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Aims
- Review the properties and assumptions of methods for population-adjusted treatment comparisons, including Matching-Adjusted Indirect Comparisons (MAIC) and Simulated Treatment Comparisons (STC).
- Provide guidance on their use in health technology appraisal.


Background
In SOTA submissions, a company wishes to compare their treatment with one of a comparator C. Standard indirect comparisons can only be used to assess evidence that is in fact different to effects modifiers between the population, and require a common comparator or control network — neither of which may exist.

Effect modification is present on a given scale, relative effects \( d_{BC} = \frac{\text{HR}_B}{\text{HR}_C} \) between treatments that are specific to a given population. Population adjustment methods seek to use available IPD to adjust for any between-trial differences, or even unconnected networks, under certain conditions (assumptions).

In a connected network with AC as a control, state of the art methods (e.g. MAIC) can be used with standardisation to produce a common comparator (Figure 2).

In a network where there isn’t a common comparator or there are single-study analysts, an unanchored comparison is the only option (Figure 4).

Methods for population adjustment
Population adjustment methods are focused on two types:
1. Propensity score methods that are Matching-Adjusted Indirect Comparisons (MAIC) and Simulated Treatment Comparisons (STC).
2. Outcome models which incorporate evidence from a common comparator network and use standardisation to produce a common comparator (e.g. MAIC).

Recommendations
The focus of the following recommendations is to establish clinical validity, transparency, and consistency in the use of population adjustment methods.

Recommendation 1
Population adjustment methods are focused on two types of evidence: unanchored and anchored.

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

Recommendation 2
Unanchored comparisons require all covariates to be adjusted for, as predictions of the treatment difference are irrelevant if they cannot be obtained for the correct target population.

Evidence and outcome models
- Propensity score methods, such as MAIC and STC, are not appropriate for population adjustment analysis.
- For a common indirect comparison, propensity score weighting methods should adjust for all effect modifiers (in imbalance or not), as well as prognostic variables. Outcome models should adjust for all effect modifiers in imbalance and any prognostic covariates and effect modifiers that impact model fit.
- For an unanchored comparison, propensity score weighting and outcome regression methods should adjust for all effect modifiers and prognostic variables, in order to reliably predict effect modification.

Recommendation 3
Indirect comparisons should be carried out on the linear scale, with the same link function that are usually specified for these outcomes.

Recommendation 4
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.

Population adjustment methods are only useful for making decisions if they can produce estimates for the appropriate target population, the shared effect modifier assumption may be required to allow a meaningful comparison.

Processes for population-adjusted indirect comparison
Anchored
1. Provide evidence for effect modifier cut-offs on a suitable transformed scale.
   - Propensity score reweighting
   - Outcome regression

2. Provide evidence that effect modifiers are in substantial imbalance between studies.
   - Propensity score methods such as MAIC and STC are not appropriate for population adjustment analysis.
   - For a common indirect comparison, propensity score weighting methods should adjust for all effect modifiers (in imbalance or not), as well as prognostic variables. Outcome models should adjust for all effect modifiers in imbalance and any prognostic covariates and effect modifiers that impact model fit.

3. Estimate the weights using the method of propensity scores to match effect modifier distributions between the studies.

4. Predict outcomes on treatments A and B in the AC trial using the outcome model.

5. From the anchored indirect comparisons in the AC population:
   - \( \hat{\delta}_{AC} = \hat{\beta}_{AC} \exp(x_{BA} \cdot \hat{\beta}_X) \)

6. Calculate standard errors using a robust standard error estimator, bootstrapping, or Reparameterisation technique.

7. If justified, use the shared effect modifier assumption to transport the \( \hat{\delta}_{AC} \) estimates into the target population for the decision. Otherwise, estimate the representation of the AC population on the target treatment network.

8. Present the distribution of estimated weights, and effect modifier estimates.

Unanchored
1. Fit an outcome model in the AC trial, which includes all effect modifiers and prognostic variables.
   - Linear with generalised linear models (GLM),effect modification is defined with respect to this outcome model.

2. Estimate the weights using the method of propensity scores to match effect modifier distributions between the studies.

3. Predict transformed outcomes on treatments A and B in the AC trial using the outcome model.

4. From the unanchored indirect comparisons in the AC population:
   - \( \hat{\delta}_{AC} = \exp(\hat{\beta}_{AC} \cdot x_{BA}) \)

5. Calculate standard errors using a robust standard error estimator, bootstrapping, or Reparameterisation technique.

6. Present the distribution of estimated weights, and effect modifier estimates.

References