NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

The appraisal committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy, and maternity?

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Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document, and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using nivolumab in combination with fluoropyrimidine- and platinum-based combination chemotherapy in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 13 April 2022

Third appraisal committee meeting: TBC

Details of membership of the appraisal committee are given in section 5.

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1 Recommendations

1.1 Nivolumab with platinum- and fluoropyrimidine-based combination chemotherapy is not recommended, within its marketing authorisation, as an option for untreated HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma in adults whose tumours express PD-L1 with a combined positive score (CPS) of 5 or more.

1.2 This recommendation is not intended to affect treatment with nivolumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

There are no curative treatment options for HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more. The usual treatment is palliative chemotherapy. Most people have platinum- and fluoropyrimidine-based chemotherapy with capecitabine plus oxaliplatin (XELOX) or fluorouracil plus oxaliplatin with folinic acid (FOLFOX).

Clinical trial evidence shows that nivolumab with XELOX or FOLFOX increases the length of time before gastric, gastro-oesophageal junction or oesophageal adenocarcinoma get worse compared with XELOX or FOLFOX alone. Evidence also shows that people live longer if they have nivolumab with XELOX or FOLFOX compared with XELOX or FOLFOX alone. But, it is unclear how long people lived beyond the trial period and for how long nivolumab's benefit lasted.

People with these conditions on average have a short life expectancy, so nivolumab meets NICE's criteria to be considered a life extending treatment at the end of life.

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However, even taking this into consideration, nivolumab is not cost effective. So, nivolumab is not recommended.

2 Information about nivolumab

Marketing authorisation indication

2.1 Nivolumab (Opdivo, Bristol Myers Squibb) is indicated for use 'in combination with fluoropyrimidine- and platinum-based combination chemotherapy for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for nivolumab.

Price

2.3 The list price of nivolumab is £439 per 40 mg/4 ml concentrate for solution for infusion vial; £1,097 per 100 mg/10 ml concentrate for solution for infusion vial; and £2,633 per 240 mg/24 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed August 2021).

2.4 The company has a commercial arrangement. This makes nivolumab available to the NHS with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee considered evidence from a number of sources. See the committee papers for full details of the evidence.

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The condition

Gastric, gastro-oesophageal junction and oesophageal adenocarcinoma have a poor prognosis and a large impact on quality of life

3.1 The patient experts explained that gastric, gastro-oesophageal junction and oesophageal adenocarcinoma significantly impact quality of life. They explained that major symptoms include difficulty swallowing and malnutrition, which can lead to severe fatigue, weight loss and the need to use a feeding tube. These symptoms can be painful and distressing, limiting people's ability to live normally and participate in social events. Diagnosis is often at an advanced stage, and around 40% of all new cases are diagnosed in people aged 75 and over. Gastric, gastro-oesophageal junction and oesophageal adenocarcinoma are more common in men than women, although the patient experts report that increasing numbers of younger people and women are being diagnosed. The committee concluded that advanced gastric, gastro-oesophageal junction and oesophageal adenocarcinoma have a poor prognosis and a large impact on quality of life.

People would welcome a new treatment option

3.2 The patient and clinical experts explained that there are no curative treatment options for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma. Standard first-line treatment for people with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 and no significant comorbidities is palliative chemotherapy. NICE's guideline on oesophago-gastric cancer: assessment and management in adults recommends dual therapy with fluorouracil or capecitabine plus cisplatin or oxaliplatin, or triple therapy with epirubicin. The clinical experts explained that dual therapy regimens are preferred and that most people would have capecitabine and oxaliplatin (XELOX). This is because oxaliplatin is better tolerated than cisplatin and has a shorter infusion time. Some people may be offered

fluorouracil with oxaliplatin and folinic acid (FOLFOX). People having FOLFOX treatment need more hospital visits (every 2 weeks) thanpeople having XELOX (every 3 weeks). The patient and clinical experts agreed that there is unmet clinical need in this population. Nivolumab is an immunotherapy and has a different mechanism of action to chemotherapy. NICE's technology appraisal guidance recommends pembrolizumab with platinum- and fluoropyrimidine-based chemotherapy for untreated HER2-negative advanced oesophageal and gastro-oesophageal junction cancer in adults whose tumours express PD-L1 with a combined positive score (CPS) of 10 or more. The committee noted that some people would be eligible for nivolumab plus chemotherapy but not pembrolizumab plus chemotherapy. As a result, there remains an unmet need in people with gastric cancer and a CPS of between 5 and 10 who cannot have pembrolizumab. The committee concluded that patients and clinicians would welcome a new treatment for untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma.

XELOX is the key comparator for this appraisal

3.3 The company suggested that XELOX and FOLFOX were the relevant comparators for this appraisal. The evidence review group (ERG) agreed with this approach and noted that most people would have XELOX because it is more convenient and cheaper than FOLFOX. Clinical experts also confirmed the company's approach and noted that dual chemotherapy regimens have similar efficacy. The committee concluded that XELOX was the key comparator for this appraisal.

Clinical evidence

Nivolumab plus chemotherapy improves progression-free survival and overall survival compared with chemotherapy alone

3.4 CheckMate 649 (n=1,581) was an open label randomised multicentre trial (including 38 patients from 5 UK centres) that compared nivolumab plus XELOX or FOLFOX with XELOX or FOLFOX alone. It included people with untreated and unresectable, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma who had an ECOG performance status of 0 to 1. People with known HER2-positive status and untreated central nervous system metastases were excluded from the study. The average age in the trial was 60.1 years. The primary outcomes were progression-free survival and overall survival in people whose tumours express PD-L1 with a CPS of 5 or more (n=955). Results from the latest data cut were based on a minimum follow-up of 24 months and showed that:

- nivolumab plus chemotherapy improved progression-free survival compared with chemotherapy alone (hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.60 to 0.81)
- nivolumab plus chemotherapy improved overall survival compared with chemotherapy alone (HR 0.70, 95% CI 0.61 to 0.81).

The committee noted that this data was mature (meaning that more than half the trial population had disease progression or died during the follow-up period). The committee concluded that adding nivolumab to platinum- and fluoropyrimidine-based combination chemotherapy improved progression-free survival and overall survival compared with chemotherapy alone.

CheckMate 649 data is generalisable to NHS clinical practice

3.5 In the first committee meeting, the ERG heard clinical advice suggesting that the trial population aged 60.1 years and with an ECOG performance

status of 0 to 1 (see section 3.4) was younger and fitter than the population seen in NHS clinical practice. The ERG thought the best available estimates were that people seen in the NHS with advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma had an average age between 64 and 66 (Cancer Research UK and Royal Marsden Hospital Trust data). The clinical experts explained that average age of the trial population is expected to be lower than that of people seen in the NHS with these conditions. They agreed there is no evidence that treatment would be less effective in older people and stated that treatment should be based on patient fitness and comorbidities, regardless of age and performance status. The company noted that the trial age is aligned with UK data sources and that there is limited evidence to suggest outcomes differ between ECOG performance status scores. The committee concluded that CheckMate 649 data is generalisable to NHS clinical practice.

Long-term remission and cure

Some people may have long-term remission, but their life expectancy may be shorter than the general population

3.6 The company considered that evidence from CheckMate 649 suggested that the hazard of progression or death in people whose disease had not yet progressed decreases over time and plateaus at 30 months. The company proposed that people who had no disease progression 30 months or more after starting treatment were in 'long-term remission'. The company's estimates of the risk of dying in people with long-term remission were the same as the general population. The ERG noted that this meant the company assumed that people whose cancer had not progressed by 30 months after starting treatment were cured and had the same lifespan as the general population. The company considered that other evidence showing long-term survival in some people supports this assumption, for example, COUGAR-02, ATTRACTION-2, Chau 2009 and

Royal Marsden Hospital data. The ERG considered that none of the long-term evidence supported the cure assumption. The number of people in CheckMate 649 at 30 months was too low for conclusions about cure to be made. The clinical experts agreed that long-term data supporting a cure assumption does not exist. However, the clinical and patient experts explained that long-term survival is likely for some people because this has been seen with other immunotherapy treatments. The clinical expert said that about 4% of people could be expected to achieve long-term remission with chemotherapy and that they expect nivolumab could double the number to 8%. The NHS clinical lead noted that disease in long-term remission can relapse, but this is uncommon. The clinical experts said that people in long-term remission have a low burden of disease and their quality of life is good. However, their fitness is unlikely to return to pre-treatment levels because of long-term toxicities with chemotherapy, such as irreversible neuropathy. They expected the mortality rate in people with long-term remission to be higher than that of the general population because they previously had advanced cancer and cytotoxic chemotherapy. The committee concluded that some people are likely to have long-term remission, but it was unclear if they were cured. The committee further concluded that people in whom disease did not recur would still be expected to have a shorter life expectancy than people who have not had this type of advanced cancer and chemotherapy.

The company's economic model

The company's updated model is suitable for decision making

3.7 In the first committee meeting, the company used a cohort-based semi-Markov model with 4 states: pre-progression, progressed disease, long-term remission, and death. All people in the pre-progression state at 30 months entered the long-term remission state and were assumed to have the same risk of dying as the general population and were assumed to be effectively cured (see section 3.6). The ERG explained that the

company's model was unnecessarily complicated and differed from the 3-state partitioned survival models often used in NICE appraisals of cancer treatments. The model did not use overall survival data directly, even though this was as mature as the progression-free survival data used to derive overall survival estimates. The company modelled overall survival indirectly by using blinded independent central review progression-free survival data from CheckMate 649. The ERG explained that the company's model survival estimates were higher than the overall survival seen in the trial. Because the company's model did not correspond with the CheckMate 649 data, the ERG stated that the model long-term survival estimates and cost-effectiveness results lack reliability. It suggested that a 3-state partitioned survival model could use the survival data from CheckMate 649 directly. The committee agreed with the ERG that 3-state partitioned survival models are suitable and noted that the inclusion of the long-term remission state in the company's original model made the model unsuitable for decision making. After consultation, the company presented a new partitioned survival model, which the committee concluded was appropriate for decision making.

Survival modelling

Progression-free survival is modelled appropriately.

3.8 In the updated company base case, long-term survival with nivolumab was estimated using a semi-parametric approach. Kaplan–Meier estimates were directly used from CheckMate 649 for the first 6.44 months; a cut off chosen to reflect the fact that high frequency assessments, which could influence the timing of progression-free survival measurements, had ended. After this point, each treatment arm was extrapolated using a log-normal distribution. The ERG agreed with the modelling approach and distribution choice, noting that there was no clinical evidence other than CheckMate 649 to choose between alternative parametric distributions. The committee concluded the method

and distribution chosen for the projection of progression-free survival beyond the trial data was appropriate.

The approach to modelling overall survival needs further exploration

3.9 Overall survival was also modelled by the company using a semi-parametric method, using Kaplan–Meier data from CheckMate 649 for the first 6.44 months, then extrapolating the data using a Gompertz distribution. The company had also added excess mortality associated with the condition to the mortality of the general population, to get an all-cause mortality hazard. The ERG considered this a potentially good approach, but explained it thought that the company had implemented it inappropriately in the model and may have double-counted deaths. The ERG's alternative approach modelled overall survival directly to follow overall survival from the trial. The ERG noted that its approach meant that at some point the mortality hazards (chance of dying) of people with the condition would be modelled to be lower than the mortality hazards in the general population. This was implausible, so the ERG set the mortality hazard so it would never be lower than the general population. The ERG explained that the correction may still not be accurate because the committee agreed in the first committee meeting that there is likely to be an excess mortality even in remission, related to having had advanced cancer and cytotoxic chemotherapy (see section 3.6). The ERG also preferred a different distribution, the generalised gamma, to extrapolate overall survival beyond the available trial data. The ERG stated that although the company-preferred Gompertz and the generalised gamma both had good statistical fit to the trial data, the mortality hazards met those of the general population later when using the generalised gamma than the Gompertz. That is, using the ERG's approach rather than the company's model, fewer treated people would have the same risk of death as the general population and it would take longer for them to reach that point. The committee considered this was more plausible. However, the company did not agree that its modelling approach was implemented

incorrectly. It further noted that its approach did not result in the modelled mortality hazards meeting those of the general population. The clinical experts explained that, in terms of morbidity, the impact of advanced cancer and the toxicities associated with treatment mean that people with these conditions have a higher risk of other malignancies and a higher expected mortality than the general population. The committee was not able to resolve the disagreement between the company and the ERG about the implementation of the company's approach in the model. The ERG's amendment of the overall survival calculated by the company using the Gompertz distribution resulted in a greater overall survival benefit for nivolumab plus XELOX than predicted by the company. However, the use of the generalised gamma distribution as favoured by the ERG, reduced it. The committee concluded that further clarification was needed from the company on its methodology to enable it to determine whether the company or ERG approach for modelling overall survival was more appropriate.

The Gompertz model and treatment waning give a plausible 20-year survival estimate of about 3%, but this is uncertain

3.10 The committee noted, when using the ERG approach, both the Gompertz and generalised gamma parametric distributions (see section 3.9) produced similar overall survival estimates until 5 years. But, beyond this point the estimates became markedly different in the nivolumab plus XELOX arm. The ERG-amended company base case (Gompertz) predicted that after 20 years, 5.9% of people treated with nivolumab plus XELOX would be alive, compared with 0.5% predicted by the ERG's preferred generalised gamma distribution. In the XELOX-only arm, the ERG-amended company base case (Gompertz) predicted that 0.9% of people would be alive after 20 years, compared with 0.2% predicted by the ERG's preferred generalised gamma distribution. Overall, using the Gompertz distribution in the ERG-amended company base case resulted in a greater modelled overall survival benefit for nivolumab plus XELOX

compared with XELOX alone than using the ERG's preferred generalised gamma. The committee noted that it had not been presented with similar estimates up to 20 years for the company base case without the ERG amendments included. In line with previous nivolumab submissions, the ERG also explored a scenario in which any treatment effect from nivolumab with XELOX compared with XELOX alone is not maintained for life. The committee noted that the summary of product characteristics for nivolumab specifies that it can be taken for a maximum of 2 years. The scenario set the mortality hazard for those treated with nivolumab plus XELOX to be equal to that of those treated with XELOX alone at 5 years (that is, 3 years after treatment with nivolumab has stopped for all patients). When this was applied to the ERG-amended company base case using the Gompertz distribution, the proportion of people estimated to be alive in the nivolumab plus XELOX arm at 20 years was 3.1%. The clinical experts explained that a long-term benefit after treatment with nivolumab had stopped was plausible, however the potential for some treatment waning should be accounted for. Of the 3 estimates of 20-year survival with nivolumab plus XELOX (5.9% Gompertz, 3.1% Gompertz with treatment waning, and 0.5% generalised gamma) the clinical experts considered the estimates using the Gompertz distribution and including waning were plausible. The committee concluded that using the modelling approach that took into account treatment waning and resulted in a predicted 20-year survival with nivolumab plus XELOX of around 3% was plausible, but with no means to validate, remained highly uncertain.

Other assumptions and inputs in the economic model

Utility values, model baseline age and adjustments for missed doses are appropriate for decision making

3.11 After technical engagement both the company and ERG made several changes and agreed on the following assumptions and inputs:

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- Applying the company's new adjustment of costs for chemotherapy and nivolumab for missed doses.
- Setting the model's mean baseline age to 64.15 years based on Cancer Research UK data, instead of CheckMate 649 data.
- Using the company's utility values based on CheckMate 649 data.

The CheckMate 649 data that was used to inform utility values cannot be reported here because it is academic in confidence. The clinical experts agreed with the company's and ERG's approach. The committee concluded that the utility values, model baseline age and adjustments for missed doses used in the model were appropriate for decision making.

Cost-effectiveness estimates

The cost-effectiveness estimate using the most plausible overall survival estimate is highly uncertain

3.12 The deterministic cost-effectiveness results include nivolumab's confidential discount (see section 2.4). The company's base case (using Gompertz distribution to model overall survival) resulted in deterministic incremental cost-effectiveness ratios (ICERs) of £45,383 per quality-adjusted life year (QALY) gained compared with XELOX, and a probabilistic ICER of £47,873 per QALY gained. The ERG-amended company base case without treatment waning produced ICERs of £41,738 per QALY gained and, with treatment waning applied, £49,840 per QALY gained. The ERG's exploratory base case used a generalised gamma distribution for modelling overall survival (see section 3.10) without treatment waning, which resulted in ICERs of £58,816 per QALY gained and, with treatment waning accounted for, £70,681 per QALY gained. The ERG had not presented probabilistic results so it was not possible to assess if the probabilistic ICERs would be similar or higher than the deterministic results presented by the ERG. The committee had already concluded that treatment waning should be accounted for and the 20-year survival estimate of 3.1% with nivolumab plus XELOX using the

ERG's approach with a Gompertz distribution was plausible. The committee agreed that an ICER of £49,840 should be used in its decision making but the uncertainty around this ICER should be taken into account.

End of life

End of life criteria are met

3.13 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It considered whether nivolumab with platinum- and fluoropyrimidine-based combination chemotherapy meets the end of life criteria for people with untreated HER2-negative advanced gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more. The company and ERG both agreed, based on their analyses, that average life expectancy in this population is less than 24 months. The observed median overall survival benefit with nivolumab plus XELOX or FOLFOX in CheckMate 649 was larger than the additional 3 month extension to life needed by the criteria (the data cannot be reported here because it is academic in confidence). The committee concluded that nivolumab met the end of life criteria.

Because of the uncertainty, an ICER comfortably under £50,000 per QALY gained would be necessary for this technology to be considered cost effective

3.14 NICE's guide to the methods of technology appraisal notes that the appraisal committee does not use a precise maximum acceptable ICER above which a technology would automatically be defined as not cost effective, or below which it would. Also, consideration of the cost effectiveness of a technology is necessary, but is not the sole basis for decision making. Therefore, NICE considers that the influence of other factors upon the decision to recommend a technology is greater when the

ICER is closer to the top of the acceptable range. Judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee had concluded that end of life criteria applied. However, the committee noted the high level of uncertainty, specifically around:

- the long-term modelled overall survival estimates after 5 years
- the long-term survival benefit of nivolumab plus XELOX compared with XELOX alone.

It further noted that the most appropriate ICER for decision making (£49,840) was very close to the maximum that would be acceptable in the context of the additional weighting for treatments meeting the criteria for use at the end of life and was deterministic. It was unclear whether the equivalent (preferred) probabilistic ICER would be significantly higher. The committee agreed that, given the uncertainty, it could only be comfortable that nivolumab represented a cost-effective use of NHS resources if the ICER was comfortably below £50,000 per QALY gained.

Further clarity on the company's modelling approach is needed

3.15 In the second committee meeting, the company disagreed with the ERG's comment that it had implemented its approach for modelling overall survival incorrectly in the model. The committee was aware that because the company had submitted a new model in response to the committee's request at the first meeting that the company had not had a chance to formally respond to the ERG critique of its new model. The committee also noted that it had not seen equivalent long-term overall survival projections to 20 years using the company's approach. The committee agreed the company should:

- explain why their modelling approach should be considered correct

- provide overall survival estimates for 5 years, 10 years and 20 years using the company base case, both including treatment waning and not
- provide cost-effectiveness estimates for a scenario that includes an assumption on treatment waning.

Equalities

There are no equality issues relevant to the recommendations

3.16 No equality or social value judgement issues were identified.

Conclusion

Nivolumab is not recommended

3.17 The committee considered the company's new model to be appropriate for decision making. Extrapolation of CheckMate 649 overall survival data using a semi-parametric approach with a Gompertz distribution and accounting for treatment waning produced plausible 20-year survival outcomes and an ICER of £49,840 per QALY gained. However, the most appropriate method to model overall survival remains unclear and the long-term survival estimates are highly uncertain. The committee agreed that, given the uncertainty, this ICER did not represent a cost-effective use of NHS resources even taking into account its conclusion that nivolumab meets the end of life criteria. The committee concluded that both the company base case and the committee's preferred ICER for decision making were higher than a level that would assure the committee that nivolumab was cost effective. This means that nivolumab cannot be recommended for treating HER2-negative, advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma that expresses PD-L1 with a CPS of 5 or more.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
March 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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