National Institute for Health and Clinical Excellence

Single Technology Appraisal (STA)

Lenalidomide for the treatment of newly diagnosed multiple myeloma

Response to consultee and commentator comments on the draft remit and draft scope

Comment 1: the draft remit

Section	Consultees	Comments	Action
Appropriateness	Celgene Ltd	Yes, Celgene Ltd. agrees that it is appropriate to refer this topic to NICE for appraisal.	Comment noted.
	CSAS	This is appropriate	Comment noted.
	Myeloma UK	The draft scope suggests appraising lenalidomide in two separate settings: 1. In the induction setting in combination with an alkylating agent and / or corticosteroid 2. In the maintenance setting as monotherapy or in combination with a corticosteroid We do not believe it is appropriate to proceed with the first proposed intervention outlined in the scope - lenalidomide in the induction setting - at this time. There is only limited data available on lenalidomide in the induction / initial treatment setting. The licensing studies which are currently being considered by the EMA do not address the critical questions needed to assess the role of lenalidomide as an induction treatment and therefore are unlikely to generate the data needed for HTA purposes; their focus is primarily on its role as a maintenance treatment. We consider that the second proposed intervention for the appraisal - lenalidomide in the maintenance setting - is an appropriate topic for referral to NICE.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. If the proposed marketing authorisation (as first-line treatment) is accepted by the EMA, it will not be possible for NICE to make recommendations on the use of lenalidomide beyond the explicit terms of its marketing authorisation.

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		Lenalidomide maintenance offers a promising treatment strategy in this setting to improve outcomes for myeloma patients. Lenalidomide is the first maintenance drug for myeloma to be considered for marketing approval by the EMA. An appraisal of its clinical and cost-effectiveness for adoption in the NHS is regarded as of high importance by the UK myeloma community.	
	UK Myeloma Forum, BSH & RCP.	We do not believe that it is appropriate to refer the first part of this topic to NICE for appraisal. That is, we do not believe it is appropriate to refer the intervention: lenalidomide in the induction setting. On the other hand, we believe it is appropriate to refer the second part of this topic, ie. lenalidomide in the maintenance setting. See below under 'Additional comments'.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. If the proposed marketing authorisation (as first-line treatment) is accepted by the EMA, it will not be possible for NICE to make recommendations on the use of lenalidomide beyond the explicit terms of its marketing authorisation.
Wording	Celgene Ltd	No. Celgene's submission to EMA is essentially an application for maintenance treatment in the ndMM setting and it is therefore not appropriate to include Lenalidomide separately, for only induction treatment within the scope.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. The wording of the remit has been amended to the following: To appraise the clinical and cost effectiveness of lenalidomide within its licensed indication as initial and maintenance therapy for newly diagnosed multiple myeloma in people for whom autologous stem cell transplant is not

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			appropriate.
	CSAS	Yes	Comment noted.
	Myeloma UK	We suggest the draft remit / appraisal objective will need to be reworded to reflect the appraisal of lenalidomide in the maintenance setting. The wording will depend on the agreed appraisal strategy - please see attached additional comments.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. If the proposed marketing authorisation (as first-line treatment) is accepted by the EMA, it will not be possible for NICE to make recommendations on the use of lenalidomide beyond the explicit terms of its marketing authorisation.
	UK Myeloma Forum, BSH & RCP.	No. We suggest the following wording: "To assess the clinical and cost effectiveness of lenalidomide as monotherapy or in combination with a corticosteroid (dexamethasone or prednisolone) within its licensed indication as maintenance therapy for the treatment of newly diagnosed multiple myeloma in people who have previously received induction chemotherapy and for whom autologous stem cell transplantation is not appropriate."	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. The wording of the remit has been amended to the following: To appraise the clinical and cost effectiveness of lenalidomide within its licensed indication as initial and maintenance therapy for newly diagnosed multiple myeloma in people for whom autologous stem cell transplant is not appropriate.
Timing Issues	Celgene Ltd	Results from study MM-015 showed a significant increase in PFS when patients were randomised to the maintenance lenalidomide arm. However [redacted]	Comments noted.

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		[redacted]	
	Myeloma UK	Myeloma UK believes that this is a valuable technology for the maintenance setting and a timely appraisal is important. However, NICE, the manufacturer and consultees should all be confident about the availability of relevant data prior to undertaking the appraisal. If relevant data are not available it may be appropriate to undertake the appraisal at a later date. We look forward to discussing this matter with all stakeholders at the scoping workshop and ascertaining an appropriate timeframe for this appraisal on that basis.	Comments noted.
	UK Myeloma Forum, BSH & RCP.	Our organisations agree that it is important that new technologies are appraised in a timely way so as to ensure that new agents become available to patients as quickly as possible. Lenalidomide is the first maintenance drug to be considered for marketing approval by the EMEA, and has the potential to benefit the majority of patients with this cancer. It is appropriate that this technology is appraised through the STA process.	Comment noted.
Additional comments on the draft remit	UK Myeloma Forum, BSH & RCP.	We believe that there are insufficient data available for the appraisal of the technology as induction therapy because the phase 3 study (MM-015) was designed as a study of extended therapy. This is reflected in the wording of the licence application. Thus it would be most appropriate to appraise the technology in the maintenance setting, in patients who have received induction therapy with thalidomide, bortezomib or lenalidomide in combination with an alkylating agent (melphalan or cyclophosphamide) and/or corticosteroid (dexamethasone or prednisolone). The inclusion of several induction regimens is in line with current	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. If the proposed marketing authorisation is accepted by the EMA, it will not be possible for NICE to make recommendations on the use of lenalidomide beyond the explicit terms

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		NICE guidance on initial therapy for patients not suitable for stem cell transplantation, i.e. the use of thalidomide or bortezomib, in combination with an alkylating agent (melphalan or cyclophosphamide) and/or corticosteroid (dexamethasone or predniosIone).	of its marketing authorisation.

Comment 2: the draft scope

Section	Consultees	Comments	Action
Background information	Celgene Ltd	Background information is sufficient for the purpose of a scoping exercise.	Comment noted.
	CSAS	Average survival between 4 and 6 years' may be quite high. Recent data from the Office for National Statistics (source Myeloma UK) reported that a third of patients now survive to 5 years. Cancer Research UK also reports 59% survive to one year and 23% to 5 years.	The scope has been updated to reflect this information.
	Myeloma UK	It is important to clarify that the term "induction" treatment - which aims to kill as many myeloma cells as possible - is normally only used in the context of a subsequent stem cell transplantation and high-dose chemotherapy treatment. Myeloma patients for whom autologous stem cell transplant (ASCT) is not appropriate do not receive induction but "initial" or "first-line" treatment instead. Ongoing maintenance treatment subsequent to either ASCT or initial treatment (for non-ASCT patients) is considered an important strategy to prolong treatment response and therefore delaying the time to relapse.	All references to *induction treatment* in this scope have been replaced with the description *initial treatment*.
	UK Myeloma Forum, BSH & RCP.	Under background, paragraph 3, line 13. We suggest that the sentence "Two frequently used combinations are cyclophosphamide, thalidomide and dexamethasone (CTD) and melphalan, prednisolone and thalidomide (MPT)" be changed to "The most commonly used regimens are melphalan and prednisolone (MP), cyclophosphamide, thalidomide and dexamethasone (CTD), melphalan, prednisolone and thalidomide (MPT) and melphalan, prednisolone	The scope has been updated to include reference to MPV. At the scoping workshop, clinical specialists explained that MP alone is seldom adopted as an initial treatment strategy (although some people who commence treatment with MPV or MPT are unable to tolerate the novel therapy and end up on MP alone). Therefore, it has not been added to the description of current treatment.

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		and bortezomib (MPV)". This would more accurately reflect current clinical practice.	
The technology/ intervention	Celgene Ltd	In the maintenance setting, Lenalidomide is administered as monotherapy only, until disease progression. It is not given in combination with a corticosteroid and Celgene requests NICE to make this correction in the scope on page 2/5.	We are aware of research in which lenalidomide is being investigated in combination with corticosteroids in the maintenance setting. For example, study lenalidomide is administered with dexamethasone in study MM-020. At the scoping workshop, clinical specialists explained that lenalidomide would normally be used as monotherapy in the maintenance setting in NHS practice. Therefore, we note ongoing investigation of lenalidomide in combination with steroids in describing the technology, but have limited the definition of the intervention to be appraised to monotherapy (see below).
	CSAS	Yes	Comment noted.
	Janssen	Lenalidomide has also been assessed in combination with the steroid dexamethasone (low dose and high dose). It would be appropriate to also consider this combination in the scope of this appraisal.	At the scoping workshop, clinical specialists explained that lenalidomide would normally be used as monotherapy in the maintenance setting in NHS practice. Therefore, we note ongoing investigation of lenalidomide in combination with steroids in describing the technology, but have limited the definition of the intervention to be appraised to monotherapy (see below).
	Myeloma UK	We do not believe it is appropriate to consider lenalidomide in combination as a stand-alone treatment in the induction (initial / front-line treatment) setting.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. Therefore, the intervention in the scope is now defined as:

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			"Initial treatment with lenalidomide in combination with melphalan and prednisolone followed by maintenance treatment with lenalidomide alone".
	UK Myeloma Forum, BSH & RCP.	We suggest that the phrase "increases foetal haemoglobin production by CD34+ haematopoietic stem cells" in paragraph 1 line 5 be removed, as it is irrelevant to the appraisal remit.	The suggested deletion has been made.
Population	Celgene Ltd	The population mentioned for the induction setting in isolation is not relevant because, as mentioned previously, the expected license is essentially for maintenance treatment. The population mentioned under the maintenance setting is appropriate for consideration.	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. Therefore, the population in the scope is now defined as: "People with newly diagnosed or previously untreated multiple myeloma for whom autologous stem cell transplantation is not appropriate".
	CSAS	Yes	Comment noted.
	Myeloma UK	We do not believe it is appropriate to consider lenalidomide in the induction (initial / front-line treatment) setting. Myeloma UK believes there to be several options for pursuing this appraisal in the maintenance setting which need to be considered. If the appraisal can consider the technology beyond the licensed indication we propose that the description of the population prior to receiving maintenance treatment is slightly amended:	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. Therefore, the population in the scope is now defined as: "People with newly diagnosed or previously untreated multiple myeloma for whom autologous stem cell transplantation is not appropriate".

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		1. replace the words 'which is' to 'who are' 2. replace 'who have previously undergone induction chemotherapy only' with 'following initial treatment only' We consider this is necessary to reflect the fact that this patient group receives 'initial' rather than 'induction' treatment. It also better reflects the various different initial treatment options, which are not restricted to what is generally understood as 'chemotherapy'.	
	UK Myeloma Forum, BSH & RCP.	As detailed above, we do not believe it is appropriate to appraise lenalidomide in the induction (initial therapy) setting. Thus the description of the population should read “people with multiple myeloma who have undergone initial chemotherapy only and who are not suitable for autologous stem cell transplantation".	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. Therefore, the population in the scope is now defined as: “People with newly diagnosed or previously untreated multiple myeloma for whom autologous stem cell transplantation is not appropriate”.
Comparators	Celgene Ltd	For comparators within the maintenance setting, 'watchful waiting' is considered the most appropriate comparator in view of the high unmet medical need in the area of maintenance treatment and the lack of available licensed alternatives in this setting. Thalidomide maintenance and corticosteroid therapy, on the other hand, are not considered appropriate comparators in the maintenance setting, as they are not routinely used in clinical practice in the UK.	Comment noted. During the scoping workshop it was agreed that patients would not receive active pharmacological treatment in the maintenance phase and so it would be appropriate to limit the comparators to best supportive care in this setting.
	CSAS	These are appropriate, except that corticosteroids are	Comment noted. Corticosteroids as monotherapies

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		unlikely to be used as monotherapy without chemotherapy for induction of untreated myeloma. Trials have also compared lenalidomide with placebo (in combination with melphalan and prednisone) for induction, and lenalidomide with placebo for maintenance.	for initial treatment of multiple myeloma are no longer included as comparators in the final scope.
	Janssen	In the induction setting: - the combination therapy comprising of melphalan and prednisolone is a relevant comparator in frail patients. - corticosteroid monotherapy is not a relevant comparator in this appraisal. - the combination comprising of thalidomide and dexamethasone is a relevant comparator.	The final scope contains the following comparators for the initial treatment phase: - Cyclophosphamide, thalidomide and attenuated dexamethasone (CDTa) - Melphalan, thalidomide and prednisolone (MPT) For people who are unable to tolerate, or have contraindications to thalidomide: - Melphalan, bortezomib and prednisolone (MPV) For people who are unable to tolerate, or have contraindications to bortezomib and thalidomide: - Melphalan and prednisolone (MP)
	Myeloma UK	We consider that the appraisal should appraise lenalidomide in the maintenance setting only. It is not appropriate to appraise lenalidomide in either an induction or initial treatment setting due to the lack of evidence and the scope of the licence application. There are no approved or standard treatments in the NHS for the maintenance setting. Neither thalidomide monotherapy nor corticosteroids are currently routinely used in the NHS in this setting. Therefore it would not be appropriate to compare lenalidomide to	The proposed marketing authorisation specifies that lenalidomide would be indicated for maintenance treatment following initial treatment with melphalan, prednisolone and lenalidomide. During the scoping workshop it was agreed that patients would not receive active pharmacological treatment in the maintenance phase and so it would be appropriate to limit the comparators to best supportive care in this setting.

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		either of these treatments in this appraisal. It would be more appropriate to compare the technology with a no maintenance treatment / watchful waiting strategy. This is also the comparator used in the national Myeloma XI study.	
	UK Myeloma Forum, BSH & RCP.	Considering only the comparators in the maintenance setting, we suggest that the only valid comparator is best supportive case ('watchful waiting'). This is the comparator used in the national studies, MM IX and MM XI. The other comparators, thalidomide monotherapy and corticosteroid monotherapy should be removed as they are not standard therapy.	Comment noted. During the scoping workshop it was agreed that patients would not receive active pharmacological treatment in the maintenance phase and so it would be appropriate to limit the comparators to best supportive care in this setting.
Outcomes	Celgene Ltd	Yes. In the pivotal trial(s) progression-free survival (PFS) was used as primary endpoint, while response rates, overall survival, OS and QoL, amongst others, were collected as secondary endpoints. Progression free survival is a valuable end point in itself even in the absence of overall survival (given that the data has not yet matured). Trial specific post progression survival will be modelled separately in order to illustrate this point.	Comment noted.
	CSAS	Response could be defined, e.g. whether this relates to blood paraprotein or light chains in the urine.	Comment noted. Response criteria are well defined according to published standards (European Group for Blood and Bone Marrow Transplant/ International Myeloma Working Group). It was agreed that there was sufficient consensus on these definitions and that therefore it was not necessary to amend the outcome measure in the scope.
	Myeloma UK	These are appropriate outcome measures. Progression-free survival (PFS) is a particularly	Comment noted.

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		important outcome measure in myeloma which is incurable and characterised by repeated relapses and remissions. Periods of remission become increasingly shorter as the myeloma cells become resistant to treatment. The primary objective of maintenance treatment is to extend the duration of response to treatment and to achieve as long a period of PFS as possible. It is therefore a more relevant endpoint than overall survival. PFS is usually associated with improved quality of life as active myeloma disease is slowed down or prevented from returning.	
	UK Myeloma Forum, BSH & RCP.	The most important outcome measure is progression free survival, or time to progression. Extended progression free survival is itself a measure of benefit. Multiple myeloma is incurable, and disease course is characterised by repeated relapses separated by remissions (termed plateau phases) that become increasingly shorter as the cancer cells become resistant to therapy. With each subsequent relapse, quality of life decreases as complications accumulate, including bone pain and fractures, infections and kidney damage. Hence the first plateau phase is associated with best quality of life, and management should aim to maximise its duration. Overall survival is also important, but is increasingly influenced by subsequent treatments, and data from clinical trials is affected by patients crossing over from treatment to control arms. Overall survival as a parameter of benefit is best addressed in a lifetime study of myeloma patients. Adverse effects and health-related quality of life are clearly important outcomes	Comment noted.

Section	Consultees	Comments	Action
		measures.	
Economic analysis	Celgene Ltd	A life time model will be appropriate for any economic analysis.	Comment noted.
	UK Myeloma Forum, BSH & RCP.	Our organisations agree that it is important that new technologies are appraised in a timely way so as to ensure that new technologies become available to patients as quickly as possible. The time horizon is appropriate, and further data will be available from the current national MM XI study. We would point out that while the QALY has been developed as a tool to standardize measurement of benefit between interventions in different diseases, it may not accurately reflect patient-centred benefits in cancer, because these patients are coming from a very different level of functioning and expectation. Thus, in patients with a severe disease whose prospects of health are poor, more value and significance should be attached to smaller QALY gains. We encourage NICE to consider the use of quality modifying tools in the final evaluation.	Comment noted. NICE provides supplementary advice on end-of-life criteria, which is taken into account when appraising treatments which may be life-extending for patients with short life expectancy, and which are licensed for indications affecting small numbers of patients with incurable illnesses. The Appraisal Committee will decide whether end-of-life criteria are met based on the evidence submitted.
Equality	Celgene Ltd	Myeloma mostly affects the elderly population, who often face other concomitant conditions. Such patient populations may also have mobility issues. Equality of access may be achieved by ensuring that the benefits of newer treatments reach these patients.	Comment noted.
	CSAS	No issues	Comment noted.
	UK Myeloma Forum, BSH & RCP.	Myeloma is twice as common in Black populations, and so restriction of access to effective therapies could be seen as discriminatory to this group.	Comment noted. However, no further evidence has been provided of differential access to therapy or prognosis in populations of African and African-Caribbean family origin.

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Other considerations	CSAS	These are appropriate	Comment noted.
	Janssen	The following subgroups should be examined in this appraisal: - Cytogenetics subgroups - Duration of maintenance therapy with lenalidomide	During the scoping workshop it was agreed that, although cytogenetic subgroups, may in the future, enable the identification of people who may respond most reliably to treatment with lenalidomide or its comparators, there is no expectation that the evidence-base for these proposed appraisals will enable discrimination between such groups.
Innovation	Celgene Ltd	The technology has an immunomodulatory mode of action which is not found in any other treatment licensed for this disease in the maintenance setting. Lenalidomide is an oral therapy and therefore can be self-administered. This can be of immense help to patients who have mobility problems. However this benefit is unlikely to be reflected in the standard QALY measure.	Comment noted. During the scoping workshop, clinical specialists expressed the view that it is the availability of a package of pharmacological treatments, rather than any single technology (including lenalidomide), that has enabled clinicians to aim to treat multiple myeloma as a chronic disease. For this reason, they did not necessarily agree that lenalidomide alone represented a true 'step-change' in the management of multiple myeloma. It was also noted that lenalidomide is an oral therapy, and this may be an important benefit to patients that is unlikely to be captured in the standard QALY measure.
	Myeloma UK	The use of maintenance treatment is widely regarded as having the potential to make a substantial impact on the duration and quality of response experienced by patients following initial treatment.	Comment noted. During the scoping workshop, clinical specialists expressed the view that it is the availability of a package of pharmacological treatments, rather than any single technology

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		There is currently an unmet need with regard to an approved, standard maintenance strategy for myeloma treatment in the UK. The evidence suggests that lenalidomide is an effective maintenance treatment in this patient population. As the first treatment to receive an anticipated licence for maintenance, it offers a potential step-change in the management of myeloma in the UK.	(including lenalidomide), that has enabled clinicians to aim to treat multiple myeloma as a chronic disease. For this reason, they did not necessarily agree that lenalidomide alone represented a true 'step-change' in the management of multiple myeloma. It was also noted that lenalidomide is an oral therapy, and this may be an important benefit to patients that is unlikely to be captured in the standard QALY measure.
	UK Myeloma Forum, BSH & RCP.	Yes. This is a step-change in the management of people with this cancer who are not eligible for stem cell transplantation. No other technology has produced such an impressive prolongation of initial plateau phase. The longer a patient remains in plateau phase following initial therapy, the greater the probability that newer and more effective treatment will be made available.	During the scoping workshop, clinical specialists expressed the view that it is the availability of a package of pharmacological treatments, rather than any single technology (including lenalidomide), that has enabled clinicians to aim to treat multiple myeloma as a chronic disease. For this reason, they did not necessarily agree that lenalidomide alone represented a true 'step-change' in the management of multiple myeloma.
Questions for consultation	CSAS	The most appropriate comparators are as listed: thalidomide or bortezomib in combination with melphalan or cyclophosphamide and prednisolone or dexamethasone	The final scope contains the following comparators for the initial treatment phase: - Cyclophosphamide, thalidomide and attenuated dexamethasone (CDTa) - Melphalan, thalidomide and prednisolone (MPT) For people who are unable to tolerate, or have contraindications to thalidomide: - Melphalan, bortezomib and prednisolone

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			(MPV) For people who are unable to tolerate, or have contraindications to bortezomib and thalidomide: - Melphalan and prednisolone (MP)
	Janssen	Induction with cyclophosphamide-thalidomide-dexamethasone is a routine treatment option in the UK. Doxorubicin-based regimens are not routinely used as induction therapy in UK clinical practice. Interferon alpha is not routinely used as maintenance therapy in UK clinical practice. In the maintenance setting, watchful waiting is a reasonable comparator	The final scope contains the following comparators for the initial treatment phase: - Cyclophosphamide, thalidomide and attenuated dexamethasone (CDTa) - Melphalan, thalidomide and prednisolone (MPT) For people who are unable to tolerate, or have contraindications to thalidomide: - Melphalan, bortezomib and prednisolone (MPV) For people who are unable to tolerate, or have contraindications to bortezomib and thalidomide: - Melphalan and prednisolone (MP)
Additional comments on the draft scope	Myeloma UK	Myeloma UK believes that this is an important appraisal and that it is vital to ensure it results in a sensible pathway of access to lenalidomide maintenance by myeloma patients within a context of the myeloma treatment pathway, NHS clinical practice and available evidence. There are a number of options available to pursue this appraisal, each with its own implications for the appraisal and for access by patients. We look forward to discussing these at the scoping meeting. Please see attached comment form	Comment noted.

Section	Consultees	Comments	Action
		for detailed comments.	
	UK Myeloma Forum, BSH & RCP.	We wish to draw your attention to the fact that the above is a joint response from the major professional groups delivering care to patients with myeloma UKMF, BSH, RCP, and RCPath. We look forward as a group to being able to explore the above views in greater depth at the scoping exercise on April 18.	Comment noted.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

Department of Health
Healthcare Improvement Scotland
Marie Curie Cancer Care
MHRA
MSD Ltd
Royal College of Nursing
Welsh Assembly Government