National Collaborating Centre for Cancer

Myeloma in adults:

diagnosis and management

Clinical Guideline

Appendices A - F

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Appendix A: The cost effectiveness of alternate imaging strategies for diagnosis in secondary care of patients with suspected myeloma

A.1 Background

Bone disease is a common feature in myeloma and soft tissue lesions could also be present. Therefore patients with a plasma cell disorder suspected to be myeloma undergo imaging to identify anatomical lesions caused by the disease.

Skeletal survey with secondary imaging by CT or MRI for equivocal and negative results with suspicion of myeloma is the primary imaging investigation used in UK. Skeletal survey is a combination of plain radiographs which includes commonly affected sites (e.g. skull, spine, chest, humeri, femora). It is readily available, low cost with relatively low radiation exposure. However this form of imaging is potentially less sensitive than other imaging techniques available. It is possible some patients who have a normal skeletal survey do have lesions that just cannot be seen on plain films. Other techniques include computed tomography (CT), magnetic resonance imaging (MRI) and FDG positron emission tomography CT (PET-CT). These imaging techniques are potentially more sensitive and specific than the skeletal survey. However, they are more costly and may increase radiation burden (especially PET-CT and CT). They are also used at the treatment planning stage and many patients with a positive diagnosis of myeloma would go on to receive these imaging techniques. In patient groups with suspected myeloma where the prevalence is likely to be high it may be optimal, in terms of both costs and health outcomes to perform this imaging for diagnosis avoiding the need for this additional imaging at the treatment planning stage. Uncertainty remains around whether performing cross-sectional imaging earlier is cost effective and if so which imaging modalities are optimal.

A.2 Existing economic evidence

A systematic literature review was performed to assess the current economic literature for this topic. The review identified 463 possibly relevant economic papers relating to myeloma. Of these, no papers were deemed relevant for this topic and therefore no papers were included in the review of existing economic evidence.

A.3 De novo economic model

The current economic literature did not adequately address the decision problem; therefore a de novo economic evaluation was created to assess cost effectiveness. All analyses were conducted in Microsoft Excel 2007.

A.3.1 Aims of analysis

The aim of the economic analysis was to assess the cost effectiveness of skeletal survey compared to whole body CT (WB-CT), MRI spine with plain radiograph of the long bones (MRI spine), whole body MRI (WB-MRI) and PET-CT for diagnosis in secondary care patients with a plasma cell disorder suspected to be myeloma. Bone scans were not

considered in the economic model as it was unclear, at this point in time, how they would fit into a clinical pathway for diagnosing myeloma. All analyses were conducted from a National Health Service (NHS) and Personal Social Services (PSS) perspective although in line with the scope of the guideline only diagnosis in a secondary care setting was considered.

A.3.2 Type of analysis

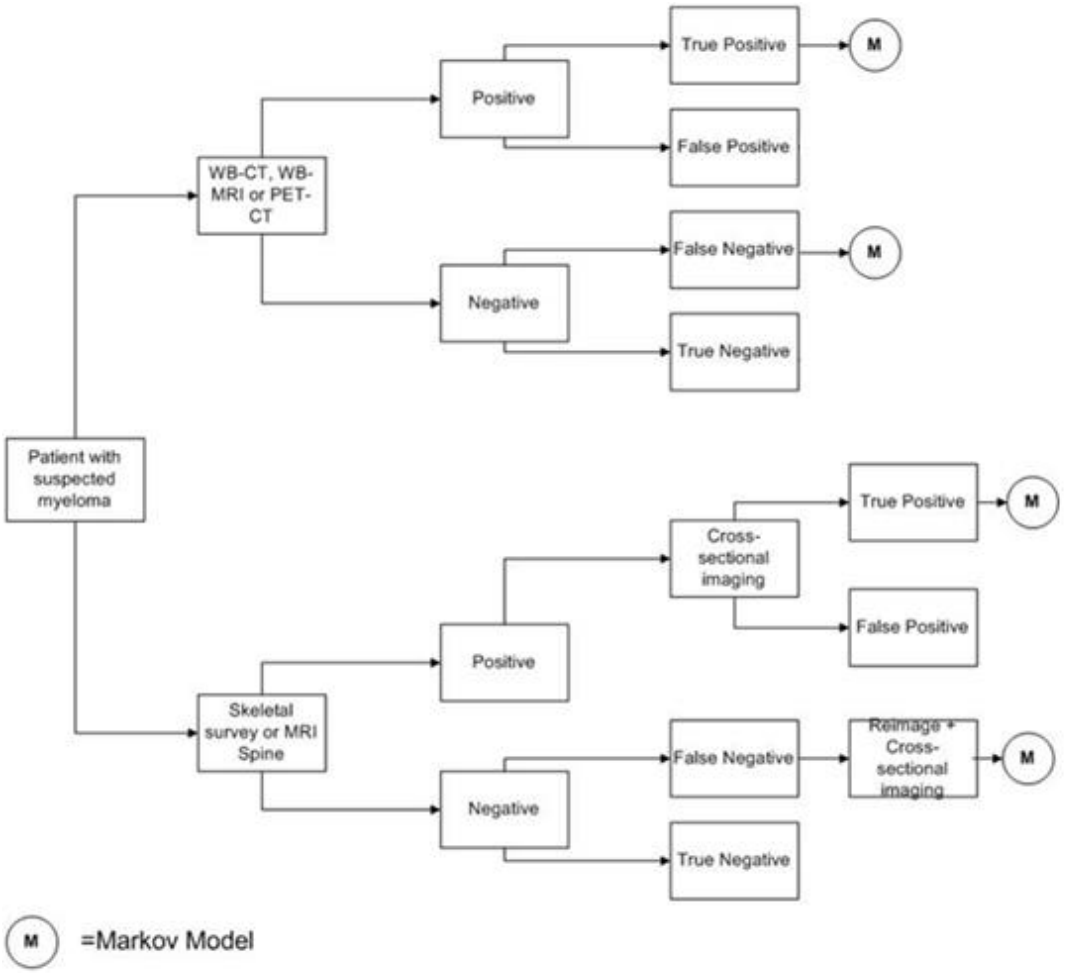
A decision tree model was created to estimate the proportion of people correctly diagnosed using each competing imaging strategy. Following the decision tree portion of the model all people with myeloma were assigned to a simple Markov model with two states, alive and dead, with transition probabilities dependent on whether myeloma was correctly diagnosed or not. All people with correct non-myeloma diagnoses (true negatives) and incorrect myeloma diagnoses (false positives) were not followed up after the decision tree component as they are assumed to have equal resource use and quality of life across all interventions after this point. All models were created in Microsoft Excel 2007.

A.3.3 Model structure

The economic model considered five potential diagnostic imaging interventions skeletal survey, WB-CT, MRI spine (with plain radiograph of the long bones), WB-MRI and PET-CT.

Patients receive either a positive or negative result based upon the diagnostic accuracy of the imaging modality. Following a positive diagnosis decisions need to be made about treatment requiring cross-sectional imaging. Patients in the skeletal survey or MRI spine arm of the model receive cross-sectional imaging to guide treatment decisions, assumed to be WB-CT in the base case, if initial imaging is positive for myeloma. People in the WB-CT, WB-MRI or PET-CT arms are assumed to have received sufficient imaging to be able to make these treatment decisions. Therefore, following positive imaging for myeloma, will receive no further imaging for the purposes of either diagnosis or treatment planning. The structure of the model is shown in Figure 1.

Figure 1: Structure of the economic model



Following the initial decision tree portion of the model people with myeloma enter one of three Markov models based on their time from first symptoms upon entering the model and whether they received a correct diagnosis or not. Discussion of the alternate Markov models is presented later.

The model assumes that people with myeloma who receive a false negative result from imaging will receive diagnostic reimaging six months later which would always correctly diagnose myeloma. All these patients would be entered into the Markov model for diagnosis after six months of first symptoms.

All people receiving chemotherapy treatment whether appropriately or not would have a decreased quality of life from the adverse events of treatment. It was deemed very unlikely, given the relatively intensive observation of patients with myeloma that patients falsely diagnosed would not go on to be correctly diagnosed before active treatment. False positives were therefore assumed to receive a correct diagnosis at cross-sectional imaging or at a reimaging six months later. Therefore, the only impact of a false positive diagnosis was an increase in resource use through additional imaging. As above these people would not be followed up in the Markov portion of the model. Whilst incorrect diagnoses are likely to lead to increased anxiety in patients no evidence was identified around their effect on ‘quality of life’ and therefore was not explored in the economic model.

A.3.41 Prevalence

2 A systematic review identified no studies reporting on the prevalence of myeloma amongst
3 people receiving diagnostic imaging for plasma cell disorders suspected to be myeloma.
4 Prevalence figures therefore had to be estimated from other myeloma populations. For the
5 base case prevalence figures were taken from 1684 patients at the US Mayo clinic in 2006
6 with a M protein in the serum or urine. The study estimated that 19.8% had myeloma, 54.7%
7 monoclonal gammopathy of undetermined significance (MGUS) and the remaining 25.5%
8 other lymphoproliferative disorders (Kyle & Rajkumar, 2007). Two other similar studies were
9 identified: one involved 930 cases of m-protein in secondary care in Malmö between 1975
10 and 1989 (Bird et al., 2009) and one based at a large district general hospital in Italy involved
11 730 cases over a ten year period from 1973 to 1983 (Malacrida et al. 1987) (Table 1). Both
12 studies, despite being in a European setting and perhaps more reflective of a UK population,
13 were over 25 years old and may not match current diagnostic criteria. Both these alternate
14 prevalence estimates were used as a one-way sensitivity analysis.

15 **Table 1: Summary of estimated prevalence of Myeloma, MGUS and other discorders**
16 **in imaged population**

	Myeloma	MGUS	Other
USA (Kyle & Rajkumar, 2007)	19.8%	54.7%	25.5%
Sweden (Bird et al., 2009)	19%	72%	4%
Italy (Malacrida et al. 1987)	25.6%	69.6%	4.8%

A.3.517 Diagnostic accuracy

18 Eight studies considering interventions included as part of the economic modelling were
19 identified by the accompanying clinical evidence review (Alexandrakis,et al., 2001; Sohn et
20 al., 2002; Alper et al., 2003; Zamagni et al., 2007; Myslivecek et al., 2008; Sager et al., 2011;
21 Cascini et al., 2013; Erten et al., 2007). Two other studies were identified which only covered
22 interventions outside of those considered in the economic analysis (Catalano et al., 1999;
23 Svaldi et al., 2001). Evidence was found on all included interventions apart from WB-CT.

24 The evidence assessed using QUADAS-2 was of moderate to low quality. The risk of bias in
25 the included studies was generally low or unclear due to underreporting with regards to the
26 timing and blinding of the index and reference tests. There was great uncertainty in the
27 patient selection methods as many studies did not report this and it was unclear whether a
28 consecutive or random sample of patients had been recruited and if inappropriate exclusions
29 had been avoided. It was therefore impossible to tell how representative they are of the
30 patient group that would be seen in NHS practise. Some studies were highlighted as having
31 a high risk of bias in the patient selection category as the population did not include a control
32 group (i.e. negative reference standard results) meaning that the specificity of the test could
33 not be determined. The reviewer highlighted to the Guideline Committee (GC) that only 4 of
34 the 10 included studies included negative cases (not myeloma) to determine specificity. his
35 again implies that the patient populations are not generalisable given that the majority of
36 cases seen during diagnosis would be negative for myeloma. It also makes it unclear
37 whether studies which reported a high sensitivity did so at the expense of a lower specificity
38 and consequently more false positives.

39 Given these issues with the included evidence, especially the issues of applicability, patient
40 selection and lack of negative cases in the patient cohorts the GC found it difficult to give
41 weight to the values reported in the evidence review and to estimate values for inclusion in
42 the economic model. This was particularly true around values of specificity. The base case
43 values used in the economic model (Table 2), whilst based on the evidence review where
44 possible are intended to be illustrative and not an estimate or ranking of the diagnostic

accuracy of the different imaging modalities. From the GC's clinical experience and supported somewhat by low quality evidence MRI was assumed to be the most diagnostically accurate, in terms of both sensitivity and specificity.

Table 2: Sensitivity and specificity used in the base case economic model

	Sensitivity	Specificity	Source (Sensitivity,Specificity)
Skeletal Survey	64%	50%	Sohn, Illustrative value
WB-CT	94%	94%	Illustrative value, Illustrative value
MRI spine	93%	95%	Myslivecek, Illustrative value
WB-MRI	100%	95%	Cascini, Illustrative value
PET-CT	90%	35%	Sager, Zamagni

Given the lack of or weak evidence around the diagnostic accuracy estimates they were extensively explored during sensitivity analysis. Sensitivity and specificity were also assigned a wide, uninformative uniform distribution, between 50% and 100% during probabilistic sensitivity analysis. This was deemed sufficient to cover all potential sensitivity and specificity values based on the GCs clinical experience. As this range was at odds with the only value of specificity reported for PET-CT in the evidence review the diagnostic accuracy of this intervention was explored during a separate deterministic sensitivity analysis varying both sensitivity and specificity between 0% and 100%. As insufficient evidence on specificity was identified to estimate the trade-off between sensitivity and specificity both were considered as independent variables in all sensitivity analyses with no covariance assigned between them.

Whilst the GC's clinical experience considered both MRI and WB-CT to have a higher sensitivity than skeletal survey it was deemed inappropriate, given the absence of robust evidence, to give either narrower or more favourable distributions during the PSA. It should be noted though that if WB-CT and MRI are more diagnostically accurate the PSA would represent a conservative estimate for the cost effectiveness of both interventions.

A.3.6 Population demographics

The age and sex of our modelled cohort was likely to be similar to that reported in the Kariyawasan et al (2007) study used for the clinical inputs in the model described in detail below (Kariyawasan et al. 2007). The study, based at one myeloma centre in London, UK estimated an average age of 65 years and was 58.3% male. No evidence was identified that the accuracy of diagnosis or quality of life differed by age or sex. Furthermore all patients in the cohort followed up in the Markov model would have myeloma for the remainder of their lives. Therefore, general population survival and quality of life were not used in the model. The sex and age of the cohort therefore have no influence on the outcome of the economic evaluation and are intended to be illustrative of the likely population cohort in the UK. As these demographics were not linked to the results it was futile to alter these during sensitivity analysis.

A.3.7 Clinical inputs

The accompanying evidence review did not identify any papers that reported clinical outcomes from differing imaging strategy. The link between diagnostic accuracy and clinical outcomes and quality of life therefore had to be modelled.

A systematic review identified two studies which linked time to diagnosis to survival and myeloma related complications (Friese et al., 2009; Kariyawasan et al., 2007). Kariyawasan et al (2007) investigated the relationship between time to diagnosis of myeloma and number of complications and survival. Kariyawasan et al (2007) was a retrospective study of 92 patients with myeloma who attended one London based myeloma centre between 2001 and

2006. Patients' medical records were analysed to look at time of first symptom, time of diagnosis, complications at time of diagnosis and presenting physician. The study concluded that time to diagnosis predicted both the number of complications and disease free survival of people with myeloma.

Friese et al (2009) was a US retrospective study of 5483 patients diagnosed with myeloma from the Surveillance, Epidemiology and End Results programme (SEERs). The study used this retrospective data to look at the time between anaemia or back pain symptoms and myeloma diagnosis. The study again estimated the relationship between time to diagnosis and complications. The study did not consider overall or disease free survival. The study concluded that time to diagnosis did not predict outcomes in patients with myeloma (OR 0.9, CI 0.8-1.1)

In the base case economic model outcomes from Kariyawasan et al (2007) were used. Even though the study size was significantly smaller than Friese et al (2009) the patient group and treatment pathway was more likely to be reflective of that in the NHS. A sensitivity analysis was performed that assumed there was no improvement in patient outcomes from prompter diagnosis (a de-facto cost-minimisation analysis) to investigate the robustness of the results to these differing conclusions.

Kariyawasan et al (2007) grouped time from first symptoms to diagnosis into three groups 0-3 months, 3-6 months and greater than 6 months. The outcomes from these groupings were used to inform the Markov models. Some patients presenting in secondary care for imaging for suspected myeloma would already have a delay between first symptoms and diagnosis. Patients were therefore assigned a time since first symptom before entering the decision tree portion of the model and were not all assumed to start at 0-3 months. Kariyawasan et al (2007) reported presenting physician and time since first symptom. The model used data from those initially presenting at GP as this group represents where the majority of patients will be referred from in practise and is exclusively outside of secondary care, making diagnostic imaging one of the first interventions in secondary care. The proportion of patients in each group is reported in Table 3.

The model assumed that the time between first symptom and diagnosis in people with a correct diagnosis would be identical to the time between first symptom and presentation (i.e. diagnosis would be made shortly after presentation in secondary care) and would enter the Markov model corresponding to this. People with a false non-myeloma diagnosis were assumed to have an additional 6 months until diagnosis and would always enter the 'greater than 6 months' Markov model. Table 3 shows the Markov model entered by time from first symptom at presentation in secondary care and the results of diagnostic imaging.

Table 3: Time from first symptom to presentation and Markov pathway following diagnostic result

Time from first symptoms to presentation	Proportion of model cohort on entry	Markov entered True Positive Result	Markov entered False Negative result
0-3 months	21.6%	0-3 months	>6 months
3-6 Months	21.6%	3-6 Months	>6 months
>6 months	56.9%	>6 months	>6 months

A.3.8 Complications

Complication rates used in the model were identical to those reported in Kariyawasan et al. (2007). Kariyawasan et al (2007) reported five different types of complications: infection, neurological, renal disease, bone disease and anaemia (Table 4). Complication rates were significantly higher in the 'greater than 6 months' group than for the 'less than 3 months' and '3-6 month' groups. All patients in the 'greater than 6 months' reported at least one of these

five complications at presentation with only 61% in the 'less than 3 months group'. Complications were assigned to the cohort, based on the time from first symptoms to diagnosis, before entering the Markov portion of the model.

Table 4: Proportion of complications at presentation for time from first symptoms to diagnosis

	Time from first symptoms to diagnosis		
Complication	**0-3 Months**	**3-6 Months**	**>6 Months**
Infection	7.1%	4.8%	11.6%
Neurological	10.7%	4.8%	7.0%
Renal Disease	21.4%	19.1%	55.8%
Bone Disease	25.0%	38.1%	62.8%
Anaemia	7.1%	38.1%	93.0%

A.3.96 Health-related quality of life

Health related quality of life values used in the model were taken from one mapping study (Proskorovsky et al., 2014) reporting values collected during one consecutive patient cohort study (Jordan et al., 2014). Proskorovsky et al (2014) used health related quality of life (HRQoL) data collected from 154 patients with a current diagnosis of myeloma presenting for routine care at five UK and six German sites. Patients who had received either an autograft transplantation or an innovative myeloma treatment in the last three months were excluded. The cohort was 63% male and had a mean age of 66 years almost identical to that assumed as the cohort for the economic model.

Three quality of life instruments were completed by participants. The EORTC QLQ-C30, EORTC QLQ-MY30 (a myeloma specific supplement to the QLQ-30) and the EQ-5D. As the EQ-5D with UK general population preference weights is NICE's preferred valuation method for HRQoL in adults (National Institute for Health and Care Excellence, 2014) these were the only values used in the economic model. The EQ-5D is a self administered questionnaire made up of five dimensions (self-care, mobility, pain, usual activity and anxiety/depression) consisting of three levels of severity ('extreme', 'some' and 'none'). These responses were converted into one summary measure using UK general population preference weights. The measure could theoretically return utility values between -0.594 to 1 (representing perfect health).

Proskorovsky et al (2014) reported their utility values for four groups: Asymptomatic, Mildly Symptomatic, Moderately Symptomatic and Severely Symptomatic based on the number and the severity of the symptoms reported. Summary of the utility values and the definition for each grouping is presented in Table 5. For the economic model people with no complications reported had a utility value equal to that of the asymptomatic group and those presenting with any complication had a utility value equal to that of the moderately symptomatic group. A deterministic sensitivity analysis tested the alternate assumption of using asymptomatic and severely symptomatic and the mildly and moderately symptomatic values for the 'no complications' and complications groups respectively.

Table 5: Symptom level and reported utility value

Symptom Level	Definition	Utility Value
Asymptomatic	Patient had no symptoms/AEs	0.923
Mildly Symptomatic	≥1 mild symptom/AE no moderate or severe symptoms/AE	0.806
Moderately Symptomatic	≥1 moderate symptom/AE no severe symptoms/AE	0.675
Severely Symptomatic	≥1 severe symptom/AE	0.501

AE: Adverse Event

A.3.10 Overall survival

Survival for the three Markov models was based on an annual probability of survival based on the person's Durie-Salmon stage of myeloma at the time of diagnosis, disaggregated again by time from first symptoms to diagnosis, reported in Kariyawasan et al (2007) (Table 6).

Table 6: Percentage of cohort in each Durie-Salmon stage by time between first symptom and diagnosis

Time from first symptoms to diagnosis	Durie-Salmon Stage					
	1a	1b	2a	2b	3a	3b
0-3 Months	42%	4%	36%	11%	4%	4%
3-6 Months	38%	0%	38%	10%	14%	0%
>6 Months	14%	2%	33%	21%	19%	10%

The annual probability of survival for each stage was based on one retrospective study of the clinical and laboratory data of 10,750 previously untreated people with myeloma from 17 institutions including centres in Europe and North America between 1981 and 2002 (Greipp et al., 2005). As part of developing an updated staging system the study reported median survival for each Durie-Salmon stage. These median values were converted to annual probabilities of survival using standard conversion formulas. The probabilities were assumed to remain constant across all years of the economic model.

The Greipp et al (2005) study finds the lowest median survival amongst Durie-Salmon stage 1b patients reporting a lower median survival than for both stage 2b and 3b. This is most likely as a result of low numbers of stage Ib patients in the study population (n=27). Stage 1b also make ups only a small proportion of patients in the economic model (<3%) and these counterintuitive inputs are likely to have little influence on outcomes. Median survival and annual probabilities of survival are reported in Table 7.

This data predates the use of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) in the treatment of myeloma which have led to survival significantly improving in patients. Given that more contemporary survival data, grouped by stage, was not identified by the accompanying evidence search a sensitivity analysis was performed for a 10%, 25% and 50% improvement in overall survival to test the robustness of the results to differing assumptions around survival.

Table 7: Estimates of median and annual probability of survival used in the economic model

Durie-Salmon Stage	Median Survival (Months)	Annual Probability Survival
1a	69	88.6%
1b	22	68.5%
2a	58	86.6%
2b	34	78.3%
3a	45	83.1%
3b	24	70.7%

The Markov models and thus the economic model as a whole had a time horizon of 10 years. This was considered sufficient to cover all significant differences in costs and quality of life between the different imaging modalities.

A.3.11 Radiation burden

Increased exposure to radiation from WB-CT scans has been associated with an increased risk of lifetime cancer attributable to imaging (Smith-Bindman et al., 2009). It was estimated that one whole body CT would increase the risk of lifetime cancer by 0.04% per scan over a 5 year period. Given the difficulties in modelling cancer attributable to imaging, quality of life detriments and costs as a result of increased exposure to radiation these were not explicitly considered in the economic model. An increased incidence of cancer attributable to imaging would weigh against some imaging modalities in the economic evaluation.

A.3.12 Costs

A.3.12.1 Imaging costs

The costs of the differing imaging modalities were taken from NHS reference costs apart from skeletal survey for which reference costs were not reported (Table 8). Skeletal survey costs were taken from internal recharge costs used in one UK myeloma centre. (King's College Hospital, personal communication, April 4, 2015) Whilst the NHS reference costs gave a value for MRI spine this did not include the additional long bone radiographs needed for myeloma diagnosis. In the absence of cost evidence around this it was estimated by the GC that the additional cost would be half that of skeletal survey. The GC also felt that the NHS reference costs might not be fully reflective of the true cost of imaging given differences in myeloma imaging compared to other haematological conditions. Therefore a deterministic sensitivity analysis was performed using internal recharge costs from the one UK myeloma centre for imaging costs. (The 50% assumption around long bone radiography remained during this sensitivity analysis).

Table 8: Imaging costs used in the base case analysis and probabilistic sensitivity analysis

	Reference Cost	Source	PSA	Internal recharge Cost
Skeletal Survey	£108.82	Internal recharge (Personal correspondence)	Triangular(£54,163)	£108.82
CT(Whole body)	£147.17	NHS Reference Costs	Gamma(α=8.2, β=17.9)	£149.05
MRI (Spine)	£199.01	NHS Reference Costs+50% cost Skeletal Survey	Gamma(α=17.8, β=11.2)	£115.08
MRI (Whole Body)	£203.06	NHS Reference Costs	Gamma(α=10.0, β=20.2)	£209.28
PET-CT	£651.96	NHS Reference Costs	Gamma(α=7.0, β=92.7)	£397.77

A.3.12.21 Appointment costs

All appointment costs were taken from NHS reference costs. The initial appointment costs for diagnosis of myeloma were assumed equal to one 'consultant led non-admitted first appointment' in clinical haematology. Appointment costs for a repeat screening following a false negative or for cross-sectional imaging following a positive result with either skeletal survey or MRI spine were assumed to be equal to that of one 'consultant led non-admitted follow-up appointment' in clinical haematology (Table 9).

A.3.12.38 Complication costs

It was assumed that the complications encountered at the time of diagnosis would be treated as part of general treatment for myeloma. The cohort were unlikely therefore to experience additional treatment, medical appointments or other resource use as a result of these complications. With a lack of evidence around costs associated with these complications it was assumed that they would result in one additional consultant led appointment costed as 'consultant led non-admitted follow-up appointment'. These complication costs were explored during probabilistic sensitivity analysis (Table 9).

Table 9: Other costs used in the base case analysis and probabilistic sensitivity analysis

	Cost	Source	PSA
First Appointment	£212.83	NHS Reference Costs	Gamma(α=5.3, β=40.2)
Subsequent Appointments	£156.41	NHS Reference Costs	Gamma(α=5.8, β=27.1)
Complication Costs	£156.41	NHS Reference Costs	Gamma(α=5.8, β=27.1)

A.3.12.48 Resource use associated with treatment of myeloma

Management for myeloma can potentially lead to great resource use especially when novel treatments and transplantation are used. The accompanying evidence review found no evidence that resource use differed, post diagnosis by either modality used or time from first symptoms to diagnosis. The GC's own clinical experience suggested that neither of these factors would lead to any significant difference in resource use even if expensive management strategies were being used. The GC felt even if there was a difference as a result of imaging modality or time from first symptoms to diagnosis it would be difficult to estimate the size and direction of that difference. Earlier diagnosis may lead to somewhat improved long-term outcomes but this may also result in more lines of novel treatments. The reverse could also be true that those with worse outcomes end up using a greater amount of resources given their greater need for treatment for major complications and for palliative care. With an equipoise around the management associated resource use it was assumed that they would be equal between all imaging modality. Thus management costs, post treatment for complications at diagnosis, were assumed to be equal between all interventions in the economic analysis and were therefore not considered.

All costs in the economic model were already at 2014 prices, the latest for which inflation figures were available. Therefore it was unnecessary to inflate any costs.

A.3.12.56 Discounting

All costs and QALYs were discounted at 3.5% per annum as recommended by the NICE Guidelines Manual (National Institute for Health and Care Excellence, 2014).

A.3.13 Sensitivity analysis

For the base case analyses a range of deterministic and threshold sensitivity analyses were conducted to test the robustness of the results of the economic analysis to different input parameters. PSA was also conducted around the base case to assess the combined parameter uncertainty in the model. In this analysis, the base case values that are utilised in the base case are replaced with values drawn from probability distributions.

A.3.14 Incremental net monetary benefit

All results are presented as incremental net monetary benefit (INMB). INMB is a representation of cost effectiveness where incremental QALY gains, compared to the comparator intervention, are converted into a monetary value by multiplying by a willingness to pay per QALY. For example if an intervention had a QALY gain of 0.5 compared to the comparator and the willingness to pay per QALY was £20,000, the monetary value of the QALY gain would equal £10,000. INMB is then calculated by subtracting total incremental cost from this monetary value of a QALY. For our analysis the 'willingness to pay' per QALY is equal to £20,000, NICE's conventional threshold, unless otherwise stated. Interventions which report a positive INMB are cost effective compared to the comparator with those reporting a negative value not being cost effective. The 'preferred' intervention would be the one which reports the highest INMB.

A.3.15 Results

A.3.15.1 Deterministic base case results

Table 10 shows the base case results for the different imaging modalities. WB-CT, MRI spine and WB-MRI are cost effective when compared to skeletal survey alone with them all being cost saving and health improving. WB-MRI showed the largest rise in incremental QALYs although this was directly as a result of it being illustratively assigned the highest sensitivity. WB-CT had the highest INMB although it was only marginally higher than that of WB-MRI. PET-CT was the only intervention to report a negative INMB. Table 10 shows the base case results for the different imaging modalities. WB-CT, MRI spine and WB-MRI are cost effective when compared to skeletal survey alone with them all being cost saving and health improving. WB-MRI showed the largest rise in incremental QALYs although this was directly as a result of it being illustratively assigned the highest sensitivity. WB-CT had the highest NMB although it was only marginally higher than that of WB-MRI. PET-CT was the only intervention to report a negative NMB.

Table 10: Deterministic base case results for a willingness to pay of £20,000 per QALY

	Incremental Cost	Incremental QALYs	INMB
Skeletal Survey	Reference	Reference	Reference
WB-CT	-£ 142.40	0.0119	£ 379.49
MRI spine	-£ 33.39	0.0115	£ 262.57
WB-MRI	-£ 92.06	0.0142	£ 376.56
PET-CT	£ 792.85	0.0103	-£ 587.37

These results were consistent when the other two estimates of prevalence were used. The estimate with the largest proportion of myeloma patients gave the highest values of INMB for the cross-sectional imaging approaches although the INMB of PET-CT remained negative (Table 11). This was true for the other two prevalence estimates of myeloma and WB-CT and WB-MRI remained cost saving and health improving. This is as a result of the large number of repeat visits given the low specificity of skeletal survey although this assumption is explored later. The prevalence of myeloma needed for the INMB of WB-MRI to remain

positive is 7% and 10% when a sensitivity/specificity are both assumed to be 80% and 90% respectively. Similar values were found for WB-CT.

Table 11: Incremental net monetary benefit under differing prevalence levels

	USA (Kyle & Rajkumar, 2007)	Sweden (Bird et al., 2009)	Italy (Malacrida et al. 1987)
Prevalence Myeloma	**19.8%**	**19%**	**25.6%**
Skeletal Survey	Reference	Reference	Reference
WB-CT	£ 379.49	£ 368.36	£ 463.23
MRI spine	£ 262.57	£ 254.11	£ 326.26
WB-MRI	£ 376.56	£ 363.37	£ 475.84
PET-CT	-£ 587.37	-£ 600.27	-£ 490.32

A.3.15.24 Probabilistic base case results

The probabilistic base case results are shown in Table 12. The probabilistic results use the mean values of the 10,000 iterations of the PSA. As the diagnostic accuracy of all imaging modalities were given an identical distribution during the PSA, the average diagnostic accuracy for all interventions would be identical over a large number of iterations. Consequently as a result there would be no difference in QALYs between modalities and the incremental QALYs would be equal to zero. Therefore only incremental costs were reported. In our probabilistic results the strategy of WB-CT ends up being the least costly option followed by skeletal survey, WB-MRI and MRI spine. This is also a de facto cost minimisation and shows WB-CT as a preferred option when we assume promptness of diagnosis has no impact on health outcomes as reported in Friese et al. (2009).

Table 12: Probabilistic base case results

	Incremental Cost
Skeletal Survey	Reference
WB-CT	-£ 10.96
MRI spine	£ 93.84
WB-MRI	£ 60.61
PET-CT	£ 639.84

A.3.16 Sensitivity/specificity

The GC expressed difficulty estimating diagnostic accuracy values for the different imaging modalities. A range of sensitivity analyses were therefore carried out to test the robustness of any conclusions to these parameters. As there was particular difficulty in estimating specificities for the interventions, especially as studies in the accompanying evidence review often did not report this, a sensitivity analysis was performed assuming an arbitrary specificity (80%) for all imaging interventions. All other values were identical to the base case. Two other sensitivity analyses were performed, one assuming 80% sensitivity across all imaging modalities and one assuming both 80% sensitivity and specificity (Table 13). When 80% specificity is assumed in all interventions then the ranking of interventions remains the same with WB-CT remaining the preferred option. Similar results are seen for 80% sensitivity although WB-CT remained the preferred option. When 80% sensitivity and specificity is assumed for all interventions there will be no difference in QALYs between interventions so the preferred option will also always be the least costly. In this analysis WB-CT was the preferred option. Whilst the GC acknowledge there was a paucity of evidence around diagnostic accuracy it was unlikely that skeletal survey would have sensitivity and specificity equal to WB-CT and WB-MRI and that these sensitivity analyses give a favourable estimate around skeletal survey. The conclusions were identical when both 60% and 100%

specificities were used. Whilst these results were explicitly arbitrary they provided a starting point for threshold sensitivity analysis presented below (Table 13).

Assuming a starting point of perfect diagnostic accuracy if skeletal survey had sensitivity less than 4 percentage points or a specificity less than 12 percentage points of that of WB-CT then WB-CT became both cost saving and health improving. For the same to be true of MRI these values needed to be 5 percentage points and 15 percentage point respectively. Higher values were needed for the same to be true of MRI spine although it never became the preferred option over either WB-CT or WB-MRI. PET-CT was never preferred to skeletal survey, or any of the other intervention, for any values of diagnostic accuracy. These conclusions were not sensitive to the starting point in terms of sensitivity and specificity with the results being consistent for all starting values of sensitivity and specificity.

Table 13: Incremental net monetary benefit around different sensitivity and specificity assumptions

	Sensitivity			Specificity			Both=		
	80%	60%	100%	80%	60%	100%	80%	60%	100%
Skeletal Survey	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
WB-CT	£122	£114	£129	£272	£272	£272	£14	£7	£22
MRI Spine	£16	£12	£19	£153	£153	£153	-£94	-£97	-£90
WB-MRI	£61	£50	£73	£260	£251	£269	-£55	-£76	-£34
PET-CT	-£830	-£877	-£783	-£369	-£450	-£288	-£611	-£740	-£483

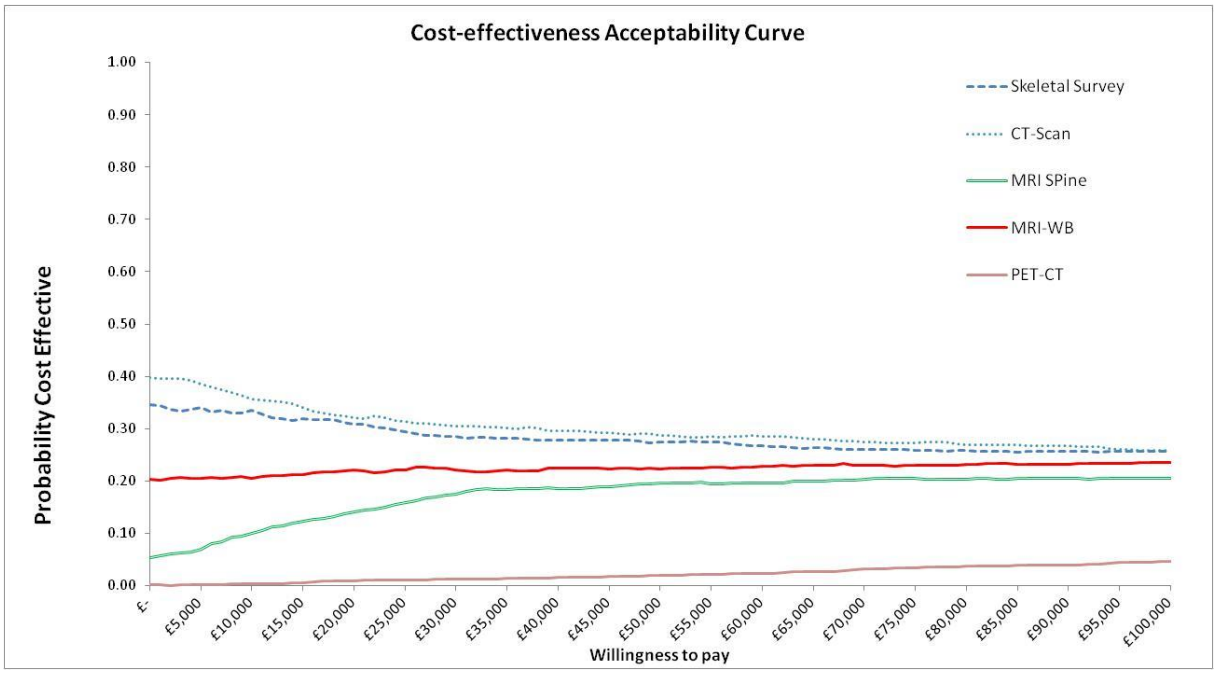
A.3.17 Utility values and survival

The use of alternate methods of estimating the utility values did not change the conclusions of the analysis. Given the large uncertainty around the diagnostic accuracy of the imaging modalities even with perfect information around these utilities there would still be considerable uncertainty around the QALY outcomes in the economic model. The same was true for survival with improvements in survival increasing the INMB of all cross sectional imaging approaches in the base-case. As the difference in QALYs were assumed to be zero in the probabilistic analysis neither of these sensitivity analyses influenced these results.

A.3.18 Probabilistic sensitivity analysis

It can be seen from the cost effective acceptability curve (Figure 2) that WB-CT remains the most likely preferred option for all willingness to pay values up to £100,000 followed closely by skeletal survey. At £20,000 per QALY there is a 32% probability that WB-CT is the preferred option closely followed by skeletal survey (31%). MRI spine and PET-CT only become the most probable preferred option for values significantly exceeding the NICE threshold of £20,000. Even at a zero willingness to pay threshold, where the least costly option is preferred, WB-CT still remains the preferred option in 40% of iterations. Given that the diagnostic accuracy of all interventions were given an identical distribution during PSA, for an infinite willingness to pay, all interventions had an equal probability of being the preferred option.

Figure 2: Cost effectiveness acceptability curve



When the values during an iteration of the PSA are favourable to cross-sectional imaging approach then one of three options (WB-CT, MRI and PET-CT) would be preferred compared to two options (skeletal survey and MRI Spine) for when the iterations are unfavourable. This could potentially underestimate the true cost effectiveness of a cross-sectional approach by 'diluting' the results across three interventions. Therefore, the CEAC analysis was re-run to just compare WB-CT (Figure 3) and WB-MRI (Figure 4) to skeletal survey.

Under these direct comparisons both WB-CT and WB-MRI were the preferred option when compared to skeletal survey both for a willingness to pay of £20,000 and £0 (where the least costly option is preferred). Again as the diagnostic accuracy of the imaging modalities have identical distributions during PSA the probability of being the preferred option is identical across all interventions at an infinite willingness to pay.

Figure 3: Cost effectiveness acceptability curve: WB-CT versus skeletal survey

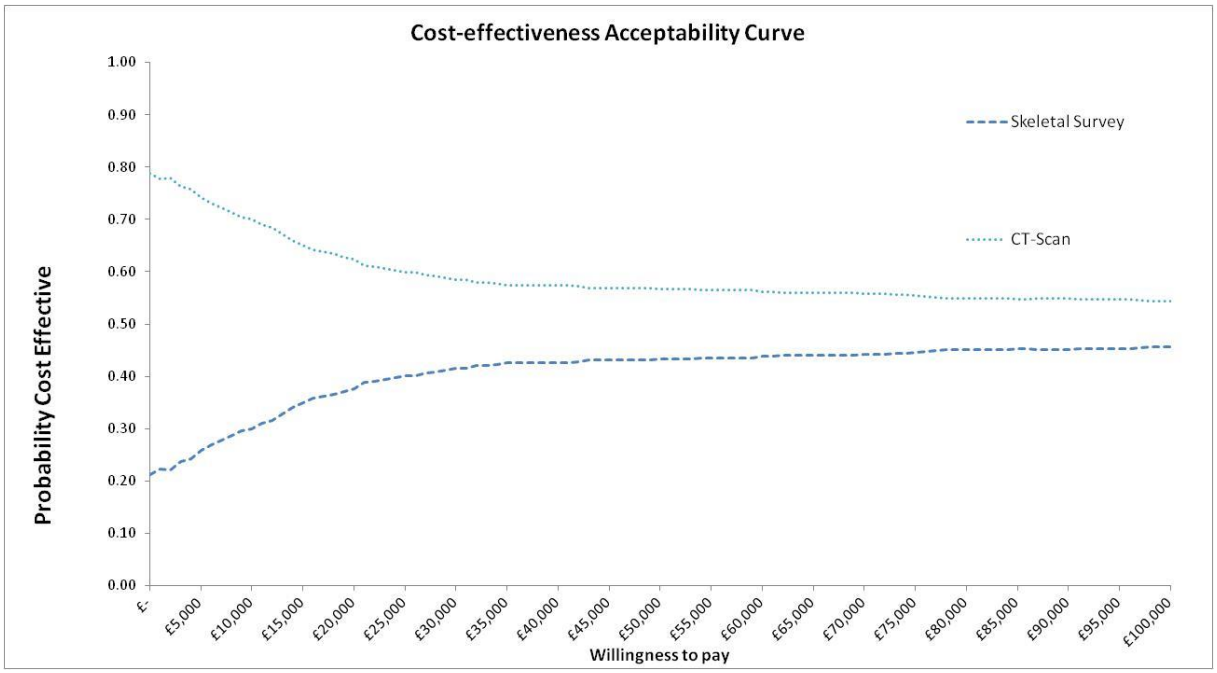
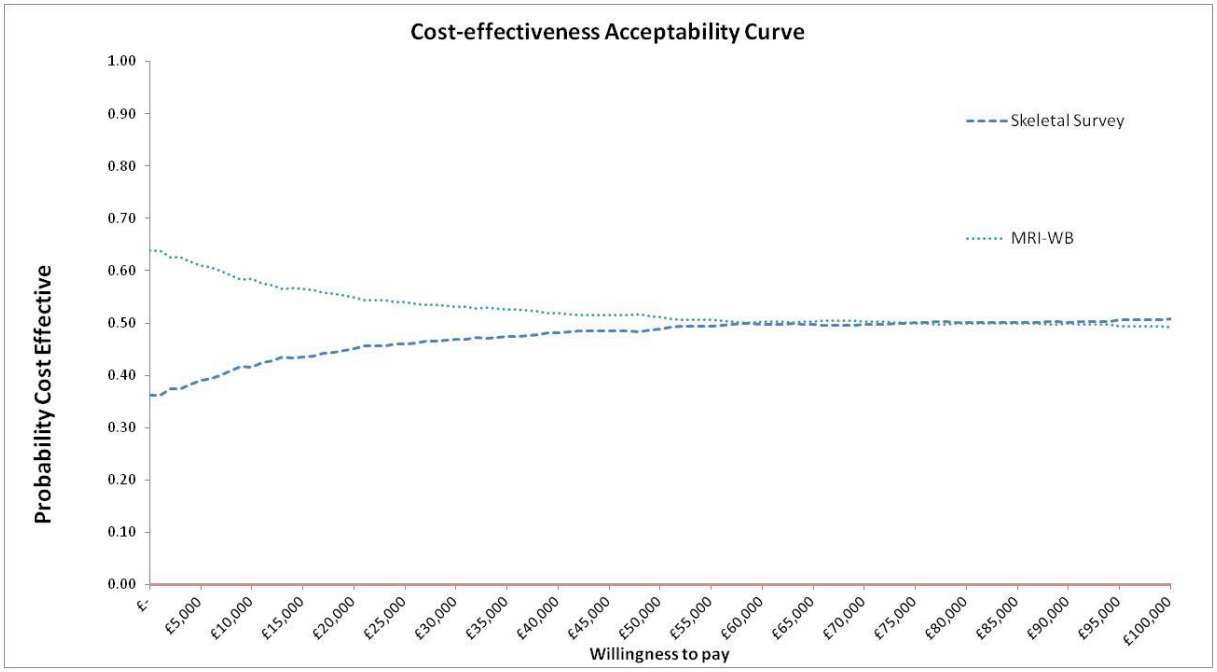


Figure 4: Cost effectiveness acceptability curve: WB-MRI versus skeletal survey



A.3.19 Conclusion

Even under the very conservative assumption that there is no difference in diagnostic accuracy between the different imaging modalities there is a strong case that an approach of using cross-sectional imaging at the time of diagnosis is a cost effective strategy for diagnosis in patients with a plasma cell disorder suspected to be myeloma. The main driver of this result appears to be the avoidance of the need for further cross-sectional imaging to guide treatment decisions, following a positive result on skeletal survey. Even under these conservative assumptions this approach could be both cost saving and health improving even with the use of WB-CT or WB-MRI being the preferred option in greater than 50% of cases even when the health provider's willingness to pay per QALY is zero. The case

becomes stronger when the cross-sectional imaging starts to have a higher diagnostic accuracy than skeletal survey with the illustrative base case values again suggesting an approach using either WB-CT or WB-MRI could be cost saving and health improving. It is unclear which is the most cost-effective between WB-CT and WB-MRI given a paucity of good evidence around diagnostic accuracy and the decision sensitivity to differences in diagnostic accuracy between both. Whilst it was the GCs opinion that MRI was the most sensitive of the considered imaging modalities it was difficult to quantify by exactly how much, if at all, without higher quality evidence.

These conclusions do not hold true for lower prevalences of myeloma where the number of subsequent cross-sectional imaging following skeletal survey is likely to be much lower. The WB-CT or WB-MRI imaging is therefore very unlikely to be cost effective as a general screening tool for all paraproteinaemias and it is important that the patient population is carefully defined. A looser definition and therefore a lower prevalence amongst the imaged population could lead to harm through increased radiation burden and through inefficiently allocated resources.

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Appendix B: The cost-effectiveness of balloon kyphoplasty and vertebroplasty compared to non-surgical management for the treatment of vertebral collapse in patients with myeloma.

B.1 Background

Bone disease remains the most common presenting feature of myeloma. The development of bone damage in myeloma is due to cancerous cells in bone tissue (causing weak/soft spots, making bones fragile and easy to fracture. When myeloma affects the vertebral spine, it causes severe pain usually affecting the back and that often spreads around the chest or abdomen in the distribution of spinal nerves. Myeloma in the neck vertebrae can lead to pain going down the shoulders and arms, whereas disease affecting the lowest segments of the spine (lumbar and sacral levels) causes pain affecting the legs.

Spinal bone disease can sometimes lead to collapse of one or more vertebrae, which causes very serious consequences including acute severe pain. The core aims of the management of spinal bone disease in myeloma are decompression, stabilization and pain control. Non-surgical management (NSM) consists of pain management using drugs (analgesics), radiotherapy, and external bracing/orthotics. Radiotherapy is effective for pain relief and most patients need one or two fractions; however it may take several weeks for the full effect and some patients experience a pain 'flare' in the early days after treatment.

Faster-acting interventions include procedures such as vertebroplasty (VP) or balloon kyphoplasty (BKP), in which plastic cement is injected into the diseased vertebrae (vertebral cement augmentation). These cement techniques can be performed by either surgeons or non-surgeons (typically radiologists) unlike open spinal surgery which is performed almost exclusively by either orthopaedic surgeons or neurosurgeons. For these reasons cement techniques are referred to as NSM in clinical practise although for clarity are not included in that definition within this report. Side-effects are usually mild and temporary but may be problematic in a few patients.

There is uncertainty around whether BKP and VP are cost effective when compared to NSM. Upfront treatment costs will be higher with both BKP and VP although could lead to increased quality of life and reduced resource use post treatment.

B.2 Existing economic evidence

A systematic literature review was performed to assess the current economic literature for this topic. The review identified 463 possibly relevant economic papers relating to myeloma. Of these, no papers were deemed relevant for this topic and therefore no papers were included in the review of existing economic evidence.

B.3 De novo economic model

The current economic literature did not adequately address the decision problem; therefore a de novo economic evaluation was created to assess cost effectiveness. All analyses were conducted in Microsoft Excel 2007.

B.3.1 Aims of analysis

The aim of the economic analysis was to assess the cost effectiveness of BKP and VP compared to NSM for the treatment of vertebral compression fractures (VCFs) patients with myeloma. Therefore, both cement techniques were compared only to NSM. All analyses were conducted from a National Health Service (NHS) and Personal Social Services (PSS) perspective.

B.3.2 Type of analysis

The analysis was a retrospective economic evaluation based on outcomes and resource use reported in the one RCT identified for vertebral cement augmentation in the accompanying clinical evidence review (Berenson et al., 2011). The trial compared BKP to NSM for the treatment of VCFs in 134 patients with cancer.

The trial was based at 22 sites in Australia, Canada, Europe and the USA in patients aged at least 21 years who had between one and three VCFs as well as scoring at least 4 on the pain numeric rating score and at least 10 on the Roland-Morris Disability Score. Patients were excluded if they had osteoblastic tumours, primary bone tumours or plasmacytoma in the index VCF. Patients were also excluded if they were in any phase 1 anticancer trial, had substantial clinical morbidities, were unsuitable for BKP or needed significant additional treatment, over NSM or BKP for index VCF.

The patient group had an average age of 64 years and was 58% male with an average estimated symptomatic fracture age of 3.5 months. The trial included cancers other than myeloma with 62% of the trial population having another cancer diagnosis with sub-group analysis by cancer type not presented. As the interventions considered in the analysis are for the treatment VCF rather than the underlying cancer the Guideline Committee thought it would be unlikely that outcomes would be different between cancer type over the one year follow-up of the trial.

The study had a large amount of crossover with patients randomised to NSM allowed to switch to BKP after one month follow-up. 38 (72%) of the 52 patients randomised to NSM group, who completed one month follow-up, crossed over to BKP. Therefore three groups were presented in the results by the authors: patients randomised to BKP, patients randomised to NSM who ultimately received BKP (crossover) and those who continued with NSM (NSM group). The authors reported no differences in the baseline characteristics of the three groups although differences at time of crossover were not reported.

B.3.3 Clinical input data

All clinical inputs for the model were based on evidence identified in the accompanying evidence review.

Low quality evidence did not show any difference in clinical outcomes between VP and BKP. For the base case therefore the clinical outcomes were assumed to be identical between the two interventions. The Guideline Committee hypothesised that it was possible that BKP had improved clinical outcomes and greater quality of life through restoration of lost body height. Whilst there would be a proportion of patients for which both BKP and VP would be suitable it was often the case that the nature of the VCF or patient characteristics would make one of the interventions clinically inappropriate. As there was also no randomised comparative evidence comparing BKP to VP they were both compared to NSM in the base-case economic evaluation but not with each other. Given this potential difference in quality of life between the two cement techniques a threshold sensitivity analysis was performed to look at the difference required for the more expensive intervention to become the preferred option.

B.3.4 Patient groups

RCTs are conventionally analysed using an intention to treat (ITT) approach to reduce bias due to non-random loss and crossover of participants. The ITT approach analyses patients by how they were randomised regardless of whether they adhered to the treatment they were randomised to or not. As the Berenson et al trial had large crossover the ITT approach may not fully capture the true outcomes of the interventions being considered. The study also did not report the characteristics of the crossover group at the time of crossover and it was unclear as to whether these patients differed significantly to those who remained in the NSM groups.

The Guideline Committee therefore considered that an 'as treated' comparison comparing all patients who ultimately received BKP to those who remained in NSM would most accurately estimate the difference in effectiveness between the two groups. It would also reflect more closely practice within the NHS where patients are likely to wait at least one month for cement techniques- a time after which the majority of patients in the NSM arm had crossed over to BKP. Consequently, for the purpose of the de novo economic evaluation two further groups were created from the trial results- a 'cement technique received' group pooling the BKP and crossover groups and a NSM-ITT group pooling the NSM and crossover group (i.e. those randomised to NSM). In the base case an 'as treated' approach was taken comparing the BKP and crossover group (cement technique received group) to the NSM group. A secondary analysis based on ITT principles was also conducted comparing the NSM-ITT group to those randomised to BKP.

B.3.5 Utilisation of non-surgical interventions for VCFs at one month

The study reported the utilisation of seven non-surgical interventions at baseline and one month post randomisation between those randomised to BKP and to NSM. The changes in the use of these interventions are shown in Table 14. Bed rest, whilst reported by the trial was excluded from the economic model as the financial cost of this would fall outside the perspective of the NHS and PSS whilst impact upon quality of life has been captured in the quality of life measures reported by the trial and discussed later.

There were no baseline difference (p-value<0.05) in utilisation of non-surgical interventions between the BKP and NSM group. A pooled percentage from the trial was therefore used for the baseline utilisation in the economic analysis. Changes in utilisation were statistically significantly lower (p-value<0.05) for the BKP group in all interventions other than wheelchair use, physical therapy and radiation therapy. As no patients crossed over before one month the NSM group was identical for both the 'as treated' and ITT analysis.

Table 14: Percentage of patients in model cohort receiving non-surgical interventions at baseline and percentage point change in utilisation between base-line and one month follow-up.

	Percent baseline	BKP	NSM
Walking Aids	33%	-9.0%	1.5%
Bracing	14%	-12.7%	-1.4%
Wheelchair	6%	-4.8%	-2.0%
Physical Therapy	14%	-10.4%	-3.6%
Any Medication	86%	-40.5%	-17.0%
Radiation Therapy	4%	-0.9%	11.3%

For the crossover group, the use of non-surgical interventions was assumed to be equal to BKP for the base case 'as treated' analysis but equal to NSM during the ITT analysis. The difference in utilisation was assumed to be maintained for one year.

B.3.6 Future VCFs

Whilst further VCFs are common in patients receiving both cement techniques and NSM, the accompanying systematic review found no evidence on whether there was a difference in the incidence of future VCFs between the interventions. In lieu of evidence it was assumed that the incidence between the groups was identical. Resultantly, both costs and outcomes of these future events were assumed identical and were not explicitly included as part of the de novo economic analysis.

B.3.7 Adverse events

Device related adverse events were observed during the trial in the BKP group. Two patients had extravasation, one had superficial wound infection and two had symptomatic fractures one of which was as a result of cement leakage. Two patients had arrhythmia, attributable to anaesthesia but this was resolved. The Guideline Committee felt that these adverse events were likely to be rare and that the additional costs and quality of life detriment were likely to be significantly outweighed by underestimates of costs and quality of life detriments in the NSM arms. Whilst the costs and quality of life detriments of these adverse events were not explicitly considered in the economic evaluation, costs attributable to adverse events of surgery were included (discussed later).

B.3.8 Survival

Survival for the economic analysis was taken from a prospective observational study of outcomes and survival in 39 patients with myeloma receiving VP in an NHS setting (Chew et al., 2011). The population had a mean age of 60 years at the time of treatment. The study reported a median survival of 20 months with a one year survival of 90% and five year survival of 40%. Survival was assumed to be identical for both the cement technique and NSM groups given the paucity of information to the contrary identified by the systematic review.

B.3.9 Time horizon

Two time horizons were used for the economic evaluation-a one year and five year. The one year analysis covered the duration of the Berenson et al (2011) trial. It was unclear from the accompanying evidence review whether differences in quality of life remained more than one year post surgery. The Guideline Committee thought that the difference was likely to remain after one year and until further VCF or death and that the one year time horizon would represent a conservative estimate of any outcomes from cement techniques. Therefore, a five year time horizon was also modelled. As no evidence was identified around the effectiveness of BKP or VP post one year, two assumptions were investigated based on the Guideline Committee's clinical experience. The first assumption was that the difference in quality of life between the groups at one year would remain for the entirety of the five year time horizon reflecting that increased mobility and reduced pain may continue significantly past one year. The second assumption was that in the group with the highest quality of life the difference would taper down at a constant rate until equal to the comparison group at five years. This was to reflect that patients were likely to experience further VCFs over the time horizon which would diminish their quality of life.

The analysis also conservatively assumed that the difference in costs between the two groups would be identical after the first year. A sensitivity analysis was run for this model though that also assumed that the difference in costs not attributable to cement techniques, during the first year, would continue in all years.

A five year time horizon was considered adequate to capture all differences between the two groups as the majority of patients would have either died or had a secondary VCF during this time.

B.3.10 Quality of Life

The main measure of health related quality of life (HRQoL) in the trial was the The Short Form (36) Health Survey (SF-36) physical component summary score (PCS). The SF-36 is a patient completed generic health survey made up of eight components (vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health). These are used to calculate two summary scores, a physical component (PCS) and mental component, on a scale of 0 (worse possible health) to 100 (best possible health). The change in SF-36 PCS from baseline for the BKP and NSM group, and from time of treatment for crossover group, is shown in Table 15. These were given a normal distribution and varied across their reported range during probabilistic sensitivity analysis (PSA).

Table 15: Change in SF-36 PCS score following treatment

Follow-up	1 Month	3 Month	6 Month	12 Month
BKP	9.2	9.6	8.8	10.6
Crossover	8.8	10.8	10.4	10.6
NSM	-0.2	1.2	-0.8	1.2
Cement Technique Received	9.0	10.1	9.4	10.6
NSM-ITT	5.7	7.5	7.4	8.3

Changes in the SF-36 PCS were converted to UK population preference EQ-5D weights using a mapping algorithm (Ara & Brasier, 2008). The EQ-5D UK tariff is NICE's preferred measure of health related quality of life in adults (National Institute for Health and Care Excellence, 2014). This was the only algorithm identified for mapping from mean SF-36 component scores to EQ-5D scores. The algorithm showed good predictive value with predicted mean EQ-5D score being correct to within 2 decimal places in both datasets used to build the algorithm and external datasets used in validation. However, the algorithm was not validated in myeloma or cancer patients although it was shown to have good predictive value in a range of health conditions associated with VCF including walking impairment and lower back pain.

Berenson et al. (2011) reported a summary score for the SF-36 PCS whilst the Ara & Brazier (2008) algorithm needs the mean individual component scores. The proportion of the change in SF-36 scores attributable to each of the four physical components were assumed to be identical to that reported in the Fracture Reduction Evaluation (FREE) trial. The FREE trial was an RCT comparing BKP and NSM in patients with VCFs across 8 European centres. Although the study population included patients with myeloma these accounted for less than 2% of the study population; the majority being osteoporosis patients. The proportion attributable to each physical component is shown in Table 16. Only the physical component contributions were used and all scores were inflated to sum to 100%.

Table 16: Contribution to overall SF-36 score for each physical component

	Contribution (%)	
	BKP	NSM
Physical Functioning	34%	34%
Role limitations due to physical health	-13%	-12%
Bodily Pain	55%	56%
General Health Perceptions	24%	22%

Given the changes in the SF-36 score and the contributions to each component in Table 16 changes in EQ-5D scores were estimated for the group using the Ara &Brazier (2008) algorithm. The analysis used 'Model EQ (1)' of the seven reported by Ara & Brazier (2008) as

this did not require an age variable which was not reported for the NSM group post one month and not reported for the crossover group at all. The use of the age variable increases the predictive precision by less than 1%. The converted EQ-5D scores are reported in Table 17.

We assumed that all patients started with a baseline quality of life weight of 0.4392 the pre-treatment mean EQ-5D score based on 11 consecutive patients, receiving VP in an NHS setting (Chew, O'Dwyer & Edwards, 2013). As economic evaluation is primarily an incremental analysis and the choice of baseline quality of life will have no effect on the incremental results this assumption was not tested during sensitivity analysis.

Table 17: Estimated EQ-5D scores following treatment

Follow-up	Baseline	1 Month	3 Month	6 Month	12 Month
BKP	0.4392	0.4667	0.4679	0.4655	0.4709
Crossover	0.4392	0.4657	0.4717	0.4705	0.4709
NSM	0.4392	0.4386	0.4428	0.4368	0.4428
Cement Technique Received	0.4392	0.4662	0.4693	0.4674	0.4709
NSM-ITT	0.4392	0.4563	0.4617	0.4613	0.4643

Berenson et al also reported a summary score for the mental component of the SF-36 for one month post-randomisation showing a mean difference between the groups of 11.1 points (95% CI 10.7-11.5) between the groups in favour of BKP. As this was only reported at one month and not for the duration of the trial the contribution of the mental component to overall quality of life was not included in the base case analysis. A sensitivity analysis was performed giving an additional quality of life increment to those receiving BKP or VP to capture this non-physical improvement in quality of life. Using the algorithm described above for SF-36 mental component scores a mean difference in terms of the EQ-5D of 0.054 was estimated at one month. Assuming that this difference persists over the time horizon of the model this equated to an additional 0.054 and 0.270 QALYs for patients surviving the entirety of the one year and five year time horizons respectively.

B.3.11 Costs

Costs were inflated to 2014 prices, using the hospital & community health services (HCHS) index (Curtis, 2014) and converted using the appropriate purchasing power parity where appropriate (National Institute for Health and Care Excellence, 2014). All costs are presented in Table 18.

Table 18: Unit costs

	Value	Source	PSA Distribution
Total Cost BKP	£3369	(Chew et al., 2013)	Gamma(α=119.7, β=34.0)
Total Cost VP	£2213	(Chew et al., 2013)	Gamma(α=35.4, β=62.5)
Annual cost pharmaceutical treatment	£132	(Puffer et al., 2004)	Triangular(£66,£264)
Annual cost radiotherapy	£431	(Botteman et al., 2011)	Triangular(£216,£863)
Annual cost bracing	£500	NHS Correspondence	Uniform(£250,£1000)
Annual cost wheelchair	£91	(Curtis, 2014)	Triangular(£46,£182)
Annual cost walking	£91	(Curtis, 2014)	Triangular(£46,£182)

	Value	Source	PSA Distribution
aids			
Annual cost physical therapy	£312	(Department of Health, 2015)	Gamma(α=25.1, β=12.4)
Annual Non-specific NSM costs	£0	Guideline Committee Estimate	Uniform(£0,£3552)

B.3.11.1 Treatment costs

The costs of VP were taken from 11 consecutive patients receiving VP for spinal metastases at one NHS hospital. Resource use was collected prospectively using structured questionnaires and costed using NHS reference costs where possible. For items of equipment an estimation of their lifespan, number of uses and maintenance costs to calculate a cost per hour per patient. Staff costs were based on published salaries for consultant radiologist, a registrar in half of cases, two radiographers and four nurses. Costs of complications, inpatient stay and drug costs were all included.

Chew et al estimated an average cost of £2213.25 per patient. This consisted of a cost of £744 for the VP kit and other costs of £1469. Chew et al (2011) considered this was a likely overestimate of the true cost as it was weighted heavily by one patient with widespread metastatic bronchial carcinoma. An alternate non-kit cost of £996 was used during sensitivity analysis equal to the average cost if all patients were treated as a day case or overnight stay. Treatment costs other than the kit cost were assumed to be identical for both VP and BKP.

The cost of the BKP kit was taken from NICE TA279 looking at BKP and VP in the treatment of osteoporotic vertebral compression fractures. It noted a list price for a BKP kit including low viscosity cement of £2600 however it noted an average selling price of £1900. Whilst the average selling price was deemed the most appropriate to use in the de novo economic evaluation it was still likely to be an overestimate of the true costs. BKP kit costs are commercially sensitive and likely to differ widely between institutions. This value was therefore given a wide distribution for PSA.

B.3.11.2 Non-surgical management costs

The annual cost of analgesic medication was taken from a study estimating the costs associated with VCFs from an NHS perspective using Hospital Episode Statistics and Personal Social Services Research Unit data (Puffer et al., 2004). The study estimated an annual cost of pharmaceutical treatments of £132. No cost data was identified for myeloma patients specifically although the costs of pharmaceutical interventions were likely to be similar to this patient group.

Radiation therapy costs were taken from a cost-effectiveness analysis of zoledronic acid in the prevention of skeletal related events for patients with bone metastases secondary to advanced renal cell carcinoma (Botteman et al., 2011). The study estimated an average cost of radiotherapy of £431 using HRG codes and NHS reference costs and considering a NHS+PSS perspective.

Bracing costs of £500 were estimated using correspondence with one NHS trust. Costs of wheelchair and walking aids were taken from PSSRU data (Curtis, 2014). A cost of £91 was used representing the unit cost of the use of self or attendant propelled chair per year. Physical therapy costs were estimated from NHS Reference Costs. Six appointments were assumed equal to a cost of £312 (Department of Health, 2015). These costs were applied to both arms of the model in line with utilisation reported in Table 14.

There was potential resource use that was not reported by the trial and consequently not included in the base case analyses. The Guideline Committee felt that the most important missed resource use was doctor and nurse time spent fitting, adjusting and advising on

bracing and wheelchair use and time spent tailoring pharmaceutical treatment for pain. By virtue of greater utilisation in the NSM arm the underestimate would be larger than for the cement technique arms. Previous economic evaluations of spinal interventions, in non-myeloma patient populations have found significantly higher resource use, post surgery amongst non-surgical arms compared to surgical arms (Lewis et al., 2011; Bala et al., 2008). With a paucity of evidence it was difficult to accurately estimate this cost. Therefore, threshold sensitivity analysis was performed to estimate the additional cost needed in the NSM arm to reduce the cost per QALY to the £20,000 NICE threshold. During PSA a non-specific cost was added to the NSM arm ranging from £0 (no underestimate of cost) to £3552 equal to the total annual healthcare related cost of VCFs (Puffer et al., 2004) representing a plausible upper limit to the underestimation of costs. In the absence of evidence the Guideline Committee were unable to come to a consensus on a 'most probable' value and it was therefore deemed appropriate to use a wide uniform distribution.

B.3.11.3 Imaging costs

Costs of imaging pre-treatment were not included in this de novo economic evaluation as these were assumed to be performed as part of a patient's regular follow-up and would be identical between the two groups.

B.3.11.4 Discounting

All costs and QALYs were discounted at 3.5% per annum as recommended by the NICE Guidelines Manual (National Institute for Health and Care Excellence, 2014).

B.3.12 Sensitivity analysis

For the base case analyses a range of deterministic and threshold sensitivity analyses were conducted to test the robustness of the results of the economic analysis to different input parameters. PSA was also conducted around the base case to assess the combined parameter uncertainty in the model. In this analysis, the values that are utilised in the base case are replaced with values drawn from a distribution used to reflect the uncertainty around parameter estimates. The PSA analysis was run for 10,000 iterations for both BKP and VP and for both a one year and five year time horizon.

B.3.13 Results

B.3.13.1 Deterministic base case results-one year time horizon

Table 19 and Table 20 show the base case results for BKP and VP respectively. Both cement procedures led to an increase in costs and QALYs. Total QALYs are equal between both cement techniques given the assumptions of the model with BKP having higher incremental costs owing to its increased kit cost. Both incremental cost effectiveness ratios (ICERs) are above the NICE threshold of £20,000 per QALY although as noted earlier they are likely to offer conservative estimates of both incremental QALYs and NSM total costs.

Table 19: Base case deterministic results for balloon kyphoplasty

Outcome	BKP	NSM	Incremental
Total Cost	£3,485	£304	£3,181
Total QALYs	0.4429	0.4170	0.0260
Cost per QALY gained			**£122,498**

Table 20: Base case deterministic results for vertebroplasty

Outcome	VP	NSM	Incremental
Total Cost	£2,329	£304	£2,025
Total QALYs	0.4429	0.4170	0.0260
Cost per QALY gained			**£77,987**

B.3.13.2 Deterministic results five year time horizon

Table 21 and Table 22 show the base case results for BKP and VP respectively when a five year time horizon is assumed with a continuing difference in quality of life. Whilst the ICERs are reduced under the longer time horizon they still both remain above £20,000 per QALY.

Table 21: Five year time horizon deterministic results for balloon kyphoplasty

Outcome	BKP	NSM	Incremental
Total Cost	£3,485	£304	£3,181
Total QALYs	1.5678	1.4748	0.093
Cost per QALY gained			**£34,209**

Table 22: Five year time horizon deterministic results for vertebroplasty

Outcome	VP	NSM	Incremental
Total Cost	£2,329	£304	£2,026
Total QALYs	1.5678	1.4748	0.093
Cost per QALY gained			**£21,779**

B.3.13.3 Probabilistic base case results

Table 23, Table 24, Table 25 and Table 26 show the base case probabilistic results calculated from the mean results of the PSA. The probabilistic results show an increased cost for NSM whilst the cement technique costs and QALYs for both groups remain consistent compared to the deterministic results. This is as a result of the non-specific NSM costs which is set equal to zero during the deterministic analysis but is always a greater than zero value during PSA. Other than for BKP in the conservative one year time horizon analysis all ICERs are now below the NICE £20,000 threshold. As NSM costs were almost certainly underestimated in the deterministic analysis these results are potentially more reflective of the true cost effectiveness.

Table 23: Base case probabilistic results for balloon kyphoplasty one year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,515	£2,191	£1,325
Total QALYs	0.4429	0.4170	0.0259
Cost per QALY gained			**£51,085**

Table 24: Base case probabilistic results for vertebroplasty one year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,338	£2,168	£170
Total QALYs	0.4429	0.4169	0.0260
Cost per QALY gained			**£6,544**

Table 25: Base case probabilistic results for balloon kyphoplasty five year time horizon

Outcome	BKP	NSM	Incremental
Total Cost	£3,519	£2,172	£1,347
Total QALYs	1.5680	1.4773	0.0908
Cost per QALY gained			**£14,842**

Table 26: Base case probabilistic results for vertebroplasty five year time horizon

Outcome	VP	NSM	Incremental
Total Cost	£2,354	£2,166	£188
Total QALYs	1.5681	1.4737	0.0944
Cost per QALY gained			**£1,994**

B.3.14 Deterministic sensitivity analysis

Deterministic sensitivity analysis was carried out to test alternate assumptions and how these influence the results of the economic evaluation (Table 27). The use of a non-kit cost of £996, assuming that all patients are treated on an overnight or outpatient reduced the ICER for both cement techniques. The ICER only dropped below £20,000 for the VP under the five year time horizon. The same was true when difference in costs between interventions continued past the first year. The addition of the mental component to the quality of life scores reduced the ICER below £20,000 for both cement technique options under the five year time horizon. Tapering of quality of life did not result in either ICER dropping below £20,000 per QALY.

Table 27: Deterministic sensitivity analysis results-ICER for alternative assumptions

	BKP-1 Year	BKP-5 year	VP-1 Year	VP-5 Year
Non-kit cost reduced to £996	£104,276	£29,120	£59,765	£16,690
Mental component added	£39,743	£11,726	£25,302	£7,471
Difference in costs continue post one year	N/A	£30,590	N/A	£18,171
Tapering quality of life after 1 year	N/A	£50,743	N/A	£32,309

B.3.14.1 Threshold analysis

A threshold analysis was performed to see how much extra NSM needed to cost, per patient, before the ICER reduced below £20,000 per QALY (Table 28). All the additional costs were lower than the upper limit of the PSA range.

Table 28: Additional NSM costs required for ICER to be below £20,000 per QALY

	1 Year Time Horizon	5 Year Time Horizon
BKP	£2662	£1322
VP	£1506	£166

Threshold analysis also showed that BKP needed to provide an additional 0.054 QALYs over the lifetime of a patient to give the same ICER when compared to VP. Given the assumptions of the model this was irrespective of the time horizon.

B.3.14.2 ITT Analysis

An alternative ITT analysis was carried out against all results and deterministic sensitivity analyses. ITT in all cases significantly increased the cost of the NSM arm (due to the cost of surgery now added to patients who crossed over) as well as increasing the total QALYs. The incremental cost and QALYs between cement techniques and NSM were reduced in all scenarios although the cost per QALY was generally consistent with the 'As Treated' results. The ITT analysis did not alter the results, in terms of being above or below £20,000 per QALY, in any scenario.

B.3.15 Probabilistic sensitivity analysis

B.3.15.1 Cost effectiveness plane

Despite the ICER for BKP being above the £20,000 threshold compared to NSM, for both the deterministic and probabilistic results, during PSA under a one year time horizon BKP was below the threshold in 26.1% of iterations (Figure 5). Under the five year time horizon this figure increased to over 64.2% meaning BKP was cost effective at the £20,000 threshold in over half of iterations (Figure 6). BKP was cost saving and health improving in 12.5% of iterations for both time horizons. VP was cost effective at a £20,000 threshold in 59.6% and 89.4% of iterations for the one year and five year time horizons respectively (Figure 7 - 8). VP was health improving and cost saving in 44.7% of iterations. For both interventions the majority of iterations were in the North-East quadrant suggesting a more costly yet effective intervention. These results are echoed in the cost effectiveness acceptability curves (Figure 9 - 12).

Figure 5: Cost effectiveness plane for balloon kyphoplasty with a one year time horizon

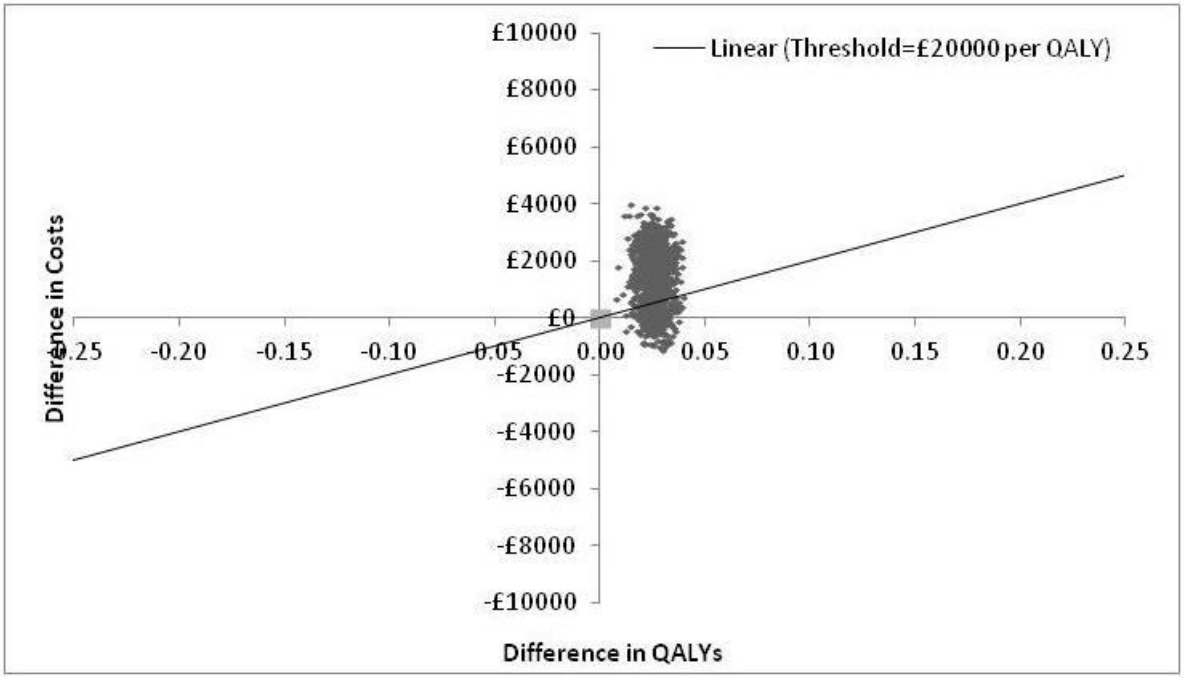


Figure 6: Cost effectiveness plane for balloon kyphoplasty with a five year time horizon

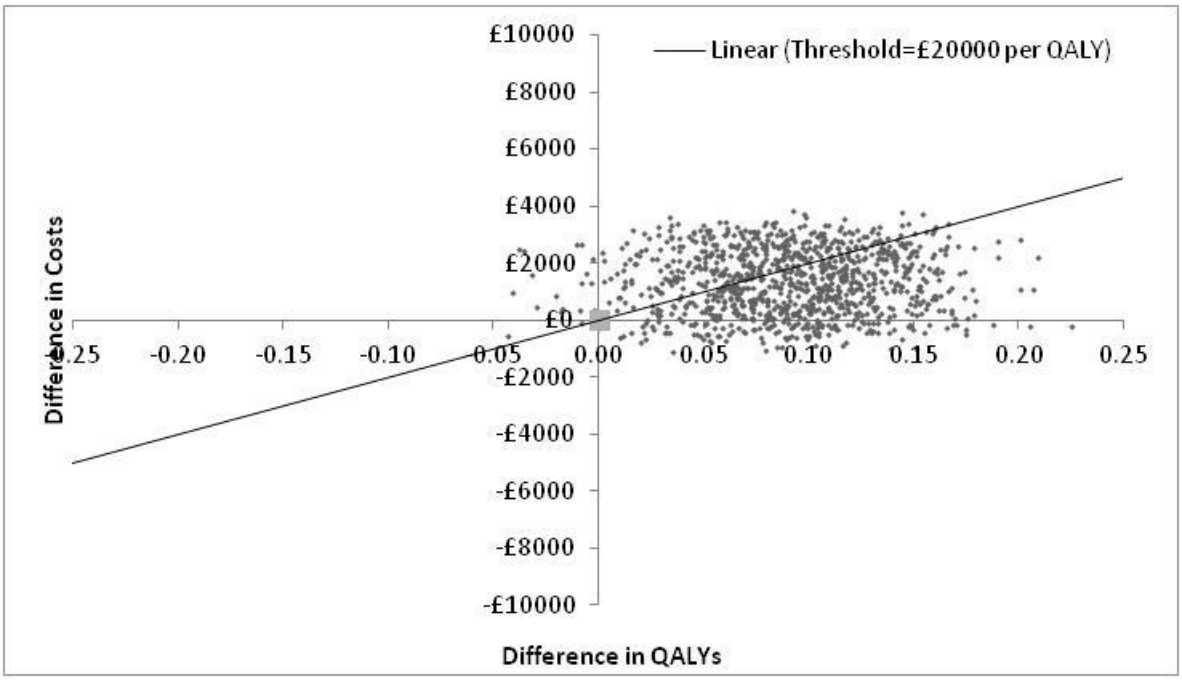


Figure 7: Cost effectiveness plane for vertebroplasty with a one year time horizon

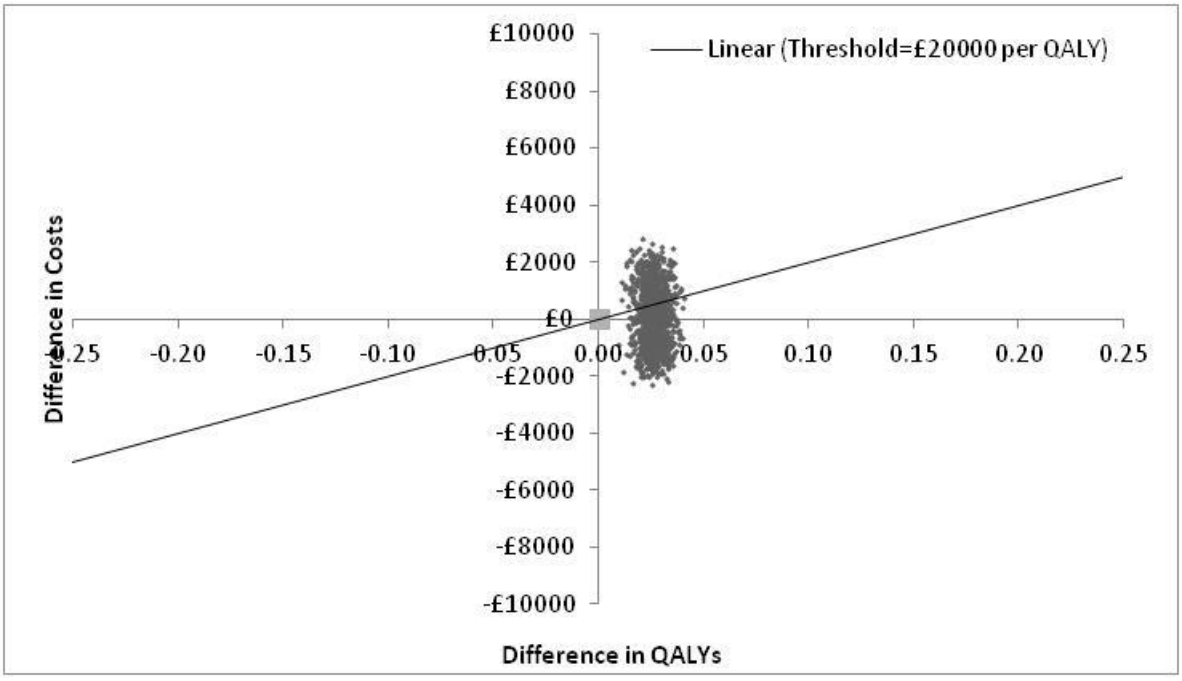


Figure 8: Cost effectiveness plane for vertebroplasty with a five year time horizon

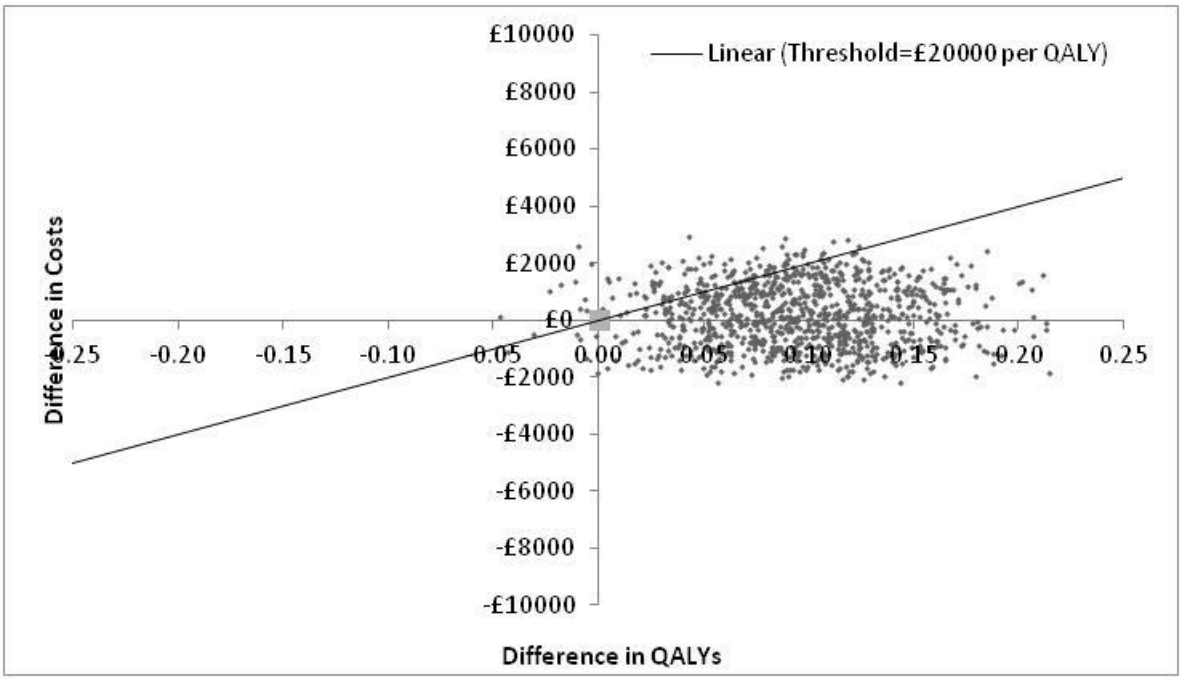


Figure 9: Cost effectiveness acceptability curve for balloon kyphoplasty with a one year time horizon

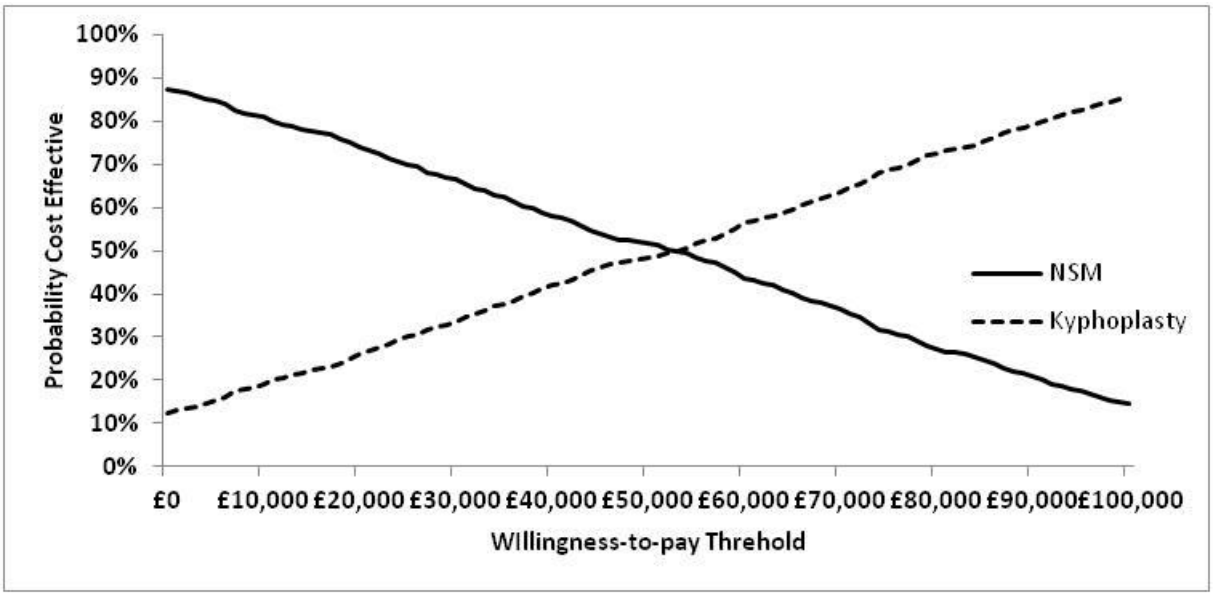


Figure 10: Cost effectiveness acceptability curve for balloon kyphoplasty with a five year time horizon

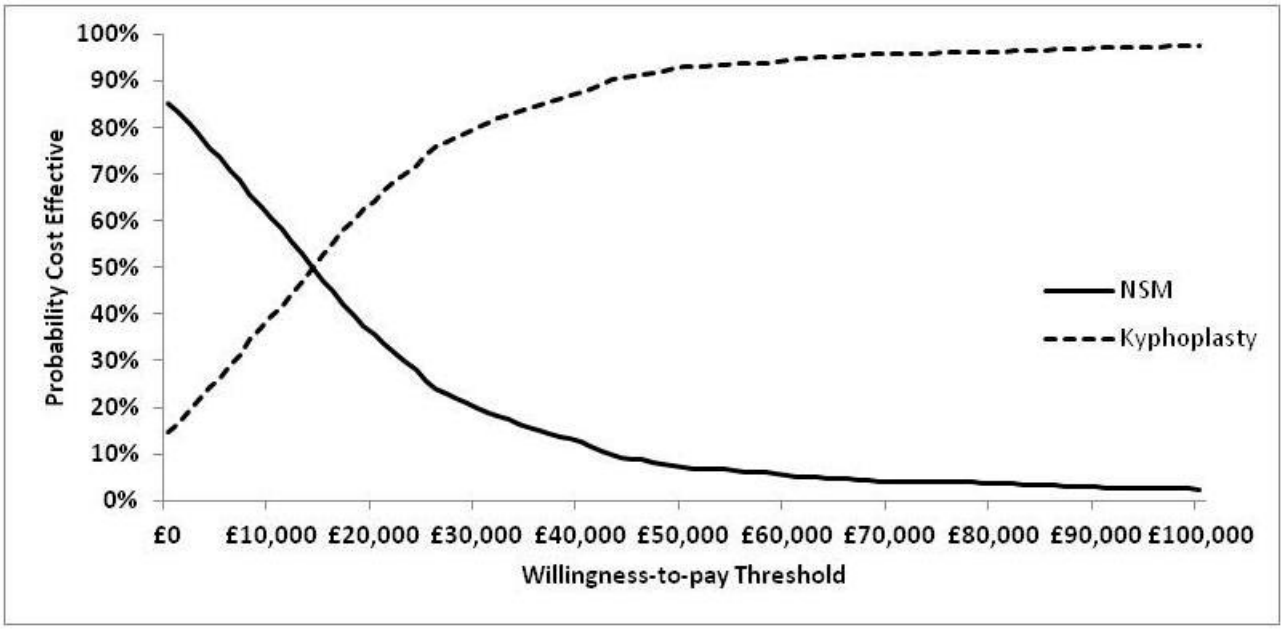


Figure 11: Cost effectiveness acceptability curve for vertebroplasty with a one year time horizon

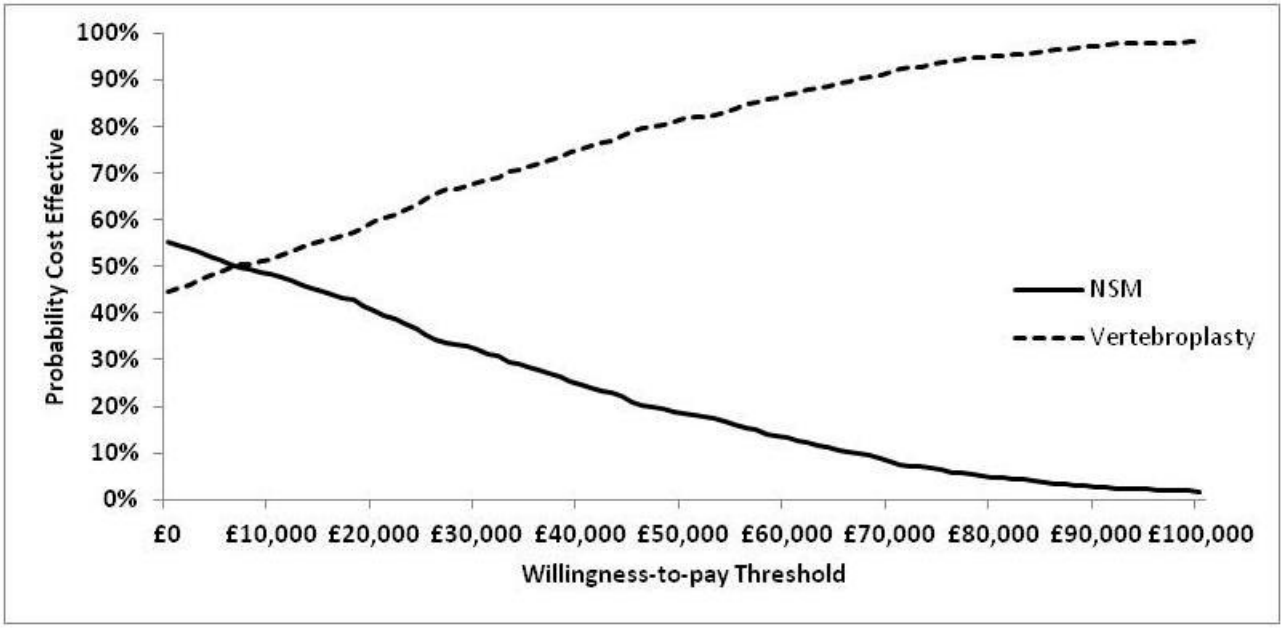
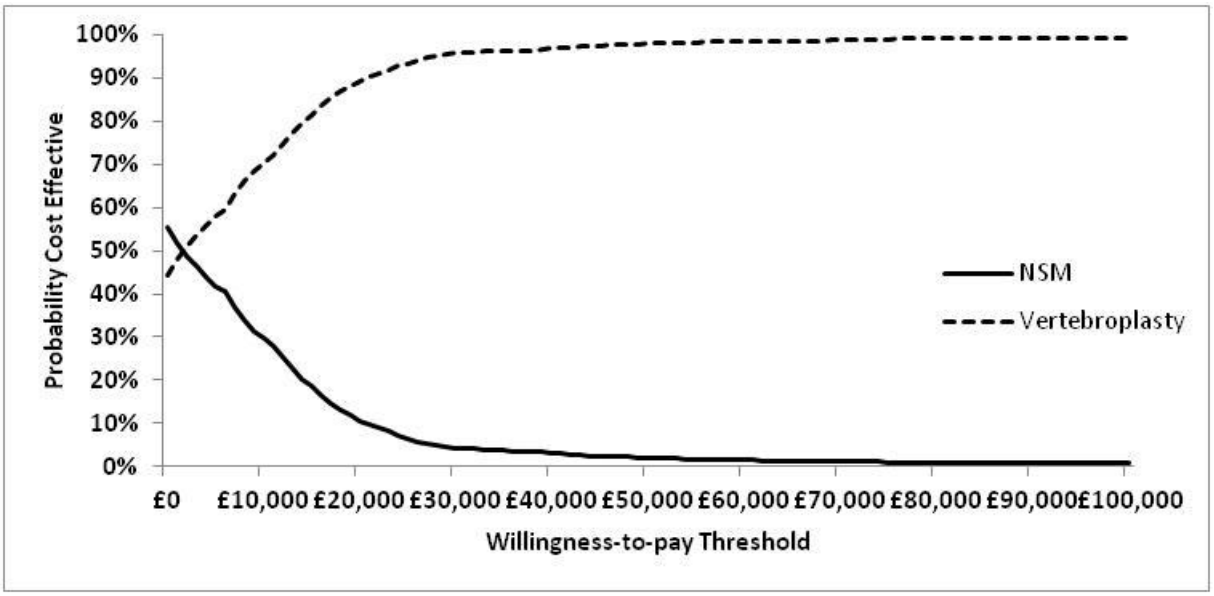


Figure 12: Cost effectiveness acceptability curve for vertebroplasty with a five year time horizon



B.3.16 Conclusions

The results of the base case analysis showed that BKP and VP were not cost effective over a one year time horizon and only VP was cost effective over a five year time horizon. However, when considering the probabilistic results, both cement techniques were shown to be cost effective with a five year time horizon with VP also cost effective under a one year time horizon. Furthermore, during PSA and under a five year time horizon both cement techniques were cost effective in the majority of iterations with VP being cost saving and health improving in 40% of cases.

The results were shown to be particularly sensitive to the costs of NSM. Threshold sensitivity analysis showed that even if our economic analysis only modestly underestimates the true cost of NSM or the effectiveness of cement techniques then both VP and BKP would likely be cost effective.

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Appendix C: Abbreviations

AlloSCT	Allogeneic stem cell transplantation
ASCT	Autologous stem cell transplantation
BKP	Balloon kyphoplasty
BP	Bisphosphonates
CI	Confidence Interval
GC	Guideline Committee
GVHD	Graft versus host disease
ICER	Incremental Cost Effectiveness Ratio
LETR	Linking Evidence to Recommendations
PCL	Plasma cell leukaemia
MDT	Multi disciplinary team
MGUS	Monoclonal gammopathy of undetermined significance
NPV	Negative Predictive Value
NSM	Non-surgical management
ONJ	Osteonecrosis of the jaw
PET-CT	Positron emission tomography CT
PPV	Positive Predictive Value
QALY	Quality Adjusted Life Years
QADAS	Quality Assessment of Diagnostic Accuracy Studies
SREs	Skeletal related events
VCFs	Vertebral compression fractures
VP	Vertebroplasty
VTE	Venous thromboembolism
WBCT	Whole body computed tomography

Appendix D: Glossary

Allogeneic stem cell transplantation (AlloSCT)

A complex procedure involving administration of high-dose cytotoxic therapy (chemotherapy with or without radiotherapy) followed by transplant of peripheral blood or bone marrow stem cells (and rarely cord blood) from a sibling or unrelated donor. This is usually followed by immunosuppression.

Amyloid

The product (immunoglobulin light chain fragments) of a group of abnormal plasma cells which is deposited in a variety of organs as an insoluble protein and is resistant to degradation.

Asymptomatic

Without obvious signs or symptoms of disease. Cancer may cause symptoms and warning signs, but, especially in its early stages, cancer may develop and grow without producing any symptoms.

Autologous stem cell transplantation (ASCT)

A procedure involving administration of high-dose chemotherapy followed by transplant of peripheral blood or bone marrow stem cells previously harvested from the patient

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis or inform the choice of treatment of a disease.

Cast nephropathy

The formation of plugs (urinary casts) in the renal tubules from free immunoglobulin light chains filtered from the blood. This leads to renal failure.

Chemotherapy

The use of medication (drugs) that is toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Cohort studies

Research studies in which groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it, or patients within the cohort are compared with each other.

Computed tomography (CT)

Imaging technique in which the person lies on a table within a x-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3-D views.

Cost effectiveness analysis

A type of economic evaluation that compares the costs and benefits of different treatments. In cost-effectiveness analysis benefits are measured in clinical outcome units, for example, additional heart attack prevented, life years gained, etc. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio.

False negative

An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.

Cytogenetics

A branch of genetics that is concerned with the study of the structure and function of the genetic material in a cell, especially the chromosomes. It includes routine analysis of chromosomes, as well as molecular cytogenetics such as fluorescent *in situ* hybridization (FISH) and other molecular techniques.

Dialysis

A process for removing waste and excess water from the blood, and is used primarily as an artificial replacement for lost kidney function in people with kidney failure.

Evidence table

A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

False positive

An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease

Fluorescence in situ hybridisation (FISH)

A molecular test carried out on biopsy or cytology samples to show whether extra or abnormal copies of specific genes or genetic material are present or absent.

GRADE

The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Graft versus host disease (GVHD)

A common complication following an allogeneic stem cell transplant. Immune white blood cells in the transplant (graft) recognize the recipient (the host) as "foreign." The transplanted immune cells then attack the host's body cells.

Health economics

The study of the allocation of scarce resources among alternative health care treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.

Heterogenous

A term used to describe the amount of difference between observations, results or effects.

Hypercalcaemia

Raised calcium level in the blood

Hyperviscosity

Increased viscosity of the blood potentially leading to pathological complications

Immunohistochemistry

The process of detecting antigens (e.g., proteins) in the cells of a tissue section, by using antibodies binding specifically to antigens in biological tissues.

Immunophenotyping

A technique used to study the protein expressed by cells. It is usually done on liquid specimens and involves the labelling of white blood cells with antibodies directed against surface proteins on their membrane. The labelled cells are processed in a flow cytometer, a laser-based instrument capable of analyzing thousands of cells per second. The whole procedure can be performed on cells from the blood, bone marrow or spinal fluid in a matter of a few hours.

Immunosuppression

A reduction in the efficacy of the immune system due to disease, treatment or both.

Kyphoplasty

A minimally invasive spinal surgery procedure used to treat painful, progressive vertebral compression fractures. Kyphoplasty involves the use of a balloon to restore the height and shape of the vertebral body. This is followed by application of bone cement to strengthen the vertebra

Light chain deposition

A rare disease characterised by the deposition of the light chain part of the immunoglobulin molecule usually in the kidneys.

Lymph

Almost colourless fluid that bathes body tissues and is carried by lymphatic vessels. It contains cells that help fight infection and disease.

Lymph nodes or glands

Small bean-shaped organs located along the lymphatic system. Nodes filter bacteria or cancer cells that might spread through the lymphatic system and to other parts of the body.

Magnetic resonance imaging (MRI)

A type of scan which uses a magnetic field and radio waves to produce images of sections of the body.

Meta analysis

Results from a collection of independent studies (investigating the same issue) are pooled, using statistical techniques to synthesise their findings into a single estimate of an effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to pool statistically results in this way.

Microarray technologies

A genetic test used to analyse very small amounts of RNA and DNA. It is a chip technology that enables the analysis of large amounts of genetic information in a short period of time.

Monoclonal gammopathy of undetermined significance (MGUS)

A common plasma cell disorder characterised by a low level monoclonal protein (<30g/L), less than 10% bone marrow plasma cells and the absence of myeloma related organ disease.

Monoclonal protein (paraprotein)

Monoclonal protein or paraprotein is a single immunoglobulin molecule produced in excess indicating a plasma cell disorder

Morbidity

Detrimental effects on health.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1,000, 10,000 or 100,000 people.

Multi disciplinary team (MDT)

A team with members from different health care professions and specialties (e.g. urology, oncology, pathology, radiology, nursing). Cancer care in the NHS uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.

Neuropathy

Damage to or disease affecting nerves, which may impair sensation, movement, gland or organ function, or other aspects of health, depending on the type of nerve affected.

Osteoclastic activity

Increased activity of the osteoclast cells that lead to increased bone resorption

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Paraprotein – see monoclonal protein

Plasma cells

The type of white blood cell which produces antibodies

Plasma cell leukaemia (PCL)

A plasma cell disorder characterised by >2 x 10^9/L circulating plasma cells in the peripheral blood

Plasmapheresis

The removal, treatment, and possible return of blood plasma (or components of blood plasma) from the circulating blood using a plasmapheresis machine (cell seperator).

Platelets

The small blood cells involved in stopping bleeding

Polymerase chain reaction techniques

A technology in molecular biology used to amplify a single copy or a few copies of a piece of DNA, generating thousands to millions of copies of a particular DNA sequence.

Positron emission tomography CT (PET-CT)

A medical imaging technique using a device which combines a positron emission tomography (PET) scanner (which utilises a radioactive tracer to show functional activity) with an x-ray computed tomography (CT) scanner. Images acquired from both devices can be taken sequentially, in the same session, and combined into a single superposed image.

Prevalence

The proportion of a population found to have a condition

Primary care

Services provided in a community setting, outside hospitals (secondary care), with which people usually have first contact.

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Specific characteristics of a cancer or the person who has it which might affect the patient's prognosis.

Prospective study

A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen.

Protein electrophoresis

The use of electrical currents to separate and characterise proteins in the blood to help diagnose myeloma

Psychosocial support

A general term for any non-therapeutic intervention that helps a person cope with stressors in the home or at work.

Qualitative research

Research in which the outcomes are usually recorded in words, rather than with numbers. Often used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)

A measure of health outcome, which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0-1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research

Research which uses numerical measurement techniques (e.g. measuring survival times after treatment).

Radiotherapy

The use of radiation, usually high energy x-rays to control the growth of cancer cells.

Randomised controlled trial (RCT)

An experimental clinical trial (study) investigating the effectiveness of different treatments in which participants are assigned at random to different groups which receive the intervention being assessed or a 'control' treatment. RCTs give the most reliable (i.e. least biased) form of evidence on clinical effectiveness.

Rare

A disease or a cancer that affects fewer than 1 in 2000 people

Relapse

Where cancer starts to grow again after treatment.

Sensitivity

In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To judge fully the accuracy of a test, its Specificity must also be considered.

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other setting. The analysis is repeated using different assumptions to examine the effect on the results.

Skeletal survey

A series of plain x-rays of the skeleton including skull, spine, pelvis and long bones used to detect myeloma-related bone disease

Specificity

In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To judge fully the accuracy of a test, its Sensitivity must also be considered.

Survival

Survival is the time alive after diagnosis of a disease

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Thrombo-embolism

Thromboses are abnormal blood clots in the veins. These can break off and block the blood flow, especially in the lungs. This is called embolism

Vertebroplasty

Vertebroplasty is an image-guided, minimally invasive, nonsurgical therapy used to strengthen a broken vertebra (spinal bone) that has been weakened by osteoporosis or by+ cancer. Percutaneous vertebroplasty involves the injection of acrylic bone cement into the vertebral body in order to relieve pain and/or stabilise the fractured vertebrae and in some cases, restore vertebral height.

Appendix E: Guideline scope

E.1 Guideline scope

E.1.1 Guideline title

Myeloma: diagnosis and management of myeloma

E.1.1.1 Short title

Myeloma

E.1.2 The remit

The Department of Health has asked NICE: 'to develop a guideline on the diagnosis and management of multiple myeloma'.

E.1.3 Clinical need for the guideline

The management of myeloma is complex and challenging. It increasingly involves the use of expensive drugs. The guideline will aim to raise standards nationally while allowing clinical flexibility and defining a common pathway for patients at various stages of their illness, and of different ages and levels of fitness. Although a consistent approach to management is desirable, it needs to reflect the very different groups of patients with myeloma from the fit and suitable for transplant, fairly fit but not suitable for transplant to patients who are extremely frail and/or unwell.

E.1.3.1 Epidemiology

a) Myeloma is the 17th most common cancer in the UK and the 14th most common cancer in men, according to figures from 2009. Incidence rates have remained stable over the past 10 years.

b) In 2010, 4672 people were diagnosed with myeloma in the UK.

c) Myeloma occurs most commonly in older people, with 71% of cases diagnosed in people aged 65 years and over. Incidence increases with age, peaking in those aged 85 years and over.

d) Myeloma is almost twice as common in men and women of African-Caribbean family origin compared with people of other family origins.

e) Although there have been substantial improvements in the duration and quality of survival during the past 15 years, myeloma remains incurable. Median survival is currently about 5 years. A significant minority (10%) of patients die within 3 months of diagnosis.

f) Survival rates are higher in younger patients. This is thought to be partly a result of differences in treatment options for younger and older patients.

g) Myeloma is usually preceded by an asymptomatic monoclonal gammopathy of undetermined significance (MGUS). It is important to distinguish between MGUS and myeloma at the time of diagnosis.

E.1.3.2 Current practice

a) The non-specific clinical presentation of myeloma (bone pain, symptoms of impaired renal function, anaemia, hypercalcaemia and hyperviscocity) often results in delayed diagnosis; 38% of cases are diagnosed only after emergency admission to hospital.

b) Diagnosis of myeloma is made using international criteria published by the International Myeloma Working Group in 2003. The use of genetic profiling to give predictive and prognostic information is increasing.

c) Several novel drug treatments have been licensed in the past 10 years, but there is some variation in the regimens used and the timing of using these drugs. High-dose chemotherapy with stem cell transplantation is a standard of care for patients who are fit enough for this procedure.

d) Symptom-based and supportive management are especially important because of the complex nature of the disease and side effects of its treatment. Management may include radiotherapy, bisphosphonate treatment, pain control, treatment of bone and renal complications, and psychosocial support.

e) A specialist multidisciplinary approach should involve the core multidisciplinary team (MDT) (as defined in Improving outcomes in haematological cancers [NICE cancer service guidance]) but also a wider group of specialists including: graduate and biomedical scientists, clinical oncologists, spinal surgeons, radiologists, renal physicians, orthopaedic surgeons and oncology pharmacists. There should also be links to community care through the GP.

f) When determining treatment for patients with myeloma, their response to previous treatment, frailty, previous toxicities and comorbidities need to be considered.

E.1.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

E.1.4.1 Population

Groups that will be covered

- Adults (aged 16 years and over) referred to secondary care with suspected myeloma, including those with MGUS.
- Adults (aged 16 years and over) with newly diagnosed or relapsed myeloma.
- Adults (aged 16 years and over) with high-risk myeloma, including primary plasma cell leukaemia.
- No patient subgroups have been identified as needing specific consideration.

Groups that will not be covered

- Children and young people (under 16 years) with suspected or diagnosed myeloma.
- People with:
  - solitary plasmacytoma in the absence of myeloma
  - amyloid light-chain (AL) amyloidosis in the absence of myeloma
  - paraproteins secondary to other conditions.

E.1.4.2 Healthcare setting

All settings in which NHS-funded care is provided.

E.1.4.3 Management

Key issues that will be covered

a) The specific information and support needs of patients with myeloma and their families and carers at diagnosis and treatment planning, and during and after treatment (including end of life care).

b) The role of centralised specialist laboratories offering integrated diagnostic reporting in the diagnosis of Myeloma has been removed from the scope and added as a topic within the update of the Improving Outcomes in Haematological Cancers service guidance, which is now in development. For more information please see http://www.nice.org.uk/guidance/indevelopment/gid-cgwave0747.

c) The role of specialist diagnostic investigations, including trephine biopsy, immunophenotyping, cytogenetics and molecular technologies, in diagnosing MGUS and standard and high-risk myeloma.

d) Imaging investigations at diagnosis.

e) The local and regional service provision needed for adequate disease management and equity of access.

f) Primary disease management for newly diagnosed myeloma, including autologous stem cell transplantation.

g) The management of primary plasma cell leukaemia.

h) The management of asymptomatic myeloma.

i) The most effective salvage therapies for relapsed and/or refractory myeloma.

j) The role of allogeneic stem cell transplantation in both primary treatment and treatment of relapsed myeloma (salvage therapy).

k) The management of neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain).

l) The prevention and management of bone disease, including spinal bone disease, for patients with myeloma.

m) The prevention of thrombosis for patients with myeloma.

n) Prophylaxis of infection for patients with myeloma.

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o) The management of renal disease for patients with myeloma.

p) Follow-up for patients with myeloma.

q) The management of treatment-related fatigue for patients with myeloma.

Issues that will not be covered

a) The management of MGUS.

b) The role of consolidation and maintenance therapy after primary management of myeloma. Consolidation and maintenance therapy are the subject of two NICE technology appraisals that are in development. The guideline will cross refer to these, in line with NICE process, and therefore will not be investigating this issue.

E.1.4.4 Main outcomes

a) Overall survival.

b) Disease-related morbidity.

c) Disease-related mortality.

d) Treatment-related morbidity.

e) Treatment-related mortality.

f) Progression-free survival.

g) Time to next treatment.

h) Treatment response rate.

i) Renal outcome.

j) Psychological wellbeing.

k) Diagnostic accuracy.

l) Number and length of admissions to hospital after diagnosis.

m) Health-related quality of life.

n) Patient-reported outcomes.

E.1.4.5 Review questions

Review questions guide a systematic review of the literature. They address only the key issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience. Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

Numbers in square brackets refer to the key issues listed in section 1.4.3.

a) What are the specific information and support needs of patients with myeloma and their families and carers

i. at diagnosis and treatment planning

ii. during treatment

iii. during follow-up

iv. at the end of life? [1.4.3a]

b) What is the most effective way to deliver diagnostic services for suspected myeloma? [1.4.3b]

c) What is the optimal laboratory testing strategy for suspected myeloma? [1.4.3c]

d) Can investigations done at the diagnosis of myeloma, including trephine biopsy, immunophenotyping and cytogenetic and molecular genetic tests accurately predict

treatment outcomes (for example, can they identify patients with a poor prognosis for whom an alternative treatment approach may be preferable)? [1.4.3c]

e) What is the optimal imaging strategy (including skeletal survey and spinal MRI) for patients with newly diagnosed myeloma? [1.4.3d]

f) Should MRI results guide treatment decisions in patients with newly diagnosed asymptomatic myeloma? [1.4.3d]

g) What is the optimal configuration of local and regional services for radiological imaging, the management of renal disease, spinal disease and bone disease, and palliative care for patients with myeloma? [1.4.3e]

h) Which patients with myeloma should be considered for autologous stem cell transplantation? [1.4.3f]

i) What are the most effective primary treatments for patients with primary plasma cell leukaemia? [1.4.3g]

j) What are the most effective primary treatments (including observation) for patients with asymptomatic myeloma? [1.4.3h]

k) What are the most effective post-third line systemic therapy regimens for patients with relapsed or refractory myeloma? [1.4.3i]

l) In which patients with relapsed or refractory myeloma is a second transplantation more effective than other therapy? [1.4.3i]

m) Which patients with myeloma should be considered for allogeneic stem cell transplantation? [1.4.3j]

n) What is the most effective way to manage neuropathy in patients with myeloma (excluding pharmacological management of neuropathic pain)? [1.4.3k]

o) What is the most effective method of preventing bone disease in patients with myeloma? [1.4.3l]

p) What is the most effective treatment for non-spinal bone disease in patients with myeloma (including external beam radiotherapy and surgical intervention)? [1.4.3l]

q) What is the most effective treatment for spinal bone disease in patients with myeloma (including external beam radiotherapy and surgical intervention)? [1.4.3l]

r) What is the most effective method for prevention of thrombosis in patients with myeloma? [1.4.3m]

s) What is the most effective prophylactic strategy for infection in patients with myeloma (including immunoglobulin, antibiotics, growth factors and vaccinations)? [1.4.3n]

t) What is the optimal management of renal disease in patients with myeloma? [1.4.3o]

u) What is the optimal follow-up protocol for patients with myeloma (including duration, frequency, investigations and onward referral)? [1.4.3p]

v) Which interventions are most effective in reducing fatigue in patients being treated for myeloma? [1.4.3q]

E.1.4.6 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the

economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in The guidelines manual.

E.1.4.7 Status

Scope

This is the final scope.

Timing

The development of the guideline recommendations will begin in March 2014.

E.1.5 Related NICE guidance

E.1.5.1 Published guidance

NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

NICE guidance to be incorporated

This guideline will incorporate the following NICE guidance:

- Bortezomib and thalidomide for the first-line treatment of multiple myeloma. NICE technology appraisal guidance 228 (2011). [Incorporation into the guideline is subject to a NICE technology appraisal review proposal.]
- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy. NICE technology appraisal guidance 171 (2009). [Incorporation into the guideline is subject to a NICE technology appraisal review proposal.]
- Bortezomib monotherapy for relapsed multiple myeloma. NICE technology appraisal guidance 129 (2007). [Incorporation into the guideline is subject to a NICE technology appraisal review proposal.]

Other related NICE guidance

- Referral for suspected cancer. NICE clinical guideline NG12. (June 2015).
- Acute kidney injury. NICE clinical guideline 169 (2013).
- Neuropathic pain - pharmacological management. NICE clinical guideline 173 (2013).
- Denosumab for the prevention of skeletal-related events in adults with bone metastases from solid tumours. NICE technology appraisal guidance 265 (2012).
- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Patient experience in adult NHS services. NICE clinical guidance 138 (2012).
- Anaemia management in people with chronic kidney disease. NICE clinical guideline 114 (2011).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Epoetin alfa, epoetin beta and darbepoetin alfa for cancer treatment-induced anaemia. NICE technology appraisal guidance 142 (2008).
- Balloon kyphoplasty for vertebral compression fractures. NICE interventional procedure guidance 166 (2006).

- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Percutaneous vertebroplasty. NICE interventional procedure guidance 12 (2003).

E.1.5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Bortezomib for consolidation therapy after autologous stem cell transplantation for the treatment of multiple myeloma. Publication date TBC
- Care of the dying adult. Publication date TBC.
- Bortezomib for induction therapy prior to high dose chemotherapy and autologous stem cell transplantation for the treatment of multiple myeloma. NICE technology appraisal guidance. Publication expected May 2014.
- Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy with bortezomib (partial review of TA171). NICE technology appraisal guidance. Publication expected July 2014.
- Pomalidomide for treating relapsed and refractory multiple myeloma previously treated with both lenalidomide and bortezomib. NICE technology appraisal guidance. Publication expected February 2015.

E.1.5.3 Related quality standard

End of life care for adults. NICE quality standard 13 (2011).

E.1.6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS: 5th edition
- The guidelines manual.
- Information on the progress of the guideline will also be available from the NICE website.

Appendix F:People and organisations involved in producing the guideline

F.1 Members of the Guideline Committee

Guideline Committee Chair	
Professor Curly Morris	Consultant Haematologist, Altnagelvin Hospital, Londonderry
Guideline Committee Lead Clinician	
Dr Guy Pratt	Senior lecturer, Cancer Sciences Honorary Consultant Haematologist, Birmingham
Guideline Committee Members	
Professor Sam Ahmedzai	Emeritus Professor, Palliative Medicine, Sheffield
Alan Chant	Patient and carer member
Andrea Guy	Clinical Nurse Specialist and Stem Cell Transplant Coordinator, Myeloma and Related Plasma Cell Disorders, London
Dr Matthew Jenner	Consultant Haematologist, Southampton
Nicola Montacute	Palliative Care Clinical Nurse Specialist, Somerset
Dr Nicola Mulholland	Consultant Radiologist and nuclear medicine physician, honorary senior lecturer, London.
Monica Morris	Clinical Nurse Specialist, Middlesex
Lesley Roberts	Patient and carer member
Dr Hamdi Sati	Consultant Haematologist, Swansea
Professor John Snowden	Consultant Haematologist & Director of Blood and Marrow Transplantation, Sheffield
Dr Matthew Streetly	Consultant Haematologist, London
Jane Woodward	Patient and carer member

Declarations of interest

Name	Interest declared	Category	Decision
Curly Morris	Received reimbursement of travel and subsistence expenses, and registration fee to attend the American Society for Haematology Meeting in Atlanta.	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Curly Morris	Received financial support from Celgene to attend the International Myeloma Workshop in Kyoto, Japan. Money was paid to Altnagelvin Haematology Laboratory Trust Funds	Non-personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Curly Morris	Received financial support from Mundi Pharma to attend the	Non-personal pecuniary Non-	Declare and can participate in

Name	Interest declared	Category	Decision
	European Blood and Marrow Transplant Meeting in London. Money was paid to Altnagelvin Haematology Laboratory Trust Funds	specific	discussion of all topics as expenses not beyond reasonable amounts.
Curly Morris	Member of the trial management group and involved in designing the the trial protocol for Myeloma X trial (phase III on the role of a second autologous stem cell transplant in patients with relapsed myeloma following high dose rate chemotherapy and autologous stem cell rescue). Funded by CRUK.	Non-personal pecuniary Specific	Declare and can participate in discussion of all topics as research not funded by the healthcare industry.
Curly Morris	Principal investigator and involved in designing the trial protocol for an Irish Clinical Oncology Research Group (ICORG) sponsored phase II trial of Bortezomib, Adriamycin and Dexamethasone (PAD) in patients with relapsed and refractory myeloma. Costs and free drug from Jansen Cilag.	Non-personal pecuniary Specific	Declare and must withdraw from discussion of any topics which include PAD as an intervention until 12 months after publication of the results
Curly Morris	Received reimbursement of travel expenses from the organisers for speaking on myeloma to data managers at the European Blood and Marrow Transplant meeting	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as expenses not beyond reasonable amounts
Curly Morris	The Binding Site Ltd have offered to reimburse travel and subsistence expenses for attendance at their conference in Edinburgh.	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as expense not beyond reasonable amounts
Curly Morris	Will receive reimbursement of travel and subsistence expenses from EMBT for chairing a session and presenting on maintenance and consolidation post transplant in myeloma patients at their conference in Turin	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as expenses not beyond reasonable amounts.
Curly Morris	Has accepted an honorarium from Celgene to attend International Myeloma Workshop in Rome in September.	Personal pecuniary non-specific	Declare and participate in discussion of all topics as expenses not beyond reasonable amounts.
Guy Pratt, Clinical Lead	Receives an annual payment from the Binding Site Ltd for being a member of their advisory board and providing general clinical advice. This involves overseeing, as chief investigator, a study recruiting normal blood donors from within	Personal pecuniary Specific	Declare and must withdraw from discussion of any topics which include interventions made by Binding Site Ltd

Name	Interest declared	Category	Decision
	the company for control samples.		
Guy Pratt	Received honorarium from Celgene for chairing a meeting on general myeloma issues.	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as conflict has now expired.
Guy Pratt	Received honorarium from Janssen for a presentation on Waldenstroms.	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as Waldenstroms is not being investigated by the guideline.
Guy Pratt	Received support for travel, accommodation and subsistence expenses from Binding Site Ltd to attend an educational meeting in Japan.	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Guy Pratt	Received support from the Italian Haematology Society to attend and present a lecture on Immunodeficiency in Multiple Myeloma	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Guy Pratt	Chief investigator (and designed trial protocol) for the PICCLE trial (parp inhibitor olaparib in relapsed chronic lymphocytic leukaemia). Astra Zeneca provided free drug support and the trial was supported by Leukaemia Lymphoma Research.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as chronic lymphocytic leukaemia is not being investigated by the guideline
Guy Pratt	Principal investigator for the PADIMAC trial (Phase II study of bortezomib, adramycin, dexamethasone (PAD) therapy in previously untreated myeloma patients). Funded by Leukaemia Lymphoma Research	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials and not funded by pharmaceutical industry.
Guy Pratt	Principal investigator for the GOYA study (GA-101 +CHOP versus RCHOP chemotherapy in untreated Diffuse Large B-cell NHL). Funded by Roche	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as diffuse large B-cell NHL is not being investigated by the guideline
Guy Pratt	Principal investigator for the Lilly Myeloma trial (A Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase 2/3 Study of Tabalumab in Combination with Bortezomib and Dexamethasone in relapsed by Myeloma). Funded by Lilly	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.

Name	Interest declared	Category	Decision
Guy Pratt	Principal investigator for the Gilead CLL study (A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Idelalisib (GS-1101) in Combination with Bendamustine and Rituximab for Previously Treated Chronic Lymphocytic Leukemia). Funded by Gilead	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as chronic lymphocytic leukaemia is not being investigated by the guideline
Guy Pratt	Co-investigator (involved in designing the trial protocol) for the TEAMM trial (trial assessing the benefit of antibiotic prophylaxis with levofloxacin, and its effect on health care associated infections in patients with newly diagnosed symptomatic myeloma). Funded by NIHR Health Technology Assessment.	Non-personal pecuniary Specific	Declare and can participate in discussion of all topics as research not funded by the healthcare industry.
Guy Pratt	Co-investigator (involved in designing the trial protocol) for the BAP trial (bezafibrate/medroxyprogesteron in chronic lymphocytic leukaemia, acute myeloid leukaemia and non-Hodgkin's lymphoma). Funded by Queen Elizabeth Hospital Trust.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as chronic lymphocytic leukaemia, acute myeloid leukaemia and NHL are not being investigated by the guideline
Guy Pratt	Member of the trial management group for a randomised phase II trial R2W in Waldenstron's macroglobulinaemia funded by Cancer Research UK. Involved in trial design, protocol amendments and answering clinical queries.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as Waldenstroms is not being investigated by the guideline
Guy Pratt	Member of the data monitoring committee (checks safety data) for the LenaRIC trial (Phase II study of the adjuvant use of lenalidomide in patients undergoing reduced intensity conditioning allogenic transplantation for multiple myeloma). Funded by CTAAC	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Guy Pratt	Member of the data monitoring committee (checks safety data) for HA-1 trial (A phase I clinical trial of the vaccination of healthy human volunteers against the minor histocompatibility antigen (mHAg) HA-1 using a DNA and MVA 'prime/boost' regimen).	Non-personal pecuniary Non-specific	Declare and participate in discussion on all topics vaccination strategies are not being investigated by the guideline
Guy Pratt	Co-author on an evidence	Personal non-	Declare and participate

Name	Interest declared	Category	Decision
	based position statement on bendamustine in multiple myeloma, on behalf of the UK Myeloma Forum and Myeloma UK.	pecuniary	in discussion on all topics as conclusions of the paper were based on a review of the published evidence.
Guy Pratt	Co-author on an evidence based position statement on maintenance and consolidation in multiple myeloma, on behalf of the UK Myeloma Forum and Myeloma UK.	Personal non-pecuniary	Declare and participate in discussion on all topics as conclusions of the paper were based on a review of the published evidence and the guideline will not be investigating maintenance and consolidation therapy for myeloma.
Guy Pratt	Registration fee for attendance at the British Society of Haematology Annual Meeting in Birmingham was paid by Janssen.	Personal pecuniary Non-specific	Declare and participate in discussion of topics as payment was no beyond reasonable amounts.
Guy Pratt	Will receive an honorarium for chairing a medical advisory board for Takeda on ixazomib.	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as ixazomib is not being investigated by the guideline.
Guy Pratt	Will receive an honorarium for chairing a medical advisory board for Amgen on carfilzomib.	Personal pecuniary Specific	Declare and must withdraw from topics which include carfilzomib as an intervention until October 2015
Guy Pratt	Will receive reimbursement of travel and subsistence expenses from the Binding Site Ltd to attend the American Society of Haematology Conference in San Francisco.	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as payment not beyond reasonable expenses.
Guy Pratt	Will receive reimbursement of travel and subsistence expenses from The Binding Site Ltd to attend their meeting in Edinburgh.	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as payment not beyond reasonable expenses.
Guy Pratt	Giving a presentation on the management of myeloma for Sebia UK Ltd in Birmingham.	Personal non-pecuniary Non-specific	Declare and participate in discussion of all guideline topics as no payment was received.
Guy Pratt	Will receive reimbursement of travel and subsistence expenses from Helena Biosciences Europe for giving a talk on international standards for diagnosis and relapse in myeloma in Barcelona	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as payment was not beyond reasonable expenses.
Guy Pratt	Has accepted an honorarium	Personal	Declare and participate

Name	Interest declared	Category	Decision
	from Takeda to attend International Myeloma Workshop in Rome in September.	pecuniary non-specific	in discussion of all topics as expenses not beyond reasonable amounts.
Hamdi Sati	Reimbursed for travel expenses to attend the European Haematology Association annual meeting by Napp Pharmaceuticals	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Hamdi Sati	Local principle investigator for the Myeloma X trial (A phase III study to determine the role of a second autologous stem cell transplant as consolidation therapy in patients with relapsed multiple myeloma following prior high dose chemotherapy and autologous stem cell rescue). Funded by CRUK	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Hamdi Sati	Local principle investigator for the Myeloma XI trial (Randomised comparisons in myeloma patients of all ages of thalidomide, lenalidomide and bortezomib combinations and maintenance lenalidomide). Funded by CTAAC	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Hamdi Sati	Local principle investigator for the MM1 trial (investigating whether adding MLN9708 to the combination of lenalidomide and dexamethasone, improves survival in patients with relapsed myeloma). Funded by Millenium Pharmaceuticals.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Hamdi Sati	Local principle investigator for the PASS observational study (A non-interventional observational post authorisation safety study of subjects treated with lenalidomide). Funded by Celgene	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Hamdi Sati	Local principle investigator for the PREAMBLE observational study (non-interventional observational study aimed at understanding the real world effectiveness of novel agents used in treating multiple myeloma and their impact on patient-reported outcomes). Funded by Bristol Myers Squibb.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Hamdi Sati	Is a signatory on a myeloma endowment fund (generated by patient donations, no direct	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as no

Name	Interest declared	Category	Decision
	contributions from pharmaceutical industry). Used to fund small projects and provide additional resource for ongoing research projects.		contributions to the fund from the healthcare industry.
Hamdi Sati	Received reimbursement of travel and subsistence expenses from SHIRE for attending the 19th annual EHA meeting in Milan.	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as expenses not beyond reasonable amounts.
Hamdi Sati	Received reimbursement of travel and subsistence expenses from Celgene to attend the European Multiple Myeloma Academy meeting in Vienna.	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as expenses not beyond reasonable amounts
Hamdi Sati	Received reimbursement of travel, subsistence and registration expenses from Bristol-Myers Squibb to attend the American Society of Haematology meeting in San Francisco.	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as expenses not beyond reasonable amounts
Hamdi Sati	Is the local principle investigator for a trial examining ixazomib maintenance therapy post Autologous stem cell transplant in newly diagnosed multiple myeloma patients. Trial is sponsored by TAKEDA	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as not supervisory responsibility on trials and the guideline is not covering maintenance therapy.
Hamdi Sati	HS declared that he has been offered travel and accommodation to attend the 7th international meeting in Edinburgh 16-17 April 2015. Educational sponsorship by Binding site.	personal pecuniary non-specific	HS can participate in discussion on all topics as not receiving expenses beyond reasonable amount.
Hamdi Sati	HS declared that he has been offered an educational grant covering registration, travel and accommodation to attend the EHA 2015 meeting from BMS.	personal pecuniary non-specific	HS can participate in discussion on all topics as not receiving expenses beyond reasonable amount.
Hamdi Sati	HS declared that he is the local Principal Investigator for Tourmaline C16021 protocol trial examining the role of Ixazomib maintenance in transplant ineligible patients, sponsored by Takeda.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as not supervisory
Hamdi Sati	Has accepted an honorarium from Takeda to attend International Myeloma Workshop in Rome in September.	Personal pecuniary non-specific	Declare and participate in discussion of all topics as expenses not beyond reasonable amounts.
John Snowden	Received an honorarium from MSD for chairing a meeting on	Personal pecuniary Specific	Declare and must withdraw from topics

Name	Interest declared	Category	Decision
	antifungal drugs.		which include antifungal drugs as an intervention until October 2014
John Snowden	Received an honorarium from Celgene for chairing a meeting on myeloma drugs.	Personal pecuniary Specific	Declare and must withdraw from topics which include myeloma drugs manufactured by Celgene (thalidomide, lenalidomide and pomalidomide) as an intervention until January 2015
John Snowden	Received an honorarium from MSD for attending an advisory board on Posoconazole	Personal pecuniary Specific	Declare and must withdraw from topics which include posoconazole (antifungal) as an intervention until October 2014
John Snowden	Received reimbursement of accommodation, travel, subsistence and registration fee from MSD, to attend the American Society for Hematology conference in New Orleans	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
John Snowden	Co-applicant on a research grant from Pfizer to investigate characterisation of central brain processing of chemotherapy-induced peripheral neuropathy	Non-personal pecuniary Specific	Declare and must withdraw from topics which include pregablin as an intervention (manufactured by Pfizer for treating peripheral neuropathy). As pharmacological management of neuropathic pain has been excluded from the topic on management of neuropathy, JS can participate in discussion of this topic.
John Snowden	Local principle investigator for the Myeloma XI trial (Randomised comparisons in myeloma patients of all ages of thalidomide, lenalidomide and bortezomib combinations and maintenance lenalidomide). Funded by CTAAC	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the RIC UCBT trial (Transplantation of umbilical cord blood from unrelated donors in patients with haematological diseases using a reduced intensity conditioning	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as transplantation of umbilical cord blood is not being investigated by the guideline and

Name	Interest declared	Category	Decision
	regimen). Funded by The Sue Harris Bone Marrow Trust.		has no supervisory responsibility on trials.
John Snowden	Local principle investigator for the MAC UCBT trial (Transplantation of umbilical cord blood from unrelated donors in patients with haematological diseases using a myeloablative conditioning regimen). Funded by The Sue Harris Bone Marrow Trust.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as transplantation of umbilical cord blood is not being investigated by the guideline and has no supervisory responsibility on trials.
John Snowden	Local principle investigator for the LenaRIC trial (Phase II study of the adjuvant use of lenalidomide in patients undergoing reduced intensity conditioning allogenic transplantation for multiple myeloma). Funded by CTAAC.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the ProT-4 trial (Phase II study to evaluate the efficacy of prophylactic transfer of CD4 lymphocytes after T-cell depleted reduced intensity HLA-identical sibling transplantation for haematological cancers). Funded by Leukaemia and Lymphoma Research.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as transfer of lymphocytes after transplantation is not being investigated by the guideline and has no supervisory responsibility on trials.
John Snowden	Local principle investigator for the Myeloma IX trial (A randomised trial comparing second generation vs third generation bisphosphonates, induction chemotherapy regimens (CVAD vs CTD, and MP vs CTDa) and thalidomide maintenance vs no maintenance therapy). Funded by MRC	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the Myeloma X relapse (intensive) trial (to determine whether a high-dose procedure with autologous transplant is superior to low-dose consolidation therapy following re-induction chemotherapy in patients with replapsed myeloma). Funded by CRUK	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the RICAZA trial (Phase II study of the tolerability of adjunctive azacitidine in patients undergoing reduced intensity allogeneic stem cell transplantation for acute myeloid leukaemia). Funded by	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as transplantation for acute myeloid leukaemia is not being investigated by the guideline and has no

Name	Interest declared	Category	Decision
	Celgene.		supervisory responsibility on trials.
John Snowden	Local principle investigator for the Living with advanced relapsed myeloma study (cross sectional observational study to identify preventable and manageable late effects). Funded by Myeloma UK.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for a Phase 2, Multi-centre, Randomised, Open-Label, Parallel Group Study to Evaluate the Effect of VELCADE on Myeloma related Bone Disease. Funded by Janssen-Cilag Ltd.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the UK Haplo Trial (A UK multicentre phase II study of haploidentical stem cell transplantation in patients with haematological malignancies). Funded by Leukaemia Lymphoma Research.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Local principle investigator for the HLA Epitope trial (HLA epitope matched platelet transfusion in aplastic anaemia, MDS and AML patients) Funded by NHS Blood and Transplant (NHSBT)	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as aplastic anaemia, myelodisplastic syndrome and acute myeloid leukaemia are not being investigated by the guideline and no supervisory responsibility on trials.
John Snowden	Principle investigator of a charitable grant from Royal Hallamshire Hospital Leukaemia and Research Fund, for a bolt-on study to Myeloma X, relating to supportive care in myeloma.	Non-personal pecuniary Specific	Declare and can participate in discussion of all topics as research not funded by the healthcare industry.
John Snowden	Co-investigator on the MUK5 trial (A phase II randomised trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs cyclophosphamide, velcade and dexamethasone (CVD) for first relapse or primary refractory multiple myeloma). Funded by Myeloma UK	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Co-investigator on the TEAMM trial (trial assessing the benefit of antibiotic prophylaxis with levofloxacin, and its effect on health care associated	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.

Name	Interest declared	Category	Decision
	infections in patients with newly diagnosed symptomatic myeloma). Funded by NIHR Health Technology Assessment.		
John Snowden	Co-investigator on the AML 17 trial (Working parties on leukaemia in adults and children trial in AML or high risk MDS 17). Funded by CRUK	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as leukaemia, AML and MDS are not being investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the FiTT study (Investigating the effectiveness of co-morbidity assessment in male patients with myeloma and prostate cancer). Funded by Weston Park Hospital Cancer Charity and Sheffield Teaching Hospitals NHS Foundation trust.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Co-investigator on the AML 15 trial (Working parties on leukaemia in adults and children AML trial 15). Funded by MRC.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as leukaemia is not being investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the AML 16 trial (A programme of development for older patients with AML and high risk MDS). Funded by CRUK.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as AML and MDS are not being investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the MCL MiniAllo trial (Phase II study of low intensity allogeneic transplantation in Mantle Cell Lymphoma). Funded by CRUK, Genzyme Therapeutics, National Institute for Health Research Cancer Network (NRCN).	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as mantle cell lymphoma is not being investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the ORCHARRD trial (Ofatumumab rituximab chemoimmunotherapy ASCT relapsed refractory DLBCL). Funded by GlaxoSmithKline.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as diffuse large B cell lymphoma is not being investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the FIGARO trial (A randomised trial of the FLAMSA-BU conditioning regimen in patients with AML	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as AML and MDS are not being

Name	Interest declared	Category	Decision
	and MDS undergoing allogeneic stem cell transplantation). Funded by Leukaemia and Lymphoma Research.		investigated by the guideline no supervisory responsibility on trial.
John Snowden	Co-investigator on the MUK 4 trial (phase II trial of combination treatment with Vorinostat, bortezomib and dexamethasone in patients with relapsed multiple myeloma). Funded by Myeloma UK	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Co-investigator on the SarCaBon trial (A randomised phase II trial of Saracatinib versus placebo for cancer-induced bone pain). Funded by MRC	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
John Snowden	Member of the UK Myeloma Forum. Involved in writing the evidence-based position statement: 'The use of consolidation and maintenance treatment in myeloma'	Personal non-pecuniary Non-specific	Declare and participate in discussion on all topics as conclusions of the paper were based on a review of the published evidence and the guideline will not be investigating maintenance and consolidation therapy for myeloma.
John Snowden	Member of the UK Myeloma Forum has been involved in writing the evidence-based position statement: 'The use of bendamustine in myeloma'	Personal non-pecuniary	Declare and participate in discussion on all topics as conclusions of the paper were based on a review of the published evidence.
John Snowden	Executive member of the UK Myeloma Forum, a non-profit organisation for the support of UK health professionals and scientists in the myeloma field.	Personal non-pecuniary	Declare and participate in discussion on all topics as interest does not impact on content of the guideline.
John Snowden	Co-author on the following abstract, which were prepared by BresMed on behalf of Celgene: Stradwick S, Freemantle N, Snowden J, Rodrigues F, Brereton N. 2012. Comparative Effectiveness of Lenalidomide plus Dexamethasone for the Treatment of Refractory/Relapsed Multiple Myeloma: A Systematic Review and Mixed Treatment Comparison. Blood (ASH Annual Meeting Abstracts); 120 (21): A4076.	Personal non-pecuniary	Declare and must withdraw from discussion of any topics which include drugs manufactured by Celgene as interventions (pomalidomide, thalidomide, lenalidomide) until November 2013
John Snowden	Co-author on the following abstract, which were prepared	Personal non-pecuniary	Declare and must withdraw from

Name	Interest declared	Category	Decision
	by BresMed on behalf of Celgene: Stradwick S, Freemantle N, Vickers A, Rodrigues F, Monzini M, Brereton N, Snowden. 2013. Comparative Effectiveness of Lenalidomide Plus Dexamethasone Versus Bortezomib Subcutaneous for the Treatment of RRMM. Presented at the 14th International Myeloma Workshop (IMW); Kyoto, Japan; April 3–7.		discussion of any topics which include drugs manufactured by Celgene as interventions (pomalidomide, thalidomide, lenalidomide) until April 2014
John Snowden	Received reimbursement of travel expenses from the organisers for speaking on quality in transplantation at the Joint Accreditation Committee in Autoimmune Diseases meeting	Personal pecuniary Non-specific	Declare and participate in discussion on all guideline topics as expenses not beyond reasonable amounts.
John Snowden	Will receive an honorarium for from Sanofi for attending an advisory board on the mobilising agent plerixafor and possibly some future currently unlicensed drugs	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as plerixafor is not being investigated by the guideline.
Matthew Jenner	Received an honorarium from Napp Pharmaceuticals for attending an advisory board on bendamustine.	Personal pecuniary Specific	Declare and must withdraw from any topics which include bendamustine as an intervention until December 2014
Matthew Jenner	Received payment from Janssen for giving an interview on the delivery of bortezomib in the community setting	Personal pecuniary Specific	Declare and must withdraw from any topics which include bortezomib as an intervention until December 2014
Matthew Jenner	Received payment from Celgene for chairing a debate on drug treatment of relapsed myeloma.	Personal pecuniary Specific	Declare and must withdraw from topics which include myeloma drugs manufactured by Celgene (thalidomide, lenalidomide and pomalidomide) as an intervention until November 2014.
Matthew Jenner	Received reimbursement of travel and subsistence from Napp Pharmaceuticals to attend the American Society of Haematology meeting in New Orleans	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Matthew Jenner	Received reimbursement of travel and subsistence from Janssen to attend the International Myeloma	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not

Name	Interest declared	Category	Decision
	Workshop in Japan		beyond reasonable amounts.
Matthew Jenner	Has been offered reimbursement of travel and subsistence expenses from Celgene to attend the European Haematology Association	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Matthew Jenner	Is local principle investigator for the MM1 trial (investigating the effect of adding MLN9708 to the combination of lenalidomide and dexamethasone, improves survival in patients with relapsed myeloma). Funded by Millenium Pharmaceuticals.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Is local principle investigator for the FOCUS trial (Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma). Funded by Onyx Pharmaceuticals	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Is local principle investigator for the MUK five trial (phase II randomised trial of carfilzomib, cyclophosphamide and dexamethasone (CCD) vs cyclophosphamide, velcade and dexamethasone (CVD) for first relapse or primary refractory multiple myeloma). Funded by Myeloma UK	Non-personal pecuniary	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Is local principle investigator for the MUK four trial (Phase II Trial of combination treatment with Vorinostat, Bortezomib and Dexamethasone in participants with Relapsed Multiple Myeloma). Funded by Myeloma UK.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Is local principle investigator for the Myeloma IX trial (randomised trial comparing second generation vs third generation bisphosphonates, induction chemotherapy regimens (CVAD vs CTD, and MP vs CTDa) and thalidomide maintenance vs no maintenance therapy). Funded by the Medical Research Council.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Is local principle investigator for the Myeloma X trial (phase III on the role of a second autologous stem cell transplant	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory

Name	Interest declared	Category	Decision
	in patients with relapsed myeloma following high dose rate chemotherapy and autologous stem cell rescue). Funded by Cancer Research UK		responsibility on trials.
Matthew Jenner	Is local principle investigator for the Myeloma XI trial (Randomised comparisons in myeloma patients of all ages of thalidomide, lenalidomide and bortezomib combinations and maintenance lenalidomide). Funded by CTAAC	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Jenner	Signatory for a charitable hospital fund used for education and development for healthcare professionals. No contribution to this fund from the pharmaceutical industry.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as no contributions to the fund from the healthcare industry.
Matthew Jenner	Was part of the group who developed evidence based guidelines on myeloma for the BCSH.	Personal non-pecuniary	Declare and participate in discussion on all topics as interest does not impact on content of the guideline.
Matthew Jenner	Is chief investigator for the MUK four trial investigating bortezomib and dexamethasome with vorinostat in relapsed myeloma. Involved n designing the trial protocol. The trial is funded by Myeloma UK.	Non-personal pecuniary Specific	Declare and participate in discussion of all guideline topics as the trial is not funded by the pharmaceutical industry
Matthew Jenner	Is local PI for the Pollux study. A randomised phase III study investigating lenalidomide and dexamethasone +/- daratumumab in relapsed myeloma. The study is funded by Janssen.	Non-personal pecuniary	Declare and participate in discussion of all guideline topics as not involved in designing the trial protocol and no supervisory responsibility for trial
Matthew Jenner	Received reimbursement of travel and subsistence expenses and an honorarium from Amgen Oncology for taking part in an advisory board on carfilzomib.	Personal pecuniary Specific	Declare and withdraw from discussion of topics that include carfilzomib as an intervention until September 2015. Chairpersons action that can be asked questions on the evidence base but must not participate in drafting recommendations
Matthew Jenner	Received reimbursement of travel and subsistence expenses and an honorarium from Takeda UK for participating in an advisory	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as interventions manufactured by

Name	Interest declared	Category	Decision
	board on myeloma		Takeda are not being investigated by the guideline
Matthew Jenner	invited to present on cytogenetics at an educational symposium at the British Society of Haematology Annual Scientific Meeting. MJ will only receive reimbursement of travel expenses	personal pecuniary Non-specific	Declare and participate in discussion on all topics as not receiving expenses beyond reasonable amount
Matthew Jenner	member of the Myeloma XI trial management group. Myeloma X1 trial is investigating different chemotherapy schedules in newly diagnosed myeloma. These include schedules containing different combinations including thalidomide, lenalidomide, bortezomib and carfilzomib. The trial is primarily funded through CTAAC (Cancer Research UK). Sponsor is University of Leeds.	non-personal pecuniary Specific	can declare and participate in all discussion as research not funded by the healthcare industry
Matthew Jenner	MJ declared that he has been offered economy class travel, accommodation and registration for the European Haematology Association Annual Meeting in Vienna, 11-14 June 2015 by Janssen.	personal pecuniary non-specific	MJ can participate in discussion on all topics as not receiving expenses beyond reasonable amount.
Matthew Jenner	MJ declared that he has been offered economy class travel, accommodation and registration for the American Society of Hematology Annual Meeting in Orlando, 5-8th December 2015 by Janssen.	personal pecuniary non-specific	MJ can participate in discussion on all topics as not receiving expenses beyond reasonable amount.
Matthew Streetly	Received payment from Celgene for attending an advisory board on lenalidomide usage in myeloma	Personal pecuniary Specific	Declare and must withdraw from any topics which include lenalidomide as an intervention until June 2014.
Matthew Streetly	Received reimbursement of travel and subsistence expenses from Janssen, for attending the International Myeloma Workshop	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Matthew Streetly	Received payment from Celgene for giving a presentation on “Optimising Myeloma therapy"	Personal pecuniary Specific	Declare and must withdraw from topics which include myeloma drugs manufactured by Celgene (thalidomide, lenalidomide and pomalidomide) as an intervention until November 2014.

Name	Interest declared	Category	Decision
Matthew Streetly	Received payment from Celgene for giving presentations on "Pomalidomide Case Histories"	Personal pecuniary Non-specific	Declare and must withdraw from any topics which include pomalidomide as an intervention until November 2014.
Matthew Streetly	Received payment from Janssen for giving a presentation on "Transplant: what is the data telling us?". Provided data on induction chemotherapy prior to transplant.	Personal pecuniary Specific	Declare and must withdraw from any topics which include induction chemotherapy as an intervention until October 2014. Induction chemotherapy is not being investigated by the guideline as there is a NICE Technology Appraisal in development in this area. Therefore MS will be able to participate in discussion of all topics
Matthew Streetly	Received payment from Celgene for giving a presentation on "Pomalidomide Background: Summary of Recent Data"	Personal pecuniary Non-specific	Declare and must withdraw from any topics which include pomalidomide as an intervention until September 2014.
Matthew Streetly	Received payment from Janssen for giving a presentation on "Managing Patient's Expectations"	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as subject of presentation is not specific to the content of the guideline.
Matthew Streetly	Received payment from Celgene for giving a presentation on "Myeloma treatment in South East London"	Personal pecuniary Specific	Declare and must withdraw from topics which include myeloma drugs manufactured by Celgene (thalidomide, lenalidomide and pomalidomide) as an intervention until February 2014.
Matthew Streetly	Had a consultative role on the Burden of Relapse study (a non-treatment related clinical study examining the impact (physical, psychological, economic) of periods of remission in comparison to periods of disease activity). Received payment from Celgene for teleconference participation every few months and review of data	Personal pecuniary Specific	Declare and must withdraw from topics which include myeloma drugs manufactured by Celgene (thalidomide, lenalidomide and pomalidomide) as an intervention until January 2015.
Matthew Streetly	Chief investigator of the MM013 study (Phase 2 multicentre,	Non-personal pecuniary Non-	Declare and must withdraw from topics

Name	Interest declared	Category	Decision
	open-label study to determine the efficacy and safety of pomalidomide in combination with low dose dexamethasone in subjects with relapsed or refractory myeloma). Trial funded by Celgene. Not involved in designing the trial protocol.	specific	which include pomalidomide as an intervention. Chair persons action that can be asked questions on the evidence base but must not be involved in drafting recommendations.
Matthew Streetly	Local principle investigator for the PADIMAC study (Phase II study of Bortezomib, Adriamycin and Dexamethasone (PAD) therapy for previously untreated patients with multiple myeloma: Impact of minimal residual disease (MRD) in patients with deferred ASCT). Funded by Leukaemia & Lymphoma Research	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Streetly	Local principle investigator for the TEAMM trial (trial assessing the benefit of antibiotic prophylaxis with levofloxacin, and its effect on health care associated infections in patients with newly diagnosed symptomatic myeloma). Funded by NIHR Health Technology Assessment.	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Streetly	Local principle investigator for the CLARION trial (Randomized, Open-label Phase 3 Study of Carfilzomib, Melphalan, and Prednisone versus Bortezomib, Melphalan, and Prednisone in Transplant ineligible Patients with Newly Diagnosed Multiple Myeloma). Funded by Onyx Therapeutics	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Streetly	Local principle investigator for the CNTO328 trial (Siltuximab (compared with placebo) in Patients With High-risk Smoldering Multiple Myeloma). Funded by Janssen	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Streetly	Local principle investigator for the PASS observational study (A non-interventional observational post authorisation safety study of subjects treated with lenalidomide). Funded by Celgene	Non-personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Matthew Streetly	Priniciple investigator for phase III trial in relapsed myeloma (patients randomised between daratumumab with lenalidomide and dexamethasone versus	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.

Name	Interest declared	Category	Decision
	lenalidomide and dexamethasone alone). Trial is funded by Janssen		
Matthew Streetly	Written a position statement for the UK Myeloma Forum, about horizon scanning for new agents in myeloma. Statement does not advocate any particular agents.	Personal non-pecuniary	Declare and participate in discussion on all topics as interest does not impact on content of the guideline.
Matthew Streetly	Planning to write a review of the long-term follow up data for a trial on pomalidomide.	Personal non-pecuniary	
Matthew Streetly	Is being sponsored to attend the American Society of Haematology Meeting in San Francisco by Janssen. Sponsorship covers flights accommodation and conference registration.	Personal pecuniary Non-specific	Declare and participate in discussion on all topics as sponsorship is not beyond reasonable amounts.
Matthew Streetly	accepted a travel award from Janssen Pharmaceuticals to attend the International Myeloma workshop in Rome in September 2015	Personal pecuniary Non-specific	Declare and can participate in discussion of all topics as expenses not beyond reasonable amounts.
Sam Ahmedzai	An honorarium from MSD was paid to his department for giving a lecture on 'The Science of Symptoms'	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as subject of presentation is not specific to the content of the guideline.
Sam Ahmedzai	An honorarium from Creative Ceutical was paid to his department for taking part in a teleconference to set up an interview study of quality of life in advanced breast cancer	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as advanced breast cancer is not being investigated by the guideline.
Sam Ahmedzai	An honorarium from Amgen was paid to his department for giving a lecture on metastatic bone disease.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as metastatic bone disease is not being investigated by the guideline.
Sam Ahmedzai	An honorarium from Napp Pharmaceuticals was paid to his department for taking part in an advisory board on pain.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as management of pain is not being investigated by the guideline.
Sam Ahmedzai	An honorarium from Prostrakan was paid to his department for giving a lecture on introduction to nausea and vomiting and its management	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as management of nausea and vomiting is not being investigated by the guideline.
Sam Ahmedzai	An honorarium from	Non-personal	Declare and participate

Name	Interest declared	Category	Decision
	Archimedes was paid to his department for participating in the Archimedes Academy. Participation includes chairing the meeting and helping to select topics and speakers. Also gave a lecture on 'Update on pain control', and took part in a debate on end of life care.	pecuniary Non-specific	in discussion of all topics as subject of presentation is not specific to the content of the guideline.
Sam Ahmedzai	An honorarium from the World Association for Sleep Medicine was paid to his department for participating in their symposium	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as subject of presentation is not specific to the content of the guideline.
Sam Ahmedzai	An honorarium from Gruenthal was paid to his department for participating in an advisory board on education and awareness strategies for breakthrough cancer pain	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as breakthrough cancer pain is not being investigated by the guideline.
Sam Ahmedzai	An honorarium from Bayer was paid to his department for taking part in a meeting on Sativex	Non-personal pecuniary Specific	Declare and can participate in discussion of all topics as pharmacological management of neuropathic pain has been excluded from the topic on management of neuropathy.
Sam Ahmedzai	Chief investigator a study to investigate characterisation of central brain processing of chemotherapy-induced peripheral neuropathy. Funded by Pfizer	Non-personal pecuniary Specific	Declare and must withdraw from topics which include pregablin as an intervention (manufactured by Pfizer for treating peripheral neuropathy). As pharmacological management of neuropathic pain has been excluded from the topic on management of neuropathy, SA can participate in discussion of this topic.
Sam Ahmedzai	Chief investigator for an observational study looking at a new treatment for opioid-induced constipation in cancer patients. Study is funded by Astra Zeneca.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as management of opioid induced constipation is not being investigated by the guideline.
Sam Ahmedzai	Chief investigator for a study of an experimental new opioid for pain control in cancer patients. Study is funded by Grunenthal	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as pain control is not being investigated

Name	Interest declared	Category	Decision
			by the guideline.
Sam Ahmedzai	Chief investigator for a study on a pain killer for cancer and non-cancer patients. Study is funded by Mundi Pharma	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as pain control is not being investigated by the guideline.
Sam Ahmedzai	Chief investigator for a study to measure the response to 'Standard laxative treatment' (SLT) in patients with opioid-induced constipation, across several European countries. Study is funded by Mundi Pharma.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as management of opioid induced constipation is not being investigated by the guideline.
Sam Ahmedzai	Chief investigator for a study to investigate HRQOL of triple negative breast cancer patients. Funded by Creative Ceutical	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as breast cancer is not being investigated by the guideline.
Sam Ahmedzai	Is co-investigator of a trial of an experimental drug to treat bone cancer pain in cancer patients. Trial is funded by the MRC and Astra Zeneca.	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as pain control is not being investigated by the guideline and no supervisory responsibility on trials.
Sam Ahmedzai	Fund holder for the SPORG research group. Money is spent on supportive and palliative care research. No contributions to the fund from pharmaceutical companies	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as no contributions to the fund from the healthcare industry.
Sam Ahmedzai	Received an honorarium and reimbursement of travel expenses from Mundipharma for lectures given during the Pain Forum lecture tour in South East Asia and Brazil on: 'pain in special populations' 'assessing and treating pain in patients with substance abuse concerns' case presentations on cancer pain, palliative care, neuropathic pain and non-malignant pain. adequacy of opioid analgesic consumption at country, global and regional levels.	Personal pecuniary Specific	Declare and must withdraw from topics which include analgesics as interventions (Mundipharma make analgesics) until April 2015.
Sam Ahmedzai	Received reimbursement of travel and subsistence expenses to attend the European Hyponatraemia Network conference in Zurich from Otsuka	Personal pecuniary Non-specific	Declare and participate in discussion of all topics as payment was not beyond reasonable amounts.
Sam Ahmedzai	Gave a lecture on 'issues	Non-personal	Declare and participate

Name	Interest declared	Category	Decision
	associated with therapeutic opioids - – an evidence-based approach to pain management' at the World Institute of Pain in Maasticht. Travel and subsistence expenses were reimbursed by Mundipharma for attending and an honorarium from Mundipharma was paid to the University of Sheffield	pecuniary Non-specific	in discussion of all topics as payment was not beyond reasonable amounts and pain management is not being investigated by the guideline.
Sam Ahmedzai	Meeting with Chugai to discuss potential research into weight loss in cancer in collaboration with NCRI.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as weight loss as a symptom is not being covered by the guideline and the research is not funded by the healthcare industry.
Sam Ahmedzai	SA declared that he has met with Chugai, in his capacity as chair of the NCRI studies group, to discuss a potential study on weight loss in cancer.	Non-personal pecuniary Non-specific	SA can participate in discussion on all topics as weight loss as a symptom is not being covered by the guideline and the research is not funded by the healthcare industry.
Sam Ahmedzai	Appointed (January 2015) by Royal College of Physicians to be their Clinical Lead for the National Care of the Dying Audit. Funded post (1 PA per week) that will be paid direct to SA. Role is to advise and lead the RCP audit team in designing a new format for the National Care of the Dying Audit, overseeing its application and helping RCP to announce and disseminate the results.	Personal pecuniary Non-specific	Declare and participate in discussion on all topics as not specific to myeloma.
Nicola Mulholland	Principle investigator for a trial on biomarkers in lymphoma. Involved in designing the trial protocol. Funded by The Elimination of Leukaemia Fund.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as lymphoma is not being covered by the guideline and the research is not funded by the healthcare industry.
Nicola Mulholland	Sub-investigator for the ZEST study (Zevalin for older people with diffuse large B cell lymphoma). Funded by Spectrum Pharmaceuticals. Involvement is to administer the drug – not involved in collecting or analysing the data	Non-personal pecuniary Non-specific	Declare and participate in discussions on all topics as diffuse large B cell lymphoma is not being investigated by the guideline and no supervisory responsibility on trial.
Nicola Mulholland	Investigator on a phase I/II	Non-personal	Declare and participate

Name	Interest declared	Category	Decision
	study of 177Lu-HH1 (Betalutin™) radioimmunotherapy for treatment of relapsed CD37+ non-Hodgkin's Lymphoma. Funded by Nordic Nanovector AS	pecuniary Non-specific	in discussion on all topics as non-Hodgkin Lymphoma is not being investigated by the guideline
Nicola Mulholland	Investigator on the NETTER-1 clinical trial. A phase III trial study comparing treatment with 177LU-DOTA0-Tyr3-Osctreotate to Octreotate LAR in patients with inoperable, progressive, somatostatin receptor positive, midgut carcinoid tumors. Trial funded by Advanced Accelerator Applications.	Non-personal pecuniary Non-specific	Declare and participate in discussion on all topics as midgut carcinoid tumours are not being investigated by the guideline.
Nicola Mulholland	Investigator on the Foxfire study. An open-label randomised phase III trial of 5-Fluorourcacil, OXaliplatic and Folinic acid +/- interventional radio-embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer	Non-personal pecuniary Non-specific	Declare and participate in discussion on all topics as colorectal cancer is not being investigated by the guideline.
Nicola Mulholland	In the process of applying for an ARSAC licence to be an investigator on a phase III, randomised placebo controlled, double blind study of oral ixazomib citrate (MLN9708) maintenance therapy in patients with multiple myeloma following autologous stem cell transplant. Funded by Millenium Pharmaceuticals	Non-personal pecuniary Non-specific	Declare and participate in discussion on all topics as maintenance therapy is not being investigated by the guideline.
Nicola Mulholland	Will receive an honorarium and reimbursement for travel and subsistence expenses from Sirtex for attending their quest investigator study in Sweden	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as Sirtex manufacture interventions for the treatment of liver cancer and liver cancer is not being investigated by the guideline
Nicola Mulholland	Will receive reimbursement of travel and subsistence expenses from TheraSphere for attending their training session in Germany	Personal pecuniary Non-specific	Declare and participate in discussion of all guideline topics as payment not beyond reasonable amounts and TheraSphere manufacture interventions for the treatment of liver cancer and liver cancer

Name	Interest declared	Category	Decision
			is not being investigated by the guideline.
Nicola Mulholland	Declared that she has been sponsored to undertake a study on lymphoma. This was classified as personal pecuniary non-specific meaning that NM can participate in discussion on all topics as the guideline is not covering lymphoma.	Non-personal pecuniary Non-specific	Declare and participate in discussion on all topics as topic not covered in the guideline.
Andrea Guy	Attended a symposium on pomalidomide organised by Celgene. No fee received. Symposium was to present the data on this drug	Personal non-pecuniary	Declare and participate in discussion of all topics as no fee received.
Andrea Guy	Local principle investigator on myeloma lifestyle study on the management of fatigue. Trial is funded by Cancer Research UK. Celgene have funded a physiotherapist's salary to work on the trial.	Non personal pecuniary Specific	Declare and participate in discussions on all topics as no supervisory responsibility on trials.
Andrea Guy	Attended the European Multiple Myeloma Academy educational meeting in Vienna. Travel expenses paid by event organisers.	Personal pecuniary Non specific	Declare and participate in discussion of all guideline topics as payment was not beyond reasonable amounts.
Monica Morris	Received honorarium for attending a nurse educational event held by Janssen on the supportive care needs of patients with myeloma.	Personal pecuniary Specific	Declare and must withdraw from any topics which involve the supportive needs of patients until May 2014.
Monica Morris	Provided advice for Janssen on the content of a nurse educational leaflet on the management of patients on Bortezomib. No payment was received.	Personal non-pecuniary Specific	Declare and participate in discussion of all guideline topics as no payment was received and a colleague is to take over the work for the duration of the guideline.
Monica Morris	Planning to publish the findings of her MSc research into the experience of myeloma family carers. No financial support was provided for the research.	Personal non-pecuniary Specific	Declare and participate in discussion of all guideline topics as no payment was received.
Monica Morris	Has been invited to take part in an advisory group for Myeloma UK looking at their research strategy. Travel and subsistence expenses will be paid by Myeloma UK. No honorarium or other payment will be received.	Personal pecuniary Non specific	Declare and participate in discussion of all guideline topics as payment is not beyond reasonable amounts.

Name	Interest declared	Category	Decision
Monica Morris	Will receive reimbursement of travel and subsistence expenses from Celgene for attending the Myeloma Academy educational event in Vienna	Personal pecuniary Non specific	Declare and participate in discussion of all guideline topics as payment is not beyond reasonable amounts.
Monica Morris	Will receive an honorarium from Novartis for attending a nursing advisory board meeting on Panobinostat	Personal pecuniary Non specific	Declare and participate in discussion of all guideline topics as panobinostat is not being investigated by the guideline.
Monica Morris	Acts as a reviewer for the myeloma section of the Cancer Research UK patient information website (CancerHelp UK). This review is done every 2 years. Receives a small payment from CRUK.	Personal Pecuniary Non-specific	Declare and participate in discussion of all topics as review is on myeloma in general and it is not funded from the healthcare industry.

F.2 Organisations invited to comment on the guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

5 Borough's Partnership NHS Foundation Trust	Abbott Molecular
Addenbrookes Hospital	Aintree University Hospital NHS Foundation Trust
Allocate Software PLC	Amgen UK
Association for Palliative Medicine of Great Britain	Association of Anaesthetists of Great Britain and Ireland
Association of Chartered Physiotherapists in Oncology and Palliative Care	Belfast Health and Social Care Trust
Binding Site Group Ltd	Bristol Myers Squibb Pharmaceuticals Ltd
British Association of Spinal Surgeons	British Dietetic Association
British Lymphoma Pathology Group	British Medical Association
British Medical Journal	British National Formulary
British Nuclear Cardiology Society	British Nuclear Medicine Society
British Psychological Society	British Red Cross
British Society of Interventional Radiology	British Society of Paediatric Gastroenterology Hepatology and Nutrition
BSPGHAN	Caplond Services
Care Quality Commission	Celgene UK Ltd
Cheshire and Merseyside SCN	counselling for prisoners network
Covidien Ltd.	Croydon Clinical Commissioning Group
Croydon Council	Croydon University Hospital
Cumbria Partnership NHS Foundation Trust	CWHHE Collaborative CCGs
Department of Health	Department of Health, Social Services and Public Safety Northern Ireland

DePuy UK	
East and North Hertfordshire NHS Trust	East Kent Hospitals University NHS Foundation Trust
East of England Strategic Clinical Network	Ethical Medicines Industry Group
Faculty of Dental Surgery	Five Boroughs Partnership NHS Trust
Gloucestershire Hospitals NHS Foundation Trust	GP update / Red Whale
Health and Care Professions Council	Health and Social Care Information Centre
Healthcare Improvement Scotland	Healthcare Infection Society
Healthwatch East Sussex	Herts Valleys Clinical Commissioning Group
Humber NHS Foundation Trust	Isabel Hospice
Janssen	Janssen Cilag Ltd
Johnson & Johnson Medical Ltd	Lanes Health
Launch Diagnostics	Leukaemia & Lymphoma Research
Leukaemia CARE	Liverpool Community Health
London cancer alliance	London North West Healthcare NHS Trust
Macmillan Cancer Support	Manchester Royal Infirmary
Mastercall Healthcare	Medical Directorate Services
Medicines and Healthcare Products Regulatory Agency	Medtronic
Milton Keynes Hospital NHS Foundation Trust	Milton Keynes NHS Foundation
Ministry of Defence	Muslim Doctors and Dentists Association
Myeloma UK	Napp Pharmaceuticals Ltd
National Association of Primary Care	National Atrial Fibrillation Clinical Policy Forum
National Clinical Guideline Centre	National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health	National Collaborating Centre for Women's and Children's Health
National Deaf Children's Society	National Institute for Health and Care Excellence
National Institute for Health Research Health Technology Assessment Programme	National Institute for Health Research
National Patient Safety Agency	Newcastle upon Tyne Hospitals NHS Foundation Trust
NHS Barnsley Clinical Commissioning Group	NHS Choices
NHS Chorley and South Ribble CCG	NHS Connecting for Health
NHS Cumbria Clinical Commissioning Group	
NHS England	NHS Hardwick CCG
NHS Health at Work	NHS Improvement
NHS North East Lincolnshire CCG	NHS Plus
NHS Sheffield	NHS Somerset CCG
NHS South Cheshire CCG	NHS Wakefield CCG
NHS Warwickshire North CCG	NHS West Cheshire CCG
Norfolk and Suffolk Palliative Care Academy	North of England Commissioning Support
Northern Health and Social Care Trust	Nottingham City Council
Novartis Pharmaceuticals	Nursing and Midwifery Council
Nutricia Advanced Medical Nutrition	Nutrition and Diet Resources UK
Older People's Advocacy Alliance	Oxford University Hospitals NHS Trust
Oxfordshire Clinical Commissioning Group	Pfizer
Primary Care Pharmacists Association	Primrose Bank Medical Centre

Public Health Agency for Northern Ireland	Public Health England
Public Health Wales	Public Health Wales
Queen Elizabeth Hospital King's Lynn NHS Trust	Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust
Roche Diagnostics	Roche Products
Royal College of Anaesthetists	Royal College of General Practitioners
Royal College of General Practitioners in Wales	Royal College of Midwives
Royal College of Nursing	Royal College of Obstetricians and Gynaecologists
Royal College of Paediatrics and Child Health	Royal College of Pathologists
Royal College of Physicians	Royal College of Psychiatrists
Royal College of Radiologists	Royal College of Speech and Language Therapists
Royal College of Surgeons of England	Royal Cornwall Hospitals NHS Trust
Royal National Institute of Blind People	Royal Pharmaceutical Society
Royal Surrey County Hospital NHS Trust	Sandoz Ltd
Scottish Intercollegiate Guidelines Network	Sebia
Serious Hazards of Transfusion	Sheffield Teaching Hospitals NHS Foundation Trust
Smith & Nephew UK Limited	Social Care Institute for Excellence
Society and College of Radiographers	Somerset, Wiltshire, Avon and Gloucestershire Cancer Services Operational Group
South Eastern Health and Social Care Trust	South London & Maudsley NHS Trust
South Wales Cancer Network	South West Yorkshire Partnership NHS Foundation Trust
Southern Health & Social Care Trust	St Helens and Knowsley Teaching Hospitals NHS Trust
St Josephs Hospice	Staffordshire and Stoke on Trent Partnership NHS Trust
Stockport Clinical Commissioning Group	Takeda UK Ltd
TB Action Group	The British Society for Haematology
The Institute of Cancer Research	The Patients Association
uMotif Digital Health	University College London
University Hospital Birmingham NHS Foundation Trust	University Hospitals Birmingham
University Hospitals Coventry and Warwickshire NHS Trust	Velindre NHS Trust
Vexim UK Ltd	Welsh Government
Welsh Scientific Advisory Committee	West Suffolk Hospital NHS Trust
Western Health and Social Care Trust	Western Sussex Hospitals NHS Trust
Wigan Borough Clinical Commissioning Group	York Hospitals NHS Foundation Trust
Yorkshire and Humber Strategic Clinical Network	

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F.3 Individuals carrying out literature reviews and complementary work

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Manager	
Katrina Blears	National Collaborating Centre for Cancer, Cardiff
Kimberley Cox	National Collaborating Centre for Cancer, Cardiff
Jennifer Stock	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Dr Mia Schmidt-Hansen	National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Angharad Morgan	National Collaborating Centre for Cancer, Cardiff
Information Specialists	
Elise Hasler	National Collaborating Centre for Cancer, Cardiff
Senior Health Economist	
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Health Economist	
James Hawkins	National Collaborating Centre for Cancer, Cardiff

F.4 Expert advisors to the Guideline Development Group

Mr Max Gibbons	Consultant Orhtopaedic Surgeon
Mr Melvin Grainger	Consultant Orthopaedic Spinal Surgeon, Birmingham
Dr David Wilson	Consultant Radiologist, Oxford
Dr Isabel Syndikus	Clinical Oncologist, Liverpool

Declarations of interest

Name	Interest declared	Category	Decision
Max Gibbons	Receives payment and reimbursement of travel expenses from Oxford BioMet, 3 times per year, for giving a lecture on knee replacement. Last lecture given in July 2014	Personal pecuniary Non-specific	Declare and participate in discussion of topic as interest is not specific to the content of the guideline and will not be involved in drafting recommendations
Max Gibbons	Co-signatory of a charitable trust fund for bone tumour research at the University. Fund	Non-personal pecuniary Non-specific	Declare and participate in discussion of topic as interest is not

Name	Interest declared	Category	Decision
	is used to fund travel expenses for Fellows.		specific to the content of the guideline and will not be involved in drafting recommendations
Melvin Grainger	Will be teaching on a cadaver course for Consultant level spinal surgeons in May 2015 run by Depuy Synthes. Involvement is to demonstrate 3 operative procedures – posterior vertebroectomy, cervical pedicle screws and cervical corpectomy. These procedures relate to spinal reconstruction but are not specific to myeloma. Will be able to claim a fee for giving the training but has not done so yet.	personal pecuniary Non-specific	Declare and participate in discussion of topic as interest is not specific to myeloma and will not be involved in drafting recommendations.
Melvin Grainger	Received an educational grant from Stiker to attend Eurospine conference in October 2014.	Personal pecuniary Non-specific	Declare and participate in discussion of topic as interest is not specific to the content of the guideline and will not be involved in drafting recommendations.
Melvin Grainger	Attended inaugural meeting of myeloma spinal working group chaired by Mr Sean Molloy and supported by Myeloma UK in January 2013. Have subsequently been given opportunity to comment on development of potential pathway for treatment of spinal myeloma, although had little direct input. This had lead to the submission of a paper entitled 'Optimising the management of patients with spinal myeloma disease' to the British Journal of Haematomolgy in March 2015 (I am not aware of acceptance/rejection of this paper as of today). The paper was submitted by Dr. Charalampia Kyriakou on behalf of the myeloma spinal working group.	Personal non-pecuniary Non-specific	Declare and participate in discussion of topic as interest is not specific to the content of the guideline and will not be involved in drafting recommendations.
Melvin Grainger	Received a request from NICE to comment on Pediguard (an instrument for inserting pedicle screws that is used in general spinal surgery). No fee received.	Personal non-pecuniary	Declare and participate in discussion of topic as interest is not specific to myeloma and will not be involved in drafting recommendations.

Name	Interest declared	Category	Decision
Isabel Syndikus	Is an investigator on the PATCH (PR09) trial, a randomised phase II trial studying how well the oestrogen skin patch works compared with luteinizing hormone releasing hormone analogue in treating patients with locally advanced or metastatic prostate cancer. Funded by Imperial College London	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the POUT trial, a phase III randomised trial of peri-operative chemotherapy versus surveillance in upper tract urothelial cancer. Funded by Cancer Research UK.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and bladder cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the PROMPTS trial, a prospective randomised phase III study of observation versus screening MRI and pre-emptive treatment in castrate resistant prostate cancer patients with spinal metastasis. Funded by Cancer Research UK.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the RADICALS trial, investigating radiotherapy and androgen deprivation in combination after local surgery in patients with prostate cancer. Funded by the Medial Research Council	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the STAMPEDE trial, a randomised controlled trial investigating systemic therapy in advancing or metastatic prostate cancer. Funded by the Medical Research Council.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the RAPPER trial, an assessment on genetic polymorphisms for predicting the effects of radiotherapy. Funded by the Christie Hospital NHS Foundation Trust	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry.
Isabel Syndikus	Is an investigator on the UK Genetic Prostate Cancer Study. Funded by the Institute for Cancer Research	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the

Name	Interest declared	Category	Decision
			pharmaceutical industry and prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the BAYER 88-8223 trial, a phase III randomised double blind placebo controlled trial of radium 223 dichloride in combination with abiraterone acetate and prednisone/prednisolone in the treatment of asymptomatic or mildy symptomatic chemotherapy-naive subjects with bone predominant metastatic castration resistant prostate cancer. Funded by Bayer in collaboration with Janssen.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics and prostate cancer is not being covered by the guideline.
Isabel Syndikus	Is an investigator on the FAST FORWARD trial, a randomised trial testing a 1-week course of curative whole breast radiotherapy against a standard 3-week schedule in terms of local cancer control and late adverse effects in patients with early breast cancer. Funded by the Institute for Cancer Research.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and breast cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the NCRN464 trial, a randomised double blind placebo controlled phase I/II trial of RNActive derived cancer vaccine in symptomatic or minimally symptomatic patients with metastatic castrate refractory prostate cancer. Funded by CureVac GmbH.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the PIVOTOL trial, a randomised phase II trial of prostate and pelvic versus prostate alone radiotherapy treatment volumes using high dose IMRT for locally advanced prostate cancer. Funded by the Institute for Cancer Research	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on the SCORAD III trial, comparing single radiotherapy treatment with a course of radiotherapy treatments for cancer pressing on the spinal cord. Funded by Cancer Research UK	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry.

Name	Interest declared	Category	Decision
Isabel Syndikus	Is an investigator on the SUPREMO trial, investigating radiation therapy of standard therapy in treating women with stage II breast cancer who have undergone mastectomy. Funded by the Medical Research Council.	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and breast cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator on a study of GDC-0068 or GDC-0980 with abiraterone acetate versus abiraterone acetate in patients with castration-resistant prostate cancer previously treated with docetaxel chemotherapy. Funded by Genetech	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as prostate cancer is not being investigated by the guideline.
Isabel Syndikus	Is an investigator for the National Study of Hodgkin's Lymphoma Genetics. Funded by the Lymphoma Research Trust and the Leukaemia Research Foundation	Non-personal pecuniary Non-specific	Declare and participate in discussion of all topics as the trial is not funded by the pharmaceutical industry and Hodgkin's Lymphoma is not being investigated by the guideline.
David Wilson	Runs a private radiology practice. St Lukes Radiology in Oxford.	Personal Pecuniary Non specific	
David Wilson	President elect of the British Institute of Radiology	Personal non-pecuniary Non-specific	
David Wilson	Is the audit leave for Medica – a tele-radiology company that do outsourced work for the NHS. Leads the team responsible for auditing their work to check it is of the correct standard	Personal pecuniary Non-specific	Declare and participate in discussion of topic L3 as will not be involved in drafting the recommendations
David Wilson	Is a partner in European Imaging and uses their facilities to see private patients	Personal pecuniary Non-specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations
David Wilson	Is a partner in the Oxford Clinic (an orthopaedic practice) and uses their facilities to see private patients	Personal pecuniary Non-specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations
David Wilson	Has a private radiology practice (St Lukes Radiology Oxford) which also does outsource work for the NHS on musculoskeletal radiology	Personal pecuniary Non-specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations
David Wilson	Wife works for his private radiology practice – St Lukes Radiology	Personal family interest Non-specific	Declare and participate in discussion of topic as will not be involved

Name	Interest declared	Category	Decision
			in drafting recommendations
David Wilson	Is in the process of planning a multi-centre prospective randomised controlled trial comparing vertebroplasty with radiotherapy in patients with myeloma induced spinal fractures. It trial goes ahead will be chief investigator (involved in designing the trial protocol). Trial hoped to be funded by CRUK.	Non-personal pecuniary Specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations
David Wilson	Treasurer of the European Society of Skeletal Radiology	Personal non-pecuniary Non-specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations
David Wilson	President Elect of the British Institute of Radiology	Personal non-pecuniary Non-specific	Declare and participate in discussion of topic as will not be involved in drafting recommendations

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