Extended value appraisal (EVA) – a proposal for the NICE Methods Review

April 2020

Context

This proposal sets out a case for evolving the NICE value framework with an approach that we consider will enable NICE to recommend the right medicines, that society needs, now and in the future. We have fully considered our previous discussions with NICE on this topic, the work undertaken during the value-based assessment consultation, what we have heard matters to patients, what the academic literature says, approaches taken in other HTA markets, and what we believe is necessary to ensure the UK remains a priority launch market.

The Association of the British Pharmaceutical Industry (ABPI) shares the Government's vision to ensure the UK becomes the best place in the world to discover, develop and deliver innovative medicines for patients. Improving the medicines access environment will benefit both patients and the UK economy. The NICE Methods Review has a key part to play in this in reviewing NICE's processes and methods for evaluating new technologies to ensure they are fit for purpose and suitable for appraising the innovations of today and the future.

Current challenges/gaps in technology appraisal decision making

1. **Cost/QALY decision making with a rigid threshold is not flexible enough to appropriately evaluate an increasing number of new medicines**

Using the QALY for decision making allows a comparable measure of health for different technologies in different therapy areas, taking into account the quantity and quality of life they give to patients. However, it is well recognised that there are limitations to the QALY and the value it can capture which is relevant to patients, the NHS and society. In the evaluation of new medicines, NICE couples cost/QALY decision making with an explicit threshold (which has not changed since NICE's inception), resulting in a rigid approach and significant challenges for appraising specialist and rare disease medicines. NICE is one of the few HTA bodies to use such an explicit threshold approach to decision making. The threshold itself has not increased over time, even in line with inflation. With a rapid evolution in science and the types of medicines coming through the pipeline, there is a need to consider how the threshold can be applied in a more flexible way for decision making if UK patients are to receive the best possible healthcare.

NICE Appraisal Committees are in principle allowed to take into account a range of considerations alongside cost-effectiveness, on a case-by-case basis and grounded on social value judgements[1]. At present, the only explicit QALY modifier in the NICE Technology Appraisal decision framework is applied to life-extending, end of life (EoL) treatments. Some new cancer treatments which treat patients at the end of their life can have a QALY weighting applied (a maximum of 1.7).

Since NICE last reviewed its methods, the medicines pipeline has changed from being predominantly treatments for chronic conditions and late stage cancers to one that is producing more targeted therapies for complex, sub-sections of diseases with increasingly small patient populations. 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. These therapies are finding it challenging to navigate NICE's methods of evaluation that are primarily the same as those for medicines treating well-established, chronic diseases.

The NICE Citizen's Council held a meeting in 2008 to discuss in what circumstances NICE should recommend interventions where the cost per QALY is above the threshold range of £20,000 to £30,000. A clear majority of the attendees agreed with a number of scenarios when NICE should do this, which are incorporated into our proposal of additional value elements. In addition, some of the key points pulled out in the report include[2]:

- *"NICE is asking the public's permission to breach the threshold, and on that we agree"*
- *"Severity, orphan medicines, need and the desirability of innovation should all be reasons to breach the threshold"*
- *"Allowing an appraisal panel to depart from the threshold is one sign of a humane society"*
- *"It's important to take account of patient groups that don't have a loud voice"*
- *"Cost effectiveness is important, but the EQ5D and how it is used to calculate QALYs need to be reformed"*
- *"It is clear from the votes that the great majority of us do not think that a view based solely on formulaic considerations of health economics is a satisfactory basis on which to make recommendations about the use of medicine or other interventions by the NHS. Judgements also need to take account of other factors".*

The NICE Citizen's Council does not appear to have been active for a number of years, with their last report produced in 2015. It is unclear if the Citizens Council will continue to operate and inform NICE's work or whether the topics previously considered will be revisited given societal change. Linked to this and how NICE applies judgements, is the recent update of the principles that guide the development of NICE guidance and standards which has superseded the Social Value Judgements (SVJ) document. The SVJ document provides important information about how NICE applies social value judgements in its decision making which we think is important to retain and the new methods manual will need to

[1] Shah, K.K., Cookson, R., Culyer, A.J. and Littlejohns, P., 2013. NICE's social value judgements about equity in health and health care. *Health Economics, Policy and Law*, 8(2), pp.145–165.

[2] Report on NICE Citizens Council meeting. Departing from the threshold. November 27-29, 2008.

sufficiently cover this given the limited coverage in the newly published principles document. As well as being an important document for NICE's external stakeholders and customers, we consider the SVJ document to be one of the key documents that NICE's advisory bodies would read to understand the context of their decision making.

2. **The is a significant gap between the thresholds used and the acceptance of different levels of uncertainty between the Technology Appraisal (TA) and Highly Specialised Technologies (HST) evaluation programmes**

Many orphan and rare disease medicines are ineligible for HST evaluation because of the narrow criteria required for entry so they are routed into the STA process. There is a significant gap between the thresholds used, evidence considered, and acceptance of different levels of uncertainty between these programmes. A recent report summarises the challenges orphan medicines being appraised by the STA process face, and that only 13% have been recommended within their full marketing authorisation between 2013-2017[3]. These challenges include:

- Evidence generation is problematic as patient populations are small and often heterogeneous making it difficult to recruit and identify trial participants.
- There is generally a lack of epidemiological and natural history data.
- Validated endpoints to predict long-term effects can be lacking.
- There is often a lack of consensus on comparators or no active comparator.
- Companies need to cover the costs of R&D and earn a return on investment which necessitates charging a high price per patient; cost recovery can be particularly challenging for small companies.

NICE has acknowledged that traditional cost effectiveness methods have limitations and created a specific HST evaluation programme with its own process and decision-making framework. Until April 2017, decision-making criteria were broad and included the nature of the condition, the impact of the new technology, and impact beyond direct health benefits; it excluded the incremental cost per QALY as a dominant criterion.

The ongoing review of the HST criteria is important and ABPI thinks there is just cause for a broader consideration of rare disease medicines that can utilise this appraisal route. In addition to the work the other relevant Task and Finish Groups will do (e.g. managing uncertainty and types of evidence), there remains a need to see if the gap between TA and HST can be bridged somewhat through the introduction of modifiers.

3. **The current end of life criteria are too narrow, with a binary output, and are becoming less relevant as standard of care improves**

Whilst the current EoL modifier gives QALY weight (up to x1.7) to treatments that offer an extension to life (>3 months) when life expectancy is short (<24 months), it is not applicable for a number of treatments that offer potential life extension and/or improved quality outside of these narrow criteria. As

[3] MAP BioPharma. Access to Orphan Medicines: A Case for Change. February 2019.

better therapies are developed and standard of care is improving, the criteria are becoming less relevant and harder to meet. Cancer medicines are being developed for use earlier in the treatment pathway, which offers better care for patients and aligns to the prevention agenda if the cancer can be treated before it becomes a chronic condition. In 2019, only 7 out of 37 cancer appraisals (19%) met the EoL criteria, compared to 42% in 2016[4].

Eligibility of technologies for the EoL modifier is determined by binary (yes/no) criteria which do not capture different degrees of severity of the condition. Perhaps most importantly, the current EoL modifier cannot be engaged for treatments that predominantly improve quality of life because of the selection criteria. This is inconsistent with empirical evidence where severity defined in terms of QALY loss from disease receives more societal support than severity based on life expectancy only.

4. The UK must demonstrate its support for innovation and reimbursement of clinically important medicines to retain a priority launch market status

Alongside delivering on the commitments in the Life Sciences Industrial Strategy and NICE's commitment in the newly published 'Principles that guide the development of NICE guidance and standards' to support innovation, the Methods Review offers the Government and NICE a significant opportunity to send a strong signal globally that the UK supports pharmaceutical innovation and is an attractive place to continue to (1) invest in and undertake clinical trials, and (2) launch medicines earlier than in other markets. Now the UK has left the European Union, such signals have never been more important, and NICE has a pivotal role to play in sending them. Early feedback from ABPI's members on the de-prioritisation of the UK in their global organisation plans and launch decisions is highly concerning and highlights the necessity of making impactful changes through the Methods Review.

Evolving the value assessment framework

Over the years, a number of other factors have been proposed by different stakeholders for NICE to consider in its decision making in a quantitative or qualitative manner. Making difficult decisions about the funding of new medicines is not an exact science – overly academic and/or rigid approaches risk limiting access to valuable and innovative technologies.

ABPI would like to see a system that provides more flexibility in the consideration of other elements of value beyond the NICE reference-case cost per QALY calculation and that how these value elements have been taken into account in decision making is more systematic and transparent. It is acknowledged that NICE has previously rejected proposals to formally adopt multi-criteria decision analysis (MCDA) tools and that implementing a full MCDA approach may be seen as too complex and challenging in today's environment. It should be noted though that there are varying degrees of MCDA and an evolved decision making framework does not need to introduce undue complexity.

ABPI believes there is scope and an opportunity to introduce additional modifiers and review the deliberative elements considered by Committees, including how these are described/presented in the decision making framework. The selected approach should provide a structure for decision making that

[4] ABPI analysis of cancer appraisals meeting EoL criteria. Jan 2020.

leaves room to exercise judgement; acknowledging that where judgement weighs more heavily, how the decision was arrived at may be less clear. Greater weight should also be placed on clinical and patient input during the appraisal.

Severity QALY modifier

The inclusion of severity as a revised QALY modifier in the NICE decision-making framework has strong foundations.

Equity principles

Health gains accrued to worse off population groups might be valued more by society, even though their ability to benefit from treatment may be smaller than for other population groups[5]. Where it is shown that society is willing to make this efficiency-equity trade-off, this provides the basis to apply special weights to QALYs generated by treatments for more severe conditions.

Societal preferences

There has been a growing body of literature providing evidence on how society wishes to prioritise NHS funding. A recent review of studies (conducted by the Office of Health Economics in August 2019) found evidence of societal support for prioritising resource allocation based on severity when QoL is involved in its definition. In addition, the NICE Citizen's Council concluded in 2008 (by 24 to 2) that NICE and its advisory bodies should take into account the severity of a disease when making decisions[6].

Methodological developments

- **Measurement**: a number of approaches have been proposed and tested to quantify severity. The absolute shortfall (AS) and proportional shortfall (PS) are two possible approaches which are in line with the QALY framework (hence combining both quality and length of life).
    - AS measures the amount of future health that will be lost as a result of the disease. AS takes high values when the total health loss over the lifetime is large. As a consequence, the same disease will determine higher AS for younger than older patients, because the former group is generally characterised by better prospective health than the latter one. AS can be described as a 'fair innings' approach – based on the assumption that everyone is entitled to some 'normal' level of health achievement[7].
    - PS is the amount of health lost relative to the remaining expected health without the disease. PS combines AS with consideration of the severity of disease in more disadvantaged patients' groups because the prospective health loss is weighted according to the remaining lifetime health (i.e. if the remaining lifetime health is poor, more weight will be given to the prospective health loss). It can therefore recognise severity of illness in

[5] Nord, E., 1999. *Cost-value analysis in health care: making sense out of QALYs*. Cambridge University Press.
Nord, E., 2005. Concerns for the worse off: fair innings versus severity. *Social science & medicine*, 60(2), pp.257–263.
[6] Report on NICE Citizens Council meeting. Quality Adjusted Life Years (QALYs) and the severity of illness. 31 January – 2 February 2008.
[7] NICE DSU Briefing Paper. Department of Health proposals for including burden of illness into value based pricing: a description and critique. July 2013.

elderly populations. PS may favour the treatment of life-threatening diseases over chronic but not life-threatening diseases because in the former case the life expectancy of patients is very short. PS contains elements of 'fair innings' and 'prospective health' arguments[7] and could be described as a 'sudden shortening of life' approach which significantly impacts a patients opportunity to have a 'good death'.

- **Inclusion in decision-making**: for an explicit consideration of severity, different approaches have been defined and used in practice. These range from more deliberative approaches, applying flexibility around the application of the baseline threshold based on committee judgements, to more quantitative ones, applying explicit QALY modifiers to the incremental cost-effectiveness ratio or the threshold.

Policy environment in the UK

Introducing a QALY weighting for life-extending medicines at the end of life and in the HST programme demonstrates a departure from the equal QALY weighting approach, and that the position 'a QALY is a QALY' is not strictly true for the UK Government or NICE.

NICE has recognised the importance of considering severity concerns repeatedly, in official documents, published literature and TA guidance[8]. In 2013, when a value-based assessment (VBA) was proposed and NICE was asked to develop a method to expand its value framework to include burden of illness and wider societal benefits, a number of measurement tools and decision-making approaches were defined and extensively debated. At the time, the opportunity to introduce a broader value assessment framework was missed because an approach was not found that was acceptable to all healthcare stakeholders who participated in the consultation process. However, there was broad support for the incorporation of burden of illness as one of the criteria to be considered and NICE committed to working with the system partners to develop a method that could be implemented[9].

Using PS and AS scores, depending on the disease and patient population in question, would provide a different, more equitable approach for introducing a severity based modifier. Further details on how this could be implemented in NICE's methods, in a manner that absorbs the EoL QALY weighting, are provided in Annex 1.

Policy environment outside the UK

An increasing number of countries with an HTA system (QALY-driven or not) have introduced an explicit way to ensure their recommendations or funding decisions are informed by severity considerations. The Dutch and Norwegian approaches are examples of how in practice severity modifiers can be included in advanced HTA systems in a flexible way.

[8] Rawlins, M., Barnett, D. and Stevens, A., 2010. Pharmacoeconomics: NICE's approach to decision-making. *British journal of clinical pharmacology*, 70(3), pp.346–349
[9] NICE Board papers. September 2014.

In the US, proposed changes to the ICER value assessment framework include the introduction of 'other potential benefits and disadvantages' for appraisal committee voting[10]. Specifically, empirical results for both absolute and proportional QALY shortfall will be provided to support voting on a single question on 'health loss without this treatment' (on a three-level scale) to be included as a contextual consideration of the appraisal committee meeting.

Rarity QALY modifier

A broad definition of a rare disease is: "A rare disease is a health condition that affects a small number of people compared with other prevalent diseases in the general population"[11]. There are three broad arguments for the inclusion of rarity as a QALY modifier: ethical principles, empirical support and economic theory.

Ethical principles

Ethical support for special consideration of rarity are based on principles of egalitarianism and rights-based arguments including non-abandonment and the right to a minimum standard of health care.

- Egalitarian principles hold that all persons should be treated equally and should be entitled to equality in access to healthcare and equality of outcomes. Where outcomes are unequal, resources should be allocated in a way that reduces the inequality between the better and worse off. By definition, rare disease medicines are associated with small patient populations and relatively low demand compared to more common diseases. Therefore, rare disease medicines tend to be more expensive to develop on a per patient basis than medicines for more common (higher demand) conditions. If rare disease medicines are held to the same cost-effectiveness thresholds as medicines for more common conditions, it can put patients with rare diseases at a disadvantage in terms of equality of access to effective medications and equality of health outcomes.

- Similar to egalitarianism, the right of non-abandonment holds that society should not abandon individuals who are suffering from a serious condition, and that social justice requires treating everybody with dignity and respect as a human being[12]. Denying treatment on the basis of cost to persons with a rare disease violates this principle and those set out in the NHS Constitution. Likewise, the right to a minimum of health care holds that "social solidarity requires that all members of the society have access to a decent minimum standard of healthcare because it is the right and fair thing to do"[13]. This argument is similar to egalitarian arguments around equality of access.

[10] ICER, 2019. *2020 Value Assessment Framework. Proposed Changes. August 21, 2019*. [online] Available at: https://icer-review.org/wp-content/uploads/2019/05/ICER_2020_VAF_Proposals_082119-1.pdf
[11] Richter, Trevor, et al. "Rare disease terminology and definitions—a systematic global review: report of the ISPOR rare disease special interest group." *Value in Health* 18.6 (2015): 906-914.
[12] Simoens, Steven. "Pricing and reimbursement of orphan medicines: the need for more transparency." *Orphanet journal of rare diseases* 6.1 (2011): 42.
[13] Zelei, Tamás, et al. "Systematic review on the evaluation criteria of orphan medicines in Central and Eastern European countries." *Orphanet journal of rare diseases* 11.1 (2016): 72.

Empirical support

Dragojlovic et al. (2015)[14] point out that much of the literature in this area "suggests that most members of the public are (1) not familiar with, and do not have pre-existing preferences for, the prioritisation of orphan-medicine funding; and (2) reluctant to engage with scenarios in which the funding of treatments for rare diseases must result in the reduction of care for those suffering from common diseases." These two factors create significant barriers to using existing evidence about the societal value of treating rare diseases to inform orphan-medicine funding policies. This suggests that the 'top of the head' preferences elicited in most studies may not be reflective of what might be observed following a full public debate on the topic and therefore the current evidence regarding citizen preferences for orphan-medicine funding policies may not provide reliable evidence for policy makers seeking to understand public preferences over the allocation of scarce resources.

From the literature that does report on this topic, the public seems to support equal priority for rare and common conditions when costs are equivalent, but support for equal priority falls in scenarios where the cost of treating rare conditions is greater than the cost of more common conditions. It is worth noting, though, that a small but significant proportion of respondents in previously conducted empirical studies have expressed a willingness to prioritise rare conditions even when the cost was higher. In addition, an Israeli study[15] found that whilst a minority of respondents favoured prioritising high cost medicines for small numbers of patients with rare diseases, a strong majority (66%) favoured prioritising medium cost medicines that may be beyond the reach of most patients but could also benefit a relatively larger number. This can be viewed as support for prioritising medicines for 'merely rare' rather than ultra-rare conditions.

Economic theory

Economic theory states that resources should be allocated in the way that generates the greatest value. In the context of health, this allocation of resources includes a 'socially optimal' level of research & development (R&D) into innovative treatments for diseases, including rare diseases.

Given the small population and low sales volumes inherent in rare conditions, the total market revenues available to recoup the costs of R&D are typically lower than for more common conditions. This typically means that manufactures need to charge a higher price for medicines which treat rare diseases to achieve a rate of return (RoR) comparable to medicines for more common conditions or accept a lower RoR on R&D into rare disease medicines. Economic theory predicts that R&D will be driven by expected RoR, so if health systems wish to ensure a 'socially optimal' level of investment into R&D for rare conditions, they must 'incentivise' R&D to overcome the lower potential revenues typically associated with rare conditions. A key mechanism to incentivise such R&D is an adjusted cost-effectiveness threshold when considering medicines for rare diseases/indications – or equivalently, a QALY modifier

[14] Dragojlovic, Nick, et al. "Challenges in measuring the societal value of orphan medicines: insights from a canadian stated preference survey." *The Patient-Patient-Centered Outcomes Research* 8.1 (2015): 93-101.
[15] Guttman, Nurit, et al. "What should be given a priority–costly medications for relatively few people or inexpensive ones for many? The Health Parliament public consultation initiative in Israel." *Health Expectations* 11.2 (2008): 177-188.

– which would allow a higher price per unit of health benefit (QALY) than medicines for more common conditions[16].

Policy environment in the UK

There is some recognition in the UK that medicines developed for small patient populations require a different approach for HTA. However, this is not consistent across the devolved nations. For example, NICE and SMC have separate HTA processes for consideration of some ultra-rare conditions (the HST evaluation programme and ultra-orphan pathway, respectively) but these take very different approaches and have different selection criteria. SMC applies a more flexible approach than NICE when considering rare (not ultra-orphan) disease medicines, accepting a higher level of uncertainty in the economic case and considering additional factors in decision making without an explicit threshold.

NICE does not give special consideration to conditions defined as rare by the EMA definition (less than 5 cases in in 10,000 population). The NICE HST evaluation programme is highly restrictive in its consideration of rarity and has seven criteria that a medicine must meet for selection. This gap between consideration of rare and ultra-rare conditions means that medicines for 'merely rare' conditions face the same cost-effectiveness threshold and decision making parameters as more common conditions, potentially disadvantaging these patients and not accounting for the higher R&D costs typically associated with these medicines.

There is a disparity between the regulatory incentives for rare disease medicines (including the fast tracking of their licensing approval) with HTA policy. Regulatory incentives have served to encourage the research and development of new medicines for rare diseases with a high unmet need. However, without considering the system as a whole and looking at how rare disease medicines are appraised through HTA, these incentives are worth less to manufacturers and patients don't benefit from access to the medicines.

Compared to other European jurisdictions, England, Scotland and Wales were the only jurisdictions that authorised less than half of rare disease medicines with an EMA marketing approval[17]. These countries also had the longest mean and median times between EMA authorisation and HTA recommendation. A comparison of NICE's review times for rare disease medicines and medicines for non-rare diseases found that median time to first decision for rare disease medicines was 24.0 months compared to 17.2 months for medicines for non-rare disease medicines[18].

There has been a call from stakeholders, including patient organisations and industry, for several years to reform the NICE TA process for rare disease medicines. Introducing a QALY weight for rare disease medicines in addition to the proposed modifier for severity would help bridge the gap between the

[16] Berdud, Mikel, M. F. Drummond, and Adrian Towse. "Establishing a reasonable price for an orphan medicine." *OHE Research Paper. London, Office of Health Economics* (2018). Available at: https://www.ohe.org/publications/establishing-reasonable-price-orphan-medicine [Accessed August 8, 2019].
[17] Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J. and Garau, M., 2019. Comparing access to orphan medicinal products in Europe. *Orphanet Journal of Rare Diseases*, 14(1), p.95. 10.1186/s13023-019-1078-5.
[18] Zamora, B., Maignen, F., O'Neill, P., Mestre-Ferrandiz, J. and Garau, M., 2019. Comparing access to orphan medicinal products in Europe. *Orphanet Journal of Rare Diseases*, 14(1), p.95. 10.1186/s13023-019-1078-5.

maximum QALY weighting used within Technology Appraisals (set out in the parameters of the Modifiers Task and Finish group specification as £50,000 per QALY gained) and the HST baseline threshold.

Other important value elements – deliberative/qualitative modifiers

There are a number of other value elements which are important to patients, the NHS and society which are not adequately captured by the QALY. These are well explored in the literature (for example in 'Defining elements of value in health care – a health economics approach: an ISPOR special task force report'[19] published in Value in Health last year). ABPI went through a process as part of the EVA work to understand which value elements are a priority from both an industry and patient perspective (this work has been shared with the Modifiers Task and Finish Group).

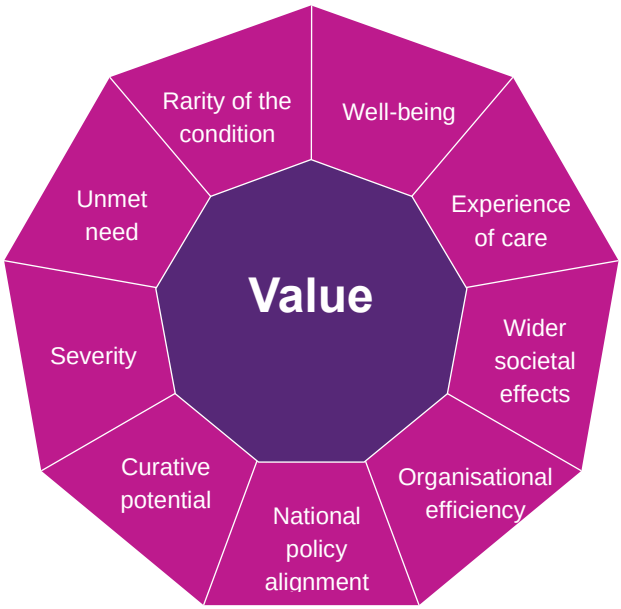

Figure 1 – prioritised list of value elements which should be considered in HTA decision making

A targeted literature review was conducted, and comparisons made with other HTA systems for discussion in a series of workshops with industry representatives and patient organisations to define a prioritised list that considers what matters most to patients (see Figure 1). Further work was done to explore how these elements of value could potentially be measured and incorporated into a decision making framework. Some of the elements can be more easily defined in a quantitative (e.g. severity through a PS or AS score) or binary (e.g. rarity which may trigger a modifier through an agreed definition) way. Others may be more of a contextual factor best suited to a Committee deliberation, for example the difference in experience of care a patient receives with a new treatment.

[19] Lakdawalla DN et al. Defining elements of value in health care – a health economics approach: an ISPOR special task force report. Value in health 21 (2018) 131-139.

There are existing ‘designations’ in the system that recognise very innovative treatments that address high unmet need, for example the Promising Innovative Medicine (PIM) designation and a subsequent Early Access to Medicines (EAMS) scientific opinion. The Accelerated Access Collaborative (AAC) is also tasked with selecting highly innovative medicines that should be accelerated through the system. These designations should be accounted for in the NICE methods so that the medicines are not only prioritised from a scheduling perspective but considered as highly innovative in their evaluation, invoking additional flexibility to recognise this.

ABPI suggests that in addition to quantitative QALY modifiers considering severity and rarity, an agreed list of additional value elements is incorporated into NICE’s methods, encouraging evidence to be submitted by companies and other relevant stakeholders e.g. clinicians and patient experts. These additional value elements should be discussed at Committee meetings, enabling some flexibility to be applied where appropriate. The final appraisal determination should set out how the additional value elements were taken into account in the Committee’s decision making. This could help improve patient input into the appraisal in a more structured way, making it clearer where their input has impacted on a decision, and could enhance NICE’s communication of decisions to broader stakeholders.

Concluding remarks

There is a good rationale for considering additional value elements in the evaluation of new medicines. Some will be underpinned by more theoretical arguments and empirical evidence than others. The Modifiers Task and Finish Group should consider both the academic evidence and the more humanistic rationale for how we want to be making decisions about access to new medicines, to determine whether they warrant inclusion in a decision making framework. The Patient Involvement Group should be included in these discussions to ensure the views of patients and what matters to them are central to the dialogue.

Appendix 1 - Severity QALY modifier

Proposal

Replace the end of life (EoL) modifier in the Technology Appraisal methods so it considers 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):

Proportional shortfall score	**QALY weight***
<0.4	1
0.40 – 0.7	1.3
>0.7	1.7

Absolute shortfall score	**QALY weight***
<12	1
12 – 20	1.3
>20	1.7

**QALY weightings for severity are independent of additional modifiers which may alter baseline threshold, such as degree of certainty around the ICER and under capture of health utility gained.*

Proposed amend to the NICE methods guide:
The Appraisal Committee will consider applying modifier weights to QALYs to incorporate severity of disease:

- where either the proportional shortfall of a disease lies between 0.4-0.7, or the absolute shortfall lies between 12-20, a weight of 1.3 may be applied
- where either the proportional shortfall of a disease is greater than 0.7, or the absolute shortfall is greater than 20, a weight of 1.7 may be applied.

In order to capture severity for the specific patient population of interest, proportional and absolute shortfall should be considered at the 'indication' level, based on undiscounted QALYs accrued in the 'standard care' arm of the cost-effectiveness model and population norm undiscounted QALYs. This method was considered under NICE's Value Based Assessment (VBA) proposals for burden of illness and wider societal impact, along with an approach of considering shortfall at the higher 'condition' level, based on ICD codes. It is important that a measure of severity is able to differentiate according to stage of disease, since, for example, the amount of healthy life forgone by a patient with a late stage cancer is likely to vary significantly from that of a patient at the early stage of the same cancer type. The required information to implement the proposed approach at the indication level will be readily available from the appraisal process.

Rationale for using both proportional and absolute shortfall

Proportional shortfall can be thought of as the **proportion of healthy life forgone** by a patient afflicted by a particular condition, as compared with a person of similar age and gender who does not have the condition. Most often it is defined as the proportion of remaining QALYs that the individual is expected to lose as a result of the condition and is bound between 0 and 1. A proportional shortfall of 0 indicates that the disease does not result in any loss of QALYs, therefore the individual will not receive any fewer QALYs than a healthy individual. A proportional shortfall of 1 indicates that the disease related QALY loss is so great that the individual loses all their remaining QALY expectation, effectively dying immediately. Proportional shortfall contains elements of 'fair innings' and 'prospective health' arguments (DSU 2013) and could be described as a 'sudden shortening of life' approach which significantly impacts a patients opportunity to have a 'good death'.

Absolute shortfall can be thought of as the **amount of healthy life forgone** by a patient afflicted by a particular condition, as compared with a person of similar age and gender who does not have the condition. Most often it is defined as the total amount of future health (QALYs) that the individual is expected to lose as a result of their condition. Absolute shortfall takes high values when the total health loss over the lifetime is large. As a consequence, the same disease will determine higher absolute shortfall for younger than older patients, because the former group is generally characterised by better prospective health than the latter one. Absolute shortfall can be described as a 'fair innings' approach – based on the assumption that everyone is entitled to some 'normal' level of health achievement (DSU 2013).

It is reasonable to conclude that society cares about absolute losses of quality of life and life expectancy, and that larger losses are considered to be more important than smaller losses. Absolute shortfall is greater where losses are greater and therefore is in line with this value judgement. It has also been argued that the measurement of the severity of a disease should be characterised using a proportional measure. That is, the proportion of expected future health that is lost is important to consider, where losing a higher proportion corresponds to a more severe disease (Stolk et al., 2004).

Both measures characterise the severity of a condition in a legitimate way, however both have limitations:

- Absolute shortfall may be relatively small for older individuals, even those that are close to the end of their lives (which is considered to be a severe case, as per the EoL criteria).
- Proportional shortfall may not be high for younger individuals with severe, debilitating, chronic conditions that are experienced over a significant number of years.

Given that these are opposing flaws it can be argued that these measures should be used in a complimentary manner in order to avoid disadvantaging certain patient populations. 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). However, 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.

The use of **either** proportional **or** absolute shortfall to characterise the severity of a condition can also be supported on ethical grounds. Each measure is unable to characterise all conditions that many would consider to be severe (for example proportional shortfall does not adequately reflect the severity of conditions affecting younger patient populations e.g. severe allergic asthma and Crohn's disease), **therefore the proposal allows for either measure to be used so as not to disadvantage certain patient populations**. This is a key difference from the 2013 VBA proposal. In the VBA work, the DSU reported that there is some empirical support for both absolute and proportional shortfall as a definition of burden of illness and that there are mixed societal preferences for each definition (DSU 2013). The VBA consultation responses also expressed a mixed view as to whether proportional or absolute shortfall should be used to define 'burden of illness' (NICE Board papers, item 04, Sep 2014). **This proposal addresses these challenges, offering NICE a solution to incorporate 'burden of illness' into decision making that is not compromised by a seemingly unresolvable technical debate between use of proportional or absolute shortfall**.

Applying a QALY modifier using this approach also incorporates some consideration of unmet need, given proportional and absolute shortfall scores will account for the current standard of care.
We strongly believe the proposal provides a predictable and transparent approach to how severity of disease can be taken into account in Appraisal Committee decision making.

QALY weightings

The proposed maximum QALY weightings in this proposal have been set according to the parameters set out in the Modifiers Task and Finish group specification – *"the group will not consider a change in the maximum QALY weighting currently used within TA (i.e. £50,000 per QALY gained)".* During the 2013 VBA consultation, NICE applied a maximum QALY weighting of 2.5 (on a £20,000 threshold). At that time, 73% of respondents to the consultation said a maximum weight of 2.5 did not function as a reasonable maximum (NICE Board papers, item 04, Sep 2014). Given that the VBA consultation was seven years ago, and NICE has recognised the need to evolve to appropriately evaluate medicines in the pipeline, **ABPI strongly suggests the limitations set by this parameter are re-considered**. The proposal should be implemented to allow the right medicines, that will greatly benefit society, to be recommended by NICE.

The proposal has considered the weights given to proportional and absolute shortfall in the Netherlands and Norway, respectively. Both HTA markets have operationalised a flexible approach using these measures of severity.

Thresholds applied in the Netherlands based on proportional shortfall score (Reckers-Droog et al. 2018):

Proportional shortfall score	**Maximum reference value per QALY gained (EUR)**
0.10-0.40	20,000
0.41-0.70	50,000
0.71-1.00	80,000

QALY weights applied in Norway based on absolute shortfall score (Summary of a government working group report, 2015):

Absolute shortfall score	QALY weight	Equivalent willingness to pay (NOK)
0-3.9	1	275,000
3-7.9	1.4	385,000
8-11.9	1.8	495,000
12-15.9	2.2	605,000
16-19.9	2.6	715,000
20+	3	825,000

The current QALY weighting given to EoL medicines also needs to be considered, to ensure these medicines can generate an equivalent QALY weighting (which has been operationalised as the application of a maximum QALY weight of 1.7 within the normal range of maximum acceptable ICERs). This was a key concern raised by industry and patient groups during the VBA consultation suggesting NICE should only consider replacing the EoL modifier when it is shown that a different approach leads to the same, or similar, outcomes (NICE Board papers, item 04, Sep 2014). A proportional shortfall score >0.7 seems appropriate for medicines which would currently meet the EoL criteria.

Appendix references

NICE Decision Support Unit Briefing Paper. Department of Health proposals for including burden of illness into value based pricing: a description and critique. July 2013

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Stolk, E.A., van Donselaar, G., Brouwer, W.B. and Busschbach, J.J., 2004. Reconciliation of economic concerns and health policy. PharmacoEconomics, 22(17), pp.1097-1107.

Summary of a report from a working group: Severity of illness and priority setting in Norway, November 2015. https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/summary_the_magnussen_report_on_severity.pdf Original report with QALY weightings listed on page 48 (in Norwegian) https://www.regjeringen.no/contentassets/d5da48ca5d1a4b128c72fc5daa3b4fd8/paa_ramme_alvor.pdf