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

David M Phillippo, University of Bristol
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METHODS FOR POPULATION-ADJUSTED INDIRECT
COMPARISONS IN SUBMISSIONS TO NICE

REPORT BY THE DECISION SUPPORT UNIT

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David M. Phillippo,¹ A. E. Ades,¹ Sofia Dias,¹
Stephen Palmer,² Keith R. Abrams,³ Nicky J. Welton¹

¹ School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road,
Bristol BS8 2PS, UK
² Centre for Health Economics, University of York
³ Department of Health Sciences, University of Leicester

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

AB trial: IPD

\[ Y_i, T_i, X_{1i}, X_{2i}, \ldots \]

AC trial: IPD

\[ Y_i, T_i, X_{1i}, X_{2i}, \ldots \]
Background

Common scenario: limited IPD

• Several recent methods make use of mixed data

AB trial: IPD

\[
\begin{array}{cccc}
Y_i & T_i & X_{1i} & X_{2i} & \ldots \\
\end{array}
\]

AC trial: aggregate data

\[
\bar{Y}_A, \bar{Y}_C, \bar{X}_1, \bar{X}_2, \ldots, \sigma_A, \sigma_C, f_X(\cdot)
\]
# Population adjustment: MAIC and STC

## Matching-Adjusted Indirect Comparison
- Population reweighting method
- Weight AB individuals to balance covariate distribution with AC trial
- Estimate outcomes on A and B in AC trial using weights
- Check distribution of weights, effective sample size
- AB and AC population must have sufficient overlap
  - Compare covariate distributions, inclusion/exclusion criteria
  - Not the only approaches, but at present the most popular

## Simulated Treatment Comparison
- Outcome regression method
- Fit regression model in AB trial
- Estimate outcomes on A and B in AC trial using regression model
- Standard model checking, AIC/DIC, examine residuals...
Population adjustment

Two possible forms of indirect comparison

Anchored

Unanchored
Population adjustment

Two possible forms of indirect comparison

**Anchored**

\[
\hat{\Delta}_{BC(AC)} = \frac{g(\bar{Y}_{C(AC)}) - g(\bar{Y}_{A(AC)})}{(g(\hat{Y}_{B(AC)}) - g(\hat{Y}_{A(AC)}))}
\]

**Unanchored**

\[
\hat{\Delta}_{BC(C)} = \frac{g(\bar{Y}_{C(C)}) - g(\hat{Y}_{B(C)})}{(g(\hat{Y}_{B(C)}) - g(\hat{Y}_{B(C)}))}
\]

- 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**

- **Form of comparison**: Standard indirect comparison
- **Constancy assumption**: Constancy of relative effects
  \[ d_{AB(AB)} = d_{AB(AC)} \]
- **Valid only if**: No effect modifiers in imbalance
- **Data**: Only requires aggregate data

**Anchored population-adjusted indirect comparison**

- **Constancy assumption**: Conditional constancy of relative effects
- **Valid only if**: All effect modifiers known and adjusted for
- **Data**: Requires IPD on at least one trial

**Unanchored population-adjusted indirect comparison**

- **Constancy assumption**: Conditional constancy of absolute effects
- **Valid only if**: All effect modifiers and prognostic variables known and adjusted for
- **Data**: 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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