NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Briefing paper for methods review working party on treatment sequences and downstream costs

The briefing paper is intended to provide a brief summary of the issues that are proposed for discussion by the Methods Review Working Party to inform an update to the Institute's Guide to Methods of Technology Appraisal. It is not intended to reflect a comprehensive or systematic review of the literature. The views presented in this paper are those of the authors and do not reflect the views of the Institute.

1 Review of the 'Guide to Methods of Technology Appraisal'

The Institute is reviewing the 'Guide to the methods of technology appraisal', which underpins the technology appraisal programme.

The original Methods Guide was published in February 2001, and revised versions were published in 2004 and 2008. The Methods Guide provides an overview of the principles and methods used by the Institute in assessing health technologies. It is a guide for all organisations considering submitting evidence to the technology appraisal programme and describes appraisal methodology.

The revised draft of the Methods Guide will be available for a 3-month public consultation, expected to begin in June 2012. We encourage all interested parties to take part in this consultation.

2 Background

2.1 Relevance of topic to NICE technology appraisals

In some technology appraisals, a new intervention may be positioned at several points in an existing sequence of treatments. As such, the comparison in the economic evaluation can be between alternative sequences of treatments, rather than a head to head comparison between the intervention and a specific comparator treatment. Rather than **X** (new treatment) vs A vs B (comparators), the evaluation may be (**X**,A,B)[*] vs (A,**X**,B) vs (A,B,**X**), which is equivalent to evaluating **X** at 1st, 2nd or 3rd line. Due to the impact that a treatment may have on the long run costs and benefits accrued, and potentially whether a patient progresses to subsequent treatments in a sequence, a lifetime perspective is required, and therefore the economic analyses have attempted to model the possible alternative sequences.

This is particularly common in technology appraisals of chronic conditions (for example rheumatoid arthritis). In such appraisals, it has been necessary for sequences of 5 of more treatments to be modelled and compared with each other. In fact, this only represents a small proportion of the overall potential sequences of rheumatoid arthritis therapies. The selection of the alternative sequences, and the assumptions and evidence used to model the sequences can have a substantial impact on the incremental cost effectiveness of competing decision alternatives.

The current methods guide highlights that the "...*main technology of interest, its expected place in the pathway of care, the comparator(s) and the relevant patient group(s) will be defined in the scope developed by the Institute"* (5.2.6). Also *"…many technologies have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic diseases. In such instances, a lifetime time horizon for clinical and cost effectiveness is appropriate"* (5.2.14). It is specific when stating; *"Sometimes both technology and comparator form part of a treatment sequence, in which*

[*] For clarity, a sequence of treatments is presented within parentheses. The order in the parentheses represents their order in the sequence. A treatment in bold represents an addition into the sequence

case the appraisal may need to compare alternative treatment sequences" (2.2.4).

Therefore, the Methods Guide suggests that the modelling of sequences of therapies should be considered if the scope defines alternative possible positions of the new technology. However the Methods Guide does not at present provide specific guidance with respect to modelling sequences of treatments.

A second, related problem arises when standard NHS care given either alongside or after the treatment of interest has been given, is very costly and/or not very effective. In this situation, the effect of a significant proportion of the modelled cohort surviving long enough to receive these downstream treatments may make a new, effective intervention appear cost ineffective, purely because it increases the opportunity to receive subsequent cost ineffective treatments. This situation is challenging for the Appraisal Committee, with new interventions that do extend survival appearing cost ineffective purely because of the downstream treatments. This situation can be deconstructed into two components. Firstly, whether direct costs (related to the primary condition) and/or indirect costs (unrelated to the primary condition) should be included in the economic evaluation. In particular, whether these costs should be included if they occur in additional life-years gained as a result of the intervention. Secondly, how can the impact of the inclusion or exclusion of these costs be made transparent, to aid the Committee when these challenging situations occur?

The Methods Guide's principal comment on this issue is in its recommendation for a life-long time horizon (5.2.14). It does suggest alternative scenarios for extrapolation beyond trial data, but it does not provide specific guidance on how to compare alternative scenarios with respect to downstream treatment possibilities.

2.2 Introduction to modelling treatment sequences

There are a number of issues that surround modelling sequences of treatments within the context of a NICE Technology Appraisal.

Firstly, the order in which the treatments are given within the sequences may have an impact on the effectiveness and the costs of the technologies. If the sequence (A,B) is identical to A and B in isolation, then what is inferred is that the costs and effects are not influenced by the position in the sequence, and therefore the sequence should begin with the most cost effective treatment.

However, it is often the case that the sequence as a whole must be considered, because it is not the case that the cheapest or most cost effective in isolation necessarily comes first in the most cost effective sequence. The position in a sequence may have an influence on factors that affect cost effectiveness (e.g. shorter duration on treatment, a lower chance of response).

A second important issue that can occur is that limited possible treatment sequences are modelled and the new intervention is added to the original treatment sequence. For example, an existing treatment sequence of 3 technologies (A,B,C) exists for a condition, and a new intervention technology **X** is modelled at the beginning of the treatment sequence compared with the original treatment sequence (**X**,A,B,C). In this example, the addition of the new technology to the start of the treatment sequence raises questions. Firstly, will a treatment 'drop out' of the sequence if **X** was recommended at first line? Secondly, does (A,B,C) represent the full treatment sequence that is routinely delivered in the NHS? Is (A,B,C) more complicated, because in fact NICE guidance allows for conditional sequences (e.g. first line options (A or B), second line options (C, or if B at first line then A)).

If a complex conditional (set of) sequence(s) has emerged as standard practice in the NHS, then the question arises as to whether the appraisal of the new technology should look to identify the 'optimal' sequence of treatments and use this as the comparator. If previous NICE guidance has recommended treatment options that would no longer be cost effective in comparison with the new technology (perhaps dominated by it), then a review of all treatments using the multiple technology appraisal process would be required to update the previous guidance. An MTA review of all treatments may require a factorial set of sequences to be modelled and evaluated, which

despite representing a computationally and empirically challenging task, may allow the optimal sequence of treatments to be identified.

Hypothetical example

Existing NICE Guidance recommends:

First line: A or B or C
Second line: D or E or F

All (9) possible sequences have slightly different estimates of costs and QALYs. The sequence (A,D) has been identified as optimal, and it is more effective and less costly than (C,F).

The question is, when evaluating **X** as a new treatment, should it be recommended if it improves the optimal sequence (A,D), and offers a positive net gain to the NHS, or should it be recommended because it can improve the sequence (C,F), but the new sequence is not optimal compared to (A,D).

If the latter, this would mean that the NHS has not gained by recommending **X**, and in reality it is unlikely that **X** will see uptake in the NHS or capture any market share. **X** may represent a 'me too' product, or may have other attributes of value for specific groups of patients.

Finally, it is unlikely to be sufficient to model the new intervention at only one point of the treatment sequence if the marketing authorisation permits its use elsewhere in the sequence (for example [A,**X**,B,C] or [A,B,**X**,C] may be potential options to be modelled). In fact, a manufacturer may only present one position of their treatment (perhaps the position that would capture the greatest market share), whereas the treatments' optimal position (from an NHS perspective) may be at a later point in the sequence, which represents a less desirable position for the manufacturer.

Related to the example above, if there are a number of technologies included in the sequences, it can become increasingly challenging to know what the true treatment effects are likely to be for every technology in every position in

the sequence. For example, if treatments have been studied in clinical trials as first-line treatments, but then are placed second or third-line in a sequence, the efficacy of these treatments in the sequence may be very different from that observed in the trial. The corollary is that, as seen frequently with modelling treatment sequences, there is a danger that what is modelled has moved dramatically from the available trial evidence. It could be argued that validation of trial evidence, by the use of expert opinion or other external data, may help ensure that modelled treatment effects appropriate reflect reality. In particular, treatment effect decrements have been used in NICE appraisals, which suggest that a treatment's effectiveness 'down the line' is diminished. These decrements could potentially be informed by external data, such as registries, or expert opinion; however they would be open to potential bias. Observational studies could potentially be used to estimate treatment effects, although the limitations of this approach have been widely discussed.

2.3 Related and unrelated downstream costs

Another problem occurs when the costs and effects of cost ineffective downstream treatments are included within the calculations of cost effectiveness of a new technology. This situation is most common in appraisals of technologies that are life-extending, for example, technologies that prolong life in terminal diseases such as cancer. For example, consider a technology that extends life by approximately 3 years, the treatment (and therefore treatment costs) are incurred for a short proportion of this time, say 3 months. The rest of the increased survival is associated with additional treatment costs that are a result of living with the condition (such as monitoring, palliation and so on). In this case, downstream but related (to the original condition) costs have been included. The effect of including these downstream related treatment costs can result in very high cost effectiveness ratios for the new technology compared with standard NHS care, simply because the new technology increases survival such that more time is spent in the expensive treatment state.

The Methods Guide makes no explicit comment regarding which (related or unrelated) future health care costs should be included in the economic

analysis. Costs could be related or unrelated to the condition for which the treatment was provided, and could be specific to time that would have been lived anyway, or specific to time that has been gained as a result of the treatment being appraised. This issue has been raised in previous literature (Meltzer, 1997), and as part of a briefing paper for the last update of the Methods Guide (Miners, 2007). As Miners states; *"is it possible to establish whether a tumour that develops 10 years after radiotherapy, but in a different location to the original tumour, is related or unrelated to the index tumour or radiotherapy?"*

Future related health costs are likely to be a necessity, in that the initiation of a treatment reflects a decision about a course of action for the patients' condition, and therefore an evaluation of its cost effectiveness should include health costs attributed by that treatment on the condition. However it may lead to age-discrimination, and would be contrary to current NICE methods that prioritise treatments that offer life extension at the end of life.

Gold (1997) provide a useful taxonomy of induced costs in cost effectiveness analyses (see Table 1).

The identification of future health care treatments which are cost ineffective may provide a disinvestment opportunity for the NHS, and offer a clear representation of 'the margin', from which cost effectiveness analyses have emerged. However it may be that these apparently cost ineffective treatments have attributes for which society may potentially be willing to pay for (end of life therapy, rule of rescue).

Table 1: Gold et al. Future costs (table derived from p.47)

Category	Sub-category	Details	Considerations for NICE
Costs **related** to the intervention, incurred during years of life that would have been lived without the intervention	-	These include related diseases in the original lifespan, and adverse events.	These costs are routinely included in NICE appraisals where a life-long time horizon is required.
Costs **unrelated** to the intervention, incurred during years of life that would have been lived without the intervention		By definition these are costs that are the same irrespective of the intervention, and so will be cancelled out in the analysis.	Because these costs would cancel out in an analysis, is it not necessary for NICE to require these costs to be included.
Costs that incur in years of life **added** (or subtracted) by an intervention	Health care costs related to the primary disease	Health care costs which occur after the initial treatment, and extend into the years of life added (or subtracted) by the intervention.	Downstream treatments and activities may not be cost effective, and may be provided due to other attributes. These may 'wash out' the cost effectiveness of the initial treatment.
	Health care costs for other diseases	Costs for diseases unrelated to the intervention and occurring in added years of life.	If interventions are compared across different age groups and these costs are included, the ranking of cost effectiveness will alter from the same set but with these costs excluded.
	Non health care costs	Relates to the perspective of the overall analysis.	Should be considered alongside any alteration in the perspective of NICE's decision-making.

2.4 What the current Methods Guide advises with respect to treatment sequences and downstream costs

The Methods Guide provides the following statements regarding sequences and future health care costs:

The time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect all important differences in costs or outcomes between technologies being compared (section 5.2.13)

Many technologies have impacts on costs and outcomes over a patient's lifetime. This is particularly the case with treatments for chronic diseases. In such instances, a lifetime time horizon for clinical and cost effectiveness is appropriate (5.2.14).

Sometimes both technology and comparator form part of a treatment sequence, in which case the appraisal may need to compare alternative treatment sequences (2.2.4).

There is limited discussion of modelling treatment sequences in the 2008 Methods Guide. It is acknowledged as a possibility in Section 2.2.4, but no further guidance on when and how treatment sequences should be modelled is provided.

3 Proposed issues for discussion

After consideration of the developments in this methodological area, the current Methods Guide and the requirements of the Institute's Technology Appraisal Programme, it is proposed that the following key questions are discussed by the Methods Guide Review Working Party.

- Under what circumstances is it acceptable to model only individual lines of therapy, rather than treatment sequences? Should downstream treatments be assumed to incur the same cost between groups?

- Should future health care costs **related** to the primary disease which are incurred due to life extension be included in the economic analysis?

- Should future health care costs **unrelated** to the primary disease which are incurred due to life extension be included in the economic analysis?

What could be the impact of providing further direction on when the modelling of treatment sequences is appropriate?

- How can the methods guide ensure that modelling of treatment sequences is undertaken consistently across appraisals?

- Should explicit guidance on aspects of modelling treatment sequences be given?

    - When and how should sequences be identified? Which should be modelled?

    - What effectiveness estimates and model parameters can be reasonably used when a treatment is included in different places in different sequences?

    - What level of primary and sensitivity analyses should be reasonably expected?

What could be the possible consequences of including further guidance in the methods guide on exactly how downstream costs should be modelled?

- What can be done in the situation where a cost ineffective treatment is given either in combination with an intervention, or given after an intervention, such that it results in the intervention itself appearing cost-ineffective?

    - Should downstream treatments that are cost ineffective be included for the primary analysis, or just limited to a secondary analysis?

- Should a head-to-head comparison of the technologies of interest (i.e. with no downstream treatments included) be requested?

What are the potential consequences of recognising this issue in the methods guide and providing guidance on how it could be approached?

4 References

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