NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL OF VIDAZA® (AZACITIDINE)

MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

20 MARCH 2009

1. Description of technology under assessment

1.1. Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

Name: Vidaza® (azacitidine).

Pharmacotherapeutic group: Pyrimidine analogue. It is a first-in-class epigenetic therapy that is believed to exert its disease-modifying effect through its incorporation into RNA and DNA, resulting in DNA hypomethylation and direct cytotoxicity in abnormal haematopoietic cells in the bone marrow.[1,2]

ATC code: L01BC07.

1.2. Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

The European Commission granted a marketing authorisation valid throughout the EU for Vidaza to Celgene Europe Ltd on 17 December 2008.

Azacitidine was designated as an orphan medicinal product (EU/3/01/084) on 6 February 2002 for the treatment of myelodysplastic syndromes (MDS).

1.3. What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

The licensed indication is as follows:

Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- Intermediate-2 and high-risk MDS according to the International Prognostic Scoring System
- Chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder

- Acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.[1]

1.4. To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Azacitidine is currently being used in the NHS as part of a Named Patient Programme which was initiated in February 2006.

Celgene-sponsored ongoing trials assessing azacitidine are outlined in Table 1.1.

Table 1.1. Celgene-sponsored trials

Status	Phase	Location	Title
Recruiting	Phase I	USA	A Phase I, open label, dose-escalation study to evaluate the safety, pharmacokinetics and pharmacodynamics of oral azacitidine in subjects with MDS and AML
Recruiting	Phase I	USA	A Phase I, open label, dose-ranging study to evaluate the pharmacokinetics and safety of azacitidine administered subcutaneously and as different oral formulations in subjects with MDS, AML, lymphoma and multiple myeloma
Recruiting	Phase I	USA	A Phase I, open label, multicentre, parallel group study to assess the pharmacokinetics and safety of subcutaneous azacitidine in adult cancer patients with and without impaired renal function

AML: acute myeloid leukaemia; MDS: myelodysplastic syndromes

Celgene is supporting international investigator-initiated trials assessing azacitidine alone or in combination with other therapies in MDS, AML and myelofibrosis.

The anticipated launch date of azacitidine in the UK is between March and July 2009.

1.5. Does the technology have regulatory approval outside the UK? If so, please provide details.

As of 21 January 2009, azacitidine has regulatory approval in the countries and regions described in Table 1.2.

Table 1.2. Countries in which azacitidine has regulatory approval

Country	Date of authorisation	Indication
USA	19/05/2004	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
	26/01/2007	Approved for intravenous administration (same indication).
	21/08/2008	Approval of overall survival supplement.
South Korea	27/01/2006	Treatment of MDS.
Switzerland	24/02/2006	Treatment of high-risk MDS such as refractory bicytopenias or pancytopenias with or without ringed sideroblasts (RCMD, RCMD-RS) or RAEB.
Israel	09/07/2006	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
Philippines	27/09/2006	Treatment of patients with MDS and their subtypes.
Hong Kong	25/03/2007	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
Lebanon	20/08/2007	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
Thailand	10/10/2007	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
Turkey	10/10/2007	Treatment of high-risk MDS, such as refractory bicytopenia or pancytopenia with or without ringed sideroblasts (RCMD, RCMD-RS) or RAEB type I and type II (RAEB-1 and RAEB-2), which is defined according to the WHO classification of MDS.
Argentina	09/11/2007	Treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T and CMML.
EU	17/12/2008	Treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with: • Intermediate-2 and high-risk MDS according to the IPSS • CMML with 10–29% marrow blasts without myeloproliferative disorder • AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification.

AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; IPSS: International Prognostic Scoring System; MDS: myelodysplastic syndromes; RA: refractory anaemia; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation; RARS: refractory anaemia with ringed sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; RCMD-RS: refractory cytopenia with multilineage dysplasia and ringed sideroblasts; WHO: World Health Organization

1.6. Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Azacitidine will be subject to an assessment by the Scottish Medicines Consortium. The timelines of the assessment have not been finalised.

1.7. For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Formulation: Vidaza (azacitidine) 25 mg/ml powder for suspension for injection.

Azacitidine will be available in glass vials containing 100 mg of azacitidine as a white lyophilised powder. The powder is reconstituted with water for injections (4 ml) prior to use.[1]

Pack size: 1 vial of 100 mg azacitidine.

[redacted]

1.8. What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for seven days, followed by a rest period of 21 days (28-day treatment cycle).[1]

It is recommended that patients be treated for a minimum of six cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression.[1]

Patients should be monitored for haematological response/toxicity and renal toxicities; a delay in starting the next cycle or a dose reduction may be necessary.[1]

1.9. What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

The acquisition cost of azacitidineis £321 per vial (25 mg/ml powder for injection).

1.10. What is the setting for the use of the technology?

Azacitidine treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents.[1]

1.11. For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Laboratory tests

Liver function tests and serum creatinine should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.[1]

Method of administration

Reconstituted azacitidine should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red or hardened.[1]

Other therapies administered at the same time

Before receiving azacitidine, patients should be given prophylactic anti-emetics to minimise nausea and vomiting.[1]

2. Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults who are not eligible for haematopoietic stem cell transplantation with higher-risk (International Prognostic Scoring System [IPSS] intermediate-2 risk and high-risk) myelodysplastic syndromes (MDS), chronic myelomonocytic leukaemia (CMML), or acute myeloid leukaemia (AML) (<30% blasts).	Adult patients who are not eligible for haematopoietic stem cell transplantation with: • Intermediate-2 and high-risk MDS according to the IPSS • CMML with 10–29% marrow blasts without myeloproliferative disorder • AML with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.
Intervention	Azacitidine (Vidaza).	Azacitidine (Vidaza).
Comparator(s)	• Best supportive care (BSC) (such as blood transfusions, erythropoietin and granulocyte colony-stimulating factor, with infection prophylaxis). • Chemotherapy (such as cytarabine and anthracyclines) – low- and high-dose.	The comparators considered in this application are: • BSC alone • BSC and low-dose chemotherapy • BSC and standard chemotherapy.

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.	The outcome measures to be considered include: • Overall survival • Progression-free survival • Response rates • Time to transformation to AML • 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 (QALY). 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.	A Markov cohort-based economic model will be used to assess the cost-effectiveness of Vidaza compared with three conventional care regimes in the treatment of MDS: • BSC • Low-dose chemotherapy • Standard chemotherapy. Cost-effectiveness will be expressed in terms of incremental cost per QALY. Costs will be considered from an NHS and Personal Social Services perspective. The time horizon will be the lifetime of a patient due to the chronic nature of the condition.
Subgroups to be considered	If the evidence allows, consideration will be given to the subgroup of patients with chromosome 7 abnormalities.	Consideration will be given to the subgroup of patients with chromosome 7 abnormalities to the extent that the data permit.
Special considerations, including issues related to equity or equality	N/A	Celgene considers that azacitidine fulfils the criteria for the appraisal of end-of-life treatments set out in the supplementary advice for appraising life-extending, end-of-life treatments issued by NICE in January 2009.[3]

3. Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- *The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.*
- *The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.*
- *The indication(s) and any restriction(s).*
- *The recommended course of treatment.*
- *The main comparator(s).*
- *Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.*
- *The main clinical results of the randomised trials and any relevant non RCTs.*
- *In relation to the economic evaluation, details of:*
  - *the type of economic evaluation and justification for the approach used*
  - *the pivotal assumptions underlying the model/analysis*
  - *the mean costs, outcomes and incremental ratios from the evaluation.*

<u>The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug</u>

Azacitidine (Vidaza®) received approval for marketing throughout the EU on 17 December 2008 (see Section 1.2). Azacitidine is a pyrimidine analogue (ATC code: L01BC07). It is a first-in-class epigenetic therapy that is believed to exert its disease-modifying effect through its incorporation into RNA and DNA, resulting in DNA hypomethylation and direct cytotoxicity in abnormal haematopoietic cells in the bone marrow (see Section 4.3).

The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price

Azacitidine is available in a pack size of one vial containing 100 mg of azacitidine powder and is reconstituted by suspension in 4 ml of sterile water for injections prior to use (see Section 1.7). The acquisition cost is £321 per vial (see Section 1.9).

The indication(s) and any restriction(s)

Azacitidine is indicated (see Section 1.3) for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with:

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder
- Acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization (WHO) classification.

MDS comprises a heterogeneous group of clonal haematological disorders that are characterised by ineffective haematopoiesis leading to peripheral blood cytopenias and progressive bone marrow (BM) failure. This results in an increased risk of transformation to AML (see Section 4.1.1). The primary treatment goals are to increase survival and delay leukaemic transformation. Currently, no treatment strategies other than allogeneic SCT offer meaningful potential to change the natural history of the disease (see Section 4.5).

The recommended course of treatment

One treatment cycle consists of a daily subcutaneous injection of 75 mg/m^2 of body surface area for seven days, followed by a 21-day rest period. Treatment is for a minimum of six cycles and should be continued for as long as the patient continues to benefit, or until disease progression (see Section 1.8).

The main comparator(s)

The main comparator is best supportive care (BSC), with or without chemotherapy, and the key clinical evidence was obtained in a multicentre, randomised, head-to-head comparison of azacitidine and BSC (Study AZA-001; see Section 6.3).

Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised

trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies

Study AZA-001 included 358 patients with MDS who were randomised at a ratio of 1:1 to receive azacitidine or conventional care regimens (CCRs) in the form of BSC alone, low-dose chemotherapy or standard-dose chemotherapy. These three regimens together formed the combined CCR group. Before randomisation, investigators preselected the most appropriate of the three CCRs for all patients on the basis of age, general condition, co-morbidities and patient preference. Patients randomised to azacitidine (n=179) received azacitidine 75 mg/m^2 for seven days every 28 days. Patients randomised to CCR (n=179) received the investigator preselected treatment option: BSC alone (n=105), low-dose chemotherapy (n=49) or standard-dose chemotherapy (n=25) (see Sections 6.3.3–6.3.4).

The main clinical results of the randomised trials and any relevant non RCTs

The primary efficacy endpoint in Study AZA-001 was time to death from any cause. Secondary efficacy endpoints were time to transformation to AML, haematological response and improvement according to International Working Group criteria for MDS, independence from red blood cell (RBC) transfusions for 56 consecutive days or more, number of infections requiring intravenous antimicrobials, and occurrence of adverse events (AEs) (see Section 6.3.9).

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).

Economic evaluation

The type of economic evaluation and justification for the approach used

The economic evaluation performed is a cost–utility analysis, based on a lifetime Markov model. The model encompasses outcome measures for costs, health outcomes and incremental cost-effectiveness. Outcomes for costs include those relating to drugs and medications, monitoring, routine follow-up and adverse event (AE) management. Health effects are expressed in terms of life-years (LYs) and quality-adjusted life-years (QALYs). The model outcomes are expressed in terms of cost per LY and per QALY gained. Probabilistic sensitivity analysis (PSA) is performed to examine the overall effect of the uncertainty in the model.

The pivotal assumptions underlying the model/analysis

- Three-year trial data are extrapolated to provide a lifetime cohort model.
- The number of modelled cycles of treatment is that observed in Study AZA-001.
- Patients can die when in either the MDS or the AML health state.
- It is assumed that all patients spend an equal amount of time in an AML state, regardless of the treatment arm from which they progressed.

- Once patients progress to the AML state, all patients receive BSC-type treatment, regardless of their previous treatment arm.
- In the model, resource utilisation relating to the routine management of patients undergoing treatment is based on expert opinion gathered from consultant haematologists in the UK.
- It assumed that there is no wastage for any drug overage for the cost calculations of low-dose or standard dose chemotherapy. Wastage is included in the cost of azacitidine.
- Utilities for patients treated with azacitidine and BSC are based on mapping European Organisation for Research and Treatment of Cancer scores from Study CALGB 9221 to EQ-5D values using a published algorithm.

The mean costs, outcomes and incremental ratios from the evaluation

Table 3.1. Mean costs, outcomes and incremental ratios from the evaluation

Comparator	Mean costs incurred	Marginal outcomes (years)	Marginal outcome (QALYs)	Incremental cost per QALY gained
Best supportive care	£97,828	2.60	1.55	**£63,295**
Low-dose chemotherapy	£84,812	2.58	1.44	**£58,837**
Standard-dose chemotherapy	£65,804	2.48	1.39	**£44,523**

Key: QALY: quality-adjusted life-year

Azacitidine can be considered to fulfil the criteria for the appraisal of end-of-life treatments set out in the supplementary advice for appraising life-extending end-of-life treatments issued by NICE in January 2009.

4. Context

4.1. Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.

4.1.1. Myelodysplastic syndrome

Myelodysplastic syndrome (MDS) comprises a heterogeneous group of clonal haematological disorders that are characterised by ineffective haematopoiesis leading to one or more peripheral blood cytopenias and progressive bone marrow (BM) failure. This results in an increased risk of malignant transformation to acute myeloid leukaemia (AML).[4-7]

The pathogenesis of MDS is complex and has not been fully characterised. Models have been proposed whereby MDS develops along a multistep process, during which a haematopoietic stem cell is mutated and attains a growth advantage. The resulting mutated cell clone causes morphological dysplasia, impaired cell differentiation and haematopoiesis, and genomic instability. The immune system is impaired as a result of altered cytokine secretion and apoptotic pathways: in early MDS, excessive apoptosis is thought to contribute to cytopenias and a cellular BM, whereas in later stages of MDS, decreased apoptosis and subsequent clonal expansion is thought to promote progression to AML; BM failure results.[8] Overall, an estimated 20–30% of MDS patients will eventually progress to develop AML. However, even in the absence of progression to AML, the prognosis for MDS patients is poor: frequent complications include infections as a result of neutropenia, which may be fatal, and life-threatening haemorrhages as a result of thrombocytopenia.[7]

MDS may arise *de novo,* or secondary to chemotherapy and/or radiation therapy for other diseases. The causes of *de novo* MDS are not entirely understood, although factors such as exposure to mutagenic chemicals or ionising radiation are thought to contribute.[9]

For the whole spectrum of MDS, the patient's symptoms are a direct consequence of cytopenias and cell function abnormalities. Common presenting symptoms include fatigue and a lack of energy, sometimes coupled with symptoms of anaemia such as dyspnoea upon exertion. Bruising or bleeding can occur, and in about 10% of

patients recurrent infections are the presenting symptom, most often of bacterial aetiology.[10]

4.1.2. Classification of MDS

MDS is classified on the basis of the findings of morphological examinations of the blood and BM. The two most recognised classifications are the French-American-British (FAB) and World Health Organization (WHO) classifications. The FAB classification (1982) groups MDS into five subtypes,[11] while the more widely used WHO classification (2001) uses the FAB classification as its backbone and classifies MDS into eight subtypes (see Table 4.1).[12,13]

Table 4.1. FAB classification criteria for MDS and equivalent WHO classification[12,13]

FAB classification	Equivalent WHO classification	% blasts* in BM	% blasts in PB	Other criteria
RA	RA RCMD	<5	<1	N/A
RARS	RARS RCMD-RS 5q- syndrome MDS-U	<5	<1	Also >15% ringed sideroblasts in BM
RAEB	RAEB-1 RAEB-2	5–20	<5	N/A
RAEB-T	AML‡	21–30	≥5	Alternatively presence of Auer rods† in blasts
CMML	MDS/MPD‡	≤20	<5	Also absolute monocytosis (>1 x 10^9/l)

* Blasts are immature blood cells

† Auer rods are needle-like granular inclusions seen in malignant myeloid cells

‡ AML and MDS/MDP are not classified as MDS by the WHO

Key: AML: acute myeloid leukaemia; BM: bone marrow; CMML: chronic myelomonocytic leukaemia; FAB: French-American-British; MDS/MPD: myelodysplastic syndrome/myeloproliferative disorder; MDS-U: myelodysplastic syndrome, unclassified; PB: peripheral blood; RA: refractory anaemia; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation; RARS: refractory anaemia with ringed sideroblasts; RCMD: refractory cytopenia with multilineage dysplasia; RCMD-RS: refractory cytopenia with multilineage dysplasia, ringed sideroblasts; WHO: World Health Organization

In addition to the FAB and WHO classifications, the International Prognostic Scoring System (IPSS; 1997) provides a method for evaluating clinical prognostic risk categories for patients with MDS. It identifies three critical factors that relate to clinical outcome in terms of survival and AML evolution, namely risk-based cytogenetic subgroups (karyotype good, intermediate and poor), the BM blast percentage and the number of cytopenias (see Table 4.2).[14]

Table 4.2. The IPSS classification of MDS, showing survival and progression to AML[14]

	Score value				
Prognostic variable	0	0.5	1.0	1.5	2.0
Marrow blasts (%)*	<5	5–10	N/A	11–20	21–30
Karyotype[†]	Good	Intermediate	Poor		
Cytopenias[§]	0/1	2/3			

Risk category (% IPSS population)	Overall score	Median survival (years) in the absence of therapy	Median time (years) for 25% of patients to progress to AML in the absence of therapy
Low (33%)	0	5.7	9.4
Intermediate-1 (38%)	0.5–1.0	3.5	3.3
Intermediate-2 (22%)	1.5–2.0	1.2	1.1
High (7%)	≥2.5	0.4	0.2

* Patients with 20–30% blasts may be considered as MDS or AML

[†] Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex (≥3 abnormalities) or chromosome 7 abnormalities; Intermediate = other abnormalities. This excludes karyotypes t(8;21), inv16 and t(15;17), which are considered to be AML not MDS

[§] Cytopenias: neutrophil count <1,800/µl, platelets <100,000/µl, haemoglobin <10 g/dl

Key: AML: acute myeloid leukaemia; IPSS: International Prognostic Scoring System

The IPSS provides clinicians with a useful tool for evaluating and treating patients according to the actual prognosis of their disease. As shown in Table 4.2, the median survival prognosis for higher-risk (categories intermediate-2 and high) MDS patients is substantially worse than that for lower-risk (categories low and intermediate-1) patients (approximate survival times: ≤1 year versus ≥3 years).[14]

4.1.3. Epidemiology of MDS

Given the rarity of MDS and its poor prognosis, it is difficult to ascertain incidence and prevalence accurately. MDS can affect all ages; however, it is predominantly a condition of the elderly, with the highest occurrence seen in patients >65 years of age.[4,5] The reported incidence varies widely, depending on the region under consideration. Table 4.3 summarises the incidence in selected EU countries.[15-22]

Table 4.3. Incidence of MDS in selected EU countries[15-22]

Country	Study period	Region (population)	Incidence per 100,000
France	1980–90 1993–96	Burgundy (493,931) Bayonne (290,000)	3.2 7.7
Germany	1975–90	Düsseldorf (575,000)	4.1
Spain	1994–98	Ourense (346,913)	8.1
Sweden	1978–92	Jönköping (303,000–310,000)	3.6
UK	1981–90 1985–93 1984–88	Bournemouth (226,000) Somerset (413,500) England and Wales (16 million)	12.6 9.3 3.6

Most epidemiological knowledge to date has been obtained from statistical studies of selected regional populations, making a true reflection of the figure across a wider population difficult to obtain.[3,19] An increase in the incidence of MDS has been noted in recent years, but this is predominantly attributed to wider recognition and diagnosis of the condition and the introduction of an improved classification system.[3]

In the UK, registries on MDS were collected in Bournemouth, Somerset, and England and Wales in the 1980s and 1990s. In addition, the Haematological Malignancy Research Network (University of York) estimates an age-standardised rate of 3.3 per 100,000.[23]

A survey performed on behalf of Celgene found that 38% of MDS patients in the UK have higher-risk disease (IPSS risk category intermediate-2 or high).[24]

4.1.4. Prognosis

The prognosis of MDS is poor: about 20–30% of patients eventually progress to AML, which may be refractory to therapy; other patients die of disease complications relating to BM failure: infections arising from neutropenia kill 40–65% of patients, while haemorrhage due to thrombocytopenia is a less common but still major problem.[7]

While MDS across all IPSS risk categories is potentially life-threatening, both the rate of transformation to AML and the death rate are higher in higher-risk patients. Median overall survival is only 0.4 years and 1.2 years in IPSS risk categories high and intermediate-2 respectively, compared with 3.5 years and 5.7 years in risk categories intermediate-1 and low respectively.[4,14]

Patients in IPSS risk categories intermediate-2 or high (and FAB subtypes refractory anaemia with excess blasts [RAEB] or refractory anaemia with excess blasts in transformation [RAEB-T]) also demonstrate more rapid BM failure, alongside an increased prevalence of cytopenias.[14] As a consequence, they have a greater need for transfusions and a higher risk of infections and bleeding, eventually leading to death.[25]

The IPSS assigns a high score value – and hence poor prognosis – to patients with a poor karyotype (defined as ≥3 abnormalities or chromosome 7 abnormalities) (see Table 4.2).[14] Because of this poor prognosis, patients with chromosome 7 abnormalities were identified by NICE in the scope for this appraisal as a subgroup meriting consideration.

Health-related quality of life (QoL) of patients with MDS is likely to be severely compromised by cytopenic symptoms such as fatigue, haemorrhagic episodes, infections requiring hospitalisation and treatment with intravenous medications, as well as the need for frequent transfusions of blood products.

4.1.5. Treatment pathway and options

MDS management is complicated due to the advanced age of the patient population and their inability to tolerate standard-dose chemotherapy, as well as the coexistence of non-haematological morbidities.[4] Treatment of all MDS patients should consider both management of symptoms and prolongation of survival. Aside from clinical response, benefit may also be obtained from haematological improvement, a decrease in transfusion dependence and a decrease in time to progression to AML.[26,27] Patients need to be managed on an individual basis, with age, performance status, major comorbid conditions, psychosocial status and availability of a caregiver being taken into consideration when deciding treatment choice, dose and length.[4] Management decisions should be taken with the full involvement of the patient.[5]

Overall, there are currently three main treatment options for MDS: low-dose chemotherapy, standard-dose chemotherapy and best supportive care (BSC). BSC aims to control the symptoms of BM failure and improve the QoL of the patient, primarily through the use of red blood cell (RBC) and/or platelet transfusions, antibiotics and, to a limited extent, cytokines, erythropoietin (EPO) or granulocytic growth factors (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]). The use of EPO is generally restricted to low-risk MDS patients.[5] BSC is essentially a palliative care option and no difference in time to progression to AML or overall survival has been observed in MDS patients treated with BSC compared with cytarabine.[28] BSC is the treatment of choice for patients with lower-risk MDS. While also typically being the most common form of treatment for patients with higher-risk MDS, it is preferred only in those who are not candidates for low-dose or standard-dose chemotherapy.[5]

UK and US guidelines are largely in agreement regarding their interventions of choice for MDS. In summary, patients with low-risk MDS (IPSS risk category low) should be offered BSC if they have symptomatic cytopenias.[4,5] Patients aged <65 years in IPSS risk category intermediate-1 should be assessed for eligibility for stem cell transplantation (SCT) and treated within a clinical trial where available.[5] Older

patients, and patients aged <65 years who are unfit for allogeneic SCT, should receive BSC. Standard-dose chemotherapy is not recommended in this group.[4,5]

Patients with higher-risk MDS (IPSS risk category intermediate-2 or high) should be assessed for standard-dose chemotherapy and SCT if aged <65 years;[4,5] ineligible patients should receive BSC and should be considered for treatment with azacitidine or decitabine[4] (which is not available in the UK) or investigational therapy within a clinical trial where available.[5] These recommendations are summarised in Figure 4.1 (see Section 4.6).[4,5]

4.2. What was the rationale for the development of the new technology?

Azacitidine was originally developed as a cytarabine analogue. However, it acts epigenetically, primarily through hypomethylation of specific gene promoter regions, in contrast to cytarabine, which is believed to exert its clinical benefit through a cytotoxic effect.[29] The discovery that the methylation status of the *p15*$^{(INK4B)}$ gene in MDS was related to disease progression provided the rationale to investigate whether altering the methylation patterns could impact on the natural history of the disease.[30] The Cancer and Leukemia Group B (CALGB) conducted studies of single-agent low-dose azacitidine which demonstrated clinical benefit.

There is a considerable unmet treatment need in higher-risk MDS patients, owing to the high morbidity, greater transfusion burden, rapid progression to AML and high mortality in this population. UK treatment guidelines for MDS suggest that, from a patient QoL perspective, a stable augmented haemoglobin concentration may be preferable to the cyclical fluctuations of RBC transfusions.[5] Thus, there is a need for novel forms of treatment that can improve haematological parameters, and azacitidine fulfils this criterion.

4.3. What is the principal mechanism of action of the technology?

Hypermethylation of CpG islands spanning the promoter regions of tumour suppressor genes is commonly associated with cancer.[31-33] Azacitidine inhibits the methylation of newly synthesised DNA by inhibiting DNA methyltransferase.[2,34,35] Azacitidine is believed to exert its antineoplastic activity through its incorporation into RNA and DNA, resulting in DNA hypomethylation and direct cytotoxicity in abnormal haematopoietic cells in the BM. DNA hypomethylation may allow for the re-expression of genes involved in normal cell cycle regulation and differentiation. The cytotoxic effects of azacitidine may be due in part to its incorporation into RNA, with

subsequent inhibition of protein synthesis, and/or its ability to activate DNA damage pathways, which leads to apoptosis.[2,31,36,37]

In a study by Uchida *et al,* progressive hypermethylation of the 5' CpG island of *CDNK2B* was observed in 78% of patients with higher-risk MDS, compared with 8% of patients with low-risk MDS.[30] In other studies, hypermethylation of *CDNK2B* correlated with blastic BM involvement and increased with disease progression toward AML.[38-41]

4.3.1. Cytotoxicity

The cytotoxicity of azacitidine is proportional to dose and exposure time.[37] Although the mechanisms of cytotoxicity are complex and multifaceted, there is general agreement that the incorporation of azacitidine into DNA and RNA, and inhibition of protein synthesis, are all critically important factors for its activity.[42]

Cytotoxicity is greatest in cells that are proliferating (S-phase) and metabolically active, while non-proliferating cells are relatively insensitive to azacitidine.[37] Cytotoxic effects may also be mediated through induction of the DNA damage response pathways. In particular, this involves azacitidine-induced responses initiated by the cell following damage to DNA to ensure the damaged DNA is not propagated.[43-45]

4.4. What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Azacitidine is indicated for higher-risk (IPSS risk category intermediate-2 or high) MDS patients who are ineligible for SCT. According to UK and US guidelines, patients with higher-risk MDS should be assessed for suitability to receive standard-dose chemotherapy (most commonly used regimens contain cytarabine with any of an anthracycline, etoposide and/or fludarabine) and SCT if aged <65 years (depending on fitness and eligibility).[4,5] Patients ineligible for standard-dose chemotherapy or SCT should receive BSC and be considered for treatment with azacitidine or decitabine[4] (which is not available in the UK) or investigational therapy within a clinical trial where available.[5]

4.5. Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Higher-risk MDS patients have a poor prognosis and limited treatment options are available. With the exception of allogeneic SCT, no existing treatment strategies have shown a significant overall survival benefit.[46] A resource use survey undertaken

by Celgene as part of the health economic sections of this submission has indicated that a quarter of the UK haematologists experienced in treating MDS do not routinely use low-dose chemotherapy. This behaviour may reflect divided physician beliefs about the benefits of low-dose chemotherapy, as UK guidelines state that there is insufficient evidence to recommend its routine use.[5] Furthermore, standard-dose chemotherapy in elderly patients with higher-risk MDS can be detrimental, with increased treatment toxicity, a higher rate of infections and haematological complications.[47]

UK and US guidelines provide a treatment framework; however, patients need to be managed on an individual basis. Age, performance status, major comorbid conditions, psychosocial status and availability of a caregiver must be taken into consideration when deciding treatment choice, dose and length.[4]

4.6. Provide details of any relevant guidelines or protocols.

Evidence-based guidelines used in UK practice for the clinical management of MDS have been published in English by the British Society for Haematology (2003)[5] and, more recently, by the National Comprehensive Cancer Network in the USA (2009).[4] Guidelines for France, Italy and Spain are available but have not been considered in this submission. The UK and US guidelines are broadly similar, using the IPSS score to determine the severity of MDS and advocating a prognostic model for decision-making, as shown in Figure 4.1.[4,5]

The UK guidelines set out three treatment options for higher-risk MDS patients:

- Standard-dose chemotherapy plus SCT
- Standard-dose chemotherapy alone
- BSC/investigational therapy.[5]

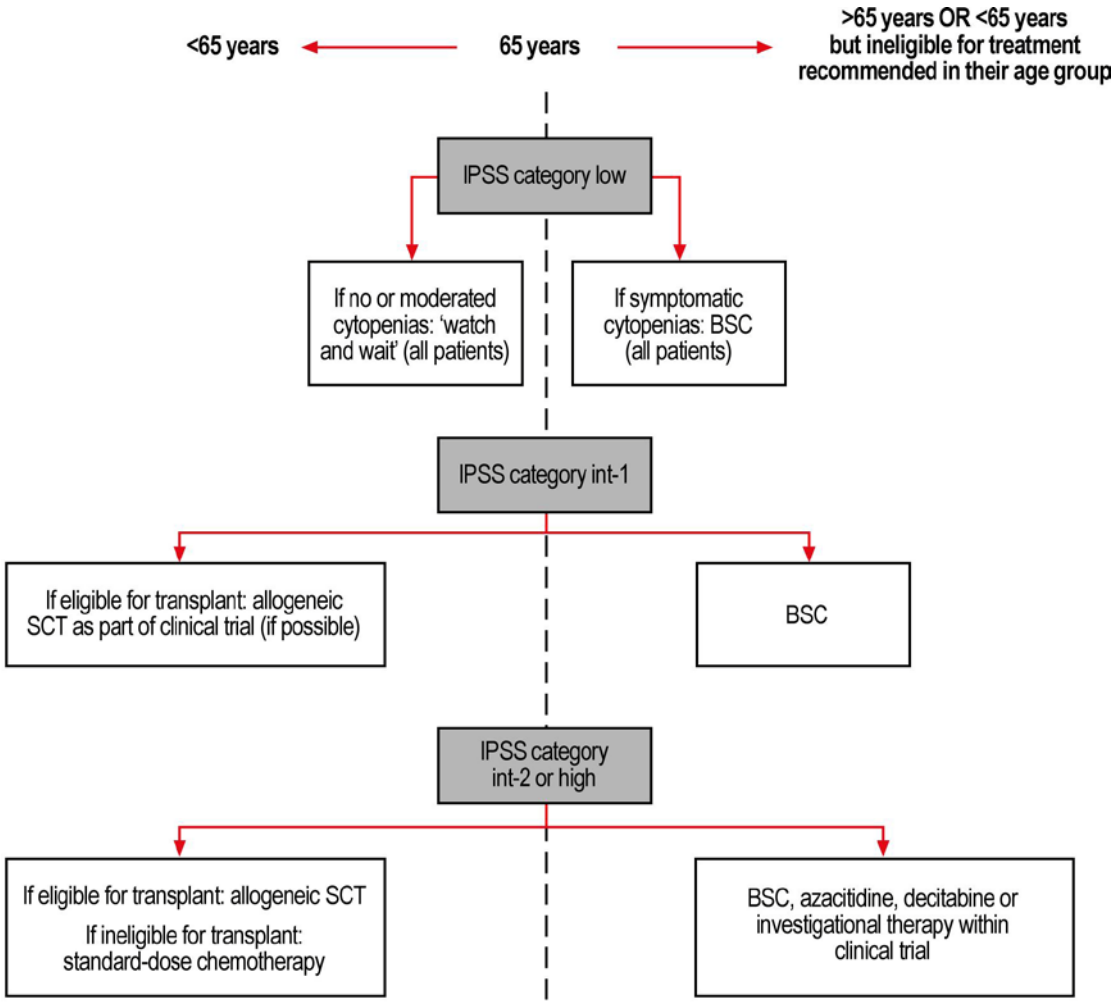
All patients <65 years should be considered for eligibility for SCT early after diagnosis. In this group of high-risk patients, SCT should only be considered for those responding to remission-induction chemotherapy.[5]

Both patients >65 years and those <65 years who are ineligible for SCT should be considered for standard-dose chemotherapy alone. Most commonly used regimens contain cytarabine with any of an anthracycline, etoposide and/or fludarabine. In patients for whom standard-dose chemotherapy alone is not recommended, intensive remission-induction chemotherapy should be offered only if SCT is proposed as consolidation.[5]

If patients do not fall into any category for which chemotherapy plus SCT is recommended, they should be offered BSC or investigational therapies within clinical research protocols.[5]

Although low-dose chemotherapy is not recommended in the UK guidelines,[5] in practice many clinicians will consider treatment with low-dose chemotherapy for those patients who are not fit to receive standard-dose chemotherapy.

Figure 4.1. Diagram of treatment recommendations for MDS[4,5]



Key: BSC: best supportive care; int-1: Intermediate-1; int-2: Intermediate-2; IPSS: International Prognostic Scoring System; SCT: stem cell transplantation

5. Equity and equality

5.1. Identification of equity and equalities issues

Are there any issues relating to equity or equalities (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

5.1.1. Life-extending, end-of-life treatments and azacitidine

Myelodysplastic syndrome (MDS) patients who are eligible for treatment with azacitidine have a poor prognosis and very limited life expectancy, with the only alternatives being best supportive care (BSC) with or without low-dose or standard-dose chemotherapy.

Celgene considers that azacitidine fulfils the criteria for the appraisal of end-of-life treatments set out in the supplementary advice for appraising life-extending end-of-life treatments issued by NICE in January 2009.[48]

- The median life expectancy of eligible MDS patients is very limited – 0.4 years and 1.2 years respectively for patients in the International Prognostic Scoring System (IPSS) categories high and intermediate-2[14] – and is less than the two years specified in the guidance.
- Azacitidine provides a significant advantage in overall survival of 9.4 months (p=0.0001) compared with current conventional care regimens (CCRs) and nearly doubles the two-year survival rate from 26.2% to 50.8% (p<0.0001).
    - Azacitidine extends overall survival by 10.6 months compared with BSC alone (p=0.0045).
    - Azacitidine extends overall survival by 9.2 months compared with BSC plus low-dose chemotherapy (p=0.0006).
    - Azacitidine extends overall survival by 9.4 months compared with BSC plus standard-dose chemotherapy (p=0.51).[46]
- Although other standard treatments are available through the NHS for the treatment of patients with higher-risk MDS, none have demonstrated comparable benefits for patients ineligible for stem cell transplantation.
- The higher-risk MDS patient population for whom azacitidine is indicated is small.[17,20,22,23] Celgene estimates an annual incidence of approximately 700 patients in England and Wales.[23,24,49]
    - Azacitidine has been designated as an orphan drug for the treatment of both MDS and acute myeloid leukaemia (AML) in the EU.[50,51]

How has the analysis addressed these issues?

In the health economic analysis, the average age of patients in the trial is identified, then the average utility of a person of that age[52] is multiplied by the life-years gained to estimate the average utility gain for all patients with survival benefit. In addition, the average utility gain required by a patient with survival benefit to generate a cost per quality-adjusted life-year of £20,000 or £30,000 is calculated.

5.1.2. Chromosome 7 abnormalities

Patients who present a karyotype with monosomy 7 or –7q/del(7q) have a poor prognosis in MDS. A recent retrospective study demonstrated that MDS/AML patients with chromosome 7 abnormalities have poor overall survival (33% survival after three years) and a higher relapse rate than patients with normal cytogenetics.[53] The IPSS considers patients with chromosome 7 abnormalities to have poor cytogenetics and assigns them a higher risk score than patients with normal or good cytogenetics.[14]

Study AZA-001 identified 57 out of 358 patients with these chromosome 7 abnormalities. The median increase in overall survival with azacitidine (n=30) was 8.5 months (threefold) compared with CCR (n=27) consisting of BSC alone, BSC with low-dose chemotherapy or BSC with standard-dose chemotherapy.[46] At two years, a significant fourfold overall survival advantage was observed with azacitidine compared with CCR (33% and 8% of patients respectively; p=0.03).[54] This study demonstrates significant clinical benefit of azacitidine in patients with chromosome 7 abnormalities.

How has the analysis addressed these issues?

A separate cost-effectiveness analysis has been performed for this subgroup of patients (see Section 7.2.2.1.1).

6. Clinical evidence

6.1. Identification of studies

6.1.1. Search strategy

Two comprehensive searches were undertaken to identify all relevant studies on 9 March 2009. The search terms used to find azacitidine required a very broad search strategy (see Appendix 2). This approach was taken because few references were anticipated given that azacitidine, although developed in the 1960s, is a relatively new drug in this disease area. However, with regard to the comparator treatments, the search was expected to retrieve a relatively large number of references because such treatments have been used in this disease area for many years. The search strategy for the comparator treatments was refined through consultation with physicians. This ensured that all relevant studies were identified, while limiting the number of irrelevant references retrieved.

The following electronic databases were searched:

- 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 included both MeSH subject headings and free-text terms for the drug intervention (for example, Vidaza), the condition (for example, myelodysplastic syndromes) and the comparators (for example, supportive care). Terms were combined with the Boolean operators ‘or’ or ‘and’ as appropriate. Wherever possible, a filter was applied to ensure selection of randomised controlled trials (RCTs) during the ‘comparator’ searches. This filter could only be applied in databases that routinely held this information; for example, MEDLINE. The full search strategies can be found in Appendix 2.

6.1.2. Inclusion and exclusion criteria

Only Phase III RCTs were included. These studies were deemed acceptable if they were published in peer review journals or, as in the case of the intervention (azacitidine), if the company provided unpublished full clinical study reports (CSRs). Studies published in abstract form were excluded due to the difficulty in accessing full details of the trial methods and results. Published abstracts which utilised trial data from azacitidine trials are listed for information in Section 6.2.

Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with: intermediate-2 and high-risk myelodysplastic syndrome (MDS) according to the International Prognostic Scoring System (IPSS); or chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder; or acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization (WHO) classification in Europe.[1] Therefore, it was felt appropriate to include studies in which the majority of enrolled subjects were similar to the patient population for which azacitidine is indicated. For this reason only studies in which at least 50% of enrolled patients met the above-mentioned criteria were included in the evidence review.

When considering patients with higher-risk MDS (IPSS risk category intermediate-2 or high), there are currently three primary therapeutic options for treatment in Europe: best supportive care (BSC), low-dose chemotherapy and standard-dose chemotherapy.[4,5] Consequently, the interventions of interest in this evidence review were azacitidine and the comparator treatments most relevant to the UK: BSC alone, BSC and low-dose chemotherapy, or BSC and standard-dose chemotherapy. Types of study outcome included overall survival, progression-free survival, response rates, time to transformation to AML, adverse effects of treatment and health-related quality of life (QoL).

6.2. Study selection

6.2.1. Inclusion and exclusion criteria

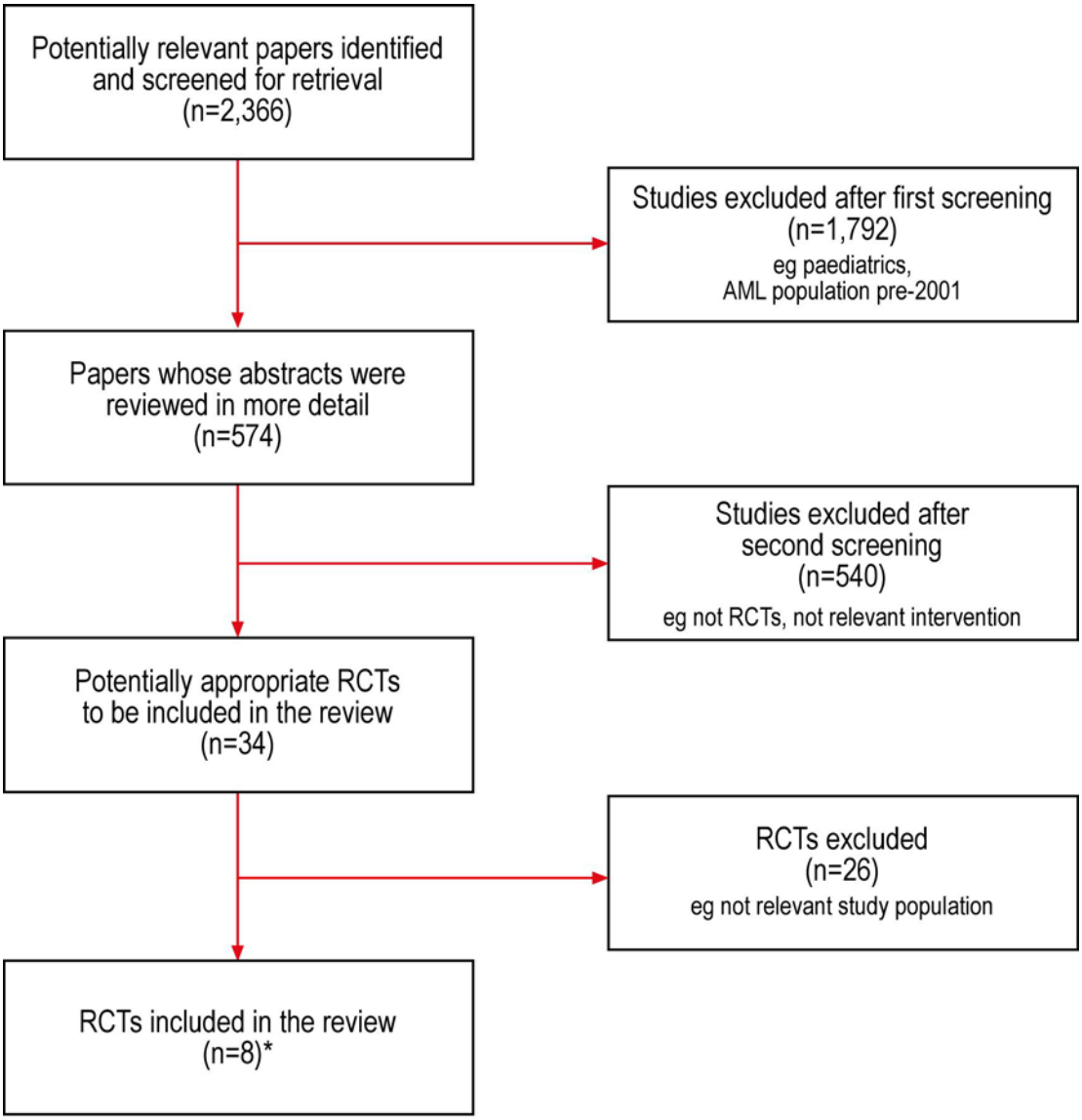
The literature searches retrieved 2,366 papers that were potentially relevant to the decision problem (see Figure 6.1 for a description of the process of study selection). Routine database commands were used to identify and exclude papers which were clearly irrelevant (n=1,792). For example, all studies which included a population of only AML patients and which were published prior to 2001 were excluded. These

studies would not have included the subset of AML patients which were of interest for this decision problem. Specifically, the population of interest for this decision problem includes only AML patients with 20–30% blasts and multilineage dysplasia according to the WHO classification[12] (see Section 1.3 for licensed indications). However, up until 2001, when the WHO classification was published, this subset of patients would have been classified as refractory anaemia with ringed sideroblasts in transformation (RAEB-T) according to French-American-British (FAB) classification criteria.[11]

The abstracts of the remaining 574 papers were read to identify potentially appropriate RCTs for the review. Some of these studies included a mixed population of AML and MDS patients. As described earlier in the inclusion criteria, if at least half of the study participants were patients with higher-risk MDS, CMML 10–29% blasts or AML 20–30% blasts, then the study was included. At the end of this stage of the selection process, 34 papers were ordered for a more detailed evaluation. Twenty-six papers were excluded, leaving eight published studies. Two CSRs for azacitidine were provided by the company (Study CALGB 9221 and Study AZA-001).[55,56] The results of the latter study were identified in the literature searches (Fenaux *et al,* 2009).[46]

Study CALGB 9221 did not meet the inclusion criteria for this review because the study sample did not contain at least 50% higher-risk MDS patients.[55] In total, therefore, eight published studies were identified for this systematic review (one published study of azacitidine and seven studies related to comparator treatments (BSC, low-dose chemotherapy and standard-dose chemotherapy).

Figure 6.1 Process of selecting studies for inclusion in the review



* Two Phase III RCTs of azacitidine were provided by the company in the form of CSRs, only one of which met the inclusion criteria for this systematic review; that is, the study population comprised higher-risk MDS patients.That study (Fenaux *et al*, 2009) was identified in the literature review

Key: AML: acute myeloid leukaemia; CSR: clinical study report; MDS: myelodysplastic syndrome; RCT: randomised controlled trial

6.2.2. Complete list of RCTs

Table 6.1 shows the full list of studies that met the inclusion criteria in this systematic review of the clinical evidence for azacitidine and relevant comparator treatments. In the 2009 study by Fenaux *et al,* the clinical effectiveness of the intervention therapy, azacitidine, was compared with that of a conventional care regimen (CCR) including BSC.[46] Of the seven published comparator treatment Phase III trials, three assessed standard-dose chemotherapy in at least one study arm,[57-59] two assessed low-dose

chemotherapy[28,60] and three included at least one study arm in which all patients received BSC.[28,61,62]

Table 6.1. List of Phase III RCTs included in the systematic review

Study	Study reference	Sample size	Intervention and comparator
1	Study AZA-001[46]	358	Azacitidine + BSC vs CCR
2	Bernasconi, 1998[57]	105	SDC vs SDC + G-CSF
3	Miller, 1992[28]	141	LDC vs BSC
4	Ossenkoppele, 2004[58]	134	SDC + G-CSF vs SDC + G-CSF + fludarabine
5	Verbeek, 1999[59]	31	SDC vs SDC + G-CSF
6	Zwierzina, 2005[60]	180	LDC vs LDC + GM-CSF vs LDC + interleukin
7	Kantarjian, 2006[61]	170	Decitabine + BSC vs BSC alone
8	Thompson, 2000[62]	66	GM-CSF + epoetin alfa + BSC vs GM-CSF + BSC

Key: BSC: best supportive care; CCR: conventional care regimen; G-CSF: granulocyte colony-stimulating factor, GM-CSF: granulocyte-macrophage colony-stimulating factor; LDC: low-dose chemotherapy; SDC: standard-dose chemotherapy

6.2.2.1. Azacitidine Phase III RCTs

The efficacy of azacitidine has been evaluated in two Phase III clinical studies.

- CALGB 9221 was a prospective, open label, multicentre, randomised, controlled Phase III study conducted by the Cancer and Leukemia Group B (CALGB) under the auspices of the National Cancer Institute.[55]
- AZA-001 was an international, multicentre, controlled, open label, randomised, parallel-group, comparative Phase III study conducted by Pharmion (now Celgene).[46]

Study CALGB 9221 cannot be included in this review because it does not meet the inclusion criteria, specifically because the study population included both low- and high-risk MDS patients. However, a brief description of the study is appropriate here as it provides background information and supports the rationale for the pivotal trial of azacitidine (Study AZA-001) in higher-risk MDS patients.

Silverman *et al* conducted a Phase III study (CALGB 9221) which randomised 191 patients to subcutaneous (SC) azacitidine at 75 mg/m^2/day for seven days every 28 days, versus BSC. Patients in the BSC arm whose disease worsened were permitted to cross over to receive azacitidine. Nearly half of the BSC group met crossover criteria and thus received azacitidine treatment. CALGB response criteria were used in this study because patient enrolment predated International Working Group (IWG) criteria. Responses occurred in 60% of patients in the azacitidine arm (7% complete remission [CR], 16% partial remission [PR], 37% haematological improvement)

compared with 5% (improved) receiving BSC (p<0.001). As seen previously in other trials, most responses were seen in the third or fourth month.[63]

Median time to leukaemic transformation or death was 21 months for azacitidine versus 13 months for BSC (p=0.007). Transformation to AML occurred as the first event in 15% of patients treated with azacitidine and 38% of patients receiving BSC (p<0.001), suggesting a significant delay in leukaemic transformation in azacitidine-treated patients. Eliminating the confounding effect of early crossover to azacitidine, a landmark analysis after six months showed median survival of an additional 18 months for azacitidine and 11 months for BSC (p=0.03).[63]

QoL assessment found significant advantages for patients initially randomised to azacitidine. Patients in the azacitidine arm experienced significantly greater improvement in fatigue (p=0.001), dyspnoea (p=0.0014), physical functioning (p=0.0002), positive affect (p=0.0077) and psychological distress (p=0.015) than those in the BSC arm.[63,64]

In conclusion, this study found that azacitidine treatment results in significantly higher response rates, improved QoL, reduced risk of leukaemic transformation, and improved survival compared with BSC.[65]

The full list of publications and references derived from Study CALGB 9221 is shown in Table 6.2.

Table 6.2. Publications and references associated with Study CALGB 9221

Study	Publications/references
1	Celgene Ltd. Data on file: Additional Analyses to CALGB 9221: A Randomized Phase III Controlled Trial of Subcutaneous 5 Azacitidine (NSC # 102816) vs. Observation in Myelodysplastic Syndromes, 2004.
2	Kornblith AB, Herndon JE 2nd, Silverman LR, Demakos EP, Odchimar-Reissig R, Holland JF *et al.* Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. *J Clin Oncol* 2002; **20:** 2441–2452.
3	Silverman LR, McKenzie DR, Peterson BL, Demakos EP, Malone NT, Holland JF *et al.* Azacitidine Prolongs Survival and Time to AML Transformation in High-Risk Myelodysplastic Syndrome (MDS) Patients ≥ 65 Years of Age. *Blood (ASH Annual Meeting Abstracts)* 2005; **106:** Abstract 2524.
4	Silverman LR, McKenzie DR, Peterson BL, Odchimar-Reissig R, Hinkle R, Backstrom JT *et al.* Rates of Infection and Bleeding Are Not Increased in Patients with Myelodysplastic Syndromes (MDS) Treated with Azacitidine Compared with Supportive Care. *Blood (ASH Annual Meeting Abstracts)* 2005; **106:** Abstract 2525.
5	Silverman LR, McKenzie DR, Peterson BL, De Castro CM, Ellerton J, Knapp KN *et al.* Response Rates Using International Working Group (IWG) Criteria in Patients with Myelodysplastic Syndromes (MDS) Treated with Azacitidine. *Blood (ASH Annual Meeting Abstracts)* 2005; **106:** Abstract 2526.
6	Silverman LR, Peterson BL, Holland JF, Stone RM, Powell BL, Larson RA *et al.* Transfusion independence in patients with myelodysplastic syndromes treated with azacitidine. *J Clin Oncol (Meeting Abstracts)* 2006; **24:** Abstract 6576.
7	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.
8	Silverman LR, McKenzie DR, Peterson BL, Demakos EP, Holland JF, Larson RR *et al.* Analysis of Survival, AML Transformation, and Transfusion Independence in Patients with High-Risk Myelodysplastic Syndromes (MDS) Receiving Azacitidine Determined Using a Prognostic Model. *Blood (ASH Annual Meeting Abstracts)* 2005; **106:** Abstract 2523.
9	Silverman LR, McKenzie DR, Peterson BL, Stone RM, Powell BL, Mayo C *et al.* Response Rates in Patients with Acute Myeloid Leukemia (AML), Treated with Azacitidine, Using WHO and International Working Group (IWG) Criteria for Myelodysplastic Syndrome (MDS). *Blood (ASH Annual Meeting Abstracts)* 2005; **106:** Abstract 1848.
10	Silverman LR, McKenzie DR, Peterson BL, Holland JF, Backstrom JT, Beach CL *et al.* Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol* 2006; **24:** 3895–3903.

Study AZA-001 is considered pivotal in supporting the clinical benefit of azacitidine in higher-risk MDS patients in Europe. Primary efficacy findings were presented in an abstract at the 2007 American Society of Hematology annual meeting[66] and were published in full in March 2009 in *The Lancet Oncology.*[46] Further analyses of survival in patient subsets have been published in abstract form.[27,67] The publications and references derived from Study AZA-001 are shown in Table 6.3.

Table 6.3. Publications and references associated with Study AZA-001

Study	Publications/references
1	Fenaux P, Mufti GJ, Santini V, Finelli C, Giagounidis A, Schoch R *et al.* Azacitidine (AZA) Treatment Prolongs Overall Survival (OS) in Higher-Risk MDS Patients Compared with Conventional Care Regimens (CCR): Results of the AZA-001 Phase III Study. *Blood (ASH Annual Meeting Abstracts)* 2007; **110:** Abstract 817.
2	Fenaux P, Gattermann N, Seymour J, Hellström-Lindberg E, Mufti GJ, Duehrsen U *et al.* Effect of azacitidine (AZA) vs low-dose Ara-C (LDAC) on overall survival (OS), hematologic response, transfusion independence, and safety in patients (pts) with higher-risk myelodysplastic syndromes (MDS). *Haematologica* 2008; **93**(Suppl 1): Abstract 0224.
3	Fenaux P, Mufti GJ, Hellström-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.
4	Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Sanz G *et al.* Azacitidine Prolongs Overall Survival (OS) and Reduces Infections and Hospitalizations in Patients (Pts) with WHO-Defined Acute Myeloid Leukemia (AML) Compared with Conventional Care Regimens (CCR). *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** Abstract 3636.
5	List AF, Fenaux P, Mufti GJ, Hellström-Lindberg E, Gore S, Bennett JM *et al.* Effect of azacitidine (AZA) on overall survival in higher-risk myelodysplastic syndromes (MDS) without complete remission. *J Clin Oncol (Meeting Abstracts)* 2008; **26:** Abstract 7006.
6	Mufti GJ, Fenaux P, Hellström-Lindberg E, Santini V, List AF, Gore S *et al.* Treatment of high-risk MDS patients (pts) with -7/del(7q) with azacitidine (AZA) versus conventional care regimens (CCR): Effects on overall survival (OS). *J Clin Oncol (Meeting Abstracts)* 2008; **26:** Abstract 7033.
7	Santini V, Fenaux P, Mufti GJ, Hellström-Lindberg E, List AF, Silverman LR *et al.* Patient outcome measures during prolonged survival in patients (Pts) with high-risk myelodysplastic syndromes (MDS) treated with azacitidine (AZA). *J Clin Oncol (Meeting Abstracts)* 2008; **26:** Abstract 7028.
8	Santini V, Fenaux P, Mufti GJ, Hellström-Lindberg E, Silverman LB, List A *et al.* Management and Supportive Care Measures of Adverse Events (AEs) in Higher-Risk MDS Patients (Pts) Treated with Azacitidine (AZA). *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** Abstract 1653.
9	Santini V, Fenaux P, Vey N, Hofmann WK, Robak T, Bacigalupo A *et al.* European inter-country treatment selection differences do not alter overall survival benefit shown with azacitidine vs conventional care regimens in higher-risk myelodysplastic syndromes. *Haematologica* 2008; **93**(Suppl 1): Abstract 0236.
10	Seymour JF, Fenaux P, Silverman LB, Mufti GJ, Hellström-Lindberg E, Santini V *et al.* Effects of Azacitidine (AZA) Vs Conventional Care Regimens (CCR) in Elderly (>=75 years) Patients (Pts) with Myelodysplastic Syndromes (MDS) from the AZA-001 Survival Trial. *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** Abstract 3629.
11	Silverman LR, Fenaux P, Mufti GJ, Santini V, Hellström-Lindberg E, Gattermann N *et al.* The Effects of Continued Azacitidine (AZA) Treatment Cycles on Response in Higher-Risk Patients (Pts) with Myelodysplastic Syndromes (MDS). *Blood (ASH Annual Meeting Abstracts)* 2008; **112:** Abstract 227.

6.2.2.2. Phase III RCTs of comparators to azacitidine

In total, seven Phase III RCTs of comparator interventions were identified for inclusion in the systematic review. In each RCT, the therapy or its comparator comprised either BSC or chemotherapy or both (see Table 6.1 for a full list of intervention and comparator studies).

6.2.3. Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

Celgene has an active publication strategy for 2009–10. Over the next 12 months, several further publications supporting the use of azacitidine in higher-risk MDS patients are expected. These are detailed in Table 6.4.

Table 6.4. Anticipated publications over the next 12 months

Anticipated lead author	Anticipated journal of publication	Anticipated publication date	Details of planned publication
Lyons	*J Clin Oncol*	Published online in March 2009	Haematological response to three alternative dosing schedules of azacitidine in patients with MDS
Silverman	To be confirmed	Quarter 4, 2009	Effects of continued azacitidine treatment cycles on response in patients with higher-risk MDS (This follows on from Abstract 227 presented by Silverman *et al* at the ASH 2008 Annual Meeting)
Fenaux	To be confirmed	Quarter 4, 2009	Azacitidine prolongs overall survival compared with CCR in patients with AML as defined by the WHO (This follows on from Abstract 3636 presented by Fenaux *et al* at the ASH 2008 Annual Meeting)
Fenaux	To be confirmed	Quarter 4, 2009	Azacitidine results in significant prolongation of overall survival and haematological response compared with low-dose chemotherapy (This follows on from Abstract 0224 presented by Fenaux *et al* at the EHA 2008 Congress)
List	To be confirmed	Quarter 4, 2009	Effect of azacitidine on overall survival in higher-risk MDS patients without complete remission (This follows on from Abstract 7006 presented by List *et al* at the ASCO 2008 Annual Meeting)
Santini	To be confirmed	Quarter 4, 2009	Practical management of the most frequently observed adverse events with azacitidine treatment (This follows on from Abstract 1653 presented by Santini *et al* at the ASH 2008 Annual Meeting)
Seymour	To be confirmed	Quarter 4, 2009	Effects of azacitidine versus CCR in elderly patients with MDS (This follows on from Abstract 3629 presented by List *et al* at the ASH 2008 Annual Meeting)

Key: AML: acute myeloid leukaemia; ASCO: American Society of Clinical Oncology; ASH: American Society of Hematology; CCR: conventional care regimen; EHA: European Hematology Association; MDS: myelodysplastic syndrome; WHO: World Health Organization

6.3. Summary of methodology of relevant RCTs for azacitidine

Study AZA-001 is considered pivotal in supporting the clinical benefit of azacitidine in higher-risk MDS patients. This section will describe methods and results as reported

by Fenaux *et al.*[46] Where more detailed descriptions are required; for example, with regard to blinding methods, data will be cited from the full CSR for Study AZA-001.[56]

6.3.1. Background and explanation of rationale for Study AZA-001

The efficacy of azacitidine in treating MDS has been evaluated in several open label clinical studies. The dosage regimen used in all of the studies except one was 75 mg/m^2 given by continuous intravenous (IV) infusion or SC injection daily for seven days every four weeks, with dose adjustments based on toxicity and clinical response. In a randomised, controlled, Phase III study of azacitidine versus BSC alone conducted in MDS patients (Study CALGB 9221), azacitidine produced higher response rates than BSC alone, and appeared to alter the natural course of MDS with longer time to evidence of AML and with evidence of improved survival.[63]

The aim of Study AZA-001 was to compare the effect of azacitidine plus BSC with CCRs plus BSC on overall survival in higher-risk MDS patients. Based on the published results of the CALGB 9221 study in MDS, which demonstrated a significant benefit for azacitidine compared with BSC for clinical response, a trend toward improved survival, and a delay in disease progression, it was considered unethical by clinical advisors to initiate a long-term comparative study involving only a therapy already shown to be significantly inferior to azacitidine.[63] Furthermore, it was cautioned that ethics committees in some of the participating countries would likely not approve a protocol that compared a drug with known benefits with BSC alone without the option of some active treatment. At the time of protocol development, there were differences in regional practices and there was no single standard of care shown to improve survival in the treatment of MDS. Low-dose chemotherapy and standard-dose chemotherapy, although not proven to affect survival, were accepted therapies for MDS used in local practice in the countries in which this study was to be conducted. Therefore, the three CCR options chosen for the current study included BSC alone, low-dose chemotherapy plus BSC and standard-dose chemotherapy plus BSC.

6.3.2. Patient population

To be eligible for Study AZA-001, patients had to have a diagnosis of primary MDS and:

- Be aged at least 18 years with a life expectancy of at least three months
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2

- Have an IPSS classification of intermediate-2 or high risk
- Have a diagnosis of MDS, defined as RAEB or RAEB-T according to the FAB classification, or CMML according to the modified FAB classification, with peripheral monocytosis (monocytes >1 x 10^9/l), dysplasia in one or more myeloid cell lines, 10–29% blasts in the bone marrow (BM) and a white blood cell (WBC) count <13,000 x 10^6/l
- Have had no prior treatment of MDS with transplantation or cytotoxic therapy
- Have a low probability of proceeding to BM transplantation or SCT following remission.[46,56]

Patients with therapy-related MDS, previous azacitidine treatment, or planned allogeneic SCT were excluded.[46]

6.3.3. Randomisation and allocation to treatment

Study AZA-001 was conducted as an international, multicentre, controlled, open label, randomised, parallel-group, comparative Phase III study of azacitidine versus CCR. Study subjects were MDS patients with IPSS intermediate-2 or high-risk disease and either RAEB or RAEB-T according to the FAB classification (defined as 5–20% and 21–30% blasts respectively, with RAEB-T being equivalent to AML according to the current WHO classification).[12,46]

The CCR consisted of three options, one of which was to be assigned to the patient by the investigator prior to randomisation. These were:

- BSC alone.
- Low-dose chemotherapy plus BSC
- Standard-dose chemotherapy plus BSC.[46]

Qualifying patients were then randomised at a ratio of 1:1 to receive treatment with:

- Azacitidine SC for seven days every 28 days plus BSC
- Or the investigator assigned CCR plus BSC.[46]

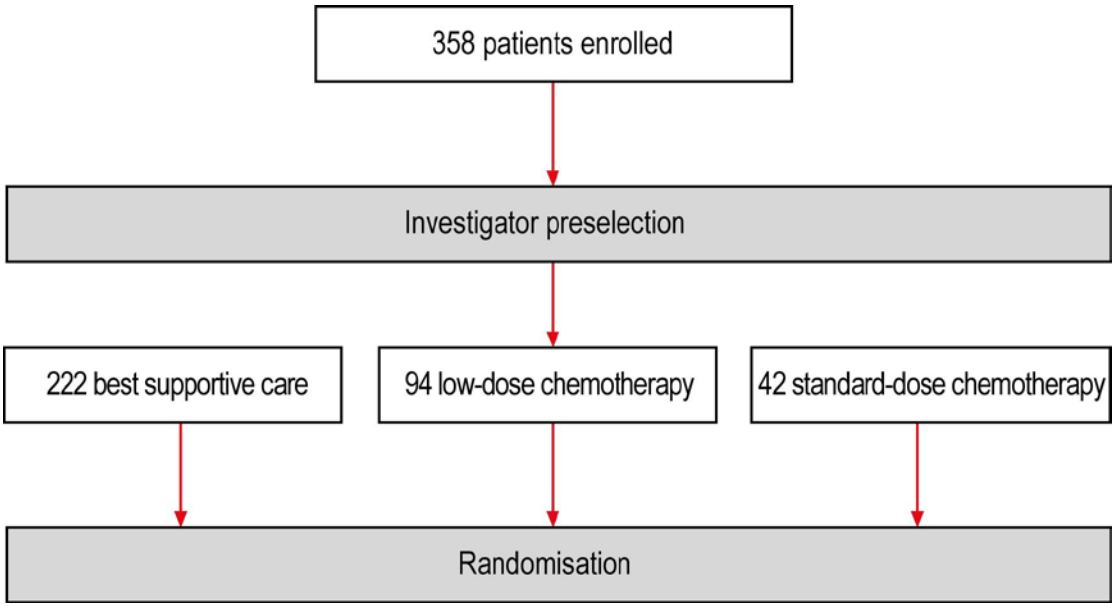
Azacitidine was given as an SC injection at a dose of 75 mg/m^2/day on Days 1–7 of a 28-day cycle. CCR consisted of BSC alone (including transfusions, antibiotics and growth factors) or with the addition of either low-dose chemotherapy (initial dose of cytarabine 20 mg/m^2/day for 14 days, repeated every 28 days for at least four cycles) or standard-dose chemotherapy (induction with IV cytarabine 100–200 mg/m^2/day for seven days plus three days of IV daunorubicin 45–60 mg/m^2/day [or alternatively IV idarubicin 9–12 mg/m^2/day or IV mitoxantrone 8–12 mg/m^2/day] followed by a

maximum of two consolidation cycles consisting of reduced doses of the drugs used for induction). Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) were permitted based on criteria described in the protocol, but erythropoietin was not allowed during the course of the study.[46]

A total of 738 patients were screened in the study; 380 failed screening, most often because eligibility criteria were not met (301/738, 40.8%). Of those not meeting eligibility criteria, the most common reason was diagnosis of AML, followed by low IPSS score and FAB classification other than RAEB or RAEB-T.[56]

The study used blocked randomisation that stratified patients by FAB and IPSS classifications to ensure a balanced assignment of patients to the two treatment groups. Randomisation was done centrally, with allocation by telephone; patients were assigned to treatment in blocks of four within each stratum. The randomisation sequence was computer generated independently by Pharmaceutical Product Development (Wilmington, NC, USA). Before randomisation, investigators preselected the most appropriate of the three CCRs for all patients on the basis of age, general condition, co-morbidities and patient preference. Patients randomised to CCR were to receive the investigator preselected treatment option (see Figure 6.2) Patients were not permitted to cross over between any of the treatment groups during the study.[46]

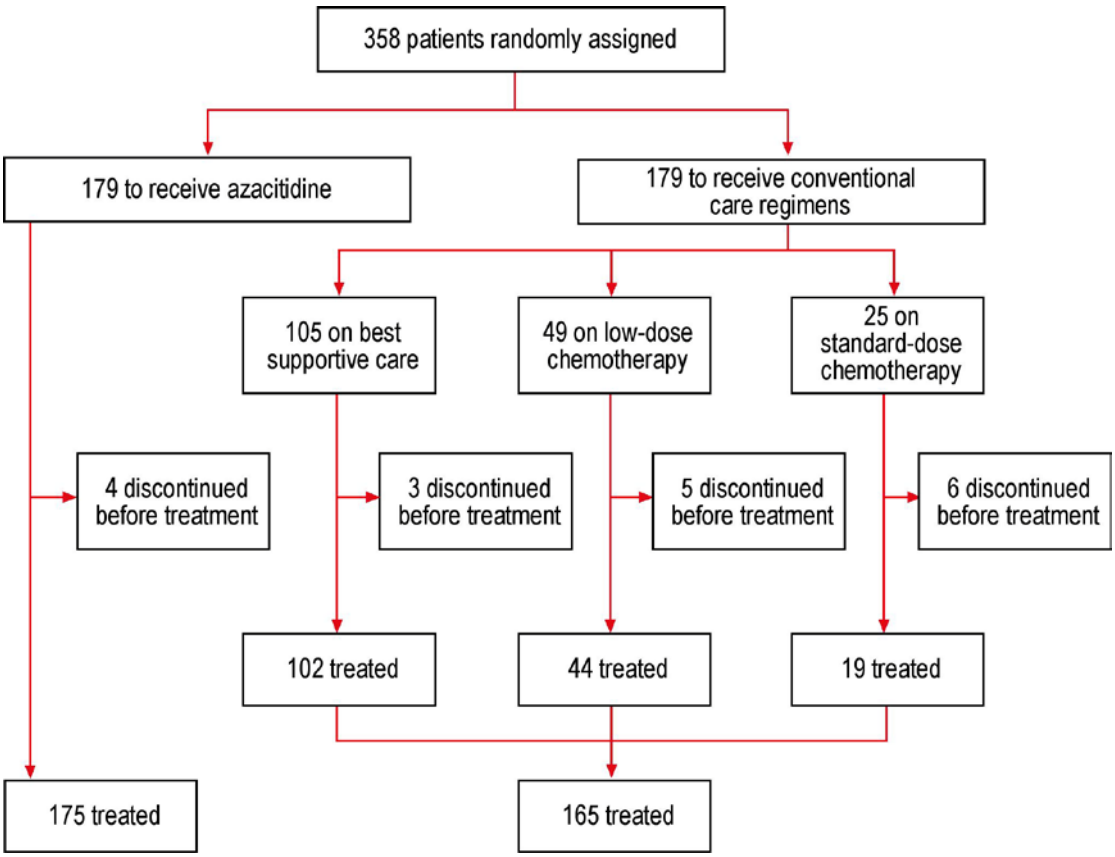
Figure 6.2. Investigator preselection[46]



6.3.4. Patient disposition

Between 13 February 2004 and 7 August 2006, 358 patients (intention-to-treat [ITT] population) at 79 sites in 15 countries were randomly assigned to receive either azacitidine (n=179) or CCR (n=179). Of those assigned to CCR, 105 were to receive BSC, 49 low-dose chemotherapy and 25 standard-dose chemotherapy (see Figure 6.3).[46] Randomised patients who withdrew from the study prior to receiving treatment included four from the azacitidine treatment group, three from the BSC-only group, five from the low-dose chemotherapy group and six from the standard-dose chemotherapy group. The reasons for withdrawal were: adverse events (AEs; n=2), withdrew consent (n=9), death (n=1) transformation to AML (n=2); protocol violation (n=3) and sponsor decision (n=1).[56]

Figure 6.3. Trial profile[46]



6.3.5. Blinding

This was an open label study. However, certain subjective evaluations, such as eligibility to enter the study and haematological response (but not haematological improvement), were to be made by an independent central reviewer in addition to

local evaluations by the investigator. The central pathology reviewer and adjudicator, as well as the central cytogenetic reviewer, were to be blinded to patient treatment assignment and their evaluations were to be used for the statistical efficacy analyses. The Independent Review Committee (IRC) which reviewed and confirmed MDS FAB and WHO diagnoses, IPSS classifications, and IWG response findings and durations was blinded to investigative site, patient identification numbers, patient initials, and investigative site number. This was accomplished by the use of dummy patient identifiers which were unique for each patient and not the actual patient number used in the study. The interim efficacy analysis was conducted by an independent third-party statistician.[56]

6.3.6. Participants

In summary, the number of patients randomised to azacitidine or all CCRs was comparable in terms of age, baseline severity of MDS (as measured by the IPSS, FAB and WHO classifications), ECOG performance status and time since original diagnosis (see Table 6.5).[46]

Table 6.5. Baseline demographics and disease characteristics by treatment group and investigator preselection[46]

	Total ITT		BSC only (n=222)		Low-dose chemotherapy (n=94)		Standard-dose chemotherapy (n=42)	
	Azacitidine (n=179)	CCR (n=179)	Azacitidine (n=117)	BSC (n=105)	Azacitidine (n=45)	LDC (n=49)	Azacitidine (n=17)	SDC (n=25)
Age (years)	69 (42–83)	70 (38–88)	69 (52–83)	70 (50–88)	69 (42–82)	71 (56–85)	63 (45–78)	65 (38–76)
≤64	57 (32%)	43 (24%)	33 (28%)	24 (23%)	14 (31%)	7 (14%)	10 (59%)	12 (48%)
≥65	122 (68%)	136 (76%)	84 (72%)	81 (77%)	31 (69%)	42 (86%)	7 (41%)	13 (52%)
Sex								
Men	132 (74%)	119 (67%)	81 (69%)	67 (64%)	39 (87%)	35 (71%)	12 (71%)	17 (68%)
Women	47 (26%)	60 (34%)	36 (31%)	38 (36%)	6 (13%)	14 (29%)	5 (29%)	8 (32%)
FAB classification								
RAEB	104 (58%)	103 (58%)	69 (59%)	68 (65%)	27 (60%)	25 (51%)	8 (47%)	10 (40%)
RAEB-T	61 (34%)	62 (35%)	38 (33%)	30 (29%)	15 (33%)	19 (39%)	8 (47%)	13 (52%)
CMML	6 (3%)	5 (3%)	5 (4%)	4 (4%)	1 (2%)	1 (2%)	0	0
AML	1 (1%)	1 (1%)	0	0	1 (2%)	0	0	1 (4%)
IPSS classification								
Intermediate-1	5 (3%)	13 (7%)	4 (3%)	9 (9%)	1 (2%)	2 (4%)	0	2 (8%)
Intermediate-2	76 (43%)	70 (39%)	48 (41%)	46 (44%)	22 (49%)	21 (43%)	6 (35%)	3 (12%)
High	82 (46%)	85 (48%)	57 (49%)	46 (44%)	19 (42%)	21 (43%)	6 (35%)	18 (72%)
Karyotype risk								
Good	83 (46%)	84 (47%)	53 (45%)	47 (45%)	24 (53%)	28 (57%)	6 (35%)	9 (36%)
Intermediate	37 (21%)	39 (22%)	25 (21%)	23 (22%)	7 (16%)	12 (25%)	5 (29%)	4 (16%)
Poor	50 (28%)	50 (28%)	33 (28%)	31 (30%)	13 (29%)	8 (16%)	4 (24%)	11 (44%)
Missing	9 (5%)	6 (3%)	6 (5%)	4 (4%)	1 (2%)	1 (2%)	2 (12%)	1 (4%)
WHO classification								
RAEB-1	14 (8%)	17 (10%)	8 (7%)	13 (12%)	3 (7%)	3 (6%)	3 (18%)	1 (4%)
RAEB-2	98 (55%)	95 (53%)	63 (54%)	60 (57%)	27 (60%)	24 (49%)	8 (47%)	11 (44%)
CMML-1	1 (1%)	0	1 (1%)	0	0	0	0	0
CMML-2	10 (6%)	5 (3%)	8 (7%)	3 (3%)	1 (2%)	0	1 (6%)	2 (8%)
AML	55 (31%)	58 (32%)	36 (31%)	27 (26%)	14 (31%)	20 (41%)	5 (29%)	11 (44%)
Indeterminate	1 (1%)	4 (2%)	1 (1%)	2 (2%)	0	2 (4%)	0	0
ECOG performance status								
0	78 (44%)	80 (45%)	47 (40%)	36 (34%)	21 (47%)	29 (59%)	10 (59%)	15 (60%)
1	86 (48%)	86 (48%)	59 (50%)	59 (56%)	21 (47%)	17 (35%)	6 (35%)	10 (40%)
2	13 (7%)	10 (6%)	11 (9%)	8 (8%)	1 (2%)	2 (4%)	1 (6%)	0
Missing	2 (1%)	3 (2%)	0	2 (2%)	2 (4%)	1 (2%)	0	0
Time since original diagnosis (years)								
<1	92 (51%)	95 (53%)	53 (45%)	53 (51%)	29 (64%)	28 (57%)	10 (59%)	14 (56%)
1–2	37 (21%)	45 (25%)	29 (25%)	27 (26%)	7 (16%)	12 (25%)	1 (6%)	6 (24%)
2–3	20 (11%)	10 (6%)	14 (12%)	6 (6%)	4 (9%)	3 (6%)	2 (12%)	1 (4%)
≥3	30 (17%)	29 (16%)	21 (18%)	19 (18%)	5 (11%)	6 (12%)	4 (24%)	4 (16%)

Data are median (range) or number (%)

Key: AML: acute myeloid leukaemia; BSC: best supportive care; CMML: chronic myelomonocytic leukaemia; CCR: conventional care regimen; ECOG: Eastern Cooperative Oncology Group; FAB: French-American-British; IPSS: International Prognostic Scoring System; ITT: intention to treat; LDC: low-dose chemotherapy; RAEB: refractory anaemia with excess blasts; RAEB-T: RAEB in transformation; SDC: standard-dose chemotherapy

6.3.7. Treatment period

As shown in Table 6.6, of all patients who discontinued treatment during the study, 70 (39.1%) discontinued azacitidine treatment versus 98 (54.7%) who discontinued CCR. Within this CCR group, the percentage of discontinuations was highest for the standard-dose chemotherapy patients (72.0%) and lowest for BSC-only patients (44.8%). Note that discontinuations included those patients randomised but not treated. In azacitidine patients, the most common reason for discontinuing study

treatment was progression, which occurred in 12.8% of patients (n=23) and was similar to the percentage of patients in the CCR group overall (11.2%; n=20). In CCR patients overall, the most common reason for discontinuing treatment was withdrawal of consent for treatment, 20.7% (n=37), compared with 8.4% of azacitidine patients (n=15); in the BSC and standard-dose chemotherapy groups, these patients accounted for almost half of the patients who discontinued.[56]

Table 6.6. Reasons for discontinuation of study drug[56]

	Number (%) of patients				
		CCR			
Reason*	**Azacitidine (n=179)**	**BSC (n=105)**	**Low-dose chemotherapy (n=49)**	**Standard-dose chemotherapy (n=25)**	**CCR total (n=179)**
Discontinued treatment prior to study closure	70 (39.1)	47 (44.8)	33 (67.3)	18 (72.0)	98 (54.7)
Adverse event	19 (10.6)	3 (2.9)	5 (10.2)	2 (8.0)	10 (5.6)
Protocol violation	1 (0.6)	3 (2.9)	2 (4.1)	2 (8.0)	7 (3.9)
Lost to follow-up†	1 (0.6)	0	0	1 (4.0)	1 (0.6)
Withdrew consent for treatment (remained in follow-up)	15 (8.4)	22 (21.0)	8 (16.3)	7 (28.0)	37 (20.7)
Sponsor decision	0	0	1 (2.0)	1 (4.0)	2 (1.1)
Non-responder	11 (6.1)	7 (6.7)	9 (18.4)	2 (8.0)	18 (10.1)
Progression	23 (12.8)	10 (9.5)	7 (14.3)	3 (12.0)	20 (11.2)
Discrepant central and local pathology review	0	1 (1.0)	0	0	1 (0.6)
Missing‡	0	1 (1.0)	1 (2.0)	0	2 (1.1)

* Patients who discontinued treatment due to death or transformation to AML are not included in the reasons for discontinuation above since these patients were considered to have completed the study (study endpoints)
† Patients were lost to follow-up during the treatment period; however, contact was re-established during the follow-up period before becoming lost to follow-up again. Therefore, these patients are counted as lost to follow-up both during the treatment and follow-up periods
‡ Reason for discontinuation was not documented
Key: AML: acute myeloid leukaemia; BSC: best supportive care; CCR: conventional care regimen

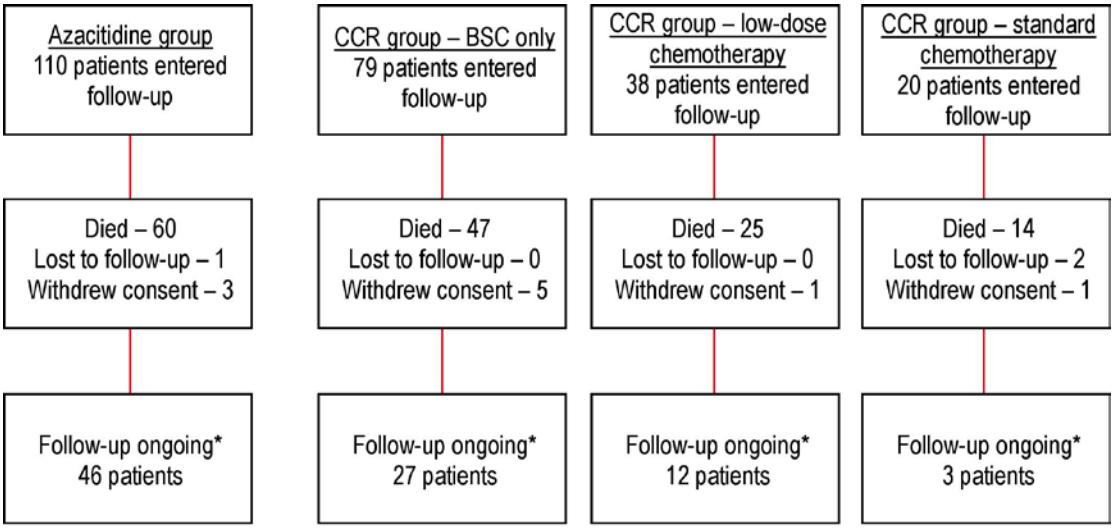
6.3.8. Follow-up period

The follow-up period was the time from the last treatment visit until study closure. Patients followed up included those who discontinued treatment for any reason other than death or being lost to follow-up, and did not withdraw consent for follow-up. The majority of patients (more than 60% of patients within each of the treatment arms) entered follow-up (see Figure 6.4). As a reflection of the shorter duration of the treatment period for the CCR group, the percentage of patients entering the follow-up period was higher in the CCR group overall (76.5%; n=137) than in the azacitidine group (61.5%; n=110).[56]

During the follow-up period, the percentage of patients who withdrew consent or who were lost to follow-up (that is, contact was permanently lost with no further data

collection) was low in both the azacitidine and CCR groups: four azacitidine patients (2.2%) versus nine CCR patients (5.0%) (see Figure 6.4). At study closure, 46 azacitidine patients (25.7%) and 42 CCR patients (23.5%) were continuing to be followed. Follow-up was terminated on the date of the close-out study visit for each patient, except for azacitidine patients, who were permitted to enter an extension phase upon fulfilment of particular criteria and at the discretion of the investigator (see Section 6.3.8.1). The median duration of the follow-up period was 11.77 months for azacitidine patients; in the CCR regimens overall, the duration was 14.49 months.[56]

Figure 6.4. Follow-up period for Study AZA-001[56]



* Patients were still in follow-up at the time of study closure. Follow-up was terminated at the time of the final study close-out visit
Key: BSC: best supportive care; CCR: conventional care regimen

6.3.8.1. Patient eligibility for the AZA-001 extension study

Upon completion of the Study AZA-001 protocol, and at the discretion of the investigating physician, patients who were randomised to receive azacitidine and were continuing to receive azacitidine at the time of study closure, had completed 12 months of study treatment and follow-up, and who did not meet any of the criteria for mandatory withdrawal had the option of entering an extension protocol.[68] At the end of the study, 40 azacitidine patients entered the AZA-001 extension study.[69]

6.3.9. Outcomes

Efficacy analyses were by ITT. Safety analyses included all patients who received at least one dose of study drug and one or more safety assessments thereafter. The

primary endpoint was overall survival, analysed by comparison of the azacitidine and combined CCR groups. Secondary efficacy endpoints were time to transformation to AML, haematological response and improvement assessed with IWG 2000 criteria for MDS,[70] independence from red blood cell (RBC) transfusions for 56 consecutive days or more, number of infections requiring IV antimicrobials, and occurrence of AEs.[46]

6.3.10. Statistical analysis and definition of study groups

This study was designed with 90% power – on the basis of a log-rank analysis – to detect a hazard ratio (HR) of 0·60 for overall survival in the azacitidine group compared with that in the CCR group, with a two-sided alpha of 0·05. The protocol specified that about 354 patients were to be randomly assigned over 18 months and then monitored for at least 12 months of treatment and follow-up, resulting in at least 167 deaths over the 30-month trial period. Recruitment and a minimum follow-up of at least 12 months for all patients, however, necessitated a longer study period. With a study period of 42 months and 195 deaths, the study had 95% power under the assumptions of the design.[46]

Overall survival was defined as the time from randomisation to death from any cause. Patients who remained alive were censored at the time of last follow-up. Time to transformation to AML was measured from randomisation to development of 30% or greater BM blasts. Patients free from transformation to AML were censored for this analysis at the time of last adequate BM sample. Randomisation and analyses were stratified by FAB subtype and IPSS group.[46]

Time-to-event curves were estimated with the Kaplan–Meier method[71] and compared with stratified log-rank tests (primary analysis). Stratified Cox proportional hazards regression models[72] were used to estimate HRs and associated 95% confidence intervals (CIs). The primary analysis of overall survival between the azacitidine and combined CCR groups used the stratified Cox proportional hazards model without any covariate adjustments to estimate the HR. Cox proportional hazards regression with stepwise selection was used to assess the baseline variables of sex, age, time since original diagnosis of MDS, ECOG performance status, number of previous RBC transfusions, number of previous platelet transfusions, measurements of haemoglobin, platelets, absolute neutrophil count and lactate dehydrogenase, BM blast percentage, and presence or absence of cytogenetic –7/del(7q) abnormality. The final model included ECOG performance status, lactate dehydrogenase,

haemoglobin, number of previous RBC transfusions, and presence or absence of the cytogenetic –7/del(7q) abnormality. Supportive overall survival analyses used the final Cox proportional hazards model.[46]

The consistency of treatment effect across subgroups was assessed with the difference in likelihood ratio between the full model with treatment subgroup and treatment-by-subgroup interaction, and the reduced model without the interaction. Additional supportive efficacy analyses by investigator preselection compared the azacitidine subgroups with the individual treatments that comprised CCR.[46]

Haematological response, transfusion independence and haematological improvement in the azacitidine and CCR groups were compared with Fisher's exact test. The rate of infection requiring IV antimicrobials was calculated with the number of recorded infections treated with IV antimicrobials divided by the total number of patient-years of follow-up. The relative risk (RR) of infection was calculated as the rate of infection in patients taking azacitidine compared with the rate in those receiving CCR. The Mantel–Haenszel estimate of the common RR, the associated 95% CI and the test that it equals unity were calculated.[73] Analyses were done with SAS (version 9.13).[46]

6.3.11. Critical appraisal of relevant RCTs

Study AZA-001 was a multicentre, open label, Phase III, randomised, parallel-group, controlled trial of azacitidine versus CCR in higher-risk MDS patients. The study was conducted at 79 investigational sites in Australia, the EU (including the UK), Russia, and the USA. At the time of protocol development, there were differences in regional practices and there was no single standard of care shown to improve survival in the treatment of MDS.[46] This was also true for the UK.

To minimise potential bias in the selection of the CCR, the intended CCR was chosen at the time of screening, and before randomisation to azacitidine or CCR. Patients were centrally randomised using the Interactive Voice Response System, which was operated through PPD Ltd, a contract research organisation in the UK. Although this was an open label trial, individual patient treatment assignment was blinded to the central reviewers and the IRC. Justification of sample size was provided.[56]

Patients in both the azacitidine and CCR study groups were well balanced with regard to baseline demographics and disease classification. All efficacy analyses

were of the ITT population, defined as all randomised patients, who were analysed according to their randomised treatment rather than the treatment actually received. The statistical analysis was appropriate to the study question.[56]

The dosage regimen used in all of the studies except one was 75 mg/m^2 given by continuous IV infusion or SC injection daily for seven days every four weeks, with dose adjustments based on toxicity and clinical response.[56] This is the same dosage regimen detailed in the Vidaza Summary of Product Characteristics.[1]

How do the RCT participants compare with patients who are likely to receive the intervention in the UK? Consider factors known to affect outcomes in the main indication, such as demographics, epidemiology, disease severity, setting.

Study AZA-001 was international and multicentre in design with 79 investigative sites in 15 countries. Patients enrolled in the study were representative of those with higher-risk MDS in demographic characteristics, presenting signs and symptoms, and subtypes on the FAB classification. In the comparison of azacitidine with the three most common treatments in higher-risk MDS, including two active treatments, treatment decisions were made in light of different treatment practices influenced by regional, national and local guidelines and consensus criteria. The study investigators consulted the Düsseldorf MDS Registry to confirm that the proportions of patients selected to the BSC, low-dose chemotherapy and standard-dose chemotherapy groups were consistent with treatment practices. For these reasons, the results are applicable to the improvement of the treatment of MDS internationally.[46]

6.4. Results of the Phase III RCT for azacitidine

6.4.1. Efficacy results

Baseline characteristics were well balanced between the azacitidine and CCR groups. The investigator preselection subgroups showed some imbalances as expected: namely, patients selected to receive standard-dose chemotherapy were younger and had better ECOG performance status and higher-risk disease (see Table 6.5).[46]

Azacitidine was given for a median of nine cycles (interquartile range [IQR] 4–15), and 151 (86%) of 175 patients who received azacitidine remained on 75 mg/m^2 per day throughout the study with no dose adjustments. The median azacitidine cycle

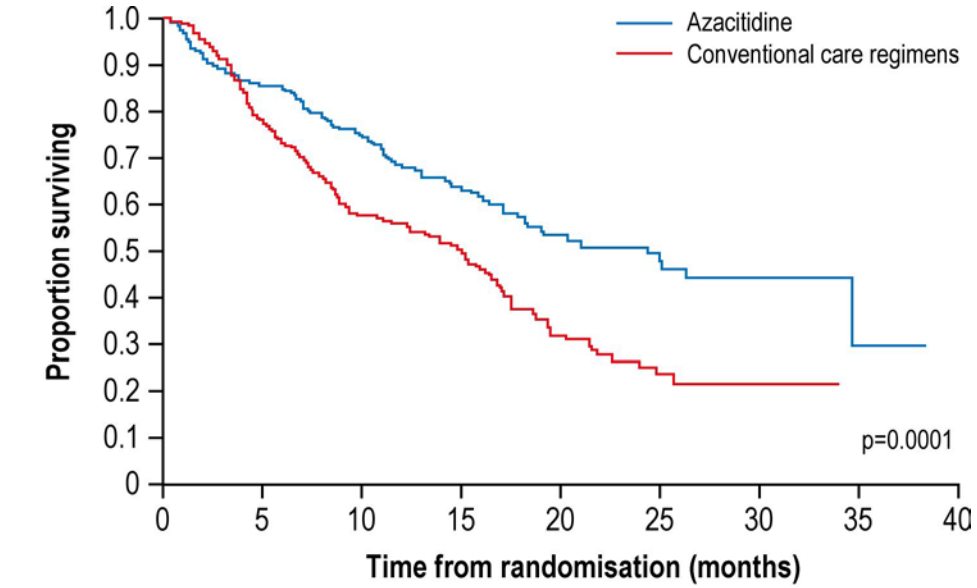
length was 28 days (IQR 28–35); 862 (54%) of the 1,611 cycle lengths were 28 days, 413 (26%) were 29–35 days and 336 (21%) were longer than 35 days.[46] The mean azacitidine cycle length reported in the AZA-001 CSR was 36.1 days.[56]

Low-dose chemotherapy was given for a median of four and a half cycles (IQR 2–8); 59 (29%) of the 201 cycle lengths were 28 days, 82 (41%) were 29–35 days, and 60 (30%) were longer than 35 days; the overall median was 35 days (IQR 28–36). Standard-dose chemotherapy was given for a median of one cycle (IQR 1–3) and BSC for a median of 6·2 months (IQR 3·6–10·3).[46]

6.4.1.1. Primary endpoint

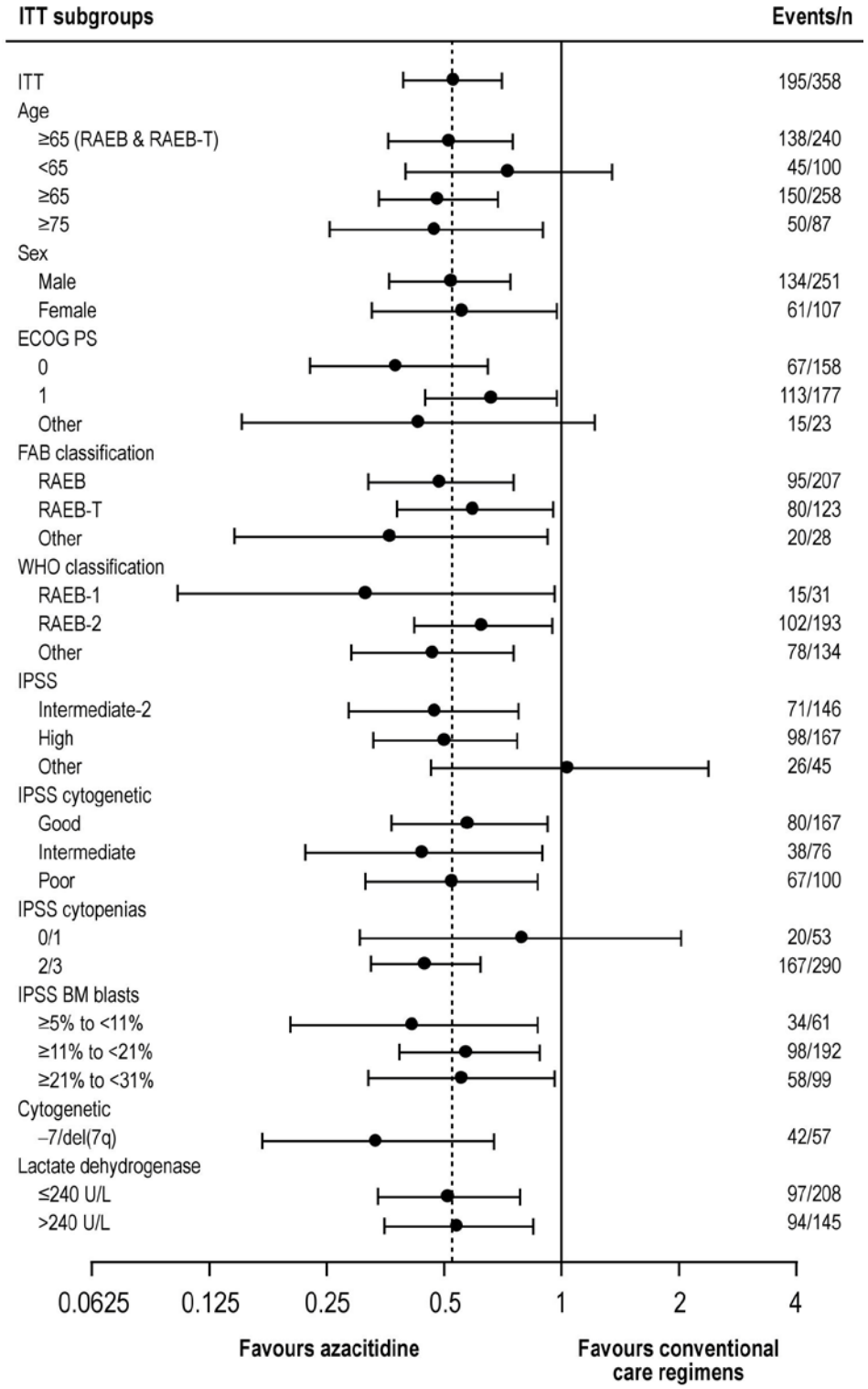
At the time of last follow-up, 82 patients in the azacitidine group had died compared with 113 in the CCR group. After a median follow-up of 21·1 months (IQR 15·1–26·9), median Kaplan–Meier overall survival was 24·5 months (IQR 9·9–not reached) in the azacitidine group compared with 15 months (IQR 5·6–24·1) in the CCR group, a difference of 9·4 months (stratified log-rank p=0·0001; see Figure 6.5). The HR for overall survival was 0·58 (95% CI 0·43–0·77). Kaplan–Meier survival curves for the azacitidine and CCR groups separated permanently after about three months, at which time 140 (78%) of 179 patients receiving azacitidine had completed three cycles of treatment (see Figure 6.5). At two years, on the basis of Kaplan–Meier estimates, 50·8% (95% CI 42·1–58·8) of patients in the azacitidine group were alive compared with 26·2% (95% CI 18·7–34·3) in the CCR group (p<0·0001).[46]

Figure 6.5. Overall survival[46]



The supportive analysis of all predefined subgroups of patients showed consistency of the azacitidine effect on overall survival compared with CCR (see Figure 6.6). In particular, overall survival was better for azacitidine than CCR in all the cytogenetic subgroups on the IPSS (poor prognosis: HR=0·53, 95% CI 0·32–0·87, p=0·012; intermediate prognosis: HR=0·44, 95% CI 0·22–0·88, p=0·021; and good prognosis: HR=0·59, 95% CI 0·37–0·92, p=0·021). In patients with –7/del(7q), median Kaplan–Meier overall survival was 13·1 months (IQR 3·9–24·5, 95% CI 9·9–24·5) in the azacitidine group (n=30) compared with 4·6 months (IQR 2·9–9·3, 95% CI 3·5–6·7) in the CCR group (n=27), giving an HR of 0·34 (95% CI 0·17–0·67, p=0·0017; see Figure 6.6).[46]

Figure 6.6. Hazard ratio and 95% CI for overall survival in the ITT analysis[46]



Hazard ratios and CIs determined with stratified Cox proportional hazards model adjusted for treatment, subgroup, ECOG performance status, lactate dehydrogenase, haemoglobin, number of previous red blood cell transfusions, and presence or absence of the cytogenetic –7/del(7q) abnormality. No subgroup-by-treatment interactions were significant (p>0·20). The horizontal axis uses a logarithmic scale. The dotted line is the hazard ratio in the primary ITT analysis; the hazard ratio and CI are from the stratified Cox regression model with treatment as the only term

Key: BM: bone marrow; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; FAB: French-American-British; IPSS: International Prognostic Scoring System; ITT: intention to treat; RAEB: refractory anaemia with excess blasts; RAEB-T: RAEB in transformation

In addition, a subgroup analysis of AML patients (median age 70 years) in Study AZA-001, which was presented by Fenaux *et al* at the American Society of Hematology 2008 Annual Meeting, found that median Kaplan–Meier overall survival was 24.5 months in the azacitidine group compared with 16.0 months in the CCR groups (HR=0.47, 95% CI 0.28–0.79, p=0.004). The two-year survival rate was 50% in the azacitidine group compared with 16% in the CCR group (p=0.0007).[74]

Furthermore, sensitivity analyses exploring the effect of the eight patients who received allogeneic SCT included in the ITT analyses determined that they did not affect the significance of the overall survival results.[46]

Similar to the primary overall survival comparison (azacitidine versus CCR), results from the investigator preselection subgroup analysis of overall survival showed significant differences favouring the study drug between azacitidine and BSC (9·6 months, p=0·0045) and azacitidine and low-dose chemotherapy (9·2 months, p=0·0006). The difference in the comparison between azacitidine (n=17) and standard-dose chemotherapy (n=25), however, was not significant (9·3 months, p=0·51; see Table 6.7). This may be because of the small number of patients in the analysis.[46]

6.4.1.2. Secondary endpoints

6.4.1.2.1 Time to transformation to AML

Median time to transformation to AML was 17·8 months (IQR 8·6–36·8, 95% CI 13·6–23·6) in the azacitidine group compared with 11·5 months (IQR 4·9–not reached, 95% CI 8·3–14·5) in the CCR group (HR=0·50, 95% CI 0·35–0·70, p<0·0001). Results from the investigator preselection subgroup showed a significant difference in time to transformation to AML for azacitidine versus BSC. Time to progression to AML did not differ significantly in the comparisons of azacitidine with either low-dose or standard-dose chemotherapy (see Table 6.7).[46]

Table 6.7. Comparison of overall survival and time to progression to AML for groups according to investigator preselection[46]

	BSC only (n=222)				**Low-dose chemotherapy (n=94)**				**Standard-dose chemotherapy (n=42)**			
	Azacitidine (n=117)	BSC (n=105)	HR (95% CI)	p-value	Azacitidine (n=45)	LDC (n=49)	HR (95% CI)	p-value	Azacitidine (n=17)	SDC (n=25)	HR (95% CI)	p-value
Overall survival (months)	21·1 (10·5–NR)	11·5 (5·7–NR)	0·58 (0·40–0·85)	0·0045	24·5 (8·4–34·7)	15·3 (4·9–25·8)	0·36 (0·20–0·65)	0·0006	25·1 (10·0–NR)	15·7 (8·2–24·1)	0·76 (0·33–1·74)	0·51
Time to transformation to AML (months)	15·0 (8·8–27·6)	10·1 (3·9–19·8)	0·41 (0·27–0·63)	<0·0001	15·0 (7·3–25·5)	14.5 (4·9–19.2)	0·55 (0·28–1·11)	0·097	23·1 (6·4–25·4)	10·7 (4·6–15·4)	0·48 (0·16–1·45)	0·19

Data are median (IQR)

HRs calculated with stratified Cox proportional hazards model adjusted for treatment, subgroup, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase, haemoglobin, number of previous red blood cell transfusions, and presence or absence of cytogenetic –7/del(7q) abnormality

No subgroup-by-treatment interactions were significant (p>0·20)

Key: AML: acute myeloid leukaemia; BSC: best supportive care; HR: hazard ratio; LDC: low-dose chemotherapy; NR: not reached; SDC: standard-dose chemotherapy

6.4.1.2.2 Response rates

The proportion of patients in the azacitidine group who achieved CR and PR was quite low, although significantly higher than in the CCR group (see Table 6.8). In the investigator preselection analysis, the proportion of patients achieving CR with azacitidine was significantly higher than with either BSC or low-dose chemotherapy, but not higher than with standard-dose chemotherapy. The proportion of patients achieving PR with azacitidine was significantly higher than with BSC, but not higher than with the other two treatments. The proportion of patients with any haematological improvement was significantly higher with azacitidine than with either BSC or low-dose chemotherapy, but not higher than with standard-dose chemotherapy (see Table 6.8).[46] Despite the relatively low CR and PR rates with azacitidine, overall survival was significantly prolonged with azacitidine compared with CCR (see Section 6.4.1.1). Analysis suggests that achievement of CR is not essential to improve survival, with PR and haematological improvement also associated with a survival benefit.[27]

Time to disease progression, relapse after CR or PR, and death were significantly longer in the azacitidine group (median 14·1 months, IQR 4·2–27·6) than in the CCR group (median 8·8 months, IQR 3·8–not reached; log-rank p=0·047). The proportions of erythroid and platelet improvements were higher in the azacitidine group than in the CCR group (see Table 6.8), but there was no significant difference in the frequency of major neutrophil improvement between the two treatment groups. Duration of haematological response (CR and PR and any haematological improvement) was significantly longer in the azacitidine group (median 13·6 months, IQR 5·9–26·4; 95% CI 10·1–16·3) than in the CCR group (median 5·2 months; IQR 2·9–12·2; 95% CI 4·1–9·7; log-rank p=0·0002). Median duration of CR plus PR in the azacitidine group was 3·2 months (IQR 2·2–4·4; 95% CI 2·4–4·2) versus 3·0 months (IQR 2·1–4·0; 95% CI 2·1–4·0; log-rank p=0·48) in the CCR group.[46]

Fifty (45%) of 111 patients (95% CI 35·6–54·8%) who were dependent on RBC transfusions at baseline in the azacitidine group became transfusion-independent compared with 13 (11·4%) of 114 (95% CI 6·2–18·7%) in the CCR group (p<0·0001).[46]

Table 6.8. Haematological response and improvement by treatment groups and investigator preselection[46]

	Total ITT (n=358)			BSC only (n=222)			Low-dose chemotherapy (n=94)			Standard-dose chemotherapy (n=42)		
	Azacitidine (n=179)	CCR (n=179)	p-value*	Azacitidine (n=117)	BSC (n=105)	p-value*	Azacitidine (n=45)	LDC (n=49)	p-value*	Azacitidine (n=17)	SDC (n=25)	p-value*
Haematological response												
Any remission	51 (29%)	21 (12%)	0·0001	32 (27%)	5 (5%)	<0·0001	14 (31%)	6 (12%)	0·042	5 (29%)	10 (40%)	0·53
CR	30 (17%)	14 (8%)	0·015	14 (12%)	1 (1%)	0·0008	11 (24%)	4 (8%)	0·047	5 (29%)	9 (36%)	0·75
PR	21 (12%)	7 (4%)	0·0094	18 (15%)	4 (4%)	0·0058	3 (7%)	2 (4%)	0·67	0	1 (4%)	1·00
Stable disease	75 (42%)	65 (36%)	0·33	52 (44%)	41 (39%)	0·50	15 (33%)	18 (37%)	0·83	8 (47%)	6 (24%)	0·18
Haematological improvement†												
Any improvement	87/177 49%)	51/178 (29%)	<0·0001	57/115 (50%)	32/105 (31%)	0·0058	24/45 (53%)	12/48 (25%)	0·0061	6/17 (35%)	7/25 (28%)	0·74
Major erythroid improvement	62/157 (40%)	17/160 (11%)	<0·0001	39/100 (39%)	8/96 (8%)	<0·0001	19/43 (44%)	4/41 (10%)	0·0005	4/14 (29%)	5/23 (22%)	0·70
Major platelet improvement	46/141 (33%)	18/129 (14%)	0·0003	27/89 (30%)	8/78 (10%)	0·0020	14/37 (38%)	6/31 (19%)	0·12	5/15 (33%)	4/20 (20%)	0·45
Major neutrophil improvement	25/131 (19%)	20/111 (18%)	0·87	13/85 (15%)	13/66 (20%)	0·52	9/33 (27%)	3/28 (11%)	0·12	3/13 (23%)	4/17 (24%)	1·00

Data are number (%) or number with improvement/number with data (%)

Haematological response and improvement based on International Working Group 2000 criteria for myelodysplastic syndromes

* p-value from Fisher's exact test for comparing patients with response between the azacitidine group and the combined group of CCR, or within investigator preselection, between azacitidine and the individual CCR

† Haematological improvement can include CR and PR

Key: BSC: best supportive care; CCR: conventional care regimen; CR: complete remission; ITT: intention to treat; LDC: low-dose chemotherapy; PR: partial remission; SDC: standard-dose chemotherapy

6.4.2. Safety results

The rate of infections treated with IV antimicrobials per patient-year in the azacitidine group was 0·60 (95% CI 0·49–0·73) compared with 0·92 (95% CI 0·74–1·13) in the CCR group (RR=0·66; 95% CI 0·49–0·87; p=0·0032). There was a significant interaction of treatment by investigator preselection for the rate of infection (p=0·0004). In the investigator preselection analysis, per-patient-year rates were similar when comparing azacitidine (0·66) and BSC (0·61; RR=1·09; 95% CI 0·74–1·65; p=0·69), but significantly lower with azacitidine (0·44) compared with low-dose chemotherapy (1·0; RR=0·44; 95% CI 0·25–0·86; p=0·017) and with azacitidine (0·64) versus standard-dose chemotherapy (2·3; RR=0·28; 95% CI 0·13–0·60; p=0·0059).[46]

The most common Grade 3 or 4 AEs were peripheral blood cytopenias for all treatments (see Table 6.9). 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 Table 6.9).[46]

Table 6.9. Deaths, discontinuations and Grade 3 or 4 haematological toxicity by treatment group and investigator preselection[46]

	Total ITT (n=358)		BSC only (n=222)		Low-dose chemotherapy (n=94)		Standard-dose chemotherapy (n=42)	
	Azacitidine (n=179)	CCR (n=179)	Azacitidine (n=117)	BSC (n=105)	Azacitidine (n=45)	Low-dose chemotherapy (n=49)	Azacitidine (n=17)	Standard-dose chemotherapy (n=25)
Deaths	82 (46%)	113 (63%)	53 (45%)	66 (63%)	20 (44%)	31 (63%)	9 (53%)	16 (64%)
Deaths during first three months* of treatment	20 (11%)	16 (9%)	13 (11%)	9 (9%)	5 (11%)	7 (14%)	2 (12%)	0
Safety population	175	165	114	102	45	44	16	19
Discontinuation before study completion due to haematological adverse events[†]	8 (5%)	4 (2%)	3 (3%)	2 (2%)	4 (9%)	2 (5%)	1 (6%)	0
Grade 3 or 4 toxicity[‡]								
Neutropenia	159 (91%)	126 (76%)	104 (91%)	70 (69%)	40 (89%)	39 (89%)	15 (94%)	17 (90%)
Thrombocytopenia	149 (85%)	132 (80%)	93 (82%)	72 (71%)	42 (93%)	42 (96%)	14 (88%)	18 (95%)
Anaemia	100 (57%)	112 (68%)	62 (54%)	67 (66%)	29 (64%)	34 (77%)	9 (56%)	11 (58%)
Baseline grade 0–2 progressed to Grade 3 or 4 during treatment[‡]								
Neutropenia	67/80 (84%)	46/76 (61%)	45/53 (85%)	22/46 (48%)	14/18 (78%)	19/24 (79%)	8/9 (89%)	5/6 (83%)
Thrombocytopenia	72/97 (74%)	68/94 (72%)	49/69 (71%)	29/54 (54%)	17/20 (85%)	29/30 (97%)	6/8 (75%)	10/10 (100%)
Anaemia	84/156 (54%)	83/130 (64%)	52/103 (51%)	48/79 (61%)	25/40 (63%)	28/37 (76%)	7/13 (54%)	7/14 (50%)

Data are number (%) or number/number with data (%)

* Three months = 91 days

[†] Study completion defined as 12 months after the last patient was randomised

[‡] National Cancer Institute's Common Toxicity Criteria toxicities based on laboratory data

Key: BSC: best supportive care; CCR: conventional care regimen; ITT: intention to treat

6.5. Summary description of comparator RCTs

6.5.1. Relevant comparator Phase III RCTs

Although there is no single standard of care proven to improve survival in the treatment of MDS, the three most commonly used treatments in higher-risk MDS are BSC, low-dose chemotherapy and standard-dose chemotherapy.[46] The literature search identified seven published Phase III RCTs of these three therapies, for patients with higher-risk MDS (see Table 6.10).[28,57-62]

Table 6.10. List of comparator Phase III RCTs included in the systematic review

Study	Study reference	Sample size	Intervention and comparator
1	Bernasconi, 1998[57]	105	SDC vs SDC + G-CSF
2	Miller, 1992[28]	141	LDC vs BSC
3	Ossenkoppele, 2004[58]	134	SDC + G-CSF vs SDC + G-CSF + fludarabine
4	Verbeek, 1999[59]	31	SDC vs SDC + G-CSF
5	Zwierzina, 2005[60]	180	LDC vs LDC + GM-CSF vs LDC + interleukin
6	Kantarjian, 2006[61]	170	Decitabine + BSC vs BSC alone
7	Thompson, 2000[62]	66	GM-CSF + epoetin alfa + BSC vs GM-CSF + BSC

Key: BSC: best supportive care; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; LDC: low-dose chemotherapy; SDC: standard-dose chemotherapy

Of these seven studies, three included at least one study arm which received standard-dose chemotherapy with or without additional therapies such as G-CSF.[57-59] Two studies included at least one study arm which received low-dose chemotherapy with or without G-CSF,[60,61] and three studies included study arms that received BSC with or without GM-CSF.[28,61,62] These studies will be grouped by type of therapy for the purposes of this clinical effectiveness review.

6.5.2. Standard-dose chemotherapy Phase III studies

Table 6.11 lists the Phase III RCTs which included a standard-dose chemotherapy arm and presents descriptions of the chemotherapy regimens administered.[57-59] For the purpose of comparison, the table also includes a description of the standard-dose chemotherapy regimen used in Study AZA-001.[46] This regimen was an accepted therapy used in local practice in the countries in which Study AZA-001 was conducted. It, therefore, provides an up-to-date description of a currently accepted and widely used chemotherapy regimen for purposes of comparison.

Table 6.11. Descriptions of standard-dose chemotherapy regimens

Study	Study period	Chemotherapy regimen
Bernasconi (a), 1998[57]	1992 start	Idarubicin 12 mg/m^2 IV on Days 1 and 2, etoposide 60 mg/m^2/12 hr IV infusion for 5 days, cytarabine 120 mg/m^2/12 hr IV bolus for 5 days
Bernasconi (b), 1998[57]	1992 start	As above plus G-CSF, SC 5 µg/kg/day, starting 48 hr after the end of chemotherapy until granulocyte count >1 x 10^9/l
Verbeek (a), 1999[59]	1990–95	Cytarabine (1 g/m^2) on Days 1, 2, 8 and 9 and mitoxantrone (10 mg/m^2) on Days 3, 4, 10, 11
Verbeek (b), 1999[59]	1990–95	As above plus GM-CSF (250 µg/m^2) as single SC injection once daily, started 48 hr prior to chemotherapy and continued until neutrophil recovery
Ossenkoppele (a), 2004[58]	1996–2001	2,000 mg/m^2 cytarabine IV in a 4-hr infusion on Days 1 through 5, plus 5 µg/kg/day G-CSF (filgrastim) SC starting 24 hr before cytarabine
Ossenkoppele (b), 2004[58]	1996–2001	As above plus 25 mg/m^2 fludarabine IV in 30 min on Days 1 through 5 starting 4 hr before cytarabine infusion
Study AZA-001[46]	2004–06	IV cytarabine 100–200 mg/m^2/day for 7 days plus 3 days of IV daunorubicin 45–60 mg/m^2/day (or alternatively IV idarubicin 9–12 mg/m^2/day or IV mitoxantrone 8–12 mg/m^2/day)

Key: G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; IV: intravenous; SC: subcutaneous

Table 6.12 shows baseline characteristics of patients enrolled in standard-dose chemotherapy study arms.[46,57-59] One of the inclusion criteria for the effectiveness review specified that at least 50% of study patients should be classified as higher-risk MDS patients: IPSS intermediate-2 or high; or CMML with 10–29% marrow blasts; or AML with 20–30% blasts and multilineage dysplasia, according to the WHO.[12] Table 6.12 shows that the severity of MDS varies greatly among these studies. For example, in the study by Bernasconi *et al,* at least 40% of patients had AML rather than higher-risk MDS.[57] This compares with the study by Verbeek *et al* in which there were no patients in this category[59] and Study AZA-001 which had 4% of patients in the AML category.[46]

Table 6.12. Characteristics of patients in standard-dose chemotherapy study arms

Study	Number in study arm	Population description							
		Age	ECOG PS	FAB MDS classification %					Other
		Median (range)	0, 1, 2	RA	RARS	RAEB	RAEB-T	CMML	AML
Bernasconi (a), 1998[57]	52	57 (25–66)	All pts 0–3			23	35		42
Bernasconi (b), 1998[57]	53	58 (22–69)	All pts 0–3			25	36		40
Verbeek (a), 1999[59]	15	57 (20–73)	NR			21*	69	10	
Verbeek (b), 1999[59]	16	57 (20–73)	NR			21*	69	10	
Ossenkoppele (a), 2004[58]	69	65 (24–75)	WHO PS 61, 33, 6	1		22	32	14	30
Ossenkoppele (b), 2004[58]	65	66 (48–75)	WHO PS 60, 38, 2	5	2	23	22	15	34
Study AZA-001[46]	25	65 (38–76)	60, 40, 0			40	52		4

* Reported for study sample and not by study arm

Key: AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FAB: French-American British; MDS: myelodysplastic syndrome; NR: not reported; PS: performance status; RA: refractory anaemia; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation; RARS: refractory anaemia with ringed sideroblasts; WHO: World Health Organization

Clinical effectiveness results are summarised for standard-dose chemotherapy study arms in Table 6.13.[46,56-59] Specifically, the main focus is on overall survival to enable comparisons with the primary outcome in Study AZA-001. Studies of standard-dose chemotherapy did not consistently report progression-free survival or time to transformation to AML. However, a majority did report response rates and these are presented here along with response rates for the chemotherapy arm of Study AZA-001. Infection rates were presented as a measure of safety of the chemotherapy regimen. In particular, life-threatening or WHO Grade 3 or 4 infections were presented if they were reported in the original paper.

Table 6.13. Summary of efficacy results for standard-dose chemotherapy study arms

Study	Number in study arm	Median overall survival in months (CI)	Response rates			Infection rates
			CR (%)	PR (%)	CR+PR (%)	
Bernasconi (a), 1998[57]	52	18.7* (range 10–22)	17 (33)	10 (19)	27 (52)	Number of life-threatening infections = 8
Bernasconi (b), 1998[57]	53	19.0* (range 10–24)	23 (43)	16 (30)	39 (74)	Number of life-threatening infections = 2
Verbeek (a), 1999[59]	15	6 (NR)	5 (39)			Incidence of Grade 3 or 4 infection = 47%
Verbeek(b), 1999[59]	16	11 (NR)	5 (31)			Incidence of Grade 3 or 4 infection = 47%
Ossenkoppele (a), 2004[58]	69	NR	45 (65)			Frequency of Grade 3 or 4 infection = 58%
Ossenkoppele (b), 2004[58]	65	NR	46 (71)			Frequency of Grade 3 or 4 infection = 67%
Study AZA-001[46]	25	15.7 (8.2–24.1)	9 (36)	1 (4)	10 (40)	% (n) patients with febrile neutropenia = 37% (7/19)[56]

* Survival data only reported for responders (n=27/52 and 39/53)

† Median survival for combined conventional care regimens including standard-dose chemotherapy, low-dose chemotherapy and BSC alone

Key: CI: confidence interval; CR: complete remission; NR: not reported; PR: partial remission

Median overall survival data for the complete study sample, were reported for one small study only (Verbeek *et al;* n=31). In the standard-dose chemotherapy arm, median survival was six months compared with 11 months in patients receiving standard-dose chemotherapy and G-CSF.[59] Bernasconi *et al* reported median (range) survival of 18.7 (10–22) months for responders (n=27/52) in the chemotherapy only arm and 19.0 (10–24) months for responders (n=39/53) in the chemotherapy plus G-CSF arm of the trial. The study reports that no patients showed a relapse-free survival greater than 11 months.[57] One of the larger studies in this group (Ossenkoppele *et al)* did not report median survival. However, it did report the probability of overall survival at 24 months (24% for the standard-dose chemotherapy arm and 39% for the standard-dose chemotherapy with fludarabine arm).[58]

Response rates varied considerably between trials, ranging from 33% to 71% of patients achieving CR. Rates of infection were relatively high, with over 60% experiencing Grade 3 or 4 infections in one study.[58] Verbeek *et al* reported that two patients became transfusion-independent, one (7%) of 15 in the low-dose chemotherapy arm and one (6%) of 16 in the BSC arm.[59] No other studies reported transfusion independence rates.

6.5.3. Low-dose chemotherapy Phase III studies

Table 6.14 lists the Phase III RCTs which included a low-dose chemotherapy arm and presents descriptions of the chemotherapy regimens administered.[28,60] The table also includes a description of the low-dose chemotherapy regimen used in Study AZA-001.[46]

Table 6.14. Descriptions of low-dose chemotherapy regimens

Study	Study period	Chemotherapy regimen
Miller, 1992[28]	NR	Cytarabine self-administered in a dosage of 10 mg/m^2 by SC injection every 12 hr for 21 consecutive days
Zwierzina (a), 2005[60]	NR	Cytarabine at a dose of 2 x 10 mg/m^2/day by SC injection for 14 days
Zwierzina (b), 2005[60]	NR	As above plus rhGM-CSF 150 µg given by SC injection twice daily from Day 8 to 21
Study AZA-001[46]	2004–06	Cytarabine at initial dose of 20 mg/m^2/day for 14 days

Key: IV: intravenous; rhGM-CSF: recombinant human granulocyte-macrophage colony-stimulating factor; SC: subcutaneous

Unlike the standard-dose chemotherapy studies, patient populations in the two low-dose chemotherapy studies were mostly high-risk MDS, with no AML patients in the study arms (see Table 6.15).[28,46,60] In the study by Miller *et al* the patient population was classified into all FAB MDS subtypes,[28] including lower- and higher-risk categories, while in the study by Zwierzina *et al,* most patients were in the higher-risk categories.[60]

Table 6.15. Characteristics of patients in low-dose chemotherapy study arms

Study	No in study arm	Population description							
		Age	ECOG PS %	FAB MDS classification %					Other
		Median (range)	0, 1, 2	RA	RARS	RAEB	RAEB-T	CMML	AML
Miller, 1992[28]	53	70 (19–85)	96% had ECOG ≤2	12	5	52	20	13	
Zwierzina (a), 2005[60]	69	65 (28–80)	WHO PS 0–2			56	44		
Zwierzina (b), 2005[60]	68	65 (28–83)	WHO PS 0–2			64	36		
Study AZA-001[46]	49	71 (56–85)	59, 35, 4			51	39	2	

Key: AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FAB: French-American British; MDS: myelodysplastic syndrome; NR: not reported; PS: performance status; RA: refractory anaemia; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation; RARS: refractory anaemia with ringed sideroblasts; WHO: World Health Organization

The highest overall median survival in low-dose chemotherapy studies was 17.8 months in patients randomised to low-dose cytarabine (see Table 6.16).[28,46,56,60] This

compared with a median overall survival of 11.6 months in the same study in patients randomised to G-CSF in addition to low-dose cytarabine.[60] The lowest overall median survival in the low-dose chemotherapy studies was 6.8 months.[28] As expected, response rates were lower than in standard-dose chemotherapy studies and, correspondingly, rates of infection were also lower.

Table 6.16. Summary of efficacy results for low-dose chemotherapy study arms

Study	Number in study arm	Median overall survival in months (CI)	Response rates			Infection rates
			CR (%)	PR (%)	CR+PR (%)	
Miller, 1992[28]	53	6.8 (NR)	6 (11)	11 (21)	17 (33)	Number of life-threatening infections = 6
Zwierzina (a), 2005[60]	69	17.8 (NR)	12 (20)	7 (11)	19 (32)	Number of Grade 3 or 4 infections = 2
Zwierzina (b), 2005[60]	68	11.6 (NR)	8 (14)	7 (12)	15 (26)	Number of Grade 3 or 4 infections = 8
Study AZA-001[46]	49	15.3 (4.9–25.8)	4 (8)	2 (4)	6 (12)	% (n) patients with febrile neutropenia = 2% (1/44)[56]

Key: CI: confidence interval; CR: complete remission; NR: not reported; PR: partial remission

Miller *et al* reported a decrease in transfusion requirements for both the low-dose chemotherapy arm (from 87% to 75%) and the BSC arm (from 84% to 78%) between baseline and three months' follow-up. However, the difference between study arms was not significant.[28]

6.5.4. BSC Phase III studies

Table 6.17 lists the Phase III RCTs which included a BSC arm and presents descriptions of the therapies administered.[28,61,62] The table also includes a description of the BSC regimen used in Study AZA-001.[46] This regimen was an accepted therapy used in local practice in the countries in which Study AZA-001 was conducted.

Table 6.17. Descriptions of BSC regimens

Study	Study period	Therapies
Miller, 1992[28]	NR	RBC and platelet transfusions as needed. Did not receive chemotherapy, androgens or corticosteroids while on study
Kantarjian, 2006[61]	2001–04	RBC or platelet transfusion. Haematopoietic colony-stimulating factors given as per treatment guidelines
Thompson (a), 2000[62]	NR	GM-CSF 0.3–5.0 mg/kg/day plus epoetin alfa 150 IU/kg 3 times/week. BSC not described further although RBC transfusions were administered
Thompson (b), 2000[62]	NR	GM-CSF as above plus placebo epoetin alfa
Study AZA-001[46]	2004–06	Blood product transfusions, antibiotics, myeloid growth factors (G-CSF and GM-CSF) for neutropenic infections until the end of the study. Treatment with erythropoietin was not permitted

Key: BSC: best supportive care; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; NR: not reported; RBC: red blood cell

All patient populations in the three studies which included a BSC study arm were classified as MDS patients. However, within the MDS classification, the disease severity varied widely (see Table 6.18).[28,46,61,62] For example, in one study (Thompson *et al),* over 40% of patients were categorised as RA and RARS, two of the lower-risk MDS subtypes,[62] compared with 20% (Kantarjian *et al)*[61] and 17% (Miller *et al)*[28] in the other two studies.

Table 6.18. Characteristics of patients in BSC study arms

Study	No in study arm	Population description							
		Age	ECOG PS %	FAB MDS classification %					Other
		Median (range)	0, 1, 2	RA	RARS	RAEB	RAEB-T	CMML	AML
Miller, 1992[28]	49	70 (34–85)	96% had ECOG ≤2	12*	5	52	20	13	
Kantarjian, 2006[61]	81	70 (62–74)	WHO PS 35, 59, 5	15	5	53	17	10	
Thompson (a), 2000[62]	45	62 (21–95)	Zubrod PS 0–2	29	13	56	2		
Thompson (b), 2000[62]	21	63 (25–84)	Zubrod PS 0–2	33	14	48	5		
Study AZA-001[46]	105	70 (50–88)	34, 56, 8			65	29	4	

* Statistics for whole study group, not by study arm

Key: AML: acute myeloid leukaemia; CMML: chronic myelomonocytic leukaemia; ECOG: Eastern Cooperative Oncology Group; FAB: French-American British; MDS: myelodysplastic syndrome; NR: not reported; PS: performance status; RA: refractory anaemia; RAEB: refractory anaemia with excess blasts; RAEB-T: refractory anaemia with excess blasts in transformation; RARS: refractory anaemia with ringed sideroblasts; WHO: World Health Organization

Only two studies other than Study AZA-001 reported survival statistics (see Table 6.19).[28,46,56,61,62] The highest overall median survival was 14.9 months (Kantarjian *et al)*[61] and the lowest was 5.1 months (Miller *et al)*.[28] The highest rate of infection reported was 4% for Grade 3 or 4 neutropenia (Kantarjian *et al)*.[61]

Table 6.19. Summary of efficacy results for BSC study arms

Study	Number in study arm	Median overall survival in months (CI)	Response rates			Infection rates
			CR (%)	PR (%)	CR+PR (%)	
Miller, 1992[28]	49	5.1 (NR)	0 (0)	0 (0)	0 (0)	Number of life-threatening infections = 2
Kantarjian, 2006[61]	81	14.9 (NR)	0 (0)	0 (0)	0 (0)	% of patients with Grade 3 or 4 febrile neutropenia = 4%
Thompson(a), 2000[62]	45	NR	NR	NR	NR	NR
Thompson(b), 2000[62]	21	NR	NR	NR	NR	NR
Study AZA-001[46]	105	11.5 (5.7–not reached)	1 (1)	4 (4)	5 (5)	% of patients with febrile neutropenia = 7% (7/102)[56]

Key: CI: confidence interval; CR: complete remission; NR: not reported; PR: partial remission

Miller *et al* found small decreases in transfusion requirements in patients in the BSC arm after three months' follow-up, but these were not statistically significantly different from decreases in patients in the low-dose chemotherapy arm.[28] Thompson *et al* reported that the percentage of patients receiving RBC transfusions was not statistically significantly different between the BSC plus GM-CSF arm and the BSC alone arm (76% and 90% respectively).[62] The percentage of patients receiving transfusions in the BSC arm in the Kantarjian *et al* study did not change significantly over time.[61]

In the above Phase III trials of comparator therapies (standard-dose chemotherapy, low-dose chemotherapy and BSC), no study found a statistically significant difference in survival between different treatment arms, regardless of intervention or comparator being investigated.

6.6. Summary of survival results for azacitidine and commonly used treatments

6.6.1. Overall survival

No meta-analyses were carried out on survival results from Phase III trials of comparator therapies. Within the group of three studies of standard-dose chemotherapy, only one study (Verbeek *et al)* reported overall survival data for the complete study sample.[59] In the group of two low-dose chemotherapy studies, study populations were substantially different with regard to the mix of patients with lower- and higher-risk MDS. In the group of three BSC studies, two reported relevant survival data. However, treatments were very different between these two studies. For example, no growth factors were used in the 1992 study by Miller *et al,*[28] while growth factors were used by 41% of patients in the 2006 study by Kantarjian *et al.*[61]

Table 6.20 shows overall survival data from studies included in this review for the three commonly used therapies in higher-risk MDS: standard-dose chemotherapy, low-dose chemotherapy and BSC. In addition, for purposes of comparison, the table includes survival results for patients in Study AZA-001 according to investigator preselection.[46] For example, in Study AZA-001, 42 patients were preselected by investigators for standard-dose chemotherapy before randomisation. After randomisation, 17 of those patients received azacitidine and 25 received standard-dose chemotherapy.[46] Results are reported for both subgroups.

Table 6.20. Overall survival for comparator treatments for MDS and azacitidine

Treatment group	Treatment in each study arm	n	Median overall survival in months (CI) for all study patients
Standard-dose chemotherapy			
Bernasconi, 1998[57]	SC	52	NR
Bernasconi, 1998[57]	SC + G-CSF	53	NR
Verbeek, 1999[59]	SC	15	6 (NR)
Verbeek, 1999[59]	SC + GM-CSF	16	11 (NR)
Ossenkoppele, 2004[58]	SC + G-CSF	69	NR
Ossenkoppele, 2004[58]	SC + G-CSF + fludarabine	65	NR
Study AZA-001[46]	SC	25	15.7 (8.2–24.1)
Study AZA-001[46]	Azacitidine*	17	25.1 (10.0–not reached)
Low-dose chemotherapy			
Miller, 1992[28]	Low-dose cytarabine	53	6.8 (NR)
Zwierzina, 2005[60]	Low-dose cytarabine	68	17.8 (NR)
Zwierzina, 2005[60]	Low-dose cytarabine + GM-CSF	64	11.6 (NR)
Study AZA-001[46]	Low-dose cytarabine	49	15.3 (4.9-25.8)
Study-AZA-001[46]	Azacitidine**	45	24.5 (8.4–34.7)
Best supportive care			
Miller, 1992[28]	BSC not including growth factors	49	5.1 (NR)
Kantarjian, 2006[61]	BSC including growth factors	81	14.9 (NR)
Thompson, 2000[62]	BSC + GM-CSF	45	NR
Thompson, 2000[62]	BSC – no GM-CSF	21	NR
Study AZA-001[46]	BSC including growth factors	105	11.5 (5.7–not reached)
Study AZA-001[46]	Azacitidine†	117	21.1 (10.5–not reached)
Conventional care regimens			
Study AZA-001[46]	SC, low-dose cytarabine or BSC	179	15 (5.6–24.1)
Azacitidine			
Study AZA-001[46]	Azacitidine	179	24.5 (9.9–not reached)

* Patients who were preselected by clinicians for SC prior to randomisation and who were then randomised to azacitidine

** Patients who were preselected for low-dose chemotherapy and then randomised to azacitidine

† Patients who were preselected for BSC and then randomised to azacitidine

Key: BSC: best supportive care; CI: confidence interval; G-CSF: granulocyte-colony stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor; NR: not reported; SC: standard-dose chemotherapy

Overall median survival was reported in only one of the three standard-dose chemotherapy studies identified (Verbeek *et al)*. Median survival was 11 months in the standard-dose chemotherapy arm and six months in the standard-dose chemotherapy arm with added G-CSF.[59] This compared with median survival of 15.7 months for patients who were both preselected for standard-dose chemotherapy, and randomised to standard-dose chemotherapy in Study AZA-001. For those patients who were preselected for standard-dose chemotherapy but randomised to azacitidine, median survival was 25.1 months. The difference in survival between the two groups was not statistically significant (p=0.51).[46]

Median survival in the two low-dose chemotherapy studies ranged from 6.8 months (Miller *et al)*[28] to 17.8 months (Zwierzina *et al)*.[60] This compared with median survival of 15.3 months for patients who were both preselected for low-dose chemotherapy and randomised to low-dose chemotherapy in Study AZA-001. For those patients who were preselected for low-dose chemotherapy but randomised to azacitidine, median survival was 24.5 months (p=0.0006).[46]

Median survival was reported in two of the three studies with BSC arms: these were 5.1 months (Miller *et al)*[28] and 14.9 months (Kantarjian *et al)*.[61] This compared with median survival of 11.5 months for patients who were both preselected for BSC and randomised to BSC in Study AZA-001. For those patients who were preselected for BSC but randomised to azacitidine, median survival was 21.1 months (p=0.0045).[46]

6.6.2. Secondary efficacy results

Secondary endpoints from Study AZA-001 further support the results of the overall survival benefit with azacitidine. Specifically, treatment with azacitidine was associated with a delay in time to transformation to AML or death and a delay in time to AML. The Kaplan–Meier median time to death or transformation to AML was significantly longer in the azacitidine group (13.0 months) compared with the combined CCR group (7.6 months; stratified log-rank p=0.0025) with a corresponding 32% (95% CI 0.53–0.87; p=0.0027) reduced risk of transformation to AML or death.[56]

Haematological AEs were among the AEs most frequently reported by azacitidine patients; the two most frequent AEs were thrombocytopenia (69.7%) and neutropenia (65.7%). Other haematological AEs frequently reported included anaemia and leucopenia. These AEs were reported at higher percentages in azacitidine patients than BSC-only patients. Of note, however, is the fact that azacitidine did not increase the risk of events of infection (RR=0.90) or bleeding (RR=0.96) when compared with BSC only. In contrast, both standard-dose chemotherapy and low-dose chemotherapy were associated with increased risks for both of these AEs relative to azacitidine.[56]

Among comparator studies included in this review, few reported time to transformation to AML. WHO Grade 3 or 4 infection rates were extracted wherever possible. However, there was a lack of consistency in how AEs were reported between trials. With regard to infection rates, for example, some studies reported the number of ‘life-threatening’ AEs only. In general, the highest infection rates were

found in standard-dose chemotherapy arms and lowest in low-dose chemotherapy and BSC study arms.

6.7. Discussion of clinical effectiveness results for azacitidine and comparator treatments for higher-risk MDS

In the absence of eligibility for allogeneic SCT, current guidelines recognise three common treatment regimes for patients with higher-risk MDS.[4,5] However, these three CCRs – BSC, low-dose chemotherapy and standard-dose chemotherapy – have failed to show any survival benefit in higher-risk MDS patients.[46]

Azacitidine is the first licensed drug to demonstrate a significant overall survival benefit in higher-risk MDS patients. Study AZA-001, which is considered pivotal in supporting the clinical benefit of azacitidine, has shown prolonged overall survival of 9.4 months (p=0.0001) compared with CCR in higher-risk patients. In addition, azacitidine was found to lower the risk of progression to AML in patients with higher-risk MDS compared with treatment with CCR.[46]

Azacitidine also resulted in a significant reduction in RBC transfusion dependence (p<0.0001) and a significantly lower rate of infections requiring IV antimicrobials (p=0.0032) compared with CCR.[46] In addition, Kornblith *et al* found that azacitidine significantly improved a range of QoL measures compared with BSC in Study CALGB 9221.[65]

Among the seven studies of comparator therapies which met the inclusion criteria for this review, none reported median overall survival higher than that reported for azacitidine in Study AZA-001 (24.5 months).[46] The highest overall median survival reported in RCTs of comparator therapies was 17.8 months. This was among patients in the low-dose chemotherapy arm of a trial (Zwierzina *et al)* which compared low-dose cytarabine with low-dose cytarabine plus GM-CSF (median survival for the latter group was 11.6 months; the difference was not significant).[60] Indeed, in all of the RCTs that reported survival results, none, with the exception of Study AZA-001, showed any statistically significant differences in overall survival between treatment arms.

While there were no statistically significant differences in survival between treatment arms of the individual trials of comparator therapies, there was much variation in survival between studies in the review. For example, the lowest median overall survival was reported in a small study (Verbeek *et al;* n=31) of standard-dose

chemotherapy (11 months) versus standard-dose chemotherapy with GM-CSF (six months),[59] while one of the highest median overall survival rates was in a study arm (Kantarjian *et al)* which received only BSC (14.9 months).[61] However, it is difficult to make direct comparisons between therapies with regard to survival because of differences in disease severity among patient populations, and different treatment regimens used. For example, growth factors were not used in the 1992 study by Miller *et al* in which the lowest median survival was reported,[28] while in the 2006 study by Kantarjian *et al* which reported the highest median survival, 41% of patients received growth factors.[61]

In Study AZA-001, median overall survival in the azacitidine group exceeded that in the CCR group by 9·4 months, with a two-year survival rate that was nearly doubled. Furthermore, comparisons with the supportive investigator preselection analysis showed that treatment with azacitidine was associated with a significant improvement in overall survival compared with low-dose chemotherapy or BSC. However, the difference in median overall survival between the azacitidine and standard-dose chemotherapy groups was not statistically significant, possibly because of the small number of patients in this analysis (n=42).[46]

Increased survival time is the primary goal of treatment for patients with higher-risk MDS. However, with the exception of allogeneic haematopoietic SCT, which is suitable for only a few patients with MDS,[75] no previous treatment strategies have shown a significant overall survival benefit. The results of Study AZA-001 indicate that azacitidine significantly lengthens overall survival in patients with higher-risk disease.

6.8. Non-RCT evidence

This review did not include non-RCT evidence.

6.9. Interpretation of clinical evidence

6.9.1. Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The decision problem is whether azacitidine should be used in place of standard-dose chemotherapy, low-dose chemotherapy or BSC to treat high-risk MDS patients not considered eligible for SCT. The evidence base has been sought to show the

efficacy of azacitidine and the efficacy of the comparator regimes, as demonstrated in clinical trials. There is considerable variation in the age of the studies, the outcomes considered and medicines used concomitantly with the regimes of interest. Information on the age and nature of the studies has been provided to allow assessment of the comparability of results.

Higher-risk MDS patients have a poor prognosis and limited treatment options are available. The primary treatment goal is increased survival time. However, with the exception of allogeneic SCT, no existing treatment strategies have shown a significant overall survival benefit.[46] In addition, UK guidelines state that there is insufficient evidence to recommend the routine use of low-dose chemotherapy,[5] while standard-dose chemotherapy in elderly patients with higher-risk MDS can be detrimental, with increased treatment toxicity, a higher rate of infections and haematological complications.[47]

Azacitidine is the first licensed drug to demonstrate a clinically and statistically meaningful survival benefit in higher-risk MDS patients. In Study AZA-001, the survival advantage with azacitidine was 9.4 months (p=0.0001) compared with CCR in higher-risk patients, with the survival advantage being consistent across all subgroups.[46] In contrast, none of the Phase III RCTs included in this systematic review reported a statistically significant survival difference between chemotherapy and BSC.

None of the clinical trials of azacitidine or comparator treatments included in this review included QoL as a study outcome. This is despite the fact that the QoL of patients with MDS is likely to be severely compromised by cytopenic symptoms such as fatigue, haemorrhagic episodes, infections requiring hospitalisation and treatment with IV medications, as well as the need for frequent transfusions of blood products.[76-79] However, Study AZA-001 reported a significant reduction in RBC transfusion dependence (p<0.0001) and a significantly lower rate of infections requiring IV antimicrobials (p=0.0032) for azacitidine compared with CCR;[46] while in Study CALGB 9221, Kornblith *et al* found that azacitidine significantly improved a range of QoL measures compared with BSC.[65] These findings indicate that azacitidine results in a marked improvement in patient well-being.

In contrast, although some studies of comparator treatments reported change in blood transfusion requirements between baseline and after treatment as a study endpoint, in general these changes were small and did not differ significantly

between study arms. Most of the trials also included infection rates as part of routine reporting of the incidence of AEs related to treatment. Unfortunately, given the lack of uniformity of reporting of infection rates, it was not possible to directly compare differences between treatments.

6.9.2. Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Study AZA-001, which compared azacitidine with CCRs, was international and multicentre in design, with 79 investigative sites in 15 countries. In the comparison of azacitidine with the three most common treatments in higher-risk MDS, including two active treatments, treatment decisions were made in light of different treatment practices influenced by regional, national and local guidelines and consensus criteria. For these reasons, the results are applicable to the improvement of the treatment of MDS internationally.

7. Cost-effectiveness

7.1. Published cost-effectiveness evaluations

7.1.1. Identification of studies

The search strategy used to identify any published cost-effectiveness literature is shown in Appendix 3.

7.1.2. Description of identified studies

The search strategy returned five studies, which are listed below in Table 7.1. All five of these studies have been excluded for either having an inappropriate comparator or being a study in pre-2001 acute myeloid leukaemia (AML) patients, who are not the subset of AML patients of interest in this decision problem.

Table 7.1. List of studies identified and reasons for exclusion

Study	Study reference	Reason for exclusion
1	Goss TF, Szende A, Schaefer C, Totten PJ, Knight R, Jädersten M *et al.* Cost effectiveness of lenalidomide in the treatment of transfusion-dependent myelodysplastic syndromes in the United States. *Cancer Control* 2006; **13**(Suppl): 17–25.	Inappropriate comparator
2	Marie JP, Wdowik T, Bisserbe S, Zittoun R. Cost of complete remission induction in acute myeloblastic leukemia: evaluation of the cost-effectiveness of a new drug. *Leukemia* 1992; **6:** 720–722.	Pre-2001 AML population
3	Nomura K, Kawasugi K, Morimoto T. Cost-effectiveness analysis of antifungal treatment for patients on chemotherapy. *Eur J Cancer Care (Engl)* 2006; **15:** 44–50.	Inappropriate comparator
4	Pashko S, Jacobs J, Santorsa J. The cost-effectiveness of idarubicin/cytosine arabinoside versus daunorubicin/cytosine arabinoside in the treatment of adults with acute myeloid leukemia. *Clin Ther* 1991; **13:** 353–360.	Pre-2001 AML population
5	Uyl-de Groot CA, Löwenberg B, Vellenga E, Suciu S, Willemze R, Rutten FF. Cost-effectiveness and quality-of-life assessment of GM-CSF as an adjunct to intensive remission induction chemotherapy in elderly patients with acute myeloid leukemia. *Br J Haematol* 1998; **100:** 629–636.	Pre-2001 AML population

Key: AML: acute myeloid leukaemia

7.2. De novo economic evaluation(s)

7.2.1. Technology

7.2.1.1. How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The indication under consideration in the economic evaluation is that detailed in the Vidaza Summary of Product Characteristics (SmPC).[1]

Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (SCT) with:

- Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS)
- Chronic myelomonocytic leukaemia (CMML) with 10–29% marrow blasts without myeloproliferative disorder
- Acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization (WHO) classification.[1]

Consistent with the scope of the decision problem for this technology appraisal, the economic evaluation considers patients with MDS as per the indication and reflects the mix of patients from Study AZA-001.

7.2.1.1.1 Dose, frequency and duration of use

The dosing data from Study AZA-001 showed the average administered dose of azacitidine to be 134.0 mg (SD 25.4 mg). Analysis of the dosing data showed that a mean of 1.91 vials (SD 0.28) were required per dose of azacitidine during the course of the trial. Patients received seven doses per treatment cycle as per the licensed indication.[56]

The trial protocol stated that patients should receive treatment every 28 days; however, the actual mean observed treatment cycle in the trial was 36.1 days.[56] This increase in cycle length was due to protocol treatment being postponed until blood counts had recovered. The 36.1 days is a mean cycle length calculated on a per-cycle basis. It is an average of the average cycle length of patients that received azacitidine.

The mean duration of treatment with azacitidine in the trial was 13.4 months.[56]

7.2.1.2. Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators.

There is no treatment discontinuation rule for the use of azacitidine in this indication. The SmPC states that treatment with azacitidine should be continued *until progression or so long as the patient continues to benefit*.[1]

Patients are recommended to be treated to progression regardless of response. It is possible to determine from haematological responses those patients that respond well to azacitidine.[46]

The economic evaluation is based on survival; therefore, there is no reason to apply a discontinuation rule.

7.2.2. Patients

7.2.2.1. What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient population considered in the economic evaluation matches that of the licensed indication. Treatment choice for these patients within the licensed indication depends on their age, Eastern Cooperative Oncology Group (ECOG) performance status and the presence of co-morbidities. Patients are therefore generally divided into three groups:

- Those suitable for best supportive care (BSC) alone
- Those suitable for low-dose chemotherapy (and BSC)
- Those suitable for standard-dose chemotherapy (and BSC).

These are the treatment arms that are modelled within the economic evaluation.

7.2.2.2. Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

Patients who present with a karyotype with monosomy 7 or –7q/del(7q) have a poor prognosis in MDS. A recent retrospective study demonstrated that MDS/AML patients with chromosome 7 abnormalities have poor overall survival (33% survival after three years) and a higher relapse rate than patients with normal cytogenetics.[53] At baseline in Study AZA-001, 57 of the 358 patients in the total population were classified in this subgroup.[46] These patients were extracted from the data set and analysed separately.

7.2.2.3. Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

Other than those included in Section 7.2.2.2, no additional patients subgroups were considered.

7.2.2.4. At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

All modelled patients enter the model on treatment initiation and exit the model at death irrespective of the treatment regimen.

Patients on active therapy enter the model at the first dose. Patients treated with azacitidine, low-dose chemotherapy or standard-dose chemotherapy are assumed to have been pretreated with appropriate premedication (for example, anti-emetic medication) before entering the model and have an initial pretreatment cost applied.

Patients on BSC alone are assumed to enter the model at the same time as they would have entered the model if they had been randomised to one of the active therapy arms.

Patients exit the model at death. This assumption is applied to all treatment arms.

7.2.3. Comparator technology

The economic evaluation reflects the main therapeutic options for treatment of higher-risk MDS patients (IPSS risk categories intermediate-2 or high)[4] and compares azacitidine with:

- BSC
- Low-dose chemotherapy (plus BSC)
- Standard-dose chemotherapy (plus BSC).

7.2.3.1. BSC

BSC aims to control the symptoms of bone marrow failure and improve the quality of life (QoL) of the patient, primarily through the use of red blood cell and/or platelet transfusions, antibiotics and, to a limited extent, cytokines, erythropoietin or granulocytic growth factors. BSC is essentially a palliative care option and for patients with higher-risk MDS it is preferred only in those who are not candidates for low-dose or standard-dose chemotherapy.

7.2.3.2. Low-dose and standard-dose chemotherapy

According to UK and US guidelines, patients with higher-risk MDS should be assessed for suitability to receive standard-dose chemotherapy.[4,5] Although low-dose chemotherapy is not recommended in the UK guidelines,[5] in practice many clinicians will consider treatment with low-dose chemotherapy for those patients who are not fit to receive standard-dose chemotherapy.

A low-dose chemotherapy regimen of cytarabine 20 mg/m^2/day administered subcutaneously for 14 days every 28–42 days is considered. BSC as described above is provided in addition to low-dose chemotherapy.[46]

A standard-dose chemotherapy regimen consisting of the following agents is considered:

- Induction chemotherapy
  - Cytarabine 100–200 mg/m^2/day administered intravenously (IV) on Days 1–7
  - An anthracycline (daunorubicin 45–60 mg/m^2/day, idarubicin 9–12 mg/m^2/day or mitoxantrone 8–12 mg/m^2/day) administered IV on Days 1–3[46]
- Consolidation chemotherapy

- Cytarabine 100–200 mg/m^2/day administered IV for three to seven days, and the same anthracycline that had been administered during induction given IV on Days 1 and 2
- The first of a maximum of two consolidation cycles delivered 28–70 days after the start of induction
- The second induction cycle delivered 28–70 days after the previous cycle[46,56]

Although other chemotherapy agents are available, they are not considered here. There is no evidence that the regimes omitted are superior.

The three above-mentioned treatment options were all included in the comparator arm of Study AZA-001[46] and are also included as comparator arms in the economic model presented.

7.2.4. Study perspective

The perspective of the economic evaluation is that of the NHS and Personal Social Services in England and Wales, as requested in the NICE reference case.

7.2.5. Time horizon

A lifetime horizon was adopted for the base-case analysis. MDS patients have a short life expectancy and a high proportion of patients will die within the first few years of diagnosis. However, some patients will have an extended survival and it is important to capture the costs and benefits associated with these patients. Study AZA-001 – the Phase III clinical study on which the model is based – was a three-year study. The model extrapolates data from the study until a point where the entire cohort has suffered mortality.

Alternative analysis timeframes also reported in the sensitivity analysis are:

- A three-year time timeframe reflecting the trial period of Study AZA-001
- A year-on-year analysis showing the effect on the incremental cost-effectiveness ratio (ICER) of increasing the model timeframe by one year at a time.

7.2.6. Framework

a) Model-based evaluations

7.2.6.1. Please provide the following.

- *A description of the model type.*
- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*
- *A list of all variables that includes their value, range (distribution) and source.*
- *A separate list of all assumptions and a justification for each assumption.*

7.2.6.1.1 Description of the model type

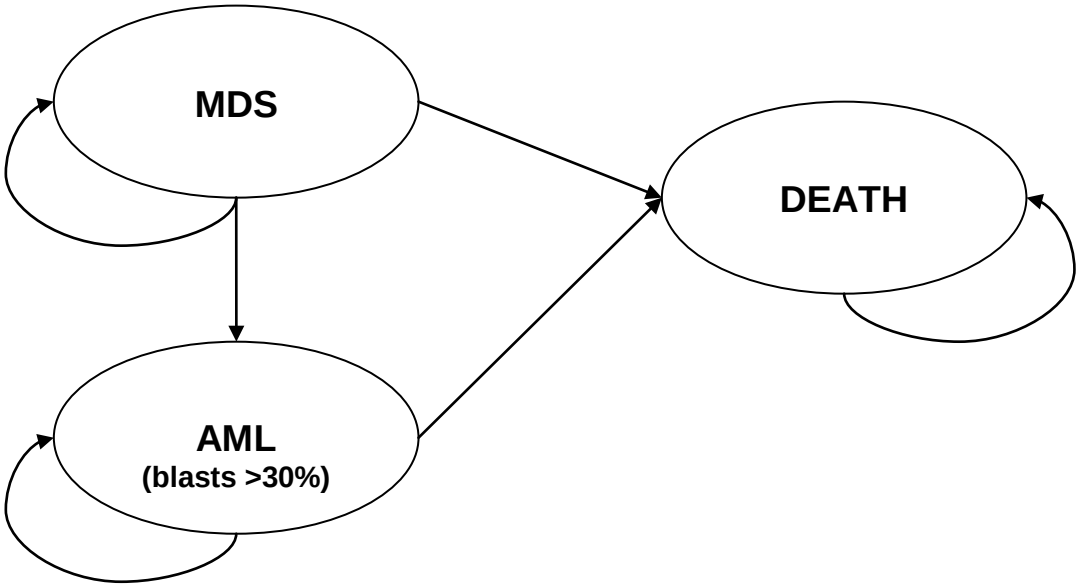
The evaluation performed is a cost–utility analysis, based on a lifetime Markov model. The model encompasses outcome measures for costs, health outcomes and incremental cost-effectiveness. Outcomes for costs include those relating to drugs and medications, monitoring, routine follow-up and adverse event (AE) management. Health effects are expressed in terms of life-years (LYs) and quality-adjusted life-years (QALYs). The model outcomes are expressed in terms of cost per LY and per QALY gained. Probabilistic sensitivity analysis (PSA) is performed to examine the overall effect of the uncertainty in the model.

7.2.6.1.2 Schematic of the model

The model is divided into three health states. The transitions between these states are shown in Figure 7.1. The health states are defined as:

- **MDS** – patients in this state are either intermediate-2 or high-risk MDS according to the IPSS, CMML with 10–29% marrow blasts without myeloproliferative disorder or AML with 20–30% blasts and multilineage dysplasia, according to the WHO classification.
- **AML (blasts >30%)** – patients in this health state have progressed from the MDS state and have AML with blasts >30%. These patients are AML patients according to the French-American-British (FAB) classification and have more severe disease (blasts >30%) compared with patients classified as AML according to the WHO (blasts 20–30%).
- **Death** – patients in this state have suffered mortality.

Figure 7.1. Schematic of the health economic model



7.2.6.1.3 List of all variables in the model

A list of all the variables in the model is shown in Table 7.2.

Table 7.2. List of variables in the model

Variable	Value	Range	Source
Overall survival curves			
Azacitidine (BSC) Weibull alpha	0.987	SD (0.023)	Study AZA-001
Azacitidine (BSC) Weibull beta	29.599	SD (2.135)	Study AZA-001
BSC Weibull alpha	1.127	SD (0.033)	Study AZA-001
BSC Weibull beta	16.273	SD (1.918)	Study AZA-001
Azacitidine (LDC) Weibull alpha	0.938	SD (0.041)	Study AZA-001
Azacitidine (LDC) Weibull beta	30.130	SD (2.289)	Study AZA-001
LDC Weibull alpha	1.161	SD (0.089)	Study AZA-001
LDC Weibull beta	17.101	SD (2.289)	Study AZA-001
Azacitidine (SDC) Weibull alpha	0.989	SD (0.069)	Study AZA-001
Azacitidine (SDC) Weibull Beta	25.480	SD (3.369)	Study AZA-001
SDC Weibull alpha	1.701	SD (0.099)	Study AZA-001
SDC Weibull beta	15.923	SD (2.856)	Study AZA-001
Azacitidine (BSC) log-logistic alpha	1.51	SD (2.856)	Study AZA-001
Azacitidine (BSC) log-logistic beta	0.048	SD (0.005)	Study AZA-001
BSC log-logistic alpha	1.49	SD (0.300)	Study AZA-001
BSC log-logistic beta	0.093	SD (0.020)	Study AZA-001
Azacitidine (LDC) log-logistic alpha	1.08	SD (0.025)	Study AZA-001
Azacitidine (LDC) log-logistic beta	0.048	SD (0.005)	Study AZA-001
LDC log-logistic alpha	1.41	SD (0.302)	Study AZA-001
LDC log-logistic beta	0.083	SD (0.021)	Study AZA-001
Azacitidine (SDC) log-logistic alpha	1.17	SD (0.019)	Study AZA-001
Azacitidine (SDC) log-logistic beta	0.057	SD (0.005)	Study AZA-001
SDC log-logistic alpha	2.27	SD (0.401)	Study AZA-001
SDC log-logistic beta	0.084	SD (0.006)	Study AZA-001
Treatment cessation			
Azacitidine Weibull alpha	1.378	SD (0.012)	Study AZA-001
Azacitidine Weibull beta	11.732	SD (1.01)	Study AZA-001
LDC Weibull alpha	1.375	SD (0.010)	Study AZA-001
LDC Weibull beta	6.102	SD (0.012)	Study AZA-001
SDC Weibull alpha	2.152	SD (0.015)	Study AZA-001
SDC Weibull beta	2.095	SD (0.019)	Study AZA-001
Blood/platelet transfusion			
Number of units of blood per cycle			
Azacitidine	1.48	SD (0.21)	Study AZA-001
Best supportive care	2.42	SD (0.32)	Study AZA-001
Low-dose chemotherapy	2.75	SD (0.38)	Study AZA-001
Standard-dose chemotherapy	2.82	SD (0.40)	Study AZA-001
Number of units of platelets per cycle			
Azacitidine	1.15	SD (0.09)	Study AZA-001
Best supportive care	0.61	SD (0.05)	Study AZA-001
Low-dose chemotherapy	2.22	SD (0.12)	Study AZA-001
Standard-dose chemotherapy	4.42	SD (0.43)	Study AZA-001
Adverse event rate per cycle			
Azacitidine (see Appendix 10)			
Low-dose chemotherapy (see Appendix 10)			
Standard-dose chemotherapy (see Appendix 10)			
Best supportive care			
Neutropenia	0.08		Study AZA-001
Leucopenia	0.00		Study AZA-001
Febrile neutropenia	0.02		Study AZA-001
Pyrexia	0.04		Study AZA-001
Pneumonia	0.02		Study AZA-001

Key: BSC: best supportive care; LDC: low-dose chemotherapy; SDC: standard-dose chemotherapy

7.2.6.1.4 Assumptions (A) and justifications (J)

(A) Three-year trial data are extrapolated to provide a lifetime cohort model.
(J) MDS is a chronic end-of-life illness and to fully capture the costs and benefits associated with treatment, a lifetime model is required.

(A) The Vidaza SmPC states that treatment should be initiated every 28 days, but the model assumes a five-week (35-day) cycle.
(J) Although the protocol suggests that a 28-day (four-week) cycle is appropriate, in Study AZA-001 the observed cycle length was 36.1 days. As the model is based on efficacy results demonstrated in the clinical trial, the dosing cycle must also be based on the actual observed data. A 35-day cycle was chosen rather than a 36.1-day cycle for the sake of simplicity. This is a slightly conservative assumption as the fewer treatment cycles the patient incurs, the lower the total cost of azacitidine.

(A) Patients can die when in either the MDS or the AML health state.
(J) Clinicians have advised that some patients die without progressing to AML and therefore a transition between MDS and death should be included in the model. This is further supported by evidence from Study AZA-001 in which patients died without disease progression (transformation to AML).

(A) There is currently no evidence to suggest a treatment effect on the time spent in an AML health state by patients. It is assumed that all patients spend an equal amount of time in an AML state, regardless of the treatment arm from which they progressed.
(J) This is supported by evidence from the clinical trial, which shows that there is no statistical difference between treatment arms for time spent in AML, and by clinical experts, who indicated that they would not expect to see any difference.

(A) The number of modelled cycles of treatment is that observed in Study AZA-001.
(J) It is good practice for the assumptions about the rules on dosing to be taken from the same source as the efficacy values used.

(A) Once they progress to the AML health state, all patients receive BSC-type treatment, regardless of their previous treatment arm.
(J) The aim of the model is to investigate the treatment of MDS only. The treatment of AML was therefore held constant by the simplifying assumption that only BSC would be used.

(A) Patients treated with azacitidine receive seven days of treatment per 35-day model cycle.
(J) This reflects azacitidine's licence (patients to receive seven days of treatment per treatment cycle) and the length of treatment cycle in Study AZA-001.

(A) In the model, resource utilisation relating to the routine management of patients undergoing treatment is based on expert opinion gathered from consultant haematologists in the UK.
(J) There are few usable healthcare resource use data reported in Study AZA-001. Furthermore, of the 358 patients in the trial, only 23 were from UK centres. It was therefore difficult to determine appropriate healthcare resource use data from the trial. To supplement the trial data, a survey of UK haematologists was performed, as it was felt that expert opinion would provide the best means to acquire relevant UK-based healthcare resource use data in the treatment of MDS patients.

(A) Azacitidine is assumed to cost £321 per vial, with only a 100 mg vial available.
(J) This reflects the current market price and vial availability.

(A) It is assumed that there is no wastage for any drug overage for the cost calculations of low-dose or standard-dose chemotherapy. However, wastage is included in the cost of azacitidine.
(J) This is a simplifying assumption and is conservative as it will underestimate the drug costs associated with low-dose or standard-dose chemotherapy.

(A) Patients incur AEs based on the data from Study AZA-001. The model cycle rate is calculated for each treatment arm and applied while the patients are still on active therapy. After treatment has ceased and patients are still in the MDS state, they are assumed to incur the BSC annualised AE rate.
(J) During active treatment there is an increased risk of treatment-related AEs occurring; however, over time the rate of AEs is shown to fall. This is best reflected by modelling the five-week rates observed in the trial.

(A) Costs for AEs are accrued during the model. However, AEs in the model do not yield any utility decrements.
(J) The mapped utility data are based on longitudinal recordings and will likely include utility decrements for patients suffering AEs. This may potentially cause double-counting of AE-associated disutility. Furthermore, given the paucity of utility

data in this patient population, estimating utility decrements for AEs would have introduced significant uncertainty into the model.

(A) Utilities for patients treated with azacitidine and BSC are based on mapping European Organisation for Research and Treatment of Cancer (EORTC) scores from Study CALGB 9221 to EQ-5D values using a published algorithm by McKenzie et al.[80] *QoL scores for low-dose and standard-dose chemotherapy reported by the SF-12 QoL instrument in Sekeres* et al[81] *are mapped to EQ-5D values by applying a published algorithm by Gray* et al.[82] *Other possible mapping methodologies are examined in the sensitivity analysis.*

(J) There were no usable utility data available in Study AZA-001 and so alternative sources had to be found. The CALGB 9221 and Sekeres *et al* data sets feature similar patients to Study AZA-001 and the mapping exercises from EORTC and SF-12 scores to EQ-5D values use published peer-reviewed algorithms.

7.2.6.2. Why was this particular type of model used?

The treatment pathway for MDS patients is straightforward and requires few health states to describe the natural course of the disease. Furthermore, there is no requirement for 'memory' in the model. Therefore, a Markov cohort-based model was considered most appropriate. The Markov approach represents an appropriate way of modelling a chronic disease when patients pass through a series of clearly defined and mutually exclusive health states.

7.2.6.3. What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The patient pathway is straightforward in this disease area: patients start with MDS and then either die or experience disease progression (transform to AML). After transformation to AML, they subsequently die. The chosen model structure best reflects this three-health-state patient pathway. No other structures were considered.

7.2.6.4. What were the sources of information used to develop and inform the structure of the model?

The main source of information that informed the structure of the model was Study AZA-001. The structure was then validated by a panel of expert haematologists.

7.2.6.5. Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

All relevant features of the condition are considered.

7.2.6.6. For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model is constructed with a five-week (35-day) cycle. The mean azacitidine treatment cycle in Study AZA-001 was 36.1 days (SD 10.4).[56] However, for ease of construction, the model was divided into five-week (35-day) cycles, which closely mirror the mean azacitidine cycle duration. Although the trial protocol defined a four-week treatment month, the actual observed dosing period in the trial was mostly five weeks. This time period reasonably reflects the minimum time over which the pathology and symptoms of MDS differ.

7.2.6.7. Was a half-cycle correction used in the model? If not, why not?

Yes, a half-cycle correction was applied.

7.2.6.8. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Overall survival and the associated costs are extrapolated beyond the three-year time horizon of the pivotal clinical trial. To estimate the model cycle transition probability to the mortality state and the lifetime extrapolation, survival curves were constructed for each treatment arm using individual patient-level data from Study AZA-001. The survival curves were built utilising the maximum likelihood estimate-generating parameter estimates in STATA to construct either a Weibull or a log-logistic fit to the data. The quality of fit was assessed using the Akaike Information Criterion (AIC) and was found to be similar for both parametric functions.

The patients treated with azacitidine are stratified according to their prerandomisation arm, so that like-for-like patient groups are compared (for example, only patients that had been preselected by the investigating physician as suitable for treatment with standard-dose chemotherapy before randomisation to azacitidine are compared with patients randomised to receive standard-dose chemotherapy).

Details on how the curve fits were performed are given in Appendix 4.

The Kaplan–Meier plots of the individual patient-level data and the curve fits for each treatment arm are shown in Figures 7.2a to 7.2f.

Figure 7.2a. Observed overall survival and fitted survival curves for BSC patients

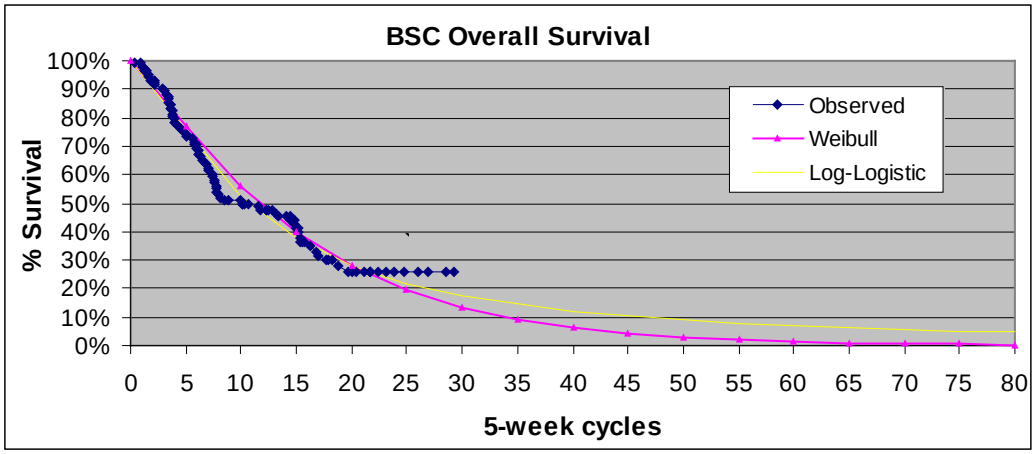


Figure 7.2b. Observed overall survival and fitted survival curves for azacitidine patients preselected for BSC

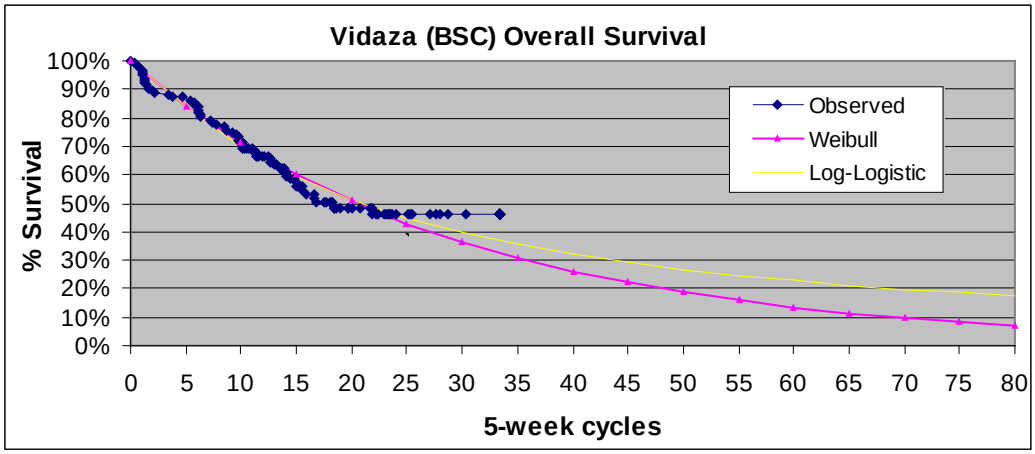


Figure 7.2c. Observed overall survival and fitted survival curves for low-dose chemotherapy patients

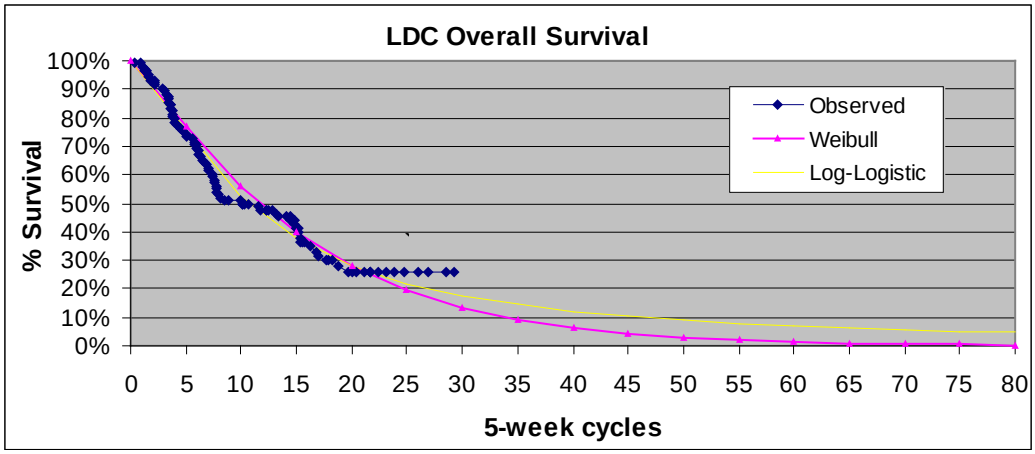


Figure 7.2d. Observed overall survival and fitted survival curves for azacitidine patients preselected for low-dose chemotherapy

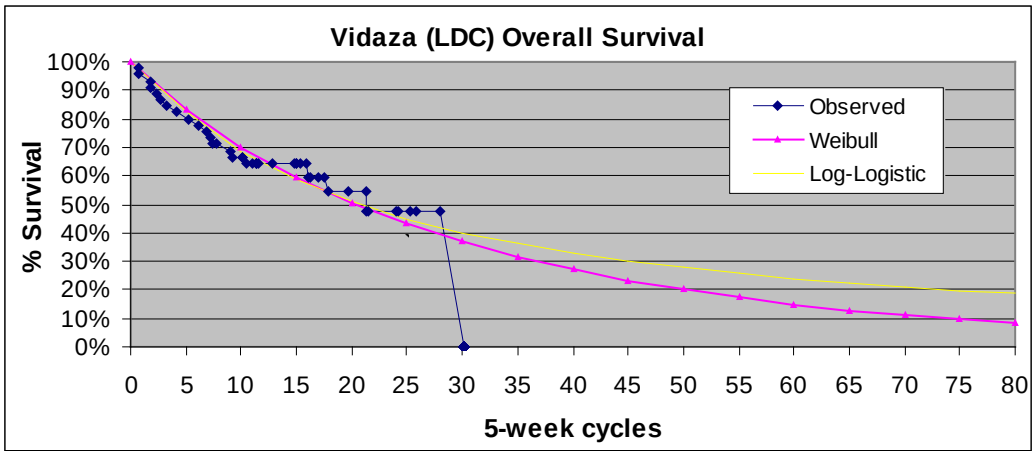


Figure 7.2e. Observed overall survival and fitted survival curves for standard-dose chemotherapy patients

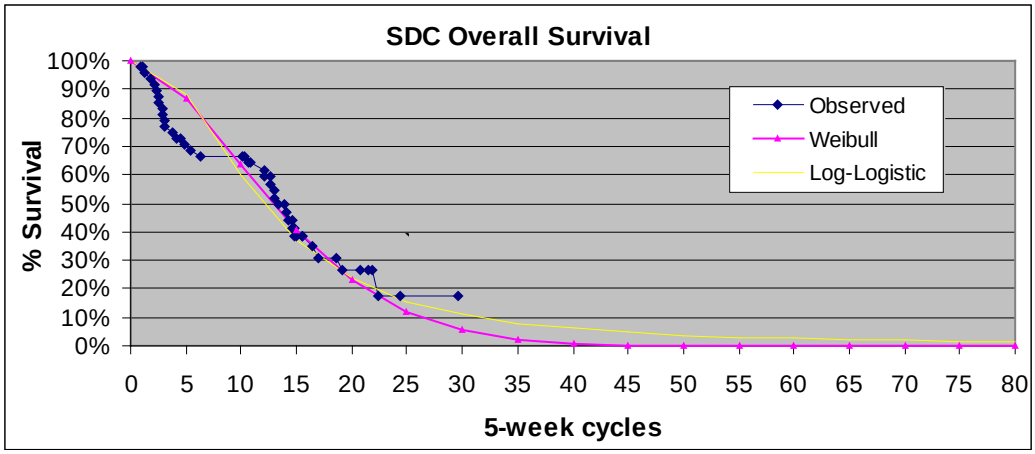
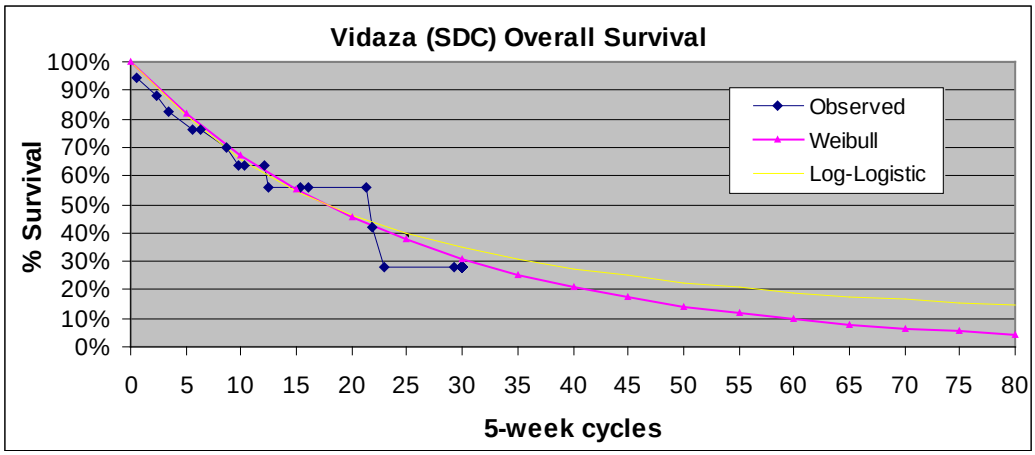


Figure 7.2f. Observed overall survival and fitted survival curves for azacitidine patients preselected for standard-dose chemotherapy



The curve fits to the trial survival data were analysed using the AIC. AIC values are based on model fit (how well the observed data fit the model) and the principle of parsimony (simple models are better, so there is a penalty for added parameters). Further details on the AIC are given in Appendix 4.

The AIC values for each curve and treatment arm are shown in Table 7.3 below.

Table 7.3. AIC values for each curve fit

Preselected treatment	Treatment arm	Curve type	AIC value
Best supportive care	Azacitidine	Weibull	741.6
		Log-logistic	741.5
	Best supportive care	Weibull	524.1
		Log-logistic	518.2
Low-dose chemotherapy	Azacitidine	Weibull	745.9
		Log-logistic	745.7
	Low-dose chemotherapy	Weibull	251.4
		Log-logistic	252.3
Standard-dose chemotherapy	Azacitidine	Weibull	742.3
		Log-logistic	742.4
	Standard-dose chemotherapy	Weibull	124.5
		Log-logistic	124.3

Key: AIC: Akaike Information Criterion

The AIC statistics show that there is very little to choose between the Weibull and log-logistic curve fits to the observed overall survival data. There is, however, a difference when the tail of the curve fits is examined. This difference is not captured by the AIC. The log-logistic curve has a significantly shallower tail and thus has better long-term mean survival that the Weibull fit. It is important, therefore, that the chosen curve type is consistent for each of the treatment arms, so that equivalent assumptions are made as to the shape of the tail.

[redacted]

[redacted]

[redacted]

[redacted]

For the base case in the economic evaluation, a log-logistic fit is assumed as this is likely to be a more appropriate curve for modelling survival data. A scenario where a Weibull fit is used will be examined in sensitivity analysis.

The modelled median and mean survival times using the log-logistic and Weibull fit are compared with the observed median survival times in Tables 7.4a and 7.4b. (modelled five-week cycles are converted to four-week cycles so that comparison with the trial results can be made). The modelled median survival times are slightly different from the trial medians, due to the curve fits which extrapolate the long-term survival. This is mainly caused by the numerous censoring points around the median survival in the observed data and in the tail of the curve, which drive the curve shape.

Patients have an increased mortality risk when in the AML health state. It is assumed that the risk of mortality in AML is independent of the patient's previous treatment arm and the pooled mortality rate is used across all treatment arms. This results in an AML mortality rate of 0.135 per cycle. This rate is applied to all patients in the AML health state. The rate of mortality of patients in the MDS health state is calculated by adjusting the rate so that the overall survival rate described above is maintained.

Table 7.4a. Modelled and trial survival statistics – log-logistic extrapolation

Preselection	Active treatment	Trial-reported median overall survival (months)	Modelled median overall survival (months)*	Modelled mean overall survival (months)
BSC	Azacitidine	21.11	26.02	52.08
	BSC	11.54	13.38	24.79
	Difference	9.57	12.64	27.29
LDC	Azacitidine	24.46	25.89	54.12
	LDC	15.31	14.90	28.67
	Difference	9.15	10.99	25.45
SDC	Azacitidine	25.08	21.94	45.69
	SDC	15.74	14.92	19.64
	Difference	9.34	7.02	26.05

* Converted from five-week cycles
Key: BSC: best supportive care; LDC: low-dose chemotherapy; SDC: standard-dose chemotherapy

Table 7.4b. Modelled and trial survival statistics – Weibull extrapolation

Preselection	Active treatment	Trial-reported median overall survival (months)	Modelled median overall survival (months)*	Modelled mean overall survival (months)
BSC	Azacitidine	21.11	25.52	37.20
	BSC	11.54	14.69	19.48
	Difference	9.57	10.83	17.72
LDC	Azacitidine	24.46	25.48	38.79
	LDC	15.31	16.38	24.75
	Difference	9.15	9.10	14.04
SDC	Azacitidine	25.08	21.98	32.01
	SDC	15.74	16.05	17.76
	Difference	9.34	5.93	14.25

* Converted from five-week cycles
Key: BSC: best supportive care; LDC: low-dose chemotherapy; SDC: standard-dose chemotherapy

b) Non-model-based economic evaluations

7.2.6.9. Was the evaluation based on patient-level economic data from a clinical trial or trials?

This approach was not used.

7.2.6.10. Provide details of the clinical trial, including the rationale for its selection.

Not applicable.

7.2.6.11. Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable.

7.2.6.12. Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable.

7.2.6.13. Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not applicable.

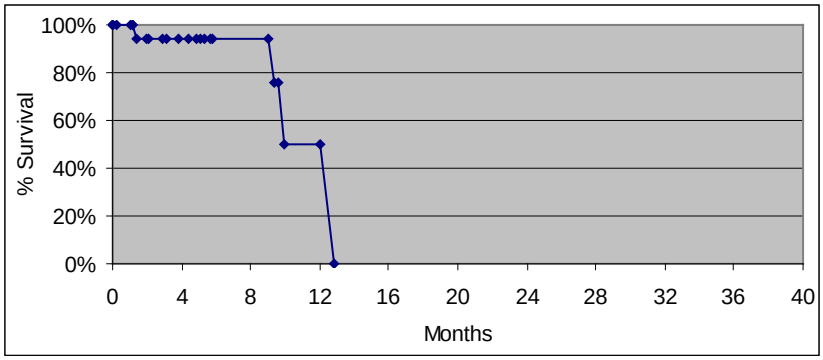
7.2.7. Clinical evidence

7.2.7.1. How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

Disease progression occurs when the patient progresses to AML. While this is recorded in the clinical trial, there is a large number of censored data points, which makes estimation of the time to transformation to AML difficult in each treatment arm. (Figure 7.4 shows the Kaplan–Meier curve for a standard-dose chemotherapy patient's progression to AML, which demonstrates the number of censored points and the difficulty in fitting a curve through the data points).

Clinicians have advised that there is no reason to expect any difference between treatment arms in the time spent in AML. Therefore, rather than forward estimating the time to AML progression from randomisation, the model calculates the pooled time in AML across all treatment arms and back calculates the time to AML progression from the survival curves.

Figure 7.4. Kaplan–Meier plot of time to AML progression for a standard-dose chemotherapy patient, demonstrating large number of censor points



The pooled median time spent in AML across all treatment arms is 3.65 five-week cycles. This average time is used to recalculate the progression to AML curves based on the survival curves. These are shown in Figure 7.5a to 7.5f.

It is assumed that the progression to AML curves maintain the same shape as the survival curve for each treatment arm, but the curve median is adjusted so that:

AML curve median = survival curve median – 3.65

The details of how these curve fits are performed are given in Appendix 4.

Figure 7.5a. Overall survival and fitted progression to AML curve for BSC patients

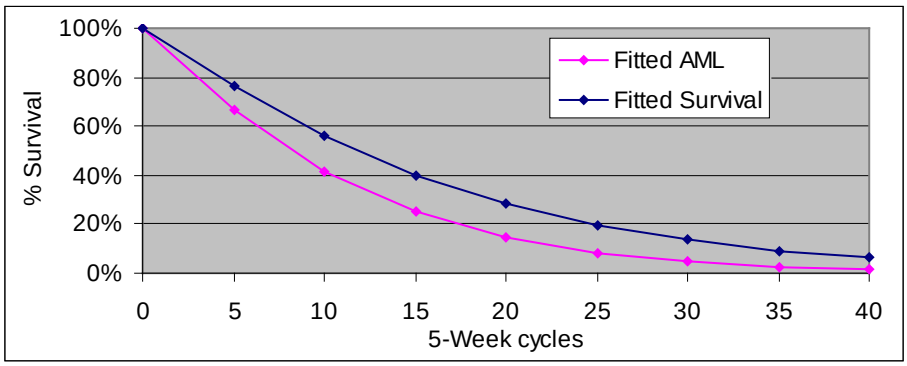


Figure 7.5b. Overall survival and fitted progression to AML curve for azacitidine patients preselected for BSC

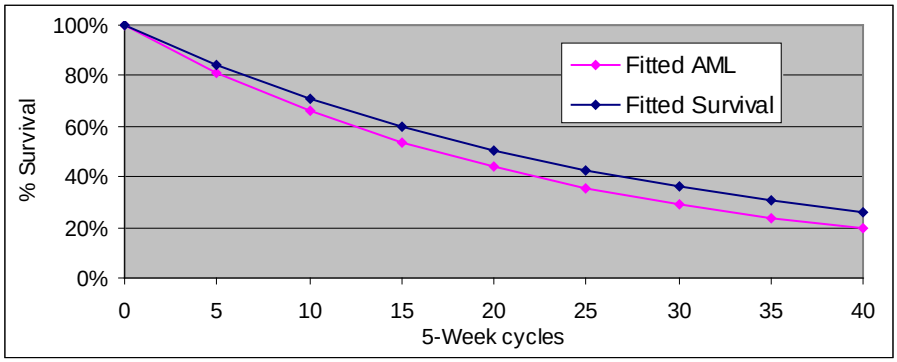


Figure 7.5c. Overall survival and fitted progression to AML curve for low-dose chemotherapy patients

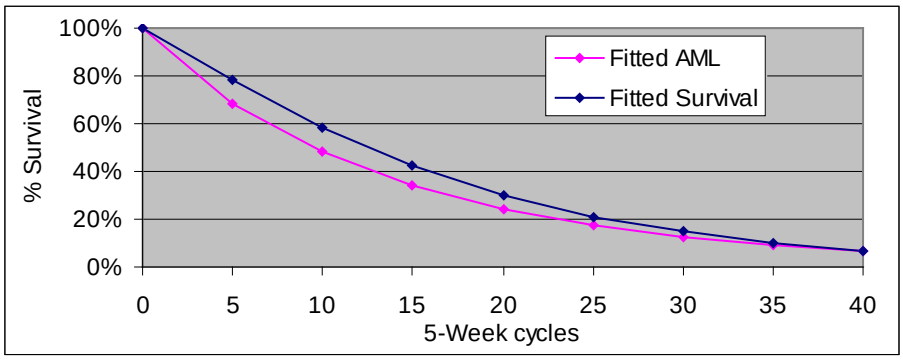


Figure 7.5d. Overall survival and fitted progression to AML curve for azacitidine patients preselected for low-dose chemotherapy

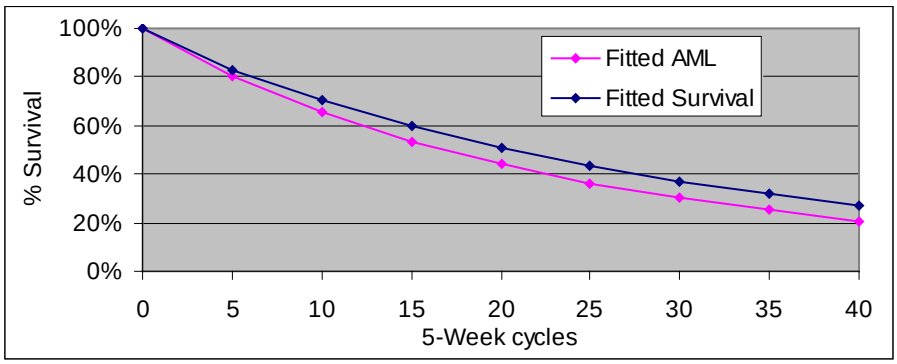


Figure 7.5e. Overall survival and fitted progression to AML curve for standard-dose chemotherapy patients

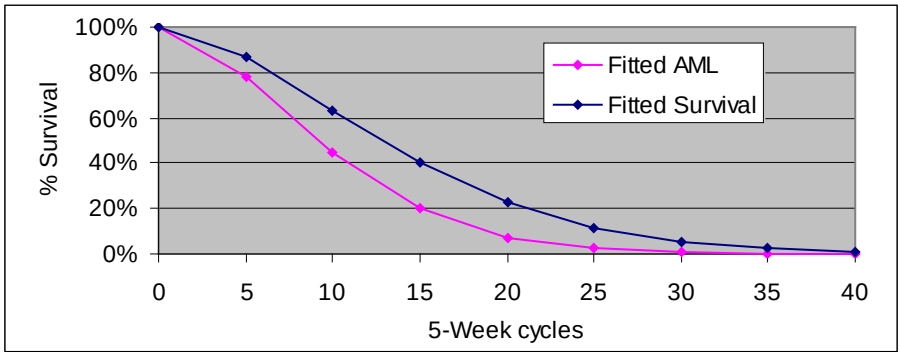
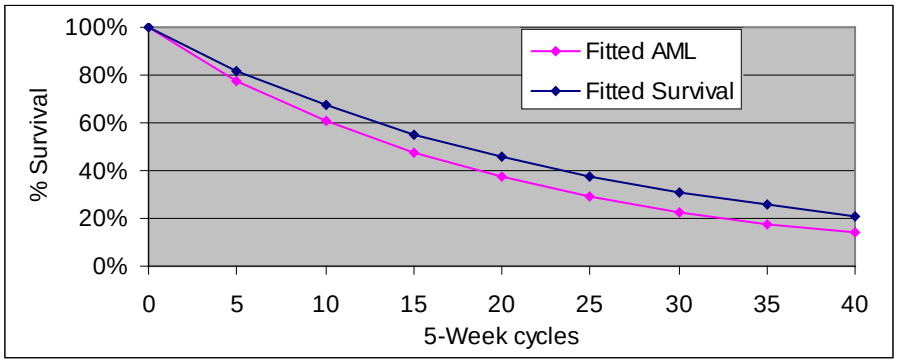


Figure 7.5f. Overall survival and fitted progression to AML curve for azacitidine patients preselected for standard-dose chemotherapy



7.2.7.2. <u>How were the relative risks of disease progression estimated?</u>

Relative risks of disease progression to AML were estimated using the pooled average time to progression and calculating the time to progression based on the overall survival curves as described in Section 7.2.7.1.

The relative risk of mortality is calculated by fitting survival curves to the observed data in each trial arm as described in Section 7.2.6.8.

7.2.7.3. <u>Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?</u>

No intermediate outcome measures were modelled.

7.2.7.4. Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

AEs associated with each treatment arm are included in the economic model. These are modelled using the observed rates from the clinical trials. All the serious Grade 3 and 4 events are modelled. It is assumed that any other AEs incur negligible costs. The modelled events are:

- Neutropenia
- Leucopenia
- Febrile neutropenia
- Abdominal pain
- Pyrexia
- Pneumonia
- Sepsis.

Anaemia and thrombocytopenia were excluded from this list because it is assumed that these AEs will be included in the modelling of blood and platelet transfusions due to anaemia and thrombocytopenia respectively, as observed in the trial.

There are, however, some difficulties in correctly applying the rate of AEs to the modelled treatment arms. The rates recorded in the trial are subject to decay. The rates are higher during initial treatment and then the effects dissipate over time. However, this rate of decay is difficult to determine and match to the extrapolated model. Three scenarios are therefore examined.

1. The AE rate observed in the clinical trial over the mean treatment period for each active treatment arm is applied initially. This is then switched to the AE rate for BSC thereafter. It is assumed that the AE rate cannot drop below that of the annualised rate for BSC. This is the base-case scenario.

2. The annualised AE rate for each treatment arm from the clinical trial is applied to patients in every cycle for which they are in the MDS health state. When patients transform to AML, it is assumed that they incur the annualised AE rate for BSC. The results of this scenario will be examined in a sensitivity analysis.

3. It is assumed that the annualised AE rate for each treatment arm from the clinical trial is applied to patients only when they are undergoing treatment.

Thereafter, they switch to the annualised rate for BSC. The results of this scenario will be examined in a sensitivity analysis.

Scenarios 2 and 3 will demonstrate the lowest and highest rates of AEs respectively when applying AEs rates to the model. Scenario 1 attempts to best reflect the experience of patients in clinical practice.

The modelled AEs are associated with incurred costs. The costs associated with each AE are discussed in Section 7.2.9.1. QoL detriments are not individually modelled as it is assumed that these are captured in the observed longitudinal QoL measurements and so could potentially lead to double-counting of utility scores as discussed in Section 7.2.8.3.

7.2.7.5. Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was not used to estimate any clinical parameters.

7.2.7.6. What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

No further assumptions were made regarding clinical evidence.

7.2.8. Measurement and valuation of health effects

7.2.8.1. If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects are expressed in terms of LYs gained and QALYs gained.

7.2.8.2. Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

The measured health effect values were:

- MDS and treated with azacitidine
- MDS and treated with BSC
- MDS and treated with low-dose chemotherapy
- MDS and treated with standard-dose chemotherapy
- Transformation to AML.

Health effects were not measured for individual AEs as these were assumed to be captured by the longitudinal QoL measurements for each MDS health state, and so could lead to double-counting of utility detriments as described in Section 7.2.8.3.

7.2.8.3. How were health effects measured and valued?

There are very few data on the utility of MDS patients in the literature and Study AZA-001 did not contain any measurement of QoL. A project was therefore commissioned by Celgene to source utility values from an alternate data set. Data were acquired from Study CALGB 9221 in which MDS patients were treated with either azacitidine or BSC and in which EORTC scores were collected (reported by Kornblith *et al)*.[65] The EORTC scores were converted to EQ-5D utility scores using a mapping algorithm described in a recent publication by McKenzie *et al*.[80] This maps EORTC QLQ-C30 functioning, symptoms and global quality scores from an individual patient level into EQ-5D scores.

The CALGB 9221 data set recorded EORTC scores at four assessment points on Days 0, 50, 106 and 182. These have all been converted to EQ-5D utility scores, as shown in Table 7.5. Full details of this mapping process are given in Appendix 5.

In the CALGB 9221 data set, some patients were allowed to crossover from the BSC arm to the azacitidine arm. Kornblith *et al* state that 'After a minimum period of four months, those on the supportive care arm could cross over to the azacitidine arm based on strict criteria concerning disease progression'.[65] Two analyses were performed to address this. First, the utilities of censored patients were mapped when they crossed over to azacitidine from BSC. This approach is used in the base-case analysis. Second, the utilities were mapped on an intention-to-treat basis (ITT). The results of this investigation show that there is negligible difference in resultant utility scores with either methodology. The effect of using ITT utility scores is shown in a sensitivity analysis.

Table 7.5. EQ-5D utility scores at four assessment points, mapped from Study CALGB 9221 data

Treatment arm	**EQ-5D score *(SD)***			
	Day 0	**Day 50**	**Day 106**	**Day 182**
Azacitidine	0.67 *(0.22)*	0.70 *(0.20)*	0.74 *(0.20)*	0.80 *(0.21)*
BSC	0.67 *(0.22)*	0.69 *(0.20)*	0.68 *(0.22)*	0.72 *(0.22)*

Key: BSC: best supportive care

The values presented in Table 7.5 are used in the base case analysis. However, patients in the CALGB 9221 data set were slightly younger and healthier at baseline than those in Study AZA-001. A sensitivity analysis was therefore performed to downward adjust the utility scores from the CALGB 9221 mapping to reflect the reduced health status of patients in this trial. Regression analysis was also performed on the CALGB 9221 dataset to assess whether a relationship could be found between baseline utility scores and baseline patient characteristics. An equation could then be determined to adjust the utility scores to the patients in the AZA-001 data set. Details of this analysis are shown in Appendix 6. The results of this downward adjustment are negligible and the utility scores are hardly affected (see Table 7.6). However, the effect of applying this adjustment is examined in a sensitivity analysis.

The utility analysis results specifically show that there is a treatment effect on the QoL of patients in the MDS health state. Patients treated with azacitidine have a better QoL than those treated with BSC, and this difference increases with increasing length of treatment. The utility scores seen at 182 days are assumed to remain constant for the remainder of the patient's time in the MDS health state.

Table 7.6. Effect of the utility adjustment to account for the more severe condition of AZA-001 patients compared with CALGB 9221 patients

Scenario	Treatment arm	Assessment at Day			
		0	50	106	182
Utility score before adjustment	Azacitidine	0.67	0.70	0.74	0.80
	BSC	0.67	0.69	0.68	0.72
Utility score after adjustment	Azacitidine	0.65	0.68	0.73	0.79
	BSC	0.65	0.67	0.67	0.71
Difference in utility due to adjustment	Azacitidine	0.02	0.02	0.01	0.01
	BSC	0.02	0.02	0.01	0.01

Key: BSC: best supportive care

The CALGB 9221 data set only contains patients treated with azacitidine and BSC and does not identify any chemotherapy patients. A literature search was performed which identified a paper by Sekeres *et al*.[81] This reported SF-12 scores for low-dose and standard-dose chemotherapy patients. These values were also converted either to SF-6D using a mapping algorithm by Brazier *et al*[83] or to EQ-5D utility values using two alternative mapping methods by Franks *et al*[84] and Gray *et al*.[82]

Individual patient-level data from Sekeres *et al* for patients treated with low-dose and standard-dose chemotherapy were used to map from SF-12 QoL data to EQ-5D.

These scores are presented in Table 7.7. Again, it is assumed that the utility score at Day 365 remains constant for the rest of the MDS health state. However, by Day 365 there are few patients remaining in the Sekeres *et al* data set and so a sensitivity analysis is performed assuming the utility score remains constant after Day 182, which matches the assumption for azacitidine and BSC patients.

No adjustments to match Study AZA-001 data were possible as no individual patient-level characteristics with which to perform this analysis were reported by Sekeres *et al*. The patients in the Sekeres *et al* data set can, however, be assumed to be comparable to Study AZA-001 patients.

Even if patient-level characteristics *had* been available from Sekeres *et al* in order to perform multivariate regression analyses on utilities, this would not be expected to significantly influence low-dose and standard-dose chemotherapy utility values, since this was not the case either in the above-mentioned utility mapping exercise for azacitidine and BSC utilities from the CALGB 9221 data set. Furthermore, BSC patients were preselected in Study AZA-001 but not in Study CALGB 9221, while low-dose and standard-dose chemotherapy patients from the Sekeres *et al* publication can be expected to have followed the same preselection process as in Study AZA-001. Consequently, there are potential reasons to believe that the low-doe and standard-dose chemotherapy patient populations were more similar in Study AZA-001 and the Sekeres *et al* trial than was the case for BSC patients in Study AZA-001 trial and Study CALGB 9221.

One validation of the analysis, however, is that at baseline patients should all be of a similar health status regardless of treatment arm. This is reflected in the Day 0 utility scores which are all 0.66–0.67 (see Table 7.7).

Table 7.7. Utility scores for low-dose and standard-dose chemotherapy patients

Treatment arm	**Mean utility score *(SD)***						
	Day 0	**Day 14**	**Day 42**	**Day 70**	**Day 98**	**Day 182**	**Day 365**
Low-dose chemotherapy	0.67 *(0.08)*	0.70 *(0.09)*	0.71 *(0.15)*	0.72 *(0.13)*	0.70 *(0.06)*	0.85 *(0.08)*	0.67 (0.22)
Standard-dose chemotherapy	0.66 *(0.13)*	0.61 *(0.10)*	0.66 *(0.10)*	0.69 *(0.12)*	0.72 *(0.16)*	0.74 *(0.18)*	0.83 *(0.10)*

There are no reported values for patients with AML. It was therefore assumed that the AML utility value is the same as that of baseline MDS (0.67). Since duration in the AML health state is modelled identically irrespective of which treatment arm patients entered initially, the effect of this assumption will only be realised in the discounting of utilities and so will have minimal effect on the cost-effectiveness. The effect of varying the AML utility score will be examined in a sensitivity analysis.

7.2.8.4. Were any other generic or condition-specific preference based measures used in the clinical trials?

There were no other generic or condition-specific preference-based measures used in the clinical trials.

7.2.8.5. Were any health effects excluded from the analysis? If so, why were they excluded?

AEs do not have AE-specific utility detriments modelled. This was to prevent any potential double-counting of the health effect due to the capture of longitudinal utility data described in Section 7.2.8.3.

7.2.9. Resource identification, measurement and valuation

7.2.9.1. What resources were included in the evaluation?

Resource use profiles for the management of MDS and AML (blasts >30%) were collected separately using a structured questionnaire (for example, routine follow-up). Additionally, resource use profiles for patients with MDS were collected based on their therapy. Treatment-associated costs (for example, administration of treatment, monitoring, concurrent medication and administration of blood products) are applied while patients receive the allocated therapy; upon treatment cessation, the treatment-associated costs of BSC are applied until disease progression (transformation) to AML. Subsequently, the costs associated with AML management are applied until death.

The following components of healthcare resource use were obtained using the structured questionnaire and are presented in the tables below:

- Routine follow-up appointments
- Laboratory and monitoring tests
- Administration of treatment with BSC, chemotherapy or azacitidine
- Medication (premedication, treatment and concurrent medication).

Table 7.8. Routine follow-up for patients with MDS or AML[85,86]

	Mean routine follow-up (per month)	Cost per consultation	Source
MDS			
Consultant haematologist	2.0	£103.00	NHS Reference Costs 2006/07
AML (blasts >30%)			
Nurse	3.0	£9.00†	PSSRU
Consultant haematologist	2.7	£103.00	NHS Reference Costs 2006/o7
Nurse	3.7	£9.00†	PSSRU

† It is assumed that each nurse contact is 20 minutes in mean duration at a cost of £27 per hour

Arithmetic means of the disease monitoring tests for MDS by treatment arm and AML and their associated costs are described in Table 7.9.

Table 7.9. Mean number of regular laboratory and disease monitoring tests[86]

Tests	Cost (£)	Source	Frequency (mean number of tests per month)				
			MDS (treatment arm)				AML
			BSC	LDC	SDC	AZA	
Full blood count	3.05	NHS reference costs DAP823	5.8	6.3	17.1	6.5	5.8
Biochemistry profile (U&Es)	1.48	NHS reference costs DAP841	2.9	2.8	6.7	2.9	2.2
Liver function tests (LFTs)	1.48	NHS reference costs DAP841	1.2	1.8	4.6	1.8	1.2
Blood cultures	7.23	NHS reference costs DAP831	0.0	0.0	0.6	0.0	0.0
Group & save/cross match	3.05	NHS reference costs DAP823	1.4	1.4	1.8	1.4	1.1
Bone marrow aspirate (BMA)	1.48	NHS reference costs DAP841	0.3	0.4	0.8	0.7	0.3
Bone marrow trephine biopsy (BMT)	1.48	NHS reference costs DAP841	0.2	0.3	0.4	0.3	0.2
Bone marrow cytogenetics	20.62	NHS reference costs DAP838	0.3	0.6	0.5	0.6	0.3

Key: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

Medication costs for premedication prior to MDS treatment and concurrent medication treatment patterns were collected by from the structured questionnaire. Details regarding the dose, frequency and duration of treatment were elicited and the treatment costs were weighted accordingly to the treatment patterns and relevant drug costs from the *British National Formulary*.[87] Details of the prescribing treatment patterns are given in Appendix 8. The costs associated with low-dose chemotherapy

and standard-dose chemotherapy were based on the Study AZA-001 protocol dosage regimens. A summary of these costs is detailed in Table 7.10.

Table 7.10. Summary of medication costs

	Cost per cycle (£)				
	MDS (treatment arm)				AML
Medication	**BSC**	**LDC**	**SDC**	**AZA**	
Premedication	0.00	6.97	0.00[†]	46.53	0.00
Active treatment	0.00	18.52	Ind: 665.79	4,381.65	0.00
			Con: 453.74		
Concurrent medication	94.73	128.75	210.39	129.46	144.07

[†] Assumed to be covered in HRG costs for inpatient stay associated with SDC administration

Key: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; Con: consolidation chemotherapy; Ind: induction chemotherapy; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

The costs of treatment administration for each MDS treatment obtained from the haematologist interviews are described in Table 7.11.

Table 7.11. Administration of treatment[85]

	Mean time per cycle (mins)	Cost per hour (£)	Source
Best supportive care			
Consultant	6.2	106.00	PSSRU
Senior doctor	4.8	40.00	PSSRU
Foundation house officer	29.2	31.80[†]	PSSRU
Nurse	58.7	27.00	PSSRU
Low-dose chemotherapy			
Senior doctor	1.2	40.00	PSSRU
Foundation house officer	7.3	31.80[†]	PSSRU
Nurse	126.5	27.00	PSSRU
District nurse	199.2	29.00	PSSRU
Hospital pharmacist	64.6	28.00	PSSRU
Standard-dose chemotherapy			
Inpatient stay	28 days	N/A	N/A
Azacitidine			
Consultant	12.3	106.00	PSSRU
Foundation house officer	5.0	31.80[†]	PSSRU
Nurse	253.1	27.00	PSSRU
Hospital pharmacist	107.7	29.00	PSSRU

[†] Foundation house officer 2: assumed a cost per hour of £31.80 based on average cost per hour of a specialty doctor and foundation house officer

For each disease-related complication or treatment-related AE incorporated into the model, information on the proportion of patients who would receive treatment was

collected. Arithmetic means of the proportion of patients who would receive treatment for each of the complications of AEs were used in the model. For disease-related complications such as anaemia and thrombocytopenia, the blood product usage as recorded in Study AZA-001 was directly used for resource use estimations for the different treatment comparators. The costs associated with transfusions are applied on a cycle basis as derived from the trial and summarised in Table 7.12. Upon progression to AML, the blood product transfusion rate for the BSC arm of MDS is used until death.

Table 7.12. Blood product administration and costs[88,89]

		Units of blood product (mean number of units) per cycle			
		MDS (treatment arm)			
Blood product	**Cost (£)***	**BSC**	**LDC**	**SDC**	**AZA**
Packed red cells	295.25	2.42	2.75	2.82	1.48
Platelets	220.00	0.61	2.22	4.42	1.15

* Indexed to 2008

Key: AML: acute myeloid leukaemia; AZA: azacitidine; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

The costs of treatment for all Grade 3 or 4 AEs were taken from the NHS Reference Costs by appropriate specialty and the rate of treatment derived from expert opinion (see Table 7.13). As detailed earlier, blood product use was taken directly from Study AZA-001 as the treatment rate for anaemia and thrombocytopenia.

Table 7.13. Grade 3 or 4 AE treatment rate and costs[86,90]

Adverse event	**Proportion of patients treated**	**National average cost**
Neutropenia*	37%	£1,234
Leucopenia*	32%	£1,234
Febrile neutropenia	83%	£4,894
Pyrexia**	91%	£4,894
Pneumonia**	91%	£4,894
Sepsis**	93%	£4,894

* Assumed to be SA08F – *Other Haematological or Splenic Disorders without CC*

** Assumed to be treated the same as febrile neutropenia, as advised by expert haematologists

A summary of the healthcare resource use included in the model is shown in Table 7.14.

Table 7.14. Summary of per-cycle healthcare resource use in the economic evaluation

Healthcare resource use	Azacitidine	BSC	LDC	SDC (consolidation/ induction)
MDS (on active treatment)	***£5,794.54***	***£1,724.25***	***£2,001.23***	***£13,010.88/ £12,798.83***
MDS (off treatment)	***£1,563.36***	***£1,724.25***	***£2,175.60***	***£2,681.73***
Cost components				
Premedication	£46.53	£0.00	£6.97	£0.00
Treatment administration	£188.51	£54.78	£188.00	£9,629.98
HRG costed adverse events	£0.00	£0.00	£0.00	£698.00
Active treatment cost	£4,381.65	£0.00	£18.56	£665.79/ £453.74
Follow-up appointments	£302.93	£302.93	£302.93	£302.93
Blood products	£688.22	£849.11	£1,300.46	£1,806.59
Concurrent medication (on active treatment)	£129.46	£94.63	£128.75	£210.52
Concurrent medication (off active treatment)	£94.63	£94.63	£94.63	£94.63
Routine tests (on active treatment)	£57.24	£42.46	£55.56	£107.31
Routine tests (off active treatment)	£42.46	£42.46	£42.46	£42.46
AML treatment	***£1,814.27***	***£1,814.27***	***£1,814.27***	***£1,814.27***
Adverse events	£380.34	£380.34	£380.34	£380.34
Follow-up appointments	£398.29	£398.29	£398.29	£398.29
Blood products	£849.11	£849.11	£849.11	£849.11
Concurrent medication	£144.07	£144.07	£144.07	£144.07
Routine tests	£42.46	£42.46	£42.46	£42.46
Annualised adverse events*	***£433.88***	***£380.34***	***£682.09***	***£2,666.76***

* Adverse events are based on the annualised rate of incidence. The model base case uses a varying cycle rate which cannot be displayed here

Key: AML: acute myeloid leukaemia; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

7.2.9.2. How were the resources measured?

Where possible, healthcare resource use was determined from Study AZA-001. Treatment dosing and units of blood products transfused are both estimated from Study AZA-001. Where healthcare resource use data were not available, data on NHS resources used to treat MDS and AML (>30% blasts) were obtained by interviewing with a structured questionnaire thirteen haematologists who specialise in the treatment of MDS.[90] These specialists were selected to provide a broadly representative geographical spread across England and Wales in order to incorporate any regional variation. NHS resources covered in the questionnaire included routine follow-up, frequency of laboratory and disease monitoring, concurrent medications and treatment of disease or treatment-related AEs. Further details of this questionnaire are presented in Appendix 7.

7.2.9.3. Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Healthcare resource use was determined from Study AZA-001 where possible, in line with the baseline and relative risk of disease progression. Where data were not available from the clinical trial, estimates of resource consumption were elicited using expert clinical opinion as described in Section 7.2.9.2 (see Appendix 8 for details of the healthcare resource questionnaire).

7.2.9.4. Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)?

Patients are assumed to receive treatment for MDS until the end of the treatment period, as observed in the clinical trial, after which they receive BSC until disease progression, and then treatment for AML until death. Appropriate resource use is therefore modelled throughout the lifetime of the patient.

There are two key resource use assumptions.

- Patients that are in the MDS health state but are no longer receiving active therapy are treated with BSC.
- Patients that have progressed to AML receive the same treatment irrespective of their previous MDS treatment regime.

Both these assumptions have been made with the guidance of expert haematologists to reflect UK clinical practice.

7.2.9.5. What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

Drug costs were taken from the *British National Formulary (BNF)*.[87] NHS costs were taken from the NHS Reference Costs 2006/07[86] and indexed to 2008 prices using the 2008 pay and price index from the Personal Social Services Research Unit (PSSRU).[85]

A key driver of cost-effectiveness in the comparison with standard-dose chemotherapy is the cost of the inpatient stay required when administering treatment.

The base-case approach presented here uses the NHS Reference Costs 2006/07 to price the standard-dose chemotherapy inpatient stay. Due to the severity of higher-risk MDS patients and the AML-type chemotherapy that these patients receive, the

most appropriate HRG code was assumed to be SA25F – *Acute Myeloid Leukaemia without CC.* This has a national average unit cost of £3,915 with an average length of stay of 9.48 days. The national average unit cost of days beyond the average length of stay is £226 per day. Other appropriate HRG codes are SA06F – *Myelodysplastic Syndrome without CC,* which is likely to underestimate the cost of treatment as it includes lower-risk MDS patients that would not receive chemotherapy, and SA17F – *Malignant Disorders of Lymphatic/Haematological systems without CC,* which is often used by hospitals to code AML chemotherapy patients. The costing analysis set out below is repeated for these codes and used to cost the standard-dose chemotherapy inpatient stay in sensitivity analysis.

A survey of UK haematologists reported the mean length of inpatient stay associated with the administration of standard-dose chemotherapy as 28 days (range 21–42 days). Including pretreatment costs and pharmacology, this results in a base-case cost for standard-dose chemotherapy inpatient stay of £10,232 (indexed to 2008 prices).

By using the SA25F (without complications) HRG code to cost the inpatient stay, it is assumed that this cost does not include the cost of treating AEs. The best available source for costing these events is again the NHS Reference Costs 2006/07. However, it is important to be careful not to double-count the cost of hospital stay, as these patients are already costed for being in hospital by the SA25F code. For each AE reference cost, the model only includes the increased daily cost above the average daily cost of code SA25F (£431.71) multiplied by the average length of stay of the AE multiplied by the rate. This results in a total additional cost due to AEs of £698 and a total inpatient stay cost of £10,930. A breakdown of this analysis is presented in Table 7.15.

Table 7.15. Analysis of the additional costs associated with standard-dose chemotherapy inpatient stay using NHS Reference Costs 2006/07

Adverse event	AE rate over first 28 days	National average unit cost	Proportion of patients treated	Average length of stay	Average cost per day	Extra cost per day	Additional cost to SDC
Neutropenia*	15.80%	£1,234	37%	2.44	£505	£78	£11
Leucopenia*	26.30%	£1,234	32%	2.44	£505	£78	£16
Febrile neutropenia	15.80%	£4,894	83%	7.43	£659	£227	£221
Pyrexia**	15.80%	£4,894	91%	7.43	£659	£227	£242
Pneumonia**	5.30%	£4,894	91%	7.43	£659	£227	£81
Sepsis**	8.13%	£4,894	93%	7.43	£659	£227	£127

* Assumed to be SA08F – *Other Haematological or Splenic Disorders without CC*

** Assumed to be treated the same as febrile neutropenia, as advised by expert haematologists

Key: AE: adverse event; SDC: standard-dose chemotherapy

In February 2009, the Department of Health published an updated NHS tariff (Payment by Results 2009/10 based on HRG 4.0) for implementation from April 2009.[91] This includes new tariff costs for the HRG codes used in the analysis above. The new costs are designed to have stripped out many of the associated costs of treatment. Thus, when costing the treatment of MDS and the associated complications, more costs have to be added back in to ensure that the full cost of treatment is captured. The cost of treatment using the NHS 2009/10 tariff is presented as a sensitivity analysis.

The 2009/10 elective spell tariff for HRG code SA25F has increased to £4,473; however, this cost is now associated with a 60-day inpatient stay. The new price results in an average cost per day of £75. This cost clearly does not include the cost of treatment of any AEs. The same methodology described above is applied to cost the related AEs, resulting in an additional cost associated with AEs of £1,601. A breakdown of this analysis is shown in Table 7.16. This results in an inpatient stay cost for standard-dose chemotherapy patients of £7,252. The effect of using this figure is examined in a sensitivity analysis.

Table 7.16. Analysis of the additional costs associated with standard-dose chemotherapy inpatient stay using NHS tariff for 2009/10

Adverse event	AE rate over first 28 days	National tariff cost	Proportion of patients treated	Elective long-stay trim point (days)	Average cost per day	Extra cost per day	Additional cost to SDC
Neutropenia*	15.80%	£1,270	37%	11	£115	£40	£26
Leucopenia*	26.30%	£1,270	32%	11	£115	£40	£37
Febrile Neutropenia	15.80%	£5,530	83%	22	£251	£176	£506
Pyrexia**	15.80%	£5,530	91%	22	£251	£176	£555
Pneumonia**	5.30%	£5,530	91%	22	£251	£176	£186
Sepsis**	8.13%	£5,530	93%	22	£251	£176	£291

* Assumed to be SA08F – *Other Haematological or Splenic Disorders without CC*

** Assumed to be treated the same as febrile neutropenia as advised by expert haematologists

Key: AE: adverse event; SDC: standard-dose chemotherapy

7.2.9.6. What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

The unit cost of azacitidine is £321 per 100 mg vial. No price discounts are presented.

7.2.9.7. Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

No additional infrastructure is required for drug administration. It is anticipated that azacitidine will be administered within the current secondary day-care setting.

7.2.9.8. Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, resources were measured using a UK clinician survey and valued using published NHS reference costs.

7.2.9.9. Were resource values indexed to the current price year?

All resources are valued at 2008 prices with the exception of those taken from the *BNF,*[87] which are at the current price, and those taken from the NHS Reference Costs 2006/07,[86] which were uplifted to 2008 prices using the PSSRU pay and price index.[85]

7.2.9.10. Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

Assumptions have been made as to the average dose per patient and the number of 100 mg vials required to provide the average dose. These are detailed in Section 7.2.1.1.1. Assumptions have also been made as to the cost of an inpatient stay for the administration of standard-dose chemotherapy. These are detailed in Section 7.2.9.5.

Azacitidine requires a seven-day continuous treatment cycle, which means that patients will be required to receive treatment over a weekend. It is assumed in the model that no additional costs are required above the cost of normal administration.

While this may underestimate the overall cost, it is envisaged that hospitals will introduce systems that will minimise the impact of weekend administration.

7.2.10. Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, an annual discount rate of 3.5% was used for costs and for health benefits.

7.2.11. Sensitivity analysis

7.2.11.1. Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

The main uncertainty in the model is the application of AEs. In the base case, the AEs are based on patient-level trial data and are time-dependent while patients are on treatment. Once patients are off treatment, they assume the annualised AE rate for BSC. Two alternative scenarios are considered.

1. The annualised AE rates for azacitidine, BSC, low-dose chemotherapy and standard-dose chemotherapy are applied in each cycle in which the patient is on treatment. Once patients move off treatment, the annualised AE rate for BSC is used.

2. The annualised AE rates for azacitidine, BSC, low-dose chemotherapy and standard-dose chemotherapy are applied to patients throughout their time in MDS.

The results of this analysis are presented in Table 7.21 in the sensitivity analysis section.

7.2.11.2. Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

A full PSA analysis was undertaken. The distributions and their sources are presented in Appendix 9 and the results of the PSA are presented in Section 7.3.1.1.

7.3. Results

7.3.1. Base-case analysis

7.3.1.1. What were the results of the base-case analysis?

Deterministic cost-effectiveness results are shown for the base-case parameters in Table 7.17. A detailed breakdown of these results in shown in Table 7.18. These results show that azacitidine provides a significant incremental overall survival gain of more than two years versus the comparator arms. However, this comes at a price, with marginal cost increases ranging from £97,829 in the comparison with BSC to £61,940 in the comparison with standard-dose chemotherapy. Azacitidine patients also have an improved QoL, which is demonstrated by QALY gains of 1.55 compared with BSC and 1.39 compared with standard-dose chemotherapy. These results lead to an ICER of £63,295 compared with BSC, £58,837 compared with low-dose chemotherapy and £44,523 compared with standard-dose chemotherapy.

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

Table 7.18. A detailed breakdown of the cost-effectiveness results

a) Azacitidine versus BSC

Item	Azacitidine (prerandomised to BSC)				BSC		
	In MDS on treatment	In MDS off treatment	In AML	Total	In MDS on treatment	In AML	Total
Number of 5-week cycles	10.50	32.32	6.45	49.27	16.02	6.17	22.19
Number of months	13.13	40.40	8.07	61.59	20.02	7.71	27.73
Cost	**£64,845.59**	**£62,815.91**	**£11,702.99**	**£139,364.49**	**£30,348.12**	**£11,187.67**	**£41,535.79**
Premedication	£488.76			£488.76			
Treatment administration	£1,980.26	£2,200.89		£4,181.15	£964.09		£964.09
HRG costed adverse events							
Pharmacology	£46,028.44			£46,028.44			
Follow-up appointments	£3,182.26	£12,171.90		£15,354.16	£5,331.86		£5,331.86
Blood/platelet transfusion	£7,229.58	£27,652.55		£34,882.13	£14,944.91		£14,944.91
Concurrent medication on treatment	£1,359.94			£1,359.94	£1,665.61		£1,665.61
Concurrent medication off treatment		£3,802.36		£3,802.36			
Routine tests on treatment	£601.33			£601.33	£747.33		£747.33
Routine tests off treatment		£1,706.04		£1,706.04			
AML treatment							
Follow-up appointments			£2,569.87	£2,569.87		£2,456.71	£2,456.71
Adverse events			£2,454.05	£2,454.05		£885.69	£885.69
Concurrent medication			£926.48	£926.48		£5,237.38	£5,237.38
Blood/platelet transfusion			£5,478.63	£5,478.63		£261.90	£261.90
Routine tests			£273.96	£273.96		£2,345.99	£2,345.99
Annualised AEs		£15,282.17		£15,282.17	£6,694.31		£6,694.31
Decaying AEs	£3,975.01			£3,975.01			

Key: AE: adverse event; AML: acute myeloid leukaemia; BSC: best supportive care; MDS: myelodysplastic syndrome

b) Azacitidine versus low-dose chemotherapy

Item	Azacitidine (prerandomised to LDC)				LDC			
	In MDS on treatment	In MDS off treatment	In AML	Total	In MDS on treatment	In MDS off treatment	In AML	Total
Number of 5-week cycles	10.77	34.60	6.34	51.71	6.07	13.56	6.27	25.89
Number of months	13.46	43.25	7.93	64.64	7.59	16.94	7.83	32.36
Cost	**£66,700.32**	**£67,250.38**	**£11,501.15**	**£145,451.85**	**£14,628.33**	**£34,646.72**	**£11,365.26**	**£60,640.32**
Premedication	£501.16			£501.16	£42.29	£872.31		£914.60
Treatment administration	£2,030.48	£2,356.26		£4,386.74	£1,141.03			£1,141.03
HRG costed AEs				£0.00				£0.00
Pharmacology	£47,195.71			£47,195.71	£112.65			£112.65
Follow-up appointments	£3,262.96	£13,031.17		£16,294.13	£1,838.62	£4,824.25		£6,662.88
Blood/platelet transfusion	£7,412.92	£29,604.67		£37,017.59	£7,892.98	£20,709.95		£28,602.93
Concurrent medication on treatment	£1,394.43			£1,394.43	£781.46			£781.46
Concurrent medication off treatment		£4,070.79		£4,070.79		£1,507.04		£1,507.04
Routine tests on treatment	£616.58			£616.58	£337.20			£337.20
Routine tests off treatment		£1,826.48		£1,826.48		£676.18		£676.18
AML treatment				£0.00				£0.00
Follow-up appointments			£2,525.55	£2,525.55			£2,495.71	£2,495.71
Adverse events			£2,411.73	£2,411.73			£2,383.23	£2,383.23
Concurrent medication			£910.50	£910.50			£899.75	£899.75
Blood/platelet transfusion			£5,384.14	£5,384.14			£5,320.52	£5,320.52
Routine tests			£269.24	£269.24			£266.06	£266.06
Annualised AEs		£16,361.00		£16,361.00		£6,056.99		£6,056.99
Decaying AEs	£4,286.09			£4,286.09	£2,482.11			£2,482.11

Key: AE: adverse event; AML: acute myeloid leukaemia; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome

c) Azacitidine versus standard-dose chemotherapy

Item	Azacitidine (prerandomised to SDC)				SDC			
	In MDS on treatment	In MDS off treatment	In AML	Total	In MDS on treatment	In MDS off treatment	In AML	Total
Number of 5-week cycles	10.51	25.97	6.39	42.88	2.22	8.27	6.62	17.10
Number of months	13.14	32.47	7.99	53.60	2.78	10.33	8.27	21.38
Cost	**£65,663.22**	**£50,486.44**	**£11,595.81**	**£127,745.46**	**£28,491.12**	**£25,311.33**	**£12,002.90**	**£65,805.35**
Premedication	£489.04			£489.04				
Treatment administration	£1,981.39	£1,768.90		£3,750.29	£21,383.90	£517.00		£21,900.90
HRG costed AEs				£0.00	£1,549.95			£1,549.95
Pharmacology	£46,054.76			£46,054.76	£1,219.61			£1,219.61
Follow-up appointments	£3,184.08	£9,782.80		£12,966.89		£2,859.21		£2,859.21
Blood/platelet transfusion	£7,233.71	£22,224.92		£29,458.64	£4,011.63	£17,051.35		£21,062.99
Concurrent medication on treatment	£1,360.72			£1,360.72	£467.47			£467.47
Concurrent medication off treatment		£3,056.04		£3,056.04		£893.19		£893.19
Routine tests on treatment	£601.68			£601.68				
Routine tests off treatment		£1,371.18		£1,371.18		£400.75		£400.75
AML treatment				£0.00				
Follow-up appointments			£2,546.33	£2,546.33			£2,635.02	£2,635.02
Adverse events			£2,431.58	£2,431.58			£2,516.27	£2,516.27
Concurrent medication			£918.00	£918.00			£953.16	£953.16
Blood/platelet transfusion			£5,428.45	£5,428.45			£5,617.53	£5,617.53
Routine tests			£271.45	£271.45			£280.91	£280.91
Annualised AEs		£12,282.59		£12,282.59		£3,589.82		£3,589.82
Decaying AEs	£4,757.83			£4,757.83				

Key: AE: adverse event; AML: acute myeloid leukaemia; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

7.3.2. Sensitivity analyses

7.3.2.1. <u>What were the main findings of the sensitivity analyses?</u>

A PSA was performed to examine the combined effect of the uncertainty in all the variable parameters. Values were sampled from the uncertainty distributions associated with each parameter. Where there were no estimates of parameter uncertainty, ±30% intervals were assumed.

In the PSA, 10,000 sets of parameters were estimated and the marginal costs and QALYs calculated. The results of these analyses are presented as scatter plots in Figures 7.6a to 7.6c and cost-effectiveness acceptability curves (CEACs) in Figures 7.7a to 7.7c.

Figure 7.6a. Scatter plot PSA results for patients preselected for BSC

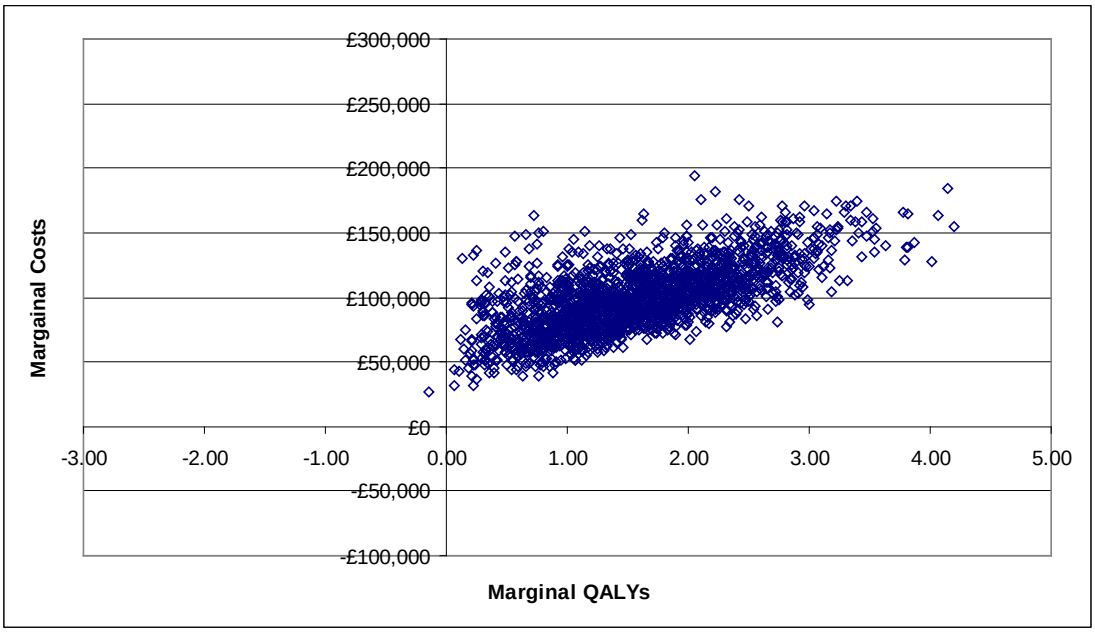


Figure 7.6b. Scatter plot PSA results for patients preselected for low-dose chemotherapy

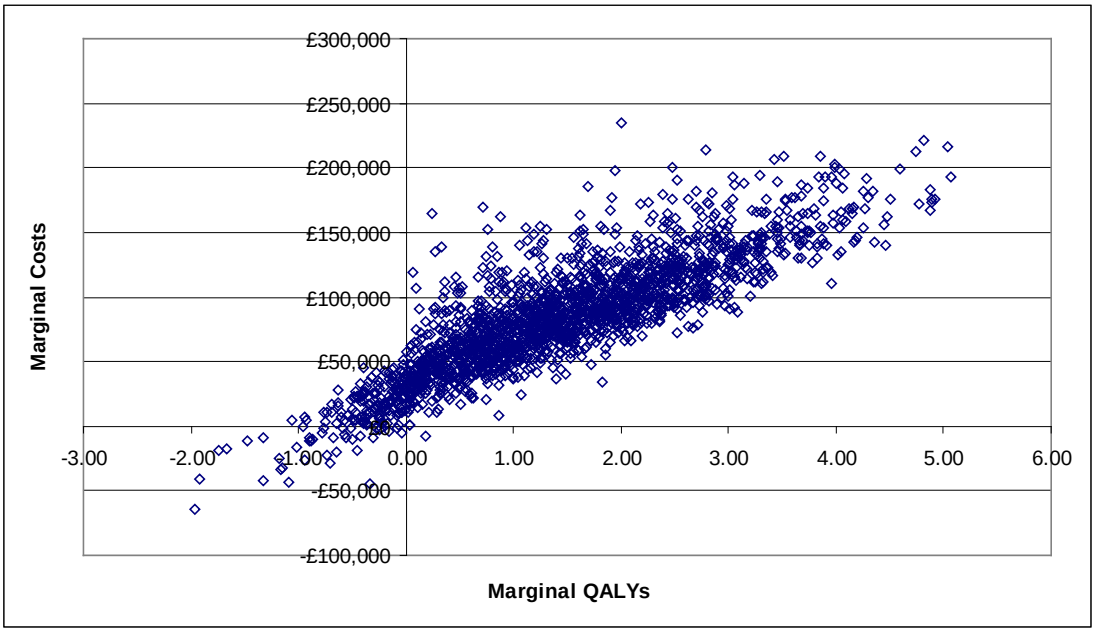


Figure 7.6c. Scatter plot PSA results for patients preselected for standard-dose chemotherapy

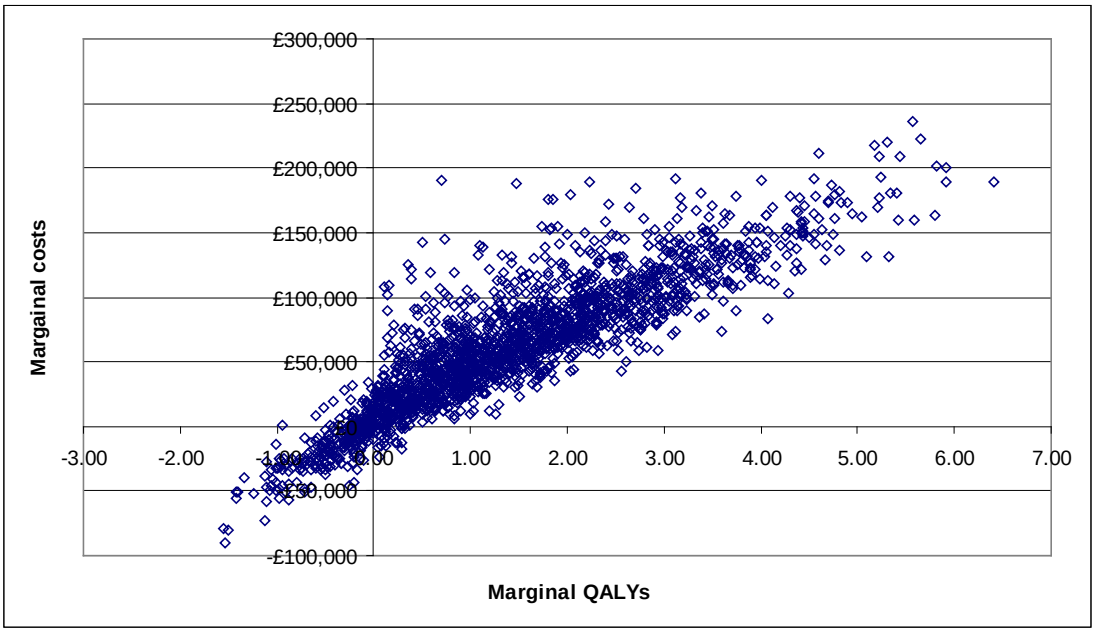


Figure 7.7a. CEAC for patients preselected for BSC

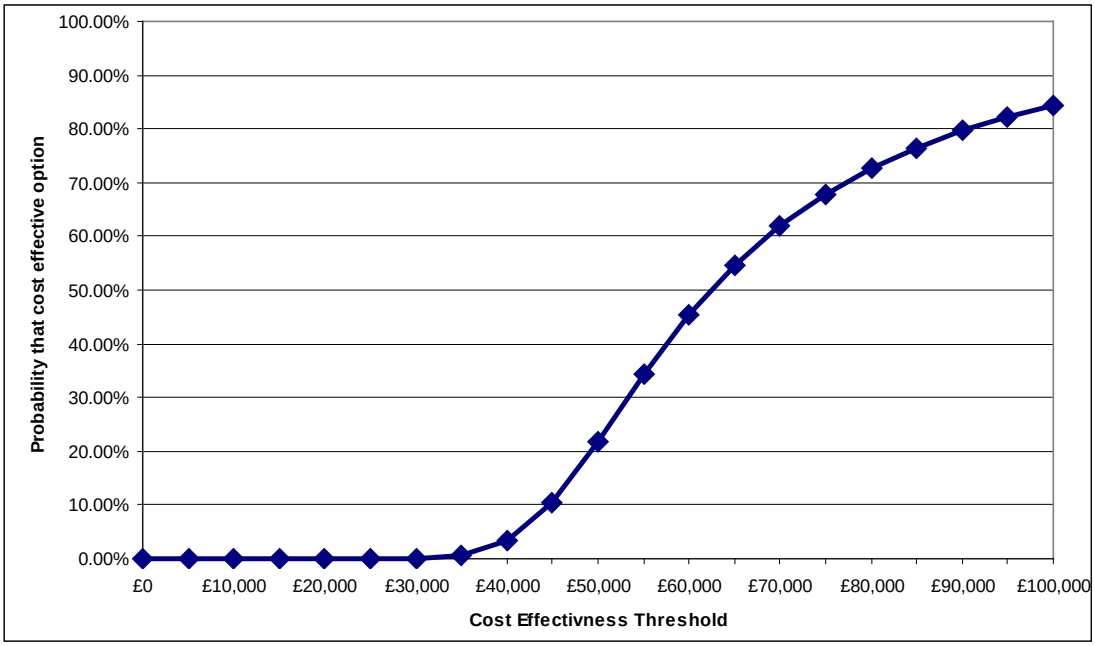


Figure 7.7b. CEAC for patients preselected for low-dose chemotherapy

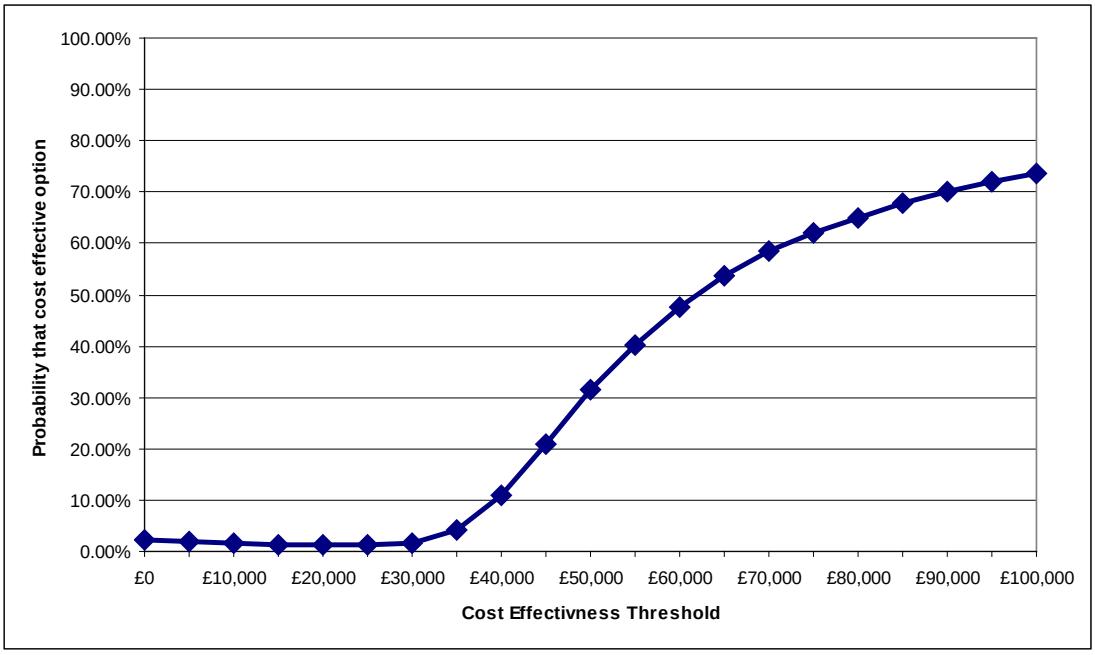
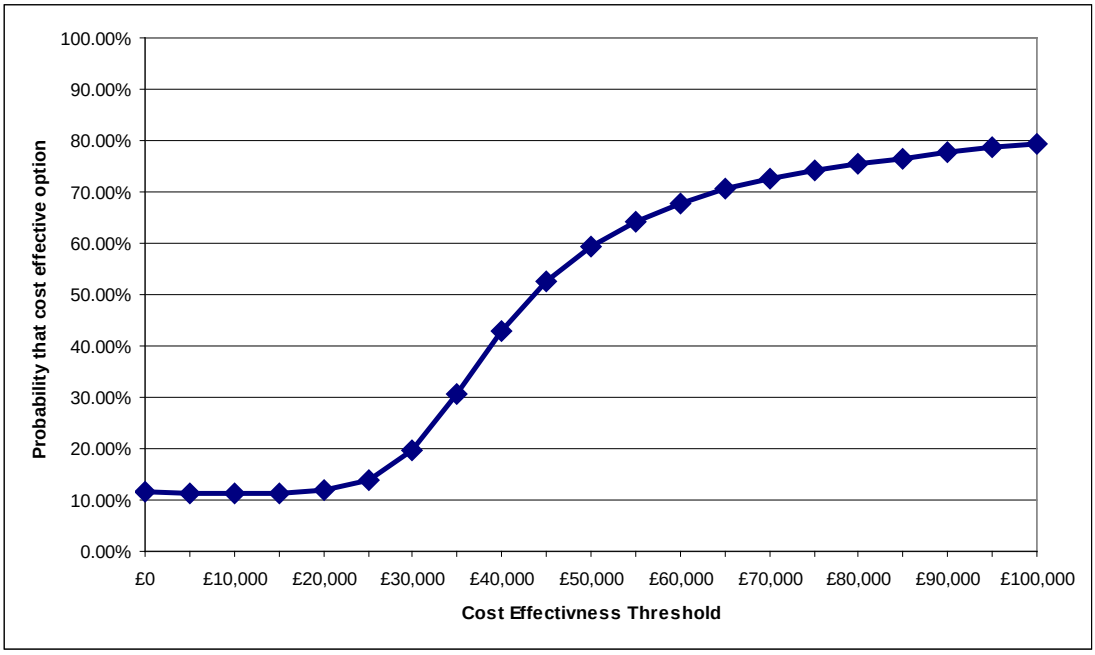
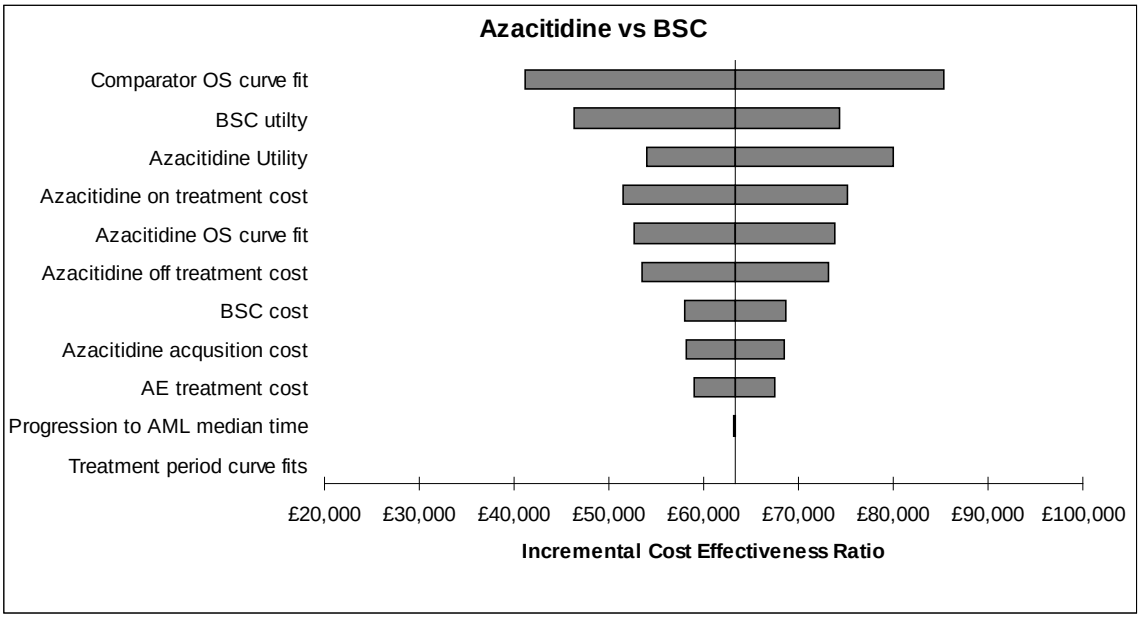


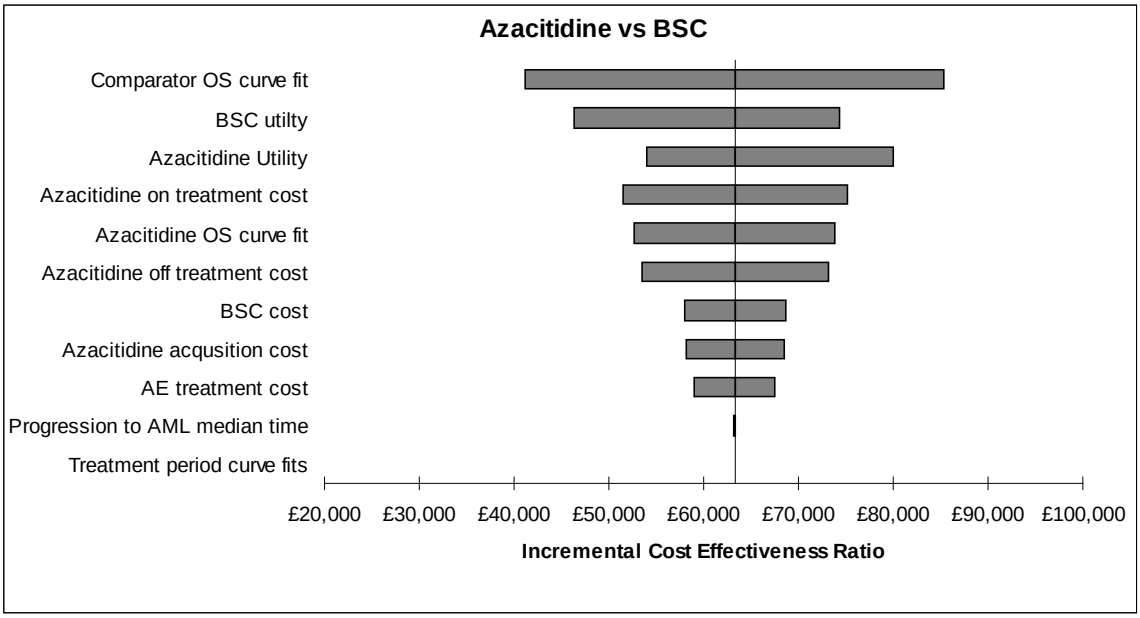
Figure 7.7c. CEAC for patients preselected for standard-dose chemotherapy

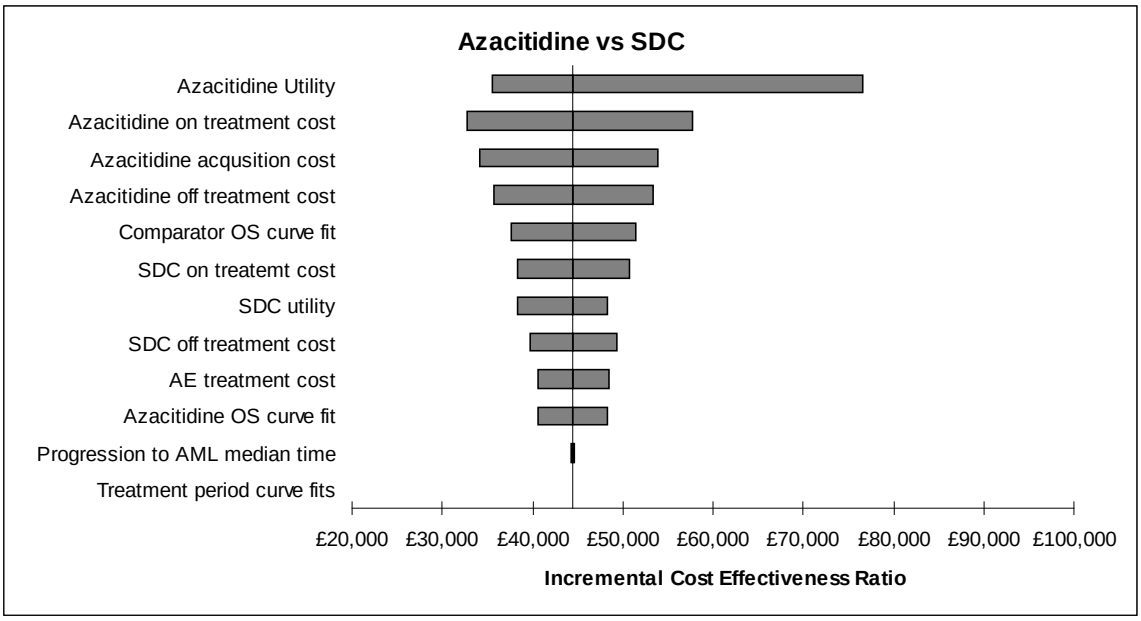


One-way sensitivity has been performed by applying the upper and lower boundary given by the distribution around each of the parameters in the model. Where distributions were unavailable, a ±30% range was assumed. Tornado diagrams for each treatment arm are shown in Figure 7.8 below.

Figure 7.8. Tornado diagrams for the one-way sensitivity analysis







7.3.2.1.1 Choice of parametric curve fit for extrapolation of overall survival

In the base case, survival is extrapolated by fitting a log-logistic curve to the observed survival in Study AZA-001. An alternate curve fit is a Weibull curve, which has a similar AIC but a steeper tail, meaning that the estimated long-term survival for each of the treatment arms is reduced. The effect of using a Weibull curve to estimate survival for each treatment arm is shown in Table 7.19.

Table 7.19. Sensitivity analysis results of fitting a Weibull curve to extrapolate overall survival

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£102,473	2.07	£71,650	0.94	**£76,413**
BSC	£30,823	1.13			
Preselected for low-dose chemotherapy					
Azacitidine	£106,335	2.14	£68,556	0.96	**£71,264**
LDC	£37,779	1.18			
Preselected for standard-dose chemotherapy					
Azacitidine	£95,357	1.72	£35,973	0.69	**£52,338**
SDC	£59,385	1.04			

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

7.3.2.1.2 Azacitidine having a disease-modifying effect

A sensitivity analysis is performed in which we assume that the azacitidine treatment arms have a disease-modifying affect compared with the comparator treatments. This is estimated by assuming the log-logistic fit for the azacitidine cohort and a Weibull fit for the comparator arms. The results of this analysis are presented in Table 7.20.

Table 7.20. Results of a sensitivity analysis assuming a log-logistic fit for the azacitidine treatment arms and a Weibull fit for the comparators

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£139,364	3.00	£108,542	1.87	**£57,974**
BSC	£30,823	1.13			
Preselected for low-dose chemotherapy					
Azacitidine	£145,452	3.12	£107,673	1.94	**£55,389**
LDC	£37,779	1.18			
Preselected for standard-dose chemotherapy					
Azacitidine	£127,745	2.57	£68,361	1.53	**£44,641**
SDC	£59,385	1.04			

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

7.3.2.1.3 Application of adverse events

In the base case, AEs are modelled from the patient-level data from the trial, calculating the AE rate by five-week cycle. In the model, these time-dependent rates

are applied while patients are on treatment. Once patients are off treatment, they assume the annualised AE rate for BSC. Two alternative scenarios are considered.

1. The annualised AE rates for azacitidine, BSC, low-dose chemotherapy and standard-dose chemotherapy are applied in each cycle in which the patient is on treatment. Once they move off treatment, the annualised AE rate for BSC is used.

2. The annualised AE rates for azacitidine, BSC, low-dose chemotherapy and standard-dose chemotherapy are applied to patients throughout their time in the MDS health state.

The results of these analyses are shown in Table 7.21. The results show that there is little difference between the base case and Scenario 1, where the annualised AE rates are used during the treatment period. When the annualised AE rates are assumed to have effect throughout patients' time in the MDS health state, the ICER increases compared with BSC and low-dose chemotherapy due to the increased cost in the azacitidine extended survival period. However, compared with standard-dose chemotherapy, the ICER decreases due to the high annualised AE rate in this treatment arm.

Table 7.21. Sensitivity analysis of the methodology of applying AE rates

Comparator treatment arm	AE methodology		
	Base case	Annualised rate on treatment (1)	Annualised rate in MDS (2)
BSC	£63,295	£60,056	£62,237
Low-dose chemotherapy	£58,837	£53,655	£57,285
Standard-dose chemotherapy	£44,523	£42,958	£27,680

Key: AE: adverse event; BSC: best supportive care; MDS: myelodysplastic syndrome

7.3.2.1.4 Modelled time horizon

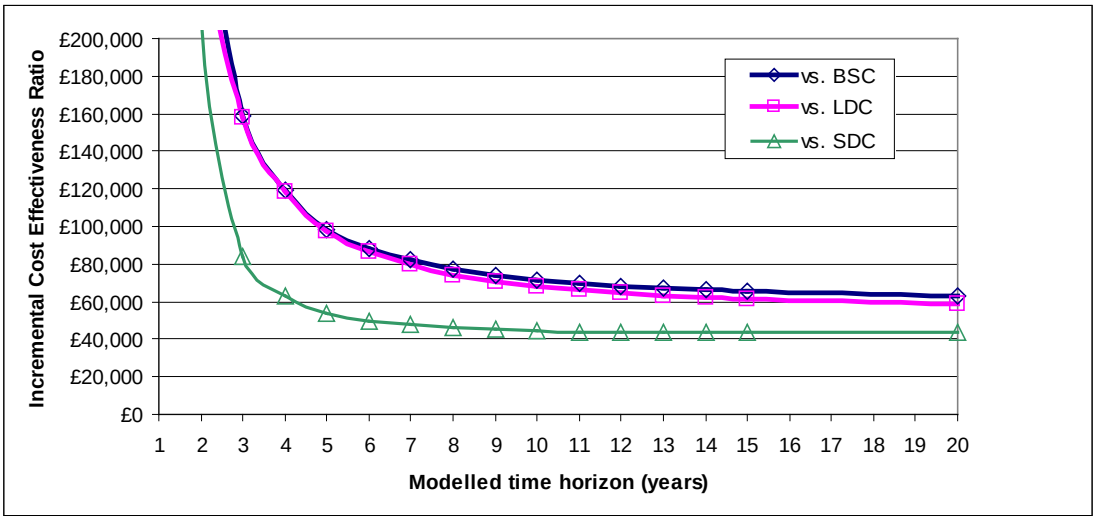
Two sensitivity analyses are performed examining the modelled time horizon. The first examines the effect of only modelling for the three-year period of Study AZA-001. The results of this analysis are shown in Table 7.22. The second analysis examines the effect on the ICER for each treatment arm of changing the model time horizon from one year through to lifetime. The results of this analysis are presented in Figure 7.9.

Table 7.22. Results of a sensitivity analysis using a three-year time horizon, reflecting the AZA-001 trial period

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£81,698	1.34	£54,144	0.34	**£159,019**
BSC	£27,554	1.00			
Preselected for low-dose chemotherapy					
Azacitidine	£77,431	1.38	£48,464	0.30	**£161,730**
LDC	£28,967	1.08			
Preselected for standard-dose chemotherapy					
Azacitidine	£80,316	1.28	£20,775	0.25	**£83,932**
SDC	£59,541	1.03			

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

Figure 7.9. Results of sensitivity analysis varying the modelled time horizon

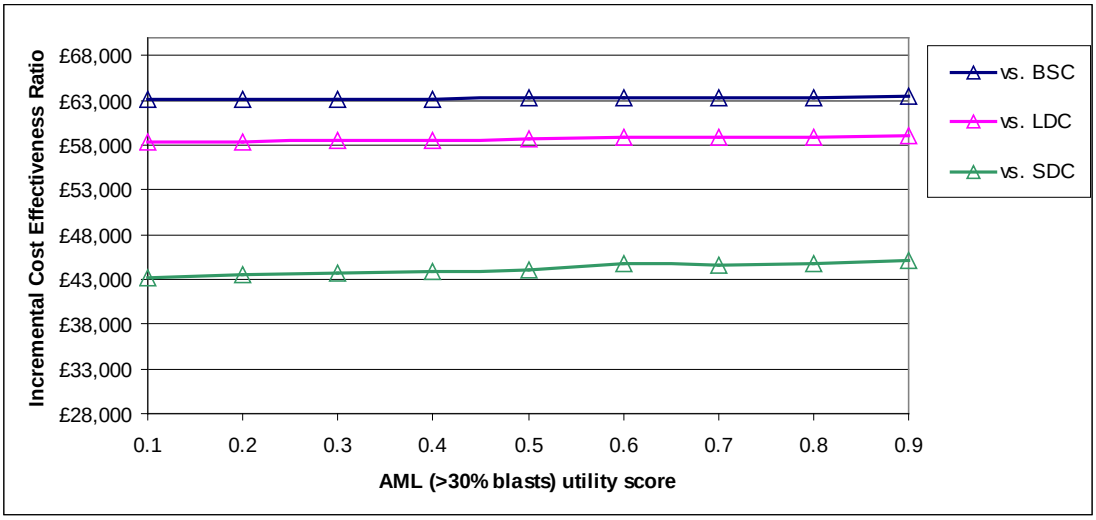


7.3.2.1.5 The utility value assigned to AML

There are no utility values available in the literature for patients that are in the AML (blasts >30%) health state. In the base case, this value is assumed to equal the baseline MDS utility score of 0.67.

The effect on the ICER of varying this figure is examined in a sensitivity analysis, the results of which are shown in Figure 7.10. The analysis shows that varying the utility score of the AML (blasts >30%) health state has minimal effect on the ICER.

Figure 7.10. Results of sensitivity analysis varying the AML utility value



7.3.2.1.6 Longitudinal utility scores.

The utility scores used in the base case are based on longitudinal data from two independent studies. The model assumes that the last recorded utility value is used as the constant MDS utility value beyond the end of the utility data. However, the values recorded at later time points are in some cases based on small numbers of patients. A sensitivity analysis is performed which fixes the utility scores at earlier time points to remove the potential effect of small patient numbers. When the utility score is fixed, the fixed value is applied for the remainder of the patient's time in the MDS health state. The results of this analysis are shown in Table 7.23 and demonstrate that this assumption has little effect on the ICER.

Table 7.23. Results of sensitivity analysis fixing the utility scores at different longitudinal time points

Comparator treatment arm	Time point from which utility scores are fixed			
	Baseline	50 days	106 days	182 Days
Best supportive care	£63,295	£72,379	£68,450	£63,295
Low-dose chemotherapy	£58,837	£67,351	£63,666	£58,837
Standard-dose chemotherapy	£44,523	£51,133	£48,266	£44,523

7.3.2.1.7 Adjusted azacitidine and BSC utility values

The utility values for patients in the azacitidine and BSC arms are mapped from EORTC scores from Study CALGB 9221. The patients in the CALGB 9221 data set were slightly younger and healthier at baseline than those in Study AZA-001. A regression analysis was performed to adjust the mapped utility values to account for

the differences in these baseline characteristics. This is detailed in Appendix 6 and the utility values are shown in Table 7.6. The results of using these values are shown in Table 7.24.

Table 7.24. Results of sensitivity analysis using alternative weighting assumptions for healthcare resource use questionnaire results

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£139,364	2.97	£97,829	1.53	**£64,100**
BSC	£41,536	1.44			
Preselected for low-dose chemotherapy					
Azacitidine	£145,452	3.08	£84,812	1.42	**£59,591**
LDC	£60,640	1.66			
Preselected for standard-dose chemotherapy					
Azacitidine	£127,745	2.54	£61,940	1.37	**£45,104**
SDC	£65,805	1.17			

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

7.3.2.1.8 HRG-4 reference costing

Recently released HRG-4 reference costs are used in a sensitivity analysis, the details of which are described in Section 7.2.9.5. AE costings are updated for azacitidine, BSC and low-dose chemotherapy. Standard-dose chemotherapy has an updated inpatient stay cost as described above. The results of this analysis are presented in Table 7.25.

Table 7.25. Results of sensitivity analysis using HRG-4 reference costs

Treatment option	Costs incurred	QALYs gained	Marginal costs	Marginal QALYs gained	Cost per QALY gained
Preselected for BSC					
Azacitidine	£147,981	3.00	£103,930	1.55	**£67,243**
BSC	£44,051	1.46			
Preselected for low-dose chemotherapy					
Azacitidine	£154,611	3.12	£89,739	1.44	**£62,256**
LDC	£64,872	1.68			
Preselected for standard-dose chemotherapy					
Azacitidine	£135,186	2.57	£76,369	1.39	**£54,892**
SDC	£58,817	1.18			

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

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7.3.2.1.10 End-of-life treatments – a quantitative analysis

A sensitivity analysis has been performed exploring the potential impact on the cost-effectiveness of applying methodology proposed by NICE for end-of-life treatments.[48]

Two analyses have been performed and are presented in Tables 7.27 and 7.28.

1) The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full QoL anticipated for a health individual of the same age.

Table 7.27. Impact of greater QALY weight

Comparator	Incremental costs (£)	Incremental LYs gained	Incremental QALYs	ICER (original)	Incremental QALYs (max*)	ICER (max QALY)
BSC	£97,829	2.60	1.55	**£63,295**	2.03	£48,154
LDC	£84,812	2.58	1.44	**£58,837**	2.00	£42,312
SDC	£61,940	2.48	1.39	**£44,523**	1.98	£31,239

* Assuming a health-related quality of life of 0.78, 0.78 and 0.80 for patients receiving BSC, LDC and SDC based on the average ages observed in Study AZA-001 and utility scores for individuals of that age.[48,52]
Key: BSC: best supportive care; ICER: incremental cost-effectiveness ratio; LDC: low-dose chemotherapy; QALY: quality-adjusted life-year; SDC: standard-dose chemotherapy

2) The magnitude of the additional weight that would need to be assigned to the QALY benefits in this patient group for the cost-effectiveness of the technology to fall within the threshold range.

Table 7.28. Magnitude of additional weight to reduce ICER to relevant thresholds

	Relative weights			
	Original ICER		New ICER with increased QALY weight	
Comparator	**£20,000/QALY**	**£30,000/QALY**	**£20,000/QALY**	**£30,000/QALY**
Best supportive care	3.16	2.11	2.41	1.61
Low-dose chemotherapy	2.94	1.96	2.12	1.41
Standard-dose chemotherapy	2.23	1.48	1.56	1.04

Key: ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

7.3.2.2. What are the key drivers of the cost effectiveness results?

The key drivers of cost-effectiveness in the model are the assumption of the parametric function used to extrapolate overall survival and the cost associated with the inpatient stay for administration of standard-dose chemotherapy.

7.3.3. Interpretation of economic evidence

7.3.3.1. Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There is no published literature available with which to compare the results of this analysis.

7.3.3.2. *What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?*

The economic evaluation captures the performance of azacitidine compared with the main comparators and utilises the evidence from Study AZA-001 effectively. Although there are a number of uncertainties about the best value of parameter inputs to use, sensitivity analysis suggests that these variations are not too significant for the conclusions. The most important uncertainties are estimated survival, in particular the appropriate shape of the fitted curve, and the cost and length of stay associated with the administration of standard-dose chemotherapy.

7.3.3.3. *What further analyses could be undertaken to enhance the robustness/completeness of the results?*

Further analysis to confirm the shape of the survival curve could be undertaken once further data become available.

8. Assessment of factors relevant to the NHS and other parties

8.1. What is the estimated annual budget impact for the NHS in England and Wales?

We have estimated the first-year budget impact for the NHS in England and Wales following the introduction of azacitidine to be £2.8 million for patients with higher-risk myelodysplastic syndrome (MDS). We estimate this to increase to £11.4 million by Year 5. This is based on 131 patients treated in Year 1, increasing to 270 patients by Year 5 (see Table 8.1).

Table 8.1 Budget impact summary for the use of azacitidine in higher-risk MDS patients

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact – without azacitidine					
Best supportive care	£4,499,613	£6,804,213	£8,195,889	£9,024,946	£9,637,997
Low-dose chemotherapy	£3,042,974	£4,697,157	£5,828,101	£6,551,333	£7,107,751
Standard-dose chemotherapy	£8,971,907	£10,930,620	£11,834,630	£12,294,307	£12,605,886
Total	£16,514,494	£22,431,990	£25,858,619	£27,870,586	£29,351,634
Budget impact – with azacitidine					
Best supportive care	£4,099,648	£6,098,632	£7,213,462	£7,783,377	£5,250,837
Low-dose chemotherapy	£2,069,222	£2,948,752	£3,337,248	£3,354,488	£3,196,582
Standard-dose chemotherapy	£6,579,399	£7,413,049	£7,337,054	£6,869,007	£6,255,804
Azacitidine	£6,575,794	£11,342,267	£15,461,376	£19,372,212	£26,069,625
Total	£19,324,062	£27,802,699	£33,349,139	£37,379,084	£40,772,848
Net budget impact	£2,809,568	£5,370,709	£7,490,520	£9,508,498	£11,421,214

The figures for any given year are calculated from the cost of the patients starting treatment in that year and the cost of the patients who started treatment in previous years but continue to accrue treatment costs.

Detailed present and proposed budget impact results are also presented for each of the treatment strategies in Tables 8.2 and 8.3.

Table 8.2. Detailed budget impact in higher-risk MDS patients – present

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Best supportive care					
Number of patients	294	297	299	301	303
Proportion of total patients treated	45%	45%	45%	45%	45%
MDS treatment costs	£3,636,897	£5,076,721	£5,967,374	£6,527,073	£6,955,539
AML treatment costs	£862,716	£1,727,493	£2,228,515	£2,497,873	£2,682,458
Total BSC cost	£4,499,613	£6,804,213	£8,195,889	£9,024,946	£9,637,997
Low-dose chemotherapy					
Number of patients	163	165	166	167	169
Proportion of total patients treated	25%	25%	25%	25%	25%
MDS treatment costs	£2,610,292	£3,799,498	£4,642,333	£5,205,336	£5,649,983
AML treatment costs	£432,682	£897,659	£1,185,768	£1,345,996	£1,457,768
Total LDC cost	£3,042,974	£4,697,157	£5,828,101	£6,551,333	£7,107,751
Standard-dose chemotherapy					
Number of patients	196	198	199	201	202
Proportion of total patients treated	30%	30%	30%	30%	30%
MDS treatment costs	£8,223,869	£9,373,939	£9,891,994	£10,186,373	£10,399,897
AML treatment costs	£748,038	£1,556,681	£1,942,636	£2,107,934	£2,205,989
Total SDC costs	£8,971,907	£10,930,620	£11,834,630	£12,294,307	£12,605,886
Total budget impact	£16,514,494	£22,431,990	£25,858,619	£27,870,586	£29,351,634

Key: AML: acute myeloid leukaemia; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

Table 8.3. Detailed budget impact in higher-risk MDS patients – with azacitidine

Patient starts treatment in:	Year 1	Year 2	Year 3	Year 4	Year 5
Best supportive care					
Number of patients	268	264	259	254	249
Proportion treated	41%	40%	39%	38%	37%
MDS treatment costs	£3,313,617	£4,544,014	£5,241,189	£5,616,032	£3,525,344
AML treatment costs	£786,030	£1,554,618	£1,972,273	£2,167,345	£1,725,492
Total BSC cost	£4,099,648	£6,098,632	£7,213,462	£7,783,377	£5,250,837
Low-dose chemotherapy					
Number of patients	111	99	86	74	61
Proportion of total patients treated	17%	15%	13%	11%	9%
MDS treatment costs	£1,774,999	£2,373,225	£2,638,440	£2,643,130	£2,519,242
AML treatment costs	£294,223	£575,527	£698,807	£711,358	£677,340
Total LDC cost	£2,069,222	£2,948,752	£3,337,248	£3,354,488	£3,196,582
Standard-dose chemotherapy					
Number of patients	144	132	120	107	94
Proportion of total patients treated	22%	20%	18%	16%	14%
MDS treatment costs	£6,030,837	£6,321,736	£6,067,671	£5,610,085	£5,068,714
AML treatment costs	£548,561	£1,091,312	£1,269,382	£1,258,922	£1,187,090
Total SDC costs	£6,579,399	£7,413,049	£7,337,054	£6,869,007	£6,255,804
Azacitidine					
Number of patients	131	165	199	234	270
Proportion of total patients treated	20%	25%	30%	35%	40%
MDS treatment costs	£6,339,614	£10,740,054	£14,487,374	£18,051,731	£24,305,762
AML treatment costs	£236,180	£602,213	£974,003	£1,320,481	£1,763,864
Total azacitidine costs	£6,575,794	£11,342,267	£15,461,376	£19,372,212	£26,069,625
Total budget impact	£19,324,062	£27,802,699	£33,349,139	£37,379,084	£40,772,848

Key: AML: acute myeloid leukaemia; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard-dose chemotherapy

8.2. What number of patients were assumed to be eligible? How was this figure derived?

Step 1: Population of England and Wales

We used 2006-based population projections compiled by the Office for National Statistics for England and Wales for 2006 to estimate the population in 2009 and the following five years (see Table 8.4).[49]

Table 8.4. Population projections for England and Wales[49]

	Forecast population		
Year	**England**	**Wales**	**Total**
2006	50,762,900	2,965,900	53,728,800
2007	51,094,200	2,979,400	54,073,600
2008	51,487,600	2,993,400	54,481,000
2009	51,888,300	3,007,700	54,896,000
2010	52,296,600	3,022,600	55,319,200
2011	52,706,500	3,037,600	55,744,000
2012	53,113,300	3,052,600	56,166,100
2013	53,514,500	3,067,700	56,582,200

Step 2: Incidence and prevalence of MDS

Due to the rarity of MDS and its poor prognosis, it is difficult to ascertain incidence and prevalence accurately. Furthermore, given the poorer prognosis of higher-risk MDS patients (median survival of 0.4 months and 1.2 years in the International Prognostic Scoring System [IPSS] risk categories high and intermediate-2 respectively,[4,14] the use of incidence of MDS is likely to reflect the eligible patient population.

Based on an estimated age-standardised rate of 3.3 per 100,000,[23] the estimated number of patients with MDS in England and Wales is given in Table 8.5.

Table 8.5. Number of patients with MDS in England and Wales

Year	England	Wales	Total
2009	1,712	99	1,812
2010	1,726	100	1,826
2011	1,739	100	1,840
2012	1,753	101	1,853
2013	1,766	101	1,867

Step 3: Number of patients with higher-risk MDS

Based on a survey performed on behalf of Celgene, it was estimated that 38% of MDS patients in the UK have higher-risk disease (IPSS risk categories intermediate-2 and high).[24] The estimated number of patients with higher-risk MDS is given in Table 8.6.

Table 8.6. Number of patients with higher-risk MDS in England and Wales

Year	England	Wales	Total
2009	651	38	688
2010	656	38	694
2011	661	38	699
2012	666	38	704
2013	671	38	710

Step 4: Number of eligible patients with higher-risk MDS and ineligible for SCT

It is estimated that only 5% of the higher-risk MDS population will be eligible for stem cell transplantation (SCT).[92] The estimated number of patients with higher-risk MDS in England and Wales is given in Table 8.7.

Table 8.7. Number of eligible patients with higher-risk MDS and ineligible for SCT in England and Wales

Year	England	Wales	Total
2009	618	36	654
2010	623	36	659
2011	628	36	664
2012	633	36	669
2013	638	37	674

8.3. What assumption(s) were made about current treatment options and uptake of technologies?

The current treatment patterns for higher-risk MDS patients are presented in Table 8.8.

Table 8.8. Current treatment patterns

Treatment	Percentage of patients treated
Best supportive care	45%
Low-dose chemotherapy	25%
Standard-dose chemotherapy	30%

There are three standard-dose chemotherapy regimens: cytarabine and daunorubicin, cytarabine and idarubicin, and cytarabine and mitoxantrone. It is assumed that these three regimens are all used in the same proportion (that is, 33.3% each).

8.4. What assumption(s) were made about market share (where relevant)?

We have assumed an uptake of azacitidine in higher-risk MDS patients of 20% in Year 1, increasing to 40% by Year 5 (see Table 8.9). We predict that 20% of this uptake will be from patients receiving BSC alone, 40% from patients treated with low-dose chemotherapy and 40% from patients treated with standard-dose chemotherapy.

Table 8.9. The uptake of azacitidine in the next five years

Year	Percentage of patients treated with azacitidine
1	20%
2	25%
3	30%
4	35%
5	40%

8.5. What unit costs were assumed? How were these calculated?

The unit costs used in the model for azacitidine and low-dose chemotherapy are £4,381.65 and £18.52 respectively per cycle. The cost of a cycle of induction standard-dose chemotherapy is £665.79, with a cost of £453.74 per cycle of subsequent consolidation, based on an average of the potential dosage regimens of cytarabine and an anthracycline. Details of the cost of each treatment are presented in Appendix 8.

8.6. In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

The costs used for this resource implications section are taken directly from the economic model as presented in Section 7 of this submission.

8.7. Were there any estimates of resource savings? If so, what were they?

There are no estimated overall savings for azacitidine.

8.8. Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The impact of azacitidine on all relevant resource savings and additional resources has been included in this economic analysis.

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10. Appendices

10.1. Appendix 1: Vidaza Summary of Product characteristics

10.2. Appendix 2: search strategy for section 6

The following information should be provided.

10.2.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter).

The following databases were searched:

- 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.

10.2.2. The date on which the search was conducted.

Two comprehensive searches were undertaken to identify all relevant studies on 9 March 2009. The search terms used to find azacitidine required a very broad search strategy. This approach was taken because few references were anticipated given that azacitidine this is a relatively new drug in this disease area. However, with regard to the comparator treatments, the search was expected to find a relatively large number of references given that such treatments have been used in this disease area for a long time. Therefore, the search strategy for comparator treatments was carefully refined to ensure that all relevant studies were identified and to limit the number of irrelevant references found.

10.2.3. The date span of the search.

There were no date limits applied to the search; therefore, each database was searched covering its full date span as detailed below.

- MEDLINE (Ovid) – 1950 to search date
- MEDLINE In-Process (Ovid) – search date
- EMBASE (Ovid) – 1980 to search date
- The Cochrane Library (Wiley InterScience) – issue 4, 2008

- CINAHL (Ovid) – 1982 to search date
- Science Citation Index (ISI Web of Knowledge) – 1900 to search date
- Social Sciences 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 (DARE, NHS EED, HTA) – search date
- AMED (Ovid) – 1985 to search date
- PsycINFO (Ovid) – 1967 to search date

10.2.4. The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The searches included both MeSH subject headings and free-text terms for the drug intervention (for example, Vidaza), the condition (for example, myelodysplastic syndromes) and the comparators (for example, supportive care). Terms were combined with the Boolean operators 'or' or 'and' as appropriate. Wherever possible, a filter was applied to ensure selection of randomised controlled trials (RCTs) during the 'comparator' searches. This filter could only be used in databases that routinely held this information; for example, MEDLINE. The full search strategies can be found below.

The following search strategy was used to find studies related to azacitidine.

1 Azacitidine/
2 vidaza.af.
3 nsc 102816.af.
4 nsc102816.af.
5 azacitidine.af.
6 or/1-5
7 exp Myelodysplastic Syndromes/
8 Myelodysplastic Syndrome$.af.
9 7 or 8
10 6 and 9

The following search strategy was used to find studies related to comparators to azacitidine. Specifically, the search looked for studies related to conventional care including best supportive care (BSC) and chemotherapy.

1 *Myelodysplastic Syndromes/

2 myelodysplastic syndrome$.ti.
3 MDS.ti.
4 *Leukemia, Myeloid, Acute/
5 acute myeloid leukaemia.ti.
6 acute myeloid leukemia.ti.
7 AML.ti.
8 *Leukemia, Myelomonocytic, Chronic/
9 chronic myelomonocytic leukaemia.ti.
10 chronic myelomonocytic leukemia.ti.
11 CMML.ti.
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13 best supportive care.mp.
14 supportive care.mp.
15 conventional care.mp.
16 chemotherapy.mp. or *Drug Therapy/
17 cytotoxic.mp.
18 *Antineoplastic Agents/
19 antineoplastic agent$.ti.
20 anti neoplastic agent$.ti.
21 anti-neoplastic agent$.ti.
22 *Cytarabine/
23 cytarabine.ti.
24 cytosine arabinoside.mp.
25 *Anthracyclines/
26 anthracycline$.ti.
27 *Daunorubicin/
28 daunorubicin.ti.
29 *Idarubicin/
30 idarubicin.ti.
31 *Mitoxantrone/
32 mitoxantrone.ti.
33 *Etoposide/
34 etoposide.ti.
35 fludarabine.mp.
36 13 or 15 or 14
37 21 or 18 or 19 or 16 or 17 or 20
38 22 or 24 or 23

39 27 or 25 or 32 or 28 or 30 or 26 or 31 or 29
40 38 and 39
41 35 or 33 or 34
42 40 or 41
43 42 and 37
44 36 or 43
45 standard chemotherapy.mp.
46 intensive chemotherapy.mp.
47 non-intensive chemotherapy.mp.
48 low-dose chemotherapy.mp.
49 high-dose chemotherapy.mp.
50 49 or 46 or 45 or 48 or 47
51 50 or 44
52 51 and 12
53 randomized controlled trial.pt.
54 controlled clinical trial.pt.
55 randomized controlled trials/
56 random allocation/
57 double blind method/
58 single blind method/
59 clinical trial.pt.
60 exp Clinical Trial/
61 (clin$ adj25 trial$).ti,ab.
62 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
63 placebos/
64 placebos.ti,ab.
65 random.ti,ab.
66 research design/
67 or/53-66
68 52 and 67

10.2.5. Details of any additional searches, for example searches of company databases (include a description of each database).

The company provided full clinical study reports for the two Phase III randomised controlled trials that were included in the review.

10.2.6. The inclusion and exclusion criteria.

The following criteria were used to select studies for inclusion in the effectiveness review.

10.2.6.1. Type of study participants

- Intermediate-2 and high-risk MDS according to the International Prognostic Scoring System.
- Chronic myelomonocytic leukaemia with 10–29% marrow blasts without myeloproliferative disorder.
- Acute myeloid leukaemia (AML) with 20–30% blasts and multilineage dysplasia, according to the World Health Organization classification.

10.2.6.2. Type of intervention

Azacitidine (Vidaza).

10.2.6.3. Types of comparators

- BSC alone.
- BSC and low-dose chemotherapy.
- BSC and standard-dose chemotherapy.

10.2.6.4. Types of study

- Phase III RCTs published in peer review journals.
- Unpublished study reports related to the intervention.

Studies published in abstract form were excluded due to the difficulty in accessing full details of the trial methods and results.

10.2.6.5. Types of study outcome

- Overall survival.
- Progression-free survival.
- Response rates.
- Time to transformation to AML.
- Adverse effects of treatment.
- Health-related quality of life.

10.2.7. The data abstraction strategy.

The following data items were extracted from all included studies:

- First author and year of publication
- Details of intervention and comparator
- Population description
- Primary and secondary outcomes to be examined
- Baseline characteristics of study participants: age, gender, Eastern Cooperative Oncology Group performance status, disease classification
- Study results: survival and other outcomes.

10.3. Appendix 3: search strategy for section 7

The following information should be provided.

10.3.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter).

The following databases were searched:

- 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.

10.3.2. The date on which the search was conducted.

The search was conducted on 9 March 2009.

10.3.3. The date span of the search.

There were no date limits applied to the search; therefore, each database was searched covering its full date span as detailed below.

- MEDLINE (Ovid) – 1950 to search date
- MEDLINE In-Process (Ovid) – search date
- EMBASE (Ovid) – 1980 to search date
- The Cochrane Library (Wiley InterScience) – issue 4, 2008
- CINAHL (Ovid) – 1982 to search date
- Science Citation Index (ISI Web of Knowledge) – 1900 to search date
- Social Sciences 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 (DARE, NHS EED, HTA) – search date
- AMED (Ovid) – 1985 to search date
- PsycINFO (Ovid) – 1967 to search date

10.3.4. The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1 *Myelodysplastic Syndromes/
2 myelodysplastic syndrome$.ti.
3 MDS.ti.
4 *Leukemia, Myeloid, Acute/
5 acute myeloid leukaemia.ti.
6 acute myeloid leukemia.ti.
7 AML.ti.
8 *Leukemia, Myelomonocytic, Chronic/
9 chronic myelomonocytic leukaemia.ti.
10 chronic myelomonocytic leukemia.ti.
11 CMML.ti.
12 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11

The database was then searched for any reference with the terms:

- Cost effectiveness
- Cost-effectiveness
- Economic
- Economics

10.3.5. Details of any additional searches, for example searches of company databases (include a description of each database).

No company database searches were performed.

10.4. Appendix 4: Curve fitting in the health economic model

10.4.1. Survival curve fits

Survival curves were fitted to the Kaplan–Meier data and extrapolated using the maximum likelihood methodology. Two curve fits were estimated: a Weibull and a log-logistic curve. Details of these fits are presented below.

Weibull

The Weibull curve is parameterised by a shape parameter α and scale parameter β and the cumulative survival at time t, S(t), calculated by:

$$S(t) = 1-e^{-(t/\beta)\alpha}$$

Log-logistic

The log-logistic curve is parameterised by a shape parameter λ and scale parameter p and the cumulative survival at time t, S(t), calculated by:

$$S(t) = 1 / (1+((p*t)^{\lambda}))$$

The cumulative survival is calculated at the start of each cycle and the rate of change used to determine the probability of suffering mortality in that cycle.

10.4.2. Progression to AML curve fits

We assume that the progression to acute myeloid leukaemia (AML) curves maintain the same shape as the survival curve for each treatment arm, but the curve median is adjusted so that:

$$\text{AML curve median} = \text{survival curve median} - 3.65$$

Weibull

The new Weibull curve is constructed with two parameters: a shape parameter α and a scale parameter β. We assume that the shape parameter is kept the same as the survival curve and the new scale parameter β_{aml} is calculated for median M_{aml} using the formula:

$$\beta_{aml} = M_{aml} / \ln(2)^{(1/\alpha)}$$

where M_{aml} is the median for the AML curve and α is from the survival curve.

Log-logistic

The new log-logistic curve is constructed with two parameters: a shape parameter α and a scale parameter β. We assume that the shape parameter is kept the same as the survival curve and the new scale parameter β_{aml} is calculated for median M_{aml} using the formula:

$$\beta_{aml} = 1/ M_{aml}$$

where M_{aml} is the median for the AML curve.

10.5. Appendix 5: Report on mapping from EORTC scores to EQ-5D values

10.6. Appendix 6: Regression methodology

10.6.1. Regression results

This appendix summarises the regression methodology undertaken to estimate which variables have a statistically significant impact on utility.

Prior to the regression, the CALGB 9221 dataset required substantial cleaning; however, even after cleaning, it still had a few remaining inconsistencies. Where data were missing, reasonable assumptions were made to fill in missing values; for example, by looking at answers given to different questions. Dummy variables were used to statistically capture the qualitative responses such as 'yes' and 'no', or a range from 'no improvement' to 'complete improvement'. These were entered along with all quantitative variables, such as age or percentage of leukaemia cells, into a regression using ordinary least squares methodology. The initial regression contained 51 explanatory variables (all with equivalent variables in the CALGB 9221 dataset) against a cardinal measure of utility as the dependent variable.

A 'stepwise' approach was taken, removing the least statistically significant variables and then re-estimating the regression model. This was repeated until the model contained only statistically significant variables. Most of the variables were not statistically significant and so were removed. Three models are presented below.

Table 10.6.1. Variables contained in the three models

Variable	Explanation
Age	**The age of a patient**
Perf_1	**Patient is ambulatory and capable of light work**
Perf_2	**Patient is not capable of work, spends <50% of time in bed**
Infect_1	**Patient has an infection of Pneumonia**
Antibio	**Patient is having to take antibiotics**
Platel	**Patient is having to have a transfusion of Platelets**
Constant	**The value of utility if all of the variables above had a value of 0**

The first model incorporates all the variables listed above. The variables (with the exception of Age and Platelets) are all significant at the 5% level. All the variables apart from Age have negative coefficients. Again, this is to be expected, as having any of these health problems is likely to lead to a decrease in utility. For example, taking antibiotics is a signal that the patient is unwell and being treated for an illness; as such, they suffer a decrease in utility. In the long run the antibiotics should make

them better off, but this is likely to be reflected in the period straight after they have stopped taking the antibiotics. Perf_1 is a better health state than Perf_2, so we would expect to see a higher negative value for Perf_2, and we do in all three models. These small logical checks give us confidence that the models are interpreting the data correctly. The Constant coefficient is positive, which is also what one would expect to see. If the patient had nothing wrong with them (all other variables set to zero), one would expect them to have a high utility. The Age variable has a positive coefficient which is likely to be due to the fact that elderly patients might psychologically accept their MDS disease state more than younger patients. Age is the least statistically significant variable; it is not significant at the 10% level.

Model 1: With all three models, the adjusted R-squared value (which examines the variation in the dependent variable that is explained by the explanatory variables, but penalises for using additional explanatory variables) is fairly low. Model 1's value is 0.1872. However, this again is expected, as there are many different variables that are not included in the model which would each explain people's variation in utility to some (albeit limited) extent.

In terms of testing the validity of the regression model, it performs well. There is no autocorrelation in the errors as the Durbin–Watson statistic is very close to 2. The F-test shows that the null hypothesis of the coefficients on the variables being jointly equal to zero can be rejected emphatically (p=0.00). In this model, we do not reject the null hypothesis that the errors are normally distributed according to the Jarque–Bera normality test at the 10% significance level (p=0.129), meaning the model displays the positive characteristic of having normally distributed errors. In successive models, although the errors display less normality, we do not reject the null hypothesis of normally distributed errors at the 5% level.

```
R-SQUARE =   0.2141     R-SQUARE ADJUSTED =   0.1872
 VARIANCE OF THE ESTIMATE-SIGMA**2 =  0.41444E-01
 STANDARD ERROR OF THE ESTIMATE-SIGMA =  0.20358
 SUM OF SQUARED ERRORS-SSE=   7.2526
 MEAN OF DEPENDENT VARIABLE =  0.65844
 LOG OF THE LIKELIHOOD FUNCTION =  35.0136

                    ANALYSIS OF VARIANCE - FROM ZERO
                      SS          DF            MS                F
 REGRESSION        80.880          7.         11.554           278.797
 ERROR             7.2526        175.       0.41444E-01        P-VALUE
 TOTAL             88.133        182.       0.48425            0.000


 VARIABLE   ESTIMATED  STANDARD   T-RATIO        PARTIAL STANDARDIZED
ELASTICITY
   NAME    COEFFICIENT   ERROR     175 DF   P-VALUE CORR. COEFFICIENT  AT MEANS
 AGE       0.25356E-02 0.1549E-02   1.637     0.103 0.123     0.1151     0.2626
 PERF_1   -0.14436     0.3350E-01  -4.310     0.000-0.310    -0.3199    -0.1169
 PERF_2   -0.22156     0.5344E-01  -4.146     0.000-0.299    -0.3208    -0.0407
 INFECT_1 -0.27859     0.1219      -2.286     0.023-0.170    -0.1575    -0.0070
 ANTIBIO  -0.12716     0.4778E-01  -2.662     0.009-0.197    -0.1841    -0.0233
 PLATEL   -0.18886E-02 0.9599E-03  -1.967     0.051-0.147    -0.1349    -0.0101
 CONSTANT  0.61590     0.1042       5.911     0.000 0.408     0.0000     0.9354

 DURBIN-WATSON = 2.0143    VON NEUMANN RATIO = 2.0254    RHO = -0.00838
 RESIDUAL SUM = -0.27103E-13  RESIDUAL VARIANCE =  0.41444E-01
 SUM OF ABSOLUTE ERRORS=   30.042
 R-SQUARE BETWEEN OBSERVED AND PREDICTED = 0.2141
 RUNS TEST:   94 RUNS,   97 POS,    0 ZERO,   85 NEG  NORMAL STATISTIC =
0.3577
 COEFFICIENT OF SKEWNESS =  -0.3147 WITH STANDARD DEVIATION OF 0.1801
 COEFFICIENT OF EXCESS KURTOSIS =  -0.3657 WITH STANDARD DEVIATION OF 0.3583

 JARQUE-BERA NORMALITY TEST- CHI-SQUARE(2 DF)=    4.0998 P-VALUE= 0.129
```

Model 2: This model removes the Age variable as it is not significant at the 10% level and the coefficient seems to have the wrong sign. In this model, the variable for Platelets becomes insignificant at the 5% level (it has moved from a p-value of 0.051 in Model 1 to 0.08 in this model), but we now reject that the errors are normally distributed at the 10% level, and the adjusted R-squared value has fallen slightly to 0.1794.

```
 R-SQUARE =   0.2021     R-SQUARE ADJUSTED =   0.1794
 VARIANCE OF THE ESTIMATE-SIGMA**2 =  0.41839E-01
 STANDARD ERROR OF THE ESTIMATE-SIGMA =  0.20455
 SUM OF SQUARED ERRORS-SSE=   7.3637
 MEAN OF DEPENDENT VARIABLE =  0.65844
 LOG OF THE LIKELIHOOD FUNCTION =  33.6306

                    ANALYSIS OF VARIANCE - FROM ZERO
                      SS          DF            MS                F
 REGRESSION        80.769          6.         13.462           321.745
 ERROR             7.3637        176.       0.41839E-01        P-VALUE
 TOTAL             88.133        182.       0.48425            0.000


 VARIABLE   ESTIMATED  STANDARD   T-RATIO       PARTIAL STANDARDIZED
ELASTICITY
   NAME    COEFFICIENT   ERROR     176 DF   P-VALUE CORR. COEFFICIENT  AT MEANS
 PERF_1   -0.13632     0.3329E-01  -4.095     0.000-0.295    -0.3020    -0.1103
 PERF_2   -0.20268     0.5243E-01  -3.866     0.000-0.280    -0.2934    -0.0372
 INFECT_1 -0.25144     0.1213      -2.073     0.040-0.154    -0.1422    -0.0063
 ANTIBIO  -0.12673     0.4800E-01  -2.640     0.009-0.195    -0.1835    -0.0233
 PLATEL   -0.16811E-02 0.9561E-03  -1.758     0.080-0.131    -0.1201    -0.0090
 CONSTANT  0.78099     0.2630E-01   29.69     0.000 0.913     0.0000     1.1861
```

Model 3: This model does not contain variables for Age or Platelet transfusions. While all are now statistically significant at the 5% level, the adjusted R-squared value has fallen slightly further.

```
R-SQUARE =   0.1880     R-SQUARE ADJUSTED =   0.1697
 VARIANCE OF THE ESTIMATE-SIGMA**2 =  0.42334E-01
 STANDARD ERROR OF THE ESTIMATE-SIGMA =  0.20575
 SUM OF SQUARED ERRORS-SSE=   7.4931
 MEAN OF DEPENDENT VARIABLE =  0.65844
 LOG OF THE LIKELIHOOD FUNCTION =  32.0459

                     ANALYSIS OF VARIANCE - FROM ZERO
                       SS          DF            MS                F
 REGRESSION        80.640          5.         16.128           380.974
 ERROR             7.4931        177.       0.42334E-01        P-VALUE
 TOTAL             88.133        182.       0.48425            0.000


 VARIABLE   ESTIMATED  STANDARD   T-RATIO       PARTIAL STANDARDIZED
ELASTICITY
   NAME    COEFFICIENT   ERROR     177 DF   P-VALUE CORR. COEFFICIENT  AT MEANS
 PERF_1   -0.14000     0.3342E-01  -4.189     0.000-0.300    -0.3102    -0.1133
 PERF_2   -0.21202     0.5247E-01  -4.041     0.000-0.291    -0.3069    -0.0389
 INFECT_1 -0.28019     0.1209      -2.318     0.022-0.172    -0.1584    -0.0070
 ANTIBIO  -0.12743     0.4828E-01  -2.639     0.009-0.195    -0.1845    -0.0234
 CONSTANT  0.77871     0.2643E-01   29.47     0.000 0.911     0.0000     1.1827
```

10.6.2. Summary

Model 1 has the highest adjusted R-squared value, but contains two variables that are insignificant at the 5% level. Model 2, which removes Age, has a slightly lower adjusted R-squared value and a slightly worse Jarque–Bera score for normally distributed errors. Model 3 again has a slightly lower R-squared value, but all the variables are statistically significant at the 5% level. In the models without Age, all the signs of the coefficients are as expected and there is no sign of autocorrelation in any of the models. Model 3 would appear to be the most econometrically sound out of the three.

One caveat of this analysis is that the data had numerous missing variables. The data have been cleaned using reasonable assumptions. Moreover, the variables that remained significant were ones where the data had no problems. The results are robust enough to conclude from analysis of these data that both the performance variables – the impact of pneumonia and taking antibiotics – have statistically significant effects on a patient's utility.

10.7. Appendix 7: Example of healthcare resource use questionnaire

10.8. Appendix 8: Medication resource use

Table 10.8.1. Medication unit costs

Medicine (generic)	Form	Strength (mg)	Pack size (unit doses)	Pack cost (£)
Acyclovir	Oral	200	25	2.54
Allopurinol	Oral	100	28	0.47
Azacitidine*	Parenteral	100	1	321.00
Caspafungin	Parenteral	500	1	325.67
Chlorphenamine	Parenteral	10	10	1.62
Chlorhexidine	Mouthwash	N/A	300	1.93
Ciprofloxacin	Oral	100	6	1.23
Cyclizine	Oral	50	20	1.48
Cytarabine	Parenteral	100	1	3.90
Daunorubicin	Parenteral	20	1	44.76
Domperidone	Oral	10	30	1.36
Filgrastim	Parenteral	0.3	1	68.41
Fluconazole	Oral	200	7	0.52
Granisetron	Oral	1	10	65.49
Idarubicin	Parenteral	5	1	87.36
Itraconazole	Oral	100	4	3.90
Lansoprazole	Oral	15	28	2.50
Levofloxacin	Oral	250	5	7.23
Metoclopramide	Oral	10	28	0.44
Mitoxantrone	Parenteral	20	1	100.00
Omeprazole	Oral	10	28	8.85
Ondansetron	Oral	8	10	60.74
Piperacillin/tazobactam	Parenteral	2.25	1	7.96
Prednisolone	Eye-drops	N/A	1	2.00
Senna	Oral	7.5	60	1.49
Tranexamic acid	Oral	500	60	7.47

All drug costs taken from: *British National Formulary,* 2009. **57.**

* Drug cost for azacitidine taken from: *Monthly Index of Medical Specialities,* March 2009.

Table 10.8.2. Premedication per cycle of treatment

Medication	Proportion treated	Mean daily dose (mg)	Mean duration (days)
Low-dose chemotherapy			
Domperidone	7.7%	60.0	14.0
Metaclopramide	23.1%	40.0	9.0
Ondansetron	7.7%	16.0	7.0
Standard-dose chemotherapy			
Allopurinol	30.8%	275.0	10.3
Cyclizine	7.7%	150.0	12.0
Domperidone	15.4%	60.0	11.8
Granisetron	7.7%	3.0	3.0
Metaclopramide	15.4%	45.0	10.0
Ondansetron	61.5%	14.5	9.1
Azacitidine			
Chlorphenamine	15.4%	10.0	14.5
Metaclopramide	23.1%	40.0	6.3
Ondansetron	53.8%	11.4	9.7
Senna	7.7%	11.3	7.0

Table 10.8.3. Concurrent medication costs

Medication	Proportion treated	Mean daily dose (mg)	Daily dose range (mg)	Duration per 28-day month	Weighted cost per month (£)
MDS health state with best supportive care					
Acyclovir	15.4%	600.0	400–800	28.0	1.31
Allopurinol	15.4%	300.0	N/A	21.5	0.17
Ciprofloxacin	38.5%	1000.0	N/A	28.0	22.08
Chlorhexidine	15.4%	40.0*	N/A	28.0	1.11
Fluconazole	23.1%	116.7	50–200	23.3	0.16
Itraconazole	15.4%	400.0	N/A	28.0	16.80
Levofloxacin	7.7%	500.0	500	28.0	6.23
Omeprazole	7.7%	20.0	N/A	28.0	1.36
Ondansetron	7.7%	16.0	N/A	28.0	26.16
Tranexamic acid	7.7%	1500.0	N/A	14.0	0.40
MDS health state with low-dose chemotherapy					
Acyclovir	23.1%	600.0	N/A	19.3	1.36
Allopurinol	23.1%	300.0	N/A	23.7	0.28
Ciprofloxacin	30.8%	1000.0	N/A	28.0	17.66
Chlorhexidine	15.4%	40.0*	N/A	28.0	1.11
Domperidone	7.7%	60.0	N/A	8.5	0.18
Fluconazole	23.1%	116.7	50–200	23.3	0.16
Itraconazole	23.1%	466.7	400–600	28.0	29.40
Levofloxacin	7.7%	500.0	N/A	28.0	6.23
Omeprazole	15.4%	500.0	N/A	28.0	2.72
Ondansetron	15.4%	16.0	N/A	18.3	36.09
MDS health state with standard-dose chemotherapy					
Acyclovir	38.5%	640.0	400–800	22.8	2.89
Allopurinol	23.1%	300.0	N/A	23.7	0.28
Caspofungin	7.7%	50.0	N/A	6.0	15.12
Ciprofloxacin	38.5%	1000.0	N/A	28.0	22.08
Chlorhexidine	15.4%	40.0*	N/A	28.0	1.11
Fluconazole	23.1%	116.7	50–200	23.3	0.16
Itraconazole	46.2%	433.3	200–600	23.8	43.35
Levofloxacin	7.7%	500.0	N/A	28.0	6.23
Omeprazole	15.4%	20.0	N/A	28.0	2.72
Ondansetron	15.4%	16.0	N/A	28.0	52.33
Piperacillin/tazobactam	7.7%	13500.0	N/A	6.0	22.04
MDS health state with azacitidine					
Acyclovir	15.4%	600.0	N/A	28.0	1.31
Allopurinol	23.1%	300.0	N/A	28.0	0.33
Ciprofloxacin	30.8%	1000.0	N/A	28.0	17.66
Chlorhexidine	15.4%	40.0*	N/A	28.0	1.11
Domperidone	7.7%	60.0	N/A	8.5	0.18
Fluconazole	23.1%	116.7	50–200	19.0	0.14
Itraconazole	30.8%	450.0	400–600	28.0	37.80
Levofloxacin	7.7%	500.0	N/A	28.0	6.23
Omeprazole	15.4%	20.0	N/A	28.0	2.72
Ondansetron	15.4%	18.0	N/A	18.3	36.09
AML health state					
Acyclovir	38.5%	680.0	600–800	28.0	2.84
Allopurinol	30.8%	300.0	N/A	28.0	0.14
Ciprofloxacin	46.2%	1083.3	500–750	28.0	28.70
Chlorhexidine	15.4%	40.0*	N/A	28.0	1.11
Domperidone	7.7%	60.0	N/A	28.0	0.59
Fluconazole	23.1%	100.0	N/A	28.0	0.16
Hydroxyurea	7.7%	750.0	N/A	28.0	0.39
Itraconazole	38.5%	440.0	200–600	28.0	37.80
Lansoprazole	7.7%	30.0	N/A	28.0	0.38
Omeprazole	15.4%	15.0	10-20	28.0	2.04
Ondansetron	15.4%	16.0	N/A	28.0	52.33
Tranexamic acid	7.7%	1500.0	N/A	28.0	0.80

* Chlorhexidine mouthwash mean daily dose is expressed in ml

Table 8.10.4. Unit costs

Treatment	Medication	Dose and regimen	Cycle cost (range)
Azacitidine	Azacitidine	75 mg/m^2/day for 7 days	£4,381.65* (range: N/A)
Low-dose chemotherapy	Cytarabine	20 mg/m^2/day for 14 days	£18.56 (range: N/A)
Standard-dose chemotherapy‡	Cytarabine and an anthracycline	Please refer to relevant rows below for the dose and regimen for each standard-dose chemotherapy	Induction: £665.79 (£324.17–1,004.80) Consolidation: £453.74 (£226.00–679.75)
	Cytarabine and daunorubicin	Induction: cytarabine 100–200 mg/m^2/day on Days 1–7 and daunorubicin 45–60 mg/m^2/day on Days 1–3 Consolidation: cytarabine 100–200 mg/m^2/day for 3–7 days and idarubicin 45–60 mg/m^2/day on Days 1 and 2	Induction: £668.40 (£559.73–777.06) Consolidation: £455.48 (£362.17–548.78)
	Cytarabine and idarubicin	Induction: cytarabine 100–200 mg/m^2/day on Days 17 and idarubicin 9–12 mg/m^2/day on Days 1–3 Consolidation: cytarabine 100–200mg/m^2/day for 3-7 days and idarubicin 9-12mg/m^2/day on days 1 and 2	Induction: £1,004.40 (£848.07–1,161.49) Consolidation: £679.75 (£554.40–805.09)
	Cytarabine and mitoxantrone	Induction: cytarabine 100-200 mg/m^2/day on Days 1–7 and mitoxantrone 8–12 mg/m^2/day on Days 1–3 Consolidation: cytarabine 100–200 mg/m^2/day for 3–7 days and mitoxantrone 8–12 mg/m^2/day on Days 1 and 2	Induction: £324.17 (£250.11–398.23) Consolidation: £226.00 (£155.76–296.23)

* The azacitidine cycle cost is based on the mean number of vials administered per dose in Study AZA-001 and assumes wastage of any vial overage in the cost

† The per-cycle cost assumes an equal proportion of each of the three potential cytarabine and anthracycline combinations used in the UK. The standard-dose chemotherapy costs are based on a body surface area of 1.7 m^2, assume no wastage and use the lowest available vial price (cost/mg) of each medication to estimate the cycle cost

10.9. Appendix 9: Probabilistic sensitivity analysis parameter distribution

Variable	Mean value	SD	Distribution
Utilities			
Azacitidine day 0	0.67	0.22	Beta(2.39,1.18)
Azacitidine day 50	0.70	0.20	Beta(2.98,1.28)
Azacitidine day 106	0.74	0.20	Beta(2.82,0.99)
Azacitidine day 182	0.80	0.21	Beta(2.1,0.53)
BSC day 0	0.67	0.22	Beta(2.39,1.18)
BSC day 50	0.69	0.20	Beta(3,1.35)
BSC day 106	0.68	0.22	Beta(2.38,1.12)
BSC day 182	0.72	0.22	Beta(2.28,0.89)
SDC day 0	0.66	0.13	Beta(8.1,4.17)
SDC day 14	0.61	0.1	Beta(13.9,8.89)
SDC day 42	0.66	0.1	Beta(14.15,7.29)
SDC day 70	0.69	0.12	Beta(9.56,4.29)
SDC day 98	0.72	0.16	Beta(4.95,1.93)
SDC day 182	0.74	0.18	Beta(3.65,1.28)
SDC day 365	0.83	0.1	Beta(10.88,2.23)
LDC day 0	0.67	0.08	Beta(22.48,11.07)
LDC day 14	0.70	0.09	Beta(17.45,7.48)
LDC day 42	0.71	0.15	Beta(5.79,2.36)
LDC day 70	0.72	0.13	Beta(7.87,3.06)
LDC day 98	0.70	0.06	Beta(40.13,17.2)
LDC day 182	0.85	0.08	Beta(16.08,2.84)
LDC day 365	0.67	0.22	Beta(2.39,1.18)
Survival			
Azacitidine (BSC) Weibull alpha	0.987	0.023	Norm(0.987,0.023)
Azacitidine (BSC) Weibull beta	29.599	2.135	Norm(29.599,2.135)
BSC Weibull alpha	1.127	0.033	Norm(1.127,0.033)
BSC Weibull beta	16.273	1.918	Norm(16.273,1.918)
Azacitidine (LDC) Weibull alpha	0.938	0.041	Norm(0.938,0.041)
Azacitidine (LDC) Weibull beta	30.13	2.289	Norm(30.13,2.289)
LDC Weibull alpha	1.161	0.089	Norm(1.161,0.089)
LDC Weibull beta	17.101	2.289	Norm(17.101,2.289)
Azacitidine (SDC) Weibull alpha	0.989	0.069	Norm(0.989,0.069)
Azacitidine (SDC) Weibull Beta	25.48	3.369	Norm(25.48,3.369)
SDC Weibull alpha	1.701	0.099	Norm(1.701,0.099)
SDC Weibull beta	15.923	2.856	Norm(15.923,2.856)
Azacitidine (BSC) log-logistic alpha	1.51	2.856	Norm(1.51,2.856)
Azacitidine (BSC) log-logistic beta	0.048	.005)	Norm(0.048,.005))
BSC log-logistic alpha	1.49	0.300	Norm(1.49,0.300)
BSC log-logistic beta	0.093	0.020	Norm(0.093,0.020)
Azacitidine (LDC) log-logistic alpha	1.08	0.025	Norm(1.08,0.025)
Azacitidine (LDC) log-logistic beta	0.048	0.005	Norm(0.048,0.005)
LDC log-logistic alpha	1.41	0.302	Norm(1.41,0.302)
LDC log-logistic beta	0.083	0.021	Norm(0.083,0.021)
Azacitidine (SDC) log-logistic alpha	1.17	0.019	Norm(1.17,0.019)
Azacitidine (SDC) log-logistic beta	0.057	0.005	Norm(0.057,0.005)
SDC log-logistic alpha	2.27	0.401	Norm(2.27,0.401)
SDC log-logistic beta	0.084	0.006	Norm(0.084,0.006)

Variable	Mean value	SD	Distribution
Costs			
MDS on treatment azacitidine	£5,795	£887	Norm(5795,887)
MDS on treatment BSC	£1,724	£264	Norm(1724,264)
MDS on treatment LDC	£2,001	£306	Norm(2001,306)
MDS on treatment SDCC	£13,011	£1,991	Norm(13011,1991)
MDS on treatment SDCI	£12,683	£1,941	Norm(12683,1941)
MDS off treatment azacitidine (BSC)	£1,563	£239	Norm(1563,239)
MDS off treatment BSC	£1,724	£264	Norm(1724,264)
MDS off treatment LDC	£2,176	£333	Norm(2176,333)
MDS off treatment SDC	£2,682	£410	Norm(2682,410)
AML	£1,814	£278	Norm(1814,278)

Key: AML: acute myeloid leukaemia; BSC: best supportive care; LDC: low-dose chemotherapy; MDS: myelodysplastic syndrome; SDC: standard chemotherapy; SDCC: consolidation SDC; SDCI: induction SDC

10.10. Appendix 10: Adverse event rates per cycle

Patients that are on treatment for myelodysplastic syndrome in the model have an increased rate of adverse event (AEs) that changes over time. This was modelled by calculating the five-week AE rate from the clinical trial data for each treatment arm. As patients receive background best supportive care (BSC), it was assumed that patients could not incur more than one occurrence of each AE per cycle and that the five-week rate could not drop below the annualised BSC cycle rate for each AE. This approach was not used for the BSC arm, which applies an annualised rate every cycle, and standard-dose chemotherapy, which has treatment-related AEs included as part of the HRG costed package. The cycle rates are shown in the tables below.

Table 10.10.1. BSC annualised cycle AE rate. Used as a 'floor' AE rate in the model

	Best supportive care	
Adverse event	**Annual rate**	**Cycle rate**
Neutropenia	0.83	0.08
Leucopenia	0.03	0.00
Febrile neutropenia	0.22	0.02
Pyrexia	0.46	0.04
Pneumonia	0.22	0.02
Sepsis	0.05	0.00

Table 10.10.2. Five-week AE rates for azacitidine patients preselected for BSC

Cycle	Neutropenia	Leucopenia	Febrile neutropenia	Pyrexia	Pneumonia	Sepsis
1	9.65%	4.39%	2.63%	4.41%	2.11%	1.07%
2	7.96%	1.83%	2.11%	4.41%	2.75%	0.48%
3	7.96%	1.96%	2.11%	4.41%	2.11%	0.48%
4	9.59%	3.20%	2.11%	4.41%	2.11%	0.48%
5	7.96%	1.11%	2.11%	4.41%	2.11%	1.01%
6	7.96%	1.21%	2.11%	4.41%	2.11%	0.48%
7	7.96%	2.67%	2.11%	4.41%	2.11%	0.48%
8	7.96%	0.29%	2.11%	4.41%	2.11%	2.01%
9	7.96%	1.78%	2.11%	4.41%	2.11%	0.48%
10	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
11	11.16%	4.46%	2.11%	4.41%	2.11%	0.48%
12	7.96%	2.72%	2.72%	4.41%	2.11%	1.10%
13	7.96%	3.31%	2.11%	4.41%	2.11%	0.48%
14	7.96%	0.29%	3.73%	4.41%	2.11%	0.48%
15	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
16	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
17	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
18	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
19	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
20	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%

Table 10.10.3. Five-week AE rates for azacitidine patients preselected for low-dose chemotherapy

Cycle	Neutropenia	Leucopenia	Febrile neutropenia	Pyrexia	Pneumonia	Sepsis
1	7.96%	4.44%	4.44%	4.41%	4.44%	0.48%
2	13.89%	9.26%	2.31%	4.41%	2.31%	2.31%
3	10.05%	2.51%	2.11%	4.41%	2.51%	0.48%
4	8.47%	5.65%	2.11%	4.41%	2.11%	0.48%
5	7.96%	0.29%	2.11%	4.41%	2.11%	1.00%
6	9.74%	3.25%	2.11%	4.41%	2.11%	0.48%
7	7.96%	0.29%	3.40%	4.41%	2.11%	0.48%
8	7.96%	0.29%	2.11%	4.41%	2.11%	2.32%
9	8.20%	0.29%	2.11%	4.41%	2.11%	1.01%
10	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
11	9.71%	0.29%	2.11%	4.41%	2.11%	0.48%
12	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
13	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
14	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
15	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
16	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
17	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
18	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
19	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
20	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%

Table 10.10.4. Five-week AE rates for azacitidine patients preselected for standard-dose chemotherapy

Cycle	Neutropenia	Leucopenia	Febrile neutropenia	Pyrexia	Pneumonia	Sepsis
1	18.75%	12.50%	6.25%	4.41%	2.11%	3.01%
2	19.48%	6.49%	2.11%	6.49%	2.11%	2.98%
3	7.96%	0.29%	2.11%	4.41%	14.08%	0.48%
4	15.38%	0.29%	2.11%	4.41%	2.11%	0.48%
5	8.47%	8.47%	2.11%	4.41%	2.11%	0.48%
6	9.80%	0.29%	2.11%	4.41%	2.11%	0.48%
7	7.96%	0.29%	2.11%	4.41%	2.11%	1.41%
8	11.11%	0.29%	2.11%	4.41%	2.11%	0.48%
9	22.22%	11.11%	2.11%	4.41%	2.11%	0.48%
10	11.90%	0.29%	2.11%	4.41%	2.11%	0.48%
11	7.96%	0.29%	2.11%	4.41%	2.11%	1.76%
12	14.29%	0.29%	2.11%	4.41%	2.11%	0.48%
13	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
14	14.29%	0.29%	2.11%	4.41%	2.11%	0.48%
15	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
16	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
17	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
18	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
19	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
20	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%

Table 10.10.5. Five-week AE rates for low-dose chemotherapy patients

Cycle	Neutropenia	Leucopenia	Febrile neutropenia	Pyrexia	Pneumonia	Sepsis
1	15.91%	2.27%	2.27%	4.41%	2.27%	0.48%
2	7.96%	0.29%	2.11%	7.32%	4.88%	0.48%
3	7.96%	0.29%	2.11%	4.41%	2.94%	1.98%
4	10.34%	0.29%	2.11%	4.41%	2.11%	0.48%
5	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
6	7.96%	0.29%	2.11%	4.41%	2.11%	2.65%
7	10.53%	0.29%	2.11%	4.41%	2.11%	0.48%
8	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
9	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
10	7.96%	0.29%	2.11%	4.41%	2.11%	3.10%
11	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
12	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
13	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
14	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
15	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
16	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
17	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
18	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
19	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%
20	7.96%	0.29%	2.11%	4.41%	2.11%	0.48%