusted indirect comparison
Constancy assumption	Constancy of relative effects $d_{AB(AB)} = d_{AB(AC)}$	Conditional constancy of relative effects Predict $d_{AB(AC)}$ from AB trial	Conditional constancy of absolute effects Predict $Y_{B(C)}$ from B trial
Valid only if	No effect modifiers in imbalance	All effect modifiers known and adjusted for	All effect modifiers and prognostic variables known and adjusted for
Data	Only requires aggregate data	Requires IPD on at least one trial	Requires IPD on at least one trial

Assumptions and properties

MAIC and STC produce estimates of relative treatment effect that are specific to the AC population

- This is unlikely to be representative of the decision target population
- If so, population-adjusted estimates are irrelevant for the decision…
- Can make use of the shared EM assumption, if justified
- Further research ongoing

Recommendations for use in HTA

1. Anchored vs. unanchored
2. Justifying anchored comparisons
3. Justifying unanchored comparisons
4. Variables to adjust for
5. Scale of comparison
6. Target population

Reporting guidelines and example R code available online

Recommendation 1

When connected evidence with a common comparator is available, a population-adjusted anchored indirect comparison may be considered. Unanchored indirect comparisons may only be considered in the absence of a connected network of randomised evidence, or where there are single-arm studies involved.

- Anchored comparisons are always preferred to unanchored comparisons
- Unanchored comparisons require much stronger assumptions

Recommendation 2

Submissions using population-adjusted analyses in a connected network need to provide evidence that they are likely to produce less biased estimates of treatment differences than could be achieved through standard methods.

- Justification for moving away from standard methods required
  - Altered decision scenario
  - Consistency between appraisals

See the NICE Methods Guide…

NICE Methods Guide

Treatment effect modifiers

5.2.7 Many factors can affect the overall estimate of relative treatment effects obtained from a systematic review. Some differences between studies occur by chance, others from differences in the characteristics of patients (such as age, sex, severity of disease, choice and measurement of outcomes), care setting, additional routine care and the year of the study. Such potential treatment effect modifiers should be identified before data analysis, either by a thorough review of the subject area or discussion with experts in the clinical discipline.

NICE (2013)

Recommendation 2 (continued)

a) Evidence must be presented that there are grounds for considering one or more variables as effect modifiers on the appropriate transformed scale. This can be empirical evidence, or an argument based on biological plausibility.

b) Quantitative evidence must be presented that population adjustment would have a material impact on relative effect estimates due to the removal of substantial bias.

- Anchored comparisons should be justified with evidence for effect modification prior to analysis
- Judge possible magnitude of bias in relation to relative treatment effect, clinical importance

Recommendation 3

Submissions using population-adjusted analyses in an unconnected network need to provide evidence that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects, and present an estimate of the likely range of residual systematic error in the "adjusted" unanchored comparison.

- For unanchored comparisons, need to justify that we are doing any better than a naïve comparison of arms
- Otherwise amount of bias is unknown, likely substantial, and could exceed size of treatment effect

Recommendation 4

a) For an anchored indirect comparison, propensity score weighting methods should adjust for all effect modifiers (in imbalance or not), but no prognostic variables. Outcome regression methods should adjust for all effect modifiers in imbalance, and any other prognostic variables and effect modifiers that improve model fit.

- For anchored comparisons, only adjustment for EMs is necessary to minimise bias
- Adjusting for other variables may unnecessarily reduce precision

Recommendation 4

b) For an unanchored indirect comparison, both propensity score weighting and outcome regression methods should adjust for all effect modifiers and prognostic variables, in order to reliably predict absolute outcomes.

- For unanchored comparisons all covariates must be adjusted for, as predictions of absolute outcomes are required

Recommendation 5

Indirect comparisons should be carried out on the transformed linear scale, with the same link functions that are usually employed for those outcomes.

- Effect modification defined with respect to this scale
  - MAIC is not "scale-free"
- Consistency between appraisals

Recommendation 6

The target population for any treatment comparison must be explicitly stated, and population-adjusted estimates of the relative treatment effects must be generated for this target population.

- If there are effect modifiers, then the target population is crucial
- An "unbiased" comparison is not good enough for decision making, must also be in the correct population
- Can use the shared EM assumption, if justified

Key issues

- Performance and robustness of methods not known – need thorough simulation study
- Decision target population must be defined, and estimates produced for this population
- Analysis from different perspective *will* give different results
- Evidence for effect modification is required for HTA
- Unanchored comparisons are very hard to justify

Thank you

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