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
Royal College of Pathologists and the British Committee for Standards in Haematology	I believe that the role of azacitidine in MDS and AML has been analysed in enormous detail during a NICE process that has now been running for twenty months. I suppose we should acknowledge that more than 1000 patients will have been diagnosed with a form of high risk MDS that might be suitable for azacitidine therapy during that time period.	Comment noted.
Royal College of Pathologists and the British Committee for Standards in Haematology	The recent ACD, following the successful appeal against the FAD, is comprehensive and confirms once again the clinical effectiveness yet relative expensive nature of the treatment in terms of the predicted incremental cost per QALY. I cannot argue with the findings of the ACD which is very thorough and I will not cover all the ground again. However, I feel the need to re-iterate most strongly my total support for the provision of azacitidine for appropriate MDS and AML patients in the UK.	Comment noted. Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
Royal College of Pathologists and the British Committee for Standards in Haematology	The recent Executive meeting of The UK MDS Forum on November 15th 2010 emphasised the utter confusion and inequality across the UK in terms of access to this drug. Some patients in England now have ready (though perhaps temporary) access to the drug via the new Interim Cancer Drug Fund. The lists produced by clinically-led panels for strategic health boards have, to date, ranked azacitidine very highly amongst drugs to be funded by this mechanism. This is to be welcomed and is a 'real world' judgement of this drugs worth and emphasises to the NICE appraisal committee the importance attached to this drug by clinicians and commissioners providing NHS care. However, some of the ten strategic health boards in England have yet to draft a list and hence azacitidine remains largely unavailable in these regions. In Scotland the drug is not available because of a negative SMC decision with no prospect of this being re-visited until the NICE process is completed. In Wales and Northern Ireland the drug is also currently unavailable. A positive NICE decision is clearly very important in providing a more level playing field for access to this drug across the UK.	The Committee's recommendations apply to the NHS in England and Wales and do not distinguish between PCTs. Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.

Consultee	Comment	Response
Royal College of Pathologists and the British Committee for Standards in Haematology	I still believe that a negative decision represents indirect discrimination against elderly people. This is because the licensed indication for azacitidine is for patients 'ineligible for stem cell transplant.' Denying the licensed indication, therefore, has a disproportionately larger impact on elderly people than on younger people with the identical diagnosis, in terms of access to effective therapy, because elderly people cannot receive stem cell transplantation. From my experience of training on equality legislation, this scenario seems very similar to examples that are commonly cited as types of indirect discrimination. Furthermore, there are examples of some PCTs providing access to azacitidine as a 'bridge to transplant.' This represents a somewhat lateral interpretation of the licensed indication and compounds the inequality towards elderly patients in whom this drug is frequently their only hope of effective therapy. I accept that a legal opinion has been sought on this, but I remain unconvinced that this would not be considered a strong example of indirect discrimination by many people presented with this scenario.	Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4. The recommendation applies to all people and does not distinguish between people based on age.
Royal College of Pathologists and the British Committee for Standards in Haematology	As stated in my original written evidence, I would emphasise once again the nihilism that currently exists for the treatment of these elderly people with MDS. 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. A negative decision from NICE will certainly add MDS to the list of diseases, predominantly affecting the elderly, with relatively poor survival compared to many of our European neighbours.	Comment noted; please see the above response. Please also note that funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions may differ across countries. The Institute recognises that guidance from other European organisations may differ from its own guidance, because of different criteria for making decisions.
Royal College of Nursing	**Has the relevant evidence has been taken into account?** This seems appropriate	Comment noted. No change required.

Consultee	Comment	Response
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** The summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by these patients. The preliminary views on resource impact and implications should be in line with established standard clinical practice	Comment noted. The Committee considered the evidence before it in the context of current clinical practice (see FAD section 4.2). Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
Royal College of Nursing	**Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** There are no comments to make at this stage	Comment noted. No change required.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	The Committee considered that its recommendation does not differently impact on any group currently protected by the equalities legislation.

Consultee	Comment	Response
NCRI/RCP/RCR/ACP/JCCO	The recommendation to not support the use of azacitidine in the NHS in England is naturally disappointing. Whilst we accept that NICE is working within its mandate, it is clear that drugs to treat orphan diseases such as high-risk MDS may need to be considered separately from high cost high disease incidence agents.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4. Please note that NICE has not received direction from the Department of Health that treatments for rare conditions ('orphan' or 'ultra-orphan') should be appraised differently from any other treatments.
NCRI/RCP/RCR/ACP/JCCO	**Has all of the relevant evidence been taken into account?** Yes. The evidence supplied by the manufacturer and by the UK MDS Support Group following the appeal has been considered by the DSU. There is no more evidence available to our knowledge	Comment noted. No change required.
NCRI/RCP/RCR/ACP/JCCO	**Are the summaries of clinical and cost-effectiveness reasonable interpretation of the evidence?** Yes. Whilst one could argue that there is a group of patients in whom a preference would be expressed by most Haematologists for therapy with low dose cytarabine rather than supportive care or intensive chemotherapy, this group cannot be precisely defined and as such will overlap with the other groups. In this regard, the criteria defined by the manufacturer following extensive consultation with the UK experts and review of the literature are reasonable but not precise. The Appraisal Committee continues to accept the clinical effectiveness of azacitidine. The data used to create the weighted average ICER are reasonable and based on the best estimate of management of MDS in the community hospitals in UK, namely the HMRN dataset.	Comment noted. The Committee concluded that a weighted average of conventional care regimens should be calculated using the HMRN registry data.

Consultee	Comment	Response
NCRI/RCP/RCR/ACP/JCCO	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Within the mandate of NICE these recommendations are sound. However, they compare less favourably with international practice.	Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4. Funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions may differ across countries. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.
NCRI/RCP/RCR/ACP/JCCO	**Are there any aspects of the recommendations that need particular consideration?** No. This has been extensively discussed in the appeal process	Comment noted. No change required.
MDS UK Patient Support Group	**Has all of the relevant evidence been taken into account?** Yes, to the best of our knowledge, all the evidence that currently exists has been considered. Azacitidine is the only effective first-line treatment for MDS, but the diversity of the group of conditions embraced as MDS, and the nature of the patient population available with their co-morbidities, make the accumulation of valid clinical trial data difficult and time-consuming.	The Committee recognised both that the population for which azacitidine is licensed is small (see FAD section 4.23) and that azacitidine represents an important change in the treatment of patients with myelodysplastic syndromes (see FAD section 4.24). Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.

Consultee	Comment	Response
MDS UK Patient Support Group	We ask NICE to stand by its recognition of the clinical effectiveness of azacitidine in terms of the significant increase in survival time that it provides for patients with high-risk MDS, and the greatly enhanced quality of that survival time. The evidence also indicates a lower risk of progression to AML and higher rates of complete remission, partial remission, haematological improvement and independence of blood transfusion.	The Committee concluded on the basis of the clinical-effectiveness evidence and the evidence from the clinical specialists and patient experts that azacitidine is a clinically effective treatment for myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia (see FAD section 4.8).
MDS UK Patient Support Group	We request that NICE give a provisional recommendation for use of azacitidine in the NHS for high-risk MDS, subject to the presentation of more evidence on the accumulated experience of use in a larger population of MDS patients over a longer period of time. The data submitted through the physician survey was by definition an estimate of use, since azacitidine has not been easily available throughout the UK. Having the drug available for a period of time would vastly increase the chances of producing more reliable, complete and valid information about its use in MDS.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
MDS UK Patient Support Group	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We believe that the clinical summaries are a reasonable interpretation of the trial evidence.	Comment noted. No change required.
MDS UK Patient Support Group	We are concerned that the evidence on cost effectiveness is based on a number of assumptions. The most important one, in the absence of additional trial data, is that patients will continue on a full dose of azacitidine for the duration of their treatment, however long that might be. A number of patients will go on to a maintenance dosage, either due to an effective response or because of impaired tolerance, which could reduce the cost by up to 65%, once control of the aberrant cell production is established. Even allowing for issues around vial size and wastage, this could still result in a considerable reduction in the cost of treatment of the order of at least 50% compared with continuing full dose treatment.	The Committee can only consider evidence with which it is presented. The Committee was presented with no evidence to support an assumption that any dose other than that which is specified in the Summary of Product Characteristics will be used in clinical practice.

Consultee	Comment	Response
MDS UK Patient Support Group	Experience with azacitidine is limited because of the relatively small number of patients available for and suitable for treatment, the logistics of undertaking large scale trials, and the additional difficulty of defining the criteria for stratification to maintenance treatment as opposed to full dose treatment. Until such trial data becomes available, we recommend that provisional approval be given for azacitidine to be available for use in treatment of patients with MDS with a recommendation that a controlled trial be established to evaluate the benefits and effectiveness of maintenance treatment in suitable patients. A similar situation was addressed in the Netherlands recently, where approval for azacitidine was given for a limited number of years, allowing the accumulation of necessary data, whilst not depriving patients of this life-line of treatment in the process.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
MDS UK Patient Support Group	Currently there is important on-going research about the efficacy of azacitidine to establish pre-treatment markers of potential response, which would help identify sub-groups of patients who would have a higher rate of response, thereby improving both clinical efficacy and cost-effectiveness. Preliminary research from King's College London seems to indicate a higher response rate to azacitidine in some sub-groups of patients. This data is currently being prepared for publication.	The Committee took note of the ongoing research to establish pre-treatment markers of potential response to azacitidine. No evidence was provided as to how this research would impact on the cost effectiveness of azacitidine and therefore this evidence has not been referred to in the FAD.
MDS UK Patient Support Group	Data on efficacy in the subgroup of patients with the del-7 chromosomal abnormality is also not yet clear. Until such data is published, and it is clearly established that it presents advantages in this patient group, we believe it is wholly unethical to deprive all patients of the benefit of this drug, condemning them to continued poor quality of life, reduced life expectancy or premature death.	The manufacturer did not present cost effectiveness evidence for the subgroup of patients in the trial with the -7/del (7q) chromosomal abnormality. The recommendation applies to the entirety of the population in the licensed indication. Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
MDS UK Patient Support Group	In addition partial responders draw some benefit from the treatment as a haematological improvement, as opposed to an increase in overall survival, can make a significant difference to the quality of life of these patients.	Comment noted.

Consultee	Comment	Response
MDS UK Patient Support Group	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** The negative recommendations do not appear to be sound on the basis of the very clear evidence for the clinical efficacy of azacitidine. The recommendations appear to be driven entirely on the basis of the apparent lack of cost effectiveness based on the current health economic modelling. If the costs could be controlled, then we believe that the STA would result in a positive recommendation for azacitidine on grounds that it is manifestly more clinically effective than many of the other drugs used in the treatment of cancer which have been approved by NICE in recent years. We believe that the only barrier which exists to its availability to MDS patients is its present cost. If that obstruction can be removed, then azacitidine should become a recommended treatment for use in the NHS in England - a development that we would support most strongly.	Comment noted. Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
MDS UK Patient Support Group	**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?** We are not aware of any. However, NICE stated that no data was presented on efficacy in sub-groups of patients, such as those patients unable to receive transfusions for religious reasons. We believe it would be inappropriate to positively discriminate such patients. This drug should be made available to all those who need it.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.
MDS UK Patient Support Group	**Are there any equality -related issues that need special consideration and are not covered in the appraisal consultation document?** Not that we are aware.	Comment noted.

Consultee	Comment	Response
MDS UK Patient Support Group	**Additional comments** The majority [around 84%] of the population of the United Kingdom live in England, to which NICE's recommendations apply. However the remaining 16% of the British population living in Scotland, Wales and Northern Ireland also have needs for medication for the treatment of MDS. Though NICE has no power there, the corresponding evaluatory bodies in those countries look to NICE for guidance, especially in specialist areas such as this. We are extremely concerned that a negative recommendation for azacitidine in England will be replicated throughout the rest of the United Kingdom, thereby denying even more patients of access to this highly effective treatment on grounds of cost alone. This is of particular importance, given the fact that the Interim Cancer Drug Fund is unavailable in those areas, and neither will the substantive cancer drug funding from next April be available for those British citizens living in Scotland, Wales and Northern Ireland.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4. Funding decisions for drugs are each individual country's national responsibility using nationally agreed criteria. Therefore funding decisions may differ across countries. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions.
MDS UK Patient Support Group	If cost is the sole barrier to a positive recommendation and thus availability of azacitidine, then we would encourage NICE to find a means of having a dialogue with the manufacturer in which the nature of cost barriers might be explored. We realise that this is not part of the remit of NICE but believe that this is an issue for the Department of Health, especially in the light of the recently announced recommendations for reforms in the NHS and the role of NICE in the future.	Azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4.

Consultee	Comment	Response
	A summary of the key points that have been addressed by Celgene We have focussed primarily on new observations and decisions made by the Appraisal Committee since the FAD was published in March 2010: • Application of end of life criteria • Approach to comparators • Sensitivity analyses relating to "blended" approach We have also provided updated cost-effectiveness analyses, based on the models preferred by NICE, to reflect a revised patient access scheme (PAS) currently under consideration by DoH and PASLU. [redacted] The scheme is under consideration by PASLU and DoH. If accepted, ministerial approval is expected in time for the Appraisal Committee meeting scheduled on 6 January 2010.	Comments noted. Please note that azacitidine is now recommended as a treatment option for adults who satisfy the conditions specified in FAD section 1.1 **and** if the manufacturer provides azacitidine at the reduced cost agreed under the patient access scheme, as described in FAD section 2.4. Please also see the responses to individual comments below.
	ACD section 4.8 - Clinical Effectiveness Celgene agree with the summarisation of the clinical evidence and remain pleased that the Committee recognises the clinical value of azacitidine.	Comment noted. No change required.
	ACD section 4.23 - End of Life Criteria Celgene agrees with the Committee's determination that azacitidine within this appraisal fulfils the criteria for consideration as a life-extending, end-of-life treatment. Importantly, we note that this determination has been made in the context of azacitidine's comparison with all conventional care types combined (i.e. a 'blended' comparison).	Comment noted.

Consultee	Comment	Response
	ACD Section 4.19 - Approach to comparators ***Identification of Subgroups*** The pivotal azacitidine clinical trial, AZA-001, allows the calculation of incremental cost-effectiveness ratios (ICERs) within the pre-selected subgroups set out in the AZA-001 trial. The subgroups are as follows: • Pre-selected for supportive care (BSC) • Pre-selected for supportive care plus low-dose chemotherapy (LDC) • Pre-selected for supportive care plus standard dose chemotherapy (SDC) Until the last Appraisal Committee meeting, Celgene and NICE had been working with cost-effectiveness comparisons of azacitidine to "conventional care" in each of these three subgroups. After further consideration, including the investigation of further evidence submitted by Celgene, the Appraisal Committee has concluded that it cannot make evidence-based recommendations based on the ICERs calculated in each subgroup, because there is insufficient robust evidence to allow the subgroups to be identified in clinical terms for NICE guidance. Given the Appraisal Committee's conclusions in this regard, it was determined in the ACD that the most appropriate ICER for the appraisal of azacitidine would be obtained by the use of a weighted average of incremental costs and QALYs estimated for each of the pre-specified subgroup comparisons. Celgene would agree that this approach follows logically from the Committee's conclusions with regard to subgroups.	Comment noted. No change required.

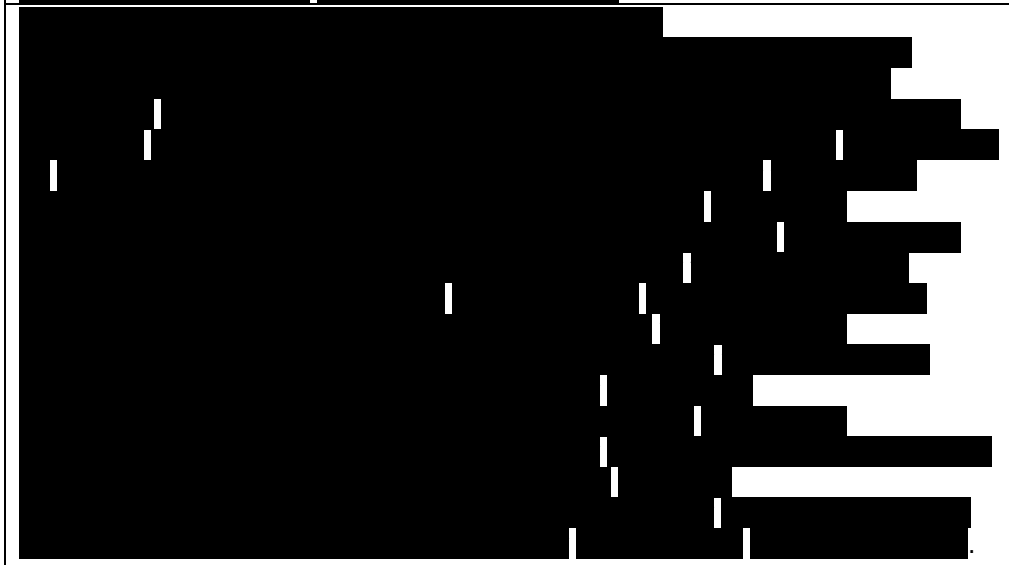
Consultee	Comment	Response
	Alternative approaches The DSU asserted that the ideal way of assessing azacitidine's cost effectiveness would be an incremental analysis involving each of the treatment options ordered according to their level of benefit. Thus, incremental costs and QALYs would be calculated for: • LDC versus BSC • Azacitidine versus LDC However, the Appraisal Committee and DSU acknowledged that it would be difficult to adjust such an analysis for the fact that patients who are eligible for BSC, LDC and SDC are often likely have substantially different clinical profiles. Eligibility for each of the three conventional care options is not entirely mutually exclusive – patient and clinician preference are known to play a role – but an incremental approach which fails to account for patient differences would carry little meaning and we noted that this observation was made during the Appraisal Committee meeting. For this reason, and because of the Committee's stated position with regard to the identification of subgroups, the weighted average approach was taken instead. However, some of the concerns which were raised regarding a fully incremental approach have been maintained, as described on the following page.	Comment noted. Please see responses below.

Consultee	Comment	Response
	Adjustment to weighted average ICER The weighted average ICER analysis presented by Celgene gave a value of £56,945/QALY gained. The Celgene ICER weighted incremental costs and QALYs for BSC, LDC and SDC subgroup analyses according to the proportions of patients pre-allocated to BSC, LDC and SDC in the AZA-001 trial. Clinical experts attending NICE Appraisal Committee hearings as well as written evidence statements collected during this appraisal have confirmed that the allocation of patients to subgroups in AZA-001 trial reflects current UK clinical practice. Celgene's evidence submission prior to this ACD provided real-life clinical data from the Haematological Malignancies Research Network (HMRN) patient registry. This registry captures current usage of BSC, LDC and SDC in UK clinical practice for MDS patients although not specifically in the population falling under the azacitidine marketing authorisation (HMRN registry includes data from all MDS patients). The Appraisal Committee carried out an adjustment to the weighted average ICER, using treatment allocation proportions observed in HMRN registry. The ACD states that the proportions (69% for BSC, 13% for LDC and 18% for SDC) are sourced from the Int-2/high-risk subgroup in the HMRN registry, but this seems at odds with the data in the HMRN report as well as in the DSU addendum to the Assessment Report. It would appear that the Committee actually used treatment allocations seen in the subgroup of MDS patients with the RAEB disease subtype – a subset of the azacitidine license (approx. 58% of the AZA-001 population). For clarity, we have presented the weighting alternatives together with corrected percentages and recalculated ICERs in Table 1. [Table 1 "Weighted average ICERs based on treatment allocations in AZA-001 and HMRN registry" included but not reproduced here]	The Committee understood that among the people classified as IPSS intermediate-2 or high risk in the HMRN registry, approximately 59% of patients received best supportive care alone, 12% received low-dose chemotherapy plus best supportive care and 29% received standard-dose chemotherapy plus best supportive care. The Committee considered the ICERs calculated using a weighted average of these proportions. The FAD has been amended to reflect this (see section 4.21).
	The Appraisal Committee has stated that it considers the most plausible ICER to be one which is based on the treatment allocations seen in the HMRN registry for MDS Int-2/high-risk patients. If we understand correctly, preference is given to these weightings over those available in AZA-001 for two reasons: ***1. The Committee considers that the HMRN registry may provide a more representative picture of current UK clinical practice than the AZA-001 trial.*** 2. ***The Committee considers that the weighted average ICER provided by***	The Committee heard from the clinical specialists that the HMRN registry, a UK database of over 600 patients, provided a representative estimate of the management of MDS in the UK. It noted that the HMRN registry includes a wider range of patients than those covered by the marketing authorisation for azacitidine but acknowledged clinical advice that within the HMRN registry, the subset of

Consultee	Comment	Response
	Celgene may be an underestimate due to the inclusion of incremental costs and benefits of azacitidine versus LDC. Since LDC is likely to be cost-ineffective compared to BSC it was felt that an element of double counting is introduced by involving a comparison of azacitidine against a therapy (LDC) which the Institute would probably not recommend as a cost-effective use of NHS resources. The adjustment carried out in Table 1 was also considered an appropriate way of increasing the ICER to account for this consideration. We would like to comment on this approach briefly. We feel that the adjustments carried out in Table 1 form a useful sensitivity analysis for the weighted average approach. However, we do not believe that the adjustments are a sound basis for the calculation of a 'preferred' ICER, especially given the Committee's stated objectives in applying these adjustments. Our comments against each of the Committee's stated objectives are set out below: 1. ***The Committee considers that the HMRN registry may provide a more representative picture of current UK clinical practice than the AZA-001 trial.*** The HMRN registry provides current insight into which treatments MDS patients are receiving. In principle, we consider the adjustments in Table 1 to be a useful sensitivity analysis. However, the HMRN registry captures information in all MDS patients, not just those indicated in the azacitidine license. This introduces uncertainty as to whether the adjustments provide a more realistic ICER for the UK than would be obtained by using the AZA-001 data. The Committee has attempted to address this uncertainty by applying treatment proportions seen in Int-2/high-risk or RAEB subsets only; both of these subsets are part of the azacitidine license and around 88% of patients in the AZA-001 trial were classified as Int-2/high-risk. But this adjustment does not control for the other clinical characteristics on which the HMRN registry patients may differ substantially from those in the azacitidine license. The most important of these are shown below: a. Transfusion requirements at time of treatment allocation b. Age and ECOG status c. Cytogenetic profile d. Eligibility for stem cell transplantation (azacitidine license explicitly rules out transplant-eligible patients) e. Number of cytopenias	patients classified as having IPSS intermediate-2 or high-risk myelodysplastic syndromes provided the best available estimate of the proportion of patients receiving each of the conventional care regimens in the patient population for whom azacitidine is licensed. The Committee concluded that a weighted average of conventional care regimens should be calculated using the HMRN registry data (for the subset of patients having IPSS intermediate-2 or high-risk myelodysplastic syndromes) rather than the AZA-001 data (see FAD section 4.20). The Committee heard from the clinical specialists that the group of patients eligible for chemotherapy could only be broadly described because of the current lack of consensus among UK haematologists about whether chemotherapy is appropriate for patients with certain comorbidities or disease-specific characteristics, and because of the inability to quantify clinician and patient preference for treatment (FAD section 4.2).

Consultee	Comment	Response
	All of these characteristics have the potential to influence treatment allocation. Stem cell transplantation eligibility is of particular concern. The HMRN data suggest that 28.5% of Int-2/high-risk patients received intensive chemotherapy or SDC, a finding which goes against expert testimony heard in earlier Appraisal Committee meetings and the Appeal hearing. Over the course of this appraisal, experts have generally indicated that SDC is rarely given in azacitidine-licensed patients; this treatment tends rather to be reserved for patients being prepared to undergo stem cell transplantation. For these reasons we cannot agree with the Committee that its adjustment to the ICER provides a more accurate reflection of UK clinical practice than the data from AZA-001.	

Consultee	Comment	Response
	2. ***The Committee considers that the weighted average ICER provided by Celgene may be an underestimate due to the inclusion of incremental costs and benefits of azacitidine versus LDC.*** The adjustment to the ICER is felt to partially compensate for a modelling issue which is often important when evaluating the cost-effectiveness of multiple therapies relative to one another. We cannot accept the link drawn in the ACD between this modelling issue and the adjustment in Table 1 for two reasons: a. We disagree in principle with the notion that the conventional care regimens need to be considered together with azacitidine in an incremental analysis. We believe that the Committee's concerns about the cost-ineffective increment between LDC and BSC are not relevant to this appraisal. This is a single technology appraisal of azacitidine versus conventional care. LDC, SDC and BSC are all part of the conventional care regimen for MDS and decisions as to whether a patient will be treated with LDC or BSC are not subject to cost-effectiveness evaluation in clinical practice – the relative difference in budget impact is small (£2,000 over a lifetime). The way in which conventional care options are used and assigned has been observed to vary in surveys carried out by Celgene, and patient preference plays a role. This is why the patients in AZA-001 were pre-allocated to BSC, LDC and SDC and thereafter effectively considered as subgroups of a main comparison of azacitidine to "conventional care regimens". b. If the Committee's concern about the cost-ineffectiveness of LDC compared to BSC is to be taken on board, an adjustment based on parameters which are unrelated to this concern seems arbitrary and inaccurate.	The Committee understood that the weighted average approach assumes that each conventional care regimen is the most cost-effective treatment option available for the patient group for whom it is used. It heard from the DSU that the necessary evidence to test this assumption is not available, given the remit of this appraisal, and therefore the use of a weighted average would result in some uncertainty in the ICER produced. It further heard from the DSU that if the cost effectiveness of each of the individual conventional care regimens was not established, the magnitude and direction of uncertainty in the weighted average ICER is unknown (see FAD section 4.19). Taking into account the limitations of the available evidence and in the absence of a satisfactory alternative, the Committee hesitantly concluded that any decision on the cost effectiveness of azacitidine would need to be made using the weighted average.
	Presentation of Revised Patient Access Scheme Based on our understanding of the ACD, the cost-effectiveness estimates from Table 1 represent the three ICERs most preferred by the Appraisal Committee, and trust that our corrections to the weighted averages are sufficiently clear. In this ACD response, we present updated ICERs based on a revised simple patient access scheme (PAS) which we have submitted for consideration by the DoH and PASLU. If accepted, we expect to receive ministerial approval for this PAS in time for the Appraisal Committee meeting on 6 January 2011.	Comments noted.

Consultee	Comment	Response
	[redacted]  We expect that PASLU and DoH will provide further details of the scheme to NICE in due course. [Table included but not reproduced here]	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
	None received.	

Comments received from commentators

Commentator	Comment	Response
	None received.	

Comments received from members of the public

Role*	Section	Comment	Response
		None received.	

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