Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer

Technology appraisal guidance
Published: 15 January 2020
www.nice.org.uk/guidance/ta619
Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.
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1 Recommendations

1.1 Palbociclib with fulvestrant is recommended for use within the Cancer Drugs Fund as an option for treating hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer in people who have had previous endocrine therapy only if:

- exemestane plus everolimus is the most appropriate alternative to a cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitor and
- the conditions in the managed access agreement for palbociclib with fulvestrant are followed.

1.2 This recommendation is not intended to affect treatment with palbociclib with fulvestrant 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

As agreed during the technical engagement stage, this appraisal focuses on the population who have breast cancer that is resistant to endocrine therapy. This includes people whose disease has progressed up to 12 months after neoadjuvant or adjuvant endocrine therapy or after 1 line of endocrine therapy for advanced disease. The main alternative treatment for this population is everolimus with exemestane.

Clinical trial evidence suggests that, compared with fulvestrant alone, palbociclib with fulvestrant increases the length of time before the disease progresses in people who have had previous endocrine treatment. However, it is uncertain whether people having palbociclib with fulvestrant live longer because the final overall survival data are not yet available. The results of indirect comparisons of palbociclib with fulvestrant and everolimus with exemestane are very uncertain.

The cost-effectiveness estimates are also very uncertain. Most of the plausible estimates are likely to be higher than what NICE normally considers an acceptable use of NHS resources. Therefore, palbociclib with fulvestrant cannot be recommended for routine use in the NHS.
Palbociclib with fulvestrant has the potential to be cost effective for the population considered in this appraisal, but more data are needed to resolve the uncertainties in the clinical evidence. Therefore, palbociclib with fulvestrant is recommended for this population in the Cancer Drugs Fund while these data are collected.
2 Information about palbociclib

Marketing authorisation indication

2.1 Palbociclib (Ibrance, Pfizer) is indicated ‘for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or in combination with fulvestrant in women who have received prior endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist’.

Dosage in the marketing authorisation

2.2 The recommended dose is 125 mg, taken orally, once daily for 21 consecutive days, followed by 7 days off treatment (28-day cycle). Treatment should be continued as long as the patient is having clinical benefit from therapy or until unacceptable toxicity happens.

Price

2.3 The cost is £2,950 for a 21-capsule pack of 125 mg capsules (excluding VAT; British national formulary online, accessed October 2019). The company has a commercial arrangement. This makes palbociclib available to the NHS with a discount. 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 (section 5) considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that:

- For decision making it is appropriate to focus on the population with endocrine-resistant disease presented by the company. This includes people whose disease has progressed up to 12 months after neoadjuvant or adjuvant endocrine therapy or after 1 line of endocrine therapy for advanced disease.
- Everolimus with exemestane is the key comparator for the population with endocrine-resistant disease.
- NICE’s end-of-life criteria are not met because the estimates of the extension to life are not sufficiently robust and overall survival in the comparator arm is longer than 2 years (see technical report, issue 8, page 38).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 2, page 10), and took these into account in its decision making. It discussed the following issues (technical report, issues 1 to 7), which were outstanding after the technical engagement stage.

Treatment pathway

People with advanced breast cancer would welcome another treatment option

3.1  Advanced breast cancer is an incurable condition. The patient experts explained that a diagnosis of advanced breast cancer affects people’s physical and mental health. They stated that the potential of palbociclib plus fulvestrant treatment to postpone or avoid chemotherapy is important to patients because chemotherapy can substantially reduce quality of life. The patient experts explained that people highly valued being able to continue their usual activities with minimal impact on lifestyle. They noted that palbociclib with fulvestrant...
has a convenient daily oral administration and a favourable side-effect profile compared with alternative treatment options. They also highlighted the importance of people living for longer without their disease progressing, therefore in better health. Second-line treatment for hormone receptor-positive, human epidermal growth factor receptor (HER2)-negative locally advanced or metastatic breast cancer for people whose disease has progressed up to 12 months after neoadjuvant or adjuvant endocrine therapy or after 1 line of endocrine therapy includes everolimus with exemestane. The cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors abemaciclib and ribociclib with fulvestrant have also been recommended for this population, but only within the Cancer Drugs Fund (see NICE’s technology appraisal guidance on abemaciclib and ribociclib). The committee concluded that another treatment option with a different side-effect profile, which would delay the need for chemotherapy, improve quality of life and extend how long people live before their disease progresses would be welcomed by people.

Clinical evidence

PALOMA-3 has more patients who previously had chemotherapy than in current clinical practice but the results are still relevant to the NHS

3.2 PALOMA-3 is a multicentre double-blind randomised placebo-controlled trial comparing palbociclib and fulvestrant (n=347) with placebo and fulvestrant (n=174) in adults with hormone receptor-positive, HER2-negative advanced breast cancer. It enrolled 521 women of any menopausal status whose disease progressed during or soon after (neo)adjuvant endocrine therapy or endocrine therapy for advanced disease. The ERG considered that the population included in the trial represented people in England who would currently be eligible for treatment with palbociclib plus fulvestrant. But the committee noted that a proportion of the trial population had previously had chemotherapy for advanced disease. Trials for the other CDK 4/6 inhibitors, abemaciclib and ribociclib, plus fulvestrant had excluded this subgroup. The clinical experts explained that the treatment pathway had changed so that the proportion of people having first-line chemotherapy for advanced disease was declining. The committee concluded that the results from PALOMA-3 were relevant, although it noted that the proportion of patients who had previously had chemotherapy for advanced disease was higher than expected in current NHS clinical practice.
Progression-free and overall survival

Palbociclib with fulvestrant increases progression-free survival compared with fulvestrant alone but the overall survival data are uncertain

3.3 The primary outcome measure of PALOMA-3 was investigator-assessed progression-free survival. Treatment with palbociclib plus fulvestrant increased median progression-free survival compared with fulvestrant alone from 4.6 months to 11.2 months (hazard ratio [HR] 0.50; 95% confidence interval [CI] 0.398 to 0.620, p<0.0001). Palbociclib plus fulvestrant resulted in a median 6.9 months gain in overall survival, although this was not statistically significant (median 34.9 months for palbociclib plus fulvestrant compared with 28.0 months for placebo plus fulvestrant [HR 0.81; 95% CI 0.64 to 1.03, p=0.09]). Although 60.2% of the trial population had died at the time of the latest analysis, the committee noted that PALOMA-3 was not powered to detect a difference in overall survival and further overall survival trial data were expected. The committee concluded that palbociclib with fulvestrant increased progression-free survival compared with fulvestrant alone, but its effect on overall survival is currently uncertain.

An overall survival advantage of palbociclib plus fulvestrant is likely given the CDK 4/6 inhibitor class effect

3.4 The committee recalled that PALOMA-3 included a proportion of people who had previously had chemotherapy for advanced disease. It noted that a significant proportion had also had 2 or more prior systemic therapies to treat their advanced disease. A clinical expert stated that, had the population in PALOMA-3 been similar to the trial populations for abemaciclib and ribociclib, a larger benefit with palbociclib plus fulvestrant would probably have been seen. The clinical experts also explained that clinicians consider all CDK 4/6 inhibitors to have similar efficacy and considered it likely that an overall survival advantage with palbociclib plus fulvestrant in PALOMA-3 would have been seen had the trial been powered for this. Recently published results from trials for abemaciclib (MONARCH-2) and ribociclib (MONALEESA-3) using more mature survival data showed statistically significant increases in overall survival. Taking into account the differences in trial populations, the committee concluded that it was likely there would be an overall survival advantage for people who had
treatment with palbociclib plus fulvestrant compared with fulvestrant alone. Also, further data from PALOMA-3 could potentially address the uncertainty in survival.

Palbociclib plus fulvestrant is an additional treatment option that some people may prefer

3.5 Treatment discontinuation with palbociclib plus fulvestrant reported in PALOMA-3 was much lower than reported for everolimus plus exemestane in the BOLERO-2 trial, which compared everolimus plus exemestane with exemestane alone. The committee noted that palbociclib plus fulvestrant is generally well-tolerated and resulted in very few people permanently stopping treatment in the trial. The most common adverse event for people taking palbociclib plus fulvestrant was neutropenia, which is not necessarily associated with symptoms, but may lead to dose interruptions and discontinuation. The clinical experts explained that everolimus plus exemestane is associated with significant toxicity, which restricts its use for people who are elderly, frail and have comorbidities such as diabetes. They noted that although clinicians agreed that all CDK 4/6 inhibitors have similar efficacy, the side-effect profile for each CDK 4/6 inhibitor is different. People taking ribociclib need additional monitoring, regular electrocardiogram assessments and liver function tests during treatment; abemaciclib is associated with an increased incidence of diarrhoea. The choice of CDK 4/6 inhibitor in clinical practice depends on its side-effect profile and whether a person is able to tolerate treatment. The committee recalled the patient experts' statement that palbociclib plus fulvestrant has manageable side effects, which cause minimal disruption to daily activities, and that people would value a range of treatment options. The committee concluded that palbociclib plus fulvestrant is an additional treatment option that some people may prefer.

Network meta-analysis

Both the company's and ERG's methods comparing palbociclib plus fulvestrant with everolimus plus exemestane are highly uncertain

3.6 Because there are no direct trials comparing palbociclib plus fulvestrant with everolimus plus exemestane, the company did network meta-analyses (NMAs).
The company's NMAs comparing progression-free survival and overall survival across the treatments used a single hazard ratio from each trial, based on the proportional hazards assumption that this is constant over time. Because this assumption appeared not to be appropriate for some of the studies in the network, the company amended its NMAs to use a fractional polynomial method, which allows the hazard ratios to vary over time according to a fitted parametric model. The ERG agreed with the principle of the fractional polynomial approach but had concerns about the uncertainty and clinical plausibility of the company's relative survival outputs (modelled hazard ratios as a function of time) using this method. Because of these concerns and the variability of results produced by the different fractional polynomial models, the ERG could not confidently select the most suitable fractional polynomial model to use in the progression-free and overall survival NMAs. Instead, the ERG used the progression-free survival data from the placebo plus fulvestrant arm of PALOMA-3 and the pooled overall survival data from both arms of PALOMA-3 to generate lower bound estimates of progression-free survival and overall survival for everolimus plus exemestane. The ERG assumed the clinical effectiveness of everolimus plus exemestane was no worse than the clinical effectiveness of fulvestrant. It reiterated that this was not the same as assuming clinical equivalence for everolimus plus exemestane and fulvestrant. The ERG explained that because there was no statistically significant difference in overall survival between the 2 arms of the trial, it preferred to pool the overall survival data (from the palbociclib plus fulvestrant and placebo plus fulvestrant arms) and use this larger data set to represent the assumption that everolimus plus exemestane is no worse than fulvestrant. The company noted that the efficacy of everolimus plus exemestane compared with fulvestrant had not been assessed in a head-to-head trial so an indirect treatment comparison using data for everolimus plus exemestane from BOLERO-2 was the best option. The clinical experts confirmed that clinicians consider everolimus plus exemestane to be more effective than fulvestrant. They did not consider that using the outcomes of fulvestrant monotherapy as a proxy for those of everolimus plus exemestane would be clinically plausible. The company also considered that it was inappropriate to pool the data from both arms based on lack of statistical significance, especially when the trial was not powered to detect differences in overall survival. The committee noted that if there was an overall survival benefit in the palbociclib plus fulvestrant arm, as was possible, then any overall survival advantage was being passed to fulvestrant. The committee was aware that there were several alternative methods other than the fractional
polynomial approach that can be used when the proportional hazards assumption is violated, but the ERG said that these could not be explored because of time constraints. The ERG accepted that clinicians consider everolimus plus exemestane to be clinically superior to fulvestrant. It noted that its approach allowed for alternative outputs that could be considered lower bound estimates of the effectiveness of everolimus plus exemestane. The committee agreed that both the company’s and ERG’s approaches were uncertain. These approaches may have introduced more uncertainty and assumptions than the standard method assuming proportional hazards, so the committee was unable to choose a preferred approach on which to base its decision. It noted that more survival data from PALOMA-3 would reduce the uncertainty. The committee concluded that results from both the company’s approach using fractional polynomial NMAs and the ERG’s approach of using fulvestrant monotherapy as a proxy for everolimus and exemestane were highly uncertain.

The company's economic model

3.7 The company presented a partitioned survival model with 3 health states: pre-progression survival, post-progression survival and death. The post-progression state was further divided by line of treatment, followed by best supportive care. The company used parametric curves to model progression-free survival and overall survival over a lifetime time horizon. A second-order fractional polynomial NMA was used to estimate progression-free survival for palbociclib plus fulvestrant and everolimus plus exemestane in the company's base case. These curves were used directly in the model to estimate transition probabilities over time. The ERG amended the company's model. It modelled progression-free survival on palbociclib plus fulvestrant and everolimus plus exemestane using progression-free survival data from PALOMA-3 and extrapolating using an exponential curve. The ERG’s approach produced a greater progression-free survival gain. Overall survival estimates for palbociclib plus fulvestrant in the company’s updated base case, after the technical engagement stage, were calculated using a Weibull curve fitted to the overall survival data from PALOMA-3. Overall survival estimates for everolimus plus exemestane were calculated from the fractional polynomial NMA. The ERG
modelled overall survival by extrapolating the pooled trial data (see section 3.6) using an exponential curve. Mean overall survival irrespective of treatment arm was the same using this approach. This meant that the ERG’s method predicted no overall survival gain with palbociclib plus fulvestrant compared with everolimus plus exemestane. The committee recalled the clinical expert’s statements that clinicians consider everolimus plus exemestane to be more efficacious than fulvestrant and did not consider that using the outcomes of fulvestrant monotherapy as a proxy for those of everolimus plus exemestane would be clinically plausible. The committee was also concerned that the company’s base-case model was based on fractional polynomial NMA, which it considered uncertain (see section 3.6). The committee concluded that the model structure was appropriate for decision making. However, data inputs to the models used by both the company and ERG could not robustly predict the relative survival benefit of palbociclib plus fulvestrant.

Both the company's and ERG's methods to model time to treatment discontinuation are uncertain

3.8 In the company's model, time to treatment discontinuation for palbociclib plus fulvestrant was estimated by applying a hazard ratio to the progression-free survival data from PALOMA-3. This meant that time to treatment discontinuation was shorter than progression-free survival. In the absence of data for everolimus plus exemestane, time to treatment discontinuation was assumed be equal to progression-free survival using the results of the fractional polynomial NMA. The ERG considered that using 2 different approaches to model the same effect was arbitrary and inconsistent. Instead the ERG used time to treatment discontinuation data from the palbociclib plus fulvestrant and placebo plus fulvestrant arms of PALOMA-3 to model time to treatment discontinuation for people having palbociclib plus fulvestrant and everolimus plus exemestane respectively. The company stated that it was not unusual for time to treatment discontinuation to be shorter than progression-free survival because people can stop treatment for various reasons and continue to derive benefit from treatment while off therapy. The clinical experts noted that most people having palbociclib plus fulvestrant continue treatment until disease progression. Also, everolimus plus exemestane is likely to be stopped more often than fulvestrant monotherapy before progression. Therefore, it is inappropriate to model time to treatment discontinuation to be equal to progression-free survival for everolimus plus exemestane, which results in the
cost of everolimus in the model being inflated. The clinical expert also explained that the ERG's approach using treatment duration for fulvestrant from PALOMA-3 to model time on treatment for everolimus plus exemestane was inappropriate. This is because there is clinical consensus that everolimus plus exemestane is more efficacious than fulvestrant monotherapy. The committee concluded that although the ERG's approach may produce more clinically plausible estimates than the company's, there was considerable uncertainty with both approaches. This could be addressed by collecting further time-on-treatment data.

**Subsequent therapy assumptions used by both the company and ERG are uncertain**

3.9 The company's base case included 2 active lines of subsequent therapy after disease progression. This was based on NICE's technology appraisal guidance on abemaciclib. The committee noted that subsequent therapy options differed greatly between people having palbociclib plus fulvestrant and people having everolimus plus exemestane. The company assumed that people spend nearly 5 months taking subsequent treatments and 16 months to 18 months in the best supportive care health state. The ERG considered that the mean time spent taking subsequent therapies was underestimated and the mean time spent in the best supportive care health state was overestimated in the company’s model. It presented alternative values to the company’s, with a maximum duration of subsequent therapy because of the structure of the company’s model. The clinical experts noted that in clinical practice patients have multiple subsequent treatments and for longer than both the company's and ERG's estimates. Most people are likely to have at least 2 lines of further therapy. During the technical engagement stage, it was suggested that a scenario assuming the same subsequent therapies for both palbociclib plus fulvestrant and everolimus plus exemestane should be considered. The ERG explained that in the company's model, people who had palbociclib plus fulvestrant could have everolimus plus exemestane as a later line of treatment and this had a significant impact on the costs in the model. It noted that a scenario assuming the same subsequent therapies for palbociclib plus fulvestrant and everolimus plus exemestane did not reflect clinical practice because the proportion of people having everolimus plus exemestane or exemestane monotherapy as later lines of treatment were excluded. The committee agreed that because of the variability in subsequent therapy options after disease progression with palbociclib plus
fulvestrant and everolimus plus exemestane, it was unclear how long patients would have subsequent therapies and what the subsequent therapies would be. The committee therefore concluded that both the company’s and ERG’s assumptions about subsequent therapies were uncertain and collecting further data could potentially reduce this uncertainty.

The costs of consultant appointments in different health states in the company's model are uncertain

3.10 In the company's model, consultant's appointments were costed:

- every 6 months for the pre-progression health state
- every 2 months for the post-progression first subsequent therapy health state
- every month for the post-progression second subsequent therapy health state.

The ERG considered that 1 appointment per month irrespective of health state represented NHS clinical practice. The clinical experts explained that patients see a consultant every 2 to 3 months once established on palbociclib plus fulvestrant. The committee agreed that the company's assumption of a consultant appointment every 6 months in the pre-progression health state was not frequent enough, but the ERG's assumption of 1 per month was too frequent. Therefore, the committee concluded that the costs of consultant appointments in different health states in both the company's and the ERG's models were not appropriate.

Cost-effectiveness results

The most plausible ICERs for palbociclib plus fulvestrant are uncertain

3.11 The committee considered the cost effectiveness of palbociclib plus fulvestrant in people who could have exemestane plus everolimus. The company's base case included the confidential patient access scheme for palbociclib, but not the confidential patient access scheme for everolimus (which reduces the costs of exemestane plus everolimus). Without the discount for everolimus, the company's base-case incremental cost-effectiveness ratio (ICER) compared with everolimus plus exemestane was £8,176 per quality-adjusted life year (QALY) gained. The ERG made some changes to the company's model in its
preferred base case, including:

- estimating progression-free survival, overall survival and time to treatment discontinuation using PALOMA-3 data (see sections 3.6 to 3.8)
- amending subsequent therapy assumptions to the ERG’s preferred assumptions (see section 3.9)
- removing daily oral drug wastage costs
- including monthly oncologist consultations in every health state (see section 3.10).

The committee did not accept all the assumptions in either the company’s or ERG’s preferred base case. It concluded that the plausible ICERs from both approaches were uncertain.

**Palbociclib with fulvestrant cannot be recommended for routine commissioning**

3.12 Depending on the assumptions made, when the confidential discount for everolimus was included, both the company’s and ERG’s ICERs varied from marginally below to above the range that would be considered a cost-effective use of NHS resources. The exact ICERs are commercial in confidence and cannot be reported here. However, because there was a high level of uncertainty in the clinical evidence depending on the approach taken to compare palbociclib plus fulvestrant with everolimus plus exemestane, the committee concluded that palbociclib with fulvestrant could not be recommended for routine commissioning.

**Cancer Drugs Fund**

**Palbociclib plus fulvestrant is recommended for use in the Cancer Drugs Fund**

3.13 Having concluded that palbociclib plus fulvestrant could not be recommended for routine use, the committee then considered whether it could be recommended for treating hormone receptor-positive, HER2-negative, advanced breast cancer after endocrine therapy within the Cancer Drugs Fund. It discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE’s Cancer Drugs Fund methods guide.
(addendum). The committee was aware that there will be more overall survival data from PALOMA-3 in 2020 and 2021. It agreed that further treatment-effectiveness data would make the results of the extrapolation in the model and the cost-effectiveness results more reliable. The committee agreed that there were several uncertainties, including:

- the results of the network meta-analysis (see section 3.6)
- the extrapolation of overall survival (see section 3.7)
- time to treatment discontinuation (see section 3.8)
- time on subsequent therapies and details of subsequent therapies (see section 3.9).

Some of these uncertainties could be resolved by collecting further data. The committee considered that, based on the cost-effectiveness analyses including the proposed commercial access agreement, there was plausible potential for palbociclib plus fulvestrant to be cost effective compared with exemestane plus everolimus. It therefore concluded that palbociclib plus fulvestrant met the criteria to be considered for inclusion in the Cancer Drugs Fund. It recommended palbociclib plus fulvestrant for use within the Cancer Drugs Fund as an option for people with hormone receptor-positive, HER2-negative, advanced breast cancer after endocrine therapy, only if:

- exemestane plus everolimus is the most appropriate alternative to a CDK 4/6 inhibitor and
- the conditions in the managed access agreement are followed.
4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. This means that, if a patient with hormone receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer has had endocrine therapy and the doctor responsible for their care thinks that palbociclib plus fulvestrant is the right treatment, it should be available for use, in line with NICE’s recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England’s Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.
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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ISBN: 978-1-4731-3649-6
Accreditation

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