Myeloma
Consultation on draft guideline - Stakeholder comments table

19 August 2015 – 1 October 2015

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

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West Midlands Regional Genetics Laboratory, Birmingham Women's Healthcare NHS Trust, Birmingham	General	General		As a laboratory which has provided genetic analysis for multiple myeloma for many years we have a clear interest in this particular disorder. We were pleased with the fact that these draft guidelines recognise the importance of testing for prognostic information in myeloma.	Thank you for your comment
Napp Pharmaceuticals Limited	General	General		Thank you for the opportunity to take part in the consultation on the NICE Myeloma draft guideline. On this occasion Napp does not wish to make any comments.	Thank you for your comment
Celgene Ltd	General	General		[i] Dimopolous MA, Roussou M, Gkotzamanidou M, *et al*. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. *Leukemia*. 2013;27:423-429. [ii] San Miguel JF, Schlag R, Khuageva NK *et al.* Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med* 2008;359:906–17. [iii] Benboubker L, Dimopoulos MA, Dispenzieri A *et al.* Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med* 2014;371:906–17. [iv] Dimopoulos M, Cheung M, Roussel M, *et al.* Impact of	Thank you for your comment and for providing these references to support statements made in your other comments. We have responded to these other comments individually.

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				Renal Impairment on Outcomes After Treatment with Lenalidomide and Low-Dose Dexamethasone in Patients with Newly Diagnosed Multiple Myeloma: FIRST Trial Results. *Poster presentation P247 at the 20th Annual European Hematology Association Congress*, June 11-14 2015. [v] Ludwig H, Miguel JS, Dimopoulos MA *et al.* International Myeloma Working Group recommendations for global myeloma care. *Leukemia* 2014;28:981–92. [vi] Quach H, Ritchie D, Stewart AK *et al.* Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. *Leukemia* 2010;24:22–23. [vii] Roussou M, Kastritis E, Christoulas D. Reversibility of renal failure in newly diagnosed patients with multiple myeloma and the role of novel agents. *Leukemia Research*. 2010;34:1395-1397. [viii] Sonneveld P, Dimopoulos M, Ramasamy K, *et al*. Treatment With Pomalidomide and Low-Dose Dexamethasone in Patients With Relapsed or Refractory Multiple Myeloma and Renal Impairment Including Those on Dialysis. *Poster presentation PO326 at the 15th Annual International Myeloma Workshop Congress*, September 23-26 2015. [ix] Medicines.org.uk. eMC. Velcade 3.5mg powder for solution for injection – summary of product characteristics. Last updated 9 February 2015. Available from: http://www.medicines.org.uk/emc/medicine/17109	

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				(Accessed April 2015). [x] Richardson PG, Sonneveld P, Schuster MW. Reversibility of symptomatic peripheral neuropathy with bortezomib in the phase III APEX trial in relapsed multiple myeloma: impact of a dose-modification guideline. *BMJ.* 2009;144:895-903. [xi] Cho J, Kang D, Lee JY, et al. Impact of dose modification on intravenous Bortezomib-induced peripheral neuropathy in multiple myeloma patients. Support Care Cancer. 2014;22:2669-2675. [xii] Arnulf B, Pylypenko H, Grosicki S, et al. Updated Survival Analysis Of A Randomized Phase III Study Of Subcutaneous Versus Intravenous Bortezomib In Patients With Relapsed Multiple Myeloma. Haematologica. 2012;97:1925-1928. [xiii] Bird J, Owen RG, D'Sa S, *et al.* Guidelines For The Diagnosis And Management Of Multiple Myeloma 2014. Available from: http://www.bcshguidelines.com/documents/MYELOMA_GUIDELINE_Feb_2014_for_BCSH.pdf. [xiv] Dimopoulos MA, Palumbo A, Attal M et al. Optimising the use of lenalidomide in relapsed or refractory multiple myeloma: consensus statement. Leukemia. 2011 May;25(5):749-60. [xv] Delforge M, Facon T, Bravo M-L, *et al*. Lenalidomide plus Dexamethasone Has Similar Tolerability and Efficacy in Treatment of Relapsed/Refractory Multiple Myeloma Patients with or without History of Neuropathy. Blood	

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				(ASH Annual meeting abstract). 2009; 114:abstract 3873	
West Midlands Regional Genetics Laboratory, Birmingham Women's Healthcare NHS Trust, Birmingham	General	General		These brief comments have been submitted after the document has been reviewed by a group composed of Clinical Scientists from our Hemato-Oncology Genetics section. Whilst we have reviewed the whole document our interest has naturally been concerned primarily with the timing and composition of genetic testing. The briefness of the comments reflects our broad agreement with the relevant recommendations. We think this is a very positive set of guidelines and we look forward to their implementation and the improvement of patient care they will result in.	Thank you for your comment
Department of Health	General	General		Thank you for the opportunity to comment on the draft for the above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Thank you for your comment
Myeloma UK	Full	General		**Treatment for newly diagnosed and relapsed patients** The treatment sections, repeating the NICE technology appraisal guidelines, are fairly straightforward. However, as mentioned previously this is subject to the interpretation of NHS England. Ideally, healthcare professionals should be able to interpret the guidance in a way that best suits their	Thank you for your comment and for providing this information. Whilst NICE guidelines are not intended to replace clinical judgement, there is still an expectation that they will be followed.

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				patients – however, as it stands, it doesn't allow for flexibility. Myeloma UK is hopeful that as the details emerge about the new cancer drugs fund mechanism and as the treatment algorithms are implemented, they are developed to allow more innovation on the NHS.	Due to existing/ongoing NICE Technology Appraisals on myeloma, it has not been possible for the Guideline Committee to review the evidence and develop recommendations on primary disease treatment, salvage therapy for relapsed myeloma or consolidation/maintenance therapy after primary management in this guideline.
Royal College of Nursing	General	General	General	The Royal College of Nursing RCN) welcomes this draft guidance. It is timely. The RCN invited members caring for people with cancer and also involved in palliative care to review the draft guideline. The comments below include comments from our members.	Thank you for your comment
Royal College of Nursing	General	General	General	The provisional recommendations seem appropriate and are to be welcomed.	Thank you for your comment
Royal College of Nursing	General	General	General	Our members are pleased to note that communication and support is accorded a high priority in this guidance. It is considered that if communication and support can be got right for individual patients and their families, much else will fall into place; patients and families will be effectively cared for and will be aware of this.	Thank you for your comment
Gloucestershire Hospitals	General	General	General	Comments on the resource impact of the guidance are as follows:	Thank you for your comment and for indicating those recommendations you think will have additional resource

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NHS Foundation Trust				1. Adoption of Serum FLC for all patients to exclude myeloma rather than urine testing for light chains 2. For all diagnostic bone marrows: a. Use of flow cytometry to identify the plasma cell phenotype b. Use of FISH on CD 138 selected plasma cells to identify adverse prognostic groups c. Use of immunohistochemistry to identify p53 expression and Ki67 staining 3. For all patients suspected of myeloma, adoption of whole body MRI rather than skeletal surveys (plain Xrays) 4. Use of intravenous immunoglobulin for all patients with hypogammaglobulinemia 5. Use of acyclovir for all patients on immunomodulatory drugs and high dose steroids (in essence almost all patients having treatment) 6. Universal screening for Hepatitis B, C and HIV	implications. We have passed it to the NICE implementation support team to inform their support activities for this guideline
Royal College of General	Full	General	General	The full guidance is comprehensive.	Thank you for your comment

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Practitioners					
Royal College of Radiologists	Full	General	General	The Royal College of Radiologists considers that the guidelines make very little reference to radiotherapy except mentioning the lack of trials. The guidelines are difficult to navigate, but they do not appear to be any dose or indications recommended. The College feels that this is an opportunity missed.	Thank you for your comment. Due to the limited evidence available on the use of radiotherapy for spinal and non-spinal bone disease, the Guideline Committee invited an expert to input in this topic area. Despite this there was a lack of consensus within the Guideline Committee as to the optimal dose schedule, and so they were not able to make any recommendations on dose and indications. This has been explained in the linking evidence to recommendations text that accompanies these recommendations.
Myeloma UK	Full	General	General	Myeloma UK welcomes the creation of the NICE Guideline on "Myeloma in adults: diagnosis and management". The guideline contains a number of valid and important recommendations for good quality treatment and care of myeloma patients in the NHS. One issue to note is that there are other guidelines that are set to be published, specifically created by NHS England, that are likely to impact on the implementation of the NICE guidelines. The NHS England Algorithm, which amalgamates NICE guidance/guidelines and other routinely available	Thank you for your comment We would hope that the recommendations in this guideline will be included in the NHS England algorithm thus ensuring consistency between the 2 documents.

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				treatments, will be compulsory for NHS England regional teams across the NHS and some of the recommendations contained within this could potentially differ to those contained within the NICE guideline. There is the potential for improved joint-working between NICE and NHS England to ensure that both sets of guidance are complementary.	
Myeloma UK	Full	General	General	The guideline would benefit from a section on the management of pain in myeloma in the section on preventing and managing complications.	Thank you for your comment. When the scope of the guideline was developed it was agreed that the management of pain was not specific to just people with myeloma, whereas the management of neuropathic pain was very specific to this patient group. We therefore prioritised investigating the management of neuropathic pain. Therefore we are not able to make any recommendations on the management of pain in myeloma patients.
Myeloma UK	Full	General	General	The guideline would benefit from a discussion about appropriate end-of-life and palliative care for myeloma patients.	Thank you for your comment. End of life and palliative care per se was not identified as a priority area for inclusion in the scope and as such we are not able to make any recommendations on this. However, where appropriate, aspects of palliative care have been included as interventions in other topics investigated by the guideline and recommendations

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					made accordingly. There is existing NICE guidance on Care of the Dying Adult and improving supportive and palliative care guidelines
Myeloma UK	Full	General	General	Whilst potentially outwith the scope of the Guideline, the relapse section would benefit from a discussion about best practice in treating myeloma patients after Revlimid at second relapse, as this is an area of clinical diversity in the NHS and is an uncertain time for patients.	Thank you for your comment. We agree that this is an area of uncertainty. Because NICE has developed a suite of technology appraisal guidance on myeloma it was not possible for the Guideline Committee to develop recommendations on the use of Revlimid at second relapse. Recommendations in this guideline are intended to complement the existing technology appraisals.
Association for Palliative Medicine	Short	General	General	We welcome of the inclusion of palliative care for patients with myeloma throughout this document.	Thank you for your comment
Janssen	Short	General	General	Janssen is concerned that, whilst developing this NICE guideline, an opportunity has been missed to clarify the optimal treatment pathway for people with myeloma, in the context of interventions available through the National Cancer Drugs Fund and/or NHS England routine commissioning.	Thank you for your comment. Due to existing/ongoing NICE Technology Appraisals on myeloma, it has not been possible for the Guideline Committee to review the evidence and develop recommendations on primary disease

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					treatment, salvage therapy for relapsed myeloma or consolidation/maintenance therapy after primary management in this guideline. Therefore we are not able to clarify the optimal treatment pathway. Drugs listed in the Cancer Drugs Fund are outside our remit for consideration in clinical guidelines.
Janssen	Short	General	General	Currently, the guideline offers incomplete guidance for the treatment of patients beyond 1st relapse. Janssen is concerned that the absence of a suggested best practice care for patients with multiply relapsed myeloma is a critical omission from the draft guideline. It is not clear that the evidence for technologies routinely used in the myeloma treatment pathway, but for which there are no plans for appraisal by the NICE Centre for Health Technology Evaluation, has been considered. We are concerned that will result in the continuation of variation in practice and uncertainty about best practice, which the guideline is designed to diminish (page 32 of Developing NICE guidelines: the Manual). Janssen considers that the guideline should recognise that there is therefore a significant unmet need for a standard of care for patients with relapsed and/or refractory multiple myeloma and consider recommendations to provide a solution.	Thank you for your comment. Due to existing/ongoing NICE Technology Appraisals on myeloma, it has not been possible for the Guideline Committee to review the evidence and develop recommendations on primary disease treatment, salvage therapy for relapsed myeloma or consolidation/maintenance therapy after primary management in this guideline. Therefore we are not able to clarify the optimal pathway for the treatment of patients beyond first relapse.

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Royal College of General Practitioners	Short	General	General	The focus of these guidelines is on the specialist care of people with myeloma. The provision of information around the disease to patients is welcomed.	Thank you for your comment
Leukaemia CARE	Short	General	General	Throughout the 'communication and support' section there are numerous references to providing information and support 'at diagnosis, at the beginning and end of each treatment, at disease progression and at transition to end of life care'. We think that there needs to be reference to providing support to patients during treatment. For example, patients diagnosed with smouldering myeloma whose disease does not require treatment and are placed on "watch and wait". At present the guideline does not take into account their ongoing need for information and support after initial diagnosis (and before starting treatment).	Thank you for your comment. The time points included in the recommendation were intended to be illustrative of key times when information/support would be needed. They were not intended to be an exhaustive list. However we have amended the recommendation to clarify that these are the time points of 'particular' importance – so that this doesn't exclude any other times.
Leukaemia CARE	Short	General	General	We are concerned about whether there are procedures in place to make amendments to the guidelines to ensure that they reflect changes to clinical practice. For example, there will be a need to incorporate ongoing and future NICE appraisals and guidelines.	Thank you for your comment. NICE have a robust process for reviewing published guidelines to determine if they need to be updated. This process will be followed for the Myeloma guideline. More information can be found on the NICE website.
Leukaemia CARE	Short	General	General	We feel there needs to be further information on treatment options that have not been recommended by NICE, but are funded via alternative routes. For example, on page 18 there is reference to the use of pomalidomide which is not	Thank you for your comment. Drugs listed in the Cancer Drugs Fund are outside our remit for consideration in clinical guidelines.

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				recommended by NICE but is currently available via the Cancer Drugs Fund (until 4th November 2015)	
Myeloma UK	Full	7		**Key research recommendations** We largely agree with the key research recommendations. In terms of the recommendations 1 and 2, there have been interesting studies undertaken at The Institute for Cancer Research (ICR), London which have showed promising results for the use of diffusion-weighted MRI scans in the diagnosis and monitoring of treatment responses in myeloma patients. The ongoing research into this at the ICR should be monitored and there is also the potential to develop other studies into this to determine its use in myeloma clinical practice. Whilst not a trial/research as such, as there are a number of important treatment options coming down the line for myeloma patients for the same relapsed and/or refractory indication (elotuzumab, Farydak® [panobinostat], Kyprolis® [carfilzomib], daratumumab and ixazomib) – future work needs to be done with myeloma clinicians to establish which order these should be used in the myeloma treatment pathway to improve patient outcomes. This is particularly pertinent as we will need answers to these questions as the drugs start to go through the NICE appraisal process. Another avenue for further research is experience of different	Thank you for your comment Thank you for this information. We anticipate that all MRI technologies could be included in the research we have recommended. We agree and would anticipate that manufacturer and academic led clinical trials of these interventions should help inform these decisions. When developing the guideline, the

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				groups of myeloma patients in treatment and care. There is a small body of evidence to suggest that myeloma patients from a black and minority ethnic (BME) community have a varying experience of the NHS in issues such as access to information and clinical trials. This is an issue that could benefit from further research to establish if this is the case and why.	Guideline Committee looked for any evidence that showed a particular group were being disadvantaged within each of the topics. We did not find any evidence to support making specific recommendations about access to information and clinical trials for myeloma patients from the BME community. Consequently we are not able to make any recommendations for research in this area. However, should such research be published in the future, this could be taken into account during future updates of this guideline.
				Finally, we also need to understand the best treatment options for myeloma patients with high-risk myeloma – particularly if the guideline recommends testing for patients with this type of disease.	Our recommendations for identifying high-risk myeloma were to provide prognostic information to these patients rather than treatment options. Whilst development of effective treatment options for high-risk myeloma may result from our recommendations, we did not investigate the most effective treatment for high-risk disease and are consequently not able to make recommendations for research in this area.

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Myeloma UK	Full	18		**The algorithm** In relation to Comment 1 (above), the NHS England Algorithm and the NICE Guideline Algorithm are likely to be confused, and given the compulsory nature of the NHS England algorithm – it is likely to take precedent. The NHS England algorithm also interprets some aspects of NICE guidance slightly differently, so clinical practice is likely to vary to that recommended in the NHS England algorithm. As mentioned above, joint working between NICE and NHS England is crucial.	Thank you for your comment. The algorithm is a pictorial representation of the recommendations that have been made in this guideline. It is not intended to be a complete pathway of care as we have not investigated all areas of myeloma management. Therefore it is possible that the two algorithms will differ. Whilst NICE guidelines are not intended to replace clinical judgement, there is still an expectation that they will be followed.
Myeloma UK	Full	18		**Communication and support** This is a very important recommendation for patients and carers. Information tailored to the individual needs and preferences is key. There is evidence to suggest that myeloma patients from a BME have different support and information needs. These should be factored into considerations for information as well, particularly as myeloma is more prevalent in these communities.	Thank you for your comment. We agree. When developing the guideline, the Guideline Committee looked for any evidence that showed a particular group were being disadvantaged within each of the topics. We did not find any evidence to support making specific recommendations about access to information and clinical trials for myeloma patients from the BME community. Consequently we are not able to make

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					any recommendations for research in this area. However, should such research be published in the future, this could be taken into account during future updates of this guideline.
				This section would benefit from more detailed information about the types of information that are available and how to access them. In addition, information can be written, verbal and online – which could perhaps be differentiated.	We have recommended that information is provided on how to access peer support and patient support groups. We do not think it is necessary to specify all the potential information formats in the recommendations.
				The National Cancer Patient Experience Survey identifies that patients have a much better experience when they have access to Clinical Nurse Specialists (CNS) as they are able to meet the complex information and support needs of patients and their families. We know that there is variation in access to CNS and in the absence of this, there needs to be clear plans in place to ensure that myeloma patients are able to access the information they require and to assess the holistic needs of patients. This can be affected by issues such as the time clinicians have available to speak to patients about this, so ensuring that there are provisions in place within the clinic for patients to go and collect information, would be beneficial.	Our question investigated what the specific information and support needs of people with myeloma were. We did not look at who should provide this information and so are not able to make any recommendations on this.

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				Particular emphasis should be given to providing information, communication and support to patients and their families at the end of life. Myeloma patients may also have need for information in the remission stages, as there is a constant worry for patients about relapsing. This should also be taken into account and is likely to be required from interaction with general practitioners.	We specify in our first recommendation that 'transition to end of life care' is one of the key points at which information and support should be provided. Our second recommendation states that information on the relapse and remission cycle should be provided.
Bristol-Myers Squibb	Full	18	1	The algorithm does not take into account treatments available via the Cancer Drugs Fund and it differs from that currently under production by NHS England. BMS believes that two differing algorithms will create confusion for clinicians and patients.	Thank you for your comment. Drugs listed in the Cancer Drugs Fund are outside our remit for consideration in clinical guidelines and therefore are not included in the algorithm. The algorithm is a pictorial representation of the recommendations that have been made in this guideline. It is not intended to be a complete pathway of care as we have not investigated all areas of myeloma treatment. Therefore it is possible that the two algorithms will differ.
Bristol-Myers	Full	19	9	[lines 9-12] It is positive to see that the draft guideline recognises that age and cultural background are important	Thank you for your comment. Our recommendations on information and

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Squibb				factors to consider when assessing a patient's information needs. However, this should not just affect the level of information given to the patient, but also the mechanism of delivery. For example 1) Some older patients may prefer to have information delivered verbally 2) The way information is delivered (not just the content) needs to take account of cultural sensitivities – especially with regard to the black African and black Caribbean populations where myeloma incidence is higher. BMS would recommend that Clinical Nurse Specialists be explicitly trained to be sensitive to the age and cultural needs of patients when delivering information.	support do not specify the mechanism for delivery. We would expect healthcare professionals to use their clinical judgement when determining how best to deliver information. We acknowledge that there is a higher incidence of myeloma in black African-Caribbean people. However we did not find any evidence to support making different recommendations for this group with regard to information delivery. We would expect healthcare professionals to be aware of cultural sensitivities when delivering information. We are not able to make recommendations about how Clinical Nurse Specialists should be trained.
Bristol-Myers Squibb	Full	20	6	[lines 6-7] The evidence that we have gathered from discussions with patient groups and clinicians suggests that patients with black African and black Caribbean heritage do not have access to information that is culturally sensitive. This is of specific concern as multiple myeloma is twice as common within these racial groups.	Thank you for your comment. We acknowledge that there is a higher incidence of myeloma in black African-Caribbean people. However we did not find any evidence to support making different recommendations for this group with regard to information delivery. We

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					would expect healthcare professionals to be aware of cultural sensitivities when delivering information.
Leukaemia CARE	Short	4	5	[lines 5-6] Within the guideline there is reference to advising family members or carers about "available support services". We would like clarification on whether this includes signposting to charitable organisations or solely NHS services. Additionally, there does not appear to be an equivalent reference to signposting to support services for the patient – only their family members or carers.	Thank you for your comment. We have amended the recommendation to clarify there are a range of local and national support services available. This could include both charitable organisations and NHS services. Provision of information to people with myeloma on how to access peer support and patient support groups has been recommended in 1.1.2
Bristol-Myers Squibb	Full	24	General	[pages 24-41] The draft guideline should also consider tests that can be performed in primary care to aid and accelerate the diagnosis of multiple myeloma. Research published in the Lancet (*Lyratzopoulos G., et al. 2012*) found that 50.6% of multiple myeloma patients attended three or more GP consultations before receiving a hospital referral. This was compared to 7.4% of breast cancer patients, 10.1% of melanoma patients, and 41.3% of pancreatic cancer patients. It has also been made clear from our conversations with clinicians that delayed diagnosis is of primary concern. NICE	Thank you for your comment. Recommendations on testing for myeloma in primary care have been made in NG12 (Suspected cancer: recognition and referral) and are outside the scope of this guideline. The Myeloma Guideline Committee commented on these recommendations during the consultation on NG12. This information will be shown in the NICE Pathway.

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				has recently published guidelines to aid the diagnosis of suspected cancers (NG12, *Suspected cancer: recognition and referral*) which contains the following recommendations with regards to multiple myeloma: Myeloma 1.10.4 Offer a full blood count, blood tests for calcium and plasma viscosity or erythrocyte sedimentation rate to assess for myeloma in people aged 60 and over with persistent bone pain, particularly back pain, or unexplained fracture. 1.10.5 Offer very urgent protein electrophoresis and a Bence‑Jones protein urine test (within 48 hours) to assess for myeloma in people aged 60 and over with hypercalcaemia or leukopenia and a presentation that is consistent with possible myeloma. 1.10.6 Consider very urgent protein electrophoresis and a Bence‑Jones protein urine test (within 48 hours) to assess for myeloma if the plasma viscosity or erythrocyte sedimentation rate and presentation are consistent with possible myeloma. 1.10.7 Refer people using a suspected cancer pathway referral (for an appointment within 2 weeks) if the results of	

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				protein electrophoresis or a Bence‑Jones protein urine test suggest myeloma. BMS believes that the Guideline Development Group should explicitly consider the earlier recommendations made by NICE during the development of the guideline.	
West Midlands Regional Genetics Laboratory, Birmingham Women's Healthcare NHS Trust, Birmingham	Full	27	26	[lines 26-32] We agree that Cytogenetic FISH analysis is not suitable for diagnosis of Myeloma or MGUS.	Thank you for your comment
UK Myeloma Forum / Royal College of Physicians	Short	4	26	[lines 26-27] We feel this would be of little utility unless MRD assays are standard of care, and /or can be used to direct therapy	Thank you for your comment. We would expect that the investigations in recommendation 1.2.4 would become the new standard of care for diagnosing myeloma.
Myeloma UK	Full	28	7	**Laboratory investigations for people with suspected myeloma** There is ongoing research into the role of SFLCA tests in primary care and also in secondary care. These are likely to	Thank you for your comment. NICE have a robust process for reviewing published guidelines to determine if they need to be updated. This process will be followed for

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				provide insight into their role in improving diagnosis of myeloma and in monitoring response to treatment and will need to be factored into this Guideline and other related diagnostic guidelines.	the Myeloma guideline. More information can be found on the NICE website. This issue will be highlighted to the surveillance team and considered in future updates. Recommendations on testing for myeloma in primary care have been made in NG12 (Suspected cancer: recognition and referral) and are outside the scope of this guideline. The Myeloma Guideline Committee commented on the NG12 recommendations during the consultation.
UK Myeloma Forum / Royal College of Physicians	Short	5	1	Include haematology and biochemistry investigations, beta2 microglobulin, LDH, urate	Thank you for your comment. These interventions were not investigated in the guideline as the Guideline Committee agreed that their use was not controversial. Instead the guideline focused on those interventions where there was uncertainty/variation in practice. Consequently we are not able to include haematology and biochemistry investigations, Beta2 microglobulin, LDH and urate in the recommendations. We have amended the background to

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					this topic in the full version of the guideline to clarify this.
UK Myeloma Forum / Royal College of Physicians	Short	5	21	We are concerned that immuno-histochemistry for p53 is not a validated biomarker for del(17p)	Thank you for your comment. We have removed reference to p53 deletion from this recommendation.
Myeloma UK	Full	34	46	**Laboratory investigations to provide prognostic information** Myeloma patients commonly report that bone marrow aspirate is an investigation that negatively impacts on them. It is a painful test, access to anaesthesia is variable and patients tell us they dread attending appointments. Myeloma UK welcomes any measure that can be put in place to ensure that patients do not have to undergo repeat bone marrow aspirate. A potential factor in the implementation of this recommendation is that the quality of bone marrow samples taken can vary. Use of scanning mechanisms such as diffusion-weighted MRI scans should be considered to reduce the need for bone marrow aspirate.	Thank you for your comment and for providing this information Thank you for your comment The Guideline Committee did not look at evidence for the use of diffusion-weighted MRI scans as it is not established practice in the UK. In addition, it does not provide cytogenetic information.

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				Fluorescence in-situ hybridisation (FISH) Whilst this is an important diagnostic test in myeloma, access in the UK is patchy. In addition, using it in combination with other tests to identify high-risk myeloma is important, however we need to ensure that identifying these groups of patients can lead to appropriate treatment options – rather than have to follow NHS England treatment algorithms to the exact word. Algorithms need to be adapted to factor these sub-groups of patients in.	Improving access to FISH will be a matter for commissioners to consider when implementing this guideline. Our recommendations for identifying high-risk myeloma were to provide prognostic information to these patients rather than treatment options. Whilst development of effective treatment options for high-risk myeloma may result from our recommendations, we did not investigate the most effective treatment for high-risk disease and are consequently not able to make recommendations in this area.
West Midlands Regional Genetics Laboratory, Birmingham Women's Healthcare NHS Trust, Birmingham	Full	34	General	The one suggestion we would like to make is that provision is made for testing for the t(14;20) [IGH-MAFB]. Whilst this is a relatively less frequent it is recognised as an adverse genetic marker (Boyd et al, Leukaemia 2011 p1-7 – MRC XI Trial). This test should only be performed if an IGH rearrangement is identified during the t(4;14) and t(14;16) FISH but without an actual IGH-FGFR3 or IGH-MAF rearrangement.	Thank you for your comment. We have recommended that testing for t(14;20) is considered. As documented in the Linking Evidence to Recommendations section, this was because there was only a small volume of evidence for this being a prognostic marker for high-risk disease.

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University Hospitals Birmingham NHS Foundation Trust	Full	34	Para 2	We welcome the recommendation to perform FISH on CD-138 selected bone marrow plasma cells. However, this will be a challenge to implement in practice as there is remarkable inconsistency across England in commissioning of this particular tests- both in whether it is funded at all and also by whom.	Thank you for your comment. We acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline
West Midlands Regional Genetics Laboratory, Birmingham Women's Healthcare NHS Trust, Birmingham	Full	34	Prognosis - general	Firstly it is clearly a benefit for the patient to only have one bone marrow aspirate which can serve for diagnostic and prognostic testing. By isolating and storing CD138+ cells and not proceeding with genetic FISH analysis until the diagnosis is confirmed via the other methods (serum free light chain analysis etc.) we can be economical with testing and only test cases with a positive diagnosis of myeloma.	Thank you for your comment. We agree.
The Society and College of Radiographers	Full	42	3.1	The Society and College of Radiographers is pleased to see that observational studies should be carried out comparing the effectiveness of whole-body MRI, fluorodeoxyglucose positron emission tomography CT (FDG PET-CT) and whole-body low-dose CT in detecting lesions that may determine the start of treatment for people with newly diagnosed myeloma.	Thank you for your comment
Royal	Full	51	11	Costs of WB-MRI- £203- does this include diffusion weighted	Thank you for your comment. Diffusion

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College of Radiologists				imaging (which is essential)? It is essential to take into account the number of patients undergoing conventional skeletal survey x-ray studies in the UK, and to appreciate that if they were all now to have WB DW (whole body diffusion weighted) MRI, which is probably the optimum test - this would require significant investment in: • buying more MRI scanners (and upgrading old machines), and buying many more body coils (4 per scanner to be used simultaneously to provide the required body coverage from head to mid-thigh) to accommodate this • radiographers with special training in overlapping coil placement, in WB DW MRI scanning, and in post processing the images into whole body stacks and "3D" MIP-type (maximum intensity projection) images to make them easily interpretable • radiologists trained in interpreting diffusion weighted whole body MR imaging • post processing software integrated onto PACS – picture archiving and communication systems (preferably) and/or standalone 3rd party workstations to "stitch together" the stacks of images acquired from the multiple overlapping body sections (head, neck, chest, abdomen, pelvis and upper thighs) which need to be acquired in T1 and Diffusion-weighted sequences (as a minimum, preferably also with T2 weighted sequences), and also software to render these diffusion weighted	weighted MRI was included as an intervention in the evidence search undertaken for this question. However no evidence was found and no costs were identified to inform the de novo economic analysis. Consequently non-diffusion weighted MRI was used in the clinical evidence and the base case model used the NHS reference cost for non-diffusion weighted WB-MRI. It was however acknowledged that this was likely to be an underestimate of the true cost of imaging and higher costs around MRI imaging were investigated during sensitivity analysis (see Appendix A). The Guideline Committee only consider cost effectiveness and not overall costs or resource impact when making recommendations. However we acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline.

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				data acquired as "mipped" (maximum intensity projection) whole body sequences for easy, reproducible and comparative interpretation. Without such software the vast numbers of images acquired in separate sequences are extremely difficult to view and interpret.	
British Society for Skeletal Radiologists	Short	5	29	The Imaging guidance with WBMR and Low dose CT is evidence based and supported by the BSSR, with the caveat that significant additional funding and resources will be needed for practical service delivery.	Thank you for your comment. The Guideline Committee only consider cost effectiveness and not overall costs or resource impact when making recommendations. However, we acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline.
UK Myeloma Forum / Royal College of Physicians	Short	5	29	We do not feel there is sufficient evidence to support this, and are unsure how readily available whole body MRI is, or if there is guidance on protocols, reporting and interpretation to inform clinical management	Thank you for your comment. Although some of the studies only included small numbers of patients, one of the studies on whole body MRI contained a large number of patients. The Guideline Committee considered there to be sufficient clinical evidence, along with evidence of cost effectiveness to support recommening the use of whole body MRI.

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					We acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Radiologists	Short	5	29	The College agrees with this recommendation. However, it will have major impact on demand for MRI (magnetic resonance imaging) capacity, extra coils etc. In addition, training of radiographers and radiologists to report this technique, but we agree this is the optimum modality for assessment of potential and proven disease, and also the modality of choice for assessing myeloma relapse. The cost implications of introducing whole body MRI for all suspected myeloma are likely to be significant.	Thank you for your comment. The Guideline Committee were aware that this recommendation may have a significant resource impact and this topic was therefore prioritised for de novo economic analysis (see Appendix A). The results of this analysis were used to inform development of the recommendations. This is documented in the Linking Evidence to Recommendations section in the full version of the guideline. The Guideline Committee only consider cost effectiveness and not overall costs or resource impact when making recommendations. However, we acknowledge that there may be challenges with implementing this recommendation and have passed it to

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					the NICE implementation support team to inform their support activities for this guideline
British Society for Skeletal Radiologists	Short	6	15	[lines 15-18] The proper implementation and compliance of clinical services with this guidance will require Additional time with a minimum 1 session needed for MDT prep, reporting and reviews of this additional workload.	Thank you for your comment. The cost impact of these recommendations was considered by the Guideline Committee and is documented in the Linking Evidence to Recommendations Section in the full guideline. The Guideline Committee agreed that the recommendations are likely to result in more cross sectional imaging, which will increase costs. However, this increase would be offset against a decrease in the number of skeletal surveys being performed. The Guideline Committee also considered that cross sectional imaging is already being done following skeletal surveys. We acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline.

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British Society for Skeletal Radiologists	Short	6	22	The recommendation will be a challenging change in practice as the services suggested will not only require additional manpower in the form of radiographers and radiologists but will also need to take into account the specialist scanner procurement costs and rooms as most radiology departments are currently working at or exceeding their capacity.	Thank you for your comment. We acknowledge that there may be challenges with implementing this recommendation and have passed it to the NICE implementation support team to inform their support activities for this guideline.
Royal College of Radiologists	Short	21	20	The College agrees that further research into the optimum imaging modality as stated in this paragraph.	Thank you for your comment.
Bristol-Myers Squibb	Full	73	1	[lines 1-8, 24] There is need for geriatrician involvement in the management of elderly patients with multiple myeloma (who make up the majority of the myeloma population). Geriatrician involvement in treatment decisions and ongoing management has been shown to be key in other haematological malignancies affecting the elderly (*see Leukaemia Care – Addressing the management of MDS in elderly patients: a time for change)*. As such, BMS believe this should be recognised within the guideline.	Thank you for your comment. We recognise that treatment is being extended to older patients. Recognition of the frailty of these patients needs to be taken in consideration on a daily basis by the treating haematologist/oncologist. Therefore it would be more appropriate for a haematologist (with a special interest in delivering chemotherapy to the elderly) to be involved rather than the intermittent involvement of a geriatrician. However, the Guideline Committee did not consider that this needed to be specified in the recommendations.
Bristol-Myers Squibb	Full	73	1	[lines 1-13] It is important that consideration be given to the characteristics of the multiple myeloma patient population. Many are likely to be elderly and/or have other comorbidities,	Thank you for your comment and for providing this information. The Guideline Committee made recommendations

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				making it unfeasible to travel large distances for treatment. Infrastructure should therefore be put in place to ensure specialist centres are working with local hospitals and other care providers to ensure patients are receiving treatment in a setting that is most appropriate for them. BMS believes the recommendation on care to be delivered locally by the treating hospital (especially with regard to systemic anti-cancer therapy) may not go far enough to meet the needs of the patients and NHS England's vision for care to be increasingly delivered in the patient's own community. The *NHS Five Year Forward View* (October 2014) outlines the need for new models of care that are built around the needs of patients. The traditional divide between primary care, community services, and hospitals are increasingly a barrier to the personalised and coordinated health services patients need (page 16). There is specific reference to models of integrated out-of-hospital care – the '*Multispecialty Community Provider',* as well as integrated hospital and primary care – '*Primary and Acute Care Systems'* (page 4). During 2015, NHS England has established 'vanguard' sites for the new care models programme, with the aim of supporting and improving integration of services. Each vanguard site will take a lead on the development of new care models, which will act as the blueprints for the NHS moving forward and the inspiration to the rest of the health	about what services should be available and whether these should be based at the local hospital (because they would be needed frequently by patients and would involve non-complex management) or at the regional level (because they are more specialist/complex and affect fewer patients). However they did not make any recommendations on location and structure of services because there was no evidence to inform this and different requirements are needed in different geographical areas. We have clarified this in the Linking Evidence to Recommendations section. If evidence is gathered from vanguard sites this could be considered during future updates of the guideline.

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				and care system. These new vanguard sites will eventually see people benefiting from fewer trips to hospital, with more services available in the community, single points of contact, and access to blood tests, dialysis and chemotherapy closer to home (Care Quality Commission, March 2015). *Does the NICE Guideline Development Group intend to use evidence gathered from these vanguard sites, to develop new models of care for multiple myeloma patients which are built around treatment in the community?* The Independent Cancer Taskforce's latest report '*Achieving world-class cancer outcomes: a strategy for England 2015-2020*' (July 2015) states that one model being developed in several forms is that of delivery in community settings; for example nurses from a secondary care provider delivering chemotherapy in GP premises. It states that the majority of patients prefer receiving chemotherapy closer to home where possible (page 38) and recommends that NHS England should encourage the delivery of chemotherapy in community settings by sharing examples of good practice nationally (Recommendation 33). The report also recommends that for patients at the end of life, providing more coordinated care in the community, closer to people's homes, would result in better outcomes for people (page 60). There is emerging evidence that providing	Thank you for providing this information.

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				services to support patients within the community can be cost-effective through preventing emergency readmissions and less intensive use of acute resources (page 59). There is also a specific recommendation that NHS England should evaluate, through new or existing vanguards, whether the establishment of community oncology nurse services and community pharmacy services could cost effectively assist with management of consequences of treatment and treatment adherence (Recommendation 72).	
Association for Palliative Medicine	Short	7	10	[lines 10-17] We support the recommendation that "Each hospital treating myeloma… should provide local access to supportive and palliative care." However, the list that follows this is unclear – the services outlined would not necessarily be typical of those within a supportive & palliative care service. Perhaps re-wording this paragraph would make this clearer, eg: • supportive and palliative care~~, including~~ • psychological support services • a 24-hour acute oncology and/or haematology helpline • physiotherapy • occupational therapy • dietetics • medical social services	Thank you for your comment. We have changed 'including' to 'supported by' to make our recommendations clearer.

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				• critical care Rather than having the lower 7 points as sub-points of "supportive and palliative care"	
University Hospitals Birmingham NHS Foundation Trust	Full	73	24	[lines 24 and on] The introduction of a specific myeloma MDT is not evidence-based, is not recommended in the IOG and is not resourced. This would present a significant resource and logistical challenge for no demonstrated gain.	Thank you for your comment. We have not recommended a specific MDT for myeloma. We have recommended that the MDT includes healthcare professionals who specialise in myeloma to assist with discussion. However this MDT could equally discuss patients with other haematological malignancies.
Bristol-Myers Squibb	Full	73	24	BMS welcomes the recommendation for support and palliative care services to be available locally, however it should be clear that these services need to be culturally sensitive to the needs of the black African and black Caribbean populations (within which myeloma incidence is high).	Thank you for your comment. We acknowledge that there is a higher incidence of myeloma in black African-Caribbean people. However we did not find any evidence to support making different recommendations for this group with regard to support and palliative care services.
Bristol-Myers Squibb	Full	73	24	We welcome the recommendation that each hospital treating multiple myeloma should provide local access to "clinical trials via the myeloma MDT".	Thank you for your comment.
Myeloma UK	Full	73	24	**Service organisation** NHS England has also created a range of service specifications on chemotherapy and also on the provision of bone marrow transplantation services. These will impact on	Thank you for your comment and for providing this information.

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				the NICE guideline to an extent and should be considered to prevent for cross-over in working and recommendations – particularly as these are likely to be included in NHS England contracts. A number of these recommendations, including 24 hour access to psychological support and social services are likely to depend on the availability of key workers, such as CNS. Whilst this is beyond the remit of NICE, the ability to have these implemented fully depends on good workforce planning and is particularly an issue in remoter areas of England and Wales. Recommendations could also potentially be made on issues such as comorbidities, particularly in the older/frailer sub-group of patients and also on the coordination of care between primary, secondary and tertiary care. All services need to be sensitive to the cultural, information and holistic needs of patients.	Thank you for this information – we agree. The Guideline Committee have made recommendations on what services should be available. However, given the lack of evidence, it was not possible to make specific recommendations for particular sub-groups of patients. Co-ordination of care will be a matter for implementation of the guideline. We agree and would expect that this would happen when the recommendations in the guideline are implemented.
Bristol-	Full	73	9	[lines 9-13] The guideline does not take into account the	Thank you for your comment. It is not

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Myers Squibb				future intravenous capacity planning that is likely to be required to cope with the forthcoming increase in intravenous therapies for multiple myeloma (kyprolis, elotuzumab, daratumumab), and the impact that the improved efficacy and hence longer treatment that these advances will bring. It is also suggested that the availability of more sensitive ways of assessing myeloma may identify specific groups of patients with smouldering myeloma who may benefit from earlier treatment with either the same chemotherapy treatments used to treat myeloma patients or specific treatments for asymptomatic myeloma. Again, infrastructure needs to be in place to cope with the expected increased demand.	possible for this guideline to make recommendations on future intravenous capacity planning for new drugs that are not yet available.
Leukaemia CARE	Short	1	General	We would like to determine the exact remit/scope of this guideline. On page one it states that it covers 'the diagnosis and management of myeloma in people aged over 16', but it also states that 'the services that hospitals that treat myeloma should provide for adults aged over 18 are also covered'. Further examples of references to either 16 or 18 can be found on pages 6, 7, 20. We are concerned that for myeloma patients aged between 16 to 18, there is the potential for either gaps in guidance or overlaps/conflicts in guidance (where there are multiple pieces of guidance in the same area).	Thank you for your comment and for highlighting this inconsistency. We have made sure that the recommendations are now consistent.
UK Myeloma	Short	7	29	Because of the relatively limited access to early phase trials,	Thank you for your comment. We accept

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Forum / Royal College of Physicians				this would be inappropriate	that there is variation in access to early phase trials. We hope that our recommendation will help to improve this.
Bristol-Myers Squibb	Full	86	General	[pages 86-88, 258] Comorbidity, frailty scores and other performance status measures (along with geriatrician assessment) should be used for determining patient fitness for *all* systemic therapy. It is not appropriate that these tools only be used for first autologous stem cell transplant.	Thank you for your comment. These recommendations are based on a clinical question investigating who should have autologous stem cell transplantation. Therefore we are restricted to making only recommendations within this topic area.
Leukaemia CARE	Short	General	General	On page 9 it states that "Do not use age or the level of renal impairment alone to assess the suitability of people with myeloma for first autologous stem cell transplant." On page 18 it states "When assessing whether people with relapsed myeloma are suitable for a second autologous stem cell transplant, take into account… age, frailty and comorbidities." We take exception to the reference to patient age in the assessment of patients' treatment options. Ageism is proscribed by the NHS and by NICE. To determine a patients treatment options by virtue of 'age' contradicts everything the NHS and NICE have been set up to follow. The patient is either fit enough to receive treatment or not fit enough to receive treatment, their age is irrelevant.	Thank you for your comment and for pointing out this inconsistency. We have amended the recommendations on second autologous stem cell transplantation to refer to 'resilience' rather than age.
Leukaemia CARE	Short	9	General	We feel that when considering stem cell transplantation there needs to be inclusion of patient views and patient choice.	Thank you for your comment. It is standard practice that patient views and

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				Stem cell transplants are a specific example where there are numerous factors to assess (e.g. religious) that may impact on patients willingness to receive a particular treatment option. At present, the guidance does not appear to take this into account.	informed choice would be taken into consideration for all management decisions. The purpose of highlighting the person's understanding of the procedure, its risks and benefits, in the recommendations on allogeneic transplant was that there is currently uncertainty over the benefits of this procedure, but the risks are known to be significant compared with those of other treatments (e.g. autologous transplant).
UK Myeloma Forum / Royal College of Physicians	Short	9	17	[lines 17-29] Our view is that the evidence to support this treatment is controversial, hence it can only be recommended as part of a clinical trial. The list of considerations illustrates how complex this area is, and does not give any guidance as to how to use the factors to guide therapy	Thank you for your comment. The Guideline Committee have already made a recommendation for further research in this area (see the full guideline). As documented in the Linking Evidence to Recommendations section, the weak quality and inconsistent nature of the available evidence did not enable the Guideline Committee to recommend who should have allogeneic stem cell transplantation. However, we have now amended the recommendation to highlight that allogeneic transplant is only suitable for a small group of people, and also to emphasise recruitment into relevant clinical trials.

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Myeloma UK	Full		7	Plasma cell leukaemia Velcade and Revlimid in the newly diagnosed setting represent viable treatment options for patients with plasma cell leukaemia, although Revlimid is not approved by NICE in this setting. Patients may therefore struggle to get access to this in the NHS unless they are applied through the individual funding request process or to the Cancer Drugs Fund.	Thank you for your comment. Based on the available evidence bortezomib and lenalidomide based combinations are effective for the treatment of primary plasma cell leukaemia. This is therefore what we have recommended. We appreciate that there may be difficulties in accessing these drugs but this will be a matter for commissioners to consider when implementing this guideline.
Celgene Ltd	Full		29	The only data included for bortezomib based regimens and lenalidomide based regimens come from a 'very low quality' small single centre study from a centre in Greece of only 43 patients receiving a bortezomib combination and only 28 receiving a lenalidomide combination (with an unreported split in this group between lenalidomide and low-dose dexamethasone (Rd) and lenalidomide plus melphalan and prednisone (MPR))i. Data for patients suffering from renal impairment has been collected for both bortezomib and lenalidomide in large, high quality randomised trials (VISTAii and MM-020iii respectively). The data from MM-020 for lenalidomide has recently been presented at EHA 2015iv. Data on 1,234 patients with mild, moderate or severe renal impairment is captured (412	Thank you for your comment. The low quality of the evidence has been acknowledged in both the evidence section of the guideline and the Linking Evidence to Recommendations section that accompanies the recommendations. The purpose of this question was to investigate effective treatments for patients with acute renal disease caused by myeloma. The relevant data from the VISTA trial was included in our evidence base. Data from the MM-020 trial on renal impairment presented at EHA 2015 has not been published in full and was therefore was not included in the evidence base for this question.

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				patients receiving continuous Rd, 419 patients receiving Rd for 18 cycles and 403 patients receiving thalidomide, melphalan and prednisone (MPT). The data shows that for patients with mild and moderate renal impairment progression free survival (PFS) and time to second anti-myeloma therapy were improved with continuous Rd vs. MPT and OS benefits were also observed for these groups of patients treated with continuous Rd. In patients with severe renal impairment, OS and PFS was also improved for patients receiving continuous Rd. The IMWG consensus statement on managing patients with renal impairmentv states that lenalidomide is effective in this setting and can reverse renal insufficiency in a significant subset of patients, when it is given at reduced doses, according to renal function. Celgene believe the conclusions presented on comparative efficacy between bortezomib and lenalidomide based regimens are misleading and poorly informed. Please reconsider this section based upon the evidence from higher quality trials which are available.	As you state, the IMWG statement on managing patients with renal impairment is based on consensus. Therefore they differ to those in this guideline which was based on a review of the available, relevant evidence. We disagree and consider that our recommendations are based on the best-available evidence for those patients with acute renal disease caused by myeloma.
Celgene Ltd	Full		All	[pages 113-116] As described above in comment number 2, data exists comparing a thalidomide based regimen (MPT) and a lenalidomide based regimen (Rd) from MM-020.	Thank you for your comment. The purpose of this question was to investigate effective treatments for

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				This should be presented in this section especially as the data comes from a more robust source than much of the data presented in this section of the guideline.	patients with acute renal disease caused by myeloma. Data from the MM-020 trial on renal impairment presented at EHA 2015 has not been published in full and was therefore not included in the evidence base for this question.
Celgene Ltd	Full		32	[lines 32-37] Immunomodulatory drugs (IMiDs™) should not be considered as a class and are not classified as chemotherapy. Thalidomide, lenalidomide and pomalidomide have different chemical structures and mechanisms of action and it is incorrect based upon the available data to present them as identical in respect to efficacy and side-effect profiles.vi Again, conclusions are drawn from a single 'very-low quality' single centre study from a centre in Greece with only 17 patients receiving bortezomib and dexamethasone combinations and only 47 patients receiving IMiDs; of which there is an unreported split between lenalidomide and thalidomide combinations and no patients receiving pomalidomide.vii As highlighted above, data for bortezomib and lenalidomide have been presented in VISTA and MM-020. MM-020 also presents comparative data between a thalidomide based regimen (MPT) and a lenalidomide based regimen (Rd). For pomalidomide, data is available from the ongoing randomised	Thank you for your comment. We have changed the text in brackets to '(IMiDs-based therapy)'. However the subheading reflects the interventions investigated in the study so we are not able to separate out the different IMiDs. The low quality of the evidence has been acknowledged in both the evidence section of the guideline and the Linking Evidence to Recommendations section that accompanies the recommendations. The purpose of this question was to investigate effective treatments for patients with acute renal disease caused by myeloma. The relevant data from the VISTA trial was included in our evidence base. Data from the MM-020 trial on renal impairment presented at EHA 2015 has not been published in full and was

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				MM-013 phase II trialviii and has been presented at IMW 2015viii. Data is presented for only 45 patients with moderate or severe renal insufficiency (including those undergoing dialysis) and shows that initial efficacy results are promising with an overall response rate of 25% in patients with moderate renal insufficiency. Celgene believe the conclusions drawn are again misleading and that the IMiDs should be separated and discussed based upon the best available evidence.	therefore not included in the evidence base for this question. We disagree and consider that our recommendations are based on the best-available evidence for those patients with acute renal disease caused by myeloma.
Celgene Ltd	Full		1	Based upon comment numbers 1-3 presented above, Celgene believe that lenalidomide and pomalidomide should be included under the recommendations section as options.	Thank you for your comment. The purpose of this question was to investigate effective treatments for patients with acute renal disease caused by myeloma. Data from the MM-020 trial on renal impairment presented at EHA 2015 has not been published in full and was therefore not included in the evidence base for this question. Published trials of pomalidomide have concentrated on relapsed and refractory myeloma and have excluded people with eGFR <45ml/min and therefore are not relevant to this question. Therefore we have not changed the recommendations as you suggest.

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Celgene Ltd	Short		8	[lines 8-17] As per comment number 1 on the full clinical guideline, Celgene, believe lenalidomide should be included as an option.	Thank you for your comment. The purpose of this question was to investigate effective treatments for patients with acute renal disease caused by myeloma. Data from the MM-020 trial on renal impairment presented at EHA 2015 has not been published in full and was therefore not included in the evidence base for this question. Therefore we have not changed the recommendations as you suggest.
Myeloma UK	Full		Table	Perhaps important to stress the use of zoledronic acid in myeloma patients who are newly diagnosed. Myeloma UK is pleased to see the benefits of zoledronic acid stressed as we have come across variation across England and Wales in its provision – although this is starting to resolve itself since the patent has been removed in Western Europe.	Thank you for your comment. We consider that our recommendation to offer zoledronic acid to prevent bone disease would already encompass patients who are newly diagnosed with myeloma.
Association for Palliative Medicine	Short		3	[lines 3-5] We support the referral of patients in this situation to specialists in palliative care	Thank you for your comment.
The Society and College of Radiographers	Full		7	The Society and College of Radiographers feels these recommendations are good: The Guideline Committee noted that whilst the evidence for the use of radiotherapy in the management of non-spinal bone disease comes from solid tumours, there is recognition that myeloma is more radiosensitive than most solid tumours.	Thank you for your comment.

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				Given this the Guideline Committee agreed to recommend that radiotherapy is used in these instances. Based on expert advice, the Guideline Committee also noted that the dose of radiotherapy normally used in myeloma means retreatment The Guideline Committee agreed that the recommendations take into account that surgery may not be suitable for all patients and where this is the case radiotherapy has been recommended instead, thereby reducing the potential risks associated with surgery. In addition, the Guideline Committee considered that radiation toxicity is lower outside the spine.	
The Society and College of Radiographers	Full		35	The Society and College of Radiographers welcomes the Guidelines Committees research recommendation: The Guideline Committee made a research recommendation for radiotherapy as although there was Guideline Committee agreement (informed by expert advice) about the role for radiotherapy in the management of non-spinal bone disease, there was uncertainty on the optimal schedule.	Thank you for your comment.
Medtronic UK	Short		25 3	Re: Cement augmentation – recommendations from the International Myeloma Working Group J Clin Oncol. 2013 Jun 20;31(18):2347-57. The aim of the International Myeloma Working Group was to develop practice recommendations for the management of multiple myeloma (MM) – related bone disease4.	Thank you for your comment and for providing us with the recommendations from the IMWG on cement augmentation. The Guideline Committee noted that the evidence in this area was of low quality.

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				Methodology: An interdisciplinary panel of clinical experts on MM and myeloma bone disease developed recommendations based on published data through August 2012. Expert consensus was used to propose additional recommendations in situations where there were insufficient published data. Levels of evidence and grades of recommendations were assigned and approved by panel members Recommendations*: Balloon kyphoplasty (BKP) should be considered for symptomatic vertebral compression fractures (VCFs) and is the procedure of choice to improve QoL in patients with painful VCFs (grade A) The role of vertebroplasty for patients with myeloma is less clear, because there are no randomized trials of vertebroplasty among patients with myeloma Furthermore, a meta analysis of 59 studies (56-case series) showed that BKP seemed to be more effective than vertebroplasty in relieving pain secondary to cancer-related VCFs and was associated with lower rates of cement Leakage. BKP arrests progressive vertebral collapse in this patient group.	Consequently, they invited experts (an Interventional Radiologist and a Spinal Surgeon) to input in this topic area and inform the development of these recommendations. As stated in the Linking Evidence to Recommendations section in the full guideline 'The Guideline Committee made recommendations for the use of cement augmentation but did not specify kyphoplasty or vertebroblasty as expert advice suggested that it is not a case of one intervention being better than the other but that each is suitable in different patient circumstances.' These recommendations were also supported by the health economic analysis.
Association for Palliative Medicine	Short		16	As well as referencing NICE guidance on neuropathic pain & opioids, we would suggest the guidance include a line as per the section on non-spinal bone disease, ie:	Thank you for your comment. Palliative care was not included as an intervention in the review question protocol on the

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				"Consider seeking advice from or referral to specialists in palliative care or pain medicine for people with complex spinal bone disease."	management of spinal bone disease and therefore we are not able to include it in our recommendations. However, the Guideline Committee consider that seeking advice from palliative care/pain medicine for these patients should form part of standard care.
UK Myeloma Forum / Royal College of Physicians	Short	13	11	This should be changed from and/or to and	Thank you for your comments. We have made this change.
Celgene Ltd	Full	211	1	The recommendation that patients with grade 3 or 4 neuropathy should temporarily stop neuropathy inducing treatment could put patients at risk. If a patient has grade 4 neuropathy, it would be safer to switch treatment than have a treatment break and the Summary of Characteristics for bortezomib recommends that treatment should be discontinued.ix	Thank you for your comment. There is no evidence to determine whether temporarily stopping treatment or switching to an alternative treatment is the best course of action when someone develops grade 3 or 4 neuropathy. The Guideline Committee agreed to recommend temporarily stopping treatment because this allowed for the possibility of the neuropathy resolving and re-introduction of the previous therapy if this was proving effective against the myeloma. We have now added a recommendation to clarify that if neuropathy does not improve despite

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					stopping myeloma treatment and further treatment is required, switching to treatments less likely to cause neuropathy should be considered.
Celgene Ltd	Full	211	1	For patients receiving bortezomib who develop neuropathic symptoms it is recommended that they switch to subcutaneous injections. Neither Richardson et al 2009x or Cho et al 2014xi make any reference to switching to subcutaneous bortezomib for intravenous bortezomib. Cho et al 2014 reference a paper by Arnulf et al 2012xii which does not actual present any data to show the impact of switching from intravenous to subcutaneous bortezomib on resolution of peripheral neuropathy and also excludes patients with grade 2 or higher peripheral neuropathy. Taken in isolation, the intravenous arm actually demonstrated higher resolution or improvement in peripheral neuropathy than the subcutaneous arm. Celgene are concerned that this recommendation is not evidence based and cannot be supported. Instead, dose reduction or selection of an alternative therapy such as lenalidomide should be considered, as highlighted by the BCSH 2014 guidelinesxiii which state that lenalidomide may be appropriate for patients with either disease or treatment-related neuropathy and that patients with ≥grade 2 peripheral neuropathy should receive a lenalidomide-based regimen	Thank you for your comment. We have already recommended dose reduction as an option for people receiving bortezomib who develop neuropathic symptoms. We did not include the Amulf (2012) trial because it is a straight comparison of subcutaneous versus IV bortezomib which was not a comparison listed in the review question protocol. Although it is true that in this trial peripheral neuropathy was less likely with subcutaneous administration (38% vs 53%) most cases resolved in both treatment arms. The Guideline Committee, based on their clinical experience and knowledge of the available literature, were aware that subcutaneous delivery of bortezomib had previously been shown to have a much lower rate of neuropathy compared with intravenous delivery. As such they recommended changing the method of

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					delivery as an option if a person developed neuropathic symptoms while on intravenous bortezomib. We have added text to the Linking Evidence to Recommendations section to clarify this. Because of the limited effective options for treating myeloma, the Guideline Committee sought to maintain the maximal duration and depth of response. We have now added a recommendation to clarify that if neuropathy does not improve despite stopping myeloma treatment and further treatment is required, switching to treatments less likely to cause neuropathy should be considered.
Celgene Ltd	Full	211	1	Lenalidomide is not mentioned as treatment option for patients experiencing neuropathy. In study MM-020iii grade 3 / 4 peripheral sensory neuropathy was more common with MPT (9.4%) than Rd (1.1%). In addition, the low levels of peripheral sensory neuropathy with Rd did not increase with long term use. An expert panel consensus groupxiv looking at the optimal use of lenalidomide in relapsed refectory multiple myeloma highlighted that peripheral neuropathy, is a relatively common and cumulative side effect of bortezomib and thalidomide, but is rarely seen with lenalidomide.	Thank you for your comment. Due to existing/ongoing NICE Technology Appraisals on myeloma, it has not been possible for the Guideline Committee to review the evidence and develop recommendations on treatments for myeloma in this guideline. This question was investigating the most effective management for those people

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				In a sub-analysis of data from studies MM-009/010xv in patients receiving lenalidomide and dexamethasone in relapsed and refractory multiple myeloma, patients with existing peripheral neuropathy received a similar mean daily dose of lenalidomide as those who did not have neuropathy. The mean treatment duration, response rate, TTP and OS were also similar in patients with and without existing neuropathy Celgene believe that a recommendation should be made in this section for the use of lenalidomide and specific dose reduction steps should be outlined as they are for bortezomib.	who experience neuropathy as a result of their myeloma treatment. This question was not about preventing peripheral neuropathy by selecting therapies less likely to cause it. The only evidence found on dose modification related to bortezomib and recommendations were made accordingly. As documented in the Linking Evidence to Recommendations section the Guideline Committee agreed that temporarily stopping, and dose reduction of any other treatment related neuropathy was appropriate. We have now added a recommendation to clarify that if neuropathy does not improve despite stopping myeloma treatment and further treatment is required, switching to treatments less likely to cause neuropathy should be considered.
Association for Palliative Medicine	Short	14	1	[lines 1-15] Again, we would suggest including a line to say ""Consider seeking advice from or referral to specialists in palliative care or pain medicine for people with complex neuropathic pain."	Thank you for your comment. Palliative care was not included as an intervention in the clinical question on the management of spinal bone disease and therefore we are not able to include it in our recommendations. However, the

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					Guideline Committee consider that seeking advice from palliative care/pain medicine for these patients should form part of standard care.
Celgene Ltd	Short	14	1	[lines 1-15] As per comment number 6 and 7 on the full clinical guideline, Celgene, believe there is not a sufficient evidence base to support switching from intravenous to subcutaneous bortezomib and that lenalidomide should be included as an option.	Thank you for your comment. The Guideline Committee, based on their clinical experience and knowledge of the available literature, were aware that subcutaneous delivery of bortezomib had previously been shown to have a much lower rate of neuropathy compared with intravenous delivery. As such they recommended changing the method of delivery as an option if a person developed neuropathic symptoms while on intravenous bortezomib. We have added text to the Linking Evidence to Recommendations section to clarify this. Because of the limited effective options for treating myeloma, the Guideline Committee sought to maintain the maximal duration and depth of response. We have now added a recommendation to clarify that if neuropathy does not improve despite stopping myeloma treatment and further treatment is

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					required, switching to treatments less likely to cause neuropathy should be considered.
Janssen	Short	14	5	[lines 5-9] Janssen is concerned that the recommendation at paragraph 1.8.8 is incomplete in that it does not communicate the importance of the cumulative dose of bortezomib when introducing dose reductions. When reducing bortezomib dose in the presence of neuropathic symptoms, consideration should be given to extending the treatment duration. Evidence: Post-hoc analysis of the VISTA study suggests that in the front-line non-transplant setting, a higher cumulative bortezomib dose is associated with improved OS. Patients receiving a cumulative bortezomib dose equal or superior to 39mg/m2 experienced a median OS of 66.3 months, compared to those receiving 39mg/m2 or less, who experienced a median OS of 46.2 months (hazard ratio adjusted for age 0.561; log-rank test, p=0.0002). To overcome the confounding effects of early deaths due to toxicity or other reasons, a landmark analysis of OS was conducted at 180 days among patients alive at that time point according to whether they received a total cumulative bortezomib dose of <39 or ≥39 mg/m2. In this analysis, OS from the landmark remained significantly longer in patients who received a cumulative bortezomib dose of ≥39 vs <39 mg/m2 (median 60.4 vs 50.3 months, HR 0.709, p=0.0356).	Thank you for your comment. This section is about the management of neuropathy not preventing it. We are therefore not able to make recommendations about cumulative dose as this is outside the scope of the guideline.

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				[Source: Mateos, MV. et al. Higher Cumulative Bortezomib Dose Results in Better Overall Survival (OS) in Patients with Previously Untreated MM Receiving VMP in the Phase 3 VISTA study. Poster Presented at 55th ASH Annual Meeting and Exposition 2013].	
UK Myeloma Forum / Royal College of Physicians	Short	14	7	We would be surprised if any units are not using the subcutaneous route	Thank you for your comment and for providing this information
Myeloma UK	Full	211	Table	Peripheral neuropathy Recommendations should also cover treatment/management of myeloma patients with long-term peripheral neuropathy. In addition, perhaps discussion of myeloma treatments/methods of administration that are less prone to inducing neuropathy.	Thank you for your comment. There is existing NICE guidance on the pharmacological management of neuropathic pain in adults. We have added a recommendation to cross-refer to this guidance. Due to existing/ongoing NICE Technology Appraisals on myeloma, it has not been possible for the Guideline Committee to review the evidence and develop recommendations on treatments for myeloma in this guideline.
UK Myeloma Forum / Royal	Short	15	13	Erythropoietin should be used with caution	Thank you for your comment. We agree – we have included a specific target haemoglobin in our recommendation.

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College of Physicians					
UK Myeloma Forum / Royal College of Physicians	Short	16	1	Include beta2 microglobulin and LDH	Thank you for your comment. This question focussed on longitudinal monitoring not staging at relapse, therefore we have not included these tests in the recommendations.
UK Myeloma Forum / Royal College of Physicians	Short	17	11	Measurement of response using paraprotein, explain IMWG guidance for definition of relapse	Thank you for your comment. These recommendations are from TA129 and have been incorporated in this guideline in line with NICE processes. We are not able to make any amendments to them
Celgene Ltd	Short	16	15	[pages 16-17, lines 15-28, 1-27] As per comment number 8 on the full clinical guideline, a statement in the recommendation section that highlighted ongoing guidance and advised that if positive, the guidance should be referred to and followed would help to future-proof the clinical guideline.	Thank you for your comment. It is not possible to highlight guidance in development in the recommendation section.
UK Myeloma Forum / Royal College of Physicians	Short	16	15	Include guidance on when to initiate salvage therapy, see IMWG guidelines regarding rate of rise in M-protein, or if clinical relapse	Thank you for your comment. The only salvage therapy investigated by this guideline was who would be suitable for a second autologous stem cell transplant. Therefore we are not able to make recommendations on any other salvage therapies or their timings.
Celgene Ltd	Full	246	17	There is an ongoing appraisal for lenalidomide (Part review TA171) which could produce guidance before the clinical	Thank you for your comment. It is not possible to highlight guidance in

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				guideline is published. A statement in the recommendation section that highlighted this ongoing guidance and advised that if positive, the guidance should be referred to and followed would help to future-proof the clinical guideline.	development in the recommendation section.
UK Myeloma Forum / Royal College of Physicians	Short	17	25	How many cycles of bortezomib? The wording suggests to treat indefinitely until ….."consider it appropriate to stop"?	Thank you for your comment. These recommendations are from TA129 and have been incorporated in this guideline in line with NICE processes. We are not able to make any amendments to them.
UK Myeloma Forum / Royal College of Physicians	Short	18	12	[line 12-16] How should these factors be taken into account, eg should ISS 3 be an indication for a salvage transplant?	Thank you for your comment. The first two recommendations in this section clarify what action to take based on response to the first autologous stem cell transplant. These were based on evidence. We have also clarified that a 'good' response to first autologous stem cell transplant is required. However the Guideline Committee did not have enough evidence to suggest how the other factors should be taken into account.
UK Myeloma Forum /	Short	18	6	"completed reinduction therapy" and ? achieved at least a PR or SD? These terms need definitions	Thank you for your comment. We have clarified in the recommendation that this

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Royal College of Physicians					means 'completed re-induction therapy without disease progression...'
Celgene Ltd	Short	18	17	[lines 17-26] As per comment number 9 on the full clinical guideline, this section is also inconsistent with all other sections of the document and gives the impression that the document was finished hastily. For example, the section on first relapse on page 246 provides the full recommendation for bortezomib. After 2 prior treatments, NICE guidance TA171 recommends lenalidomide plus dexamethasone. The full guidance should be presented here. Celgene believes a failure to do so could cause confusion for clinicians and patients as to which treatment options are available to them. A statement around ongoing appraisals in this section could also help future-proof the document as a number of different agents are currently under review with NICE.	Thank you for your comment. These recommendations have now been incorporated into the guideline.
Celgene Ltd	Full	260	2	[lines 2-7] This section is inconsistent with all other sections of the document and gives the impression that the document was finished hastily. For example, the section on first relapse on page 246 provides the full recommendation for bortezomib. After 2 prior treatments, NICE guidance TA171 recommends lenalidomide plus dexamethasone. The full guidance should	Thank you for your comment. These recommendations have now been incorporated into the guideline.

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				be presented here. Celgene believes a failure to do so could cause confusion for clinicians and patients as to which treatment options are available to them. As per comment number 8, a statement around ongoing appraisals in this section could also help future-proof the document as a number of different agents are currently under review with NICE.	

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Consultation on draft guideline - Stakeholder comments table

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