



Deposited via The University of Sheffield.

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/id/eprint/221638/>

Version: Accepted Version

---

**Article:**

Gibbons, C.L. and Latimer, N.R. (2024) Prevalence of immature survival data for anti-cancer drugs presented to the National Institute for Health and Care Excellence between 2018-2022. Value in Health. ISSN: 1098-3015

<https://doi.org/10.1016/j.jval.2024.11.013>

---

© 2024 The Authors. Except as otherwise noted, this author-accepted version of a journal article published in Value in Health is made available via the University of Sheffield Research Publications and Copyright Policy under the terms of the Creative Commons Attribution 4.0 International License (CC-BY 4.0), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>

**Reuse**

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here: <https://creativecommons.org/licenses/>

**Takedown**

If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing [eprints@whiterose.ac.uk](mailto:eprints@whiterose.ac.uk) including the URL of the record and the reason for the withdrawal request.

**Now published in *Value in Health*:**

Gibbons CL, Latimer NR. Prevalence of Immature Survival Data for Anti-Cancer Drugs Presented to the National Institute for Health and Care Excellence between 2018-2022. *Value in Health* 2024 Dec 24;S1098-3015(24)06791-3. doi: 10.1016/j.jval.2024.11.013

**ABSTRACT**

***Objectives***

Between 2015 and 2017, 41% of NICE cancer single technology appraisal (STA) decisions relied upon immature survival data. This occurs when clinical trials that form the evidence base in support of new or existing technologies suffer from limited follow-up. During this period, NICE did not negatively recommend any cancer technologies that used immature data. This suggests a potential incentive to submit to NICE with immature data to avoid rejection. Using immature survival data in cost-effectiveness evaluations has resulted in importantly different conclusions, compared to cost-effectiveness re-estimations using matured data. We assessed the reliance on immature survival data in NICE decision-making of cancer treatments, appraised after 2017.

***Methods***

A structured literature review of NICE cancer STAs published between 2018 and 2022 was conducted. The relationship between data maturity and NICE recommendations was assessed, and the extent to which past decisions were later reviewed was explored.

***Results***

56% (n=57) of NICE's cancer recommendations relied upon immature survival data. 54% (n=31) of these received a positive recommendation, 39% (n=22) were placed into the Cancer Drugs Fund (CDF) and 7% (n=4) received a negative recommendation. STAs with mature data received a similar proportion of negative recommendations. Only one non-CDF recommendation based on immature data was reappraised using updated survival data.

### ***Conclusion***

The majority of NICE cancer technology decisions are based on immature survival data and receive positive recommendations. Non-CDF decisions are unlikely to be reappraised. Consequently, many technologies could receive an inappropriate recommendation based on immature data and not be subsequently rectified.

**Keywords: NICE, immature survival data, decision-making, oncology, health technology assessment**

## **Highlights**

1. Previous research showed that between 2015 and 2017, 41% of NICE cancer technology appraisals relied on immature survival data in its decision-making. NICE did not give a negative recommendation to technologies that submitted with immature survival data, which suggests a potential incentive for companies to submit to NICE with immature data to avoid rejection. It has been shown that basing decision-making on immature survival data can result in importantly different conclusions.
2. Since 2018, the reliance on immature survival data in NICE cancer technology appraisals has increased. The majority of recommendations were positive, with a few negative recommendations. The proportion of Cancer Drugs Fund (CDF) recommendations to resolve data maturity uncertainties has remained similar. As non-CDF recommendations are rarely reappraised, it is likely that inappropriate recommendations could be made based on immature survival data, with these not subsequently being rectified once the data matures.
3. With the aim of accelerating patient access to new and effective treatments, the pressure to speed up decision-making is increasing. This demand for speed means that resources may not be allocated efficiently in the long-term, and sub-optimal decisions are likely to be made. NICE and other health technology assessment authorities should be cautious

when making recommendations based on immature survival data, particularly when their decisions are unlikely to be reappraised.

## **Introduction**

The incidence of cancer is rising in the UK and around the world,[1] as are the number of pharmaceutical technologies manufactured to treat it. With demand increasing for more innovative and effective treatments, such as gene therapies, the cost of new drugs is rising significantly. Consequently, the affordability to patients and health care providers is declining.[2-3] To ensure that resources are allocated efficiently and health gains are maximised within limited national budgets, some countries have established health technology assessment (HTA) authorities to assess the cost and clinical effectiveness of technologies to ensure the benefits of providing one treatment over another exceed opportunity costs.[4–8] For example, the National Institute of Health and Care Excellence (NICE),[9] appraises new and existing technologies to make recommendations for use within NHS England.[10] Around half of NICE’s appraisals are cancer treatments and NICE recommended 10 times more cancer technologies in 2021 compared to the early 2000s.[11] It is important that HTA authorities provide evidenced-based evaluations that are both swift and thorough to provide patients quick access to treatments, but also to ensure decisions represent the best allocation of resources.[12]

Most new interventions are more effective and expensive,[13] therefore, decision-makers tend to use pre-specified willingness-to-pay thresholds to inform whether a technology is cost-effective against treatments in current practice. Typically, differences in expected costs and health

outcomes e.g., quality-adjusted life years (QALYs) are compared to determine an incremental cost-effectiveness ratio (ICER), a measure of the marginal cost per extra unit of health gained.[5,14] ICERs are then compared against the specified threshold. For example, NICE considers most technologies relative to the maximum acceptable ICER range of £20,000 to £30,000 per QALY gained.[5] In specific circumstances, NICE allows decision modifiers, such as QALY weightings to reflect society's increased willingness-to-pay for severe and rare diseases.[5]

In HTA, there is a strong preference for direct clinical evidence from high-quality data collection, in particular, from randomised controlled trials (RCTs).[5] Clinical trials often provide the main clinical effectiveness evidence, but at the time of evaluation, these may be incomplete or have limited follow-up.[15] This is because NICE, like other HTA authorities, aims to recommend treatments around the same time as manufacturers receive their marketing authorisation from regulators such as the Medicines and Healthcare products Regulatory Agency (MHRA) and the European Medical Agency (EMA).[4-6,12,16-17] A NICE recommendation is subject to regulatory approval, which is a separate assessment to make sure that medicines available in the UK are safe and effective.[16] When overall survival (OS) is a key endpoint, limited survival data can be a problem because OS will be a crucial part of the QALY calculation. Therefore, it is necessary that HTA authorities consider the important health and economic differences between interventions over a lifetime horizon.[5,18-20]

Incomplete data is often seen in early-stage cancers appraisals, where many people survive longer than the trial. When only a small proportion of people in the trial have experienced an event of interest e.g., death, the data can be considered immature.[21] Although no formal numerical definition of immature survival data exists, some consider it to be when less than 50% of events

have occurred.[21-22] The fewer the events, the more immature the data, and therefore the larger the uncertainty is around the overall time-to-event e.g., mean survival. When the data is incomplete, statistical inference methods such as extrapolation are needed to estimate the treatment costs and health benefits beyond the trial period.[5,20] Given extrapolated data is unobserved, a large amount of uncertainty can prevail around which survival model should be used, because different models can provide different results, which can ultimately lead to different reimbursement decisions.[23-24] Therefore, when data is immature and dependence on the unobserved data grows, uncertainty rises.

As treatments become more effective and people live longer, the reliance on immature survival data in HTA decisions is likely to increase.[25] Approaches to provide rapid patient access whilst addressing data maturity uncertainty have been adopted globally, such as Accelerated Approval Programmes, by regulators like the EMA and the Food and Drug Administration.[17,26] Similarly, NHS England has a Cancer Drugs Fund (CDF), into which the NICE Committee can recommend a treatment is placed, whereby it is funded through a managed access agreement whilst further data are collected.[27-28] This is for drugs the NICE Committee thinks “might” be cost-effective, but there is sufficient uncertainty not to recommend the drug for routine commissioning.

### ***Rationale***

Since 2018, NICE has published over 300 recommendations across all disease areas,[29] that may have been affected by immature data. This is important because NICE’s decisions affect which treatments patients can and cannot access through the NHS. Although there were efforts to minimise the impact of evidence uncertainties on patient access e.g., the CDF, it is possible that inappropriate decisions are made by NICE, and other HTA authorities because of this reliance.

The impact of immature data has been researched within the context of NICE's decision-making of cancer and non-cancer topics.[25,30] A pivotal piece of literature reviewed cancer single technology appraisals (STAs) between 2015-2017 and found that there was a reliance on immature data (41%), that was often characterised by single-arm, early phase trials or interim analyses.[12,21] When the key evidence was mature, 50% of STAs received negative recommendations compared to 0% of those with immature data.[21] This indicates a potential incentive for companies to submit to NICE with immature data to avoid a negative recommendation.[5,21] The study also reconstructed the model from NICE technology appraisal (TA) 381 to re-estimate cost-effectiveness using the latest survival data and found that ICERs halved.[21] This was because the predicted survival benefits were lower when based on immature data, compared to those predicted using matured data. This could have changed NICE's original decision and demonstrates the potential implications of using immature survival data in HTA decision-making.[21,31]

Approximately 35% of cancer drugs are placed into the CDF, where there is a mandated agreement to reappraise the technology at the end of a data collection period.[5,21] For cancer drugs not placed into the CDF, there is a key concern that decisions made based on immature data are not subsequently reappraised once the data matures. NICE's 2014 process guide stated that "*when NICE publishes guidance, a suggested time for its review is given*".[32] NICE's 2022 process guide states that "*guidance will not have a fixed review date, except for guidance with recommendations for use with managed access*".[5] For non-managed access recommendations, reappraisals are only done when there is believed to be sufficient new evidence available that could change the existing recommendation.[5] The frequency of these reappraisals is unknown, especially in the context of decisions made with immature survival data.

To update previous findings and investigate the current trends around data maturity in NICE submissions and recommendations, this paper reviews the prevalence of immature survival data used in NICE cancer STAs between 2018 and 2022.[21-22,25,31] Furthermore, as a previously unexplored area of research, this paper provides an overview of NICE’s approach to reappraising non-managed access recommendations and investigates the success of the CDF at resolving data maturity uncertainties.

### ***Objectives***

A structured literature review (SLR) was conducted in two stages: a review of NICE cancer STAs since 2018 and an exploration of NICE reappraisals since 2018 (CDF and non-CDF).

The objectives for the first part of the SLR were to assess the current:

- reliance on immature survival data when submitting to NICE with a cancer technology,
- relationship between NICE’s recommendation and the use of immature data,
- trend of immature data and NICE decision-making in comparison to previous findings prior to 2018.

The objectives for the second part of the SLR were to:

- Section A: CDF reappraisals
  - determine whether the CDF data collection period is sufficient to resolve data maturity uncertainties.
  - assess the relationship between data maturity and reappraisal decisions.
- Section B: Non-CDF reappraisals

- understand the type and frequency of reappraisals conducted by NICE for non-managed access technologies.
- identify the rationale for the reappraisals

## **Methods**

### ***Search***

A manual search of the NICE website was completed in July 2022, to identify NICE cancer TAs published between 1<sup>st</sup> January 2018 and 5<sup>th</sup> July 2022. This was a continuation of the previous review that concluded on December 31<sup>st</sup>, 2017.[21]

### ***Study selection***

Excluded from all analyses were TAs that were non-cancer, terminated and not STAs (see Appendices, Table A.1). In line with previous reviews, no restriction of cancer type or severity was imposed.[21] For Part One analyses, STAs that were reappraisals were excluded to avoid confounding the results on the use of immature data. This is because more mature data would likely have been available for the update.[5,21] In Part Two, only NICE reappraisals (CDF and non-CDF) were included.

### ***Data extraction***

Relevant information was collected using a data extraction form developed based on a previous study (see Appendices, Table A.2).[21] One author extracted all relevant data. Where there was any concern about the interpretation of the data extracted the second author provided assistance. Information was gathered by searching NICE appraisal documents: Committee papers (including the company submission and the External Assessment Group (EAG) report), Committee slides

and the Final Draft Guidance. For Part Two, this included documents from both the original and reappraisal. If any trial details were unavailable, the clinical trial registry and published papers were used.

Given the lack of formal definitions, classifying data maturity was consistent with previous review methodology.[21] EAG and Committee statements were used to determine if STAs used ‘mature’, ‘immature’, ‘partial information’ and ‘not mentioned’ data. This was done systematically by searching the NICE appraisal documents using the terms ‘mature’, ‘immature’, ‘maturity’ and ‘immaturity’. Evidence that was deemed to have ‘partial information’ were situations where multiple clinical trials were presented but the maturity of all was not discussed, or different trials were considered to have different maturity levels so a firm conclusion could not be made. To determine the relationship between data maturity and maturity statements, the proportion of deaths in the key trials was extracted from every STA.

### ***Data analysis***

The extracted data was tabulated and analysed using narrative synthesis.

## Results

### *Part One: Review of NICE cancer TAs.*

304 NICE STAs were published between January 2018 and July 2022. 202 appraisals were excluded: 32 reappraisals, 50 terminated appraisals, 114 non-cancer indications, and 6 multiple technology appraisals (Figure 1) (see Appendices, Table A.3). 102 NICE cancer STAs were included for data extraction.

### *Definition of maturity*

EAGs and Committees determined maturity by the proportion of death events in the pivotal trial. The average proportion of deaths in STAs classified as being based on immature data was 25%, and was 55% for those classified as being based on mature data (see Table 1).

The relationship between maturity statements and the proportion of death events appeared to centre around 50%, with 89% of “immature” STAs involving trials in which less than 50% of patients had died, and 80% of “mature” STAs involving trials in which more than 50% of patients had died (Figure 2). However, 50% is not an explicit threshold for maturity as it was not applicable for 6 (6%) appraisals.

### *Prevalence of immature survival data*

In 57 (56%) STAs, pharmaceutical companies used immature survival data in their submission to NICE (see Table 1 and Appendices, Table A.4). Nine (9%) STAs used mature data, and in the remaining STAs data maturity was undetermined, with either no mention (n=34, 33%) or partial

information (n=2, 2%) provided . The EAG and Committee commented on data maturity in 65% of STAs.

### *Characteristics of mature and immature data*

Evidence characteristics differed mostly by analysis type e.g., interim, or final. Forty-five (79%) STAs with immature data presented interim data-cuts, compared to 4 (40%) STAs with mature data (see Table 1 and Appendices, Table A.5). Interim analyses had a smaller proportion of observed death events compared to final analyses (29% vs 44%).

The use of early phase trials or single-arm study designs was higher in immature STAs than mature (32% [n=18] versus 11% [n=1] for each of study characteristic). However, Phase 3 RCTs were most common overall (Figure 3). Early phase or single-arm trials were often presented as supporting secondary evidence. Three (5%) immature STAs submitted multiple trials of different designs e.g., RCT and single-arm trial, and 2 (3%) presented trials of different phases e.g., 3 and early phase.

### *Data maturity and NICE recommendations*

Positive recommendations (full and optimised [recommendation for a population smaller than stated in the marketing authorisation]) were given to 31 (54%) STAs that used immature data and 8 (89%) with mature data (see Table 1 and Appendices, Table A.6). Zero (0%) mature STAs received a recommendation into the CDF compared to 22 (39%) of the immature STAs (Figure 4).

A similar proportion of mature and immature STAs were negatively recommended (11%, n=1 versus (7%, n=4). Negative decisions were due to ICERs that were too high (n=3, 60%), or because the CDF would not have resolved the uncertainty (n=2, 40%).

### ***2.3.2 Part Two: NICE reappraisals***

#### *Section A: CDF*

24/304 (8%) of NICE TAs published between 2018-2022 were CDF reappraisals. Multiple reasons contributed to the original CDF recommendations, but OS was a key uncertainty in 96% (n=23) (see Appendices, Table A.7). Average data maturity upon entering the CDF was 37%.

The mean duration of additional data collection in the CDF was 32.1 months and on average the data matured to 56% complete (Figure 5). EAG and Committee statements were used to determine the post-CDF maturity classification. 13 (54%) were considered mature, 9 (38%) were immature and 3 (13%) were undetermined. Twelve (100%) mature STAs and 7 (78%) immature STAs received a positive recommendation. Two (22%) immature STAs received negative recommendations because the ICER was too high. Fifteen (63%) STAs had remaining uncertainties relating to data maturity, economic modelling or other clinical concerns (see Appendices, Table A.8). These received positive recommendations when the ICER was acceptable.

#### *Section B: Non-CDF*

NICE published 3 guidance updates and 5 reappraisals between 2018-2022. Guidance updates were due to commercial arrangement changes, and only 1 reappraisal for an STA that was originally deemed to be based on immature survival data (see Appendices, Table A.9). The mean time between the original and the reappraisal was 51 months (range: 16-120 months). Three STAs that originally received negative recommendations, resulted in full (n=1; reappraised with mature data), optimised (n=1) and negative (n=1) recommendations. Two STAs retained their original optimised recommendation.

## Discussion

Since 2018, the reliance on immature survival data in NICE cancer appraisals has increased from 41% in the three previous years, to 56%.[21] This means that more than half of NICE's decisions for cancer technologies are based on data where the true survival benefit is highly uncertain. In NICE appraisals, immature data is often defined by the EAG and Committee as when fewer than 50% of trial participants have died. However, in some circumstances, such as when technologies claim to be curative, a higher maturity threshold is used. This suggests that no explicit threshold of immaturity exists. Immature survival data was mostly characterised by interim analyses from Phase 3 RCTs, but having final analyses does not guarantee mature survival data. In fact, the average maturity was below 50% for both interim and final analyses in the reviewed appraisals. Therefore, making final analyses a requirement for HTA would not resolve data maturity uncertainties. The prevalence of single-arm or early phase trials remained higher in appraisals that were deemed to be based on immature data.[21] However, these were often presented as secondary sources of evidence when the main evidence was uncertain. This is consistent with NICE's methods guide that states that it will consider other evidence types, to complement RCTs, when evidence is limited.[5] Overall, findings suggest that data immaturity will continue to be a key source of uncertainty in HTA of cancer treatments.

In Tai *et al.*'s review of the maturity of survival data used in NICE appraisals, the authors observed that cancer drugs submitted with immature data were never given negative recommendations.[21] Our review found a similar proportion of STAs with mature and immature data were given a negative recommendation (7% vs 11%), indicating that submitting with immature data does not guarantee a positive recommendation. Instead, negative recommendations were more likely when ICERs were too high or where clinical uncertainties could not be resolved

within the CDF. However, this finding is unlikely to deter companies from submitting to HTA authorities with immature data due to pressures around expediting appraisals and making treatments available to patients quickly. Indeed, industry feedback suggests that the current route to NHS provision of treatments is too slow.[33]

The relationship between data maturity, positive recommendations, and placement in the CDF, has remained similar over time. Most STAs that used immature data received positive recommendations (54% in 2018-2022 versus 65% in 2015-2017) and a similar proportion were placed into the CDF (39% in 2018-2022 versus 35% in 2015-2017).[21] However, this shows that more STAs with immature data were positively recommended than referred into the CDF, which may be a concern given the data maturity recommendations were based on. Ultimately, this means that most decisions made based on immature data will not be subject to reappraisal.

Between 2018 and July 2022, only one cancer STA in which the original decision was deemed to be based on immature survival data and was not placed into the CDF was reappraised when more mature evidence became available. Importantly, this is not because there was no new published survival evidence for cancer treatments appraised in recent years. For example, Tai *et al.*'s review identified several STAs for which updated survival data had become available since the original NICE decision was made. However, these were not the technologies found to be reappraised within this review.[21] This indicates that reappraisals of NICE decisions for treatments that are not placed in the CDF are extremely rare, and that decisions based on immature survival data are unlikely to be reappraised after the data matures.

The combined impact of our key findings that: a) the reliance on immature survival data in NICE's decision-making is rising; b) STAs with immature data more often result in positive treatment recommendations than recommendations to place the drugs into the CDF, and c) non-

CDF recommendations are rarely reappraised, could equate to a large loss of allocative efficiency in the NHS, and other health care systems. It is likely that inappropriate recommendations could be made for many technologies based on immature survival data, and these decisions are not subsequently reappraised and rectified once the data matures. The need for quick patient access is recognised, but these findings suggest that more patients may miss out in the long-run due to the opportunity costs of recommending treatments that are not cost-effective or not recommending treatments that are in fact cost-effective.

Cost-effectiveness was the primary driver of positive recommendations in the CDF reappraisals, which aligns with NICE's remit. Interestingly, when uncertainties remained e.g., data immaturity, Committees often increased its cost-effectiveness threshold or chose pessimistic scenarios. This was to reduce the risk of approving cost-ineffective treatments when the true cost-effectiveness was uncertain. This suggests that whilst cost-effectiveness is the most important decision-making factor, Committees vary their requirements to offset remaining uncertainties, including those associated with immature survival data. However, it is important to note that arbitrarily increasing the cost-effectiveness threshold is unlikely to prevent inappropriate recommendations based on immature data, as it is unlikely to be possible to predict what impact further data collection will have on the results. Therefore, it would be preferable for decisions made based on immature survival data to be reappraised when more mature evidence is available.

### ***Applications***

This paper looked specifically at NICE, however, the key messages regarding the importance of reappraising decisions are relevant for all HTA authorities.

Given that national healthcare budgets are unlikely to increase in real terms substantially over time, but technology prices continue to rise, HTA authorities need to ensure that they are

minimising ineffective spending and resource wastage.[34] As demonstrated, once positive and negative reimbursement decisions have been made, they often remain unrevised. To ensure there is a sustainable healthcare system, an area of consideration for HTA authorities could be disinvestment. The concept of disinvestment is to partially or fully withdraw the funding of technologies that are not cost-effective, to reinvest or reallocate resources to health technologies that may be more cost and clinically effective.[34] This could benefit patients as this would free up resources to fund new treatments. In NICE's 2022 methods guide, they state circumstances in which guidance may be withdrawn.[5] However, the reasons for removal do not include the re-evaluation of clinical evidence, except for technologies in managed access.

The pressure to speed up decision-making and therefore the speed at which treatments reach and provide benefit to patients is increasing.[33] This is particularly given the MHRA's new International Recognition Procedure, which is increasing the speed at which technologies are coming to market and HTA authorities.[16] Proposing that every recommendation is reappraised is implausible because many HTA authorities have limited capacity. Initially, benefits could be achieved by only reappraising decisions made with immature data once the data has matured. NICE currently relies upon the submission of new evidence that could affect the recommendation before it reappraises decisions.[5] However, it seems unlikely that manufacturers would choose to provide additional data that may suggest that their product would no longer be cost-effective and potentially face the withdrawal of their drug from NHS routine commissioning. NICE could expand their mandatory reappraisals to non-CDF recommended technologies that used immature data. Given that maturity statements are not consistently provided, an objective maturity threshold could be used to determine eligibility at the time of the original appraisal. However, as discussed, one threshold may not apply to all technologies. This reassessment method would

remain time consuming and be subject to resource challenges so more investigation into HTA disinvestment is required.

### ***Limitations and further research***

The CDF was relatively successful at resolving data maturity uncertainties, with 92% subsequently receiving a positive recommendation. This includes 100% of those considered mature when exiting the CDF (50%), indicating an association between increased data maturity and positive decisions. Despite its relative success, since 2018, only 39% of NICE cancer STAs based on immature survival data resulted in recommendations placing drugs into the CDF. Future research should investigate why this proportion is not higher. STAs with immature data should also be reappraised once data has matured.

A limitation of our study is that we did not extract the key reasons driving the NICE decision-making process for the appraisals reviewed in Part One. Hence, we cannot be certain that data maturity was a key driver in all of these appraisals. However, our analyses allow us to assess the relationship between data maturity and NICE decision-making, and our Part Two review provided information on the factors influencing decisions, demonstrating that data maturity was an important factor.

In 2020, NICE was involved in producing rapid COVID-19 guidelines.[35] Reappraising recommended technologies was unlikely a priority and therefore the data sampled may not be an accurate representation of NICE's reappraisal process. Future research should continue to monitor the frequency of NICE non-managed access reappraisals. Furthermore, only 65% of STAs included maturity statements, therefore, more appraisals could have used immature data but were not categorised as such in our analyses. To see whether conclusions remain, further research could apply a broader categorisation of immature data e.g., trials with fewer than 50% of

death events. The true implications of immature survival data on HTA decision-making have not been verified. Only one case study has evaluated NICE's decision-making using both immature and mature survival data within a reconstructed economic model.[21] To assess the generalisability this finding, additional research is needed to explore the true scale and impact of immature survival data on decisions made by NICE.

As the reliance on immature data and extrapolation is increasing, methods to overcome this dependency might be required. For example, NICE's 2022 real-world evidence framework encourages the use of real-world data to resolve knowledge gaps and reduce uncertainties.[36] It states that NICE already uses real-world data to inform guidance, for example, where there is insufficient evidence available for decision-making because follow-up is limited. Literature is expanding on the use of external data and information within HTA, with new methods being proposed. One approach is the use of Bayesian Hierarchical Network Meta-Analysis.[37-38] This allows information, such as treatment effects, to be borrowed from technologies in the same class where more mature trial evidence is available. Whilst this relies upon strong assumptions of clinical similarity between treatments, it suggests that there may be methods available to help improve the reliability of extrapolations based on immature data. However, fundamentally uncertainty will remain, and analyses and recommendations should be checked when more mature data becomes available. Future research should investigate what approaches to address data maturity concerns are being presented and accepted in HTA submissions e.g., real-world data, Bayesian Hierarchical Network Meta-Analysis or pessimistic scenario analyses.

## **Conclusion**

This review found that immature survival data routinely contributes to decisions made by NICE. The reliance on immature survival data is more prevalent since 2017, yet the proportion of technologies recommended into the CDF remains similar. This is a concern given that we found that non-managed access recommendations are rarely reappraised, despite more mature data becoming available. The demand for quick access to new and effective treatments in the short-term means that resources may not be allocated efficiently in the long-term, and inappropriate decisions are likely to be made. Therefore, NICE, and other HTA authorities, should be cautious when making recommendations based on immature survival data.

## References

1. Cancer Research UK. Cancer incidence statistics. Available at:  
<https://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence#heading-Zero>. [Accessed January 12, 2024].
2. Morgan SG, Bathula HS, Moon S. Pricing of pharmaceuticals is becoming a major challenge for health systems. *BMJ* 2020;368:l4627.
3. Conti R, Frank R, Gruber J. Addressing the trade-off between lower drug prices and incentives for pharmaceutical innovation. 2021.
4. CADTH Methods and Guideline. Guidelines for the Economic Evaluation of Health Technologies: Canada. (4th ed). Ottawa: CADTH; 2017
5. NICE. NICE health technology evaluations: the manual, Process, and methods. Available at:  
<https://www.nice.org.uk/process/pmg36/resources/nice-health-technology-evaluations-the-manual-pdf-72286779244741> [Accessed January 12, 2024].
6. Commonwealth of Australia (2016) Guidelines for preparing a submission to the Pharmaceutical Benefits Advisory Committee. Available at:  
<https://pbac.pbs.gov.au/content/information/files/pbac-guidelines-version-5.pdf> [Accessed January 12, 2024].
7. Haute Autorité de Santé. Choices in methods for economic evaluation – HAS. Available at:  
[https://www.has-sante.fr/upload/docs/application/pdf/2020-11/methodological\\_guidance\\_2020\\_choices\\_in\\_methods\\_for\\_economic\\_evaluation.pdf](https://www.has-sante.fr/upload/docs/application/pdf/2020-11/methodological_guidance_2020_choices_in_methods_for_economic_evaluation.pdf)  
[Accessed January 12, 2024].

8. International Society for Pharmacoeconomics and Outcome Research. Pharmacoeconomic guidelines around the world. Available at: <https://www.ispor.org/heor-resources/more-heor-resources/pharmacoeconomic-guidelines>. [Accessed January 12, 2024].
9. NICE. What we do. Available at: <https://www.nice.org.uk/about/what-we-do>. [Accessed January 12, 2024].
10. Department of Health and Social Care. 2022-23 Variation to the Financial Directions to NHS England Available at: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1087059/variation-to-2022-to-2023-nhs-financial-directions.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1087059/variation-to-2022-to-2023-nhs-financial-directions.pdf) [Accessed January 12, 2024].
11. NICE. Technology appraisal data: cancer appraisal recommendations. Available at: <https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance/data/cancer-appraisal-recommendations> [Accessed January 12, 2024].
12. Lux MP, Ciani O, Dunlop WC, Ferris A, Friedlander M. The Impasse on Overall Survival in Oncology Reimbursement Decision-Making: How Can We Resolve This? *Cancer Manag Res* 2021;13:8457–71.
13. York Health Economics Consortium. Cost-Effectiveness Plane. Available at: <https://yhec.co.uk/glossary/cost-effectiveness-plane/> [Accessed January 12, 2024].
14. York Health Economics Consortium. Incremental Cost-Effectiveness Ratio (ICER). Available at: <https://yhec.co.uk/glossary/incremental-cost-effectiveness-ratio-icer/> [Accessed January 12, 2024].

15. Latimer NR, Adler AI. Extrapolation beyond the end of trials to estimate long term survival and cost effectiveness. *BMJ Medicine* 2022;1(1):e000094.
16. UK Government. Medicines & Healthcare products Regulatory Agency: International Recognition Procedure. 2024. Available at:  
<https://www.gov.uk/government/publications/international-recognition-procedure/international-recognition-procedure>. [Accessed January 12, 2024].
17. European Medicines Agency. Final report on the adaptive pathways pilot. Available at:  
[https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot\\_en.pdf](https://www.ema.europa.eu/en/documents/report/final-report-adaptive-pathways-pilot_en.pdf). [Accessed January 12, 2024].
18. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;313(7052):275–83.
19. Owens DK, Siegel JE, Sculpher MJ, Salomon JA. Designing a Cost-Effectiveness Analysis. In: *Cost-Effectiveness in Health and Medicine*. Oxford University Press 2016;p. 75–104.
20. Haacker M, Hallett TB, Atun R. On time horizons in health economic evaluations. *Health Policy Plan* 2020;35(9):1237–43.
21. Tai TA, Latimer NR, Benedict Á, Kiss Z, Nikolaou A. Prevalence of Immature Survival Data for Anti-Cancer Drugs Presented to the National Institute for Health and Care Excellence and Impact on Decision-making. *Value in Health*. 2021;24(4):505–12.
22. Dyer M, Wagner P, Wiinberg L, Ryan J. PCN134 Assessing the Relationship between Immature and Mature Overall Survival (OS) Outcomes on HTA Decision-Making: A Study of UK Nice Decisions and the Case for Coverage with Evidence Development. *Value in Health* 2021;24:S44.

23. Delos Santos S, Witzke N, Arciero VS, Rahmadian AP, Everest L, Chan KK. Reassessing the net health benefit (NHB) of FDA approved cancer drugs with evolution of evidence using the American Society of Clinical Oncology Value Framework (ASCO-VF). *Journal of Clinical Oncology* 2020;38(15\_suppl):7011–7011.
24. Everest L, Blommaert S, Chu RW, Chan KKW, Parmar A. Parametric Survival Extrapolation of Early Survival Data in Economic Analyses: A Comparison of Projected Versus Observed Updated Survival. *Value in Health* 2022(4):622–9.
25. Lee D, Amadi A, Sabater J, Ellis J, Johnson H, Kotapati S, et al. Can We Accurately Predict Cost Effectiveness Without Access to Overall Survival Data? The Case Study of Nivolumab in Combination with Ipilimumab for the Treatment of Patients with Advanced Melanoma in England. *Pharmacoecon Open* 2019;3(1):43–54.
26. U.S Food and Drug administration. Accelerated Approval Program. Available at: <https://www.fda.gov/drugs/information-health-care-professionals-drugs/accelerated-approval-program>. [Accessed January 12, 2024].
27. NHS England. Cancer Drugs Fund. Available at: <https://www.england.nhs.uk/cancer/cdf/>. [Accessed January 12, 2024].
28. NICE. Managed Access. Available at: <https://www.nice.org.uk/about/what-we-do/our-programmes/managed-access>. [Accessed January 12, 2024].
29. Davies C, Briggs A, Lorgelly P, Garellick G, Malchau H. The “Hazards” of Extrapolating Survival Curves. *Medical Decision-making* 2013;33(3):369–80.

30. NICE. Published Guidance, NICE advice and quality standards. Available at:  
<https://www.nice.org.uk/guidance/published?ngt=Technology+appraisal+guidance>.  
[Accessed January 12, 2024].
31. NICE. Guide to the processes of technology appraisal. Available at:  
<https://www.nice.org.uk/process/pmg19/resources/guide-to-the-processes-of-technology-appraisal-pdf-72286663351237> [Accessed January 12, 2024].
32. Bullement A, Meng Y, Cooper M, Lee D, Harding TL, O'Regan C, et al. A review and validation of overall survival extrapolation in health technology assessments of cancer immunotherapy by the National Institute for Health and Care Excellence: how did the initial best estimate compare to trial data subsequently made available? J Med Econ 2019;22(3):205–14.
33. HM Government. Pro-innovation Regulation of Technologies Review: Life Sciences. 2023. Available at: [Life sciences report - Pro-innovation Regulation of Technologies.pdf \(publishing.service.gov.uk\)](#) [Accessed January 12, 2024].
34. Kamaruzaman H, Grieve E, Wu O. Disinvestment in healthcare: a scoping review of systematic reviews. International Journal of Technology Assessment in Health Care 2022;38(1):e69.
35. NICE. COVID-19. Available at: <https://www.nice.org.uk/guidance/conditions-and-diseases/respiratory-conditions/covid19> [Accessed January 12, 2024].
36. NICE. NICE real-world evidence framework. Available at:  
<https://www.nice.org.uk/corporate/ecd9/chapter/overview#key-messages> [Accessed July 16, 2024].

37. Heeg B, Verhoek A, Tremblay G, et al. Bayesian hierarchical model-based network meta-analysis to overcome survival extrapolation challenges caused by data immaturity. *Journal of Comparative Effectiveness Research* 2023;12(3).
38. Heeg B, Verhoek A, Tremblay G, et al. MSR77 Bayesian Hierarchical Model-Based Network Meta-Analysis to Overcome Survival Extrapolation Challenges Caused by Immature Data: Application in Previously Treated Metastatic Non-Small Cell Lung Cancer (NSCLC) PD-L1>1%. *Value in Health* 2022;25(12).

**Table 1: Evidence characteristics and NICE recommendations for NICE cancer STAs, categorised by maturity**

| Category                              |                | Immature | Mature |
|---------------------------------------|----------------|----------|--------|
| N (%)                                 |                | 57 (56)  | 9 (9)  |
| Average maturity (%)                  |                | 25       | 55     |
| Observed deaths more than 50% (%)     |                | 11       | 80     |
| <b>Evidence characteristics N (%)</b> |                |          |        |
| Analysis type                         | Interim        | 45 (79)  | 4 (44) |
|                                       | Final          | 21 (21)  | 5 (56) |
| Trial design                          | Single arm     | 18 (32)  | 1 (11) |
|                                       | RCT            | 36 (63)  | 8 (89) |
|                                       | Mixed          | 3 (5)    | 0 (0)  |
| Trial phase                           | 1 or 2 (early) | 18 (32)  | 1 (11) |
|                                       | 3              | 37 (65)  | 8 (89) |
|                                       | Mixed          | 2 (3)    | 0 (0)  |
| <b>NICE recommendation N (%)</b>      |                |          |        |
| Full                                  |                | 22 (39)  | 4 (44) |
| Optimised                             |                | 9 (16)   | 4 (44) |
| Negative                              |                | 4 (7)    | 1 (11) |
| CDF                                   |                | 22 (39)  | 0 (0)  |

Note: % do not add to 100% due to rounding. Data was only collected for STAs determined as immature or mature by EAGs or Committees

Abbreviations: CDF, cancer drugs fund; EAG, external assessment group; RCT, randomised controlled trial; STA, single technology appraisal