Methods for the assessment of the effectiveness of treatment sequences for clinical and economic decision making in the NHS

Lewis R1, Hughes DA1, Wilkinson C1, Woolacott N2, Ruiz F3, Williams NH1, Philips CJ4, Sutton A5

BACKGROUND: Treatment sequencing is the order in which interventions are administered within a treatment pathway. The effectiveness of treatments may differ according to their pharmacology and positioning in the pathway. Policy and clinical decisions based on the optimum sequence rather than the effectiveness or cost-effectiveness of individual treatments are becoming increasingly important, but it is both impractical and prohibitively costly to evaluate all conceivable treatment sequences in randomised controlled trials (RCTs). RCTs of individual treatments used at single points in the treatment pathway provide poor evidence on sequencing effects (FIG 1-3), and generally fail to consider the long term impact of multiple treatments. Alternative data sources are longitudinal studies based on patient registries, but these are subject to selection bias and confounding. Sequencing questions are frequently addressed using decision analytic modelling, which makes full use of the best available data, supplemented by judgements and assumptions where the evidence is absent. These are tested in sensitivity analyses.

OBJECTIVES: To assess existing methods of modelling treatment sequences and identify assumptions made in relation to treatment sequencing effects.

METHODS: A comprehensive literature review of MEDLINE, Embase and the Cochrane library, supplemented by Internet and hand searches. Due to scarce relevant indexing terms and no clear methodological taxonomies, a conventional systematic search was combined with a pragmatic and iterative process. Only studies that investigated the use of an active treatment after treatment failure were considered. Studies were categorised according to their overall modelling approach, decision problem, and assumptions used.

RESULTS: 86 relevant modelling studies were identified. Modelling approaches included decision trees, Markov cohort models, Individual-patient simulation (IPS) state transition models, and discrete event simulations (DES). Modelling approaches based on IPS, including DES, were used as they provide more flexibility than cohort based models, especially for handling patient histories, whilst cohort models were used as they benefit from being simpler and easier to implement. No study systematically tested different modelling approaches for sequences. Most studies applied simplifying assumptions to treatment effects obtained from RCTs of single treatments. These assumptions were generally not validated, or their impact assessed.

Simplifying assumptions used in modelling studies:
1. Treatment effect is independent of positioning in treatment sequence.
2. Treatment effect is dependent on the number of previous treatments used, but independent of the type of treatments used.
3. Treatment effect is the same as an alternative (substitute) treatment used at the same point in the sequence.
4. Treatment effect decreases by the same set amount at each point in the sequence (representing diminishing effect).
5. Treatment effect is reduced, in line with a reduction factor, when used at a later point in the sequence (treatment effect adjusted using a reduction factor).
6. Observational studies provide an un-biased estimate of treatment effect.

CONCLUSIONS: Considering the limited evidence base, it is unclear whether complex modelling is required or the more commonly used Markov cohort structure would suffice. The impact of using simplifying assumptions to represent sequencing effects is increased uncertainty around the effectiveness and cost-effectiveness of treatments, the extent of which is unknown. There needs to be greater recognition of this in decision making with further research needed to evaluate it.

Contact: Ruth Lewis r.lewis@bangor.ac.uk

Acknowledgements: The research was funded by an NIHR Doctorate fellowship supported by the Welsh Assembly Government