NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Nivolumab for treating locally advanced unresectable or metastatic urothelial carcinoma after platinum-containing chemotherapy

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using nivolumab 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?

Issue date: [October 2017]

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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 determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using nivolumab 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: 9th November 2017

Second appraisal committee meeting: 23rd November 2017

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

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1 Recommendations

1.1 Nivolumab is not recommended, within its marketing authorisation, as an option for treating locally advanced unresectable or metastatic urothelial carcinoma in adults after platinum-containing therapy.

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

Treatment options for people with locally advanced unresectable or metastatic urothelial carcinoma after platinum-containing therapy are limited; they are usually offered docetaxel, paclitaxel and best supportive care.

Nivolumab has been studied in a clinical trial, but it has not been directly compared with other treatments. Based on the available evidence, it is difficult to establish the magnitude of the clinical benefit for nivolumab compared with current clinical practice.

Nivolumab meets NICE's criteria to be considered a life-extending end-of-life treatment. It is likely to extend people's lives by more than 3 months, but there is a lack of evidence comparing nivolumab with other treatments.

The committee's estimate of the most plausible ICER was based on the ERGs base-case analysis. The committee considered the most plausible ICER would be between £67,205 and £86,030 per QALY gained (these were the ICERs for nivolumab compared with paclitaxel and docetaxel, respectively). The committee therefore agreed that the most plausible

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estimate of the ICER was £76,000 per QALY gained, which is higher than what NICE normally considers acceptable for end-of-life treatments.

Nivolumab could not be recommended for routine use in the NHS. It does not appear to have the potential to be cost effective and is therefore not suitable for use within the Cancer Drugs Fund for people with unresectable or metastatic urothelial cancer after platinum-containing therapy.

2 The technology

Nivolumab (Opdivo, Bristol-Myers Squibb)	
Marketing authorisation	Nivolumab as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of platinum-containing therapy.
Recommended dose and schedule	3 mg/kg by intravenous infusion every 2 weeks.
Price	£439 per 40-mg vial or £1,097 per 100-mg vial (excluding VAT; British national formulary online, accessed September 2017). The company has agreed a patient access scheme with the Department of Health. If nivolumab had been recommended, this scheme would provide a simple discount to the list price of nivolumab with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Bristol-Myers Squibb and a review of this submission by the evidence review group (ERG). See the committee papers full details of the evidence.

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The condition

Urothelial carcinoma substantially decreases quality of life

3.1 Urothelial carcinoma causes a number of symptoms, including haematuria (blood in the urine) and increased frequency, urgency and pain associated with urination. The patient experts commented that chemotherapy is associated with unpleasant adverse effects such as fatigue, nausea and vomiting and places people at a greater risk of infection. The committee was aware that many people with the disease are older and may have comorbidities, which can affect the choice of treatment. The committee recognised that locally advanced or metastatic urothelial carcinoma has a significant impact on quality of life.

Clinical management

There is unmet need for effective treatment options

3.2 Initial treatment is usually with a cisplatin-containing chemotherapy regimen. Treatment options for people with disease progression after platinum-containing chemotherapy include docetaxel, paclitaxel or best supportive care. The clinical experts explained that none of these treatments offer lasting benefit and that prognosis is poor even for people having their first therapy. The patient experts explained that the adverse effects of chemotherapy can have a major negative impact on quality of life and that regular hospital visits for treatment disrupt usual activities. The clinical experts noted that there have been no new treatments for locally advanced or metastatic urothelial carcinoma for a number of years and that, unlike for other cancers, there is no targeted or personalised treatment yet available. The committee concluded that there is an unmet need for effective treatment options for people with locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy.

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Comparators

Paclitaxel, docetaxel and best supportive care are relevant comparators for people who have had platinum-containing chemotherapy

3.3 The company submitted clinical and cost-effectiveness analyses comparing nivolumab with paclitaxel, docetaxel, and best supportive care, although the NICE scope also included re-treatment with first-line platinum-containing therapy. The committee understood that because nivolumab is an immunotherapy with a different adverse effect profile to taxanes (such as paclitaxel and docetaxel), there may be some people for whom nivolumab is suitable who would otherwise choose best supportive care. It recognised that the introduction of immunotherapy may change clinical practice in the future, but that best supportive care is currently a treatment option for urothelial carcinoma and is therefore a relevant comparator. The committee understood that re-treatment with first-line chemotherapy was used before a standard second-line treatment option became available, and that now most clinicians would use a taxane. The clinical experts explained that re-treatment would be most likely for disease that had responded well, in people whose disease has not progressed for a long period of time after first-line treatment and are fit enough to have re-treatment with platinum. However, this choice is driven more by the clinician than the patient. The clinical experts explained that paclitaxel is used as current standard of care in the UK because of its availability and favourable adverse-effect profile compared with docetaxel, but the committee understood that these treatments could otherwise be considered clinically equivalent. The committee concluded that docetaxel, paclitaxel, and best supportive care are appropriate comparators, but re-treatment with first-line chemotherapy is not.

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Clinical trial evidence

The CheckMate studies are broadly generalisable to UK clinical practice

3.4 The clinical effectiveness evidence for nivolumab comes from 2 phase II, single-arm trials; CheckMate 275 and CheckMate 032. The trials included:

- 270 patients with locally advanced unresectable or metastatic urothelial carcinoma with disease progression or recurrence after treatment with at least 1 platinum-containing agent (CheckMate 275), and
- 78 patients with carcinoma of the renal pelvis, ureter, bladder, or urethra and disease progression after treatment with at least 1 platinum-containing chemotherapy (CheckMate 032).

There is a lack of UK patients in the trials and fewer patients with an ECOG performance status of 0 compared with those seen in clinical practice, which might impact the generalisabilty of the results. The ERG stated that 23% of people in CheckMate 032 switched to nivolumab in combination with ipilimumab upon disease progression. The committee noted that this would bias the efficacy results from this study, but acknowledged that when pooled with CheckMate 275 the proportion of patients switching treatment in the entire pooled population is low, and therefore the impact is minimal. It also noted a difference in the mean age of people in the trial (66 years) compared with the mean age in clinical practice, which the experts suggested is around 75 years. The clinical experts explained that this could suggest a role for using nivolumab in younger people whose disease has newly progressed. The committee accepted that the patient populations in the CheckMate studies are broadly generalisable to those seen in UK practice.

The CheckMate studies provide efficacy estimates for nivolumab but no randomised controlled trial evidence is available

3.5 The latest available data from CheckMate 275 reported the objective response rate at 20.0% (95% confidence interval [CI] 15.4 to 25.3) and

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median overall survival was 8.57 months (95% CI 6.05 to 11.27). In CheckMate 032 the objective response rate was 24.4% (95% CI 15.3 to 35.4) and median overall survival was 6.51 months (95% CI 1.91 to not estimable). The committee was concerned that without a trial directly comparing nivolumab with other treatments, it is difficult to reliably assess the relative treatment benefit of nivolumab. The committee also noted that the trial data are immature and based on a small numbers of patients, and therefore there is considerable uncertainty in the results. The clinical experts highlighted that people whose disease responds to treatment with an immunotherapy such as nivolumab can have a lasting response, good quality of life and prolonged survival. They explained that the novel mechanism of action of immunotherapies such as nivolumab represents a step change in clinical practice. The committee concluded that it would be challenging to accurately assess the relative treatment benefit of nivolumab without any available randomised control trial evidence.

Indirect comparison

The results of the simulated treatment comparison need to be treated with caution because the analysis was unanchored

3.6 Nivolumab has only been studied in single-arm trials for previously treated urothelial cell carcinoma, so to compare nivolumab with the relevant comparators the company did a simulated treatment comparison and network meta-analysis. This was an unanchored comparison because none of the evidence included in the analysis shared a common comparator. The committee was aware that bias is introduced into a simulated treatment comparison if all important prognostic factors are not accounted for. It considered that it is unlikely that all of the important prognostic factors had been accounted for in the simulated treatment comparison, and that this therefore impacts the robustness of the results. The ERG explained that the way to test the external validity of the simulated treatment comparison is the out-of-sample method, which could be used to assess the presence of bias in the comparison model. The

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committee heard from the company that because of the limited availability of data this validation method would not provide an accurate estimation of bias. The ERG noted that the impact of using alternative prognostic factors in the prediction model could have been assessed in a sensitivity analysis, and should have been undertaken to test the robustness of the comparison. The committee concluded that, because of the concerns regarding the robustness of the simulated treatment comparison, the results of the analysis need to be treated with caution.

The network meta-analysis produced results which were inconsistent with current clinical expectations about the effectiveness of nivolumab

3.7 The company linked the results of the individual simulated treatment comparisons together through a network meta-analysis, using a fractional polynomial model. The committee noted that this is not a conventional modelling approach for a network meta-analysis and it was concerned that a lack of evidence in the network increased the reliance on the modelling to estimate relative treatment benefit of nivolumab. The ERG explained that the fractional polynomial modelled was a highly flexible form of analysis. However, it expressed reservations about the robustness of the fractional polynomial model as incremental cost effectiveness ratio (ICER) estimates were highly sensitive to the parameterisation of the model. It also noted that including the results from a simulated treatment comparison, which was not robust, would affect the meta-analysis results, although it is unclear to what extent. The committee agreed that, the results of the indirect comparison need to be treated with caution because the optimal parameterisation of the fractional polynomial is unknown and the network of evidence is sparse. The relative treatment effect for nivolumab was estimated based on the results of the network meta-analysis. The committee heard from the company that nivolumab is expected to have a long-lasting effect because of its novel mechanism of action. The committee understood that results from the company's network meta-analysis suggest that, compared to docetaxel, the relative effectiveness of nivolumab decreases with time. The committee was

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concerned that the estimates from the network meta-analysis produced results that are inconsistent with current clinical expectations about the effectiveness of nivolumab. The committee concluded that relative effectiveness estimates inferred from the network meta-analysis are associated with uncertainty which needs to be accounted for in its decision-making.

Adverse events

Nivolumab is well tolerated

3.8 The clinical experts explained that in their experience of using nivolumab, it is well tolerated and has a preferable adverse-effect profile compared to the comparator chemotherapies. They stated that the rate of serious adverse effects from nivolumab are broadly similar to those observed for chemotherapies. They noted that the mortality risk from current treatments has decreased as clinical understanding improves following more wide spread use of the treatment. The committee noted that a similar trend could occur if nivolumab was recommended, with treatment-related mortality dropping as clinical understanding improves. It noted that it is challenging to make a robust comparison of adverse events without randomised control trial evidence. The committee acknowledged that nivolumab is associated with some rare but unpleasant and potentially serious adverse events that are specific to immunotherapy, but it concluded that nivolumab may be a tolerable alternative to chemotherapies as more experience is gained with this type of treatment.

Assumptions used in economic model

The use of standard parametric time-to-event survival analysis is preferred to a response-based approach

3.9 The company stated that standard parametric time-to-event models are unsuitable for modelling the possible sustained and long-term response to treatment which is expected with nivolumab. To account for this the

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company modelled survival using a response-based analysis. This modelled survival for people until a pre-determined time point (landmark), when survival was individually assessed according to response to treatment. The company opted for an 8-week landmark point, based on the median time to response in the CheckMate trials. The ERG explained that alternative landmarks were not fully explored and therefore the impact on the ICER was not appropriately assessed. The company used the Kaplan–Meier estimates up until the landmark, when generalised gamma curves were fitted to the separate responder and non-responder curves. The ERG stated that the company did not provide a mathematical justification to support their argument that a different response cannot be accurately described by standard parametric survival models. It explained that standard approaches are flexible enough to accurately model different responses, without needing to introduce unnecessary assumptions in to the analysis. The ERG preferred to estimate overall and progression-free survival by fitting a generalised gamma function to the trial data. The committee agreed with the ERG that the company's approach introduced unnecessary complexity into the modelling of survival.

3.10 The clinical experts explained that people with urothelial cancer who have been previously treated with a platinum-containing chemotherapy have a mean life expectancy of around 12 months and that survival at 5 years is uncommon. The committee understood that the overall survival data for nivolumab are too immature to provide a reference for the estimates generated in the survival models. The committee noted that the 5-year survival of people on other immunotherapies is approximately 10%, and accepted that this estimate could be an acceptable reference to validate the estimates produced by the different modelling approaches. The clinical experts stated that around 2 to 3% of people would be expected to be alive 5 years after treatment with current standard of care. With this in mind, the committee noted that the slope of overall survival curve for responders was nearly flat, suggesting that the proportion of responders

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alive would drop slowly. The committee agreed that the responder curve produced an implausible estimation of survival in the long term because the response-based model approach does not appear to accurately characterise survival outcomes in this population. It was concerned that the company's model overestimated the number of patients who would be alive at 5 years. It noted that patients surviving past 5 years are effectively considered cured, a claim which was not supported by the evidence. The committee heard from the company that estimates for 5-year survival in the response-based model were 17% for nivolumab and around 3 to 6% for standard of care (values derived from the company's economic model). The committee heard from the ERG that the 5 year survival estimates when using their preferred survival model was 11% for nivolumab and between 1-3% for taxanes. The committee preferred the ERG's approach to survival modelling because it produces estimates that are more consistent with those expected in this patient population. It concluded that the response-based approach used unnecessary assumptions and resulted in implausibly high estimates of overall survival. The committee preferred the use of conventional parametric time-to-event survival analysis in its calculation of the most plausible ICER.

Pooling of utility estimates from CheckMate 275 and CheckMate 032 in the model is appropriate for this appraisal

3.11 EQ-5D data were collected directly in CheckMate 275, which is the preferred measure of health-related quality of life in adults. Pre-progression utilities (0.718) and post-progression utilities (0.603) were derived from CheckMate 275, with missing values being imputed. Disutilities for adverse events were derived from the literature. The ERG explained that the utility decrements used by the company were inconsistent with those used in a previous nivolumab appraisal. It also highlighted that the company's use of utilities from only CheckMate 275 in its base-case is inconsistent with the pooling of other outcomes from CheckMate 275 and CheckMate 032. The company provided utilities pooled from both CheckMate 032 and CheckMate 275; when using these

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utilities in the model it resulted in a decrease in the ICERs for all comparisons. The committee noted in the company's estimation of the treatment effect of nivolumab, both CheckMate studies were pooled, and it agreed that a consistent approach should be taken for estimating utility values. The committee concluded that the pooling of utility estimates from the 2 trials was acceptable in this case.

Cost-effectiveness estimates

The most plausible ICER is based on the ERG's base-case

3.12 The company's probabilistic base-case ICERs are £54,220 per quality-adjusted life year (QALY) gained compared with docetaxel and £46,209 per QALY gained compared with paclitaxel. The ERG made 10 amendments to the company's base-case:

- Corrected errors relating to background mortality
- Corrected errors in calculating dose intensity
- Included gemcitabine plus cisplatin in the base-case
- Used overall survival only to calculate the responder and non-responder proportions used for response-based time to treatment discontinuation analysis
- Excluded all adverse events which occurred in less than 5% of people in the CheckMate studies
- Used pooled utilities from CheckMate 275 and CheckMate 032
- Used body surface area and weight from CheckMate 275 only
- Removed patient characteristics and comparator treatment costs from the probabilistic sensitivity analysis
- Used a non-response-based, conventional, survival analysis
- Assumed that only doses delayed by 7 days or more are missed doses.

The change from the company's preferred response-based modelling approach to a conventional time-to-event survival analysis approach had the largest impact on the ICER. The ERG's preferred probabilistic ICERs

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incorporating all of the 10 amendments are £86,030 per QALY gained compared with docetaxel and £67,205 per QALY gained compared with paclitaxel.

Docetaxel and paclitaxel are the relevant comparators for estimating the ICER

3.13 The committee accepted all of the ERG's amendments apart from the inclusion of gemcitabine and cisplatin as a relevant comparator. It heard from the clinical experts that docetaxel and paclitaxel could be assumed to be clinically equivalent, but because of differences in tolerability they are given in different frequencies. The committee agreed that docetaxel and paclitaxel are the most relevant treatments to compare with nivolumab for decision making.

The committee's estimate of the most plausible ICER is more than £50,000 per QALY gained

3.14 The committee agreed that the response-based approach did not accurately characterise the survival outcomes expected in this population, which led it to accept the ERG's analysis as a basis for estimating the most plausible ICER. It noted that the network meta-analysis resulted in estimates which were inconsistent with current clinical expectations (see section 3.7) and recalled that any analyses using these estimates needed to be treated with caution. The committee's estimate of the most plausible ICER is based on the ERGs base-case analysis. It considered that the most plausible ICER is between £67,205 and £86,030 per QALY gained (the ICER comparing nivolumab with paclitaxel, and the comparison with docetaxel respectively). The committee therefore concluded that its most plausible estimate of the ICER is £76,000 per QALY gained.

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PD-L1 subgroups

There is insufficient evidence to suggest that PD-L1 expression is predictive of survival outcomes or treatment response

3.15 The committee considered whether there were any subgroups for whom nivolumab may be more cost effective. Nivolumab inhibits the PD-L1 protein and therefore it may be more clinically and cost effective in people with higher levels of PD-L1 expression. In CheckMate 275, there was a statistically significant difference in median overall survival in people with PD-L1 >1% (11.63 months) compared to those <1% (5.95 months). Similar trends were observed for progression-free survival outcomes in both CheckMate studies. The committee noted that nivolumab appears to be more clinically effective in people with higher levels of PD-L1 based on the subgroup analyses presented by the company. The clinical experts stated that there is not enough evidence to separately assess the effectiveness of nivolumab according to PD-L1 expression. The committee considered the regulators interpretation of the clinical evidence, it noted that 12-month survival in the PD-L1 <1% subgroup appeared similar to observed in larger trials for singe-agent chemotherapy. The committee concluded that there is insufficient evidence to suggest that PD-L1 expression is predictive of outcome and it was unable to make recommendations for any subgroups based on PD-L1 expression.

End of life

Life expectancy for people with urothelial carcinoma is less than 24 months

3.16 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's Cancer Drugs Fund technology appraisal process and methods.

3.17 For people with locally advanced or metastatic disease who have had previous chemotherapy, data from the company's model and from the

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literature show that overall survival is much less than 24 months for people having treatment with standard care. The clinical experts agreed that they would expect people with locally advanced or metastatic urothelial carcinoma who have been previously treated with a platinum-containing chemotherapy to live for less than 24 months. The committee concluded that the population meets the short life expectancy criterion.

Nivolumab is likely to extend life by at least 3 months

3.18 The committee noted that because of the lack of phase III data directly comparing nivolumab with other treatments it is difficult to make robust conclusions about overall survival gain. However, data from the company's model and from the literature suggest a difference in median survival of at least 16 months. The committee noted the ERG's comments that these estimates are from the economic model, based on comparison of single-arm studies and therefore very weak evidence. The committee acknowledged the limitations in the evidence but concluded that, on balance, it is likely that nivolumab extends life by more than 3 months.

Nivolumab meets the criteria for end-of-life treatments

3.19 The committee recognised that there are important limitations in the evidence available. It concluded that the end-of-life criteria are likely to be met for this population, although it has not been presented with robust evidence for the extension-to-life criterion.

Routine commissioning

Nivolumab is not recommended for routine use in the NHS

3.20 The committee concluded that the most plausible ICERs (see section **Error! Reference source not found.**) are higher than those usually considered a cost-effective use of NHS resources for end-of-life treatments. The clinical and cost-effectiveness estimates are highly uncertain because they are based on the simulated treatment comparison. The committee did not recommend nivolumab for routine use

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in the NHS for people with locally advanced unresectable or metastatic urothelial carcinoma after platinum-containing therapy.

Cancer Drugs Fund

3.21 Having concluded that nivolumab could not be recommended for routine use, the committee considered if it could be recommended for treating metastatic or unresectable urothelial cancer after platinum-containing therapy within the Cancer Drugs Fund. The committee discussed the new arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting the addendum to the NICE process and methods guides.

Nivolumab does not have the potential to be recommended for routine use

3.22 The committee's preferred ICERs are all substantially higher than the range usually considered a cost-effective use of NHS resources for end-of-life treatments. The committee concluded that there is no plausible potential that nivolumab will satisfy the criteria for routine use in this population, not least because there are no planned or ongoing studies that could address the key clinical uncertainties identified. It did not recommend nivolumab for use within the Cancer Drugs Fund as an option for people with metastatic or unresectable urothelial cancer after platinum-containing therapy.

Other factors

3.23 No equality issues were identified.

3.24 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism is not relevant in considering the cost effectiveness of nivolumab.

3.25 The company did not highlight any additional benefits that had not been captured in the QALY.

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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.

Gary McVeigh
Chair, appraisal committee

Lindsay Smith
Vice chair, appraisal committee
September 2017

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 D.

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.

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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.

Thomas Paling
Technical Lead

Christian Griffiths
Technical Adviser

Kate Moore
Project Manager

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