

National Institute for Health and Care Excellence

Review of methods for health technology evaluation programmes: proposals for change

Executive Summary

1. This is NICE's second stage consultation on proposed changes to the way we develop recommendations across our health technology evaluation programmes – our programmes that evaluate medicines, devices and diagnostic technologies. We are seeking your views on 4 areas where we are making changes.
2. Committee assess the benefits and costs of new treatments against the current treatments in the healthcare system in order to decide whether the new treatment is good value for money. The proposed changes would see patients receive innovative new treatments sooner by allowing greater flexibility over decisions about their cost effectiveness. This means that NICE will be able to support the introduction of valuable innovative technologies, bringing health benefits for patients and good value to the NHS. At the same time, we will remain robust, efficient and able to meet the challenges of advancing health technology.
3. The proposals include:
 - **Greater emphasis on medicines for people with severe diseases**
4. Currently NICE committees can recommend treatments with a higher cost for people who are in their last months of life. However, there is no evidence that society values treatments at the end of life over other treatments. Evidence does show that society values health gains from treatments for very severe diseases over other treatments. We propose it would be fairer to move beyond the end of life 'modifier', which mainly focused on treatments for cancers, to put more weight on treatments for people with severe diseases across all types of disease.

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5. We will also be working with research partners to look at how much additional weighting society is willing to put on severe disease to see whether the level we currently use is appropriate. Because the NHS has a finite budget, if extra money is spent on a certain treatment for a severe disease because their health gains are given greater importance, then other treatments in the NHS could be displaced or not funded. The outcome of this research would also tell us what the impact of placing greater importance to severe diseases would be on health funding elsewhere in the system.

- **Flexibility in accepting uncertainty in specific situations**

6. When treatments are developed for rare conditions or for children, or when the treatments are highly innovative and complex, it is often difficult to carry out enough research to demonstrate the benefits of the treatment beyond the time period of the clinical trial. This means there can be uncertainty about the long-term benefits of these treatments. In these situations, the NICE committee producing the guidance has the flexibility where there is still some uncertainty because of the challenges of collecting evidence to recommend the technologies that fall into these categories. Still, the evidence base should be as strong as possible, and any limitations to it should be explored as usual.

- **Putting more emphasis on the role of the whole evidence base**

7. We propose broadening the types of evidence used in decisions about clinical and cost-effectiveness outside of the usual gold standard randomised controlled trials. This means we will use more evidence from patients' lived experience which reflects what it is like to live with a condition in real life and will clarify the circumstances in which different types of evidence have strengths or limitations.

- **Ongoing work on health inequalities**

8. Health inequalities are the gaps in health status and in access to health services between different groups, for example, those with different socioeconomic status or different ethnicity, or populations in different geographical areas. We know how important reducing health inequalities is and agree that there is a strong case for introducing a 'modifier' into decision

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making that allows committees to give greater importance to technologies that help to reduce health inequalities. This is a priority for NICE, but we are also clear that it has to be carried out thoroughly and consistent with the ongoing work at NICE on health inequalities. This means that we won't be introducing a modifier for health inequalities at this time. We are working toward resolving the challenges around health inequalities in the coming months within the current review and/or future methods.

- **Discounting rate.**

9. Discounting is a way for an economic analysis to adjust costs and benefits that will happen in the future, because generally people prefer to have benefits sooner but spend money later. This is done by including a 'discount rate' in the analysis. Our current discount rate is 3.5%. We found evidence that we should change our discount rate to 1.5%, and this could make a particularly big difference to some treatments, like gene therapies. However, this overlaps with several other issues outside NICE and across the NHS. Having considered this further, we still think we should change the discount rate to 1.5% as soon as we can, but the other overlapping issues need to be addressed for this to happen. In the meantime, we will keep the current discount rate.
10. Following the completion of this review, NICE will move to a new approach to updating our methods where we will update specific sections more regularly to respond to emerging health technologies. We will also put in place an improved process for identifying new health technologies, these will include digital technologies, genomics and antimicrobials.
11. The main benefits of the overall methods changes proposed in the consultation are:
 - Increased clarity, consistency and transparency for stakeholders on the evidence needed for each type of evaluation which could lead to faster decisions as committees should receive the evidence that is expected at the outset of an evaluation
 - Improvements to the information and evidence that is available to committees to inform their recommendations

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- Increased consistency and transparency on the recommendations made in NICE's health technology evaluation programmes.

Introduction

12. This review of health technology evaluation methods has 2 stages. In the first stage, we considered the evidence and considerations affecting our methods to establish whether there is a case for changing them. In the second stage, we now consider the consultation responses from stakeholders to those cases for change, and put forward proposals for implementing the changes into a refined structured decision-making framework for the updated unified programme manual.
13. Once this update of our methods is published, future updates will use a more modular and iterative approach, moving away from a cycle of updating every 4-6 years to allow us to flexibly pick up on emerging science and methods. We have already identified health inequalities, genomics, digital technologies, antimicrobial resistance and societal preferences for health benefits in severe diseases as topics that will be considered in these future updates and are keen to receive ideas for other topics as part of this consultation.
14. We have had the benefit of receiving extensive input and expertise from a wide variety of stakeholder groups, including patients, clinicians, academics, committee members and life sciences companies, through our working group and steering group meetings, and task and finish groups involving more than 160 participants and more than 30 meetings.
15. To inform the second stage consultation, which is focused on ways to implement the proposed changes, the contribution of external stakeholders on the working group, steering group and task and finish groups was different to that in the first phase of the review. During this second phase, the external stakeholders helped guide the NICE team in their exploration of the materials that would be reviewed by the NICE Board.
16. Three mostly internal task and finish groups focused on the components required to complete the methods review, as well as extensive input from the

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NICE Board. Reports of the task and finish groups are made available with this consultation.

- The Consultation task and finish group (a NICE internal-only task and finish group) reviewed, collated and summarised the feedback received during the first stage consultation.
- The Developing the Manual task and finish group produced a structured decision-making framework and unified manual for the Technology Appraisals Programme, the Highly Specialised technologies Programme, the Medical Technologies Evaluation Programme and the Diagnostics Assessment Programme ensuring they are aligned where appropriate.
- The Benefits Realisation task and finish group described the impacts of the methods review on all elements of the health and life sciences ecosystem and considered how the updated methods interact with each other and with other developments in the healthcare and health technology landscape, giving particular consideration to issues of equality and fairness, within NICE's legal and ethical duties.

Case for change and consultation

17. In the first stage of this review, we presented the case for changing NICE's methods of health technology evaluation. The consultation document presented 56 proposals across 5 broad topics:

- Valuing the benefits of health technologies
- Understanding and improving the evidence base
- Structured decision making
- Challenging technologies, conditions and evaluations
- Aligning methods across programmes

18. The consultation received responses from 196 organisations and individuals, across the life sciences industry, patient organisations, academia and the NHS (Table 1). The responses received informed the development of the changes proposed to the methods.

Table 1 Consultation responses by organisation type

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| Respondent | Percentage |
|---|---|
| Industry | 40% (pharmaceutical industry 22%; device industry 6%; industry body 5.5%; consultancy 5%; diagnostic industry 1.5%) |
| Patient organisations | 23% |
| Academic organisations | 10% |
| Responses from individuals | 10% (academic individual comment 5%; other 5%) |
| NHS, professional and devolved nation organisations | 8% (NHS organisations 4%; professional organisations 3%; devolved nation organisations 1%) |
| Other organisations | 5% |
| NICE and committee members | 4% |

19. Responses to the consultation were reviewed in detail, taking into account the range of overall support by stakeholder type, evidence and reasoning presented. The findings from this review informed the current proposals. Generally, stakeholders welcomed the various cases for change and expressed broad support for most of the proposals, but not all. Challenges were raised across several key topics.

20. The report prepared by the Consultation task and finish group provides a detailed summary of the individual case for change proposals under each topic area, and where relevant, additional issues or topics outside the consulted proposals raised by stakeholders.

Summary of proposals for the second consultation

21. The second consultation presents proposed updates to NICE's methods for health technology evaluation, developed into a refined structured decision-making framework and an updated programme manual. The proposals are built on the responses to the first consultation and the input of the many internal and external people in the task and finish groups, the working group and steering group. Even with the breadth and depth of the review, and the involvement of so many different stakeholders with varying perspectives, consensus was reached on most areas; however, not unexpectedly, there were some points upon which consensus could not be reached. The proposals represent NICE's view of the best available methodological evidence and

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practical considerations, while also carefully balancing the risks, benefits and opportunity costs to the health system.

22. The following sections present a high-level summary of the key updates proposed for inclusion in the unified manual (a-t) according to the 5 broad topics from the first consultation.

23. Appendix I provides greater detail on the evidence that was considered, the rationale and judgements NICE has made, to come to these proposals.

24. The 3 task and finish group reports are provided as supporting information to accompany this consultation.

Valuing the benefits of health technologies

Severity

- a. The review underpinning the first consultation concluded that there is evidence to indicate that society would favour prioritising treatment for severe diseases compared with the limited evidence that society would favour prioritising treatments at end of life. Allowing for the introduction of a severity modifier and removing the current end-of-life modifier was a case for change that was supported by respondents in the first consultation.
- b. This second consultation focusses on how such a change could be implemented. Whilst there is evidence that society values severe conditions more highly, to date there has been limited exploration of how society would wish this preference to be applied in health technology evaluation. In particular, there is limited information on the opportunity cost trade-off that society is willing to accept when attributing a higher value to severe conditions. As a consequence we are not yet able to use research evidence to define the magnitude of a severity weighting in an NHS context, or specify the amount of health displacement that should be accepted as a consequence.
- c. Because of the limited evidence for specifying the magnitude of severity weighting, we intend to explore how and to what extent society values health benefits in severe diseases, acknowledging that this could be less, the same

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or more than that currently applied through the end of life modifier. We consider it critical for this significant piece of research to be commissioned as soon as possible as it could take some time. The research would aim to generate evidence to further inform:

- the degree to which society favours severe diseases considering the health benefits that might be displaced as a consequence and
- the QALY weighting that should be applied.

The outcome this research would inform a future modular update of the methods for health technology evaluation.

- d. In order to avoid delay while this research is in progress, we have developed an approach to implement a severity modifier that can be used now to replace the current end of life modifier. This approach also takes into account the wider policy and system implications and interdependencies of a change in the application of quality-adjusted life year (QALY) weights, including the potential impacts on NHS spending and resource allocation that could arise when prioritising treatments focused on severe diseases.
- e. This approach is based on using proportional and absolute QALY shortfall. 'QALY shortfall' provides a robust, transparent and logical reflection of the severity of a health condition that measures the amount of health lost as a result of a condition, using QALYs as a standard, common measure of health across health conditions. QALY shortfall may be presented in either absolute or proportional terms. Absolute shortfall measures the total amount of health lost, while proportional shortfall measures the fraction of remaining health lost. Proportional and absolute shortfall measure different aspects of a severe disease. We propose to use both absolute and proportional QALY shortfall for quantifying severity of disease, whichever implies the higher severity, in order to capture and recognise a full picture of the severity of the condition. We have set the cut-offs for the levels of severity taking into account the number of topics (conditions) that would be eligible, for cancer and non-cancer, and by reflecting on the experience with applying the end-of-life modifier.

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- f. In the absence of evidence for specifying severity weights, our current approach takes an “opportunity cost neutral” analysis to severity – that is our basic principle aims to reallocate the weights applied to incremental QALYs currently invested in end-of-life treatments to those for severe disease. Using this basic principle, there is a wide range of scenarios for how these QALY weights might be distributed to different conditions depending on their severity as measured by absolute and proportional shortfall. In this consultation we propose 2 possible approaches that show different ways of reallocating the additional QALY weights historically applied through the end of life modifier, whilst accepting that there are other possibilities. The 2 approaches presented here use a 2-step approach according to severity and provide precise detail on QALY shortfall levels and weightings which are clear for committees, patients, companies and all other NICE stakeholders.
- g. We seek views on an approach where a QALY weight of x1.2 is applied for conditions with an absolute QALY shortfall of 12–18 or a proportional shortfall of 0.85–0.95, and a weight of x1.7 is applied for an absolute shortfall of ≥18 or a proportional shortfall of ≥0.95 (Option 1). (See sections 1.2 – 1.25 of Appendix I). This scenario essentially translates to a cost effectiveness level of £36,000 per QALY gained for the QALY weight of 1.2, and an upper limit for cost-effectiveness of £50,000 per QALY gained, similar to that currently employed for end of life. Some illustrative examples are included in [NICE’s Note on proportional versus absolute shortfall](#).
- h. We also describe an alternative approach (Option 2) which reduces the highest severity weighting to 1.5 but increases the middle QALY weight to 1.25. This option increases the QALY weight for the larger number of topics with medium severity to £37,500 per QALY gained, and lowers the QALY weight for the smaller number of topics with the highest severity from £50,000 per QALY gained to £45,000 per QALY gained, compared with option 1.

Table 2 Severity modifier proposed options

| Proportional shortfall | Absolute shortfall | Option 1 QALY weight | Option 2 QALY weight |
|------------------------|--------------------|----------------------|----------------------|
| <0.85 | <12 | 1 | 1 |
| ≥0.85<0.95 | ≥12<18 | x1.2 | x1.25 |

| | | | |
|-------|-----|------|------|
| ≥0.95 | ≥18 | x1.7 | x1.5 |
|-------|-----|------|------|

Uncertainty

- i. Uncertainty remains an important consideration in decision-making and will specifically impact technologies/populations for which evidence generation is particularly difficult, including rare diseases, evaluations in children and innovative and/or complex technologies. We describe when we expect committees to apply flexibility when considering evidence in circumstances concerning technologies/populations for which evidence generation is particularly difficult. (See sections 1.26 – 1.35 of Appendix I).

Health Inequalities

- j. There remains a case to include consideration of whether recommending a technology can reduce health inequalities within health technology evaluations. To implement benefits on reducing health inequalities in technology assessment as a formalised modifier requires further work. The outstanding challenges and complexities will be resolved in the coming months. (See sections 1.36 – 1.41 of Appendix I)

Highly specialised technologies

- k. The revised modifiers are relevant across all NICE health technology evaluation processes, except for the highly specialised technology programme, and are considered within the relevant context and decision-making framework. (See sections 1.42 – 1.46 of Appendix I).
- l. The highly specialised technologies programme will continue to apply the magnitude of benefit modifier as described in the Interim Process and Methods of the Highly Specialised Technologies Programme. (See section 1.47 of Appendix I).

Discounting

- m. We maintain our view that there is an evidence-based case for changing the reference-case discount rate to 1.5% for costs and health effects. We recognise the wider policy and fiscal implications and interdependencies

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raised by system stakeholders to such a change, including the potential impacts on NHS spending and resource allocation, that extend beyond the reach of this review. We accept the need for further consideration of a change to 1.5% through wider policy discussions, including through the Voluntary Scheme for Branded Medicines Pricing and Access. NICE welcomes the opportunity to be able to work with stakeholders and, to inform discussions, we will collect information on the effects of a change in discount rate in future health technology appraisals.

- n. The existing reference-case rate will be retained in the meantime (See sections 1.48 - 1.52 of Appendix I).
- o. The provision for non-reference-case discounting at 1.5% in certain circumstances will also be retained, with some clarification to the best way it can be used.

Understanding and improving the evidence base

- p. The proposed cases for change to the methods for sourcing, synthesising and presenting evidence, calculating the costs of introducing health technologies emphasising the primary importance of accurately reflecting prices paid in the NHS, and considering health-related quality of life will be implemented into the methods guidance (See section 2 of Appendix I). Further guidance on real-world evidence, including a framework for real-world evidence generation, will be provided by NICE through various activities, not just this methods review.

Structured decision making

- q. The manual explains how the committees should evaluate the evidence and make the judgements that lead to its final conclusions taking the changes to the methods into account. As before, the structured decision-making framework requires that the committee makes judgements on the appropriate and relevant comparator technologies. Next, committees will consider the full range of clinical evidence available applying their judgement on the clinical effectiveness of the technology being evaluated. The committee will then consider whether a severity modifier applies to the technology in question. If a

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severity QALY weighting applies, it is applied to the QALYs gained, which should be used to calculate the most plausible ICER. When considering the most plausible ICER, the committee will take into account uncertainty, as well as any managed access or commercial arrangements that may be in place. Finally, the committee may consider uncaptured benefits, non-health objectives as well as any remaining uncertainty due to the nature of the technology for which evidence generation is particularly difficult. The principle that underlies the committee decision-making is that of the opportunity cost of programmes that could be displaced by the introduction of new technologies, to maximise the health benefit gained from a fixed NHS budget (See section 3 of Appendix I). Other topics such as subgroups, when net-benefit approaches should be used, technologies which are not cost-effective at low or £0 cost and similar technologies are also addressed in section 3 of Appendix I.

- r. Equalities considerations will continue to be taken into account throughout health technology evaluations.

Challenging technologies, conditions and evaluations

- s. Methods refinements proposed through reviewing key challenges for technologies such as advanced therapy medicinal products (ATMPs), histology-independent cancer treatments and other emerging technologies, will be incorporated into the manual (See section 4 of Appendix I). Additional clarification will be provided for proposals including the use of threshold analyses and cure proportion modelling.

Aligning methods across programmes

- t. A draft single, unified methods manual covering the Technology Appraisals Programme, the Highly Specialised Technologies Programme, Medical Technologies Evaluation Programme and Diagnostics Assessment Programme is presented. It aligns as much as possible the methods across NICE's programmes for health technology evaluation, while retaining relevant differences (See section 5 of Appendix I). The unified manual highlights throughout that evidence and uncertainties will be considered appropriately for the context in which they are being considered, including the type of

technology, evaluation and condition. Proposals to align the use of cost comparison analysis are incorporated into the unified manual.

Impact

25. The Benefits Realisation task and finish group assessed and summarised the benefits associated with the proposed changes to methods that were consulted on after the first stage of the methods review. All new and updated methods adopted by NICE are expected to be associated with some benefits. It is recognised that not all stakeholders or population groups will be affected by every change to the methods or experience the benefits associated with the changes equally. In addition, some benefits may be more visible than others and realising benefits in some areas may have unavoidable consequences for others. Those unavoidable consequences also need to be considered to fully understand the impact of the methods review.

26. The main benefits of the methods changes are:

- Increased clarity, consistency and transparency for stakeholders on the evidence needed for each type of evaluation which could lead to faster decisions as committees should receive the evidence that is expected at the outset of an evaluation
- Improvements to the information and evidence that is available to committees to inform their recommendations
- Increased robustness, consistency and transparency on the recommendations made within and across NICE's health technology evaluation programmes
- Improvements for potential patient access to treatments – particularly through the application of the modifiers and other new methods which should result in fewer terminated evaluations.

27. The task and finish group identified some concerns about potential impacts, including effects on access to particular technologies, implementation challenges, and impacts on prices for health technologies and on NHS spending. Other risks include an increase in workload for the NICE CHTE staff and other stakeholders to manage the additional evidence that will be required

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by the new methods. This is an area of concern and one which has been laid bare by the impact of COVID-19 over the past year and a half.

28. The scale and impact of the proposals on both the workload of NICE and its stakeholders are being explored. It is anticipated that some of the proposals will be resource releasing whereas others will be resource incurring. The impact of the proposals will be analysed during the consultation and confirmed once responses to the consultation have been received, and the final methods confirmed. NICE will continue to monitor and assess the impact of the methods changes on its stakeholders and staff going forward.

29. The task and finish group also made recommendations for future activities that are needed to assess the benefits that may be realised once the unified manual is finalised.

Equality impact assessment

30. The impact on equality has been considered for some changes to the manual, but a formal equality impact assessment will need to be carried out once the full revised methods are finalised. This work is planned and will take place ahead of the final publication of the unified manual.

Future proofing

31. Future updates of the methods of health technology evaluation will use a more modular and iterative approach, moving away from a cycle of updating every 4 to 6 years. We have already identified health inequalities, genomics, digital technologies, antimicrobial resistance technologies and societal preferences for health benefits in severe diseases as topics that will be considered in future phases of methods review. These topics will be prioritised as soon as possible, but the precise timing depends on other activities and developments across the healthcare system.

Appendix I: Discussion and rationale for proposals

1. Valuing the benefits of health technologies

- 1.1. Based on the first stage of the review and consultation responses received, we propose to update how we consider factors that affect our decisions (referred to as 'modifiers'), incorporating the severity of disease and refining our approach to uncertainty and innovative technologies. Although we maintain our view that there is a case to change how we value costs and health effects in the future (through 'discounting'), wider policy and system implications and interdependencies need to be addressed in order for the change to be implemented. The existing reference case rate will be maintained in the meantime, and so will the option for committee to apply a different approach in exceptional circumstances.

Severity of disease

- 1.2. The first phase of the methods review identified limited evidence that society places additional value for life-extending treatments at the end of life. Conversely, the review found greater evidence that society values health benefits in very severe conditions highly. Recognising that there is a definite degree of overlap between severity of disease and end of life, the review therefore identified a case to replace the current end of life modifier with one that considers disease severity which encompasses both shortening of life and loss of quality of life. Such a modifier would require careful consideration and design in order to be implemented. There was strong support for this case for change in the first consultation, with recognition this also depends on how it is implemented.
- 1.3. We therefore retain our view that there is a case to introduce a modifier for severity of disease. To implement this as a modifier, there are 3 key considerations:
- How to measure severity

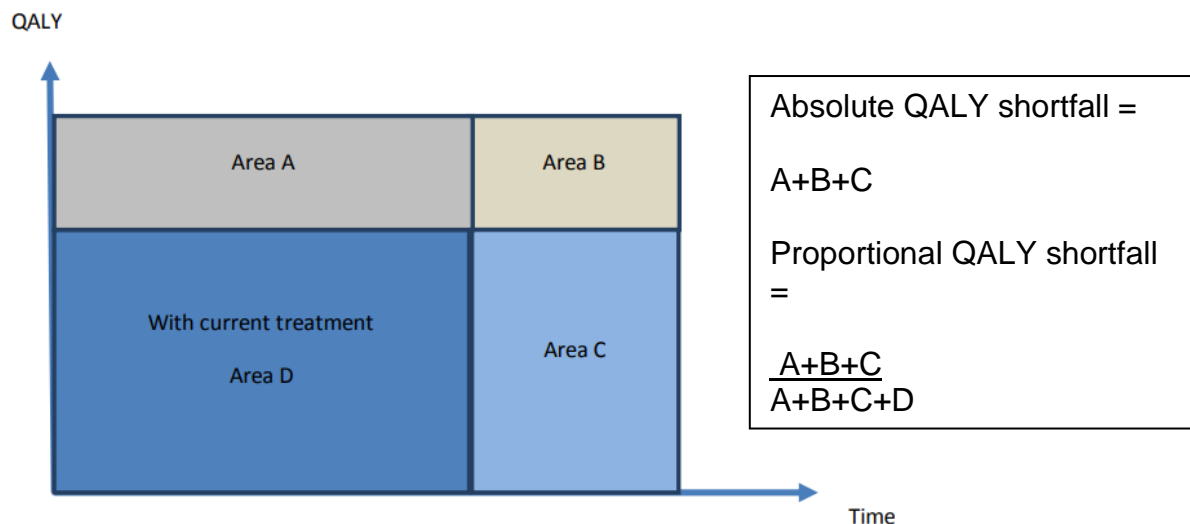
- The underlying principles for the modifier: the overall nature of the modifier and extent of its operation
- How to design and implement the modifier in practice, within the identified principles.

Measuring severity

- 1.4. To implement a severity modifier, a definition and measurement approach is needed that captures the severity of all health conditions in a common, consistent and transparent way. In this context, the severity of health conditions may perhaps be most intuitively understood as the amount of health that is lost as a result of the condition. We identify that 'QALY shortfall' provides a robust, transparent and logical reflection of the severity of health condition that fulfils these considerations: it measures the amount of health lost as a result of the condition, using QALYs as a standard, common measure of health across health conditions.
- 1.5. QALY shortfall may be presented in either absolute or proportional terms. Absolute shortfall measures the total amount of health lost, while proportional shortfall measures the fraction of remaining health lost. Proportional and absolute shortfall measure different aspects of a severe disease. For example, a high absolute shortfall may reflect a condition that arises in childhood and affects quality and length of life over a long period, whereas a high proportional shortfall may reflect a condition that is life threatening (even if the total amount of health lost is relatively smaller). Moreover, absolute and proportional measures each have different strengths and limitations in different circumstances. We therefore propose to use both absolute and proportional QALY shortfall for quantifying severity of disease, whichever implies the higher severity, in order to capture and recognise a full picture of the severity of the condition.
- 1.6. Absolute QALY shortfall for a particular condition is defined as total health potential in the general population (that is, without the specific condition in the question; $A+B+C+D$ in figure 1) minus the health expected for people with the condition in question who are having current treatment (D). Proportional QALY shortfall for a condition is defined as the ratio of absolute QALY shortfall

(A+B+C) divided by total health potential in the general population (without the condition; A+B+C+D).

Figure 1 QALY shortfall diagram



Underlying principles: nature and extent of the modifier

- 1.7. The introduction of any modifier must, like all of NICE’s work, take into account the costs and benefits of recommending a health technology in the context of health displaced elsewhere in the NHS by additional spending. When an additional weighting factor or modifier is taken into account for a technology such that QALY gains are given greater weight leading to a higher incremental cost per QALY being accepted, there is greater displacement of health elsewhere. Therefore, the impact of using a modifier has knock-on effects on budgets and priorities across the health service that must be considered carefully. NICE’s role is to ensure the effective use of NHS resources, taking into account clinical benefits, societal values, costs and displacement of care.

- 1.8. The proposed severity modifier will work quantitatively, in a similar way to the end-of-life modifier; that is, by applying a weighting to health benefits gained (a QALY weight). As outlined in the first stage of the review, we maintain our perspective that health benefits are of equal value (regardless of other characteristics of the technology and people having those benefits), apart

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from in very exceptional circumstances. As was the case for the end-of-life criteria, the starting point is that the severity modifier should be applied as an exception.

- 1.9. The critical question for the severity modifier, then, is how much more should health benefits for severe diseases be valued, that is the magnitude which the modifier should be applied within a framework of exceptionality, to support valuable innovations for severe diseases. In doing this, we must also recognise the knock-on effects and the health that is displaced by applying an additional QALY weight, as is currently the case with the end of life modifier.
- 1.10. While there is clear evidence that society values highly health benefits in severe diseases, there is not enough evidence to clearly define the magnitude of that societal value (and the amount of health displacement we are willing to accept). We consider it critical for this significant piece of research to be commissioned as soon as possible as it could take some time. The research would aim to generate evidence to further inform the degree to which society favours severe diseases considering the health benefits that might be displaced as a consequence, and the QALY weighting that should be applied. The outcome of this research would inform a modular update of the methods for health technology evaluation.
- 1.11. Retaining the current end-of-life modifier in the meantime would not be optimal given the limited evidence for societal value (as identified in the first stage) and the clear support for its replacement with severity expressed in the consultation. We therefore need a pragmatic approach to establish a severity modifier. Taking the existing end-of-life exception as a benchmark, we can see 3 possibilities: that society values health benefits for severe conditions more, similarly or less than applied under end of life.
 - If there is greater value, we would be able to expand the overall magnitude of the modifier, providing additional support for innovations for severe conditions. However, there then would be greater displacement of health elsewhere in the NHS, all other things being equal.

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- If there is less value, the overall magnitude of the modifier would be smaller than for end of life. While this would reduce health displacement, it would arguably undervalue the impacts of severe conditions and the prospects for access to the innovative treatments that could ameliorate them relative to what was achieved with end of life.

- 1.12. In that context, we propose as a starting point a severity modifier with an overall magnitude similar to that applied under the current end-of-life criteria. This allows us to support and value health technologies for the most severe conditions consistent with evidence of societal value, while maintaining a level of health displacement similar to that which has operated for more than 10 years. This has the effect of maintaining the current displacement or opportunity costs compared with end-of-life. We can achieve this by implementing the severity quantitative modifier such that it has an average QALY weighting per topic equivalent to that which has been applied under end-of-life.
- 1.13. The case for change consultation anticipated that a severity modifier would be more broadly applicable than the previous end of life criteria, and would move beyond cancer into a broader range of conditions. We retain our view that this principle should be achieved. In practice, end-of-life conditions are normally, by definition, severe. It would therefore be appropriate if the severity modifier, as far as possible, captured technologies that would have met the end-of-life criteria.
- 1.14. The final principle is how to reflect the range of severities seen in health technology evaluations whilst maintaining the principle of exceptionality in the application of weightings. To achieve this, we propose a 2-step severity modifier with medium and higher ranges of severity.

Designing and implementing the modifier

- 1.15. In order to design a practical, implementable modifier within these established principles, we need to establish:

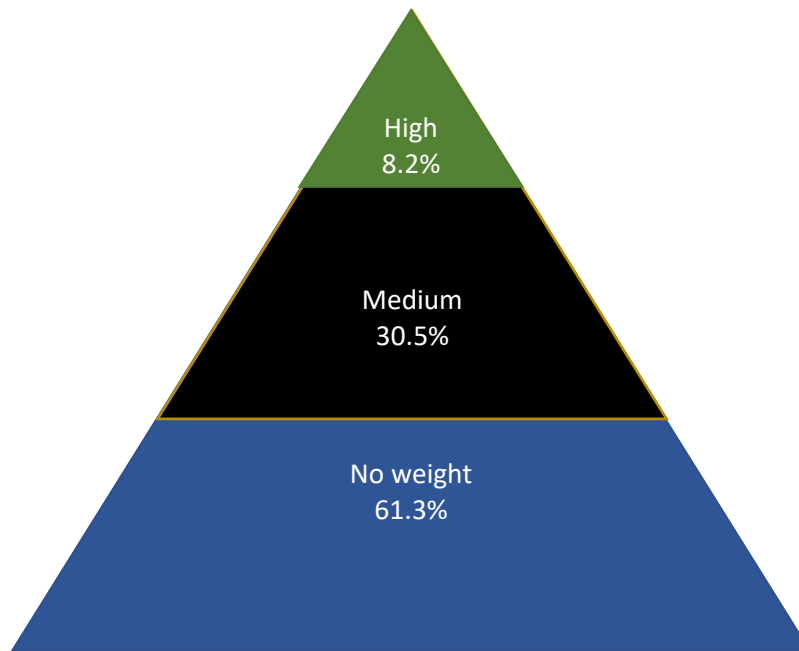
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- The levels of absolute and proportional shortfall at which each step of the modifier should be applied
- The QALY weights to apply to each step, such that, when combined with the absolute and proportional shortfall levels, they establish an average QALY weighting per topic equivalent to end-of-life.

1.16. To inform this, a retrospective review of health technology appraisal decisions (n=364 decisions for which shortfall data could be calculated) conducted between January 2011 and November 2019 was undertaken, and absolute and proportional QALY shortfall values were calculated for each topic. We found that approximately 18% of decisions received the end-of-life weighting (n=65). This retrospective review directly represent previous evaluations and is the best available evidence for developing the severity modifier for future topics.

1.17. Taking into account this review and further detailed deliberation, we identified levels for absolute and proportional shortfall that we consider represent an appropriate level of severity of disease at which to apply a QALY weight, and which capture a suitable range of topics (both cancer and non-cancer), within the principle of exceptionality (see Table 3). In the retrospective review, the total number of past decisions that would have received a weight would be 141 (39%); more than double that under end-of-life. Of these, a fifth (that is, 8% of all decisions) fall into the higher severity range, with the remainder falling into the medium range (Figure 2). This therefore retains the principle of exceptionality by applying the greatest weight to the most severe conditions, while spreading the QALY weight more fairly through both a greater number and greater variety of conditions.

Figure 2 Pyramid of exceptionality



- 1.18. With the 2-step approach and the proposed severity levels, there is a choice about how much weighting to apply to each level. One can achieve the same average QALY weighting in many different ways; for example, one could use a steep gradient with a very high weight applied in the highest severity, or a shallower gradient such that more even weights are applied in the medium and higher severity categories. We present for consultation 2 options (Table 3). Each option has relative strengths and limitations in different circumstances. We propose as Option 1, a 2-step approach where a QALY weight of x1.2 can be applied for conditions with an absolute QALY shortfall of 12–18 or a proportional shortfall of 0.85–0.95, and a weight of x1.7 can be applied for an absolute shortfall of ≥ 18 or a proportional shortfall of ≥ 0.95 .
- 1.19. We also propose an alternative 2-step approach (Option 2) which reduces the highest severity weighting to x1.5 but increases the middle QALY weight to x1.25 (see Table 3).

Table 3 Proposed Severity modifier options

| | Proportional QALY shortfall | Absolute QALY shortfall | Option 1 QALY weight | Option 2 QALY weight |
|-------------------------|------------------------------------|--------------------------------|-----------------------------|-----------------------------|
| No additional weight | <0.85 | <12 | 1 | 1 |
| Medium severity weight | ≥0.85<0.95 | ≥12<18 | x1.2 | x1.25 |
| Highest severity weight | ≥0.95 | ≥18 | x1.7 | x1.5 |

1.20. The difference between option 1 and 2 is the application of different weightings to the topics captured within each severity category. Option 1 uses the original maximum weight used in end-of-life (x1.7) for the most severe category, and a weighting of x1.2 for the middle severity category. Option 2 gives a lower weighting compared to end-of-life for the highest severity category of x1.5 and a slightly higher weighting of x1.25 compared to option 1, for the middle severity category. Within the overall opportunity cost neutral paradigm the choice is whether to have a small number of topics with a very high weight, while the larger group of middle severity topics get a x1.2 weighting, or to give the highest severity group a weighting that is not as high as the level that end-of-life was given for all topics in order to distribute the weighting more evenly across both categories. The number and type of topics that are captured in the medium and high severity categories remain the same in both options (see **Table 4** and Table 5).

Table 4 QALY comparison of EOL and severity modifier options topics

| Modifiers | # of recs | End of life applied | End of Life not applied | Severity modifier Option 1 High | Severity modifier Option 1 Medium | Severity modifier Option 1 No weight | Severity modifier Option 2 High | Severity modifier Option 2 Medium | Severity modifier Option 2 No weight |
|-----------------------------|------------------|----------------------------|--------------------------------|--|--|---|--|--|---|
| QALY Weighting | - | x1.7 | x1.0 | x1.7 | x1.2 | x1.0 | x1.5 | x1.25 | x1.0 |
| End of life | 65 | 65 | 0 | 14 | 44 | 7 | 14 | 44 | 7 |
| Non-end of life, cancer | 88 | 0 | 88 | 12 | 33 | 43 | 12 | 33 | 43 |
| Non-end of life, non-cancer | 211 | 0 | 211 | 4 | 34 | 173 | 4 | 34 | 173 |
| All recommendations | 364 | 0 | 299 | 30 | 111 | 223 | 30 | 111 | 223 |

Table 5 QALY weighting comparison for EOL and severity modifier

| Modifiers | # of recs | EOL | Severity modifier Option 1 | Severity modifier Option 2 |
|--------------------------------|------------------|------------|-----------------------------------|-----------------------------------|
| Mean QALY weight per appraisal | - | 1.125 | 1.119 | 1.117 |

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- Option 1: Topics which would originally have met end-of-life and which remain in the high severity range are not affected as the x1.7 weighting is the same as the maximum weighting for end-of-life. Topics which have met end-of-life previously but are in the middle severity category can now effectively consider a maximum of £36,000 per QALY gained instead of £50,000. Approximately 19 out of 25 past routinely recommended end-of-life topics in the middle severity category for which we had ICERs could move from recommended to not recommended if companies did not modify their value proposition to accommodate the new modifier. 10 end-of-life topics in the middle severity category were not recommended and 4 were recommended within the CDF, and 5 did not specify an ICER. 83 topics that did not meet the end-of-life criteria may have met the criteria for a severity weighting.
- Option 2: Topics which would originally have met end-of-life and which remain in the high severity range would now receive a x1.5 weighting which effectively equates to a maximum ICER of £45,000 per QALY gained. Of the 10 past end-of-life topics which would receive the higher severity weighting, 4 would still be recommended without changing value proposition. 2 were not recommended and 2 were recommended within the CDF. With the slightly higher weighting of x1.25 for the middle severity category (equivalent to £37,500 per QALY gained), the same number of end-of-life topics (19) as with option 1, would move from recommended to not recommended, again assuming companies would not respond by lowering their prices. 83 topics that did not meet the end-of-life criteria may have met the criteria for a severity weighting (at a different level to option 1).

- 1.21. The QALY weighting is applied within the structured decision-making framework to the incremental QALYs gained by using the intervention. The application will be based on the committee's assessment of the totality of the evidence for the specific condition indication in question, including the economic model submitted by the company, critique by the academic group, and evidence on the natural history of the condition of interest.
- 1.22. We recognise that these are 2 representations of a range of possible options that could be used to apply a QALY weight. We have provided an insight in the reasons for choosing one or the other (see Section 1.11). While our main focus is the impact on health displacement, we also have to take into account wider policy and system implications and interdependencies of a change in

CONFIDENTIAL UNTIL PUBLISHED

the application of QALY weights, including the potential impacts on NHS spending and resource allocation. The choice of options presented here has been informed by these considerations and takes into account the significant degree of uncertainty inherent in forecasting the effect of a policy change such as this on, in particular, pharmaceutical spend and prices. Furthermore, health system and wider governmental partners have confirmed that implementation of these options is feasible within the near term financial constraints.

Impact of the proposed modifier

- 1.23. The introduction of the severity modifier supports innovation in treatments for the most severe diseases – encompassing the majority of end-of-life cancer treatments as well as some cancer treatments which did not previously meet the end-of-life criteria, non-cancer medicines, earlier-stage treatments, treatments for rare diseases and others. The modifier will provide clarity on the value attributed to innovation in specific disease areas, allowing companies to plan pricing and launch strategies well in advance. The severity modifier is also likely to lead to more technologies that have important benefits for people with the most severe conditions becoming available.
- 1.24. The application of the severity modifier will be considered on a case-by-case basis by individual committees, based on the totality of evidence and the precise condition and indication under consideration. With the proposed approach, there are very few topics (7) which met the end-of-life criteria previously, but which would not receive an additional weighting with the severity modifier. The main reason why these conditions, such as advanced melanoma, would not receive a severity weighting is that although people's life expectancy may be less than 2 years with the relevant comparator, quality of life can remain good for most of that period. However, it is also important to note that with the proposed approach, from our retrospective review, we have identified examples of evaluations that might (based on the evidence at that time) have received a severity modifier spanning a broad range of conditions, from cancer (both end-of-life and non-end-of-life indications), to musculoskeletal, inflammatory and mental health conditions.

CONFIDENTIAL UNTIL PUBLISHED

- 1.25. Some important equality considerations were highlighted during the development of the severity modifier. In particular equality considerations around age were considered. The end-of-life criteria, as defined, tended to be applied to treatments for diseases which affect older people and was rarely applied to diseases affecting younger people and children. The severity modifier proposed should capture severe diseases at any age range. Equalities considerations have also previously been raised for absolute and proportional QALY shortfall; this is mitigated by the consideration of both absolute and proportional measures together, alongside established flexibilities in applying the methods in the context of equalities concerns.

Uncertainty

- 1.26. We consulted on proposals to clarify and codify the circumstances where committees can apply flexibilities when considering decision uncertainty. Committees have previously exercised flexibilities in these circumstances, but it is not explicitly referred to in the existing methods guides. There was a high level of support to this proposal in principle, but stakeholders were keen to understand how the proposal would be implemented.
- 1.27. The unified manual now clarifies that when considering the degree of certainty in the cost effectiveness, where committees will normally be more cautious when they are less certain, committees will be mindful that there are circumstances where generating evidence is complex, difficult and for which further data collection to resolve uncertainty is not realistic or feasible. These circumstances normally occur specifically in rare diseases, diseases affecting children and for highly innovative and complex technologies. The review made clear that this must not overlap with other modifiers to create 'double counting'.
- 1.28. Submissions to NICE should include the highest level of evidence generation possible for the context in which the technology is being evaluated. There are always likely to be deficiencies in the evidence base available for an evaluation. Despite such weaknesses in the evidence base, decisions still have to be made about the use of technologies. Analyses exploring the

CONFIDENTIAL UNTIL PUBLISHED

limitations of the evidence should be explicit, with attempts to overcome these limitations. The impact of the limitations of the data on the results of the analysis should be quantified as fully as possible.

1.29. In all evaluations, judgements about the acceptability of the technology as an effective use of NHS resources will specifically take account of the degree of certainty around the clinical and cost effectiveness. In particular, the Committee will normally be more cautious about recommending a technology when they are less certain about the evidence presented. However, the committee will be mindful that there are certain technologies/populations for which evidence generation is particularly difficult because they are:

- Rare diseases
- For use in population that is predominantly children (<18 years old)
- Innovative and complex technologies.

1.30. In all cases, Committees must consider the nature, scale and consequences of the decision uncertainty and risks and any measures that may mitigate those risks (such as commercial and managed access arrangements). Committees should be cautious in accepting a higher degree of uncertainty in circumstances where the highest standard possible of evidence generation has not been achieved.

1.31. When considering uncertainty, the Committee should take into account the likelihood of decision error and the consequences for patients and the NHS. There should be an explicit reference to the potential benefits and risks to patients based on the level of decision uncertainty and whether these can or cannot be mitigated. Committees should also consider the risks to other patients in the NHS of using the technology, based on the most plausible cost effectiveness estimates.

1.32. Technologies may be considered to be innovative and complex if, in the Committee's judgment, technologies provide a step-change in treatment and the uncertainty generated is due to the innovative nature or complexity of the technology.

CONFIDENTIAL UNTIL PUBLISHED

- 1.33. Committees may take into account if technologies have been designated rare or innovative by system partners.
- 1.34. Committees should be satisfied the technology is potentially cost effective and that the remaining uncertainty is related to the condition or technology.
- 1.35. This is a clarification of existing uncertainty considerations and provides alignment of access with regulatory and commercial and managed access systems. It also ensures that innovative technologies and treatments for children or rare diseases have the potential to be recommended without barrier or delay.

Health inequalities

- 1.36. The first stage of the methods review identified evidence that the UK population prioritises seeking a fair distribution of health across society. The review highlighted evidence that people are willing to generate less health overall if the health is generated in disadvantaged groups, particularly when this is driven by socioeconomic factors. A case for change for a modifier that considers health inequalities was consulted upon.
- 1.37. During the consultation, stakeholders generally agreed with the concept of a health inequalities modifier for technologies which could reduce inequality, but noted that opportunity cost must be considered alongside any modifier introduced.
- 1.38. Addressing health inequalities is an important priority, and a broad and complex area that will require ongoing consideration across all of NICE, as described in our Principles and NICE Strategy. Health technology evaluation is not necessarily expected to be the main route to resolve such challenges. Nevertheless it is crucial that, when issues of health inequality do arise in an evaluation, we are able to clearly and transparently consider them within decision making.
- 1.39. We therefore maintain our view that evaluations should include consideration of whether recommending a technology can reduce health inequalities within health technology evaluations. The existing methods, NICE's statutory duties,

CONFIDENTIAL UNTIL PUBLISHED

the NICE Principles and routine deliberative decision-making, combined, provide the flexibility to take into account relevant considerations for individual evaluations, and this may include health inequalities if it arises. Even so, there remains a case to include a formal modifier. In order to do so, we first need to fully explore the remaining important challenges and complexities within health inequalities. Based on our findings from this stage of the review, it is likely that a health inequalities modifier would be a qualitative consideration, usually being considered within the normal cost-effectiveness ranges. This would take into account the evidence of societal value linked to socioeconomic disadvantage, although we also note the importance of other sources of inequality. However, in order to formally establish this, it will be important in particular to understand different definitions and origins of inequalities, the roles of different parts of the health system (including health technologies) in addressing them, the effects of displacement and opportunity cost, and methods and evidence for assessing and measuring health inequalities. This links with ongoing NICE-wide work exploring how health inequalities can be systematically considered across all our work and the opportunities to strengthen NICE's role in addressing health inequalities, allowing us to ensure a consistent approach across the institute. We will work towards resolving these challenges in the coming months, within the current methods review and/or future iterative methods updates, in order to build the established case for change into a formalised, defined modifier within the decision-making framework for health technology evaluations.

- 1.40. For completeness, it should be emphasised that the consideration of health inequalities described here is separate from wider consideration of equalities, within NICE's legal and moral duties to eliminate unlawful discrimination and promote equality. Such equality considerations remain, as always, a vital and integral part of all NICE health technology evaluations.
- 1.41. The exploration of health inequalities as a consideration in health technology evaluations emphasises NICE's commitment to addressing health inequalities, albeit as only small part of our work in this area. While there exist other and perhaps better mechanisms to address inequalities, beyond health technology

CONFIDENTIAL UNTIL PUBLISHED

evaluation, resolving the outstanding questions to introduce a modifier presents an important addition to the methods that has the potential to directly redress some discrete health inequalities. Moreover, such a committee consideration will support innovations that help address inequalities and unfairness in health across society and that particularly benefit disadvantaged groups.

Alignment of the application of modifiers across programmes

- 1.42. The case for change identified in the first stage was that the application of modifiers across evaluation programmes should be as consistent as possible. The nature of some modifiers, however, do not lend themselves to be applied to all programmes, and therefore, the draft manual will provide clear direction how and when the modifiers apply. Although how they are used may differ across programme, the fundamental nature of the decision making and value for money frameworks in different programmes will not change.
- 1.43. For the Technology Appraisals programme, the modifiers above apply directly as described.
- 1.44. For medical technologies evaluated through the medical technologies evaluation programme, which uses a cost saving decision rule, the concepts of a quantitative QALY weight or a qualitative modifier that allows a higher ICER are not applicable. Nevertheless, it is appropriate that the committee can take into account relevant factors in its deliberations, in line with societal value. Therefore, the modifiers described are not applicable as QALY weights, but should be considered deliberatively within decision making. This may be particularly relevant for uncertainty; the committee will consider uncertainty and risk proportionately, taking into account the likelihood and consequences of decision error and the specific circumstances of the evaluation, including the nature of the technology and the evidence challenges encountered in the medical technology ecosystem. It may not be necessary to quantify severity using absolute and proportional shortfall for medical technologies.
- 1.45. For diagnostics, the uncertainty consideration is relevant so is applied as described, and will be considered proportionately for the context of diagnostic

CONFIDENTIAL UNTIL PUBLISHED

technologies. For severity of disease, it is unclear whether the societal value of severity is relevant for diagnostics.

- 1.46. The relevance of severity of disease is likely to differ for diagnostic technologies compared with treatment interventions. Importantly, diagnostic technologies tend to sit somewhat upstream within a pathway of care, and may influence care decisions, treatment choices and hence health outcomes over time. They can influence the care pathway both for people with a condition and those without (that is, negative diagnoses). Taking into account the effects of population mix (people with and without the condition), and disease trajectory (how many people go on to develop a particular symptom, complication or stage of disease, and when), absolute and proportional QALY shortfall at the point of using the technology may not reflect the severity of disease in a diagnostic context in the same way as they do for a treatment intervention. Moreover, there is an important drive across the NHS for earlier diagnosis of conditions. Because of these considerations, a severity modifier such as that proposed above is unlikely to reflect the societal value and severity of disease in a way that is relevant to the diagnostics context. We therefore anticipate that the severity modifier will not normally be applicable in diagnostic evaluations. Further work is needed to explore elements of value that are relevant to diagnostics; this work can be explored in future modular updates (potentially combined with genomics).
- 1.47. Highly specialised technologies evaluations are built on different ethical and normative principles and so use a different decision and modifier framework, based on a different cost per QALY level and which takes into account the magnitude of benefit associated with the technology. Stage 1 identified that there was no case to change the current framework for HST because of its exceptional nature. The severity of the condition is already implicitly captured in HST, because topics selected for HST must be severe; therefore no additional severity modifier is applied. Uncertainty is a relevant consideration in HST and must be taken into account and considered proportionately for the context of very rare conditions. Because of this, the additional consideration permitted when evidence collection is difficult (for rare diseases, children and

innovative technologies) is already implicitly accounted for within the HST committee's framework, so it is not considered that further adjustment will be needed.

Discounting

- 1.48. The methods review identified a case for changing NICE's preferred (reference-case) discount rate from 3.5% to 1.5% per year for costs and health effects. It concluded that the best available evidence supported a discount rate of 1.5%, applied to both costs and health effects, and considered that the argument that the 2% 'wealth effect' does not apply to health (as described in the HM Treasury Green Book) is important. However, it also identified important policy and affordability implications and interdependencies that go beyond the reach of the methods review. These include the effect of the change on healthcare costs/resources, and dynamic and distributional consequences across the health system.
- 1.49. The consultation highlighted broad interest in this topic. We note that many stakeholders expressed support for changing the discount rate, although others explored issues such as the impact on healthcare resources and the potential for differential discounting of costs and health effects.
- 1.50. In our assessment of the best available evidence, and taking into account the views expressed in consultation and the policy and system considerations, we maintain our view that there is a case for changing the reference-case discount rate to 1.5% for costs and health effects. We recognise the wider policy and fiscal implications and interdependencies raised by system stakeholders to such a change, including the potential impacts on NHS spending and resource allocation, that extend beyond the reach of this review. We accept the need for further consideration of a change to 1.5% through wider policy discussions, to impact on the Voluntary Scheme for Branded Medicines Pricing and Access that runs to the end of 2023. NICE welcomes the opportunity to be able to work with stakeholders and, to inform future discussions, we will collect information on the effects of a change in discount rate in future health technology appraisals.

CONFIDENTIAL UNTIL PUBLISHED

1.51. Until policy and system implications can be addressed, the existing reference-case discount rate of 3.5% will be retained.

Non-reference case discounting

1.52. In that context, there is a need to consider the provisions for non-reference-case discounting within NICE's methods. We propose to retain the provision for non-reference-case discounting at 1.5%, with some clarification. We are not proposing to expand the circumstances for the application of non-reference-case discounting which would have similar policy and affordability implications to changing the reference-case discount rate. We propose the following changes:

- Clarify further the role of the non-reference-case discount rate, its use in different types of evaluations, and the relevance of irrecoverable costs.
- Remove the reference to a particular duration of effect, allowing committees to use their judgement to determine the circumstances in which they wish to explore the impact of non-reference case discounting. This is intended to address a potential equality issue with the existing criteria (which stated that benefits should normally be sustained over at least 30 years).
- Amend the consideration of uncertainty as this applies whether or not reference or non-reference case discount rates are applied.

CONFIDENTIAL UNTIL PUBLISHED

| Current methods | Proposed methods |
|--|--|
| <p>Reference case</p> <p>Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. For the reference case, the same annual discount rate should be used for both costs and (currently 3.5%).</p> <p>The specific discount rate varies across jurisdictions and over time. The Institute considers that it is usually appropriate to discount costs and health effects at the same annual rate of 3.5%, based on the recommendations of the UK Treasury for the discounting of costs.</p> <p>Sensitivity analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis (see section <non-reference-case>).</p> | <p>Reference case</p> <p>Cost-effectiveness results should reflect the present value of the stream of costs and benefits accruing over the time horizon of the analysis. For the reference case, costs and health effects should be discounted at the same rate, of 3.5% per year.</p> <p>Alternative analyses using rates of 1.5% for both costs and health effects may be presented alongside the reference-case analysis, in specific circumstances.</p> |

CONFIDENTIAL UNTIL PUBLISHED

| Current methods | Proposed methods |
|---|--|
| <p>Non-reference-case</p> <p>In cases when treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference-case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved. Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.</p> | <p>Non-reference-case</p> <p>The committee may consider analyses using a non-reference-case discount rate of 1.5% per year for both costs and health effects, if, in the committee’s judgement, all of the following criteria are met:</p> <ul style="list-style-type: none"> • The technology is for people who would otherwise die or have a very severely impaired life; • It is likely to restore them to full or near-full health; and • The benefits are likely to be sustained over a very long period. <p>When considering analyses using a 1.5% discount rate, the committee must take particular account of plausible long-term health benefits in its deliberations. The committee will need to be confident that there is a highly plausible case for the maintenance of benefits over time when using a 1.5% discount rate</p> <p>Further, the committee will need to be satisfied that any irrecoverable costs associated with the technology (including, for example, its acquisition costs and any associated service design or delivery costs) have been appropriately captured in the economic model and/or mitigated through commercial arrangements.</p> |

2. Understanding and improving the evidence base

2.1. Most cases for change in this area were well received by stakeholders.

2.2. There was support to refresh and clarify the methods guidance on sourcing, assessing and presenting evidence, including:

- no change to the general preference for randomised controlled trials (RCTs), when feasible, to inform estimates of treatment effects
- an emphasis on the role of a comprehensive evidence base, including non-RCTs and real-world evidence, and the circumstances in which different types of evidence have strengths or limitations
- additional guidance on the use of RCT and non-RCT evidence, assessment and reporting of study quality, risk of bias and confounding, and presenting evidence

Guidance on the use of real-world evidence (RWE)

2.3. There was a large response and strong support for the proposals around the use of real-world evidence, but stakeholders considered many areas required further clarification.

2.4. NICE acknowledges the broad range of applicability of RWE in health technology evaluations, we therefore propose to articulate how and when RWE will be considered in decision-making and to explain what the expectations are around the identification of evidence and data. The methods review presents improved guidance on the use of RWE and the principles for developing and presenting high quality evidence. These principles are common across applications of RWE.

2.5. A real-world evidence framework has been developed which provides guidance on research governance encompassing study planning and protocols, conduct and reporting of results, and for assessment of data quality and relevance the use of real-world data to inform health technology assessment. It is focused on the development of new evidence which may be generated from prospective data collection or the retrospective use of existing data.

2.6. Many of these applications are particularly relevant in the context of medical technologies and diagnostics – either (or both) because of the challenges in collecting clinical trial evidence in this context, and because of the nature of

CONFIDENTIAL UNTIL PUBLISHED

the information and outcomes needed. Examples include access and usability outcomes, effects of tests on clinical decision making and care choices, and health service outcomes (such as referral rates and service design).

- 2.7. It is acknowledged that there are challenges associated with collecting high quality evidence, particularly in certain contexts. While our guidance stresses the value of high-quality RWE, we do not place any restrictions on the types of evidence that we will accept: any evidence can be considered, and will be considered in context with its strengths, limitations and uncertainties, proportionately for the context in which it is evaluated, how it is used in the evaluation, and how any uncertainties affect the benefits and risks of the technology.

Costs

- 2.8. Non-reference-case analyses in which a particular cost is apportioned or adjusted will be allowed in defined circumstances. These circumstances may include when there is an established plan to change practice or service delivery, when there is a formal arrangement with relevant stakeholders, or when introducing the technology will have substantial, identifiable health benefits not captured in health technology evaluations.
- 2.9. Some health technologies may have a substantial impact on non-health outcomes or costs to other government bodies. These impacts are usually identified during scoping. Costs incurred outside the NHS and PSS will always be agreed with the Department of Health (or other relevant government bodies as appropriate) and detailed in the final scope. For these non-reference analyses the benefits and costs to other government bodies will be presented separately from the reference-case analysis.
- 2.10. The case for change proposed a hierarchy for the sources of prices for medicines that should be used when commercial arrangements in place. However, further review has identified that such a hierarchy may not fully reflect the complexities of the medicines pricing environment, and some further concerns were raised during the consultation. This proposal has therefore been revisited.

CONFIDENTIAL UNTIL PUBLISHED

- 2.11. As far as possible, estimates of unit costs and prices for particular resources should be used consistently across evaluations.
- 2.12. As noted in the first stage of the review, the most important principle is that evaluations must use prices that reflect as closely as possible the prices that are paid in the NHS, while acknowledging and exploring any uncertainties and variation. In practice, when multiple commercial arrangements are in place for a particular medicine, the patient access scheme (PAS) price is frequently not the best reflection of the true price in the NHS. Consequently, a hierarchy that prioritises the PAS price is unlikely to be helpful. Nevertheless, the previously proposed hierarchy did helpfully highlight the relative strengths and limitations of PAS, electronic market information tool (eMIT), tariff and Commercial Medicines Unit prices; it showed that any of these prices can be appropriate to use in an evaluation, as long as their limitations are acknowledged and explored.
- 2.13. We therefore propose that the unified manual will emphasise the fundamental principle, that the price used must reflect as closely as possible the prices that are paid in the NHS for use in the population under consideration. It will note that the committee should take into account the transparency, national availability and guaranteed duration of the prices in its deliberations. Information on the advantages and limitations of a PAS, eMIT and Commercial Medicines Unit prices will be provided, and uncertainties in pricing should be accounted for in the analysis. For Commercial Medicines Unit prices, in order to capture the range of prices and any corresponding impacts on cost effectiveness, the committee should consider analyses based on both the lowest and the highest available prices across regions in its decision making; for pragmatism, academic groups may use as a base case for sensitivity and scenario analyses the mid-point between the highest and lowest prices. These methods are relevant across all types of technology evaluation, whenever a medicine with a commercial arrangement is considered in the analysis.

Understanding and presenting uncertainty

- 2.14. As well as exploring how uncertainty is considered as a modifier in decision making, the review suggested there was a case to update NICE's methods for understanding, characterising and presenting uncertainty in health technology evaluations. Uncertainty should be fully and robustly characterised (both quantitatively and qualitatively) to clearly identify the nature, size and effect of uncertainties across evaluations.
- 2.15. Further exploration of different types of uncertainty, and ways to visualise it have highlighted challenges around establishing an agreed visualisation framework. The implementation of the visualisation framework will be accomplished through submission templates and need not be part of the manual.
- 2.16. The use of Expected Value of Perfect Information (EVPI) will not be adopted into the NICE methods. Stakeholders raised concerns about this proposal and the majority disagreed with it. It was noted that the added value of EVPI and how it would be used in decision-making was unclear as experiences from other countries suggested that its added value to decision making is minimal. There were concerns that it would add complexity to decision making, and the additional burden for analysts and reviewers may not be worth it. On the other hand, some stakeholders argued that the proposal did not go far enough and should include expected value of partially perfect information (EVPPPI) and expected value of sample information (EVSI).

3. Structured decision-making

- 3.1. Most proposals under this topic area were well received. However, some proposals need further clarification and stakeholders had some concerns.

General recommendations

- 3.2. We have updated and clarified how clinical and cost-effectiveness analyses should be presented and considered (including incremental and pair-wise analyses and subgroup analyses).

Net benefit approaches

- 3.3. The methods currently allow presenting net health or net monetary benefits alongside incremental cost-effectiveness ratios. Net benefit approaches may be particularly relevant when there are several interventions or comparators, when the differences in costs or QALYs between comparators is small, and when technologies are in the south-west quadrant; when net benefits are presented, net health benefits are preferred. Although not a fundamental change in methods, the updated manual will clarify when the use of net benefit approaches could be helpful for decision-making.

Subgroups

- 3.4. NICE's recommendations often consider the clinical and cost effectiveness of technologies in defined subgroups of the population, and there is substantial methodological guidance to ensure that this is done robustly. Minor changes to the manual have been made to support good conduct of subgroup analyses, including presenting absolute and relative treatment effects and reviewing the credibility of subgroup effects.
- 3.5. A clarification of the use of subgroups by committees has been included in the updated manual. This explains that committees may choose not to recommend a technology for a particular subgroup for which the technology is not cost-effective (that is, to make an optimised recommendation) even when the technology is found to be clinically and cost-effective for the whole population. Such a decision must be methodologically, clinically and ethically appropriate, and must take into account the benefits and harms of including or excluding a particular group. There was some concern that this might raise equality issues, however, equality impact assessments remain in place and are conducted at each stage of an evaluation and the clarification of a methodological approach to subgroups on its own does not raise an active equality issue that needs to be considered further.

Technologies which are not cost effective at low or £0 cost

- 3.6. In cases where survival is increased by a technology in a population which the NHS is currently providing expensive treatments, the company may make a

CONFIDENTIAL UNTIL PUBLISHED

case for submitting a non-reference-case analysis with the background care costs removed. Where a technology is administered in combination with another treatment, commercial solutions may be proposed by the company.

- 3.7. This was an area of debate during both stages of the methods update and the decision to accept a non-reference case for technologies which are not cost-effective at low or £0 cost is to recognise those situations which are beyond the company's control and provide a potential solution to this issue, and also to acknowledge the work the ABPI is doing to allow commercial negotiations in combination therapy situations. The impact of this change will, along with the other changes made to the methods, be monitored periodically.

4. Challenging technologies, conditions and evaluations

- 4.1. The comments received on the proposals in this workstream were supportive, but came with a call for further clarity or guidance on some of the proposals.
- 4.2. New methods resulting from the case for change and consultation with respect to challenging technologies, conditions and evaluations include:
- using scenario analyses to explore the effects of different assumptions about long-term benefits, potentially including threshold analysis for treatment effect duration
 - highlighting the importance of conducting RCTs for clinical development wherever possible, with thorough justification when not the case
 - recommending that companies conduct analyses in subpopulations to address generalisability of results
 - assumptions and extrapolations concerning the long-term effectiveness of these technologies including any waning of the therapeutic effect, should be substantiated by evidence from (ideally) comparative trials using validated clinical endpoints.
- 4.3. Controlled clinical trials are necessary to assess the prognostic and/or predictive value of biomarkers. The expression of a biomarker by a tumour is not a sufficient condition to assume that a product targeting this biomarker will be efficacious.

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- 4.4. When basket trials are used, they should include relevant internal comparators, use a random allocation of treatments, use appropriate clinical endpoints (with a validated relationship with the overall survival and quality of life of the patients) and enrol all patient groups relevant to the indication. Any deviations from this standard should be justified.
- 4.5. Biases associated with external comparisons should be explored. Other efficient approaches to clinical development should also be considered for these products such as platform trials.
- 4.6. Assumptions about homogeneity, heterogeneity and generalisability of subgroups to clinical practice must be clearly presented, tested and fully explored. Bayesian hierarchical models can be used in this context.
- 4.7. Cure-proportion modelling could be considered to explore the trajectories of different subpopulations without necessarily assuming a 'cure'. Curative assumptions should be supported by appropriate long-term clinical evidence.

5. Aligning methods across programmes

- 5.1. The methods manual has been aligned across our health technology evaluation programmes and an overarching decision-making framework has been developed. The methods provide a consistent approach for cost comparison analysis which can be used in relevant circumstances in all health technology evaluation programmes. However, there are unique features of technologies such as diagnostics and medical technologies which do not lend themselves to a single approach to technology evaluation. As a result, there are some differences in the way which the structured decision-making framework applies in each programme. These differences are explained and clear in the methods manual.