NICE National Institute for Health and Care Excellence

Use of disease-specific reference models in economic evaluations: NICE position statement

Corporate document
Published: 30 September 2025

www.nice.org.uk/corporate/ecd18

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Introduction

NICE helps practitioners and commissioners get the best care to people fast, while ensuring value for the taxpayer. We do this by developing guidance, advice and information through a diverse range of programmes that share the same core process of identification, assessment (including economic evaluation) and interpretation of evidence.

The government's 10 Year Health Plan for England sets out how NICE will take a whole lifecycle approach to updating guidance to drive smarter spending in the NHS. This broad programme of work includes bringing our different types of guidance together so that users can easily find the recommendations they need and so that inconsistencies between different guidance on the same topic are reduced (see NICE's information on bringing our guidance together by topic). This requires a consistent approach to economic evaluation within care pathways.

Background

A common disease or condition will typically have several pieces of NICE guidance about it, with each piece supported by a health economic model that weighs up the costs and benefits of alternative options. Usually, a model is built by a different modelling team for each piece of guidance. The NICE reference case has supported consistent methods across assessments, but some inconsistencies persist. Inconsistencies in modelling can lead to inconsistencies between recommendations, which can negatively impact the care that people receive (see the appendix).

This position statement sets out NICE's view on the use of disease-specific reference models and disease-specific reference case extensions in the economic evaluation of interventions considered by its evaluation programmes. It aims to:

- indicate NICE's plans for developing and implementing disease-specific reference models and case extensions in high-priority clinical areas
- outline what NICE expects from companies, external assessment groups (EAGs), guideline developers and committee members when it has issued a reference case extension
- describe how NICE would identify disease areas where a reference case extension can bring value to NICE and the wider system.

Terminology

NICE reference case

NICE's manuals outline the methods that it considers most appropriate for estimating clinical effectiveness and value for money. Health economic modelling teams should follow these methods, referred to as the reference case in NICE's health technology evaluation manual (and cross-referred to in NICE's guidelines manual). For example, the reference case specifies that, in most cases, the quality-adjusted life year should be used as the measure of overall health gain.

Disease-specific reference case extension

Disease-specific reference case extensions are extensions to the existing NICE reference case. A disease-specific reference case extension specifies the characteristics a model should have in a specific disease area or condition, rather than providing a fully implemented model. The level of detail will vary by disease and could include any of the following:

- lists of outcomes (including adverse events), comparator treatment strategies and population subgroups to be captured
- a conceptual model containing the specific relationships between different health states and outcomes
- specific input assumptions and datasets to be used.

The aim of a reference case extension at NICE is to signal what NICE considers current best practice in how an economic analysis for a particular disease should be designed. It should be used for all guidance development for a specific disease or condition unless there are strong justifications not to.

The term should not be shortened to 'reference case' unless it is clear from the context that it is the disease-specific reference case extension that is being referred to.

Disease-specific reference model

Disease-specific reference models evaluate a wide set of interventions within a particular disease area or condition (adapted from Haji Ali Afzali and Karnon 2011). These are developed independently of the companies, populated using best available evidence and validated. They are executable models that are available to companies submitting health technologies for assessment by health technology assessment (HTA) bodies and guideline developers.

NICE's position

Disease-specific reference case extensions

1. To enable standardised health economic modelling approaches to inform guidance development, NICE will develop reference case extensions in selected disease areas or conditions.

2. Some of the evidence on which the reference case is based will be stronger for some elements than others. Where there is clearly a best approach, the extension will make it clear that a specific element is 'required'. Where there is some uncertainty, an assumption or method will be 'recommended'. Reference case extensions will also evolve as new evidence becomes available (for example, elements may be revised from 'recommended' to 'required').

3. Reference case extensions will only add detail to the NICE reference case and will not contradict it.

4. Deviations from reference case extensions should be explained and justified by companies, EAGs and guideline developers, and agreed through committees and NICE's quality assurance processes. NICE will keep the reference case extensions under review to assess whether updates are needed.

5. The reference case extension development process will include extensive engagement opportunities. Workshops during the design of a reference case extension will allow patient advocates, clinicians, commissioners, industry stakeholders, health economic modellers and data scientists to give feedback and be involved in the process.

6. All stakeholders will be invited to participate in a non-competitive space (that is, a reference case extension is not developed as part of a specific appraisal) to avoid any perceived unfair advantages to any particular stakeholder.

7. When NICE is aware of a model (or models) that meets one of its reference case extensions, it will notify stakeholders.

8. In some circumstances, NICE will consider building its own reference model.

9. NICE acknowledges the operational challenges of developing and using reference models, such as model ownership, resourcing and maintenance, and management of confidential company data, and will continue to explore their use.

10. If NICE decides a reference model would be useful, it will consider doing any of the following:

- adapting a model that is already being developed within NICE processes (for example, for guideline updates or for multiple technology appraisals [MTAs])
- using an existing model that can be adapted for NICE's purposes
- developing a new model.

Topic selection

11. Selection of topics for future disease-specific reference case extensions will focus on NICE's high-priority clinical areas.

12. Prioritisation will also consider which areas can gain significant benefit from a prescribed approach. For example, where:

- committees, EAGs, stakeholders or NICE technical staff have identified significant methodological weaknesses or inconsistencies in modelling approaches in existing models, or
- modelling methods are not yet well established, such as when there are new technologies in the pipeline that will significantly change the management of a disease area or condition, or
- there is a high level of innovation in a disease area and the volume of new products being developed in parallel risks inconsistent approaches to modelling.

13. NICE's intention to develop a reference case extension for a disease area or condition will be signalled to external stakeholders through our usual processes to ensure that any model development can be aligned.

Next steps

14. NICE's first disease-specific reference case extension will be released for consultation in 2026 for the treatment of obesity and weight-related comorbidities. The development process will include a literature review of cost–utility analyses and expert input from:

- clinical experts and patient representatives
- health economist analysts and modellers
- industry stakeholders
- commissioners of NHS services.

15. The conceptual model developed by NICE's HTA Lab for metabolic dysfunction-associated steatohepatitis (MASH) will be adapted into a disease-specific reference case extension in 2026 to 2027.

16. A governance process, with stakeholder input, will be developed to support the transparent and proportionate selection of topics for the development of a reference case extension.

17. To promote adherence to a disease-specific reference case extension, the scoping process of technology appraisals (TAs) and guidelines will be adapted to signpost to reference case extensions in the scoping document. In TAs and health technology evaluations, company submissions and EAG report templates will be adapted to include a description of how the company's analysis adhered to the disease-specific reference case extension. All products will capture committee assessment of how well the reference case extension has been implemented.

18. A NICE process will be developed for maintaining reference case extensions as the evidence base grows. The process will also include retiring reference case extensions if it is decided that the benefits of maintaining them are not justified.

19. NICE will consider resourcing and technologies for ongoing maintenance and updating of reference models and reference case extensions. It will also consider how other programmes at NICE, such as the HTA Lab, can support more dynamic updating of existing models (see NICE's information on the future of HTA with AI).

20. NICE will assess and learn from using disease-specific reference case extensions in NICE evaluations. It will consider whether the opportunities outweigh the challenges to NICE's guidance development processes. This position statement will be reviewed following implementation of the MASH and obesity reference case extensions.

21. An update to NICE's methods manuals concerning the use of disease-specific reference case extensions will be considered where appropriate.

22. NICE will continue to explore and build on collaborative opportunities with other HTA agencies (for example, see information on NICE's international collaborations).

If you have any questions or comments about this position statement, please contact us at the following email address: ReferenceModels@nice.org.uk.

Summary

23. Disease-specific reference models and case extensions can provide several benefits to NICE, companies and the health and care system, through greater consistency in methods, more efficient use of time, and greater transparency in decision making (see the appendix).

24. Implementing reference models has challenges, as they are resource-intensive to build and maintain, and there are barriers to incorporating them into existing NICE processes. NICE will explore reducing these barriers, including by exploring new information technologies and collaborating with HTA organisations internationally.

25. This position statement describes how NICE will develop and use disease-specific reference case extensions across its guidance production programmes. Disease-specific reference case extensions are being taken forwards first in the areas of MASH and obesity.

References

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Wang J, Pouwels X, Ramaekers B et al. (2024) A Blueprint for Multi-use Disease Modeling in Health Economics: Results from Two Expert-Panel Consultations. Pharmacoeconomics 42(7): 797–810.

NICE guidance

- Cabozantinib with nivolumab for untreated advanced renal cell carcinoma (2024) NICE technology appraisal guidance 964
- NICE health technology evaluations: the manual (2022) NICE guideline PMG36 (accessed July 2025)
- Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (2016) NICE technology appraisal guidance 375
- Developing NICE guidelines: the manual (2014) NICE guideline PMG20 (accessed July 2025)

Appendix: Anticipated benefits and challenges of a standardised approach to modelling methods

Disease-specific reference models have emerged in NICE products on several occasions over the years. This includes:

- models developed by external assessment groups (EAGs) for multiple technology appraisals (MTAs) being adapted for single technology appraisals (STAs; for example, in rheumatoid arthritis, NICE technology appraisal TA375)
- guideline models adapted for health technology evaluations
- bespoke whole pathway models developed for guidelines (for example, in atrial fibrillation and prostate cancer [Lord, Willis, Eatock et al. 2013])
- pathway models developed for technology appraisals (TAs; for example, in renal cell carcinoma, NICE technology appraisal guidance TA964).

However, they have not been adopted formally by NICE or applied across all NICE products.

For some diseases, multiple NICE STAs and other guidance exist that cover the same parts of a clinical pathway (the same 'decision space'). This can lead to inconsistencies in economic model inputs and assumptions since companies, EAGs and NICE developers build their own models. Despite a rigorous quality assurance process, these inconsistencies may affect committee decisions and can result in inconsistencies between different pieces of guidance within a condition.

Disease-specific reference models or reference case extensions may enable more robust decisions to be made when recommending technologies by encouraging consistent assumptions and approaches to modelling across NICE's guidance products (Haji Ali Afzali and Karnon 2011; Haji Ali Afzali, Karnon, Merlin et al. 2012). More consistent modelling approaches across guidance products will help bring our different types of guidance together so that users can easily find the recommendations they need.

Where there are multiple models in the same decision space, the same assumptions and

parameters might be discussed separately for each model. This repetitive scrutiny of different models by EAG staff and committees creates inefficiencies in the evaluation process (Wang, Pouwels, Ramaekers et al. 2024). A standardised approach may allow for a quicker decision-making process and better use of time spent by committees, EAGs and NICE in evaluating, developing and validating new economic models. Committee meeting discussions could focus on building consensus around new key issues rather than revisiting matters that have already been addressed in previous discussions.

Using disease-specific reference models can also promote transparent decision making through sharable models. A standardised approach to modelling a disease also has advantages for companies, such as:

- facilitating early value assessment for technologies in development
- creating greater clarity about model structures and inputs that are likely to be acceptable to the committee
- potentially reducing the cost of developing new economic models to support NICE evaluations.

The development and maintenance of reference models need adequate resourcing to ensure their continual robustness and prevent them from becoming out of date (Sampson, Arnold, Bryan et al. 2019, Haji Ali Afzali, Karnon, Merlin et al. 2012). Their development and maintenance can be supported by innovation in methodology, such as through AI-facilitated approaches for updating or adapting existing models, or the use of real-world data to ensure that the model outputs reflect real-world practice in England (Reason, Rawlinson, Langham et al. 2024; Fleurence, Bian, Wang et al. 2025).

Reference models require academic credibility and rigour to be suitable for decision making. Models will undergo independent critical appraisal and consultation before they are used for decision making. Involvement of patients and clinicians will ensure that any model assumptions reflect care pathways and current practice, and that models capture what matters most to the people who will be affected by decisions for new medicines.

Disease-specific reference case extensions can potentially provide many of the benefits of fully implemented reference models. They can be used for the fair and consistent:

- evaluation of new technologies, and
- updating of existing guidance.

ISBN: 978-1-4731-7230-2