NICE National Institute for Health and Care Excellence

NICE guidance

Bisphosphonates for treating osteoporosis

Technology appraisal guidance
Published: 9 August 2017
Last updated: 8 July 2019

www.nice.org.uk/guidance/ta464

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

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.

Contents

This guidance partially replaces TA160 and TA161.

1 Recommendations

1.1 Oral bisphosphonates (alendronic acid, ibandronic acid and risedronate sodium) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) are recommended, within their marketing authorisations, as options for treating osteoporosis in adults:

- who are eligible for risk assessment as defined in NICE's guideline on osteoporosis (recommendations 1.1 and 1.2) and NICE's quality standard on osteoporosis and
- who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in NICE's guideline on osteoporosis (recommendations 1.3 to 1.12) and NICE's quality standard on osteoporosis and
- when bisphosphonate treatment is appropriate, taking into account their risk of fracture, their risk of adverse effects from bisphosphonates, and their clinical circumstances and preferences.

1.2 The choice of treatment should be made on an individual basis after discussion between the responsible clinician and the patient, or their carers, about the advantages and disadvantages of the treatments available. If generic products are available, start treatment with the least expensive formulation, taking into account administration costs, the dose needed and the cost per dose.

1.3 These recommendations are not intended to affect treatment with alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid that was started in the NHS before this guidance was published. Adults having treatment outside these recommendations 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

Alendronic acid, ibandronic acid, risedronate sodium and zoledronic acid are bisphosphonates, licensed for treating osteoporosis. Currently clinicians offer bisphosphonates to people with osteoporosis who are eligible for risk assessment and who have a high fracture risk.

To simplify the criteria for treatment and bring the guidance into line with NICE's guideline on osteoporosis, the evidence on bisphosphonates has been reviewed. A new network meta-analysis confirms that bisphosphonates are more effective at reducing the risk of fracture than placebo.

Risk assessment tools are used in clinical practice (FRAX and QFracture), in line with NICE's guideline on osteoporosis. These tools measure risk differently and can give different levels of risk in the same person.

Oral and intravenous bisphosphonates are recommended because new analyses show they are cost effective for people who have been assessed as being at higher risk of osteoporotic fragility fracture using the methods recommended in NICE's guideline on osteoporosis and NICE's quality standard on osteoporosis.

2 The technologies

2.1 The technologies being considered in this appraisal can be used at any point in the treatment pathway, within their marketing authorisations. Costs may vary in different settings because of negotiated procurement discounts.

Table 1 Summary of the technologies

Drug, dosage form and dosage	Indication	Price
Alendronic acid (generic) tablets, 10 mg once a day	• Treating postmenopausal osteoporosis • Preventing and treating corticosteroid-induced osteoporosis in postmenopausal women not receiving hormone replacement therapy • Treating osteoporosis in men	28-tablet pack = £1.69
Alendronic acid (generic) tablets, 70 mg once a week	• Treating postmenopausal osteoporosis	4-tablet pack = £0.72
Alendronic acid (generic) oral solution, 70 mg/ 100 ml once a week	• Treating postmenopausal osteoporosis	4 × 100 ml = £27.36
Ibandronic acid (generic) tablets, 150 mg once a month	• Treating postmenopausal osteoporosis	1-tablet pack = £1.13

Ibandronic acid (generic) injection, 3 mg/3 ml once every 3 months	• Treating postmenopausal osteoporosis	3-ml prefilled syringe = £10.27 (Price based on eMIT database [data from 12-month period to end December 2015])
Risedronate sodium (generic) tablets, 5 mg once a day	• Treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures • Preventing osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women	28-tablet pack = £8.60 (Price based on eMIT database [data from 12-month period to end December 2015])
Risedronate sodium (generic) tablets, 35 mg once a week	• Treating postmenopausal osteoporosis to reduce risk of vertebral or hip fractures • Treating osteoporosis in men at high risk of fractures	4-tablet pack = £0.85
Zoledronic acid (generic) intravenous infusion, 50 micrograms/ml once a year	• Treating postmenopausal osteoporosis and osteoporosis in men (including corticosteroid-induced osteoporosis)	100-ml solution for infusion bag = £7.36 (Price based on eMIT database [data from 12-month period to end December 2015])

Note: prices based on national drug tariff.

3 Committee discussion

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

Nature of the condition

Osteoporosis can have a significant impact on a person's quality of life

3.2 Osteoporosis is a progressive skeletal disorder. It is characterised by low bone mass and deterioration of the structure of bone tissue leading to an increase in bone fragility and risk of fracture. The patient experts explained that fractures can be painful, have a significant impact on a person's independence and increase mortality. The clinical experts emphasised that it is important to prevent fragility fractures, particularly in people at the highest risk of fracture. The committee concluded that osteoporotic fragility fractures are debilitating, also affecting family and friends, and that preventing these would preserve the quality of life of the person and their carers.

Clinical management of the condition

Bisphosphonates are offered to people with the highest risk of osteoporotic fragility fractures

3.3 The clinical experts explained that bisphosphonates are generally well tolerated and are an important option in treating osteoporosis. The committee understood that bisphosphonates are usually offered to people with high fracture risk who typically have several risk factors, such as parental history of hip fracture, alcohol intake of 4 or more units per day and rheumatoid arthritis (see NICE's technology appraisal guidance on primary prevention of osteoporotic fragility fractures and

secondary prevention of osteoporotic fragility fractures). Sometimes they are offered to people with comorbidities that can lead to osteoporotic fractures. The committee noted consultation comments on the assessment report that intravenous treatment needs to be available for people who are unable to take or tolerate oral bisphosphonates (such as those with impaired cognitive function). The committee concluded that bisphosphonates are an important treatment option, which clinicians prescribe for people at the highest risk of having osteoporotic fractures.

The technology appraisal guidance on osteoporosis needs to be simplified and aligned with the clinical guideline

3.4 The committee was aware of the guidance on using bisphosphonates.

- Alendronic acid was recommended as an option for primary prevention of osteoporotic fragility fractures in postmenopausal women with a high risk of fracture; and risedronate and etidronate for those at higher fracture risk.
- Alendronic acid was recommended as an option for secondary prevention of osteoporotic fragility fractures in postmenopausal women with a high risk of fracture; and risedronate and etidronate for those at higher fracture risk.

3.5 The committee understood from the clinical experts that they have concerns about NICE's technology appraisal guidance because:

- It is based on assessing the risk of osteoporotic fragility fractures taking into account a number of specific clinical factors, which may not be readily known.
- It is difficult to implement because the criteria for using each treatment are complex.
- It is not linked to NICE's guideline on osteoporosis, which refers to a treatment threshold associated with risk assessment rather than clinical factors.
- It does not include recommendations for men.

- There are now more bisphosphonate treatments available, such as ibandronic acid and zoledronic acid, which are not covered by the guidance.
- Since publication a number of bisphosphonates have generic versions and as a result their price has dropped significantly.

The committee concluded that there is a need to align the NICE guideline and NICE technology appraisal guidance, to simplify the guidance, to include recommendations for men, and to reflect the current price of bisphosphonates.

Assessing fracture risk

QFracture and FRAX assess risk in different ways; the recommendations should be based on using either tool

3.6 The committee recognised that assessing fracture risk is important to guide treatment. It noted that the absolute risk of an osteoporotic fracture over 10 years is usually assessed using tools such as FRAX or QFracture, which are both recommended in the NICE guideline. The committee noted comments from consultees and heard from clinical experts that the 2 tools have important differences in their approach to calculating fracture risk. The committee heard that each tool includes different risk factors, and that only FRAX accounts for the competing risk of mortality. The committee further noted that FRAX can be used with or without bone mineral density but that QFracture does not incorporate bone mineral density. It heard from clinical experts that FRAX is used more often than QFracture, possibly because FRAX is included in the National Osteoporosis Guideline Group's guideline. However, it noted that QFracture is also widely used in clinical practice. The committee understood that the risk level for an individual person from each tool could be very different and the 2 tools were not interchangeable. The committee agreed that the risk assessment tools were different and that it was not possible to determine which, if either, provided a more accurate and comprehensive risk assessment of fracture. It concluded that NICE guidance needed to account for the variation in practice and differences between the tools, and therefore agreed that its recommendations should be

based on a level of risk determined by either tool.

National Osteoporosis Guideline Group

The National Osteoporosis Guideline Group's guideline provides a treatment threshold for clinicians

3.7 The committee was aware of the recent publication of a NICE accredited guideline by the National Osteoporosis Guideline Group for preventing and treating osteoporosis. The committee understood that the guideline recommended:

- treatment for people with a high risk of fragility fracture
- measuring bone mineral density and then assessing the risk of osteoporotic fragility fractures in people with intermediate risk.

The committee noted that the guideline recommended treatment thresholds, which the recent NICE quality standard on osteoporosis reflected. The committee acknowledged that the thresholds may be used to determine when to offer treatment in clinical practice. However, it recognised that the recommendations to use these thresholds did not take cost effectiveness into account.

Clinical effectiveness

Using a class-effect network meta-analysis model to assess clinical effectiveness is appropriate

3.8 The committee considered the assessment group's network meta-analysis to determine the effectiveness of the bisphosphonates compared with placebo. It noted that 27 studies providing fracture data and 35 studies providing bone mineral density data were included in the network meta-analysis designed to develop a class-effect model, that is, the treatment effects are assumed to come

from a common distribution based on the class of drug. The network meta-analysis assessed clinical effectiveness for:

- vertebral fracture
- hip fracture
- wrist fracture and
- femoral neck: bone mineral density only.

The committee concluded that the methods used for the meta-analysis were appropriate.

Pooling the efficacy results for bisphosphonates is appropriate, but cost effectiveness needs to be assessed for each treatment

3.9 The committee noted that the assessment group presented the network meta-analysis results for each treatment individually and for all bisphosphonates as a class. The committee discussed whether the bisphosphonates could be considered as a class. It heard that in clinical practice the treatments were considered to be interchangeable. It acknowledged comments from consultees that the efficacy estimates of the oral and intravenous bisphosphonates should be pooled for each fracture site. The committee noted that there were differences between the bisphosphonates in administration methods, persistence and adverse events. It therefore concluded that the efficacy estimates should be pooled, but the cost effectiveness for each treatment would need to be considered individually.

Bisphosphonates are more effective than placebo in reducing fracture risk

3.10 The committee considered the pooled efficacy estimates in the network meta-analyses, which suggest that:

- All treatments are associated with a statistically significant reduced risk of

vertebral fracture compared with placebo (hazard ratio [HR] 0.45; credible interval [CrI] 0.31 to 0.65).

- All treatments are associated with a statistically significant reduced risk of hip fracture compared with placebo (HR 0.67; CrI 0.48 to 0.96).
- None of the treatments are associated with a statistically significant reduced risk of wrist fracture compared with placebo (HR 0.81; CrI 0.46 to 1.44).
- None of the treatments are associated with a statistically significant reduced risk of proximal humerus fracture compared with placebo (HR 0.79; CrI 0.58 to 1.11).

The committee concluded that all bisphosphonates (oral and intravenous) are more clinically effective than placebo in reducing fracture risk.

Assessment group's economic model

The model structure is appropriate for decision-making

3.11 The committee was aware that the assessment group developed a de novo economic model to compare the cost effectiveness of oral bisphosphonates (alendronic acid, risedronate sodium, ibandronic acid) and intravenous bisphosphonates (ibandronic acid and zoledronic acid) and no treatment. The model was a discrete event simulation model that simulates patients with different characteristics, and calculates the costs and benefits after each event, such as fractures or death. The clinical events included in the model were hip fracture, wrist fracture, vertebral fracture, proximal humerus fracture and death. Time to event estimates were calculated using the FRAX and QFracture assessment tools. The committee concluded the model structure was appropriate for decision-making.

Population in the economic model

The model includes adults assessed for risk of osteoporotic

fragility fracture

3.12 The committee noted that, in line with the final scope, the assessment group modelled a population of adults assessed for risk of osteoporotic fragility fracture, according to the recommendations in NICE's guideline on osteoporosis. These state that assessment of fracture risk should be considered:

- in all women aged 65 years and over and all men aged 75 years and over
- in women aged under 65 years and men aged under 75 years in the presence of risk factors, for example:
  - previous fragility fracture
  - current use or frequent recent use of oral or systemic glucocorticoids
  - history of falls
  - family history of hip fracture
  - other causes of secondary osteoporosis
  - low BMI (less than 18.5 kg/m^2)
  - smoking
  - alcohol intake of more than 14 units per week for women and more than 21 units per week for men.
- Fracture risk should not be routinely assessed in people aged under 50 years unless they have major risk factors (for example, current or frequent recent use of oral or systemic glucocorticoids, untreated premature menopause or previous fragility fracture), because they are unlikely to be at high risk.

The modelled population is appropriate because it includes men and women

3.13 The committee recalled that one of the objectives of this technology appraisal was to make recommendations for men (see section 3.5), and it was assured by the assessment group that the modelled population included both men and

women. The committee concluded that the modelled population was appropriate because it matched the final scope and included both men and women.

Duration of treatment in the economic model

The duration of treatment in clinical practice is uncertain

3.14 The clinical experts explained that there is uncertainty about the recommended treatment duration for someone prescribed a bisphosphonate. Depending on the person's fracture risk, treatment for up to 60 months may be recommended. However, the treatment duration assumed in the model (based on studies reporting mean duration of treatment) was lower than this; 6 months for oral bisphosphonates, 13 months for intravenous ibandronic acid and 14 months for zoledronic acid. The committee understood that there are factors that may influence the person adhering to treatment. For example, the initial discussion between the clinician and the patient about the aim of treatment and the correct method of administration, the regular telephone follow-up to encourage patients to adhere to treatment, and help the person has in managing any adverse effects during the initial treatment period. The committee recognised that this support varies across England, which would affect how long the person stays on treatment. The committee concluded that the model may have underestimated the duration of treatment in clinical practice. But given the relatively low acquisition cost of bisphosphonates, this is likely to affect the effectiveness of treatment more than its cost, and modelling longer treatment duration would improve the cost effectiveness of bisphosphonates.

Survival estimates in the economic model

It is plausible that the survival curve for FRAX is similar to that for QFracture

3.15 The committee was aware of the assumptions made by the assessment group about the fracture-free survival curve for FRAX. The assessment group noted

that the parametric curve for fracture-free survival in QFracture was a Gompertz curve, and it had assumed that the fracture-free survival curve for FRAX would also follow a Gompertz curve with the same shape but a different rate of fracture. The committee acknowledged that the assessment group made this assumption because it did not have access to the underlying data for FRAX. The committee considered whether it was reasonable to assume that the 2 survival curves would be similar, particularly considering that the algorithm for FRAX takes mortality risk into account whereas QFracture does not. The committee concluded that there were limitations of this method, but agreed it was an appropriate approach given the lack of information on FRAX.

Utilities in the economic model

The model appropriately captures the impact on health-related quality of life of a fracture or entering a nursing home

3.16 The committee was aware that the utility values used in the model for those who have not had a fracture, or moved to a nursing home, depended on age and sex, and were based on EQ-5D data for the UK general population. It noted:

- Disutility associated with fractures was accounted for by applying a fracture disutility multiplier (rather than a decrement) to the pre-fracture utility value. Values for hip, wrist and spine fractures were based on the KOFOR/ICUROS study because this was the only study to provide pre- and post-fracture EQ-5D values for these fractures. It also had the largest sample size and reported similar results to other studies. Values from Zethraeus et al. (2002) were used for proximal humerus fractures because no other studies reported a value for this fracture site.
- Disutility associated with moving into a nursing home was accounted for by applying a utility multiplier of 0.625 to the pre-fracture utility value. This was based on a prospective cohort study that collected EQ-5D values from 90 patients with hip fractures, a proportion of whom moved into a nursing home after fracture. Several publications report a lower multiplier of 0.4. However, this was based on expert opinion rather than EQ-5D scores.

The committee concluded that it was satisfied that the impact of a fracture or of moving to a nursing home on health-related quality of life had been adequately captured in the model.

Cost of bisphosphonates in the economic model

Using the lowest cost for each bisphosphonate is appropriate

3.17 The committee was aware that generic versions of the bisphosphonates are available, and it heard from clinical experts that these are regarded as being the same as the branded drug in clinical practice. The clinical experts explained that the most appropriate bisphosphonate would be prescribed at the lowest available cost, and that sometimes this would be outside of that formulation's marketing authorisation. The committee heard that the assessment group used the lowest available cost for each bisphosphonate in the model. However, since the model was run some prices have decreased slightly, which the committee acknowledged should be taken into account in the cost-effectiveness results. The committee concluded that using the lowest available cost for each bisphosphonate in the cost-effectiveness modelling reflected clinical practice and was appropriate.

Nursing home costs

The costs of nursing homes and residential care are captured in the model

3.18 The committee noted that the initial assessment group report had considered nursing home and residential care together, and applied the costs of residential care to both. The patient expert explained that nursing home costs are much greater than residential home costs. Additionally, the level of care provided in nursing homes and in residential care is very different. Nursing homes provide medical care for people who can no longer care for themselves and residential care provides independent living with limited support. The committee

acknowledged that many people moving into residential care or nursing homes do so for reasons other than a fragility fracture. Therefore they may already be in a nursing home or residential care before fracture. The committee considered that given the differences between nursing homes and residential care, the costs of each setting should be considered individually. In the revised analyses, the assessment group separated nursing home and residential care costs. The revisions resulted in the annual cost of new admission to long-term care reducing from £36,600 to £23,500. The committee concluded that on balance the costs of nursing care and residential care in the model were appropriately captured.

Adverse events in the economic model

The model reflected the range of adverse events associated with treatment

3.19 The economic model captured some adverse events including gastrointestinal symptoms, which are associated with oral bisphosphonates (alendronic acid, risedronate sodium, ibandronic acid) and flu-like symptoms, which are associated with intravenous bisphosphonates (zoledronic acid and ibandronic acid). The committee was concerned that osteonecrosis of the jaw was not included in the model. The assessment group explained that there was not enough evidence for it to be included. Although not all adverse events have been included the committee was satisfied that the model reflected an adequate range of adverse effects associated with treatment.

Cost-effectiveness results

Conclusions on cost effectiveness should not be made, irrespective of the fracture risk tool used

3.20 The assessment group presented separate results based on using FRAX or QFracture to assess fracture risk. The committee was aware that both tools are widely used in clinical practice. It was also aware that they can provide a different

probability of fracture risk for the same person, which means that the cost-effectiveness estimates could vary depending on which tool was used to determine risk. Because of this, the committee considered that it was appropriate to estimate cost effectiveness using each risk assessment tool separately. However, the committee also recalled the need to simplify the recommendations on preventing osteoporotic fragility fractures, and link them to existing NICE guidance in this disease area. Because of this, the committee concluded that if feasible, it was appropriate to recommend treatment at a level of fracture risk irrespective of the tool used, to complement other NICE guidance on preventing osteoporotic fragility fractures.

Oral bisphosphonates are cost effective for people with at least a 1% fracture risk

3.21 The committee was aware that the assessment group provided results as incremental net benefits to allow cost effectiveness to be assessed across different 10-year fracture risk probabilities. It noted that the results were provided when valuing a quality-adjusted life year (QALY) at £20,000 per QALY gained and at £30,000 per QALY gained. At £20,000 per QALY gained oral bisphosphonates were cost effective (that is, the incremental net benefit of bisphosphonates was positive) at:

- around 1% probability of fracture risk when using QFracture and
- any treatment threshold when using FRAX.

The committee concluded that oral bisphosphonates were cost effective for people with at least a 1% fracture risk.

Intravenous bisphosphonates are cost effective for people with at least a 10% fracture risk

3.22 The committee considered the incremental net benefits of intravenous ibandronic acid and intravenous zoledronic acid. It noted the risk level at which the treatments were cost effective (that is, at which the incremental net benefit of

bisphosphonates was positive):

- ibandronic acid:
  - QFracture: at 13.7% and 10.1% (at £20,000 and £30,000 per QALY gained respectively)
  - FRAX: at 10.3% and 6.8% (at £20,000 and £30,000 per QALY gained respectively).
- zoledronic acid:
  - QFracture: at 15.9% and 10.9% (at £20,000 and £30,000 per QALY gained respectively)
  - FRAX: at 10.1% and 6.4% (at £20,000 and £30,000 per QALY gained respectively).

3.23 The committee noted that the prices of zoledronic acid and ibandronic acid are now lower than those used in the cost-effectiveness model and reasoned that this would lower the risk level at which treatments became cost effective. Therefore the committee concluded that intravenous bisphosphonates were cost effective for those with at least a 10% fracture risk.

Equality issues

Consideration should be given to people who cannot take oral bisphosphonates

3.24 The committee noted the potential equality issue raised during scoping; some people will have difficulty adhering to the complex instructions for taking oral bisphosphonates, which will affect treatment benefit. For example, people with dementia, learning disabilities, those unable to remain upright for the specified time period, and people for whom oral bisphosphonates might be contraindicated such as those with oesophageal stricture. The committee agreed that consideration should be given to this group and people who are unable to tolerate the recommended treatment.

Conclusion

Oral and intravenous bisphosphonates are recommended for some people

3.25 The committee noted its earlier conclusion that oral bisphosphonates were cost effective for people with at least a 1% fracture risk and that intravenous bisphosphonates were cost effective for those with at least a 10% fracture risk. It recommended oral and intravenous bisphosphonates as options for treating osteoporosis at these risk levels in people eligible for risk assessment. The committee considered those who are unable to tolerate oral bisphosphonates and agreed that for this group, intravenous bisphosphonates would be a cost-effective use of NHS resources.

Other factors

3.26 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of any of the technologies in this appraisal.

4 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh Ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has osteoporosis and the doctor responsible for their care thinks that bisphosphonates are the right treatment, they should be available for use, in line with NICE's recommendations.

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 B.

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.

Henry Edwards
Technical Lead

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Update information

March 2020: Background information about the appraisal deleted from sections 1 and 4 of the guidance.

July 2019: Recommendations and section 4 of the guidance updated in line with the July 2019 review decision. Patient decision aid updated to reflect the changes to recommendations.

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