

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE**

**SPECIAL HEALTH AUTHORITY**

**UPDATE REPORT ON THE APPLICATION OF THE 'END-OF-LIFE'  
SUPPLEMENTARY ADVICE IN HEALTH TECHNOLOGY  
APPRAISALS**

The Board is asked to receive the report

Carole Longson, Director, Centre for Health Technology Evaluation  
Peter Littlejohns, Clinical and Public Health Director

July 2009

# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## SPECIAL HEALTH AUTHORITY

### UPDATE REPORT ON THE APPLICATION OF THE 'END-OF-LIFE' SUPPLEMENTARY ADVICE IN HEALTH TECHNOLOGY APPRAISALS

#### 1 Introduction

1.1. Supplementary advice to the 2008 'Guide to the Methods of Technology Appraisals' was issued to the Appraisal Committee on 2<sup>nd</sup> January 2009 (Appendix 1). It is expected to be taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. The supplementary advice will apply when such treatments have an incremental cost effectiveness ratio (ICER) in excess of the upper end of the range normally approved by the Appraisal Committee

1.2. The supplementary advice states that :

*"The Institute intends to ensure that the supplementary advice is robust for the long-term and that it achieves its intended purpose. It will therefore be subject to a methodological evaluation. The Institute will design and manage this evaluation, the results of which will be published and used to make modifications to the supplementary advice, if necessary."*

1.3. This report (Appendix 2) covers the first 4 months of the implementation of the supplementary advice. The Supplementary Advice has been applied on a number of occasions. Although there has been considerable discussion by committee members on the application and interpretation of most of the end of life criteria, its application appears to have been undertaken consistently. However it is still early days with only one guidance document having been published using the new criteria. In addition there was an appeal against the lapatinib appraisal which fell outside the timescale of the report but the outcome of the appeal was announced recently and the implications of the panel's decision are incorporated into this cover paper.

#### 2 Issues for Board Consideration and guidance

2.1 Section 1.1 of the advice states: "the additional advice will apply when such treatments have an incremental cost effectiveness ration (ICER) in excess of the upper end of that normally approved by the Appraisal Committee, using the 'reference case' outlined in the Institute's Guide to the Methods of Technology Appraisal" .This ICER is also referred to

TITLE: UPDATE REPORT ON THE APPLICATION OF THE 'END-OF-LIFE' SUPPLEMENTARY ADVICE IN HEALTH TECHNOLOGY APPRAISALS

DATE: 22 JULY 2009

REF: 09/055

in Section 1.4). **There have been various interpretations of which ICER is being referred to and it would help if the advice could be clarified to highlight that it refers to the committee's view of the most plausible ICER .**

- 2.2 It could be that two very similar interventions for the same disease, will both meet the criteria for the application of the supplementary advice. If they are appraised a short time apart e.g. within three months of each other, then strict accordance with the criteria could mean that the first intervention may be accepted and the second rejected as it no longer represents a new treatment for which no alternative is available within the NHS. This highlights the extreme end of the general issue faced by the committee in deciding when there are or are not alternative treatments with comparable benefits in the NHS. **The Board is asked to provide clarification as to how to proceed with such 'fast-followers'.**
- 2.3 There have been differing interpretations of the criterion 'no alternative treatment with comparable benefits is available through the NHS'. One interpretation is that this statement was intended to imply an important 'step change' in treatment which is in line with the principles of 'rewarding' innovation. The alternative interpretation is that it is an extension of the three-month gain criterion. **The Board is asked to affirm that this criterion is intended to refer to 'step-change' innovations.**
- 2.4 There are a number of technical issues in applying the criteria, including whether it should be the mean or median survival used to establish whether the treatment provides an anticipated survival gain, and whether quality of life benefits during progression free survival should be included in addition to survival benefit. These issues are explored in the report and the committee's preferred approach is described. **The Board is asked to agree with this approach.**
- 2.5 Criterion 2.1.4 refers to "the treatment is licensed or otherwise indicated for small patient populations". The Committee has interpreted this, as directed elsewhere in the document, to mean the cumulative population (across all diseases) for which the treatment is licensed. The logic of this is that guidance expected manufacturers to reserve exceptionally high prices for drugs with a small market. Some commentators however would prefer the population size criterion to mean just the population covered by an appraisal. Arguably any population could be considered as 'small' if divided into subgroups . **The Board is asked to confirm that the 'population' is intended to mean 'cumulative population across all indications' . Advice is also requested with respect to the need to review existing guidance under the supplementary advice should the cumulative population be subsequently increased due to subsequent marketing authorisations.**

- 2.6 The Appeal panel has recently released its decision on the appraisal of Lapatinib and upheld the appeal on 2 grounds. The first ground reflected the timing of the issuing of the supplementary advice during the appraisal process . *“ The appeal panel decided it could not exclude the possibility that if the company had been given clear instructions and adequate opportunity to engage in the process, and the Appraisal Committee had had more time to consider the company’s submission than the then the Appraisal Committee might have reached a different conclusion. Whether or not it does so on reconsideration is entirely a matter for the committee”* (paragraph 31). **As this reflects the timing of this particular appraisal there is no further advice requested from the Board.**
- 2.7 However the appeal point relating to the *“Appraisal Committee’s application of the Supplementary Advice ..... was overly restrictive and unfair”* does require further clarification from the Board. Paragraph 46 states *” The Appeal Panel did not accept the Committee’s approach to the meaning of the requirement that life extension should “normally be of at least an additional 3 months, compared to current NHS treatments,” The Appeal Panel concluded that the Appraisal Committee was not correct to have read that as requiring a minimum of an average of 3 months in absolutely every case. It would , in compelling circumstances, be open to the Appraisal Committee to accept an average of less than 3 months. However in paragraph 47 the Appeal Panel further states “that the Supplementary Advice is itself already a policy dealing with a departure from normal policy in exceptional circumstances. Clear and strong justification would be required for an exceptional departure from what is already an exceptional policy, particularly if the departure is more than nominal. It might be that such compelling circumstances would almost never be present. Nonetheless, the Committee was mistaken to have thought that it had no discretion at all to apply the Supplementary Advice where the mean survival is shown to be less than 3 months” . In paragraph 48 the Appeal Panel states that it “allowed the appeal on this point in so far as the Committee should consider whether, exceptionally, a life extension of less than 3months might be acceptable in this case. **The Board is invited to consider the nature of what “exceptional” might mean and give further guidance.***
- 2.8 The Board is asked to note Section 6.5 of the report which describes the preliminary implicit “weights” given to QALYs when interventions are considered appropriate for use in the NHS using the supplementary advice.
- 2.9 The supplementary advice states:

*“that the Institute will normally recommend to the Department of Health that it should give consideration to a data collection exercise for treatment recommended for use on the basis of the criteria set out in section 2. The purpose of this will be to assess the extent to which the*

*anticipated survival gains are evident when the treatments involved are used in routine practice. The outcome of this exercise will be evaluated when the guidance for that treatment is reviewed.”*

To date the Committee has recommended two such schemes but implementation remains problematic. Preliminary discussions with the DH have suggested that there might be systems available for cancer drugs but not for other disease areas.

- 2.10 The supplementary advice highlights that “*the Institute intends to ensure that the supplementary advice is robust for the long-term and that it achieves its intended purpose*” (see paragraph 1.2) therefore **the Board is asked to agree that further research is required to test the assumptions of the EOL advice and to advise on the nature of that research.**

Carole Longson, Director, Centre for Health Technology Evaluation  
Peter Littlejohns, Clinical and Public Health Director

July 2009

## Appendix 1

### SUPPLEMENTARY ADVICE TO THE 2008 'GUIDE TO THE METHODS OF TECHNOLOGY APPRAISALS'

#### 1 Summary

- 1.1 This document sets out supplementary advice to the Appraisal Committees, to be taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. The additional advice will apply when such treatments have an incremental cost effectiveness ratio (ICER) in excess of the upper end of the range normally approved by the Appraisal Committees, using the 'reference case' outlined in the Institute's *Guide to the Methods of Technology Appraisal*, and which may offer demonstrable survival benefits over current NHS practice.
- 1.2 The current appraisal methodology recognises that there will be circumstances in which it may be appropriate to recommend the use of treatments with high reference case incremental cost effectiveness ratios. It states (with reference to the Institute's standard appraisal criteria) that: *'Above a most plausible ICER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the technology as an effective use of NHS resources.'* The Appraisal Committee has, in the past, made recommendations above the normal threshold range when it has explicitly identified additional benefits not readily captured in the reference case. This has occurred when the treatment involved has been life-extending, licensed or otherwise indicated for small populations with incurable illnesses.
- 1.3 In developing this supplementary advice, the Institute has taken account the Appraisal Committees' previous decisions, together with the relevant principles in the guide to the use of Social Value Judgements. It has also had regard to the consideration given by the Citizens Council, at its meeting in November 2008, to the circumstances in which it might be appropriate to support the use of treatments outside the Institute's cost per quality adjusted life years (QALY) threshold range. In addition, the Institute has taken account of its responsibility to recognise the potential for long term benefits to the NHS of innovation. In this context, it considers it appropriate for its Appraisal Committees to have regard to the importance of supporting the development of innovative treatments that are anticipated to be licensed for small groups of patients who have an incurable illness.
- 1.4 The objective of this supplementary advice is to ensure that the Appraisal Committees fully consider all the benefits which it is appropriate to take into account in appraising treatments designed to

extend life, at the end of life for small populations and in particular to ensure that where benefits are not, or not adequately captured in the reference case, that the Appraisal Committees are provided with an appropriate supplementary analysis. For this supplementary advice to be applied, a treatment will need to have been through an appraisal by NICE where the most plausible reference case point estimate for the ICER exceeds the upper end (£30,000) of the range normally considered by the Appraisal Committees to represent a cost effective use of NHS resources. Each candidate treatment will also need to meet the criteria set out in section 2.

- 1.5 The Institute will normally recommend to the Department of Health that it should give consideration to a data collection exercise for treatments recommended for use on the basis of the criteria set out in section 2. The purpose of this will be to assess the extent to which the anticipated survival gains are evident when the treatments involved are used in routine practice. The outcome of this exercise will be evaluated when the guidance for that treatment is reviewed.

## **2 Criteria for appraisal of end of life treatments**

- 2.1 This supplementary advice should be applied in the following circumstances and when all the criteria referred to below are satisfied:
- 2.1.1 The treatment is indicated for patients with a short life expectancy, normally less than 24 months and;
- 2.1.2 There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment, and;
- 2.1.3 No alternative treatment with comparable benefits is available through the NHS, and;
- 2.1.4 The treatment is licensed or otherwise indicated, for small patient populations.
- 2.2 When the conditions described in 2.1 are met, the Appraisal Committee will consider:
- 2.2.1 The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, and;
- 2.2.2 The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold

range.

2.3 In addition, the Appraisal Committees will need to be satisfied that:

2.3.1 The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (taking account of trials in which cross-over has occurred and been accounted for in the effectiveness review). and;

2.3.2 The assumptions used in the reference case economic modelling are plausible objective and robust.

### **3 Review of the resulting guidance**

3.1 The guidance produced using these criteria will be subject to review in accordance with the Institute's current arrangements. The review will normally take place no later than 2 years after the guidance has been issued. The review can be either brought forward or delayed, depending on the outcome of any data collection exercise or the availability of other new evidence.

3.2 Treatments approved following the application of the supplementary advice will not necessarily be regarded or accepted as standard comparators for future appraisals of new treatments introduced for the same condition. Second and subsequent licences for the same product will be considered on their individual merits. The Appraisal Committee will take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria outlined above

### **4 Implementation and evaluation**

4.1 This supplementary advice will be effective from 5 January 2009.

4.2 The Institute intends to ensure that this supplementary advice is robust for the long-term and that it achieves its intended purpose. It will therefore be subject to a methodological evaluation. The Institute will design and manage this evaluation, the results of which will be published and used to make modifications to the supplementary advice, if necessary.

## Appendix 2

### REPORT ON THE APPLICATION OF THE 'END-OF-LIFE' CRITERIA JUNE 2009

#### 1 Introduction

- 1.1. This report outlines the supplementary advice on end-of-life treatments issued to the Appraisal Committee and provides a synopsis of the application of the criteria during the Appraisal Committee meetings held between January and April 2009. It also highlights the interpretation of the criteria by the Appraisal Committee and identifies issues in the application of the criteria faced by the Appraisal Committee.

#### 2 Background:

- 2.1. Supplementary advice to the 2008 'Guide to the Methods of Technology Appraisals' was issued to the Appraisal Committee on 2<sup>nd</sup> January 2009. The supplementary advice document states:
- 2.2. "This supplementary advice is to be taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. The supplementary advice will apply when such treatments have an incremental cost effectiveness ratio (ICER) in excess of the upper end of the range normally approved by the Appraisal Committee, using the 'reference case' outlined in the 2008 'Guide to the Methods of Technology Appraisal'. For this supplementary advice to be applied, all the following criteria must be met:
- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.
  - There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
  - No alternative treatment with comparable benefits is available through the NHS.
  - The treatment is licensed or otherwise indicated for small patient populations.
- 2.3. In addition, when taking these criteria into account, the Appraisal Committee must be persuaded that the estimates of the extension to life are robust and that the assumptions used in the reference case economic modelling are plausible, objective and robust. The Appraisal Committee will also take into account the cumulative

population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria outlined above.

- 2.4. When the conditions in 2.2. are met, the Appraisal Committee will consider:
- The impact of giving greater weight to quality adjusted life years (QALYs) achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age, and
  - The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range.

### 3 Methods

- 3.1. All appraisals discussed at Appraisal Committee meetings between January 2009 and April 2009 were reviewed with regard to the application of the end-of-life supplementary advice. A data collection table has been produced, capturing the details of each appraisal and the considerations of the Appraisal Committee with regard to the end-of-life criteria (see Appendix A, Table 1). For appraisals in which the end-of-life criteria were considered to be relevant, additional information was recorded (see Appendix A, Table 2). Data collection was completed by a designated health technology analyst, and the data were then checked by the analysts involved in the individual appraisals.

### 4 Results

- 4.1. This analysis is based on 11 Appraisal Committee meetings held between January and April 2009. Sixteen appraisals (14 single technology appraisals and two multiple technology appraisals totalling 22 technologies) were discussed. During this period, six of the 16 appraisals (totalling nine technologies) were discussed twice by the Appraisal Committee. This was a similar number to the same period in 2008.
- 4.2. Of the 16 appraisals, eight (11 technologies) were not associated with a life expectancy of 24 months or less (Appendix A, Table 1). These technologies were not considered in the context of the end-of-life criteria by the Appraisal Committee:
- Rivaroxaban for venous thromboembolism.
  - Tenofovir disoproxil fumarate for hepatitis B.

- Mifamurtide for non-metastatic osteosarcoma.
- Rituximab (first-line) for chronic lymphocytic leukaemia.
- Alitretinoin for chronic eczema.
- Romiplostim for thrombocytopenic purpura.
- Donepezil, rivastigmine, galantamine, and memantine for Alzheimer's disease.
- Ustekinumab for psoriasis.

Of these eight appraisals, three were discussed for the first time by the Appraisal Committee and therefore had not, at that stage, been subject to consultation. However, it is unlikely that later in the appraisal process, for example after ACD consultation, these appraisals would be considered as fulfilling the end-of-life criteria.

4.3. Two further technologies were not discussed in the context of the end-of-life criteria:

- Pemetrexed (first-line) for non-small cell lung cancer.
- Cetuximab for colorectal cancer.

Pemetrexed for lung cancer was not discussed in the context of the end-of-life criteria, because at the first Appraisal Committee meeting the most plausible ICER was not established. After this ICER has been established this technology may, if relevant, be discussed in the context of the end-of-life criteria at the next Committee meeting for this appraisal (scheduled for 24<sup>th</sup> June). Cetuximab for colorectal cancer was not discussed in the context of the end-of-life criteria because the most plausible ICER accepted by the Appraisal Committee was less than £30,000 per QALY gained.

4.4. The remaining six appraisals (nine technologies) were discussed in the context of the end-of-life criteria. The following three technologies were considered not to fulfil all of the criteria for being a life-extending, end-of-life treatment (the primary reason for not meeting the criteria is given in brackets):

- Cetuximab for squamous cell carcinoma of the head and neck (evidence indicates that extension to life associated with the treatment is less than 3 months in this population).
- Bevacizumab for renal cell carcinoma (licensed for other indications that have large eligible patient populations).

- Lapatinib for advanced and/or metastatic breast cancer (evidence indicates that extension to life associated with the treatment is less than 3 months in this population).

See Appendix B for the Appraisal Committee considerations of each of these technologies.

4.5. Of the six appraisals (nine technologies) that were discussed in the context of the end-of-life criteria, the following six technologies were considered to fulfil the criteria for being a life-extending, end-of-life treatment and were not licensed for other indications with large eligible patient populations (most plausible ICERs, as considered by the Appraisal Committee, in brackets):

- Sunitinib (first-line) for renal cell carcinoma (less than £50,000 per QALY gained).
- Sorafenib (second-line) for renal cell carcinoma (£65,900 per QALY gained).
- Temsirolimus for renal cell carcinoma (more than £102,000 per QALY gained).
- Lenalidomide for multiple myeloma (more than £43,800 per QALY gained).
- Sunitinib for gastrointestinal stromal tumours (£31,800 per QALY gained).
- Sorafenib for hepatocellular carcinoma (£64,800 per QALY gained).

See Appendix C for the Appraisal Committee considerations of each of these technologies.

4.6. For the technologies that were considered to fulfil all of the end-of-life criteria (see section 4.5), the impact of giving greater weights to QALYs gained through treatment with the technology in the later stages of terminal diseases was assessed. For this, as per the supplementary advice, the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age was used. The range of the magnitude of the implicit QALY weightings that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the current threshold range was discussed by the Appraisal Committee. Tabulations of the weightings were available for the Appraisal Committee at the meetings and were included within the evaluation reports distributed to consultees and commentators. The magnitude of the implicit QALY weights that would need to be assigned to the original QALY

benefits was considered to be acceptable by the Appraisal Committee for the following technologies:

- Sunitinib (first-line) for renal cell carcinoma.
- Lenalidomide for multiple myeloma.
- Sunitinib for gastrointestinal stromal tumours.

For the other three technologies, the magnitude of the implicit QALY weights that would need to be assigned to the original QALY benefits was not considered to be acceptable by the Appraisal Committee. See Appendix D for tables of the range of QALY weightings considered by the Appraisal Committee.

## 5 Discussion:

### 5.1. *The application of the criteria*

5.1.1. In establishing whether a treatment is indicated for patients with a short life expectancy (normally less than 24 months), the Appraisal Committee used the median overall survival from the control arm of the pivotal trials as presented by the manufacturers. For five technologies, the trial data were either immature and the median overall survival in the control arm in the trials had not been reached, or the overall survival in the control arm was confounded by crossover. In these cases, the Appraisal Committee accepted the median overall survival estimates from available observational data (for example, the evidence on survival with dexamethasone, which was the comparator in the lenalidomide for multiple myeloma appraisal, came from observational data) or from estimates of progression-free survival (for example for bevacizumab for renal cell carcinoma). The use of survival estimates derived from data extrapolation in the economic models was not used by the Appraisal Committee for establishing the normal life expectancy of a condition with standard treatment alone.

5.1.2. In establishing whether there is sufficient evidence to indicate that the treatment offers an extension to life (normally of at least an additional 3 months), the Appraisal Committee considered the difference in median overall survival from the pivotal trials, as well as the mean incremental life years gained from the economic model. In general, the estimates from the trials and the economic models were similar, for example cetuximab for head and neck cancer; 2.7 months was established from the trial and 2.2 months from the economic model. The Committee did not accept that cetuximab provided the required extension to

life, as both estimates indicated that survival was less than 3 months. However, in the case of sorafenib for hepatocellular carcinoma, the estimate of life extension from the trial was 2.8 months compared with an estimate of 6.1 months from the economic model. In this case, the Appraisal Committee noted the difference in estimates, and agreed that sorafenib could be considered under the end-of-life supplementary advice. In some cases the data on life extension were immature or confounded by crossover. The Appraisal Committee accepted estimates of progression-free survival from the pivotal trials, as these estimates were considered to give a good indication that the anticipated overall survival gain would be of sufficient magnitude to meet the criteria in the supplementary advice.

- 5.1.3. In order to establish whether or not there are alternative treatments with comparable benefits available through the NHS, the Appraisal Committee considered whether the technologies appraised provide a 'step change' or 'marked change' in the treatment options for the condition. For example, in the case of lenalidomide, the Appraisal Committee spent a substantial amount of time discussing this issue, partly because lenalidomide is a derivative of thalidomide which has already been used for the treatment of multiple myeloma and partly because lenalidomide was, after ruling out its plausibility as an earlier treatment, being appraised as a last-line treatment. The Appraisal Committee took the view that this new last-line treatment was a step change because other options had been tried and so only best supportive care was the comparator. The issue was complicated by the timing of this appraisal and the appraisal of bortezomib for multiple myeloma (technology appraisal 129). Bortezomib also has a marketing authorisation for the treatment of multiple myeloma and could have been considered as an alternative treatment; however, bortezomib was not recommended by NICE for the treatment of multiple myeloma in second or subsequent relapses by NICE, as the most plausible reference-case ICERs were £77,000 for second relapse and £107,000 for subsequent relapse. Therefore, bortezomib was not recommended to be routinely available in the NHS. The manufacturer of bortezomib highlighted that if the appraisal of bortezomib had happened after the supplementary advice regarding 'end-of-life' treatments was put in place, bortezomib could have been recommended through the advice and lenalidomide would have been rejected on the grounds of another treatment being available.

- 5.1.4. There have also been cases in which the treatment being appraised is given in addition to (and at the same time as) the current standard of care, for example bevacizumab plus interferon-alfa was considered to represent a marked change compared to interferon-alfa alone).
- 5.1.5. In establishing whether the treatment is licensed or otherwise indicated for small patient populations, the population size has been based on the incidence of a condition, rather than the prevalence. In order to fulfil the end-of-life criteria, by definition, the 'life expectancy associated with a condition must be short'; therefore incidence and prevalence should not differ greatly. The Appraisal Committee has also taken into account the cumulative population for which each product is licensed when considering the strength of any case for justifying decisions that employ the end-of-life criteria. For example, bevacizumab is licensed for first-line treatment of advanced and/or metastatic renal cell carcinoma (population size approximately 4000); however, it is also licensed for the treatment of breast cancer, colorectal cancer, and lung cancer (the total population size was not estimated precisely) and therefore the Appraisal Committee considered that it did not fulfil the broader policy objectives of the end-of-life supplementary advice. The Appraisal Committee made a similar observation for cetuximab for head and neck cancers, although the estimates of the cumulative licensed population have not been precisely estimated. For the other technologies which were considered in the context of the end-of-life criteria and which are licensed for other indications (for example sunitinib for renal cell carcinoma and gastrointestinal stromal tumours), the cumulative population sizes were still 'small' and so the Appraisal Committee felt that they currently fulfil the end-of-life criteria. It has been proposed by one consultee that the Appraisal Committee should assign an even greater QALY weighting to 'ultra-orphan' conditions/treatments. However, the Appraisal Committee considered that, as no further direction or supplementary advice had been issued and as the end-of-life criteria do not recognise such a distinction, ultra-orphan conditions should not be treated differently from other 'end-of-life' conditions or technologies.
- 5.1.6. In establishing whether the estimates of the extension to life and the assumptions in the economic modelling are robust, the whole trial population estimates and estimates from subgroups have, where appropriate, typically been viewed by the Appraisal Committee as robust (for example, sorafenib for renal cell carcinoma). However, some

subgroups were not considered to fulfil the end-of-life criteria, as they were not clearly defined by the manufacturer and small, and therefore the evidence was not considered robust (for example temsirolimus for renal cell carcinoma had subgroups determined broadly and unclearly by type of histology that comprised 18% of trial population; less than 80 people). There have also been circumstances in which the manufacturer has presented post hoc subgroup data, typically in response to consultation, suggesting a greater extension to life in a subgroup compared with the whole trial population (for example, sunitinib for renal cell carcinoma, cetuximab for head and neck cancer and lapatinib for breast cancer). In these cases the Appraisal Committee considered the rationale for the provision of the subgroup data. In the cases of cetuximab for head and neck cancer and lapatinib for breast cancer, the post hoc subgroup analyses were considered to be without robust biological/clinical plausibility. In the case of sunitinib for renal cell carcinoma, the subgroup data were used as a means of overcoming a methodological problem for the patient group as a whole (that is, the trial allowed the use of novel second-line treatments and this did not reflect current UK practice).

## 5.2. *Calculation of QALY weights*

5.2.1. A technical issue has arisen regarding how relative QALY weights should be calculated. The first way of calculating the relative QALY weight is to factor in all QALYs generated during both the 'progression free' period and the 'progressed' period of life extension. The second way of calculating the relative QALY weight, and one that may be argued is technically more accurate, is to include only the QALYs gained through extension of life and not the QALYs gained through improved quality of life during any extended 'progression free' period. The use of the second approach would increase the weight that needs to be applied. The numerical value of this increase depends on the proportion length of the progression-free period relative to the period in the progressed state and the relative difference in utilities generated between the progression free and the progressed health state.

5.2.2. The Committee has adopted the first, simpler approach. It has first assumed that end-of-life candidate technologies would, for reasons of innovation and exceptional severity of illness, merit consideration towards the upper end of the normal threshold range ie £30,000 per QALY. It has then calculated the QALY weighting that would need to be

assumed for a “favourable” decision on the ratio of calculated ICER to 30,000. In the case of sunitinib in renal cell carcinoma, for example, the preferred analysis had sunitinib at (just under) £50,000 per QALY. The Committee noted that a ‘positive decision’ implied valuing the end of life QALYs for RCC patients 70% higher than those for patients in circumstances that did not meet end of life criteria.

### 5.3. *Additional Issues:*

- 5.3.1. The end-of-life criteria were discussed at the first Appraisal Committee meetings for cetuximab for head and neck cancer and sorafenib for hepatocellular carcinoma. However, in the case of sunitinib for gastrointestinal stromal tumours the Appraisal Committee discussed the end-of-life criteria at the second meeting, after the most plausible ICER had been established. For lapatanib, the appraisal committee reviewed the applicability of the criteria as issued for consultation at their second meeting and the Institute requested the committee to meet a third time to consider the application of the final criteria. The Appraisal Committee’s considerations of the end-of-life criteria were released in FADs, and their application and resulting recommendations had therefore not been through a consultation process.
- 5.3.2. The end-of-life criteria were not considered by the Appraisal Committee unless the treatment was indicated for patients with a short life expectancy; that is, this criterion was always the first to be considered. For most of the appraisals in which the end-of-life criteria were considered, the Appraisal Committee had deliberations on all of the criteria. For cetuximab for head and neck cancer the Appraisal Committee accepted that there was evidence that cetuximab did not provide substantial extension to life and also took into account the fact that cetuximab is also licensed for other indications with large eligible populations. For lapatinib for breast cancer, the Appraisal Committee’s discussion of the end-of-life criteria finished as soon as it agreed that there was evidence that lapatinib did not substantially extend life.
- 5.3.3. Many of the appraisals that were considered in the context of the end-of-life criteria also included patient access schemes that had been agreed by the Department of Health. In general, these schemes were in place before the Committee discussed the end-of-life criteria. However, in the cases of bevacizumab for renal cell carcinoma and sorafenib for renal cell carcinoma patient access schemes were proposed by the manufacturer and agreed by the

Department of Health after the supplementary advice on the end-of-life criteria had been published.

- 5.3.4. For the three technologies that have been considered as fulfilling the end-of-life criteria and have been recommended by the Appraisal Committee, the research recommendations have reflected the need for rigorous data collection on the life-extending benefits of the treatments, as set out in the supplementary advice on appraising life-extending, end of life treatments. The review dates for these appraisals are also within two years of the publication date of the guidance, also in accordance with the supplementary advice.

## 6 Summary:

- 6.1. A total of nine technologies out of the 22 that were discussed between January and April 2009 were considered in the context of the end-of-life criteria, that is they were associated with a short life expectancy (less than 24 months). Of these nine technologies, six were considered to fulfil the end-of-life criteria and of these six, three technologies were then recommended as treatment options by the Appraisal Committee.
- 6.2. The sequence of steps the Committee have followed has usually been:
- (1) Is this an EOL technology at all? ie. is life expectancy on current therapy less than about 24 months. This step rules out all non-fatal and many chronic diseases.
- If yes*
- (2) Is it necessary to consider EOL criteria i.e. is the standard calculation ICER more than £20,000 to £30,000?
- If yes*
- (3) Are the criteria (short life expectancy, 3 month+ gain, step change, robust evidence, small cumulative patient population) met?
- If yes*
- (4) Is the implied QALY multiplier acceptable?
- 6.3. , There has been significant discussion by the Appraisal Committee on the application and interpretation of most of the individual end-of-life criteria.

- 6.4. The most significant discussions by the Appraisal Committee have been about the interpretation of 'small patient population', whether any other treatments are available on the NHS with comparable benefits (that is does the treatment constitute a 'marked change' in treatment options), and whether the treatment provides a sufficient extension to life (including subgroups).
- 6.5. Of the six technologies that have fulfilled all of the criteria, the Appraisal Committee has judged acceptable the magnitude of the additional QALY weighting that would be required to bring the cost-effectiveness within an acceptable range for three technologies. The range of QALY weightings for all six technologies that fulfilled the criteria was reported in the evaluation reports and detailed in Appendix D of this report. So far the Committee has *de facto* accepted a highest weighting of 1.7 (relative to a pre EOL threshold of £30,000 per QALY gained noting that this is 2.5 relative to a pre EOL threshold of 20,000 per QALY gained).
- 6.6. The review dates of the three technologies that have been recommended after fulfilling the end-of-life criteria are within 2 years of the publication of guidance. It is possible that the technologies that are recommended under the end-of-life criteria will at review stage no longer fulfil the criteria, for example because they may receive marketing authorisations for additional indications with larger eligible patient populations.

## Appendix A

Table 1 - End-of-life data collection

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Colorectal cancer (1st line): <b>Cetuximab</b> 06-Jan-09 (B)	3 <sup>rd</sup> meeting: ACD 2	£69,300 (vs FOLFORI); £63,200 (vs FOLFOX); 'best-case' 29,900 – 'high degree of uncertainty'	N.R.	N.R.	N.R.	N.R.	N.R.	N.R.
Colorectal cancer (1st line): <b>Cetuximab</b> 01-Apr-09 (B)	4 <sup>th</sup> meeting: FAD	£26,700 - £33,300	N.R.	N.R.	N.R.	N.R.	N.R.	No (treatment was C/E)
Head & neck cancer (squamous cell carcinoma): <b>Cetuximab</b> 06-Jan-09 (B)	1 <sup>st</sup> meeting: ACD1	Manufacturer: £121,000 'considerable uncertainty' ERG: £166,000-£208,000	Yes – median OS 7 months on chemo alone ( <i>from RCT, note that this is not reported in the considerations section in ACD</i> )	No – increment of 0.187 life years gained = 68 days vs chemo ( <i>from model</i> )	Not addressed in detail	Yes-approx 3000 per year with recurrent/metastatic SCCHN and cetuximab given to a smaller proportion.	High degree of uncertainty around ICERs	No

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Head & neck cancer (squamous cell carcinoma): <b>Cetuximab</b> 03-Mar-09 (B)	2 <sup>nd</sup> meeting: FAD	Base-case as above; after consultation manufacturer submitted subgroups ICERs: £92,800 for those aged <65 years and KPS ≥ 90 and £124,400 for those aged <65 and KPS ≥ 80	The Committee noted from the EXTREME trial that life expectancy for patients treated with chemotherapy alone was unlikely to be more than 24 months and could be as low as 7 months.	No-2.7 months from RCT and 0.187 life years gained ~2.2 months ( <i>from model</i> ). Subgroup (Aged <65 years and KPS ≥ 90): 3.7 months	N.R. in detail. Extended median survival gained from the addition of cetuximab, not considered to represent a marked change from current treatment (platinum-based chemotherapy) for SCCHN.	Noted that cetuximab is licensed for other indications with much larger populations.	The Committee considered the EoL criteria only in relation to the estimate of overall survival for the whole trial population.  Subgroups not considered reliable; 'uncertainty' in life extension in subgroups	No
Multiple myeloma: <b>Lenalidomide</b> 06-Jan-09 (B)	2 <sup>nd</sup> meeting: ACD2	2+ prior therapies: 'more than' £43,800 2+ prior therapies (inc thalidomide): 'more than' £41,300 . (Note ICERs include patient access scheme)	Yes – as low as 9 months from MRC obs data	Yes – increment median OS 9.4 months vs dex. (from RCTs; whole trial data)	Yes – thalidomide no evidence of effect in 2 <sup>nd</sup> /3 <sup>rd</sup> relapse & bortezomib not recommended by NICE in 2 <sup>nd</sup> /3 <sup>rd</sup> relapse; also no evidence of the availability of thalidomide in the NHS	Yes – no other licensed indications.	Yes	Yes

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Multiple myeloma: <b>Lenalidomide</b> 03-Mar-09 (B)	3 <sup>rd</sup> meeting: FAD	As above	As above	As above	As above	As above – note population ~2100	Yes	Yes
Renal cell carcinoma: <b>Sunitinib (1<sup>st</sup>-line)</b> 14-Jan-09 (C)	3 <sup>rd</sup> meeting: FAD	'Most plausible' ICER < £50,000,	Yes – potentially as low as 12 months (from RCT)	Yes – incremental median OS 6 months for ITT and 14 months for 'no-post study treatment group' (from RCT)	Yes – considering that bevacizumab is not recommended	Yes	Yes	Yes
Renal cell carcinoma: <b>Sunitinib (2<sup>nd</sup>-line)</b> 11-Mar-09 (C)	4 <sup>th</sup> meeting: FAD	Not considered clinically effective, therefore no ICER established	N.A.	N.A.	N.A.	N.A.	N.A.	No
Renal cell carcinoma: <b>Bevacizumab</b> 14-Jan-09 (C)	3 <sup>rd</sup> meeting: ACD2	£82,700 – 'lowest plausible ICER'.	Yes – potentially as low as 12 months (from RCT)	Yes – although OS was not reached but PFS and model suggestive	Yes	No – has number of other licenses for larger cancers; breast, lung, colorectal	Yes	No

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Renal cell carcinoma: <b>Bevacizumab</b> 11-Mar-09 (C)	4 <sup>th</sup> meeting: FAD	£53,800 (reduced due to PAS), 'lowest plausible ICER'	As above	As above	As above	As above	Yes	No
Renal cell carcinoma: <b>Sorafenib</b> 14-Jan-09 (C)	3 <sup>rd</sup> meeting: ACD2	£65,900 - £74,200,	Yes – potentially as low as 6 months (from RCT)	Yes - although OS was not reached but PFS and model suggestive	Yes-licensed for 2 <sup>nd</sup> -line or unsuitable for IFN	Yes	Yes	Yes
Renal cell carcinoma: <b>Sorafenib</b> 11-Mar-09 (C)	4 <sup>th</sup> meeting: FAD	£65,900	As above	As above	As above	As above	As above	Yes
Renal cell carcinoma: <b>Temsirolimus</b> 14-Jan-09 (C)	3 <sup>rd</sup> meeting: ACD2	£102,000	Yes – potentially as low as 7 months (from RCT)	Yes – incremental median OS 3.6 months (from key RCT)	Yes-licensed for poor prognosis	Yes (see comments)	The RCT data and the economic model were considered robust.  Subgroup data presented by manufacturer not considered robust (therefore not EoL)	Yes

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Renal cell carcinoma: <b>Temsirolimus</b> 11-Mar-09 (C)	4 <sup>th</sup> meeting: FAD	£102,000; 'too low' as vial price increased	As above	As above	As above	As above	As above	Yes
Breast cancer (advanced & metastatic): <b>Lapatinib</b> 22-Jan-09 (A)	3 <sup>rd</sup> meeting: FAD	£93,825 (£69,932 with PAS) for lap+cap vs cap mono.	Yes – approx 15 months on capecitabine alone	No – 1.9 incremental months gained; not statistically significant (from RCT), 2.3 months from model  Subgroup presented by the manufacturer with OS > 3 months	Not addressed in detail	Yes~2000 patients per year	The RCT data and the economic model were considered robust.  Subgroup data presented by manufacturer not considered robust (therefore not EoL)	No
VTE: <b>Rivaroxaban</b> 22-Jan-09 (A)	2 <sup>nd</sup> meeting: FAD	ICER < £30,000 (dominated comparators)	Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
Thrombocytopenic purpura: <b>Romiplostim</b> 03-Feb-09 (B)	Non-quorate meeting	Non-quorate meeting – no discussion at this meeting						

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Thrombocytopenic purpura: <b>Romiplostim</b> 01-Apr-09 (B)	1 <sup>st</sup> meeting: ACD	Manufacturer ICERs: £14,000 - £16,000 'substantial underestimate'	Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
GIST: <b>Sunitinib</b> 11-Feb-09 (C)	1 <sup>st</sup> meeting: ACD	Manufacturer £27,400 - £77,100 'considerable uncertainty'	N. R.	N. R.	N.R.	N.R.	N.R.	N.R.
GIST: <b>Sunitinib</b> 08-Apr-09 (C)	2 <sup>nd</sup> meeting: FAD	'most plausible' ICER: £31,800	Yes – potentially as low as 9 months (from RCT)	Yes – 9 incremental months gained from RCT and model	Yes – BSC only alternative	Yes (although note licensed for RCC)	Yes	Yes
Hepatitis B: <b>Tenofovir disoproxil fumarate</b> 11-Feb-09 (C)	1 <sup>st</sup> meeting: ACD	Less than £20,000	Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
Hepatitis B: <b>Tenofovir disoproxil fumarate</b> 08-Apr-09 (C)	2 <sup>nd</sup> meeting: FAD	As above.	As above.	N.A.	N.A.	N.A.	N.A.	No.

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Osteosarcoma (non-metastatic): <b>Mifamurtide</b> 18-Feb-09 (A)	1 <sup>st</sup> meeting: N.A.	Confidential	Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
Osteosarcoma (non-metastatic): <b>Mifamurtide</b> 22-Apr-09 (A)	Has not received marketing authorisation; appraisal on hold (no ACD released for consultation)							
Leukaemia (chronic lymphocytic, 1 <sup>st</sup> -line) <b>Rituximab</b> 03-Mar-09 (B)	1 <sup>st</sup> meeting: ACD	£13,000 - £30,000	N.A.	N.A.	N.A.	N.A.	N.A.	No
Non small cell lung cancer (1 <sup>st</sup> -line): <b>Pemetrexed</b> 19-Mar-09 (A)	1 <sup>st</sup> meeting: ACD	No base-case ICER established	N.A.	N.A.	N.A.	N.A.	N.A.	N.R.
Eczema (chronic): <b>Alitretinoin</b> 01-Apr-09 (B)	1 <sup>st</sup> meeting: ACD	£13,000 - £31,000	Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No

Appraisal Topic (Cttee)	Meeting #	Base-case ICER + uncertainty	Short life-expectancy?	Extension to life?	No alternative treatments with comparable benefits?	Indication being considered affects small populations AND Licensed for other indications?	Robust data?	Fulfil EOL?
Hepatocellular carcinoma (advanced and metastatic): <b>Sorafenib</b> 08-Apr-09 (C)	1 <sup>st</sup> meeting: ACD	'manufacturer base-case £64,800; 'considerable uncertainty'	Yes - Survival in placebo arm of key RCT 7.9 months	Yes - Extension to life of 2.8 months observed in RCT. Manufacturer's model indicated predicted life years gained 0.51 reflecting a gain in OS of 6.1 months.	Yes – BSC is only alternative	Yes - Approx. 2340 new cases of HCC per yr in England and Wales. Population eligible for sorafenib [advanced HCC] approx. 700	Yes	Yes
Alzheimer's disease: <b>Donepezil, rivastigmine, galantamine and memantine</b> (review) 22-Apr-09 (A)	Review meeting		Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
Psoriasis: <b>Ustekinumab</b> 22-Apr-09 (A)	1 <sup>st</sup> meeting: ACD		Life expectancy > 24 months	N.A.	N.A.	N.A.	N.A.	No
N.R. Not reported; N.A. not applicable; C/E cost effective								

Table 2 – Additional details of appraisals considered in the context of the end-of-life criteria.

Appraisal Topic (Cttee)	Eligible for EoL?	QALY weightings: acceptable/ reported?	Patient Access Scheme?	Research recommendations?	Comments
Head & neck cancer (squamous cell carcinoma): <b>Cetuximab</b> 06-Jan-09 (B)	No	N.A.	No	None	Some of the criteria were not addressed in detail for this appraisal because one of the 'earlier' criteria was already not met. Both median overall survival taken from the RCT and LYG taken from the model considered. No detail of size of populations for other licensed indications of cetuximab In combination; manufacturer presented subgroups after consultation that had increased extension to life (~3.7 months) (note colorectal cancer license not discussed)
Multiple myeloma: <b>Lenalidomide</b> 06-Jan-09 (B)	Yes	Acceptable – no explicit QALY weighting reported	Yes- costs beyond 26 cycles rebated	Rigorous data collection is needed on the life-extending benefits of lenalidomide when it is used in people who have had two or more prior therapies	Quite a significant consultation response about whether lenalidomide is a real innovative product considering that it is a derivative of thalidomide. Also bortezomib received a 'no' before EoL was in play and might have been looked upon differently.
Renal cell carcinoma: <b>Sunitinib (1<sup>st</sup>-line)</b> 14-Jan-09 (C)	Yes	Yes – QALY weights N.R.	Yes- 1 <sup>st</sup> cycle of sunitinib free to NHS	Rigorous data collection is needed on the life-extending benefits of (1 <sup>st</sup> -line) sunitinib when no further treatments are received	* Note that sunitinib has another indication but because that is also for a small population the criterion applies (mentioned in FAD?)

Appraisal Topic (Cttee)	Eligible for EoL?	QALY weightings: acceptable/ reported?	Patient Access Scheme?	Research recommendations?	Comments
Renal cell carcinoma: <b>Bevacizumab</b> 14-Jan-09 (C)	No	N.A.	Yes - bev rebate after 10g given to a patient within a year. All IFN costs rebated	None related to bevacizumab	
Renal cell carcinoma: <b>Sorafenib</b> 14-Jan-09 (C)	Yes	QALY weights N.R. but thought 'too great'	Yes – 1 <sup>st</sup> pack free to NHS	1 <sup>st</sup> -line sorafenib vs BSC for people unsuitable for immunotherapy with a poor or intermediate prognosis 2 <sup>nd</sup> -line sorafenib vs BSC for people in whom a non-immunotherapy based treatment has failed or who are unsuitable for immunotherapy	* Note that sorafenib has another indication but because that is also for a small population the criterion applies  Second-line; not considered differently
Renal cell carcinoma: <b>Temsirolimus</b> 14-Jan-09 (C)	Yes	QALY weights N.R. but thought 'too great'	No	1 <sup>st</sup> -line temsirolimus vs BSC for people unsuitable for immunotherapy with poor prognosis	* Note that temsirolimus has another indication but because that is also for a small population the criterion applies Proposed as an Ultra-orphan; not considered differently

Appraisal Topic (Cttee)	Eligible for EoL?	QALY weightings: acceptable/ reported?	Patient Access Scheme?	Research recommendations?	Comments
Breast cancer (advanced & metastatic): <b>Lapatinib</b> 22-Jan-09 (A)	No	N.A.	Yes	A guidance recommendation for 'only in research'.  RCT of lapatinib + capecitabine vs. trastuzumab-containing regimens and other chemotherapy regimens after trastuzumab. Study of clinical and cost effectiveness of trastuzumab continued after disease progression	Some of the criteria were not addressed in detail for this appraisal because one of the 'earlier' criteria was already not met.  Incremental months gained; 2.3 months from model
Gastrointestinal stromal tumours: <b>Sunitinib</b> 11-Feb-09 (C)	Yes	QALY weightings acceptable as "close to one".	Yes (1 <sup>st</sup> cycle of sunitinib free to NHS)	Rigorous data collection is needed on the life-extending benefits of sunitinib.	Minded no issued after first meeting. EoL discussed at second meeting after most plausible ICER established.
Hepatocellular carcinoma (advanced and metastatic): <b>Sorafenib</b> 08-Apr-09 (C)	Yes?	QALY weightings would be too great to be acceptable (not explicitly reported)	No (though discussing with DH)	None	Note that the trial OS was less than 3 months – the Committee agreed that this was around the level that met the criteria. Also noted that model OS was more than double this (although not many patients providing data by the end of the time horizon that informed this median).

## **Appendix B – Appraisal Committee considerations of technologies that did not fulfil the end-of-life criteria**

### **Cetuximab for squamous cell carcinoma of the head and neck**

The Committee discussed whether cetuximab, in combination with platinum-based chemotherapy for the treatment of recurrent and/or metastatic SCCHN, fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee considered the criteria only in relation to the estimate of overall survival for the cohort population because it did not consider the subgroup data to be robust (see sections 4.3 and 4.4). The Committee noted from the EXTREME trial that life expectancy for patients treated with chemotherapy alone was unlikely to be more than 24 months and could be as low as 7 months. The Committee observed that the trial data suggested that cetuximab plus platinum-based chemotherapy extended median survival by 2.7 months compared with platinum-based chemotherapy alone. The Committee were concerned about the uncertainty associated with this estimate because of the wide confidence interval. It was also aware that the predicted life years gained from the economic modelling for this group was 0.187, reflecting a gain in overall survival of approximately 2.2 months. The Committee therefore did not consider that this estimate of gain in overall survival was in keeping with the criteria relating to extension of life or that the addition of cetuximab represented a marked change from current treatment for SCCHN.

The Committee also understood that an estimated 3000 people in England and Wales are diagnosed with recurrent and/or metastatic SCCHN every year, however based on the evidence from clinical specialists, cetuximab plus platinum-based chemotherapy would be appropriate for only a small proportion of these patients (that is, those whose disease was unsuitable for local treatment and who were well enough to receive platinum-based chemotherapy). However, the Committee understood that it should take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria for appraising life-extending, end-of-life treatments. It noted that cetuximab was licensed for a number of other indications involving much larger patient groups.

In summary, the Committee was not persuaded that the use of cetuximab plus platinum-based chemotherapy fulfilled all the criteria to be considered as a life-extending, end-of-life treatment. The Committee came to this conclusion taking into account the importance of supporting the development of innovative treatments licensed for small groups of patients who have an incurable illness.

### **Bevacizumab for advanced and/or metastatic renal cell carcinoma**

The Committee next discussed whether bevacizumab plus IFN- $\alpha$  for the treatment of advanced and/or metastatic RCC fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with IFN- $\alpha$  treatment alone was unlikely to be greater than 24 months and was potentially as low as 12 months. The Committee agreed that it was likely that bevacizumab plus IFN- $\alpha$  would increase overall survival by more than 3 months in comparison with IFN- $\alpha$  alone. It had heard that RCC does not respond well to IFN- $\alpha$  alone, but considered that bevacizumab plus IFN- $\alpha$  does represent a marked change in the treatment of advanced and/or metastatic RCC. The Committee was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. However, the Committee understood that it should take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria for appraising life-extending, end-of-life treatments. It noted that bevacizumab was licensed for a number of other indications involving much larger patient groups. The Committee noted that the manufacturer argued that the use of bevacizumab was restricted in the UK and that, in effect, the valid patient population for bevacizumab is small. However the Committee considered that this point did not override its view that bevacizumab is licensed for a relatively large population across its range of indications. In summary, the Committee was not persuaded that bevacizumab plus IFN- $\alpha$  meets all the criteria for a life-extending end-of-life treatment, given the size of the patient populations (in RCC and other cancers) for whom it is licensed.

### **Lapatinib for advanced and/or metastatic breast cancer**

On this basis the Committee understood that the main RCT reported a median overall survival for patients receiving capecitabine monotherapy of approximately 15 months (65.9 weeks). It is estimated that approximately 2000 patients with HER2-overexpressing metastatic breast cancer per year are receiving second- or third-line chemotherapy and are therefore eligible to be offered treatment with lapatinib. The Committee observed that the trial data suggest that lapatinib plus capecitabine extends survival relative to capecitabine alone. However, it noted that the main RCT reported a gain in overall survival of approximately 1.9 months which did not reach conventional levels of statistical significance (lapatinib plus capecitabine 17.1 months versus capecitabine alone 15.2 months, HR 0.90; 95% CI 0.71 to 1.12,  $p = 0.3$ ). The Committee was also mindful of the results from the economic model, but noted that this provided an estimate of life years gained of 0.19 reflecting a gain in overall survival of approximately 2.3 months. Therefore, the Committee did not consider that the size of the possible benefit was in

TITLE: UPDATE REPORT ON THE APPLICATION OF THE 'END-OF-LIFE' SUPPLEMENTARY ADVICE IN HEALTH TECHNOLOGY APPRAISALS

DATE: 22 JULY 2009

REF: 09/055

keeping with the supplementary advice from NICE for consideration of life-extending, end-of-life treatments.

In summary, the Committee accepted the estimates of clinical-effectiveness reported in the main lapatinib RCT. However, the Committee did not consider that lapatinib had demonstrated that it was cost effective in comparison with capecitabine or vinorelbine, either with or without the patient access scheme. The Committee was mindful that trastuzumab may be continued following progression of disease but considered that the data submitted by the manufacturer of lapatinib had demonstrated that trastuzumab was not cost effective compared with capecitabine. The Committee noted the blended comparator proposed by the manufacturer, which enabled the calculation of a single ICER comparing lapatinib with current standard care. The Committee considered it inappropriate to mix mutually exclusive healthcare technologies. Therefore the Committee did not accept the use of the blended comparator with the application of the patient access scheme. The Committee was not persuaded that lapatinib fulfilled the criteria described in the supplementary advice from NICE for consideration of end of life treatments. The Committee concluded that the use of lapatinib was not a cost effective use of NHS resources, and recommended that lapatinib should only be used in the context of further research.

The Committee was informed by NICE that an additional subgroup analysis had been submitted by the manufacturer of lapatinib the day before the Appraisal Committee meeting. In line with the published process, the Committee was not required to consider the late submission. However, the Committee chose to look at the document submitted by the manufacturer in order to assess whether the data presented in the document would be likely to materially affect the conclusions already reached. In the document the manufacturer identified a group of patients from the main RCT who had received less than three prior treatment regimens. The manufacturer argued that these patients more appropriately matched those enrolled in the trastuzumab RCT and that the clinical- and cost-effectiveness results from this subgroup should therefore be considered. The Committee considered whether in principle that it was clinically possible that this subgroup of patients might respond to lapatinib differently. The Committee was concerned that the subgroup was based on a small number of patients, and that very little information was provided on how the subgroup was identified, and on the patients involved. The Committee also noted that there was no exploration of the possibility that the differences in the efficacy observed for this subgroup could have occurred by chance. The Committee considered that the data analysis could, at this stage, generate a useful hypothesis for future research but it could not materially affect the conclusion that lapatinib should only be used in the context of clinical trials.

## **Appendix C – Appraisal Committee considerations of technologies that did fulfil the end-of-life criteria**

### **Sunitinib (1st-line) for advanced and/or metastatic renal cell carcinoma**

The Committee next discussed whether sunitinib for advanced and/or metastatic RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. Although the Committee noted that sunitinib was to be aimed at more patient groups than just people with RCC, such as people with gastrointestinal stromal tumours, this was the first indication for which it was being appraised. It therefore considered that for this appraisal, sunitinib should be regarded as meeting this criterion for an end-of-life treatment. The Committee noted from the clinical trials that the normal life expectancy with IFN- $\alpha$  treatment alone was unlikely to be greater than 24 months and was potentially as low as 12 months. The Committee also noted that evidence from the sunitinib trial suggested that sunitinib increased survival by more than 3 months in comparison with IFN- $\alpha$  alone. It was further persuaded that sunitinib provided a step-change in the first-line treatment of advanced and/or metastatic RCC and noted that more than 20% of the public and patients that responded in consultation highlighted this impressive benefit from sunitinib. In summary, the Committee was satisfied that sunitinib currently meets the criteria for being a life-extending end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

### **Sorafenib (2nd-line) for advanced and/or metastatic renal cell carcinoma**

The Committee next discussed whether sorafenib for the treatment of advanced RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months. The Committee considered that even though the sorafenib trial was terminated early, this was done after a report of increased progression-free survival in the sorafenib arm. The Committee considered that it was likely that sorafenib would increase overall survival by more than 3 months in comparison with best supportive care. It also agreed that sorafenib provided an improvement in the treatment of advanced RCC. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. Therefore the Committee was satisfied that sorafenib meets the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this consideration was robust.

### **Temsirolimus (1st-line) for advanced and/or metastatic renal cell carcinoma**

The Committee next discussed whether temsirolimus for the treatment of advanced and/or metastatic RCC fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with IFN- $\alpha$  treatment alone was unlikely to be greater than 24 months and was potentially as low as 7 months for patients with a poor prognosis. The Committee considered that evidence from the temsirolimus trial suggested that temsirolimus increased survival by more than 3 months compared with IFN- $\alpha$  alone and it considered temsirolimus to be an improvement in treatment for advanced and/or metastatic RCC. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000 and that temsirolimus was licensed for people with a poor prognosis and so had a very small patient population. The Committee agreed that the criterion for the robustness of evidence was convincing for the overall trial data, but not for the subgroup data. In summary, the Committee was satisfied that temsirolimus met the criteria for being a life-extending, end-of-life treatment for the whole trial population.

### **Lenalidomide for multiple myeloma**

The Committee next discussed whether the subgroup of people with multiple myeloma who had received two or more prior therapies, and the benefit provided by lenalidomide, fulfilled the criteria for consideration as an appraisal of a life-extending, end-of-life treatment. The Committee noted from the clinical trials and the MRC data that normal life expectancy without lenalidomide was unlikely to be greater than 24 months and was potentially as low as 9 months. The Committee considered that evidence from the lenalidomide trials suggested that lenalidomide increased survival by more than 3 months compared with dexamethasone, and that crossover in the dexamethasone arm means that this benefit is likely to have been underestimated. The Committee considered that the potential alternatives, thalidomide and bortezomib, were unlikely to be routinely available on the NHS, as discussed in section 4.4. The Committee noted from the manufacturer's submission that the estimated eligible population was approximately 2100. In summary, the Committee was satisfied that the population and the technology of interest meet the criteria for accepting that this is an appraisal of a life-extending, end-of-life treatment and that the evidence presented for this consideration was supported by robust data.

### **Sunitinib for gastrointestinal stromal tumours**

The Committee then discussed whether sunitinib for unresectable and/or metastatic malignant GIST, given after intolerance or resistance to imatinib, fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It was aware that in England and Wales the total number of people concerned was between 90 and 150. The Committee noted from the RCT that the life expectancy for unresectable and/or metastatic malignant GIST, following intolerance or resistance to imatinib, with best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 9 months. The Committee also noted that the evidence from the RPSFT analysis of the trial suggested that sunitinib increased survival by more than 3 months compared with best supportive care. The Committee noted the comments from patient experts and clinical specialists highlighting the important benefits of sunitinib and was persuaded that sunitinib provided a marked change in the treatment of unresectable and/or metastatic malignant GIST that is intolerant or resistant to imatinib. In summary, the Committee was satisfied that sunitinib met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

### **Sorafenib for hepatocellular carcinoma**

The Committee discussed whether the benefit provided by sorafenib in HCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It noted from the clinical studies that normal life expectancy without sorafenib was unlikely to be greater than 24 months and was potentially as low as 7.9 months. The Committee considered that evidence from the clinical studies of sorafenib plus BSC suggested that it increased survival by more than 2.8 months compared with placebo plus BSC, and the manufacturer's economic model predicted a gain in overall survival of 6.1 months. The Committee considered that the potential alternative, doxorubicin, was unlikely to be used routinely in the UK (see section 4.4). The Committee noted from the manufacturer's submission that the estimated eligible population was approximately 700 new cases per year. In summary, the Committee was satisfied that the population and sorafenib met the criteria for an appraisal of a life-extending, end-of-life treatment, and that the evidence presented was supported by robust data.

**Appendix D – Implicit QALY weightings considered by the Appraisal Committee**

**Sunitinib (1<sup>st</sup>-line), sorafenib (2<sup>nd</sup>-line) and temsirolimus (1<sup>st</sup>-line) for advanced and/or metastatic renal cell carcinoma**

This is based on i) the mean age of diagnosis for renal cell using the ICD codes CD64:66, 68 as in the assessment report and ONS data for cancer registrations 2004 and ii) weights from the York MVH study (Kind, Hardman and Macran (1999) CHE Discussion paper 172)

**mean age (yrs) at diagnosis:** 66 males 67 females  
**utility in this age group** 0.78

<i>IC</i>	<i>I LYG</i>	<i>IQ (original)</i>	<i>ICER (original)</i>	<i>IQ (max)</i>	<i>ICER (max Q)</i>	Relative weights			
						<i>Original Q</i>		<i>max Q</i>	
<b>Scenario</b>						<b>20,000</b>	<b>30,000</b>	<b>20,000</b>	<b>30,000</b>

Sunitinib vs IFN, using Committee's preferred assumptions (and no restriction on time of administration of IFN):

31921	0.86	0.59	54103	0.6708	47586	2.71	1.80	2.38	1.59
-------	------	------	-------	--------	-------	------	------	------	------

Temsirolimus vs IFN, using manufacturer's model with Assessment Group IFN administration costs

13717	0.221	0.134	102366	0.17238	79574	5.12	3.41	3.98	2.65
-------	-------	-------	--------	---------	-------	------	------	------	------

Sorafenib vs BSC, using 'failed IFN' subgroup with patient access scheme and new price

20153	0.425643	0.31	65929	0.33200154	60702	3.25	2.17	3.04	2.02
-------	----------	------	-------	------------	-------	------	------	------	------

## Lenalidomide for multiple myeloma

**Table 1: Quantitative exploration of QALY gains from the December ERG model with a price cap at two years<sup>1</sup>**

Scenarios	Incremental costs (£)	Incremental life-year gained	Incremental QALYs (original)	ICER (original, £/QALY)	Incremental QALYs (max)*	ICER (max QALY)	Relative Weights			
							Original QALY		Max QALY	
							20000	30000	20000	30000
>1 prior therapy with modeled dexamethasone survival curve fitted to either median or mean of MRC data										
Fitted to median	56,170	2.78	1.86	30,200	2.25	24,964	1.51	1.01	1.25	0.83
Fitted to mean	54,291	1.81	1.24	43,800	1.47	36,932	2.19	1.46	1.87	1.23
>1 prior therapy including prior thalidomide with modeled dexamethasone survival curve fitted to either median or mean of MRC data										
Fitted to median	49,275	2.55	1.7	29,100	2.07	23,804	1.46	0.97	1.19	0.79
Fitted to mean	47,531	1.71	1.15	41,300	1.39	34,195	2.07	1.38	1.7	1.14
*Assuming a health related quality of life of 0.81 for a healthy individual in this population based on van Agthoven and colleagues (2004)										

<sup>1</sup> Based on data from “Hoyle M, Rogers G, Garside R et al, The clinical and cost-effectiveness of lenalidomide for multiple myeloma in people who have received at least one prior therapy: an evidence review of the submission from Celgene: Addendum to the report submitted on 1<sup>st</sup> September 2008.” Calculations by the technical team at the National Institute for Health and Clinical Excellence 5 January 2009.

### Sunitinib for gastrointestinal stromal tumours

This is based on i) the mean age of diagnosis for GIST using the ESMO Guidelines Working Group Report, 2007 and ii) weights from the York MVH study (Kind, Hardman and Macran (1999) CHE Discussion paper 172)

*mean age (yrs) at diagnosis:* 60

*utility in this age group* 0.8

						Relative weights			
<i>IC</i>	<i>I LYG</i>	<i>IQ (original)</i>	<i>ICER (original)</i>	<i>IQ (max)</i>	<i>ICER (max Q)</i>	<i>Original Q</i>		<i>max Q</i>	
						£20,000	£30,000	£20,000	£30,000
15928	0.77	0.5	31856	0.616	25857	1.59	1.06	1.29	0.86

### Sorafenib for hepatocellular carcinoma

**Table 2: Quantitative exploration of QALY gains from the manufacturer's model<sup>2</sup>**

Scenarios	Incremental costs (£)	Incremental life-year gained	Incremental QALYs (original)	ICER (original, £/QALY)	Incremental QALYs (max)*	ICER (max QALY)	Relative Weights			
							Original QALY		Max QALY	
							20000	30000	20000	30000
Base case	23,232	0.51	0.36	64,754	0.4	58,080	3.20	2.16	2.90	1.94

<sup>2</sup> Based on data from the manufacturer's submission for the STA of 'Sorafenib for the treatment of HCC'

\* Calculations by the technical team at the National Institute for Health and Clinical Excellence April 2009.

