Population-adjusted treatment comparisons
Estimates based on MAIC and STC

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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: Effect Modifiers

- **Effect modifiers** alter the effect of treatment relative to control

- **Prognostic variables** affect absolute outcomes but not the relative treatment effects
Prognostic Variable

Effect Modifier

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Background: Effect Modifiers

• Effect modifiers may also be prognostic
• We are only concerned with individual level effect modifiers
  • Not possible to adjust for study characteristics
• Effect modifiers must be prespecified
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: Target Population

• A decision has a pre-specified target population
  • e.g. UK population for NICE TA

• Methods for population adjustment produce estimates in a specific target population
  • This may not match the target population for the decision!
Background

Ideal scenario: full individual patient data (IPD)

- “Gold standard” – IPD meta-regression

AB trial: IPD

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

AC trial: IPD

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

Common scenario: limited IPD

• Several recent methods make use of mixed data
Population adjustment: MAIC

Matching-Adjusted Indirect Comparison

• Weight individuals in the AB trial to balance covariate distributions with the AC trial
• Take a weighted mean to estimate mean outcomes on A and B in the AC trial
• Similar idea to Propensity Score reweighting

Signorovitch et al. (2010)
Population adjustment: MAIC

- AB and AC population must have sufficient overlap
  - Compare covariate distributions, inclusion/exclusion criteria
  - Check distribution of weights
  - Compute Effective Sample Size (ESS) \( \approx \frac{(\sum w)^2}{\sum w^2} \)
- Traditional Propensity Score “balance checking” not necessary/possible
Population adjustment: STC

Simulated Treatment Comparison (STC)

• Create an outcome regression model in the AB trial
• Use this to predict mean outcomes on treatments A and B in the AC trial

Ishak et al. (2015)
Population adjustment: STC

- AB and AC population must have sufficient overlap
  - Avoid extrapolation
  - Compare covariate distributions, inclusion/exclusion criteria
- Use standard tools for model checking
  - AIC/DIC, examine residuals, ...
Population adjustment: MAIC and STC

• Extensive computation is not required

• Can be implemented in standard statistical software and routines (SAS, R, STATA, ...)
  • A worked example in R is available accompanying the TSD on the NICE DSU website
Population adjustment

Two possible forms of indirect comparison

Anchored

Unanchored
Population adjustment

Two possible forms of indirect comparison

Anchored

\[ B \text{ vs. } C = (C - A) - (B - A) \]

Unanchored

\[ B \text{ vs. } C = C - B \]

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

Some form of *constancy* assumption

- Constancy of relative effects
  - Relative A vs. B effect constant across studies
  - No EMs in imbalance
  - Used by standard indirect comparisons
- **Conditional** constancy of relative effects
- **Conditional** constancy of absolute effects
Assumptions and properties

Conditional constancy of relative effects

• Used by anchored population-adjusted indirect comparisons
• Requires all effect modifiers to be known
• Respects randomisation, prognostic variables are cancelled out
• A reasonable relaxation of constancy of relative effects
Assumptions and properties

**Conditional constancy of absolute effects**

- Used by *unchanched* population-adjusted indirect comparisons
- Requires all effect modifiers and prognostic variables to be known
- Ignores randomisation
- Widely regarded as *infeasible*
Assumptions and properties

Other assumptions:

- Studies are *internally valid*
- Lack of joint distribution leads to additional assumptions about correlations between covariates
Assumptions and properties

Both 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...
Shared Effect Modifier Assumption

- Satisfied by active treatments which:
  - Have the same set of effect modifiers
  - Change in treatment effect for each EM is the same for all treatments

- Likely to be valid for treatments in the same class
- If valid for treatments B and C then an estimate of B vs. C is valid for any population
Recommendations

Motivation of the recommendations

• Reproducibility, consistency, transparency
• Minimising bias and maximising precision
Recommendations

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

- Unanchored comparisons require much stronger assumptions, so anchored comparisons are always preferred
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.

• Applies to anchored comparisons
• Justification is necessary for moving away from standard methods
• Effect modification alters the decision scenario
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.

• Combine between-trial difference in EMs with knowledge of likely strength of interaction

• Judge possible 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.

• Applies to 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 5

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

- Better statistical properties
- Effect modification defined with respect to this scale
- Interpretability
  - Biologically and clinically, as well as statistically
- 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
Recommendation 7

• Reporting guidelines available in the TSD
• Largely correspond to recommendations 1-6, reporting the evidence and justification at each step
Thank you

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