Reviewing implementation in practice of the NICE Health Technology Evaluation Manual

August 2024

Executive summary

In 2019, the National Institute for Health and Care Excellence (NICE) initiated a significant review of the methods and processes used to evaluate health technologies. The review concluded in early 2022 with the publication of a new manual, with NICE stating *"the changes will give patients earlier access to innovative new treatments by allowing greater flexibility over decisions about value for money and consideration of a broader evidence base"*.[1] At the time, the Association of the British Pharmaceutical Industry (ABPI) welcomed the changes, but raised concerns that they did not sufficiently meet the level of ambition that had been anticipated by many stakeholders, including the pharmaceutical industry and as set out in the government's Life Sciences Vision. This ultimately risked patients not being able to access innovative medicines in England.[2] The updated Health Technology Evaluation (HTE) Manual has now had more than two years to bed in, and the impact of the changes is starting to become apparent.

To help monitor the impact of the 2022 HTE Manual, the ABPI launched a new initiative – Continuous NICE Implementation Evaluation (CONNIE)[3] – to collect feedback from companies on the implementation of the key changes that were made. This report is the second in the ABPI's CONNIE series, which aims to review company feedback and explore trends. This latest analysis now captures feedback from 39 completed evaluations, which is representative of 76 per cent of all topics that have concluded in the analysis timeframe.

Given the challenging broader commercial environment in the context of a capped Voluntary Scheme for Branded Medicines Pricing, Access and Growth (VPAG) and the critical juncture at which the UK currently finds itself, it is more important than ever to ensure NICE's methods and processes are robust, fit for purpose, and can adequately value and support the introduction of new medicines and significant indications into the NHS.

Key insights from the analysis

- **Severity modifier:** the severity modifier has been applied in eight topics (21 per cent of all topics). The average quality-adjusted life year (QALY) weighting across the entire sample (1.073) is lower than the average QALY weighting used by NICE to design the severity modifier (1.119) and also lower than the average QALY weighting that was calculated to be 'opportunity cost neutral' compared to the previous end-of-life criteria (1.125). This indicates that the severity modifier is so far being applied on a more conservative basis than is needed to just deliver opportunity cost neutrality, as per its design, taking away value that was previously available with the end-of-life modifier and disproportionately impacting cancer medicines. A severity modifier applied on a more conservative basis than designed risks increasing the number of topics not recommended and therefore restricting access to treatments for patients with severe diseases. This result is consistent with NICE's own findings on the severity modifier utilisation since implementation.

- **Uncertainty:** companies reported four topics (10 per cent) where NICE committees accepted greater uncertainty and it was clear how this impacted decision-making – on two occasions for rarity and on a further two occasions for innovation. Companies' anecdotal experience suggests this result is driven by improved explicit communication from NICE about existing uncertainty management rather than improved acceptance of uncertainty management from NICE committees. These results cannot yet be considered reflective of NICE's aims towards a greater acceptance of uncertainty as outlined in the HTE Manual.
- **Non-reference case flexibilities:** despite eight topics (21 per cent) making a case for non-reference case flexibilities (e.g. 1.5 per cent discount rates and wider societal perspectives), NICE is yet to grant any topic a non-reference case flexibility. Two of these topics were ultimately not recommended for use by NICE.
- **Technical engagement:** companies reported mostly positive experiences from the 29 topics (74 per cent) that had technical engagement with companies, reporting that in 21 of these topics (54 per cent), technical engagement helped to resolve at least some of the key issues. There were no topics which had not had technical engagement if the company had requested it. There was a decrease in the number of appraisals that required only one committee meeting (31 per cent in in H2 2023/24 vs. 71 per cent in H1 2023/24). Resolving some uncertainties/questions at the technical engagement stage can support better use of committee meeting time and ensure there is a focus on what matters to the committee decision-making.
- **Additional flexibilities**: there were a few topics where companies pursued additional flexibilities, such as surrogate endpoints, carer quality of life (QoL) and real-world evidence (RWE). However, in topics where these were used, companies reported mostly positive experiences.

Recommendations

1. The ABPI recommends that NICE immediately reviews the severity modifier to adjust downwards the cut-off levels used to determine the degree of severity so that more medicines can benefit. Any changes necessary should be made quickly to ensure that the NHS does not go backwards in serving patients suffering from severe diseases.
2. The ABPI recommends that NICE should replace the opportunity cost-neutral approach to implementing the modifier. Instead, NICE should use an approach that is evidence-based and better reflects societal preferences for helping people with severe disease to access innovative treatments.
3. There remain disparities in positions on the implementation of the acceptance of uncertainty between company-reported results in CONNIE and NICE's findings. The ABPI recommends that NICE works further with industry to understand these disparities. The ABPI wishes to work collaboratively with NICE on potential solutions that may assist committees in making recommendations accepting a higher degree of uncertainty, in line with the HTE Manual.
4. NICE should bring to life the commitments set out in the HTE Manual to offer non-reference case flexibilities, including to allow relevant topics to use a 1.5 per cent discount rate and a wider societal perspective to allow more patients to benefit from innovative medicines.
5. Given mostly positive experiences reported by companies when using broader methods flexibilities – such as surrogate endpoints, carer QoL and RWE – companies should explore all opportunities to use the flexibilities offered. We recommend that NICE continues to work with companies to encourage their use where appropriate.
6. NICE should regularly report on the impact of its methods (and process) changes and duly consider the need for further, timely evolution of the HTE Manual within the new modular update process. The ABPI recommends that the modular update process is brought to life as soon as possible in line with VPAG commitments and NICE should publish clear timelines for when the first updates will be considered and delivered.

Introduction

Following an extensive review of the methods and processes used in its health technology evaluations, NICE published an updated HTE Manual in January 2022.[4] NICE stated, *"the changes will give patients earlier access to innovative new treatments by allowing greater flexibility over decisions about value for money and consideration of a broader evidence base".*[5] Key changes included:

- Giving additional weight to health benefits in the most severe conditions to allow more equitable access to treatments for these conditions, alongside withdrawing the end-of-life modifier that was introduced in 2009.
- Adopting new approaches to the evidence NICE considers in its assessments. For example, improving how real-world evidence from the lived experiences of patients can be used in evaluations.
- Allowing more flexibility for NICE's independent committees in cases where it is particularly difficult to generate enough evidence. Sometimes, research into conditions affecting children, rare diseases or where the new treatment is innovative or complex can be problematic. The changes were intended to allow NICE's committees to consider uncertainty more appropriately and to manage the risks to patients and the NHS while preventing inappropriate barriers to valuable innovations.
- Adopting a clearer vision, and clearer principles and routing criteria for treatments for very rare diseases that NICE will evaluate under its Highly Specialised Technologies (HST) Programme. This was intended to improve the efficiency, predictability and clarity when routing topics to the programme and build upon NICE's ambition to provide fairer access to highly specialised medicines and treatments within the NHS.
- Earlier engagement with NHS England and companies about commercial/managed access proposals that allow NHS patients to receive a treatment while further data is collected on its effectiveness. There will also be greater clarity around the circumstances in which NICE committees can make a managed access recommendation.

The ABPI welcomed the changes but raised concerns when the new HTE Manual was published that the outcome of the review did not meet the level of ambition that was anticipated by many stakeholders, including the pharmaceutical industry and as set out in the government's Life Sciences Vision. This risked negatively impacting patient access to some new medicines/indications at a critical time when the UK needs to be seen as an attractive priority launch market on the global stage.[6]

NICE made commitments to closely monitor the impact of the HTE Manual in practice and to adopt a more agile, modular approach to making further updates to its methods and processes. To support these endeavours, the ABPI launched a new initiative – CONNIE[7] – to collect continuous feedback from its members on the implementation of the key changes in the HTE Manual. CONNIE captures member feedback on completed evaluations only. Therefore, CONNIE does not consider feedback on the recent trend of increased NICE terminations or discontinued topics.[8]

In December 2023, the ABPI published the first report presenting the CONNIE data to review the impact of the updated NICE HTE Manual (CONNIE: Round 1).[9] Key insights included: the severity modifier being applied on a more conservative basis than needed to deliver opportunity cost neutrality, as per its design; companies reporting no evidence of committees accepting greater uncertainty in the evidence base; and positive signs for committees accepting surrogate endpoints and RWE.

As companies continue to provide feedback monitoring the implementation of the updated NICE HTE Manual to the ABPI and the CONNIE database grows, the ABPI plans to publish six-monthly updates in the CONNIE series to continuously review the impact of the updated NICE HTA Manual. The current report (CONNIE: Round 2) represents the second report in this series.

Note - CONNIE captures company feedback and the analysis presented does not attempt to determine whether modifiers and flexibilities should, or should not, have been applied in any particular evaluation.

CONNIE analysis

1. Sample

Building on the 20 topics outlined in the first CONNIE report (CONNIE: Round 1), this latest report (CONNIE: Round 2) includes an additional 19 topics. Therefore, the total sample includes data for 39 topics that have completed their evaluation (to publication of final guidance), up to March 2024, using the updated methods set out in the HTE Manual. The sample includes 31 (79 per cent) single technology appraisals (STA), six (15 per cent) cost comparison appraisals and two (5 per cent) HST evaluations.[10] The sample represents 76 per cent of all topics using the updated methods set out in the HTE Manual that have concluded in the period to March 2024.

Date of final guidance publication

Where analysis of trends over time are of interest, this and future reports will present results within half-yearly time periods. Topics are categorised by the date of publication of final guidance, with half one (H1) covering appraisals with final guidance from April to September and half two (H2) covering appraisals with final guidance from October to March. Table 1 outlines the number of topics from the CONNIE: Round 1 and CONNIE: Round 2 reports by date of final guidance publication.

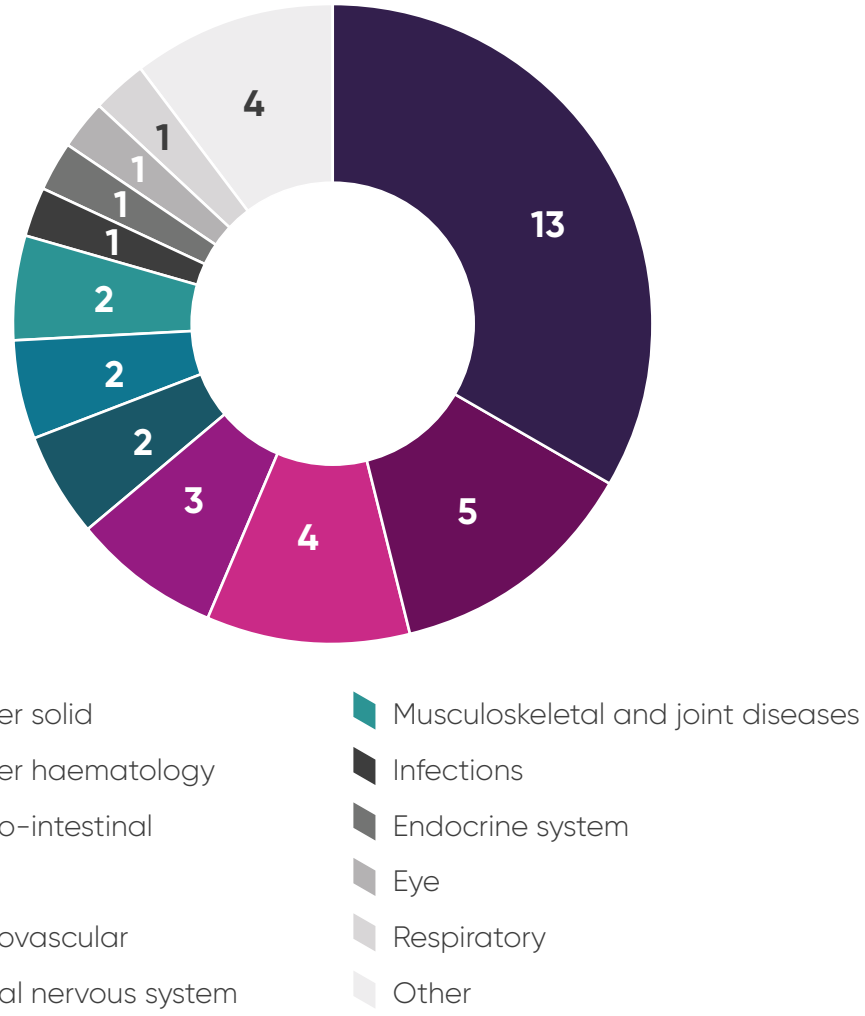
Table 1: CONNIE rounds by date of final guidance publication

	H2 2022/23 topics (%)	H1 2023/24 topics (%)	H2 2023/24 topics (%)	Total
CONNIE: Round 1	7 (78%)	13 (76%)	0 (0%)	20 (51%)
CONNIE: Round 2	2 (22%)	4 (24%)	13 (100%)	19 (49%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)

Sample characteristics

- Fourteen (39 per cent) new active substances and 25 (61 per cent) licence extensions
- Thirty (77 per cent) monotherapies, six (15 per cent) combination therapies with generics, and three (8 per cent) combination therapies with other branded medicine(s)
- Twenty-three (59 per cent) common indications, 13 (33 per cent) orphan indications, and three (8 per cent) ultra-orphan indications
- The sample does not contain any ATMPs
- Eighteen (46 per cent) cancer medicines
- Twenty-two (56 per cent) first in class, nine (23 per cent) second in class, five (13 per cent) third in class, two (5 per cent) fourth in class, and one (3 per cent) other/unknown position in class
- The evidence submissions were reviewed by 11 Evidence Assessment Groups (EAGs)
- The topics covered a representative range of all five NICE appraisal committees

Figure 1: Breakdown of topics by therapy area



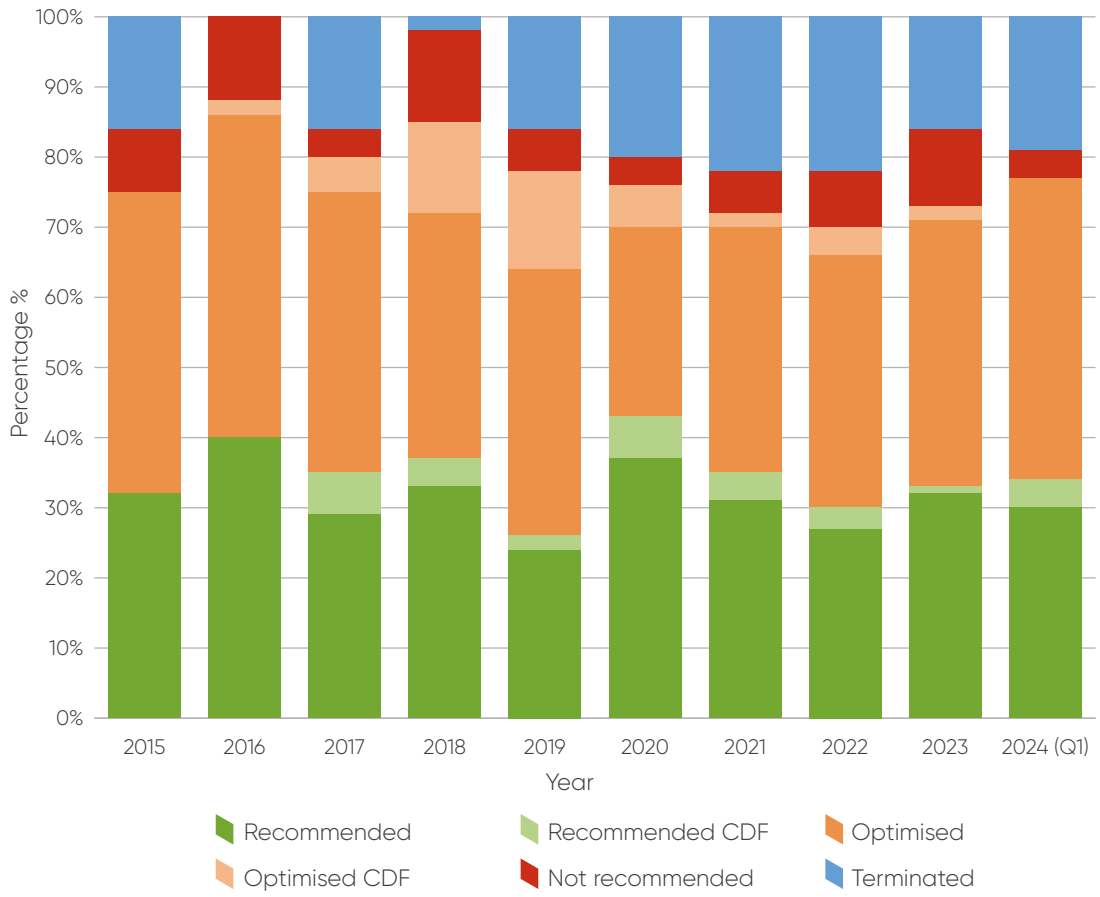
2. NICE guidance outcomes

Twenty-four (62 per cent) of the topics were fully recommended, seven (18 per cent) were optimised, three (8 per cent) were recommended for use in the CDF and five (13 per cent) were not recommended (Table 2). In order to validate the CONNIE dataset, a comparison of technology appraisal outcomes was conducted against a broader data set over a longer period (Figure 2). The CONNIE dataset outcomes reflect a higher proportion of fully recommended topics, a lower proportion of optimised topics, and a comparable proportion of topics not recommended and topics in the CDF. Largely, the CONNIE dataset is representative of a typical NICE sample with respect to outcomes. CONNIE only captures data for completed evaluations, so the results and insights in this report do not include topics that NICE has terminated.

Table 2: NICE guidance outcomes for CONNIE topics

	H2 2022/23 topics (%)	H1 2023/24 topics (%)	H2 2023/24 topics (%)	Total
Recommended	7 (78%)	11 (65%)	6 (46%)	24 (62%)
Optimised	1 (11%)	3 (18%)	3 (23%)	7 (18%)
Recommended – CDF	1 (11%)	1 (6%)	1 (8%)	3 (8%)
Optimised – CDF	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Not recommended	0 (0%)	2 (12%)	3 (23%)	5 (13%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)

Figure 2: NICE guidance outcomes for all topics (proportion)[11]

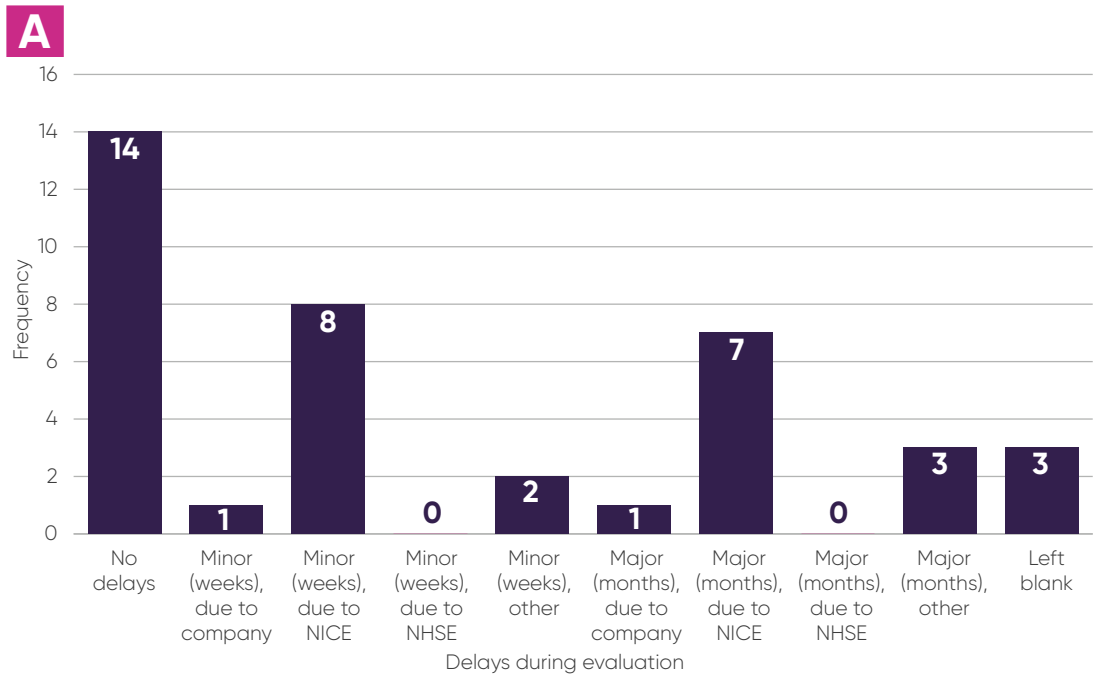


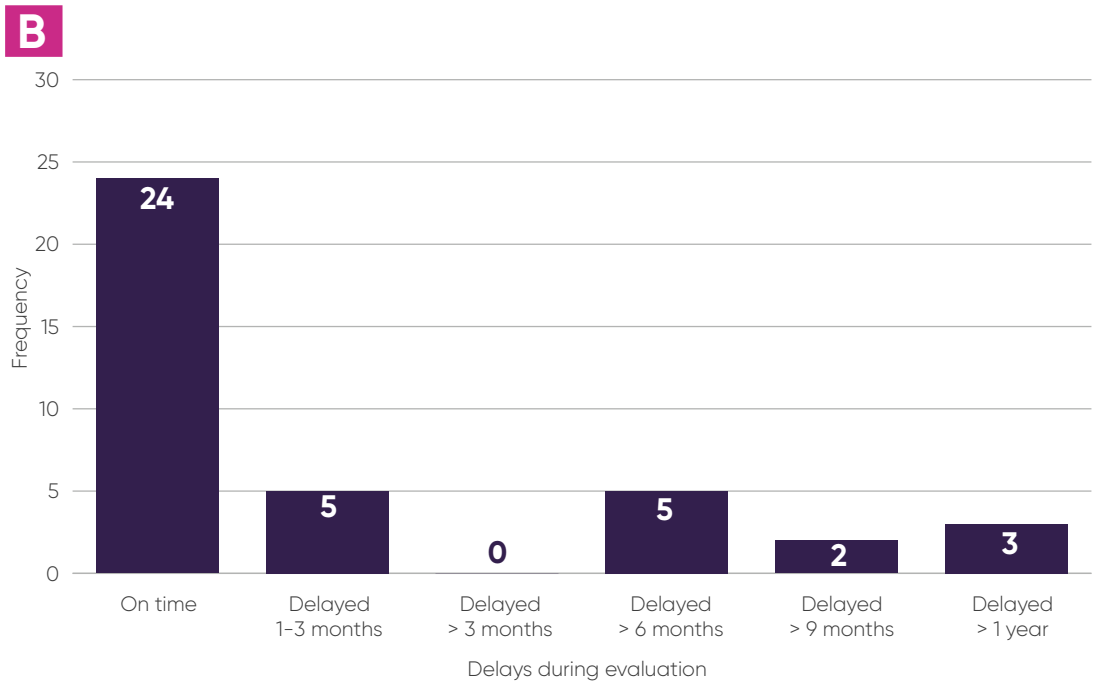
3. Process steps and timing

Evaluation scheduling (reported as companies receiving an invitation to participate) was on time for 28 (72 per cent) topics. Four topics (10 per cent) were delayed by NICE and five topics (13 per cent) were delayed by companies. Some delays were reported during the evaluation process for 22 topics (56 per cent), these were predominantly due to NICE (15 topics, 38 per cent, as per Figure 3A).

There were also delays to publication of final guidance in 15 topics (38 per cent, as per Figure 3B) and in 10 (26 per cent) of these topics, delays were greater than six months.

Figure 3: Delays reported during the evaluation (A) and to final guidance publication (B)





Topics are scoped at the beginning of the evaluation process to define what questions the evaluation will answer and what will and will not be included, providing a framework and defining the issues for consideration. NICE has flexibility to vary the consultation timing for developing the scope and to determine the degree of engagement that is required.[12] Twenty topics (51 per cent) had no scoping engagement, indicating they were probably not in a new or complex disease area/care pathway. Of the 19 topics where scoping was held, six (15 per cent) had a full workshop, four (10 per cent) had a short/abbreviated workshop, and nine (23 per cent) had a call instead of a workshop.

Technical engagement and appraisal committee meetings

Technical engagement is a process step to allow discussions between a company, the EAG and the NICE technical team to identify and consider any evidence gaps, issues and potential resolutions ahead of the committee meeting. It can also be used to consider any commercial or managed access proposals.[11] Twenty-nine topics (74 per cent) had technical engagement. Of these, in five topics (13 per cent) technical engagement helped to resolve key issues, in 16 topics (41 per cent) technical engagement helped to resolve some key issues, and in eight topics (21 per cent) technical engagement did not help to resolve any key issues. The technical engagement step is no longer a mandatory part of the process, but the ABPI considers it a high-value process step and that it should be utilised when there are significant uncertainties and/or questions about the evidence base. It was promising to see there were no instances where there was no technical engagement despite a company request.

Most of the topics concluded with the need for only one committee meeting (see Table 3). The average number of committee meetings was 1.47. In H2 2023/24, there was a decrease in the number of appraisals that required only one committee meeting (31 per cent vs. 71 per cent in H1 2023/24). A potential driver of this could be appraisal committees being increasingly risk averse and preferring to go to second committee meetings before making a decision. Resolving some uncertainties/questions at the technical engagement stage can support better use of committee meeting time and ensure focus on what matters to the committee decision-making. In each of the five topics where companies reported technical engagement helped to resolve key issues, just one committee meeting was required.

Table 3: Number of topics with technical engagement and number of appraisal committee meetings needed to conclude each topic

Technical engagement	ABPI CONNIE analysis H2 2022/23, topics (%)	ABPI CONNIE analysis H1 2023/24, topics (%)	ABPI CONNIE analysis H2 2023/24, topics (%)	ABPI CONNIE analysis total, topics (%)
Technical engagement helped to resolve key issues	0 (0%)	4 (24%)	1 (8%)	5 (13%)
Technical engagement resolved some issues	4 (44%)	8 (47%)	4 (31%)	16 (41%)
Technical engagement didn't resolve issues	1 (11%)	3 (18%)	4 (31%)	8 (21%)
No technical engagement (agreed by company)	4 (44%)	2 (12%)	4 (31%)	10 (26%)
No technical engagement (despite company request)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)
Appraisal committee meetings	**ABPI CONNIE analysis H2 2022/23, topics (%)**	**ABPI CONNIE analysis H1 2023/24, topics (%)**	**ABPI CONNIE analysis H2 2023/24, topics (%)**	**ABPI CONNIE analysis total, topics (%)**
1	5 (56%)	12 (71%)	4 (31%)	21 (54%)
2	1 (11%)	4 (24%)	8 (62%)	13 (33%)
3	1 (11%)	1 (6%)	0 (0%)	2 (5%)
Left blank	2 (22%)	0 (0%)	1 (8%)	3 (8%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)
Average number of committee meetings	1.43	1.35	1.67	1.47

4. Severity modifier

One of the biggest changes made in the updated HTE Manual was the removal of the end-of-life modifier and its replacement with a new severity modifier. The ABPI supported broadening NICE's definition of 'severity' beyond just imminently life-threatening conditions.

However, in the absence of evidence to clearly define the magnitude of societal value for health benefits in severe diseases, the severity modifier was implemented in an opportunity cost neutral way and designed to have an overall magnitude similar to that applied under the end-of-life modifier for its initial implementation until it could be evolved further using an evidence-based approach informed by research.

In NICE's retrospective analysis (of 364 decisions between January 2011 and November 2019), approximately 18 per cent received the end-of-life QALY weighting (x1.7).[13] In designing the new severity modifier to be opportunity cost neutral, NICE estimated 8.2 per cent of topics should receive the higher QALY weighting, 30.5 per cent should receive the lower QALY weighting and 61.3 per cent should receive no weighting.[14]

This approach caused the ABPI and our members significant concerns, as the proportional and absolute QALY shortfall cut-offs that NICE applied were seen as too challenging to adequately support access to medicines that treat very severe conditions. This ultimately means that patients risk losing access to innovative medicines in England.

Table 4 shows the results for the company-reported utilisation of the severity modifier against NICE's intended design for the severity modifier. Across the sample, 2.2 topics received the higher QALY weighting (x1.7), 5.8 topics received the lower QALY weighting (x1.2), and 29 (78%) topics received no QALY weighting.[15]

Table 4: Percentage of topics applicable for severity modifier when designed, compared to percentage of topics the severity modifier was applied to in its implementation (committee-assigned QALY weights)

Technical engagement	Design	Implementation				
	Severity modifier design (%)	NICE data, topics (%)	ABPI CONNIE analysis H2 2022/23, topics (%)	ABPI CONNIE analysis H1 2023/24, topics (%)	ABPI CONNIE analysis H2 2023/24, topics (%)	ABPI CONNIE analysis total, topics (%)
Higher QALY weight (x1.7)	8.2%	2 (3%)	2 (25%)	0.2 (1%)	0 (0%)	2.2 (6%)
Lower QALY weight (x1.2)	30.5%	11 (17%)	0 (0%)	2.8 (16%)	3 (25%)	5.8 (16%)
No QALY weight (x1.0)	61.3%	51 (80%)	6 (75%)	14 (82%)	9 (75%)	29 (78%)
Total	100%	64 (100%)	8 (100%)	17 (100%)	12 (100%)	37 (100%)

Another way to review whether the modifier is being implemented as opportunity cost neutral is to look at the average QALY weighting granted per topic (Table 5). The average QALY weighting used by NICE to design the severity modifier was 1.119 and the average QALY weighting that was calculated to be opportunity cost neutral to the end-of-life criteria (2009–21) was 1.134. The average QALY weighting in the total CONNIE sample of 1.073 is less than the average QALY weighting under end-of-life and the severity modifier design. Hence, results suggest the severity modifier is being applied on a more conservative basis than needed to deliver opportunity cost neutrality. A severity modifier applied on a more conservative basis than designed risks increasing the number of topics not recommended and therefore restricting access to treatments for patients with severe diseases.

There was strong alignment between the company-proposed, EAG-proposed, and committee-assigned QALY weights (identical in 97 per cent of topics) indicating that, while there are concerns about whether the current cut-offs are set to meet opportunity cost neutrality, there is limited evidence in the results of conflicting views over the application of the modifiers to the existing cut-offs.

Table 5: Average QALY weightings

	Source	Average QALY weighting
Design	NICE methods review analysis (2009–21)	1.134
	NICE methods review analysis (2011–19)	1.125
	Severity modifier design[16]	1.119
Implementation	NICE data[17]	1.056
	ABPI CONNIE analysis total	1.073
	ABPI CONNIE analysis H2 2022/23	1.175
	ABPI CONNIE analysis H1 2023/24	1.041
	ABPI CONNIE analysis H2 2023/24	1.050

The ABPI does not believe there has been any change to the mix of the severity of conditions ('case mix') being assessed by NICE to explain why there is a lower number of medicines benefiting from the weighting than expected. This is supported by NICE's analysis of average QALY weighting, which showed no clear trend over time from 2009 to 2021. It is considered extremely unlikely that the underutilisation of the severity modifier is explainable by a sudden change in case mix of severity across the past two years since the introduction of the new HTE Manual.

Given that the severity modifier replaced the oncology-specific end-of-life criteria, the application of the severity modifier in oncology topics is of particular interest. Under end-of-life, oncology topics had an average QALY weighting of 1.297 (Table 6). Under NICE's design for the severity modifier, oncology topics were designed to have an average QALY weighting of 1.220. At the time, industry raised concerns over the impact this loss of QALY weighting would have on patient access for innovative oncology medicines. Of the 18 oncology topics in CONNIE, 2.2 (12.2 per cent) received the higher x1.7 QALY weighting, 4.8 topics (26.7 per cent) received the lower x1.2 QALY weighting and 11 topics (61.1 per cent) received no weighting, which represents an average QALY weighting of 1.139.[14] Of these 18 topics, four (22.2 per cent) ultimately were not recommended by NICE. In five topics (27.8 per cent), companies reported that the topic would previously have been eligible for the end-of-life criteria, representing an average QALY weighting of 1.194. This suggests that for oncology topics, the severity modifier has taken away value that was previously available with the end-of-life modifier. Companies report that this is a key driver for the increased proportion of non-recommended oncology topics in the sample, restricting oncology patient access.

Table 6: Average QALY weighting for oncology topics under end-of-life versus severity modifier design versus CONNIE

	Higher QALY weight (x1.7)	Lower QALY weight (x1.2)	No QALY weight (x1.0)	Average QALY weighting
NICE methods review analysis (2011–19), oncology topics under end-of-life criteria[16]	42.5%	0.0%	57.5%	1.297
NICE methods review analysis (2011–19), oncology topics severity modifier design[16]	17.0%	50.3%	32.7%	1.220
ABPI CONNIE analysis, oncology topics under severity modifier	12.2%	26.7%	61.1%	1.139
ABPI CONNIE analysis, modifier oncology topics would have received under end-of-life criteria	27.8%	0.0%	72.2%	1.194

The ABPI recommends that NICE immediately reviews the severity modifier to adjust downwards the cut-off levels used to determine the degree of severity so that more medicines can benefit. Any changes necessary should be made quickly to ensure that the NHS does not go backwards in serving patients suffering from severe diseases.

The degree to which patient access to medicines for treating patients with severe disease is prioritised relative to less severe disease should represent societal preferences. However, currently, there is no robust evidence-based understanding of these societal preferences. The ABPI recommends that NICE should replace the opportunity cost-neutral approach to implementing the modifier. Instead, NICE should use an approach that is evidence-based and better reflects societal preferences for helping people with severe disease to access innovative treatments.

5. Managing uncertainty

The HTE Manual states:

"6.2.34 The committee will be mindful that there are certain technologies or populations for which evidence generation is particularly difficult because they are:

- *rare diseases*
- *for use in a population that is predominantly children (under 18 years old)*
- *innovative and complex technologies*

In these specific circumstances, the committee may be able to make recommendations accepting a higher degree of uncertainty. The committee will consider how the nature of the condition or technology(s) affects the ability to generate high-quality evidence before applying greater flexibility."[18]

Companies reported four topics (10 per cent) where the committee accepted greater uncertainty and it was clear how it impacted decision-making (Table 7). Of these four topics, greater flexibility was given on two occasions for rarity and on a further two occasions for innovation.

Table 7: Uncertainty management

	H2 2022/23, topics (%)	H1 2023/24, topics (%)	H2 2023/24, topics (%)	Total
Greater acceptance and clear how impacted decision-making	0 (0%)	2 (12%)	2 (15%)	4 (10%)
Claimed to be greater acceptance but unclear how impacted decision-making	1 (11%)	1 (6%)	0 (0%)	2 (5%)
Unsure if greater flexibility/ acceptance of uncertainty was applied	4 (44%)	4 (24%)	2 (15%)	10 (26%)
No flexibility/greater acceptance applied	3 (33%)	10 (59%)	8 (62%)	21 (54%)
Left blank	1 (11%)	0 (0%)	1 (8%)	2 (5%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)

A key result from CONNIE: Round 1 was that no companies reported committees accepting greater uncertainty in the evidence base and it being clear how this had impacted decisions. In response to this NICE maintained committees were making recommendations accepting a higher degree of uncertainty during the confidential part of committee discussions ('Part II' of meetings). The current results do represent an improvement on the previous CONNIE report as the proportion of topics where companies reported they were unsure if greater flexibility/ acceptance of uncertainty was applied decreases with time. However, anecdotal experience from companies suggests this result is driven by improved explicit communication from NICE about existing uncertainty management rather than improved acceptance of uncertainty management from NICE committees. While improved communication from NICE is preferred, it's unlikely to give patients earlier access to innovative new treatments by allowing greater flexibility over decisions, as per NICE's stated aims.

These results cannot be considered reflective of NICE's aims towards a greater acceptance of uncertainty, for the particular circumstances specified and set out in the HTE Manual. For example, only two topics reported committees accepting a higher degree of uncertainty for rarity despite 16 topics being orphan or ultra-orphan indications.

On a number of occasions, companies have reported appraisal committees being increasingly inflexible on uncertainty. When appraisal committees use an incremental cost-effectiveness ratio (ICER) threshold for decision-making, a threshold between £20,000 and £30,000 is used, with the level of uncertainty in an appraisal influencing which decision-making threshold within this range is used. The severity modifier is applied to this ICER threshold. Anecdotal evidence from companies suggests that there has been a recent increase in NICE using a decision-making ICER threshold to the lower end of the £20,000 to £30,000 range based on the level of uncertainty in an appraisal. Companies have suggested that the impact of uncertainty driving to the lower end of the ICER threshold has, in some instances, negated any additional benefit from a severity modifier. This makes cost-effectiveness at a given price more challenging in an appraisal and ultimately impacts patient access.

There remain disparities in positions on the implementation of the acceptance of uncertainty between company-reported results in CONNIE and NICE's findings. The ABPI recommends that NICE works further with industry to understand these disparities. The ABPI wishes to work collaboratively with NICE on potential solutions that may assist committees in making recommendations accepting a higher degree of uncertainty, in line with the HTE Manual.

6. Non-reference case flexibilities

Non-reference case flexibilities

The updated HTE Manual intended to allow greater flexibility in decision-making, where this was deemed appropriate, along with permitting the consideration of a broader evidence base.[19] Companies made a case for non-reference case flexibility in eight topics (21 per cent). Of these eight topics, four (10 per cent) were for a 1.5 per cent discount rate to be applied and two (5 per cent) were for adopting a wider societal perspective (the remaining two were not specified). Despite eight topics making a case for non-reference case flexibilities, none were granted them. Two of these topics went on to be not recommended by NICE.

NICE's decision not to change the reference case discount rate despite an evidence-based case for change was disappointing and something that the ABPI is seeking to resolve. The retention of a 3.5 per cent discount rate in the reference case puts greater emphasis on being able to utilise the non-reference case flexibility. The analysis shows that committees continue not to apply this, and reflects NICE's restrictive criteria for non-reference case discounting. This risks limiting patient access in treatments that have long-term health benefits and societal cost savings outside of the health system.

NICE should bring to life the commitments set out in the HTE Manual to offer non-reference case flexibilities, including allowing relevant topics to use a 1.5 per cent discount rate and a wider societal perspective to allow more patients to benefit from innovative medicines.

Health-related quality of life (HRQoL)

The HTE Manual states the EuroQol five-dimension (EQ-5D) is the preferred measure of HRQoL in adults but recognises it may not be available and/or the most appropriate measure. The EuroQol five-dimension 3 level version (EQ-5D-3L) was used in 12 topics (31 per cent) and the EuroQol five-dimension 5 level version (EQ-5D-5L) was mapped to the EQ-5D-3L in 13 topics (40 per cent). Companies submitted disease-specific instruments to measure HRQoL in two topics (accepted once and rejected once). Companies also submitted vignettes to measure HRQoL in two topics (also accepted once and rejected once). The ABPI is encouraged to see examples of additional flexibilities available to companies and accepted by committees.

Surrogate endpoints

Surrogate endpoints sometimes need to be used to demonstrate treatment effect when final clinical endpoints are unavailable. The HTE Manual recognises this and advises on the type of evidence that should be provided to demonstrate the relationship between the surrogate and final endpoint. Ten topics (26 per cent) used surrogate endpoints for main treatment effect parameter(s), and these were accepted or partially accepted by the committee in nine topics (23 per cent) (see Table 8). Although the sample size is small, it is encouraging to see committees applying flexibility for accepting an increasing number of surrogate endpoints when final endpoints are not available and that companies are providing good quality evidence to demonstrate the surrogate relationship.

Table 8: Surrogate endpoints used for main treatment effect parameter(s)

		H2 2022/23, topics (%)	H1 2023/24, topics (%)	H2 2023/24, topics (%)	Total
No surrogate endpoints submitted		8 (89%)	12 (71%)	9 (69%)	29 (74%)
PFS (for OS)	Submitted and accepted	0 (0%)	2 (12%)	0 (0%)	2 (5%)
	Submitted and partially accepted	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Submitted and not accepted	0 (0%)	1 (6%)	0 (0%)	1 (3%)
Other surrogate endpoints	Submitted and accepted	1 (11%)	2 (12%)	3 (23%)	6 (15%)
	Submitted and partially accepted	0 (0%)	0 (0%)	1 (8%)	1 (3%)
	Submitted and not accepted	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total		9 (100%)	17 (100%)	13 (100%)	39 (100%)

Carer quality of life (QoL)

The majority of topics reported no inclusion of carer QoL (32, 82 per cent) or left the response blank (five, 13 per cent). In the remaining two additional topics, both of which were HSTs, carer QoL was included in ICER calculations and was partially accepted. No topics have reported either the full acceptance of carer QoL or have had the use of carer QoL rejected by NICE committees.

For HST evaluations, the HTE Manual states:

1.2.7 "For highly specialised technologies, the committee will consider the following additional factors in its deliberations around clinical effectiveness: the overall size of the health benefit to patients, and when relevant, carers."

For all evaluations, the HTE Manual states:

4.3.17 "Evaluations should consider all health effects for patients, and, when relevant, carers. When presenting health effects for carers, evidence should be provided to show that the condition is associated with a substantial effect on carer's health-related quality of life and how the technology affects carers."

The ABPI encourages companies, where relevant, to generate and submit evidence to support the evaluation of medicines that impact carer QoL to ensure the full benefit of all health effects can be considered in NICE evaluations, in line with NICE guidance. This should not be limited just to HST topics.

Real-world evidence (RWE)

Another key update to the HTE Manual was to provide more flexibility for considering broader evidence sources used in evaluations. Company experience had previously been that committees have very limited appetite to accept RWE, especially if used to estimate treatment effect. CONNIE captures whether RWE has been used to estimate treatment effect as a) a primary source, b) an adjustor of the primary source, or c) a validator of the primary source.

Companies used RWE as the primary source to estimate treatment effect in two topics (5 per cent) and as a validator of the primary source in nine topics (23 per cent) (Table 9). In these 11 topics, companies reported some degree of acceptance from committees in five (45 per cent) and no acceptance from committees in one topic (9 per cent), with five topics unsure/left blank.

Table 9: RWE used by company

	H2 2022/23, topics (%)	H1 2023/24, topics (%)	H2 2023/24, topics (%)	Total
RWE used to estimate treatment effect – primary source	1 (11%)	1 (6%)	0 (0%)	2 (5%)
RWE used to estimate treatment effect – adjustor of primary source	0 (0%)	0 (0%)	0 (0%)	0 (0%)
RWE used to estimate treatment effect – validator of primary source	3 (33%)	4 (24%)	2 (15%)	9 (23%)
RWE not used to estimate treatment effect	5 (56%)	11 (65%)	10 (77%)	26 (67%)
Left blank	0 (0%)	1 (6%)	1 (8%)	2 (5%)
Total	9 (100%)	17 (100%)	13 (100%)	39 (100%)

A key result from the CONNIE: Round 1 analysis was that there were encouraging signs that NICE's committees are being more accepting of RWE when it is used to estimate treatment effect. Although numbers are small, the current report, in comparison to the CONNIE: Round 1 report, demonstrates a slight drop in companies submitting RWE. Where RWE is submitted by companies, CONNIE results indicate NICE committees are willing to accept the evidence. Where relevant, the ABPI encourages companies to continue to use RWE in NICE evaluations to make the most of flexibilities offered by NICE.

Conclusion

This is the second report in the CONNIE series to monitor the impact of the 2022 HTE Manual. It is of significant concern that the data suggests that the design of the severity modifier is still not being applied in an opportunity cost neutral manner, taking away value that was previously available with the end-of-life modifier and disproportionately impacting cancer medicines. The situation seems to have deteriorated further between CONNIE: Round 1 (to September 2023) and CONNIE: Round 2 (to March 2024).

It will be critical to continue monitoring the application of the severity modifier to understand how many topics it has been applied to (and at which QALY weighting). There is an urgency to complete research to inform further evolution of the modifier. Until this is available, the ABPI recommends the absolute and proportional QALY shortfall cut-offs are adjusted downwards to enable more medicines to benefit from it, in line with NICE's estimates for implementation in an opportunity cost neutral way.

Disappointingly, the results also outline the lack of any utilisation of non-reference case flexibilities of a 1.5 per cent discount rate and a wider societal perspective in topics so far, despite these being requested by companies in eight topics.

However, although the numbers are small, where additional flexibilities for surrogate endpoints, carer QoL and RWE have been utilised, companies have reported mostly positive experiences, which is an encouraging result.

Recommendations

1. The ABPI recommends that NICE immediately reviews the severity modifier to adjust downwards the cut-off levels used to determine the degree of severity so that more medicines can benefit. Any changes necessary should be made quickly to ensure that the NHS does not go backwards in serving patients suffering from severe diseases.
2. ABPI recommends that NICE should replace the opportunity cost-neutral approach to implementing the modifier. Instead, NICE should use an approach that is evidence-based and better reflects societal preferences for helping people with severe disease to access innovative treatments.
3. There remain disparities in positions on the implementation of the acceptance of uncertainty between company-reported results in CONNIE and NICE's findings. The ABPI recommends that NICE works further with industry to understand these disparities. The ABPI wishes to work collaboratively with NICE on potential solutions that may assist committees in making recommendations accepting a higher degree of uncertainty, in line with the HTE Manual.
4. NICE should bring to life the commitments set out in the HTE Manual to offer non-reference case flexibilities, including to allow relevant topics to use a 1.5 per cent discount rate and a wider societal perspective to allow more patients to benefit from innovative medicines.

5. Given mostly positive experiences reported by companies when using broader methods flexibilities – such as surrogate endpoints, carer QoL and RWE – companies should explore all opportunities to use the flexibilities offered. We recommend that NICE continues to work with companies to encourage their use where appropriate.
6. NICE should regularly report on the impact of its methods (and process) changes and duly consider the need for further, timely evolution of the HTE Manual within the new modular update process. The ABPI recommends that the modular update process is brought to life as soon as possible in line with VPAG commitments and NICE should publish clear timelines for when the first updates will be considered and delivered.

The ABPI will continue working with its members to collect feedback and help support NICE's monitoring of the impact of the key changes made in the HTE Manual.

We would like to thank our members for supporting us with evidence generation and NICE for continuing to engage in a collaborative way to support our joint ambition to ensure the methods and processes used to evaluate technologies enable timely patient access to clinically and cost-effective medicines.to evaluate technologies enable timely patient access to clinically and cost-effective medicines.

Endnotes

1 NICE, 'NICE publishes new combined methods and process manual and topic selection manual for its health technology evaluation programmes', January 2022, available at https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/changes-to-health-technology-evaluation

2 HM Government, 'Life Sciences Vision', 2021, available at https://www.gov.uk/government/publications/life-sciences-vision

3 To find out more about CONNIE, please contact the ABPI's Value and Access team.

4 NICE, 'NICE health technology evaluations: the manual', 31 January 2022, available at https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

5 NICE, 'NICE publishes new combined methods and process manual and topic selection manual for its health technology evaluation programmes', 31 January 2022, Available at https://www.nice.org.uk/news/articles/nice-publishes-new-combined-methods-and-processes-manual-and-topic-selection-manual-for-its-health-technology-evaluation-programmes

6 ABPI, 'ABPI analysis on NICE's changes for evaluating new medicines: Next steps', 31 January 2022, available at https://www.abpi.org.uk/media/blogs/2022/january/abpi-analysis-on-nice-s-changes-for-evaluating-new-medicines-next-steps

7 To find out more about CONNIE, please contact the ABPI's Value and Access team.

8 Recent data demonstrates the EFPIA 2024 Patient W.A.I.T. Indicator. https://efpia.eu/news-events/the-efpia-view/efpia-news/new-data-from-efpia-reveals-multiple-factors-leading-to-unequal-access-to-medicines-for-patients-across-europe/

9 ABPI, ABPI CONNIE: Round 1, 18 December 2023, available at https://www.abpi.org.uk/publications/reviewing-the-impact-of-the-updated-nice-health-technology-evaluation-manual-connie/

10 All percentages represent proportion of total CONNIE sample (n=39) unless otherwise stated.

11 ABPI analysis of NICE Technology Appraisal Outcome data available on the NICE website, May 2024. The analysis includes terminated NICE appraisals.

12 NICE, 'NICE health technology evaluations: the manual', 31 January 2022, available at https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

13 NICE, 'Review of methods for health technology evaluation programmes: proposals for change', August 2021.

14 Proportional QALY shortfall (PS) must be between 0.85 and 0.95 or absolute QALY shortfall (AS) must be between 12 and 18 for a medicine to receive a x1.2 QALY weighting. PS must be at least 0.95 or AS must be at least 18 for a medicine to receive a x1.7 QALY weighting.

15 One topic was split based on population subgroups with 1/5 subgroups receiving the higher QALY weighting (x1.7) and 4/5 subgroups receiving
the lower QALY weighting (x1.2). Where fractions of appraisals are reported, this represents differing severity modifiers applied to subpopulations within an appraisal.

16 NICE, 'Review of methods for health technology evaluation programmes: proposals for change', August 2021.

17 Taken from NICE analysis on appraisal topics that have been to NICE committee until December 2023. Analysis includes 64 topics, of which 46 have had final guidance published.

18 NICE, 'NICE health technology evaluations: the manual', 31 January 2022, available at https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

19 NICE, 'NICE publishes new combined methods and process manual and topic selection manual for its health technology evaluation programmes', 31 January 2022, available at https://www.nice.org.uk/news/articles/nice-publishes-new-combined-methods-and-processes-manual-and-topic-selection-manual-for-its-health-technology-evaluation-programmes

The Association of the British Pharmaceutical Industry

A company limited by guarantee registered in England & Wales number 09826787

Registered office 2nd Floor Goldings House, Hay's Galleria, 2 Hay's Lane, London, SE1 2HB

COM-0173-0724