

**MYELODYSPLASTIC SYNDROMES - AZACITIDINE: A CRITICAL  
APPRAISAL OF ADDITIONAL EVIDENCE SUBMITTED BY CELGENE  
AND THE MDS FOUNDATION**

REPORT BY THE DECISION SUPPORT UNIT

September 2010

Sarah Davis<sup>1</sup>, Allan Wailoo<sup>1</sup>, Christopher Carroll<sup>1</sup>

<sup>1</sup> University of Sheffield, UK

Decision Support Unit  
ScHARR  
University of Sheffield  
Regent Court  
30 Regent Street  
Sheffield  
S1 4DA

## **EXECUTIVE SUMMARY**

This DSU report provides a critical appraisal of the evidence submitted by Celgene and the MDS Foundation in response to NICE's requests following the appeal decision. The DSU was asked to assess whether the quality of life data from the MDS Foundation remove uncertainty around the utility estimates and whether these estimates have been appropriately incorporated into the Celgene economic model. The DSU considers that the utility values submitted by the MDS Foundation are not appropriate for use in the base-case cost-effectiveness analysis. In addition, the incorporation of the new utility data does not substantially alter the cost-effectiveness estimates.

The DSU was asked to assess whether the data submitted by Celgene regarding current practice patterns and the characteristics of patients receiving each of the comparative care regimens give a comprehensive view of UK clinical practice and allow a clear definition of subgroups. The DSU considers that the data recently submitted by Celgene provide neither a comprehensive view of UK clinical practice nor permit a robust, evidence-based definition of MDS sub-groups eligible for low dose chemotherapy treatment.

The DSU was asked to consider whether any special consideration is required due to the incorporation of patient preference within the trial design of the AZA-001 trial. In Celgene's submission they have provided a literature review describing the main concerns facing patient preference trials, but they also state that these trials have limited relevance to the AZA-001 trial, as they all involve patients in the actual assignment to control or active treatment which was not the case in the AZA-001 trial. The DSU would agree with this position. However, the fact that the AZA-001 trial used a combination of clinical judgment and patient preference to determine allocation to one of the three conventional care regimens does have implications, as this makes it difficult to identify a pre-specified group of patients from within the UK azacitidine indicated population who can be expected to be similar to those patients pre-selected to receive either BSC or LDC within the AZA-001 trial.

## CONTENTS

<b>1. INTRODUCTION</b> .....	<b>5</b>
1.1. BACKGROUND.....	5
<b>2. QUALITY OF LIFE DATA FROM THE MDS FOUNDATION</b> .....	<b>7</b>
2.1. SZENDE ET AL. ....	8
2.2. COMPARISON OF SZENDE ET AL. WITH CELGENE BASE-CASE. ....	9
2.3. SUMMARY.....	10
<b>3. COST-EFFECTIVENESS RESULTS USING QUALITY OF LIFE DATA FROM THE MDS FOUNDATION</b> .....	<b>11</b>
3.1. METHOD USED TO MODEL UTILITY BASED ON TRANSFUSION STATUS .....	11
3.2. OTHER ISSUES IDENTIFIED.....	12
3.3. RESULTS.....	14
3.4. SUMMARY.....	16
<b>4. CURRENT UK PRACTICE PATTERNS AND CHARACTERISTICS OF PATIENTS RECEIVING THE COMPARATIVE CARE REGIMENS</b> .....	<b>17</b>
4.1. LITERATURE REVIEW .....	17
4.1.1. <i>Assessment summary</i> .....	17
4.1.2. <i>Conclusion</i> .....	18
4.2. HAEMATOLOGIST SURVEY .....	18
4.2.1. <i>Assessment summary</i> .....	18
4.2.2. <i>Conclusion</i> .....	20
4.3 CELGENE HOSPITAL SURVEY .....	20
4.3.1 <i>Assessment summary</i> .....	21
4.3.2 <i>Conclusion</i> .....	21
<b>5. ISSUES ARISING FROM THE INCORPORATION OF PATIENT / PHYSICIAN PREFERENCE IN THE TRIAL DESIGN OF AZA-001</b> .....	<b>23</b>
<b>6. CONCLUSIONS</b> .....	<b>25</b>
<b>7. REFERENCES</b> .....	<b>26</b>
<b>APPENDIX:</b> .....	<b>28</b>

## TABLES AND FIGURES

Table 1 Transfusion-based utility scores reported by Szende et al (Table 1.6 of Celgene's post-appeal submission).....	12
Table 2 Utility scores for treatment arms in the model (Table 1.7 of Celgene's post-appeal submission with headings corrected) .....	12
Table 3 Deterministic base-case results* using original utility estimates [probabilistic estimates shown in brackets].....	15
Table 4 Deterministic results using transfusion based utility estimates (UK data from Szende et al) but no other change to base-case assumptions* [probabilistic estimates shown in brackets].....	15
Table 5 Deterministic results using transfusion based utility estimates (All patient data from Szende et al) but no other change to base-case assumptions* [probabilistic estimates shown in brackets] .....	16

## **ABBREVIATIONS AND DEFINITIONS**

ACD	Appraisal Consultation Document
AML	Acute myelogenous leukemia
BSC	Best supportive care
CCR	Conventional care regimen
CMML	Chronic myelomonocytic leukemia
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	Euroqol-5D quality of life instrument
ICER	Incremental cost-effectiveness ratio
IPSS	International Prognostic Scoring System
FAB	French-American-British classification of MDS
FAD	Final appraisal determination
LDC	Low dose chemotherapy
SDC	Standard dose chemotherapy
MDS	Myelodysplastic syndromes
PSA	Probabilistic Sensitivity Analysis
TTO	Time-trade-off
VAS	Visual analogue scale

# 1. INTRODUCTION

## 1.1. BACKGROUND

In March 2010 a Final Appraisal Determination (FAD) was issued on the use of azacitidine for the treatment of myelodysplastic syndromes, chronic myelomonocytic leukaemia and acute myeloid leukaemia. The FAD was appealed against and the Appeal Panel upheld the appeal points made by four appellants under Ground 2. All of these points related to the fact that the Appraisal Committee considered best supportive care alone to be the most appropriate comparator for economic modelling. The comparator arm of the pivotal trial (Study AZA-001) included three conventional care regimens (CCRs) best supportive care alone, low-dose chemotherapy (plus best supportive care), and standard-dose chemotherapy (plus best supportive care). The Appeal Panel requested that the Appraisal Committee reconsider the guidance issued, taking account of both best supportive care and low-dose chemotherapy as comparators. In order to inform the Committee's re-consideration of these issues, NICE requested that Celgene submit further information on;

- current clinical practice to explore the proportions of people receiving low-dose chemotherapy (plus best supportive care) and those receiving best supportive care alone
- the clinical characteristics of people receiving low-dose chemotherapy (plus best supportive care) in routine clinical practice

The Appeal Panel also requested that the Appraisal Committee examine additional data on quality of life which was offered by the MDS Foundation in their response to the ACD. The Committee had not previously considered this data as it was offered after the ACD was issued and it was considered that it was unlikely to change the Committee's decision. In order to inform the Committee's re-consideration of their recommendations, NICE requested that the MDS Foundation submit their additional data on quality of life and health utility values in MDS. NICE also requested that Celgene conduct an additional cost-effectiveness analysis incorporating the health utility data made available by the MDS Foundation to estimate the ICERs for the whole entire population and for the groups eligible to receive low-dose chemotherapy (plus best supportive care), and best supportive care alone.

During the Appeal hearing the design of the pivotal trial (Study AZA-001) and in particular the manner in which patient preference had been involved in determining treatment allocation

was raised and it was discussed that trials involving patient preference may need to be considered differently from other trials. NICE therefore requested that Celgene submit information on the interpretation of patient preference trials to inform the Committee's deliberations.

### ***Aims and objectives of the DSU review***

This DSU report provides a critical appraisal of the evidence submitted by Celgene and the MDS Foundation in response to NICE's requests following the appeal decision. These recent submissions are referred to as the post-appeal submissions, whereas references made to the manufacturer submission refer to the original submission made by Celgene. The report addresses three questions;

1. Do the quality of life data from the MDS Foundation remove uncertainty around the utility estimates and to what extent have the utility data provided by the MDS Foundation been appropriately incorporated into the Celgene model? (addressed in sections 2 and 3)
2. Do the data submitted by Celgene regarding current practice patterns and characteristics of patients receiving each of the comparative care regimens give a comprehensive view of UK clinical practice and allow a clear definition of subgroups? (addressed in section 4)
3. Is there anything that the Committee has to consider differently from other trials results when it makes its judgement on the clinical effectiveness of azacitidine due to the incorporation of patient / physician preference within the study design of AZA-001? (addressed in section 5)

## **2. QUALITY OF LIFE DATA FROM THE MDS FOUNDATION**

In the pivotal trial of azacitidine (Study AZA-001), no utility data were collected. Therefore, in the manufacturer submission alternative methods were used to estimate the incremental QALYs associated with azacitidine therapy. In a different study (CALGB 9221), patients were treated with either azacitidine or BSC. This was a study of patients with myelodysplastic syndromes but was not included in the clinical effectiveness review because the patient population was of a lower IPSS risk category than the population specified in the marketing authorisation for azacitidine. In this study the EORTC quality of life instrument was administered to patients at baseline, and days 50, 106 and 182. It is possible to estimate the EQ5D utility value from these EORTC scores using a published regression model (McKenzie 2009). This published regression model was based on a separate dataset of patients with oesophageal cancer that filled in both the EORTC instrument and the EQ5D.

Three issues of relevance to the utility estimates were noted in the FAD: that i) fatigue and ii) independence from blood transfusions, were not fully reflected in the estimation of benefits and that iii) oesophageal cancer is a very different condition to myelodysplastic syndrome. These issues were again raised at appeal. None of the Appeal points raised in relation to the utility data were upheld. However, the Appeal Panel “requests the Appraisal Committee to examine the data on quality of life, and consider the utilities available to it from MDS UK”.

Several additional pieces of information, of relevance to the estimation of health state utilities have been submitted since that time by the MDS Foundation, namely a published paper estimating utility values from MDS patients (Szende 2009) and two other papers providing general quality of life information for this patient group (Steensma 2008, Heptinstall 2008). The paper by Heptinstall uses data obtained from the MDS Foundation’s internet forum and copies of the questionnaires provided to patients who took part in these forums were also submitted. These additional sources of information were critically reviewed by the DSU to establish whether they addressed the issues noted in the FAD/appeal. Whilst the papers by Steensma et al and Heptinstall identify factors which influence quality of life in MDS patients, the results do not provide information that could be used in the economic model or that would provide insight into whether the current base case analysis undervalues the health benefit of azacitidine. These papers were therefore not considered further by the DSU and this section of the report focuses on the utility values from Szende et al study. The potential

impact of these additional utility estimates on the ICER estimates has also been assessed (see section 3).

### **2.1. SZENDE ET AL.**

This paper reports the results of a valuation exercise in which myelodysplastic patients are asked to value different, hypothetical health states described using vignettes by Time Trade Off (TTO) and Visual Analogue Scales (VAS). Authors include those whose affiliations are given as the MDS foundation and Celgene Corporation. Patients are drawn from the US, France, Germany and the UK. Vignettes were reported as being developed from existing literature and reports from MDS patient discussion forums. The health state labeled as “living in transfusion independence” had a mean TTO valuation of 0.84 (sd 0.16) and the state labeled “Living with transfusion dependency” a mean valuation of 0.6 (sd 0.28). Celgene have included the results from this study as a sensitivity analysis in their post-appeal submission. The method and results of this analysis are discussed in section 3.

There are several issues associated with the Szende study that require comment:

1. Whilst the study claims to be an investigation of the value of transfusion-free living, the description of the health states are not restricted to transfusion. The vignettes cover a range of health domains. These cover symptoms (e.g. fatigue, mental health, discomfort), activities (e.g. the degree of interference with family and social life) as well as the amount of time spent at a health care provider. The valuations are therefore of descriptions reflecting the typical patient that is transfusion dependent/independent rather than transfusion dependency *per se*.
2. The sample size is small (n=47), of whom only 21 were from the UK. Celgene have submitted two cost-effectiveness sensitivity analyses, one using the UK specific data and the other using data from the whole study. Reporting in the paper does not provide details of how many patients provided valuations on which the mean results are based. It is stated that 4 patients did not understand the TTO.
3. Whilst this is a study of patients with MDS, the valuation is not of their own health. They are of hypothetical states described as vignettes. It is therefore questionable whether this facet of the study offers any real advantage over the previous approach



which relied on estimating the relationship between EQ5D and EORTC based on the responses of patients with a different type of cancer.

4. Standard TTO exercises including those used to generate the EQ5D UK tariff, are based on a ten year life expectancy. This study used a five year period in order that the exercise was more relevant to the patients. This is appropriate to the setting but may yield differing valuations to the standard 10 year period.

## **2.2. COMPARISON OF SZENDE ET AL. WITH CELGENE BASE-CASE.**

In the base-case economic model, it is the case that transfusion independence is not a benefit that is valued directly. However, the EORTC quality of life instrument does capture directly several of the elements of transfusion independence that are relevant and also feature in the vignettes in the Szende et al study. In particular, the EORTC includes items that ask the extent to which treatment has interfered with family life and social activities. The EORTC instrument also captures elements of transfusion independence indirectly by valuing symptoms and restrictions on activities that are associated with it. Again, there is substantial overlap with the dimensions included in the vignettes for the valuation study.

The Szende et al. study does offer the potential advantage that the study population comprises patients with myelodysplastic syndromes. This is only a potential advantage to the base case approach however. This is because the patients are not asked to value their own health states but hypothetical states that they are unlikely to have experienced. Direct valuation of health states is also not consistent with the standard approach to valuations used by NICE where valuations are derived from the general public.

Whilst the base case analysis draws, in part on a study of patients with oesophageal cancer, this is not used to demonstrate a treatment effect. This is used to estimate the relationship between the symptoms described on the EORTC quality of life instrument and the EQ5D.

Furthermore, the design of the base case analysis does come from a study of patients taking azactidine versus those that are not in patients in the appropriate disease area, albeit that they are at a lower level of severity. Thus, the adverse events that are associated with the treatment are captured to some extent in a way that the data supplied by MDS do not.

We therefore agree with Celgene that the Szende et al study does not provide information that is more appropriate for use in the base-case cost –effectiveness analysis.

Despite this conclusion, it is also necessary to consider whether the data provided by MDS provide evidence that the base case analysis underestimates the health benefits of azacitidine. We do not agree that the new data demonstrate the value of transfusion independence. The Szende et al study demonstrates that patients attach lower value to the vignettes that have been labeled as depicting patients typically found to be transfusion dependent. This is not equivalent to valuing transfusion independence. The approach does not isolate transfusion dependence/independence from associated symptoms and therefore, it is not possible to conclude which of these components contribute to the difference in the observed valuations. Since many of the components, particularly the symptomatic elements are included in the EORTC and EQ5D instruments, it is not possible to establish whether the base case approach values all or only some of the relevant issues.

### **2.3. SUMMARY**

The approach taken in the Celgene base-case is an appropriate, practical approach to estimating QALYs in the absence of any direct evidence. There is no evidence to support the claim that this approach underestimates the health benefits of azacitidine, despite the fact that neither fatigue nor transfusion dependence feature directly in the EQ5D instrument. The new data submitted by the MDS Foundation do not alter this conclusion.

### **3. COST-EFFECTIVENESS RESULTS USING QUALITY OF LIFE DATA FROM THE MDS FOUNDATION**

Celgene have included in their post-appeal submission a revised economic analysis in which health utility for patients in the MDS health state is determined solely by whether or not the patient has achieved independence from red blood cell transfusions. The utility values applied in the model have been updated but all other aspects of the model have remained unchanged and incorporate the “NICE preferred base-case assumptions” which are described in the Celgene post-appeal submission as “Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine”.

#### **3.1. METHOD USED TO MODEL UTILITY BASED ON TRANSFUSION STATUS**

In the revised analysis, the utility applied in each arm is calculated based on the proportion who are transfusion independent and transfusion dependent for that arm, from the AZA-001 study, and the time trade-off utilities, from the Szende et al study, for these two health states. The model does not incorporate data on a third health state, “reduced transfusion burden”, which is also available from the Szende et al study. This is probably because of the way transfusion status was defined and reported in the AZA-001 study as described below. A constant utility is applied to patients within the MDS health state for the whole model timeframe. The same utility value is applied for the MDS health state for all comparator treatments (BSC, LDC, SDC) as it is based on the proportion achieving transfusion independence across the whole comparator arm which includes all three comparator treatments. The model is set up to use either the full results from Szende et al or the UK specific values from this study. The values used are summarised in Tables 1 and 2. As described in section 2, the reporting in the paper by Szende et al does not provide details of how many patients provided valuations on which the mean results are based so it is not possible to calculate exact standard errors for these estimates.

**Table 1 Transfusion-based utility scores reported by Szende et al (Table 1.6 of Celgene's post-appeal submission)**

<i>Health state</i>	<i>Mean utility score (standard deviation)</i>	
	<i>UK patients</i>	<i>All patients</i>
MDS transfusion independent	0.85 (0.15)	0.84 (0.16)
MDS transfusion dependent	0.65 (0.29)	0.60 (0.28)

**Table 2 Utility scores for treatment arms in the model (Table 1.7 of Celgene's post-appeal submission with headings corrected)**

<i>Health state</i>	<i>Proportion of patients who are transfusion independent</i>	<i>Weighted MDS utility score</i>	
		<i>UK patients</i>	<i>All patients</i>
Comparators (BSC, LDC, SDC)	27.9%	0.71	0.67
Azacitidine	60.3%	0.77	0.74

The source of the data used to estimate the proportion that are transfusion independent is not described in detail within the Celgene post-appeal submission. However, the data on the proportion achieving transfusion independence, presented in Table 1.7 of the Celgene post-appeal submission, agrees with data presented in Table 11-17 of the Clinical Study Report (Celgene 2007) for the AZA-001 trial which describes red blood cell transfusion status whilst the patient is on-treatment. Here, on-treatment was defined as the time between randomisation and the date of last treatment study visit, and a patient was considered to be transfusion independent if the patient had no transfusions during any 56 consecutive days or more during this period.

The application of constant utility values to the whole model timeframe effectively assumes that all patients in the MDS health state remain either transfusion dependent or transfusion independent throughout their treatment period and beyond until they either die or progress to AML. Given that the trial outcome used to define transfusion status only required 56 consecutive days without transfusion, it does not seem reasonable to extrapolate this outcome until death or progression to AML. Neither does it seem reasonable to apply the trial outcome from the start of treatment as the quality of life gains of being transfusion independent are unlikely to be achieved from the first day of treatment.

### **3.2. OTHER ISSUES IDENTIFIED**

In the original model, the utility of the AML health state was set equal to the baseline utility in the azacitidine arm (0.67) which was the same as the baseline utility in the BSC and LDC

arms. However, in the revised model, the utility for the AML state is still set equal to the starting utility in the azacitidine arm, which incorporates the treatment effect of azacitidine on transfusion independence and results in a higher utility being applied for AML (e.g 0.77 when using the UK specific data) than for the transfusion dependent MDS state. It appears counterintuitive that the utility of AML should be higher in this analysis than in the previous analysis and that it should be higher than for some MDS health states. The revision of this value is not discussed in the post-appeal submission. An analysis using the estimate applied previously has been undertaken by the DSU as this was felt to be more reasonable than the approach taken in the revised analysis.

The ICERs presented in the Celgene's post-appeal submission are based on the deterministic base-case analysis. No PSA analysis is provided for the scenario using the revised utility values and the model does not appear to be set up to provide a PSA analysis as some of the utility values used in the PSA are not updated to reflect the revised utility estimates. The DSU have amended the model to provide a PSA analysis. In this analysis, beta distributions were used to describe uncertainty in the proportion of patients achieving transfusion independence. Beta distributions were also fitted to the utility estimates from Szende et al, but in order to estimate the standard errors around the mean, we had to assume that all 47 patients recruited in the study were included in the analysis when estimating the mean utility for the whole study population and that all of the 21 UK patients were included when estimating the UK specific utility results.

In addition to presenting results for patients pre-selected to receive BSC and patients pre-selected to receive LDC, the manufacturer has also presented a "blended comparison" which estimates the cost-effectiveness across the whole indicated population. This analysis assumes that the distribution of conventional care regimens (BSC, LDC and SDC) used in the trial is replicated within the whole indicated population. Issues regarding the use of "blended comparisons" have been addressed by the DSU in a previous appraisal (NICE 2010). The DSU considers that the appropriate approach to economic analysis, as reflected in the NICE 'Guide to the methods of technology appraisal' and general economic literature, would be to consider all treatment options in a single incremental analysis comparing each successive alternative from the least effective to most effective and excluding any dominated (more costly and less effective) treatments. Where it is possible to specify subgroups with identifiable characteristics for which the comparator interventions differ, it would be

appropriate to conduct an incremental analysis within each subgroup, rather than using a blended approach to estimate cost-effectiveness across a heterogeneous population.

In addition to these concerns, the exact method used to calculate the “blended comparison” is not described in detail within Celgene’s post-appeal submission. It is stated that “the weightings applied were consistent with the patient allocation observed in the AZA-001 trial, specifically 62% for BSC, 26% for LDC and 12% for SDC”. However, when attempting to replicate these figures, the DSU found that the mean costs and QALYs cited in Table 1.1 of their submission could only be replicated by applying the weightings from each trial arm individually. This gave weightings of 65%, 25%, and 9% for the azacitidine arm and 59%, 27% and 14% for the CCR arm for BSC, LDC and SDC respectively. This clearly introduces a source of bias into the comparison as the proportion receiving SDC is higher in the CCR arm and, as is stated in the manufacturer submission, patients selected to receive standard-dose chemotherapy were younger and had better ECOG performance status and higher-risk disease. (Celgene 2009)

### **3.3. RESULTS**

Table 3 shows the model results for the deterministic base-case presented by Celgene in their post-appeal submission which uses the original utility data, and the “NICE preferred base-case assumptions” which are described as “Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine”. As the mean incremental costs and QALYs from the PSA were not presented by the manufacturer, the DSU ran the PSA using the submitted model and these results are shown within square brackets within Table 3.

**Table 3 Deterministic base-case results\* using original utility estimates [probabilistic estimates shown in brackets]**

<i>Treatment option</i>	<i>Costs incurred, £</i>	<i>QALYs gained</i>	<i>Incremental costs, £</i>	<i>Incremental QALYs</i>	<i>ICER, £</i>
<b><i>Pre-selected for BSC</i></b>					
Azacitidine	91,753	2.04	63,756 [61,663]	1.01	63,177 [61,022]
BSC	27,998	1.03		[1.01]	
<b><i>Pre-selected for LDC</i></b>					
Azacitidine	101,355	2.44	65,671 [62,499]	1.34	49,030 [47,841]
LDC	35,684	1.10		[1.31]	
<b><i>Pre-selected for SDC</i></b>					
Azacitidine	91,534	1.91	47,475 [43,138]	0.93	51,252 [46,406]
SDC	44,060	0.98		[0.93]	

\* Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine

Table 4 shows the model results when using the UK specific utility data from Szende et al to estimate transfusion based utility values. The figures presented here differ slightly from those presented in the Celgene post-appeal submission as we have corrected the model to use the baseline utility from the trial as the estimate of utility in the AML state as it did previously, although this correction had negligible impact on the ICERs.

**Table 4 Deterministic results using transfusion based utility estimates (UK data from Szende et al) but no other change to base-case assumptions\* [probabilistic estimates shown in brackets]**

<i>Treatment option</i>	<i>Costs incurred, £</i>	<i>QALYs gained</i>	<i>Incremental costs, £</i>	<i>Incremental QALYs</i>	<i>ICER, £</i>
<b><i>Pre-selected for BSC</i></b>					
Azacitidine	91,753	2.02	63,756 [61,581]	0.98	65,023 [62,961]
BSC	27,998	1.04		[0.98]	
<b><i>Pre-selected for LDC</i></b>					
Azacitidine	101,355	2.39	65,671 [62,407]	1.31	49,995 [47,330]
LDC	35,684	1.08		[1.32]	
<b><i>Pre-selected for SDC</i></b>					
Azacitidine	91,534	1.87	47,475 [43,335]	0.91	51,997 [45,381]
SDC	44,060	0.96		[0.95]	

\* Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine

Table 5 shows the model results when using the utility data from the whole study population reported by Szende et al (rather than UK specific data) to estimate transfusion based utility values. Again, the figures presented here differ slightly from those presented in the Celgene post-appeal submission due to our correction to the AML utility value, but this correction had negligible impact on the ICERs.

**Table 5 Deterministic results using transfusion based utility estimates (All patient data from Szende et al) but no other change to base-case assumptions\* [probabilistic estimates shown in brackets]**

<i>Treatment option</i>	<i>Costs incurred, £</i>	<i>QALYs gained</i>	<i>Incremental costs, £</i>	<i>Incremental QALYs</i>	<i>ICER, £</i>
<b><i>Pre-selected for BSC</i></b>					
Azacitidine	91,753	1.96	63,756 [61,557]	0.96 [0.96]	66,190 [63,830]
BSC	27,998	1.00			
<b><i>Pre-selected for LDC</i></b>					
Azacitidine	101,355	2.32	65,671 [62,465]	1.29 [1.29]	51,066 [48,348]
LDC	35,684	1.04			
<b><i>Pre-selected for SDC</i></b>					
Azacitidine	91,534	1.82	47,475 [43,047]	0.89 [0.87]	53,168 [49,290]
SDC	44,060	0.93			

\* Weibull curve fit to survival data, no vial sharing and a patient access scheme discount of 7% to the acquisition cost of azacitidine

### 3.4. SUMMARY

As discussed in section 2, the Szende study does not provide information that is more appropriate for use in the base-case cost-effectiveness analysis than the approach previously taken in the Celgene base-case. Having said that, none of the analyses using the revised utility estimates from the Szende study resulted in significant change to the cost-effectiveness estimates. Some concern is expressed regarding the possibility that the utility gain in the analysis using the revised utility values may overestimate benefit as it assumes that transfusion independence achieved for a minimum of 56 days during the trial is achieved on the first day of treatment and maintained either until AML progression or death. The blended comparison does not appear to have been estimated in the manner described in Celgene's post-appeal submission and appears to be potentially biased. The blended comparison is also not considered by the DSU to be an appropriate approach to economic analysis in this context.



## **4. CURRENT UK PRACTICE PATTERNS AND CHARACTERISTICS OF PATIENTS RECEIVING THE COMPARATIVE CARE REGIMENS**

The aim of section 1 of Celgene's post-appeal submission was to provide more comprehensive data on the proportions of people receiving LDC (plus BSC) and those receiving BSC alone, and to define the clinical characteristics of those who receive LDC plus BSC in routine clinical practice in the UK. The purpose of this section is to critically review the data submitted on UK clinical practice and explore the definition of eligible sub-groups. The manufacturer submitted data from four sources to address these questions:

- a literature review;
- a survey of a sample of "UK haematologists" conducted by the manufacturer;
- the manufacturer's own survey of a sample of hospitals;
- data from the Haematological Malignancies Research Network Registry.

### **4.1. LITERATURE REVIEW**

#### *4.1.1. Assessment summary*

The purpose of this review was to identify patient clinical characteristics found in studies of MDS patients that are associated with better outcomes. Eleven studies (references 37-47 in Celgene 2010) were identified indicating seven or more characteristics that may determine a patient's eligibility for LDC. Only two of these studies were conducted in the UK (Burnett 2007, Mufti 1983) and only one has been published since 1991 (Burnett, 2007). This was an "informal review" (Celgene 2010, p.8) rather than a systematic review. It is not clear whether the studies identified represent all relevant studies, or exactly how the final list of clinical characteristics were derived (eg. whether a characteristic associated with "better outcomes" in one study, but not in another, was included). The final list reported in the results (Celgene 2010, p.12) appears to exclude toxicity and administration, which were identified from the literature (Celgene 2010, p.11), and includes ECOG Performance status and the Haematopoietic Cell Transplantation-specific Comorbidity Index (HCTCI), which "is not currently in routine clinical use in the UK" (Celgene 2010, p.12), but which is then listed as one of the characteristics "most widely used in the UK in MDS patients" to assess suitability

for LDC. It is stated that other clinical characteristics were also identified through the assistance of a single clinical expert (p.12), but there are no additional characteristics listed in Q2 (p.58) of the survey, only full details of relevant co-morbidities and criteria relating to a prognostic scoring system (IPSS), which is being used also as a measure of eligibility for LDC treatment.

#### *4.1.2. Conclusion*

The literature review offers very limited evidence either on current clinical practice in the UK in terms of the clinical characteristics of patients receiving LDC or eligibility criteria for receiving the comparative care regimens.

## **4.2. HAEMATOLOGIST SURVEY**

### *4.2.1. Assessment summary*

A survey of 72 “UK haematologists” was conducted to identify estimated proportions of patients receiving the various comparative regimens, the clinical characteristics of the patients receiving these regimens, and the role of patient preference in treatment choice. The survey does not provide data on the relative proportions of eligible patients receiving the comparative care regimens, but rather presents clinicians’ estimates of patients receiving each regimen, eg. only approximately one third of the responding haematologists reported that they gave LDC plus best supportive care to four or more patients in any year from 2008-2010; and only 7% (5 respondents) estimated they had given this regimen to 10 or more patients. Almost two thirds of the respondents estimated to have given best supportive care alone to six or more patients over the same period. A completed critical review checklist for the survey is provided in Table A1 (Boynton 2004), but a summary of the key points affecting the reliability and validity of the survey and its findings is presented below.

- The survey appears to apply only to azacitidine-eligible patients but this criterion is not specified.
- The survey instrument was not piloted (only content was assessed by a single relevant clinician); nor was the survey validated or tested for reliability.

- There are insufficient details to enable an assessment of the design, distribution or administration of the survey.
- There is no information on the ethical approval that is a probable requirement for a survey of NHS staff (Dept. Of Health 2005)
- The sampling of survey respondents was opportunistic and self-selecting (voluntary), with a high risk of selection bias. No characteristics of the respondents were reported (other than that 5/72 were designated as “specialists” [criteria not reported]; the submission admits to the lack of details concerning the respondents p.21). The number of institutions represented by this sample is not reported. Criteria for inclusion in or exclusion from the survey were not reported. It is therefore unclear how representative the sample is of UK haematologists who treat MDS. The submission also admits that some respondents may be reporting data on the same patients (p.20). It is not possible to generalise to UK clinical practice based on this sampling method (Boynton 2004).
- A self-report survey was not an appropriate tool for collecting data on any of these questions (Q1-Q7 in the survey), and especially not on prevalence and patient numbers, due to problems such as response bias (Adams 1999). A prospective cohort study would be a much more appropriate method. It is also not clear whether the data provided are the result of clinicians’ retrospective case note review or simple self-report only; the latter especially would generate data with a high risk of bias and uncertainty. Even the responses to Q2 (criteria that may affect treatment recommendation) may be unreliable, as previous research has demonstrated clinician self-report and actual practice can differ substantially (Adams 1999).
- There are inconsistencies within the survey which may further affect the validity of the instrument (i.e. is it measuring what it claims to measure?): IPSS Int-1 is listed as an exclusion criterion (i.e. respondents are only to consider patients with IPSS Int-2 and High Risk in their responses) but it is included in Q2 as a criterion for suitability for LDC treatment. This question may therefore not be measuring responses relating exclusively to the intended population (azacitidine-eligible patients).
- Q2 should have an open field for any relevant clinical characteristics not identified by the literature review: one aim of the survey was to identify all characteristics of eligible patients who may receive LDC in the UK in order to identify specific sub-groups of eligible patients; the existing instrument limits this to a pre-determined set of characteristics only.

- The survey is aiming to measure how far patient preference affects treatment options (Q6 and Q7). However, it is not appropriate to ask clinicians to recall an estimate of the proportion of patients over an undefined period who have opted for a course of treatment which is different from the recommended treatment based on “clinical suitability”. Only a prospective cohort study of patients could generate valid and reliable data on this.
- Q7 also poses a question that is not logical, i.e. respondents are asked to estimate the percentage of occasions when patients who are not suitable for LDC plus BSC request that they should not receive LDC. The submission states that the respondents report that 35% of patients not deemed suitable prefer still to have LDC, and that 30% deemed suitable prefer not to have LDC (p.19); however, the survey data also indicate that 32% deemed unsuitable prefer not to have LDC (p.79), i.e. that haematologists would allow about 32% of patients regarded as “clinically inappropriate” for LDC “to forego the treatment after accounting for personal preference”. There is therefore an issue with these questions and the validity of the responses.
- The respondents’ answers to Q3-7 appear to relate to an indefinite period.
- It is unclear what proportion of the population respondents are commenting on in Q1, Q3-7 are MDS IPSS Int-2 and High Risk, CMML or AML.

#### *4.2.2. Conclusion*

There is a high risk of bias in this survey: it has not been validated and its reliability has not been evaluated; there are issues with the validity of some items; and the sampling of respondents and the external validity of the data are both highly questionable. Consequently this survey cannot provide valid or reliable data on: 1) the proportions of UK MDS azacitidine-eligible patients receiving BSC alone or LDC plus BSC; 2) the clinical characteristics of UK MDS patients who receive LDC in current clinical practice; 3) the extent to which patient preference may affect the treatment choices of UK MDS patients. The data provided are estimates based on the self-report and retrospective recall of a sample of clinicians, the details of which is unknown.

### **4.3 CELGENE HOSPITAL SURVEY**

#### *4.3.1 Assessment summary*

This ongoing survey reports interim data from 23 hospitals, including 8 “specialist MDS centres” on proportions of MDS patients (not just azacitidine-eligible patients) receiving the comparative care regimens. However, exact proportions are not reported; only an inexact graph is provided. Furthermore, insufficient information is provided on the Celgene survey to assess the reliability and validity of the survey and its data. The following are unclear: the representativeness of this sample of hospitals; the time period to which the data relate; the methods of data collection.

#### *4.3.2 Conclusion*

This survey offers data of limited value (the data relate to a broader population than the population of interest) concerning the estimated numbers and proportions of UK MDS patients receiving the various relevant regimens. It provides no data on the clinical characteristics of patients who are eligible for LDC or the influence of patient preference in treatment choices.

### **4.4 YORK REGISTRY DATA**

#### *4.4.1 Assessment summary*

This survey reports data from the Haematological Malignancies Research Network registry maintained by the University of York on 22 hospitals within the Yorkshire and Humber region on proportions of MDS, CMML and AML patients (though not just azacitidine-eligible patients) receiving the comparative care regimens over a period of 5 years from 2004-2009. However, insufficient information is provided on the collection of the York Registry data to assess the reliability and validity of these data. The methods of data collection (i.e. routine, objective data collection) are unclear. Nevertheless, these data do indicate the following: 29% (n=28) CMML; 18% (n=120) AML; and 11% (n=11) of IPSS Int-2 and 15% (n=4) of IPSS High Risk MDS patients (who are azacitidine-eligible), in this geographical area receive LDC plus best supportive care. Respective, comparable percentages of patients receiving best supportive care alone, for each of these conditions are: 30% (CMML); 20% (AML); and 53% and 48% (IPSS Int-2 and High Risk).

#### *4.4.2 Conclusion*

The York Registry provides the relatively most objective and reliable data on numbers of patients receiving the various treatment regimens, but, as the submission states, these cover all MDS patients, as well as not covering all azacitidine-eligible patients (which include CMML and AML). It provides no data on the clinical characteristics of patients who are eligible for LDC or the influence of patient preference in treatment choices.

#### **4.5 OVERALL SUMMARY**

The submission interrogated four different sources to answer the questions on current practice patterns for, and characteristics of UK azacitidine-eligible MDS patients who receive the various comparative care regimens. A haematologist survey, a hospital survey and Registry data were used to provide an estimate of the number and proportion of UK azacitidine-eligible MDS patients receiving the comparative care regimens. However, only the York Registry offered relatively reliable data on this, albeit with limitations. The data indicate that as many as 15% of MDS patients, 18% of AML patients and 29% of CMML patients (both generally, not azacitidine-eligible patients alone) may receive LDC plus best supportive care, though the exact eligibility criteria for receiving LDC in this sample is unknown. Despite being AML and CMML patients generally, rather than those who are azacitidine-eligible, these figures are similar to, or lower than the proportion who received LDC in the AZA-001 trial, which was 26%. This figure is higher than the most comparable data provided by the York Registry, although the population in the trial is different. A literature review and haematologist survey were used to identify the clinical characteristics of those UK MDS patients eligible for LDC, but despite some apparent consistency in the eligibility of some variables (eg. symptomatic cytopenias) both approaches were limited in their conduct and external validity. These sources therefore only provide a limited evidence-based indication of possible eligibility criteria for LDC, especially as some of the data indicate variation in practice. The haematologist survey was also used to estimate the effect of patient preference on the choice of LDC as a treatment, but this approach was neither valid nor appropriate for answering this question. The data presented therefore provide neither a comprehensive view of UK clinical practice nor permit a robust, evidence-based definition of MDS sub-groups eligible for LDC treatment.

## **5. ISSUES ARISING FROM THE INCORPORATION OF PATIENT / PHYSICIAN PREFERENCE IN THE TRIAL DESIGN OF AZA-001**

In the AZA-001 trial, azacitidine was compared with conventional care regimens (CCRs) using a fully randomised comparison. There were three treatments available within the CCR arm of the trial. These were best supportive care (BSC) alone, low dose chemotherapy with best supportive care (LDC) and standard dose chemotherapy with best supportive care (SDC). Before randomisation, investigators determined which one of these three treatment options was most appropriate for each patient. The choice of CCR preselected for each patient was recorded for all patients prior to randomisation. Patients were then randomly assigned one-to-one to receive azacitidine or their pre-selected CCR. Those assigned to receive one of the CCR options were not to be transferred to another treatment option within conventional care and were not to be transferred to the azacitidine treatment arm at any time during study.

The study used blocked stratified randomization to ensure a balanced assignment of patients to the azacitidine and CCR trial arms, but patients were stratified based on classification of MDS (FAB) and prognosis (IPSS) and not on their preselected CCR. It should therefore be noted that the usual concerns regarding the validity of subgroup analyses would apply to any subgroup analysis of treatment outcomes by pre-selected CCR.

The method used by the investigator to determine the preselected CCR is described in the main study publication “as clinical judgment on the basis of age, ECOG performance status, and comorbidities”. (Fenaux 2009) In the manufacturer’s original submission the basis for selection is described as “age, general condition, co-morbidities and patient preference”. Whilst this gives us an idea of which factors the investigators took into account when selecting the most appropriate CCR, it does not allow us to identify a consistent set of characteristics that differentiate exactly between those patients who were preselected to receive BSC and those who were preselected to received LDC or SDC. It is therefore difficult to identify those patients in clinical practice who are likely to have similar characteristics and similar outcomes to those within each of the pre-selected CCR subgroups.

The term “patient preference trial” has been used to describe trial designs which try to take account of any potential interaction between the effectiveness of the treatment being studied and the patient’s preference to receive either the study treatment or the comparator. In Celgene’s submission they have provided a literature review describing the main concerns facing patient preference trials but they also state that these trials have limited relevance to the AZA-001 trial, as they all involve patients in the actual assignment to control or active treatment which was not the case in the AZA-001 trial. The DSU would agree with this position and have therefore not examined in detail the literature review provided by Celgene.

In summary, whilst some account may have been taken of patient preference in the AZA-001 trial to determine the pre-selected CCR, it was not used to inform allocation between the azacitidine and CCR. However, the pre-selected CCR was used to define pre-specified subgroups and analyses were conducted comparing azacitidine to CCR by pre-specified CCR subgroup. The usual concerns regarding the validity of subgroup analyses would apply to any analysis of treatment outcome by pre-selected CCR. Finally, due to the use of clinical judgment and patient preference to determine allocation to the pre-selected CCR, it is not possible to identify a consistent set of characteristics that differentiate exactly between those patients who were preselected to receive BSC and those who were preselected to receive LDC or SDC.



## 6. CONCLUSIONS

The DSU considers that the utility values from the Szende study, submitted by the MDS Foundation, are not more appropriate for use in the base-case cost-effectiveness analysis than the approach previously taken in the Celgene base-case. There is no evidence to support the claim that the approach previously used underestimates the health benefits of azacitidine, despite the fact that neither fatigue nor transfusion dependence feature directly in the EQ5D instrument. The new data submitted by the MDS Foundation do not alter this conclusion. In addition, the incorporation of the new utility data does not substantially alter the cost-effectiveness estimates.

The fact that the AZA-001 trial used a combination of clinical judgment and patient preference to determine allocation to one of the three conventional care regimens makes it impossible to identify a consistent set of characteristics that differentiate exactly between those patients who were preselected to receive best supportive care and those who were preselected to receive either low dose chemotherapy or standard dose chemotherapy. It is therefore difficult to identify a pre-specified group of patients from within the UK azacitidine indicated population who can be expected to be similar to those patients receiving either BSC or LDC within the AZA-001 trial. Furthermore, the data recently submitted by Celgene provide neither a comprehensive view of UK clinical practice nor permit a robust, evidence-based definition of MDS sub-groups eligible for low dose chemotherapy treatment.

## 7. REFERENCES

Adams AS, Soumerai SB, Lomas J, Ross-Degnan D. Evidence of self-report bias in assessing adherence to guidelines. *Int J Qual Health Care* 1999;11:187-92.

Boynton P, Greenhalgh T. Selecting, designing, and developing your questionnaire. *BMJ* 2004; 328 (7451): 1312-15.

Burnett AK, Milligan D, Prentice AG et al. A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and highrisk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; 109: 1114–1124.

Celgene Ltd. Data on file: Clinical study report: A Multicenter, Randomized, Open-Label, Parallel-Group, Phase 3 Trial of Subcutaneous Azacitidine Plus Best Supportive Care Versus Conventional Care Regimens Plus Best Supportive Care for the Treatment of Myelodysplastic Syndromes (MDS) (AZA PH GL 2003 CL 001), December 2007.

Celgene Ltd. Single technology appraisal of Vidaza® (azacitidine): Manufacturer / sponsor submission of evidence. March 2009.

Department of Health. *Research governance framework for health and social care: Second edition*. 2005.

Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A *et al*. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10**: 223–232.

Heptinstall. Quality of Life in Myelodysplastic Syndromes. *ONCOLOGY Nurse Edition* 2008; 22 (8).

[http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH\\_4108962](http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4108962) (accessed 20/09/2010)

McKenzie L, van der Pol M. Mapping the EORTC QLQ C-30 onto the EQ-5D Instrument: The Potential to Estimate QALYs without Generic Preference Data. *Value Health* 2009; 12: (1): 167-171.

Mufti GJ, Oscier DG, Hamblin TJ, Bell AJ. Low doses of cytarabine in the treatment of myelodysplastic syndrome and acute myeloid leukemia. *N Engl J Med* 1983; 309: 1653–1654.

NICE. Lapatinib for the treatment of women with previously treated advanced or metastatic breast cancer: Final appraisal determination. National Institute for Health and Clinical Excellence, May 2010.

Steensma DP, Heptinstall KV, Johnson VM, Novotny PJ, Sloan JA, Camoriano JK, Niblack J, Bennett JM, Mesa RA. Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): Results of a large internet-based survey. *Leukemia Research* 2008; 32 (5): 691-698

Szende A, Schaefer C, Goss TF et al. Valuation of transfusion-free living in MDS: results of health utility interviews with patients. *Health Qual Life Outcomes* 2009; 7: 81

## APPENDIX:

**Table A 1 Critical appraisal checklist for a questionnaire study from: Boynton P, Greenhalgh T. Selecting, designing, and developing your questionnaire. BMJ 2004; 328 (7451): 1312-15.**

Research question and study design	
<p>1. What information did the researchers seek to obtain?</p>	<p>1) Numbers of patients treated with BSC, LDC, SDC, azacitidine and other Treatments: a) Respondents were asked to estimate these numbers in the years 2008, 2009 and 2010</p> <p>2) Which clinical characteristics (of those usually measured in MDS patients) would make them more or less likely to treat with LDC</p> <p>3) The proportion of patients judged to be clinically “appropriate”, “inappropriate” or “borderline” for treatment with LDC</p> <p>4) The proportion of cases in which a patient’s preference would override the above clinical judgments of eligibility for LDC</p> <p>Note: these responses were only to relate to patients satisfying the criteria outlined at the beginning of the survey. These criteria appear to relate to three different patient groups (MDS, CMML, AML), but no “either”, “or” is provided; these groups appear to be treated as one in the survey. These inclusion criteria are also not explained or justified anywhere. They appear, by implication (eg. p.20) to represent azacitidine-eligible patients only, but this is not specified.</p>
<p>2. Was a questionnaire the most appropriate method and if not, what design might have been more appropriate?</p>	<p>No. Self report (retrospective also) is an extremely weak form of data collection. Prospectively collected observational data are required to answer all questions.</p>
<p>3. Were there any existing measures (questionnaires) that the researchers could have used? If so, why was a new one developed and was this justified?</p>	<p>No. Development of new survey tool was justified.</p>
<p>4. Were the views of consumers sought about the design, distribution, and administration of the questionnaire?</p>	<p>Yes and No. Item development was guided by a literature review only but the final list of items was checked by an appropriate clinical expert (and as a result one item was revised). It is not clear whether haematologists were consulted about the distribution or administration of the survey.</p>

<b>Validity and reliability</b>	
5. What claims for validity have been made, and are they justified? (In other words, what evidence is there that the instrument measures what it sets out to measure?)	None. There is no statement relating to the validity of the survey. However, Q2 includes a question about patients with an IPSS score of Int-1, who are actually excluded from the survey, according to the Summary, which states that responses should relate to IPSS Int-2 and High risk only. It is therefore not measuring what it set out to measure. Results for these data are included in the analysis: pp.70, 73.
6. What claims for reliability have been made, and are they justified? (In other words, what evidence is there that the instrument provides stable responses over time and between researchers?)	None. There is no statement relating to the reliability of the survey.
<b>Format</b>	
7. Was the title of the questionnaire appropriate and if not, what were its limitations?	Title: "Haematologist survey" only
8. What format did the questionnaire take, and were open and closed questions used appropriately?	Closed questions only
9. Were easy, non-threatening questions placed at the beginning of the measure and sensitive ones near the end?	Not applicable
10. Was the questionnaire kept as brief as the study allowed?	Yes.
11. Did the questions make sense, and could the participants in the sample understand them? Were any questions ambiguous or overly complicated?	Questions appear to make sense. No question appears overly ambiguous.
<b>Instructions</b>	
12. Did the questionnaire contain adequate instructions for completion—eg example answers, or an explanation of whether a ticked or written response was required?	Six questions require percentages; one question 25-30 Likert-type responses

13. Were participants told how to return the questionnaire once completed?	Not reported
14. Did the questionnaire contain an explanation of the research, a summary of what would happen to the data, and a thank you message?	Not reported
<b>Piloting</b>	
15. Was the questionnaire adequately piloted in terms of the method and means of administration, on people who were representative of the study population?	Unclear
16. How was the piloting exercise undertaken—what details are given?	One relevant clinician was consulted on the content of the survey only.
17. In what ways was the definitive instrument changed as a result of piloting?	The wording of one item was changed.
<b>Sampling</b>	
18. What was the sampling frame for the definitive study and was it sufficiently large and representative?	Unclear. Invitations were submitted to two sources: the “contacts database of a commercial survey company” and the mailing list of a relevant clinical forum. This appears to be a form of opportunity sampling, i.e. participants are selected from a group who are available at the time of study. This approach is usually used for canvassing the opinions of a known group of participants. However, it cannot generate reliable results that can be generalised to the wider population. This is also the case because inclusion criteria for the survey participants were not specified; there are no data on the proportion of potentially relevant clinicians represented by the sample; there are no data on the proportion of potentially relevant institutions represented by the sample; and no response rate was reported (number of individuals approached / number of individuals responding). There is therefore a high risk of selection bias in the sample. It is also admitted that some of the respondents may be reporting on the same patient (p.20).

<p>19. Was the instrument suitable for all participants and potential participants? In particular, did it take account of the likely range of physical/mental/cognitive abilities, language/literacy, understanding of numbers/scaling, and perceived threat of questions or questioner?</p>	<p>No. May not be applicable.</p>
<p><b>Distribution, administration and response</b></p>	
<p>20. How was the questionnaire distributed?</p>	<p>Not reported. Post/email/face-to-face? Note: There does not appear to be any ethical approval for the survey of NHS staff, which is normally required (DoH 2005)</p>
<p>21. How was the questionnaire administered?</p>	<p>Not reported.</p>
<p>22. Were the response rates reported fully, including details of participants who were unsuitable for the research or refused to take part?</p>	<p>No</p>
<p>23. Have any potential response biases been discussed?</p>	<p>No</p>
<p><b>Coding and analysis</b></p>	
<p>24. What sort of analysis was carried out and was this appropriate? (eg correct statistical tests for quantitative answers, qualitative analysis for open ended questions)</p>	<p>Descriptive statistics and a linear regression analysis. Yes, this approach is appropriate for analysing percentages.</p>
<p>25. What measures were in place to maintain the accuracy of the data, and were these adequate?</p>	<p>Not reported.</p>
<p>26. Is there any evidence of data dredging—that is, analyses that were not hypothesis driven?</p>	<p>Unclear</p>
<p><b>Results</b></p>	
<p>27. What were the results and were all relevant data reported?</p>	<p>There are some anomalies, which affect validity: the survey reports that sample clinicians report that approximately one third of patients who do not fit criteria for BSC/LDC did not receive it because of patient preference. It is unclear why clinicians would report that patients not considered eligible for LDC are specifying that they wish to opt out of LDC.</p>

<p>28. Are quantitative results definitive (significant), and are relevant non-significant results also reported?</p>	<p>Results are not significant</p>
<p>29. Have qualitative results been adequately interpreted (e.g. using an explicit theoretical framework), and have any quotes been properly justified and contextualised?</p>	<p>Not applicable</p>
<p><b>Conclusions and discussion</b></p>	
<p>30. What do the results mean and have the researchers drawn an appropriate link between the data and their conclusions?</p>	<p>The haematologist survey has substantial limitations, so any conclusions based on its data cannot be considered robust.</p>
<p>31. Have the findings been placed within the wider body of knowledge in the field (eg via a comprehensive literature review), and are any recommendations justified?</p>	<p>An informal literature review has been performed, and data from a second survey, and Registry data are also provided.</p>