Conflicts of interest

I have no actual or potential conflicts of interest in relation to this presentation.

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Network meta-analysis in HTA submissions: methodological advances

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With thanks to: David Phillippo, Hugo Pedder

Context

METHODOLOGICAL ADVANCES

- Submissions to reimbursement authorities usually involve synthesis of the relevant evidence, often using indirect treatment comparisons or network meta-analysis methods
- Methods used should follow ‘best practice’ and agencies often provide guidance on this.
- But new methods or extensions to current methods appear all the time
  - Can be hard to know which methods are valid or will be accepted by agencies.

Methodological guidance

POLL

Do you support having methods guidance for evidence synthesis in HTA submissions?

- Yes
- No

Outline

REVIEW OF RECOMMENDATIONS

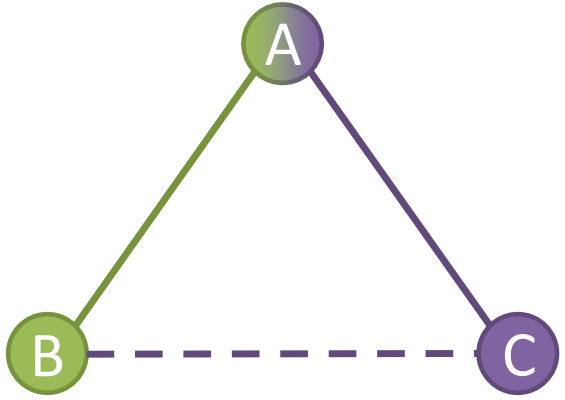
- **April 2020** NICE Decision support Unit: critical review of existing and emerging methods for evidence synthesis on clinical effectiveness for decision-making in HTA (http://nicedsu.org.uk/chte2020-sources-and-synthesis-of-evidence/)
- Provide some examples of recommendations
  - Population adjustment methods
    - Anchored and unanchored comparisons
  - Combining randomised and non-randomised evidence
  - Model-based NMA: time course and dose-response models (briefly)

Population adjustment methods

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)



Population adjustment methods

CURRENT METHODS: MAIC, 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
- AB and AC populations must have good overlap

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

Simulated Treatment Comparison

- 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, including that all effect modifiers adjusted for**
- **Obtain estimates in the AC ("competitor") population**
- **Only applicable to simple ITC setting (AB vs AC) – not to wider networks**

Population adjustment methods

METHODOLOGICAL CHALLENGE: UNANCHORED COMPARISONS

- Incorporation of evidence in disconnected networks or from single arm studies
- MAIC, STC proposed
- Issues outlined for anchored case also apply here

- In addition 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

Technical Support Document 18

METHODS GUIDANCE ON POPULATION ADJUSTMENT

- December 2016: NICE DSU Technical Support Document 18
  - Explained theory behind MAIC and STC methods
  - Made recommendations on the use of population-adjusted estimates in submissions to NICE – noted these were provisional as the properties of the methods not fully evaluated.
  - Proposed minimum requirements for reporting
- Highlighted several key limitations of these methods
- Not meant as an endorsement of the use of MAIC in HTA

  (STC used to a lesser extent)

Population adjustment methods

NEW METHOD: ML-NMR

Multi-**L**evel **N**etwork **M**eta-**R**egression*

- Integration approximation method
  - estimates relative treatment effects at two levels: the population level (which is the target for inference) and the IPD level
  - Integrating over the covariate distributions gives estimates that are more precise than those obtained by STC
- Can provide estimates for **any target population**, not just for AggD population
- Applicable to any connected network with any mixture of IPD and AggD
  - If IPD available for all studies → standard IPD meta-regression
  - If no effect modifiers adjusted for → standard NMA model
- R package using Stan available on CRAN: *multinma*

*Phillippo et al. (2020a) doi: 10.1111/rssa.12579

Population adjustment methods

DEVELOPMENTS FOR ANCHORED COMPARISONS

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 AggD studies
- All make additional assumptions
- Need to acknowledge limitations when using methods
- MAIC performed poorly in a simulation study*: move away from using this
- In the simple indirect comparison situation use STC or ML-NMR: performed similarly in simulation study*
- When larger networks available use ML-NMR
  - R package *multinma* includes extensive examples to facilitate use

*Phillippo et al. (2020b) https://doi.org/10.1002/sim.8759

Population adjustment methods

DEVELOPMENTS FOR UNANCHORED COMPARISONS

Recommendations for practice

- STC or ML-NMR may reduce bias in unanchored comparisons
  - but potential for bias cannot be eliminated without further comparative, randomised data
- STC/ML-NMR can be used to support decision-making but their limitations need to be acknowledged
  - estimate systematic bias using out-of-sample or in-sample methods
- Current research underway to identify how best to quantify the extent of error that is likely to be present in submissions based on these methods (funded by the MRC)
- **Unclear <u>when</u> or <u>if</u> methods should be used in HTA**

Combining randomised and non-randomised evidence

WHEN IS IT LIKELY TO BE USEFUL?

- When evidence from RCTs is sparse
  - Non-randomised evidence can be considered to increase precision of estimates
  - To connect otherwise disconnected networks
- Additional biases in observations evidence need to be taken into account
  - **Otherwise we weaken the evidence instead of strengthening it!**
  - This is the main area of methodological development, but still no consensus on which methods should be used
  - Research recommendations

Combining randomised and non-randomised evidence

Recommendations for practice

- Careful consideration of whether the observational data are sufficiently credible
- A bias-adjusted base-case should be used
  - other methods as sensitivity analyses
- Methods that attempt to down-weight and adjust the observational evidence prior to inclusion in the synthesis are preferred
  - hierarchical model, design-adjusted analysis
- Naïve pooling of randomised and non-randomised evidence is not recommended
  - may be useful as a first step analysis, or as a sensitivity analysis.

Model-based NMA

MBNMA*

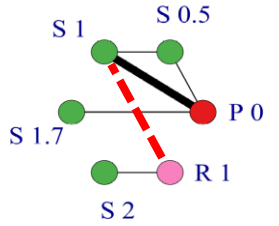
- Model-based meta-analysis (MBMA) used in drug development to inform decision-making and future trial designs
  - use of complex dose and/or time course models
  - Tends to be arm-based and not respect randomisation
- Model-based NMA combines MBMA with NMA
  - **respects randomization**
  - allows estimation and prediction for multiple time point or doses
  - using plausible physiological time-course or dose-response models.
  - Allows assessment of evidence consistency across comparisons
- R packages available on CRAN: *MBNMAtime*, *MBNMAdose*

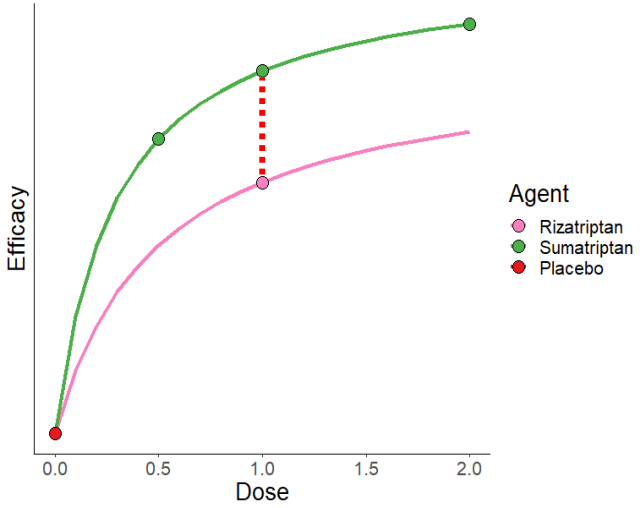
*Pedder et al. (2019) https://doi.org/10.1002/jrsm.1351; Mawdsley et al (2016) doi:10.1002/psp4.12091

Model-based NMA

CONNECTING NETWORKS*

- To date not used in NICE TA submissions (??)
  - respects randomisation in the original trials
- Can be used to connect networks using the assumed dose-response relationship
  - Estimates functional relationships for dose-response models (eg Emax model)
- Allows interpolation to predict outcomes for doses not in the original trials





*Pedder et al. (2021) doi:10.1177/0272989X20983315

Conclusion/Discussion

- Methodological development happening all the time
  - Refinements, improvements, new methods
- Hard to keep HTA guidance up to date
- Often methods motivated by real practical problems that occur in HTA
  - So could have immediate use but…
  - …how to be sure methods will be accepted if not explicit in guidance?

Thank you

 @sdias_stats

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