ASSESSING TECHNOLOGIES THAT ARE NOT COST-EFFECTIVE
AT A ZERO PRICE

REPORT BY THE DECISION SUPPORT UNIT

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ABOUT THE DECISION SUPPORT UNIT

The Decision Support Unit (DSU) is a collaboration between the Universities of Sheffield, York and Leicester. We also have members at the University of Bristol, London School of Hygiene and Tropical Medicine and Brunel University. The DSU is commissioned by The National Institute for Health and Care Excellence (NICE) to provide a research and training resource to support the Institute's Technology Appraisal Programme. Please see our website for further information www.nicedsu.org.uk

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EXECUTIVE SUMMARY

There are several scenarios under which clinically effective technologies may be found not to be cost-effective even if they are zero priced. There may be costs associated with delivering the technology which remain even when the price is reduced to zero and these costs alone may outweigh the health benefits achieved. But even in the situation where a clinically effective technology can be acquired and delivered for zero cost, there are scenarios in which that technology may fail to demonstrate cost-effectiveness because it increases other aspects of resource use. We have described four related but different scenarios in which clinically effective treatments result in additional time being spent in health states with high resource use and/or low health-related quality of life either during or after the treatment period. We have also examined case studies identified from the National Institute for Health and Care Excellence’s (NICE’s) previous appraisals to determine if the factors illustrated in these scenarios are present and whether they contributed to the conclusion that a technology was not cost-effective even when it was zero priced. We found examples of three of the four scenarios within the case studies we examined and in some cases these factors contributed to the conclusions that the technology being appraised would not be cost-effective even if it were zero priced.

The NICE methods guide states that costs which are considered to be unrelated to the technology or condition of interest may be excluded from the cost-effectiveness analysis. We have reviewed the methodological literature around the exclusion of unrelated costs from cost-effectiveness analyses to determine whether there is a case for excluding some of the costs incurred in periods of additional survival in the case studies we identified. In the majority of the case studies, the costs incurred during periods of additional survival were related to either the technology being appraised or the condition the technology was intending to treat. These cannot therefore be considered to be unrelated costs. In one case study which examined a treatment in patients with end-stage renal disease requiring dialysis, the decision about whether to consider the dialysis costs to be related or unrelated seemed to be dependent on whether the condition of interest was end-stage renal disease or the particular complication of end-stage renal disease that the technology is indicated to treat. Given the fairly arbitrary judgement this requires and the fact that there is still a real opportunity cost to patients elsewhere within the NHS of extending dialysis treatment, an alternative would be to include all related and unrelated costs within the cost-effectiveness analysis. This would
allow an ICER to be constructed which is both internally consistent, in its approach to costs and benefits, and externally consistent with the decision makers remit of allocating healthcare budgets to increase population health gain, as described in the methodological literature we reviewed.

We acknowledge that new technologies that are administered in combination with existing treatments may struggle to demonstrate cost-effectiveness if those existing treatments are themselves not cost-effective or if their cost-effectiveness falls very close to NICE’s threshold. In some cases a new technology may only be cost-effective at a positive price if discounts are offered on other technologies which are given alongside the new technology. Whilst this may be perceived as a disincentive for investment in new technologies in diseases where there are existing high cost therapies, the cost-effectiveness of the new technology will improve when lower cost generic / biosimilar formulations of existing therapies become available. It might also increase the incentive to develop technologies which provide a more effective alternative to existing therapies instead of technologies which further add to the treatment burden by being administered alongside existing therapies. There is also an incentive here for NICE to ensure that it does not recommend technologies with poor or marginal cost-effectiveness since if these are incorporated into standard care any future technology which prolongs the duration of standard care may fail to demonstrate cost-effectiveness. In some situations it may also be worth exploring whether there is a case for disinvesting from existing treatments that form part of standard care particularly if those existing treatments have not been previously appraised by NICE or if the benefits estimated at the time of appraisal have not been realised.

Whilst we have mainly focused on the issues related to costs incurred in added life years it is also important to consider if the benefits have been properly accounted for in the cost-effectiveness model. Consideration should be given to whether all of the health benefits occurring during periods of high resource usage have been properly accounted for, particularly for interventions such as palliative care where there may be benefits falling on carers in addition to patients or where benefits which may not properly captured by generic quality of life measures. It is also worth considering whether there may be some treatments, such as dialysis and palliative care, which society may consider worthwhile despite their poor cost-effectiveness and whether the value placed on these treatments by society may not be fully captured by the health benefits accrued by either the patients themselves or their carers.
If those wider societal benefits cannot be quantified, then excluding the cost of treatment, whilst including any health gains would provide a lower bound on the incremental cost-effectiveness ratio (ICER).

In addition we discuss how treatments which are cost-effective in the general population may not be cost-effective in particular groups of patients with high background care costs. The Institute’s existing ‘Social Value Judgements’ policy would preclude separate recommendations being made for patients with different characteristics if the differences in the recommendations are based solely on differences in the background care costs. Even in cases where there are high background care costs across the whole population specified in the scope of the appraisal, it may still be important for the Committee to consider whether there are any legal or ethical reasons for recommending the treatment, including the need to distribute health resources in the fairest way in society as a whole.
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<td>ACD</td>
<td>Appraisal consultation document</td>
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<td>BSC</td>
<td>Best supportive care</td>
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<td>DSU</td>
<td>Decision Support Unit</td>
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<td>EDT</td>
<td>Early disease time</td>
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<td>ERG</td>
<td>Evidence Review Group</td>
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<td>ESRD</td>
<td>End-stage renal disease</td>
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<td>FAD</td>
<td>Final appraisal document</td>
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<tr>
<td>FOLFOX</td>
<td>Oxaliplatin plus Fluorouracil plus folic acid</td>
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<td>HER2+</td>
<td>Human epidermal growth factor 2 positive</td>
</tr>
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<td>HPV</td>
<td>Human papillomavirus</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>HRQoL</td>
<td>Health-related quality of life</td>
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<td>ICER</td>
<td>Incremental cost-effectiveness ratio</td>
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<td>Life-years</td>
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<td>MS</td>
<td>Manufacturer submission</td>
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<td>MTA</td>
<td>Multiple technology appraisal</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NICE</td>
<td>National Institute for Health and Care Excellence</td>
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<td>PC</td>
<td>Palliative care</td>
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<td>PFS</td>
<td>Progression-free survival</td>
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<td>PPS</td>
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<td>QALY</td>
<td>Quality-adjusted life-year</td>
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<td>SHPT</td>
<td>Secondary hyperparathyroidism</td>
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<td>SPC</td>
<td>Summary of product characteristics</td>
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<tr>
<td>STA</td>
<td>Single technology appraisal</td>
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<tr>
<td>TA</td>
<td>Technology appraisal</td>
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<td>TAG</td>
<td>Technology assessment group</td>
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<td>XELOX</td>
<td>Oxaliplatin plus capecitabine</td>
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1. INTRODUCTION

In a recent National Institute for Health and Care Excellence (NICE) appraisal of a new drug (pertuzumab) in metastatic breast cancer the appraisal consultation document (ACD) concluded that pertuzumab, when used in accordance with its licensed indication, did not represent a cost-effective use of NHS resources. The manufacturer had indicated in their comments on the ACD that when using plausible assumptions (those preferred by the evidence review group) there was no price at which pertuzumab would be cost-effective (it was not cost-effective at zero price). The issue driving this relatively high incremental cost-effectiveness ratio (ICER) appeared to be that the drug was given in combination with another drug (also the comparator) and any additional progression-free survival (PFS) was accompanied by the costs of both pertuzumab and the comparator drug. In view of the fact that the technology was associated with substantial benefits in terms of both progression-free and overall survival, the Institute’s Guidance Executive decided not to issue the Final Appraisal Documents (FAD) pending further exploration of the issue.

The Decision Support Unit (DSU) was asked to explore the circumstances in which clinically effective technologies are not cost-effective even at a zero price. In the light of this exploration, the DSU was asked to consider the usual rules for assessing cost-effectiveness and their appropriateness or otherwise in these circumstances.

This review

The DSU was asked to consider real and/or hypothetical examples in which a technology is not cost-effective at zero price and to describe the factors that contribute to this. The DSU was also asked to consider whether, in relation to these situations, there are circumstances in which it might be justifiable to depart from the usual range of acceptable ICERs, or otherwise adapt the methods of assessing cost-effectiveness. The DSU was asked to address these issues through;

1. A review of previous NICE appraisals where technologies have been found to be not cost-effective at zero price and consideration of the factors that contributed to this.
2. A consideration of those situations where similar factors are likely to also occur.
3. A literature search for any previous discussion of this issue in the health economic literature.
4. A discussion of any alternative approaches to assessing the cost-effectiveness of clinically effective technologies that are not cost-effective at any positive price.

2. DESCRIPTION OF GENERALISED SCENARIOS

There are several ways in which a new technology which is clinically effective may fail to demonstrate cost-effectiveness even when it is zero priced. Firstly whilst the technology itself may be acquired at zero cost, there may be costs incurred for administering the intervention, such as outpatient or day case procedure costs. There may also be specific investigations required to assess eligibility for treatment or to monitor the patient following treatment. These additional costs associated with delivering the technology must be offset by sufficient quality-adjusted life-year (QALY) gains if the technology is to be deemed cost-effective.

Secondly, for a drug to be clinically effective, it must result in additional QALYS being gained either by improving overall survival and / or by allowing a greater proportion of the patient’s life-expectancy to be spent in a health state with better health-related quality of life (HRQoL). Whilst both of these will improve the patient’s life-time QALY profile, they may also have an impact on health resource use. We illustrate four such scenarios below.

Scenario 1

For patients with on-going healthcare needs, additional survival may be associated with additional resource use. In patients with high resource use and / or low HRQoL, the cost of additional resource incurred during the additional life-years gained may outweigh the QALYs gained during the period of additional survival. In these circumstances, clinically effective treatments which increase survival may not be cost-effective.
Figure 1: Additional survival results in the existing standard of care being provided for longer

<table>
<thead>
<tr>
<th>Intervention (Drug A + BSC)</th>
<th>Comparator (BSC)</th>
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<tr>
<td>Drug Cost&lt;sub&gt;A&lt;/sub&gt;</td>
<td>BSC_cost</td>
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<td>BSC_cost</td>
<td>ΔBSC_cost</td>
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<tr>
<td>Time, years</td>
<td>Time, years</td>
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<td>ΔLYs</td>
<td>ΔLYs</td>
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<td>QALY</td>
<td>QALY</td>
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<tr>
<td>Time, years</td>
<td>Time, years</td>
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Figure 1 illustrates this for the case where Drug A is given in addition to best supportive care (BSC) resulting in an increase of life expectancy (ΔLYs) and a QALY gain (ΔQALY).

In the general case Drug A will not be cost-effective if;

\[
\lambda \times ΔQALY - (\text{Drug Cost}_A + \Delta BSC \_cost) < 0
\]

where \( \lambda \) is the cost-effectiveness threshold being applied by the decision maker.

However, in the case where Drug A can be purchased (and administered) for no additional cost, it is still possible that Drug A will not be cost-effective if;

\[
\lambda \times ΔQALY < \Delta BSC \_cost
\]

or alternatively if we prefer to think in terms of annualized costs and utility values which are constant during the period of additional survival then this expression reduces to;

\[
\lambda \times \frac{ΔQALY}{ΔLYs} < \frac{\Delta BSC \_cost}{ΔLYs}
\]

\[
\lambda \times \text{Utility} < \text{Annualized BSC cost}
\]
We can conclude from this that drugs which increase survival in patients with high ongoing care costs and/or a low HRQoL may fail to demonstrate cost-effectiveness even if they can be acquired and administered at zero cost.

**Scenario 2**

It is often the case that health states with better HRQoL are associated with lower healthcare costs and therefore clinically effective treatments which delay the onset of more severe health states are often cost saving. However, if transition to a worse disease state results in the patient discontinuing high cost treatments then delaying the on-set of more severe disease may increase the patient’s life-time resource use. In this case, then the QALY gains of delaying progression to the more severe health state may not outweigh the additional resource use of increased stay in the less severe state.

*Figure 2: Increased time spent in early disease state results in additional time on intensive treatment regimen*
Figure 2 illustrates a situation where a new technology, Drug A, is given alongside the current standard of care, Drug B, for the duration of the early disease state with the comparator being current standard care (Drug B) alone. The new technology results in additional time ($\Delta\text{EDT}$) being spent in the early disease health state and treatment with Drug A and Drug B is continued for the duration of early disease. All costs and QALYs accrued after progression to the late disease state are assumed equal between the new technology and the current standard of care and therefore are not included in Figure 2. We can see from Figure 2 that there are two types of additional costs for the new technology; those that relate directly to the drug and administration costs for technology A, and those that relate to the increased usage of B. Even if Drug A can be acquired and administered at zero cost, the net benefit (NB) for intervention compared to comparator would be:

$$\text{NB} = (\lambda \times \Delta\text{QALY}) - (\Delta\text{Admin}_B + \Delta\text{Drug}_{\text{Cost}B})$$

Therefore it may not cost-effective to add Drug A to standard care even if it can be acquired and administered at zero cost, if the costs of delivering standard care outweigh the benefits of adding A to standard care.

**Scenario 3**

**Figure 3 Increased time spent in a later disease state with additional healthcare needs**
Figure 3 illustrates a third scenario where a new technology may not be cost-effective even when it can be acquired and administered at zero cost. In this scenario the intervention results in additional survival but that increased time is being spent in a late disease health state which has high costs and low HRQoL. The costs have been separated here into best supportive care (BSC), and palliative care (PC). We have assumed that the level of resource use for best supportive care is not increased after moving to the late disease state (i.e \( \text{BSC\_cost}_1 = \text{BSC\_cost}_2 \)) and all additional costs are captured under palliative care (PC\_cost\_2) which only occurs in the late disease state. If all other costs (i.e drug and administrative costs) are assumed equal between the intervention and comparator strategies, then the cost-effectiveness is determined by comparing the net benefit realized from the additional QALY gain against the additional best supportive care and palliative care cost, ie.

\[
\text{NB} = \lambda \times \Delta \text{QALY} - (\Delta \text{BSC\_cost}_2 + \Delta \text{PC\_cost}_2)
\]

From this we can see that if either category of cost is sufficiently high relative to the utility of the late disease state it will result in a negative net benefit. If the palliative care costs are set to zero then we have a scenario which is similar to that illustrated in Figure 1, where it is the continuation of current treatments within the period of additional survival which adversely affect the cost-effectiveness of a life-prolonging intervention. However, if the best supportive care costs are set to zero then we have a new situation where it is the addition of new treatments during the period of additional survival which adversely affect the cost-effectiveness of the life-prolonging intervention.

**Summary of Scenarios 1 to 3**

In all of the scenarios illustrated above, it is the balance between the costs incurred and QALYs gained for the health state in which the additional survival is being spent that determines whether the additional survival has a positive or negative net benefit. If new technologies are given alongside existing technologies which are not themselves cost-effective, or if the benefits of healthcare given later in the disease care pathway do not outweigh the costs of that later care, then this may mean that the new technology may fail to demonstrate cost-effectiveness even if it can be acquired and administered at zero cost.
**Scenario 4**

A final scenario is illustrated in Figure 4. Here the drug under appraisal (Drug A) increases life-expectancy, but in the period of additional survival the patient goes on to have a high cost event which is not experienced in the comparator arm. Even if Drug A can be obtained at zero cost, it may fail to demonstrate cost-effectiveness if the cost of treating the later event is sufficiently high and outweighs the additional QALYs gained in the years of additional survival. The distinction being drawn between this scenario and the ones illustrated above is that the event may be related to the disease being treated by Drug A or it may be due to a completely unrelated disease. In the latter case, the only relationship between the administration of Drug A and the high cost event is that Drug A increases the duration of survival thereby increasing the patient’s chance of experiencing the high cost event during their lifetime.

**Figure 4: Patient survives longer but experiences a high cost event later in life**
3. CASE STUDIES FROM PREVIOUS NICE APPRAISALS

Section 3 examines case studies identified from previous NICE appraisals which have been selected because they share some characteristics with the general scenarios described in Section 2. These examples were identified using the authors’ knowledge of previous NICE appraisals and on advice from the NICE Technical Team. A systematic search through previous TAs to identify all relevant case studies was not conducted. In some cases, such as in the pertuzumab example mentioned in the introduction, explicit statements were made during the appraisal regarding the likely cost-effectiveness when assuming a zero price, whilst in other cases this issue was not explicitly raised during the appraisal.

The descriptions of the case studies provided below are based on the relevant evidence review group (ERG) reports and manufacturer submissions (MS) for those appraisals without access to any of the executable models described within those documents.

3.1. Cinacalcet in end-stage renal disease

Cinacalcet is licensed for the treatment of secondary hyperparathyroidism (SHPT) in patients with end-stage renal disease (ESRD) on maintenance dialysis therapy.³ Almost all people with ESRD have SHPT.³ Dialysis therapy is a high cost medical intervention. The technology assessment group (TAG) for the TA of cinacalcet (TA117) estimated the average cost of dialysis to be £15,643 (Table 105 of HTA report).⁴ The highest utility value applied to patients in the TAG cost-effectiveness model was 0.6735 (Table 76 of the HTA report).⁴ The ratio of costs and benefits for additional time spent on dialysis would therefore be in excess of £20,000 per QALY when excluding all other healthcare costs associated with the management of ESRD. Therefore a life-extending treatment in this patient population may fail to demonstrate cost-effectiveness, at a £20,000 per QALY threshold, unless it also demonstrates a substantial improvement in quality of life or results in substantial cost savings compared to the current standard care of care. This is an example of the scenario illustrated in Figure 1, where the dialysis costs represent the costs of best supportive care in this population.
3.2. Pertuzumab

Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with Human epidermal growth factor 2 (HER2)-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.\(^5\) The ERG report for the NICE appraisal of pertuzumab states that the addition of pertuzumab to the treatment regimen of trastuzumab and docetaxel in this patient population provides improved PFS.\(^6\) At the first data cut (median follow-up of 19 months) there was a difference of 6.1 months in median PFS between the arms as measured by the independent review facility (18.5 months vs 12.4 months, hazard ratio [HR] 0.62, 95% CI: 0.51 to 0.75), with similar findings at the first and second data cut (median follow-up of 30 months) for local investigator assessed PFS.\(^6\) Although a significant difference in overall survival was reported at the second data cut, the ERG and Committee considered there to be uncertainty in the magnitude of the overall survival gain due to immaturity of the data.\(^1,6\) The Summary of Product Characteristics (SPC) states that treatment with pertuzumab should continue until disease progression or unmanageable toxicity and that if trastuzumab treatment is discontinued, treatment with pertuzumab should also be discontinued.\(^5\) Therefore, any gain in PFS would result in additional costs for ongoing treatment with both pertuzumab and trastuzumab.

The MS gives the mean cost per 3 week cycle for trastuzumab as £1,629.60 for the initial dose and £1,222.20 for the maintenance dose (page 143 of the MS).\(^7\) The cost of acquiring docetaxel is substantially lower at £35 per cycle (page 144 of the MS).\(^7\) The cost of administering all three drugs on day 1 of each 21 day cycle is given as £248 for the first dose and £197 for each subsequent cycle with an additional pharmacy dispensing cost of £9.40 per cycle (Table 27 of the MS).\(^7\) In addition to these costs, the economic model described in the MS includes a cost for best supportive care of £157 per month (Table 29 of the MS).\(^7\) Therefore, we calculate the annualized cost of remaining in the progression-free health state to be £27,253 even when assuming a zero price for pertuzumab. These costs would also be incurred by any patient receiving the comparator intervention of trastuzumab combined with docetaxel. These costs associated with the progression-free state act to increase the ICER because treatment with pertuzumab results in an increased duration of PFS.
If we ignore any other factors influencing overall costs (i.e. assume that the cost of monitoring, treatment of adverse events and second-line cancer therapies are similar between the pertuzumab and comparator arm), and assume no difference in post-progression survival (PPS), then the cost-effectiveness model simplifies to a trade-off between the QALY gains associated with additional PFS and the acquisition cost of pertuzumab. This is similar to the scenario illustrated in Figure 2 above. To determine whether this additional survival will increase or decrease the ICER, it is necessary to determine whether the additional survival results in a positive or negative change in net benefit. Given the costs described above, the utility value for the progression-free health state for advanced breast cancer would have to be over 0.90 to give a positive net benefit event when applying a willingness to pay threshold of £30,000 per QALY and assuming a zero price for pertuzumab. Given that none of the utility values applied in the manufacturer’s model were above 0.785 (Table 25 of the MS), we can say that it is unlikely that pertuzumab would be cost-effective even at zero price in this population if its clinical benefits are limited to extending survival in the progression free state.

3.3. Vinflunine

In the NICE guidance for vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272) it is stated, “When a vial price of £0 was used, the ICER was £27,478 per QALY gained.” According to Table B42 of the MS, vinflunine in addition to best supportive care (BSC) resulted in additional PFS, PPS and overall survival (OS) compared to BSC. A substantial (41%) proportion of the additional life-years (LYs) gained are accrued due to additional time spent in the post-progression health state even though treatment with vinflunine was ceased after disease progression. According to Table B42 of the MS there is an overall gain of 0.268 in discounted LYs with 0.158 of this relating to gains in PFS and 0.110 of this relating to gains in PPS.

In this appraisal, the costs per month of providing best supportive care were high at £585 and £1340 in the vinflunine arm for the pre- and post- progression states respectively (Table B39 of the MS). The utility values applied to these states were 0.65 and 0.25 respectively (Table B35 of the MS). Therefore, there is a negative net benefit associated with increased PPS when applying a £30,000 per QALY threshold. This is similar to the scenario described in Figure 3 above.
In the case of vinflunine, the ICER is under the upper range of ICERs that are considered to be cost-effective when applying a vial price of £0 and therefore based on the manufacturer’s estimates of cost-effectiveness it would be possible to set a positive price at which this clinically effective treatment would be reimbursed providing the Committee were willing to apply a threshold of £30,000 per QALY in this case. However, the high cost and low utility value for time spent in the PPS state for this health condition means that treatments which have a positive effect on PPS would be less cost-effective than those which have a negative effect on PPS for this population.

3.4. Cetuximab for head and neck cancer

Cetuximab is licensed for the treatment of patients with recurrent and/or metastatic squamous cell cancer of the head and neck in combination with platinum-based chemotherapy.10 In the ERG report for the TA of cetuximab for this indication (TA172), a threshold analysis was presented (on page 69) which showed that the ICER compared to platinum-based chemotherapy was £37,403 when assuming that cetuximab was zero priced.11 The ERG report cites three reasons for this high ICER. Firstly cetuximab requires more frequent administration than the platinum-based chemotherapy. Secondly, cetuximab is indicated for use until disease progression meaning that any increase in progression free survival also increases the cost of administering cetuximab. Finally, “because cetuximab is associated with better survival, patients experience a longer period during which they are eligible to gain benefit from other follow-on treatments and palliative care, all of which involve additional NHS cost.”

However, it can be seen from the figures presented by the ERG that 95% (4480/4709) of the incremental cost (when assuming a zero price) is related to drug administration, suggesting that the provision of follow-on treatments and palliative care during the period of additional survival are not the main drivers of incremental cost in this case.11 So whilst the scenario illustrated in Figure 3 may have a small negative impact on the ICER, it is not the main driver of the high ICER when assuming a zero drug price.

The drug administration costs presented by the ERG are not broken down into those related to cetuximab administration and those related to the provision of platinum-based
chemotherapy. However the low incremental cost attributable to drug acquisition for other treatments (as presented on page 69 of the ERG report) suggests that the additional administration costs are largely attributable to cetuximab.\textsuperscript{11}

In the first 18 weeks of cetuximab administration, it is given along-side platinum-based chemotherapy.\textsuperscript{12} We can calculate the cost of extending treatment on this platinum-based chemotherapy using the drug costs and administration costs per cycle using the data presented in the MS.\textsuperscript{12} Using the proportions receiving cisplatin (62.8\%) and carboplatin (37.2\%) based chemotherapy from Table H8, and the drug costs per cycle presented in Table H10 (£712 and £292.44), we can see that the mean drug cost per cycle in the comparator arm was £448.52 per 3 week cycle. The cost of administration for platinum-based chemotherapy are £1184 per cycle based on the unit costs presented in Table H11 (£296) and the duration of inpatient stay (4 days per 3 week cycle) presented in Table H3 of the MS. Therefore the background costs of platinum-based chemotherapy are equivalent to £41,045 per annum. So, even if this health state were associated with full utility, it would not be cost-effective to prolong survival in this state. This suggests that the scenario illustrated in Figure 2 may have a role to play in this example. However, in this case, the impact on the ICER of prolonged survival on the platinum-based chemotherapy regimen is limited due to the fact that the platinum-based chemotherapy was stopped at 18 weeks with only the cetuximab treatment being continued until disease progression. Therefore, any increase in PFS that occurred after this 18 week time-point would not incur additional costs for providing background platinum-based chemotherapy.

It appears that in this case study, the ERG’s conclusions that the ICER exceeded £30,000 per QALY when assuming a zero price for cetuximab are being driven by the high costs associated with administering chemotherapy during the period of PFS, and the vast majority of these appear to be related to the administration of cetuximab due to its more frequent administration and the fact that it is continued beyond the 18 weeks limit for administration of platinum-based chemotherapy. So, whilst the scenarios illustrated in Figure 2 and 3 may play some role in increasing the ICER for cetuximab, it is the fact that cetuximab cannot be administered for zero cost that is driving the conclusion that it would not be cost-effective even if it were zero priced.
3.5. Bevacizumab for metastatic colorectal cancer

TA 212 considered the use of bevacizumab in combination with oxaliplatin and either fluorouracil plus folic acid (FOLFOX) or capecitabine (XELOX) for the treatment of metastatic breast cancer.\textsuperscript{13} This case study was considered to have similar characteristics to the scenario illustrated in Figure 2 as it involves the addition of a new technology to one of two existing high cost treatment regimens (FOLFOX or XELOX) and compares the cost-effectiveness of combined treatment with the new technology (B+FOLFOX or B+XELOX) against these existing treatment regimens. Treatment is indicated until progression of the underlying disease,\textsuperscript{13} therefore, as in the pertuzumab example described above, we have a situation where an increase in PFS would result in additional time being spent on both the new technology (bevacizumab) and the background existing treatment regimen (FOLFOX or XELOX). Table 23 of the MS gives the administration costs applied in the manufacturer’s cost-effectiveness model.\textsuperscript{14} In the comparator arms these were £526 per month for XELOX and ranged from £1024 to £1735 per month for FOLFOX depending on the exact administration method. The costs of administering these regimens in combination with bevacizumab were similar. It can be seen that for the FOLFOX regimen, the administration costs alone may exceed £20,000 per annum making it difficult for this regimen to be combined in a cost-effective manner with any technology which increases the duration of treatment with FOLFOX. Therefore this is another example of the scenario illustrated in Figure 2.

3.6. Summary of case studies

Several examples have been found within previous NICE TAs in which a clinically effective treatment has extended the period spent by a patient within a high cost health state. Where the costs accrued during this additional survival are not offset by the QALYs gained from additional time spent in this health state, this additional survival has the effect of pushing up the ICER for the clinically effective treatment. In some cases, the balance of costs and benefits associated with prolonged survival may mean that a technology whose only clinical benefit is to increase survival in that health state will fail to demonstrate cost-effectiveness even when it is zero priced.

Sometimes the high costs associated with additional survival are attributable to the ongoing administration of high cost drug therapies which are administered along-side the treatment
being appraised, but are also considered to represent current best practice in patients not receiving the treatment being appraised. In other cases, it is the cost of providing best supportive care to a population with high healthcare needs and low quality of life which is driving the ICER upwards. Finally, in one example, it appears that the main factor driving the ICER above commonly accepted thresholds, when assuming a zero price, is the cost of administering the technology being appraised rather than the cost of treatments given alongside that technology, although, the costs of administering concomitant chemotherapy treatments were also high in this example. No examples were identified which matched the characteristics of scenario 4 in which the increased duration of life-expectancy places patients at risk of requiring high cost future interventions.

4. LITERATURE REVIEW

In Section 2 we identified that a clinically effective technology may be found not to be cost-effective, even when assuming a zero price, if it results in an increased amount of time being spent in a health state associated with a high level of NHS resource use. This situation runs counter to the usual expectation that treatments which improve survival will be cost-effective if they are provided at a reasonable cost, and it is being driven by the high costs accrued during periods of additional survival. There is a reasonable amount of existing literature on the methodological issue of which costs incurred during added life-years should be included in cost-effectiveness analyses.\textsuperscript{15-38} We decided to examine this literature to identify whether there could be a case for excluding certain types of costs accrued during periods of additional survival. In Section 5 we go on to examine how any principles for excluding certain types of costs identified in the literature might be applied in practice within the case studies we examined and within the TA programme as whole.

Some of the literature regarding the inclusion of costs incurred during periods of additional survival focuses on the distinction between medical costs accrued during added life-years and the broader costs to society, such as changes in consumption and production.\textsuperscript{16,27,28,33} This issue is not relevant within the context of NICE TAs as the perspective for the reference case is limited to costs related to NHS and personal social services (PSS) resources.\textsuperscript{39}
However, even for those costs falling within the reference case perspective, a distinction has been drawn in the literature between those costs that are related and unrelated to the technology of interest.\textsuperscript{32,35} The NICE methods guide states in section 5.5.7, “Costs related to the condition of interest and incurred in additional years of life gained as a result of treatment should be included in the reference-case analysis. Costs that are considered to be unrelated to the condition or technology of interest should be excluded.”\textsuperscript{39} Therefore, under the existing NICE methods for TA, it would be acceptable to exclude costs which are considered to be unrelated to the condition or technology of interest.

The example of life-extending treatment in patients with ESRD requiring maintenance dialysis therapy has been used in the literature to illustrate the case for excluding such unrelated costs.\textsuperscript{21} Grima \textit{et al.} argue that dialysis costs can be considered to be unrelated and excluded if, “the need for or intensity of dialysis is not impacted by the therapy of interest and incremental dialysis costs are due exclusively to extension of life”. They argue that this definition of unrelated costs may apply not only to therapies for unrelated conditions, such as statins, but also to therapies for conditions that are a consequence of renal failure or the use of dialysis. They also argue that the decision to provide dialysis, despite its poor cost-effectiveness, has already been taken and therefore dialysis patients should not be denied subsequent treatments for co-morbid conditions due to the high background costs of providing dialysis.

van Baal \textit{et al.} disagree that unrelated costs should be excluded.\textsuperscript{34} They argue that Grima \textit{et al.} have ignored the real opportunity costs of life prolonging treatments in patients with ESRD and that the resources spent on additional dialysis for these patients could generate more health gains by being allocated to other patient groups. They argue that it is better to ignore the distinction between unrelated and related costs, and to include in the analysis all medical costs as these represent real opportunity costs within the healthcare sector. They suggest that if treatments which are cost-effective in other populations are found not to be cost-effective in patients with high background care costs, then the ethical and equity concerns that this finding raises should be dealt with in a process separate from the estimation of cost-effectiveness.

Several authors have attempted to define more specifically what is meant by ‘related’ and ‘unrelated’ costs in order to determine what can be excluded from the analysis on this basis.
Nyman tried to approach the definition by requiring that a consistent approach be taken between the estimation of incremental costs and incremental benefits in the ICER.\textsuperscript{27} In his definition any resource use which influences the incremental QALYs gained should be included in the incremental cost. Using Nyman’s rationale, van Baal \textit{et al.}\textsuperscript{35} define a disease as being related to an intervention if the intervention influences its prognosis and/or its age and sex specific incidence rate. Under this definition they claim that the gain in QALYs during life years that would also have been lived without the interventions cannot be attributed to medical care for unrelated diseases and that differences in healthcare costs of unrelated disease occur only if an intervention increases life expectancy. In the scenario illustrated by Figure 4, the high cost future event may be considered to be unrelated under this definition if the intervention being appraised is an intervention to prevent early death such as childhood vaccinations and the high cost future event is something like stroke whose incidence increases with age but whose incidence or prognosis is not influenced by childhood vaccinations. Conversely, the cost incurred in the additional life years gained would be considered to be related if the intervention was smoking cessation in teenagers and the high cost future event was lung cancer treatment.

In a later paper,\textsuperscript{37} van Baal \textit{et al.} go back to the theoretical definition first proposed by Garber and Phelps that unrelated costs are conditionally independent of prior expenditures in order to address the issues around postponement of the high costs incurred in the last year of life.\textsuperscript{17} If a treatment postpones death by avoiding death from a particularly cause, for example cervical cancer prevention through human papillomavirus (HPV) vaccination, it is important to consider whether the costs of end of life care for that individual are really avoided or whether they are simply postponed until a later point when death occurs due to a disease unrelated to cervical cancer, such as stroke. Gandjour \textit{et al.} showed that ignoring the costs incurred in the last year of life from unrelated diseases would overestimate the cost-effectiveness of interventions which prevent early death from a particular disease.\textsuperscript{40} van Baal \textit{et al.} discuss how costs that are related to time to death can be considered to be related to life-extending treatments, as they are end of life costs which are postponed by the treatment, whereas costs which are related only to age can be considered not to be related.\textsuperscript{37} They point out that this definition is not based on defining related and unrelated diseases, but on defining related and unrelated costs as some costs falling within a particular disease area may be conditionally dependent whilst others falling in the same disease area may not be. However, they argue that
separating costs into related and unrelated components is an unnecessary complication which can be avoided if all life-time healthcare costs are included in the analysis.

Rappange et al. argue that the ICER should incorporate both unrelated and related medical costs and the health benefits resulting from both these types of costs as this allows an ICER to be constructed which is internally consistent as suggested by Nyman et al. and externally consistent with the decision makers remit of allocating healthcare budgets to increase population health gain.32

5. ALTERNATIVE APPROACHES TO APPRAISING TREATMENTS WHICH ARE NOT COST-EFFECTIVE AT ZERO PRICE

5.1. Defining costs incurred during added life-years as being unrelated
If one accepts the position put forward by Grima et al.,21 that costs unrelated to the technology being appraised can be excluded from the ICER, and that costs incurred solely due to increased survival can be classified as unrelated, then it may be possible to argue that some of the costs identified in the examples described in Section 3, could be excluded from the ICER. This could be argued for populations where the costs of providing best supportive care in addition to the technology being appraised are high and not affected by the technology being appraised except through its impact on survival. The most obvious example of where this definition of unrelated costs could be applied is the dialysis example described by Grima et al.,21 but it could be argued that it also applies in cases where the best supportive care costs are high such as in the vinflunine example.8

In the cinacalcet case study described above, both the TAG and the manufacturer excluded dialysis costs from their base-case cost-effectiveness analysis, although dialysis costs were included in a sensitivity analysis for the TAG model.4 Whilst the TAG stated that it was arguable that SHPT is so closely associated with ESRD that the costs of dialysis should be included, it also stated that dialysis is a very expensive treatment that has already been accepted as standard for this population, although it may not be deemed cost-effective. The TAG also acknowledged that this is a, “methodological issue of considerable controversy”. The FAD for this appraisal does not describe whether the TA Committee considered the
exclusion of dialysis costs to be appropriate or not in this case. ³ Based on NICE’s current methods guidance, the decision to include or exclude dialysis costs would depend on whether those costs are ‘related to the condition of interest’ or not. The position could be taken that cinacalcet is indicated for SHPT which happens to occur in patients with ESRD but that the ESRD is an unrelated pre-existing condition in this population and therefore the costs of dialysis could be excluded. The rationale for exclusion then comes down to a fairly arbitrary decision as to whether SHPT or ESRD is the ‘condition of interest’ for that appraisal. For this reason, van Baal et al. argue that it is better to include all costs rather than trying to draw distinctions between related and unrelated costs.³⁴ It could also be argued that the costs in the last weeks before death are high regardless of the cause of death and therefore the costs for end of life care should be excluded as unrelated for the appraisal of a specific technology because similar costs would be experienced later in life if that individual died of another cause. However, this approach would contradict the definition of related costs put forward by van Baal et al. in which costs which are related to proximity to death are considered to be related to life-extending treatments.³⁷ Furthermore, in the case studies we have examined, the postponement of end of life costs beyond the model horizon has not been an issue as the models have generally taken a life-time approach in accordance with NICE methods guidance.⁴,⁷,⁹,¹²,¹⁴,³⁹ It may also be argued that technologies which constitute the current standard of care or best practice in the NHS and whose delivery or effectiveness is not affected by the addition of the technology being appraised, except through its impact on survival, could also be considered to be unrelated. This logic might also be applied to the costs of treatment with FOLFOX or XELOX alongside bevacizumab for colorectal cancer in TA212 or the treatment with trastuzumab alongside pertuzumab for advanced breast cancer.¹,¹³ However, it would be difficult to argue that the benefits of these technologies are in no way affected by the concomitant administration of the technology being appraised given that they are administered at the same time and with the same treatment intent. Furthermore, without trials examining the separate and combined effects of these treatments (e.g pertuzumab versus trastuzumab versus both combined) it is impossible to say whether they have independent effects on outcomes.
The disadvantages of trying to exclude some of the costs attributable to prolonged survival are those outlined in the literature described in Section 4. The most relevant of these within the context of NICE is the opportunity cost, in terms of health gains forgone in other patient populations, of ignoring costs which differ between the treatment and comparators outlined in the decision problem. These opportunity costs are in no-way diminished by the fact that the costs accrued in the added life-years have been defined as being unrelated to the technology being appraised.

There are also practical difficulties in separating related and unrelated costs. One way to think about the distinction between related and unrelated costs is to consider which future costs the decision maker is committing to by making a recommendation for or against the technology being appraised and whether the estimate of benefit assumes that those future resources will be available. If there are treatments available now which may or may not be available in future, then it may be better to exclude both the costs and the effects of those treatments from the analysis. However, estimating the future health gains in the absence of future care may be difficult as we may only have data on the health gains given current care provision. For example, estimates of general population life-expectancy are often utilised within cost-effectiveness models but these estimates may be dependent on maintaining the current provision of healthcare. Furthermore, excluding all costs and benefits of unrelated future care will only yield an unbiased estimate of the ICER if it can be assumed that all future care will be provided at the cost-effectiveness threshold. If unrelated future care yields a negative net benefit due to higher costs than can be justified by the QALY gains, then excluding future costs and benefits will produce an overly optimistic estimate of the cost-effectiveness of the technology being appraised. If the converse is true, and future benefits can be achieved at below the cost-effectiveness threshold, then excluding future costs and benefits will result in an ICER estimate that is overly pessimistic.

It is hard to see how the definitions of ‘unrelated’ medical costs can be applied to many of the examples described in Section 3. In particular, it is hard to see how the health gains associated with care provided alongside the technology of interest with the same treatment intent can be considered to be unrelated to the health gains attributable to the technology of interest. The examples of unrelated costs given in the literature are often much more clearly unrelated than those considered here and look more like the scenario illustrated in Figure 4. It might be possible to argue convincingly that the health benefits of stroke treatments provided
in later life are unrelated to the effectiveness of childhood vaccinations which allow the patient to survive long enough to be at risk of stroke. However, in the examples considered in Section 3, the costs incurred in the added life-years are actually incurred during or soon after treatment with the technology of interest and are related to treatment of the same condition. It is therefore likely that their ability to produce health benefit will interact in some way with the health gains attributable to the technology being appraised. None of the examples we identified were similar to scenario 4 in which a healthcare cost is incurred during the period of additional survival which may be completely unrelated to the disease being treated by the technology under appraisal.

The exclusion of certain costs from cost-effectiveness analyses on the basis that they are unrelated might lead to inconsistencies being introduced between sequential appraisals of drugs for similar indications. For example, in the appraisal of vinflunine described above, the high costs of best supportive care in the post-progression state meant that any increase in PPS would drive the ICER upwards. It could be argued that the care provided after progression is an unrelated cost as the increased need for such care in patients receiving vinflunine is purely drive by their increased survival. These costs could then be excluded from the ICER on this basis. However, one could conceive that another drug for the same indication may be developed in the future which has the effect of reducing PPS by increasing PFS. For this second drug, accounting for the costs of best supportive care incurred during PPS within the ICER would serve to reduce the ICER and it would seem perverse not to account for the real cost savings that are attributable to this second drug when determining whether it is a cost-effective use of NHS resources. In practice, this problem could be solved by conducting an incremental analysis comparing both drugs within an MTA and applying a consistent approach to defining costs as being related or unrelated within that incremental analysis. However, there is a risk that an inconsistent approach may be taken across different TAs if sequential STAs are used to evaluate multiple drugs within a disease area and each draws a different line between related and unrelated costs.

Rappange et al.\textsuperscript{32} point out that excluding unrelated costs incurred during added life-years will have distributional consequences if the approach is applied consistently across many TAs and cost-effectiveness in each case is determined by comparison to a single threshold. Under these conditions, the exclusion of future unrelated costs favours treatments which result in additional survival other those that result in quality of life gains. They also states that it
favours preventative treatments aimed at older populations over those aimed at younger population as the costs incurred in future life-years are discounted more in younger populations. However, this bias towards favouring treatments aimed at older populations is unlikely to play out in many of the examples identified above, where life-expectancy is low and therefore discounting has a minimal impact on the ICER.

In those cases where the new technology being appraised is being given alongside a very high cost existing intervention, it may be better to re-examine whether the current standard of care represents good value for the NHS. In the pertuzumab example, a previous NICE appraisal (TA34) considered the cost-effectiveness of trastuzumab in combination with taxane therapy (combination trastuzumab was only licensed for use with paclitaxel at the time of TA34) and the committee concluded that the true ICER for combination therapy compared to taxane therapy was likely to be under the £37,500 per QALY gained estimated by the manufacturer. However, the figures used to populate the economic model submitted for the appraisal of pertuzumab suggest that even if the cost per QALY for trastuzumab in combination with docetaxel is under £30,000 per QALY, as believed by the Committee in TA34, there is probably little room left under the NICE threshold to allow additional life-extending therapies to be added cost-effectively.

As more and more technologies pass through the NICE process it may be that it becomes commonplace for new technologies which are given in addition to existing therapies to struggle to demonstrate cost-effectiveness if those existing therapies have been priced at a level that achieves an ICER just under NICE’s threshold. Disinvestment from existing high cost technologies may be warranted in some cases, although this is not an option where the new technology is licensed for use in addition to the existing technology. In these cases it may be that a positive price for the new technology which represents good value to the NHS can only be achieved by obtaining a discounted price on both new and existing technologies. There is precedent for manufacturers proposing cost reductions on drugs given alongside the technology being appraised as the manufacturers of bevacizumab proposed a patient access scheme which involved cost reductions for both bevacizumab and oxaliplatin in TA 212. The need to offer discounts on existing technologies to achieve a positive price on new technologies may be perceived by manufacturers as producing a disincentive to develop drugs in areas where there are existing high cost therapies. However, any disincentive is time-limited by the patent duration on existing therapies as the expectation is that generic and
biosimilar products will emerge allowing existing therapies to be acquired at lower cost. In the case of TA212, where a cost reduction was offered on oxaliplatin when given alongside bevacizumab, the Committee concluded that oxaliplatin was already available at a substantially discounted price though NHS procurement contracts. A difficulty in demonstrating cost-effectiveness for technologies which add-on to existing high cost treatment may also increase the incentive for industry to develop technologies which provide a more effective alternative to existing therapies instead of technologies which further add to the treatment burden by being administered alongside existing therapies.

5.2. Properly accounting for benefits

We have focused here on which costs should be incorporated within the analysis, but it is also important to consider whether the benefits have also been properly accounted for. In the case of vinflunine described above, one of the factors contributing to the high ICER for vinflunine was the low utility of the post-progression state. There are several issues which may be relevant when trying to properly account for benefits within the model. Firstly there may be a lack of evidence meeting the NICE reference case for health state utility valuations on which to base utility estimates leading to an underestimation of the direct health benefits to patients. Secondly, generic measures of health utility may fail to detect differences in quality of life that are important to patients particularly at the end of life. Thirdly, the reference case allows for all health benefits to be included whether they fall to patients or to others such as carers. In some of the case studies, the costs of palliative care, provided as part of best supportive care, were substantial. In the vinflunine case study, 14% of the incremental cost was attributable to palliative care costs incurred post progression. It could be argued that good quality palliative care provides benefits to carers, who avoid the psychological distress of seeing their loved one suffer, and these benefits have not been captured within the manufacturer’s analysis.

Finally, there may be some treatments, such as dialysis and palliative care, which society may consider worthwhile despite their poor cost-effectiveness. The value placed on these treatments by society may not be captured by the health benefits accrued by either the patients themselves or their carers. NICE already accepts analyses which explore the additional value placed on ‘life-extending treatment at the end of life’ through the application of end of life QALY weights. There may be other situations where a QALY weight could
be applied to reflect societal preferences that are not captured within the health benefits already included in the QALY, although this would require a change to the current NICE methods guide. Calculating the ICER including the benefits of the treatment of the high cost background treatment, but excluding the cost, as was done for dialysis within the cinacalcet appraisal, provides a lower bound on the ICER as it assumes that all of the excluded costs are justified by the value of the non-QALY benefits.

5.3. Ethical or legal reasons for accepting a higher ICER

There may be situations, as for the dialysis example described by Grima et al., where a new technology is cost-effective in the general population, where average healthcare costs are low, but not cost-effective in a specific population who are already receiving a high cost maintenance treatment which would not itself be considered cost-effective but is part of the NHS standard of care none the less. As described earlier, in such populations any life-extending treatment is likely to be found not to be cost-effective unless it generates substantial quality of life gains or cost savings in addition to extending survival.

NICE’s existing ‘Social Value Judgements: Principles for the development of NICE guidance, (2nd Edition)’ policy states, “NICE can recommend that use of an intervention is restricted to a particular group of people within the population (for example, people under or over a certain age, or women only), but only in certain circumstances. There must be clear evidence about the increased effectiveness of the intervention in this subgroup, or other reasons relating to fairness for society as a whole, or a legal requirement to act in this way.” Under this policy it would not be possible for NICE to make different recommendations for people with high background care costs than for the general population as a whole if the difference in those recommendations was driven solely by a difference in the background costs of care in the two populations.

In the case studies we have identified, the high background care costs, such as dialysis for patients with SHPT in the appraisal of cinacalcet, were incurred by the whole population included within the scope of the appraisal. It may therefore not be relevant to consider whether the intervention would be cost-effective in other populations who have lower background care costs, particularly if the intervention would not be indicated in those populations. However, if the background care costs in the population defined in the scope
were found to be too high to allow a life-extending treatment to be cost-effective despite being delivered for zero cost, the Committee may still wish to consider whether there are any legal or ethical reasons for recommending the treatment despite the high ICER. This would be in line with NICE existing Social Value Judgement policy which describes the need to ‘distribute health resources in the fairest way within society as a whole’.41

6. CONCLUSIONS

Having considered the examples identified within the NICE TA programme and the methodological literature on this issue, we would argue that all costs which differ between the technology being appraised and the comparator technologies identified in the decision problem should be included within the ICER, provided they fall within the NHS and PSS perspective, as this provides an ICER which reflects the real opportunity cost of recommending the technology being appraised and is consistent with the objective of the NICE TA programme.39 Whilst this would result in a slightly broader inclusion of costs than included within the current NICE methods guide,39 in practice none of the costs included in the case studies examined here would have been excluded under the current NICE methods, with the possible exception of dialysis costs in the appraisal of cinacalcet. The rationale for exclusion in this case comes down to a fairly arbitrary decision as to whether SHPT or ESRD is the ‘condition of interest’ for that appraisal. For this reason, we would agree with van Baal et al. that it is better to consider all costs which differ regardless of whether they fall within the ‘condition of interest’.34

The TA Committee may also wish to consider whether the health benefits to both the patients and their carers of all the care falling within the NHS and PSS budget has been adequately captured in the cost-effectiveness analysis, as including the costs of all NHS and PSS resource use without capturing the full health benefits may under estimate the value of the technology and the value of the care provided alongside it.

The TA Committee may wish to consider whether the population is currently receiving a high cost intervention which does not meet commonly accepted thresholds for cost-effectiveness but which is deemed to be an acceptable use of NHS resources for other reasons and whether the only impact of the technology being appraised on the requirement for this high cost
background intervention is through its effect on survival. The Committee may wish to consider whether there are some additional benefits to society of providing that existing high cost intervention which are not captured in the health benefits accrued by patients or other people. If those additional benefits cannot be quantified, then calculating the ICER including the health benefits of the background intervention, but not its costs would provide a lower bound on the ICER. If there are no additional benefits to society outside of those already captured within the ICER, then the Committee may wish to recommend that existing intervention for appraisal to determine whether the NHS should disinvest from that technology.

Finally, in accordance with their existing policies, the Committee may also wish to consider whether there are any legal or ethical reasons for recommending the treatment when the ICER is in excess of the range usually considered to represent good value for the NHS.
7. REFERENCES


