NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia

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

Definitions:

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

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

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

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

Comments received from consultees

Consultee	Comment	Response
Celgene[1]	Overall survival gain (pages 4-5, Response to ACD, full text not reproduced here)	Comments noted. The Committee considered the goodness of fit of the survival curves presented. The Committee concluded that the most plausible ICER was derived from the manufacturer's sensitivity analysis which used the Weibull distribution to model overall survival, as it provided the best fit to the long-term survival data (see FAD section 4.8).
Celgene[1]	Survival in the AML state (page 7, Response to ACD, full text not reproduced here)	Comments noted. The Committee considered that the way in which the time patients spend in the 'acute myeloid leukaemia' health state is modelled may impact on the modelled total treatment costs, as it would affect the proportion of patients remaining on treatment and the amount of treatment received (see FAD section 4.10).
Celgene[1]	Administration costs of azacitidine (page 7, Response to ACD, full text not reproduced here)	Comments noted. The Committee concluded that the modelled increased costs of weekend administration were reasonable, noting that the associated impact on the ICERs was relatively low (see FAD section 4.10).

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Consultee	Comment	Response
Celgene[1]	Calculation of mortality rate (pages 7-8, Response to ACD, full text not reproduced here)	Comments noted. The Committee agreed that the way in which the health-state-specific mortality rates were calculated did not affect the model's estimates of overall survival. The FAD has been amended accordingly.
Celgene[1]	Utilities (page 8, Response to ACD, full text not reproduced here)	Comments noted. The based on the results of sensitivity analyses carried out by the manufacturer, the Committee concluded that impact on the ICER of underestimating utility gains owing to treatment was likely to be small (see FAD section 4.9).
Celgene[1]	Age-dependent mortality (page 8, Response to ACD, full text not reproduced here)	Comments noted. The cost-effectiveness of azacitidine was considered in light of the correction made for the inclusion of age-dependent mortality in the model (see FAD sections 4.6 – 4.14).
Celgene[1]	Economic model functionality (page 9, Response to ACD, full text not reproduced here)	Comments noted. The cost effectiveness of azacitidine was re-considered by the Committee in light of these corrections (see FAD sections 4.6 – 4.14).

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Consultee	Comment	Response
Celgene[1]	Treatment patterns in the UK (page 10-11, Response to ACD, full text not reproduced here)	Comments noted. The Committee concluded that these data showed pronounced variations in treatment patterns, indicating that there is no nationally recognized standard of care for this patient population, particularly with regard to patients' eligibility to receive chemotherapy. The Committee concluded that in the absence of consistent evidence on the proportion of people indicated for treatment with azacitidine that would be eligible to receive chemotherapy, best supportive care was the most appropriate comparator, as it was received by the majority of patients in the trial (see FAD section 4.2).
Celgene[1]	[redacted] (pages 12-13, Response to ACD, full text not reproduced here)	Comments noted.
Celgene[1]	Vial sharing (page 13, Response to ACD, full text not reproduced here)	Comments noted. The Committee concluded that the analyses incorporating estimated vial sharing did not produce plausible results due to the difficulties in implementing a vial-sharing scheme efficiently and therefore would not form the basis for its decision on the use of azacitidine in the NHS (see FAD section 4.7).

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Consultee	Comment	Response
Celgene[1]	Factual inaccuracies (page 13, Response to ACD, full text not reproduced here)	Comment noted. Section 2.3 of the FAD has been amended accordingly.
Celgene[1]	Updated base-case analysis (pages 14-24, Response to ACD, full text not reproduced here)	Comments noted. The cost effectiveness of azacitidine was re-considered by the Committee in light of these updated results (see FAD sections 4.6 – 4.14).
Celgene[1]	Survival curve selection (page 25, Response to ACD, full text not reproduced here)	Comments noted. The Committee considered the goodness of fit of the survival curves presented (see FAD section 4.8). The Committee concluded that the most plausible ICER was derived from the manufacturer's sensitivity analysis which used the Weibull distribution to model overall survival, as it provided the best fit to the long-term survival data.
Celgene[1]	Extrapolation of overall survival gain with azacitidine compared to comparators analysed and calculation of mortality rates (pages 25-29, Response to ACD, full text not reproduced here)	Comments noted. The cost-effectiveness of azacitidine was considered in light of the correction made for the inclusion of age-dependent mortality in the model (see FAD sections 4.6 – 4.14).

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Consultee	Comment	Response
Celgene[1]	Calculation of period in acute myeloid leukaemia (pages 30-31, Response to ACD, full text not reproduced here)	Comments noted. The Committee considered that the way in which the time patients spend in the 'acute myeloid leukaemia' health state is modelled may impact on the modelled total treatment costs, as it would affect the proportion of patients remaining on treatment and the amount of treatment received (see FAD section 4.10).
Celgene[1]	Probablistic sensitivity analysis (PSA) assumptions (page 31, Response to ACD, full text not reproduced here)	Comments noted. The cost effectiveness of azacitidine was re-considered by the Committee in light of these corrections (see FAD sections 4.6 – 4.14).
Celgene[1]	Amended and additional model functionality (pages 31-33, Response to ACD, full text not reproduced here)	Comment noted. The cost effectiveness of azacitidine was re-considered by the Committee in light of these corrections (see FAD sections 4.6 – 4.14).
Department of Health	Thank you for the opportunity to comment on the appraisal consultation document for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted.

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Consultee	Comment	Response
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above appraisal. We are content with the technical detail of the evidence supporting the appraisal and have no further comments to make at this stage	Comment noted.
Harrow PCT	You may be aware that I was unable to participate as a consultee at the appraisal meeting due to lack of timely submission of paperwork by the cancer network who were acting on behalf of Harrow PCT and I attended the meeting as a member of the public. I have therefore not had an opportunity to express some of these comments earlier.	Comment noted.
Harrow PCT	*Do you consider that all of the relevant evidence has been taken into account?* Yes	Comment noted.

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Consultee	Comment	Response
Harrow PCT	*Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?* The cost of transfusion seems not to have been considered in a comprehensive manner. For example, a patient with myelodysplasia undergoing an episode of uncomplicated transfusion will usually be given 3 units of red cells every 3-4 weeks. Should platelet transfusion be required, usually this will be on a regular basis i.e. 1 unit every week or so. The cost of an episode of red cell transfusion thus includes Cost of x units of red cells - standard cost Cost of cross match and issue of blood -standard cost Cost of medical and nursing care provided for the 8-10 hours of transfusion -no HRG exists, variation in cost across UK but costed as day patient or in-patient for <2 days Cost to the NHS by use of donor time/donor product- if we assume a donor spends 1-2 hrs donating blood- hence cost to society in terms of loss of time from work; the need to comply with national guidance on streamlining use of blood and blood products Cost to the patient in time lost for transfusion Cost of complications- such as refractoriness to random donor products, iron overload. These costs add up to more than just the cost of the unit of blood product. In the assessment of the ACD, the need for transfusion is significantly improved by Azacytidine in some patient groups. In my opinion, it would be useful to consider the transfusion costs more completely.	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC (including the costs of transfusion) were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable. As per the NICE reference case (see sections 5.2.7 to 5.2.10 of the NICE methods guide), costs incurred outside the NHS or PSS (i.e., those owing to time away from work) were not incorporated.

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Consultee	Comment	Response
Harrow PCT	*Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* I believe that the cost- effectiveness has to be re-addressed after calculating the true costs of transfusion. As it stands, I believe that the cost-effectiveness analysis is incomplete.	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC (including the costs of transfusion) were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.
Harrow PCT	*Are there any equality related issues that need special consideration that are not covered in the ACD?* No	Comment noted.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	We believe that not enough evidence has been taken into account regarding the decline in health over time for patients receiving only best supportive care (BSC), in comparison with patients receiving active treatment with azacitidine (Vidaza). Best Supportive Care (BSC) compares very unfavourably with this new technology. BSC does not represent a treatment as such for high-risk MDS. BSC merely deals with chronic symptoms of the condition. Transfusions have to be administered in increased frequency and rapidly lead to a much worse quality of life, and decline in health. Each transfusion at the hospital is increasingly taxing for these patients. BSC does not stop the progression of the condition. Azacitidine is the only drug that will enable these patients to live longer with an improved quality of life. *4.7….." It (the Committee) - understood that, given the patient distribution in the UK, best supportive care was the most appropriate comparator. The Committee considered that chemotherapy was not an appropriate comparator since there was limited evidence of statistically significant clinical effectiveness."*	As per the NICE Reference Case, the comparators are meant to represent current and best practice in the NHS. The Committee noted data which showed pronounced variations in treatment patterns, which indicated that there is no nationally recognized standard of care for this patient population, particularly with regard to patients' eligibility to receive chemotherapy. The Committee concluded that in the absence of consistent evidence on the proportion of people indicated for treatment with azacitidine that would be eligible to receive chemotherapy, best supportive care was the most appropriate comparator, as it was received by the majority of patients in the trial (see FAD section 4.2).

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	We strongly feel that health related Quality of Life issues – in particular fatigue, was understated: (as acknowledged by the Committee in sections 4.5 & 4.9.) The patient expert statements as well as many other patient testimonies we have come across are all consistent with the fact that quality of life is immensely improved for patients receiving azacitidine. Many patients who respond to azacitidine become transfusion **independent** and their haemoglobin levels remain at a high and healthy level. Quality of life for patients with this incurable sub-type of the condition is the most important factor for them. A treatment that relieves daily fatigue and breathlessness is of immeasurable benefit to patients.	The Committee understood that the utility gains owing to treatment with azacitidine (including those attributable to reduced fatigue and transfusion independence) were likely underestimated by the model (see FAD section 4.5). The Committee concluded, however, that the result of this underestimation would be minimal because changes in utility estimates did not produce large changes in the ICER (see FAD section 4.10).
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	Patients do not need any or as many hospitals visits as with BSC, hence reducing the cost burden to the NHS.	Comment noted. Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	Patients are able to regain a much higher degree of independence and are able to participate in social activities again – improving the patients' experience (as aimed for in the Cancer Reform Strategy).	The Committee understood that the utility gains owing to treatment with azacitidine (including those attributable to reduced fatigue and transfusion independence) were likely underestimated by the model (see FAD section 4.5). The Committee concluded, however, that the result of this underestimation would be minimal because changes in utility estimates did not produce large changes in the ICER (see FAD section 4.10).

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	Patient testimony gathered from more than 100 Patient and Family Forums worldwide through both written questionnaires administered to MDS patients and through verbal, taped and transcribed quality of life conversations at these Forums provide strong evidence that fatigue is the major reason that MDS patients experience an extremely diminished quality of life. Blood transfusions rank second only to fatigue in their effect on patients' quality of life. The time involved in travel to the transfusion centre, to receive the transfusions, and the necessity to have an accompanying caregiver imposes a hardship on patients' lives and those of their caregivers. With repeated transfusions the burden becomes higher as the disease progresses as does the risk for for end organ complications arising from iron overload. Patients treated with azacitidine report that their quality of life both from the standpoint of relief from debilitating fatigue and freedom from transfusions has a huge impact on their quality of life and their ability to function in normal activities of daily living. The MDS Foundation will be happy to share this information with NICE. *4.5……. "The Committee noted that no quality of life data were collected in the AZA-001 trial, although such data collected in CALGB 9221 suggested improvements in overall health with azacitidine."* *4.9 "The Committee considered the ERG's concerns that the manufacturer's estimate of patients' quality of life included in the model lacked face validity. The patient experts and clinical specialists stated that treatment with azacitidine reduces symptoms (such as fatigue) and the need for blood transfusions, both of which are probably associated with a degree of disutility. The Committee noted that the manufacturer's model produced* ***small gains*** *in health-related quality of life as a result of treatment with azacitidine, and that* ***greater independence*** *from blood transfusions was not included in the utility estimate. It noted that the manufacturer had estimated utility by mapping to the EQ-5D, and that the EQ-5D does not include fatigue as a dimension, although some effects of this symptom on ability to undertake normal activities would be captured. The Committee considered that reduced fatigue resulting from treatment with azacitidine may not have been completely captured in the modelled utility values……The Committee concluded that the manufacturer's model may have underestimated the gains in health-related quality of life resulting from treatment with azacitidine, but noted that the degree of underestimation was not known".*	The Committee understood that the utility gains owing to treatment with azacitidine (including those attributable to reduced fatigue and transfusion independence) were likely underestimated by the model (see FAD section 4.5). The Committee concluded, however, that the result of this underestimation would be minimal because changes in utility estimates did not produce large changes in the ICER (see FAD section 4.10).

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	Overall survival may not be the most important outcome for all of the patients – good quality of life in the last 1-2 years of survival is equally important and the ability to participate actively in life. *4.8…. "The ERG stated that the most important influence on the model's outputs was overall survival,.."*	The Committee understands the importance of quality of life. Section 4.8 of the ACD was meant to describe the extent to which various inputs into the model played a role in determining the final ICER. To say "*that the most important influence on the model's outputs was overall survival*" was to say that the ICER was more sensitive to changes in estimates of survival than to changes in estimates of health-related quality of life. The FAD has been amended to correct this misunderstanding (see section 4.10).

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	*Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?* • Yes. As stated in section 4.6, the Committee concluded on the basis of evidence from clinical specialists and patient experts that azacitidine is a clinically effective treatment for MDS, CMML and AML, and that in section 4.2 from clinical specialists that current treatment for 90 % of this group of patients is best supportive care (BSC). However we disagree with the committee's conclusion on cost-effectiveness. The Committee should take into consideration that the incremental cost effectiveness ratio per quality adjusted life year gained (ICER per QALY) is of necessity going to be high, because the base comparator (BSC) is going to be low. This is an unfortunate test of cost-effectiveness, when the condition (MDS) being treated has not seen any real advance in medical treatment for some time, and any new treatment being introduced would suffer from the same fate.	The incremental cost effectiveness ratio takes into account both the costs and gains in quality-adjusted survival attributable to azacitidine, relative to those attributable to BSC. Considerations about the cost effectiveness are explained in the Guide to the Methods of Technology Appraisal section 6.2.6.10 and 6.2.6.11.
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	• BSC and risk of increased infections: Under BSC, patients may suffer from a lower immunity and may be prone to increased infections, requiring a higher number of hospital stays, antibiotics – hence increasing overall costs for the care of this group of patients.	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	• Shortage of blood supply AND related costs: We realise that this point may not be considered within the remit of NICE, but there is an issue on availability of blood for transfusion and the impact on the NHS. Currently, the National Blood Service is emphasising the additional pressures being created by people who have, or may have, flu being excluded from donation. It seems that one of the major specifically attributable costs of best supportive care is transfusion. In the first month of azacitidine treatment, patients may require more frequent transfusions (study by Kornblith et al), but transfusion independence reached by many patients subsequently, provides savings on a financial as well as a social level (reducing the pressure for additional blood donors; scarce blood supplies can be directed elsewhere in the NHS). The sub-group of patients requiring frequent blood transfusions (i.e. weekly or bi-monthly) or also requiring platelets would represent an additional cost-saving to the NHS services. Similarly, when patients develop an immunity to transfusions, the cost of cross-matching on-going transfusions further increases the cost to the NHS. *4.14 …"The Committee considered whether there were any subgroups of patients for whom azacitidine would be considered a cost-effective use of NHS resources, and whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. The Committee noted that azacitidine may be of specific benefit to those who are unable to receive blood transfusions for clinical or religious reasons. The Committee noted that patients treated with azacitidine required fewer blood transfusions than those treated with best supportive care."*	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	*Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* • No – the recommendation for further research (Point 6.1 – Study on health related Q-O-L values) will mean increased delay translating into continued severely impaired quality of life for many patients and/or earlier than necessary death for many. The MDS Foundation (an international patient advocacy organization) will be happy to share quality of life data gathered worldwide with NICE. In addition, the Foundation has developed a quality of life tool that is currently undergoing validation. The Foundation will be happy to provide NICE with all data gathered from MDS patients on an ongoing basis for future support of azacitidine use.	The recommendations for further research will not dictate the timings of a review of guidance on the use of azacitidine. The recommendations for further research are given only in the hopes of stimulating research to fill evidence gaps which have come to light during the appraisal.
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	• Equally, (Point 8.1) the proposed review by the Guidance Executive in November 2012, will also definitely mean depriving hundreds of patients of a better quality of life, and will mean earlier than necessary death for many. Furthermore it will provide a further burden on blood supplies, especially at critical times of diminished number of blood donors.	Please note that the proposed review time has been amended to February 2013 to reflect the updated FAD publication date.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	*Are there any equality related issues that need special consideration that are not covered in the ACD?* • Equality on a European level – the UK should strive to be leaders in innovative medicine. The major European countries have already adopted the use of azacitidine. By not adopting innovative treatments early on, the UK cannot establish itself as a world leader in promoting innovation in MDS.	Funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions can differ across countries. Organisations in other European countries may not take cost effectiveness into consideration when making their recommendations. NICE, however, is obliged to take cost effectiveness into consideration in its decision making.
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	• A negative decision by NICE will make it less likely that patients going through the Individual Funding Request process with their Primary Care Trusts (PCTs) will have azacitidine funded. Moreover, the chances of a successful outcome for patients will vary depending on the individual PCT, thereby denying patients equal access to this technology. The only other alternative is to apply to use private insurance, an option not open to most patients.	The Committee's recommendations apply to the whole of the NHS and do not distinguish between PCTs. Although individual choice is important for the NHS and its users, they should not have the consequence of promoting the use of interventions that are not clinically and/or cost effective.

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Consultee	Comment	Response
MDS UK Patient Support Group, Rarer Cancers Forum, Leukaemia CARE, Leukaemia Research Fund, Leukaemia Society, Macmillan Cancer Support	• The NHS Confederation states: "Every NHS patient deserves to be treated with fairness, dignity and respect and that should be no different for elderly people using the service". The vast majority of these patients are on average 70 years old – hence it is important they should receive the same level of effective care as a younger working population.	Comment noted. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age. The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation.
Royal College of Nursing.	Nurses working in this area of health have reviewed the Appraisal Consultation Document of technology appraisal for Myelodysplastic syndromes – azacitidine. There are no further comments to submit at this stage on behalf of the Royal College of Nursing. Thank you for the opportunity to review this document. We look forward to participating in the next stage of the appraisal.	Comment noted.

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Comments received from clinical specialists and patient experts

Nominating organisation		Comment	Response
Patient expert	Paul A. Harford	I am naturally disappointed to learn from the ACD the committee's preliminary decision is not to recommend azacitidine for the treatment of the conditions above. However, I do gain some comfort that those of us currently receiving azacitidine can continue to do so.	Comment noted.
Patient Expert	Paul A. Harford	**Sections 2.3 & 3.8** The appraisal has been made on the basis of azacitidine being injected subcutaneously daily for 7 days, followed by a rest period of 21 days. The dosage is 75mg/m2 involving 9 vials for one cycle. In my treatment I receive an equal dosage of in total 750mg over 5 days which I calculate to be 7.5 vials. Bearing in mind weekend treatment is not required and what appears to be a lower dosage, I ask whether the cost effectiveness is improved to a more reasonable and acceptable level?	The Committee considered the impact varying the costs of weekend administration would have on the ICER. The impact was shown to be minimal (see FAD section 4.11).

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Nominating organisation		Comment	Response
Patient Expert	Paul A. Harford	**Section 4.5** It is disappointing that no quality of life data were collected in the AZA-001 trial. However, patient experts did confirm the improvement in health and increased ability to perform normal activities of daily living. I have already confirmed my improved health from my azacitidine treatment which I have received form April 2008. The improvement was a quick one in that no blood transfusions have been necessary since July of 2008. A most important feature of this has been a consistent haemoglobin and platelet level within the normal parameters. The problem with blood transfusions was the decline in haemoglobin level in the period between each transfusion which were necessary every 3 weeks involving either 2 or 3 units. Best Supportive Care treatment only therefore offered a temporary respite compared with no decline with treatment with azacitidine. What has not been mentioned with care by blood transfusions is the increasing risk of iron (ferritin) content in the blood. One other important factor is the risk of infection on Best Supportive Care because of a breakdown in one's immune system. I did experience an infection as result. I had to be hospitalized for 6 days, after which I was treated for a period of 14 days with intravenous anti-biotics.	Comments noted. The Committee considered all of the evidence submitted, which includes not only the clinical trial evidence, but statements from patients and clinical experts. The Committee understood that the utility gains owing to treatment with azacitidine (including, but not limited to those attributable to transfusion independence) were likely underestimated by the model (see FAD section 4.5). The Committee concluded, however, that the result of this underestimation would be minimal because changes in utility estimates did not produce large changes in the ICER (see FAD section 4.10). Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Nominating organisation		Comment	Response
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	In keeping with my written and verbal evidence to the NICE Committee meeting of 1st July 2009 robustly supporting the introduction of azacitidine as the treatment of choice for patients suffering with the appropriate categories of MDS, AML and CMML, I am very disappointed at the preliminary recommendation to reject on the basis of cost effectiveness. I am certain that haematology colleagues throughout the UK will be similarly dismayed. As stated in my original written evidence, I would emphasise once again the nihilism that currently exists for the treatment of these elderly people. The denial of the first and only widely applicable effective treatment for this group of patients would re-enforce this nihilism. It would also strongly re-enforce the recently publicised very negative perception that elderly patients with malignant diseases are poorly served in the UK. I believe denying access to azacitidine would indirectly discriminate against elderly people and generate issues of equality with respect to access to effective therapy. I address this important issue in heading 4 along with my comments for each of the other headings below.	Comment noted. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age. The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation.

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Nominating organisation		Comment	Response
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	*1) Do you consider that all of the relevant evidence has been taken into account?* I agree that the main focus of evidence for the licensed indication is The AZA 001 trial. I also believe that important data supporting a survival benefit and quality of life benefit comes from the randomised trial of Lewis R Silverman et al. I accept that this included patients with lower risk MDS but it highlighted the benefit of azacitidine for MDS across high risk and low risk FAB groups and was the initiator of the AZA 001 trial. I understand that there are extended follow up data available from the AZA 001 study which might inform the cost effectiveness model and these data should be presented by the company.	Comment noted. Data from the long-term extension study of the AZA-001 trial were considered by the Committee (see FAD sections 3.1 & 3.13).
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	*2) Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?* I am delighted that the ACD acknowledges and accepts the evidence of significant clinical effectiveness for azacitidine use within the licensed indication. It should be emphasized that for the vast majority of elderly patients with disease falling within the licensed indication there is currently no effective therapy and these patients receive supportive care only. That azacitidine has shown a survival benefit of some 10 months compared to conventional care is, to my mind, a major clinical development in the care of these patients.	Comments noted. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age.

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Nominating organisation		Comment	Response
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	From the point of view of the cost-effectiveness model I accept that the evidence of the ERG presented on 1st July suggests that there is a lack of face validity with the submitted model, especially in terms of the size of the actual benefit gained and the realistic nature of the predicted survival tail. It is important that these are addressed by the company. There clearly are some deficiencies in the AZA 001 trial in terms of assessing time to AML and the lack of quality of life data. However, there are plenty of examples within clinical practice to date of remissions and survival being measured in several years with azacitidine. The revised model produced by the ERG generated a high incremental cost but it is clear that aspects of this type of modeling are controversial. I believe that the clinical effectiveness, clearly proven by a randomized and peer reviewed trial, published in a high quality journal, should in this instance over- ride the high cost. This is because firstly there are currently no effective alternative treatments, because secondly the size of the clinical benefit achieved is very significant and because thirdly given the age of the patients and the nature of the underlying disease this is clearly an end –of-life modifying therapy.	The Committee concluded that azacitidine is a clinically effective treatment (see FAD section 4.6). The Committee similarly concluded that azacitidine meets the criteria for being a life-extending, end-of-life treatment (see FAD section 4.13). However, the Committee considered that the additional weight that would need to be assigned to the original QALY benefits in this patient group to fall within the current threshold range would be too great (see FAD section 4.14).
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	*3) Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* I consider that the ACD acknowledgement and acceptance of the clinical effectiveness is a sound interpretation of the clinical data. There are some issues with the various cost effectiveness models which need to be addressed.	Comment noted. In responses to clarification requests from the Committee, the Evidence Review Group and the Decision Support Unit, errors in the manufacturer's model were corrected. The cost effectiveness of azacitidine was re-considered by the Committee in light of these corrections.

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Nominating organisation		Comment	Response
Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	*4) Are there any equality related issues that need special consideration that are not covered in the ACD?* I think there are issues here which are currently very important. The median age of patients with MDS is well in excess of 70 years of age and only some 6% of MDS patients are diagnosed under the age of 50 years. Whilst I accept that the ACD does not directly discriminate between old and younger patients with MDS in terms of access to azacitidine it does generate issues of equality in terms of access to effective therapy. Younger patients (a minority of cases) can be effectively treated with intensive chemotherapy followed by an allogeneic stem cell transplant. Denying this young minority of patients access to azacitidine does not necessarily, therefore, deny them effective therapy. However, for the elderly majority, intensive chemotherapy and allogeneic stem cell transplantation is not an option because of toxicity. Consequently, to deny them azacitidine will be denying them the single most effective and currently applicable therapy and to my mind, therefore, indirectly discriminates against elderly people.	Comment noted. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age. The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation.

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Royal College of Pathologists and the British Committee for Standards in Haematology	Dr Dominic Culligan	A recent study by the North West Cancer Intelligence Service (NWCIS) presented at the National Cancer Intelligence Network (NCIN) claimed there had been little progress in cancer death rates in the over 75s over the last decade whereas significant benefit had been seen in the under 75s. The gap in death rates in this older age group between the UK and other countries in Europe and USA is widening. Professor Mike Richards, National Cancer Director, in response to this study is quoted in the press as saying 'This is an important study and urgent action needs to be taken on the findings. We need to ensure that cancer patients of all ages are diagnosed as early as possible and receive appropriate treatment. The findings have already been shared with the National Cancer Equality Initiative and we will be working with the NHS and other interested parties to tackle any age inequalities.' High risk MDS is a malignant disease predominantly of elderly people. Denying these elderly patients the only effective therapy currently available, would, to my mind, be a direct contradiction of the above statement by Professor Richards and would be a blatant example of sub- optimal care of elderly patients suffering with cancer in the UK.	Comment noted. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age. The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation.
NCRI/RCP/RCR/ ACP/JCCO	Professor David Bowen	*Do you consider that all of the relevant evidence has been taken into account?* Yes. I found the ERG analysis of the Celgene submission to be insightful and informative. The NICE process has been robust but can only be as good as the data presented. It is unfortunate that a detailed academic health economic analysis was presumably beyond the resources and scope of the ERG as the costs of BSC could have been more comprehensive.	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Nominating organisation		Comment	Response
NCRI/RCP/RCR/ ACP/JCCO	Professor David Bowen	*Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?* Having re-examined the healthcare resource use documentation from the Celgene submission I conclude that this could have been much more accurate if an academic health economist and expert Haematologists had been commissioned. For example the cost of blood products is not simply as quoted in table 7.12; this is merely the collection, processing and delivery cost of a unit of blood. Excluded are a number of significant costs such as hospital blood bank costs (cross matching particularly with a relatively high frequency of alloantibodies and their associated additional costs), premedication for patients with transfusion reactions (common in MDS), management of the complications of transfusion including transfusion reactions, fluid overload and iron overload. These costs are all lower in the azacitidine arm as 40% patients become red cell transfusion independent. In addition some of the HRG costs in Table 7.9 are presumably extrapolated and are wildly different from the real costs, not that this would affect the ICER significantly. Given the data presented to the ERG and having heard and understood the critique of the Markov modelling in Celgene's submission, the preliminary views on resource impact are as expected.	Comments noted. Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.

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Nominating organisation		Comment	Response
NCRI/RCP/RCR/ ACP/JCCO	Professor David Bowen	*Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?* Given the data presented to the ERG and having heard and understood the critique of the Markov modelling in Celgene's submission, the provisional recommendations of the Appraisal Committee are the only conclusion that could be reached. I now feel that there are more flaws in the Celgene health economic data than I had previously realised which could lead to a higher cost for Best Supportive Care, although the impact that this would have on the ICER is unknown. I believe that a negative recommendation by NICE will have serious ramifications for MDS patients, and for physicians and researchers with an interest in MDS which will extend beyond the health economic sphere as follows: • This will perpetuate the nihilism amongst the UK Haematology community towards the management of patients with MDS, whose median age is 75 years. This will certainly be contributing to the poor outcome for such cancer patients compared with other developed countries recently highlighted in the media and which the government has pledged to redress. • The UK will be perhaps the only developed country in which MDS, CMML and AML patients will be deprived of access to 5-azacitidine which NICE accepts as a treatment capable of prolonging survival compared with alternative therapies. 5-azacitidine is the worldwide standard of care within its' licensed indication. UK MDS patients have access to no licensed drugs, compared with other European countries who have access to two drugs (azacitidine and deferasirox) and the US which has access to 4 drugs (azacitidine, decitabine, deferasirox and lenalidomide).	In responses to clarification requests from the Committee, the Evidence Review Group and the Decision Support Unit, errors in the manufacturer's model were corrected. The cost effectiveness of azacitidine was re-considered by the Committee in light of these corrections. The Committee was aware that the categories of MDS specified by the marketing authorisation (see FAD section 1.1) predominantly effect elderly people. The recommendation, however, applies to all people and does not distinguish between people based on age. The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation. Funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions can differ across countries. Organisations in other countries may not take cost effectiveness into consideration when making their recommendations. NICE, however, is obliged to take cost effectiveness into consideration in its decision making. The Committee considered that in light of all the evidence submitted, azacitidine would not be a cost effective use of NHS resources.

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Nominating organisation		Comment	Response
		• This decision will take the wind out of the sails for the development of internationally competitive clinical trials in high-risk MDS by the NCRI Haematological Oncology MDS subgroup. A randomised phase 2/3 trials programme is under development to explore combinations of new agents with 5-azacitidine as the standard of care. This was to be highly internationally competitive and may now have to be abandoned or postponed to a future timepoint when it will no longer be competitive. This is clearly not an issue directly concerning NICE but the wider implications of NICE decisions must be acknowledged.	Comment noted.
NCRI/RCP/RCR/ ACP/JCCO	Professor David Bowen	*Are there any equality related issues that need special consideration that are not covered in the ACD?* No.	Comment noted.

Summary of comments received from members of the public

Theme	Response
Azacitidine offers a notable extension to life, and is a considerable improvement over what is currently available for treatment of patients with MDS.	The Committee concluded that azacitidine is a clinically effective treatment (see FAD section 4.6). The Committee similarly concluded that azacitidine meets the criteria for being a life-extending, end-of-life treatment (see FAD section 4.13). However, the Committee considered that the additional weight that would need to be assigned to the original QALY benefits in this patient group to fall within the current threshold range would be too great (see FAD section 4.14).

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Theme	Response
Treatment with azacitidine improves quality of life, as it decreases fatigue, reduces or eliminates transfusion dependence and allows patients to participate in usual activities again.	The Committee understood that the utility gains owing to treatment with azacitidine (including those attributable to reduced fatigue and transfusion independence) were likely underestimated by the model (see FAD section 4.5). The Committee concluded, however, that the result of this underestimation would be minimal because changes in utility estimates did not produce large changes in the ICER (see FAD section 4.10).
The costs of best supportive care have not been fully accounted for.	Following consultation on the ACD, the manufacturer was asked to clarify the way in which the costs of BSC were modelled. In light of the information provided by the manufacturer, the Committee considered the estimated costs of BSC to be reasonable.
The decision to not recommend azacitidine for use in the NHS creates an inequity in access to treatment across Europe, as azacitidine is currently used in other countries.	Funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions can differ across countries. Organisations in other countries may not take cost effectiveness into consideration when making their recommendations. NICE, however, is obliged to take cost effectiveness into consideration in its decision making. The Committee considered that in light of all the evidence submitted, azacitidine would not be a cost effective use of NHS resources.
The decision to not recommend azacitidine was based on costs and of financial convenience.	The Committee does not consider the affordability, that is to say the costs alone, of new technologies, but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3)

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