Evidence Review Group's Report

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

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Contributions of authors
Hyde, Connock and Greenheld wrote the clinical effectiveness sections.

Edlin, Round and Tubeuf analysed the economic model and wrote the cost effectiveness sections. Fry-Smith advised on searches and conducted additional searches.

Abbreviations:

AML	Acute myeloid leukaemia
Aza	Azacitidine
BSC	Best supportive care
CALGB	Cancer and Leukaemia Group B
CCR	Conventional care regimen (either BSC, LDC or SDC in the context of this report)
CMML	Chronic myelomonocytic leukaemia
ERG	Evidence Review Group
FAB	French-American-British (type of classification system for MDS)
HRQoL	Health-related quality of life
IPSS	International Prognostic Scoring System (type of classification system for MDS)
LDC	Low dose chemotherapy
SDC	Standard dose chemotherapy (analogous to intensive chemotherapy in the context of this report)
MDS	Myelodysplastic syndrome
MS	Manufacturer submission
RCT	Randomised controlled trial
WHO	World Health Organisation (type of classification system for MDS)

1 SUMMARY

1.1 Scope of the submission

The MS addresses the scope requested. In essence this was to address the effectiveness and cost-effectiveness of azacitidine relative conventional care regimens, particularly BSC, LDC and SDC, in patients with higher risk MDS, CMML and AML with 20-30% blasts on the outcomes of survival, time to progression to AML, adverse events and HRQoL.

1.2 Summary of submitted clinical effectiveness evidence

The key source of evidence on clinical effectiveness was an open label RCT by Fenaux et al [1], referred to in the MS as the AZA-001 study. It compared aza with CCR in 358 patients with higher risk MDS, CML and AML 20-30% blasts.

The AZA-001 study showed that:

- The median overall survival was 24.5 months on azacitidine, compared with 15.0 months in the CCR group (p=0.0001)
- The response rates were low (complete remission 17% aza vs 8% CCR)
- The median time to transformation to AML was greater in the azacitidine group (17.8 versus 11.5 months; p<0.0001).
- Of patients who were RBC transfusion-dependent at baseline, 45% of those on azacitidine became RBC transfusion-independent during the treatment period, compared with 11.8% in the CCR group (p<0.0001)

1.3 Summary of submitted cost effectiveness evidence

Estimates of cost per QALY gained for azacitidine in comparison with BSC, LDC and SDC are provided.

1.4 Commentary on the robustness of submitted evidence

1.4.1 Strengths

Concerning the evidence on clinical effectiveness the evidence was based on an adequately powered RCT, study AZA-001 reported by Fenaux et al in Lancet Oncology in 2009. The trial was registered and a protocol for the trial was available. The effects on survival, time to progression to AML, independence from transfusion and reduction in infections requiring intravenous antibiotics were clinically important and unlikely to have been explained by chance alone. There was no evidence that these benefits were substantially off-set by adverse events.

1.4.2 Weaknesses

Concerning clinical effectiveness the AZA-001 study was open to bias, particularly from lack of blinding and uncertainty about losses to follow-up. In addition there was no direct evidence on impact on HRQoL. There is no evidence for differences in effects between investigator pre-selected treatment groups.

The overwhelming observation however was the errors in the model which were sufficiently severe and numerous that the credibility of the estimates of cost-effectiveness provided in the MS were completely undermined.

1.4.3 Areas of uncertainty

The credibility of the estimates of cost-effectiveness is the pre-dominant issue.

Even if the model is corrected further areas of uncertainty will remain such as:

- The degree to which the size of effects may have been overestimated because of the observed biases
- The effect of aza on HRQoL in patients with higher risk MDS, CMML and AML with 20-30% blasts
- The appropriateness of separating out BSC, LDC and SDC when there are no unconfounded estimates of effect for each of these comparators

- The appropriateness of many of the parameters used in the original model relating to effectiveness, utilities and costs

1.5 Key issues

Although there are concerns about the clinical effectiveness evidence and the parameters used in the model, the over-riding issue is the fundamental validity of the estimates of cost-effectiveness presented in the MS.

2 BACKGROUND

2.1 Critique of manufacturer's description of underlying health problem

The key points concerning the health problem, as indicated in the final scope are that myelodysplastic syndromes (MDS) are a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life threatening disease, with anaemia and increased risk of bleeding and infections. MDS affects patients' quality of life due to debilitating symptoms such as fatigue and dyspnoea, treatment regimens involving hospitalisation with intravenous drug infusions and blood transfusions, and complications such as severe infections.

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), the presence of chromosome 7 abnormalities, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-I risk, intermediate-II risk or high-risk. It is estimated that higher risk MDS subgroups (intermediate-II and high-risk) form approximately 22% and 7% of the MDS population, respectively. The FAB system divides MDS into five subgroups, including chronic myelomonocytic leukaemia (CMML), which is characterised by high numbers of white blood cells in the blood and bone marrow. The WHO system, which divides MDS into eight subgroups, does not class CMML as a type of MDS, but rather within a new category of myelodysplastic-myeloproliferative overlap syndromes.

MDS are associated with an increased risk of transformation to acute myeloid leukaemia (AML). AML is a progressive form of MDS characterised by rapidly growing cancer of the blood and bone marrow. Around 30% of patients with MDS will progress to AML.

There were 1,993 people newly diagnosed with MDS in England in 2004, with over 90% of patients aged over 60 at the time of diagnosis. Median survival of patients with MDS is around 20 months but can be less than 6 months for high risk subgroups. Establishing the presence of chromosome 7 abnormalities is important as this is associated with rapid progression to AML.

The manufacturer's portrayal of the condition is consistent with these key points. Additionally they have undertaken a survey indicating that just over one third of patients (38%) with MDS have high risk disease (IPSS risk category intermediate-2 or high), slightly higher than the estimates provided in the scope. The ERG has confirmed that long term survival in high risk MDS is unusual.

2.2 Critique of manufacturer's overview of current service provision

The key points indicated in the scope are that the mainstay of treatment for MDS is best supportive care (transfusions, growth factors, antibiotics) to control the symptoms of bone marrow failure, and low-dose standard chemotherapy for some patients. Stem cell transplant is not an option for the majority of patients since the patients' age and/or co morbidities usually precludes this treatment option.

The manufacturer's portrayal of the current treatment options are consistent with this view. The MS often refers to standard dose chemotherapy as compared to low dose chemotherapy. To avoid confusion it needs to be recognised that standard dose chemotherapy is actually intensive, and indeed in the main trial providing evidence on effectiveness [1] is referred to as "intensive chemotherapy". The very limited use of high dose chemotherapy, particularly in patients over 65 years of age needs emphasis.

3 Critique of manufacturer's definition of decision problem

3.1 Indicated scope

Intervention	Azacitidine
Population	Adults who are not eligible for haematopoietic stem cell transplantation with higher-risk (IPSS intermediate-II risk and high-risk) myelodysplastic syndromes, chronic myelomonocytic leukaemia, or acute myeloid leukaemia (<30% blasts)
Comparators	• best supportive care (such as blood transfusions, erythropoietin and granulocyte-colony stimulating factor, with infection prophylaxis) • chemotherapy (such as cytarabine and anthracyclines)– low and high dose
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival (including time to transformation to AML or death) • response rates, including haematologic response and improvement • blood-transfusion independence • infections requiring IV therapy • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	If the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities. Guidance will only be issued in accordance with the marketing authorisation.

3.2 Population

The population of interest in the industry submission is consistent with the scope, both of which in turn coincide with the market authorisation.

3.3 Intervention

The submission is again consistent with the scope. The marketing authorisation indicates the dose and route of azacitidine to be 75mg/m^2 subcutaneously daily for 7 days followed by a rest period of 21 days (28 day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles, continuing for as long as the patient continues to benefit or until disease progression.

3.4 Comparators

The comparators used in the manufacturer submission are consistent with the scope.

3.5 Outcomes

The outcomes used in the manufacturer submission are consistent with the scope.

3.6 Time frame

The time frame adopted is consistent with the scope, with attempts in the economic model to extrapolate to a lifetime time horizon.

3.7 Other relevant factors

The submission considers the main genetic sub-group identified, chromosome 7 abnormalities, especially -7/del(7q)

4 CLINICAL EFFECTIVENESS

4.1 Critique of manufacturer's approach

4.1.1 Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The two main searches for studies on azacitidine and its comparators appear generally comprehensive and included the following databases:

- MEDLINE In-Process
- EMBASE
- The Cochrane Library
- CINAHL
- Citation Indexes (Science & Social Sciences)
- BIOSIS
- British Nursing Index
- CRD databases (DARE, NHS EED, HTA)
- AMED
- PsycINFO.

The searches were conducted up to March 2009.

The searches were examined by an experienced information specialist in the ERG who spotted no major errors, but several minor problems:

- The search strategy for only one database is detailed in full. It appears to be for MEDLINE but this is not stated.
- The search for Azacitidine is constructed on text and index terms capturing the intervention and one of the conditions of interest (Myelodysplastic syndrome). Terms for chronic myelomonocytic leukaemia and acute myeloid leukaemia are not represented therefore one would expect these studies to have been missed.
- The search for the comparator treatments is constructed on text and index terms capturing the interventions, conditions and a study design filter for randomised controlled trials.

- In the search for comparator treatments, while some text word terms have been searched in the title and abstract fields and also mapped to an available subject term, others have been searched in the title field only. Searching text words in all available text fields would have yielded a more comprehensive search.
- Trials registers were not searched therefore some ongoing studies may have been overlooked.
- Searching activity appears to have been limited to bibliographic databases, so as well as on-going studies being under-represented, unpublished studies may have been under-represented too.

A certain amount of re-running of searches was undertaken within the limits of the time available, as indicated in Appendix 1. No additional studies were identified.

A request for further information was made concerning on-going studies and the manufacturer provided further information indicated and summarised in a later section.

4.1.2 Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The inclusion criteria were provided in 6.1.2 and 10.2.6 in the manufacturer submission. They are clearly stated and consistent with the decision problem. An important criterion is that studies with less than 50% of participants in the intermediate-2 and high risk IPSS, CMML (10-29% blasts) and AML (20-30% blasts) are excluded and has an important consequence which is discussed later. There is no information on the number of reviewers who screened and performed the inclusion/exclusion decisions, and no copies of the forms which were used to do this. Use of routine database commands to exclude studies deserves clarification (p19) and the high proportion of hits excluded by this means (1792/2366, 76%) is a concern.

4.1.3 Table of identified studies. What studies were included in the submission and what were excluded?

The included studies are clearly identified. There is only one included study concerning the effectiveness of azacitidine, study AZA-001, the main publication for which is by Fenaux et al [1], and this is appropriately the main focus of the clinical effectiveness section of the manufacturer's submission. There are a further 7 included studies, all RCTs, on alternatives to Aza in the population of interest which are laid out on p47-54 of the MS.

Although the number of excluded studies and general reasons for exclusion are indicated in the QUOROM flow diagram in Fig 6.1 of the MS, there is no detailed list of excluded studies, particularly the 26 excluded at the final stage.

One excluded study which emerges, is CALGB 9221 [2] an earlier RCT of aza versus BSC in which there were many participants with low risk MDS, and it is thus appropriately excluded. However, because it is one of the few sources of data on health-related quality of life (HRQoL), it is repeatedly treated as though it were an included study when discussing the impact of aza in this outcome. This is inappropriate. If the data on effect on survival have been excluded because only a small proportion of the CALGB-9221 RCT are intermediate-2 and high risk MDS patients, the same argument must apply to HRQoL. The considerable efforts invested to map utilities from the HRQoL data in CALGB-9221 (10.5 in MS) relied on in the health economic analysis must also be considerably undermined by this fact, as most of the data employed again emanate from patients with lower risk MDS where the nature and severity of effects of HRQoL are likely to be different from the higher risk patients who are the object of this STA.

A request for further information was made to the manufacturer for the sub-group data relating to higher risk patients in CALGB-9221. They were able to do this for survival, but were unable to disaggregate the data for HRQoL results.

4.1.4 Details of any relevant studies that were not included in the submission?

We identified no additional completed RCTs.

The MS presented a confusing account of on-going studies, concentrating on follow-up publications of existing completed studies like AZA-001. A request for further information elicited a list of 15 on-going studies. Only one of these was a phase III RCT and none appeared relevant to this appraisal based on the detail supplied.

4.1.5 Description and critique of manufacturers approach to validity assessment

There was no structured assessment of validity as encountered in most systematic reviews. This was particularly apparent for the included studies in the comparator section of the review. Most of the key issues concerning threats to validity were touched on in 6.3 of the MS.

Because of the central importance of AZA-001 it was full re-appraised by the ERG as part of this appraisal, taking advantage of responses to requests for clarification from the manufacturer. This detailed appraisal is provided in Appendix 2.

4.1.6 Description and critique of manufacturers outcome selection

The MS reports all outcomes measured in AZA-001. This covers all the outcomes suggested in the final scope for this STA with the exception of HRQoL. Outcomes which are likely to impact on HRQoL, like freedom from transfusion and rates of infection requiring intravenous antibiotics are reported. However it is clear that there is no direct research evidence supporting the claim that “azacitidine results in a marked improvement in patient well-being” in the population of interest in this STA. The manufacturer confirms this fact in their response to a request for clarification concerning the impact of aza on HRQoL (response B3).

4.1.7 Describe and critique the statistical approach used

For azacitidine's effectiveness, meta-analysis is unnecessary because there is only a single included RCT.

For the comparators, although there is no pooling, the approach taken is to consider the arms of the RCTs included in isolation, effectively breaking randomisation. Most of the conclusions based on this part of the review thus need to be treated with caution. Fortunately these conclusions do not contribute substantially to the overall conclusions and do not feed into the economic modelling.

4.1.8 Summary statement

Although the approach to reviewing the evidence on clinical effectiveness falls short of the standards suggested by QUOROM, the evidence in the MS on azacitidine generally appears complete and relevant to the decision problem.

The exception is data on impact of aza on HRQoL. There is an attempt to suggest that data from the excluded trial CALGB-9221 provides such evidence. However the reason for exclusion, <50% of participants in higher risk conditions, invalidates the results on HRQoL as equally as on survival and time to progression to AML.

The evidence on comparators, although complete, does not contribute greatly to decision problem and can be largely disregarded.

4.2 Summary of submitted evidence

4.2.1 Summary of results

The executive summary offers the following synopsis of the evidence on clinical effectiveness, which as indicated is mainly and appropriately derived from the AZA-001 study:

Median overall survival was 24.5 months on azacitidine, compared with 15.0 months in the CCR group (p=0.0001). In a supportive analysis, this survival advantage was observed across all IPSS cytogenetic subgroups, in patients with –7/del(7q) and in elderly patients with AML. The overall survival gain was observed despite relatively low response rates. Analysis suggests that achievement of complete remission is not essential to improve survival. Partial remission and haematological improvement were also associated with survival benefit (see Section 6.4.1).

The reduction in risk of death on azacitidine compared with CCR was 42% (p=0.0002). At two years, the proportion of patients surviving was approximately twice as high in the azacitidine group as in the CCR group (50.8% versus 26.2%; p<0.0001). The median time to transformation to AML was also greater in the azacitidine group (17.8 versus 11.5 months; p<0.0001). In summary, azacitidine significantly lengthens overall survival in patients with higher-risk disease (IPSS categories intermediate-2 and high) (see Section 6.4.1).

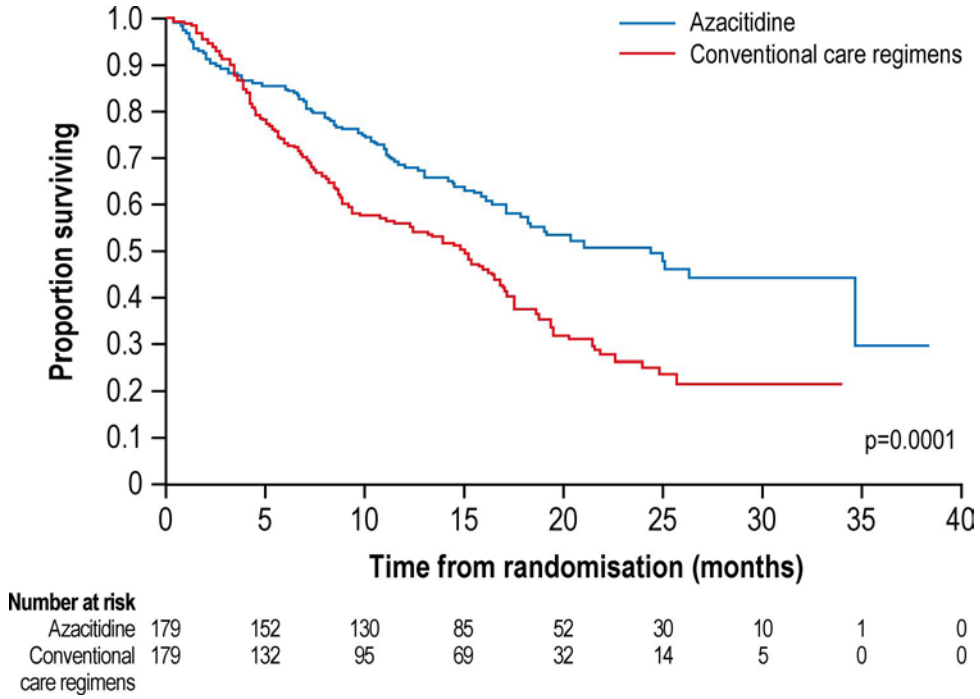
Of patients who were RBC transfusion-dependent at baseline, 45% of those on azacitidine became RBC transfusion-independent during the treatment period, compared with 11.8% in the CCR group (p<0.0001), and the duration of RBC transfusion independence was also longer in the azacitidine group that the CCR group (13.8 versus 8.8 months respectively; p=0.1584) (see Section 6.4.1).

The most frequently observed Grade 3 or 4 AEs were peripheral blood cytopenias for all treatments. The most common treatment-related non-haematological AEs included injection site reactions with azacitidine, and nausea, vomiting, fatigue and diarrhoea with azacitidine, low-dose chemotherapy and standard-dose chemotherapy. Treatment discontinuations before study completion in the azacitidine group compared with the CCR group were mostly related to haematological AEs (see Section 6.4.2).

Although seven, relevant, comparator, Phase III, randomised controlled trials were identified, three of which included a BSC arm, no meta-analysis could be

carried out and none of the therapies reviewed showed a better median overall survival, either for azacitidine or BSC, than those reported in Study AZA-001 (see Sections 6.4.1 and 6.5).

The survival curves for the primary outcome, overall survival are reproduced below. It is important to note where this figure is reproduced in black & white that in the first few months after treatment, the aza curve is below that for the CCR, only crossing over to indicate improved survival for aza after 4 months.



Consideration of the results by the investigator pre-selected groups (BSC, LDC and SDC) is also emphasised and is particularly critical in the context of the economic model. The overall AZA-001 trial result in comparison with those in each of the investigator pre-selected groups are indicated in the table below for overall survival.

Overall survival; whole trial			
Aza (n=179) Median (IQR)	CCR (n=179) Median (IQR)	HR (95% CI)	p-value
24.5 (9·9–NR)	15·0 (5·6–24.1)	0·58 (0·43–0·77)	0·0001

Overall survival; BSC investigator pre-selected group			
Aza (n=117) Median (IQR)	BSC (n=105) Median (IQR)	HR (95% CI)	p-value
21·1 (10·5–NR)	11·5 (5·7–NR)	0·58 (0·40–0·85)	0·0045
Overall survival; LDC investigator pre-selected group			
Aza (n=45) Median (IQR)	LDC (n=49) Median (IQR)	HR (95% CI)	p-value
24·5 (8·4–34·7)	15·3 (4·9–25·8)	0·36 (0·20–0·65)	0·0006
Overall survival; SDC investigator pre-selected group			
Aza (n=17) Median (IQR)	SDC (n=25) Median (IQR)	HR (95% CI)	p-value
25·1 (10·0–NR)	15·7 (8·2–24·1)	0·76 (0·33–1·74)	0·51
Abbreviations: NR not reached; IQR inter-quartile range CCR conventional care regimen; BSC best supportive care; LDC low dose chemotherapy; HDC high dose chemotherapy			

4.2.2 Critique of submitted evidence syntheses

As indicated in the ERG critical appraisal of Fenaux et al, Appendix 2, the evidence for the effectiveness of aza relative to CCR is reasonably robust with three provisos:

- Although the RCT by Fenuax et al is well conducted it remains open to bias from through lack of blinding. There are also concerns about loss to follow-up based on additional information supplied commercially-in-confidence

- The evidence of different effects in different investigator pre-selected groups is unreliable on the following grounds:

    - Some of the groups, particularly SDC are very small (aza=17; SDC (intensive chemotherapy)=25)

    - The baseline characteristics are often markedly imbalanced, again particularly for the SDC group for the characteristics IPSS classification and karyotype risk

- The difference between each of the groups although not formally tested, does not appear on the basis of the 95% CI to be more than could be accounted for by chance alone

- The evidence presented on the impact on HRQoL from the CALGB-9221 is not applicable to the patient group of interest indicated in the decision problem (intermediate-2 and high risk IPSS MDS, CMML (10-29% blasts) and AML (20-30% blasts))

4.2.3 Summary

There is some possibility of bias concerning all estimates of the effect of aza relative to CCR (consisting of BSC, LDC or SDC, depending on circumstances). It would be reasonable to consider the possibility that estimates of effect had been over estimated in sensitivity analyses in the economic model.

In addition great caution should be exercised concerning the interpretation of the evidence presented on impact on HRQoL and difference in effect between different investigator pre-selected groups.

5 ECONOMIC EVALUATION

5.1 Manufacturers review of previous economic evaluation

The MS undertook a separate search for evidence on cost-effectiveness. The following sources were searched on 9th March 2009: MEDLINE (Ovid) 1950 – search date; MEDLINE In Process (Ovid) search date; EMBASE (Ovid) 1980 – search date; Cochrane Library (Wiley InterScience) 2008 Issue 4; CINAHL (Ovid) 1982 – search date; Science Citation Index (ISI Web of Knowledge) 1900 to search date; Social Science Citation Index (ISI Web of Knowledge) 1956 to search date; BIOSIS (ISI Web of Knowledge) 1985 to search date; British Nursing Index (Ovid) 1985 to search date; CRD databases search date; AMED (Ovid) 1985 to search date and PsycINFO (Ovid) 1967 to search date.

Five potential studies were identified, as listed in Table 7.1 in the MS. All were excluded although the criteria used to screen or include/exclude were not given.

The search strategy was appraised by the ERG information specialist. The following issues were noted:

- The search strategy for only one database is detailed in full. It appears to be for MEDLINE but this is not stated.
- The search is constructed on text and index terms for the conditions of interest and 'the database was then searched for any reference with the terms: cost effectiveness; cost – effectiveness; economic and economics'. Since no further details are given it is difficult to assess the quality of the search or the likelihood of references having been missed. Also, the search is impossible to replicate.

This suggests that relevant studies may have been overlooked.

The search strategies indicated in Appendix 1 were run by the ERG, but no additional included economic evaluations were identified.

5.2 Overview of manufacturer's economic evaluation

The manufacturer provided an economic submission in both report (Word) and executable model (Excel) formats. Unfortunately, the flaws found by the ERG in this model were of a sufficient number and severity that the ERG does not believe that any confidence can be placed in the model at present. The model is not fully executable, and to the degree that it does execute, it does so due only to coding errors. When correctable errors are resolved, the model does not execute due to broken links.

For this reason, any results provided in the manufacturer's report will be inaccurate, and accurate results cannot be produced by the corrected excel model without arbitrary assumptions on the part of the ERG. Given this, the judgement of the ERG is that any results presented cannot be independently validated. NICE has requested urgent clarification from the manufacturer in order to allow the ERG to provide results from an executable model to the Committee.

The major clarifications requested by the ERG related to specific coding errors and their resolution. These include those preventing survival data from being used in the model. These took the form of IF statements which ensured that the survival data was not used at critical points, and broken links that prevented it from being used when these first errors were resolved. Other major issues related to the apparent non-discounting of costs and the non-provision of critical information, including the uncertainty attached to the time spent in acute myeloid leukaemia and important covariances between parameters characterising the survival data. In addition to these clarifications, the ERG noted that the model had important functionality removed, particularly as regards the analysis of subgroups.

5.3 Results included in manufacturer's submission

The results of the economic analyses as presented in the MS are summarised in Table 7.17 of the submission (see below).

Table 7.17. Summary of base-case cost-effectiveness results

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£139,364	3.00	£97,829	1.55	**£63,295**
BSC	£41,536	1.46			
Preselected for low-dose chemotherapy					
Azacitidine	£145,452	3.12	£84,812	1.44	**£58,837**
LDC	£60,640	1.68			
Preselected for standard-dose chemotherapy					
Azacitidine	£127,745	2.57	£61,940	1.39	**£44,523**
SDC	£65,805	1.18			

Key: BSC: best supportive care; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

It should be emphasised that the ERG's strong view is that no weight can be placed on the numerical values of the ICERs because of the severity of the problems noted above.

5.4 Comment on validity of results presented with reference to methodology used

The validity of the results is severely undermined by the problems with the model indicated above. These concerns are reinforced by issues with the face validity of the results of the model relative to the results of the main source of evidence on clinical effectiveness [1]. Thus the trial by Fenaux et al with median follow-up of 21.1 months indicates:

- An improvement in median survival of 9.5 months with azacitidine
- Little evidence of greater chance of cure with azacitidine
- Likely very low levels of long term survival irrespective of treatment

In contrast the model presented in the MS suggests an improvement in mean survival of 32 to 34 months (see MS table 7.18), considerably different from the observed difference, notwithstanding that one is a median and the other a mean. In a life-time model, although this difference might be explicable if azacitidine was bringing about an improvement in cure rate, such

improvement in cure is not compatible with the trial results, nor indeed is it claimed. Thus the difference between modelled and observed survival time, particularly its magnitude, deserves explanation and seems likely on the basis of the observed errors in the model to be mainly because the model is not performing in the way envisaged.

5.5 Summary of uncertainties and issues

The flaws found by the ERG in this model were of a sufficient number and severity that no confidence can be placed in the model results at present.

Beyond this however, even if a credible model were produced substantial uncertainty would remain concerning effectiveness, quality of life and cost parameters whose impact would need to be fully investigated anew in the revised model.

6 Additional work undertaken by the ERG

- Additional searches to confirm completeness of published data on effectiveness and cost-effectiveness
- Detailed critical appraisal of the RCT by Fenaux et al [1]
- Exploration of alternative methods of extrapolating survival and time to progression to AML from the RCT by Fenaux et al [1]
- Exploration of the sensitivity of the MS model to plausible variation in key parameters
- Attempts to fix some flaws contained in the model (inappropriate discounting, lack of incremental analysis).

Because of the potential to mislead in the presence of serious concerns about the basic validity of the current MS model, the outputs of the last three activities have not been presented in this report. It is intended that they will be re-applied to a corrected MS model when supplied.

7 Discussion

7.1 Summary of clinical effectiveness issues

The evidence on clinical effectiveness was based on an adequately powered RCT, study AZA-001 reported by Fenaux et al [1] in Lancet Oncology in 2009. The trial was registered and a protocol for the trial was available. The effects on survival, time to progression to AML, independence from transfusion and reduction in infections requiring intravenous antibiotics were clinically important and unlikely to have been explained by chance alone. There was no evidence that these benefits were substantially off-set by adverse events.

However, the AZA-001 study was open to bias, particularly from lack of blinding and uncertainty about losses to follow-up. In addition there was no direct evidence on impact on HRQoL and here is no evidence for differences in effects between investigator pre-selected treatment groups.

7.2 Summary of cost effectiveness issues

The overwhelming issue was the errors in the model which were sufficiently severe and numerous that the credibility of the estimates of cost-effectiveness provided in the MS were completely undermined.

There are residual issues concerning the model parameters, but these cannot be sensibly addressed until a credible model has been produced.

7.3 Other issues

The logistic problem of delivering a seven day treatment cycle of azacitidine where hospital pharmacies are generally closed at weekends was an important issue raised by our clinical adviser.

7.4 Implications for research

Capturing the impact of azacitidine on HRQoL has clearly been a challenge suggesting that there may need to be further research specifically on the effect of azacitidine on quality of life, but also generally on how to capture improvements in health in MDS, possibly through the development of new disease specific QoL tools.

Appendix 1.

Searches undertaken by the ERG

Clinical effectiveness

MEDLINE (Ovid) 1950 - Feb 2009

1 (azacitidine or vidaza).mp.
2 myelodysplastic syndrome$.tw.
3 myelodysplastic syndromes/
4 mds.tw.
5 or/2-4
6 chronic myelomonocytic leukaemia.tw.
7 chronic myelomonocytic leukemia.tw.
8 cmml.tw.
9 Leukemia, Myelomonocytic, Chronic/
10 8 or 6 or 7 or 9
11 aml.tw.
12 acute myeloid leukaemia.tw.
13 acute myeloid leukemia.tw.
14 Leukemia, Myeloid, Acute/
15 11 or 13 or 12 or 14
16 10 or 15 or 5
17 1 and 16
18 limit 17 to "reviews (optimized)"
19 limit 17 to "therapy (optimized)"

EMBASE (Ovid) 1980 to 2009 Week 10

1 (azacitidine or vidaza).mp.
2 myelodysplastic syndrome$.tw.
3 Myelodysplastic Syndrome/
4 cmml.tw.
5 chronic myelomonocytic leukemia.tw.
6 chronic myelomonocytic leukaemia.tw.
7 Chronic Myelomonocytic Leukemia/
8 aml.tw.
9 acute myeloid leukaemia.tw.
10 acute myeloid leukemia.tw.
11 Acute Granulocytic Leukemia/
12 6 or 11 or 3 or 7 or 9 or 2 or 8 or 4 or 10 or 5
13 1 and 12
14 limit 13 to "treatment (2 or more terms high specificity)"

Cochrane Library 2009 Issue 1

#1 azacitidine or vidaza
#2 myelodysplastic next syndrome*
#3 MeSH descriptor Myelodysplastic Syndromes, this term only
#4 mds
#5 (#2 OR #3 OR #4)
#6 chronic next myelomonocytic next leukaemia
#7 chronic next myelomonocytic next leukemia
#8 cmml
#9 MeSH descriptor Leukemia, Myelomonocytic, Chronic explode all trees
#10 (#6 OR #7 OR #8 OR #9)
#11 aml

#12 acute next myeloid next leukaemia
#13 acute next myeloid next leukemia
#14 MeSH descriptor Leukemia, Myelomonocytic, Chronic/
#15 (#11 OR #12 OR #13 OR #14)
#16 (#5 OR #10 OR #15)
#17 (#1 AND #16)

On-going studies

Sources: ClinicalTrials.gov; Current Controlled Trails *meta*Register and NIHR UK Clinical Research Network Database.
Search terms: Azacitidine, vidaza.

Economic evaluation

Ovid MEDLINE(R) 1950 to February 2009
1 (azacitidine or vidaza).mp.
2 myelodysplastic syndrome$.tw.
3 myelodysplastic syndromes/
4 mds.tw.
5 or/2-4
6 chronic myelomonocytic leukaemia.tw.
7 chronic myelomonocytic leukemia.tw.
8 cmml.tw.
9 Leukemia, Myelomonocytic, Chronic/
10 8 or 6 or 7 or 9
11 aml.tw.
12 acute myeloid leukaemia.tw.
13 acute myeloid leukemia.tw.
14 Leukemia, Myeloid, Acute/
15 11 or 13 or 12 or 14
16 10 or 15 or 5
17 1 and 16
18 economics/
19 exp "costs and cost analysis"/
20 cost of illness/
21 exp health care costs/
22 economic value of life/
23 exp economics medical/
24 exp economics hospital/
25 economics pharmaceutical/
26 exp "fees and charges"/
27 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw.
28 (expenditure$ not energy).tw.
29 (value adj1 money).tw.
30 budget$.tw.
31 or/18-30
32 31 and 17

Cochrane Library (NHS EED, HTA database) 2009 Issue 1
See clinical effectiveness strategy above

Appendix 2.

Critical appraisal of:

Fenaux P, Mufti G J, 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 myelodysplatic syndromes: a randomised, open-label, phase III study. Lancet Oncology 2009;10(3):223-32. Epub 2009 Feb 18 DOI:10.1016/S1470-2045(09)70003-8.

The appraisal is based on the information presented in the published paper, although this is generally consistent with that in the MS. It is also based on trial protocol for NCT00071799 and responses to requests for additional information.

MS refers to this trial as "AZA-001"

Design:
Open label randomised controlled trial

Funding:
Celgene Corporation

Question addressed:
Population – higher risk myelodysplastic syndromes (International Prognosis Scoring System (IPSS) intermediate-2 or high & French-American-British (FAB) definitions refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation, or chronic myelomonocytic leukaemia with at least 10% bone marrow blasts and a white blood cell (WBC) count less than $13x10^9$ cells per L.
Also patients with:

- ECOG status 0-2
- Life expectancy of at least 3 months

The following patients were excluded:

- Therapy related myelodysplastic syndrome
- Previous azacitidine treatment
- Planned allogeneic stem cell transplantation

Intervention – Azacitidine $75mg/m^2$ sub-cutaneously per day for 7 days out of every 28 days for at least six cycles. No cross-over allowed. Use of erythropoietin and darbopoetin was not permitted. Elements of best supportive care were allowed.
Azacitidine continued until study completion (12 months after last patient recruited) or discontinuation due to relapse, unacceptable toxicity or disease progression. Median cycles actually given 9 (IQR 4 to 15).

Comparator – Conventional care regimens. Best supportive care or low dose chemotherapy (cytarabine) or standard dose, intensive, chemotherapy defined

by caring physician at time of randomisation. As for the intervention arm no cross-over was allowed and use of erythropoietin and darbopoetin was not permitted. Best supportive care consisted of blood product transfusions, antibiotic treatment and granulocyte-colony-stimulating factor for neutropenic infection. Low dose chemotherapy consisted of cytarabine 20 mg/m^2 per day for 14 days out of every 28 days for at least four cycles. Standard dose, intensive, chemotherapy consisted of:

- Induction - cytarabine 100-200 mg/m^2 per day by continuous intravenous (iv)infusion for 7 days PLUS
- Induction – either iv daunorubicin 45-60 mg/m^2 per day for 3 days or iv idarubicin 9-12 mg/m^2 per day for 3 days or iv mitoxantrone 8-12 mg/m^2 per day for 3 days
- Consolidation for those who achieved complete or partial remission after induction – one or two courses of same drugs used for induction at reduced dosages

All conventional care arms, not just the best supportive care option, could receive elements of best supportive care with the exception of the eythropoeitin stimulating agents.

It was clarified in a request for further information (A6) that there were no centrally defined protocols for giving blood products, other than those that might be operating in the investigation centres.

Outcomes –

- (Primary) Overall survival
- Time to transformation to acute myeloid leukaemia (AML)
- Haematological response
- Improvement assessed with IWG 2000 criteria for myelodysplastic syndromes
- Independence from red-blood-cell transfusions for 56 consecutive days or more
- Number of infections requiring intravenous antibiotics
- Occurrence of adverse events

Length of follow-up was until 12 months after the entry of the last patient into the trial. Analysis was on the basis of intention-to-treat, except for safety analyses where a participant had to have had at least one dose of the intervention and one or more safety assessments thereafter.
Outcomes were general assessed by site investigators. There was central review of pathology and all cytogenetic data.

Outcomes stated are consistent with outcomes listed in trial registry ClinicalTrials.gov for NCT00071799.

Power calculation:
Done. Power 90%; two-sided alpha 0.05; outcome overall survival; hypothesised effect HR 0.60. Target population on these bases was 354.

Numbers considered for eligibility:
Not stated

Numbers randomised:

- Azacitidine 179
- Conventional care regimes 179
    - Best supportive care 105
    - Low dose cytarabine 49
    - Intensive chemotherapy 25

Method of randomisation – sequence generation:
Computer generated by independently by Pharmaceutical Product Development (Wilmington, NC, USA). Assigned to treatment in blocks of four within each stratum. Strata by FAB and IPSS classifications.

It was clarified in response to request for further information (item A4) that the order within each block was randomly assigned and that there were 4 strata (RAEB/Int-2;RAEB/High;RAEB-T/Int-2;RAEB-T/High).

Method of randomisation – allocation concealment:
Randomisation centrally by phone.

Baseline equivalence:
Fully reported in Table 1.
Good balance between Intervention and Conventional Care groups
This balance was not maintained for the investigator pre-selected sub-groups. In particular in the participants pre-selected for intensive chemotherapy there was and excess of poorer prognosis patients based on IPSS, karyotype risk and WHO classification in the group actually receiving intensive chemotherapy relative to the group receiving azacitidine. Results in this sub-group are thus likely to have been biased towards azacitidine.

Blinding:
Explicitly open label.
Outcomes measured by site investigators. Only pathology and cytogenetics were reviewed centrally.

Amplified in response to request for further information (A5)

A5. Please confirm that the investigators' inability to blind in AZA-001 (page 31) is likely to introduce bias. Please indicate if this bias is expected to be greater for those outcomes where blinded assessment was not possible?

The gold standard is to blind all aspects of a study. However, in certain protocols this is not feasible because of patient condition and/or the nature of the study. In Study AZA-001 certain subjective evaluations (eligibility to enter the study and haematological response, but not haematological improvement) were made by an independent central reviewer and local evaluations by the investigator, which could have introduced bias. Nevertheless, the study was blinded as far as was possible to eliminate further bias. The central pathology reviewer and adjudicators as well as the central cytogenetic reviewers were blinded to patient treatment assignment. Additionally, the Independent Review Committee which confirmed FAB and WHO MDS diagnoses, IPSS classifications and International Working Group response findings was blinded to patient information and investigative site.

Loss to follow-up:
These are not clear from journal article

This was clarified in response to request for further information A7. The reply below was marked as commercially in confidence.

Table A7.1. Reason for loss from study for azacitidine patients[4]

Month	0	5	10	15	20	25	30	35	40
Number at risk	179	152	130	85	52	30	10	1	0
Reason for loss	Number of patients								
[redacted]									

Key: AML: acute myeloid leukaemia

Table A7.2. Reason for loss from study for CCR patients[4]

Month	0	5	10	15	20	25	30	35	40
Number at risk	179	132	95	69	32	14	5	0	0
Reason for loss	Number of patients								
[redacted]									

Key: AML: acute myeloid leukaemia; CCR: conventional care regimen

Ref 4. 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), 2007.

We have assumed that the major contribution to the category [redacted] is reaching the end of the trial without an event occurring. In addition the additional information indicates that [redacted] and that the reasons for this, such as [redacted], [redacted] may be associated with higher death rates. If these participants were included there may have been a reduction in the stated effect of azacitidine.

Results:

- Overall survival
  - AZA median 24.5 months (IQR 9.9 to not reached)
  - Conventional 15.0 months (IQR 5.6 to 24.1)
  - HR 0.58 (95% CI 0.43 to 0.77) (stratified log rank p=0.0001)
  - At time of last follow-up 82 deaths in AZA & 113 in conventional care

    - 2 year survival (from K-M curves) AZA 50.8% (95% CI 42 to 59%) & Conventional 26.2% (95% CI 19 to 34%) (p<0.0001)
    - In the -7/del(7q) sub-group the differences were:
        - AZA (n=30) median 13.1 months (IQR 3.9 to 24.5)
        - Conventional (n=27) median 4.6 months (IQR 2.9 to 9.3)
        - HR 0.34 (95% CI 0.17 to 0.67) (stratified log rank p=0.0017)
    - In the investigator preselected sub-groups the differences were:
        - AZA vs best supportive care 9.6 months, p=0.0045
        - AZA vs low dose chemotherapy 9.2 months, p=0.0006
        - AZA vs intensive chemotherapy 9.3 months, p=0.51
- Time to transformation to acute myeloid leukaemia (AML)
    - AZA median 17.8 months (IQR 8.6 to 36.8)
    - Conventional 11.5 months (IQR 4.9 to not reached)
    - HR 0.50 (95% CI 0.35 to 0.70) (stratified log rank p<0.0001)
- Haematological response
    - AZA ; any remission (complete + partial) 51/179 (29%)
    - Conventional ; any remission (complete + partial) 21/179 (12%)
    - P (Fishers exact test) =0.0001
- Improvement assessed with IWG 2000 criteria for myelodysplastic syndromes
    - AZA ; any improvement 87/177 (49%)
    - Conventional ; any remission (complete + partial) 51/178 (29%)
    - P (Fishers exact test) <0.0001
- Independence from red-blood-cell transfusions for 56 consecutive days or more
    - AZA ; 50/111 (45%; 95% CI 36 to 55%) of those transfusion dependent at baseline
    - Conventional ; 13/114 (11.4%; 95% CI 6 to 19%) of those transfusion dependent at baseline
    - P <0.0001
- Number of infections requiring intravenous antibiotics
    - AZA ; 0.6 antimicrobials per patient year (95% CI 0.49 to 0.73)
    - Conventional ; 0.92 antimicrobials per patient year (95% CI 0.74 to 1.13)
    - RR 0.66 (95% CI 0.49 to 0.87)
- Occurrence of adverse events
    - Deaths – see overall survival
    - Discontinuation before study completion due to haematological adverse events: Aza 8/175 (5%) vs Con 4/165 (2%)
    - Grade 3 or 4 toxicity – neutropenia: Aza159/175 (91%) vs Con 126/165 (76%)
    - Grade 3 or 4 toxicity – thrombocytopenia: Aza149/175 (85%) vs Con 132/165 (80%)
    - Grade 3 or 4 toxicity – anaemia: Aza100/175 (57%) vs Con 112/165 (68%)

Summary of identified threats to validity based on RCT quality assessment suggested by Cochrane Collaboration		
CRITERION	MET?	NOTES
Research question clarity	Yes	
Implications of study design		RCT maximises opportunity to minimise threats to internal validity
Randomisation (sequence) adequate	Yes	
Randomisation (allocation concealment) adequate	Yes	
Baseline equivalence	Yes	NOT for individual treatment modalities with conventional care
Blinding adequate	No	None of the key parties for most of the key outcomes are blinded. Some blinding attempted in assessing response based on results of pathology. Assessment of outcomes open to bias, particularly those with subjective elements.
Loss-to-follow-up (survival) minimal	Unclear	Additional information provided on a commercially in confidence basis
CONCLUSION		
The study is open to bias from lack of blinding. This is not a criticism of the triallists, as making a trial such as this blinded may be virtually impossible. However, the absence of blinding may suggest some caution is required in interpretation as this consideration would indicate that the measured size of effect could be an overestimate. Some bias may also have been introduced through [redacted] loss to follow-up, which emerges from the cic data supplied in request to further information about loss to follow-up. The validity of estimates of effect concerning the investigator specified pre-selected treatment groups needs to be interpreted particularly cautiously in view of the small size of the sub-groups, particularly the intensive chemotherapy group. This is reinforced by the noted imbalance in the baseline characteristics.		

[1] Fenaux P, Mufti G J, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A et al. Efficacy of azacitidine compared with that of conventionalc are regimens in the treatment of higher risk myelodysplatic sundromes: a randomised, open-label, phase III study. *Lancet Oncology* 2009;**10**(3):223-32. Epub 2009 Feb 18 DOI:10.1016/S1470-2045(09)70003-8.

[2] Silverman LR, Demakos EP, Peterson BL, Kornblith AB, Holland JC, Odchimar-Reissig R *et al.* Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol* 2002; **20:** 2429–2440.