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Title: Understanding the NICE severity premium: Exploring its implementation and the implications for decision-making and patient access

***Running Title*:** Implications of NICE's severity premium

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Precis:

The expected effects of adoption of the disease severity premium by the National Institute for Health and Care Excellence (NICE) on pharmaceutical reimbursement decisions.

Abstract

Objective

To evaluate the impact of NICE's new severity modifier, which has replaced the end-of-life (EoL) premium, on future NICE recommendations, considering past decision-making patterns.

Methods

NICE technology appraisals (TAs) published between January 2020 and December 2022 were reviewed. Summary statistics were generated to assess how the new severity modifier might impact hypothetical decision-making in historical TAs.

Results

A total of 138 data points were identified from 132 TAs. While the EoL premium was applied in 46 (33%) appraisals, 57 (39%) qualify for a severity-based QALY multiplier. Only 19 (14.6%) appraisals not receiving an EoL premium met the severity criteria, the majority (17) qualifying for a 1.2x multiplier. In appraisals predicted to meet the severity criteria, 45 (79%) were in oncology, making them 4.04 (95% CI: 1.91 – 9.02) times more likely to qualify for a severity modifier than non-oncology indications. Among historically EoL indications, 42 (91%) were predicted to meet the severity criteria, making them 14.8 (95% CI: 6.37 – 37.6) times more likely to qualify for a severity modifier.

Conclusions

The new severity modifier will predominantly benefit oncology indications, continuing their previous explicit prioritisation under the EoL decision modifier. However, the new severity modifier is harder to achieve and less generous; only a fraction of appraisals qualify for the highest effective £51,000 per QALY threshold. The vast majority of indications previously approved at £50,000 per QALY would now need to meet a cost-effectiveness threshold of

less than £36,000. This may necessitate greater pricing flexibility from manufacturers, and increase the likelihood of negative recommendations.

Highlights

NICE has made major changes to the adjustment of their willingness-to-pay thresholds, replacing the 'end-of-life' premium for life extending treatments with a severity-based, tiered approach to valuing new technologies.

Based on historical decision-making, very few technologies appraised by NICE are likely to be eligible for the highest willingness-to-pay threshold, with the new severity modifier continuing to predominantly benefit oncology technologies.

The vast majority of indications previously qualifying for the £50,000 per QALY gained EoL premium would now need to meet a cost-effectiveness threshold of either £30,000 or £36,000. This more restrictive policy environment may present challenges to the introduction of new technologies into the UK, but may improve allocation of resources to where they provide the greatest benefits.

Introduction

The quality-adjusted life year (QALY) offers a standardized measure for evaluating the benefits of different healthcare technologies and serves as the foundation for the decision-making framework preferred by NICE and many other reimbursement agencies. Such frameworks assess the relative value of healthcare technologies using cost per QALY metrics such as the incremental cost-effectiveness ratio and net health benefit. Traditionally, the decision-making philosophy of NICE is based on the principle that 'a QALY is a QALY is a QALY'. This approach suggests that all QALYs hold equal value, whether gained or lost, and irrespective of the individuals or particular situational factors involved. When combined with the efficiency objective inherent to all universal healthcare systems, this approach ostensibly ties value directly and consistently to the QALYs generated by a healthcare technology, suggesting that the approval of new technologies always improves allocative efficiency.[1-3] Underlying this approach is the assumption that the primary objective of the health system is to maximise total population health. However, it is long accepted that society is concerned with the distributional consequences of decisions and unfair distribution of health resources, placing additional value on QALYs gained in certain populations, such as children and individuals with life-threatening or debilitating diseases.[4-6] To address these health equity objectives, QALYs can be weighted to encourage decisions promoting a more equitable distribution of health resources.[3,4,7] This differential QALY weighting according to who benefits from treatment can modify the structure of decision-making such that health generating resources are directed to those society perceives to need them most.

The National Institute for Health and Care Excellence's (NICE) Methods and Processes for Technology Appraisal (TA) updated in 2022 and adopted in 2023[8] incorporate a QALY weighting multiplier for disease severity. This decision modifier enables Appraisal Committees to make recommendations at variable willingness-to-pay (WTP) thresholds depending on the severity of the indication. Under the revised methods, the severity of the condition is considered in terms of both the absolute and proportional QALY shortfall associated with a disease (see Box 1) with specific criteria applied to determine whether a severity modifier is appropriate. The multiplier is applied to the incremental QALYs associated with a technology, prior to the calculation of incremental cost effectiveness ratios. The £20,000 to £30,000 threshold is therefore retained regardless of the severity modifier applied; however, the severity modifier can be interpreted as increasing the effective WTP threshold. Specifically, the 1.2x multiplier implies a maximum threshold of £36,000 per QALY gained, where the 1.7x multiplier corresponds to a maximum threshold of £51,000 per QALY gained.

Box 1 Absolute and proportional shortfall

The severity modifier, as implemented in the NICE methods update, considers the future health loss experienced by people with a condition compared with those without it. Disease severity can be characterised by the extent of shortfall in healthy life, in absolute or proportional terms.

Absolute QALY shortfall quantifies the total amount of future health a person is expected to lose due to their condition. This is calculated by subtracting the modelled total QALYs on the standard of care, from the expected total QALYs of a sex- and age-matched sample of the general population.

Proportional QALY shortfall measures the proportion of future QALYs a person is expected to lose due to their condition. It is calculated by dividing the absolute QALY shortfall by the expected total QALYs from an age and sex-matched sample of the general population.

The new severity modifier replaces NICE's 'end-of-life' (EoL) decision modifier adopted in 2009, which allowed for a higher price to be paid for life-extending treatments indicated for patients with a very short life expectancy i.e. willingness-to-pay threshold of £50,000. Research on public preferences has suggested weak support for an EoL premium, thus this shift in methods has been justified based on a stronger body of evidence supporting the

prioritisation of treatment for patients with more severe conditions.[4,9,10] The implementation of severity weights also brings England and Wales into line with several other European countries such as Norway and the Netherlands which use QALY severity weights as decision modifiers.[9] Nonetheless, replacing the EoL premium with a severity premium represents a significant policy shift, and may have far-reaching implications not only for the healthcare system, but also for the prioritisation of future research and investment. Historically, a substantial proportion of advanced cancer treatments received approval based on the EoL premium, at ICERs well above those usually considered cost-effective by NICE.[11] The introduction of the severity modifier raises questions about the continued eligibility of such treatments for prioritisation, and the future of patient access to new cancer treatments in England and Wales. Moreover, the introduction of a severity modifier may shift investment incentives, and redirect development resources towards new technologies for specific indications which now qualify for a severity modifier. Consequently, health indications unlikely to qualify for a severity modifier could see reduced investment and development attention.

In this study, we present the findings of a review of previous Technology Appraisals (TAs). The objective was to evaluate the potential impact of the severity modifier on future NICE recommendations based on previous decision-making patterns, considering both the implications for appraisals that met and did not meet the EoL criteria. Through this analysis, we aim to provide insights into the potential implications of the severity modifier for the evaluation of health technologies by NICE.

Methods

Appraisal search and selection

A list of all published NICE TA guidance for any intervention or indication published between 1st January 2020 and 31st December 2022 was compiled from the NICE website to collect a sufficiently large sample of appraisals conducted under the previous iteration of NICE's processes, introduced in mid-2018. Published documents (namely the Committee Papers, External Assessment Group (EAG) reports, Public Committee Slides, and Final Appraisal Determinations (FAD)) from full Single Technology Appraisals (STA) were independently screened by MN and MW. Updates or reconsiderations of previous STAs, including Cancer Drug Fund (CDF) rapid reconsiderations were included. Appraisals were excluded if they had been terminated.

Data Extraction

MN and MW independently extracted data from publicly available appraisal documentation. A standardised and pilot-tested data extraction form developed in MS Excel was used. Extracted data were cross-checked for validity and accuracy, and any conflicts were resolved by RH. The data extracted from each TA included: Appraisal number, publication year, indication, intervention or drug evaluated, baseline age and sex distribution of the modelled population, QALYs accrued by patients on current standard of care (SoC QALYs) in the economic model, whether the technology met the EoL criteria, and NICE committee recommendations.

Data and variables

Using the most recent tool developed by Schneider *et al.*[12] dated 15th May 2023, a hypothetical QALY severity modifier was calculated for each historical TA on the basis of extracted SoC QALYs and population characteristics. This tool estimates the absolute and proportional QALY shortfall for a population using quality-adjusted life expectancy norms

for the English population.[12] The severity modifier was categorised as 1.0x, 1.2x, or 1.7x, in alignment with the updated methods guide. The health indications were classified into thirteen principal disease areas per Kaltenthaler and colleagues.[13] These were then collapsed into a binary variable of cancer and non-cancer indications. Application of the EoL premium and NICE recommendation status were coded as binary variables (yes / no). Recommendations approved through the cancer drugs fund (CDF) was coded as yes (n = 11). Where the EoL premium was applied but SoC QALYs were redacted from available public documents, SoC QALYs were optimistically assumed to be 2.0 since EoL was only applied when life expectancy on current treatments is <24 months (n = 5).

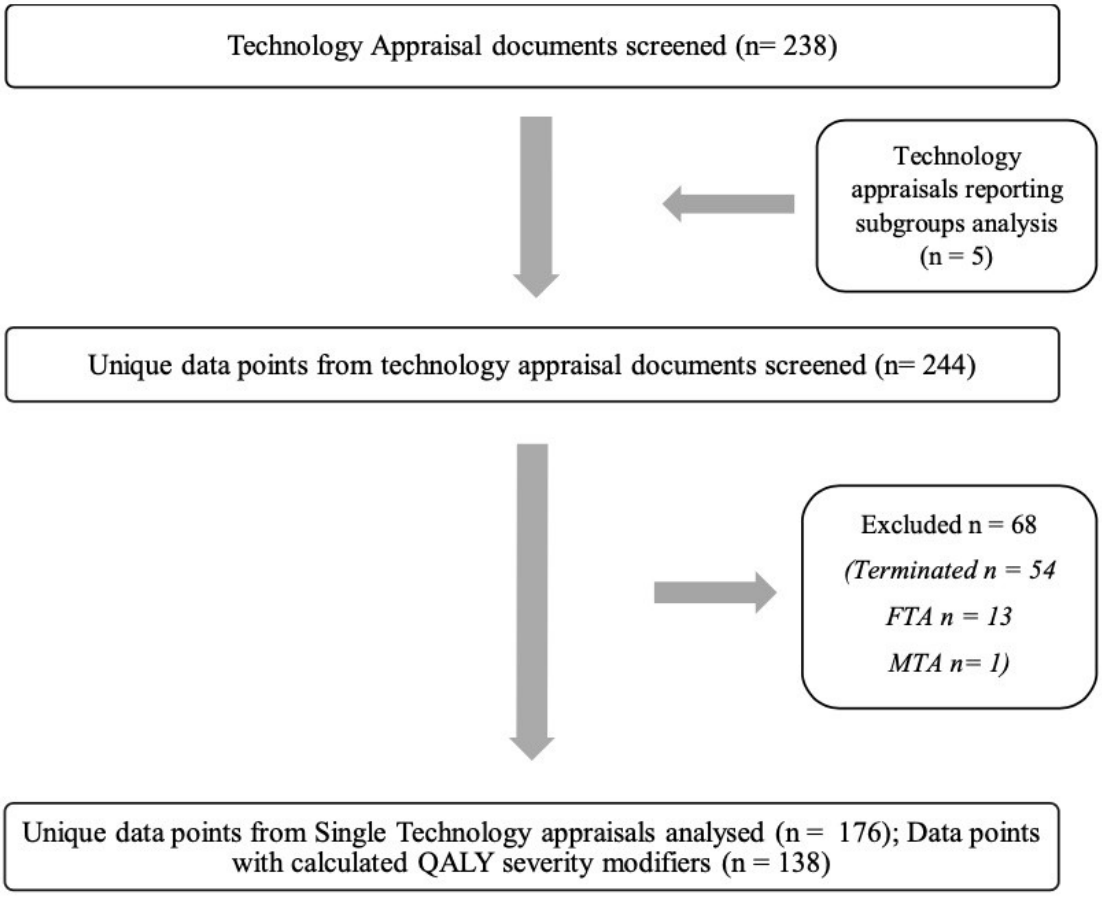
Synthesis and data analysis

Descriptive summary statistics were generated for each of the quantitative items. To evaluate how the severity modifier would impact the hypothetical approval of technologies previously classified as meeting the EoL criteria, hypothetical QALY severity multipliers calculated for previous TAs were compared against recommendation status. Contingency tables of frequency counts and percentages of the severity modifiers and respective EoL applications were presented. Fisher's exact test and odds ratios were used to assess associations between the application of a severity modifier and EoL, and recommendation status. A narrative synthesis was performed to evaluate potentially important patterns and relationships within the dataset, highlighting potential changes to NICE's decision-making in previous appraisals due to the adoption of the severity modifier. Analysis was performed in R version 4.2.1.

Results

A total of 238 technology appraisals were conducted between 1st January 2020 and 31st December 2022 (TA617 – TA854). Five of the appraisals reported a subgroup analysis in which separate decisions were made within a single appraisal. For the purposes of the analysis, these subgroups were considered as separate data points as committees would need to consider application of decision modifiers individually for each subgroup. This resulted in the identification of 244 unique data points from the 238 TAs included. Among the 244 data points 176 (72.1%) were Single Technology Appraisals (STAs) that met the inclusion criteria for further analysis as shown in Figure 1. Among the 176 STAs, 38 appraisals redacted information on the ICERs and SoC QALYs, and therefore their hypothetical severity modifiers could not be calculated. Please refer to the electronic supplementary material for a list of included STAs. The final dataset for which a severity modifier could be calculated comprised 138 data points.

Figure 1 PRISMA flow diagram of appraisal selection process.

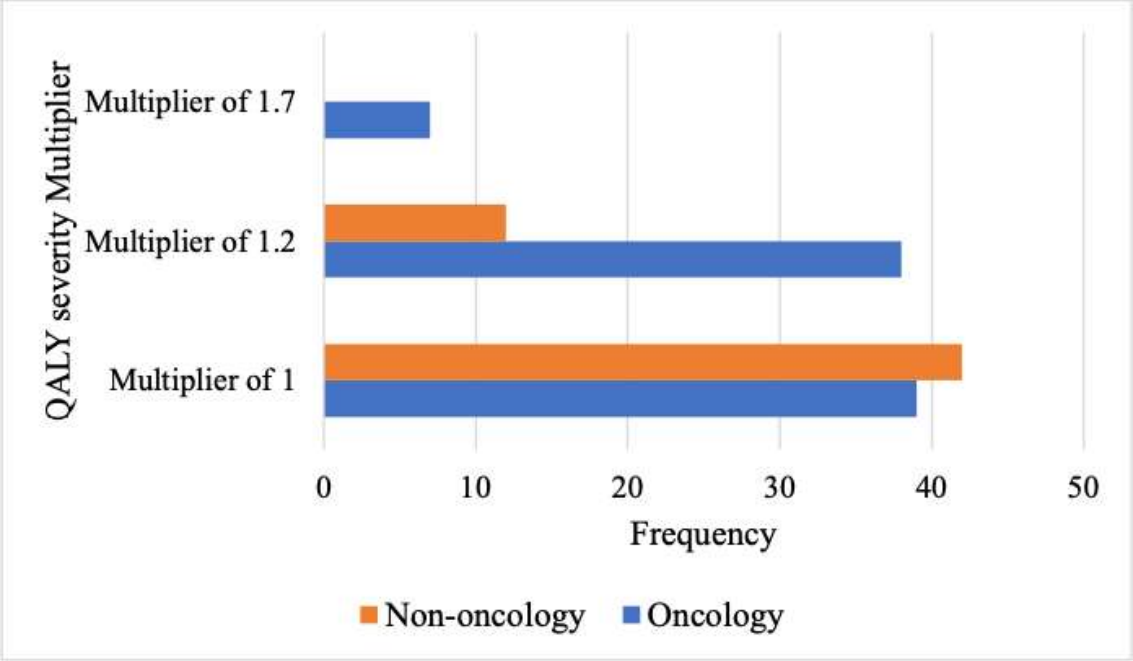


Characteristics of included appraisals

The main disease areas covered by the TAs were oncology (84/138, 61%), musculoskeletal (10/138, 7.2%), blood and immune system (9/138, 6.5%) and central nervous system (9/138, 6.5%), see Supplementary material Table 1. The majority of TAs resulted in a positive recommendation; 115 (83%) of appraisals ended with a recommendation for routine commissioning and a further 11 (8%) ended with a recommendation for use within the CDF. EoL criteria were met in 46 (33%) of TAs.

Figure 2 and Table 2 in the supplementary materials shows the hypothetical eligibility for a severity modifier by whether the appraisal considered an oncology or non-oncology indication. The results show oncology indications were much more likely to be eligible for a severity modifier than non-oncology indications. Of 57 appraisals that would have qualified for a severity modifier, 79% (n = 45) were in oncological indications. TAs in oncology were 4.04 times more likely to have a severity modifier applied than appraisals in non-oncology indications (odds ratio: 4.04, 95% CI: 1.91 – 9.02, p-value < 0.001). Seven (TA655, TA668, TA669, TA722, TA736, TA831 and TA852) oncology TAs would meet the criteria for a 1.7x QALY weighting. No appraisals in non-oncology indications would have met the criteria for a 1.7x QALY weighting. Among the 57 appraisals that would have qualified for a severity modifier, only 10 interventions non-oncology indications would have qualified for a severity modifier of 1.2x. These were as follows: TA728 (advanced systemic mastocytosis), TA699, TA624 and TA656 – all for relapsing–remitting or secondary progressive multiple sclerosis, TA804 (short bowel syndrome), TA767 (multiple scelorosis), TA753 (epileptic seizures), TA685 (Still's disease), TA854 (treatment-resistant depression) and TA651 (opioid-induced constipation).

Figure 2 Distribution of Single Technology Appraisal health focus and QALY weight multiplier



How does the severity modifier impact the approval of technologies previously classified as meeting the end-of-life criteria?

Among the 138 TAs with a complete dataset, 46 (33%) were approved with an EoL premium, while 57 (36%) would have received a QALY severity modifier as shown in Figure 3 and Table 3 in the supplementary materials. Among the TAs approved with an EoL premium, only two did not relate to oncology: TA728 (advanced systemic mastocytosis), and TA755 (spinal muscular atrophy). Of the 46 appraisals approved with an EoL premium, 37 (80%) would have received a severity-based QALY multiplier of either 1.2x (n = 32) or 1.7x (n = 5) with nine not qualifying for a QALY multiplier.

Although a small minority of appraisals would have qualified for the 1.7x QALY multiplier, it was found that TAs approved with the EoL premium were 14.8 times more likely to be eligible for a QALY multiplier (odds ratio: 14.8, 95% CI: 6.37 – 37.6, p-value < 0.001). The 37 appraisals meeting both the EoL and severity criteria were predominantly oncological

interventions with the exception of TA728. The five appraisals that met the EoL criteria and would likely be eligible for a QALY multiplier of 1.7x focused on treating advanced cancers, often after chemotherapy; TA736 (recurrent or metastatic squamous cell carcinoma of the head and neck), TA722 (relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement), TA668 (previously treated BRAF V600E mutation-positive metastatic colorectal cancer), TA831 (previously treated BRCA mutation-positive hormone-relapsed metastatic prostate cancer) and TA655 (advanced squamous non-small-cell lung cancer after chemotherapy).

In total, 20 TAs would hypothetically have qualified for a QALY multiplier of 1.2x or 1.7x, but did not receive an EoL premium when the appraisals were conducted. Out of these, two were eligible for the 1.7x multiplier; TA669, a treatment of metastatic gastric cancer or gastro-oesophageal junction adenocarcinoma after two or more treatments, and TA852, an update of the same appraisal. Among the 18 appraisals hypothetically eligible for QALY multiplier of 1.2x but not deemed to meet the EoL criteria, the seven were in oncology with 11 in other indications.

Figure 3 Distribution of Severity modifier weights and end of life status approval

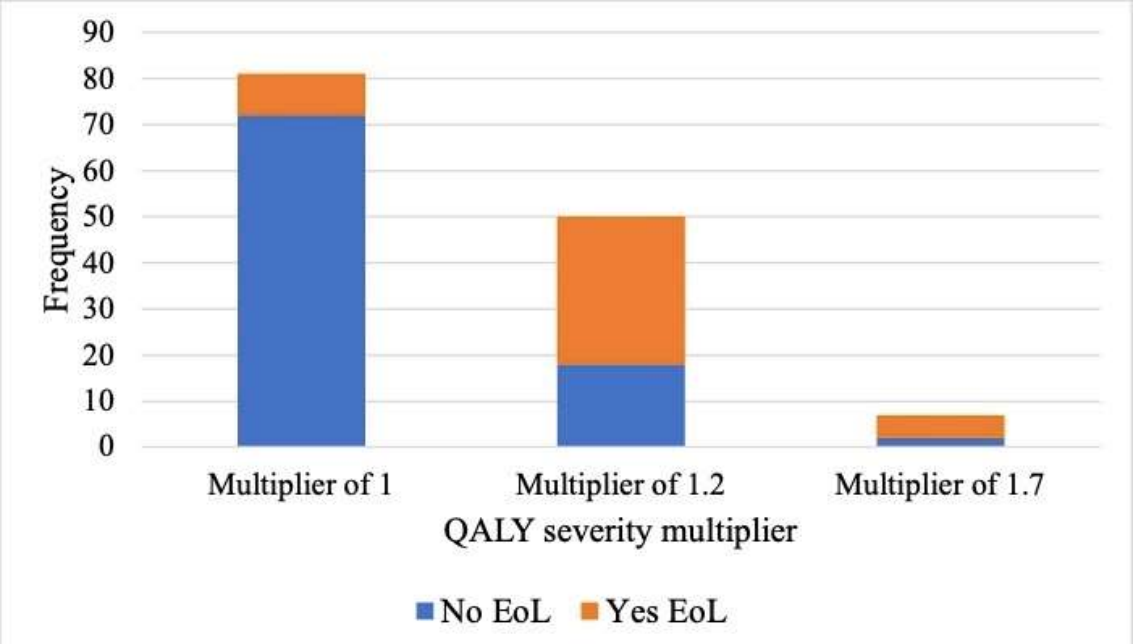


Table 1 stratifies the results into two subgroups based on whether an appraisal resulted in a positive or negative recommendation. This analysis aims to assess how the implementation of the severity modifier might impact future decision-making and the proportion of technologies receiving a positive recommendation.

Among the 138 TAs with a complete dataset, 126 (91%) received a positive recommendation. Out of these 126 TAs, 86 (68%) were considered not to meet the EoL criteria and thus would have been appraised without any decision modifier. The introduction of the severity modifier is unlikely to have affected the final recommendation in these TAs. However, it may have impacted on drug pricing in the 19 TAs (17 at multiplier of 1.2x and two at multiplier of 1.7x) found to meet the severity modifier criteria. Typically, technologies are priced to the relevant WTP threshold, and as such higher prices would have likely been acceptable in these TAs without further pricing negotiation between NHS England and the product manufacturers.

These results contrast with the 40 appraisals (32%) that met the EoL criteria and would have been considered with a QALY multiplier of 1.7x or WTP of up to £50,000 per QALY. Under the revised methods, only four of these appraisals would remain eligible for a 1.7x multiplier. Among the remaining 36 appraisals, 29 (73%) would have been eligible for a 1.2x multiplier, and 7 (18%) would not have qualified for any severity modifier. In these appraisals the revised methods may have had an impact on recommendations.

Only 12 TAs (8.7%) resulted in negative recommendations making definitive inferences difficult. However, the results suggest that the revised methods would have had limited impact. Of the six appraisals (50%) that did not meet the EoL criteria, only one - TA854, would have received a QALY multiplier of 1.2x. TA854 evaluated esketamine nasal spray for treatment-resistant depression, and while it is possible that a severity modifier may have permitted a positive recommendation, other considerations beyond the ICER were an important factor in committee recommendations for this technology. Amongst the six (50%) TAs that met the EoL criteria but resulted in negative recommendations, the introduction of the severity modifier would not have affected outcomes as it would not have allowed additional flexibility on price. In fact, in the majority (five) the effective WTP applied by the committee would have been lower.

Table 1 Distribution of hypothetical severity modifier versus end-of-life application based on whether it was approved or not for either routine use or cancer drug fund.

TAs approved for routine use or CDF					**TAs not approved for routine use or CDF**				
	End of life applied		**Total**	p-value [Ψ]		*End of life applied*		**Total**	p-value [Ψ]
QALY severity modifier	No	Yes		<0.001	*QALY severity modifier*	No	Yes		0.2
Multiplier of 1	67 (53%)	7 (5.6%)	74 (59%)		Multiplier of 1	5 (42%)	2 (17%)	7 (58%)	
Multiplier of 1.2	17 (13%)	29 (23%)	46 (37%)		Multiplier of 1.2	1 (8.3%)	3 (25%)	4 (33%)	
Multiplier of 1.7	2 (1.6%)	4 (3.2%)	6 (4.8%)		Multiplier of 1.7	0 (0%)	1 (8.3%)	1 (8.3%)	
Total	86 (68%)	40 (32%)	126 (100%)		**Total**	6 (50%)	6 (50%)	12 (100%)	

[Ψ] Fisher's exact test

Discussion

The results of this review indicate that NICE's new severity-based decision modifier will be predominantly applied in oncology indications, continuing to benefit technologies targeting advanced or metastatic cancer when there are few effective treatment options left. These findings suggest that it will be rare for indications outside oncology to satisfy the criteria for a severity modifier. Although the scope of the sample may have meant the omission of important examples, it is noteworthy that chronic conditions with a high perceived impact on quality of life are unlikely to be deemed severe enough to qualify for a severity premium using the metric implemented in NICE's updated methods.

Disease severity is currently assessed in terms of foregone QALYs within NICE's methods.[10] While this maintains internal consistency with NICE's value assessment framework, it is potentially an important factor in determining how both fatal and non-fatal conditions drive QALY shortfall. This raises the question of whether the QALY can appropriately represent the public preferences that underpin the rationale for severity-based pricing premiums. This is particularly relevant when considering debilitating conditions that the public perceives as severe, but may not be assessed as such through the lens of the functional utility-based EQ-5D-3L instrument in terms of foregone QALYs.[14,15]

The majority of topics evaluated by NICE are unlikely to be affected by the NICE methods update, as they are ineligible for both the severity-based and the former EoL decision modifier. However, there may be some impact on the prices the NHS is willing to pay for a small minority of previously non-EoL appraisals, which will now receive a severity weighting. One explanation for the lack of appraisals in which a severity premium would be applicable in this review is simply that technologies in these areas were too expensive to be recommended by NICE, and thus manufacturers focused on alternative markets rather than seeking approval in the UK. With the introduction of the severity modifier, manufacturers of

technologies for these conditions may now prioritise the UK market, thereby increasing patient access. On the other hand, it is unlikely that the introduction of the severity modifier would have changed the committee's decision for technologies previously not recommended due to pricing concerns, as typically these products were priced well above any acceptable effective WTP threshold.

Appraisals in which an EoL premium was applied were by far the most likely to also be eligible for a severity modifier. However, very few of the appraisals previously meeting the EoL criteria with a WTP threshold of £50,000 per QALY gained would qualify for the roughly equivalent 1.7x QALY severity weighting, instead being subject to an effective WTP threshold of £30,000 - £36,000 per QALY gained. This may put a significant number of future technology appraisals at risk of receiving negative recommendations or require increased flexibility on pricing from manufacturers, which may not be forthcoming. Depending on the flexibility of manufacturers capacity and willingness to lower prices, this may have an impact on the number of positive recommendations, and thus whether patients have access to these treatments on the NHS.

The acceptability of these consequences to patient groups and the wider public remains to be seen. It is easy to imagine that many will consider the new severity modifier as a retrograde step, setting too high a barrier to cost-effectiveness. However, it is important to remember that the justification for these revisions lies in the need to address criticism of the EoL premium which was often criticised for diverting much needed resources away from other NHS services.[1,16] While the severity modifier aims to address this issue, there is nonetheless the possibility of negative consequences in terms of access to new medicines which, while justifiable in cost-effectiveness terms, may not be palatable to the public and other stakeholders. This could lead to a reduction in investment or, more likely, the de-prioritisation of the UK as a pioneer market for new technologies. Additionally, such a major

change in methods may raise concerns about the validity of previous decision making, and indeed undermine the validity of decisions made on the basis of EoL premium. This is particularly problematic as new technologies will be compared against comparators which are no longer cost-effective under present methods, which further complicates NICE's process of iterative decision-making which inherently assumes the cost-effectiveness of the comparators currently in use.

Given the patterns observed in this review, it appears that fewer new technologies could be recommended, with lower prices will be offered to manufacturers. While it is not easy to establish the budgetary consequences to the NHS, which depend on several factors including epidemiology, only a small fraction of technology appraisals may be eligible for a 1.7x QALY multiplier compared to the number of appraisals meeting the EoL criteria. However, it is important to note that our analysis is based on a retrospective sample, and there is no guarantee that it will precisely reflect future patterns in NICE appraisals. It should also be noted that our interpretation is based on a technocratic approach, and may not fully capture the nuances and considerations that arise during committee deliberations. However, we believe that the trends identified in this analysis are likely to broadly reflect how the committee would have interpreted the interaction of the severity modifier with the ICERs in their recommendations.

Conclusions

The new severity modifier introduced in NICE's latest methods guide update represents an important policy shift. The findings of this review indicate that the severity modifier will predominantly benefit technologies targeting oncology indications, reinforcing the advantage previously offered to these indications under the end-of-life criteria. However, the new severity modifier appears to be more restrictive and far less generous; only a fraction of appraisals will qualify for the highest effective willingness-to-pay threshold of £51,000. This more restrictive policy environment may increase the proportion of negative recommendations and may require increased pricing flexibility from manufacturers.

While the severity modifier may present challenges with regards to patient access to new medicines, it is important to consider these consequences within the broader context of opportunity cost and NICE's overarching objective of improving societal health. The severity modifier offers an opportunity to better target the prioritisation of those interventions most valued by society and to allocate resources to where they provide the greatest health benefits.

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