Basket Weaving: Challenges with evaluation of efficacy

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Basket trials in HTA: challenges

- HTA methods are set up based on the PICO framework
  - Population, Intervention, Comparator, Outcomes
- But appraisal of histology independent (tumour-agnostic) therapies do not fit with conventional definitions of
  - **Population:** usually defined as individuals with a particular tumour type → now multiple tumour types included
  - **Comparators:** not a single comparator for all included tumours → typically single arm trials conducted
  - **Outcomes:** often only surrogate outcomes such as response are reported → need survival endpoints

HTA: health technology assessment

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Population: multiple tumours

- Often population-defining mutations are rare, or occur mainly in rare cancers
  - Overall study size moderate, but few participants in each tumour site
- Can assume

1. HTA population is defined by this mutation
   - Assume effect homogeneous across tumour sites?
     - Reasonable for response?
     - Reasonable for survival outcomes given differences in prognosis?
   - Challenge selecting comparator arm → standard of care differs by tumour site
2. HTA population defined by tumour site
   - Multiple appraisals for same intervention in each different cancer site
   - Very small sample size

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Effects across tumour types

- Accepting target population of interest is defined by mutation

1. Take effect estimate from each cancer site separately → no pooling
   - Small sample sizes, large uncertainty
2. Assume effect the same regardless of tumour site → complete pooling
   - May not be reasonable
   - Ignores known clinical heterogeneity in tumour sites leading to potential heterogeneity in effects
3. Assume effects across cancer sites are similar, but not equal
   - A BHM assumes effects are exchangeable across cancer sites (i.e., come from a common distribution) → borrowing of information across histologies
   - "partial pooling" or middle-ground between complete pooling and no pooling
   - Allows prediction of effect in a tumour site with this mutation that has not yet been observed in a trial (tumour agnostic prediction)

BHM: Bayesian hierarchical model

https://doi.org/10.3310/hta25760
https://doi.org/10.1177/0272989X20980327

BHM: assumptions

- How much borrowing is reasonable?
- What additional evidence, clinical advice, and/or model diagnostics are needed to support assumptions?
  - Different levels of borrowing across histologies can be assumed
- Should we also borrow across other
  - Interventions? E.g., other drugs targeting same/similar mutations
  - Populations? E.g., adults and children
    - Potential for greater challenges in interventions for children's cancers

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Comparator effects?

- Target population of interest is defined by mutation (not histology/cancer site)
- But **standard of care** technologies will differ by histology
  - Have a basket of comparators?
  - Compare a pooled/average histology independent effect with separate comparators for each histology?
- Most basket trials run without a comparator arm
- Where will comparator evidence come from?

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Comparator evidence

- Comparator evidence for each histology from observational evidence or (historical) trials
- Access to individual participant data for comparator to allow for adjustment?
  - Often only published aggregate data available
- Relevant population?
  - Mutation status unknown for most individuals in comparator studies or RWE
  - Is presence of mutation prognostic of response and/or disease progression?
  - Is this the same for all histologies?
- Tumour site is typically prognostic of survival, does this also interact with mutation status?

RWE: real world evidence

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Challenge for HTA…

- Challenge at NICE for appraisal of Larotrectinib (TA630) and Entrectinib (TA644)
  - Use a blended comparator and calculate a single overall ICER?
  - Calculate an ICER for each histology then average?
- Which treatment effect to use:
  - Separate effect for each histology: small sample sizes, large uncertainty
  - Average effect from BHM: accounts for heterogeneity across histologies, borrows strength across histologies (increase in precision)
  - Are BHM assumptions acceptable? NICE committee thought they might be.

ICER: Incremental cost-effectiveness ratio

https://www.nice.org.uk/guidance/ta630/
https://www.nice.org.uk/guidance/ta644/

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Histology independent comparator

- NICE appraised Larotrectinib (TA630) and Entrectinib (TA644) separately against standard of care.
- **Are some problems minimised when comparing two active histology independent technologies?**
- Populations included in basket trials both have same mutation e.g., NTRK fusion
- Some **but not all** included tumour types will be common
  - Does this cause more problems?
  - Which assumptions are reasonable?
- Using assumptions of BHM, can we avoid some of the challenges in comparing to standard of care?

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Data requirements

- To compare two histology independent technologies, ideally we would have data from a randomised basket trial comparing technology A and B.
  - However, this type of trial is unlikely to be conducted
- In HTA the manufacturer submitting for access will have IPD for their own study
- But for comparator may only have
  - Aggregate published data from historical trials
    - Aggregated mean effect (complete pooling), by histology (no pooling) or average from a BHM?
    - Response or survival outcomes
  - RWE? If one technology in use for some time
- Methodological challenge… how to adjust for confounding to get best possible estimate of comparative effect?

IPD: Individual participant data

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Thank you

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