Novel ITC and NMA methods for HTA submissions? Population adjustment

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Conflicts of interest

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Population adjustment methods

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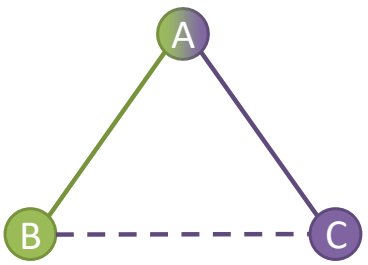
METHODOLOGICAL CHALLENGE: ANCHORED COMPARISONS

- Standard network meta-analysis (NMA) assumes that the distribution of effect modifiers is the same in all included trials.
- Often this is not the case, and we want to adjust for potential effect modifiers
- Ideally, we would have individual participant data (IPD) from all included trials, but this is rare in HTA

- Methods have been developed for one particular situation, common in HTA:
  - company has IPD for their own study (AB) but only aggregate data (AggD) for the comparator study(ies) (AC)



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Population adjustment methods

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EXISTING METHODS: MAIC, STC (SEE NICE DSU TSD 18)

Matching-**A**djusted **I**ndirect **C**omparison

- Population reweighting method
  - Weight AB individuals to balance covariate distribution with AC trial
  - Estimate outcomes on A and B in AC trial using weights
- AB and AC populations must have good overlap

  But if there is good overlap, population adjustment isn't needed!
- Signorovitch et al. (2010)

Simulated **T**reatment **C**omparison

- Create an outcome regression model in the AB trial to predict mean outcomes on treatments A and B in the AC trial
- AB and AC populations must have sufficient overlap to avoid extrapolation
- Not used as much as MAIC
- Caro and Ishak (2010)

- **Strong assumptions are made – see TSD18 for a review**
- **Obtain estimates in the AC ("competitor") population**
- **Only applicable to simple ITC setting (AB vs AC)**

https://www.sheffield.ac.uk/nice-dsu/tsds

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Challenges for HTA

- MAIC commonly used in HTA submissions when (suspected) effect modifiers are imbalanced across studies
- Presence of effect modifiers means **relative treatment effects vary** in different populations
  - need relative effect in **correct** (target) population for decision making
- MAIC creates artificial situation by forcing adjustment to aggregate data study
  - Results won't be valid for submitting manufacturer's trial population
  - Unlikely to be valid for the key population of interest for decision-making
- Only works in simple indirect comparison
  - What if more than one aggregate data study available?
  - What if larger network of evidence available?

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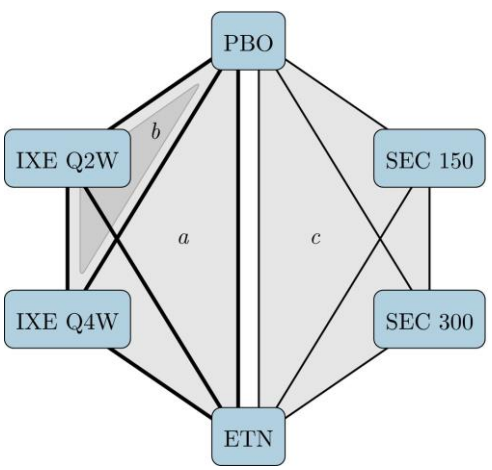
Example of HTA network

Treatments for moderate-to-severe plaque psoriasis compared with placebo over 12 weeks in four phase 3 trials.

PBO, placebo; IXE, ixekizumab; SEC, secukinumab; ETN, etanercept); IXE and SEC were each investigated with two different dosing regimens.

Thick lines indicate availability of IPD on a comparison; Thin lines indicate availability of aggregate data on a comparison.
Shading indicates comparisons made in 3 multi-arm trials (a, b, c)



In Phillippo et al 2020, https://doi.org/10.1111/rssa.12579

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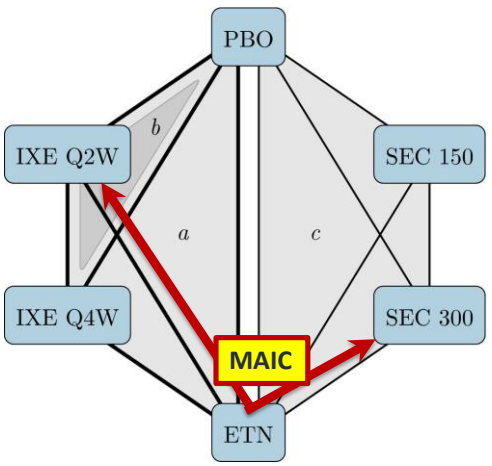
MAIC analysis previously carried out using only part of the available evidence…



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Multi-Level Network Meta-Regression (ML-NMR)

- Integration approximation method (*Phillippo et al* 2020, https://doi.org/10.1111/rssa.12579)
  - estimates relative treatment effects at two levels: the population level (target for inference) and the IPD level
  - Integrating over the covariate distributions gives estimates that are more precise than those obtained by STC (which adds additional uncertainty by simulation)
  - For non-collapsible measures (eg log odds ratios) correctly combines marginal and conditional effects (produces both marginal and conditional estimates)
- **Can provide estimates for any target population**
- Applicable to any connected network with any mixture of IPD and AggD
  - If IPD available for all studies, same as standard IPD meta-regression
  - If no effect modifiers adjusted for, reduces to standard NMA model
- R package using Stan available on CRAN: *multinma*
- Simulation study shows that it performs well (*Phillippo et al 2020* https://doi.org/10.1002/sim.8759)

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Network meta-interpolation

- Uses information on aggregate level relative treatment effects in sub-groups.
  https://doi.org/10.1002/jrsm.1608
  - E.g., trials report relative treatment effect in severe and non-severe subgroups
  - Estimates the relative treatment effect on the linear predictor scale in each trial that would be observed with any specified (target) proportion of severe patients.
- A standard NMA can then be run at the target values of the effect modifier.
- Can be extended to multiple sub-group dimensions
- Works at the level of population average conditional effects, does not estimate absolute average treatment effects in the target population.
  - Limited use in HTA.

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Consider options carefully…

- Is adjustment for population differences needed?
  - Is a simple indirect comparison or NMA suitable?
  - Is there really an important imbalance in effect modifiers?
- If effect modifiers are different in different studies, which study is most representative of the target population for decision?
  - HTA committees want representative measures
  - What do we know about effect modification? Often what modifies effects is not well understood…
  - Many discussions on how patients included in trials reflect clinical practice
  - What if patients are not comparable across trials? Which trial is most representative?
- Are we throwing away evidence? Is this desirable/defensible?

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Recommendations for practice

- All methods assume **all effect modifiers** are known and have been adjusted for
  - Unlikely to be true in practice and further limited by reporting for aggregate data studies
- All make additional assumptions – are these more acceptable than the usual assumptions of "sufficient homogeneity" of effects across studies?
  - Need to acknowledge limitations when using methods
- In the simple indirect comparison situation use STC or ML-NMR: performed similarly in simulation study; when larger networks use ML-NMR
- Be clear which is the **target population for decision**!
- **ML-NMR should be more commonly used in HTA practice**
  - Session 253: Time to Implement Multi-Level Network Meta-Regression (ML-NMR) Rather Than Matching-Adjusted Indirect Comparisons

    Tuesday 14th 17:00-18:00

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Population adjustment methods

METHODOLOGICAL CHALLENGE: UNANCHORED COMPARISONS

- Incorporation of evidence in disconnected networks or from single arm studies
- MAIC, STC proposed

  - NICE DSU TSD 18: overview of key issues – not an endorsement of the methods, highlights assumptions and minimum requirements for reporting
- Methods assume that **all effect modifiers and prognostic factors** are known, and adjusted for
  - Stronger assumption than in anchored comparisons
  - Impossible to verify even with lots of data
- Research underway for a possible extension of ML-NMR to this scenario
- Relates to methods for disconnected networks… next speaker

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Thank you

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