

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

RESEARCH AND DEVELOPMENT

Response to Consultation

Appraising life-extending, end of life treatments

1 Introduction

- 1.1 In November 2008 proposals for an addendum to the 'Guide to Methods of Technology Appraisal' were released for a five week public consultation. The proposal set 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.
- 1.2 This response document highlights the key themes from public consultation on the draft proposal and describes the subsequent changes to the document.

2 Background

- 2.1 The 'Guide to Methods of Technology Appraisal'¹, describes the concepts and principles that underlie the Appraisal Committee's appraisal of evidence and decision making.

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<http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetohemethodsoftechnologyappraisal.jsp>

- 2.2 In November 2008 proposals for an addendum to the 'Guide to Methods of Technology Appraisal' were released for public consultation. The addendum 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.
- 2.3 The consultation asked three specific questions. In addition, there was an opportunity to provide any other comments. The three questions were:
- Your view on the proposition that the Committee should be asked to place additional weight on proven survival benefits in patients with terminal illness and short life expectancy.
 - In particular, is the wording in section 2 appropriate, and will it help the Appraisal Committees achieve the objective set out in section 1?
 - Are there valid alternatives which might be used to achieve the same ends, in the short or long-term?
- 2.4 The draft proposal was amended in light of the consultation comments and a revised proposal was discussed by the Board in December 2008.
- 2.5 The Institute received around 850 comments from 300 responders to the consultation. Table 1 shows the proportions of responses by different types of organisation/individual. NHS professionals formed the largest group of respondents, followed by patients, carers and the public, and 'other' (mainly people who didn't specify their interest but including charities and people from local government).. There were responses from a number of other non-UK Health Technology Assessment organisations.
- 2.6 Many responses were multi-stranded, addressed other aspects of NICE processes/methods, and focussed on specific appraisals,

predominantly the appraisal of drugs for renal cell carcinoma. This response paper focuses on the purpose of the consultation namely the supplementary advice required for appraising life-extending, end of life treatments. General issues relating to NICE processes and methods are only addressed where they impact on this supplementary advice.

Table 1: Categories of individuals/organisations who responded to consultation

	Q 1	Q 2	Q 3	Q 4
NHS	67	64	53	59
Other	60	56	44	50
Patient/Carer/Public	38	32	29	47
Pharma	18	17	14	15
Committee	26	27	21	21
Total comments	209	196	161	192

2.7 In summary, the majority of respondents supported the proposal on the grounds that rejecting proven life-extending treatments on the grounds of cost-effectiveness was not acceptable. There was also an added concern that NICE’s existing economic methods may not fully capture the value given to extensions to life when individuals have a short life expectancy. However, many respondents noted that there are other circumstances that might also warrant special consideration and that this proposal would potentially divert resources away from other equally deserving patients. Concerns were expressed about the details of the proposal and respondents highlighted the technical/methodological problems with implementing the proposals. A need for further methodological exploration of the issues was identified.

3 Question 1: Your view on the proposition that the Committee should be asked to place additional weight on proven survival benefits in patients with terminal illness and short life expectancy.

- 3.1 Overall, 63% of respondents supported the proposition; 21% were against; 16% commented on aspects of the proposition without expressing a clear view either way.
- 3.2 Patients, carers and the public were almost entirely in favour of the proposition. NHS professionals were only just in favour, as were NHS and NHS-related organisations. Of the 'other' category, twice as many were in favour as against. Industry and charities were predominantly in favour.
- 3.3 Comments made in support of the proposal were:
- Any drug that is proven to prolong life should be given extra weight.
 - Treatment should be given regardless of cost if no alternative is available.
 - Access should be in step with other leading economies.
 - The proposals support the wider societal values of humanity and compassion.
 - The QALY (Quality-Adjusted Life Year) measure doesn't adequately capture the important issues for 'terminally ill' patients.
 - The proposals reflect NICE's existing Social Value Judgements².
 - Appreciation for NICE's intervention in an untenable situation.

² <http://www.nice.org.uk/aboutnice/howwework/socialvaluejudgements/socialvaluejudgements.jsp>

3.4 Concerns were however raised about a number of aspects of the proposal:

- The proposition is illogical and contradicts principles of appraisal and/or NICE's Social Value Judgements. There is no scientific evidence to support the proposition, particularly on societal preferences with respect to end-of-life (EoL). It would be more opportune to focus on severity of disease.
- There are ethical issues around the proposal in general and around the use of the limits specified in the proposal. The limits set (7,000 population limit and 24 months anticipated survival) are arbitrary and cannot be substantiated.
- The proposition does not consider the opportunity cost of making greater provision for end-of-life treatments. The lack of ring-fenced budget associated with the proposals will result in inequity/unfairness to other patient groups and other types of intervention, such as prevention and palliative care.
- The focus on providing medicines alone for the end-of-life is inappropriate. For this patient group, it would be more opportune to focus NHS resources on implementing the Department of Health's EoL Care Strategy³ (including non drug treatments) which may provide greater benefits. In addition, treatment-specific information needs to be provided to facilitate a better communication between doctors and patients about the true benefits and risks associated with treatments.
- There will be many technical/methodological problems with implementing the proposals, including in the interpretation of some of the limits, for example 'substantial' extension to life.
- The requirement for the treatment to have gone through a standard appraisal process will impact on the timeliness of the guidance produced by NICE.

³ <http://www.dh.gov.uk/en/Healthcare/IntegratedCare/Endoflifecare/index.htm>

- The proposal sets a precedent and will create a number of incentives for increased targeting of therapies and for raising prices for EoL medicines. There is no specified upper threshold limit. It is not clear how the proposition fits with the value-based pricing scheme. The proposals will impact on similar assessments that Primary Care Trusts make on non-NICE cancer drugs/other drugs/non-drugs.

Response

- 3.5 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. The Appraisal Committees have in the past made recommendations above the normal threshold range in circumstance when they have 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.
- 3.6 In response to concerns raised by stakeholders the Institute has felt the need to strengthen the advice given to its Appraisal Committees. 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 EoL for small populations. In particular to ensure that, where the benefits or treatments designed to extend life at the EoL are not, or not adequately, captured in the reference case, the Appraisal Committees are provided with an appropriate supplementary analysis.
- 3.7 In developing this supplementary advice, the Institute has taken account of 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 year (QALY) threshold range.

- 3.8 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.
- 3.9 The Institute however recognises that the supplementary advice is controversial and acknowledges the concerns that the advice has the potential to divert resources away from other, equally deserving patient groups. To ensure that the supplementary advice is robust for the long-term and that it achieves its intended purpose, the Institute will undertake a methodological evaluation. The results of this evaluation will be made publically available and used to make modifications to the supplementary advice, if necessary.
- 3.10 In recognition of the premium that the NHS has been asked to pay for these treatments the Institute recognises the need to ensure that the anticipated survival gains are evident when the treatments are used in routine practice. The Institute does not receive any funds to conduct the research required, therefore it will normally recommend to the Department of Health that it should give consideration to a data collection exercise.
- 3.11 The supplementary advice to the Appraisal Committees is to be taken into account at the time the appraisal is undertaken within existing process, methods and timelines. Section 2.2 of the advice specifies what supplementary analyses will be considered to ensure that this is made available to the Appraisal Committees at

the point of decision making. Similarly, any specific points of appeal relating to the application of the supplementary advice will be considered within the existing appeal process. This supplementary advice is not therefore anticipated to impact on the timeliness of any guidance produced.

- 3.12 Finally the supplementary advice is based on the premise that in circumstances where patients have a short life-expectancy, society is prepared to fund life-extending treatments that would not meet the cost-effectiveness criteria used for other treatments. The Institute does not receive funds to conduct the research required but it will work with methodological research funders to ensure that research is undertaken to validate this premise. NICE will also work with research funders and researchers to ensure the technical aspects of the current cost-utility approach with respect to life-extending, EoL treatments are investigated.

4 Question 2: In particular, is the wording in section 2 appropriate, and will it help the Appraisal Committees achieve the objective set out in section 1?

4.1 Section 2.1.1

- 4.1.1 Section 2.1.1 stated that “*the medicine is indicated, in its license for a patient population normally not exceeding 7000 new patients per annum*”. Section 1.3 expanded further ‘*exceed 7,000, with the intention of including medicines for rarer cancers and other uncommon conditions, and small groups within larger populations. The reason for selecting a small population maximum figure is that it may sometimes be the case that the costs involved in developing medicines for small groups of patients need to be reflected in a higher price, at least for the first indication.*”

- 4.1.2 A number of respondents acknowledged that limits were required to ensure that the scheme reflects the investment needed to recognise 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.
- 4.1.3 The vast majority of respondents were unhappy with the population number restriction. Clarification was also required as to whether the 7,000 population related to the overall population or sub-groups in whom the treatment was indicated. It was also felt that any limit should be based on the potential number of patients who would benefit not the size of the underlying population with a particular condition. Queries were also raised as to whether the limit related to England and Wales and from what source the population estimates should be drawn. Respondents also noted that this criterion would reward 'rare' diseases over others, would lead to sub-specialising indications by drug companies to reach this target and, with the increase in genetic markers, be open to abuse.

Response

- 4.1.4 The rationale for selecting a small population was, as stated in section 1.3 of the consultation document, to acknowledge that the costs involved in developing medicines for small groups of patients may be reflected in a higher price, at least for the first indication. NICE however acknowledges that obtaining accurate estimates on specific populations may be practically difficult and that there may be variation between estimates from different sources. In order to reflect the difficulties in estimating the precise number of patients for whom a treatment is indicated the wording has been amended to: "*the treatment is licensed or otherwise indicated for small patient populations*".

4.2 Section 2.1.2

- 4.2.1 Section 2.1.2 stated that the medicine is “*indicated for the treatment of patients with a diagnosis of a terminal illness and who are not, on average, expected to live for more than 24 months*”.
- 4.2.2 Respondents deemed this criterion to be unacceptable, arbitrary, too simplistic and to discriminate against people with conditions that may progress slowly. They also noted that overall survival was difficult to predict; in addition to variation between individuals, prognosis varies by type and stage. The criterion could favour drugs for the latter end of the treatment pathway, when quality of life may be poor, over earlier stage treatments when absolute gain in life may be greater and quality of life better.
- 4.2.3 A number of amendments were proposed including reducing the criterion to 12 or 6 months in line with definitions of ‘terminal illness’ including that given by the World Health Organisation. Clarification was also requested as to whether the 24 months was intended to be from diagnosis or from last treatment intervention; with or without existing pharmacological treatment. Also whether the average was the mean, median or mode; and what source of data should be used.

Response

- 4.3 This criterion has been revised to provide clarification. Section 2.1.1 of the final advice states that “*The treatment is indicated for patients with a short life expectancy, normally less than 24 months*”.

4.4 Section 2.1.3

- 4.4.1 Section 2.1.3 of the consultation document stated “*there is sufficient evidence to indicate that the medicine offers a substantial extension to life, compared to current NHS treatment*”.

- 4.4.2 Respondents highlighted the need to provide further clarification about what constitutes a 'substantial' extension to life. They also noted that novel treatments may offer important benefits other than just extension to life that should be taken into account. For example improved quality-of-life, reduced toxicity, less morbidity, and alternative modes of administration.
- 4.4.3 Further clarification was also requested as to what constitutes sufficient evidence. For example whether head-to-head randomised controlled trial evidence was required, or whether indirect comparisons/observational data would be acceptable. A number of respondents focussed on the definition of current NHS treatment. Points raised included that current NHS treatment might not be 'best' NHS treatment.

Response

- 4.4.4 Section 3 and Section 5 of the 2008 revised 'Guide to the Methods of Technology Appraisal' addresses the evidence that the Institute requires. The evidence required for appraising life-extending, end of life treatments will be required to meet the same standards.
- 4.4.5 In line with existing methods of appraisal, the comparator treatments will be established during the scoping phase which includes a consultation period. Section 2.2.4 of the 2008 'Guide to the Methods of Technology Appraisal' provides further clarification: *"Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance) and to the natural history of the condition without suitable treatment. There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice. For example, this may occur when new technologies are used inconsistently across the NHS. Relevant comparator technologies may also include those that do not have a marketing authorisation (or CE mark for medical devices) for the*

indication defined in the scope but that are used routinely for the indication in the NHS. Comparator technologies may include branded and non-proprietary (generic) drugs. Sometimes both technology and comparator form part of a treatment sequence, in which case the appraisal may need to compare alternative treatment sequences. The scoping process aims to specify the comparator technologies as precisely as the technology under appraisal. Evidence providers will need to give due regard to all the above considerations when selecting comparator technologies for analyses in the evidence submissions”.

4.5 Section 2.2

4.5.1 Section 2.2 of the proposal stated that *“In order to recommend use of a treatment, the Appraisal Committee will need to be satisfied that:*

- *2.2.1 The estimates of the extension to life are robust and can be shown or reasonably inferred from either progression free survival or overall survival (in trials in which cross-over has occurred and been accounted for in the effectiveness review). Life-extension inferred from modelled mortality gains, where the effects of the intervention are only on morbidity will not be sufficient, and;*
- *2.2.2 The assumptions used in the economic modelling should be plausible objective and robust, and;*
- *2.2.3 No alternative treatment with comparable benefits is available through the NHS.”*

4.5.2 A number of comments were made about the technical issues in section 2.2 and 2.3. Of particular concern was the criterion 2.2.3 and it was argued that this was against patient choice and competition because the new intervention may have alternative benefits other than extending life. Respondents requested clarification of what was intended and how comparable benefits

should be demonstrated. Other issues raised were whether the alternative treatments were only those approved by NICE, and whether it could include those not approved by NICE. Also whether it encompassed any medicine theoretically available, or only those that were routinely used.

Response

4.5.3 The wording of these criteria have been simplified and moved to Section 2.3 of the revised scheme, which states: *“In addition, the Appraisal Committee 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.”*

4.5.4 Criterion 2.2.3 has been moved to section 2.1. Section 4.4.5 of this response document highlights the guidance on comparators provided in the Section 2.2.4 of the 2008 ‘Guide to the Methods of Technology Appraisal’.

4.6 Section 2.3

4.6.1 Section 2.3 of the proposal stated *“higher ICERs (incremental cost effectiveness ratios) will need to be justified by demonstrable increases in extension to life, and a sound case for the impact of innovating for a small patient population”*.

4.6.2 Respondents stated that this criterion was ‘too loose’ and not useful. Clarification was also requested as to what would constitute ‘higher ICERs’, a ‘sound case’ and ‘demonstrable’. They also requested further detail of what impacts might be included and the

need to encourage innovation where large numbers of patients could benefit.

Response

- 4.6.3 This criterion has been removed from the final supplementary advice. Section 1.3 of the revised document now highlights the Institute's "*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.*"

5 Question 3: Are there valid alternatives which might be used to achieve the same ends, in the short or long-term?

- 5.1 A large proportion of respondents thought the question was asking whether there were alternative treatment options for the management of renal cell carcinoma.
- 5.2 A significant proportion (predominantly NHS professionals) thought NICE's current methods and processes are appropriate and should not be changed. It was noted that the current appraisals methods manual allowed latitude to recommend treatments that did not meet the existing criteria for cost-effectiveness.
- 5.3 Respondents noted that the technologies to which the scheme might apply would have a high price (acquisition cost). A number of suggestions were made to reduce the price paid by the NHS. For example, specification of the price at which the intervention would become cost effective, central renegotiation of the price or flexible pricing schemes.

- 5.4 The budget impact of accepting these high-cost technologies into the NHS was highlighted, as was the need for the budget impact to be taken into account by NICE. A number of suggestions were made to offset this including releasing resources from Primary Care Trusts and identifying treatments which should be withdrawn from the NHS. Respondents suggested ring-fenced budgets to prevent diversion of resources from other patient groups, setting a maximum total cost or cost per patient, and establishing specialist rare cancer commissioning.
- 5.5 A number of responses focussed on the need to review NICE's current cost-effectiveness threshold.
- 5.6 Many respondents questioned whether the economic approach (including the current system of calculating QALYs) used by the Institute fully captured the value placed on extensions to life in the circumstances where there is a shortened life expectancy. To address this concern a number of alternative technical methods were proposed including:
- Use of cost per year/month of expected life gain rather than cost QALY.
 - Threshold analysis to indicate how much more the benefits would need to be weighted to allow the intervention to fall below current cost per QALY threshold. The Committee could then assess acceptability of how much more benefit would need to be attributed to patients with a shortened life expectancy compared to other patient groups.
 - Non-reference case sensitivity/scenario analyses to explore the impact of giving additional weight to QALYs gained when there is a shortened life expectancy.
 - Using health utilities derived from actual patients rather than those of the general public.

- Assigning the period of survival the full age-related quality of life rather than the quality of life actually being experienced by the patient.
- Including ALL costs/benefits in the perspective taken rather than just those for the NHS/Personal Social Services.
- Commissioning of research into whether the EuroQol 5-D and other quality of life measurement tools capture all the benefits of extending survival and what weight would be assigned to QALYs from derived from patients with a short life expectancy.
- Consideration given to severity of disease rather than EoL.
- Using 'health profiles' rather than snapshot 'health states' to take into account quality of life over a specified time period.

Response

- 5.7 The price of a treatment is a key determinant of its cost-effectiveness. However, pricing issues, including flexible pricing schemes are not within NICE's remit and are the responsibility of the Department of Health. It is anticipated that some of the issues raised by consultees will be addressed through the revised Pharmaceutical Price Regulation Scheme.
- 5.8 NICE's mandate does not allow for the budget impact to be taken into account when making decisions about cost-effectiveness. This is the responsibility of the Department of Health.
- 5.9 As part of its quality assurance process NICE continually examines its methods. NICE is holding a technical workshop in February 2009 to discuss issues around the current threshold. The workshop will explore what would need to be done by NICE and by others should a need to review the threshold be identified. No decisions regarding the threshold range will be made at the workshop. In any event, the reference case ICER for treatments likely to be considered under this supplementary advice will exceed any conceivable extension to the threshold range.

5.10 The intention of the supplementary advice is to ensure that the Appraisal Committee fully consider all the benefits that it is appropriate to take into account in appraising treatments designed to extend life at the EoL for small populations. In particular to ensure that where benefits are not, or not adequately, captured in the reference case the Appraisal Committees are provided with an appropriate supplementary analysis. This objective has now been clarified in section 1.4 of the revised addendum now and Section 2.2 now provides further technical detail on the supplementary analyses that will be considered:

- *"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."*

6 Other issues raised

6.1 Evidence Development

6.1.1 Section 1.7 of the proposal stated *"Subject to agreement with the Department of Health, medicines recommended for use on the basis of the criteria set out in section 2.1, will normally be subject to an appropriately designed programme of evidence development to ensure that the anticipated survival gains are evident when it is used in routine practice. The outcome of this exercise will be evaluated when the guidance is reviewed. The design of the studies will be determined by the Institute and will need to be funded centrally. NICE will be responsible for managing the data collection exercise and assessing and reporting the outcome.*

Manufacturers will be given access to anonymised data and a summary of the results published’.

- 6.1.2 Responses to the consultation noted that £100,000 was not realistic and far more resources would be required. It was also noted that the research needed to be prioritised against other projects. A number of methodological issues were also noted including the fact that, because rare diseases/small populations were involved, recruitment of sufficient numbers of patients would be slow and difficult, possibly requiring international collaboration. The need to capture quality of life in addition to survival was also raised. Respondents also questioned what would happen in the event that it was not possible to obtain for robust estimates of relative survival benefits.

Response

- 6.1.3 As a result of the consultation and the fact that research funds would need to go through the existing NIHR prioritisation process Section 1.5 of the supplemental advice has been amended: *“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 data collection exercise 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’.*

7 Clarifications

- 7.1 In line with existing NICE processes⁴, the review date is the month and year when NICE will consult with relevant organisations on a review proposal to decide whether or not the guidance needs to be updated, and if so, how to update the guidance. The length of time between the publication of the guidance and the review date will vary depending on the available evidence for the technology, and knowledge of when ongoing research will be reported. It is possible that evidence that may make a substantial impact on the current guidance will become available in advance of the official review date for the guidance. The Institute, or consultees or commentators to the original appraisal, can identify such evidence. If the Guidance Executive considers that the emerging evidence is of particular significance and will impact on the validity of the guidance, then the review date for the guidance may be brought forward. The Institute will not review any guidance earlier than 1 year after its publication.
- 7.2 Any specific points of appeal relating to the application of the supplementary advice will be considered within the existing appeal process.
- 7.3 The Institute will not undertake a systematic retrospective review of previous decisions that the supplementary advice might impact on. This exercise would have considerable resource implications. The decision whether to review a particular guidance will be made according to existing processes as described in the 'Guide to the Technology Appraisal Process' which allow for request for the review of any guidance to be brought forward on the basis of evidence submitted to the Institute.

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http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp

- 7.4 The Institute will design and manage the evaluation which will be undertaken by an independent body. The results of the evaluation will be published and used to make modification to the supplementary advice, if necessary.
- 7.5 It is anticipated that the treatments to which this supplementary advice applies may subsequently be licensed for multiple indications. Second and subsequent licenses 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.
- 7.6 The revised proposal implemented from January 5 2009 to apply to all ongoing appraisals.