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REVIEW

A review of methodological aspects of economic evaluations used in NICE assessments for treatments in metastatic breast cancer

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ABSTRACT

Introduction: Methodological choices need to be made during model development. These choices can influence the outcome of a National Institute for Health and Care Excellence (NICE) assessment.

Areas covered: This review aims to identify, assess, and describe possible trends within the methodological aspects of economic evaluations used in NICE assessments of treatments for metastatic breast cancer (mBC). The NICE website was searched to identify technology appraisals submitted between 1 January 2009, and 31 December 2023. In this review methodological aspects are analyzed and discussed in three clusters – input data, model settings, and model outcomes – across the following characteristics: clinical trial information, quality-of-life measures, treatments used, model structure, health states, time horizon, threshold applied, and the NICE recommendations. This review provides a reference for stakeholders who want to understand previous NICE assessments of treatments for mBC, and the settings used in those, which can optimize decisions during model development.

Expert opinion: Uniformity in the methodological choices made during model development and the economic evaluations can increase transparency, increase comparability, and reduce complexity of the NICE assessment.

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KEYWORDS
Cost-effectiveness models; economic evaluations; health technology assessment; metastatic breast cancer; national institute for health and care excellence; review

1. Introduction

In the United Kingdom (UK), people have a 30% risk of developing cancer before the age of 75, with breast cancer remaining the most common cancer site with 58,756 new cases and 12,122 deaths in 2022 [1]. Approximately 61,000 people are living with metastatic breast cancer (mBC) in the UK and a recent study showed that the number of patients living with mBC is increasing, as demonstrated, for instance, by data from England [2,3]. Due to the remaining prevalence of mBC in the UK the treatment landscape for breast cancer keeps evolving [4].

A cost of incidence model using Cancer Research UK data estimated that the lifetime costs of newly diagnosed breast cancer patients in 2024, will cost the UK economy £2.6 to £2.8 billion, of which £727 million are National Health Service treatment and screening costs [5]. The National Institute for Health and Care Excellence (NICE) assesses whether a new intervention is a cost-effective use of the UK's resources. The time to reimbursement for a new intervention can be long, and the duration of a technology appraisal for treatments varies. To estimate the economic impact of new interventions, manufacturers submit cost-effectiveness analyses, which are then assessed by NICE. The results of these economic evaluations play a key role in the duration of the NICE assessments and the resulting NICE recommendation.

Outcomes of the economic evaluations are treatment-specific and highly dependent on clinical trial results used as input. However, methodological choices made when developing economic models for these evaluations, while substantiated, are not uniform. Importantly, these choices can also influence the outcome of a NICE assessment and achieving uniformity in these choices could optimize the methods of economic evaluations. Therefore, this research aims to identify, assess, and describe possible trends within the methodological aspects of economic evaluations used in NICE assessments of treatments for mBC.

2. Methods

2.1. Evidence generation

A systematic search was performed to identify NICE assessments relevant to our objective. The NICE website (nice.org.uk) was searched on 26 June 2024, using the term

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Article highlights

- This review found consensus in the model inputs by using evidence from a phase 3 RCT and using the EQ-5D questionnaire as the basis for HSUV.
- A partitioned survival model is the most frequently used model type for mBC, especially in the most recent years. Most models used the PFS, PP, and death health states with a lifetime horizon.
- Besides the use of EQ-5D data in economic evaluations, none of the analyzed characteristics showed a clear positive or negative impact on the NICE recommendation.
- The uniformity in methodological choices found in this review can increase transparency, increase comparability, and reduce complexity of the NICE assessment.

'metastatic breast cancer,' with the 'technology appraisal guidance' filter applied [6]. All technology appraisals with any recommendation ('not recommended' was also considered a recommendation) for an indication of mBC were included. Technology appraisals submitted to NICE between 1 January 2009, and 31 December 2023, were included to create an overview of technology appraisals in the past 15 years. Technology appraisals that were terminated, in development, or unavailable were excluded.

2.2. Data extraction

Data extraction was performed in Microsoft Excel by an initial set of researchers and subsequently verified and adjusted by another group. To gather the necessary data, an extraction table was created and continuously adjusted. The final appraisal document and committee papers were used as main source of information. When data was not available there, other documents were searched.

2.3. Analysis

The extracted data was analyzed in three clusters of characteristics – input data, model settings, and model outcomes. The cluster of input data included information on the clinical trials (phase II or phase III trial; single arm or double arm; use of immature overall survival (OS) data – defined as median not reported), information on the quality-of-life measurement (which was used to calculate health state utility values [HSUV] for the model) and study treatment and comparators (used in the trial; and used in the submission). The model settings cluster assessed information on the model structure (partitioned survival models, state transition models – including Markov models, semi-Markov models, state-transition models, or time-in-state models—, and other model types) the health states considered in the model (the number of health states; and which health states), and the time horizon (lifetime or based on trial duration; and length in years). The cluster for model outcomes focused on the threshold applied (stratified by line of treatment) and the final reimbursement recommendation (positive or negative recommendation).

3. Results

3.1. Selection of NICE assessments

A total of 87 technology appraisals were identified through the systematic search of the NICE website. Of those, 38 were excluded due to termination or ongoing development, 2 for being published before 2009 and 4 for being published after 2023. Another, 15 technology appraisals were excluded because they did not assess an mBC indication, and 5 were unavailable. One technology appraisal assessed two treatments for mBC separately, therefore, this technology appraisal is counted as two separate NICE assessments. In total, 24 NICE assessments were included for data extraction [7–29]. A flow diagram of the selection process; an overview of the included NICE assessments; and specific exclusion reasons per technology appraisal are provided in online resource 1.

3.1.1. Input data

3.1.1.1. Clinical trial. Most commonly (22; 92%) manufacturers submitted evidence from a phase 3 clinical trial – all of which were double-armed – as a basis of the efficacy in their economic evaluations (Figure 1). A phase 2 trial was submitted twice (8%) as that basis: one was a single-arm trial, and the other was a double-arm trial. Immature OS data was used in 21% (5) of the economic evaluations and was only used after 2016.

3.1.1.2. PRO measurement. Across the study period, the EuroQol 5D (EQ-5D) questionnaire was the most frequently used measure to calculate HSUV for the economic evaluation (63%; 15/24). None of the evaluations used the EQ-5D questionnaire before 2013; prior to that year, literature was the main source for HSUV with Cooper et al. (2003) and Lloyd et al. (2006) used most frequently [30,31]. After 2013, EQ-5D was utilized in 88% (15/17) of the economic evaluations. In the economic evaluations where EQ-5D was used, it was mapped data in 67% (10/15): in three economic evaluations another quality-of-life measure, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items (i.e. EORTC QLQ-C30), was mapped to EQ-5D; and in seven economic evaluations, the EQ-5D five level (i.e. EQ-5D-5 L) was mapped to the EQ-5D three level (i.e. EQ-5D-3 L).

3.1.1.3. Trial compound and comparator. In all NICE assessments the compound studied in the clinical trial was aligned with the compound assessed in the submission. The comparator studied in the clinical trial was aligned with the comparator used in the economic evaluations in 42% (10) of the NICE assessments. In the remaining NICE assessments, the comparator was adjusted in several ways. It was broadened through an indirect treatment comparison (ITC) in 33% (8), aligned by using comparators more relevant to UK clinical practice in 13% (3), aligned by excluding irrelevant comparators from the comparator arm in 8% (2), and in 4% (1) the

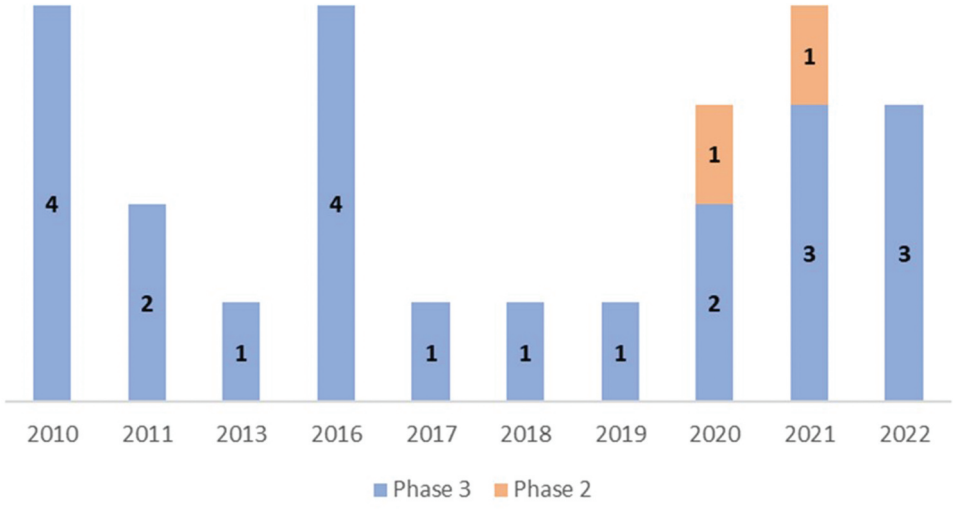

Figure 1. Number of phase 3 and phase 2 trials submitted as clinical evidence to NICE.

clinical trial was single arm, and a comparator for submission had to be selected (Figure 2).

3.2. Model settings

3.2.1. Model type

Table 1 shows that the partitioned survival model was the most frequently used model type in economic evaluations of mBC (14; 58%) followed by state-transition models (8; 33%). Other models used were a partitioned survival Markov model (1; 4%) or a cost comparison model (1; 4%). Over the years, an increase in the use of the partitioned survival model can be observed, with the partitioned survival model being used in 73% (8/11) of the models since 2017, compared to only 46% (6/13) prior to or in 2017.

3.2.2. Health states

The most common health states were a combination of progression-free survival (PFS), post-progression (PP), and death. These health states were used in 20 (83%) economic evaluations, regardless of model type (Figure 3). Since definitions differed between NICE assessments, economic evaluations using slight variations of the progression-free health state (i.e. two economic evaluations used stable disease and one used 'treated,' which was classified as comprising both stable and responsive patients) were considered equivalent to PFS. Three NICE assessments used four health states instead of three: two added PFS2, and one used on- or off treatment. One model, a cost comparison model, did not use health states.

3.2.3. Time horizon

A lifetime horizon was applied in 92% (22) of the economic evaluations. Time horizons based on trial duration were used in 8% (2). Moreover, the length of the time horizon seems to be increasing over time, with a dip in 2019, when there was only one economic evaluation that used a time horizon of 15 years (Figure 4).

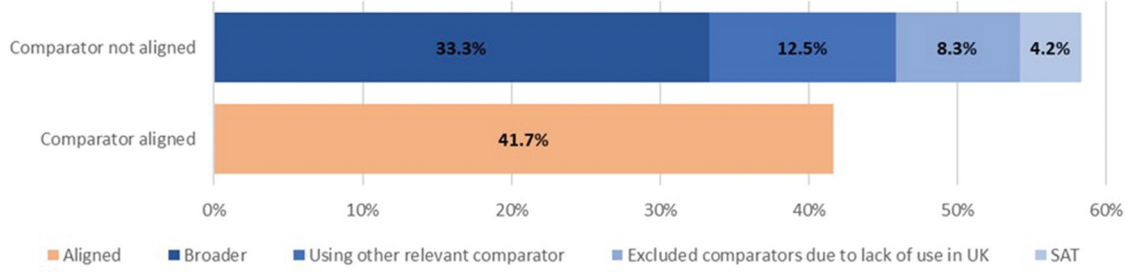

Figure 2. Alignment of comparators between clinical study and NICE submission.
Abbreviations: SAT, single-arm trial.

Table 1. Model type used in NICE assessments stratified by year of submission.

Model type	2010	2011	2013	2016	2017	2018	2019	2020	2021	2022	Total (%)
Partitioned Survival model	2	0	1	2	1	0	1	2	4	1	14 (58)
State transition model	2	2	0	1	1	1	0	1	0	0	8 (33)
Partitioned survival Markov model	0	0	0	1	0	0	0	0	0	0	1 (4)
Cost comparison	0	0	0	0	0	0	0	0	0	1	1 (4)

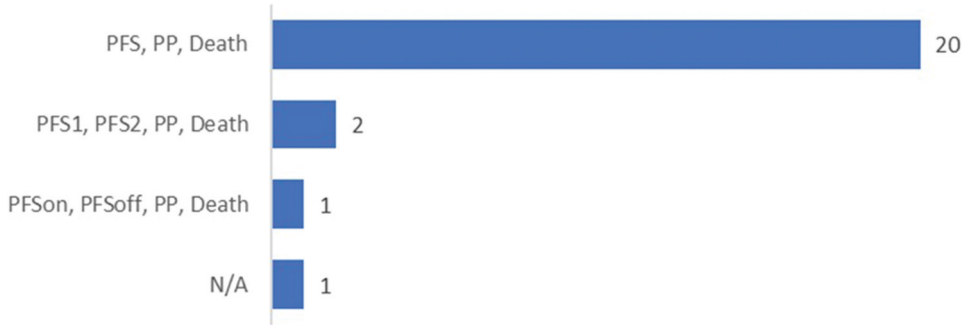

Figure 3. Health states used in the economic evaluations.

Abbreviations: N/A, not applicable; PFS, progression-free survival; PP, post progression.

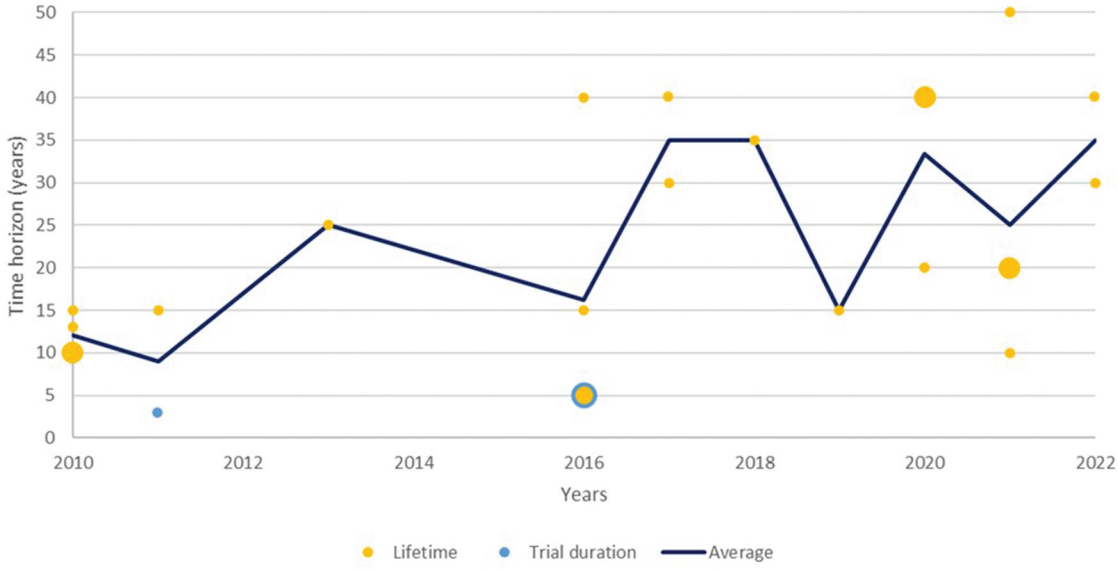

Figure 4. The average length of time horizons used in NICE assessments over time.

Average length of time horizons is represented by the blue line (—). Each yellow dot (•) represents a lifetime time horizon; each blue dot (•) represents a time horizon based on trial duration. Larger dots represent two time horizons in the same year with the same length; the yellow dot with a blue outline (i.e. 2016, time horizon 5 years) represents two time horizons with the same length, one using lifetime, one using trial duration.

3.3. Model outcomes

3.3.1. Threshold

The main result of most economic evaluation is an incremental cost-effectiveness ratio (ICER) assessed against a threshold, which determines cost-effectiveness. No clear trends were observed over time with regard to the thresholds used. The most common thresholds in the NICE assessments were £50,000 per quality-adjusted life year (QALY) and £30,000 per QALY used in 50% (12) and 30% (7) of economic evaluations, respectively (Figure 5).

3.3.2. NICE recommendation

Table 2 shows the positive and negative recommendations from NICE per investigated characteristic of the included NICE assessments. No trend could be identified over time. Moreover, there is no clear association between the NICE recommendation and clinical trial set-up (i.e. double arm or single arm, phase II or phase III, immaturity of data, comparator alignment with NICE submission) nor between model type, health states used, or threshold used and NICE recommendation. Using EQ-5D in the economic evaluation seems to be associated with a positive recommendation of NICE.

Generally, NICE has more frequently given a positive recommendation 63% (15) than a negative recommendation 38% (9). Furthermore, NICE has issued no more than one negative recommendation each year, except for the year 2010, when four negative recommendations were made.

4. Discussion

Based on our analysis of NICE assessments from 1 January 2009, to 31 December 2023, uniformity in methodological choices can be found: a partitioned survival model with three health states (PFS, PP, Death), and a lifetime horizon should be used with phase 3 double-arm clinical trial and EQ-5D data, where manufacturers should expect at least a threshold of £36,000 per QALY. These results show there is potential to explore a disease-specific model template for mBC economic evaluations, since there is sufficient overlap

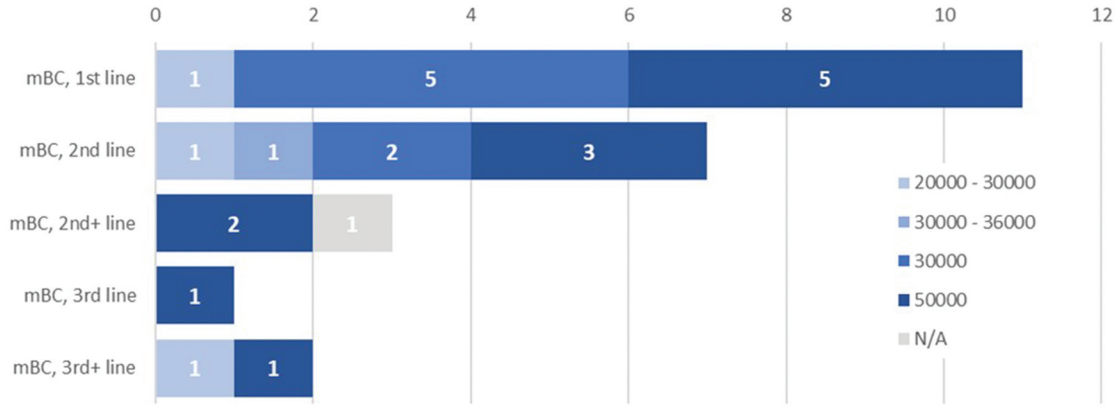

Figure 5. Different thresholds used in the assessment of different lines of treatment.

Abbreviations: mBC, metastatic breast cancer; N/A, not applicable.

Table 2. NICE recommendations based on subgroups of NICE assessments characteristics.

	Negative recommendation n (%)	Positive recommendation n (%)	Total n
Total	9 (38)	15 (63)	24
Year of NICE submission			
<2015	5 (71)	2 (29)	7
2015–2018	2 (29)	5 (72)	7
2019–2022	2 (20)	8 (80)	10
Clinical trial phase			
Phase 2	1 (50)	1 (50)	2
Phase 3	8 (36)	14 (64)	22
Clinical trial design			
Single arm	1 (100)	0 (0)	1
Double arm	8 (35)	15 (65)	23
Immature OS data used			
Yes	3 (60)	2 (40)	5
No	6 (33)	12 (67)	18
Unavailable[a]	0 (0)	1 (100)	1
EQ-5D used			
Yes	4 (27)	11 (73)	15
No	5 (63)	3 (38)	8
N/A	0 (0)	1 (100)	1
Comparator aligned with clinical study?			
Yes	3 (30)	7 (70)	10
No	1 (17)	5 (83)	6
Broader	5 (63)	3 (38)	8
Model type			
Partitioned survival model	6 (43)	8 (57)	14
State-transition model	3 (38)	5 (63)	8
Partitioned survival Markov model	0 (0)	1 (100)	1
Cost-comparison model	0 (0)	1 (100)	1
Number of health states			
3	8 (40)	12 (60)	20
4	1 (33)	2 (67)	3
N/A	0 (0)	1 (100)	1
Health states used			
PFS, PP, Death	8 (40)	12 (60)	20
Other	1 (25)	3 (75)	4
Time horizon length (years)			
0–10	3 (50)	3 (50)	6
11–20	3 (38)	5 (63)	8
21–30	2 (67)	1 (33)	3
31–40	1 (17)	5 (83)	6
41–50	0 (0)	1 (100)	1
Threshold (per QALY)			
£20,000 – £30,000	2 (67)	1 (33)	3
£30,000 – £36,000	1 (100)	0 (0)	1
£30,000	1 (14)	6 (86)	7
£50,000	5 (42)	7 (58)	12
N/A	0 (0)	1 (100)	1

[a]Unavailable due to confidentiality.

Abbreviations: EQ-5D, EuroQol 5D; N/A, not applicable; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PP, post progression; QALY, quality-adjusted life year.

between economic evaluations. A disease-specific model template could create consistency within the economic evaluations and reduce the duration of a NICE assessment by increasing familiarity with the model, reducing time for quality assessment of the model, and increasing comparability between NICE assessments. However, it also reduces flexibility, which can limit stakeholders to provide a good reflection on their interventions in clinical practice, especially with innovative interventions. Moreover, it reduces incentive to explore innovation in economic evaluations. More research and, importantly, discussion with all stakeholders involved is needed to understand if this review can contribute to a disease-specific model template.

To provide a streamlined process for NICE assessments, and ensure high-quality submissions, NICE has published a manual on health technology evaluations, which states a strong preference for high-quality randomized controlled trials (RCTs) for relative treatment effects – as RCTs minimize potential external influences when identifying the effect of one or more interventions on outcomes [32]. Phase 3 RCTs are the standard to evaluate the efficacy of one intervention versus another. As expected, most NICE assessments therefore use results of a phase 3 RCTs in their submission to NICE, a phase 2 trial was only used in two NICE assessments. Moreover, only once was a single-arm trial used as the main trial result to show the efficacy of an intervention. Meaning that, even though the increase of targeted treatments in oncology could warrant a rise of single-arm trials with smaller patient populations, the phase 3 double-arm RCT remains the golden standard.

Furthermore, our review found that the comparator used in the NICE assessments does not need to be aligned with the comparator from the clinical trial, as this was found in more than half of the NICE assessments. Most often, when unaligned, the comparator is broadened by using an ITC. Other times, it is narrowed by eliminating certain interventions from the comparator arm or a different comparator is selected. The most likely explanation is that, since mBC is a well-known disease area with multiple potential treatment options, it is not always possible to conduct a globally coordinated trial comparing the new intervention versus the standard of care in the UK. Therefore, adjustments specific to the UK must be made for the submissions to NICE. Importantly, our results did not find a negative or positive association between adjusting the comparator and the NICE recommendation.

Given the need for consistency across economic evaluations, NICE has stated that the EQ-5D is the preferred method to measure health-related quality of life in adults, recommending its use to generate utility values for economic evaluations [32]. Our results show that following the publication of the guide to the methods of technology appraisal in 2013, EQ-5D became the standard in NICE assessments in mBC [33]. Interestingly, EQ-5D had already been the preferred method of measuring health-related quality of life for NICE since 2008, but it did not have the same influence [34]. EQ-5D use is associated with a higher chance of a positive NICE-recommendation.

State-transition models and partitioned survival models are frequently used in NICE assessments for oncology drugs, accounting for 54% and 41%, respectively [35]. Comparable results were observed in our selection of NICE assessments for mBC. In 2017, NICE published technical support document (TSD) 19, reviewing the use of partitioned survival modeling for healthcare decision-making [36]. Even though TSD19 does not recommend using either partitioned survival modeling or state-transition modeling as a standard, our results suggest that the publication of TSD19 influenced the use of partitioned survival analysis in a favorable way, as we see an increase in its use after 2017.

Since PFS and OS are common outcome measures in clinical trials assessing new interventions in oncology, models with health states based on progression will be most suitable to model clinical practice. Our results confirm that economic evaluations in mBC use progression-based health states, with a three-state model using PFS, PP, and death being the most common.

Following the NICE reference case, the time horizon in economic evaluations should be '*long enough to reflect all important differences in cost or outcomes between the different technologies being compared*' [32]. Given the stage of mBC, treatments are palliative, which creates the need for lifetime horizons to capture all relevant differences between technologies. Our results confirm that lifetime horizons are used in the majority of the economic evaluations. Interestingly, they also show a trend in absolute years of the time horizon, with lifetime horizons becoming longer over time. The absolute increase of years lived in a lifetime horizon suggests patients' improved survival.

Improved survival also suggests that clinical trial duration needs to increase to obtain mature enough clinical data to use in regulatory and reimbursement processes or that less mature data will be used in these processes. Our review indeed shows an increase of immature OS data used after 2016. A review by Bell Gorrod et al. in 2019 showed that the evidence review group criticized survival functions in 71% of the NICE assessments, giving a mature survival function as one of the reasons why little or no discussion occurred [37]. This suggests that the opposite is also true; an immature survival function leads to more discussion. A limitation of the partitioned survival models arises when long-term OS extrapolations are unsure, due to the fact that the PP health state is partially determined by OS. Moreover, PFS and OS extrapolations can lead to implausible predictions (e.g. PFS crosses OS) [36]. Therefore, a state-transition model, with a structural link between PFS and OS, could optimize the technology appraisal process better. However, immature data will always result in uncertain predications, regardless of the model structure [36]. Our results show that both model types are used with immature OS.

A new intervention will be deemed cost-effective when the ICER lies beneath a threshold of £20,000 to £30,000 per QALY. Based on end-of-life criteria this threshold could change to £50,000 per QALY and based on the current disease severity modifier it can change to either £36,000 or £51,000 per QALY – based on disease severity modifier of 1.2x or 1.7x, respectively [32]. Njoroge et al. (2024) found that NICE assessments with the end-of-life threshold applied were more likely to be eligible for a disease severity modifier [38]. Our results show that in NICE assessments for

treatments of mBC commonly use the £50,000 per QALY threshold, suggesting mBC is usually regarded as end-of-life. Thus, a multiplier is expected to be applied to the threshold in most NICE assessments for treatments of mBC in the future. However, given our limited scope, no statements can be made on the level of the multiplier that will be used. Noteworthy, our results did not show a clear association between lines of treatment and a higher threshold.

Overall, the 24 identified NICE assessments were able to generate valuable insights for most of the characteristics assessed. However, this study does not show definite trends and the characteristics that were evaluated in this study – input data, model settings, and used threshold – do not show a direct association with the NICE recommendation and the methodological choices were not criticized in final appraisal documents when NICE gave negative recommendations. This review is limited in its focus on the final appraisal document and committee papers, where ERG critique could potentially be more associated with the NICE recommendation. More research should be performed to better understand the importance and impact of all relevant characteristics in economic evaluations as other factors like cost-effectiveness outcomes and model parameters (e.g. survival extrapolations, treatment costs, HSUV) are expected to be the main influencers of NICE recommendations. Furthermore, some identified insights might be representative for other countries too, since country-specific models are usually adapted from a global model, however future research with similar analyses in other countries with a cost-effectiveness focus can be done to generate truly global insights.

Using the previous NICE assessments to guide decisions during model development should be done with caution. This research gives examples of changing guidelines from end-of-life criteria to a disease severity modifier to determine the threshold as well as the publication of the guide to the methods of technology appraisal in 2013, which resulted in establishing EQ-5D as the standard method to generate utility values for the economic evaluations. Guidelines can be updated and should always be adhered to.

Multiple studies published in recent years have focused on selected characteristics of NICE assessments. Rose et al. assessed the consistency of breast cancer utility values in NICE assessments with NICE-preferred methods [39]. Njoroge et al. evaluated the impact of the NICE severity modifier [38]. Bell Gorrod et al. and Gallacher et al. assessed the survival methods used in NICE assessments [37,40]. However, to the knowledge of the authors, this is the first study that assessed methodological aspects of economic evaluations in mBC NICE assessments with the aim of identifying, assessing, and describing possible trends.

5. Conclusion

This study provides a reference for stakeholders who want to understand previous NICE assessments of treatments for mBC, and their settings used, which can optimize decisions during model development. In the economic evaluations assessed the EQ-5D was used to calculate HSUV in 63% of appraisals, a partitioned survival model was used in 58%, three health states (PFS, PP, Death) were used in 83%, and a lifetime horizon was used in 92%. From this we conclude that – following NICE assessments from 1 January 2009, to 31 December 2023—uniformity can be achieved by using a partitioned survival model with three health states (PFS, PP, Death), and a lifetime horizon, with phase 3 double arm clinical trial and EQ-5D data, where manufacturers should expect at least a threshold of £36,000 per QALY.

6. Expert opinion

New innovative therapies have contributed to a rapidly growing market for mBC treatments. However, a need for new innovative therapies remains, as mBC still is a common cancer site with a high mortality [1]. In certain countries, these innovative interventions are not only assessed for reimbursement based on their clinical effectiveness but also on their cost-effectiveness.

NICE is one of the leading, most influential, health technology assessment (HTA) bodies performing these assessments, with a core role for economic evaluations and the cost-effectiveness [41]. Given that the guidelines are broadly written and include multiple possibilities for those economic evaluations, there are various methods to model the cost-effectiveness of new interventions. Thus, methodological choices need to be made during the development of these economic evaluations, which can influence the outcome of the NICE assessments. NICE assessments are comprehensively reported and publicly available, making them a useful source to perform a review on these methodological choices and their impact.

The fact that methodological choices are made during model development, will result in structural uncertainties of the results, especially the choice of model structure [36]. Therefore, there can be merit in achieving uniformity in the methodological choices made during model development. This review showed that there is an overlap in the economic evaluations, and the methodological choices, but it also showed differences. It also revealed that none of the analyzed characteristics showed a clear positive or negative impact on the NICE recommendation. Nevertheless, this research can provide an initial reference for stakeholders who want to develop an economic model for mBC that is uniform to models previously assessed by NICE. This review can therefore help to optimize future model development for mBC through increased familiarity with the optimized model for HTA bodies, faster model development, and uniformity and transparency of HTA assessments.

That impact can be increased by future research that aims to understand the arguments behind the methodological choices that were made during model development. Moreover, insights into aspects of economic evaluations, outside of methodological characteristics – for example, efficacy outcomes included in the evaluations – should be researched to truly guide future economic evaluations, as these aspects are expected to be the main influencers of the NICE recommendation. Another focus area for future research is the

development of a disease-specific model for NICE assessments of interventions in mBC. This could improve transparency of the models and create consistency within the economic evaluations. Moreover, such a template could increase comparability of the evaluations and potentially improve the time-to-patient access.

In the future, a disease-specific model template for mBC that can be used for NICE assessments can be considered. Authors expect that such a disease-specific model template for mBC will be thoroughly researched and implemented within some HTA bodies. Broader research into additional HTA assessments can reveal international differences and similarities and can extent the development of a disease-specific model template toward international collaborations.

Declarations of interest

J Paulissen and N Postma were employees of Asc Academics at the time the research was conducted. J Paulissen is currently employed by Daiichi Sankyo Nederland B.V. S Wolters and A Postma are paid employees of Asc Academics. M Postma is advisor to Asc Academics. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Author contribution

All authors contributed to the study's conception and design. Data collection was performed by **J Paulissen**, **S Wolters**, **A Postma**, and **N Postma**. Material preparation and analysis were performed by **J Paulissen** and **S Wolters**. The first draft of the manuscript was written by **J Paulissen** and all authors were involved in the revision of the manuscript. All authors read and approved the final manuscript.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers

1. Ferlay J, Ervik M, Lam F, et al. Global cancer observatory: cancer Today. [Internet]. 2024 [cited 2024 Nov 8]. Available from: https://gco.iarc.who.int/today
2. Breast cancer now. Breast cancer facts and statistics [Internet]. [cited 2024 Jun 21]. Available from: https://breastcancernow.org/about-us/why-we-do-it/breast-cancer-facts-and-statistics/#breast-cancer-in-the-uk-2024
3. Palmieri C, Owide J, Fryer K. Estimated prevalence of metastatic breast cancer in England, 2016–2021. JAMA Netw Open. 2022;5(12):e2248069. doi: 10.1001/jamanetworkopen.2022.48069
4. Miglietta F, Bottosso M, Griguolo G, et al. Major advancements in metastatic breast cancer treatment: when expanding options means prolonging survival. ESMO Open. 2022;7(2):100409. doi: 10.1016/j.esmoop.2022.100409
5. Bush L, Misak J, Macdonald S. The cost of breast cancer [Internet]. 2024 [cited 2024 Nov 8]. Available from: https://www.demos.co.uk
6. National Institute for Health and Care Excellence [Internet]. [cited 2024 Jun 26]. Available from: https://www.nice.org.uk
7. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 1 or more anti-HER2 treatments | TA862 [Internet]. 2023 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta862
8. National Institute for Health and Care Excellence. Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy | TA836 [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta836
9. National Institute for Health and Care Excellence. Sacituzumab govitecan for treating unresectable triple-negative advanced breast cancer after 2 or more therapies | TA819 [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta819
10. National Institute for Health and Care Excellence. Alpelisib with fulvestrant for treating hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced breast cancer | TA816 [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta816
11. National Institute for Health and Care Excellence. Pembrolizumab plus chemotherapy for untreated, triple-negative, locally recurrent unresectable or metastatic breast cancer | TA801 [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta801
12. National Institute for Health and Care Excellence. Tucatinib with trastuzumab and capecitabine for treating HER2-positive advanced breast cancer after 2 or more anti-HER2 therapies | TA786 [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta786
13. National Institute for Health and Care Excellence. Abemaciclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy | TA725 [Internet]. 2021 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta725
14. National Institute for Health and Care Excellence. Trastuzumab deruxtecan for treating HER2-positive unresectable or metastatic breast cancer after 2 or more anti-HER2 therapies | TA704 [Internet]. 2021 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta704
15. National Institute for Health and Care Excellence. Ribociclib with fulvestrant for treating hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy | TA687 [Internet]. 2021 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta687
16. National Institute for Health and Care Excellence. Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer | TA639 [Internet]. 2020

[cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta639
17. National Institute for Health and Care Excellence. Abemaciclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | TA563 [Internet]. 2019 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta563
18. National Institute for Health and Care Excellence. Eribulin for treating locally advanced or metastatic breast cancer after 1 chemotherapy regimen | TA515 [Internet]. 2018 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta515
19. National Institute for Health and Care Excellence. Pertuzumab with trastuzumab and docetaxel for treating HER2-positive breast cancer | TA509 [Internet]. 2018 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta509
20. National Institute for Health and Care Excellence. Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer | TA503 [Internet]. 2018 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta503
21. National Institute for Health and Care Excellence. Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | TA495 [Internet]. 2017 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta495
22. National Institute for Health and Care Excellence. Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer | TA496 [Internet]. 2017 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta496
23. National Institute for Health and Care Excellence. Trastuzumab emtansine for treating HER2-positive advanced breast cancer after trastuzumab and a taxane | TA458 [Internet]. 2017 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta458
24. National Institute for Health and Care Excellence. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens | TA423 [Internet]. 2016 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta423
25. National Institute for Health and Care Excellence. Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer | TA263 [Internet]. 2012 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta263
26. National Institute for Health and Care Excellence. Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 | TA257 [Internet]. 2012 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta257
27. National Institute for Health and Care Excellence. Eribulin for the treatment of locally advanced or metastatic breast cancer | TA250. Internet. 2012 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta250
28. National Institute for Health and Care Excellence. Fulvestrant for the treatment of locally advanced or metastatic breast cancer | TA239 [Internet]. 2011 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta239
29. National Institute for Health and Care Excellence. Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer | TA214 [Internet]. 2011 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/guidance/ta214
30. Lloyd A, Nafees B, Narewska J, et al. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683–690. doi: 10.1038/sj.bjc.6603326
31. Cooper NJ, Abrams KR, Sutton AJ, et al. A bayesian approach to Markov modelling in cost-effectiveness analyses: application to taxane use in advanced breast cancer. J R Stat Soc Ser A Stat Soc. 2003;166(3):389–405. doi: 10.1111/1467-985X.00283
32. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual [Internet]. 2022 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/process/pmg36
• **of interest.**
33. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Internet]. 2013 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.
• **of interest.**
34. National Institute for Health and Care Excellence. Position statement on use of the EQ-5D-5L value set for England [Internet]. 2019 [cited 2024 Nov 9]. Available from: https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.
• **of interest.**
35. Bullement A, Cranmer HL, Shields GE. A review of recent decision-analytic models used to evaluate the economic value of cancer treatments. Appl Health Econ Health Policy. 2019;17(6):771–780. doi: 10.1007/s40258-019-00513-3
36. DECISION SUPPORT UNIT. NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review [Internet]. 2017 [cited 2024 Nov 9]. Available from: https://www.sheffield.ac.uk/nice-dsu.
• **of interest.**
37. Bell Gorrod H, Kearns B, Stevens J, et al. A review of survival analysis methods used in NICE technology appraisals of cancer treatments: consistency, limitations, and areas for improvement. Med Decis Making. 2019;39(8):899–909. doi: 10.1177/0272989X19881967
38. Njoroge MW, Walton M, Hodgson R. Understanding the National Institute for Health and Care Excellence severity premium: exploring its implementation and the implications for decision making and patient access. Value Health. 2024;27(6):730–736. doi: 10.1016/j.jval.2024.02.013
39. Rose M, Rice S, Craig D. Does methodological guidance produce consistency? A review of methodological consistency in breast cancer utility value measurement in NICE single technology appraisals. Pharmacoecon Open. 2018;2(2):97–107. doi: 10.1007/s41669-017-0040-5
40. Gallacher D, Auguste P, Connock M. How do pharmaceutical companies model survival of cancer patients? A review of NICE single technology appraisals in 2017. Int J Technol Assess Health Care. 2019;35(2):160–167. doi: 10.1017/S0266462319000175
41. Kumar G, Radu P, Cubi-Molla P, et al. Navigating change: a comparative analysis of health technology assessment reforms across agencies – processes, drivers, and interdependencies. Int J Technol Assess Health Care. 2025;41(1):e21. doi: 10.1017/S0266462325000133