NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
Amgen	We welcome the Institute's positive recommendation of denosumab for the prevention of skeletal-related events (SREs) in adults with bone metastases in patients with breast cancer and also in patients with other solid tumours. We are also pleased that the Appraisal Committee made amendments in response to comments on the first ACD made by Amgen (ACD II: Section 4.3.8, page 31; Section 4.3.9, page 32; Section 1.3, page 3).	Comment noted. No actions requested
Amgen	However, and with respect, we do not agree with Appraisal Committee's decision to withdraw the positive recommendation for use of denosumab in prostate cancer on the grounds that zoledronic acid is not the suitable comparator in this patient group. Amgen believe that there are strong and compelling reasons, based on the Institute's methods guide on comparator selection, why zoledronic acid should be considered an appropriate comparator for prostate cancer patients with bone metastasis in this appraisal of denosumab for SRE prevention: • Bisphosphonate use, and specifically zoledronic acid, for the prevention of skeletal-related events (SREs) in prostate cancer, is embedded in UK clinical practice, with clear evidence of use: Bisphosphonates are used in approximately half of all prostate cancer patients with bone metastasis in the UK, among which they are used more frequently as a treatment to prevent SREs (56% of patients) than they are for pain relief (42% of patients). Of prostate cancer patients receiving a bisphosphonate, 92% were given zoledronic acid. • Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. The Clinical Guideline 58 (CG58) recommendation against the use of bisphosphonate to prevent or reduce the complications of bone metastases in prostate cancer was based on inappropriate conclusions, underestimating the efficacy of zoledronic acid. This is reflected by the continued use of zoledronic acid to prevent SREs in prostate cancer patients in UK clinical practice, despite the CG58 recommendation.	Comment noted. See also individual responses in each section below. The Committee concluded that because bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal, for people with bone metastases from prostate cancer, is best supportive care (see FAD section 4.3.6). Based on the wording of the marketing authorisation, the Committee was unable to make recommendations as per the clinical guideline specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5). The Committee was not persuaded that the results of the analyses suggesting that denosumab may be associated with lower costs than zoledronic acid should change its decisions that the appropriate comparator for people with bone metastases from prostate cancer was best supportive care and that for this patient group denosumab in comparison with best supportive care had

Consultee	Comment	Response
	• Pain relief is implicitly part of the SRE prevention indication, since the SRE composite end point captures an intervention for the management of pain (i.e. radiation to the bone) and is therefore within the remit of this appraisal. Since CG58 recommends bisphosphonate use for pain relief in prostate cancer, zoledronic acid is an appropriate comparator. Regardless of clinical intent (i.e. for the relief of pain or prevention of SREs), denosumab compared to zoledronic acid, shows improved efficacy in prevention of SREs (which includes radiotherapy to the bone for pain relief) in the relevant prostate cancer population recommended to receive bisphosphonates by CG58 (i.e. patients with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed). The use of denosumab in this population, in the place of bisphosphonates, provides the NHS with a treatment option that is economically dominant, i.e. delivering improved outcomes for patients with cost savings to the NHS. Our aim within Amgen has been to deliver high quality, robust, comparative clinical trial evidence in response to HTA requirements. To this end, we have conducted the largest and most robust clinical trial programme in patients with bone metastases from solid tumours to-date, and have demonstrated unequivocal clinical superiority and dominant cost-effectiveness for denosumab against zoledronic acid, the standard of care within the UK, across all solid tumours. Despite this, we feel that NICE have made a preliminary recommendation, which will deny prostate cancer patients with bone metastases access to denosumab, based on a technicality relating to the wording of treatment intent and resulting comparator selection, whilst ignoring current UK practice, head to head clinical evidence, and principles of evidence-based medicine. Amgen believe that the preliminary recommendation for denosumab, which excludes prostate cancer patients based on a technicality in comparator selection, is perverse and will inevitably result in iniquitous access to treatment for patients with bone metastasis from advance solid tumours across the UK. We kindly request that NICE reconsider its preliminary recommendation against the use of denosumab as a treatment option in prostate cancer patients with bone metastases, and revise the recommendation to allow for the use of	not be shown to be a cost-effective use of NHS resources (see FAD section 4.3.25).

Consultee	Comment	Response
	denosumab where zoledronic acid is currently used for SRE prevention in prostate cancer in UK clinical practice, specifically: *Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from prostate cancer if:* *-zoledronic acid would otherwise be prescribed for these patients and* *-the manufacturer provides denosumab with the discount agreed in the patient access scheme.*	
Amgen	**UK bisphosphonate treatment patterns in prostate cancer** **Bisphosphonate use and treatment Intent** Bisphosphonate use, and specifically zoledronic acid, for the prevention of skeletal-related events (SREs) in prostate cancer is embedded in UK clinical practice. It is therefore an appropriate comparator for the prevention of SREs in prostate cancer in this appraisal**.** The Appraisal Committee concluded that *'because the intention of the guideline on prostate cancer (NICE clinical guideline 58) was to recommend bisphosphonates for pain relief, the appropriate comparator for patients with metastatic prostate cancer in an appraisal considering the prevention of skeletal-related events is best supportive care'* (ACD II: Section 4.3.4, page 29). We would wish to remind the Committee of the Institute's own guidelines on comparator selection, namely; Section 2.2.4 of the Guide to Methods of Technology Appraisal (June 2008), where it states that "Relevant comparators are identified, with consideration given specifically to routine and best practice in the NHS (including existing NICE guidance)' and also in Section 2.2.4 where it states 'There will often be more than one relevant comparator technology because routine practice may vary across the NHS and because best alternative care may differ from routine NHS practice.' Despite the recommendations of CG58 for bisphosphonate use only for pain relief, it is clear that there is variation in clinical use of bisphosphonates in prostate cancer across the UK, as recognised by the Appraisal Committee (Section 4.3.4, page 28). This reflects the mixed view among prostate cancer	Comment noted. The Committee discussed these chart review data, alongside other data on the clinical use of bisphosphonates submitted by consultees during the second ACD consultation. It noted that these data showed that bisphosphonates were being used in clinical practice, but that there was variation in reasons for their use. The Committee was not persuaded that these data on use should be relied on over the recommendations in the clinical guideline which state that bisphosphonates are not recommended for the prevention of skeletal related events (see FAD section 4.3.6).

Consultee	Comment	Response
	treating physicians regarding the relative benefits of bisphosphonates for pain relief or SRE prevention in the management of bone metastases. A UK patient chart review of treatment patterns shows that bisphosphonates are routinely used in approximately half of all prostate cancer patients with bone metastasis in the UK, among which they are used more frequently as a treatment to prevent SREs (56% of patients) than they are for pain relief (42% of patients): Table 1 presents the results from a UK patient chart review of 1161 prostate cancer patients with bone metastases (Kantar Health 2010), showing bisphosphonate treatment rates and reasons for initiation. The review shows that in 68% of prostate cancer patients with bone metastases, bisphosphonates were prescribed (currently or previously treated) or planned for future use. Of those currently treated, 56% were given bisphosphonates to prevent SREs and 42% to treat/prevent pain. In addition, treatment patterns from the IMS Oncology Analyzer™ for patients prescribed bisphosphonates show that zoledronic acid is the most commonly used bisphosphonate in prostate cancer, used in 92% of patients who receive a bisphosphonate; reflecting that zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer. Therefore we feel there is strong evidence demonstrating that zoledronic acid use for the prevention of SREs in patients with prostate cancer is embedded in UK clinical practice. This is backed up by clinical expert testimony, both within the assessment report (TAR: Section 3.2.1, page 11), and from the experts at the first Appraisal Committee meeting on 8th March 2012. As such, and in line with the Institute's own methods guide, both bisphosphonates (zoledronic acid) and best supportive care are relevant comparators in prostate cancer in this appraisal. ***Table 1 included but not reproduced here***	
Amgen	**Prostate cancer patient population treated with bisphosphonates** Whilst there is some variation within the UK, regarding clinical intent of bisphosphonate use in prostate cancer, i.e. why patients are treated (for pain relief or SRE prevention), there is broad agreement on the patient population treated with bisphosphonates i.e. who receives treatment; with the appraisal	Comment noted. The Committee understood from the clinical specialists that where zoledronic acid was used, it was in people with hormone-refractory (castration resistant) prostate cancer with painful bone metastases for whom other treatments

Consultee	Comment	Response
	committee recognising that in UK clinical practice, bisphosphonates are used in those patients as recommended by CG58 - 'The Committee heard from clinical specialists that where zoledronic acid is used, it is used in accordance with the guideline on prostate cancer (NICE clinical guideline 58) in people with hormone-refractory (castration resistant) prostate cancer with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed' (ACD II: Section 4.3.4, page 28). Importantly, evidence from prostate cancer Study 103 has demonstrated improved efficacy for denosumab compared to zoledronic acid for prevention of SREs (which includes radiotherapy to the bone for pain relief), in a specific subgroup of patients (with a prior SRE) which aligns with those patients recommended to receive bisphosphonates by CG58 i.e. in painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed. Baseline characteristics of the prior SRE subgroup for Study 103 show that 80% of patients had pain at baseline and 75% had received radiotherapy to the bone prior to entry into the study. The appraisal committee recognises that in UK clinical practice, bisphosphonates are used in those patients as recommended by CG58, i.e. for patients with painful bone metastases for whom other treatments including analgesics and palliative radiotherapy have failed. Importantly, evidence from prostate cancer Study 103 has demonstrated improved efficacy for denosumab compared to zoledronic acid for prevention of SREs (which includes radiotherapy to the bone for pain relief) in a specific subgroup of patients (with a prior SRE) which aligns with those patients recommended to receive bisphosphonates by CG58.	including analgesics and palliative radiotherapy have failed (see FAD section 4.3.6). However, the Committee was only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations as per the clinical guideline specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5). The Committee was not persuaded that the population of people who were currently receiving zoledronic acid for pain relief in accordance with the clinical guideline would be the same as the population who would receive denosumab if it was recommended for the prevention of skeletal related events (see FAD section 4.3.6).
Amgen	**Inadequate consultation on clinical expert advice on bisphosphonate use** Amgen believe that, within this appraisal process, efforts to obtain a complete picture of bisphosphonate clinical intent for use and efficacy, from a broadly representative group of UK clinicians, were inadequate. The NICE consultation process resulted in unbalanced testimony, since those clinical experts invited by the Institute to be present at the first Appraisal Committee meeting were not invited to attend the second meeting, even though it was clear from the ACD consultation that the topic of clinical intent for bisphosphonate use would be	Comment noted. Clinical specialists and patient experts were invited to and participated in the first Appraisal Committee meeting (see FAD sections 4.3.2, 4.3.3, 4.3.6, 4.3.8, 4.3.9, 4.3.12, 4.3.13, 4.3.14, 4.3.16, 4.3.18, and 4.3.22). In line with NICE processes, the clinical specialists attended the first Committee meeting, where they

Consultee	Comment	Response
	discussed for the first time in this appraisal. Section 3.5.36 of the Institute's MTA process guides state that 'If clarification of issues raised during the consultation period is required, the Chair of the Appraisal Committee can, at their discretion, invite one or more of the clinical specialists, NHS commissioning experts or patient experts to attend (the second Appraisal Committee meeting)'. Given the variation within the UK for bisphosphonate use in prostate cancer regarding clinical intent, Amgen would have welcomed the Chair of the Appraisal Committee exercising their discretion to allow broader clinical expert advice to be sought on the topic.	respond to questions from the Committee, provide clarification and help clarify issues about the submitted evidence (NICE guide to the MTA process section 3.5.6). The MTA process for second and subsequent Committee meetings states: If clarification of issues raised during the consultation period is required, the Chair of the appraisal Committee can, at their discretion, invite one or more of the clinical specialists to attend (NICE guide to the MTA process section 3.5.36). This process was followed in this appraisal. Based on the consultation comments, it was considered that they supported the variation in use of bisphosphonates identified by specialists and that therefore, the Appraisal Committee would be able to make a conclusion on the appropriate comparator of denosumab for the prevention of skeletal-related events, in patients with bone metastases from prostate cancer, by drawing on the evidence provided prior to and at the first Committee meeting, as well as evidence provided during the consultations on the ACDs. Therefore it was not considered necessary to invite the clinical specialists and patient experts to the second meeting. They were, additionally, encouraged to submit their comments on the appraisal consultation documents. All these steps were followed for this appraisal topic in line with usual NICE MTA process.
Amgen	**Efficacy of bisphosphonates in the prevention of SREs in prostate cancer**	Comment noted. It is not within the remit of

Consultee	Comment	Response
	patients Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. The CG58 recommendation against the use of bisphosphonates to prevent or reduce the complications of bone metastases in prostate cancer was based on inappropriate conclusions of zoledronic acid efficacy. Zoledronic acid is the only bisphosphonate with demonstrated efficacy and a license for use in prostate cancer, and is specifically indicated for SRE prevention. However, the appraisal committee states that 'The Committee understood that the [CG58] group considered evidence from a systematic review and meta-analysis and, based on that evidence, did not recommend bisphosphonates for preventing skeletal-related events in prostate cancer' (ACD II: Section 4.3.4, page 28). The CG58 recommendation was based on inappropriate conclusions on the efficacy of zoledronic acid in SRE prevention. The Cochrane review, which formed the basis of the evidence for assessment of efficacy for bisphosphonates in the prevention of SREs within CG58, conducted an inappropriate meta-analysis analysis which resulted in an underestimate of efficacy of zoledronic acid in SRE prevention in prostate cancer patients: • The Cochrane analysis assumed a bisphosphonate class effect and inappropriately pooled data for different bisphosphonates from three RCTs of bisphosphonate versus placebo. However, only the zoledronic acid RCT (Saad 2002) demonstrated statistically significant improvements in SRE prevention compared to placebo, and was the basis for approval for its licensed indication in SRE prevention. Neither of the RCTs evaluating disodium pamidronate (Small 2003) or sodium clodronate (Dearnaley 2003), showed evidence of efficacy in SRE prevention (with no significant differences from placebo) and as a consequence neither are licensed for SRE prevention or pain relief in prostate cancer. • The Cochrane analysis also included RCTs not relevant to SRE prevention: the study evaluating disodium pamidronate (Small 20034) was primarily a pain control study and did not report sufficient detail on	this appraisal to review the clinical guideline recommendations for the use of bisphosphonates in the prevention of skeletal related events and treatment of pain. The analysis by the Assessment Group for the appraisal of denosumab has not assumed a class effect and has focused on studies with skeletal-related event outcomes. It is the analysis by the Assessment Group, as well as that by the manufacturer that has informed the estimates of efficacy and cost effectiveness of denosumab, the bisphosphonates and best supportive care (see FAD section 4.3.4).

Consultee	Comment	Response
	the SRE prevention outcomes, whilst the RCT evaluating sodium clodronate (Dearnaley 20035) was a bone metastases prevention study and therefore was not in the appropriate population to assess SRE prevention. The assessment of efficacy of bisphosphonates in SRE prevention should therefore have been conducted without assumption of a class effect and only including relevant SRE data. This was the approach taken within the current technology appraisal, in which both network meta-analyses (conducted by Amgen and the Assessment Group) included only the zoledronic acid RCT (Saad 20023), whilst excluding the disodium pamidronate RCT and the sodium clodronate RCT for the reasons stated above. Both of these network meta-analyses showed a significant effect for zoledronic acid in SRE prevention in prostate cancer. The Cochrane review, through its inappropriate use and pooling of data was therefore biased against zoledronic acid and underestimated the efficacy of zoledronic acid, leading to a recommendation against its use for SRE prevention by CG58.	
Amgen	**Value of SRE prevention in patients with prostate cancer** Men with prostate cancer and bone metastases in the UK are in need of treatments for SRE prevention, which will become increasingly clinically meaningful to both patients and treating physicians because of improvements in patient survival. Prostate cancer patients with bone metastases carry the burden of terminal disease; SREs (following bone metastases) can result in incapacitating clinical sequelae including pathological fractures, radiation to bone, spinal cord compression, or surgery to bone, which can significantly add to that burden. SREs can dramatically erode quality of life, and the pain associated with bone metastases and SREs is significant, debilitating and difficult to treat. The prevention or delay of SREs can therefore provide meaningful benefits to these patients. Within the UK there were an estimated 38,151 prostate cancer patients with bone metastases in 2011. Evidence from a UK patient chart review shows that	Comment noted. The Committee considered evidence on the nature of skeletal-related events in adults with bone metastases from solid tumours and the value placed on the benefits of denosumab by people with the condition, those who represent them, and clinical specialists. It also took into account the effective use of NHS resources (see FAD section 4.3.1). The Committee recognised the impact on people of bone metastases and the value placed by them on minimising the effects of bone metastases (see FAD section 4.3.2). However, the Committee concluded that denosumab could not be recommended as a cost-effective use of NHS resources for

Consultee	Comment	Response
	79% of prostate cancer patients with bone metastases have a moderate to high risk of SREs and that 49% of patients have been, or are treated, with bisphosphonates1. Since publication of CG58 (2008), there have been a number of interventions licensed for the treatment of metastatic prostate cancer. It is reasonable to assume that these will result in improved survival among patients with metastatic prostate cancer in the UK (e.g. NICE TA259 positive recommendation for abiraterone) and as a consequence, SRE prevention will become increasingly important and clinically meaningful to both prostate cancer patients and all treating clinicians.	preventing skeletal-related events for those groups of patients for whom best supportive care is the appropriate comparator (see FAD section 4.3.24).
Amgen	**Pain relief is implicitly part of the SRE prevention indication** Pain relief is implicitly part of the SRE prevention indication, since the SRE composite end point captures an intervention for management of pain (i.e. radiation to the bone) and is therefore within the remit of this appraisal. Since CG58 recommends bisphosphonate use for pain relief in prostate cancer, zoledronic acid is an appropriate comparator. The CG58 evaluated bisphosphonates separately for pain relief and for the prevention or reduction of the complications of bone metastasis (i.e. SREs), and whilst they make a negative recommendation specifically for SRE prevention, they recommend bisphosphonates for pain relief in patients with painful bone metastases for whom other treatments including analgesics and palliative radiotherapy have failed. The Appraisal Committee however noted that 'neither denosumab nor any of the bisphosphonates has marketing authorisation for pain relief in this group and that pain relief on its own was not in this appraisal's remit' (ACD II: Section 4.3.4, page 28)'. However Amgen believes that this is an artificial distinction and that pain management is implicitly part of the SRE prevention and is therefore within the remit of this appraisal: The SRE composite end point captures an intervention for the management of pain (i.e. radiotherapy to the bone) and is an objective measure of worsening pain / pain progression, compared to patient reported outcomes that assess pain. Treatments that prevent radiotherapy to the bone	Comment noted. The Committee considered that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but understood that all were of importance to patients. However, the Committee was not persuaded that the population of people who were currently receiving zoledronic acid for pain relief in accordance with the clinical guideline would be the same as the population who would receive denosumab if it was recommended for the prevention of skeletal related events (see FAD section 4.3.6). The Committee was only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5).

Consultee	Comment	Response
	have prevented worsening pain / pain progression and so have provided pain relief. Table 2 presents the distribution of first on-study SRE by type, for the prostate cancer Study 103, and shows that radiotherapy to the bone is the most commonly reported SRE in all patients with prostate cancer (52.3% of patients) and also in the subgroup of patients with a prior SRE (55.0% of patients). Therefore, by preventing SREs in this patient population, treatments are providing pain relief. ***Table 2 included by not reproduced here***	
Amgen	**Clinical benefit and cost-effectiveness of denosumab over zoledronic acid in prostate cancer patients** Regardless of clinical intent (for relief of pain or prevention of SREs), compared to zoledronic acid, denosumab shows improved efficacy in prevention of SREs, including pain relief, in prostate cancer patients. Table 3 presents a summary of results from Study 103 in prostate cancer to show the efficacy of denosumab compared to zoledronic acid for the individual pain-related SRE component (prevention of radiation to the bone), for Patient Reported Outcome Measures (PROMs) of pain relief, as well as prevention of all SREs using the composite SRE endpoint. The data show that in prostate cancer patients, denosumab has demonstrated improved efficacy over zoledronic acid in relieving pain, as assessed using time to first radiation to the bone (an intervention for the management of pain); significantly reducing the risk of first radiation to the bone by [redacted] in patients with prostate cancer (p = [redacted], adjusted p value). There was also a significant delay in median time to first radiation to the bone compared with zoledronic acid in patients with prostate cancer (not estimable versus [redacted] weeks for zoledronic acid). Denosumab has also demonstrated improved efficacy over zoledronic acid in relieving pain, as assessed by PROMs; denosumab delayed the time to development of moderate or severe pain compared with zoledronic acid, in patients with no or mild pain at baseline (5.8 versus 4.9 months, p = 0.1416), decreased the proportion of patients who progressed to moderate or severe pain	Comment noted. The Committee discussed the efficacy data for pain-related and SRE outcomes for the prostate cancer study 103. The Committee recognised that denosumab improved skeletal related event outcomes compared to zoledronic acid, and that the outcomes for pain, although all favoured denosumab, were not all statistically significant (FAD section 4.3.10) While recognising the clinical efficacy of denosumab, the Committee did not consider that a recommendation about denosumab for the prevention of skeletal-related events would lead to a more efficient use of NHS resources where existing NICE guidance did not recommend the use of bisphosphonates for skeletal related events and only recommended the use of bisphosphonates for pain relief, because the populations, although overlapping, were not necessarily the same. The Committee was not persuaded that the results of the analyses suggesting that denosumab may be associated with lower costs than zoledronic

Consultee	Comment	Response
	(a relative decrease of 13.7% over 73 weeks) and reduced the number of patients who progressed from low analgesic use to strong opioids (a relative decrease of 11.7% over 73 weeks). Finally, denosumab has demonstrated superior efficacy over zoledronic acid in prevention of all SREs, as assessed using the composite SRE endpoint (which includes pathological fracture, radiotherapy to bone, surgery to bone or spinal cord compression); significantly reducing the risk of first on-study SRE by 18% in prostate cancer (p = 0.008, adjusted p value). There was also a significant delay in median time to first on-study SRE compared with zoledronic acid in patients with prostate cancer (20.7 versus 17.1 months, 3.6 month delay). ***Table 3 included but not reproduced here*** Importantly the results from the prostate cancer Study 103 show that denosumab provides superior efficacy to zoledronic acid in the prior SRE patient subgroup, which aligns with the patient population recommended by CG58 to receive bisphosphonate, i.e. in prostate cancer patients with painful bone metastasis for whom other treatments including analgesics and palliative radiotherapy have failed. Therefore denosumab is superior to zoledronic acid in preventing further radiotherapy to the bone (i.e. preventing pain interventions and so managing pain), in patients who have already experienced radiotherapy to the bone. Denosumab provides consistent clinical benefits over zoledronic acid for pain relief in prostate cancer, using both the objective measure of a pain management intervention (radiation to the bone) and Patient Related Outcomes Measures, in addition to clinical superiority over zoledronic acid in the prevention of composite SREs. Further, because denosumab has proven superior efficacy over zoledronic acid, this has been modelled by both Amgen and the Assessment Group to deliver superior overall health outcomes (in terms of QALYs gained) for denosumab compared to zoledronic acid, at a lower total cost. Therefore, regardless of the clinical intent for bisphosphonate use as recommended in NICE CG58, denosumab is a cost-effective alternative to zoledronic acid in prostate cancer patients with bone metastasis.	acid should change its decisions that the appropriate comparator for people with bone metastases from prostate cancer was best supportive care and that for this patient group denosumab had not be shown to be a cost-effective use of NHS resources (see FAD section 4.3.25).

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	The use of denosumab in place of bisphosphonates, in those prostate cancer patients recommended to receive bisphosphonates by CG58, provides a treatment that is dominant i.e. delivering improved outcomes for patients with cost savings to the NHS.	
Amgen	**Perverse recommendation** Denosumab has demonstrated, across three phase III RCTs, a superior, statistically significant, clinically meaningful, consistent and robust treatment effect for the reduction in the occurrence of SREs compared with zoledronic acid in breast, prostate and other solid tumours; also accompanied by clinically meaningful improvements in pain management compared to zoledronic acid. This clear clinical benefit of denosumab over the standard of care within the UK, combined with a patient access scheme offered by Amgen, has ensured that denosumab, in the relevant prostate cancer patient population (as defined by CG58) dominates the current standard of care; providing cost saving improved outcomes to the NHS. Our aim within Amgen has been to deliver high quality, robust, comparative clinical trial evidence in response to HTA requirements. To this end we have conducted the largest and most robust clinical trial programme in patients with bone metastases from solid tumours to-date and have demonstrated unequivocal clinical superiority and dominant cost-effectiveness for denosumab against zoledronic acid, the standard of care within the UK. Despite this, NICE have made a preliminary recommendation, which denies prostate cancer patients with bone metastases access to denosumab based on a technicality relating to the wording of treatment intent and resulting comparator selection, whilst ignoring current UK practice, head to head clinical evidence, and principles of evidence-based medicine. Amgen believe that the preliminary negative recommendation in prostate cancer is perverse and will inevitably result in iniquitous access to treatment for patients with advanced cancer across the UK. Amgen kindly request that NICE reconsider its preliminary recommendation against the use of denosumab as a treatment option in prostate cancer patients with bone metastases, and revise the recommendation to allow for the use of	Comment noted. The Committee concluded that because bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal, for people with bone metastases from prostate cancer, is best supportive care (see FAD section 4.3.6). The Committee did not consider that a recommendation about denosumab for the prevention of skeletal-related events would lead to a more efficient use of NHS resources where existing NICE guidance recommended the use of bisphosphonates for pain relief, because the populations, although overlapping, were not necessarily the same. The Committee was not persuaded that the results of the analyses suggesting that denosumab may be associated with lower costs than zoledronic acid should change its decisions that the appropriate comparator for people with bone metastases from prostate cancer was best supportive care and that for this patient group denosumab had not be shown to be a cost-effective use of NHS resources (see FAD section 4.3.25).

Consultee	Comment	Response
	denosumab where zoledronic acid is currently used for SRE prevention in prostate cancer in UK clinical practice, specifically: Denosumab is recommended as an option for preventing skeletal-related events in adults with bone metastases from prostate cancer if: -zoledronic acid would otherwise be prescribed for these patients and -the manufacturer provides denosumab with the discount agreed in the patient access scheme ***References included by not reproduced here***	
NCRI/RCP/RCR/ACP/JCCO	The consensus from our experts in breast cancer (including patient advocates) is to welcome the NICE guidance in that area. Our experts in prostate cancer note that support is not recommended for patients in that area. Although they would wish to see all effective drugs available for patients, they feel it would have been inconsistent for NICE to have approved denosumab in prostate cancer. This is because NICE guidance has previously not approved zoledronic acid in this disease, and other NICE appraisals have rejected drugs that, unlike denosumab, improve survival in castrate-refractory disease.	Comment noted. No action required.
Royal College of Nursing	**1. Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive. **2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with bone metastases from solid tumours. The preliminary views on resource impact and implications should be in line with established standard clinical practice. **3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area of health have reviewed the recommendations of the Appraisal Committee and do not have any other comments to add. The RCN would welcome guidance to the NHS on the use of this health	Comments noted. The Committee has taken into consideration current clinical practice and clinical guidelines in formulating its recommendations. It has also considered equalities issues (see FAD sections4.3.2-4.3.7 and 4.3.27).

Consultee	Comment	Response
	technology. **4. 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 gender, race, disability, age, sexual orientation, religion or belief?** None that we are aware of. **5. Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?** We are not aware of any specific issue at this stage. We would ask that any guidance issued should show that an equality impact analysis has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	
British Uro-Oncology Group (BUG)	The British Uro-oncology Group (BUG) network covers the spectrum of UK specialists who treat genito-urinary cancers as a special or main interest. The great majority of these specialise in the treatment of prostate cancer. To understand the current situation regarding use of zoledronic acid in metastatic castrate resistant prostate cancer (mCRPC), BUG conducted an e-alert survey with the following questions: 1. Do you currently prescribe zoledronic acid for prostate cancer? 2. Is your prescribing confined to patients who have suffered a skeletal related event (SRE)? 3. In the post-SRE situation, do you prescribe zoledronic acid: a. Mostly for the treatment of bone pain b. Mostly for the delay of further skeletal events The survey was issued by email to 200 UK Consultants (an estimated 80% of whom manage prostate cancer). In total 61 responses were received within the one-week deadline set for receipt of responses. Of the 61 responses received, 53 (87%) prescribe zoledronic acid (ZA) for prostate cancer. Out of the 53 who prescribe ZA for prostate cancer, 19 (36%) prescribe it exclusively in the post-SRE scenario whereas 31 (58%) prescribe it	Comment noted. The Committee discussed these survey data submitted by British Uro-Oncology Group during the consultation. The Committee noted that these data showed that bisphosphonates were being used in clinical practice, but that there was variation in reasons for their use. The Committee noted that the survey data had a high non-response rate that could affect the reliability of the data and overestimate the use of bisphosphonates. The Committee was not persuaded that these data on use should be relied on over the recommendations in the clinical guideline for prostate cancer. The Committee concluded that because bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related

Consultee	Comment	Response
	in other situations as well, which include hypercalcemia, delaying SRE and osteoporosis. Three respondents did not answer this question. Twenty-five (47%) of the 53 who use ZA responded that, in the post SRE situation, it was mostly for bone pain while 17 (32%) used it mostly for delay of further SREs. Nine respondents (17%) stated they use it for both these indications with equal importance. These results show that there is a high penetration of use of ZA in prostate cancer in the UK. This use is in accordance with several International Guidelines and whilst some of the use is in accordance with the NICE guidelines (i.e. solely for the control of pain) there is a significant proportion (25/53) who use ZA in prostate cancer patients with SREs to prevent/delay further SREs. The number of Consultant Oncologists responding to this questionnaire – 61 individuals – does not include all those involved nationally in the management of advanced prostate cancer, but it represents a significant proportion and therefore is likely to represent UK practice. The results of this survey are consistent with the expert advice provided by the Prostate Action representative (Dr Stephen Harland) and the BUG representative (Dr Amit Bahl) at the NICE meeting for denosumab for Bone Metastasis ACD on 8th March 2012. BUG would be grateful if NICE could consider this submission when considering the question of how denosumab might influence British oncological practice.	events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care (See FAD section 4.3.6).
Breakthrough Breast Cancer	Breakthrough welcomes the opportunity to comment on the appraisal consultation document regarding the use of denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. Denosumab is used to prevent the occurrence of skeletal related events (SREs) in patients whose cancer has spread to their bones. This spread (or metastasis) can come from breast cancer and other solid tumours and therefore denosumab will be an important treatment for some breast cancer patients. Therefore we are very pleased that NICE have provisionally recommended this drug as an option for preventing SREs in patients with bone metastases from breast cancer. Not only does denosumab show clinical effectiveness over the	Comment noted. No action required.

Consultee	Comment	Response
	traditional standard therapy but it will also serve as a treatment option for those patients for whom zoledronic acid is not suitable. SREs can occur as a result of bone metastases and are defined as pathological bone fractures, compression of the spinal cord or the need for palliative radiotherapy or major orthopaedic surgery for the treatment of bone metastasis. SREs can significantly impact on the quality of life of a patient causing disability, pain and hospitalisation so any treatments that can reduce their occurrence are welcome. If treatments can provide health benefits they may allow patients to continue with normal daily activities such as caring for their families or simply enjoying spending quality time with their loved ones, things that are very important to metastatic breast cancer patients. We are satisfied NICE have taken the relevant evidence into account in this appraisal. The current treatment for bone metastases and the prevention of SREs in advanced breast cancer patients is bisphosphonates such as zoledronic acid. Studies looking at the effectiveness of denosumab compared to zoledronic acid have found the former to be superior in delaying the time to first and multiple SREs. Denosumab has also been found to be better than zoledronic acid at delaying the worsening of pain of advanced cancer patients with bone metastases. We are unaware of any aspect of NICE's recommendation that needs particular consideration regarding any unlawful discrimination. We note that this recommendation is dependent on the manufacturer providing denosumab at a discounted rate as part of a patient access scheme already agreed with the Department of Health. We hope there are no changes to this agreement as we would be very disappointed if breast cancer patients could not gain access to this drug.	
Department of Health	I wish to confirm that the Department of Health has no substantive comments to	Comment noted. No action required.

Consultee	Comment	Response
	make, regarding this consultation.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	Comments from clinical specialists were received through their stakeholder organisations (Health Improvement Scotland and British Uro-Oncology Group [BUG]]) and presented in the relevant sections.	

Comments received from commentators

Commentator	Comment	Response
Health Improvement Scotland	The clinical and cost effectiveness summaries are all reasonable and fully applicable to NHS Scotland, having considered the relevant evidence. The provisional recommendations are a suitable basis for guidance for the NHS and the pathways and treatment options are again applicable to NHS Scotland. However, with regard to Prostate Cancer there is one salient point. The recommendations as stated do not approve the use of Denosumab as it is argued that the most relevant comparator is best supportive care, rather than Zoledronic Acid. In NHS Scotland we do have limited availability of Zoledronic Acid in some areas although it is not approved by SMC. There is some allowance for pain control of Zoledronic Acid by NICE but this is not explicitly stated for Denosumab. It might be argued that the best comparator for Denosumab in Scotland is Zoledronic Acid by virtue of the fact that limited availability exists.	Comment noted. The Committee considered the evidence submitted about current clinical practice with regard to bisphosphonates and considered that there was variation in use. It was not persuaded that the data on use should be relied on over the recommendations in the clinical guideline in determining the appropriate comparator. The Committee concluded that because bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care (See FAD section 4.3.6).
Health Improvement	I consider that all relevant evidence has been taken into account, that the summaries of clinical and cost effectiveness are reasonable interpretations of	Comment noted. No action required.

Commentator	Comment	Response
Scotland	the evidence and that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.	
Prostate Action	It is bitterly disappointing that once again NICE has blocked access to medicine for men with prostate cancer whilst recommending it for use in women with breast cancer. Yet again, gender inequality continues	Comments noted. The Committee discussed potential equalities issues, noting issues raised about gender in regard to breast and prostate cancer. The Committee noted that separate clinical trials have been carried out in these different cancer types, and that the trials showed different efficacy profiles of denosumab between the cancer types. The recommendations for the different cancer types (breast, prostate and other solid tumors) reflect the different choice of comparator for denosumab in the different cancer types. The choice of comparator was informed by the marketing authorisation for denosumab and the published clinical guidelines (see FAD section 4.3.27).
	At the first appraisal committee the clinical expert specialists invited by NICE clearly stated that they use bisphosphonates for SRE prevention in prostate cancer. It would appear that the clinical experts who gave their opinion in the first meeting have been ignored and as such were excluded for the follow on meeting at which a decision was made to reverse the initial recommendation for use in prostate cancer patients. Having nominated Steve Harland as a clinical expert for this NICE appraisal, it is surprising and disappointing that NICE did not invite him back to the second meeting. We strongly believe that the clinical experts should have been part of such discussions, especially as they had been invited by NICE to give their professional opinion.	Comment noted. Clinical specialists and patient experts were invited to and participated in the first Appraisal Committee meeting (see FAD sections 4.3.2, 4.3.3, 4.3.6, 4.3.8, 4.3.9, 4.3.12, 4.3.13, 4.3.14, 4.3.16, 4.3.18, and 4.3.22). In line with NICE processes, the clinical specialists attended the first Committee meeting, where they respond to questions from the Committee, provide clarification and help clarify issues about the submitted evidence (NICE guide to the MTA process section 3.5.6). The MTA process for second and subsequent

Commentator	Comment	Response
		Committee meetings states: If clarification of issues raised during the consultation period is required, the Chair of the appraisal Committee can, at their discretion, invite one or more of the clinical specialists to attend (NICE guide to the MTA process section 3.5.36). This process was followed in this appraisal. Based on the consultation comments, it was considered that they supported the variation in use of bisphosphonates identified by specialists and that therefore, the Appraisal Committee would be able to make a conclusion on the appropriate comparator of denosumab for the prevention of skeletal-related events, in patients with bone metastases from prostate cancer, by drawing on the evidence provided prior to and at the first Committee meeting, as well as evidence provided during the consultations on the ACDs. Therefore it was not considered necessary to invite the clinical specialists and patient experts to the second meeting. They were, additionally, encouraged to submit their comments on the appraisal consultation documents. All these steps were followed for this appraisal topic in line with usual NICE MTA process.

Commentator	Comment	Response
	We believe that pain relief and skeletal related event (SRE) prevention are two sides of the same coin and as such are not separate issues. So, radiotherapy to the bone is given to relieve bone pain and at the same time, it is also a commonly experienced SRE in prostate cancer. Therefore, it seems incongruous that pain relief is not considered to be part of the remit of this appraisal as denosumab is licensed for the prevention of SRE's, which included pain relief through preventing the need to intervene with radiotherapy to the bone.	Comments noted. The Committee considered that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but understood that all were of importance to patients. When considering the evidence the Committee is able to take account of health effects to an individual. However, the Committee is only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations as per the NICE clinical guideline in prostate cancer specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5).
National Collaborating Centre for Cancer	**Prostate Cancer** There appears to be a fundamental misunderstanding of the 2 separate clinical uses of bisphosphonates in prostate cancer namely prevention of skeletal related events and the treatment of bone pain. Skeletal related events (SRE) are a composite endpoint invented by the pharmaceutical industry to show clinical significance of bisphosphonates (and other bone targeted agents such as denosumab) when the individual endpoints in their trials failed to show significance. For a critical analysis of this read the Cochrane review of bisphosphonate for prostate cancer published in 2006. The guideline group for CG58, of which I was clinical lead, reviewed all the data and were unconvinced. Many of the endpoints that make up SRE are of little clinical relevance. Hence the recommendation not to use bisphosphonates for the prevention of skeletal related events in prostate cancer. Bisphosphates have also been shown to reduce pain from bone metastases. This is distinct from the prevention of bone pain which is one of the constituents	Comment noted. The Committee understood that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but understood that all were of importance to patients. The clinical trials for denosumab included both SRE outcomes and also pain-related outcomes (see FAD section 4.3.5) and when considering the evidence the Committee is able to take account of all health effects to an individual. The Committee considered all evidence received including the clinical guideline recommendations and the data about the current use of bisphosphonates submitted by other consultees. On balance, it

Commentator	Comment	Response
	of SRE. The evaluation report on denosumab confuses the prevention of pain that is part of SRE with the separate use of bisphosphonates for the treatment of established pain. In fact, the evaluation report does not appear to have reviewed any of the data on bisphosphonates for the treatment of pain (I am not even sure that there is any for denosumab). Again the CG58 guideline group reviewed the bisphosphonate evidence for pain relief and made a recommendation that bisphosphonates could be used for pain relief when other measures had failed. This has nothing to do with prevention of skeletal related events. Therefore, I cannot see how the Denosumab ACD can make any recommendation for prostate cancer either for skeletal related events or for the treatment of bone pain.	concluded that since bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care. (see FAD section 4.3.6)
National Collaborating Centre for Cancer	**Breast Cancer** I was not involved in the development of CG81 but the guideline group appears to have taken a much less sceptical view of bisphosphonates for the prevention of SRE than the prostate cancer guideline group. Reading the evaluation report for denosumab it is clear from the denosumab versus best supportive care comparisons that the cost effectiveness of zoledronate is questionable. Unfortunately this technology appraisal decided not to cover the comparison of zoledronate with best supportive care. It is also disappointing that the only comparator was zoledronate which is one of the most expensive bisphosphonates. There are a number of less costly generic bisphosphonates and no evidence that one bisphosphonate is superior to another. This is why the recommendations in both CG58 and CG81 do not specify a particular bisphosphonate. Using the data in the denosumab evaluation report one of the health economists at NCC-C has calculated that the ICERs for zoledronate versus best supportive care for the prevention of SREs in prostate cancer and breast cancer are £293,900 and £316,714 respectively. This not an issue for prostate cancer because CG58 makes a do not use recommendation for zoledronate. For breast cancer it appears that denosumab is only cost effective when compared to a non-cost effective treatment.	Comment noted. The Committee recognised that the submitted cost-effectiveness analyses suggested that zoledronic acid was not cost effective when compared with best supportive care. However, in view of the contradictory results from the published economic evaluations, and the recommendations about bisphosphonates in the guideline on advanced breast cancer (NICE clinical guideline 81), the Committee was persuaded that zoledronic acid was an appropriate comparator against which to appraise denosumab for patients with breast cancer and the subgroup of people with solid tumours other than breast and prostate for whom zoledronic acid is indicated. On balance the Committee, while recognising the uncertainties over the cost effectiveness of zoledronic acid, concluded that denosumab, based on current prices and with the patient access scheme, was shown to be cost effective compared with

Commentator	Comment	Response
		zoledronic acid (or other bisphosphonates in the case of metastatic breast cancer) (See FAD section 4.3.23).

Comments received from members of the public

Role*	Section	Comment	Response
Patient	**Section 1** (Appraisal Committee's preliminary recommendations)	As a prostate cancer patient, I have direct experience of SREs as I have recently had radiotherapy to my hip. It is accepted that such radiotherapy to the bone is given to prevent SREs, and also given to relieve the pain. I therefore find it illogical that NICE has chosen to separate pain relief from SRE prevention. As denosumab is licensed for the prevention of all SREs, which includes pain relief through preventing the need to intervene with radiotherapy to the bone. Therefore I think NICE should reconsider the negative recommendation in the prostate cancer setting. I am one of the lucky ones who has had bisphosphonates as part of a clinical trial and believe this has protected my bones for some time, though sadly I have now had to have radiotherapy to my hip. One of the two clinical specialists invited by NICE to provide the committee with clinical expertise at the first appraisal meeting said that they use bisphosphonates for SRE prevention in prostate cancer. However, the specialists were not invited to the second meeting, even though their view on the reason for use of bisphosphonates in prostate cancer would have been useful to this appraisal. Through this reversal of their original decision, NICE is denying	Comment noted. The Committee considered that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but understood that all were of importance to patients. However, the Committee was only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5). The Committee noted comments received and concluded that since bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care. (see FAD section 4.3.6)

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
		prostate cancer patients access to a medicine which is available to cancer patients with breast cancer or other solid tumours, despite equally convincing clinical data.	Comment noted. Clinical specialists and patient experts were invited to and participated in the first Appraisal Committee meeting (see FAD sections4.3.2, 4.3.3, 4.3.6, 4.3.8, 4.3.9, 4.3.12, 4.3.13, 4.3.14, 4.3.16, 4.3.18, and 4.3.22). In line with NICE processes, the clinical specialists attended the first Committee meeting, where they respond to questions from the Committee, provide clarification and help clarify issues about the submitted evidence (NICE guide to the MTA process section s3.5.6). The MTA process for second and subsequent Committee meetings states: If clarification of issues raised during the consultation period is required, the Chair of the appraisal Committee can, at their discretion, invite one or more of the clinical specialists to attend (NICE guide to the MTA process section 3.5.36). This process was followed in this appraisal. Based on the consultation comments, it was considered that they supported the variation in use of bisphosphonates identified by specialists and that therefore, the Appraisal Committee would be able to make a conclusion on the appropriate comparator of denosumab for the prevention of skeletal-related events, in patients with bone metastases from prostate cancer, by drawing on the evidence provided prior to and at the first Committee meeting, as well as evidence provided during the consultations on the ACDs. Therefore it was not considered necessary to invite the clinical specialists and patient experts to the second meeting. They were, additionally, encouraged

Role*	Section	Comment	Response
			to submit their comments on the appraisal consultation documents. All these steps were followed for this appraisal topic in line with usual NICE MTA process. The Committee discussed potential equalities issues, noting issues raised about gender in regard to breast and prostate cancer. The Committee noted that separate clinical trials have been carried out in these different cancer types, and that the trials showed different efficacy profiles of denosumab between the cancer types. The recommendations for the different cancer types (breast, prostate and other solid tumours) reflect the different choice of comparator for denosumab in the different cancer types. The choice of comparator was informed by the marketing authorisation for denosumab and the published clinical guidelines (see FAD section 4.3.27).
NHS Professional	**Section 1** (Appraisal Committee's preliminary recommendations)	(1) There is an error on page 5. The NICE Prostate Cancer guideline recommended bisphosphonates to relieve pain (not to prevent bone mets) only when other treatments had failed. It would be more pertinent to quote the recommendation in the same guideline that zoledronate should NOT be used to prevent SREs. (2) The Prostate cancer guideline recommendation was based on the view that zoledronate did not impact on either overall survival or quality of life, and that SREs were of uncertain clinical significance. Precisely the same considerations apply to denosumab. It has not been shown to improve either survival or quality of life, and so the case rests on whether or not SREs are clinically significant, and if so, whether the drug is cost-effective. My own view is that some SREs are definitely clinically significant (e.g. spinal	Comment noted. FAD has been updated to include the CG58 negative recommendation on use of bisphosphonates to prevent skeletal-related events (see FAD section 2.6) The Committee recognised that there were differences between treatment aims to relieve pain, prevent pain and delay worsening pain, but recognised some overlap between pain-related outcomes and skeletal-related event outcomes but understood that all were of importance to patients (see FAD section 4.3.5). The Committee also discussed the clinical importance of the skeletal related event

Role*	Section	Comment	Response
		cord compression) and that other SREs are not clinically significant (e.g. asymptomatic fractures detected only on routine imaging). Other SREs are of some significance (e.g. palliative EBRT). I think that one needs to look at the individual SREs rather than merely the composite in order to evaluate whether the drug effect is clinically significant.	outcome and concluded that it was appropriate to use skeletal related event as defined in the clinical trial as the basis of its decision (see FAD section 4.3.7).
	Section 1 (Appraisal Committee's preliminary recommendations))	(3) I think prostate cancer should be considered as a separate entity. It should not be assumed that bone mets from prostate behave and respond in the same way as bone mets from other cancers (4) in the case of prostate cancer, based on the NICE guideline from 2008, the appropriate comparator should be best standard of care and not zoledronate (5) It seems to me that the evidence concerning denosumab for SRE prevention in prostate cancer is very similar indeed to the evidence concerning zoledronate. Given that NICE Prostate Cancer Guideline in 2008 recommended that zoledronate should NOT be used, I expect the same recommendation with regard to denosumab. (6) It would seem to me bizarre for NICE to approve an expensive drug that does not improve survival or quality of life at the same time that it is rejecting drugs that do improve both survival and quality of life in CRPC.	Comment noted. The Committee concluded that because bisphosphonates are recommended for pain relief when other treatments have failed in the guideline on prostate cancer (NICE clinical guideline 58), and not for the prevention of skeletal-related events, the appropriate comparator in this appraisal for people with bone metastases from prostate cancer is best supportive care. The Committee was only able to make a recommendation in accordance with the wording of the marketing authorisation about the use of denosumab for the prevention of skeletal-related events. It was unable to make recommendations, as per the clinical guideline on prostate cancer, specifically for the use of denosumab for pain relief in people with prostate cancer (see FAD section 4.3.5).