NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Lenalidomide for the treatment of myelodysplastic syndromes associated with deletion 5q cytogenetic abnormality

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Executive summary

Myelodysplastic syndrome (MDS) is a diverse group of haematological disorders in which the bone marrow functions abnormally and insufficient numbers of mature blood cells are produced. Red blood cells, white blood cells and platelets may all be affected by MDS, resulting in life-threatening disease, with anaemia, increased risk of bleeding, infection and disease transformation to acute myeloid leukaemia (AML). MDS mostly affects the elderly, impairing quality of life due to debilitating symptoms, such as fatigue and dyspnea, as well as treatment regimens involving hospitalisation for intravenous drug infusions, blood transfusions and complications such as severe infections.

Due to its low incidence, MDS is recognised as an orphan disease by regulatory authorities in Europe and the US. The annual incidence of MDS is between two and 13 per 100,000 people and in England, 2,204 patients were newly diagnosed with MDS on 2009. Low risk and intermediate-1 risk MDS together form approximately 70% of all MDS, with deletion of chromosome 5q being the most common of the cytogenetic abnormalities, occurring in between 16% and 28% of all patients, with a further 39% to 50% of these patients being blood transfusion dependent. Just over 500 patients are estimated to fall under the indication being appraised by NICE.

MDS del(5q) is an area of unmet need, as there are currently no licensed/approved treatment options for patients, with most quickly becoming red blood cell transfusion dependent. While the major goal of treatment is to achieve transfusion independence, the mainstay of treatment remains best supportive care; that is, blood transfusions, growth factors and antibiotics.

Lenalidomide (Revlimid®) is an oral therapy with anti-neoplastic, anti-angiogenic, pro-erythropoeitic and immunomodulatory properties. A marketing authorisation is anticipated in Europe for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with del(5q) cytogenetic abnormality with or without other cytogenetic abnormalities. Lenalidomide was approved in 2005 by the FDA in this indication.

The efficacy of lenalidomide has been demonstrated in the MDS-004 clinical trial, a randomised Phase 3 study that compared the efficacy and safety of two lenalidomide doses (10 mg and 5 mg) with placebo. Cytogenetic responses were achieved in

50% patients receiving lenalidomide 10 mg and 25% of patients receiving lenalidomide 5 mg (modified intention-to-treat population). Transfusion independence lasting ≥26 weeks was achieved in 56.1% and 42.6% of patients on lenalidomide 10 mg and 5 mg, respectively. Lenalidomide responders had significantly longer AML-free survival than non-responders (p=0.0085). Patients responding to lenalidomide experienced clinically meaningful improvements in quality of life through to Week 48. Changes in health-related quality of life (HRQoL) were positively associated with haemoglobin improvement and transfusion independence status, and these were maintained with continued response to treatment. Lenalidomide is generally well tolerated; early haematological adverse events can be anticipated and managed by dose modifications and supportive care.

The cost-effectiveness of lenalidomide was determined using a Markov model developed in Microsoft® Excel. This approach was used to estimate lifetime outcomes and costs for patients with MDS del(5q). The model was designed to capture key clinical drivers within MDS del(5q): transfusion dependence, requirements for chelation, complications associated with transfusion dependence and chelation and disease transformation to AML.

The model produces a good estimation of the clinical trial data and indicates that over a lifetime horizon, patients receiving lenalidomide will spend an additional 1.7 years in a transfusion-independent state, resulting in a QALY gain of 0.89. Without a Patient Access Scheme this results in an ICER of £56,965 (see Table 1). Extensive sensitivity analysis has been conducted around key model parameters and the model results vary little within the scenarios tested.

The key driver of the model is the proportion of patients that achieve transfusion independence and remain on treatment beyond the number of cycles where the Patient Access Scheme is implemented. It should be noted that as the patient population is small (≈500 patients) the budget impact is likely to also be small – approximately £2,000 per 100,000 population in Year 1, increasing to £11,000 per 100,000 population in Year 5.

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a. mITT population included patients with centrally confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug
b. Patients received 10 mg once-daily on Days 1–21 every 28 days. Patients in the 5 mg group were treated once-daily on Days 1–28 every 28 days.
c. Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire

d. >7 points on FACT-An score

Table 1. Base-case cost-effectiveness results

	Intervention	Best supportive care
Technology acquisition cost	£68,261	£2,393
Other costs	£88,046	£103,333
Total costs	£156,308	£105,726
Difference in total costs	N/A	£50,582
LYG	5.69	4.53
LYG difference	N/A	1.16
QALYs	3.46	2.58
QALY difference	N/A	0.89
ICER	N/A	£56,965

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio

QALYs and Costs are presented with a 3.5% discount rate. LYG are undiscounted.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1. Description of technology under assessment

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

Revlimid® (lenalidomide)

Immunomodulatory drug (BNF category: Malignant disease and immunosuppression; BNF sub-category: Drugs affecting the immune response).[1]

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

The mechanism of action of lenalidomide includes antineoplastic, anti-angiogenic, pro-erythropoietic, and immunomodulatory properties. Specifically, lenalidomide:

- Inhibits proliferation of certain haematopoietic tumour cells, including multiple myeloma-affected plasma cells and del(5q) tumour cells
- Enhances T cell- and natural killer (NK) cell-mediated immunity and increases the number of NK and T cells
- Inhibits angiogenesis by blocking the migration and adhesion of endothelial cells and the formation of micro-vessels
- Augments fetal haemoglobin production by CD34+ haematopoietic stem cells
- Inhibits production of pro-inflammatory cytokines – for example, tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) – by monocytes.[2]

In MDS associated with del(5q), lenalidomide was shown to selectively inhibit the abnormal clone by increasing the apoptosis of del(5q) cells. The sensitivity to lenalidomide in MDS with del(5q) can, at least in part, be explained by the up-regulation of several tumour suppressor genes (for example, *SPARC* and *RPS14*) that have reduced expression due to haploinsufficiency caused by del(5q).[2]

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

Lenalidomide does not currently have a UK marketing authorisation for the treatment of MDS. The application is currently under consideration by the European Medicines Agency (EMA) with a Committee for Medicinal Products for Human Use opinion/decision anticipated in April 2013 and European Committee decision in June 2013.

1.4. Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

An application for lenalidomide has been submitted to the EMA and is currently under assessment with ongoing discussions.

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

An application for lenalidomide has been submitted to the EMA for use in the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1 risk MDS associated with a del(5q) cytogenetic abnormality with or without additional cytogenetic abnormalities – the same indication for which

lenalidomide has been approved by the US Food and Drug Administration in December 2005.

1.6. Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

No additional evidence for the use of lenalidomide in the indication under review is expected to be available in the next 12 months.

1.7. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Lenalidomide is already available in the UK for the treatment of relapsed refractory multiple myeloma, aside from the 2.5 mg dose, which is yet to be launched. The 2.5 mg dose is specific to the MDS indication. The marketing authorisation for treatment of MDS del(5q) is expected end of June 2013.

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

Lenalidomide has been approved for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality, with or without additional cytogenetic abnormalities, in the following countries: USA, Canada, Israel, Japan, Malaysia, New Zealand, Switzerland, Australia, Argentina, Bolivia, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Peru and Uruguay.

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

The technology may be appraised by the Scottish Medicines Consortium following the granting of a marketing authorisation.

1.10. For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 2. Unit costs of technology being appraised[2]

Pharmaceutical formulation	Lenalidomide 10 mg, 5 mg, 2.5 mg hard capsules[2]
Acquisition cost (excluding VAT)	Lenalidomide 10 mg (21 pack) for £3,780; Lenalidomide 5 mg (21 pack) for £3,570; Lenalidomide 2.5 mg (21 pack)*[1]
Method of administration	Orally: capsules should be swallowed whole, preferably with water, either with or without food[2]
Doses	Recommended starting dose is 10 mg once-daily[2]
Dosing frequency	10 mg once-daily on Days 1–21 of a 28-day cycle[2]
Average length of a course of treatment	Treatment is continued until erythroid relapse, disease progression or toxicity[2] Dosing is continued or modified based on clinical and laboratory findings (see dose adjustments).
Average cost of a course of treatment	Treatment with lenalidomide 10 mg for one cycle would cost £3,780. The average cost of a course of treatment will vary according to the number of cycles and treatment breaks and dose adjustments required. (See dose adjustments below)
Anticipated average interval between courses of treatments	NA
Anticipated number of repeat courses of treatments	Is a clinical decision and is likely to vary depending on a patient's response to treatment
Dose adjustments	Adjust dose for patients with cytopenias so treatment can resume with minimal interruptions.[3,4] Dose reduction steps to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicity judged to be related to lenalidomide: • Starting dose: 10 mg once-daily on Days 1–21 every 28 days • Dose level-1: 5 mg once-daily on Days 1–28 every 28 days • Dose level-2: 2.5 mg once-daily on Days 1–28 every 28 days Dose level-3: 2.5 mg every other day 1–28 every 28 days[2]

*Lenalidomide 2.5 mg is not available on the market, but once available a price will be confirmed.

1.11. For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12. Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

MDS are subdivided using the International Prognostic Scoring System (IPSS), and the French-American-British (FAB) and World Health Organisation (WHO) classification systems. Based on the proportion of leukaemic cells (or 'blasts'), bone marrow cytogenetic findings, and the presence of blood cytopenia, the IPSS classifies outcome as low-risk, intermediate-1 risk, intermediate-2 risk or high-risk.

Improved karyotyping (with FISH analysis for del(5q)) can lead to better diagnosis and prognostic stratification in lower-risk MDS.[5] Detection of a del(5q) abnormality provides a clear treatment option. Lenalidomide treatment should be supervised by a physician experienced in the use of anticancer therapies.[2]

1.13. Is there a need for monitoring of patients over and above usual clinical practice for this technology?

The major dose-limiting toxicities of lenalidomide include neutropenia and thrombocytopenia. A full blood count, including white cell count with differential count, platelet count, haemoglobin levels and haematocrit, should be performed at baseline, every week for the first eight weeks of lenalidomide treatment and monthly thereafter to monitor for cytopenias.[2]

It is advisable to monitor renal function in the elderly and in those with renal impairment. Cases of hypothyroidism have been reported, and monitoring of thyroid function should be considered. Close monitoring of warfarin and digoxin concentrations in patients receiving these medications is advised during lenalidomide treatment. In addition, patients with known risk factors for thromboembolism and/or myocardial infarction should be closely monitored.[2]

1.14. What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Lenalidomide is to be administered as a monotherapy for the treatment of MDS del(5q).

2. Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1. Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

MDS are a diverse group of haematological disorders, predominantly affecting individuals aged over 70. They are characterised by hypercellular or hypocellular bone marrow with abnormal cell morphology, maturation and function, and peripheral blood cytopenias, resulting from ineffective blood cell production.[6] MDS may be classified as primary (no known cause), or secondary to treatment with chemotherapy and/or radiation for other diseases. They are caused by a cumulative acquisition of genetic errors in the bone marrow. Cytogenetic abnormalities are found in the dysplastic clone of 50–80% of patients with MDS.[7,8] Common abnormalities include 5q, 7, 20q and Y chromosomal deletions, as well as trisomy 8. The most common cytogenetic abnormality in MDS is del(5q).[3] Among the more common karyotypic abnormalities, isolated del(5q) is associated with the best prognosis,[9] while multiple cytogenetic abnormalities are associated with a worse prognosis than isolated abnormalities.[10]

The most common presenting features of MDS include anaemia, weakness and fatigue, bacterial infections, and bleeding and bruising.[11-13]

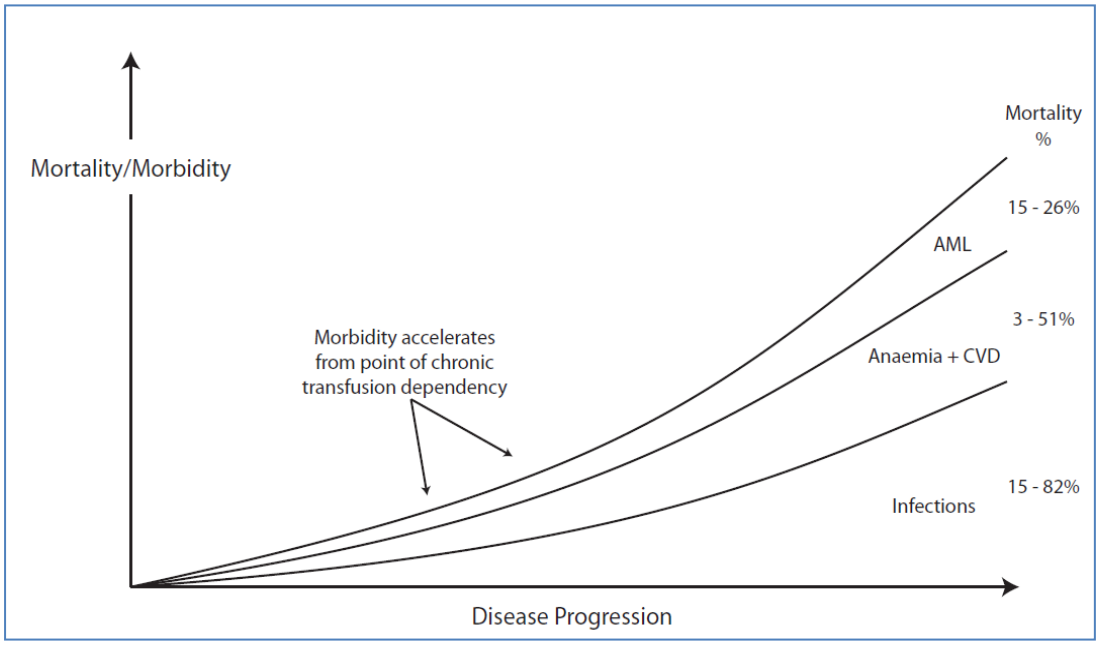
Prognosis in MDS is based on the International Prognostic Scoring System (IPSS). Based on the proportion of leukaemic cells (or ‘blasts’), bone marrow cytogenetic findings, and the presence of blood cytopenia, the IPSS classifies outcome as either low-risk, intermediate-1-risk, intermediate-2-risk or high-risk. The low-risk and intermediate-1-risk groups together form approximately 70% of all MDS cases.[3,14] Median survival with low-risk and intermediate-1-risk MDS is 5.7 years and 3.5 years, respectively, and can be less than six months for patients with high-risk MDS.[14]

Currently, patients are treated with best supportive care (BSC) and can receive RBC transfusions, iron chelation and erythropoiesis stimulating agents. A recent study

showed that the cumulative rates for progression to AML in patients undergoing BSC measured at two and five years was 12.1% and 19.9%, respectively. The same study showed that the overall survival rate for these patients measured at two and five years was 74.4% and 40.5%, respectively.[15]

MDS are associated with a number of underlying pathogenetic factors, including bone marrow dysfunction, peripheral blood cytopenias and ineffective haematopoiesis.[7,16] The primary clinical manifestations of these effects are refractory anaemia, increased risk of infection and haemorrhages, and disease transformation to AML. The majority of patients with low- or intermediate-1-risk MDS die of causes related to their underlying disease (see Figure 1).

Figure 1. An illustration of the nature of disease progression in MDS del(5q): cumulative morbidity and mortality of disease components



Mortality source data: [17-23]

2.2. How many patients are assumed to be eligible? How is this figure derived?

Due to its low incidence and nature, MDS as a whole is recognised as an orphan disease by regulatory authorities in Europe and the US.

The final scope for this NICE Single Technology Appraisal identifies a specific patient group in the licensed indication for this technology; that is, patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality with or without other cytogenetic abnormalities.[2,24]
The incidence of MDS is between two and 13 per 100,000 people, and this figure increases to 30 cases per 100,000 people per year for patients over the age of 70 years.[25] In England, 2,204 people were newly diagnosed with MDS in 2009.[26] The number of diagnosed MDS patients, derived from Hospital Episode Statistics (HES) data, is estimated at approximately 18 per 100,000.[27] Many cases remain undiagnosed. Combining HES data with published population data indicates there are approximately 11,200 diagnosed MDS patients in the UK. Del(5q) is one of the most common cytogenetic abnormalities in MDS, occurring in approximately 15% of patients.[9,14,28] It is estimated that 70% of MDS patients are of low- and intermediate-1 risk, with between 39% and 50% of these blood transfusion dependent.[29]

2.3. Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

Median survival with low-risk and intermediate-1-risk MDS is 5.7 years and 3.5 years, respectively, and can be less than six months for patients with high-risk MDS. The expected survival of patients with transfusion-dependent MDS is shorter and the risk of progression to AML is higher than in those patients who are not yet transfusion dependent. Therefore, this provides enhanced prognostic accuracy for patients with low- or INT-1-risk MDS over the course of this illness and RBC transfusion dependency at diagnosis appear to be important predictors of both reduced OS and increased risk of progression to AML.

2.4. Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

Two documents published in the UK that are relevant to the condition are the 2003 NICE cancer service guideline Improving outcomes in haematological cancers – The Manual[30] and the 2003 British Committee for Standardisation in Haematology Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes.[25]
These guidelines will be updated in December 2012 and published in March 2013.

For patients with intermediate-2 or high-risk MDS who are not eligible for haematopoietic stem cell transplantation, NICE Technology Appraisal 218 recommends azacitidine as a treatment option.[31]

2.5. Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The mainstay of treatment for MDS del(5q) is best supportive care (blood transfusions and antibiotics) to control the symptoms of bone marrow failure. Although erythropoietin (EPO) is sometimes used successfully in the early stages of MDS, over time, patients can become unresponsive to EPO and increasingly dependent on blood transfusions.[32] In addition, MDS del(5q) patients have a significantly higher level of endogenous EPO compared with non del(5q) MDS patients, making them intrinsically more resistant to EPO.[33] A review of the literature on the use of EPO and granulocyte colony-stimulating factor (G-CSF) in MDS del(5q) highlighted that the response to these treatments (EPO alone or in combination with G-CSF) seemed to be lower in MDS del(5q) than in other low-risk MDS patients.[34]

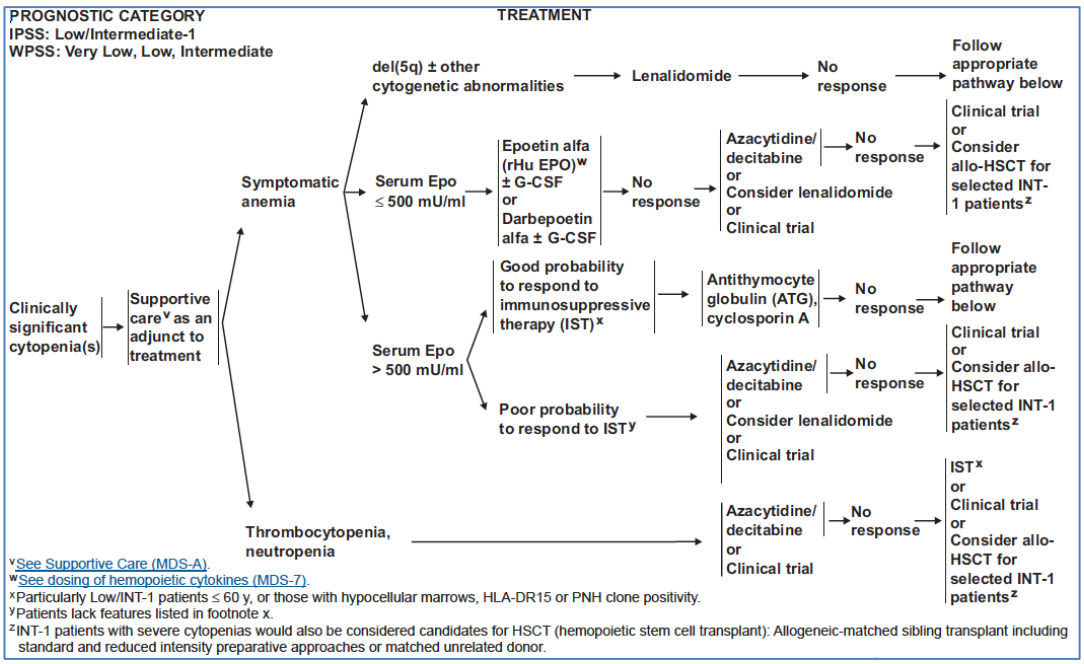
The burden of the underlying disease is exacerbated by the requirement for red blood cell (RBC) transfusions. Once patients have no therapeutic option other than receiving blood transfusions, they are chronically transfusion dependent (TD).[21,29,35,36] From the point of chronic transfusion dependency (CTD), the burden of MDS increases quickly, due to the trauma of transfusions, increased infection risk, anaemia, iron overload and the ‘multiplier effect’ of interactive co-morbidities (cardiovascular, renal, diabetic).[37] The main point at which the prognosis can be improved is before patients become chronically TD. Early intervention is, therefore, recommended to avoid patients becoming transfusion dependent, and to prevent chronic severe anaemia and the associated burden from being manifested.

The aim of intervention in MDS del(5q) should, therefore, be to reverse transfusion dependence and delay disease progression, and thus prevent the rapid deterioration

in patient health and QoL, and the premature mortality associated with it. The earlier the intervention, the more likely it is that the long-term consequences of chronic anemia can be avoided. Furthermore, the intervention removes the potential adverse events associated with blood transfusions.

In low and intermediate-risk del(5q) MDS, lenalidomide simplifies the treatment algorithm. It is indicated for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality, with or without other cytogenetic abnormalities.[2] Detection of a del(5q) abnormality provides a clear treatment option. The National Comprehensive Cancer Network in the United States recommends lenalidomide for those with del(5q) chromosomal abnormalities and symptomatic anaemia.[38]

Figure 2. National Comprehensive Cancer Network guidelines for lenalidomide



Lenalidomide not only provides symptomatic relief, but it also targets the cause of the malignancy and changes the course of the disease. In del(5q) MDS, lenalidomide seems to modify the disease predominantly by directly targeting the del(5q) clone and by a parallel pro-erythropoietic effect.[3,39-41]

By modifying the disease, lenalidomide produces significant cytogenetic responses: in the randomised controlled trial by Fenaux *et al,* 50% of patients had a complete or partial response to lenalidomide 10 mg. The onset of an erythroid response occurred

by Cycle 2 in 86% of patients. In addition, lenalidomide was shown to provide rapid and enduring transfusion independence: the median time to transfusion independence was 4.6 weeks; transfusion independence lasting ≥26 weeks was achieved in 56.1% of patients with lenalidomide 10 mg; median duration of transfusion independence was not reached, but is likely to exceed two years in lenalidomide-treated patients.[5]

In del(5q) MDS, achievement of transfusion independence ≥26 weeks with lenalidomide was associated with significantly longer OS ($p<0.0001$).[42] Achievement of transfusion independence ≥26 weeks with lenalidomide was associated with a 45% reduction in the relative risk of AML progression ($p=0.022$) and a 51% reduction in the relative risk of death ($p=0.008$).[43] Transfusion dependence is associated with reduced survival as a result of iron overload, heart failure and progression to AML.[44] Achieving long-term transfusion independence with lenalidomide increases life expectancy.[42]

Treatment of del(5q) MDS patients with lenalidomide was associated with significant improvements in HRQoL at Week 12 ($p<0.05$ versus placebo). Also, patients with del(5q) MDS responding to lenalidomide experienced clinically meaningful improvements in quality of life through to Week 48.[5] Previous HRQoL studies have shown that patients with MDS experience impairment in functioning and activities of daily living that result in worse HRQoL than those of similarly aged adults from the general population.[45,46] It was also shown that fatigue caused by chronic anaemia has a large impact on the overall HRQoL of MDS patients,[45,47] while the number of transfusions per month inversely correlated with HRQoL.[21]

It is believed that lenalidomide has the potential to improve the HRQoL of del(5q) MDS patients by lowering the symptomatic burden of comorbid anaemia and by preventing the morbidity associated with anaemia. Results from a retrospective analysis of 4,007 observation periods suggest that periods of TD are generally associated with more medical events compared with periods of TI. Furthermore, periods of TI on therapy have fewer medical events compared with TD periods – both on or off therapy: that is, lenalidomide therapy plays a role in lowering supportive care requirements and resources utilisation for many patients.[48] A similar study found that TD periods were associated with the highest incidence of infection and bleeding events compared with any of the TI periods. Similarly, hospitalisations and emergency room visits were highest for TD periods compared with any of the TI

periods. Most notably, the incidence of events during TI periods on longer courses of lenalidomide (≥3 lenalidomide cycles) approached that of periods of TI without active therapy (watch and wait). The authors concluded that it is likely that since lenalidomide treatment resulted in lower incidence of infections and clinically significant bleeds during TI periods, it is likely that lenalidomide also impacts on the underlying biology of MDS.[49]

2.6. Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

Management of MDS low and intermediate -1 del(5q) is based on the patient's IPSS and French–American–British (FAB) score, wherever possible. Treatment focuses predominantly on symptom relief – that is, reducing cytopenias, treating persistent/recurring infection, improving quality of life – and prolonging survival.[25] Red cell transfusion and iron chelation therapy are used to manage anaemia and complications of iron overload as a result of repeated transfusions.

Erythropoietin (EPO) with or without granulocyte colony stimulating factor (G-CSF) can increase haemoglobin concentration and reduce/eliminate red blood cell transfusion in selected patients with MDS. However, over time, patients can become unresponsive to EPO and increasingly dependent on blood transfusions.[32] In addition, MDS del(5q) patients have a significantly higher level of endogenous EPO compared with non del(5q) MDS patients, making them intrinsically more resistant to EPO [33]. A review of the literature on the use of EPO and G-CSF in MDS del(5q) highlighted that the response to these treatments (EPO alone or in combination with G-CSF) seemed to be lower in MDS del(5q) than in other low-risk MDS patients.[34]

For some patients, a trial of immunosuppressive therapy is recommended. Neutropenic sepsis in patients with MDS should be treated with intravenous antibiotics, the same as neutropenia in other patients (for example, post-chemotherapy).[25]

Even though lenalidomide is currently awaiting a positive indication for treating del(5q) MDS patients, there is at present ongoing prescribing in an unlicensed capacity by means of the Cancer Drugs Fund.

2.7. Please identify the main comparator(s) and justify their selection.

Currently, in the UK, the mainstay of treatment for MDS del(5q) is best supportive care (blood transfusions and antibiotics) to control the symptoms of bone marrow failure. The aim of intervention in MDS del(5q) should be to reverse transfusion dependence and delay disease progression, and thus prevent the rapid deterioration in patient health and QoL, and the premature mortality associated with it. The earlier the intervention, the more likely it is that the long-term consequences of chronic anemia can be avoided. Furthermore, the intervention removes the potential adverse events associated with blood transfusions.

To a very limited extent EPO is sometimes included within best supportive care. However, as discussed above, the evidence points to a much lower response to EPO alone or in combination with G-CSF in MDS del(5q) patients than in other low-risk MDS patients.[34]

There are no other licensed treatment options available for the treatment of MDS del(5q) patients.

2.8. Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Most adverse events tend to occur during the first 16 weeks of therapy with lenalidomide. Serious adverse reactions include: venous thromboembolism (deep vein thrombosis, pulmonary embolism) Grade 3 or 4 neutropenia, febrile neutropenia and Grade 3 or 4 thrombocytopenia.[2]

Dose adjustments are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia, or other Grade 3 or 4 toxicity judged to be related to lenalidomide.[2] Treatment depends on the severity of the condition and can include oral or intravenous antibiotics.

2.9. Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

Lenalidomide must be initiated and monitored under the supervision of physicians experienced in the management of MDS (that is, hospital specialists). It is then taken orally according to the dosing regimen stated in the SPC.[2]

It is recommended that all patients see their GP before treatment, every week for the first eight weeks and then monthly thereafter. At each of these visits a full blood count test will be carried out to monitor for cytopenias. Women of childbearing potential require pregnancy testing every four weeks as part of the Pregnancy Prevention Programme, since lenalidomide is expected to have teratogenic effects if taken during pregnancy.[2]

The elderly and those with impaired renal function will require regular monitoring. Close monitoring of warfarin and digoxin concentrations in patients receiving these medications is advised. In addition, patients with known risk factors for thromboembolism and/or myocardial infarction should be closely monitored. Physicians should carefully evaluate patients before and during treatment using standard screening for occurrence of second primary malignancies.[2]

2.10. Does the technology require additional infrastructure to be put in place?

The therapy does not require additional infrastructure to be put in place. Lenalidomide is an oral therapy.

3. Equity and equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1. Identification of equality issues

3.1.1. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

MDS predominantly affects elderly patients, many of whom have concomitant conditions. This patient population may also have mobility issues; that is, patients who are frail and live at long distances from a hospital may find difficulty in commuting to receive blood transfusions. Lenalidomide is an oral therapy, which can be taken at home, thereby ensuring equality of access.

3.1.2. How has the analysis addressed these issues?

We have not been able to incorporate these issues into our analysis and it remains an area of uncertainty.

4. Innovation

4.1.1. Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a ‘step-change’ in the management of the condition.

There is no licensed option available for the treatment of MDS in del(5q) patients and, therefore, it remains an area of unmet need. Patients currently receive blood transfusions as treatment. Lenalidomide, once licensed, would be the first genuine therapeutic option.

4.1.2. Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

Lenalidomide is an oral therapy, which has significant positive implications for patients with mobility issues; that is, patients who are frail and live at long distances from a hospital may find difficulty in commuting to receive blood transfusions. These benefits are unlikely to be captured in a QALY and, therefore, may be an underestimate.

4.1.3. Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Efforts are ongoing to capture the value of lenalidomide as an oral therapy in the treatment of MDS del(5q).

5. 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**	**Rationale if different from the scope**
Population	Adults with myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality and who are red blood cell transfusion dependent	Same as in the final scope	NA
Intervention	Lenalidomide	Same as in final scope	NA
Comparator(s)	Best supportive care including blood transfusions	Same as in final scope	Azacitadine / stem cell transplant are not appropriate comparators as the trial population did not include intermediate-2 and high risk patients
Outcomes	-overall survival -progression-free survival (including time to transformation to AML or death) -response rates, including haematologic response and improvement -frequency of blood transfusions (including blood-transfusion independence) serious infections -adverse effects of treatment -health related quality of life.	Same as above	NA

Economic analysis	Cost-effectiveness analysis	Same as in final scope	NA
Subgroups to be considered	NA	NA	NA
Special considerations, including issues related to equity or equality	NA	NA	NA

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, Personal Social Services; QALY(s), quality-adjusted life year(s)		

6. Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

Lenalidomide is expected to receive an indication for the treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q – del(5q) – cytogenetic abnormality with or without other cytogenetic abnormalities.[2]

The key evidence to support the efficacy of lenalidomide is taken from study MDS-004, a randomised Phase 3 study that compared the efficacy and safety of two lenalidomide doses (10 mg and 5 mg) with placebo in patients with low- or intermediate-1-risk MDS with a del(5q) abnormality. Results show that:

- By modifying the disease, lenalidomide produces significant cytogenetic responses:
  - Lenalidomide 10 mg and 5 mg both produced significant cytogenetic responses ($p<0.001$)
  - The cytogenetic response rates (complete and partial) in the modified intention-to-treat (mITT)[a] population were 50% with lenalidomide 10 mg and 25% with lenalidomide 5 mg (non-significant between groups)
- By modifying the disease, lenalidomide provides enduring transfusion independence:
  - Lenalidomide 10 mg and 5 mg both achieved significant transfusion independence ($p<0.001$ versus placebo)
  - Transfusion-independence lasting ≥26 weeks was achieved with lenalidomide 10 mg in 56.1% of patients and with lenalidomide 5 mg in 42.6% of patients
  - Add in the response rates used in the HE model – assessed at day 80
- By modifying the disease, lenalidomide provides rapid and long-lasting transfusion[-independence:
  - The onset of an erythroid response occurred by Cycle 2 in 86% of patients
  - The median time to transfusion independence was 4.6 weeks with lenalidomide 10 mg[b]

  - Median duration of protocol-defined or International Working Group (IWG)-defined transfusion independence was not reached, but is likely to exceed two years in lenalidomide-treated subjects
- By achieving transfusion independence, lenalidomide can increase acute myeloid leukaemia (AML)-free survival:
  - Lenalidomide responders (red cell transfusion independence for eight weeks or more) had longer AML-free survival than non-responders (six-month landmark analysis; p=0.0085)
- Lenalidomide significantly improves patients' quality of life:
  - Lenalidomide 10 mg and 5 mg were associated with significant improvements in health-related quality of life (HRQoL)[c] at Week 12 ($p<0.05$ versus placebo)
  - Patients responding to lenalidomide experienced clinically meaningful improvements in quality of life[d] through to Week 48
  - Changes in HRQoL were positively associated with haemoglobin improvement and transfusion independence status, and these HRQoL effects were maintained with continued response to treatment.
- Lenalidomide is well tolerated, allowing treatment to continue for improved long-term outcomes:
  - Grade 3–4 cytopenias may occur during early treatment cycles with lenalidomide, but decrease thereafter
  - Early haematological adverse events can be anticipated and managed by dose modifications and supportive care.[5]

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a. mITT population included patients with centrally-confirmed low- or intermediate-1-risk MDS with del(5q) and documented RBC transfusion-dependence, who received ≥1 dose of study drug
b. Patients received 10 mg once-daily on Days 1–21 every 28 days. Patients in the 5 mg group were treated once-daily on Days 1–28 every 28 days.
c. Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire
d. >7 points on FACT-An score

6.1. Identification of studies

6.1.1. Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

Literature search

A comprehensive literature search was conducted to identify all relevant clinical effectiveness evidence for lenalidomide and comparator treatments as described in the decision problem for this NICE Single Technology Appraisal. The search was based on the question, 'What is the clinical effectiveness of lenalidomide and comparator therapies when used to treat patients with low- or intermediate-1-risk MDS associated with del(5q) cytogenetic abnormality who are red blood cell (RBC) transfusion dependent?'

The following is a summary of the literature search methods that were used to ensure that all potentially relevant studies were identified in a systematic way. These included both published peer-reviewed studies, as well as abstracts from conference proceedings. The full literature search strategy and terms used are presented in section 10.2, appendix 2.

Study population

The aim of the literature review was to identify studies of adult patients with low- or intermediate-1-risk MDS, associated with a del(5q) cytogenetic abnormality, who were RBC transfusion dependent. However, the information specialist advised that this subgroup of MDS patients was unlikely to be identified through standard searches of electronic databases. The literature search, therefore, focused on identifying studies of therapies for the MDS patient population in general, to ensure that the search was as inclusive as possible. Subsequently, study selection methods were used to limit the final set of studies to those whose patient populations were relevant to the decision problem; that is, patients with transfusion-dependent

anaemia due to low- or intermediate-1-risk MDS associated with a del(5q) abnormality with or without other cytogenetic abnormalities.

Therapeutic interventions

The search was designed to identify studies investigating the clinical efficacy of lenalidomide, as well as of therapies currently used in best supportive care, defined as blood transfusion, iron chelation therapy and antibiotic therapy for infections.

Limits

No date or language limitations were specified in the search.

Databases searched

The following electronic databases were searched: MEDLINE®, Embase, The Cochrane Library, Cochrane Database of Systematic Reviews, Cochrane Register of Clinical Trials, NHS Economic Evaluations Database (NHS HEED), HTA database, Database of Abstracts of Reviews of Effects (DARE), CINAHL®, EconLit, Web of Science® databases (Science Citation Index and Conference Proceedings Citation Index).

The search combined terms to describe the intervention(s) of interest (best supportive care and lenalidomide) and the population (patients with MDS associate with a del(5q) abnormality), before applying methodological search filters, such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN), to refine the results to the appropriate types of evidence (clinical trials, systematic reviews and economic evidence). The terms within these groups were combined using the Boolean operator OR; then groups were combined using the Boolean operator AND. This approach is the standard 'building block' approach to searching.[50]

In addition to the formal searches, reference lists of included studies were scanned for additional publications of relevance to the research question.

6.2. Study selection

6.2.1. Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Study selection

Two reviewers independently inspected each reference (title and abstract) identified by the literature search and applied study selection criteria. For articles that were possibly relevant, or in cases of disagreement between the two reviewers, the full article was obtained and independently inspected. Table 3 summarises the eligibility criteria used.

Table 3. Eligibility criteria used in search strategy

Eligibility criteria	Clinical effectiveness
Inclusion criteria	**Population:** Patients with RBC transfusion-dependent, low- or intermediate-1-risk MDS with del(5q) **Interventions:** Lenalidomide or best supportive care (antibiotics, blood transfusions, growth factor therapies and iron-chelation therapies) **Outcomes:** Frequency of blood transfusions; blood-transfusion independence; overall survival; progression-free survival (including time to transformation to AML; haematological response (including change from baseline in ANC, platelet count and Hb level and haematopoietic cells evaluation); serious infections; adverse effects of treatment; health-related quality of life **Study design:** Randomised controlled trials and systematic reviews **Language restrictions:** No language restrictions were applied
Exclusion criteria	**Population:** Study patients for whom no cytogenetic abnormality was reported; patients with intermediate-2 and high-risk MDS **Interventions:** Azacitadine, chemotherapy and stem cell transplantation **Study design:** Single-arm clinical trials

Key: AML = acute myeloid leukaemia; ANC = absolute neutrophil count; Hb = haemoglobin; MDS = myeloproliferative disorders; RBC = red blood cell

Types of studies

The review included all randomised controlled trials (RCTs) that evaluated lenalidomide or therapies currently used as best supportive care (antibiotics, blood transfusions, growth factor therapies and iron-chelation therapies) in the relevant study population. RCTs were included if they compared the intervention to either an active comparator or to placebo. The review included RCTs regardless of design (parallel, crossover, open label, single- or double-blind).

Types of participants

The characteristics of patients were those relevant to the decision problem as specified in the appraisal; therefore, only studies that enrolled adult patients with International Prognostic Scoring System (IPSS) low- or intermediate-1-risk MDS, associated with a del(5q) cytogenetic abnormality, who were RBC transfusion-dependent were included.

Types of intervention

Interventions included lenalidomide and best supportive care therapies, as long as they were used for the treatment of IPSS low- or intermediate-1-risk MDS, associated with a del(5q) cytogenetic abnormality, in adult patients who are RBC transfusion-dependent.

Types of clinical outcomes

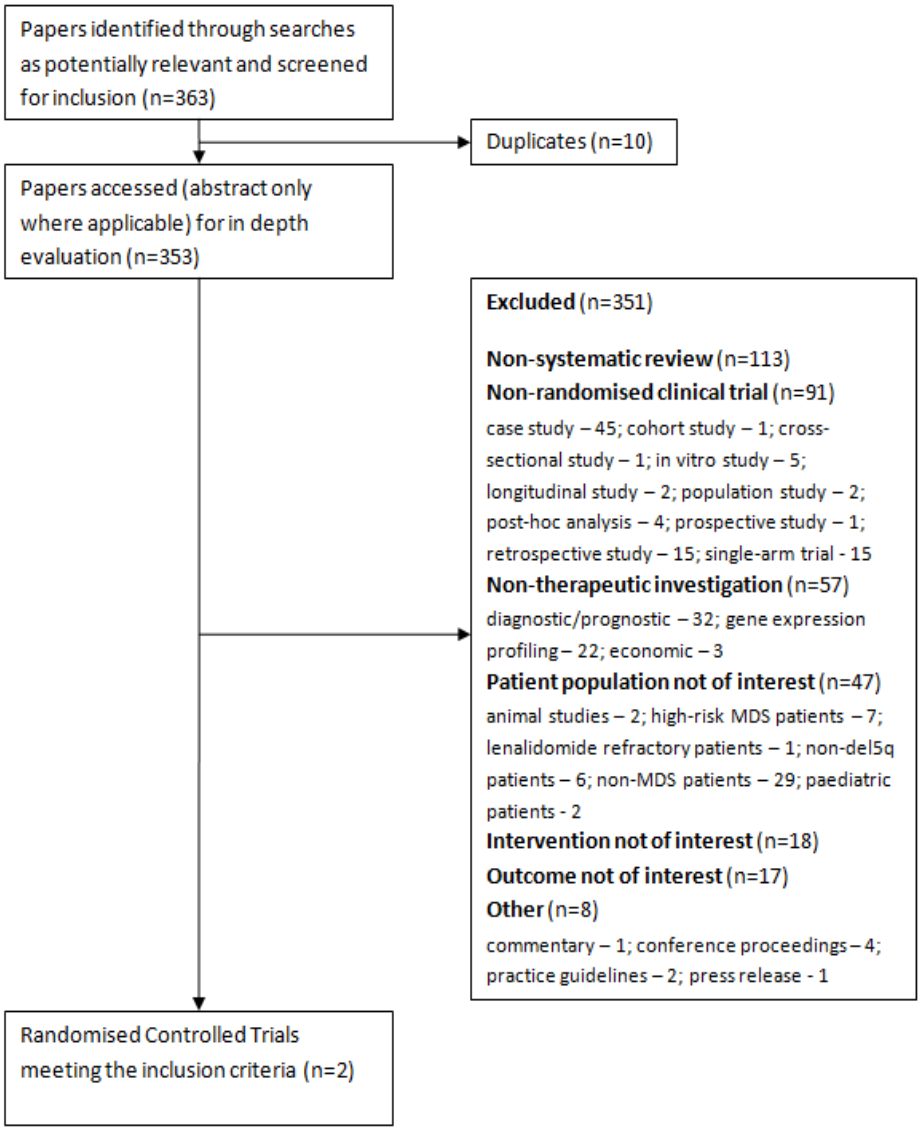
The types of clinical outcomes included were any of the following: frequency of blood transfusions; blood transfusion-independence; overall survival; progression-free survival (including time to transformation to AML; haematological response (including change from baseline in absolute neutrophil count [ANC], platelet count, hemoglobin level and haematopoietic cells evaluation); serious infections; adverse effects of treatment; HRQoL.

6.2.2. A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

A total of 363 potentially relevant papers were identified. After removing duplicates, 353 records remained (see Figure 3). Each of these papers was assessed for relevance by examination of the title and abstract. In cases where the information in the title or abstract was insufficient, the full text of the publication was obtained for

further examination. Of the 363 potentially relevant papers identified only two met the inclusion criteria (see Figure 3).[5]

Figure 3. Flow diagram of literature search process



6.2.3. When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

The review identified one relevant study of lenalidomide. This was an RCT that compared lenalidomide with placebo in patients with low- or intermediate-1-risk MDS with a del(5q) abnormality, whose condition was RBC transfusion-dependent.[5] While key results were reported in the journal article, a number of additional publications were identified that reported on secondary analyses of the original trial data. A list of these publications is shown in Table 4.[5]

Table 4. Secondary publications from original RCT data

Study	Author, year	Publication description	Main outcome reported
1	Sekeres, 2011[42]	Identification of predictive factors for overall survival in MDS patients treated with lenalidomide, using study data from MDS-004 and MDS-003 combined; n=286; abstract	List of the most important predictive factors that increase the risk of disease progression and death
2	Fenaux, 2009[43]	Preliminary results of primary and secondary outcomes at 52 weeks of study MDS-004.(Fenaux *et al*, 2011 reported results at median follow-up of 156 weeks); n=138; abstract	Primary and secondary outcomes at 52 weeks: RBC-TI ≥26 weeks; duration of TI, CyR (IWG 2000), progression to AML, and AEs
3	Fenaux, 2010[51]	Analysis of safety data from study MDS-004; n=138; abstract	Frequency, timing and management of lenalidomide-associaterd haematological AEs
4	Gohring, 2010[52]	Fluorescence R-banding and T/C-FISH analysis to determine telomere length in patients from MDS-003 and MDS-004 studies, to determine whether telomere shortening contributes to leukaemic progression in patients with MDS and del(5q); n=14; abstract	Telomere length at study entry and after treatment
5	Mufti, 2011[53]	Occurrence of trisomy 8 (8+) in patients in the MDS-004 study; n=205; abstract	Occurrence and effect on long-term outcomes of 8+ at baseline and after treatment with lenalidomide
6	Giagounidis, 2011[54]	Investigation of the effect of additional cytogenetic abnormalities on OS and AML progression in MDS-003 and MDS-004 patients; n=274; abstract	OS and AML progression by cytogenetic risk groups and transfusion independence in lenalidomide-treated patients
7	List, 2011[55]	Evaluation of predictive factors for durable RBC-TI in lenalidomide-treated patients (MDS-003 and MDS-004 combined); n=286; abstract	CyR evaluated by IWG criteria. RBC-TI for ≥8 weeks according to IWG criteria and RBC-TI for ≥26 weeks
8	Fenaux, 2010[51]	Identification of prognostic factors for AML-free survival and OS during lenalidomide-treatment in the MDS-004 study after prolonged follow-up; n=138; abstract	Median progression to AML and number of patients who died; also, prognostic factors for survival
9	Fenaux, 2010[51]	Description of the frequency, timing and management of lenalidomide-associated haematological AEs	Grade 3/4 AEs
10	Brandenburg, 2010[56]	Analysis of clinical and HRQoL data from the MDS-004 study	Reliability and validity of the FACT-AN score in patients with low or intermediate-1-Risk MDS with del(5q)

Key: AE = adverse events; AML = acute myeloid leukaemia; CyR = complete cytogenetic response; FACT-AN = Functional Assessment of Cancer Therapy-Anemia; HRQoL= health-related quality of life; IWG = International Working Group; OS = overall survival, RBC-TI = red blood cell-transfusion independence; T/C-FISH = telomere/centromere-fluorescence *in situ* hybridisation

Three other studies have also recently been identified. One was a published study in which the authors report HRQoL outcomes assessed using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) among 167 RBC transfusion-

dependent patients with IPSS Low-/Intermediate-1-risk del(5q)31 MDS treated with lenalidomide versus placebo in a randomised Phase 3 clinical trial, MDS-004.[57] The results of this study are similar to the HRQoL results reported in the main body of the MDS-004 trial (Section 6.5.3). That is, treatment with lenalidomide was shown to improve HRQoL; improvements were apparent at Week 12 and were significantly greater with lenalidomide (both 10 mg and 5 mg groups) than placebo. Specifically, in the Revicki study, mean baseline to 12 week changes in FACT-An total scores improved following treatment with lenalidomide 10 and 5 mg (+5.7 and +5.7, respectively) versus placebo (-2.8) (both $p < 0.05$). Clinically important changes in HRQoL from baseline were observed at Weeks 12, 24, 36 and 48 among RBC-transfusion independent ≥26 week responders in both treatment groups.

It should be noted that the Revicki study results differ from the trial results in two important ways. The Revicki paper reports data for the ITT population, whereas the trial reports HRQoL for the safety population. In addition, FACT-An scores were available for 81% of randomised patients in the Revicki study, while the trial only had available FACT-An scores for 71% of randomised patients.

The second was a study published online only so far, comparing long-term outcomes in lenalidomide-treated and untreated MDS patients with del(5q). The study evaluated clinical outcomes of 295 lenalidomide-treated patients from two clinical trials (MDS-003/MDS-004) and 125 lenalidomide-untreated RBC transfusion-dependent patients with del(5q) Low-/Int-1-risk MDS from a large multicentre registry.[15]

The third study was an abstract from the American Society of Haematology. The study examined lenalidomide treatment patterns and their association with reduced transfusion needs in a Medicare-enrolled population with MDS (n=23,855).[58]

Complete list of relevant RCTs

6.2.4. Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

The literature search identified two studies that appeared to be relevant to the decision problem. The key characteristics of both these studies are described in Table 5.

One RCT compared the intervention (lenalidomide) with placebo in the relevant patient group.[5] This study is clearly relevant to the decision problem and is the main focus of this submission of clinical evidence.

The second RCT assessed the effectiveness of growth factors, which are a component of best supportive care (comparator therapy) in patients with MDS. However, this relatively small study (n=30) enrolled mostly study subjects with MDS who were transfusion-independent (63.4%). Furthermore, only three patients (10%) had MDS with del(5q).[5] Given the way in which the data were presented it was not possible to determine the exact number of patients relevant to the decision problem: that is, patients with MDS associated with a del(5q) cytogenetic abnormality who were RBC dependent. This study will not be included in the main body of the submission but instead a brief description of the study and key results is provided in section 10.2.8, appendix 2.

Table 5. List of relevant RCTs[5]

Study	Intervention	N	Study duration*	Patient characteristics
Balleari *et al,* 2006	rHEPO 10,000 IU SC three times weekly	15	16 weeks	Low-risk MDS: n=30 (100%) 5q-syndrome: n=3 (10%) Transfusion-dependent: n=11 (36.7%)
	rHEPO 10,000 IU SC three times weekly + G-CSF 300 mg SC once- or twice-weekly	15		
Fenaux *et al,* 2011	Lenalidomide 10 mg on Days 1–21 (28-day cycle)	69	52 weeks	Low-risk MDS: n=205 (100%) 5q-syndrome: n=205 (100%) Transfusion-dependent: n=205 (100%)
	Lenalidomide 5 mg on Days 1–28 (28-day cycle)	69		
	Placebo on Days 1–28 (28-day cycle)	67		

Key: G-CSF = granulocyte colony-stimulating factor; MDS = myelodysplastic syndromes; rHEPO = recombinant human erythropoietin; SC = subcutaneously
* Double-blind phase

6.2.5. Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with

reference to the decision problem. If there are none, please state this.

Only the study by Fenaux *et al*[5] listed in Table 5 compared the intervention lenalidomide with an appropriate comparator (placebo) with reference to the decision problem. This study is described in detail in sections 5.3 and 5.4.

6.2.6. When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

The study by Balleari *et al*[59] (see Table 5) included a small subset of patients whose condition was possibly relevant to the decision problem. It will not be described in detail in section 5.3 or 5.4; rather, a summary of the study is included in section 10.2.8, appendix 2. The study is not further discussed in sections 5.3 and 5.4 because the data were presented in such a way that it was not possible to determine the exact number of patients relevant to the decision problem. It was reported that only three patients had MDS associated with a del(5q) cytogenetic abnormality; it is not possible to determine if those three patients were also transfusion dependent.

List of relevant non-RCTs

6.2.7. Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

No non-RCTs are included.

6.3. Summary of methodology of relevant RCTs

6.3.1. As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a

CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Background to studies

IPSS low- or intermediate-1-risk MDS with del(5q) cytogenetic abnormality is characterised by macrocytic anaemia and short response duration when treated with best supportive care, including erythropoiesis-stimulating agents (ESAs).[5] Anaemia negatively affects quality of life (QoL) and disease course.[5] RBC transfusion-dependence and subsequent iron overload are associated with poor outcomes in patients with MDS.[60,61]

The first dedicated MDS study, MDS-001, was an open label, Phase 1/2 clinical trial of 43 patients, 32 (74%) of whom were transfusion-dependent at study initiation, and 12 (28%) of whom had the del(5q) abnormality. Patients received one of three dosing regimens of lenalidomide – 10 mg daily, 25 mg daily, or 10 mg daily for 21 days of a 28-day cycle. Overall, a major erythroid response was seen in 49% of patients, and in 83% of those with a del(5q) abnormality.[5] This prompted two concurrent, single-arm Phase 2 studies of transfusion-dependent, lower-risk patients with MDS, either with (MDS-003, the registration trial) or without (MDS-002) the del(5q) lesion. The MDS-003 trial included 148 patients with the del(5q) abnormality. Most (73%) had failed on previous treatment with ESAs, and 74% had no additional cytogenetic abnormalities. Patients were treated with lenalidomide 10 mg daily for 21 or 28 days of a 28-day cycle. Sixty-seven per cent achieved transfusion independence, with a median duration of response of more than two years. Karyotype complexity, in patients with the del(5q) lesion, had no significant effect on the rate of transfusion independence (72%, 48% and 67% for patients with no, one, or two or more additional abnormalities, respectively). A complete cytogenetic response was achieved by 45% of evaluable patients.[3] In the MDS-002 study, 26% of patients became transfusion-independent – a much lower proportion than that observed in the del(5q) population in the MDS-003 study. The median duration of response was also lower, at 41 weeks, supporting a specific effect of the drug on the del(5q) clone.[5]

The 2011 Phase 3 study, which forms the main evidence base for this submission, was the first randomised, placebo controlled study of lenalidomide in MDS. This RCT (MDS-004) compared the efficacy and safety of lenalidomide (10 mg and 5 mg) against placebo in RBC transfusion-dependent patients with IPSS low- or intermediate-1-risk MDS with del(5q).[5]

The clinical data presented in sections 5.3, 5.4 and 5.5 are from the published journal article by Fenaux *et al,* 2011.[5] In sections where more detail is required, additional tables and text are taken from the full clinical study report for study MDS-004.[62]

MDS-004

Methods

6.3.2. Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

MDS-004 was a Phase 3, multicentre, randomised, double-blind, placebo controlled study that enrolled patients from 8 July 2005 to 26 June 2007 at 37 study sites in the UK, France, Germany, Italy, Spain, Belgium, Netherlands, Sweden and Israel.

Patients were randomly assigned in a 1:1:1 ratio (centrally using a validated interactive voice response system [IVRS]) to lenalidomide 10 mg/day on Days 1–21, lenalidomide 5 mg/day on Days 1–28, or placebo; all 28-day cycles. Patients were stratified according to IPSS karyotype score (0 versus >0; that is, isolated del(5q) abnormality versus del(5q)31 plus one or more additional cytogenetic abnormalities). The trial methodology is summarised in Table 6.[5]

The dose of lenalidomide or placebo was to be reduced if dose-limiting toxicities occurred, and complete blood counts were to be obtained weekly following the development of dose-limiting neutropenia or thrombocytopenia. Lenalidomide dosing was reduced as follows: lenalidomide 5 mg (starting dose), dose level −1 (5 mg every other day), dose level −2 (5 mg twice-weekly), and dose level −3 (5 mg weekly);

lenalidomide 10 mg (starting dose), dose level −1 (5 mg daily), dose level −2 (5 mg every other day), and dose level −3 (5 mg twice-weekly); patients not tolerating dose level −3 discontinued treatment. For Grade 4 neutropenia, lenalidomide was interrupted and resumed at the next dose level down when ANCs recovered to ≥500/µl. For Grade 4 thrombocytopenia, lenalidomide was interrupted and resumed at a decreased dose level when the platelet count recovered to ≥25,000/µl and <50,000/µl on two or more occasions for seven days or more; or ≥ 50,000/µl at any time. Granulocyte colony-stimulating factors (G-CSF) and granulocyte macrophage-colony stimulating factors (GM-CSF) were allowed for neutropenia.

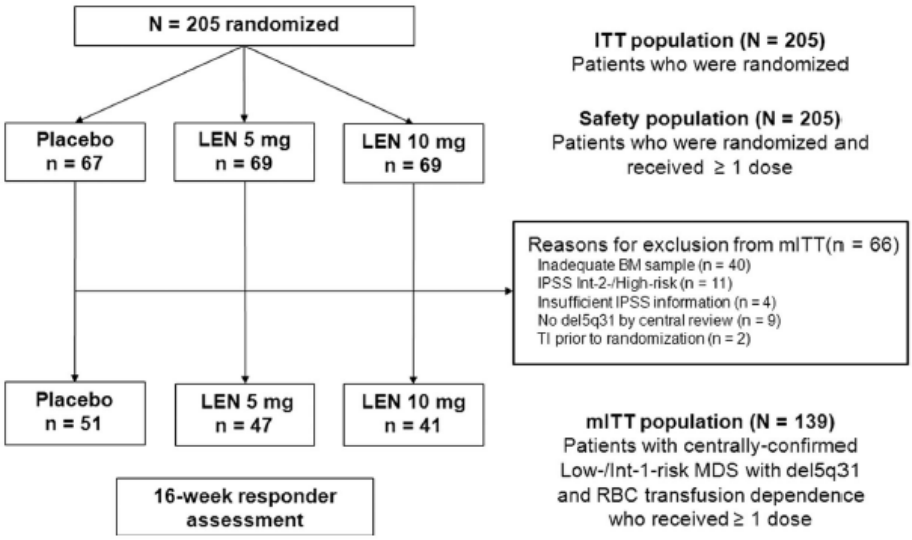
Table 6. Summary of methodology of the lenalidomide MDS-004 trial[5]

Location	Multicentre trial with participating centres in: UK, France, Germany, Italy, Spain, Belgium, Netherlands, Sweden and Israel
Design	Phase 3, randomised, double-blind, placebo controlled trial
Duration of study	Up to 52 weeks
Method of randomisation	Validated interactive voice response system
Method of blinding (care provider, patient and outcome assessor)	Not reported
Intervention(s) (n =) and comparator(s) (n =)	Lenalidomide 10 mg on Days 1–21: n=69 Lenalidomide 5 mg on Days 1–28: n=69 Placebo: n=67 (all 28 day cycles) Crossover from placebo to lenalidomide or higher lenalidomide dose allowed at 16 weeks
Primary outcomes (including scoring methods and timings of assessments)	Red blood cell transfusion-independence for ≥26 weeks
Secondary outcomes (including scoring methods and timings of assessments)	Erythroid response at 16 weeks, duration of red blood cell transfusion-independence, cytogenetic response at Weeks 12, 24 and every 24 weeks thereafter, OS, AML progression, safety, and HRQoL at Weeks 12, 24, 36, 48
Duration of follow-up	Median follow-up 1.55 years.

Key: AML = acute myeloid leukaemia; HRQoL = health-related quality of life; OS = overall survival

The 205 patients who were randomly assigned to receive lenalidomide 10 mg (n=69), lenalidomide 5 mg (n=69) or placebo (n=67) during the double-blind phase were included in the ITT and safety populations. A total of 139 patients were included in the mITT population (lenalidomide 10 mg, n=41; lenalidomide 5 mg, n=47; and placebo, n=51). Figure 4 outlines the reasons for exclusion from the mITT population.[5]

Figure 4. Study populations by randomised treatment group in the double blind phase[5]



Key: BM = bone marrow; IPSS = International Prognostic Scoring System; LEN = lenalidomide; mITT = modified intention-to-treat; RBC = red blood cell; TI = transfusion independence

Patients with at least a minor erythroid response (that is, a 50% decrease in transfusion requirements) by Week 16 were eligible to continue double-blind treatment for up to 52 weeks, or until erythroid relapse, disease progression or unacceptable toxicity. Those without minor erythroid response by Week 16 were discontinued from the double-blind phase, unblinded, and eligible for open label treatment. Those completing the double-blind phase without disease progression or erythroid relapse were unblinded and could start open label treatment at their current lenalidomide dose. Patients in the placebo or lenalidomide 5 mg groups without minor erythroid response by Week 16 or those experiencing erythroid relapse could crossover to lenalidomide 5 mg or 10 mg, respectively, in the open label extension phase. Open label treatment was continued for up to 156 weeks of total study participation. Patients with disease progression at any time and those randomly assigned to lenalidomide 10 mg without minor erythroid response by Week 16 were withdrawn from the study and were ineligible for open label treatment.[5]

Participants

6.3.3. Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the

eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Patients aged ≥18 years with investigator-documented IPSS low- or intermediate-1-risk MDS and del(5q), with or without additional cytogenetic abnormalities, and RBC transfusion-dependent anaemia (no eight consecutive weeks without RBC transfusions within the 16 weeks before randomisation) were included. Confirmation of del(5q) status (karyotype analysis) and bone marrow morphology was performed by central haematological review after randomisation.[5]

Exclusion criteria included: proliferative (white blood cell [WBC] count ≥ 12,000/µl) chronic myelomonocytic leukaemia; Grade ≥2 neuropathy; prior use of lenalidomide; treatment with recombinant erythropoietin (EPO), chemotherapy or any other investigational agent within 28-days or long-acting ESAs within eight weeks before study entry; and abnormal laboratory values (absolute neutrophil count [ANC] <500/µl, platelet count <25,000/µl, serum creatinine levels >2.0 mg/dl, serum transaminase levels more than three times the upper limit of normal [unless due to iron overload from blood transfusions], and serum total bilirubin concentration >1.5 mg/dl).[5]

6.3.4. Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Baseline patient characteristics of the mITT population were similar across treatment groups (see Table 7).[5]

Table 7. Baseline patient characteristics (mITT population)[5]

Characteristic	Placebo (n=51)	Lenalidomide 5 mg (n=47)	Lenalidomide 10 mg (n=41)	Overall (n=139)
Age, years: median (range)	70 (39–85)	66 (40–86)	68 (36–84)	69 (36–86)
Female sex, n (%)	41 (80.4)	37 (78.7)	28 (68.3)	106 (76.3)
Time since diagnosis, years: median (range)	2.4 (0.2–14.3)	2.8 (0.2–17.1)	2.5 (0.2–14.9)	2.7 (0.2–17.1)
Transfusion burden, units/8 weeks: median (range)	6 (4–12)	7 (1*–25)	6 (2–12)	6 (1*–25)
IPSS risk category (central review), n (%)				
Low	29 (56.9)	19 (40.4)	20 (48.8)	68 (48.9)
Intermediate-1	22 (43.1)	28 (59.6)	21 (51.2)	71 (51.1)
WPSS risk category, n (%)				
Very low	0	0	0	0
Low	2 (3.9)	7 (14.9)	2 (4.9)	11 (7.9)
Intermediate	33 (64.7)	23 (48.9)	26 (63.4)	82 (59.0)
High	15 (29.4)	17 (36.2)	13 (31.7)	45 (32.4)
Very high	0	0	0	0
Missing	1 (2.0)	0	0	1 (0.7)
FAB classification (central review), n (%)				
RA	35 (68.6)	32 (68.1)	28 (68.3)	95 (68.3)
RARS	8 (15.7)	5 (10.6)	8 (19.5)	21 (15.1)
RAEB	3 (5.9)	7 (14.9)	5 (12.2)	15 (10.8)
CMML	1 (2.0)	2 (4.3)	0	3 (2.2)
Other or missing	4 (7.8)	1 (2.1)	0	5 (3.6)
WHO classification, n (%)				
RA	6 (11.8)	7 (14.9)	2 (4.9)	15 (10.8)
RARS	2 (3.9)	0	2 (4.9)	4 (2.9)
RAEB-1	7 (13.7)	5 (10.6)	4 (9.8)	16 (11.5)
RAEB-2	1 (2.0)	2 (4.3)	1 (2.4)	4 (2.9)
RCMD	1 (2.0)	2 (4.3)	1 (2.4)	4 (2.9)
5q– syndrome	27 (52.9)	24 (51.1)	16 (39.0)	67 (48.2)
Unknown	5 (9.8)	7 (14.9)	14 (34.1)	26 (18.7)
Missing	2 (3.9)	0	1 (2.4)	3 (2.2)
EPO level, n(%)				
≤500 mIU/ml	21 (41.2)	13 (27.7)	14 (34.1)	48 (34.5)
>500 mIU/ml	24 (47.1)	24 (51.1)	21 (51.2)	69 (49.6)

Characteristic	Placebo (n=51)	Lenalidomide 5 mg (n=47)	Lenalidomide 10 mg (n=41)	Overall (n=139)
Missing	6 (11.8)	10 (21.3)	6 (14.6)	22 (15.8)
Prior EPO use, n (%)	24 (47.1)	24 (51.1)	24 (58.5)	72 (51.8)
Karyotype, n (%)				
Isolated del(5q)	38 (74.5)	35 (74.5)	33 (80.5)	106 (76.3)
del(5q) + ≥1additional abnormality**	13 (25.5)	12 (25.5)	8 (19.5)	33 (23.7)
ANC 0.5–1.0 x 10^9/l, n (%)	3 (5.9)	10 (21.3)	3 (7.3)	16 (11.5)
Platelet count, n(%)				
<150 x 10^9/l	8 (15.7)	11 (23.4)	8 (19.5)	27 (19.4)
25–50 x 10^9/l	0	1 (2.1)	1 (2.4)	2 (1.4)
≥150 x 10^9/l	43 (84.3)	36 (76.6)	33 (80.5)	112 (80.6)

Key: ANC = absolute neutrophil count; CMML = chronic myelomonocytic leukaemia; EPO = erythropoietin; FAB = French–American–British; IPSS = International Prognostic Scoring System; RA = refractory anaemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RCMD = refractory cytopenias with multilineage dysplasia; WPSS = WHO Prognostic Scoring System
* Only 2 patients had a transfusion burden of 1 unit/8 weeks
** 2 patients (3.9%) in lenalidomide 5 mg group and 3 (7.3%) in lenalidomide 10 mg group had del(5q) + ≥2 additional cytogenic abnormalities

Outcomes

6.3.5. Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Study endpoints

The primary endpoint was RBC transfusion independence for ≥26 consecutive weeks. Secondary endpoints included erythroid response, duration of RBC transfusion independence, cytogenetic response, overall survival (OS), AML progression, safety and HRQoL. Changes in haemoglobin levels were determined from baseline.[5]

Erythroid response was assessed using the IWG 2000[5] and 2006 criteria.[63] Duration of RBC transfusion-independence was defined (IWG 2000 criteria) as the number of days between the last transfusion before the start of the transfusion-independence period or the first dose of lenalidomide, whichever occurred later, and the first transfusion after the transfusion-independence period.[5]

Karyotyping (≥20 metaphases) and fluorescence *in situ* hybridisation (FISH; ≥100 cells evaluated) were performed. Cytogenetic response was assessed using the IWG 2000 criteria and was determined on the basis of karyotyping results.[5] OS was defined as time from randomisation to death from any cause. Time to AML progression was defined as the time from randomisation to diagnosis of AML (according to the French-American-British [FAB] criteria).[5] Disease progression to more advanced MDS subtypes is also presented. Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) and graded using the National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Patient-reported HRQoL was assessed using the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire,[5] which was administered at baseline, and Weeks 12, 24, 36 and 48.[5] Changes from baseline of ≥7 points on the FACT-An scale are associated with clinically important improvements in HRQoL.[5]

Appropriateness of measurements

Patients with MDS require long-term treatment with supportive therapies, and six-month durability of clinical response is considered a notable clinical outcome. Patients were to be treated and evaluated for up to 156 weeks in the MDS-004 trial.

The safety measures assessed were those routinely used in clinical studies evaluating the safety of investigational treatments for haematological malignancies.

The HRQoL instruments are accepted measures by which to assess the impact of anaemia-related symptoms, or their relief as a result of therapeutic intervention, on the quality of life of patients with MDS.[57]

Statistical analysis and definition of study groups

6.3.6. State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Definitions of study populations

The ITT population includes all study participants who were randomly assigned to one of the three study treatment arms. The mITT population includes all patients:

- With a documented diagnosis of MDS who met IPSS criteria for low- to intermediate-1-risk disease and had an associated del(5q) cytogenetic abnormality, confirmed by central review of an evaluable bone-marrow aspirate/optional biopsy
- With RBC transfusion-dependent anaemia, defined as not having a period of 56 days (two months) without a RBC transfusion within at least the immediate 112 days (four months) prior to Day 1 of the pre-randomisation phase
- Who have taken at least one dose of the study drug.[5]

The safety population includes all randomised patients who received a dose of study drug.[5]

Determination of sample size

Assuming response rates (RBC transfusion independence for ≥26 weeks) of 0.400 and 0.100 in the active treatment and placebo groups, respectively, a sample size of 45 patients per group (mITT population) and a two-group continuity corrected chi-square test with a 0.025 two-sided significance level (α split to adjust multiple

comparisons) has 80% power to detect differences between each active treatment group and placebo. Descriptive statistics were used to compare lenalidomide 10 mg and 5 mg; the study was not powered to detect differences between the lenalidomide groups. Initial enrolment for the study was 162 patients. On 8 June 2006, the target enrolment was expanded to 205 to ensure the prespecified number of evaluable patients (n=135).[5]

Statistical analysis

The Mantel–Haenszel procedure stratification on the IPSS karyotype score (0 versus >0) compared response rates for lenalidomide 10 mg and 5 mg versus placebo. For the primary endpoint, a stepwise modified Bonferroni procedure controlled the experiment error rate. Patients who discontinued double-blind treatment were considered treatment failures. For erythroid and cytogenetic responses, results are summarised by treatment group. Cytogenetic responses are the best post-baseline responses. Duration of response, AML progression and OS were characterised using Kaplan–Meier curves. Duration for time-to-event analyses was calculated from randomisation to the date of death or censoring (date of last contact), whichever was earliest. For the duration of RBC transfusion independence, data are included until the last date with available information on transfusions. This date is indicated as censored for patients who died or who remained RBC transfusion independent at data cut-off. Analysis of variance was used to analyse changes in haemoglobin concentration from baseline. Response rates were compared within prespecified subgroups of baseline serum or plasma EPO levels (≤500 versus >500 mIU/ml), and isolated del(5q) versus del(5q) plus at least one additional abnormality using a chi-square test. Analysis of variance was performed to compare changes in the FACT-An score from baseline at Week 12 in each lenalidomide group versus placebo. Longitudinal assessment of FACT-An scores to Week 48 for patients who achieved RBC transfusion independence for ≥26 weeks with lenalidomide is presented.[5]

A multivariate logistic regression model identified external factors that predict RBC transfusion-independence. A backward procedure eliminated the less significant (significance = $p<0.05$) factors to build the final logistic regression model. The following variables were used: treatment group (lenalidomide 10 mg versus placebo, lenalidomide 5 mg versus placebo); age (>65 versus ≤65 years); MDS duration (more than two years versus up to two years); centrally confirmed IPSS score (intermediate-1-risk versus low-risk); transfusion burden (more than four versus up to

four units/eight weeks); bone marrow blasts (≥5% versus <5%); baseline EPO level (>500 versus ≤500 mIU/ml); baseline platelet count (≥150 versus <150 x 10^9/l); and granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage CSF (GM-CSF) use (yes versus no). Age, MDS duration, and bone marrow blasts were also investigated as continuous variables.[5]

A Cox proportional hazard model was used to evaluate the effect of potential baseline risk factors and RBC transfusion independence for at least eight weeks (IWG 2000 criteria) on AML-free survival and OS, with RBC transfusion independence (for at least eight weeks) as a time-dependent covariate. A landmark analysis (six months) was performed to reduce potential bias regarding the fact that responding patients must have survived long enough to attain a response. Univariate Cox proportional hazard models first assessed each individual risk factor. Once potentially significant (p<0.15) risk factors were identified, a multivariate model simultaneously determined the most important prognostic variables using a backward elimination variable-selection approach (variables were eliminated until all remaining variables had a significance of p<0.15). These analyses included data through completion of the open label phase for patients randomly assigned to lenalidomide (dose groups combined); patients randomly assigned to placebo were excluded because all, except 11 patients, crossed over to lenalidomide 5 mg. Identification of prognostic factors for RBC transfusion independence and long-term outcomes was a predefined objective.[5]

Final data for the double-blind phase are presented for all endpoints except for duration of response, AML progression and OS, which include open label data up to data cut-off (9 July 2010; 156 weeks after last patient accrual).[5]

6.3.7. Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Prespecified examination of subgroups

The rates of remaining RBC transfusion free for 182 days or more were examined according to the following subgroups:

- Gender
- Age (≤65 years, >65 years)

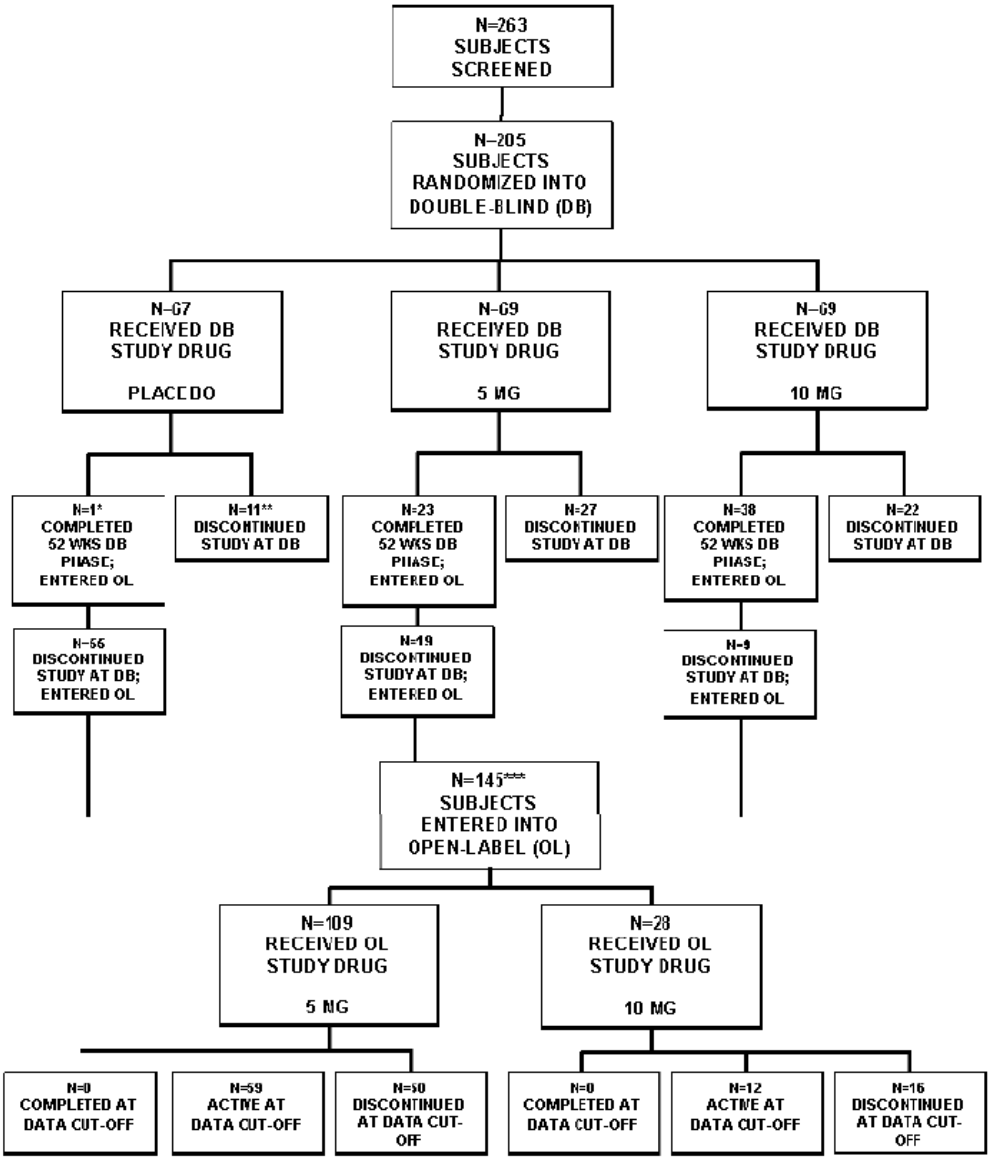
- FAB classification determined by investigator
- FAB classification determined by central haematology reviewer
- IPSS risk category determined by central reviews
- Years from MDS diagnosis to study entry (up to two years, more than two years)
- EPO category (≤500 mIU/ml, >500 mIU/ml)
- Cytogenetics – karyotype IPSS score (0, >0).[5]

Participant flow

6.3.8. Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

A total of 205 patients were enrolled in the study, with 67 being randomly assigned to the placebo arm, 69 to the lenalidomide 10 mg arm and 69 to the lenalidomide 5 mg arm. Patient disposition in the double-blind and open label treatment phases is illustrated in Figure 5 and summarised in Table 8 (double-blind phase) and Table 9 (open label phase).[5]

Figure 5. Disposition of patients through the double-blind and open label phases of MDS-004[62]



* Subject 0384005 completed 52 weeks of double-blind study drug and received 1 cycle of 5-mg open-label study drug.
** Subject 0014028 and 0344003 discontinued from the study after completing 52 weeks of double-blind study drug.
*** Of the 145 subjects who crossed over from DB to OL, seven (7) subjects were on drug holiday at the time of the cross-over and had not yet received a dose of OL study drug (as of the data cut-off 26 JUN 2008). One (1) additional subject (0374003) entered the open-label phase but had not yet taken their first dose of drug prior to the data cut-off.
NOTE: One subject (0014028) received (1) dose of 10-mg open-label study drug but was not entered into the open-label phase.

Double-blind treatment phase

A total of 205 patients were enrolled in the study, with 67 in the placebo arm and 69 each in the lenalidomide 10 mg and lenalidomide 5 mg arm. As of the 26 June 2008 data cut-off date, all 205 participants had completed/withdrawn from the double-blind phase of the study (and 145 [70.7%] had entered the open label extension phase). Table 8 summarises the patient disposition in the double-blind treatment phase.[62]

Table 8. Disposition of patients in the double-blind treatment phase by treatment regimen[62]

Disposition/ reason	**Placebo (n=67)**	**Lenalidomide 5 mg (n=69)**	**Lenalidomide 10 mg (n=69)**	**Overall (n=205)**
	n (%)	n (%)	n (%)	n (%)
Number of subjects in the ITT population	67	69	69	205
Subjects withdrawn from double-blind phase[a]	67 (100)	69 (100)	69 (100)	205 (100)
Primary reason for withdrawal from double-blind phase				
Lack of therapeutic effect	58 (86.6)	35 (50.7)	20 (29.0)	113 (55.1)
Relapse after erythroid response	1 (1.5)	1 (1.4)	1 (1.4)	3 (1.5)
Lack of erythroid response	53 (79.1)	31 (44.9)	18 (26.1)	102 (49.8)
Disease progression	4 (6.0)	3 (4.3)	1 (1.4)	8 (3.9)
Adverse event	2 (3.0)	6 (8.7)	4 (5.8)	12 (5.9)
Withdrawal of consent	2 (3.0)	1 (1.4)	3 (4.3)	6 (2.9)
Death	0 (0.0)	1 (1.4)	2 (2.9)	3 (1.5)
Protocol violation	1 (1.5)	0 (0.0)	0 (0.0)	1 (0.5)
Other[b]	4 (6.0)	26 (37.7)	40 (58.0)	70 (34.1)
Subjects entered into open label phase[a]	56 (83.6)	42 (60.9)	47 (68.1)	145 (70.7)

[a] Percentage calculated using the number of subjects in the double-blind intention-to-treat (ITT) population as the denominator
[b] Includes 64 subjects who completed the double-blind phase

The primary reasons for discontinuation in the overall population were lack of therapeutic effect (113 patients [55.1%]) and 'Other' (70 patients [34.1%], including 64 who completed the double-blind phase). The percentage of patients who discontinued due to lack of therapeutic effect decreased from 86.6% in the placebo arm to 29.0% in the lenalidomide 10 mg arm and 50.7% in the lenalidomide 5 mg arm. Conversely, the percentage of those who discontinued for 'Other' reasons (primarily completion of the double-blind phase) increased from 6.0% in the placebo arm to 58.0% in the lenalidomide 10 mg arm and 37.7% in the lenalidomide 5 mg

arm. The percentage of patients who discontinued the study as a result of AEs was low and similar across treatment groups (3.0% in the placebo arm, 5.8% in the lenalidomide 10 mg arm and 8.7% in the lenalidomide 5 mg arm). Note that the deaths only reflect those whose discontinuation page listed death as the reason for discontinuation from the study, and do not reflect the total number of deaths reported.[62]

Open label treatment phase

As of the 26 June 2008 data cut-off date, 145 study participants had entered the open label treatment phase; of those, 78 (53.8%) were still active and 67 (46.2%) had completed/withdrawn from the open-label treatment phase. The disposition of patients in the open label treatment phase is summarised in Table 9.[62]

Table 9. Disposition of subjects in the open label treatment phase by initial double-blind treatment regimen[62]

Disposition/ reason	No open label study drug (n=8)	Lenalidomide 5 mg (n=109)[a]	Lenalidomide 10 mg (n=28)	Overall (n=145)
	n (%)	n (%)	n (%)	n (%)
Number of subjects entered into open label phase	8	109	28	145
Subjects active in open label phase[b]	7 (87.5)	59 (54.1)	12 (42.9)	78 (53.8)
Subjects withdrawn from open label phase[b,c]	1 (12.5)	50 (45.9)	16 (57.1)	67 (46.2)
Primary reason for withdrawal from open label phase				
Lack of therapeutic effect	1 (12.5)	34 (31.2)	14 (50.0)	49 (33.8)
Relapse after erythroid response	0 (0.0)	17 (15.6)	4 (14.3)	21 (14.5)
Lack of erythroid response	0 (0.0)	6 (5.5)	9 (32.1)	15 (10.3)
Disease progression	1 (12.5)	7 (6.4)	1 (3.6)	9 (6.2)
Other	0 (0.0)	4 (3.7)	0 (0.0)	4 (2.8)
Adverse event	0 (0.0)	10 (9.2)	2 (7.1)	12 (8.3)
Withdrawal of consent	0 (0.0)	4 (3.7)	0 (0.0)	4 (2.8)
Death	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.7)
Other[b]	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.7)

[a] This includes all subjects who received a 5 mg dose regardless of regimen (eg once-daily, every other day, twice a week, etc)
[b] Percentage calculated using the number of subjects who entered the open label phase as the denominator
[c] The open label discontinuation CRF for subject 0014006 was not collected prior to database lock. as a result, this subject was not counted as withdrawn from open label

The 28 patients in the lenalidomide 10 mg arm included 13 who crossed over from the double-blind lenalidomide 5 mg arm. The 109 patients in the lenalidomide 5 mg arm included 56 who crossed over from the double-blind placebo arm. Of the eight patients who did not receive open label study drug, seven were on drug holiday at the time of the crossover and one had not yet taken their first dose of drug prior to the data cut-off point. The primary reason for discontinuation in the overall population was lack of therapeutic effect (49 patients [33.8%]). The percentage of patients who discontinued due to lack of therapeutic effect were 50.0% in the lenalidomide 10 mg arm and 31.2% in the lenalidomide 5 mg arm.

The percentage of patients who discontinued due to AEs was low and similar in both lenalidomide groups (7.1% in the 10 mg arm and 9.2% in the 5 mg arm). Again,

deaths only reflect subjects whose discontinuation page listed death as the reason for discontinuation from the study, and do not reflect the total number of deaths reported.[62]

6.4. Critical appraisal of relevant RCTs

6.4.1. The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2. Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

6.4.3. If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

A summary of the quality assessment of study MDS-004 is presented in Table 10. A complete quality assessment for the trial is included in section 10.3, appendix 3. MDS-004 was conducted as a double-blind study; therefore, subjects, investigators and staff, and Celgene Corporation clinical and medical representatives were unaware of treatment assignments, unless, in the opinion of the investigator, unblinding was absolutely needed to safely treat a patient. In such a case, unblinding was to occur via the IVRS. Study blister cards and bottles were labelled with the study number, patient number, visit number, expiry date, directions for use, sponsor address, and the warnings ‘Keep out of the reach of children’ and ‘For clinical trial use only’. Both study medication and placebo capsules were identical in appearance. Baseline characteristics were similar across patient groups.[5]

The mITT population was used to assess efficacy and included patients with centrally confirmed low- or intermediate-1-risk MDS with a del(5q) abnormality and documented RBC transfusion-dependence, who received more than one dose of study drug. The ITT population included patients randomly assigned to one of the study groups and was used to verify the mITT findings.[5]

Data as observed method was used to handle the missing data. The number and percentage of missing data were also presented in the tables. In the time-to-event analysis, the event which has not been observed was censored at the date of the last visit.[5]

Table 10. Quality assessment results for study MDS-004[62]

Question	Response
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in drop-outs between groups?	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes

6.5. Results of the relevant RCTs

6.5.1. Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2. The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3. For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.

- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Patients

The ITT and safety populations included the 205 patients who were randomly assigned to receive lenalidomide 10 mg (n=69), lenalidomide 5 mg (n=69) or placebo (n=67) during the double-blind phase. A total of 139 patients were included in the mITT population (lenalidomide 10 mg, n= 41; lenalidomide 5 mg, n=47; placebo, n=51). Duration of exposure data are presented in Table 11.[5]

Table 11. Duration of exposure by randomised treatment group (double-blind phase; safety population)[5]

Duration of exposure	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
≥4 weeks	63 (94.0)	67 (97.1)	63 (91.3)
≥8 weeks	62 (92.5)	62 (89.9)	59 (85.5)
≥16 weeks*	42 (62.7)	50 (72.5)	54 (78.3)
≥24 weeks	6 (9.0)	30 (43.5)	41 (59.4)
≥32 weeks	4 (6.0)	29 (42.0)	39 (56.5)
≥52 weeks	3 (4.5)	15 (21.7)	29 (42.0)

* The reduction in patient numbers after 16 weeks is the result of the crossover design of the study

Erythroid response

In the double-blind phase, significantly more patients in the mITT population achieved the primary endpoint (RBC transfusion independence for ≥26 weeks) with lenalidomide 10 mg (56.1%) and 5 mg (42.6%) than with placebo (5.9%; p<0.001 versus both lenalidomide groups). Using the IWG 2000 criteria (response fo ≥8 weeks), RBC transfusion independence rates in the mITT population were 61.0% with lenalidomide 10 mg, 51.1% with lenalidomide 5 mg, and 7.8% with placebo (p<0.001 for each comparison versus placebo). Similar results were found in the ITT population and using the IWG 2006 criteria (see Table 12).[64]

Table 12. Erythroid response, as assessed by RBC transfusion independence for ≥26 weeks or ≥8 weeks (double-blind phase; mITT and ITT populations)[5]

	RBC transfusion independence, n (%) [95% CI]		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	n=51	n=47	n=41
Protocol-defined (≥26 weeks)	3 (5.9) [1.2–16.2]	20 (42.6) [28.3–57.8]*	23 (56.1) [39.7–71.5]*
IWG 2000 (≥8 weeks)	4 (7.8) [2.2–18.9]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
IWG 2006 (≥8 weeks)	3 (5.9) [1.2–16.2]	24 (51.1) [36.1–65.9]*	25 (61.0) [44.5–75.8]*
ITT population	n=67	n=69	n=69
Protocol-defined (≥26 weeks)	4 (6.0) [1.7–14.6]	24 (34.8) [23.7–47.2]*	38 (55.1) [42.6–67.1]•
IWG 2000 (≥8 weeks)	5 (7.5) [2.5–16.6]	33 (47.8) [35.6–60.2]*	42 (60.9) [48.4–72.4]*
IWG 2006 (≥8 weeks)	4 (6.0) [1.7–14.6]	33 (47.8) [35.6–60.2]*	42 (60.9) [48.4–72.4]*

Key: CI = confidence interval; ITT = intention-to-treat, IWG = International Working group; mITT = modified ITT; RBC = red blood cell
p<0.001 versus placebo

Time to erythroid response

Among patients who achieved RBC transfusion independence for ≥26 weeks with lenalidomide (dose groups combined), onset of response occurred during Cycle 1 in 48.8% of patients, Cycle 2 in 37.2%, Cycle 3 in 9.3% and Cycle 4 in 4.7% of patients.

Duration of erythroid response

Median duration of IWG 2000-defined erythroid response (RBC transfusion independence for ≥8 weeks) was not reached in either lenalidomide group (see Figure 6), but the lower bound of the 95% confidence interval (CI) was 82.9 weeks with lenalidomide 10 mg and 41.3 weeks with lenalidomide 5 mg. Of these patients, 15 (60.0%) in the lenalidomide 10 mg group and 16 (66.7%) in the 5 mg group had ongoing responses and had been censored. Median duration of protocol-defined RBC transfusion independence (≥26 weeks) was not reached.[5]

Figure 6. Duration of IWG 2000-defined RBC-TI in patients randomly assigned to lenalidomide 10 mg or 5 mg (mITT population)[5]

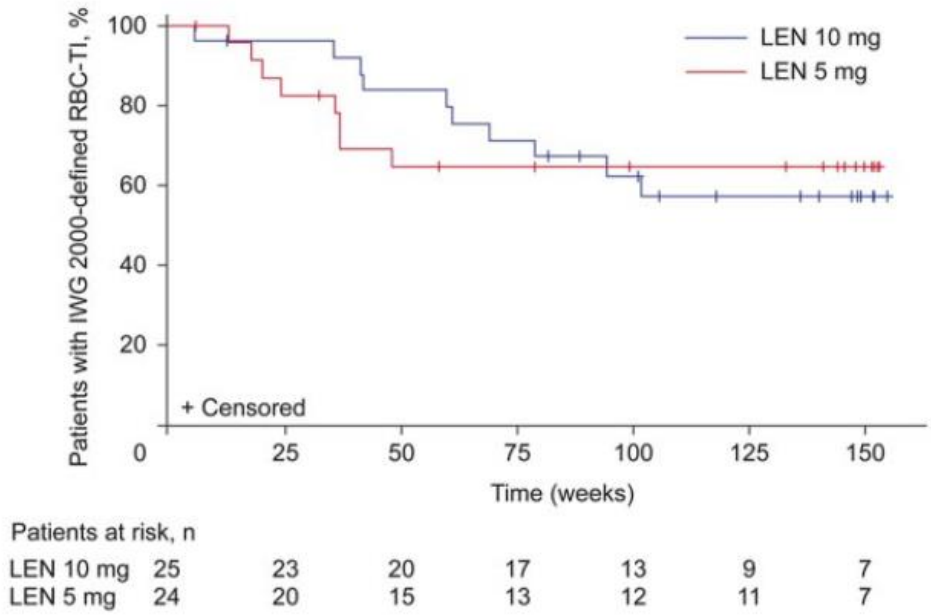
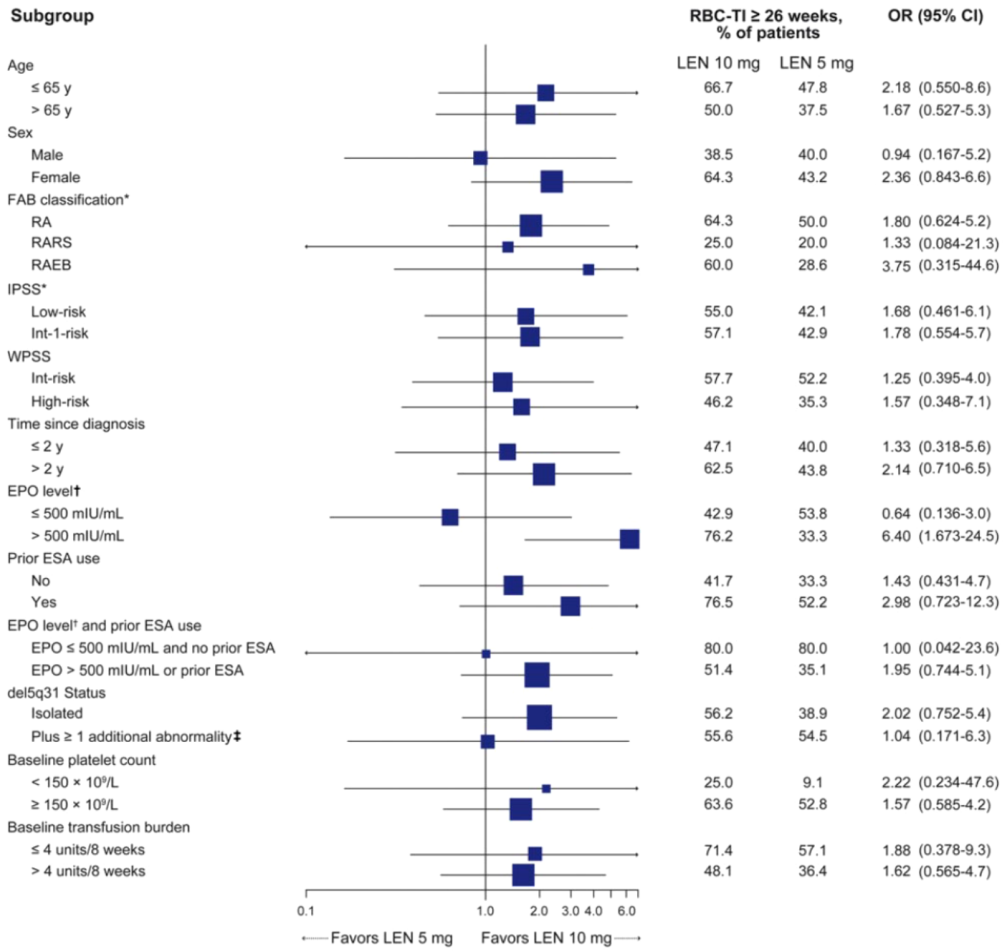


Figure represents patients who achieved RBC-TI during the double-blind phase of the study. For duration of RBC-TI, data are included until the last date with available information on transfusions. This date is indicated as censored for patients who died or who remain RBC-TI at data cut-off. Median duration of RBC transfusion follow-up for all treatment groups combined was 1.55 years (RBC transfusion follow-up for ≥1, ≥2 and ≥3 years was available for 85, 54, and 9 patients, respectively)
Key: IWG = international Working Group; LEN = lenalidomide; RBC-TI = red blood cell transfusion independence

Subgroup analysis of erythroid response (lenalidomide 10 mg versus 5 mg)

Rates of achievement of RBC transfusion independence for ≥26 week (mITT population) favoured lenalidomide 10 mg over 5 mg for most subgroups (see Figure 7). In 45 lenalidomide-treated patients with baseline EPO levels > 500 mIU/ml, the RBC transfusion independence rate was significantly higher with lenalidomide 10 mg than with 5 mg (76.2% versus 33.3%; p<0.004).[62]

Figure 7. Forest plot of subgroup analysis for achievement of RBC transfusion independence for > 26 weeks in patients randomised to lenalidomide 10 mg or 5 mg (mITT population)[62]



Horizontal bars represent 95% CI. * Based on central hematological review. † EPO level data were missing for 10 patients in 5 mg group and 6 patients in 10 mg group. ‡ Because of the small number of patients with del(5q) plus ≥2 additional abnormalities (n=5), this group was combined with the del(5q) plus 1 additional abnormality group to allow comparison with the isolated del(5q) group. Among the 5 patients randomised to lenalidomide with del(5q) plus ≥2 additional abnormalities,1 patient in the lenalidomide 5 mg group achieved RBC-TI for ≥26 weeks.
Key: CI = confidence interval; EPO = erythropoietin; ESA = erythropoiesis-stimulating agent; FAB = French–American–British; IPSS = International Prognostic Scoring System; LEN = lenalidomide; OR = odds ratio; RA = refractory anaemia; RAEB = RA with excess blasts; RARS = RA with ringed sideroblasts; RBC-TI = red blood cell transfusion independence; WPSS, WHO-based Prognostic Scoring System

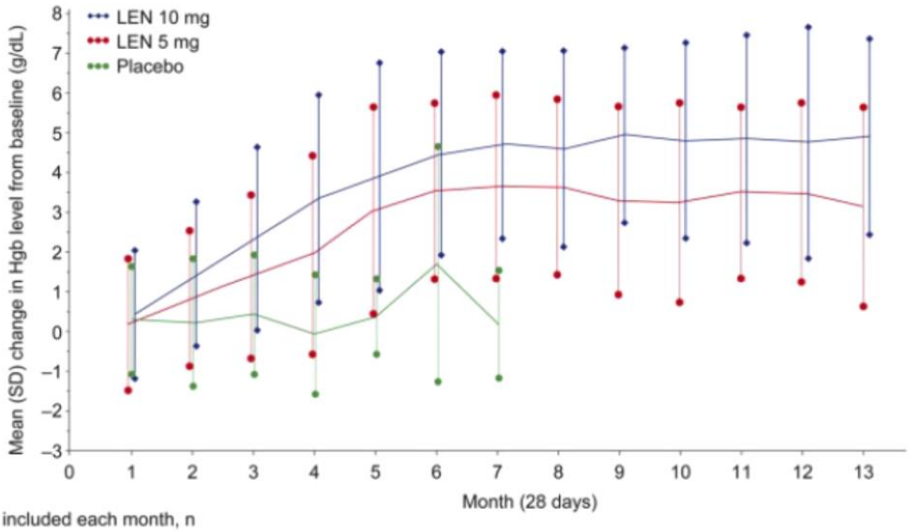
Predictors of erythroid response

A multivariate analysis based on a logistic regression model showed that factors significantly predictive of RBC transfusion independence for ≥26 weeks were lenalidomide treatment (p<0.0001 for lenalidomide 10 mg versus placebo; p=0.0004 for lenalidomide 5 mg versus placebo), higher baseline platelet count (≥150 x 10^9/l; p=0.003) and longer time since MDS diagnosis (two years or more; p=0.05).[62]

Change in haemoglobin levels

Figure 8 shows changes from baseline in haemoglobin levels (mITT population). Median maximum haemoglobin increases in patients who responded to lenalidomide (RBC transfusion independence for ≥8 weeks) were 6.3 g/dl (range 1.8–10.0 g/dl) with the 10 mg dose and 5.2 g/dl (range 1.5–8.5 g/dl) with the 5 mg dose.[62]

Figure 8. Mean haemoglobin change from baseline over time by randomised treatment group; mITT population[62]



Patients included each month, n

LEN 10 mg	40	38	38	36	29	26	24	24	24	24	23	23	18
LEN 5 mg	47	46	43	42	29	24	24	24	23	22	20	18	11
Placebo	51	50	49	47	7	5	4						

Data are mean ± standard deviation but were not calculated if the number of patients was ≤3.
Key: Hgb = haemoglobin; LEN = lenalidomide; SD = standard deviation

Cytogenetic response and progression

Cytogenetic response rates (complete plus partial) in the mITT population were 50.0% and 25.0% in the lenalidomide 10 mg and 5 mg groups, respectively (p=0.066). Complete cytogenetic response rates were 29.4% and 15.6% (p=0.29). No cytogenetic responses occurred in the placebo group (p<0.001 versus both lenalidomide groups). Cytogenetic progression (development of new independent clones as well as additional aberrations together with del[5q31]) was observed in eight of 34 patients treated with lenalidomide 10 mg (23.5%; p=0.50 vs placebo), ten of 32 treated with lenalidomide 5 mg (31.3%; p=0.17 vs placebo), and five of 35 patients receiving placebo (14.3%). Similar results were observed in the ITT population (data not shown). Median time to cytogenetic progression was 93 days (range 85–170 days) in the lenalidomide 10 mg group, 85 days (range 83–339 days)

in the lenalidomide 5 mg group, and 99 days (range 83–172 days) in the placebo group.[62]

HRQoL

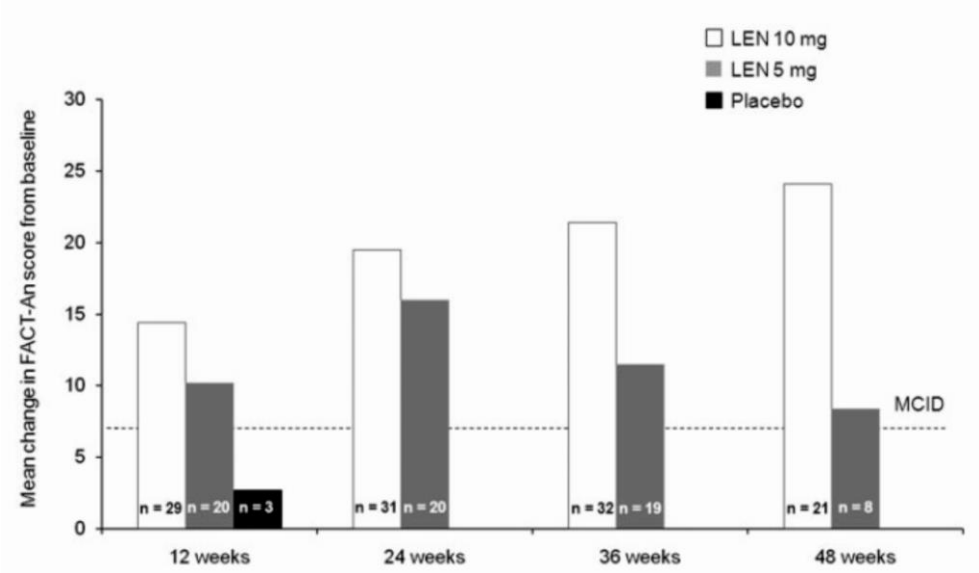
HRQoL outcomes were assessed using FACT-An among 167 RBC transfusion-dependent patients with IPSS Low-Intermediate-1-risk del(5q)31 MDS treated with lenalidomide versus placebo in the randomised Phase 3 clinical trial, MDS-004. Mean baseline to 12-week changes in FACT-An total scores improved following treatment with lenalidomide 5 mg and 10 mg (+5.7 and +5.7, respectively) versus placebo (−2.8) (both $p < 0.05$). Clinically important changes in HRQoL from baseline were observed at Weeks 12, 24, 36, and 48 among RBC-transfuction independent ⩾26 week responders in both treatment groups.

The lenalidomide treatment was associated with improvements in HRQoL compared with placebo during the initial 12 weeks of therapy. These HRQoL improvements were maintained in patients who remained on double-blind treatment with lenalidomide through 48 weeks of treatment. In addition, patients who switched from the placebo group to the lenalidomide 5 mg group after Week 12 also showed a clinically meaningful improvement in FACT-An scores. Because of the study design and missing data after Week 16, the double-blind and longitudinal results are descriptive and exploratory, yet they confirm those previously reported by Fenaux *et al* to the FACT-An TOI and subscale score outcomes.[64]

Baseline and Week 12 (that is, before crossover) FACT-An scores were available for 71% of randomly assigned patients (lenalidomide 10 mg, n=48; 5 mg, n=45; placebo, n=52). Baseline scores (mean ± standard deviation) were 121.1 ± 21.3, 124.8 ± 25.0, and 121.5 ± 28.0 among the lenalidomide 10 mg, 5 mg, and placebo groups, respectively. Mean change from baseline at Week 12 was significantly higher in the lenalidomide 10 mg (5.8 versus –2.5; $p<0.05$) and 5 mg (5.9 versus –2.5; $p<0.05$) groups than in the placebo group. Absolute change from baseline FACT-An scores exceeded 7 points (that is, minimal clinically important difference) among responders (RBC transfusion independence ≥26 weeks) at Weeks 12, 24, 36, and 48 in both lenalidomide groups (see Figure 9).[62]

Figure 9. Absolute change in FACT-An scores from baseline among patients who achieved transfusion independence for ≥26 weeks in the placebo group at

Week 12 (before crossover) and the lenalidomide 5 mg and 10 mg groups at Weeks 12, 24, 36, and 48; safety population[62]



Key: FACT-An = Functional Assessment of Cancer Therapy-Anaemia; LEN = lenalidomide; MCID minimal clinically important difference

Disease progression

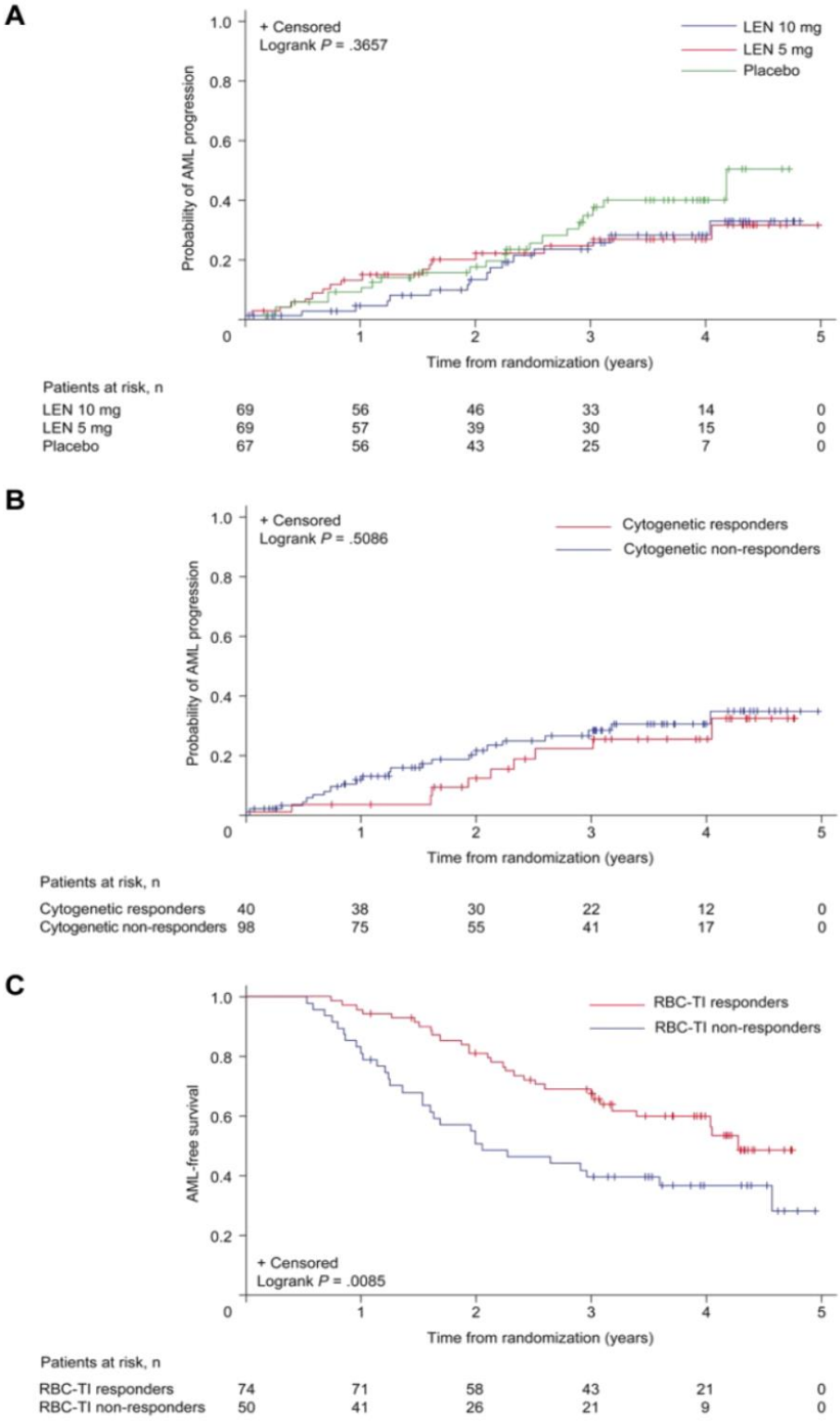
In the safety population, median duration of follow-up for AML progression (from date of randomisation to AML, death, or last known contact for non-AML survivors, whichever was earliest) was 30.9 months (range 2.1–56.5 months) in the placebo group, 36.1 months (range 0.4–57.7 months) in the lenalidomide 10 mg group and 31.8 months (range 0.8–59.4 months) in the lenalidomide 5 mg group. Before crossover at 16 weeks, two patients (3.0%) in the placebo group, none in the lenalidomide 10 mg group and two (2.9%) in the lenalidomide 5 mg group had progressed to AML. Overall, 52 patients (25.4%) progressed to AML during the double-blind and open label phases. Of 11 patients who were randomly assigned to placebo and never received lenalidomide, including three patients who completed 52 weeks of the study protocol, four (36.4%) progressed to AML; 17 of 56 patients (30.4%) who initially received placebo and then crossed over to lenalidomide 5 mg progressed to AML, as did 16 of 69 patients (23.2%) in the lenalidomide 5 mg group and 15 of 69 patients (21.7%) in the lenalidomide 10 mg group. Among patients with documented baseline del(5q) status, 33 of 135 (24.4%) patients with isolated del(5q) abnormality, eight of 38 (21.1%) patients with del(5q) plus one additional abnormality and eight of 17 (47.1%) patients with del(5q) plus two or more additional abnormalities progressed to AML. Median time to progression was not reached in the lenalidomide groups (see Figure 10 Part A). Cumulative risk of AML for the

lenalidomide dose groups combined was 16.8% (95% CI 9.8–23.7) at two years and 25.1% (95% CI 17.1–33.1) at three years.[62]

Figure 10 Part B shows time to AML progression by cytogenetic response in patients randomly assigned to lenalidomide. Lenalidomide responders (RBC transfusion independence for ≥8 weeks) had longer AML-free survival than non-responders (six-month landmark analysis; p=0.0085; see Figure 10 Part C). Time to AML progression was similar between patients included in and excluded from the mITT population (p=0.3149).[62]

During the double-blind phase, three patients (4.5%) in the placebo group, two (2.9%) in the lenalidomide 10 mg group and two (2.9%) in the lenalidomide 5 mg group progressed from refractory anaemia (RA) to RA with excess blasts (RAEB), one patient progressed from RAEB in transformation to AML (placebo group), and one from RAEB to AML (lenalidomide 5 mg group).[62]

Figure 10. Time to AML progression; safety population[62]



Results are presented (A) by randomised treatment group, (B) by cytogenetic response (complete plus partial) in patients randomly assigned to lenalidomide, and (C) by a landmark (six-month) analysis of AML-free survival by RBC transfusion independence for ≥8 weeks in patients randomly assigned to lenalidomide. The placebo group includes 56 patients (83.6%) who had not achieved at least a minor response by Week 16 and therefore crossed over to lenalidomide 5 mg

Key: AML = acute myeloid leukaemia; LEN = lenalidomide; RBC-TI = red blood cell transfusion independence

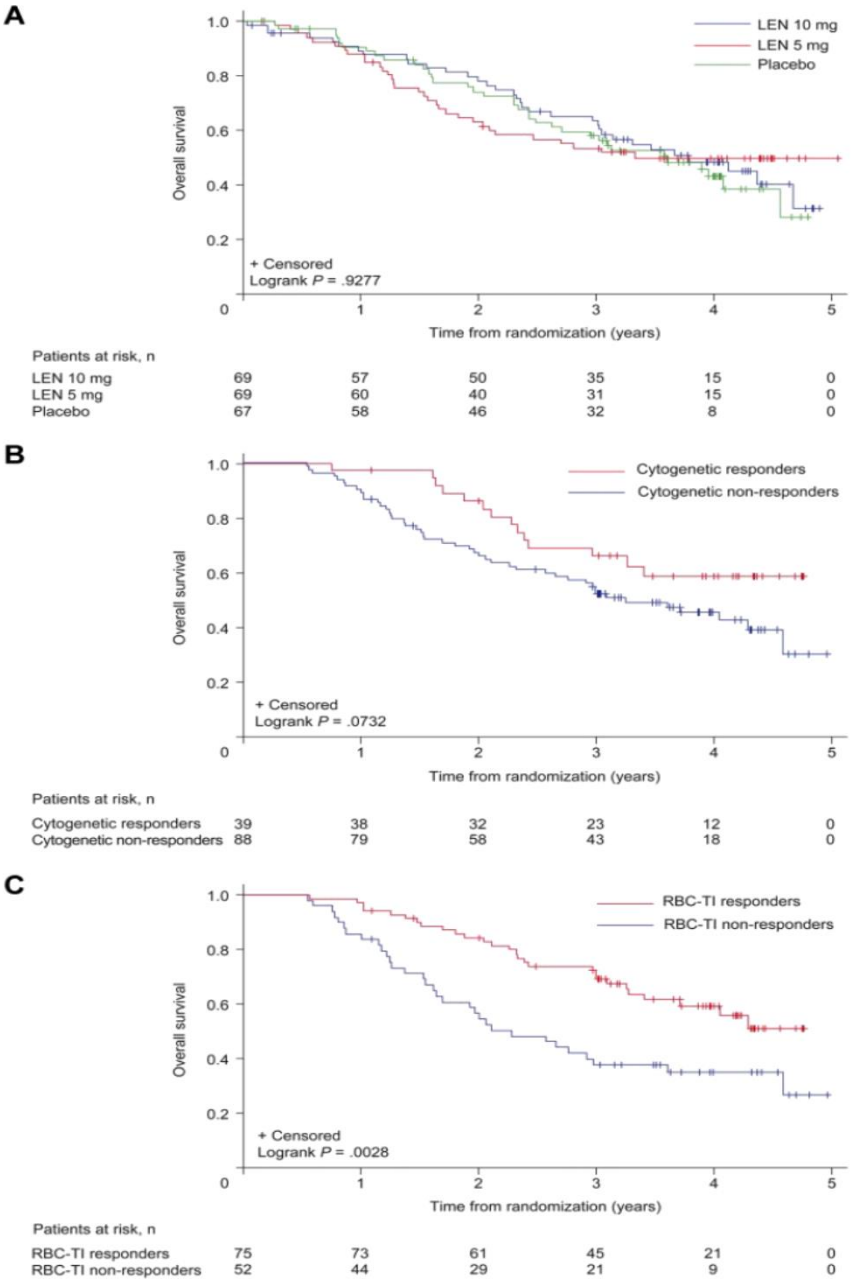
Survival

The median duration of OS follow-up was 35.9 months (range 2.1–56.5 months) in the placebo group, 36.9 months (range 0.4–57.7 months) in the lenalidomide 10 mg group and 35.5 months (range 1.9–59.4 months) in the lenalidomide 5 mg group. At data cut-off, 101 patients had died, including ten patients within 30 days of their last dose: four of 67 (6.0%) in the placebo group (infection, disease progression, myocardial infarction), four of 69 (5.8%) in the lenalidomide 10 mg group (cerebral haemorrhage because of MDS progression, septic shock [two cases], AML), and two of 69 (2.9%) in the 5 mg group (pulmonary embolism [PE], pneumonia). The case of PE was suspected by the investigator to be related to lenalidomide; the patient had a previous history of a PE, developed leukaemia, and had deep vein thrombosis and a PE in the setting of acute leukaemia.[62]

Median length of OS was 42.4 months (95% CI 31.9 to not reached), ≥35.5 months (95% CI 24.6 to not reached), and 44.5 months (95% CI 35.5 to not reached) in the placebo, lenalidomide 5 mg and 10 mg groups, respectively (see Figure 11 Part A). Three-year OS for the lenalidomide groups combined was 56.5% (95% CI 49.5–63.4%).[62]

OS was similar between patients included in and excluded from the mITT population (p=0.9218). Figure 11 also shows landmark (six-month) analyses of OS by cytogenetic response (see Part B) and by RBC transfusion independence for ≥8 weeks (see Part C).[62]

Figure 11. Duration of overall survival; safety population[62]



Results are presented A) by randomised treatment group, by landmark (six-month) analyses of overall survival, (B) by cytogenetic response (complete plus partial), and (C) by RBC transfusion independence (≥8 weeks) in patients randomly assigned to lenalidomide. The placebo group includes 56 patients (83.6%) who had not achieved at least a minor response by Week 16 and therefore crossed over to lenalidomide 5 mg.
Key: LEN = lenalidomide; RBC-TI = red blood cell transfusion independence

Cox proportional hazards model for AML-free survival and overall: six-month landmark analysis

The Cox proportional hazards model showed that in the combined lenalidomide groups, RBC transfusion independence for ≥8 weeks was associated with a 42%

reduction in the relative risk of AML progression or death (p=0.048) and a 47% reduction in the relative risk of death (p=0.021; see Table 13). Higher baseline ferritin levels, older age and higher transfusion burden were associated with a significantly increased risk of AML progression or death.[62]

Table 13. Cox proportional hazards model for AML-free survival and overall survival in patients randomised to lenalidomide: six-month landmark analysis; safety population[62]

Variables	Hazard ratio (95% CI)			
	Univariate model		Final model	
	AML-free survival	Overall survival	AML-free survival	Overall survival
Age, years*	1.02 (1.00–1.05) p=0.047	1.03 (1.00–1.05) p=0.018	1.04 (1.01–1.06) p=0.011	1.04 (1.01–1.07) p=0.003
Time since diagnosis, years	1.02 (0.97–1.08) p=0.448	1.02 (0.96–1.08) p=0.607	–	–
Transfusion burden, units/8 weeks*	1.09 (1.01–1.17) p=0.030	1.10 (1.03–1.18) p=0.004	1.08 (1.00–1.16) p=0.055	1.09 (1.02–1.17) p=0.011
Bone marrow blasts, %	1.04 (0.96–1.12) p=0.335	1.05 (0.97–1.13) p=0.233	–	–
No.of cytopenias (2 or 3 vs 1)	0.97 (0.57–1.64) p=0.900	0.95 (0.56–1.61) p=0.855	–	–
Platelet count, x 10^9/l	1.00 (1.00–1.00) p=0.059	1.00 (1.00–1.00) p=0.032	–	–
ANC, x 10^9/l	1.00 (0.91–1.09) p=0.922	1.00 (0.91–1.09) p=0.951	–	–
Haemoglobin level, g/dl	0.93 (0.70–1.23) p=0.612	0.95 (0.72–1.25) p=0.709	–	–
del(5q) + ≥1 additional abnormality vs isolated del(5q)	1.47 (0.85–2.55) p=0.169	1.22 (0.70–2.14) p=0.485	–	–
EPO level, 100 mIU/ml	0.99 (0.97–1.01) p=0.539	0.99 (0.97–1.01) p=0.390	–	–
Ferritin level, mol/l	1.01 (1.00–1.02) p=0.011	1.01 (1.00–1.02) p=0.014	1.01 (1.00–1.02) p=0.020	1.01 (1.00–1.02) p=0.019
WPSS risk (high/very high vs low/intermediate	1.40 (0.77–2.52) p=0.271	1.30 (0.73–2.33) p=0.377	–	–
RBC-TI for ≥8 weeks (yes vs no)*	0.51 (0.30–0.85) p=0.009	0.47 (0.28–0.78) p=0.003	0.58 (0.33–0.99) p=0.048	0.53 (0.31–0.91) p=0.021

Key: – = not significant; ANC = absolute neutrophil count; CI = confidence interval; EPO = erythropoietin; RBC-TI = red blood cell transfusion independence; WPSS = WHO Prognostic Scoring System

Variables are baseline, except for RBC-TI for ≥8 weeks, which is a time-dependent covariate of the six-month landmark analysis. Variables are continuous except for number of cytopenias, del(5q), WPSS and RBC-TI for ≥8weeks

* Statistically significant (p=0.05 variables in the final model)

6.6. Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1. The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

6.6.2. If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

A meta-analysis was not appropriate for this submission. The Phase 3 study, which forms the main evidence base for this submission, is the first randomised, placebo-controlled study of lenalidomide in patients with MDS.[62]

6.6.3. If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact

that each exclusion has on the overall meta-analysis should be explored.

Not applicable.

6.7. Indirect and mixed treatment comparisons

Data from head-to-head RCTs should be presented in the reference-case analysis, if available. If data from head-to-head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1. Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

A mixed treatment comparison was not an appropriate analysis for the purposes of this submission. The literature search identified only one RCT of the intervention, lenalidomide, and only one small study of a comparator treatment (best supportive care) relevant to the decision problem.[62]

6.7.2. Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Not applicable.

6.7.3. Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table XX. Summary of the trials used to conduct the indirect comparison

No. trials		Intervention	Comparator B	Comparator C	Comparator D
1	Trial 1	✓		✓	✓
1	Trial 2		✓	✓	✓
2	Trial 3 Trial 4	✓	✓		
1	Trial 5	✓		✓	
Etc.	Etc.	Etc.			
Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900					

6.7.4. For the selected trials, provide a summary of the data used in the analysis.

Not applicable

6.7.5. Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Not applicable

6.7.6. Please present the results of the analysis.

Not applicable

6.7.7. Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Not applicable

6.7.8. If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Not applicable

6.7.9. Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable

6.8. Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1. If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

No non-RCTs were considered relevant for the purposes of this submission.

6.9. Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1. If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

Not applicable

6.9.2. Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Table 14. Adverse events across randomised groups

Adverse event category[a]	Placebo (n = 67)		Lenalidomide 5 mg once-daily (n = 69)		Lenalidomide 5 mg once-daily (n = 69)	
Subjects with at least 1 AE	63	(94.0)	69	(100.0)	69	(100.0)
Subjects with at least 1 AE related to study drug	33	(49.3)	68	(98.6)	66	(95.7)
Subjects with at least 1 NCI CTCAE Grade 3–4 AE	29	(43.4)	62	(89.9)	65	(94.2)
Subjects with at least 1 related NCI CTCAE Grade 3–4 AE	13	(19.4)	61	(88.4)	61	(88.4)
Subjects with at least 1 SAE	14	(20.9)	28	(40.6)	31	(44.9)
Subjects with at least 1 SAE related to study drug	1	(1.5)	17	(24.6)	13	(18.8)
Subjects with an AE leading to discontinuation of study drug	3	(4.5)	11	(15.9)	6	(8.7)
Subjects with an AE leading to dose reduction or interruption	4	(6.0)	43	(62.3)	50	(72.5)

Key: AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

a A subject with multiple occurrences of an AE (preferred term using MedDRA dictionary version 5.1) is counted only once in the AE category.

6.9.3. Give a brief overview of the safety of the technology in relation to the decision problem.

Brief summary of adverse events

An overview of all treatment-emergent adverse events (AEs) is presented in Table 15. All treatment-emergent AEs were reported in a significantly higher percentage of lenalidomide-treated patients than placebo-treated patients. All patients in both lenalidomide groups reported at least one treatment-emergent AE. Similar percentages of patients in the 10 mg and 5 mg lenalidomide group had at least one AE related to study drug, at least one NCI CTCAE Grade 3 or 4 AE, at least one NCI

CTCAE Grade 3 or 4 AE related to study drug, at least one serious AE and at least one serious AE related to study drug. While a higher percentage of patients in the 10 mg group had at least one AE leading to dose reduction or interruption, a smaller percentage of patients in this group actually discontinued due to AEs.[62]

Table 15. Overview of adverse events (double-blind safety population)[62]

AE category*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
Patients with ≥1 AE	63 (94.0)	69 (100.00)	69 (100.0)
Patients with ≥1 AE related to study drug	33 (49.3)	68 (98.6)	66 (95.7)
Patients with ≥1 NCI CTCAE Grade 3–4 AE	29 (43.3)	62 (89.9)	65 (94.2)
Patients with ≥1 related NCI CTCAE Grade 3–4 AE	13 (19.4)	61 (88.4)	62 (88.4)
Patients with ≥1 SAE	14 (20.9)	28 (40.6)	31 (44.9)
Patients with ≥1 SAE related to study drug	1 (1.5)	17 (24.6)	13 (18.8)
Patients with an AE leading to discontinuation of study drug	3 (4.5)	11 (15.9)	6 (8.7)
Patients with an AE leading to a dose reduction or interruption	4 (6.0)	43 (62.3)	50 (72.5)

Key: AE = adverse event; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SAE = serious adverse event
* A patient with multiple occurrences of an AE (preferred term using Medical Dictionary for Regulatory Activities version 5.2) is counted only once in the AE category

Drug-related AEs

Drug-related treatment-emergent AEs reported by ≥10% of patients in any treatment group are summarised in Table 16, by descending incidence in the lenalidomide 10 mg group.[62]

Table 16. Drug-related adverse events reported in 10% or more of patients by treatment regimen; double-blind safety population[62]

System Organ Class/ preferred term*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
Patients with ≥1 AE	33 (49.3)	68 (98.6)	66 (95.7)
Blood and lymphatic System disorders			
Neutropenia	10 (14.9)	52 (75.4)	52 (75.4)
Thrombocytopenia	2 (3.0)	27 (39.1)	33 (47.8)
Leukopenia NOS	2 (3.0)	9 (13.0)	5 (7.2)
Gastrointestinal disorders			
Diarrhoea NOS	8 (11.9)	13 (18.8)	13 (18.8)
Constipation	2 (3.0)	7 (10.1)	9 (13.0)
General Disorders and Administration Site Conditions			
Fatigue	1 (1.5)	5 (7.2)	7 (10.1)
Musculoskeletal and Connective Tissue disorders			
Muscle cramp	3 (4.5)	9 (13.0)	5 (7.2)
Skin and Subcutaneous Tissue Disorders			
Pruritus	0 (0.0)	11 (15.9)	18 (26.1)
Rash NOS	1 (1.5)	10 (14.5)	3 (4.3)

Key: AE = adverse event; NOS not otherwise specified
* System Organ Class and preferred term are coded using the Medical Dictionary for Regulatory Activities version 5.2, and are listed in descending order of frequency for the 10 mg lenalidomide column. A patient with multiple occurrences of an AE counted only once in the AE category

Overall, the percentage of patients with drug-related AEs was similar in the two lenalidomide groups and was higher in those groups than in the placebo group. At least one drug-related AE was reported in 33 (49.3%) of the 67 patients in the placebo group, in 66 (95.7%) of the 69 patients in the lenalidomide 10 mg group and in 68 (98.6%) of the 69 patients in the lenalidomide 5 mg group.[62]

The drug-related AEs that were reported with the highest incidence (≥20% of the patients in any group) were:

- Blood and lymphatic system disorders: neutropenia (14.9% in the placebo group, and 75.4% in each of the lenalidomide groups) and thrombocytopenia (3.0% in the placebo group, 39.1% in the lenalidomide 5 mg group and 47.8% in the lenalidomide 10 mg group)

- Skin and subcutaneous tissue disorders: pruritus (0% in the placebo group, 15.9% in the lenalidomide group 5 mg and 26.1% in the lenalidomide 10 mg group).[62]

The percentage of drug-related AEs reported in <10% of the patients in any treatment group was generally similar in the two lenalidomide groups and higher in those groups than in the placebo group. Most of the drug-related AEs that occurred in <10% of the lenalidomide-treated patients were not reported in any of the patients receiving placebo.[62]

Grade 3 and 4 AEs

Treatment-emergent Grade 3 or 4 AEs reported by ≥2% of the patients in any treatment group are summarised in Table 17, by descending incidence in the placebo group. Overall, the percentage of patients who had Grade 3 or 4 AEs was similar inthe two lenalidomide groups and higher in those groups than in the placebo group. At least one Grade 3 or 4 AE was reported in 29 (43.3%) of the 67 patients in the placebo group, in 62 (89.9%) of the 69 patients in the lenalidomide 5 mg group and in 65 (94.2%) of the 69 patients in the lenalidomide 10 mg group.[62]

Table 17. Grade 3 or 4 adverse events reported in ≥2% of patients by treatment regimen; double-blind safety population[62]

System Organ Class/ preferred term*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69),n (%)
General Disorders and Administration Site Conditions			
Fatigue	1 (1.5)	0 (0.0)	2 (2.9)
Fall	0 (0.0)	1 (1.4)	2 (2.9)
Pyrexia	0 (0.0)	0 (0.0)	2 (2.9)
Infections and Infestations			
Pneumonia NOS	1 (1.5)	1 (1.4)	3 (4.3)
Investigations			
ALT increased	0 (0.0)	2 (2.9)	1 (1.4)
Metabolism and Nutritional Disorders			
Haemochromatosis	2 (3.0)	3 (4.3)	1 (1.4)
Musculoskeletal and Connective Tissue disorders			
Back pain	0 (0.0)	1 (1.4)	2 (2.9)
Respiratory, Thoracic and Mediastinal Disorders			
Dyspnoea NOS	2 (3.0)	1 (1.4)	2 (2.9)
Bronchitis NOS	(0 (0.0)	0 (0.0)	2 (2.9)
Pulmonary embolism	0 (0.0)	2 (2.9)	2 (2.9)
Skin and Subcutaneous Tissue Disorders			
Pruritus	0 (0.0)	0 (0.0)	2 (2.9)
Rash NOS	0 (0.0)	3 (4.3)	0 (0.0)
Vascular disorders			
Deep vein thrombosis	1 (1.5)	1 (1.4)	4 (5.8)

Key: AE = adverse event; ALT = alanine aminotransferase; NOS not otherwise specified
* System Organ Class and preferred term are coded using the Medical Dictionary for Regulatory Activities version 5.2, and are listed in descending order of frequency for the 10 mg lenalidomide column. A patient with multiple occurrences of an AE counted only once in the AE category

Deaths

The causes of death (up to the data cut-off date of 26 June 2008) for patients who died within ≤30 days of the last dose of study drug are summarised in Table 18.[62]

Table 18. Deaths that occurred during the study or within 30 days after the last dose of study drug; double-blind safety population[62]

Patient number	Age / sex	Date of last dose (study day)	Date of death (study day)	Cause of death
Starting dose assignment: placebo				
0014018	52/ Female	Unk Mar 2006 (82)	13 Apr 2006 (104)	Adult Respiratory Distress Syndrome
0044002	68 / Male	15 May 2007 (516)	17 May 2007 (518)	Adult Respiratory Distress Syndrome
Starting dose assignment: lenalidomide 5 mg				
0014014	64 / Female	13 Mar 2006 (141)	17 Mar 2006 (145)	Thrombosis – pulmonary embolism
0124003	79 / Female	20 Sep 2006 (38)	22 Sep 2006 (40)	Aspiration pneumonia
Starting dose assignment: lenalidomide 10 mg				
0014021	84 / Female	19 Apr 2006 (35)	17 May 2006 (63)	Progressive worsening of general condition –precise cause unknown
0054001	68 / Female	10 Mar 2006 (54)	28 Mar 2006 (72)	Cerebral haemorrhage due to progression of MDS
0214006	82 / Female	05 Jul 2006 (10)	07 Jul 2006 (12)	Septic shock (respiratory origin)
0264002	76 / Female	05 Nov 2007 (176)	27 Nov 2007 (198)	AML

Key: AML = acute myeloid leukaemia; MDS = myelodysplastic syndromes

Most of the deaths, across all three treatment groups, were caused by ‘Respiratory, Thoracic, and Mediastinal Disorders’ (System Organ Class term). Eight (3.9%) deaths occurred during the study or within 30 days of receiving study drug. Of those, two (3.0%) deaths occurred in the placebo group, two (2.9%) in the lenalidomide 5 mg group and four (5.8%) in the lenalidomide 10 mg group.[62]

AEs leading to discontinuation of study drug

Table 19 summarises the treatment-emergent AEs that led to discontinuation of the study drug in at least two patients in any treatment group.[62]

Table 19. Adverse events leading to discontinuation of therapy reported in two or more patients by treatment regimen; double-blind safety population[62]

System Organ Class/ preferred term*	Placebo (n=67), n (%)	Lenalidomide 5 mg (n=69), n (%)	Lenalidomide 10 mg (n=69), n (%)
Patients with ≥1 AE leading to discontinuation of study drug	3 (4.5)	11 (15.9)	6 (8.7)
Blood and Lymphatic System Disorders			
Neutropenia	0 (0.0)	4 (5.8)	1 (1.4)

Key: AE = adverse event
* System Organ Class and preferred term are coded using the Medical Dictionary for Regulatory Activities version 5.2, and are listed in descending order of frequency for the placebo column. A patient with multiple occurrences of an AE counted only once in the AE category

At least one AE leading to discontinuation of study drug was reported in three (4.5%) of the patients in the placebo group, in six (8.7%) of those in the lenalidomide 10 mg group and in 11 (15.9%) of the patients in the lenalidomide 5 mg group. The most frequently reported AE that led to discontinuation of study medication was neutropenia: four (5.8%) patients in the lenalidomide 5 mg group. All other AEs leading to discontinuation were reported in a maximum of two patients in any treatment group.[62]

In addition, AML (not otherwise specified [NOS]) led to discontinuation of study drug by one patient in the placebo group and each of the lenalidomide groups, and leukaemia (NOS) led to discontinuation of study drug by one patient in the lenalidomide 5 mg group.[62]

6.10. Interpretation of clinical evidence

6.10.1. Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

The main evidence base for this submission is the Phase 3, double-blind, placebo controlled trial (the MDS-004 study). This trial assessed the efficacy and safety of lenalidomide in 205 transfusion-dependent patients with IPSS low- or intermediate-1-risk MDS associated with a del(5q) cytogenetic abnormality. Patients received lenalidomide 10 mg/day on Days 1–21 (n=69) or 5 mg/day on Days 1–28 (n=69) of a

28-day cycle, or placebo (n=67). Crossover to lenalidomide or to a higher dose was allowed after 16 weeks.

More patients in the lenalidomide 10 mg and 5 mg groups achieved RBC transfusion independence for ≥26 weeks (primary endpoint) than in the placebo group (56.1% and 42.6% versus 5.9%; both p<0.001). Median duration of RBC transfusion independence was not reached (median follow-up 1.55 years), with 60–67% of responses ongoing in patients without progression to AML.

Cytogenetic response rates (complete and partial) were 50.0% and 25.0% in the lenalidomide 10 mg group and the lenalidomide 5 mg group, respectively (p=0.066). For the two lenalidomide groups combined, three-year OS and AML risk were 56.5% and 25.1%, respectively. RBC transfusion independence for ≥8 weeks was associated with 47% and 42% reductions in the relative risks of death and AML progression or death, respectively (p=0.021 and p=0.048).

Treatment with lenalidomide was shown to improve HRQoL; improvements were apparent at Week 12 and were significantly greater with lenalidomide (both 10 mg and 5 mg groups) than placebo. Notably, longitudinal assessment among responders (RBC transfusion independence for ≥26 weeks) demonstrated clinically meaningful improvements in HRQoL up to Week 48.

Treatment was discontinued because of AEs in 8.7% of patients in the lenalidomide 10 mg group, 17.4% in the 5 mg group and 4.5% in the placebo group. The overall incidence of deep vein thrombosis (DVT) in the MDS-004 trial was 3.6% with lenalidomide (10 mg dose, four patients, 5.8%; 5 mg dose, one patient, 1.4%) versus 1.5% with placebo, consistent with the MDS-003 study (10 mg dose, five patients, 3%). Therefore, lenalidomide monotherapy does not appear to be thrombogenic in lower-risk MDS patients with a del(5q) abnormality.[5]

In conclusion, in the Phase 3, randomised, placebo controlled MDS-004 study in patients with IPSS low- or intermediate-1-risk MDS with a del(5q) abnormality, both lenalidomide doses (10 mg and 5 mg) resulted in significant RBC transfusion independence and cytogenetic responses and were generally well tolerated with a manageable safety profile. RBC transfusion independence was durable and was associated with improvements in haemoglobin levels and HRQoL and reduced risk of death. There was no obvious increase in AML progression with lenalidomide

treatment, but continued follow-up is needed. Anticipation of haematological AEs and use of dose modifications and supportive care as needed should help achieve optimal clinical benefit from lenalidomide. Lenalidomide 10 mg was associated with a better erythroid response rate in patients with increased EPO levels (In 45 lenalidomide-treated patients with baseline EPO levels >500 mIU/ml, the RBC transfusion independence rate was significantly higher with lenalidomide 10 mg versus 5 mg (76.2% versus 33.3%; p=0.004).) a trend toward a higher cytogenetic response rate (50.0% versus 25.0%; p=0.066) and more durable HRQoL improvements, without increasing the incidence of AEs. These findings support the use of a starting dose of 10 mg, with subsequent dose reductions or interruptions if needed.[5]

6.10.2. Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

The MDS-004 trial is the first randomised, placebo controlled study to evaluate two doses of lenalidomide in a predominantly elderly patient population, and provides the opportunity to further examine the efficacy and safety profile of lenalidomide in lower-risk MDS patients with a del(5q) abnormality.[5] Results from this study have proved consistent with previous reports.[3]

Improved karyotyping (with FISH analysis for del(5q)) can lead to better diagnosis and prognostic stratification in lower-risk MDS.[5] Detection of a del(5q) abnormality provides a clear treatment option. The National Comprehensive Cancer Network in the USA recommends that those patients with del(5q) chromosomal abnormalities and symptomatic anaemia should receive lenalidomide.[38]

Lenalidomide does not just treat the symptoms; it targets the cause of the malignancy and changes the course of the disease. In the treatment of patients with lower-risk MDS, there is a shift away from supportive care and towards altering the natural history of the disease.[65] By modifying the disease, lenalidomide provides rapid and long-lasting transfusion independence. The onset of an erythroid response occurred by Cycle 2 in 86% of patients. The median time to transfusion independence was 4.6 weeks with lenalidomide 10 mg. Median duration of

transfusion independence was not reached, but is likely to exceed two years in lenalidomide-treated patients.[5]

Achieving long-term transfusion independence with lenalidomide increases overall survival and reduces the risk of AML progression. Achievement of RBC transfusion independence for ≥26 weeks was associated with significantly longer overall survival ($p<0.0001$),[42] a 45% reduction in the relative risk of AML progression ($p=0.022$) and a 51% reduction in the relative risk of death ($p=0.008$).[43]

Achieving long-term transfusion independence with lenalidomide also increases patients' QoL.[5] It is thought that this is directly related to a reduction in hospital visits and in treatments for infections.[5]

AEs and toxicities with lenalidomide are predictable and easy to manage. Grade 3–4 cytopenias may occur during early treatment cycles but decrease thereafter.[5] This allows treatment to continue for improved long-term outcomes. Often, concerns about side-effects and toxicity in the elderly mean that disease-modifying agents are not used early in the treatment pathway.[5] Active treatment of lower-risk MDS is often not initiated until evidence of disease progression is seen, even though 85% of patients with lower-risk MDS die before they progress to AML.[5]

Limitations

It has been noted that crossover from placebo to lenalidomide in the MDS-004 study confounded the ability of the trial to assess the effect of the drug on overall survival or on transformation to AML.[42] Furthermore, Fenaux *et al* point out that continued follow-up is needed to determine if lenalidomide treatment is associated with AML progression.[5]

However, a recent combined analysis of the MDS-003 and MDS-004 studies in 286 lenalidomide-treated patients with MDS del(5q) demonstrated that cytogenetic responses impacted on clinical outcomes. Achievement of cytogenetic response was associated with significantly lower overall survival ($p<0.0001$), and risk of AML progression appeared to be higher in non-responding patients ($p=0.0517$).[42]

Median follow-up duration for OS was 38.4 months (range 0.3–81.9 months) in MDS-003 and 36.1 months (range 0.4–59.4 months) in MDS-004. The analysis showed

that transfusion independence after treatment with lenalidomide was associated with increased OS and reduced risk of AML progression.[42]

6.10.3. Please 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.

Most patients with MDS require blood transfusions due to chronic anaemia. Apart from the acute risks associated with transfusions, chronic anaemia and RBC transfusion dependence impact negatively on survival and quality of life. Therefore, the major goal of treatment is to achieve transfusion independence and maintain the patient's quality of life. The objective of this Single Technology Appraisal is to evaluate the clinical effectiveness of lenalidomide within its licensed indication for the treatment of MDS associated with a del(5q) cytogenetic abnormality in people with RBC transfusion dependence. The MDS-004 study is the only RCT of lenalidomide that specifically enrolled such patients. The primary endpoint was RBC-transfusion independence for ≥26 consecutive weeks. Secondary endpoints included erythroid response, duration of RBC-transfusion independence, cytogenetic response, OS, AML progression, safety and HRQoL. Changes in haemoglobin levels were determined from baseline. The FACT-An assessment which has good reliability and validity in patients with low- or intermediate-1-risk MDS with a del(5q) abnormality is a relevant measure of HRQoL outcomes. In the MDS-004 RCT, the FACT-An scores were responsive to changes in hameoglobin levels, demonstrating the ability to detect patient-reported longitudinal changes in HRQoL associated with changes in underlying disease status.[56] Results from this study show that patients on lenalidomide met all the study endpoints. Lenalidomide provides significant clinical benefit across the spectrum of del(5q) MDS, with or without other cytogenetic abnormalities.[64]

6.10.4. Identify any factors that may influence the external validity 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 patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The MDS-004 study was designed and conducted at the request of the FDA to refine the lenalidomide dosing schedule. The lenalidomide doses for this study (10 mg and 5 mg) were selected based on the results of Phase 2 studies (CC-5013-MDS-001 and CC-5013-MDS-003), which showed that a dose of 10 mg once-daily was a safe and effective initial dose regimen, when administered either daily for 21-of-28 day cycles, or for 28-of-28 day cycles. The 10 mg dose using the 21-of-28 day cycle was chosen because Grade 4 neutropenia was reported less frequently with this regimen, while the RBC-transfusion independence rate was still comparable to that for the 28-of-28 day cycle regimen (Study MDS-003). The lower 5 mg dose (using the 28-of-28 day cycle) was included to refine the dosing schedule and determine whether this lower starting dose/regimen would be sufficient to provide adequate benefit, with potentially lesser toxicity. Currently, the most frequent schedule of utilisation of lenalidomide in MDS patients is 21/28 days, with comparable efficacy results with the 28/28-day schedule.

Erythropoiesis-stimulating agents (ESAs) are not approved for patients with transfusion-dependent, IPSS low- or intermediate-1 (INT-1)-risk MDS with del(5q). Based on the data available to date, the nature of the proposed indication is such that patients treated with transfusion-dependent anemia and IPSS low- or INT-1-risk MDS with del(5q) constitutes a population of patients who are unlikely to benefit from further treatment with ESAs.

Currently in the EU no drug is approved for patients with transfusion-dependent, IPSS low- or INT-1-risk MDS with del(5q). However, it is acknowledged that ESAs have been used for patients with IPSS lower-risk MDS with del(5q).[66]

The majority of subjects enrolled in MDS-003 (72.9%) and in MDS-004 (52.7%) had received prior ESAs. Of the 138 lenalidomide-treated subjects in MDS-004, 74 (53.6%) subjects had received prior ESA treatment with or without G-CSF and at the time of enrolment. Also, endogenous EPO levels were measured in most subjects in MDS-004, and 52% of lenalidomide subjects were documented to have

baseline levels >500 mIU/ml. Overall, 77.6% (159/205) of MDS-004 study subjects had received prior ESA treatment and/or had a baseline EPO level >500 mIU/ml.

Thus, these subjects with advanced disease, significant transfusion burdens, often with high endogenous EPO levels as well as prior history of ESA treatment, would not be expected to respond well to further treatment with ESAs, but did commonly respond well to lenalidomide.

7. Cost effectiveness

7.1. Published cost-effectiveness evaluations

Identification of studies

7.1.1. Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

A comprehensive systematic review was designed and implemented to identify all relevant economic studies. Search strategies were designed with reference to the decision problem as set out in the final scope for this appraisal. Full details of the systematic review can be found in section 10.10, ppendix 10.

Description of identified studies

7.1.2. Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

A total of 398 potentially relevant cost-effectiveness searches were identified. Following the removal of duplicates and a review of the titles and abstracts, six studies remained that met the inclusion criteria. Summary information regarding these studies is provided in the table below. Only one of these studies has some limited relevance to the decision-problem. The other five studies have not, either because they were not cost-effectiveness studies or because the interventions included were not specified in the current decision problem.

Table 20. Key characteristics of included studies

Lead author	Year	Country(ies)	n	Patient group	Type of information
Gidwani[67]	2012	US	n/a	MDS	Cost-effectiveness Markov model tracking hypothetical cohorts of MDS patients treated with azacyutidine or decitabine
El Ouagari[68]	2011	Canada	n/a	Low or int-1 risk MDS	Comparing cost-effectiveness of deferasirox with s no chelation therapy in TD patients
Kuhne[69]	2010	Germany	116	TD MDS low/int-1 risk	Economic burden
Lafeuille[70]	2008	USA	3,312	MDS	Cost of treatment with Epoetin Alfa and Darbepoetin Alfa
Goss[71]	2006	USA	n/a	Low/Int-1 risk transfusion dependent MDS associated with del-5q	Decision analytic model to compare costs and outcomes of lenalidomide with BSC
Casadevall[72]	2004	France	60	MDS & anaemia	Cost and QOL (FACT-An) for ESA+G-CSF patients vs standard care

Goss *et al* developed a decision analytic model using data from MDS-003 trial data (n = 148) for the treatment of low orintermediate-1 risk, TD MDS patients. Health state descriptions were developed based on published literature and reports from MDS patient focus group discussions. The authors then assessed QOL by conducting health utility interviews with a group of MDS patients. These interviews used the TTO method to value the health states on a scale anchored on 1 (perfect health) and 0 (death). The health states developed were TI, RT, TD and death.[71]

The model incorporated medical resources such as drugs, transfusions, and laboratory tests along with office visits and other health care resources. Based on MDS-003 data, the model assumed that a transfusion included 2 units of RBCs and 0.18 units of platelets during treatment. Additionally, estimates for the utilisation of iron chelation treatment by transfusion-dependency status were taken from the study

and the proportions were applied in each arm of the mode. Utilisation of EPO and G-CSF treatment in the best supportive care (BSC) group was taken from the Nordic study but were slightly modified in the model calculation to reflect the standard US practice (weekly dose of 40,000 IU EPO and 300 µg G-CSF).[73] The model assumed that all patients received EPO treatment as part of their care even if they did not become TI.

The model did not go on to adjust for any differences in outcomes associated with del-5q syndrome, since just 11 patients had this disease status in the 'Nordic MDS Group' (the source of BSC data alongside the placebo arm of a randomised Phase II trial; THAL-001).

In the base case 67% of lenalidomide patients were TI compared to 8.9% of BSC patients. This led to 0.61 and 0.08 TI years respectively. QALYs gained were 0.78 and 0.53 in the lenalidomide and BSC arms, respectively. The total annual treatment cost was modelled to be US$63,385 for lenalidomide, compared with US$54,940 for BSC. The annual cost of transfusions was US$7,574 and US$18,101 for patients treated with lenalidomide and BSC, respectively. Incremental cost TI year gained of lenalidomide compared to BSC was US$16,066. Incremental cost per QALY gained was US$35,050.

One-way sensitivity analyses tested assumptions on pre-treatment transfusion requirement, health utility associated with TI, TI rate with EPO, and TI rate with lenalidomide. Results were most sensitive to patients' pre-treatment annual transfusion requirements (13–17 transfusions per year) and the proportion of patients treated with lenalidomide who were TI (63%–71%), which saw the ICER range from around US$30,000 to US$40,000. The probability of cost effectiveness of lenalidomide compared to BSC exceeded 50% at cost-effectiveness thresholds over US$35,000 and was 100% at a US$50,000 threshold.

However, it is unlikely, that the one year time horizon analysed is sufficient to determine the true cost effectiveness of lenalidomide, with a relationship between transfusion dependence and decreased survival likely.

7.1.3. Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated

instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

See section 10.11, appendix 11.

7.2. De novo analysis

Patients

7.2.1. What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? 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? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

A *de novo* economic evaluation was conducted and included the patient population from the pivotal trial for Lenalidomide in MDS del5(Q) – MDS-004.[64] The population from this clinical trial reflects that of the expected license indication.

There are two analysis populations in the MDS-004 trial: intention to treat (ITT) and modified intention to treat (MITT). The ITT population consists of all trial subjects, whereas MITT is a subgroup of all patients with a documented low- to intermediate-1-diagnosis of MDS, red blood cell (RBC) transfusion-dependent anemia and at least one dose of the study drug taken. Efficacy data for both of these are reported in the trial report; however the ITT population more closely matches the relevant NICE scope and this data is used in the base case. Using the MITT population reduces the available pool of data substantially and no significant difference is observed in key endpoints between trial arms.

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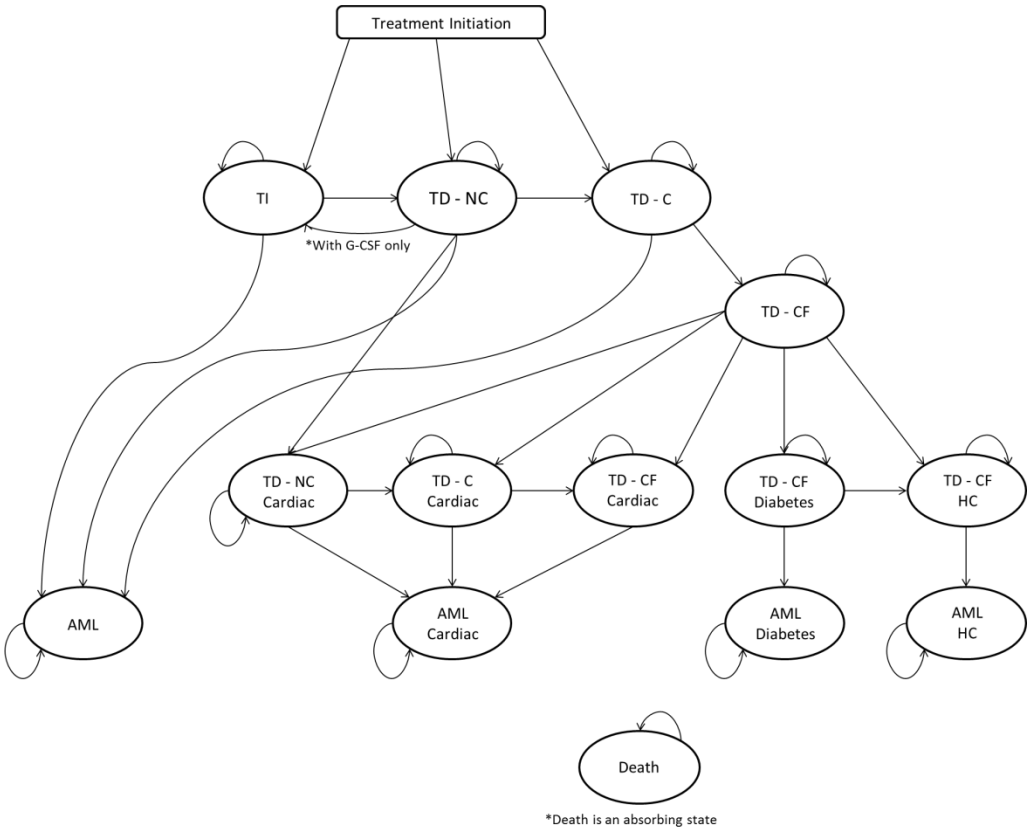
[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Model structure

7.2.2. Please provide a diagrammatical representation of the model you have chosen.

Figure 12. Model structure



TI = transfusion independent, TD = Transfusion dependent, NC = No chelation, C = Chelation, CF = Chelation Failure, Cardiac = cardiac disease, Diabetes = Diabetes, AML = acute myeloid leukemia, HC = Hepatic conditions.

7.2.3. Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

The model was developed in MS Excel using a Markov Cohort based methodology. A schematic of the model is presented in 7.2.2. The model structure has been chosen to capture the key features of MDS (Section 2.1 and Section 2.5). There are 3 key features to treatment of MDS associated with a deletion (del) 5q and these are reflected by the model:

1. A patient's transfusion requirements, i.e. whether they are transfusion independent or transfusion dependent, the latter subject to increased risk of cardiac disease;

2. Whether a patient requires iron chelation, following a certain number of RBCs and thus is at risk of other complications;
3. Whether a patient has progressed to acute myeloid leukemia (AML).

The model is primarily based on data from the MDS-004 trial, which is supplemented by data from the literature and clinical opinion.

7.2.4. Please define what the health states in the model are meant to capture.

The model consists of 14 health states as shown in Table 21. These health states were selected based upon the 3 key clinical features of MDS in 7.2.3. The complications associated with transfusion dependency and iron chelation included within the model (cardiac, hepatic and diabetes) were selected based upon the relevant adverse events detailed in Section 2.5.

Table 21. Health state descriptions

Health state	Description
TI	Transfusion independence – no requirement for red blood cell transfusions
TD - NC	Transfusion dependency with no requirement for iron chelation
TD-NC Cardiac	Transfusion dependency with no requirement for iron chelation and cardiac disease due to transfusion dependency
TD-C	Transfusion dependency with response to iron chelation
TD-C Cardiac	Transfusion dependency with response to iron chelation and cardiac disease due to transfusion dependency
TD-CF	Transfusion dependency with non-response to iron chelation
TD-CF Cardiac	Transfusion dependency with non-response to iron chelation and cardiac disease
TD-CF Diabetes	Transfusion dependency with non-response to iron chelation and diabetes from adverse reaction to iron overload
TD-CF HC	Transfusion dependency with non-response to iron chelation and hepatic complications from adverse

	reaction to iron overload
AML	Acute myeloid leukemia
AML Cardiac	AML and cardiac disease from transfusion dependency
AML Diabetes	AML and diabetes from adverse reaction to iron overload
AML HC	AML and hepatic complications from adverse reaction to iron overload
Death	Death

7.2.5. How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

As described above, 3 key aspects of the condition are captured in the model, i.e. a patient's transfusion status; whether a patient requires iron chelation following a certain number of transfusions; whether a patient has progressed to AML. The model structure reflects these clinical drivers (Sections 2.1 and 2.5).

The first stage of disease progression is defined by the whether or not a patient is dependent upon blood transfusions (transfusion dependence or independence) and the second by progression to AML. These were modelled using data from the MDS-004 trial (as described in Section 7.3.1).

7.2.6. Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 22. Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	20 years	Represents a lifetime horizon given the average patient age of 67 from the MDS-004 trial	NICE Methods Guide
Cycle length	4 weeks	Reflects the dosing interval for lenalidomide	SPC
Half-cycle correction	No	Short cycle length (28 days) therefore not required	NICE Methods Guide
Were health effects measured in QALYs; if not, what was used?	Yes	NICE reference case	NICE Methods Guide
Discount of 3.5% for utilities and costs	Yes	NICE reference case	NICE Methods Guide
Perspective (NHS/PSS)	NHS	NICE reference case	NICE Methods Guide
NHS, National Health Service; PSS, personal social services; QALYs, quality-adjusted life years			

Technology

7.2.7. Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Lenalidomide is implemented in the model as per its anticipated marketing authorisation taking into account the dose interruptions and titrations observed in the MDS-004 pivotal trial. In the base case of the model best supportive care (BSC) is

considered as per the NICE scope. This is defined as the provision of blood transfusions for transfusion dependent patients.

Since an erythropoiesis stimulating agent (ESA) is a constituent of BSC (i.e. the main comparator in the NICE final scope) to a limited extent, results from scenario comparing lenalidomide to BSC including ESA are presented as an extension of the base case. Within the MDS 004 trial 28% of UK patients had received ESA prior to the trial (52.7% of all patients had received ESA prior to the trial).

It is assumed within the base case of the model therefore that 28% of patients will receive ESA, followed by GCSF, in addition to transfusions as part of BSC

Use of ESA is implemented within the model in line with the dosing regimes detailed in the British National Formulary.[1]

7.2.8. Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the ‘response’ criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.

- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

The dosing schedule for lenalidomide in the model is taken from the MDS-004 trial, in which patients were initiated on treatment at a continuous dose of 10 mg per day. In the model, as in the trial, patients receive 21 days of continuous treatment per 28 days. Patients in the trial were allowed up to 2 treatment interruptions, usually due to adverse events (discussed below). All patients in the lenalidomide arm of the model remain on treatment until they are determined to have stopped responding to treatment (i.e. they have become transfusion dependent).

The model includes a response assessment period, during which all patients receive therapy, even if they have not responded to treatment. The length of time required to determine non-response is 84 days – or three treatment cycles.

The trial protocol specified either 56 or 182 days for the determination of transfusion status. However, after 56 days only 76.25% of MDS-004 patients who experience a major response have responded. Although the trial protocol specified either a 56 or 182 days for determination of transfusion status, the model uses an 84-day assessment period. This allows the greatest number of patients to achieve a major response: 96.25% of responders to lenalidomide do so within 84 days.

In the trial, some patients categorized as responders had one or more brief treatment interruptions. Since no lenalidomide is given during these interruptions, no treatment costs are incurred for these patients for that specified period.

As in the trial, the model accounts for two treatment interruptions during which period the patient receives no lenalidomide treatment. These are reflected in the model with 64% of ITT patients that are on treatment (non-responders and responders) experiencing a first dose interruption, matching the proportions observed in the MDS-004 trial. The cost of treatment is adjusted to take into consideration these treatment interruptions. There was no requirement for clinical outcomes to be adjusted in a similar fashion, since the efficacy data for the ITT population used within the model already accounts for these interruptions.

The mean time to interruption in the trial was 50 days. Interruptions lasted for an average of 27 days. After dose interruption patients resumed treatment at a lower dose of 5mg given for 28 days per cycle (as per the trial). Of patients experiencing a first dose interruption, 62% went on to have a second interruption after a mean time of 86 days from the start of the first interruption. The mean duration of the second interruption was 24 days. After the second dose interruption patients resumed treatment at a dose of 5mg given for 14 days per cycle (as per the trial).

Similar brief treatment interruptions and dose modifications may be expected in real life clinical practice. For example in the UK, there is a limited amount of prescribing of lenalidomide for MDS patients through the Cancer Drugs Fund. Analysis of patients starting on 10 mg lenalidomide indicated that there is a 23% probability that patients will switch to a lower dose.[74] Similar evidence is also available from the US where lenalidomide for the treatment of MDS del(5q) has been on the market since 2005.[58] Statistical associations cannot be made from available data, but it nevertheless indicates that switching to a lower dose may be expected for reasons such as AE. Patients remain on lenalidomide until they are identified as a non-responder and are taken off treatment.

No additional monitoring requirements or costs are associated with any of the dosing issues discussed above. Within the model it is assumed that patients are monitoring weekly up to 56, 2 weekly up to 84 days and 4 weekly thereafter.

7.3. Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1. Please demonstrate how the clinical data were implemented into the model.

Overview of the transitions between health states

Transition between the health states is derived as follows:

1. Whether a patient responds to treatment or not, initially is determined using 84 day response rates from the trial data:

    a. If a patient responds they enter the Transfusion Independent (TI) health state
    b. If they do not respond and <u>had not</u> previously received enough RBC units to require chelation in the trial they enter the Transfusion Dependent No Chelation (TD-NC) health state
    c. If they do not respond and <u>had</u> previously received enough RBC units to require chelation in the trial they enter the Transfusion Dependent – Chelation state (TD-C)

2. After a patient achieves initial response the probability of continued response is assessed each cycle. If they stop responding they enter the Transfusion Dependent No Chelation (TD-NC) health state. The time to non-response is estimated by the fitting of a parametric curve to the MDS-004 duration of response data.

3. From Transfusion Dependent No Chelation (TD-NC) health state patients can become Transfusion Independent only if they receive and respond to G-CSF.

4. From the Transfusion Dependent No Chelation (TD-NC) health state patients progress to the Transfusion Dependent – Chelation state (TD-C) when they have received enough RBC units to require chelation. Patients can also progress to the Transfusion Dependent Cardiac Disease (TD – NC Cardiac) according to the risk per cycle of developing cardiac disease. These data are taken from the clinical literature (ref)

5. From the Transfusion Dependent – Chelation state (TD-C) patients either respond to chelation and remain within the same health state, or fail chelation in which case they progress to the Transfusion Dependent – Chelation Failure state (TD-CF). Patients in the TD-C state also have a risk of progressing to cardiac disease in which case they enter the TD – C Cardiac state. These data are taken from the clinical literature.[75,76]

6. From the Chelation Failure state patients have a chance of developing either diabetes or hepatic complications, which are associated with cardiac failure (TD-CF diabetes and TD-CF HC). They can also still develop cardiac disease. These data are taken from the clinical literature.[75,76]

7. Patients retain any complications they have developed as they progress through the health states, including when they enter AML.

8. A patient's chance of progressing to AML is determined from the MDS-004 data, with patients in a transfusion independent state being less likely to progress to AML.

9. Within the MDS-004 trial, and in other literature, whether a patient is transfusion dependent or not significantly influences their survival with transfusion independent patients surviving longer. Therefore within the model the probability of death each cycle is determined based upon initial response status - transfusion independent patients have a lower risk of mortality. Response/non-response based probabilities of death are applied to all patients who do not have AML. Once a patient progresses to AML an increased probability of death is applied based upon published literature.

Data sources

Data from the pivotal study MDS-004 (which was also the registration trial) has been used, wherever possible, in the modelling of costs and outcomes for MDS del 5q patients. It was not possible to pool data from the earlier study, MDS-003, as this trial was an open label single arm trial, whereas MDS-004 was a placebo controlled randomized trial. Furthermore the dosing and schedules evaluation in both these trials were different.[62,64]

The sections below provide a full description of how the clinical parameters are included in the model.

Treatment response and duration of response

Treatment response

Treatment response within the model is defined as a patient achieving transfusion independence. For costing purposes, as noted earlier in Section 7.2.8, response is

determined after 84 days. Response rates are included for the ITT population according to the response time definition from the clinical trial, that is, an uninterrupted period of transfusion independence for 56 consecutive days.

Base case response rates for lenalidomide and receipt of only transfusions are taken directly from the MDS-004 trial, and are shown in Table 23 below. Placebo response rates are used for patients receiving only BSC.

Table 23. Response rates for ITT population – response defined as 56-day RBC transfusion independence

Placebo		Lenalidomide	
Mean	**95% CI (%)**	**Mean**	**95% CI (%)**
7.50%	[2.5, 16.6]	60.90%	[48.4, 72.4]

Patients receiving ESA have a greater chance of response to treatment than with transfusions alone; however, greater costs are also incurred. Within the model it has been assumed that patients will be given ESA for 3 cycles (as with lenalidomide before response is determined), non-responders will then be given G-CSF in addition to ESA for 3 cycles before response is determined.

As there was no ESA usage in the trial, available literature was used to estimate response rates in these patients.

Patients in the trial were categorised into one of three predictive groups using information from Hellström-Lindberg et al, dictating their likelihood of response to ESA + G-CSF.[77] These groups are defined as follows:

- High probability of response: Serum erythropoietin (S-Epo) of ≤ 500 U/l, and a prior transfusion requirement of < 2 RBC units per month on average.
- Intermediate probability of response: one of either S-Epo ≤ 500 U/l or a prior transfusion requirement of < 2 RBC units per month.
- Low probability of response: S-Epo of > 500 U/l, and a prior transfusion requirement of ≥ 2 RBC units per month on average.

A published study by Jädersten *et al* reports the response rates after combination therapy by predicted group, as shown in Table 24 along with the proportion of MDS-004 patients within each group.[73] Patients in the 'low' predictive group are unlikely to be treated by ESA; as such we weight the response rates for the high and intermediate probability groups with the proportion of trial patients in those groups.

Table 24. Response rates to ESA + G-CSF and distribution of MDS-004 patients by predictive group

Predictive Group	Proportion of MDS-004 Patients	ESA + G-CSF Response Rate
High probability of response	3.5%	60%
Intermediate probability of response	36.4%	18%
Low probability of response	60.1%	6%

This methodology provides an estimated response rate to ESA + G-CSF of 21.7%. However this is unlikely to be representative of ESA + G-CSF use in the UK because combination therapy is started upon the failure of ESA alone. The response rate to monotherapy with either ESA or G-CSF is assumed by Balleari et al to be half that to combination therapy;[59] published response rates to ESA range from 10-49%, compared to around 50.6% with G-CSF.[78,79] Utilising this assumption provides an ESA response rate of 10.8% and a response rate of 10.8% for G-CSF when this is added to ESA monotherapy.

Response duration

The response duration for lenalidomide in the model is based on patient level data from MDS-004 trial data. Based on observations in the clinical trial, it is assumed that over time responding patients stop responding to treatment. When this occurs, it is assumed that patients immediately move to a transfusion dependent health state. This is a conservative assumption as it discounts any potential residual treatment effects whereby patients may continue to be in some state of response to an extent and thereby also impacts transfusion dependent adverse events and mortality rates. Patients who are transfusion independent are assumed not to require iron chelation as would be expected for transfusion dependent patients. Therefore patients first move to the 'transfusion dependent – no iron chelation required' health state once they stop responding to treatment.

MDS-004 is a crossover trial in which almost half of the patients are recruited into the open label phase after completing the 52-week double blind phase. The open label crossovers of the patients are taken into account while extrapolating the response duration curves.

Log-rank tests were used to determine if there was a significant difference in response duration depending on whether a treatment was received as the first or second treatment within the trial i.e. whether crossover within the trial may have impacted upon results. The results showed that the order patients received treatment (and therefore crossover) did not have a significant impact on duration of response.

In order to determine the time that patients continued to respond to treatment response curves were calculated for ITT patients initially receiving the lenalidomide 10 mg dose. Response curves could not be calculated for patients on the placebo arm as there were insufficient responses to provide data for a reasonable curve fit (only 5 patients responded and 4 of these were censored). Therefore the lenalidomide 5 mg dose efficacy was used as a proxy to determine the response curves for the best supportive care arm in the model. This most likely overestimates the treatment effect in the comparator arm.

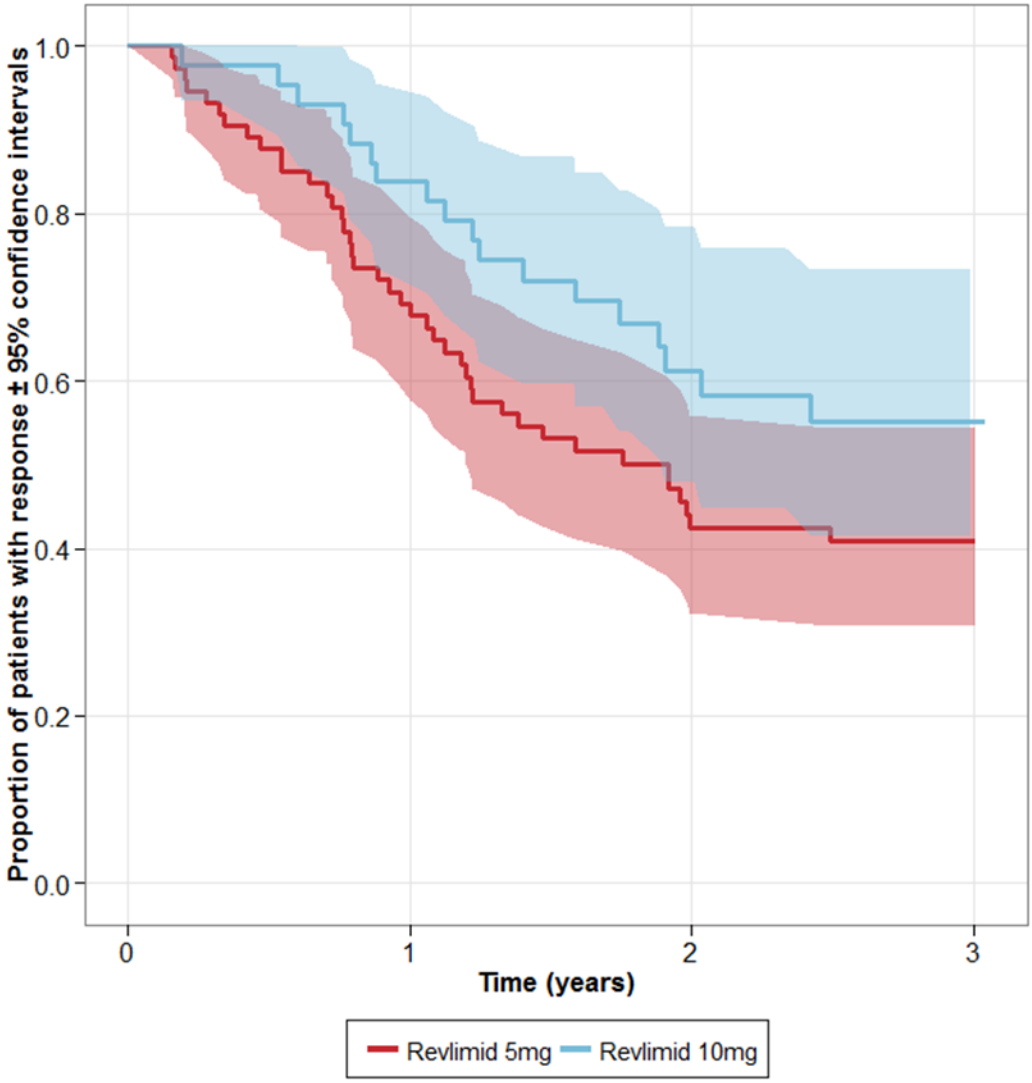
Parametric response duration curves were fitted to the data for all patients starting on either lenalidomide 10 mg or 5 mg in the trial (weibull, log logistic, lognormal and exponential functions) and the goodness of fit determined using the Integrated Brier Score (IBS) and Akaike Information Criterion (AIC). The lower the IBS value the better the fit of the model or the more reliable it is for making future predictions. This method of evaluation is generally considered superior to using AIC or BIC, although these scores are also reported.[80]

The curves with lowest AIC and IBS and the best visual fit are used for the base case model and are as follows:

- Starting dose 10 mg lenalidomide: Lognormal distribution
- Best supportive care (estimated using 5 mg lenalidomide): Lognormal distribution

Figure 13 shows the Kaplan-Meier curve for response, displaying the percentage of patients still responding at each point in time after beginning treatment. The placebo curve is not shown as there was just a single sustained responder in this trial arm.

Figure 13. Kaplan Meier Curve showing responders in lenalidomide 10 mg and 5 mg treatment arms



Revlimid 10mg	75	47	27	2
Revlimid 5mg	46	36	22	1

Numbers at risk

The assessed fitted models for response are shown in Figure 14 for both 10 mg and 5 mg lenalidomide, alongside their Kaplan-Meier plots.

Figure 15 below provides the AIC values and Integrated Brier Scores for the combined 5 mg and 10 mg lenalidomide response curves, providing a case for the use of the a lognormal fitted model with its low AIC value and low prediction error.

Figure 14. Assessed fitted models against their respective Kaplan-Meier plots

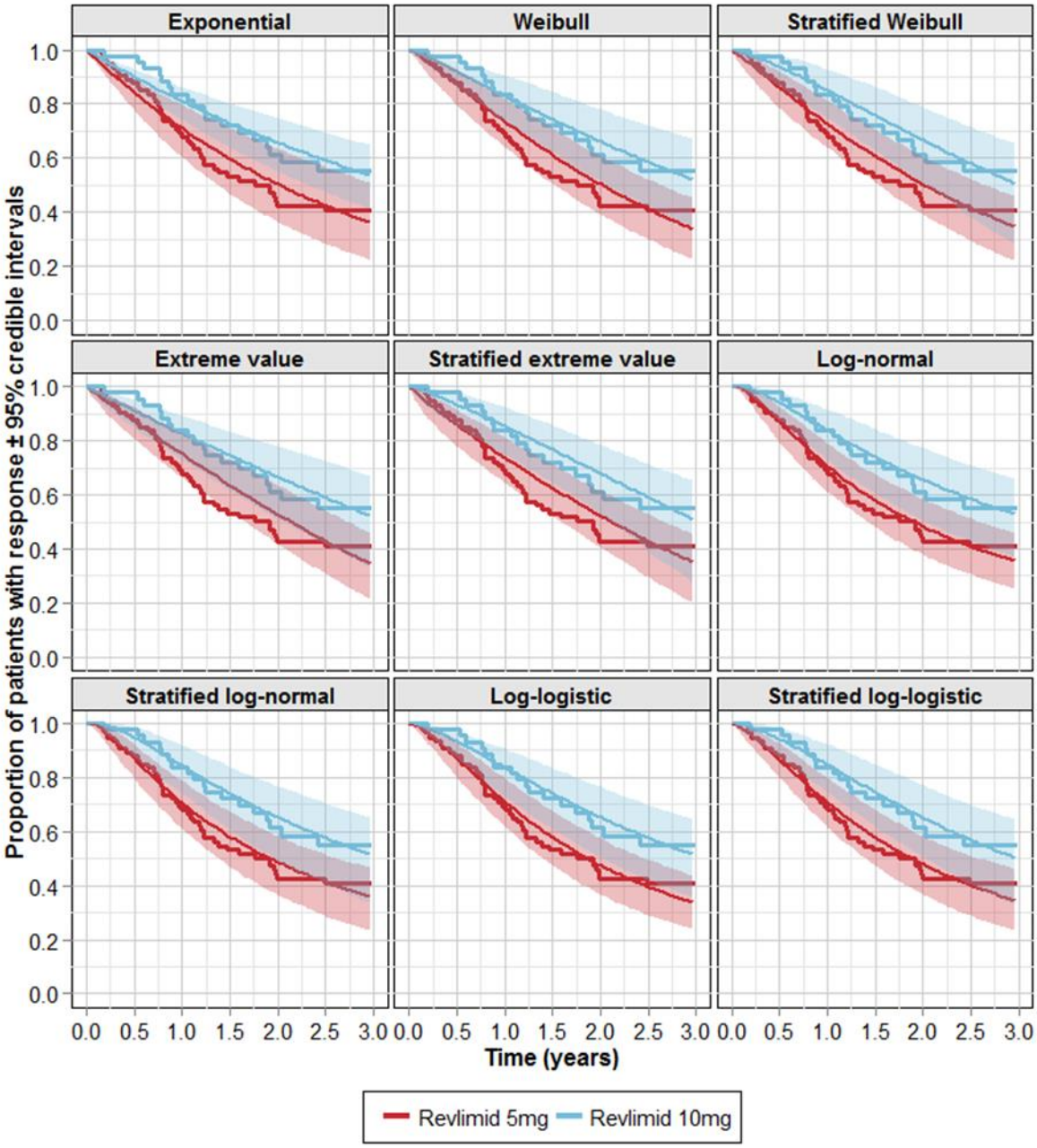


Figure 15. AIC and Integrated Brier Score values for fitted response curves

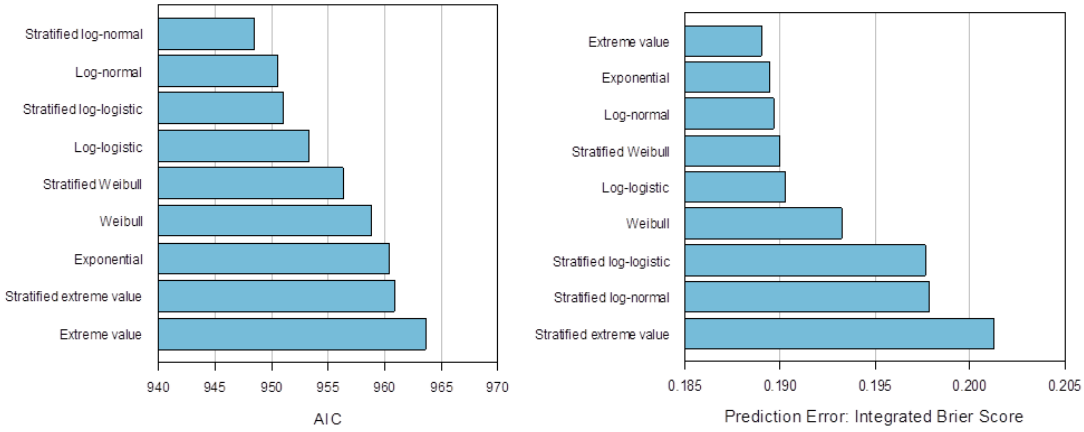
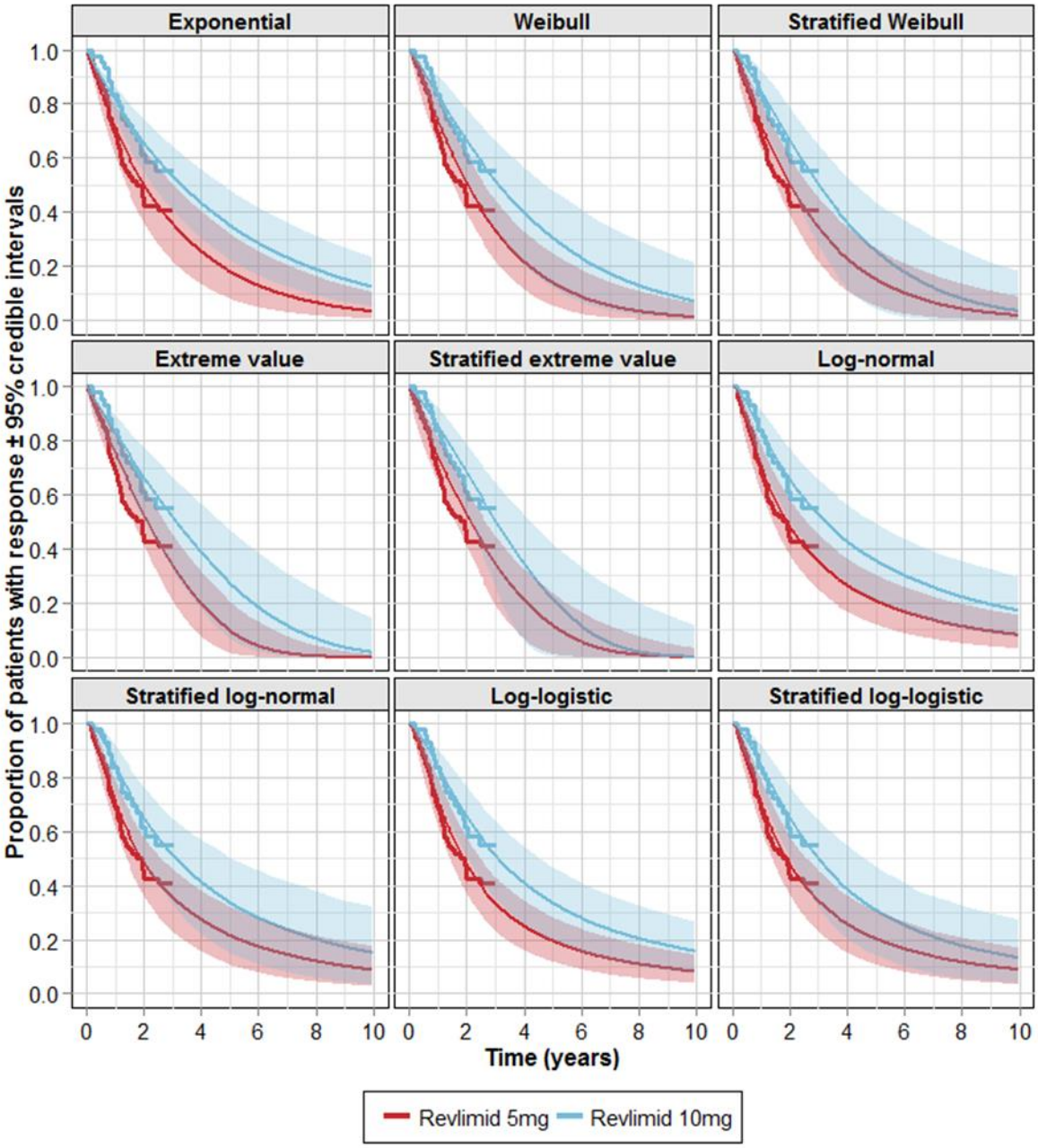


Figure 16 shows the fitted response curves over 250 treatment cycles. As previously noted, since there are insufficient placebo responders in the trial to attempt an accurate fitted curve, the 5 mg lenalidomide response curve has been used to approximate the best supportive care response time. Lenalidomide 10 mg displays a slight advantage in response duration over best supportive care; a benefit likely to be conservative in reality, since we might expect 5 mg lenalidomide to be more efficacious than placebo.

Figure 16. Response curves for lenalidomide 10 mg and best supportive care, with lenalidomide 5 mg used as a proxy for best supportive care due to insufficient observations



There is a strong correlation between the duration of lenalidomide treatment and the duration of response in the trial (correlation coefficient 0.70, p<0.001). This supports the assumption that response duration can be used as a proxy for treatment duration within the model (the exception being that 3 cycles are given at the beginning of the model for cost purposes for the determination of response).

Blood transfusions

Blood transfusion rate

It is assumed that patients in the transfusion dependent health states receive RBC transfusions and platelet transfusions for each cycle spent in these health states. An average number of RBC/platelet units transfused per cycle is estimated from patient level information from the trial and applied to all patients, each cycle, in the transfusion states.

There is no difference assumed in the RBC/platelet transfusion rates between the different iron chelation health states. For example patients in the 'transfusion dependent – no iron chelation required' health state, have the same transfusion rate as patients in the 'transfusion dependent – iron chelation' health state.

Average blood transfusion rates in the base case model are taken from the patient's individual transfusion history during the weeks recorded prior to randomisation in the MDS-004 trial data. Transfusion rates were calculated by analysing data for UK patients in the trial. An average number of RBC units transfused per cycle was calculated using patient level transfusion history during the weeks recorded prior to randomisation in the MDS-004 trial data. For patients of UK origin in the trial; mean RBC units per 28 day cycle, mean RBC units per transfusion, mean transfusions per 28 day cycle and RBC units per 8 weeks are 4.57 [CI 4.56-4.58], 2.43 [CI 2.42-2.43], 1.41 [CI 1.40-1.42] and 9.15 [CI 9.12-9.17], respectively.

Number of transfusions per cycle

Analysis of UK specific patient level data for average number of transfusions per cycle was calculated from the MDS-004 trial data. This showed that a patient receives an average of 2.4 RBC units per transfusion – based on the trial data where this number of units was provided per transfusion prior to randomisation. Using this in conjunction with the average number of RBC units required per cycle of 4.57, the patient will require 1.89 RBC transfusions per cycle. This represents the number of transfusions required to provide 4.57 RBC units.

It is assumed in the model that a patient receives an average of 3.0 platelet units per transfusion; based on the trial data where this number of units was provided per transfusion prior to randomisation. Using this in conjunction with the average number

of platelet units required per cycle of 0.06, patients are assumed to require 0.02 platelet transfusions per cycle. This represents the number of transfusions required to provide 0.06 platelet units.

Previous transfusion history

The average number of units of RBCs previously transfused is based on an analysis of UK patient's transfusion history in the base case, with all patients included as a sensitivity analysis. Patients that have had a total number of units of RBC greater than the threshold at which iron chelation is applied (see below) are excluded from this analysis as they are assumed to start the model in the iron chelation health state (8.00% of patients).

Patients that do start the model in the 'no iron chelation required' health state have received an average of 4.57 units of RBCs over the preceding weeks (25 such patients, SD: 0.86).

Transfusion dependence related complications

Patients who are transfusion dependent are at risk of complications. Within the model the risk of cardiac disease is included to represent this increased risk. The risks of incurring cardiac disease and the associated costs are discussed in further detail later in this section. Each cycle, patients are assessed as to whether complications occur.

Once a patient has cardiac disease they are assumed to incur the costs and a utility decrement for all remaining cycles until death, including following progression into AML. A conservative assumption is applied that an individual cannot progress to more than one complication.

Iron chelation

Iron chelation is initiated to avoid complications associated with iron overload. The decision to start treatment with an iron chelator is based on a patient's previous RBC transfusion history. Once a patient has received over a threshold number of units of RBCs, they are initiated on iron chelation. The threshold is usually between 20 and

30 units of RBCs.[81] We assume in the base case model that the average threshold is 25 RBC units.

Treatment choice and dose of iron chelation

There are two treatment choices assumed for iron chelation in the model; desferroxamine (DFO) and deferasirox. DFO has historically been the iron chelator most commonly used but the inconvenience and negative impact on quality of life associated with its cumbersome administration (DFO requires subcutaneous infusion for 8–12 hours per night, 3–7 times per week) leads to poor compliance, and reduced effectiveness.[82] Deferasirox is a more recent alternative to DFO and while it is more expensive , it does not have the same quality of life detriments and compliance issues. In the base case it is assumed that patients can receive either of these therapies, with the proportion on each estimated from Prescription Cost Analysis: England 2010.[83] A summary of the distribution of treatment and the doses assumed in the base case is shown in Table 25.

Table 25. Iron chelation treatments and dosing

Iron chelator	Market share	Days dosed per week	Dose (mg/kg)
IV – DFO and Desferal	29%	4-7*	40
Oral - Exjade	71%	7	20

** 5 was chosen as the base case value.*

Iron chelation response rates

The response rate for iron chelation is based on a report by Kontoghiorges et al which states:

“It is estimated that only a maximum of 66% of the patients using DFO receive it regularly without complications and achieve body iron levels within the nontoxic range, achieving serum ferritin levels below 2.5mg/l.”[75]

A response rate of 66% is therefore assumed in the model. Response and determination of non-response to iron chelation is assumed to occur in the first cycle of treatment.

Once a patient requires iron chelation they move to either the chelation or chelation failure state depending on their response. Patients that respond to treatment are assumed to continue to receive chelation up to progression to AML or death.

Iron overload complications

Patients that do not respond to iron chelation are at risk of iron overload complications. These are assumed to be diabetes mellitus and hepatic complications. The risks of incurring these are discussed in later in this section and the associated costs in section 7.36. Each cycle, patients are assessed as to whether these complications occur and a proportion of patients are moved into the iron overload failure categories for each risk.

Once a patient has diabetes or hepatic complications they are assumed to incur the costs and utility decrements of these complications for all remaining cycles until death, including following progression into AML. A simplifying assumption is applied that an individual cannot progress to more than one of these complications.

Patients previously chelated

A proportion of patients enter the model having previously received iron chelation. This is assumed to be all patients that enter the model having previously received more units of RBCs than the iron chelation threshold. In the MDS-004 trial, 8.0% of patients had received more than 25 units of blood in the 8 weeks prior to randomisation and thus were assumed to be in receipt of iron chelation. Patients that enter the model on iron chelation continue being chelated if they do not achieve transfusion independence. If they do respond to treatment and achieve transfusion independence then they stop chelation treatment and have their RBC count reset to 0.

Progression to AML

The time to development of AML was derived from individual patient level analysis of the MDS-004 trial. Estimates are made separately for transfusion dependent and transfusion independent patients.

AML progression curves are fitted to individual patient level data with appropriate choice of curve extrapolated using the selected distribution. In the base case model the weibull distribution has been chosen for these curves as this had as a relatively low IBS and low AIC and offers a more clinically realistic fit than the extreme value distribution which, despite having the lowest IBS, predicts 100% AML progression relatively quickly.

The time to progression to AML curves used within the model are shown in Figure 17.

Figure 17. Time to progression to AML curve

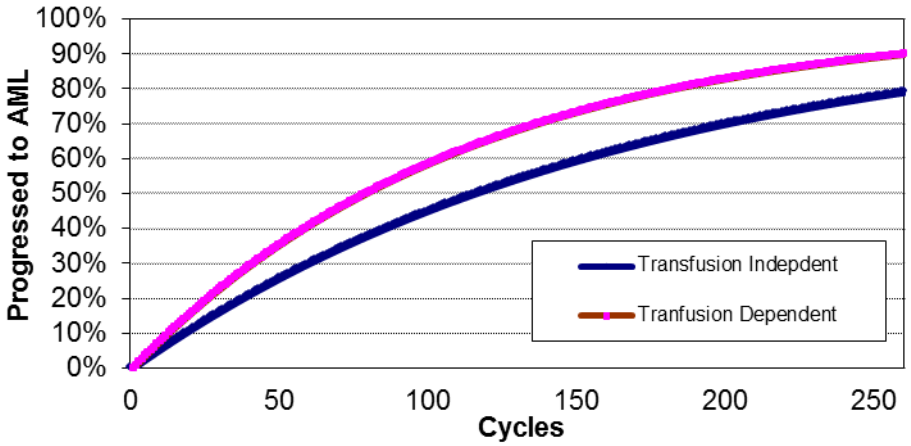
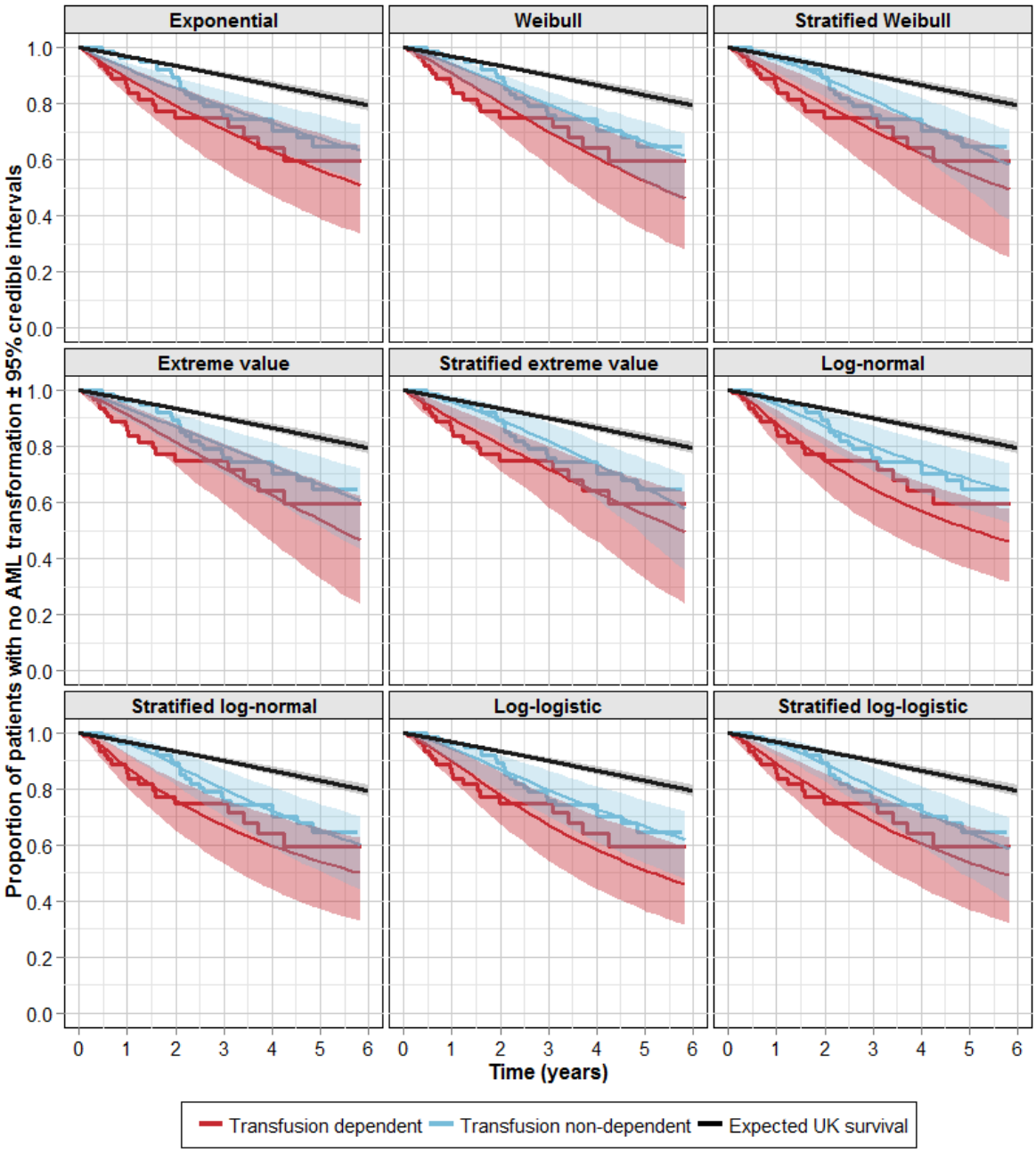


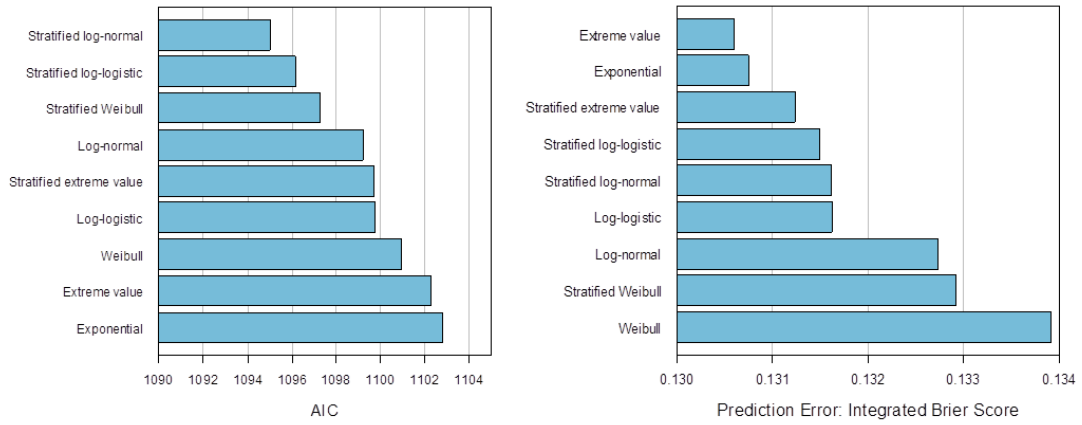
Figure 18 shows the Kaplan-Meier curve for progression to AML, showing the percentage of patients yet to progress to AML at a given treatment cycle for transfusion dependent and independent patients. The modelled curves fit the responder arms very well. Transfusion dependent patients are at a higher risk of progression to AML compared to patients who are transfusion independent.

Figure 18. Kaplan-Meier Curve showing AML progression in each treatment arm and the modelled transfusion dependent and independent groups



AIC and IBS scores associated with these models are displayed in Figure 19.

Figure 19. AIC and Integrated Brier Score values for fitted AML progression curves



Treatment and survival in AML

Treatment of patients with AML is discussed in more detail later in this section and survival of patients in AML is discussed below. An assumption is made that there is no relationship between previous treatment arm or transfusion status and a patient's treatment or survival in AML, in keeping with the properties of a markov model.

Mortality

Transfusion dependent mortality according to transfusion dependency

In a study conducted to identify the most significant prognostic factors in MDS patients, it was reported that mortality is strongly related to transfusion dependency in MDS.[20] A Cox regression model with time-dependent covariates showed that the survival of patients with MDS who developed a transfusion dependency was significantly lower than the survival of patients who did not develop a dependency (HR = 2.16). This result was supported in multivariate analyses with cytogenetic score (defined by IPSS criteria), and in Cox regression models that controlled for the cumulative units transfused and monthly transfusions separately.

Results from the MDS-004 trial have been used to estimate mortality in the model. The time until death is analysed separately for transfusion dependent and transfusion independent patients who do not enter AML and is not assumed to be otherwise related to the treatment received. A log-rank was used to test for significance for the

two patient populations. A significant difference in survival was found for transfusion dependent versus transfusion independent patients (Chi-square = 21.8, d.f. = 1, P < 0.0001).

The mortality curve for survival is modelled best by the Weibull distribution, which has a relatively low predicted error (IBS) and a low AIC (Figure 20).

Figure 20. AIC and predicted error values for fitted survival curves

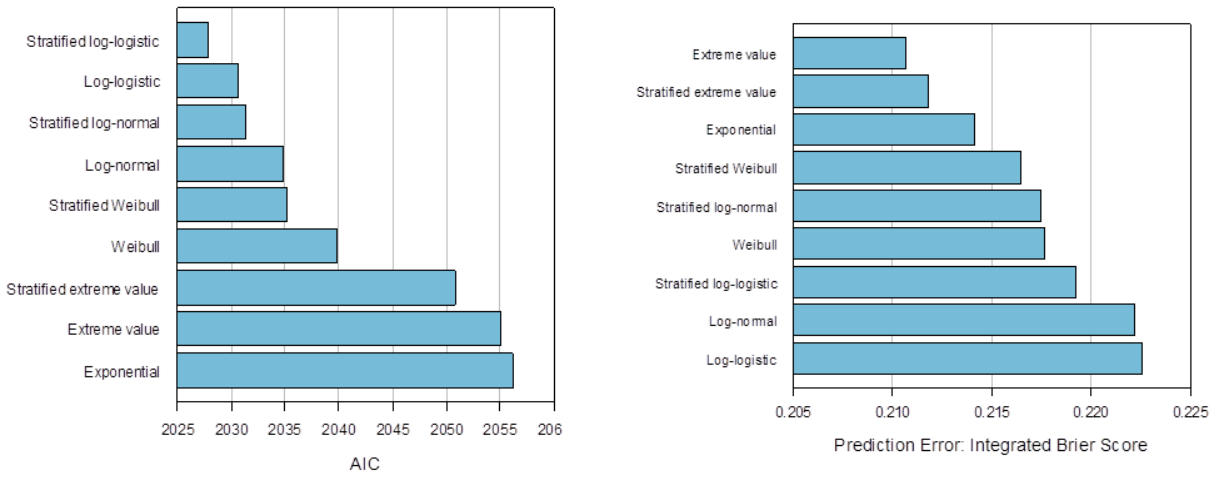


Figure 21 and Figure 22 show the curve fits for transfusion independent and dependent MDS-004 patients, respectively, alongside baseline all-cause mortality (ACM) based upon the age distribution of patients within the MDS-004 trial and the Kaplan-Meier survival curve.

In order to take account of age-related mortality within the model a Generalized Additive Model (GAM) was fitted to the ACM data, which is a regression technique based on splines able to model complex non-linear relationships. This method fits a continuous GAM for survival in ACM, which was then used to predict the probability of survival for each patient in the sample for a series of future time points; for example, the survival probability of a 60 year old after 1 year, 2 years and so on. The mean of these predicted values for the future time points was used to give the predicted baseline survival curve.

Figure 21. Assessed curve fits for survival compared to the Kaplan Meier curves and baseline all-cause mortality.

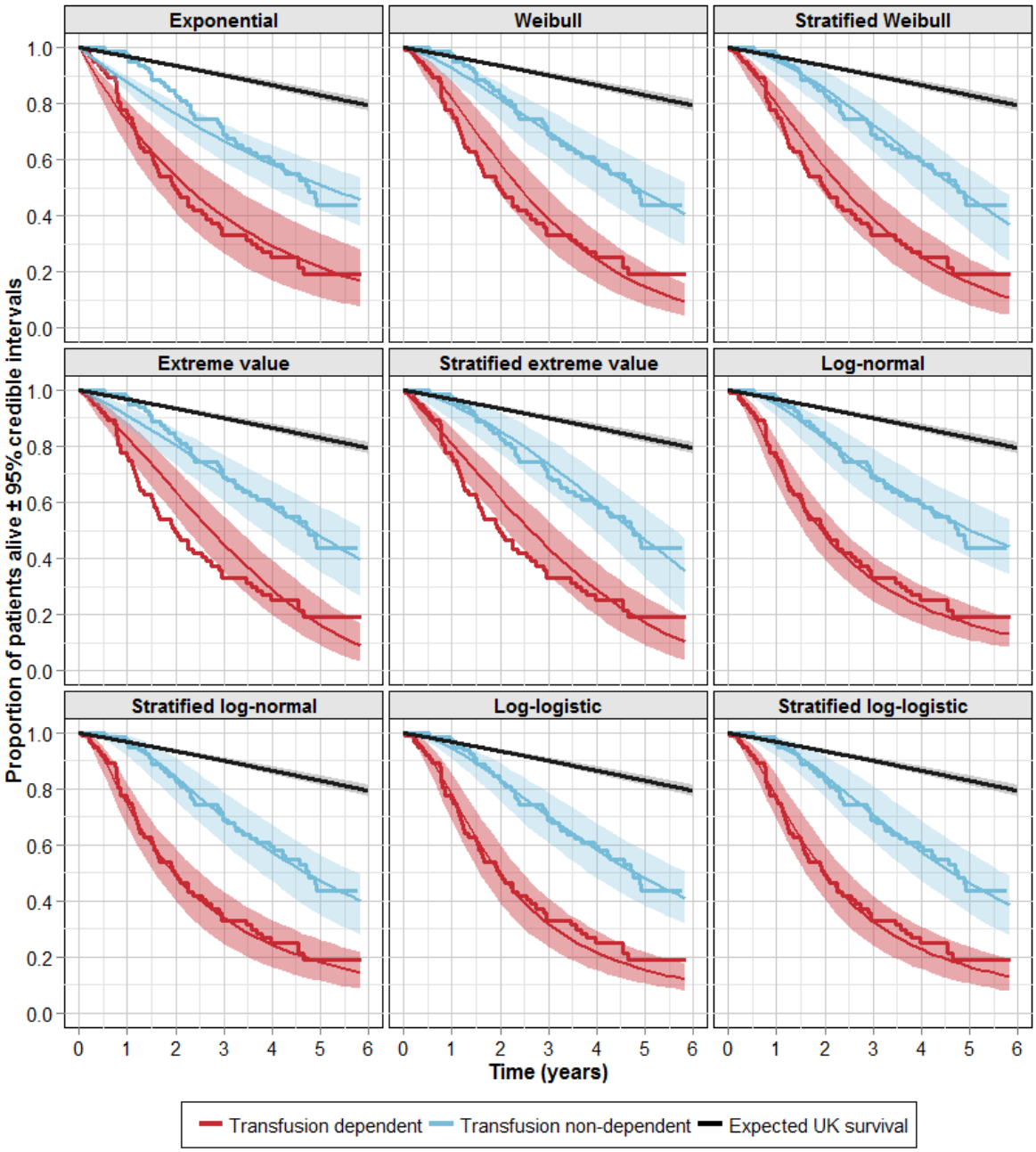
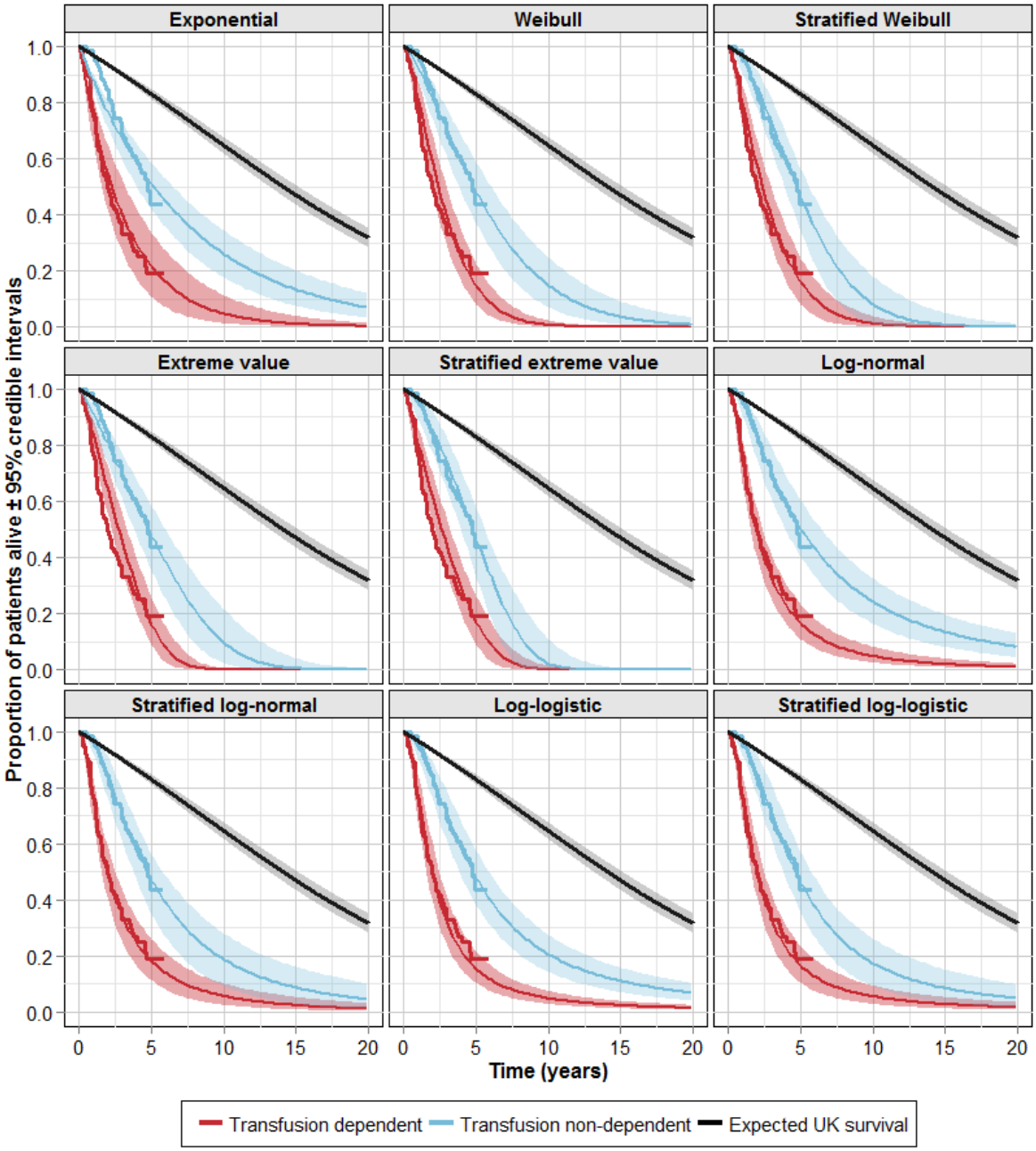


Figure 22. Assessed curve fits for transfusion dependent mortality extrapolated over a longer time horizon, compared to the Kaplan Meier curve and baseline all-cause mortality.



The survival prospects of a transfusion dependent patient are worse than for an independent patient, based upon the MDS-004 trial. This is also shown by a recent study of MDS patients with del 5q syndrome by Germing *et al*.[84]

The cross-over of patients in the MDS-004 trial at week 16, precludes any long term assessment of the impact of lenalidomide on survival compared to an untreated

cohort. Reliance on MDS-004 trial data alone to extrapolate mean survival is therefore likely to result in an underestimate. The reported median duration of OS was 42.4 months (31.9, NA), not reached and 44.5 months (35.5, NA) in patients randomized to placebo, lenalidomide 5 mg, and lenalidomide 10 mg respectively. At 4 years only 15 patients remain on the lenalidomide 5 mg and 10 mg arms and only 8 patients remain on the placebo arm.

To overcome this limitation within the trial data the median survival within the model for BSC was adjusted to match the reported median survival for the combined MDS-003 and MDS-004 trials of 3.8 years (2.9, 4.8).[19] The adjustment has been applied to the scale parameter for the overall survival curve for transfusion dependent patients keeping the hazard ratio for the difference in survival between transfusion independent and dependent patients fixed as per the MDS-004 trial.

AML mortality

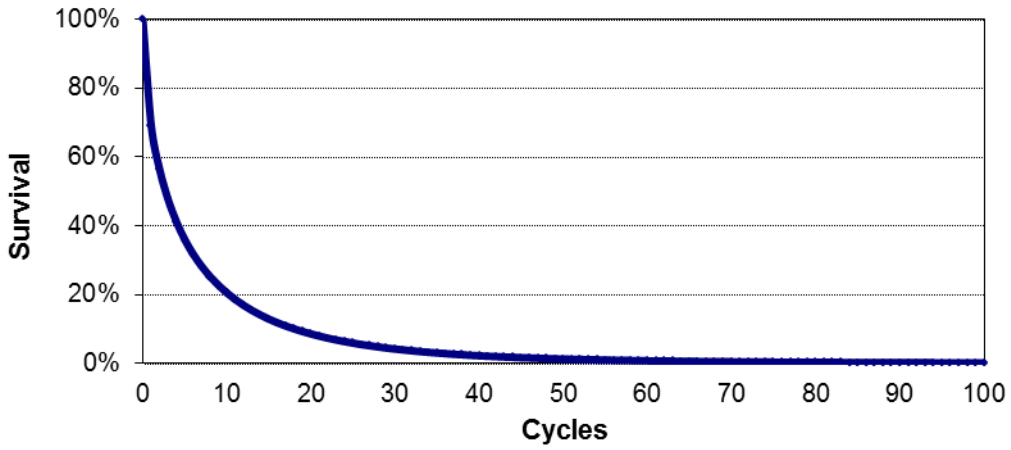
Too few patients died from AML in the lenalidomide trials to allow analysis directly from the trial data. In the model, once patients develop AML they are assigned new life expectancies based upon analysis of the results of a published study.[85] In this study 211 patients were followed after diagnosis of AML. The authors stratified the patients into three prognostic categories based on cytogenetics, leukocyte count, and the presence/absence of antecedent haematological disorders. Patients having 5q deletions and AML secondary to MDS are in the worst prognostic group, with a median survival of only 66 days from diagnosis. All patients were treated with standard chemotherapy, although the specific protocols varied.

The authors published a survival curve for the adverse risk group. This was digitised to obtain a set of survival data points, to which exponential, Gompertz, log logistic, Weibull and log normal curves were fitted. The log normal function provided the best fit based upon its AIC score. However, the weibull function was chosen to represent AML mortality because the log normal function exhibited a ‘long tail’, whereby some patients lived for an unrealistically long time. The Weibull fit does not exhibit this, with less than 1% of patients surviving for much over 4 years, and had only a marginally larger AIC score (470.71 compared to 470.14).

The mortality risk is dependent upon time spent in the state; therefore the patient’s time in AML must be recorded to correctly assign the mortality risk.

The survival curve for patients in AML is shown in Figure 23.

Figure 23. Survival time for a patient entering the AML health state



The above study and methodology was used as it was deemed a more reliable source of data to fit such a curve than the MDS-004 data, in which 56 patients die of AML. The graph above is obtained from double this number of patients (113) in the study's "at risk" group, which should provide a more dependable curve fit for AML survival.

Adverse events and complications

Lenalidomide-related adverse events

Two adverse events are included in the model for lenalidomide as the only events that were both serious enough to warrant inclusion in the model and showed a difference between rates in the lenalidomide and placebo arms in the trial.

Patients treated with lenalidomide are assumed to be at risk of incurring Grades 3 and 4 neutropenia and thrombocytopenia. The rates of grade 3/4 thrombocytopenia and neutropenia (including leukopenia) were taken from published data from the MDS-004 trial. It is unlikely that all instances of neutropenia and thrombocytopenia can be attributed to lenalidomide because MDS is characterized by these peripheral cytopenias. Therefore, the number of patients experiencing these AE was adjusted by subtracting the patients who had neutropenia and thrombocytopenia within the placebo group.

It is assumed that any lenalidomide adverse events have a constant hazard over 4 cycles. After that time there is no longer a risk of AE.

The lenalidomide AEs have a range of severity and thus it is assumed that only a proportion of patients incurring the AE require treatment. These figures are based on the MDS-004 trial data. The rates of AEs assumed and the proportion of patients treated in the base case model are presented in Table 26.

It is conservatively assumed that the adverse rates for patients receiving ESA are the same as for those receiving transfusions only.

Table 26. Lenalidomide adverse events incidence rates and proportion of patients treated

Adverse event	3 month risk	Cycle risk	Time period applied (cycles)	% Treated
Thrombocytopenia, Grade 3/4	41.90%	4	12.69%	6.00%
Neutropenia, Grade 3/4	57.50%	4	19.26%	27.70%

Iron overload and transfusion dependence complications

The model incorporates the development of cardiac disease, hepatic complications, and diabetes mellitus secondary to transfusion dependence and iron overload.
The rates of hepatic disease and diabetes mellitus complications are derived from a retrospective study of 46 patients suffering from MDS.[86] The monthly hazards of these sequelae were derived assuming the event times are distributed exponentially.

The rates of events are shown in Table 27. These risks are applied to patients in the chelation failure health state.

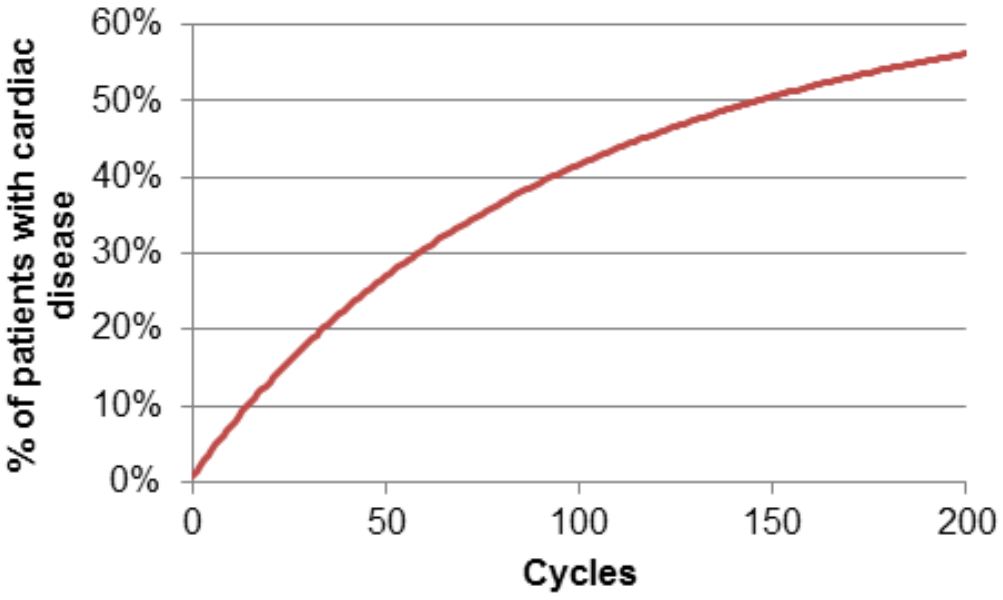
Table 27. Complications associated with iron overload

Adverse event	Annual rate	Cycle rate
Diabetes mellitus	2.70%	0.21%

Hepatic complications	8.30%	0.66%

The risk of individuals dependent on transfusions progressing to cardiac disease is discussed in a study by Malcovati *et al*.[76] Their graph was digitised to produce a set of data points, to which curve fits were tested to show the cumulative probability of cardiac disease. Of these, the Gompertz curve provided the best fit (Figure 24). The parameters for this are applied to the model to implement the risk of cardiac complications in a more sophisticated manner than a simple cycle rate.

Figure 24. Digitised cumulative probability of transfusion dependent patients progressing to cardiac disease



7.3.2. Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

See Section 7.3.1. A transition matrix cannot be provided as cycle probabilities are time dependent for treatment response duration, mortality and progression to AML.

7.3.3. Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has

not been included, provide an explanation of why it has been excluded.

Transition probabilities vary over time within the model as determined by the clinical trial data.

7.3.4. Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The intermediate outcome of transfusion independence / dependence was linked to mortality and AML progression using the relationship estimated directly from the clinical trial data. See Section 7.3.1.

7.3.5. If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable.

Summary of selected values

7.3.6. Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Table 28. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Average Number of Transfusions per month cycle	4.574	[4.197-4.951] NORMAL	Section 7.3.1
Average RBC units per Transfusion	2.426	[2.221- 2.631] NORMAL	Section 7.3.1
Average Number of platelet transfusions per month cycle	0.060	[0.021-0.099] NORMAL	Section 7.3.1
Average platelet units per Transfusion	3.000	[2.869-3.131] NORMAL	Section 7.3.1
Average proportion not responding to Chelation	0.340	[0.285-0.397] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
Chelation Initiation Threshold (RBC units transfused)	25	Not included in PSA	Section 7.3.1
Average RBC units per month - pre treatment (non chelated patients)	9.149	[8.362-9.935] NORMAL	Section 7.3.1
Proportion of patients pre chelated (≥ Chelation initiation threshold RBCs)	0.080	[0.051-0.113] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
Response Rate - lenalidomide	0.609	[0.597-0.621] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
Response Rate – Transfusions Only	0.075	[0.068-0.083] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
Response Rate - ESA	0.108	[0.078-0.142] BETA DERIVED USING STANDARD	Section 7.3.1

		ERROR.	
Response Rate - G-CSF	0.108	[0.078-0.142] BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
Monitoring Duration – Lenalidomide Period 1	2	Not included in PSA	Section 7.3.1
Monitoring Duration – Lenalidomide Period 2	1	Not included in PSA	Section 7.3.1
Monitoring Duration – Revlimid Period 3	999999 (lifetime)	Not included in PSA	Section 7.3.1
Monitoring Frequency per cycle – Lenalidomide Frequency 1	4	Not included in PSA	Section 7.3.1
Monitoring Frequency per cycle – Lenalidomide Frequency 2	2	Not included in PSA	Section 7.3.1
Monitoring Frequency per cycle – Lenalidomide Frequency 3	1	Not included in PSA	Section 7.3.1
Monitoring Duration – Best Supportive Care Period 1	999999 (lifetime)	Not included in PSA	Section 7.3.1
Monitoring Frequency per cycle – Best Supportive Care Frequency 1	1	Not included in PSA	Section 7.3.1
No treatment monitoring- Frequency per cycle	1	Not included in PSA	Section 7.3.1
Iron Chelation monitoring – Frequency per cycle	1	Not included in PSA	Section 7.3.1
Utilities - Transfusion Independent	0.85	[0.793-0.900] BETA – ALPHA AND BETA	Section 7.4.9

		DERIVED USING STANDARD ERROR.	
Utilities - Transfusion Dependent	0.65	[0.543-0.751] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
Utilities - AML	0.65	[0.543-0.751] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - DFO use	21.0%	[0.158-0.263] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - Oral Chelator use	0.0%	Not included in PSA BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - Cardiac Disease	17.9%	[0.068-0.290] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - Diabetes	12.3%	[0.050-0.196] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - Hepatic Complications	8.0%	[0.060-0.100] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.9
AE utility decrement - Thrombocytopenia	0.0%	Not included in PSA	Section 7.4.9
AE utility decrement -	0.0%	Not included in PSA	Section 7.4.9

Neutropenia			
AE Risk % Thrombocytropenia – per cycle - Lenalidomide	0.127	[0.068-0.199] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Thrombocytropenia – per cycle - Percentage of patients treated	0.060	[0.021-0.113] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Thrombocytropenia – per cycle - Lenalidomide	0.193	[0.120-0.276] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Thrombocytropenia – per cycle - Percentage of patients treated	0.277	[0.192-0.369] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Iron Chelation failures AEs – Risk of Diabetes	0.002	[0.000-0.012] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Iron Chelation failures AEs – Risk of Hepatic	0.007	[0.000-0.020] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.3.1
AE Risk % Iron Chelation failures AEs – Risk of Cardiac Disease (Gompertz) - Beta	-4.935	[-4.73584, -5.13429] MULTIVARIATE NORMAL	Section 7.3.1
AE Risk % Iron Chelation failures AEs – Risk of Cardiac Disease (Gompertz) - Gamma	-0.006	[-0.02396, 0.01157] MULTIVARIATE NORMAL	Section 7.3.1
Costs – Drug Acquisition cost – Lenalidomide cost	180.00	Not included in PSA	Section 7.4.21

10mg			
Costs – Drug Acquisition cost – Lenalidomide cost 5mg	170.00	Not included in PSA	Section 7.4.21
Costs – Drug Acquisition cost – ESA vial cost	110.620	Not included in PSA	Section 7.4.21
Costs – Drug Acquisition cost – G-CSF vial cost	52.710	Not included in PSA	Section 7.4.21
Costs – Drug Acquisition cost – Iron chelation	1383.39	Not included in PSA	Section 7.4.21
Costs – Adverse Events - Thrombocytopenia	1636.38	[1376.838-1914.517] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Adverse Events - Neutropenia	1636.38	[1376.838-1914.517] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Adverse Events - Cardiac Disease	3792.30	[3190.814-4436.882] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Adverse Events - Diabetes	3644.40	[3066.372-4263.844] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Adverse Events - Hepatic	1445.80	[1011.628-1943.531] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Other treatment costs - AML	1919.40	[1614.969-2245.643] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21

Costs – Other treatment costs – Admin Cost	234.88	[197.626-274.803] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Other treatment costs – Unit of blood	133.10	[111.989-155.723] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Monitoring costs - GP Visit	36	[30.290-42.119] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Monitoring costs - Blood count	3.09	[2.597-3.611] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Costs – Monitoring costs - Iron test	1.23	[1.035-1.439] GAMMA – ALPHA AND BETA DERIVED USING THE STANDARD ERROR	Section 7.4.21
Dosing – Lenalidomide Lenalidomide Time to interruption 1	54.2	[27.35-81.05] NORMAL DERIVED USING STANDARD ERROR	Section 7.2.8
Dosing – Lenalidomide Lenalidomide Time to interruption 2	72.1	[38.62-105.58] NORMAL DERIVED USING STANDARD ERROR	Section 7.2.8
Dosing – Lenalidomide Dosing interruption 1 days	17.5	[10.40-24.60] NORMAL DERIVED USING STANDARD ERROR	Section 7.2.8
Dosing – Lenalidomide Dosing interruption 2 days	13.9	[0-27.96] NORMAL DERIVED USING STANDARD ERROR BOUNDED AT 0	Section 7.2.8
Dosing – Lenalidomide % having 1st	0.687	[0.578-0.796] BETA – ALPHA AND BETA	Section 7.2.8

interruption		DERIVED USING STANDARD ERROR.	
Dosing – Lenalidomide -% having 2nd interruption	0.738	[0.634-0.842] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.2.8
Dosing – Lenalidomide Lenalidomide treatment days per cycle 10mg	21	Not included in PSA	Section 7.2.8
Dosing – Lenalidomide Lenalidomide treatment days per cycle 5mg (after 1st interruption)	28	Not included in PSA	Section 7.2.8
Dosing – Lenalidomide Lenalidomide treatment days per cycle (after 2nd interruption)	14	Not included in PSA	Section 7.2.8
Dosing –Average Dose Iron Chelation	28.333	Not included in PSA	Section 7.4.21
Dosing - DFO doses per week	5	[3-7] NORMAL	Section 7.4.21
Dosing – Cycles of treatment for non-responders - Lenalidomide	3	Not included in PSA	Section 7.4.21
Dosing – Chelation market share - DFO	0.291	[0.218-0.363] BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.	Section 7.4.21
Dosing – Chelation market share - Exjade	0.709	[0.532-0.887] 1- (BETA – ALPHA AND BETA DERIVED USING STANDARD ERROR.)	Section 7.4.21
Response Curves – Response Duration - Lenalidomide	Lognormal curve Beta = 1.1876778 Alpha = 7.07	Beta = [1.0413161-1.3546114]	Section 7.3.1

		Alpha = [6.8076036-7.3323964] MULTIVARIATE NORMAL	
Response Curves – Response Duration – Best Supportive Care	Lognormal curve Beta = 1.187677833 Alpha = 6.542	Beta = [1.35461137-1.041316105] Alpha = [6.34618345-6.73781655] MULTIVARIATE NORMAL	Section 7.3.1
AML curves – Transfusion Dependent	Weibull curve: Beta = 1.38803628 Alpha = 0.000225395	Beta = [1.229327372, 1.567234862] Alpha = 0.000257167, 0.000197549] MULTIVARIATE NORMAL	Section 7.3.1
AML curves – Transfusion Independent	Weibull curve: Beta = 1.38803628 Alpha = 0.00011228	Beta = [1.229327372, 1.567234862] Alpha = [9.70405E-05-0.000129913] MULTIVARIATE NORMAL	Section 7.3.1
Median Survival from MDS003 and MDS004	3.80	[2.90-4.80] TRIANGULAR	Section 7.3.1
Mortality curves – Transfusion Dependent	Weibull curve: Beta = 1.172337947 Alpha = 0.000377855	Beta = [1.061437671, 0.000494951] Alpha = [1.294825216-0.000288462] MULTIVARIATE NORMAL	Section 7.3.1
Mortality curves – Transfusion Independent	Weibull curve: Beta = 1.172337947	Beta = [1.061437671-1.294825216]	Section 7.3.1

	Alpha = 0.000255574	Alpha = [0.000207891-0.000314193] MULTIVARIATE NORMAL	
CI, confidence interval			

7.3.7. 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 intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

It is assumed that no additional patients show response to lenalidomide following the initial response assessed within the clinical trial data. Response status i.e. whether patients are transfusion independent or not, is then linked directly to AML and mortality outcomes which are extrapolated beyond the trial period based upon parametric curves fit to the data within the trial (see Section 7.3.1).

7.3.8. Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 29. Assumptions and justifications in economic model

Assumption	Justification	Reference
Response is determined at 84 days	96.25% of patients who experience a major response do so within 84 days of starting treatment	Section 7.3.1
Response is defined as a patient achieving transfusion independence – that is, a completely removed need for the transfusion of RBC – for a period of 56 consecutive days (8 weeks)	As per clinical trial	Section 7.3.1
Responding patients change transfusion status	Simplifying assumption backed up by clinical trial	Section 7.3.1

during the cycle of treatment initiation		
Non-responding patients remain on therapy until non-response is determined	Conservative assumption made for the purposes of costing	Section 7.3.1
Responding patients remain on therapy until cessation of response is determined	As per clinical trial	Section 7.3.1
Patients receive iron chelation after reaching a threshold level of units of RBCs transfused	Derived from literature	Section 7.3.1
Patients that achieve transfusion independence have their RBC count reset to 0	Simplifying assumption – likely to reflect clinical practice	Section 7.3.1
Response to iron chelation is determined in the 1st cycle of administration	Based upon available literature	Section 7.3.1
Patients that do not respond to iron chelation are at risk of complications associated with iron overload	Based upon available literature	Section 7.3.1
Patients that respond to iron chelation treatment are assumed to receive treatment up to the point of progression to AML or death	Reflects clinical practice	Section 7.3.1
The rate of progression to AML is dependent on transfusion status	Based upon clinical trial data	Section 7.3.1
Once in AML, all patients on all treatment arms are assumed to receive the same treatment. No modelling of treatment options, of blood transfusions or iron chelation occurs	Reflects clinical practice	Section 7.3.1
Patients who progress to AML with cardiac disease associated with transfusion dependence, or diabetes or hepatic complications associated with iron overload, retain all costs and utility dis-benefits associated with these conditions	Reflects clinical practice	Section 7.3.1
Mortality rates are	Based upon clinical trial	Section 7.3.1

dependent on transfusion status and whether a patient has progressed to AML	data	
Mortality rates in transfusion states are assumed to be weibull and memory-less	Based upon clinical trial data	Section 7.3.1
Mortality in AML is Weibull and requires memory of when the patient entered the AML state	Based upon available literature	Section 7.3.1

7.4. Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1. Please outline the aspects of the condition that most affect patients' quality of life.

Myelodysplastic syndromes (MDS) are characterized by ineffective hematopoiesis and persistent peripheral blood cytopenias. Anaemia is the most common disease manifestation of MDS and is estimated to be present in at least 85% of cases. Anaemia is typically associated with dizziness, headache, chest pain, shortness of breath and fatigue, and may lead to reduced mental alertness, physical weakness, poor concentration and lethargy. The side-effects can profoundly impact a patient's overall functioning and well-being. Several clinical trials have shown that erythroid response to erythropoiesis stimulating agents (ESA) and MDS response to hypomethylating agents was generally associated with an improvement in HRQL.[72,87,88]

7.4.2. Please describe how a patient's HRQL is likely to change over the course of the condition.

Patients with MDS are reported to have statistically and clinically significant differences, relative to the general population, in physical, role, emotional, cognitive and social functioning components of HRQL as well as worse fatigue and global QoL.[89]

The course of a patient's HRQL over time is likely to be determined to a significant extent by their transfusion status, and haemoglobin level as well as their age. In other words, older patients who are transfusion dependent with a depressed haemoglobin level are likely to have the poorest HRQL.

HRQL data derived from clinical trials

7.4.3. If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

No health status measure, such as EQ-5D, was included in MDS-004. HRQL data were collected in the study using the Functional Assessment of Cancer Therapy-Anaemia (FACT-An) tool as reported earlier in the clinical section of this submission (see section 6.3.5). However, these data are not consistent with the reference case and cannot be used in the cost-effectiveness analysis.

Mapping

7.4.4. If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

EQ-5D data were collected at baseline in the MDS-004 study. Attempts were therefore made to estimate EQ-5D utilities by mapping from the FACT-An data collected in the MDS-004 clinical trial. In preliminary analyses, a relationship between FACT-An and 5Q-5D was explored, making use of regression models to map observed FACT-An scores from MDS-004 to corresponding EQ-5D scores. Unfortunately, mapping models were characterised by a level of error (between baseline EQ-5D scores from the trial and those predicted by the mapping exercise) that was considered unacceptable.

HRQL studies

7.4.5. Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A comprehensive systematic search was designed and implemented to identify relevant HRQL data for patients with MDS del 5q. Full details of the searches as well as inclusion and exclusion criteria are included in Appendix 12. A further study has recently been published providing HRQL data on patients treated with lenalidomide in the MDS-004 study.[57]

7.4.6. Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.
- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

A total of 672 potentially relevant HRQL papers were identified. Having removed duplicates and applied inclusion criteria, 20 studies remained (including the recently published study by Revicki) and these are summarised in the table below.[57] Upon detailed assessement of these studies a total of 4 studies were identified that describe relevant health states, are potentially consistent with the NICE reference case and could be appropriate for cost-effectiveness analysis.

Table 30. HRQL papers identified

Lead author	Year	Country(ies)	n	Patient group	Type of information
Revicki[57]	2012	Europe	167	Low- and Int-1-risk MDS with del5q	FACT-An QOL scores
Buckstein[89]	2011	Canada	186	MDS	Assessment of QOL using the instruments EORTC QLQ-C30, FACT-An/Fatigue, EQ-5D

Lead author	Year	Country(ies)	n	Patient group	Type of information
Nilsson-Ehle[90]	2011	Sweden, Denmark	36	Elderly anaemic MDS low/int-1 risk	QOL, response rate and physical function
Oliva[91]	2011	Italy	45	Low- and Int-1-risk MDS with del-5q	QOL, efficacy, and safety of lenalidomide
Buckstein[92]	2009	Canada	73	MDS	Assessment of QOL using the instruments EORTC QLQ-C30, FACT-An/Fatigue, EQ-5D
Kelaidi[93]	2009	France	99	Low and int-1 MDS with anaemia	QOL – instrument not specified
Oliva[94]	2009a	Italy	148	Newly-diagnosed MDS	QOL-E and LASA QOL assessment scores
Oliva[95]	2009b	Italy	49	Low- and Int-1-risk MDS with del-5q	QOL efficacy, and safety of lenalidomide in the treatment of MDS with del-5q
Oliva[96]	2009c	Italy	49	Low- and Int-1-risk MDS with del-5q	QOL, efficacy, and safety of lenalidomide in the treatment of MDS with del-5q
Szende[97]	2009	UK, USA, Germany, France	47	MDS	QOL found using TTO and VAS methods.
Balleari[59]	2006	Italy	30	low-risk MDS	FACT-An QOL assessment scores
Goss[71]	2006	USA	n/a	Low/Int-1 risk transfusion dependent MDS associated with del-5q	Decision analytic model to compare costs and outcomes of lenalidomide with BSC
Spiriti[47]	2005	Italy	133	Low-risk MDS; Hb ≤ 10g/dL; stable clinical condition; life expectancy of ≥ 6 months	Response (transfusion status) and QOL (FACT-An) of patients receiving Epoetin Alfa
Stasi[88]	2005	Italy	53	Previously untreated low/int-1 risk MDS; 46 transfusion dependent	QOL measures; LASA, global fatigue scale and FACT-An assessments

Lead author	Year	Country(ies)	n	Patient group	Type of information
Casadevall[72]	2004	France	60	MDS & anaemia	Cost and QOL (FACT-An) for ESA+G-CSF patients vs standard care
Clavio[98]	2004	Italy	11	Low-risk MDS	Prospective, open label, non-randomised study of the effect on QOL (FACT-An) and brain function of high dose rHuEPO
Sekeres[99]	2004	USA	43	Elderly advanced MDS and AML	QOL measures; SF-12, FACT-An and Geriatric Depression Scale)
Hellstrom-Lindberg[77]	2003	Scandinavia	53	MDS & anaemia good and intermediate risk groups	Predictive model for EPO response and analyses of QOL
Jansen[45]	2003	The Netherlands	50	TD MDS patients	A cross-sectional study of 3 HRQoL measures (SF-36, MFI and EQ-5D VAS)
Kornblith[87]	2002	USA	191	MDS	Quality of life (EORTC QLQ-C30) and RBC transfusion requirement for azacytidine vs supportive care

Dealing first with the 16 less relevant studies that were identified which reported some HRQL data in MDS patients, a wide variety of tools were used. Studies by Balleari (2006),[59] Spiriti (2005),[47] Stasi (2005),[88] Casadevall (2004),[72] Clavio (2004),[98] Sekeres (2004)[99] and Revicki (2012)[57] used the FACT-An instrument in studies recruiting patients with MDS ranging from low-risk to advanced MDS and AML. A number of other studies reported HRQL data that had been collected using the EORTC QLQ-C30 and/or QoL-E instruments (Kornblith 2002, Hellstrom-Lindberg 2003, Oliva 2009a, 2009b and 2009c, Oliva 2011, Nilsson-Ehle 2011).[77,87,90,91,94,95] Again, patients in these studies were recruited with a range of disease severity. None of these studies provide data that is consistent with the reference case or suitable for use in cost-effectiveness analysis. A cross-sectional study by Jansen (2003) in patients from the Netherlands with transfusion dependent MDS included the SF-36

as well as the multidimensional Fatigue Inventory (MFI) and the EQ-5D VAS. The study estimated the average EQ-5D VAS for MDS patients to be 61.2. No comparable estimates were available from this study for transfusion independent patients since only dependent patients were included.[45]

Four studies were identified in the systematic searches that provided potentially relevant information for the cost-effectiveness modelling. These were Goss (2006),[71] Szende (2009),[97] Buckstein (2009)[92] and Buckstein (2011).[89] These are described in more detail below.

The study by Goss et al was an economic evaluation and has already been discussed earlier in section 7.1.2. Health state descriptions were developed based on published literature and reports from MDS patient focus group discussions. The authors then assessed QOL by conducting health utility interviews with a small group of MDS patients (n=8). These interviews used the TTO method to value the health states on a scale anchored on 1 (perfect health) and 0 (death).The health states developed were transfusion dependence, reduced transfusion requirement and transfusion independent. Health state descriptions included varying severity/intensity of problems on important QoL domains including fatigue, tiredness and social functioning. Utility estimates were 0.5 (SD=0.23) for transfusion dependent, 0.81 (SD=0.10) for reduced transfusion requirement and 0.91 (SD=0.04) for transfusion independent. Results from the Goss study are potentially consistent with the NICE reference case and could be used in the cost-effectiveness analysis. However, the small sample of patients used in the study is an important weakness and introduces considerable uncertainty.[71]

Szende (2009) reports results from a sample of 47 MDS patients in the US (n = 8), France (n = 9), Germany (n = 9) and the UK (n = 21). Patients were interviewed to elicit the utility value of TI, reduced transfusion (RT) and TD. These values were found using visual analogue scale (VAS) and time trade-off (TTO) methods. In the TTO exercise, patients were asked to make a pairwise choice between living with MDS, either transfusion dependent or independent, for five years, and living in perfect health for a shorter period of time. This was repeated until a point of indifference was obtained, at which the respondent was unable to choose a preference for either of the two available alternatives. EQ-5D characteristics were surveyed to describe the patient sample. The mean EQ-5D index value was 0.78,

and patients reported at least some problem with mobility (45%), usual activities (40%), pain/discomfort (47%), and anxiety/depression (34%).[97]

The study provides evidence that TI is associated with significantly better QOL scores ($p < 0.001$) compared to both RT and TD. Patients put a high value on being TI when their preferences are measured on a utility scale. This indicates that MDS patients are willing to trade-off length of life in order to achieve TI, especially if patients are TD, and this is reflected by the 0.60 utility score. Results were similar between countries and in all cases patients estimated a significant difference in utility between TD and TI.[97]

In the UK sample using the TTO method, the mean utility for transfusion dependent was 0.65 (SD = 0.29) and the mean utility for transfusion independent was 0.85 (SD = 0.15). The Szende study provides values that are arguably suitable for cost-effectiveness analysis and are the closest to the NICE reference case of the available data. One drawback in relation to the Szende study is that AML is not included as a separate health state since this is required for the cost-effectiveness model.[97]

A third, potentially suitable source of utility data is provided in a study by Buckstein. Data from this study is available in the form of two abstracts (2009, 2011). The 2009 abstract is a preliminary analysis of the patient population reported in the 2011 abstract. The study comprises a prospective assessment of QOL in 186 patients registered in a MDS clinic in Canada using the instruments EORTC QLQ-C30, FACT-An/Fatigue, EQ-5D and a global fatigue scale. Of the 186 patients there were only 105 with measurable IPSS scores, 81% fell into low or intermediate-1 risk categories and 5% had del-5q abnormality, 33% were TD and 43% had a haemoglobin (Hb) level of ≤100 g/L.[89,92]

Relevant utility estimates are only available from the preliminary analysis reported in the 2009 abstract and poster presentation. In this analysis, the median patient age was 73 and 60% were male. Of the 69 patients in this preliminary sample with measurable IPSS scores, 80% fell into low or intermediate-1 risk categories, 8% had del 5q syndrome, 41% were TD, 23% were receiving lenalidomide, 25% iron chelation and 19% growth factors. Eight of 32 patients who had repeated QOL assessments increased their Hb level to > 100 g/L and demonstrated increased

global QOL. The EQ-5D utility for transfusion independent patients was 0.8 (SD not given) and for transfusion dependent it was 0.63 (SD not given).[89,92]

Overall, from the available data the utility estimates from the Szende study are the most relevant and the closest to the NICE reference case.[89,92,97] The Goss study offers estimates from a very limited patient sample.[71] The Buckstein study reports a lower utility for transfusion independence compared to the Szende study (0.8 versus 0.85). However, the Buckstein data are derived from an older patient population (mean 73 years) whereas the Szende data are from a patient population of identical average age to the MDS-004 study (67 years).[89,92,97]

7.4.7. Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable

Adverse events

7.4.8. Please describe how adverse events have an impact on HRQL.

Patients with MDS del 5q typically experience a number of adverse events during the course of their disease and associated treatment. A common complication of dependence on blood transfusions is iron overload which requires iron chelation therapy. A recent technology appraisal for the treatment deferasirox (DFO) elicited utility values using the TTO technique in a cross section of the UK general population. DFO therapy was found to decrease utility by 21% compared to oral chelation, and oral chelation was found to have no adverse effect on QoL compared to no chelation.[100]

Patients who are transfusion dependent and experience iron overload are at increased risk of developing other serious complications including cardiac disease and diabetes as well as hepatic complications. Decreases in QoL associated with cardiac disease and diabetes were estimated in the Beaver Dam Health Outcomes Study utilising the Time Trade Off method. Reported decreases for cardiac disease and diabetes were 17.9% and 12.3% respectively.[101] Compensated cirrhosis has been reported to be associated with an 8% decrease in QoL on the basis of a study using the Standard Gamble and Time-Trade Off techniques.[102]

Neutropenia and thrombocytopenia occur frequently in patients with MDS, both as a characteristic of the disease and also as a result of treatment intervention. These adverse events are likely to have some effects on quality of life but since they are typically transient and manageable, QoL impairment is likely to be short-term.

Quality-of-life data used in cost-effectiveness analysis

7.4.9. Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Table 31. Data used in cost-effectiveness analysis

State	Utility value	Confidence interval	Reference in submission	Justification
Utilities - Transfusion Independent	0.85	[0.793-0.900]	Section 7.4.6	Szende (2009) study in UK patients provides estimates that are the best approximation to the NICE reference case[97]
Utilities - Transfusion Dependent	0.65	[0.543-0.751]	Section 7.4.6	As above
Utilities - AML	0.65	[0.543-0.751]	Section 7.4.6	Conservatively assumed to be same as TD state since

				not reported separately in Szende (2009) study[97]
AE utility decrement - DFO use	21.0%	[0.158-0.263]	Section 7.4.8	Published evidence to support decrement where IV chelation is used (McLeod, 2009)
AE utility decrement - Oral Chelator use	0.0%	Not included in PSA	Section 7.4.8	Published evidence to support no decrement for oral therapy (McLeod, 2009)
AE utility decrement - Cardiac Disease	17.9%	[0.068-0.290]	Section 7.4.8	Published data from the Beaver Dam study (Fryback, 1993)
AE utility decrement - Diabetes	12.3%	[0.050-0.196]	Section 7.4.8	Published data from the Beaver Dam study (Fryback, 1993)

AE utility decrement - Hepatic Complications	8.0%	[0.060-0.100]	Section 7.4.8	Assumed to be similar to decrement in cirrhotic Hepatitis C patients (Wong 1995)
AE utility decrement - Thrombocytopenia	0.0%	Not included in PSA	Section 7.4.8	Assumption
AE utility decrement - Neutropenia	0.0%	Not included in PSA	Section 7.4.8	Assumption

7.4.10. If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable.

7.4.11. Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

As described elsewhere in the submission, patient's HRQL is strongly associated with their requirement for blood transfusions and their haemoglobin level. As a result patients who are transfusion dependent experience dizziness, headache, chest pain, shortness of breath and fatigue, leading to reduced mental alertness, physical weakness, poor concentration and lethargy.[57] In contrast, patients achieving transfusion independence experience significant improvements in HRQL. There is evidence to suggest that patients responding to treatment and achieving transfusion independence experience progressive improvements in HRQL over time in parallel with increases in their haemoglobin levels.[95]

7.4.12. Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

Not applicable

7.4.13. If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable – all patients enter model in the transfusion dependent health state with a utility score reflecting this.

7.4.14. Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

Utility values are adjusted by an age-dependent factor derived from Kind *et al*, who published utility decrements with increasing age.[103] Individuals start the model at the average age of the MDS-004 model of 67 years; a weighting factor of 1 is applied to

utilities from here until the age of 74, in line with Kind et al.[103] Beyond this age, utilities are weighted by a factor of 0.936, reducing utility by 6.4%.

7.4.15. Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.4.16. Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The expected HRG coding of best supportive care for lower-risk MDS would be SA06F – 'Myelodysplastic Syndrome without CC'. The relevant PbR tariff for 2012/13 and NHS Reference Cost for 2011/12 may be found on the DH website.[104] In practice coding may vary between providers.

7.4.17. Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The intervention being appraised (Lenalidomide) is outside the tariff and therefore PbR costing approach has not been used. Costs relating to the monitoring of patients

and management of adverse events have been estimated using NHS reference costs and the literature.

Resource identification, measurement and valuation studies

7.4.18. Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

A systematic search was conducted as described earlier in section 7.4.6. No relevant costing studies were identified. The systematic searches to identify cost-effectiveness studies (as discussed earlier in section 7.4.6) included relevant search terms to identify any suitable cost studies. The full systematic searches are described in section 10.10, appendix 10. A number of cost analyses were identified in the literature. However, none of the studies related to the UK setting and since cost data are typically not considered to be generalisable no detailed review of these studies has been conducted.

7.4.19. If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Not applicable

Intervention and comparators' costs

7.4.20. Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The table below provides a summary of the treatment costs for lenalidomide compared to BSC. Lenalidomide drug costs have been taken from the British National Formulary.[1] The cost of tests has been taken from NHS Reference Costs[104] and the cost of a GP visit has been taken from the Personal Social Services Research Unit.[105]

Table 32. Unit costs associated with the technology in the economic model

Items	Intervention	Transfusion Only	ESA	Ref. in submission
Technology cost	£180 per 10mg tablet £170 per 5mg tablet	£0	£110.62 per 20,000 IU vial ESA £52.71 per 200mg vial GCSF	1.10, 1.11 and 7.4.21
Mean cost of	£3,780 per cycle	£0	£884.96 per	

technology treatment	receiving 10mg (£180 * 21 days per cycle) £4,760 per cycle receiving 5mg at 28 days per cycle (£170 * 28 days per cycle) £2,380 per cycle receiving 5mg at 14 days per cycle (£170 * 14 days per cycle)		cycle for ESA (£110.62*2 vials per week*4 weeks) £632.52 for GCSF (£52.71*3 vials per week*4 weeks)	
Administration cost	£0 – oral administration	£0	£0 - conservative	
Monitoring cost	£36 per GP visit (£30.29,£42.11) Weekly for first 56 days, 2 weekly until 84 days, every 28 days thereafter	Same cost per visit Visits every 28 days	Same cost per visit Visits every 28 days	PSSRU 2011[105]: GP surgery cost including qualifications Table 10.8b
Tests	£3.09 for full blood count (£2.60,£3.61) One of each with every GP visit	Same cost One of each with every GP visit	Same cost One of each with every GP visit	NHS 2011/12 reference costs[104] – haematology and biochemisty
Total	≤£3,956 per cycle depending on the proportion of patients receiving each dosing regime within the trial	£40.32 per cycle	£925.28 for ESA alone £1557.80 for ESA + GCSF	

(confidence interval)

Health-state costs

7.4.21. Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Drug costs

Drug acquisition prices are obtained from the British National Formulary.[1]

The price of IV iron chelation has been estimated using the average patient weight from the MDS-004 trial of 69 kg and the relative market share and prices of Desferal and DFO based upon Prescription Cost Analysis: England 2010[83] and BNF64.[1] A summary of the drug acquisition costs is presented in Table 33.

Table 33. Drug acquisition costs assumed in the base case

Treatment	Standard unit	Source	Unit price
Lenalidomide	per 10 mg tablet	BNF 64	£180.00
Lenalidomide	per 5 mg tablet	BNF 64	£170.00
Erythropoeitin (Eprex)	per 20,000 IU vial	BNF 64	£110.62
G-CSF (Neupogen)	per 300 mg vial	BNF 64	£52.71
IV iron chelation	per dose	BNF 64	£25.35
Oral iron chelation	per dose	BNF 64	£46.37

Monitoring costs

Assumptions are made for each treatment type as to the monitoring requirements. These are detailed below with the unit costs summarised in Table 34.

Lenalidomide

The frequency of monitoring associated with the initiation of lenalidomide treatment was taken directly from the summary of product characteristics: visits (and thus blood counts) occur weekly for the first eight weeks, bi-weekly for the next four weeks, and then four-weekly thereafter (at this point they are being monitored at the same frequency as patients who are not receiving treatment).

Best supportive care

Monitoring was assumed to occur once per cycle throughout treatment. This is likely to underestimate the cost for best supportive care, particularly as monitoring is likely to be more frequent for patients receiving ESA.

Iron chelation

Patients who are on iron chelation accrue the costs of four-weekly liver function tests at the monitoring visits. They do not accrue additional visit costs, as the monitoring associated with iron chelation is assumed to occur at the same time as the scheduled blood counts.

Table 34. Unit costs for monitoring requirements

Item	Standard Unit	Unit Price	Source
GP Visit	Per visit	£36.00	PSSRU 2011[105] GP surgery cost including qualifications Table 10.8b
Full Blood Count	Per Test	£3.09	NHS 2011/12 reference costs[104] – haematology
Serum Ferritin	Per Test	£1.23	NHS 2011/12 reference costs[104] - biochemistry

Blood transfusions

Blood transfusions have two associated costs, the cost of administering the blood (nurse time, ward time etc) and the cost of acquiring a unit of blood.
In some regions (e.g. the UK) the cost of administration is included in the cost of a unit of blood, in others the cost of administration has to be added on. Both options are possible in the model. A unit of blood in the UK was costed at £111.16 in 2004 prices, whilst other costs – administration costs including cross matching, equipment and an outpatient procedure – were estimated to be £196.16,[106] using inflation indices within PSSRU. Platelet transfusion was costed at £187.00.[107] These prices have been inflated to £133.10, £234.88 and £312.49 respectively (Table 35 and Table 36).

Table 35. Blood transfusion costs

Cost component	Cost
RBC unit	£133.10
Administration (non-RBC costs)	£234.88
Total cost	**£367.98**

Table 36. Blood transfusion costs

Cost component	Cost

Platelet Transfusion (Including administration)	£312.49

Cost of treating AML

Information regarding the UK cost of AML was obtained from the Health Technology Assessment for azacitadine where the treatment cost for AML was estimate as £1,844 per 28 day cycle. This cost includes costs of follow-up appointments, associated adverse events, concurrent medication and blood/platelet transfusions, and routine tests. This was inflated using PSSRU to £1,919.40 per cycle (or £68.55 per day).[105]

Complications of iron chelation and transfusion dependency

The cost of complications is taken from relevant literature. Costs have been inflated as required using values from PSSRU.[105]

Table 37. Unit costs for complications

Adverse Event	Time period	Source	Unit Price
Cardiac Disease	annual cost	Luengo-Fernandez *et al*[108]	£3,792.30
Hepatic Complications	annual cost	Wright *et al*[109]	£1,445.80
Diabetes Mellitus	annual cost	Kanavos P *et al*[110]	£ 3644.40

Table 38 shows how the costs are associated with each health state in the model.

Table 38. Costs by health state

Health state	*Lenalidomide drug & monitoring costs*	*Best supportive care drug & monitoring costs*	*Iron chelation drug & monitoring costs*	*Transfusion costs*	*AML costs*	*Cardiac disease costs*	*Hepatic complications costs*	*Diabetes costs*
TI	✓ - Lenalidomide arm	✓ - Best supportive care arm						
TD-NC		✓		✓				
TD-NC-Cardiac		✓		✓		✓		
TD-C		✓	✓	✓				
TD-C-Cardiac		✓	✓	✓		✓		
TD-CF		✓		✓				
TD-CF-Cardiac		✓		✓		✓		
TD-CF-HC		✓		✓			✓	
TD-CF-Diabetes		✓		✓				✓
AML					✓			
AML-Cardiac					✓	✓		
AML-HC					✓		✓	
AML-Diabetes					✓			✓

Adverse-event costs

7.4.22. Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

The cost of adverse events is taken from NHS Reference costs.[104] These costs are multiplied each cycle by the event rate and the proportion of patients that are treated for the adverse event (see section 7.3.1).

Table 39. Unit costs for adverse events

Adverse event	Time period	Source	Unit price
Thrombocytopenia	per episode	NHS Reference costs 2011/2012 – SA08F[104]	£1,636.38
Neutropenia	per episode	Assumed as thrombocytopenia	£1,636.38

Miscellaneous costs

7.4.23. Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No other costs are included.

7.5. Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

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

An additional health state for reduced transfusion dependency was explored during model development but rejected due to lack of data available (there were not enough patients in the trial to reliably estimate mortality and AML progression based on 3 categories of transfusion dependency).

Structural uncertainty within the model is explored for the following scenarios:

- Impact of using inputs based upon all patients in the trial rather than just UK patients:
    - Proportion of patients using ESA: 52.7%

  - Average number of RBC - pre treatment, no chelation: 8.97
  - Average RBC units per cycle for transfusion dependent patients: 4.49
  - Average Platelets (Units) per cycle for transfusion dependent patients: 0.049
- Impact of comparing to either all patients using ESA or all patients only receiving transfusions as required
- Impact of using alternative utility sources: Buckstein and Goss[71,89,92]
- Impact of altering the threshold at which chelation is given (range from 20 – 30 units)
- Impact of selecting alternative curve fits for mortality, AML and response duration (all alternative curves fitted)

7.5.2. Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

Deterministic sensitivity analysis has been carried out to establish which variables have the greatest influence on the ICER outcome. Upper and lower bounds have been determined using the distributions detailed in the full parameter list provided in Section 7.3.6 and Section 7.4.9. The following additional variables were included:

- The costs of adverse events, hepatic and cardiac complications, AML, blood and blood administration, GP visits and tests: Gamma distribution, standard error assumed to be 10% of the mean
- Hepatic complications – standard error taken from the source publication as 284.59.

The upper and lower bounds are set at the 95% confidence intervals of the distributions for each variable.

7.5.3. Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of 'priors'. If any parameters or

variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis has been carried out. Distributions are taken from Section 7.3.6 and Section 7.4.9 with the distributions for costs being calculated as specified in Section 7.5.2. The only parameters excluded from probabilistic sensitivity analysis are the unit costs of drugs as these costs are fixed and not subject to uncertainty and the number of monitoring visits carried out per cycle for lenalidomide and best supportive care as again these are fixed according to treatment protocol, the cost of these visits is varied within the analysis.

7.6. Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.6.1. For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example,

adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Table 40. Summary of model results compared with clinical data

Outcome	Clinical trial result	Model result
Median overall survival lenalidomide	5.2 years (MDS003 + MDS004) 3.7 years (MDS004)	4.7 years
Median overall survival Transfusion Only	3.8 years (MDS003 + MDS004) 3.5 years (MDS004)	3.8 years
Median time to AML progression for transfusion dependent patients	Not reached in the trial	5.4 years
Median time to AML progression for transfusion independent patients	Not reached in the trial	7.9 years
Median duration of response for patients who initially respond: lenalidomide	Not reached in the trial: lower bound of the 95% CI 1.9 years (MDS 004) 2.2 years (MDS 003)	2.1 years
Median duration of response for patients who initially respond: Placebo	Not reached in the trials (lower bound of the 95% CI 0.2 years (MDS 004)	1.5 years (evaluated based upon 5mg data)
% of patients experiencing thrombocytopenia grade 3/4	Lenalidomide 10mg: 44.9% Placebo: 3%	41.9% (difference between the two arms)
% of patients experiencing neutropenia grade 3/4	Lenalidomide 10mg: 75.4% Placebo: 17.9%	57.5% (difference between the two arms)

7.6.2. Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

Markov traces are provided in Appendix C.

7.6.3. Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

Please see Markov trace.

7.6.4. Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

All results provided within this section have been calculated without the Patient Access Scheme. Results including the Patient Access Scheme are presented in Appendix B.

Table 41. Model outputs by clinical outcomes – lenalidomide – without PAS

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Transfusion independent	1.76	1.39	£69,731.35
Transfusion dependent	3.61	1.90	£79,758.20
AML	0.32	0.17	£6,818.16
Total	**5.69**	**3.46**	**£156,307.71**
LY, life years; QALY, quality-adjusted life year			

Table 42. Model outputs by clinical outcomes – best supportive care

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Transfusion independent	0.17	0.13	£2,415.61
Transfusion dependent	4.06	2.27	£96,690.57
AML	0.30	0.17	£6,619.99
Total	**4.53**	**2.58**	**£105,726.18**
LY, life years; QALY, quality-adjusted life year			

7.6.5. Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Table 43. Summary of QALY gain by health state (including discounting)

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Transfusion Independent	1.39	0.13	1.26	1.26	74.05%
Transfusion Dependent without Iron Chelation	0.13	0.10	0.03	0.03	1.81%

Therapy					
Transfusion Dependent with Iron Chelation Therapy	1.11	1.39	-0.28	0.28	16.33%
Transfusion Dependent with Chelation Failure	0.65	0.78	-0.13	0.13	7.54%
AML	0.17	0.17	0.00	0.00	0.27%
Total	**3.46**	**2.58**	**0.89**	**1.70**	**100%**

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 44. Summary of costs by health state without PAS

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Transfusion Independent	£69,731.35	£2,415.61	£67,315.74	£67,315.74	79.71%
Transfusion Dependent	£79,758.20	£96,690.57	-£16,932.38	£16,932.38	20.05%
AML	£6,818.16	£6,619.99	£198.17	£198.17	0.23%
Total	**£156,307.71**	**£105,726.18**	**£50,581.53**	**£84,446.29**	**100.00%**

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 45. Summary of predicted resource use by category of cost without PAS

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Technology cost	£68,261.29	£2,393.04	£65,868.25	£65,868.25	78.00%
Complications: Thrombocytopenia and Neutropenia	£316.14	£0.00	£316.14	£316.14	0.37%
Iron Chelation Therapy	£33,110.04	£41,111.57	-£8,001.53	£8,001.53	9.48%
Complications: Cardiac Disease, Diabetes Mellitus and Hepatic Complications	£712.81	£756.88	-£44.07	£44.07	0.05%
Blood transfusions	£44,381.48	£52,857.69	-£8,476.21	£8,476.21	10.04%
AML	£6,818.16	£6,619.99	£198.17	£198.17	0.23%
General Monitoring	£1,153.93	£22.57	£1,131.36	£1,131.36	1.34%
Monitoring with Best Supportive	£1,524.43	£1,927.89	-£403.46	£403.46	0.48%

Care					
Monitoring with Iron Chelation Therapy	£29.43	£36.55	-£7.11	£7.11	0.01%
Total	**£156,307.71**	**£105,726.18**	**£50,581.53**	**£84,446.29**	**100%**
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

7.6.6. Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table 46. Base-case results without patient access scheme

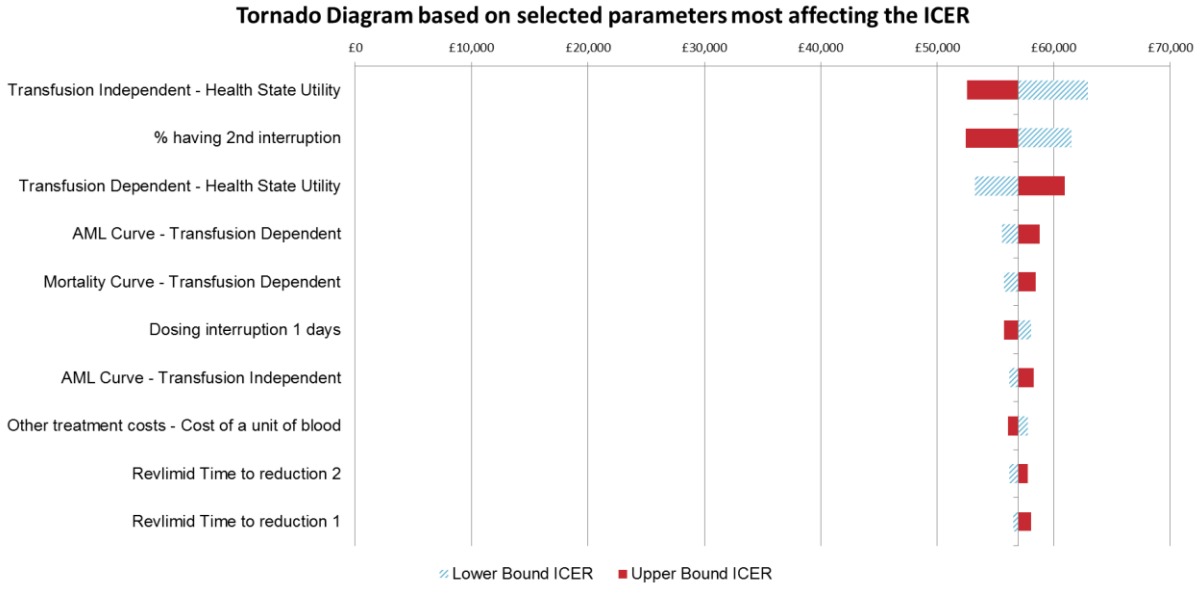
Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incrementa (QALYs)
Best supportive care	£105,726.18	4.53	2.58	-	-	-	£41,051.95	-
Lenalidomide	£156,307.71	5.69	3.46	£50,581.53	1.16	0.89	£45,131.75	£56,965.0
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses

7.6.7. Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Figure 25 shows the top 10 parameters affecting the ICER. The most influential parameter is the utility assigned to transfusion independence. The ICER is also sensitive to the parameters used for mortality and AML, the proportion of patients having dose interruptions and the health state utilities assumed for transfusion dependence. The ICER varies between £52,560 and £62,591 under deterministic sensitivity analysis.

Figure 25. Tornado diagram – top 10 parameters affecting the ICER without PAS



7.6.8. Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Probabilistic sensitivity analysis was conducted using 1000 model runs. The mean ICER using probabilistic analysis was similar to the deterministic ICER (£58,178 per QALY). 0% of observations were cost-effective at a £30,000 per QALY threshold. In all cases lenalidomide was more effective than best supportive care.

Table 47. Output from PSA

	Without PAS
Mean Incremental Costs	£50,178
Mean Incremental QALYs	0.862
Mean ICER	£58,178
% of observations cost-effective at £20,000 threshold	0%
% of observations cost-effective at £30,000 threshold	0%

Figure 26. Cost effectiveness scatter plot without PAS

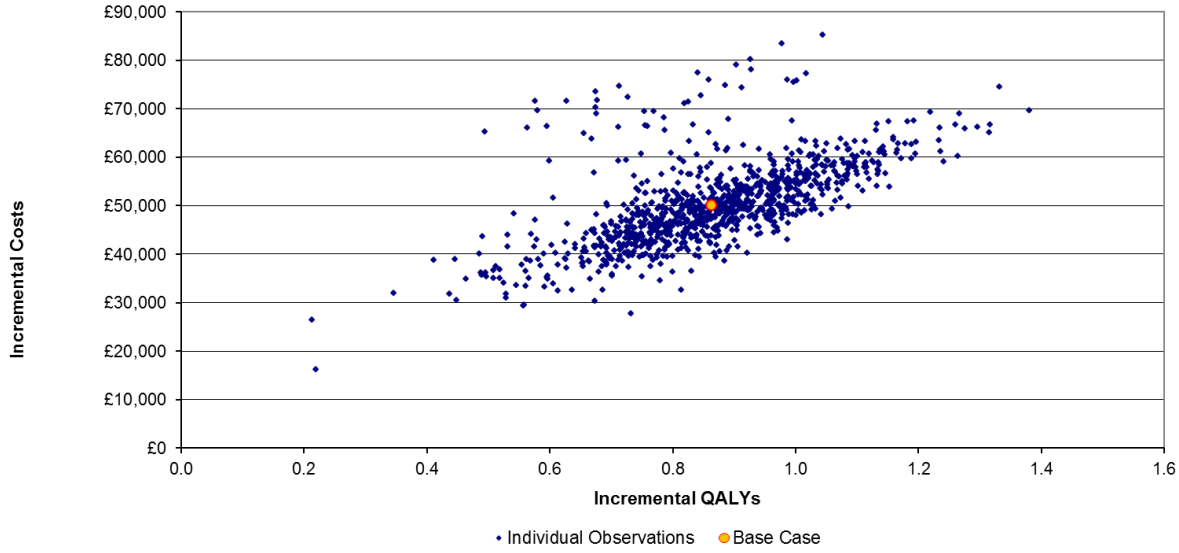
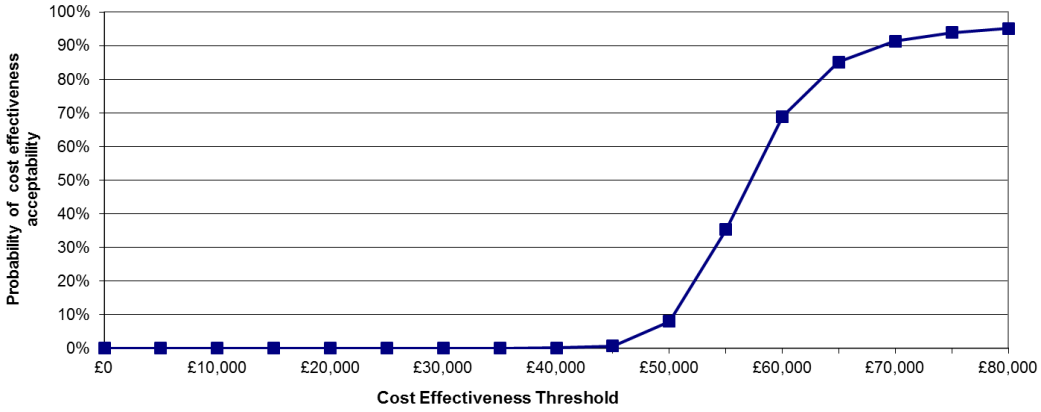


Figure 27. Cost effectiveness acceptability curve without PAS



7.6.9. Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Table 48 to Table 54 present the results of structural sensitivity analyses. The model is not overly sensitive to the curve fits assumed, the comparator used, the source of utilities used, the use of all patients rather than UK patients or the iron chelation threshold used.

Table 48. All trial patients rather than UK patients without PAS

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Best supportive care	£105,434	4.55	2.60	-	-	-	-
Lenalidomide	£156,937	5.69	3.47	£51,504	1.15	0.87	£59,500

Table 49. Comparator without PAS

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
All patients using ESA	Best supportive care	£110,270	4.59	2.65	-	-	-	-
	Lenalidomide	£156,308	5.69	3.46	£46,038	1.11	0.81	£56,623
All patients receiving only transfusions as required	Best supportive care	£103,662	4.53	2.57	-	-	-	-
	Lenalidomide	£156,308	5.69	3.46	£52,646	1.16	0.89	£58,913

Table 50. Iron chelation threshold without PAS

Threshold	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
20	Best supportive care	£104,932	4.53	2.58	-	-	-	-
	Lenalidomide	£154,687	5.69	3.46	£49,755	1.16	0.89	£55,953
30	Best supportive care	£105,103	4.53	2.58	-	-	-	-
	Lenalidomide	£156,315	5.69	3.46	£51,212	1.16	0.89	£57,761

Table 51. Source of utilities without PAS

Threshold	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Goss	Best supportive care	£105,726	4.53	2.02	-	-	-	-
	Lenalidomide	£156,308	5.69	3.08	£50,582	1.16	1.06	£47,621
Buckstein	Best supportive care	£105,726	4.53	2.61	-	-	-	-
	Lenalidomide	£156,308	5.69	3.46	£50,582	1.16	0.85	£59,323

Table 52. Curve selection – response duration without PAS

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive	£105,695	4.53	2.58	-	-	-	-

	care							
	Lenalidomide	£155,216	5.69	3.46	£49,521	1.16	0.88	£56,265
Weibull	Best supportive care	£105,777	4.53	2.57	-	-	-	-
	Lenalidomide	£154,854	5.69	3.44	£49,077	1.16	0.87	£56,403
Log-logistic	Best supportive care	£105,746	4.53	2.58	-	-	-	-
	Lenalidomide	£155,763	5.69	3.46	£50,017	1.16	0.88	£56,730
Extreme Value	Best supportive care	£105,777	4.53	2.57	-	-	-	-
	Lenalidomide	£153,262	5.69	3.43	£47,484	1.16	0.86	£55,445

Table 53. Curve selection – AML progression without PAS

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive care	£109,086	4.71	2.65	-	-	-	-
	Lenalidomide	£161,005	5.95	3.56	£51,919	1.24	0.92	£56,717
Log-logistic	Best supportive care	£106,265	4.58	2.58	-	-	-	-
	Lenalidomide	£159,434	5.88	3.53	£53,169	1.30	0.95	£56,237
Lognormal	Best supportive care	£105,476	4.56	2.56	-	-	-	-
	Lenalidomide	£161,267	5.99	3.57	£55,791	1.43	1.00	£55,514
Extreme Value	Best supportive care	£105,132	4.49	2.57	-	-	-	-
	Lenalidomide	£153,259	5.51	3.40	£48,128	1.02	0.83	£57,703

Table 54. Curve selection – overall survival without PAS

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive care	£111,225	4.85	2.69	-	-	-	-
	Lenalidomide	£162,976	6.09	3.61	£51,751	1.24	0.91	£56,646
Log-logistic	Best supportive care	£108,060	4.66	2.63	-	-	-	-
	Lenalidomide	£162,982	6.01	3.61	£54,922	1.35	0.98	£55,813
Lognormal	Best supportive care	£110,195	4.77	2.68	-	-	-	-
	Lenalidomide	£166,422	6.18	3.69	£56,227	1.41	1.01	£55,536
Extreme Value	Best supportive care	£104,078	4.45	2.54	-	-	-	-
	Lenalidomide	£151,085	5.44	3.35	£47,006	0.99	0.81	£58,117

7.6.10. What were the main findings of each of the sensitivity analyses?

The mean ICER using probabilistic analysis was similar to the deterministic ICER. Without the patient access scheme 0% of observations were cost-effective at a £30,000 per QALY threshold. In all cases lenalidomide was more effective than best supportive care.

The most influential parameter within the model without the patient access scheme is the utility associated with transfusion independence. The ICER is also sensitive to the parameters for mortality and AML, dose interruption and the transfusion dependence health state utility assumed.

Table 48 to Table 54 present the results of structural sensitivity analyses. The model is not sensitive to the curve fits assumed, the source of utility values, the comparator used, the use of all patients rather than UK or the iron chelation threshold used.

7.6.11. What are the key drivers of the cost-effectiveness results?

The key driver of the model is the proportion of patients that achieve transfusion independence and the benefits that derive from this in terms of increased utility and reduced mortality.

7.7. Validation

7.7.1. Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

Multivariate regression analyses were performed as an internal model validation process to by computing the magnitude of effect and statistical significance of various explanatory variables on response duration and mortality from other causes than AML. This provides the benefit of checking that the influence of variables obtained from the data adheres to what we might expect a priori. These analyses were undertaken prior to data being analysed with a focus on trial crossover, but still provide useful insight, as demonstrated using the log-rank test; crossover is unlikely to affect the overall results.

For the placebo treatment arm, the effect of treatment duration on response duration is understandably insignificant. Haemoglobin level is found to be the only statistically significant parameter tested, with a unit (g/dL) increase of haemoglobin reducing the duration of response by over 33 days on average.

A much stronger effect of treatment duration on response duration is observed with 5 mg lenalidomide compared to placebo. An additional day on treatment is predicted to provide an additional day of transfusion independence, backed up by a high level of statistical significance. The patient having an increased need for blood transfusions pre-treatment, and having received prior Erythropoietin / Darbopoietin (EPO), both substantially decrease response duration. This indicates that patients who have not received prior EPO and are not requiring as many blood transfusions (i.e. lower risk patients) are more likely to respond to treatment with 5 mg Lenalidomide.

The 10 mg lenalidomide treatment group also displays a significant, positive effect of treatment duration on response duration. In this treatment arm no demographic parameters – including haemoglobin levels, pre-treatment transfusion burden and receipt of prior EPO – have a statistically significant impact on response duration compared to placebo, suggesting that 10 mg lenalidomide offers a positive response extension to all patients including higher risk groups.

A longer treatment duration is shown to significantly reduce the likelihood of death, with an odds ratio of 0.997 given every additional day of treatment. Being in the 10 mg lenalidomide treatment group is shown to have a significant effect, with a large magnitude – the odds ratio is 0.068 compared to the placebo trial arm.

As may be predicted *a priori*, increasing age raises the probability of death. Higher haemoglobin levels are observed to reduce the probability of death, and drastically so with an odds ratio of 0.51.

7.8. Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.8.1. Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No analysis of subgroups was undertaken in this submission. However, as a part of ongoing regulatory discussions with the EMA certain additional analyses are being explored, which may make it possible to undertake such analysis in future.

7.8.2. Please clearly define the characteristics of patients in the subgroup.

N/a

7.8.3. Please describe how the statistical analysis was undertaken.

N/a

7.8.4. What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

N/a

7.8.5. Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

The only obvious subgroup within the clinical trial was the Modified Intention to Treat (MITT) population reported in Section 6. The ITT population used within the modelling includes all subjects that were randomized to one of the three study treatments.

The MITT population has stricter criteria including only subjects with:

- A documented diagnosis of MDS that met IPSS criteria for low- to intermediate-1-risk disease and had an associated del 5q[31] cytogenetic abnormality, confirmed by central review of an evaluable bone-marrow aspirate/optional biopsy
- RBC transfusion-dependent anemia defined as not having any 56 consecutive days (2 months) without a RBC transfusion within at least the immediate 112 days (4 months) prior to Day 1 of the Pre-Randomization Phase
- At least 1 dose of study drug taken.

Using the MITT population was not considered appropriate as it is unlikely that in real-life practice these strict criteria for use of lenalidomide would be met. Additionally the reduction in sample size for analysis (from 69 in the 10 mg arm to 41 and from 67 in the placebo arm to 51) would have lead to increased uncertainty and difficulty in fitting curves.

The proportion of patients achieving transfusion independence in the 10 mg lenalidomide arm is similar between the two subgroups (61% in the MITT and 60.9% in the ITT).

As a part of the on-going regulatory discussions with the EMA additional analyses are being explored which may identify subgroups with better outcomes relative to the

entire cohort including an investigation of whether it is possible to provide results by cytogenetic subgroup. These analyses are not yet available.

7.9. Interpretation of economic evidence

7.9.1. 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?

No analysis of subgroups was undertaken in this submission, however as a part of ongoing regulatory discussions with the EMA certain additional analysis are being explored to identify potential subgroups which may make it possible to undertake such analysis in future.

7.9.2. Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

The evaluation considers all patients identified in the decision problem

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

The main strength of the evaluation is that the MDS-004 trial was considered an appropriate basis for evidence of treatment of patients in the UK. Modelled efficacy does not therefore rely on any indirect comparison or mixed treatment comparison.

The main weakness of the evaluation is that the model required the use of pooled data from the MDS-004 and MDS-003 trials to be able to accurately evaluate survival due to low patient numbers available for longer-term analysis in the MDS-004 trial.

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

An understanding of the extent of ESA use in the UK population would enhance the robustness of the model, currently this is assumed to be zero in the base case.

Section C – Implementation

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

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1. How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The incidence of MDS is between two and 13 per 100,000 people, and this figure increases to 30 cases per 100,000 people per year for patients over the age of 70 years.[25] In England, 2,204 people were newly diagnosed with MDS in 2009.[26] Derived from Hospital Episode Statistics (HES) data, the number of diagnosed MDS patients is estimated at approximately 18 per 100,000.[27] Many cases remain undiagnosed. Combining HES data with published population data indicates there are approximately 11,200 diagnosed MDS patients in the UK. Del(5q) is one of the most common cytogenetic abnormalities in MDS, occurring in approximately 15% of patients.[9,14,28] It is estimated that 70% of MDS patients are of low- and intermediate-1 risk, with between 39% and 50% of these blood transfusion dependent.[29] Applying the above breakdown, patient population eligible for treatment in year1 and for the next 5 years is estimated in the tables below:

Table 55. Patient population eligible for treatment

Diagnosed Cases of MDS	11200
Percentage of patients with del 5q	15%
Low & Int-1 Risk	70%
Transfusion Dependent	45%
Patients eligible for lenalidomide Rx	**529**

Table 56. Patients eligible for treatment over five years

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for treatment for lenalidomide	529	534	540	545	550
(Assuming a 1% increase per year in patient population)					

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

Current treatment options for the indicated population are best supportive care inclusive of blood transfusions and no assumptions have been made regarding its uptake. To a limited extent lenalidomide is already prescribed outside of a licence in England under CDF.

8.3. What assumption(s) were made about market share (when relevant)?

Table 57. Market share assumptions

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for treatment for lenalidomide	529	534	540	545	550
(Assuming a 1% increase per year in patient population)					
Assumed uptake of treatment	12%	19%	22%	25%	25%
Net Patient Population	63	102	119	136	138

The 1% annual increase in patient population is based on an assumption of marginal increase in the general elderly population.

8.4. In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The technology being appraised falls outside the NHS tariff and no other related costs have been identified at this point.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

Treatment with 10 mg lenalidomide is assumed at current list price of £3780 for a 21-day capsule pack.

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

No resource savings have been incorporated into the budget impact estimates. In practice there is likely to be a resource saving as result of patients not requiring blood transfusions when on lenalidomide.

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

Table 58. Estimated annual budget impact

	Year 1	Year 2	Year 3	Year 4	Year 5
Current Year BI assuming 50% DoT per year	£1,439,726	£2,302,362	£2,692,552	£3,090,316	£3,121,219
Prior Year BI due to "DoT spill-over"	£0	£1,439,726	£2,302,362	£2,692,552	£3,090,316
Total Annual Budget Impact	**£1,439,726**	**£3,742,089**	**£4,994,915**	**£5,782,868**	**£6,211,535**

* Assumptions - Cycle Cost (for 10 mg cap) = £3780; pts. receive 12 cycles in a year; pts. start treatment mid year

The estimated budget impact is £1.4 million in Year 1 increasing to £6 million by Year whic translates into a budget impact of around £2000 per 100,000 population in year1 increasing to a£11000 per 100,000 population in year 5.

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

Patients who remain in transfusion independent state as a result of the treatment will not require blood transfusions. These have not been quantified or accounted for in the above estimates. There may be other wider societal benefits and these have not been included.

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10. Appendices

10.1. Appendix 1

10.1.1. SPC/IFU, scientific discussion or drafts.

10.2. Appendix 2: Search strategy for section 6.1 (Identification of studies)

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), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

- CINAHL (Cumulative Index to Nursing and Allied Healh) via EBSCO
- The Cochrane Library: Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database
- Embase via OvidSP
- MEDLINE via OvidSP
- Science Citation Index via Web of Knowledge

10.2.2. The date on which the search was conducted.

Searches were conducted the week commencing Monday 2 January 2012.

10.2.3. The date span of the search.

No date limitations were appliedto the search; for example, MEDLINE was searched from 1948 to present.

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).

CINAHL

S57 (S52 NOT S55) and (S6 and S56)

S56 S52 NOT S55

S55 S53 or S54

S54 AU anonymous

S53 SO cochrane library

S52 S50 NOT S51

S51 (MH "Animal Studies")

S50 S45 NOT S49

S49 S46 or S47 or S48

S48 PT news

S47 PT letter

S46 PT editorial

S45 S43 or S44

S44 cost or costs or economic* or pharmacoeconomic* or price* or pricing*

S43 S39 or S42

S42 S40 or S41

S41 (MH "Health Resource Utilization")

S40 (MH "Health Resource Allocation")

S39 S33 not S38

S38 S34 or S35 or S36 or S37

S37 (MH "Business+")

S36 (MH "Financing, Organized+")

S35 (MH "Financial Support+")

S34 (MH "Financial Management+")

S33 (MH "Economics+")

S32 S6 and S31

S31 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30

S30 TX allocat* random*

S29 (MH "Quantitative Studies")

S28 (MH "Placebos")

S27 TX placebo*

S26 TX random* allocat*

S25 (MH "Random Assignment")

S24 TX randomi* control* trial*

S23 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask* or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))

S22 TX clinic* n1 trial*

S21 PT Clinical trial

S20 (MH "Clinical Trials+")

S19 S6 and S18

S18 S12 not S17

S17 ((MH "Animals")) and (S13 or S14 or S15 or S16)

S16 (MH "Animals")

S15 PT editorial

S14 PT letter

S13 PT commentary

S12 S7 or S8 or S9 or S10 or S11

S11 systematic N review OR systematic N overview

S10 (MH "Literature Review+")

S9 Metaanaly*

S8 meta analysis*

S7 (MH "Meta Analysis")

S6 S4 and S5

S5 5q

S4 S1 or S2 or S3

S3 TI MDS OR AB MDS

S2 myelodysplas*

S1 (MH "Myelodysplastic Syndromes+")

The Cochrane Library

#1 MeSH descriptor: [Myelodysplastic Syndromes] explode all trees
#2 myelodysplas*:ti,ab,kw
#3 MDS:ti,ab,kw
#4 #1 or #2 or #3
#5 5q
#6 #4 and #5

Embase

1. exp myelodysplastic syndrome/
2. myelodysplas$.mp.
3. MDS.ti,ab.
4. 1 or 2 or 3
5. 5q.mp.
6. 4 and 5
7. best supportive care.mp.
8. clinical practice.mp.
9. lenalidomide.mp.
10. revlimid.mp.
11. active therap$.ti,ab.
12. placebo/
13. placebo$.mp.
14. antiinfective agent/
15. antibiotic$.ti,ab.
16. blood transfusion/
17. transfusion$.ti,ab.
18. signal peptide/
19. erythropoietin receptor/
20. erythropoietin antibody/ or erythropoietin/ or recombinant erythropoietin/
21. erythropoietin$.ti,ab.
22. EPO.ti,ab.
23. darbepoetin alfa.mp.
24. epoetin alfa.mp.
25. epoetin beta.mp.
26. epoetin theta.mp.
27. epoetin zeta.mp.
28. macrogol derivative/
29. methoxy polyethylene glycol-epoetin beta.mp.
30. granulocyte colony stimulating factor/
31. Granulocyte Colony-Stimulating Factor$.mp.
32. G-CSF.mp.
33. recombinant granulocyte colony stimulating factor/

34. filgrastim.ti,ab.
35. lenograstim.mp.
36. pegfilgrastim.mp.
37. iron chelating agent/
38. iron/ and chelation therapy/
39. iron chelation/
40. iron chelat$.mp.
41. thioctic acid/
42. Alpha lipoic acid.mp.
43. ALA.ti,ab.
44. Deferasirox.mp.
45. deferoxamine mesylate/ or deferoxamine/
46. Deferoxamine.ti,ab.
47. dimercaprol/
48. Dimercaprol.ti,ab.
49. BAL.ti,ab.
50. succimer diisopentyl ester/ or succimer tc 99m/ or succimer di sec butyl ester/ or succimer dibutyl ester/ or succimer dimethyl ester/ or succimer diisobutyl ester/ or succimer derivative/ or succimer diethyl ester/ or succimer/ or succimer dipropyl ester/ or succimer diisopropyl ester/
51. Dimercaptosuccinic acid.mp.
52. DMSA.ti,ab.
53. unithiol/
54. 2,3-dimercapto-1-propanesulfonic acid.mp.
55. DMPS.ti,ab.
56. edetic acid/
57. Ethylenediamine tetraacetic acid.mp.
58. penicillamine disulfide/ or penicillamine derivative/ or penicillamine/
59. Penicillamine.ti,ab.
60. or/7-59
61. 6 and 60
62. Meta Analysis/
63. ((meta adj analy$) or metaanalys$).tw.
64. (systematic adj (review$1 or overview$1)).tw.
65. or/62-64
66. cancerlit.ab.
67. cochrane.ab.
68. embase.ab.
69. (psychlit or psyclit).ab.
70. (psychinfo or psycinfo).ab.
71. (cinal or cinahl).ab.
72. science citation index.ab.
73. bids.ab.
74. or/66-73
75. reference lists.ab.
76. bibliograph$.ab.
77. hand-search$.ab.
78. manual search$.ab.
79. relevant journals.ab.
80. or/75-79

81. data extraction.ab.
82. selection criteria.ab.
83. 81 or 82
84. review.pt.
85. 83 and 84
86. letter.pt.
87. editorial.pt.
88. animal/
89. human/
90. 88 not (88 and 89)
91. or/86-87,90
92. 65 or 74 or 80 or 85
93. 92 not 91
94. 61 and 93
95. clinical trial/
96. randomised controlled trial/
97. randomization/
98. single blind procedure/
99. double blind procedure/
100. crossover procedure/
101. placebo/
102. randomi?ed controlled trial$.tw.
103. rct.tw.
104. random allocation.tw.
105. randomly allocated.tw.
106. allocated randomly.tw.
107. (allocated adj2 random).tw.
108. single blind$.tw.
109. double blind$.tw.
110. ((treble or triple) adj blind$).tw.
111. PLACEBO$.tw.
112. prospective study/
113. or/95-112
114. case study/
115. case report.tw.
116. abstract report/ or letter/
117. or/114-116
118. 113 not 117
119. 61 and 118

MEDLINE

1 exp Myelodysplastic Syndromes/ (14487)
2 myelodysplas$.mp. (14423)
3 MDS.ti,ab. (9146)
4 1 or 2 or 3 (22062)
5 5q.mp. (2461)
6 4 and 5 (720)
7 best supportive care.mp. (836)
8 clinical practice.mp. (78655)
9 lenalidomide.mp. (1276)

10 revlimid.mp. (73)
11 active therap$.ti,ab. (1198)
12 Placebos/ (30765)
13 placebo$.mp. (153595)
14 Anti-Bacterial Agents/ (211004)
15 antibiotic$.ti,ab. (199390)
16 Blood Transfusion/ (50152)
17 transfusion$.ti,ab. (70577)
18 "Intercellular Signaling Peptides and Proteins"/ (17035)
19 Receptors, Erythropoietin/ or Erythropoietin/ or Erythropoietin, Recombinant/ (19451)
20 erythropoietin$.ti,ab. (20076)
21 EPO.ti,ab. (8122)
22 darbepoetin alfa.mp. (914)
23 Epoetin Alfa/ (1165)
24 epoetin alfa.mp. (1461)
25 epoetin beta.mp. (424)
26 epoetin theta.mp. (2)
27 epoetin zeta.mp. (16)
28 Polyethylene Glycols/ (31607)
29 methoxy polyethylene glycol-epoetin beta.mp. (21)
30 Granulocyte Colony-Stimulating Factor/ (10290)
31 Granulocyte Colony-Stimulating Factor$.mp. (15161)
32 G-CSF.mp. (10851)
33 Filgrastim/ (1373)
34 filgrastim.ti,ab. (1256)
35 lenograstim.mp. (305)
36 pegfilgrastim.mp. (371)
37 Iron Chelating Agents/ (4585)
38 Iron/ and Chelation Therapy/ (264)
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40 Thioctic Acid/ (2597)
41 Alpha lipoic acid.mp. (1326)
42 ALA.ti,ab. (30180)
43 Deferasirox.mp. (425)
44 Deferoxamine/ (5550)
45 Deferoxamine.ti,ab. (2996)
46 Dimercaprol/ (1441)
47 Dimercaprol.ti,ab. (251)
48 BAL.ti,ab. (10170)
49 Succimer/ (1397)
50 Dimercaptosuccinic acid.mp. (2094)
51 DMSA.ti,ab. (1904)
52 Unithiol/ (481)
53 2,3-dimercapto-1-propanesulfonic acid.mp. (59)
54 DMPS.ti,ab. (500)
55 Edetic Acid/ (23459)
56 Ethylenediamine tetraacetic acid.mp. (628)
57 Penicillamine/ (7030)
58 Penicillamine.ti,ab. (6278)

59 or/7-58 (811625)
60 6 and 59 (183)
61 Meta-Analysis/ (32030)
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63 metaanaly$.tw. (1117)
64 meta analysis.pt. (32030)
65 (systematic adj (review$1 or overview$1)).tw. (33102)
66 exp Review Literature/ (1710689)
67 or/61-66 (1747119)
68 cochrane.ab. (20232)
69 embase.ab. (17581)
70 (psychlit or psyclit).ab. (858)
71 (psychinfo or psycinfo).ab. (6624)
72 (cinahl or cinhal).ab. (6708)
73 science citation index.ab. (1473)
74 bids.ab. (316)
75 cancerlit.ab. (532)
76 or/68-75 (32618)
77 reference list$.ab. (7172)
78 bibliograph$.ab. (9827)
79 hand-search$.ab. (3081)
80 relevant journals.ab. (528)
81 manual search$.ab. (1733)
82 or/77-81 (19976)
83 selection criteria.ab. (15814)
84 data extraction.ab. (7505)
85 83 or 84 (22082)
86 review.pt. (1707850)
87 85 and 86 (14536)
88 comment.pt. (490623)
89 letter.pt. (752956)
90 editorial.pt. (300969)
91 animal/ (4955043)
92 human/ (12264339)
93 91 not (91 and 92) (3632269)
94 or/88-90,93 (4746020)
95 67 or 76 or 82 or 87 (1756001)
96 95 not 94 (1602051)
97 60 and 96 (63)
98 randomized controlled trial.pt. (323376)
99 controlled clinical trial.pt. (84121)
100 randomized controlled trials/ (78273)
101 random allocation/ (73759)
102 double blind method/ (114226)
103 single blind method/ (15837)
104 clinical trial.pt. (470963)
105 exp Clinical Trial/ (670960)
106 (clin$ adj25 trial$).ti,ab. (216037)
107 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (119326)

108 placebos/ (30765)
109 placebos.ti,ab. (1669)
110 random.ti,ab. (143710)
111 research design/ (65446)
112 or/98-111 (1118907)
113 60 and 112 (48)

Science Citation Index

#40	#39 OR #38 OR #37 OR #36 OR #35 OR #34 OR #33 OR #32 OR #31 OR #30 OR #29 O OR #25 OR #24 OR #23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #1 #11 OR #10 OR #9 OR #8 OR #7 *DocType=All document types; Language=All languages;*
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#38	Topic=(Ethylenediamine tetraacetic acid) *DocType=All document types; Language=All languages;*
#37	Topic=(DMPS) *DocType=All document types; Language=All languages;*
#36	Topic=(2,3-dimercapto-1-propanesulfonic acid) *DocType=All document types; Language=All languages;*
#35	Topic=(DMSA) *DocType=All document types; Language=All languages;*
#34	Topic=(Dimercaptosuccinic acid) *DocType=All document types; Language=All languages;*
#33	Topic=(BAL) *DocType=All document types; Language=All languages;*
#32	Topic=(Dimercaprol) *DocType=All document types; Language=All languages;*
#31	Topic=(Deferoxamine) *DocType=All document types; Language=All languages;*
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#29	Topic=(ALA) *DocType=All document types; Language=All languages;*
#28	Topic=(Alpha lipoic acid) *DocType=All document types; Language=All languages;*
#27	Topic=(iron chelat*) *DocType=All document types; Language=All languages;*
#26	Topic=(pegfilgrastim) *DocType=All document types; Language=All languages;*
#25	Topic=(lenograstim) *DocType=All document types; Language=All languages;*

#24	Topic=(filgrastim) *DocType=All document types; Language=All languages;*
#23	Topic=(G-CSF) *DocType=All document types; Language=All languages;*
#22	Topic=(Granulocyte Colony-Stimulating Factor*) *DocType=All document types; Language=All languages;*
#21	Topic=(methoxy polyethylene glycol-epoetin beta) *DocType=All document types; Language=All languages;*
#20	Topic=(epoetin zeta) *DocType=All document types; Language=All languages;*
#19	Topic=(epoetin theta) *DocType=All document types; Language=All languages;*
#18	Topic=(epoetin beta) *DocType=All document types; Language=All languages;*
#17	Topic=(epoetin alfa) *DocType=All document types; Language=All languages;*
#16	Topic=(darbepoetin alfa) *DocType=All document types; Language=All languages;*
#15	Topic=(EPO) *DocType=All document types; Language=All languages;*
#14	Topic=(erythropoietin) *DocType=All document types; Language=All languages;*
#13	Topic=(transfusion*) *DocType=All document types; Language=All languages;*
#12	Topic=(antibiotic*) *DocType=All document types; Language=All languages;*
#11	Topic=(placebo*) *DocType=All document types; Language=All languages;*
#10	Topic=(active therap*) *DocType=All document types; Language=All languages;*
#9	Topic=(revlimid) *DocType=All document types; Language=All languages;*
#8	Topic=(lenalidomide) *DocType=All document types; Language=All languages;*
#7	Topic=(clinical practice) *DocType=All document types; Language=All languages;*
#6	Topic=(best supportive care) *DocType=All document types; Language=All languages;*
#5	#4 AND #3 *DocType=All document types; Language=All languages;*
#4	Topic=(5q) *DocType=All document types; Language=All languages;*
#3	#2 OR #1

	DocType=All document types; Language=All languages;
#2	Topic=(MDS) *DocType=All document types; Language=All languages;*
#1	Topic=(myelodysplas*) *DocType=All document types; Language=All languages;*

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

Celgene confirmed the list of publications that were identified and, in addition, provided the complete study reports for all relevant studies of lenalidomide.

10.2.6. The inclusion and exclusion criteria.

Types of studies

Systematic reviews of randomised controlled trials (RCTs) are the best method for revealing the effects of a therapeutic intervention. Therefore, we included all RCTs that evaluated any of the above interventions in comparison to either an active comparator or to placebo for the treatment of myelodysplastic syndromes (MDS) associated with a deletion 5q del(5q) cytogenetic abnormality in people with red blood cell (RBC)transfusion dependence. We included RCTs regardless of design (parallel, crossover, open label, single- or double-blind).

Types of participants

The characteristics of patients in the studies should be similar to those of a typical patient described in the economic model from the key clinical trial on lenalidomide. Only studies that enrolled adult patients with low- or intermediate-1-risk International Prognostic Scoring System (IPSS) MDS associated with a del(5q) cytogenetic abnormality who were RBC transfusion-dependent were, therefore, included.

Types of intervention

The interventions included were best supportive care therapies and lenalidomide, as long as they were used for the treatment of low- or intermediate-1-risk IPSS MDS associated with a del(5q) cytogenetic abnormality in adult patients who are RBC transfusion-dependent.

Types of clinical outcomes

Types of clinical outcomes included were frequency of blood transfusions; blood transfusion independence; overall survival; progression-free survival (including time to transformation to acute myeloids leukemia (AML); haematological response (including change from baseline in absolute neutrophil count (ANC), platelet count haemoglobin level and hematopoietic cells evaluation); serious infections; adverse effects of treatment; health-related quality of life (HRQoL).

The data abstraction strategy.

The data extraction table comprised data items related to the characteristics and results of the final set of included studies. Development was based on conventions in systematic reviews and the specific requirements of the clinical effectiveness evidence.

Two reviewers independently extracted data items from each included trial. In the event of disagreement between the two reviewers, a third reviewer would have extracted the data and results attained by consensus but this was not necessary.

If study duplication within publications was suspected: author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remain, the authors would have been contacted but, again, this was not necessary.

Should sequential publications from the same trial report on different clinical endpoints, all results would be extracted and details of all data sources referenced. Should multi-intervention studies be identified, descriptions of all interventions would be extracted under the characteristics of included studies table of the final database. Neither of these scenarios presented themselves.

As part of the data extraction process, trials were independently assessed for method quality using a checklist for RCTs, which estimates the risk of different types of bias.

Description of study by Balleari *et al,* 2006

The aim of this study was to compare the effects of ‘standard’ doses of recombinant human erythropoietin (rHEPO) with the combination of rHEPO and granulocyte

colony-stimulating factor (G-CSF) in the treatment of anaemic patients with low-risk MDS in a prospective randomised trial. Anaemic patients with low-risk MDS were randomly assigned to receive either rHEPO (10,000 IU subcutaneously [SC] three times per week) or the same dosage of rHEPO plus G-CSF (300 µg SC twice per week) for a minimum of eight weeks. Patients who were unresponsive to rHEPO were offered the combination therapy for a furtherr eight weeks, whereas non-responders to rHEPO plus G-CSF were considered 'off-study'. Responders continued the treatment indefinitely. Both haematological response and changes in QoL scores (Functional Assessment of Cancer Therapy-Anemia) were recorded and evaluated. Thirty consecutive patients (ten with refractory anemia [RA], five with RA with ringed sideroblasts, seven with refractory cytopenia with multilineage dysplasia, five with RA with less than 10% blasts and three with 5q-syndrome) were enrolled in the study. All of them (15 in the rHEPO arm and 15 in the rHEPO plus G-CSF arm) were evaluable after the first eight weeks of treatment. Erythroid response was observed in six out of 15 (40%) patients in the rHEPO arm and in 11 out of 15 (73.3%) patients in the rHEPO plus G-CSF arm. In four out of nine (44.4%) patients who were unresponsive to rHEPO alone, the addition of G-CSF induced erythroid response at 16 weeks. No relevant adverse effects were recorded for either treatment in any of the study patients. Erythroid response to hepatocyte growth factor was associated with a relevant improvement in QoL.[5]

Twenty responders continued the treatment. Afterwards, eight out of 20 (40%) discontinued therapy because of the following: losing response (two patients), progression to high-risk MDS (three patients) and death due to other causes (three patients). The remaining 12 are still responding and continuing treatment, with a median duration of follow-up of 28 months. Progression to acute leukaemia was cumulatively observed in four out of 30 (13.3%) patients (two in each arm).[5]

Although these data were obtained from a relatively small cohort of patients, they indicate that the rHEPO plus G-CSF treatment is more effective than rHEPO therapy alone for correcting anemia in low-risk MDS patients and for making a relevant improvement in their QoL.[5]

10.3. Appendix 3: Quality assessment of RCT(s) (section 6.4)

Study	**Balleari et al, 2006[5]**	**Fenaux et al, 2011[5]**
Selection bias		
An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups). Yes, No, Unclear, N.A.	Unclear	Yes
There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation). Yes, No, Unclear, N.A.	Unclear	Yes
The groups were comparable at baseline, including all major confounding and prognostic factors. Yes, No, Unclear, N.A.	Yes	Yes
Based on answers to above, in your opinion was selection bias present? If so what is the likely direction of effect. Low risk, Unclear/unknown risk, High risk.	Unclear	Low risk
Likely direction of effect.	Unclear	N/A
Performance bias		
The comparison between groups received the same care apart from the interventions studied. Yes, No, Unclear, N.A.	Yes	Yes
Participants receiving care were kept 'blind' to treatment allocation. Yes, No, Unclear, N.A.	Unclear	Yes
Individuals administering care were kept 'blind' to treatment allocation. Yes, No, Unclear, N.A.	Unclear	Yes
Based on answers to above, in your opinion was performance bias present? If so, what is the likely direction of effect? Low risk, Unclear/unknown risk, High risk.	Unclear	Low risk
Likely direction of effect.	Unclear	N/A
Attrition bias		
All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up) Yes, No, Unclear, N.A.	Yes	Yes
The groups were comparable for treatment completion Yes, No, Unclear, N.A.	Yes	Yes
The groups were comparable with respect to the availability of outcome data Yes, No, Unclear, N.A.	Yes	Yes
Based on answers to above, in your opinion was attrition bias present? If so, what is the likely direction of effect? Low risk, Unclear/unknown risk, High risk.	Low Risk	Low risk
Likely direction of effect.	N/A	N/A
Detection bias		
The study had an appropriate length of follow-up. Yes, No, Unclear, N.A.	Yes	Yes
The study used a precise definition of outcome. Yes, No, Unclear, N.A.	Yes	Yes
A valid and reliable method was used to determine the outcome. Yes, No, Unclear, N.A.	Yes	Yes
Investigators were kept 'blind' to participants' exposure to the intervention. Yes, No, Unclear, N.A.	Unclear	Unclear
Investigators were kept 'blind' to other important confounding and prognostic factors. Yes, No, Unclear, N.A.	Unclear	Unclear

Based on answers to above, in your opinion was detection bias present? If so, what is the likely direction of effect? Low risk, Unclear/unknown risk, High risk.	Low Risk	Low risk
Likely direction of effect.	N/A	N/A

10.4. Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

The following information should be provided.

10.4.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable

10.4.2. The date on which the search was conducted.

Not applicable

10.4.3. The date span of the search.

Not applicable

10.4.4. 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).

Not applicable

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

Not applicable

10.4.6. The inclusion and exclusion criteria.

Not applicable

10.4.7. The data abstraction strategy.

Not applicable

10.5. Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

10.5.1. A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?		
Was the concealment of treatment allocation adequate?		
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		
Is there any evidence to suggest that the authors measured more outcomes than they reported?		
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?		
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.6. Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable

10.6.2. The date on which the search was conducted.

Not applicable

10.6.3. The date span of the search.

Not applicable

10.6.4. 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).

Not applicable

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

Not applicable

10.6.6. The inclusion and exclusion criteria.

Not applicable

10.6.7. The data abstraction strategy.

Not applicable

10.7. Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1. Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable

10.8. Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Not applicable

10.8.2. The date on which the search was conducted.

Not applicable

10.8.3. The date span of the search.

Not applicable

10.8.4. 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).

Not applicable

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

Not applicable

10.8.6. The inclusion and exclusion criteria.

Not applicable

10.8.7. The data abstraction strategy.

Not applicable

10.9. Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1. Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable

10.10. Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT

- NHS EED.

Study population: the focus was on adult patients with low or intermediate risk MDS. The requirement for a del-5q was initially included within the criteria; however, since this strategy yielded very few potential hits, the search was expanded to include all MDS patients.

Therapeutic interventions: the search was designed to find studies investigating the cost effectiveness of lenalidomide as well as alternative therapies currently used as best supportive care (BSC): antibiotics, blood transfusions, growth factor therapies (erythropoiesis-stimulating agent [ESA] and granulocyte colony-stimulating factor [G-CSF]), and iron-chelation therapies.

Limits: no limits were made on date or language.

Electronic databases searched:
Utility values strategy:

- CINAHL (Cumulative Index to Nursing and Allied Health) via EBSCO
- The Cochrane Library: Cochrane Databases of Systematic Reviews, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database
- Embase via OvidSP
- MEDLINE via OvidSP
- Science Citation Index via Web of Knowledge

Economic search:

- CINAHL (Cumulative Index to Nursing and Allied Health) via EBSCO
- NHS Economic Evaluation Database (EED) via The Cochrane Library
- Embase via OvidSP
- MEDLINE via OvidSP
- Science Citation Index via Web of Knowledge

Search terms: The search combined terms to describe the intervention(s) of interest (BSC and Revlimid) and the population (MDS sufferers) before applying methodological search filters, such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN), to refine the results to the appropriate types of evidence

(economic and utilities). The terms within these groups were combined using the Boolean operator ‘or’, and then groups were combined using the Boolean operator ‘and’. This approach is the standard 'building block' approach to searching

10.10.2. The date on which the search was conducted.

Monday 6 February 2012

10.10.3. The date span of the search.

No limit

10.10.4. 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).

Utility values strategy:

CINAHL

S43	S4 and S42
	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or
S42	S41
S41	tto
S40	time tradeoff
S39	time trade off
S38	standard gamble*
S37	willingness to pay
S36	qwb

S35	quality of well-being
S34	quality of wellbeing
S33	rosser
S32	disutili*
S31	hui or hui1 or hui2 or hui3
S30	health utilit*
S29	health* year* equivalent*
S28	(MH "Health Status Indicators")
S27	daly*
S26	disability adjusted life
S25	qaly* or qald* or qale* or qtime*
S24	quality adjusted life
S23	(MH "Quality-Adjusted Life Years")
S22	(MH "Economic Value of Life")
S21	hye or hyes
S20	hql or hqol or h qol or hrqol or hr qol
S19	euroqol or euro qol or eq5d or eq 5d
S18	sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twnety or short from twenty
S17	sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen
S16	sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short

	form twelve
S15	sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short from thirtysix or short form thirty six
S14	(MH "Health Status Indicators")
S13	TI daly* OR AB daly*
S12	TI disability adjusted life OR AB disability adjusted life
S11	TI (qaly* or qald* or qale* or qtime*) OR AB (qaly* or qald* or qale* or qtime*)
S10	TI quality adjusted life OR AB quality adjusted life
S9	(MH "Quality-Adjusted Life Years")
S8	TI (economic* or pharmaco economic* or pharmoco-economic) OR AB (economic* or pharmaco economic* or pharmoco-economic)
S7	AB cost* N1 (effective* or util* or benefit* or minimi*)
S6	TI cost*
S5	(MH "Costs and Cost Analysis")
S4	S1 or S2 or S3
S3	TI MDS OR AB MDS
S2	myelodysplas*
S1	(MH "Myelodysplastic Syndromes+")

The Cochrane Library

#1 MeSH descriptor: [Myelodysplastic Syndromes] explode all trees

#2 myelodysplas*:ti,ab,kw
#3 MDS:ti,ab,kw
#4 #1 or #2 or #3
#5 MeSH descriptor: [Costs and Cost Analysis] explode all trees
#6 MeSH descriptor: [Patient Acceptance of Health Care] explode all trees
#7 cost*:ti
#8 (cost* near/2 (effective* or util* or benefit* or minimi*)):ab
#9 (economic* or pharmaco economic* or pharmoco-economic*):ti OR (economic* or pharmaco economic* or pharmoco-economic*):ab
#10 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#11 quality adjusted life:ti,ab,kw
#12 (qaly* or qald* or qale* or qtime*):ti,ab,kw
#13 disability adjusted life:ti,ab,kw
#14 daly*:ti,ab,kw
#15 MeSH descriptor: [Health Status Indicators] explode all trees
#16 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short from thirtysix or short form thirty six):ti,ab,kw
#17 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six):ti,ab,kw
#18 (sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve):ti,ab,kw
#19 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen):ti,ab,kw
#20 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twnety or short from twenty):ti,ab,kw
#21 (euroqol or euro qol or eq5d or eq 5d):ti,ab,kw
#22 (hql or hqol or h qol or hrqol or hr qol):ti,ab,kw
#23 (hye or hyes):ti,ab,kw
#24 MeSH descriptor: [Value of Life] explode all trees
#25 MeSH descriptor: [Quality-Adjusted Life Years] explode all trees
#26 quality adjusted life:ti,ab,kw
#27 (qaly* or qald* or qale* or qtime*):ti,ab,kw
#28 disability adjusted life:ti,ab,kw
#29 daly*:ti,ab,kw
#30 MeSH descriptor: [Health Status Indicators] explode all trees
#31 health* year* equivalent*:ti,ab,kw
#32 health utilit*:ti,ab,kw
#33 (hui or hui1 or hui2 or hui3):ti,ab,kw
#34 disutili*:ti,ab,kw
#35 rosser
#36 quality of wellbeing:ti,ab,kw
#37 quality of well-being:ti,ab,kw
#38 qwb:ti,ab,kw
#39 willingness to pay:ti,ab,kw
#40 standard gamble*:ti,ab,kw
#41 time trade off:ti,ab,kw
#42 time tradeoff:ti,ab,kw
#43 tto:ti,ab,kw

#44 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43
#45 #4 and #44

EMBASE
1. exp myelodysplastic syndrome/
2. myelodysplas$.mp.
3. MDS.ti,ab.
4. 1 or 2 or 3
5. best supportive care.mp.
6. clinical practice.mp.
7. lenalidomide.mp.
8. revlimid.mp.
9. active therap$.ti,ab.
10. placebo/
11. placebo$.mp.
12. antiinfective agent/
13. antibiotic$.ti,ab.
14. blood transfusion/
15. transfusion$.ti,ab.
16. signal peptide/
17. erythropoietin receptor/
18. erythropoietin antibody/ or erythropoietin/ or recombinant erythropoietin/
19. erythropoietin$.ti,ab.
20. EPO.ti,ab.
21. darbepoetin alfa.mp.
22. epoetin alfa.mp.
23. epoetin beta.mp.
24. epoetin theta.mp.
25. epoetin zeta.mp.
26. macrogol derivative/
27. methoxy polyethylene glycol-epoetin beta.mp.
28. granulocyte colony stimulating factor/
29. Granulocyte Colony-Stimulating Factor$.mp.
30. G-CSF.mp.
31. recombinant granulocyte colony stimulating factor/
32. filgrastim.ti,ab.
33. lenograstim.mp.
34. pegfilgrastim.mp.
35. iron chelating agent/
36. iron/ and chelation therapy/
37. iron chelation/
38. iron chelat$.mp.
39. thioctic acid/
40. Alpha lipoic acid.mp.
41. ALA.ti,ab.
42. Deferasirox.mp.
43. deferoxamine mesylate/ or deferoxamine/

44. Deferoxamine.ti,ab.
45. dimercaprol/
46. Dimercaprol.ti,ab.
47. BAL.ti,ab.
48. succimer diisopentyl ester/ or succimer tc 99m/ or succimer di sec butyl ester/ or succimer dibutyl ester/ or succimer dimethyl ester/ or succimer diisobutyl ester/ or succimer derivative/ or succimer diethyl ester/ or succimer/ or succimer dipropyl ester/ or succimer diisopropyl ester/
49. Dimercaptosuccinic acid.mp.
50. DMSA.ti,ab.
51. unithiol/
52. 2,3-dimercapto-1-propanesulfonic acid.mp.
53. DMPS.ti,ab.
54. edetic acid/
55. Ethylenediamine tetraacetic acid.mp.
56. penicillamine disulfide/ or penicillamine derivative/ or penicillamine/
57. Penicillamine.ti,ab.
58. or/5-57
59. "Quality of Life"/
60. (quality of life or qol).ti,ab.
61. (value adj2 (money or monetary)).tw.
62. value of life/
63. quality adjusted life year/
64. quality adjusted life.tw.
65. (qaly$ or qald$ or qale$ or qtime$).tw.
66. disability adjusted life.tw.
67. daly$.tw.
68. health status indicators/
69. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shorform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
70. (sf 6 or sf6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
71. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
72. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortfrom sixteen or short form sixteen).tw.
73. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
74. (euroqol or euro qol or eq5d or eq 5d).tw.
75. (hql or hqol or h qol or hrqol or hr qol).tw.
76. (hye or hyes).tw.
77. health$ year$ equivalent$.tw.
78. health utilit$.tw.
79. (hui or hui1 or hui2 or hui3).tw.
80. disutilit$.tw.
81. rosser.tw.
82. quality of wellbeing.tw.
83. qwb.tw.
84. willingness to pay.tw.

85. standard gamble$.tw.
86. time trade off.tw.
87. time tradeoff.tw.
88. tto.tw.
89. letter.pt.
90. editorial.pt.
91. comment.pt.
92. or/89-91
93. or/59-88
94. 93 not 92
95. 4 and 58 and 94

MEDLINE

1 exp Myelodysplastic Syndromes/ (14146)
2 myelodysplas$.mp. (14094)
3 MDS.ti,ab. (9015)
4 1 or 2 or 3 (21577)
5 best supportive care.mp. (832)
6 clinical practice.mp. (77815)
7 lenalidomide.mp. (1279)
8 revlimid.mp. (70)
9 active therap$.ti,ab. (1173)
10 Placebos/ (30448)
11 placebo$.mp. (150845)
12 Anti-Bacterial Agents/ (208316)
13 antibiotic$.ti,ab. (196869)
14 Blood Transfusion/ (49481)
15 transfusion$.ti,ab. (69554)
16 "Intercellular Signaling Peptides and Proteins"/ (15867)
17 Receptors, Erythropoietin/ or Erythropoietin/ or Erythropoietin, Recombinant/ (19730)
18 erythropoietin$.ti,ab. (19582)
19 EPO.ti,ab. (7899)
20 darbepoetin alfa.mp. (879)
21 Epoetin Alfa/ (0)
22 epoetin alfa.mp. (1447)
23 epoetin beta.mp. (416)
24 epoetin theta.mp. (2)
25 epoetin zeta.mp. (15)
26 Polyethylene Glycols/ (31273)
27 methoxy polyethylene glycol-epoetin beta.mp. (23)
28 Granulocyte Colony-Stimulating Factor/ (12021)
29 Granulocyte Colony-Stimulating Factor$.mp. (15500)
30 G-CSF.mp. (10634)
31 Filgrastim/ (0)
32 filgrastim.ti,ab. (1243)
33 lenograstim.mp. (303)
34 pegfilgrastim.mp. (364)
35 Iron Chelating Agents/ (4507)
36 Iron/ and Chelation Therapy/ (258)

37 iron chelat$.mp. (8035)
38 Thioctic Acid/ (2560)
39 Alpha lipoic acid.mp. (1338)
40 ALA.ti,ab. (29531)
41 Deferasirox.mp. (410)
42 Deferoxamine/ (5463)
43 Deferoxamine.ti,ab. (2937)
44 Dimercaprol/ (1439)
45 Dimercaprol.ti,ab. (248)
46 BAL.ti,ab. (10021)
47 Succimer/ (1374)
48 Dimercaptosuccinic acid.mp. (2056)
49 DMSA.ti,ab. (1863)
50 Unithiol/ (479)
51 2,3-dimercapto-1-propanesulfonic acid.mp. (57)
52 DMPS.ti,ab. (495)
53 Edetic Acid/ (23414)
54 Ethylenediamine tetraacetic acid.mp. (621)
55 Penicillamine/ (6923)
56 Penicillamine.ti,ab. (6190)
57 or/5-56 (798984)
58 "costs and cost analysis"/ (39243)
59 exp "Patient Acceptance of Health Care"/ (139008)
60 cost$.ti. (69860)
61 (cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab. (70320)
62 (economic$ or pharmaco economic$ or pharmoco-economic$).tw. (124922)
63 Quality-Adjusted Life Years/ (5335)
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66 disability adjusted life.tw. (883)
67 daly$.tw. (898)
68 Health Status Indicators/ (17327)
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70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1173)
71 (sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (2331)
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (19)
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74 (euroqol or euro qol or eq5d or eq 5d).tw. (2704)
75 (hql or hqol or h qol or hrqol or hr qol).tw. (5638)
76 (hye or hyes).tw. (51)
77 value of life/ (5197)
78 quality adjusted life year/ (5335)
79 quality adjusted life.tw. (4565)

80 (qaly$ or qald$ or qale$ or qtime$).tw. (3822)
81 disability adjusted life.tw. (883)
82 daly$.tw. (898)
83 health status indicators/ (17327)
84 health$ year$ equivalent$.tw. (37)
85 health utilit$.tw. (826)
86 (hui or hui1 or hui2 or hui3).tw. (726)
87 disutili$.tw. (167)
88 rosser.tw. (69)
89 quality of wellbeing.tw. (7)
90 quality of well-being.tw. (294)
91 qwb.tw. (150)
92 willingness to pay.tw. (1673)
93 standard gamble$.tw. (591)
94 time trade off.tw. (610)
95 time tradeoff.tw. (192)
96 tto.tw. (469)
97 or/58-96 (428953)
98 4 and 57 (3083)
99 97 and 98 (80)

Science Citation Index

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#43	Topic=(quality adjusted life) DocType=All document types; Language=All languages;
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#37	Topic=(Ethylenediamine tetraacetic acid) *DocType=All document types; Language=All languages;*
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#30	Topic=(Dimercaprol) *DocType=All document types; Language=All languages;*
#29	Topic=(Deferoxamine) *DocType=All document types; Language=All languages;*
#28	Topic=(Deferasirox) *DocType=All document types; Language=All languages;*
#27	Topic=(ALA) *DocType=All document types; Language=All languages;*
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#1	Topic=(myelodysplas*) *DocType=All document types; Language=All languages;*

Economic search:

CINAHL

S16	S4 AND S15
S15	S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14
S14	TI ((hql or hqol or h qol or hrqol or hr qol or pqol or qls)) OR AB ((hql or hqol or h qol or hrqol or hr qol or pqol or qls))
S13	AB (value n2 (money or monetary)) or economic model* or markov* or quality adjusted life or qaly* or qald* or qale* or qtime* or "disability adjusted life" or daly* or SF6D or "sf 6d" or "short form 6d" or shortform6d or "health* year* equivalent*" or hye or hyes or "healht utilit*" or hui or hui1 or hui2 or hui3 or disutil* or "standard gamble*" or "time trade off" or "time tradeoff" or tto
S12	AB (cost* n2 (effective* or utilit* or benefit* or minimi* or evaluat* or analy* or study or studies or consequenc* or compar* or efficienc*))
S11	AB pharmacoeconomic* or pharmaco-economic* or economic* or price* or pricing* or budget* or euroqol* or eq5d or eq-5d or finance* or financial* or fee or fees
S10	TI (value n2 money) or (value n2 monetary) or (economic model* or markov* or quality adjusted life or qaly* or qald* or qale* or qtime* or disability adjusted life year or daly* or SF6D or sf 6d or short form 6d or shortform6d) or (health* year* equivalent* or hye or hyes or health utilit* or hui or hui1 or hui2 or hui3 or disutil* or standard gamble* or time trade off or time tradeoff or tto)

S9	TI cost* or pharmacoeconomic* or pharmaco-economic* or economic* or price* or pricing* or budget* or euroqol* or eq5d or eq-5d or finance* or financial* or fee or fees
S8	(MH "Health Resource Utilization") OR (MH "Health Resource Allocation")
S7	(MH "Fees and Charges+")
S6	(MH "Costs and Cost Analysis")
S5	(MH "Economics") OR (MH "Economic Value of Life") OR (MH "Economics, Dental") OR (MH "Economics, Pharmaceutical") OR (MH "Economic Aspects of Illness")
S4	S1 or S2 or S3
S3	TI MDS OR AB MDS
S2	myelodysplas*
S1	(MH "Myelodysplastic Syndromes+")

NHS Economic Evaluation Database (EED)

#1 MeSH descriptor: [Myelodysplastic Syndromes] explode all trees
#2 myelodysplas*:ti,ab,kw
#3 MDS:ti,ab,kw
#4 #1 or #2 or #3

EMBASE

1. exp myelodysplastic syndrome/
2. myelodysplas$.mp.
3. MDS.ti,ab.
4. 1 or 2 or 3
5. best supportive care.mp.
6. clinical practice.mp.
7. lenalidomide.mp.
8. revlimid.mp.
9. active therap$.ti,ab.
10. placebo/
11. placebo$.mp.
12. antiinfective agent/
13. antibiotic$.ti,ab.
14. blood transfusion/

15. transfusion$.ti,ab.
16. signal peptide/
17. erythropoietin receptor/
18. erythropoietin antibody/ or erythropoietin/ or recombinant erythropoietin/
19. erythropoietin$.ti,ab.
20. EPO.ti,ab.
21. darbepoetin alfa.mp.
22. epoetin alfa.mp.
23. epoetin beta.mp.
24. epoetin theta.mp.
25. epoetin zeta.mp.
26. macrogol derivative/
27. methoxy polyethylene glycol-epoetin beta.mp.
28. granulocyte colony stimulating factor/
29. Granulocyte Colony-Stimulating Factor$.mp.
30. G-CSF.mp.
31. recombinant granulocyte colony stimulating factor/
32. filgrastim.ti,ab.
33. lenograstim.mp.
34. pegfilgrastim.mp.
35. iron chelating agent/
36. iron/ and chelation therapy/
37. iron chelation/
38. iron chelat$.mp.
39. thioctic acid/
40. Alpha lipoic acid.mp.
41. ALA.ti,ab.
42. Deferasirox.mp.
43. deferoxamine mesylate/ or deferoxamine/
44. Deferoxamine.ti,ab.
45. dimercaprol/
46. Dimercaprol.ti,ab.
47. BAL.ti,ab.
48. succimer diisopentyl ester/ or succimer tc 99m/ or succimer di sec butyl ester/ or succimer dibutyl ester/ or succimer dimethyl ester/ or succimer diisobutyl ester/ or succimer derivative/ or succimer diethyl ester/ or succimer/ or succimer dipropyl ester/ or succimer diisopropyl ester/
49. Dimercaptosuccinic acid.mp.
50. DMSA.ti,ab.
51. unithiol/
52. 2,3-dimercapto-1-propanesulfonic acid.mp.
53. DMPS.ti,ab.
54. edetic acid/
55. Ethylenediamine tetraacetic acid.mp.
56. penicillamine disulfide/ or penicillamine derivative/ or penicillamine/
57. Penicillamine.ti,ab.
58. or/5-57
59. exp SOCIOECONOMICS/
60. exp "Cost Benefit Analysis"/
61. exp "Cost Effectiveness Analysis"/

62. exp "Cost of Illness"/
63. exp "Cost Control"/
64. exp Economic Aspect/
65. exp Financial Management/
66. exp "Health Care Cost"/
67. exp Health Care Financing/
68. exp Health Economics/
69. exp "Hospital Cost"/
70. (financial or fiscal or finance or funding).tw.
71. exp "Cost Minimization Analysis"/
72. (cost adj estimate$).mp.
73. (cost adj variable$).mp.
74. (unit adj cost$).mp.
75. or/59-74
76. 4 and 58 and 75

MEDLINE

1 exp Myelodysplastic Syndromes/ (14154)
2 myelodysplas$.mp. (14112)
3 MDS.ti,ab. (9033)
4 1 or 2 or 3 (21602)
5 best supportive care.mp. (837)
6 clinical practice.mp. (78028)
7 lenalidomide.mp. (1287)
8 revlimid.mp. (71)
9 active therap$.ti,ab. (1174)
10 Placebos/ (30479)
11 placebo$.mp. (151089)
12 Anti-Bacterial Agents/ (208555)
13 antibiotic$.ti,ab. (197142)
14 Blood Transfusion/ (49506)
15 transfusion$.ti,ab. (69646)
16 "Intercellular Signaling Peptides and Proteins"/ (15894)
17 Receptors, Erythropoietin/ or Erythropoietin/ or Erythropoietin, Recombinant/ (19750)
18 erythropoietin$.ti,ab. (19606)
19 EPO.ti,ab. (7903)
20 darbepoetin alfa.mp. (882)
21 Epoetin Alfa/ (0)
22 epoetin alfa.mp. (1447)
23 epoetin beta.mp. (416)
24 epoetin theta.mp. (2)
25 epoetin zeta.mp. (15)
26 Polyethylene Glycols/ (31360)
27 methoxy polyethylene glycol-epoetin beta.mp. (23)
28 Granulocyte Colony-Stimulating Factor/ (12028)
29 Granulocyte Colony-Stimulating Factor$.mp. (15508)
30 G-CSF.mp. (10635)
31 Filgrastim/ (0)
32 filgrastim.ti,ab. (1245)

33 lenograstim.mp. (304)
34 pegfilgrastim.mp. (366)
35 Iron Chelating Agents/ (4509)
36 Iron/ and Chelation Therapy/ (258)
37 iron chelat$.mp. (8048)
38 Thioctic Acid/ (2562)
39 Alpha lipoic acid.mp. (1339)
40 ALA.ti,ab. (29551)
41 Deferasirox.mp. (416)
42 Deferoxamine/ (5466)
43 Deferoxamine.ti,ab. (2940)
44 Dimercaprol/ (1439)
45 Dimercaprol.ti,ab. (248)
46 BAL.ti,ab. (10029)
47 Succimer/ (1374)
48 Dimercaptosuccinic acid.mp. (2055)
49 DMSA.ti,ab. (1862)
50 Unithiol/ (479)
51 2,3-dimercapto-1-propanesulfonic acid.mp. (57)
52 DMPS.ti,ab. (496)
53 Edetic Acid/ (23418)
54 Ethylenediamine tetraacetic acid.mp. (623)
55 Penicillamine/ (6924)
56 Penicillamine.ti,ab. (6194)
57 or/5-56 (800133)
58 Economics/ (26164)
59 "costs and cost analysis"/ (39259)
60 Cost allocation/ (1905)
61 Cost-benefit analysis/ (52573)
62 Cost control/ (19003)
63 cost savings/ (7363)
64 Cost of illness/ (14591)
65 Cost sharing/ (1705)
66 "deductibles and coinsurance"/ (1318)
67 Health care costs/ (22339)
68 Direct service costs/ (955)
69 Drug costs/ (10615)
70 Employer health costs/ (1038)
71 Hospital costs/ (6667)
72 Health expenditures/ (11952)
73 Capital expenditures/ (1907)
74 Value of life/ (5197)
75 exp economics, hospital/ (17639)
76 exp economics, medical/ (13190)
77 Economics, nursing/ (3853)
78 Economics, pharmaceutical/ (2291)
79 exp "fees and charges"/ (25464)
80 exp budgets/ (11197)
81 (low adj cost).mp. (18273)
82 (high adj cost).mp. (6779)

83 (health?care adj cost$).mp. (3070)
84 (fiscal or funding or financial or finance).tw. (66542)
85 (cost adj estimate$).mp. (1197)
86 (cost adj variable).mp. (28)
87 (unit adj cost$).mp. (1273)
88 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (144237)
89 or/58-88 (402508)
90 4 and 57 and 89 (63)

Science Citation Index

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#23	Topic=(lenograstim) *DocType=All document types; Language=All languages;*
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#20	Topic=(Granulocyte Colony-Stimulating Factor*) *DocType=All document types; Language=All languages;*
#19	Topic=(methoxy polyethylene glycol-epoetin beta) *DocType=All document types; Language=All languages;*
#18	Topic=(epoetin zeta) *DocType=All document types; Language=All languages;*
#17	Topic=(epoetin theta) *DocType=All document types; Language=All languages;*
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#13	Topic=(EPO) *DocType=All document types; Language=All languages;*
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#11	Topic=(transfusion*) *DocType=All document types; Language=All languages;*
#10	Topic=(antibiotic*) *DocType=All document types; Language=All languages;*
#9	Topic=(placebo*) *DocType=All document types; Language=All languages;*
#8	Topic=(active therap*) *DocType=All document types; Language=All languages;*
#7	Topic=(revlimid) *DocType=All document types; Language=All languages;*

#6	Topic=(lenalidomide) *DocType=All document types; Language=All languages;*
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#4	Topic=(best supportive care) *DocType=All document types; Language=All languages;*
#3	#2 OR #1 *DocType=All document types; Language=All languages;*
#2	Topic=(MDS) *DocType=All document types; Language=All languages;*
#1	Topic=(myelodysplas*) *DocType=All document types; Language=All languages;*

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

Not applicable.

10.11. Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

	Study name Goss et al. 2006	
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	

6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	
15. Was the relevance of productivity changes to the study question discussed?	N/A	
16. Were quantities of resources reported separately from their unit cost?	Yes	There is a section describing the resource utilisation data but no detailed information on quantities is provided
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Methods are discussed briefly for each resource item
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	There is a section describing the model with limited detail

21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	No alternative models are discussed and there is no discussion about the suitability of the chosen structure
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	
24. Was the choice of rate justified?	N/A	
25. Was an explanation given if cost or benefits were not discounted?	No	The model has a 1 year time horizon so discounting was not required
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	A probabilistic analysis is briefly discussed, although there is very limited explanation or justification of the distributions chosen or parameters included.
28. Was the choice of variables for sensitivity analysis justified?	No	
29. Were the ranges over which the parameters were varied stated?	Yes	Ranges are quoted as part of a table displaying results of the one-way sensitivity analysis
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?		

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

10.12. Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

Study population: the focus was on adult patients with low or intermediate risk MDS. The requirement for a del(5q)was initially included within the criteria; however, since this strategy yielded very few potential hits, the search was expanded to include all MDS patients.

Therapeutic interventions: the search was designed to find studies investigating the cost effectiveness of Revlimid as well as alternative therapies currently used as best supportive care (BSC): antibiotics, blood transfusions, growth factor therapies (erythropoiesis-stimulating agent [ESA] and granulocyte colony-stimulating factor [G-CSF]), and iron-chelation therapies.

Limits: no limits were made on date or language.

Electronic databases searched: Medline, Embase, Cochrane Library, Cochrane database of systematic reviews, Cochrane register of clinical trials, NHS HEED, HTA database, DARE, CINAHL, Econlit, Science Citation Index (Web of Science), Conference Proceedings Index (Web of Science).

Search terms: The search combined terms to describe the intervention(s) of interest (BSC and Revlimid) and the population (MDS sufferers) before applying methodological search filters, such as those produced by the Scottish Intercollegiate Guidelines Network (SIGN), to refine the results to the appropriate types of evidence (economic and utilities). The terms within these groups were combined using the Boolean operator ‘or’, and then groups were combined using the Boolean operator ‘and’. This approach is the standard 'building block' approach to searching

10.12.2. The date on which the search was conducted.

Monday 6 February 2012

10.12.3. The date span of the search.

No limit

10.12.4. 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 exp Myelodysplastic Syndromes/
2 myelodysplas$.mp.
3 MDS.ti,ab.
4 1 or 2 or 3
5 best supportive care.mp.
6 clinical practice.mp.
7 lenalidomide.mp.
8 revlimid.mp.
9 active therap$.ti,ab.
10 Placebos/
11 placebo$.mp.
12 Anti-Bacterial Agents/
13 antibiotic$.ti,ab.
14 Blood Transfusion/
15 transfusion$.ti,ab.
16 "Intercellular Signaling Peptides and Proteins"/

17 Receptors, Erythropoietin/ or Erythropoietin/ or Erythropoietin, Recombinant/
18 erythropoietin$.ti,ab.
19 EPO.ti,ab.
20 darbepoetin alfa.mp.
21 Epoetin Alfa/
22 epoetin alfa.mp.
23 epoetin beta.mp.
24 epoetin theta.mp.
25 epoetin zeta.mp.
26 Polyethylene Glycols/
27 methoxy polyethylene glycol-epoetin beta.mp.
28 Granulocyte Colony-Stimulating Factor/
29 Granulocyte Colony-Stimulating Factor$.mp.
30 G-CSF.mp.
31 Filgrastim/
32 filgrastim.ti,ab.
33 lenograstim.mp.
34 pegfilgrastim.mp.
35 Iron Chelating Agents/
36 Iron/ and Chelation Therapy/
37 iron chelat$.mp.
38 Thioctic Acid/
39 Alpha lipoic acid.mp.
40 ALA.ti,ab.
41 Deferasirox.mp.
42 Deferoxamine/
43 Deferoxamine.ti,ab.
44 Dimercaprol/
45 Dimercaprol.ti,ab.
46 BAL.ti,ab.
47 Succimer/
48 Dimercaptosuccinic acid.mp.
49 DMSA.ti,ab.
50 Unithiol/
51 2,3-dimercapto-1-propanesulfonic acid.mp.
52 DMPS.ti,ab.
53 Edetic Acid/

54 Ethylenediamine tetraacetic acid.mp.
55 Penicillamine/
56 Penicillamine.ti,ab.
57 or/5-56
58 "costs and cost analysis"/
59 exp "Patient Acceptance of Health Care"/
60 cost$.ti.
61 (cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab.
62 (economic$ or pharmaco economic$ or pharmoco-economic$).tw.
63 Quality-Adjusted Life Years/
64 quality adjusted life.tw.
65 (qaly$ or qald$ or qale$ or qtime$).tw.
66 disability adjusted life.tw.
67 daly$.tw.
68 Health Status Indicators/
69 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short from thirtysix or short form thirty six).tw.
70 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
71 (sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
72 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
73 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twnety or short from twenty).tw.
74 (euroqol or euro qol or eq5d or eq 5d).tw.
75 (hql or hqol or h qol or hrqol or hr qol).tw.
76 (hye or hyes).tw.
77 value of life/
78 quality adjusted life year/
79 quality adjusted life.tw.
80 (qaly$ or qald$ or qale$ or qtime$).tw.
81 disability adjusted life.tw.
82 daly$.tw.
83 health status indicators/
84 health$ year$ equivalent$.tw.

85 health utilit$.tw.
86 (hui or hui1 or hui2 or hui3).tw.
87 disutili$.tw.
88 rosser.tw.
89 quality of wellbeing.tw.
90 quality of well-being.tw.
91 qwb.tw.
92 willingness to pay.tw.
93 standard gamble$.tw.
94 time trade off.tw.
95 time tradeoff.tw.
96 tto.tw.
97 or/58-96
98 4 and 57
99 97 and 98

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

Not applicable

10.12.6. The inclusion and exclusion criteria.

As this search was looking for HRQL evidence rather than clinical evidence, no limits were placed upon the types of study included within the search.

All studies that enrolled adult patients with MDS were included.

Studies relating to BSC therapies and Revlimid used for the treatment MDS in adult patients who are RBC transfusion dependent were included

QOL information – in the form of utilities or scores on any QOL instrument

10.12.7. The data abstraction strategy.

The data extraction table comprised data items related to the characteristics and results of the final set of included studies. Development was based on conventions in systematic reviews and the specific requirements of the cost-effectiveness evidence.

Two reviewers independently extracted data items from each included trial. In the event of disagreement between the two reviewers a third reviewer would have extracted the data and results attained by consensus, but this was not necessary.

If study duplication within publications was suspected: author names, location and setting, specific intervention details, participant numbers, baseline data and date and duration of study were assessed. If uncertainties remained, the authors would have been contacted but again this was not necessary.

If sequential publications from the same trial reported on different endpoints, all results were extracted (if possible) and details of all data sources referenced. If multi-intervention studies were identified, descriptions of all interventions were extracted under the characteristics of included studies table of the final database.

10.13. Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1. The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

Not applicable

10.13.2. The date on which the search was conducted.

Not applicable

10.13.3. The date span of the search.

Not applicable

10.13.4. 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).

Not applicable

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

Not applicable

10.13.6. The inclusion and exclusion criteria.

Not applicable

10.13.7. The data abstraction strategy.

Not applicable

11. Related procedures for evidence submission

11.1. Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission.

There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

11.2. Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential

information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as 'academic in confidence'.

Please therefore underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and information submitted under 'academic in confidence' in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be 'blacked out' from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of 'academic in confidence' information. The 'stripped' version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE's website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the 'stripped' version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been

put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.