NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

CHTE methods review

Modifiers

Task and finish group report

October 2020

Executive summary

This task and finish group has explored modifiers in decision making, and this report outlines the background, methods and conclusions of this review. Input has been sought from internal and external task and finish group members (including NICE staff, committee members, and representatives from industry, patient organisations and academia), and progress reports have been presented to the working group.

For the purpose of this report, a factor is considered a modifier if:

- it has not been included in the estimate for quality-adjusted life years (QALY) because it cannot be (that is, issues that go over and above the QALY calculation – technical 'adjustment')
- value judgements.

The NICE reference case considers that all QALYs are equal, irrespective of the population, disease area or technology with which the QALY is associated. When considering a modifier, there is inherent deviation from this reference case. With that, there is a recognition that specific populations, disease areas or technologies are considered to have a greater value to society, so other populations, disease areas and technologies have a lesser value to society. This may be appropriate, if this is morally and ethically supported by reason, coherence and available evidence.

It is essential that there is complete transparency about the modifiers that are applied in NICE decision making and, crucially, why they are being adopted (the moral case). Given the moral and ethical implications of this review, further work is likely to be needed around the defensibility of applying (or not) certain modifiers, and the support for such a policy. The input from society in terms of what elements of value should be considered (or not) in decision making will be extremely important. It is therefore likely that the modifiers presented in this review will need to be discussed in a wider forum (such as a citizens' council) that discusses social values in the context of healthcare priority setting.

Case for change

Table 1 case for change for the modifier innovation

Modifier	Innovation
Currently used?	Yes
Moral case	There is no moral case to include innovation as a modifier in itself. What is valued from an innovation are the factors that define it, such as ability to provide a substantial therapeutic improvement.
Evidence – importance to public	None identified
Evidence – importance to NHS	None identified in the literature. Key policy papers including the NHS Long-term plan and Accelerated Access Collaborative.
Evidence – other	Commentary or opinion in literature that innovation as a principle is not a social value. Evidence that the innovation modifier is applied inconsistently.
Case for change – including as modifier?	Opinion is mixed, and largely depends on how innovation is defined and applied. Case for including – to promote innovation: There is also a trend that other international health technology assessment bodies are attempting to incentivise innovation through price premiums or faster reimbursement. Case for excluding – risk of double counting (depending on definition): May not be viewed as a social value in itself. Current definition is not clear and inconsistently applied.
Case for change – definition?	Yes. Definition unclear and does not represent general view of innovation. Case to exclude technical corrections, and to avoid double counting.
Case for change – application?	Yes. Clearer definition and also more clarity on what the consequences of being defined as innovative are for decision making. Further exploration will be done to identify whether there are any characteristics left that warrant a separate innovation consideration (for example, a substantial effect on how service is delivered in the NHS, delivery mode or organisational efficiencies). Consider how best to promote and incentivise innovation beyond the application of an innovation modifier. For innovative technologies, this could be achieved through procedural changes in NICE's process, managed access solutions or both.

Table 2 case for change for the modifier end of life

Modifier	End of life
Currently used?	Yes
Moral case	There sems to be a moral case to place a higher value on the life of the patients with terminal conditions. However, these extensions of life should be replaced by or accompanied by improvements in quality of life. This would prevent prioritising specific conditions (such as cancer) compared with others.
Evidence – importance to public	Mixed. The UK public appears to support giving special consideration to end-of-life technologies. However, there is a lack of consensus among both the public and NHS as to whether this should be applied in the context of a treatment that increases life expectancy, that improves quality of life, or both.
Evidence – importance to NHS	Mixed. In a discrete choice experience, healthcare professionals ranked 'debilitating or life-threatening disease' as the third most important consideration of 5 possibilities, but lower than 'treatment benefit (extent of survival increases)'. Policy makers ranked 'debilitating or life-threatening disease' as the lowest of all considerations. However, the degree of overlap between a 'debilitating or life-threatening disease' and an end-of-life setting is not described, and possibly minimal.
Evidence – other	In past appraisals, some interventions were deemed to meet the end-of-life criteria in some populations but not for others, or against some comparators but not others. Few other international health technology assessment bodies consider 'end of life' specifically as a modifier, though most tend to consider 'severity of illness' either explicitly or implicitly.
Case for change – including as modifier?	Yes. Case for including: some evidence supporting extensions of life at the end of the life of the patients. Case for excluding or replacing: some evidence and opinion that the relevant modifiers should be based on both, extensions of life and quality of life. It is unclear whether it should solely be applied at the end of the life.
Case for change – definition?	Yes – definition should include both extensions of life and quality of life.
Case for change – application?	Yes – end-of-life criteria should be replaced by severity or burden of illness.

Table 3 case for change for the modifier magnitude of benefit

Modifier	Magnitude of benefit
Currently used?	Yes
Moral case	There is a moral case to be consistent in the application of any decision-making modifiers across different programmes.
Evidence – importance to public	No. High importance on whether a drug is clinically effective. One study identified looked specifically at whether the general public considered an additional weighting should be given for a higher magnitude of benefit. This study found a diminishing preference for higher quality-adjusted life year gains. That is, the public does not support a magnitude of benefit modifier.
Evidence – importance to NHS	None
Evidence – other	Several other international health technology assessment bodies consider magnitude of benefit as a modifier, but under the banner of what constitutes an innovative medicine.
Case for change – including as modifier?	No. Case for excluding: magnitude of benefit is a composite of several other potentially important decision-making factors, specifically burden of illness, innovation and age. These decision-making factors should be considered separately.
Case for change – definition?	Not applicable
Case for change – application?	Not applicable

Table 4 case for change for the modifier curative potential

Modifier	Curative potential
Currently used?	No
Evidence – importance to public	No. High importance on whether a drug is clinically effective. One study identified found that whether a treatment was a cure or not did not appear to influence respondent's choice in treatment
Evidence – importance to NHS	No literature identified within the targeted search.
Case for change – including as modifier?	No Case for excluding: Whether a treatment is curative, all else being equal, was not found to be an important factor to the public.
Case for change – definition?	Removal of the criteria for non-reference case discounting.
Case for change – application?	Consider if other decision-making modifiers should take into account if any additional adaptation or weighting should be applied as needed if the technology has a curative potential.

Table 5 case for change for the modifier rarity

Modifier	Rarity
Currently used?	No
Moral case	There may be a moral and ethical justification for applying a greater weight where there is an unmet need or health inequality arising from the fact a disease is rare.
Evidence – importance to public	No. Evidence strongly suggests that the public do not regard rarity on its own as an as important modifier.
Evidence – importance to NHS	No specific literature identified within the targeted search. Key policy papers have been produced in the area of treating rare diseases, showing the importance of rare diseases to the NHS and the UK in general. Rare Disease Strategy and Rare Disease Advisory Group at NHS England.
Evidence – other	Most of the countries reviewed factor rarity into their pricing or reimbursement decision-making processes. Countries often have a separate process or threshold for ultra-orphan drugs.
Case for change – including as modifier?	No Case for excluding: Evidence strongly suggests that the public do not regard rarity as an as important modifier. There are characteristics of rare diseases that may justify the need for a decision-making modifier, including the burden of illness, severity, the age of the population, and the desire to reduce health inequality. These characteristics can be captured in other modifiers and complemented by other elements in the methods review. This can also be considered within process considerations.
Case for change – definition?	Not applicable
Case for change – application?	Consider if other decision-making modifiers should consider if any additional adaptation or weighting should be applied as needed if a disease is also rare.

Table 6 case for change for the modifier age

Modifier	Age
Currently used?	No
Evidence – importance to public	Yes. Evidence is mixed but suggests the UK public may favour younger age groups.
Evidence – importance to NHS	No literature identified
Evidence – other	Of the countries reviewed, only Japan includes age as a modifier, technologies are eligible for a 5% to 20% price premium over comparators There have been 2 NICE appeal panel decisions (the technology appraisal guidance on sofosbuvir–velpatasvir–voxilaprevir for treating chronic hepatitis and the highly specialised technology guidance in development on lysosomal acid lipase deficiency - sebelipase alfa [ID737]) that relate to age, which found: 'the committee should consider whether there is anything particular to this patient group as children that should be taken into account in the appraisal' The 2010 Equality Act applies to NICE, which prohibits discrimination based on age. However, under 18-year-olds are protected against age discrimination only in relation to work During the technology appraisal on mifamurtide for osteosarcoma in children NICE amended the methods to allow for a non-reference case discounting rate of 1.5% for costs and health effects (compared with 3.5%).
Case for change – including as modifier?	Yes Case for including: Evidence suggests that the public would prioritise this age group compared to adults. Committees, and the NICE appeal panel, appear to consider diseases that affect children differently. Case for excluding: Many of the issues encountered by the committee when appraising technologies that are used to treat childhood diseases may be captured within a potential severity or burden of illness modifier. May not conform to the 2010 Equality Act.
Case for change – definition?	To explore inclusion of a modifier based on whether the population includes children. Removal of the criteria for non-reference case discounting.
Case for change – application?	The modifier should be applicable independently to any severity or burden of illness modifier.

Table 7 case for change for the modifier burden of illness

Modifier	Burden of illness
Currently used?	No
Moral case	There is a moral case to treat severe conditions differently and to value health gains in severe conditions more than in other non-severe conditions.
Evidence – importance to public	Yes. The public appears to support giving special consideration to severity of the disease.
Evidence – importance to NHS	None
Evidence – other	In the Value vases assessment (VBA) proposal there seemed to be some support for adopting severity or burden of illness. The decision support unit report highlights some correlation between end of life and burden of illness. Other international health technology assessment bodies tend to take into account 'severity of illness' either explicitly or implicitly. The NICE Citizen's council report (2008) favoured considering severity or burden of illness as a relevant modifier. The council favoured taking severity into consideration alongside cost and clinical effectiveness evidence; but not through modifying the quality-adjusted life year (QALY) measurement.
Case for change – including as modifier?	Yes Case for including: evidence supporting severity as an important value element. Case for excluding or replacing: some evidence and opinion that the relevant modifiers should be based on both extension of life and quality of life.
Case for change – definition?	Yes – definition of severity should look into shortening of life and loss of quality of life
Case for change – application?	Yes. Severity or burden of illness should replace the end-of-life criteria.

Table 8 case for change for the health inequality

Modifier	Health inequality
Currently used?	No
Moral case	There is a moral case to reduce health inequalities and to treat technologies that address these inequalities differently.
Evidence – importance to public	Consistent finding that members of the general population would be willing to trade total quality-adjusted life years (QALYs) to reduce inequality in the social distribution of (QALYs). (Williams et al. 2005, Dolan et al. 2011, Robson et al. 2017, Gibbs et al. 2019, McNamara et al. 2020).
Evidence – importance to NHS	Evidence that secondary care professionals have similar, though slightly less marked, preferences to the general public (Dolan et al. 2006, Ratcliffe et al. 2009).
Evidence – other	Most NICE citizens council members supported the proposition that NICE guidance should aim to narrow the gap between the least and most disadvantaged, even if this is not the most efficient allocation of resources (NICE 2006). There is abundant evidence that health-related inequalities have increased over the past 20 years and, although that cannot be ascribed to NICE alone, we should want to contribute to system-wide efforts to reverse the trend.

Case for change – including as modifier?	Case for including: The NHS's statutory duties and NICE's stated principles stipulate that our guidance should offer particular benefit to the most disadvantaged. Consistent evidence that the UK general population favours allocation of resources that seeks to equalise, and not just maximise, health gains. A relatively simple method has been proposed that could incorporate empirical societal preferences to modify decision-making objectively. Case for excluding: Some additional quantitative burden. Worked case studies suggest none of the appraisals reviewed would have arrived at a different conclusion if they had formally included equality. Unless compulsory in all cases, there would be no incentive for companies to do analyses showing the opportunity costs associated with their technology can be expected to increase inequality to a greater degree than the technology itself reduces it.
Case for change – definition?	Definition should include socioeconomically mediated health inequalities; other areas of inequality may be amenable to consideration (though quantitative evidence appears to be lacking).
Case for change – application?	Methods exist that use empirically quantified societal inequality aversion; these could be applied to outputs of any economic analyses on which decision-making relies. Committees would then be able to consider the impact of positive or negative recommendations (that is, if a technology that appears not to provide net health benefit should nonetheless be recommended because it would sufficiently reduce inequality or a technology that does provide net health benefit should not be recommended because it would exacerbate inequality too much).

Table 9 case for change for the uncertainty

Modifier	Uncertainty
Moral case	There is a moral case to value more highly certain gains over uncertain gains.
Currently used?	Explicitly through quality of evidence. Implicitly through preference for randomised controlled trials. Above a most plausible incremental cost-effectiveness ratio of £20,000 per quality-adjusted life year gained, judgements about the acceptability of the technology as an effective use of NHS resources specifically take account (among other things), the degree of certainty around the incremental cost-effectiveness ratio (ICER) (this is covered by the uncertainty task and finish group). In addition, the committee will want to be increasingly certain of the cost effectiveness of a technology as the impact of the adoption of the technology on NHS resources increases. Therefore, the committee may need more robust evidence on the effectiveness and cost effectiveness of technologies that are expected to have a large impact on NHS resources.
Evidence – importance to public	Literature exploring uncertainty specifically as a modifier is limited. There were no papers that specifically investigated whether the public placed a greater weight on certainty of clinical effectiveness or cost-effectiveness estimates as a decision-making modifier.
Evidence – importance to NHS	Evidence that pressures to accelerate access to 'innovative' technologies have made decision makers more tolerant (Charlton, 2019). Formalisation of an appraisal process attempts to absorb uncertainties for decision making (Calnan, 2016).
Evidence – other	Refer to 'Uncertainty' and 'Decision Making' reports produced as part of the Centre for Health Technology Evaluation (CHTE) 2020 methods review.
Case for change – including as modifier?	Not as a modifier. Not a characteristic of a patient group, the size of the health benefits or the technology. It is a feature of evidence and understanding, and there is a separate set of methods for reflecting it and handling it in decision making.
Case for change – definition?	Being considered more fully by the 'Uncertainty' and 'Decision Making' reports produced as part of the CHTE 2020 methods review.
Case for change – application?	Committees should retain their ability to believe or not in the evidence presented when considering a cost-effectiveness estimate based on the uncertainty presented and explored using the methods suggested by the uncertainty task and finish group. In their consideration, committees will be able to apply their judgement to recommend, not recommended or recommend a technology in a particular framework such as a managed access agreement.

Background

The NICE technology appraisals (TA), highly specialised technologies (HST), diagnostics advisory (DA) and medical technologies evaluation (MTE) committees (from this point forward referred collectively as 'CHTE committees'), make decisions on the grounds of cost effectiveness. While clinical and cost effectiveness are key decision-making criteria when Centre for Health Technology Evaluation (CHTE) committees make recommendations, these are not the sole basis for decision making, and other factors are legitimately considered alongside. These factors can be referred to as decision modifiers.

NICE principle 7 (2020) states that 'NICE's recommendations should not be based on evidence of costs and benefit alone. We must take into account other factors when developing our guidance. We also recognise that decisions about a person's care are often sensitive to their preferences.'

The way decision modifiers are considered by CHTE committees varies. Some are considered quantitatively and are associated with a specific additional maximum weight. Others are intended to be qualitatively considered by the committee.

NICE's decisions should in principle maximise the total health gains to the UK public, and therefore health-related benefits should be valued the same across the population (that is, quality-adjusted life year (QALY) = QALY = QALY). The modifiers work, however, makes the case for accounting for those specific circumstances or cases when deviating from the reference case in which all health-related benefits are valued the same irrespective of any other considerations is appropriate based on a moral and ethical reflection supported by reason, coherence and available evidence. This would result in reducing the total health gains to the UK public to prioritise reimbursement of specific circumstances or cases.

Current modifiers used by CHTE committees

For the **TA programme,** the methods guide states that above a most plausible incremental cost-effectiveness ratio (ICER) of £20,000 per QALY gained, judgements about the acceptability of the technology as an effective use of NHS resources specifically take account of the following factors:

- the degree of certainty around the ICER (this is under consideration by the task and finish group looking at uncertainty)
- whether the assessment of the change in health-related quality of life has been adequately captured
- the innovative nature of the technology, specifically when the substantial nature of the benefits may have not been adequately captured in the QALY calculation

- the criteria for ‘life-extending treatment at the end of life’ (through the application of a maximum weight of 1.7 to the QALY gained)
- non-health objectives of the NHS (other benefits that are considered socially valuable but are not directly related to health and are not easily captured in a cost per QALY analysis; and cost of care by family members, friends or a partner which might otherwise have been provided by the NHS or personal social services).

For the **HST programme**, the maximum acceptable ICER is £100,000 per QALY gained taking into account additional factors that include:

- the nature of the condition (morbidity, disability, impact on carers, extent and nature of treatment options)
- the impact beyond direct health benefits (including non-health objectives of the NHS, as in technology appraisals, in addition to the potential for benefits for research and innovation, delivery of specialised services, additional staffing and infrastructure).

Beyond a most plausible ICER of £100,000 per QALY gained, in addition to the same factors outlined above for the technology appraisals programme, the committee is also able to consider the magnitude of the benefit. A weight is applied to each QALY according to the number of overall QALYs gained with the new technology (no weighting if 10 or fewer QALYs gained, weight of 2 if 11 to 29 QALYs gained, weight of 3 if 30 or more QALYs gained).

For the **DA programme,** a modifier can be understood as:

- when the committee alters the level a technology’s estimated ICER must be under (for North-east quadrant) to be considered cost effective: for example, considering £30,000 cost per QALY gained, rather that £20,000 cost per QALY gained, or above £30,000 cost per QALY gained.

  In this context, modifiers include:

  - **innovative technology** – particularly if the test can solve a long standing, unmet need.
- when an expected ICER is above or below a threshold for cost effectiveness. That is, the committee does not alter the threshold they consider to be cost effective, but (for North-east quadrant)

if a technology’s estimated ICER is under this threshold, they don’t recommend for routine adoption.

If the technology’s estimated ICER is over this threshold it may still be recommended for use (for routine adoption or with or in research).

- These modifiers include: **Sunk costs** – if adopting the technology would result in large upfront costs (for example to buy a large piece of kit to run a test, or if changes to a care pathway to introduce a new test would not easily be reversed) then the committee may need greater certainty that a test is cost effective to recommend routine adoption. A recommendation for use in or with research is more likely; particularly if the ICER is near the threshold.
- **Greater uncertainty** about cost effectiveness (and if the expected ICER is near the threshold) – this increases the likelihood of a research recommendation (rather than routine adoption).
- **Uncertainty that diagnostic accuracy data used to differentiate between tests in the model are valid** (because of methodology, quality, or bias issues) or **generalisable** (because the test was done in a different population to the decision question). In this case, even tests with low ICERs may not be recommended and this often leads to a research recommendation for further diagnostic accuracy data ('better study' or in right population).
- **Uncertainty about the extent that acting on a test result in practice will lead to the magnitude of changes in care (and impact on outcomes) predicted by the model**. Linked evidence models are usually used in diagnostic assessments, starting with test accuracy data, then assuming a course of action happens based on the test result (positive or negative) that influences clinical outcomes (possibly with another link between surrogate and longer term outcomes). However, in practice, not all positive or negative tests results will be acted on in the same way, so the magnitude of change in care (and impact on outcomes) predicted by the model might not happen. This is especially the case when the test result is just one piece of information upon which decisions about care are made, or if (for prognostic tests) the result is used to help patients make decisions. In these cases, the committee may not be convinced that implementing the model in practice will have the same effect as predicted in the model, so may want further data on the impact of introducing testing on clinical outcomes to make sure that the model is accurate.
- **Ongoing research:** if research is ongoing that is likely to provide relevant outcome data, the committee may be more likely to recommend research and wait for this research to publish (particularly if there are irreversible costs to adopting technology, or the estimated ICER is near the threshold and it is likely the research data could have an effect on the decision).
- **Uncaptured benefit of technology:** if the expected ICER is above the threshold, the committee may well still recommend use if they consider

there are uncaptured benefits. For example, monitoring technologies often provided patient reassurance which is unlikely to be captured by health-related quality-of-life questionnaires, so the committee may consider that the QALYs generated by using the technology have been underestimated.

For the **MTE programme,** technologies have to be cost saving or cost neutral to get a positive recommendation and only innovative technologies are selected for guidance development. Often there is uncertainty within a cost model for a technology. When there is uncertainty about whether a technology will be cost saving or neutral, the modifiers considered within the discussion include:

- **Quality of life**: Quality-of-life benefit is not captured in MTE's cost consequence methods; however, the committee considers quality-of-life benefits (such as relief of chronic pain or sexual function improvements) as part of the clinical evidence review.
- **Equalities**: When a technology provides health benefits for populations with a protected characteristic where current standard care does not.
- **Unmet need**: When a technology is addressing an unmet need within the NHS, such as a condition or patient group who have no current treatment options, rare diseases and inequality of treatment access.
- **Resource releasing capacity**: Some technologies may cost more, but release resources downstream, for example by reducing nursing time, length of stay, likelihood of further treatments and so on. When possible, this is included in the economic model, if resource releasing costs aren't adequately captured in the model the committee can consider the impact of resource release as a modifier.
- **National issue**: When a technology addresses a national issue, such as moving secondary care to primary care or public health concerns, the committee will consider the impact the technology is likely to have in relation to the issue.
- **Innovation**: Innovation is not considered a modifier because it is used as part of the selection criteria for routing technologies to MedTech guidance.
- **Sustainability**: The medical technologies evaluation team are trying to gain more evidence about the sustainability of technologies so that the committee can consider it as a potential modifier.

The CHTE committees have discretion to consider those factors it believes are most appropriate to each evaluation, having regard to NICE's obligations on equality and human rights, considering:

- the balance between the benefits and costs of providing health services or social care in England
- the degree of need of people in England for health services or social care
- the desirability of promoting innovation in providing health services or social care in England.

Historical consideration of decision modifiers

In 2014 NICE considered a unified approach to using other factors in decision making in the consultation on "Value-Based Assessment of Health Technologies". This proposed:

- a maximum QALY weight for all decision modifiers of 2.5
- burden of illness and wider societal benefits as formal decision modifiers
- to exclude an explicit weight for end-of-life conditions.

The proposals were not adopted by NICE, after responses from consultation.

Mixed views for using a proportional QALY shortfall method (the proportion of future quality-adjusted life years expected, that is lost by having the condition) to estimate burden of illness were received, but with potential for adopting in the future.

A negative response was received for using an absolute QALY shortfall method (the amount of future QALYs expected, that are lost by having the condition) to estimate burden of illness, or to consider the wider social impact.

NICE has also previously considered, and rejected, formally adopting multi-criteria decision analysis tools, in which specific weights are given to different factors.

Decision modifiers not currently stated within the methods guides

A proposal for an **extended value assessment (EVA)** approach has been shared by the Association of British Pharmaceutical Industry (ABPI) as part of this methods review process, and is being considered as part of this work.

Sustainability has also been a factor that committees have considered in the past, particularly in the medical devices area (for example ethical supply chain, energy

efficiency in manufacturing, use of plastic and so on). This factor also fits in the current piece of work.

NICE committees must consider the different needs of **children** when they are included in an evaluation alongside adults. Two recent appeal panel decisions have suggested that committees should not only consider the needs of children, but also whether the fact that children are included should lead to any modification in the conclusions.

Project objective

Five overarching themes will be explored:

- Factors that could need a QALY weighting.
- Uncertainty and other technical reasons for adjustment.
- Ethical or social reasons for adjustment, including for disabilities and children.
- Non-health impacts including wider benefits, productivity, sustainability, and cost of care by family members.
- When the QALY doesn't fully capture benefits including rarity, innovation, unmet need, burden of the illness (severity), curative potential and if there are benefits of the technology to other licensed indications or co-morbidities.

This task and finish group will explore the application of modifiers in NICE's decision making. In particular:

- if the current modifiers are still relevant for patients and the NHS and in line with NICE's remit for CHTE committees
- whether or not there is a need to modify or adapt currently considered modifiers, for example, through the addition or amendment of specific weights
- if any additional factors currently not considered in the decision making should be taken into account, either quantitatively or qualitatively
- how positive and negative modifiers are or should be taken into account in decision making.

For the purpose of this report, a factor is considered a modifier if:

- it has not been included in the QALY because it cannot be, that is issues that go over and above the QALY calculation (technical adjustment)
- it reflects value judgements.

A factor is not considered a modifier and not included in this report if it is a factor that has not been included in the ICER or QALY but could have been (technical correction).

For a modifier to be considered as part of NICE decision making, there needs to be a clear and defensible moral case for a given characteristic being a source of additional social value. This means that the absence of that characteristic is a source of lower social value. There should also be no overlap with other potential modifiers (that is, double counting).

To incorporate a modifier into decision making, there should ideally be evidence from a UK population on how the public would weight gains in health in general compared with gains for patients with the specific characteristics. However, that should not be the sole basis to apply a modifier and there should be a moral and ethical case supported by reason, coherence and available evidence.

NICE's decisions have an overall impact on opportunity cost, and therefore the maximum health gains that can be achieved for a whole population. Applying a modifier implicitly or explicitly assumes that some elements or factors which may be addressed by a particular technology are valued more or less over and above other elements or factors. For example, under the current end-of-life criteria, technologies that extend the life of a patient (for over 3 months) at the end of their life (when life expectancy is normally less than 24 months), are valued more than other technologies that do not extend the life of the patients at the end of their lives.

The effect of this is that technologies or services may be displaced, which can lead to fewer health gains across the population. These technologies may or may not be evaluated by NICE and consideration should be given as to whether health and equity are being maximised with the available resources or whether more health is being destroyed or more inequalities have arisen because of applying certain modifiers that are likely to only apply to a selected group of technologies or conditions. Therefore, the consequences of applying modifiers should be measured, taking into account the evidence on the extent to which the characteristic in question applies to health decrements (health opportunity costs) associated with NICE decisions which impose net additional costs on the health system.

In this sense, it is essential that there is complete transparency about the modifiers that are being adopted and, crucially, why they are being adopted. Given the moral and ethical implications of this review, further work is likely to be needed around the defensibility of the application or not of certain modifiers and the support for such a

policy. The input from society in terms of what elements of value should be considered or not in decision making will be extremely important, and therefore, it is likely that the modifiers presented in this review will need to be discussed in a wider forum (such as a citizens' council) which discusses social values in the context of healthcare priority setting.

Formal equality also demands that there be consistency in how modifiers are applied across cases. That is, cases that are alike in morally relevant respects should be treated similarly, while cases that differ in morally relevant respects should be treated differently.

Project Tasks

The activities have been categorised in 2 stages. Stage 1 has 3 workstreams, comprising of:

1. How has the committee considered modifiers in its decision making?
2. Is there evidence available on whether any of the currently applied modifiers are relevant for patients and the NHS, and within NICE's remit?
3. Are there other factors beyond the currently applied other factors that should be considered?

The results from stage 1 will inform whether or not there is a case for change in how and which modifiers are described in the Methods Guide and considered by CHTE committees.

Stage 2 will build on these results to explore:

4. Should a specific framework be adopted for the consideration of additional factors?
5. What are the implications for changing the approach for the NHS (that is, what is the expected change in the proportion of positive or negative recommendations, the types of products receiving a positive recommendation, and the budget impact)?

Methods

Stage 1, workstream 1: How has the committee considered modifiers in its decision making?

Technology Appraisal and Highly Specialised Technology committees

A review of published technology appraisals (TA) and highly specialised technologies (HST) guidance was commissioned to the NICE decision support unit (DSU). This review took a pragmatic approach and aimed to understand the frequency at which factors beyond the incremental cost-effectiveness ratio (ICER) were taken into account in NICE decision making in the TA and HST programmes.

The DSU reviewed 323 TAs that published on the NICE website between May 2011 to November 2019, including 570 decisions. All HSTs that were published before January 2020 were considered (12 HSTs). Each appraisal may make more than one recommendation, either because it pertains to more than one health technology or because recommendations are made that differ by patient subgroup.

For each recommendation within the published guidance, the review captured:

- the most plausible ICER and QALY estimates,
- if the committee considered the technology to be innovative, meet the end-of-life criteria, or
- if they had discussed other factors which could potentially modify the decision such as age (children or the elderly), disability, burden or severity of illness, indirect costs including productivity costs, wellbeing, experience of care, sustainability, wider societal benefits, organisational efficiency, national policy alignment, curative potential, rarity, patient choice, impact on carers, equality, co-morbidities, benefits of the technology to other licensed indications. Because of time restrictions, a full review of the guidance for other factors was limited to guidance published between January 2018 and November 2019.

For technologies that were recommended, most ICERs fell within the acceptable threshold. When recommendations were made with above-threshold ICERs, the most plausible calculated ICER, provided or referred to in the guidance, was deemed to be an overestimate of the committee's view of the true ICER. The reasons for this were as follows:

- The committee believed that one or more of the model assumptions were unrealistic and believed that a change in the assumption would result in a lower ICER.
- The committee believed that the ICER would be below the threshold for a subgroup, however no specific ICER was calculated for the subgroup.
- The committee believed that other factors were relevant to the decision that were not or could not be incorporated into the model (that is, decision modifiers; these are discussed in the later sections of this report).

It was noted that there was also a degree of subjectivity about the interpretation of text for the innovation and other factors categorisation.

Stage 1, workstream 2: Is there evidence available on whether any of the currently applied modifiers are relevant for patients and the NHS, and within NICE's remit?

A pragmatic review of the available literature was conducted. The aim of this review was to investigate the importance to either the public or the NHS of specific decision-making modifiers that that are currently applied, or could be applied, within health technology assessment in England.

Key search terms included:

- decision-making or modifiers
- social value judgement
- health technology assessment
- UK geographic filter or National Institute of Health and Care Excellence (NICE).

The search for literature was targeted to search for papers available since the current NICE Methods Guide for technology appraisals (2013) was published.

Key papers were also solicited from experts and citation searching (forward and backwards) of included papers. During review of the available evidence it was decided to include relevant studies that had been identified from similar healthcare settings.

Stage 1, workstream 3: Are there other factors beyond the currently applied other factors that should be considered?

The literature review described above for workstream 2 also considered whether there were additional factors that should be considered.

A review of the health technology assessment (HTA) processes in other countries was one in addition to the reviews described previously. The aim of this international review was to understand how modifiers are taken into account in decision making by other HTA bodies, and to investigate whether there are any other relevant factors applied in other countries that should be considered by the task and finish group. The international review took a 2-stage approach:

1. Studies comparing pricing and reimbursement processes across different countries were reviewed to provide an initial baseline understanding. The following sources were used:

    - A EUnetHTA analysis (an analysis of HTA and reimbursement procedure in EUnetHTA partner countries, 2017) of HTA and reimbursement procedures within 31 EUnetHTA partner countries.

    - A review of the practices, processes and policies of value assessment for new medicines across 8 European countries one by Angelis et al. (2018).

    - A publication by the Office for Health Economics that assessed cost-effectiveness thresholds applied across 14 countries, and the factors (modifiers) other than cost effectiveness that are considered in decision making (Zhang & Garau, 2020).

2. Publicly available methods guides; other formal HTA body sources and legislation (where relevant) were reviewed across 14 countries, to supplement and enhance the phase 1 findings. HTA body decision outcomes (in the form of assessment reports for individual medicines) were not reviewed.

The following countries were included in the in-depth review: Australia, Canada, Czech Republic, France, Germany, Ireland, Italy, Japan, Netherlands, Poland, Portugal, Scotland, Sweden, USA. Countries were selected based on their comparability to the UK in terms of GDP and population size, as well as the availability of a publicly available methods guide. The sample was also intended to cover a range of decision-making approaches at a high level (for example cost effectiveness, clinical effectiveness, or budget impact-driven countries), as well as a wide geographic spread.

To allow comparison across countries, for each modifier HTA bodies were categorised as to whether: 1) the modifier is considered through a clear, well-defined mechanism, 2) the modifier is mentioned as a decision factor, but its importance to decision making is unclear, and 3) the modifier is not mentioned. This categorisation is qualitative and subjective, and it is also important to note that differences in the HTA processes between countries impacts how the modifiers are applied. The table in the appendix 2 of this report summarises this categorisation.

Results

Based on the preliminary results from the 3 workstreams and discussion with the task and finish group members and the methods working group, a list of key modifiers was derived. Results are detailed below, in the context of these relevant decision modifiers:

- innovation
- end of life
- magnitude of benefit
- rarity
- curative potential
- age
- burden of illness
- health inequalities
- uncertainty.

The modifiers not included in this list may be considered when looking into the specific definitions of each of the above modifiers. After consultation and exploration of the potential frameworks to apply these modifiers, other factors not currently included may need further consideration.

Innovation

NICE Principle 8 states that NICE supports innovation in the provision and organisation of health and social care services.

The Health and Social Care act (2012) requires NICE to have regard to the desirability of promoting innovation in the provision of health services or of social care in England.

The NHS long-term plan “recognises the critical importance of research and innovation to drive future medical advance, with the NHS committing to play its full part in the benefits these bring both to patients and the UK economy”.

Consideration should be given to the best route to promote and incentivise innovation at NICE, whether through the application of a specific modifier for innovation (considered as part of this report), or through procedural aspects applied to innovative technologies as part of an overall support from NICE to innovation.

Kennedy report

The current definition for innovation in technology appraisal (TA) and highly specialised technology (HST) was influenced by Sir Ian Kennedy's review of the value of innovation in 2009. In this review, Sir Kennedy states that NICE should formulate a definition of innovation for products that industry claims to be:

- new
- constitutes an improvement on existing products
- offers something more (that is, a step change in terms of outcomes for patients).

Sir Kennedy defined step change as:

- the product significantly and substantially improves the way that a current need (including supportive care) is met
- the need met is one which the NHS has identified as being important
- where appropriate, research on stratification has identified the population(s) in which the product is effective
- the product has been shown to have an appropriate level of effectiveness, for example, benefiting 70% of the intended target group. This may be all of the population who have the condition or just a subset and
- the product has a marketing authorisation for the particular indication.

Kennedy also suggested that a mechanism to incentivise innovation might include higher cost-effectiveness thresholds (for a fixed period of for example, 3 to 5 years) or granting companies the opportunity of benefiting from flexible pricing or patient access schemes. He also states that agreeing a higher cost-effectiveness threshold for innovative products may mean that the threshold for a product which is not an innovation will have to be reduced.

NICE Principles

The recently published NICE Principles (NICE 2020) explicitly state:

- Support innovation in the provision and organisation of health and social care services (principle 8).
- The importance of promoting innovation in the provision of health services and social care is set out in the Health and Social Care Act 2012. NICE aims to support this innovation by encouraging interventions that provide substantial

distinctive benefits that may not be captured by measuring health gain (that is, the estimated QALYs gained) (principle 26).

- Innovation does not necessarily lead to better outcomes than existing practice. And if innovations come at an additional cost, they may divert resources away from existing practices that are better value for money. To mitigate the risk of an innovative intervention not performing as expected NICE's committees can, in appropriate circumstances, recommend its use in the context of a managed access arrangement (principle 27).

The NICE principles refine the innovation definition as 'interventions that provide substantial benefits that may not be captured by the QALY'.

Results from the decision support unit (DSU) review on innovation

The guidance for each TA was assessed to identify if the technology was regarded as innovative, in line with the definition described in the methods guide:

- to address an unmet need
- represent a step change in treatment
- innovative benefit not captured in the ICER.

The DSU report states that there was no criterion that was universally considered sufficient, alone, to warrant defining a technology as innovative. Therefore, despite some technologies meeting individual criterion in certain examples, the technologies may not have been considered overall innovative.

Table 10: Committee considerations in relation to innovation

	No	Yes	Missing or unclear
Innovation met? (%)	461 (80.9)	105 (18.4)	4 (0.7)
Step change (%)	329 (57.7)	237 (41.6)	4 (0.7)
Unmet need (%)	425 (74.6)	141 (24.7)	4 (0.7)
Benefit not captured in the incremental cost-effectiveness ratio (%)	468 (82.1)	96 (16.8)	6 (1.1)

Where data were available on the incremental QALY, cases which were deemed to be innovative were associated with greater incremental QALY gain than those that were not.

Notably, the greatest QALY gain reported in a TA was in Nusinersen for treating spinal muscular atrophy. Spinal muscular atrophy is associated with a young age of

onset and poor quality of life, therefore resulting in substantial negative QALY for standard care. Nusinersen was considered by the committee to be an innovative treatment and address an unmet need, however they did not consider there to be any benefits of an innovative nature that were not captured in the economic analysis. As a result, this technology was recorded as not meeting the innovation criteria.

The innovation data indicates that a higher proportion of HSTs (50%) are deemed to be innovative than TAs. However, a similar proportion are regarded as having innovative benefits that are not captured in the QALY, indicating that this criterion is not independently driving the innovation definition.

Table 11: Innovation in HST evaluations

	Innovative	Step change	Unmet need	Benefit not captured in incremental cost-effectiveness ratio
HST1	Yes	Yes	Yes	–
HST2	–	–	–	–
HST3	Yes	Yes	Yes	–
HST4	–	–	Yes	–
HST5	–	–	–	–
HST6	–	Yes	Yes	–
HST7	–	Yes		–
HST8	Unclear	–	–	–
HST9	Yes	–	Yes	–
HST10	Yes	–	–	Yes
HST11	yes	Yes	Yes	–
HST12	Yes	Yes	Yes	Yes

In 2 HST evaluations (patisiran for treating hereditary transthyretin amyloidosis and voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations), the committee expanded the definition of innovation to also cover a technological step change, with the opportunity for benefit in other conditions or in a particular field.

The DSU review highlights inconsistency in how innovation has been considered and recorded by TA and HST committees. Therefore, there is a case for change in the definition of innovation. There is a need for further clarity on whether or not the current considered criteria are appropriate (that is, step change, unmet need and benefit not appropriately captured in the QALY).

Results from the literature review on innovation

No studies were identified that considered specifically the importance of innovation to the public or the NHS.

One study (Charlton, 2019), assessed the application of innovation in NICE Technology Appraisal committee decision making. The study conclusions support those of the DSU work outlined above (see results from the decision support unit (DSU) review on innovation), that is, that the definition of innovation is open to interpretation and as such has been applied inconsistency across decisions. Charlton highlights instances of contradiction in committee application, noting cases where the committee has considered whole drugs classes as innovative (disease-modifying anti-rheumatic drugs), and others where this has only been applied to the first in class (tyrosine kinase inhibitors for treating leukaemia).

Charlton also discusses concerns in the literature, raised as opinion pieces, that innovation may not be considered to have a specific social value. That the value associated with innovation lies generally with increased effectiveness or other benefits derived from the product, rather than just its innovative nature (of note, no empirical data were identified to support these view points). It further notes that "NICE already facilitates payment of a "premium" for novel technologies. All technologies appraised by NICE display some degree of novelty; for example, a drug may have been recently patented or an existing technology shown to be effective in a new application. This means that all technologies recommended by NICE are novel—or "innovative"—in some respect."

International considerations of innovation

Three of the HTA bodies reviewed consider 'innovation' explicitly, with 2 describing the factors defining innovation in some detail. Others consider some factors that may constitute innovation (for example, a substantial efficacy improvement), but they are not labelled as such. Overall, 9 of the 14 countries reviewed assess innovation either through a defined or undefined mechanism.

The Italian Medicines Agency's innovation algorithm assigns innovative status to medicines that offer high therapeutic value in an area of significant unmet need, based on robust clinical evidence (assessed using the GRADE method) (Agenzie Italiana del Farmaco, 2017). In Japan, the Ministry of Health, Labour and Welfare (MHLW) defines an innovative drug to be one that meets all of the following criteria: 1) a new, clinically useful mechanism of action; 2) a better efficacy and safety profile than comparators, and 3) an improvement in the method of treating the condition (Yamate, Update of Drug Pricing System in Japan", Ministry of Health, Labour & Welfare [accessed June 2020]). The Czech Republic has a special innovation category for 'highly innovative medical products'. Limited detail is provided in the legislation as to what constitutes such a product, but it appears to be defined by

‘clinical characteristics’ (Zakon et al 1997). Finally, while not labelled as such, the ‘improvement of medical benefit’ (ASMR) rating awarded by the Transparency Committee (TC) in France is effectively an assessment of innovation. Again, limited detail is provided as to what drives a higher ASMR rating, but it is primarily based on a medicine’s relative clinical efficacy compared with comparators. The nature of the treatment (‘symptomatic’, ‘preventative’ or ‘curative’) also factors into the TC’s decision-making process. Medicines classified as innovative in these countries are rewarded either through price premiums compared with their comparators (France and Japan), or faster reimbursement (the Czech Republic and Italy).

New legislation implementing an HTA process was introduced in Greece in 2018. While no published methods guides were identified, (Kanavos et al. 2019) describes the new process in some detail. Innovation’ is assessed in the Greek HTA methodology using the Ahlqvist-Rastad system, though it is unclear how the rating assigned counts towards the final HTA body recommendation. The factors considered by the Ahlqvist-Rastad system are unmet need, superiority compared with alternatives in terms of efficacy, safety, dosage and route of administration, and mechanism of action (class) (Vitry et al. 2013).

In summary, where innovation is a modifier for HTA bodies, the degree of efficacy improvement compared with comparators is always an important factor in deciding whether a medicine is innovative. The perceived novelty of the mechanism of action and degree of unmet clinical need are considered in some but not all of the international HTA body methods guides reviewed.

Conclusion on innovation

The DSU report and the literature highlight that the definition of innovation is unclear and this risks decision inconsistency. There is therefore a case to clarify the definition and application of the innovation criteria.

Whether innovation should remain as a relevant modifier remains unclear. There is no empirical evidence to support, or oppose the idea that society values innovative products. Concerns have been raised that NICE in its processes already provides a weight for innovation. There is however a responsibility for NICE to promote and support innovation in health technologies. The appropriate mechanism to do so is however unclear.

Proposal for stage 1: To remove innovation as a modifier, unless an appropriate, clear definition that is distinct from other decision modifiers, is identified. This means that the different factors included in the innovation definition are proposed to be separated out.

Actions for stage 2: To reflect on decision modifiers and framework to ensure the values often attributed to innovation are captured. That is, further exploration will be conducted to identify whether there are any characteristics left that warrant a

separate innovation consideration (for example, substantial impact on how service is delivered in the NHS, delivery mode or organisational efficiencies).

Consideration should be given to how best to promote and incentivise innovation beyond the application of an innovation modifier. This could be achieved through procedural changes in NICE's process or managed access solutions for innovative technologies.

Table 1 includes a summary of these conclusions.

End of life

The End-of-life criteria are routinely considered as part of the technology appraisals (TA) committee decision making. The current NICE methods guide for technology appraisals (2013) states that:

- In the case of a life-extending treatment at the end of life, the appraisal committee will satisfy itself that all of the following criteria have been met:
  - the treatment is indicated for patients with a short life expectancy, normally less than 24 months, and
  - there is sufficient evidence to indicate that the treatment has the prospect of offering an extension to life, normally of a mean value of at least an additional 3 months, compared with current NHS treatment.
- In addition, the appraisal committees will need to be satisfied that:
  - the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review), and
  - the assumptions used in the reference case economic modelling are plausible, objective and robust.

In cases where the end-of-life criteria are met, a QALY weight of up to 1.7 can be applied (essentially increasing the maximum threshold from £30,000 to £50,000 per QALY gained).

It is recognised that the end-of-life criteria have almost exclusively applied to cancer indications. This implies that extending the life of the patients with cancer, at their end of their lives, is valued more that health gains in other situations or conditions.

Perspectives on the end-of-life criteria

Sir Ian's Kennedy review (2009) cautioned against end-of-life criteria, stating that "if treated as anything other than a rare exception, the "end-of-life" category could threaten the very existence of a rational system of resource allocation in which the interests of all are weighed."

In 2014, as part of the value-based assessment consultation, a proposal was made to replace the end-of-life criteria and associated weighting with a combination of 2 modifiers: wider societal benefits and burden of illness. The proposed maximum QALY weight for all the modifiers would remain 2.5. This accounts for the range from the lowest threshold of £20,000 per QALY gained, to the highest of £50,000 per QALY gained. The modifiers that were included in the proposal were burden of illness and wider societal benefits, which would replace end of life.

The proposals were not adopted by NICE, after responses from consultation, which were inconsistent:

- the approach for burden of illness using proportional QALY shortfall received mixed views with potential for adoption in the future
- the absolute QALY shortfall approach for wider social impact received a negative response.

The Association of British Pharmaceutical Industry (ABPI) shared a proposal, as part of the current methods review, for an extended value appraisal (EVA) framework. In this proposal, the ABPI commented that the current end-of-life criteria are too narrow, with a binary output, and are becoming less relevant as standard of care improves. They state that ''advances in research and development mean we are now seeing therapies for treating patients earlier in the stages of disease, that are potentially curative and are addressing a high unmet need'' and that these technologies face a challenge under current NICE's methods. Furthermore, they also state that since standard of care has improved and better therapies are coming to the market, the end-of-life criteria are increasingly difficult to be met. They suggest replacing the end-of-life criteria with severity of disease in relation to both quantity and quality of life by introducing a QALY modifier based on either proportional or absolute shortfall score (whichever is highest and most appropriate) based on evidence available that severity defined in terms of QALY loss from disease receives more societal support than severity based on life expectancy only.

Results from the decision support unit (DSU) review on end of life

End-of-life criteria are specific to each decision made within an appraisal. As such, the DSU identified that for one technology, it may have a different end-of-life decision for different populations or comparators. For example, in NICE's guidance on

lutetium (177Lu) oxodotreotide for treating unresectable or metastatic neuroendocrine tumours the end-of-life criteria were met for pancreatic neuroendocrine tumors (NETs) but not for gastrointestinal NETs, while in cabozantinib for previously treated advanced renal cell carcinoma, cabozantinib met the end-of-life criteria when compared with axitinib, but not when compared with nivolumab.

The DSU analysis shows that in 106 (19%) decisions, the end-of-life criteria were met. Of these:

- 77 (73%) health technologies were recommended for use
- 15 (14%) health technologies were not recommended
- 14 (13%) health technologies were recommended within the cancer drugs fund.

In 464 (81%) cases, the technology did not meet the end-of-life criteria.

A slightly higher proportion of these technologies were recommended (346, 75%).

Table 12 summarises these results.

Table 12

N=570 recommendations	**Recommended**	**Not Recommended**	**Recommended through the Cancer Drugs Fund**
End of life	77 (14%)	15 (3%)	14 (2%)
No end of life	346 (61%)	94 (16%)	24 (4%)

The DSU noted inconsistencies in terms of whether decision making explicitly or implicitly applies a QALY weighting. When looking at the 'committee discussion on end of life' sections of the final appraisal documents, only 23 (22%) of the 106 recommendations that met the end-of-life criteria explicitly mention that a QALY weight can be, or has been, applied.

In the remaining interventions recommended based on the end-of-life criteria, committees implicitly applied the weighting by accepting a higher ICER (usually up to £50,000 per QALY).

The results from the DSU work raise the question about the reporting of these decisions, and whether an explicit QALY weight should be applied and referred to when applying the end-of-life criteria.

Results from the literature review on end-of-life criteria

Recent literature discussing end of life as a decision-making modifier is mixed. Charlton (2019) assesses how far NICE's current end-of-life criteria can be considered fair in terms of their alignment with NICE's ethical frameworks to achieve fair decision making. Charlton asserts that NICE has never offered any empirical or theoretical basis for its 3 end-of-life criteria, and that interviews with experts in NICE's HTA process suggest that the threshold of £50,000 per QALY for end-of-life medicines was initially introduced arbitrarily based on a political need to approve a particular cancer medicine with an ICER close to this number. Charlton also questions the relevance of NICE's end-of-life criteria, and suggests that fair-minded people may not support some of the values upon which they are based.

Several large, representative surveys have been done in the UK since the introduction of NICE's end-of-life criteria, to explore whether members of the public support giving additional weight to life-extending, end-of-life medicines. Shah et al. (2017) surveyed 3,969 adults in England and Wales considered representative of the general population. Respondents were asked to select which 1 of 2 patient profiles they would treat across 10 separate discrete choice experiment tasks. Life expectancy and quality of life with and without treatment were varied across the patient profiles based on a discrete number of levels. While respondents were significantly more likely to select a patient profile that met NICE's end-of-life criteria than one that did not, they were far more influenced by the extent of QALY gains achieved on treatment than by a patient's life expectancy in the absence of treatment. The average life expectancy in the top 50% of preferred patient profiles was almost identical to that of the bottom 50% of patient profiles. The study also indicated that respondents were more likely to favour a patient profile in which the treatment increased life expectancy rather than quality of life.

The results of a survey by Mason et al. (2018) are more supportive of attributing additional value to end-of-life medicines. The survey sample comprised of 4,902 adults considered representative of the UK population. Respondents were presented with 18 statements linked either positively or negatively to 1 of 3 viewpoints on the relative value of life extensions for people with a terminal illness. These viewpoints were derived in previous work by McHugh et al. (2015) through qualitative research with 59 participants selected to provide a broad range of experience and expertise in end-of-life considerations. Notably, none of the 3 possible viewpoints directly supported considering end-of-life medicines as a special case. Viewpoint 2 appears to come the closest, with respondents adhering to this viewpoint likely to consider that denying life-extending medicines to people who want them as being morally wrong. The survey participants were assigned to 1 of the 3 viewpoints based on their responses to the 18 statements, with a 7-point Likert scale used to indicate agreement or disagreement with each statement. Of the respondents, 49.3% were most closely aligned with viewpoint 2, which values life extension and patient choice,

but not necessarily in an end-of-life setting. A further 36.8% respondents were most closely aligned with viewpoint 1, which advocates there being no special patient groups more deserving of treatment.

In McHugh et al. (2018), 1,496 of the people answering the survey in Mason et al. (2018) were presented with 2 additional tasks. The first task was designed to represent HTA body decision making. Respondents were asked to select 1 of 3 mutually exclusive potential policies: 1) a standard cost-effectiveness test should be used for all medicines; 2) special consideration should be given to all end-of-life medicines; and 3) special consideration should be given only to those end-of-life medicines that meet specific requirements (for example, increasing life expectancy, or improving quality of life). In the second task, respondents were asked to select preferred treatments and trade off treatment options based on a fixed budget. The available treatments varied by whether they increased life expectancy or improved quality of life, and whether they were intended for use by patients at the end of life or not. In the first task, 64% of respondents answered that special consideration should be given to end-of-life medicines (either all end-of-life medicines, or only those that meet specific requirements). 45% of the sample felt that this should depend on a specific requirement, with 32% favouring a special consideration for end-of-life medicines that improve quality of life. Only 4% advocated giving special consideration for end-of-life medicines that increase life expectancy. The results of the second task further support the preference for quality-of-life gains over life extension. Only 5.6% of respondents ranked life-extending end-of-life medicines as their first choice. In contrast, 51% ranked non-end-of-Life, quality of life-improving medicines as their first choice. The relationship between the 3 viewpoints previously described for Mason et al. (2018) and the results of the 2 subsequent tasks was also assessed; 82.6% of people assigned to viewpoint 2 favoured giving special consideration to end-of-life medicines.

The results described in Rowen et al. (2016) are, among the recent surveys, the most supportive of an increased societal value judgement towards end-of-life medicines. Members of the public 3,669) were surveyed with a discrete choice experiment in which they were asked to select 1 of 2 patient profiles. Patient profiles varied depending on their life expectancy without the condition, life expectancy with and without treatment, and quality of life with and without treatment. The results for profiles that aligned with NICE's current end-of-life criteria were modelled separately to those that did not. The coefficient associated with end of life was positive and significant, indicating that respondents were more likely to select a profile that met NICE's end-of-life criteria than one that did not. QALY gains in an end-of-life population were valued 3.331 times more highly than QALY gains in a non-end-of-life population.

Other sources referenced in the publications described above present an equivocal picture as to public opinion regarding end-of-life medicines. A review by Shah et al.

(2016) identified 17 preference elicitation studies, 7 of which found justification for a positive premium for end of life, 7 found no such justification, and 3 reported mixed results. Mason et al. (2018) considered that these differences may be because of different research techniques, or could reflect a disagreement within society about the relative value of end-of-life medicines.

Overall, the quality of the evidence exploring the importance of End of Life as a decision modifier to the public in the UK is strong, with over 16,490 people surveyed across the studies described in detail. Shah et al. (2017) excluded people who had recently completed health-related surveys, but this recruitment criteria is not described for the other surveys. As such, it is possible that some respondents completed more than one of the surveys described. Study participants were representative of the UK population in terms of age and sex, with some differences noted for other characteristics, including social grade (Shah et al. (2017)) and employment status and EQ-5D score (Rowen et al. (2016)). The results of Mason et al. (2018) are somewhat more difficult to interpret than the other surveys, as none of the viewpoints explored are directly in favour of attributing additional value to end-of-life medicines. However, McHugh et al. (2018) indicates that most people with viewpoint 2 favour giving special consideration to end of life. Mason et al. (2018) is also noteworthy in that it used the relatively untested 'Q methodology' to derive the 3 viewpoints, and also employed a Likert rating scale rather than a decision choice experiment as in the other surveys. Also, as the survey used an abbreviated set of questions to determine a respondent's viewpoint, it was only 74% accurate in doing so compared with the original methodology used in McHugh et al. (2015).

Literature on the extent to which the NHS values end-of-life medicines more is sparse. In Bourke et al. (2018), 16 healthcare professionals and 24 NHS policy makers completed a discrete choice experiment and patient trade-off exercise. Policy makers were defined as members of a NICE, AWMSG or SMC appraisal committee. Although Bourke et al. (2018) was primarily focussed on societal preferences around orphan drugs, it provides limited tangential insights into end-of-life considerations. In the discrete choice experience, healthcare professionals ranked debilitating or life-threatening disease as the third most important consideration of 5 possibilities; higher than improvements to everyday life, cost per patient per year and the availability of other drug treatments, but lower than treatment benefit (extent of survival increases). Policy makers ranked debilitating or life-threatening disease as the lowest of all considerations. However, the degree of overlap between a debilitating or life-threatening disease and an end-of-life setting is not described, and possibly minimal. Bourke et al. (2018) also indicates that while extending survival is most important to healthcare professionals, it is lowly ranked by policy makers.

Furthermore, given that technologies meeting the end-of-life criteria are almost exclusively indicated in cancer conditions, there remains the question as to whether

society values life extensions in cancer more than health benefits in other conditions. Linley and Hugues (2012) state, based on a choice-based experiment in 4,118 UK adults using web-based surveys, that although disease severity seems to be viewed by society as a valid criterion for prioritising health resource, there does not seem to be such a support for preferential funding of cancer treatments.

In summary, the available literature is highly heterogeneous as to its support for treating end of life as a decision modifier. On balance, based on recent surveys, the UK public appears to support giving special consideration to end-of-life medicines. However, there is a lack of consensus among both the public and NHS as to whether this should be applied in the context of a treatment that increases life expectancy, or one that improves quality of life or both. The current end-of-life weighting applied by NICE has also been criticised as arbitrary and not evidence-based, and it remains unclear from the literature whether the applied weighting is appropriate. Rowen et al. (2016) indicates that the cost-effectiveness threshold for end-of-life medicines should be up to 3.331 times that of non-end-of-life drugs, equating to around £100,000 per QALY based on the upper limit of NICE's standard threshold. Consideration should therefore be given to the following key points:

1. whether improvement in quality of life should be included as an end-of-life criterion,

2. whether an increase in life expectancy should be kept as an end-of-life criterion, and

3. whether NICE's current cost-effectiveness threshold for end-of-life medicines is appropriate.

Considerations 1 and 2 are part of this report while 3 will be covered in stage 2.

International considerations of end of life

End of life is considered in different ways across the HTA bodies internationally, usually as severity of illness which could inherently include broader considerations than the conditions considered in NICE's methods to be at the end of life. Further detail is provided in the burden of illness section.

The Scottish Medicine Consortium treats end-of-life medicines as a special category. If the preliminary advice is not to recommend an end-of-life medicine, the company may ask for a Patient and Clinician Engagement meeting where additional evidence from patient groups and clinicians can be considered. Technologies being assessed in France and Germany are more likely to be awarded a high Improvement of Medical Benefit assessment (ASMR) rating (France) or 'added benefit' rating (Germany) if they are indicated for conditions with a high mortality risk, and can show an improvement in survival outcomes. Such ratings support a higher price

compared with comparators. However, end of life is not specifically mentioned by either HTA body.

Conclusion on end of life

Based on the application of the end-of-life criteria by the appraisal committees, the literature review and the international comparison, there is a case for change. Input from the working group and the task and finish group members supports this.

There is a case to consider health more broadly and to also capture the quality of life associated with the condition, and its improvement, rather than just life expectancy and extension when considering a technology. This would be in line with an application of a severity or burden of illness modifier and therefore, it is proposed that the end-of-life criteria are replaced by a modifier based on **severity or burden of illness**, **and QALY gains**. It is important to highlight that although there is expected to be an overlap between products that currently meet the end-of-life criteria and those that will likely meet the severity or burden of illness definition, the overlap will not be absolute. This means that some products may not be as valued as per the new severity criteria as they currently are based on the end-of-life criteria and viceversa. This is in line with the conclusions from this review that there seems to be more value

Proposal for stage 1: To replace end of life with severity or burden of illness

Actions for stage 2: to define severity or burden of illness appropriately and how it should be incorporated.

Table 2 includes a summary of these conclusions.

Magnitude of benefit

The NICE Highly Specialised Technology (HST) programme currently may apply a QALY weighting where there is significant compelling evidence that the treatment offers significant QALY gains. Depending on the number of QALYs gained over the lifetime of patients, when comparing the new technology with its relevant comparator(s), the committee will apply a weight between 1 and 3, using equal increments, for a range between 10 and 30 QALYs gained. The weighting is applied in the following way:

Table 13

Incremental quality-adjusted life years gained (per patient, using lifetime horizon)	Weight
Less than or equal to 10	1
11 to 29	Between 1 and 3 (using equal increments)
Greater than or equal to 30	3

The HST methods therefore place a greater value on treatments with a higher comparative magnitude of benefit compared to those with a low comparative magnitude of benefit.

Magnitude of benefit is currently not formally considered within any other programme at NICE.

Results from the decision support unit (DSU) review on magnitude of benefit

The DSU noted that the weight based on the magnitude of benefit, as a function of the incremental QALY gain, was applied from HST6 onwards.

In most HST cases where the appraisal calculated ICERs, technologies could be recommended solely by reference to the ICER, given the relevant weight. For example, strimvelis for treating adenosine deaminase deficiency–severe combined immunodeficiency was believed to have a maximum ICER of £120k per QALY gained. Given that the relevant QALY weight was felt to lie between 1.4 to 1.96, this would bring the ICER below £100,000. The ICER for burosumab for treating X-linked hypophosphataemia in children and young people was more uncertain because the relevant weight itself was uncertain. There are combinations of the most feasible ICER and the highest QALY weight that could bring the ICER within the programmes £100k general threshold. The ICERs for patisiran for treating hereditary transthyretin amyloidosis, voretigene neparvovec for treating inherited retinal dystrophies caused by RPE65 gene mutations and cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2 all exceeded the threshold after applying the weights agreed by committee, albeit by only a very slight amount in the case of patisiran for treating hereditary transthyretin amyloidosis.

Table 14 Incremental cost-effectiveness ratios from highly specialised technology appraisals

	Incremental cost-	Quality-adjusted life	Incremental QALY gain	Managed access scheme (MAS)

	effectiveness ratio	year (QALY) weight		or patient access scheme (PAS)
HST1	NR	–	–	–
HST2	NR	–	–	MAS and PAS
HST3	NR	–	–	MAS and PAS
HST4	dominates	–	–	PAS
HST5	dominates	–	–	PAS
HST6	NR	–	14 to 25	MAS and PAS
HST7	Dominant to £120,000	1.4 to 1.96 depending on the comparator	14 to 19.6	–
HST8	£113,000 to £150,000	Could be above 1	5.52 to 15.99	PAS
HST9	£96,697	1	–	PAS
HST10	£102,993	1	9.16	PAS
HST11	£140.300	1.2	12.1	PAS
HST12	£366,923	3	30.06	MAS

NR = most plausible ICER not reported; Dominance: A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.

Results from the literature review on magnitude of benefit

There are many studies which have shown that the general public place a high importance on whether a drug is clinically effective, however studies that looked specifically at whether the general public considered that additional weighting should be given to a drugs with a higher magnitude of benefit is limited.

Brazier et al. (2013) was commissioned by the Department of Health because of the value-based pricing proposal (2010) that there would be higher thresholds for medicines that can show greater therapeutic innovation and improvements compared with other products. The study utilised a discrete choice experiments with a large UK population sample (n=3,669) and found that respondents preferred to treat patients who had larger QALY gains at a diminishing rate. This result would suggest that, total QALY gains being equal, the UK public would prefer QALY gains spread across multiple technologies compared with a single large QALY gain.

International considerations on magnitude of benefit

As described for the innovation modifier, several international HTA bodies consider magnitude of benefit as a modifier, often under the banner of what constitutes an innovative medicine.

Relative clinical efficacy is a key driver of the Improvement of Medical Benefit assessment (ASMR) rating awarded by the Transparency committee in France, which has an important role in determining the potential for a price premium

compared with comparators. In Italy and Japan, a new medicine must show a high added therapeutic value in order to be deemed innovative and gain faster access (Italy) or a premium price (Japan) as a result. The Scottish Medicines Consortium applies a higher cost-effectiveness threshold for medicines that offer an improvement in life expectancy of greater than 3 months, or a substantial improvement in quality of life (SMC: Modifiers used in appraising new medicines). Institute for Clinical and Economic Review in the USA consider the degree of health loss without the medicine (as absolute or proportional QALY shortfall) as a contextual consideration that can influence the committee's decision within the ICER range suggested by the clinical evidence and cost-effectiveness analysis (Institute for Clinical and Economic Review: Overview of the Institute for Clinical and Economic Review value assessment framework and update for 2017-2019).

Overlap with other investigated decision-making modifiers

Comparative magnitude of benefit is influenced by several other decision-making factors included in this review, specifically burden of illness, innovation, and age. This is because a very severe disease or a disease that affects the very young leads to a large absolute QALY shortfall (see burden of illness section) and consequently a larger capacity to benefit, in terms of QALY gains.

A decision-making modifier consisting of burden of illness could be prioritising opposite ends of a large QALY gain for a very severe disease. That is, a modifier for burden of illness would prioritise the first QALY gains, whereas a magnitude of benefit modifier would prioritise the last QALY gains (but only if gained within a single technology).

Part of the Kennedy report on innovation (see innovation section) defines an innovative technology as a technology that offers something more: a step change in terms of outcomes for patients. It could be assumed that very high comparative magnitude of benefit would fall under this criterion.

Conclusions on magnitude of benefit

There is currently no strong case that magnitude of benefit should be considered as a decision-making modifier, either within the HST programme or by CHTE as a whole. There is substantial overlap with several other investigated decision-making modifiers, risking double counting of any proposed modifier weighting. The task and finish group members considered it would be more appropriate, where possible, to consider decision-making modifiers as separately as possible. Given that most or all of any potential magnitude of benefit could be captured elsewhere, it is suggested that magnitude of benefit should not be considered a separate modifier. This has implications for the HST program that will need to be considered and taken into account.

Proposal for stage 1: Removal of magnitude of benefit modifier within the HST programme.

Actions for stage 2: Not applicable.

Table 3 includes a summary of these conclusions.

Curative potential

New innovative technologies used with curative intent are increasingly being considered by NICE technology appraisal (TA) and highly specialised technology (HST) committees. Other technologies may also lead to a functional cure for a proportion of patients, that is the mortality risk and quality-of-life of those treated is equal to that of the age-adjusted general population.

Curative potential, defined as a treatment that restores a person to full or near full health, is explicitly considered by TA and HST committees when deciding on whether a non-reference case discounting rate of 1.5% should apply. However, the specific criteria also include further qualifying criteria:

- 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 time period of at least 30 years, and
- the is committee satisfied that the health effects are highly likely to be achieved, and the introduction of the technology does not commit the NHS to significant irrecoverable costs.

NICE has previously investigated whether NICE methods and decision frameworks were fit for purpose for the assessment and appraisal of regenerative medicines, a class of technology which often has curative potential (NICE 2016). The report identified that discounting rate had a very significant impact on the analyses, however this is because these are one-off technologies with a high upfront cost and not due to curative potential. The report concluded found that the current NICE appraisal methods and decision framework are applicable to regenerative medicines and cell therapies.

Results from the decision support unit (DSU) review on curative potential

Curative potential was not considered within the DSU review.

Results from the literature review on curative potential

Literature exploring curative potential as a modifier is limited. Hampson et al. (2019) did a discrete choice experiment that investigated the publics preference around curative potential. Whilst the public preferred to prioritise large QALY gains, whether a treatment was a cure did not appear to influence respondent's choice in treatment.

International considerations on curative potential

Curative potential was not considered within the international review.

Conclusions on curative potential

There is currently no strong case that curative potential should be considered as a decision-making modifier. Curative potential, that is restoration to full or near full health is currently one of the criteria within non-reference case discounting rate of 1.5%. However, the task and finish group considered that the other criteria within non-reference case discounting are the compelling grounds to consider a decision-making modifier in this case, and TA committee members noted that technologies that lead to functional cures are not considered differently by committee.

The other decision-making modifiers within non-reference case discounting are further considered within the age and burden of illness sections.

Proposal for stage 1: Recommendation to the discounting task and finish group that the criteria for non-reference case discounting should be removed or amended.

Actions for stage 2: Not applicable.

Table 4 includes a summary of these conclusions.

Rarity

The only CHTE committee which formally considers rarity a decision-making modifier is the medical technologies evaluation committee, where the committee may consider whether the technology is addressing an unmet need within the NHS. However, NICE has a separate process for the appraisal of rare diseases through the Highly Specialised Technology (HST) Appraisal Programme, which was brought into force by the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013. Rarity is a key criterion that a technology must meet to enter the HST programme, and the only criterion detailed within the legislation, which states a

“highly specialised health technology” means a health technology intended for use in the provision of services for rare and very rare conditions provided for in regulations under section 3B(1)(d) of the 2006 Act(d).

Rarity can be considered a decision-making modifier as the maximum acceptable incremental cost-effectiveness ratio (ICER), before other factors are considered, within the HST programme is £100,000 compared with £20,000 per quality-adjusted life year (QALY) gained within the technology appraisal programme. Therefore, essentially valuing QALY gains in very rare diseases (that meet the HST criteria) up to 5 times more than those gained by technologies entering the Technology Appraisal programme. Furthermore, above an ICER of £100,000 the HST programme may consider additional factors not all of which are considered by other CHTE committee. These include:

- the nature of the condition (morbidity, disability, impact on carers, extent and nature of treatment options)
- the impact beyond direct health benefits (including non-health objectives of the NHS, as in TAs, in addition to the potential for benefits for research and innovation, delivery of specialised services, additional staffing and infrastructure)
- the magnitude of benefit when comparing the new technology with its relevant comparator(s).

Where a technology meets these further factors, particularly magnitude of benefit (see magnitude of benefit section), the maximum acceptable ICER would be approximately £300,000 per QALY gained. Therefore, a QALY gained for a technology that meets the HST criteria, may be valued over 10 times greater than a QALY gained for a technology appraised within the TA programme.

Results from the decision support unit (DSU) review on rarity

Mentions of rarity in TA are sparse, and when a reference it is made, it is often done alongside other factors so it is not possible to conclude the impact of rarity on the decision on its own.

Mifamurtide for the treatment of osteosarcoma recommends the use of mifamurtide with a most plausible ICER above NICE’s threshold. One of the factors that was considered was the fact that this is for a rare condition, alongside innovation and the fact that the technology was indicated for use in children. These factors combined led to the conclusion that mifamurtide could be accepted as a cost-effective use of NHS resources.

Similarly, dinutuximab beta for treating neuroblastoma states that the committee believed a number of factors were relevant to its decision making in recommending a technology with a most plausible ICER in excess of £40k, among them rarity.

Specifically, the guidance states “the committee is prepared to be flexible in its decision-making given the rarity and severity of the disease”.

Pentosan polysulfate sodium for treating bladder pain syndrome found that for the general patient population included within the appraisal, where the comparator was best supportive care, the committee felt that the ICER was too high to recommend the technology. There was no ICER presented for the subpopulation where bladder instillations were the relevant comparator. However, the committee recommended the technology in this subpopulation, stating “the committee acknowledged that because this is likely to be a small population, the estimated impact on NHS resources is also likely to be small”. The committee concluded that the ICER in this population would be acceptable considering the small number of patients.

The reference to rarity is much more common in HST evaluations, given the nature of the programme, which is focussed on rarer conditions. One example from patisiran for treating hereditary transthyretin amyloidosis states that rarity was one of the factors that was considered when recommending the technology with a relatively high ICER.

Results from the literature review on rarity

Recent literature that explores the importance of rarity as a decision-making modifier does not support its use. Many articles reference the NICE citizens council report on Ultra Orphan drugs, NICE (2004), which found that “rarity on its own is not a factor – and the degree of severity must come into the picture”. More recently Chim et al. (2017) and Rizzardo et al. (2019) conducted large, representative surveys in Australia and Canada respectively to elicit societal preference of decision-making modifiers. These found that rarity was not regarded as important decision-making factor.

Bourke et al. (2018) specifically investigated whether the UK public placed a higher value for funding of orphan drugs compared to drugs treating common diseases, using both person trade-off and discrete choice experiment methods. The person trade-off found most respondents (54%; 95% confidence interval [CI] 50 to 59) would choose to allocate funds equally between patients treated for rare diseases and those treated for common diseases. However, the discrete choice experiment indicated a greater preference for treating a common disease over a rare disease.

Key policy papers have been produced in the area of treating rare diseases, demonstrating the importance of rare diseases to the NHS and the UK in general. The UK Strategy for Rare Diseases (2013) was produced to ensure ’no one gets left -behind just because they have a rare disease’. A key aim of the strategy that is directly relevant to the work of the modifiers task and finish group is to ‘deliver effective interventions and support to patients and families quickly, equitably and sustainably’. An action from this report was to ‘ensure that there are appropriate

procedures for evaluating the costs and benefits of treatments for patients'. The UK strategy for rare diseases did not detail what the appropriate procedures may be, nor discuss whether a weighting for rare diseases would be appropriate.

In response to this document, NHS England and Improvement produced the Implementation Plan for the UK Strategy for Rare Diseases (2018). The implementation plan broadly focussed on facilitating earlier diagnosis and intervention, improving care coordination, and promoting research.

International considerations on rarity

Most of the countries reviewed factor rarity into their pricing or reimbursement decision-making processes, and rarity is was identified by the Office of Health Economics as being one of the most commonly applied modifiers by international HTA bodies. However, the mechanism by which this is accomplished differs between countries and is often unclear. Generally the way HTA bodies approach orphan medicines can be categorised into 3 main groups:

1) orphan medicines are directly given greater weighting or a bonus of some manner during decision making,

2) higher levels of clinical data uncertainty are accepted, and

3) other modifiers are given more importance for orphan medicines. HTA bodies may apply more than one of these approaches.

The most common way in which the first of the approaches above is applied is through a higher cost-effectiveness threshold for orphan medicines. This is done by HTA bodies in Ireland, Japan, Norway, Slovakia, Sweden, the USA and Australia (in the latter case, providing other criteria are met (Angelis et al 2018)). However, for some of these HTA bodies the increased threshold is not included in their methods guides, and is instead informal and described in other sources based on primary research. In Japan, a specific price premium is in place for orphan medicines. In Germany, an additional benefit is considered proven for orphan medicines based on regulatory approval alone during the Arzneimittelmarkt-Neuordnungsgesetz (AMNOG) benefit assessment, which supports a price premium over comparators.

Some HTA bodies apply a different assessment process for rare diseases. The Italian Medicines Agency has an accelerated 100-day procedure, and the Scottish Medicines Consortium and Institute for Clinical and Economic Review (USA) have separate pathways for orphan medicines. Medicines defined as ultra orphan by the SMC are made available to prescribers for 3 years after the SMC's assessment while further clinical effectiveness data are gathered. The manufacturer may also ask for the medicine to be considered at a PACE meeting, where patients and clinicians can provide evidence on a medicine's added value. The Institute for Clinical and Economic Review applies a separate value assessment framework to orphan

medicines, where special weighting may be given to other contextual considerations (Institute for Clinical and Economic Review: Modifications to the Institute for Clinical and Economic Review value assessment framework for treatments for ultra-rare diseases).

In summary, while most HTA bodies consider rarity in some manner, there is no consistent approach. Typically, a higher cost-effectiveness threshold is applied to orphan drugs in countries where cost-effectiveness analysis is used, though these higher thresholds are not usually detailed in the HTA bodies' methods guides.

Conclusions on rarity

The funding of technologies that treat ultra-rare conditions is particularly challenging, because there are additional issues in addition to rarity. These include providing an incentive for developing medicines that would otherwise not be commercially viable, difficulties in providing a strong evidence base for appraisal, and reducing inequities of care. These challenges are reflected by how common separate processes are used to appraise ultra-orphan drugs within other similar health technology assessment bodies.

The literature strongly suggests that the public do not value rarity as a decision-making factor, however this is often investigated by assuming all else is equal. Any willingness to give greater weight to health gains for technologies appraised within the HST programme may be combining several other potential decision-making modifiers, as the technologies evaluated within the HST programme are often for diseases that are extremely severe, affect children, and have limited or no other current treatment options. NICE appraisal committees also must appraise technologies that treat diseases that have some or all of these characteristics (with similar evidence bases) but currently, other than applying flexibility during decision-making, committees are unable to apply a greater weight to health gains for these technologies. Task and finish members did not consider there was a moral or ethical justification for this disparity between programmes.

In terms of incentivising development of medicines that would otherwise not be commercially viable it is unclear whether assigning a greater weight to all rare diseases within the NICE methods is the most appropriate mechanism to achieve this goal, much less what specific weighting should apply.

It is therefore suggested that rarity should be removed as a decision-making modifier. It may be justified to consider whether rarity may have an impact when in combination with other potential modifiers, for example whether a greater value should be placed on innovative drugs for rarer diseases compared to innovative drugs for common diseases in order to provide an incentive for drug development.

Task and Finish group members did consider that there may be a moral and ethical justification for applying a greater weight where there is an unmet need or health

inequality arising from the fact a disease is rare. It should be considered whether any additional adaptation or weighting should apply to a potential health inequalities modifier (see health inequalities section).

Proposal for stage 1: Removal of rarity as a decision-making modifier

Actions for stage 2: Consider whether the proposed decision-making modifiers are equally applicable for rare compared to common diseases, and whether any additional adaptation or weighting should apply. Consider interaction between HST and TA programmes.

Table 5 contains a summary of these conclusions.

Age

NICE committees are required to consider the different needs of children when they are included in an evaluation alongside adults.

Two recent appeal panel decisions, covering one technology appraisal (TA) and one highly specialised technology (HST) topic, have suggested that committees should not only consider the needs of children, but also whether the fact that children are included should lead to any modification in the conclusions.

Results from the decision support unit (DSU) review on age

Age was considered relevant to committee decision making in 3 TA and 5 HST guidance documents reviewed by the DSU. Several different approaches have been taken to appraise methods for health-related quality-of-life estimation in children. The committee for the technology appraisal guidance on cochlear implants for children and adults with severe to profound deafness noted that the utility gain for cochlear implants in severe to profound deafness may be larger in children than adults. This assumption considerably reduced the incremental cost-effectiveness ratio (ICER) from the base case and ultimately increased committee confidence that the intervention was cost effective.

However, in NICE's technology appraisal guidance on nusinersen for treating spinal muscular atrophy, despite the committee noting that the population for spinal muscular atrophy was predominantly children and young people, the impact of age on any recommendation is not detailed in the guidance.

In NICE's guidance on ataluren for treating Duchenne muscular dystrophy with a nonsense mutation in the dystrophin gene, the committee suggested that paediatric quality-adjusted life years (QALYs) in Duchenne muscular dystrophy may not fully have been captured in the company's model. It suggested QALYs be viewed differently because of the time in a child's life when most gain happens compared with best supportive care. This differs from NICE's guidance on strimvelis for treating

adenosine deaminase deficiency–severe combined immunodeficiency where the committee concluded that the clinical and cost-effectiveness evidence reflected the age of the population, and further modifiers were not needed.

References to older populations mainly pertained to guidance implementation, such as difficulty with aspects of care for the elderly.

Results from the literature review on age

Three recent studies evaluating age as a potential decision-making modifier were reviewed; a UK discrete choice experiment to elicit preferences across multiple decision criteria (Erdem and Thompson 2014); a UK person trade-off study to estimate age-related weights for health gains to aid decision-making (Petrou et al. 2013); and a Canadian survey-based study of values in drug reimbursement decisions (Rizzardo et al. 2019). No literature was found on how the NHS values age as a potential modifier.

Erdem and Thompson (2014) used a discrete choice experiment technique combined with latent class models to explain heterogeneity in public preferences for health service innovations. Postal questionnaire data from 250 members of the general public in West Yorkshire were used for model estimation. The authors evaluated preferences for innovations according to target population (for example, people with cancer or obesity), age group, implementation time, uncertainty associated with likely effects, potential health benefits and cost. Three classes of respondents were identified, with each class having different preferences for the various attributes. In terms of preferences for age groups, Class 1 made up 54% of the sample and preferred to allocate to adults (18 to 65 years old) then young people (under 18 years old) then the elderly (over 85 years old). Classes 2 (34% of sample) and 3 (12% of sample) were both indifferent between adults and young people, however class 2 preferred not to allocate to the elderly and class 3 preferred to allocate to the elderly. There were no differences in demographics between the 3 classes. Limitations of this study include the relatively small sample size and small geographical area of survey respondents.

Petrou et al. (2013) asked 2,500 adults from the UK to complete a person trade-off exercise to determine preferences for allocating health gains (expressed in terms of life extensions) by age. They found a preference for giving more health gains to younger age groups in 85% of age comparisons. The age given the highest weight for life extension varied depending on the response aggregation method used, however overall, 30 year olds were given the highest mean relative weight. This study benefitted from a large sample size and a UK-wide respondent base. Results appear to be in broad alignment with those from Erdem and Thompson (2014), with most respondents preferring to allocate health to adults rather than the very young or very old.

Canada has a publicly funded healthcare system and faces similar drug reimbursement decision-making challenges as the UK. To gain insight into societal preferences in Canada, Rizzardo et al. (2019) did an online survey in which 2,539 adults were asked to rank 13 values relevant to drug funding prioritisation, including age. Based on survey results, values were weighted using an analytic hierarchy process. Age was ranked in the bottom 5 values by 46% of study participants and was 9th lowest in terms of weighting (only socioeconomic status, unmet need, rarity and adherence ranked lower). As acknowledged by the authors, ranking exercises can be subject to bias and other limitations. It should be noted that this study does not provide any information on whether people would prefer to weight increasing age positively or negatively as a modifier, only that age as a potential modifier ranks poorly in comparison to the other values included in the survey.

Overall, the evidence appears to be of high quality, consisting of 2 UK-based studies deemed to be directly applicable to the population under consideration (Erdem and Thompson 2014; Petrou et al. 2013) and a large Canadian study of lower applicability (Rizzardo et al. 2019). Methodological differences between studies mean that direct comparisons between results should be interpreted with caution, however, there appears to be some evidence that the UK public tends to favour younger age groups over the elderly for health allocation (Erdem and Thompson 2014; Petrou et al. 2013). Despite this, there is insufficient evidence to suggest the general public place overall importance on age as potential modifier.

Lancsar et al. (2020) found that age is a relevant factor to account for when considering QALY weighting. Based on a Discrete Choice Experiment (DCE) study done over a representative sample of the Australian population, the authors concluded that age was a relevant factor depending on the remaining life expectancy without treatment. When life expectancy is extremely short (0 to 3 months) infants and children seem to be prioritised, when it is relatively short (4 months to 2 years), they found that young adults are prioritised but when life expectancy is longer (3 to 5 years or normal) teens are prioritised.

Gu et al. (2015) did a systematic review of patient elicitation and stated preferences studies from the general public. Twenty-five studies elicited preferences for age, of which the 14 suggest the public in general favours the young over the elderly. Of these 14 studies, 8 controlled for the greater capacity to benefit of a young population compared with have an older population. Conversely 3 studies found little evidence of any preference for age, while 8 studies suggest a preference for those at a working age. Of these, 2 and 5 studies respectively controlled for confounding effect of capacity to benefit.

International considerations of age

Of the 14 HTA bodies reviewed, only the Ministry of Health, Labour and Welfare (MHLW) in Japan applies age as a modifier. Medicines with an explicit paediatric

indication, dosage or route of indication are eligible for a price premium over comparators of 5% to 20%.

Conclusion on age

Overall, the evidence of age as a decision-making modifier is mixed and may be confounded by the publics' preference for prioritising drugs where there is a large capacity to benefit. Furthermore the 2010 Equality Act applies to NICE, which prohibits discrimination based on age.

Within the 2010 Equality Act under 18s are protected against age discrimination only in relation to work. The evidence for this age group is stronger and suggests that the public would prioritise this age group compared to adults. Feedback from TA committee members within the task and finish group was that appraisals for technologies that treat paediatric conditions are often among the most challenging they must appraise, and often similar characteristics of technologies evaluated through the HST programme (see rarity section). Rare and severe conditions often start in childhood and there are often technical issues when considering drugs that treat paediatric conditions, such as collection of robust quality-of-life data or the inclusion of carer disutility.

Much of the literature controls for the potential confounding that a child has a greater capacity to benefit in comparison to an adult. This is needed to estimate whether the public place a greater value on the age of the population in of itself. However, this confounding cannot be removed in practice. A life-limiting disease in a child is much more severe, as defined by the absolute QALY shortfall, than the same disease in adults.

The current methods allow for a non-reference case discounting rate of 1.5% for costs and health effects (compared with 3.5%) where the following criteria apply:

- 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 time period of at least 30 years and
- committee satisfied that the health effects are highly likely to be achieved, and that the introduction of the technology does not commit the NHS to significant irrecoverable costs.

These criteria were introduced during the appraisal for mifamurtide for the treatment of osteosarcoma where the ICER was sensitive to the discount rate used. Given that non-reference case discounting is likely to improve cost effectiveness, these criteria are a decision modifier and combine the potential decision-making modifiers age (because there must be over 30 years of life expectancy remaining), severity, curative potential and magnitude of benefit. The task and finish group consider the

criteria for non-reference case discounting is inappropriate and that any criteria for decision-making modifiers, and their justification, should be explicitly stated.

Many of the issues encountered by committee when appraising technologies that are used to treat childhood diseases may be captured within a potential severity or burden of illness modifier. However, it is suggested that a modifier based on whether the population includes children should also be explored.

Proposal for stage 1:

- To explore a modifier based on whether the population includes children.
- Recommendation to the discounting task and finish group that the criteria for non-reference case discounting should be removed or amended.

Actions for stage 2: Consider feasibility of a modifier and application.

These conclusions are summarised in Table 6.

Burden of illness

Burden of illness is defined as the magnitude of the impact of disease with standard of care. Standard of care may include other available treatments or best supportive care, when there are no other treatments to manage the condition. Therefore, the level of unmet need is considered within the burden of illness definition. The burden of illness might for example be described as severe or debilitating, and therefore, the terms severity and burden of illness may be used interchangeably.

During the Value Based Assessment (VBA) proposal in 2014, the approach for burden of illness using proportional quality-adjusted life year (QALY) shortfall received mixed views with potential for adoption in the future. Proportional shortfall is calculated by taking the disease-related QALY loss and dividing it by the remaining QALY expectation in absence of the disease (that is, it represents the proportion of expected life that is lost due to the condition).

In the Association of British Pharmaceutical Industry's (ABPI) Extended Value Assessment (EVA), it is stated that severity defined in terms of QALY loss from disease receives more societal support than severity based on life expectancy only.

The ABPI suggests replacing end of life with severity of disease in relation to both quantity and quality of life by introducing a QALY modifier based on either proportional or absolute shortfall score (whichever is highest and more appropriate). They proposed that absolute shortfall could be applied to conditions where (for example) patients are young and expected to lose a significant amount of health (in

absolute terms). And, in situations where absolute losses are not large, but the condition is life-threatening, proportional shortfall would be more appropriate and should be used instead.

Results from the decision support unit (DSU) review on burden of illness

The DSU was able to calculate burden of illness in 364 cases (64%). Missing values happened where they were unable to identify the number of QALYs expected for the comparator (n=188), or unable to identify the model start age (n=50).

They estimated both absolute QALY shortfall and proportional shortfall. Mean absolute shortfall was 9.39 QALYs, median 9.77 and a range from 0.07 to 24.40 QALYs. Proportional Shortfall was a mean of 0.62 and median 0.64.

The cases in which the technology met the NICE end-of-life criteria had higher (mean and median) absolute shortfall and proportional shortfall than those that do not.

Table 15 Burden of illness by end-of-life status

–	End of life	End of life	No end of life	No end of life
–	**Absolute shortfall**	**Proportional shortfall**	**Absolute shortfall**	**Proportional shortfall**
mean	12.13	0.91	8.80	0.55
median	11.54	0.91	8.54	0.57

In the case of highly specialised technology (HST) evaluations, burden of illness was referred to in 9 out of 12 evaluations, being recognised as a key aspect of the condition for which the technology was being considered. There was no additional information on whether this had material impact on the committee's decision making.

In NICE's guidance on cerliponase alfa for treating neuronal ceroid lipofuscinosis type 2, for example, it is stated that the committee recognised the severity of the condition, and that "taking all these factors into account, the committee agreed that cerliponase alfa could provide value for money within the context of a highly specialised service".

However, in NICE's guidance on patisiran for treating hereditary transthyretin amyloidosis the guidance explicitly states that burden of illness was one of several factors that prompted the committee to recommend the technology, despite the high incremental cost-effectiveness ratios (ICERs).

Results from the literature review on burden of illness

There are several recent studies on the importance of burden of illness to the public, including large representative international surveys.

Rizzardo et al. (2019) did an online survey in which 2,539 Canadian adults were asked to rank 13 values relevant to drug funding prioritisation, including disease severity. Based on survey results, values were weighted using an analytic hierarchy process. Severity was ranked 4th highest in terms of weighting (only safety, ability to work, and quality of life ranked higher). This study found that disease severity was ranked higher than extension to life, and these top 5 factors were valued were 5 to 7 times more important than those values ranked the lowest (rarity and adherence).

Chim et al. (2017) did a large, broadly representative sample (n = 3,080) of the Australian population. They found that most respondents (52.7%) would prioritise treating severe diseases (rather than moderate diseases), all else being equal. However, the proportion of respondents who would prioritise treating severe disease decreases if the costs are higher, or the comparative benefits were lower (48.5% and 25.6% respectively) rather than treating moderate disease. Also, they compare the results of their study with the UK study by Linley et al. (2013) and note 'that there was a striking level of consistency between the views and preferences on allocation criteria in the general public of the UK and Australia'.

Gu et al. (2015) did a systematic review of patient elicitation and stated preferences studies from the general public. This systematic review captured studies conducted before the current methods guide was published, spanning 2 decades from 1989 to 2014. Most studies (19 out of 22) suggest that members of the general public are in general willing to give priority to a patient with more severe disease. Among these studies, 3 further highlight that severity may be one of the most important attributes to use in health care priority setting, with many studies ranking severity as one of the most important factors.

Overall, while there is strong evidence to suggest that burden of illness or disease is considered important by the public, there was less evidence on the extent or weighting the public would prioritise burden of illness as a decision-making modifier. Gu et al. (2015) found only 4 out the 22 studies reported specific weights for burden of illness, and the results were further confounded by the heterogeneity in the definitions of severity used and in the types of elicitation method. The results range from a significant (but small) weighting given to treating relatively less severe disease in a discrete choice experiment by Lancsar et al. (2011) to a person trade-off study which found returning 3 patients with severe health problems to full health was equivalent to saving one life by Nord et al. (1993).

The literature for burden of illness does not significantly overlap with that identified for end of life. The large surveys identified did not include end of life as a

consideration for the public to rank, given it was aimed at an Australian and Canadian population, where an end-of-life modifier does not apply. Gu et al. (2015) found that the most popular definitions of burden of illness is based on quality of life if untreated and only 4 out of 19 studies defined severity in terms of life expectancy if untreated (or age of onset and age of death if untreated).

More recently, Lancsar et al. (2020) explored the social value of QALYs across 4 QALY types (life-extending QALYs; quality-of-life-enhancing QALYs; QALYs generated as a mix of life extension and quality-of-life enhancement; and QALYs that extend life but simultaneously reduce quality of life). They conducted a discrete choice experiment with a nationally representative sample in age and gender to explore the Australian public's preferences for which factors should receive additional weight in priority setting and what weight they should receive. They also calculated relative priority weights across characteristics such as age and severity.

Their conclusions highlight that people valued more highly QALYs generated by a mixture of life extension and improvements in quality of life than those generated by either of these components in isolation; and both of these are weighted more highly than those QALYs which extend life but reduce quality of life. These preferences seemed to also depend on the underlying severity as measured by quality of life without treatment. The authors state that "(…) when quality of life without treatment is low, QALYs generated by improvements in quality of life receive highest weight". The results also showed that the largest weight was given to those in moderate health rather than to those with the most severe conditions, measured in terms of either quality of life or life expectancy without treatment. They stated that "(…) when the treatment generates QALYs made up of quality of life improvement only, patients who have very low quality of life without treatment (that is,, the most severe) are prioritised. When the treatment extends life or both extends life and improves quality of life, patients in moderate quality of life without treatment are prioritised. When treatment extends life but simultaneously reduces quality of life, patients in relatively high quality of life without treatment are prioritised."

Age was a relevant factor depending on the remaining life expectancy of the patients (see age section).

The NICE Citizen's council report (2008) favoured considering severity or burden of illness as a relevant modifier. The council favoured taking severity into consideration alongside cost and clinical effectiveness evidence; but not through modifying the quality-adjusted life year (QALY) measurement.

International considerations of burden of illness

Most of the countries reviewed consider 'severity of illness' either explicitly or implicitly, and it is was identified by the Office of Health Economics as being one of the most applied modifiers by international HTA bodies. Approaches vary between

countries, with most using reasonably well-defined mechanisms. For example, higher cost-effectiveness thresholds are explicitly described for more severe conditions (often oncology) in Canada, Japan, the Netherlands, and Sweden. In France, disease severity impacts a medicine's medical service rendered (SMR) rating, which determines the extent to which it will be reimbursed under the country's public healthcare system. The Institute for Quality and Efficiency in Health Care (IQWiG) in Germany cannot decide that a medicine has a major added benefit (and would thus be eligible for the greatest price premium over comparators) unless it has an impact on mortality or serious symptoms. It is worth noting that severity is also linked to unmet need in some HTAs (for example, France), which in some cases allows for a higher cost-effectiveness threshold, or higher price to be set.

However, disease severity is not always explicitly considered. For example, in the US, Institute for Clinical and Economic Review has begun to incorporate a calculation of the equal value of life years gained (evLYG) more prominently into its reports. evLYG measures gains in life length, regardless of how much a treatment improves quality of life. A greater focus on evLYG means that drugs that extend life are treated more equally regardless of the patient's severity of illness or level of disability

Conclusion on burden of illness

In line with the conclusions on end of life (see end-of-life section improvements in both quality of life and extension of life seem to be favoured over improvements in life extension only. This would be in line with an application of a severity or burden of illness modifier which looks into shortening of life and loss of quality of life, and therefore, it is suggested that a modifier based on **severity or burden of illness** should be included.

Proposal for stage 1: To include a modifier based on burden of illness.

Actions for stage 2: Develop modifier definition and application, investigating the overlap with the current end-of-life criteria.

These conclusions are summarised in Table 7.

Health inequalities

The Health and Social Care Act (2012) stipulates that the policy makers and commissioners must 'have regard to the need to reduce inequalities between the people of England with respect to the benefits that they can obtain from the health service'. In reflection of this duty, NICE's Principles (2020) state that 'our guidance should support strategies that improve population health as a whole, while offering particular benefit to the most disadvantaged' (NICE 2020).

The areas of inequality that NICE takes into account include but are not limited to people sharing the characteristics protected by the Equality Act (2010). A dedicated task and finish group has a broad remit to consider potential equality issues in the development of NICE guidance, and this document contains a separate review on evidence regarding age as a modifier of decision-making.

Also, there is specific evidence on the extent to which society would like decision makers to reflect the potential of a technology to reduce health inequalities arising from socioeconomic factors. It is well established that deprivation is a major determinant of health. The Marmot review (2010) highlighted conspicuous discrepancies in quality and length of life between people living in the poorest neighbourhoods and those living in the richest (Marmot et al. 2010). A recent update has shown that health inequalities in England have increased over the subsequent decade: for men, the difference in life expectancy at birth between least and most deprived tenth of areas grew from 9.1 years in 2010 to 2012 to 9.5 years in 2016 to 2018; for women, the gap grew from 6.8 years to 7.7 years over the same period. Indeed, women in the most deprived tenth of areas experienced a decrease in life expectancy in the 2010s (Institute of Health Equity 2020).

When NICE's citizens council considered the issue in 2006, a majority (58%) of members agreed with the proposition that it is 'appropriate for NICE to issue guidance that concentrates resources on trying to improve the health of the most disadvantaged members of our society, thus narrowing the gap between the least and most disadvantaged, even if this has only a modest impact on the health of the population as a whole' (NICE 2006).

Results from the decision support unit (DSU) report on health inequalities

Health inequalities has not been directly referred to in technology appraisal (TA) or highly specialised technology (HST) evaluations. Instead, equality issues are taken into account with regards to considerations in line with the Equalities legislation.

Results from other programmes

We are aware of only 1 instance in which a NICE decision-making committee considered evidence actively taking preferences of the type summarised above into account. This was not in CHTE; rather, it came in a public health guideline on cardiovascular disease: identifying and supporting people most at risk of dying early (PH15). On that occasion, it was suggested that a threshold as high as £120,000 per quality-adjusted life year (QALY) could apply to a programme that reduces health inequalities. However, this would only be appropriate in the circumstances that (a) the intervention in question only provides benefits to the most deprived fraction of society and (b) opportunity costs can be assumed only to apply to the least disadvantaged. The former may occasionally be true of public health programmes,

the latter will never be true of any health and social care expenditure. In the event, the committee in PH15 did not have to exercise such judgements, as all the programmes it reviewed appeared to represent good value for money without applying additional weight to the QALYs they were expected to generate.

Results from literature review on health inequalities

There have been several attempts to establish and quantify the preferences of the general public or NHS professionals regarding distribution of health benefits among less and more disadvantaged patients. Mostly, these take the form of discrete choice experiments in which participants are asked to express a preference between pairs of hypothetical healthcare programmes. One programme provides more benefit to the rich than the poor while the alternative has less of a socioeconomic gradient. By progressively lowering the amount of total health expected from the second programme, the researchers can identify the point at which participants become unwilling to trade off reduced health for more equitable distribution of gain. This provides a method of quantifying societal inequality aversion, that is, the extent to which we would prefer to equalise, rather than maximise, health gains.

Williams et al. (2005) conducted face-to-face interviews with a representative sample of York residents (n=130). Their discrete choice experiment, focusing on life expectancy only, found that the implied equity weight at the margin for those in the most deprived fifth of society relative to those in the least deprived fifth would be 6.6 (see also Dolan et al. 2011).

Dolan et al. (2006) did a similar discrete choice experiment in a sample of secondary care specialists (n=238). Their results suggest that respondents would be prepared to generate less health overall if gains fell preferentially to people who were socioeconomically disadvantaged. Respondents had equal preference for, on the one hand, a programme evenly spreading 32.41 QALYs throughout society and, on the other, a programme giving 9 QALYs to the most deprived fifth, 3 QALYs to the least deprived fifth, and 6 QALYs each to 3 intermediate categories (that is, generating 30 QALYs overall). The authors performed some additional calculations showing that these preferences are equivalent to valuing QALYs added to the most deprived population at £28,000 each, whereas those gained by the least deprived are valued at £11,200 each (see also Ratcliffe et al. 2009).

Robson et al. (2017) report a discrete choice experiment in which members of the general public in England (n = 244) expressed preferences between hypothetical health programmes distributing greater or lesser health gains more or less equally among most and least deprived populations. Their results suggest substantial concern for health inequality among the English general public. The authors state that, at current levels of quality-adjusted life expectancy, the degree of preference would equate to weighting health gains to the poorest fifth of people in society 6 to 7 times as highly as health gains to the richest fifth.

In an analogous way, Gibbs et al. (2019) did a discrete choice experiment, showing that most participants from the general population prefer asymmetric healthcare allocation favouring unemployed compared with employed people.

Taken together, this evidence reveals a relatively robust and consistent picture of inequality aversion in the UK population, albeit in a literature that is dominated by a small number of researchers performing closely related experiments.

A recent paper published by McNamara et al. (2020), which was not included in the literature review due to the time when this was published, found evidence that the public has aversion to inequalities in lifetime health, particularly when these are health inequalities presented in the context of socioeconomic inequality.

International considerations of health inequalities

Of the 14 countries, 8 (emboldened in references section) consider equity in some manner in their HTA decision making, although little detail is typically included in methods guides as to the nature of these considerations, or how they factor into the decision process. Some HTA bodies simply state that health inequalities should be considered during decision making, and allow companies to highlight potential equity considerations in their submissions (Health Information and Quality Authority [HIQA] in Ireland) or to include additional analyses that address equity-related policy concerns (Canadian Agency for Drugs and Technologies in Health [CADTH] in Canada).

The Agency for Health Technology Assessment and Tariff System (AOTMiT) (Poland), Swedish Agency for health technology assessment and assessment of social services (SBU) (Sweden) and Institute for Clinical and Economic Review (the US) provide somewhat more detail as to how health inequalities are considered as part of their assessment processes. The SBU considers whether there are ethical arguments for or against an intervention as part of a structured checklist, including the following: 1) whether there are resource or organisational limitations that may restrict access for certain patients, 2) whether doctors' views may influence the medicine's usage, causing unequal access, 3) whether there are special interests that may cause unequal access, and 4) whether access to the drug can be hindered due to structural factors (SBU appendix 9). The AOTMiT takes a similar approach, stipulating that the following points should be taken into account: 1) whether any groups be favoured or discriminated against, 2) whether access to the drug guaranteed to be equal, and 3) whether a narrow group of patients is expected to receive a large benefit (AOTMiT Health Technology Assessment Guidelines). However, the impact of the considerations above on the assessment outcomes of the SBU and AOTMiT is unclear.

Institute for Clinical and Economic Review states that where feasible, it may explore through scenario analyses methods to capture the impact of new technologies on

disparities in life expectancy across different subpopulations in the US healthcare system (Overview of the Institute for Clinical and Economic Review value assessment framework and update for 2017-2019). Institute for Clinical and Economic Review committees also vote on whether an intervention will benefit a historically disadvantaged or underserved community as a contextual consideration which can influence what they consider the most plausible incremental cost-effectiveness ratio.

In summary, only the AOTMiT, SBU and Institute for Clinical and Economic Review provide any real detail as to how health inequality concerns are considered in decision making. The AOTMiT and SBU focus on ensuring that all patients have equal access to a medicine, while Institute for Clinical and Economic Review appears to place more importance on addressing wider population inequities.

Conclusion on health inequalities

Consistent evidence that the UK general population favours allocation of resources that seeks to equalise, and not just maximise, health gains. Consideration of health inequalities is also in line with NHS's statutory duties and NICE's stated principles stipulate that our guidance should offer particular benefit to the most disadvantaged. A relatively simple method has been proposed that could incorporate empirical societal preferences to modify decision-making objectively, and could be considered. Health inequalities might not feature in all technology evaluations, but task and finish group members agreed it was an important consideration that could be addressed. More broadly, the impact of other modifiers should consider the potential disproportionate impact on lower socioeconomic groups.

Task and finish group members considered that there may be a moral and ethical justification for applying a greater weight where there are health inequalities arising from the fact a disease is rare (see rarity section). However, there was no quantitative evidence on whether this view is reflected by the UK public, nor what specific weighting should apply.

Proposal for stage 1: To incorporate a modifier relating to reducing health inequalities. Definition should include socioeconomically mediated health inequalities; other areas of inequality may be amenable to consideration (though quantitative evidence appears to be lacking).

Actions for stage 2: To clearly define the modifiers and determine appropriate application.

Table 7 includes a summary of these conclusions.

Uncertainty

As outlined by the uncertainty task and finish group, there are generally 3 types of uncertainty that are considered during decision making: **choice of data source**, **parameter uncertainty** and **structural uncertainty**. Together, these elements contribute to the overall **decision uncertainty** faced by NICE appraisal committees.

NICE appraisal committees are often asked to make decisions about technologies with limited clinical and cost-effectiveness evidence. This is particularly the case for diagnostics and medical technologies, and it is becoming increasingly common for pharmacological products because of earlier licensing decisions, the demand for early access and an increased number of treatments targeting smaller patient populations with greater specificity, such as those for rare conditions.

All methods guides across CHTE stipulate that uncertainty should be explored and appropriately captured in the analyses. The uncertainty task and finish group will explore more deeply the methods to appropriately capture and present uncertainty.

The task and finish group suggested that uncertainty could be understood as a technical correction or a factor for decision making which can be parametrised (outside the remit of this task and finish group) and not as a modifier itself. It was also suggested that uncertainty be retained as a modifier or, explored further at least, to account for risk aversion in decision making and budget impact (for example, when considering incremental cost-effectiveness ratios [ICERs] less than £20,000 per quality-adjusted life year [QALY] gained, the ICER itself is too uncertain and the impact is substantial based on quantification).

Results from the decision support unit (DSU) review on uncertainty

Uncertainty was not looked by the DSU as an independent modifier of the committee's decision making.

Results from the literature review on uncertainty

Literature exploring uncertainty as a modifier is limited. Existing literature highlights that pressures to accelerate access to innovative' technologies have made decision makers more tolerant of weakened evidence requirements (Charlton, 2019). The formalisation of appraisals by NICE has been considered an attempt to absorb uncertainties evident in the decision-making process including those arising from the level of confidence in the analysis done, the level of trust in pharmaceutical companies and patient representatives, diverse perspectives and relative expertise of the decision makers (Calnan, 2016). Despite the various levels of uncertainty that are present in appraisals, deliberations for decision making often focus on a small number of specific issues which may touch on uncertainties in the evidence presented and the analysis done. There were no papers which specifically

investigated whether the public placed a greater weight on certainty of clinical effectiveness or cost-effectiveness estimates as a decision-making modifier.

International considerations

All international health technology assessment (HTA) bodies reviewed (in bold text of references section) stipulate that the company should assess uncertainty in some manner, although most do not provide further detail as to how uncertainty factors into the committee's decision making. Where cost-effectiveness analysis is used, international HTA bodies consider structural, methodological and parameter uncertainty through sensitivity analyses. Some HTA bodies provide further detail on how the strength of a company's clinical evidence is assessed. The SBU (Sweden) uses the standard GRADE system and considers the outputs of this alongside other decision factors such as cost effectiveness and ethical considerations. The IQWiG in Germany grades the level of clinical certainty as 'low', 'medium' or 'high', with a high-quality meta-analysis generally required for an added benefit to be considered proven.

Only Institute for Clinical and Economic Review in the US details how uncertainty directly factors into decision making, as the committee votes on whether uncertainty or overly unfavourable model assumptions creates a risk that cost-effectiveness estimates are too optimistic or pessimistic.

Conclusion on uncertainty

Considering explicit ways to apply a modifier or modifiers to take into account uncertainty has a wide range of issues because the possible sources of uncertainty. Some task and finish group members suggested that uncertainty should not be a modifier because it is not a characteristic of a patient group, the type of magnitude of the health benefits or the technology. It is a feature of the evidence base and there is a separate set of methods for reflecting it and handling it in decision making.

However, committees should retain their ability to believe or not in the evidence presented when considering a cost-effectiveness estimate based on the uncertainty presented and explored using the methods suggested by the uncertainty task and finish group. In their consideration, committees will be able to apply their judgement to recommend, not recommended or recommend a technology within a particular framework such as a managed access agreement.

Proposal for stage 1: Uncertainty is being considered by the uncertainty' and the decision making task and finish groups (each producing their own reports, with collaboration). It will not be considered explicitly as a modifier by this group.

Actions for stage 2: Being considered by the uncertainty' and the decision making task and finish groups (each producing their own reports, with collaboration).

Table 8 includes a summary of these conclusions.

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Appendices

Appendix 1 – Extract from the final project specification form

5	Question(s) to be answered by the task and finish group	1. How has the committee considered each of the modifiers in decision making? - Results from DSU review on each individual modifier is included in the respective section for each modifier 2. Is there evidence available on whether any of the currently applied modifiers are relevant for patients and the NHS, and within NICE's remit? a. What is the strength of the evidence? - Results from the literature and the international reviews on each individual modifier is included in the respective section for each modifier - The strength of the evidence is not high, and therefore, it is suggested that further work is conducted in a wider forum (such as a citizens' council) which discusses social values in the context of healthcare priority setting 3. Are there other factors beyond the currently applied additional/other factors that should be considered? - The literature and international reviews did idenfity other factors. The list of the considered factors is included in the Results section.

		4. Should a specific framework be adopted for the consideration of additional factors (such as the VBA approach from 2014 or the adoption of MCDA)? a. What criteria would need to be met before they can be applied i. Are the criteria justifiable and fair (that is, not arbitrary cut offs) b. If so, how would these modifiers be applied? What weight would they receive? How are qualitative modifiers applied? c. If not, are there any additional guidance that can be provided in the methods guide? d. Does this apply for all types of technologies (HST, devices, diagnostics) - These aspects have not been considered yet and will form part of stage 2 following further work in line with the proposals set up in this review. 5. What are the implications for changing the approach for the NHS? (that is, what is the expected change in the proportion of positive or negative recommendations, the types of products receiving a positive recommendation and budget impact) a. What are the implications of conflation of the other factors? - These aspects have not been considered yet and will form part of stage 2 following further work in line with the proposals set up in this review.

Appendix 2 – Overview of 'modifiers' considered by different HTA bodies

Modifier	Australia	Canada	Czech Rep.	France	Germany
Severity	Considered as part of 'Rule of Rescue'	Higher CE threshold for oncology drugs	Impacts reimbursement levels and conditions, but importance unclear	Impacts SMR rating, which impacts reimbursement status	Not explicitly, but a high added benefit only possible for severe diseases
Unmet need	Considered as part of 'Rule of Rescue'	-	-	Impacts SMR rating. Considered on a binary scale (yes/no)	Lower burden of proof required in cases of 'dramatic effect'
Rarity	Considered as part of 'Rule of Rescue'	-	-	Usually leads to lower ASMR rating	Lower P values accepted, surrogate endpoints accepted. Added benefit proven
Innovation	-	-	Innovative products awarded temporary reimbursement	ASMR rating defines innovation and governs price premium	-
Societal/ uncaptured benefits	Considered in supplementary analysis	Productivity losses can be included in additional analysis	-	Impact on public health can impact SMR/ASMR ratings	Productivity losses due to mortality/incapacity are considered
Equity/ ethical issues	Case-by-case basis	All outcomes weighted equally in ref. case Other analyses can be presented	-	-	-
Other	-	-	-	-	-

Modifier	Ireland	Italy	Netherlands	Poland	Scotland
Severity	-	Implicitly	3 disease severity categories, with different CE thresholds	-	PACE meetings apply for end-of-life drugs
Unmet need	-	Impacts price, but no structured mechanism to its assessment	-	If decision has significant patient/budget impacts	Higher CE threshold accepted in absence of other licensed drugs
Rarity	Higher CE threshold in place, but not explicit	Innovation rating more likely. Accelerated procedure applies	-	-	PACE meetings apply. Greater uncertainty also accepted
Innovation	-	Innovation defined based on 3-dimensional algorithm	-	Drugs classified into different innovation groups	Substantial life expectancy/QoL gains – higher CE threshold
Societal/ uncaptured benefits	Impact on other Government agencies can be included	Public health benefits implicitly considered	Reference case is societal perspective, including productivity	Range of social and ethical issues considered, but impact on decision-making unclear	Added value elements discussed at PACE meetings, including productivity gains
Equity/ ethical issues	No QALY weightings in ref. case, but equity considerations should be presented	Ethical issues implicitly considered	Solidarity and affordability considered	Discrimination and equity considered, but no structured framework	-
Other	-	-	-	-	-

Modifier	Sweden	USA
Severity	Impacts CE threshold, and graded on 4-point scale	evLYG analysis included, which treats drugs equally regardless of severity
Unmet need	-	-
Rarity	Impacts CE threshold, though these are not strictly defined	Separate framework. Higher CE threshold presented ($200k)
Innovation	Only if it can be captured in CE analysis	Novelty of mechanism of action incorporated into decision process
Societal/ uncaptured benefits	Reference case is societal perspective	Delivery mechanism, risk/benefit balance and timing, QALY shortfall all considered
Equity/ ethical issues	Wide range of ethical considerations captured in 12-point checklist and process	Impact on life expectancy disparities considered in scenario analysis
Other	Environmental impact	Impact of therapy on efficacy of future treatments