Section A: General requests: Clarification on search strategies

General

A1. *In order to reproduce the searches, please confirm the following details for all database searches for sections 10.2, 10.10 & 10.12:*

- *Although the manufacturer submission (MS) states that no date limits have been applied, please provide the date span searched for each search and each individual database i.e. Medline 1946-2013/01/22*

The databases searched for clinical and adverse event evidence and those searched for cost-effectiveness and utilities evidence are shown in Tables 1 and 2 respectively.

Table 1: Databases searched for clinical and adverse event evidence

CINAHL (Cumulative Index to Nursing and Allied Health) via EBSCO - 1982-December 2011
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 – 1991-December 2011
Embase via OvidSP – 1974-December 2011
MEDLINE and MEDLINE In-Process via OvidSP – 1946-December 2011
Science Citation Index via Web of Knowledge – 1900-December 2011

Table 2: Databases searched for cost-effectiveness and utilities evidence

CINAHL (Cumulative Index to Nursing and Allied Health) via EBSCO - 1982- February 2012
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 - 1991- February 2012
Econlit via OvidSP – 1961-February 2012
Embase via OvidSP – 1974- February 2012
MEDLINE and MEDLINE In-Process via OvidSP – 1946- February 2012
Science Citation Index via Web of Knowledge – 1900- February 2012

- *Although the MS states in each section the date of the week commencing for each set of searches, please provide the exact date each individual resource was searched on.*

Table 3: Search dates

	Clinical effectiveness including adverse events	**Quality of life**	**Cost-effectiveness**
CINAHL	22/12/2011	10/02/2012	13/02/2012
Cochrane Library	20/12/2011	10/02/2012	10/02/2012
EMBASE	22/12/2011	10/02/2012	13/02/2012

	Clinical effectiveness including adverse events	**Quality of life**	**Cost-effectiveness**
MEDLINE & MEDLINE In-Process	20/12/2011	10/02/2012	13/02/2012
Science citation index	22/12/2011	10/02/2012	13/02/2012
Econlit		10/02/2012	13/02/2012
NHS EED		13/02/2012	13/02/2012

Clinical Effectiveness Searches (6.1 &10.2)

A2. *Please confirm if the Medline strategy reported in 10.2 also included the search of Medline In-Process (as requested by NICE). If not, please confirm if this was searched and provide the relevant strategy.*

Yes the same strategy was used for both Medline and Medline In-Process.

A3*.* *In section 6.1 the MS states that the Web of Knowledge Conference Proceedings Index was searched, but there is no record of this in section 10.2. Was this included in the Science Citation Index Search? If not, please confirm if this was the case and provide a strategy.*

Yes this was included in the Science Citation Index Search.

Adverse Events Searches (6.9 & 10.8)

A4. ***Priority request:*** *Please clarify whether any Adverse Events searches were undertaken? If they were carried out, please provide the full details of all searches, including the date spans, date searched and strategies used. If Adverse Events searches were not carried out, please provide further explanation for not completing these.*

Adverse events searches were carried out as part of the search for clinical evidence. The date spans are the same as those provided for the clinical evidence section.

Cost Effectiveness Searches (7.1 & 10.10)

A5. *Econlit is included in a list of databases searched in section 6.1, but there is no record of this in section 10.10 or elsewhere. Please confirm if this was searched for in the Economics section as requested by NICE. If it was, please provide the search strategy.*

The search terms are provided in Tables 4 and 5.

Table 4: Quality of life search terms

1	myelodysplas$.mp.	2	MDS.ti,ab.
3	1 or 2	4	best supportive care.mp.
5	clinical practice.mp.	6	lenalidomide.mp.
7	revlimid.mp.	8	active therap$.ti,ab.
9	placebo$.mp.	10	antibiotic$.ti,ab.
11	transfusion$.ti,ab.	12	erythropoietin$.ti,ab.
13	EPO.ti,ab.	14	darbepoetin alfa.mp.
15	epoetin alfa.mp.	16	epoetin beta.mp.
17	epoetin theta.mp.	18	epoetin zeta.mp.
19	methoxy polyethylene glycol-epoetin beta.mp.	20	Granulocyte Colony-Stimulating Factor$.mp.
21	G-CSF.mp.	22	filgrastim.ti,ab.
23	lenograstim.mp.	24	pegfilgrastim.mp.
25	iron chelat$.mp.	26	Alpha lipoic acid.mp.
27	ALA.ti,ab.	28	Deferasirox.mp.
29	Deferoxamine.ti,ab.	30	Dimercaprol.ti,ab.
31	BAL.ti,ab.	32	Dimercaptosuccinic acid.mp.
33	DMSA.ti,ab.	34	2,3-dimercapto-1-propanesulfonic acid.mp.
35	DMPS.ti,ab.	36	Ethylenediamine tetraacetic acid.mp.
37	Penicillamine.ti,ab.	38	or/4-37
39	cost$.ti.	40	(cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab.
41	(economic$ or pharmaco economic$ or pharmoco-economic$).tw.	42	quality adjusted life.tw.
43	(qaly$ or qald$ or qale$ or qtime$).tw.	44	disability adjusted life.tw.
45	daly$.tw.	46	(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.
47	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.	48	(sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
49	(sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.	50	(sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twnety or short from twenty).tw.
51	(euroqol or euro qol or eq5d or eq 5d).tw.	52	(hql or hqol or h qol or hrqol or hr qol).tw.
53	(hye or hyes).tw.	54	quality adjusted life.tw.
55	(qaly$ or qald$ or qale$ or qtime$).tw.	56	disability adjusted life.tw.
57	daly$.tw.	58	health$ year$ equivalent$.tw.
59	health utilit$.tw.	60	(hui or hui1 or hui2 or hui3).tw.

61	disutili$.tw.	62	rosser.tw.
63	quality of wellbeing.tw.	64	quality of well-being.tw.
65	qwb.tw.	66	willingness to pay.tw.
67	standard gamble$.tw.	68	time trade off.tw.
69	time tradeoff.tw.	70	tto.tw.
71	or/39-70	72	3 and 38
73	71 and 72	-	

Table 5: Cost-effectiveness search terms

1	myelodysplas$.mp.	2	MDS.ti,ab.
3	1 or 2	4	best supportive care.mp.
5	clinical practice.mp.	6	lenalidomide.mp.
7	revlimid.mp.	8	active therap$.ti,ab.
9	placebo$.mp.	10	antibiotic$.ti,ab.
11	transfusion$.ti,ab.	12	erythropoietin$.ti,ab.
13	EPO.ti,ab.	14	darbepoetin alfa.mp.
15	epoetin alfa.mp.	16	epoetin beta.mp.
17	epoetin theta.mp.	18	epoetin zeta.mp.
19	methoxy polyethylene glycol-epoetin beta.mp.	20	Granulocyte Colony-Stimulating Factor$.mp.
21	G-CSF.mp.	22	filgrastim.ti,ab.
23	lenograstim.mp.	24	pegfilgrastim.mp.
25	iron chelat$.mp.	26	Alpha lipoic acid.mp.
27	ALA.ti,ab.	28	Deferasirox.mp.
29	Deferoxamine.ti,ab.	30	Dimercaprol.ti,ab.
31	BAL.ti,ab.	32	Dimercaptosuccinic acid.mp.
33	DMSA.ti,ab.	34	2,3-dimercapto-1-propanesulfonic acid.mp.
35	DMPS.ti,ab.	36	Ethylenediamine tetraacetic acid.mp.
37	Penicillamine.ti,ab.	38	or/4-37

A6. *Please confirm if the Economics Medline strategy reported in 10.10 also included the search of Medline In-Process. If not, please confirm if this was searched and provide the search strategy.*

Please see response for A2.

Measurement of Health Effects HRQL Searches (7.4 & 10.12)

A7. *Section 10.12 includes a single generic search strategy; please clarify whether the individual search strategies for this section are those recorded in 10.10 as "Utility Values Strategies".*

This is correct.

***A8**. Please confirm if the Utilities Medline strategy reported in section 10.10 also included the search of Medline in Process, if not please confirm if this was searched and provide the search strategy.*

Yes the same strategy was used for both Medline and Medline In-Process.

***A9**. Please confirm if the search strategy for NHS EED reported for the Economics search in 10.10 was also used to inform the HRQL section (10.12).*

This is correct.

***A10.** Econlit is in the list of databases searched in section 6.1, but there is no record of this in section 10.12 or 10.10. Please confirm if this was searched in the HRQL section as requested by NICE. If it was searched, please provide the search strategy.*

This was included. See A5 for search terms.

***A11.** In section 10.12.1 the MS states that Web of Knowledge Conference Proceedings Index was searched, please clarify if this was included in the Science Citation Index Search? If not, please provide the search strategy.*

Yes this was included in the Science Citation Index Search.

Section B: Clarification on the clinical effectiveness data:

B1. ***Priority request:*** *Please provide the complete clinical study report (CSR) for the MDS-004 study, including information such as the demographic and baseline characteristics of the ITT population (Table 14.1.3.2).*

This was included in the original reference submission to NICE, file named as 'cc-5013-mds-body'. This is reattached for ease of reference.

B2*.* *Please provide a list of excluded studies by reason of exclusion, in particular the 18 studies excluded because of "intervention not of interest" and the 17 studies excluded because of "outcome not of interest".*

See Appendix 2 for the full list of excluded studies for studies where the reason was "intervention not of interest" or "outcome not of interest".

B3*.* *Please clarify how the additional publications in table 4 (page 38 of the MS) were identified, and whether there is a reason why were these not identified through the systematic search (for example, studies 3, 8, 9 and 10 seem to fulfil all inclusion criteria)?*

Studies 3, 8, and 9 are all referenced to 51 in the reference list in the submission – which is the Fenaux abstract in Journal of Clinical Oncology. Study 10 is also an abstract. The mentioned studies referenced in the table did not come up in the main search as there was no specific search for abstracts from conferences.

B4*.* *In the study population flowchart (Figure 4, page 45), please provide the reasons for exclusion from the mITT analysis by treatment arm.*

Table 6: Reasons for exclusion from the mITT analysis by treatment arm

Category/Description	Placebo QD 28 of 28 Days (N=16)	Lenalidomide 5 mg QD 28 of 28 Days (N=22)	Lenalidomide 10 mg QD 21 of 28 Days (N=28)
Inadequate BM Sample	12	11	17
INT-2 or Higher IPSS Score	2	5	4
Insufficient IPSS Information	0	1	3
No del(5q) by Central Review	2	4	3
Transfusion Independent Prior to Pre-Randomization	0	1	1

The primary reason for exclusion was "inadequate bone marrow sample." The next most frequent reasons for exclusion were "Int-2 or High Risk IPSS MDS by Central Review at baseline."

B5*.* ***Priority request:*** *Please clarify the main 'other' reasons for discontinuation for both the lenalidomide groups with the corresponding numbers (see table 8, page 55 of the MS).*

Two patients in each of the lenalidomide groups (10 mg and 5 mg) discontinued stating the reason 'other', unfortunately the CRF did not capture further detail and so we cannot expand on the reasons for these discontinuations.

B6. ***Priority request:*** *Page 56 of the MS states "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." Please clarify the actual number of deaths by treatment group and study period.*

Table 7: Summary of deaths from the DB and OL phases

Category	Placebo QD 28 of 28 Days (N=67) n (%)	Lenalidomide 5 mg QD 28 of 28 Days (N=69) n (%)	Lenalidomide 10 mg QD 21 of 28 Days (N=69) n (%)	Overall (N=205) n (%)
All subjects who died during the study	35 (52.2)	32 (46.4)	34 (49.3)	101 (49.3)
Number of subjects who died ≤ 30 days after last dose[a]	4 (6.0)	2[b] (2.9)	4 (5.8)	10 (4.9)

Overall, there were 101 (49.3%) deaths during the study period, 10 of which occurred within 30 days of the last dose of study drug. The percentages of deaths, including those that occurred within 30 days of their last dose, were comparable between the placebo group and the lenalidomide groups.

B7. ***Priority request:*** *Please provide all results reported in chapter 6.5 both for the ITT and the mITT population; including:*

Time to erythroid response – 182 days

Table 8: Time to response - subjects who became RBC-transfusion independent for at least 182 Days (mITT Population)

Statistic	Placebo (N=51)	Lenalidomide 5 mg/day (N=47)	Lenalidomide 10 mg/day (N=41)
Number transfusion independent (responders)	3	20	23
Mean (weeks)[a]	8.2	3.5	4.5
SD	13.77	3.65	4.03
Median (weeks)[a]	0.3	3.0	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

[a] Measured from the day of the first dose of study drug to the first day of the 182+ day RBC transfusion-free period.

The median times to response were 3.0 weeks (range: 0.3 – 12.3 weeks) for the 20 responders in the 5 mg lenalidomide group, 4.3 weeks (range: 0.3 – 14.7 weeks) for the 23 responders in the 10 mg lenalidomide group, and 0.3 weeks (range: 0.3 – 24.1 weeks) for the 3 responders in the placebo group.

Table 9: Time to response - subjects who became RBC-transfusion independent for at least 182 days (ITT Population)

	PLACEBO (N=67)	5 MG QD (N=69)	10 MG QD (N=69)
Time to transfusion independence (weeks)			
N	4	24	38
Mean	6.3	3.7	5.1
SD	11.93	3.62	3.74
Median	0.3	3.3	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

Time to erythroid response – 56 days

Table 10: Time to response - subjects who became RBC-transfusion independent for at least 56 days (mITT Population)

Time to Response for 56+ Day RBC Transfusion Independence (Double-blind - MITT Population)

	PLACEBO (N=51)	5 MG QD (N=47)	10 MG QD (N=41)
Time to transfusion independence (weeks)			
N	4	24	25
Mean	7.9	3.4	4.9
SD	11.27	3.39	4.06
Median	3.6	3.2	4.3
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

Table 11: Time to response - subjects who became RBC-transfusion independent for at least 56 days (ITT Population)

	PLACEBO (N=67)	5 MG QD (N=69)	10 MG QD (N=69)
Time to transfusion independence (weeks)			
N	5	33	42
Mean	6.4	4.3	5.4
SD	10.33	3.72	3.74
Median	0.3	4.1	4.6
Min, Max	0.3, 24.1	0.3, 12.3	0.3, 14.7

Duration of erythroid response

Table 12: Duration of RBC-transfusion independence response - subjects who became RBC-transfusion independent for at least 182 Days (mITT Population)

Statistic	Placebo (N=51)	Lenalidomide 5 mg QD (N=47)	Lenalidomide 10 mg QD (N=41)
Kaplan-Meier estimates			
Number of transfusion independent subjects	3	20	23
Number (%) who progressed (had a transfusion after response)	0 (0.0)	5 (25.0)	9 (39.1)
Number (%) who maintained transfusion independence (censored [a])	3 (100.0)	15 (75.0)	14 (60.9)
Median (weeks)	NA	NA	NA
95% CI (weeks)	NA, NA	NA, NA	98.3, NA
Summary statistics			
N	3	20	23
Mean	61.4	107.7	108.6
SD	10.93	52.35	40.63
Median	56.1	140.9	106.0
Min, Max	54.1, 74.0	28.3, 157.0	40.0, 158.7

Note: measured from the first of the consecutive 182 days during which the subject was free of RBC transfusions to the day before the date of the first RBC transfusion after this period.

[a] Duration of response was censored at the date of last transfusion assessment for subjects who maintained transfusion independence.

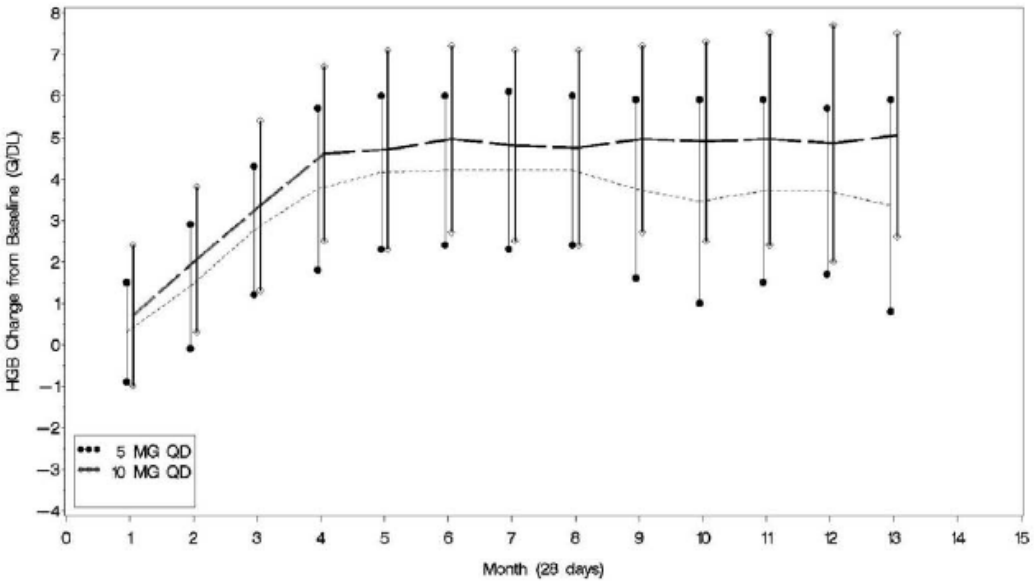
Median duration of transfusion independence for the lenalidomide treated subjects exceeded 2 years (with the median ranging between 106 and 141 weeks).

Table 13: Duration of 182+ day transfusion independence response by initial dosing regimen (ITT Population)

	PLACEBO (N=4) n (%)	5 MG QD (N=24) n (%)	10 MG QD (N=38) n (%)
Kaplan-Meier estimates			
Subjects with Transfusion Independence Response	4	24	38
Subjects who progressed (had a transfusion after response)	0 (0.0)	7 (29.2)	15 (39.5)
Subjects who maintained transfusion independence (censored[1])	4 (100.0)	17 (70.8)	23 (60.5)
Median (weeks)	NA	NA	NA
%95 CI	[NA, NA]	[NA, NA]	[98.3, NA]
Summary statistics (weeks)			
N	4	24	38
Mean	58.6	106.0	106.6
SD	10.60	52.72	42.63
Median	55.1	140.9	105.5
Min, Max	50.0, 74.0	28.3, 157.0	31.3, 158.7

Change in haemoglobin levels

Table 14: Change in haemoglobin (g/dL) from baseline (BL) to maximum value (Max) - subjects who became RBC-transfusion independent for at least 56 Days (mITT Population)



Number of subjects in each month

Placebo													
5 mg/day	20	20	20	20	20	20	20	20	20	20	16	17	10
10 mg/day	23	23	23	23	23	23	23	23	23	23	22	22	17

Note: Mean and standard deviation (SD) were not calculated if the number of subjects was ≤ 3.

Table 15: Change in haemoglobin (g/dL) from baseline to maximum value for subjects who became RBC-transfusion independent for at least 182 Days (ITT Population)

Hemoglobin Change from Baseline to Maximum Value - Responders for 182+ Day Transfusion Independence (Double-blind ITT Population)

		PLACEBO(N=67)			5 MG QD(N=69)			10 MG QD(N=69)		
	Stat	Baseline	Max	Change	Baseline	Max	Change	Baseline	Max	Change
Hemoglobin(g/dL)	N	4	4	4	24	24	24	38	38	38
	Mean	10.3	12.4	2.1	8.4	13.9	5.6	8.4	14.5	6.1
	SD	1.03	1.30	0.57	0.86	1.69	1.82	1.00	1.56	1.81
	Median	10.6	12.7	2.2	8.3	14.1	5.5	8.3	14.4	6.5
	Min, Max	8.8, 11.2	10.7, 13.7	1.5, 2.7	6.4, 9.9	10.0, 16.3	1.6, 8.6	6.2, 10.8	11.1, 18.0	2.0, 10.0

Cytogenetic response and progression

Table 16: Cytogenetic response by central review (mITT Population)

Response Category [a]	Placebo (N [b]=41)	Lenalidomide 5 mg/day (N [b]=37)	Lenalidomide 10 mg/day (N [b]=40)
	n (%)	n (%)	n (%)
Major response	0 (0.0)	5 (13.5)	10 (25.0)
Minor response	0 (0.0)	3 (8.1)	7 (17.5)
Cytogenetic progression	5 (12.2)	10 (27.0)	8 (20.0)
Not evaluable/data not available	10	10	1

[a] Best response
[b] Number of subjects evaluable for response

In the 10 mg lenalidomide treatment group, major and minor cytogenetic responses were observed in 25.0% and 17.5%, respectively; compared with 13.5% and 8.1%, respectively, in the 5 mg lenalidomide group. There were no major or minor responses in the placebo group. Cytogenetic progression was observed at a rate of 12.2% in the placebo group (median duration of exposure 16 weeks), 27% in the 5 mg lenalidomide group (median duration of exposure18 weeks) and 20 % in the 10 mg lenalidomide group (median duration of exposure, 50 weeks).

Cytogenetic relapses were too few to evaluate. Similar results were obtained for the ITT population (Table 17).

Table 17: Cytogenetic response by central review (ITT Population)

	PLACEBO (N=50)	5 MG QD (N=48)	10 MG QD (N=61)
Complete response	0 (0.0)	9 (18.8)	15 (24.6)
Partial response	0 (0.0)	4 (8.3)	12 (19.7)
Cytogenetic progression	5 (10.0)	12 (25.0)	12 (19.7)
Cytogenetic relapse	0 (0.0)	0 (0.0)	1 (1.6)
Not Evaluable	17	21	8

HRQoL

This analysis was performed as part of the safety assessment per trial protocol and included all patients. Further breakdown of this analysis to ITT or mITT is therefore not available.

Disease progression

Please refer to Fenaux (2011).

Survival

Please refer to Fenaux (2011).

B8. *The scope states: "If evidence allows, subgroups based on different cytogenetic profiles will be considered separately". Please clarify why this subgroup has not been explored in the MS (see MS, statement of the decision problem, page 28)*

B9*.* *Please clarify the following sentence on page 30 of the MS: "Add in the response rates used in the HE model – assessed at day 80".*

This sentence was included in error.

B10*.* *In section 6.3.1 of the MS it is difficult to relate study references to each of the clinical trials. Please provide all the relevant references for each of the Celgene trials (MDS-001 to MDS-004).*

MDS-001: List A *et al*, 2005

MDS-002: Raza A *et al,* 2008

MDS-003: List A *et al* 2006

MDS-004: Fenaux P *et al* 2011

B11*.* *Page 44 of the MS states that "... patients not tolerating dose level −3 discontinued treatment", please clarify which treatment options were available for these patients? BSC only or also other treatments such as azacitadine?*

Within the trial protocol patients were allowed to reduce their total dose of lenolidamide three times: firstly to 5 mg for 28 days; second to 5 mg for 14 days out of 28; and finally to 5 mg for seven days out of 28. No patients within the trial titrated down to 5 mg seven days out of 28. Any patients who discontinued on 5 mg seven days out of 28 due to adverse event would receive symptomatic treatment to manage adverse events. Patients who are non-responsive would in addition receive transfusions and potentially treatment with growth factors.

B12*.* ***Priority request:*** *Please clarify why a relatively large number of patients were excluded from the mITT population (66 out of 205), and the reasons why most of these did not fulfil the inclusion criteria (n=20) or had inadequate/insufficient information (n=44). Please clarify why it was not possible to assess people fully before randomisation?*

Following randomisation, the patients were reviewed by central lab and were accordingly assigned after the investigator assessment.

The primary reason for exclusion was "inadequate bone marrow sample." The next most frequent reasons for exclusion were "Int-2 or High Risk IPSS MDS by Central Review" at baseline.

Table 18: Reasons for exclusion from mITT analysis

Category/Description	Placebo QD 28 of 28 Days (N=16)	Lenalidomide 5 mg QD 28 of 28 Days (N=22)	Lenalidomide 10 mg QD 21 of 28 Days (N=28)
Inadequate BM Sample	12	11	17
INT-2 or Higher IPSS Score	2	5	4
Insufficient IPSS Information	0	1	3
No del(5q) by Central Review	2	4	3
Transfusion Independent Prior to Pre-Randomization	0	1	1

B13. *Please provide full definitions of Erythroid response according to the IWG 2000 and 2006 criteria.*

<u>IMW – 2000 definition (Cheson, 2000)</u>
Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, transfusion independence.

Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

<u>IMW – 2006 definition (Cheson, 2006)</u>

Erythroid response (pretreatment, < 11 g/dL)

- Hgb increase by >1.5 g/dL
- Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk.
- Only RBC transfusions given for a Hgb of < 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation.

B14. ***Priority request:*** *Please provide an overview of patients that crossed over from one arm to another with time of cross-over and from which arm to which arm and how these treatment switches were handled in the analyses.*

All patients who crossed over did at 4 months if they did not respond: placebo to 5 mg; 5 mg to 10 mg.

In the MDS-004 study, the overall OL population (split out by treatment received during the DB and OL treatment phases) was as follows:

- 16 subjects received a starting dose of 10 mg in the DB phase and continued on that starting dose in the OL phase
- 28 subjects received a starting dose of 10 mg in the DB phase crossed over (decreased) to a starting dose of 5 mg in the OL phase

- 14 subjects received a starting dose of 5 mg in the DB phase and crossed over to a starting dose of 10 mg in the OL phase
- 27 subjects received a starting dose of 5 mg in the DB phase and continued on that starting dose of 5 mg in the OL phase
- 56 subjects crossed over from placebo in the DB phase to 5-mg lenalidomide in the OL phase
- 4 subjects received lenalidomide in the DB phase, entered the OL phase but did not receive any OL study drug before discontinuing from the study.

The proportion of lenalidomide-treated subjects who completed the OL phase of the study ranged from 23.2% (in the Pbo/5 mg group) to 43.8% (in the 10 mg/10 mg group).

The initial probability of response to either lenalidomide or placebo was modelled based solely upon the double blind phase. As crossover did not significantly impact upon the duration of response to treatment (see answer to C14) the duration of response to treatment was modelled based upon the combined data set of double blind patients and crossover patients for lenalidomide. For placebo not enough patients responded to allow modelling of response duration.

As survival and AML progression were modelled on a responder / non-responder basis a time dependent covariate model was used to model the probability of either death or progression to AML accounting for response and crossover with the data set using the following format:

Table 19: Example of coding for response and crossover

ID	Start	Stop	Event	Switched	Responder
14001	0	455	1	0	Transfusion dependent
14002	0	1467	1	0	Transfusion non-dependent
14003	0	110	0	0	Transfusion dependent
14003	111	1625	1	1	Transfusion dependent

Probability of an event (Start, Stop, Event) = Responder + Switched

Responder describes whether patients became transfusion independent or not and switched describes whether the record is for the second treatment or not (if patients switched treatment).

***B15**. Please provide possible reasons why AML progression in the MDS-004 trial is so much higher compared with untreated del(5q) MDS patients in other publications (see ref 84-Germing 2012).*

Progression to AML may have been higher in MDS-004 trial compared to other trials for the following reasons:

Patients in MDS004 had a relatively high median duration from time of diagnosis to start of the trial: 2.4 years for placebo treated patients, 2.8 years for lenalidomide 5mg treated patients and 2.5 years for lenalidomide 10mg treated patients [mITT population] (Fenaux, 2011).

All patients in MDS004 were RBC transfusion-dependent, a well-known adverse prognostic factor in MDS for both OS and AML progression (Fenaux 2011)(Malcovati 2007). In comparison, only 41.6% of patients enrolled in Germing 2012 were considered to be transfusion dependent at diagnosis (Germing 2012). Univariate analysis of prognostic parameters in Germing 2012 showed that a higher proportion of transfusion dependent patients progressed to AML

The early crossover design in MDS004 prevented long-term assessment of the impact of 295 lenalidomide treatment on AML progression and OS compared with untreated patients. Analysis by Kuendgen et al, 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. In this analysis of lenalidomide-treated versus untreated RBC transfusion dependent patients with Low- or Int-1-risk MDS and del(5q), lenalidomide treatment was not associated with a greater risk of AML progression as assessed by Cox proportional hazards models with left truncation.

***B16**. Please provide a description of the FACT-An scale and provide references.*

The Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire was used to assess HRQoL. The FACT–An is composed of two subscales: the FACT-G (general) and the FACT-An (anemia). The FACT-G measures general HRQoL in cancer patients within four domains: physical, social, emotional and functional. The Anemia subscale measures the cancer-related symptoms of anemia and fatigue. Higher overall scores indicate better HRQoL (Yellen, 1997).

An additional description of FACT-An is obtained from Cella (2002):

The Functional Assessment of Cancer Therapy—Anemia (FACT-An [47 items]) consists of 5 subscales; physical well-being (PWB; 7 items), social/family well-being (SWB; 7 items), emotional well-being (EWB; 6 items), functional well-being (FWB; 7 items), and anemia symptoms (AS; 20 items). The PWB, SWB, EWB, and FWB subscales can be summed to form the FACT—General (FACT-G) score. The PWB, FWB, and AS subscales can be summed to form the Trial Outcome Index— Anemia (TOI-An).

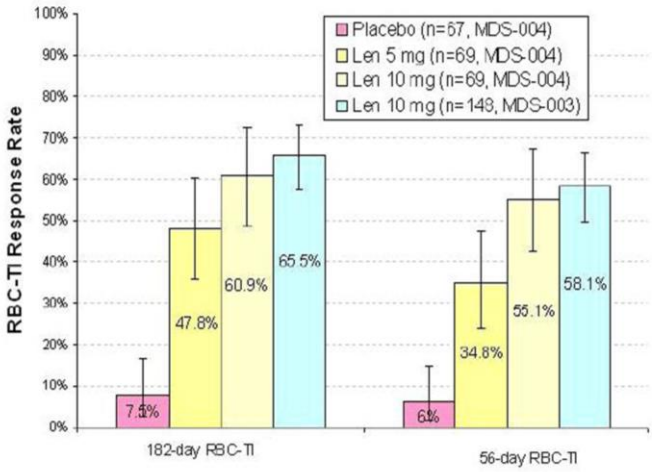
***B17**. In table 14 (page 80) of the MS, please confirm that the last column is 10mg, instead of the 5mg reported.*

Yes that is correct.

***B18.** Figure 7, page 65 of the MS presents subgroup analysis of erythroid response (lenalidomide 10mg vs 5mg). Please provide the same figure for both lenalidomide arms separately versus placebo (preferable for the ITT population, or both mITT and ITT).*

The figure is provided below.

Figure 1 Response rate for mITT and ITT populations



B19. *On page 45 of the MS it is stated that: "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." Please clarify how data for these patients were analysed in the mITT analyses – were they still followed-up for outcomes, were their results censored, what happened if they died?*

Patients randomized to lenalidomide 10 mg who did not achieve a minor erythroid response by week 16, were not entered into open label phase of the study but were all entered into a follow-up phase. These patients were followed up on a quarterly basis for AML progression and survival. For analysis of AML progression, if the patient did not report AML progression during the follow-up phase, the patient was censored at the last contact date. For patients with AML progression, they were counted as event and time from randomization to AML progression were calculated and used in statistical analysis. The same method was applied for analysis of overall survival. Patients with AML progression were followed up for survival.

B20. ***Priority request:*** *Please provide tables with adverse events as reported in chapter 6.9 for the per-protocol population.*

The safety population analysed includes all randomized subjects who received any study drug. For more information please see the CSR attached.

B21. ***Priority request:*** *Please clarify the diagnostic process for the ITT population and the mITT population and clarify how the tests used and diagnostic process of determining IPSS risk, del5q31 status and transfusion dependence in the clinical studies compares with standard NHS practice?*

Diagnosis of MDS is based on morphological evidence of dysplasia upon visual examination of a bone marrow aspirate and biopsy which can routinely be performed in NHS practice. Information obtained from additional studies such as karyotype, flow cytometry, or molecular genetics is complementary but not diagnostic (Garcia, 2011).

B22. ***Priority request:*** *In the MDS-004 trial, please explain which patients in the control arm received placebo only or placebo plus best supportive care (BSC). Please clarify what constitutes BSC in the MDS-004 trial. For instance, how many patients received erythropoiesis stimulating agent (ESA), GCSF, or blood transfusions as part of BSC; and what other treatments were allowed as part of BSC?*

In the MDS-004 trial BSC was contingent on symptoms and managed accordingly. For example, infections were treated with antibiotics; neutropenia was managed by administration of GCSF; and for patients not responding ESA was administered. Out of 67 placebo patients in the double blind phase 4 patients received no transfusions and two received transfusions and GCSF. ESA use was not permitted within the trial.

Section C: Clarification on the cost effectiveness data

C1. *Please specify the parts of the submission with clinical expert input. If clinical experts were consulted, please provide the rationales for your decisions on validation of the model structure and the main model assumptions.*

There was no external clinical input to this submission. Internal clinical input was sought for model construction and validation purposes and the model was validated against available published cost-effectiveness evidence.

To validate the model a comparison was performed against the analysis conducted by Goss et al (the only relevant cost-effectiveness study identified).

Table 20: Comparison of model results with Goss *et al* over a one year time horizon

Result	Goss *et al*	Model amended following ERG comments
Proportion transfusion independent - lenalidomide	67%	59%
Proportion transfusion independent - BSC	8.9%	7.3%
TI years - lenalidomide	0.61	0.46
TI years - BSC	0.08	0.05
QALYs - lenalidomide	0.78	0.73
QALYs - BSC	0.53	0.64

The results of the model submitted are considerably more conservative than those contained within the Goss model, particularly in relation to the utility associated with transfusion independence compared to dependence.

C2. *Please describe the search process for identifying literature on transition probabilities (e.g. probability of diabetes or cardiac disease) and costs (e.g. costs of diabetes and other complications) that were not based on the lenalidomide clinical studies. Please elaborate on the studies identified and their applicability to this study population.*

Transition probabilities and costs were identified based upon a non-systematic review conducted using PubMed.

The Jaeger paper (used for the probabilities of hepatic complications and diabetes) reports the outcomes in those patients requiring more than 50 units of transfusion during the course of the disease. The MDS-004 trial reported the transfusion burden of all patients as requiring a set number of units per 8 week period with median of 2.7 and range of 1-25.

Whilst these are different ways to evaluate the patient population, Jaeger confirms that those patients requiring a higher number of blood transfusions have a higher risk of developing cardiac failure, hepatic problems and diabetes. The age of patients and

incidence of different varieties of MDS appear to be similar to other reported retrospective analysis.

The Malcovati paper used to estimate the probability of cardiac disease is a retrospective analysis of the Italian registry evaluating the prognostic value of the WHO classification in patients with de novo MDS.

The Del5q cohort in Malcovati is about 30 patients out of 467. The median ages are comparable to the MDS004 trial: 65 and 69, however, there is a slightly higher female population in MDS 004 75% vs 50%. Apart from these differences, the populations would appear to be similar to the MDS 004 trial.

The papers used to estimate costs review the entire population based burden and costs and not just MDS patients. In the absence of any specific data to provide costs associated with CVD, hepatic disease and transfusions for MDS patients, these peer reviewed and published manuscripts provide a good cost estimate.

C3. *Page 97 of the MS describes the model structure. Please explain how patients with existing rather than acquired cardiac conditions and diabetes are accounted for? Is the treatment/outcome profile different for these patients?*

Patients with existing diabetes or cardiac conditions were not accounted for in the analysis. Due to the low number of these patients in the trial it is not possible to analyse whether their treatment outcomes are different. It would however, be expected that the risk of death would be higher for patients with these complications, but this will be accounted for in the survival estimates from the trial data. Patients with pre-existing conditions will have been taken into account in the analysis conducted for the ITT population as their outcomes are analysed along with the rest of the population. The impact of patients developing these conditions (which is greater on the BSC arm) may be underestimated as no correction is included for increased mortality in these patients due to lack of evidence. This biases against lenalidomide.

The table below shows the numbers of patients with pre-existing diabetes and cardiac conditions within the MDS-004 trial. Numbers of patients are small and are relatively evenly balanced between arms.

Table 21: Numbers of patients with pre-existing diabetes and cardiac conditions in MDS-004

	Placebo	**Lenalidomide 5 mg**	**Lenalidomide 10 mg**
Type 2 diabetes mellitus	3 (4.5%)	4 (5.8%)	5 (7.2%)
Type 1 diabetes mellitus	2 (3.0%)	1 (1.4%)	0 (0%)
Cardiac failure	3 (4.5%)	2 (2.9%)	2 (2.9%)

***C4**. Page 97 of the MS describes the model structure. Please explain why progression to more severe forms of MDS was not included within the model?*

We did not include more severe forms of MDS in the model as the model focuses on a particular position within the treatment pathway: low and int-1 risk MDS, that is to say the indication provided in the scope and not the entire treatment pathway. Progression to int-2 and high risk MDS for low risk and int-1 MDS was not measured within the clinical trial and therefore could not be included wihtin the model.

This is probably conservative as it would be expected that more patients in the control arm and non-responders would progress to severe disease which would incur more costs as a result of going onto azacitidine.

***C5**. Page 101 of the MS states that 28% of UK patients in the trial had received ESA prior to the trial but that 52.7% of all patients in the trial had received ESA prior to the trial. Please clarify the rationale for the assumption that the proportion of patients who received ESA prior to the trial is representative for ESA use during BSC in the UK.*

As no evidence is available on the use of ESA within MDS and clinical experts indicated that use was low in the NICE scoping meeting the estimates based upon prior ESA use by UK patients within the clinical trial are the most appropriate available. These are consistent with the NICE scoping statement that ESA use is low in the UK for del5q patients.

Subgroup analysis showed that prior ESA did not significantly impact the chance of transfusion independence by treatment group within the trial therefore the overuse of ESA prior to the trial compared to UK practice is unlikely to impact results.

Sensitivity analysis is provided to address the uncertainty around ESA use in the trial analysing 0% and 100% use.

***C6.** **Priority request:** Page 102 of the MS describes the assessment of response. Please clarify why a 84-day assessment period was used for determination of response rate in the HE model, while in Ch. 6 of the MS only a 56-day and 182-day assessment period were reported (as per protocol).*

Also, please explain the impact on model outcomes of using a smaller or larger number of days for the assessment period

An 84-day assessment period has been used as a pragmatic stopping rule which allows clinicians to identify responders quickly while not excluding late responders (as would be the case with a 56 day stopping rule). Additionally this fits in well with the monitoring frequency required for lenalidomide where patients switch to monthly monitoring after 84 days.

Table 22 shows the number and percentage of patients who achieved transfusion independence in each of the trial arms. By day 84 the majority of patients who will achieve transfusion independence have already done so.

Table 22: Number and percentage of patients who achieved transfusion independence

	Number of patients			% transfusion independent		
	Placebo	5 mg lenalidomide	10 mg lenalidomide	Placebo	5 mg lenalidomide	10 mg lenalidomide
28	3	16	16	4.5	23.2	23.2
56	4	27	30	6.0	39.1	43.5
84	4	32	41	6.0	46.4	59.4
112	4	33	42	6.0	47.8	60.9
140	4	33	42	6.0	47.8	60.9
168	4	33	42	6.0	47.8	60.9
182	5	33	42	7.5	47.8	60.9

As a simplifying assumption in the submitted model, all patients who respond were classed as responders from cycle 1 onwards in both arms. The model has been amended to follow the proportions in the trial with the assumption that response to ESA occurs at the same rate as response to lenalidomide 10 mg.

Table 23 presents the model ICERs according to the time response was assessed, including all model changes made in response to these questions.

Table 23: ICERs based on time response (and all changes recommended by the ERG in this document)

Response Assessed	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
56 days	Standard Care	£103,512	4.55	2.65	-	-	-	-
	Revlimid	£138,515	5.24	3.19	£35,003	0.69	0.54	£64,619
84 days	Standard Care	£103,581	4.58	2.66	-	-	-	-
	Revlimid	£150,063	5.65	3.48	£46,482	1.07	0.81	£57,243
112 days	Standard Care	£103,132	4.58	2.67	-	-	-	-
	Revlimid	£153,324	5.69	3.50	£50,192	1.11	0.83	£60,146
140 days	Standard Care	£102,728	4.58	2.67	-	-	-	-
	Revlimid	£155,104	5.69	3.50	£52,376	1.11	0.83	£63,040
168 days	Standard Care	£102,414	4.58	2.68	-	-	-	-
	Revlimid	£155,841	5.69	3.50	£53,427	1.11	0.83	£64,529
182 days	Standard Care	£102,790	4.60	2.68	-	-	-	-
	Revlimid	£155,841	5.69	3.50	£53,051	1.10	0.82	£64,795

C.7 *Please provide further explanation of 'major response' as mentioned on page 102 in the MS, indicating whether a minor response may also be obtained. Please provide definitions of major and minor response where appropriate.*

Erythroid response (which is referred to here) is classified as major if the patient achieved RBC transfusion independence and minor if the subjects' RBC transfusion requirement had decreased by ≥50% without achieving transfusion independence.

C8. ***Priority request:*** *In the last paragraph on page 102 of the MS numbers are presented about treatment interruptions. None of the numbers cited in this paragraph match the numbers used in the model [excel sheet Dosing]. Please explain the discrepancy.*

The values that are presented in the model are the correct values. The values in the submission are from an older version of the model that had not been updated to use the correct ITT population figures. Thank you for pointing it out. In Table 24, we have provided a table with the correct numbers in.

Table 24: Treatment interruption numbers as presented in the model

1st interruption

Mean time to 1st interruption	54.2	*days*	113.8	*SD*	Proportion of patients	68.70%
Length of 1st interruption	17.5	*days*	30.1	*SD*	Dose on resumption	5

2nd interruption

Mean time to 2nd interruption	72.1	*days*	141.9	*SD*	Proportion of patients	73.80%
Length of 2nd interruption	13.9	*days*	59.6	*SD*	Dose on resumption	5

C9. ***Priority request:*** *Page 103 of the MS states that treatment interruptions were experienced by 64% of the ITT patients that are on treatment. Please clarify if this 64% is based on 10 mg lenalidomide, 5 mg lenalidomide or both? Please provide the percentage of treatment interruptions per treatment arm.*

Further, 62% of the patients experiencing a first interruption also experienced a second interruption. After the second interruption patients resumed treatment at a dose of 5 mg for 14 days per cycle. Please provide sub-analyses from the trial about their response and overall survival.

Experience from the Cancer Drugs Fund indicates a 23% probability that patients will switch to a lower dose. This 23% appears low considering the 64% chance of treatment interruptions followed by treatment adjustments in the trial. Please clarify this apparent discrepancy.

This was also an error in the submission, but not the model. The correct numbers should be:

68.7% of patients in the ITT population experience dose interruption (based upon the 10mg dose) resuming treatment at a dose of 5 mg for 28 days per cycle. Of these, 73.8% experienced a second dose interruption resuming treatment at a dose of 5 mg for 14 days per cycle.

The information provided from the Cancer Drugs Fund was from a record of what has so far been dispended for the indication being appraised. This information was provided (i) to highlight that there is a need and interest from clinicians to treat patients and (ii) to suggest that dose titration may be expected in real world practice.

It is not possible to draw any reliable conclusions at this point from the Cancer Drugs Fund information as the current use of lenalidomide is off label, ad hoc and with no dosing advice provided (including no advice on dose titration in response to adverse events) which would have been available post marketing authorisation, in the SmPC and in the trial.

C10. *Page 106-107 of the MS states there was no reported ESA usage during the trial, therefore available literature was used to estimate response rates in these patients. While the response rate for ESA+G-CSF was calculated as 21.7%, this was reduced to 10.8% for ESA and G-CSF monotherapy. The published response rates to ESA range froms 10-49% for ESA compared to around 50.6% with G-CSF, so the current estimate of 10.8% appears low, please clarify the choice of estimate?*

Please see page 19 of the submission which states “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.”

It should also be noted that during the scoping workshop UK clinicians argued that ESA is not commonly used in clinical practice. The reason provided for the argument was that no tangible clinical response can be expected from this treatment. It is also noted within the literature that patients with a 5q chromosomal abnormality seem to respond to ESAs with a significantly lower response rate and significantly shorter duration of response (Santini, 2011).

C11. *On page 108 the MS states that the results show that the order patients received treatment (and therefore crossover) did not have a significant impact on duration of response. Please provide these results. Please clarify whether patient numbers are sufficient to detect significant differences?*

The results of this analysis are provided below. Given the small number of patients in this analysis, it is difficult to be able to draw any statistical conclusions from these data. However, visually it can be seen that there appears to be no indication of any difference between first and second treatments and the confidence intervals almost perfectly overlap.

Figure 2: Kaplan Meier estimates for duration of response

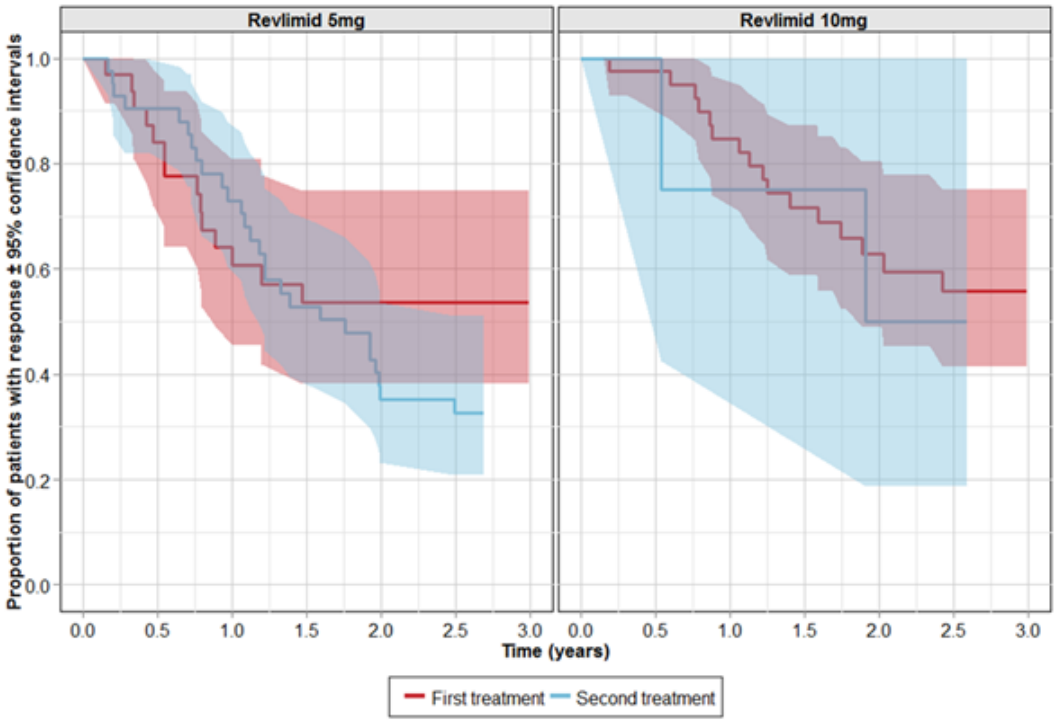


Table 25: Log-rank test for first versus second treatment

Patient group	Lenalidomide 5 mg		Lenalidomide 10 mg	
	N	Stopped responding	N	Stopped responding
First treatment	33	14	42	16
Second Treatment	42	27	4	2
Chi-square (1 df)	0.9		0.1	
P	0.332		0.808	

C12. *Please provide further rationale for why the 5mg dose efficiency was used as a proxy to determine the response curves for the best supportive care arm in the model (page 108 of the MS). Please clarify the process taken to identify the value used for BSC and to determine its appropriateness, for example searches for contextual data available in the literature.*

The response curves have been taken from 5 mg lenalidomide as there were not enough patients responding on the placebo arm of the trial to fit curves. Only five patients responded and of these only one was not censored. This was insufficient to attempt to fit curves.

As lenalidomide 5 mg is an active and effective treatment the use of this curve as a proxy for no treatment is likely an over-estimate of response duration for patients receiving only transfusions. The use of this curve as a proxy for ESA response duration is likely also an overestimate of response duration as Kelaidi *et al* (2008) indicated a mean response duration of 13 months for del5q patients, the mean and median durations of response for responding patients with the 5 mg curve used is considerably longer than this (24 months and 41 months respectively). It should be noted that the Kelaidi population includes patients who are not RBC transfusion dependent (38%) meaning that in reality response duration may be even lower for the transfusion dependent population.

It should be noted that the model is not sensitive to the assumptions regarding response duration due to the low proportions of patients responding to placebo and ESA, to which these curves are applied.

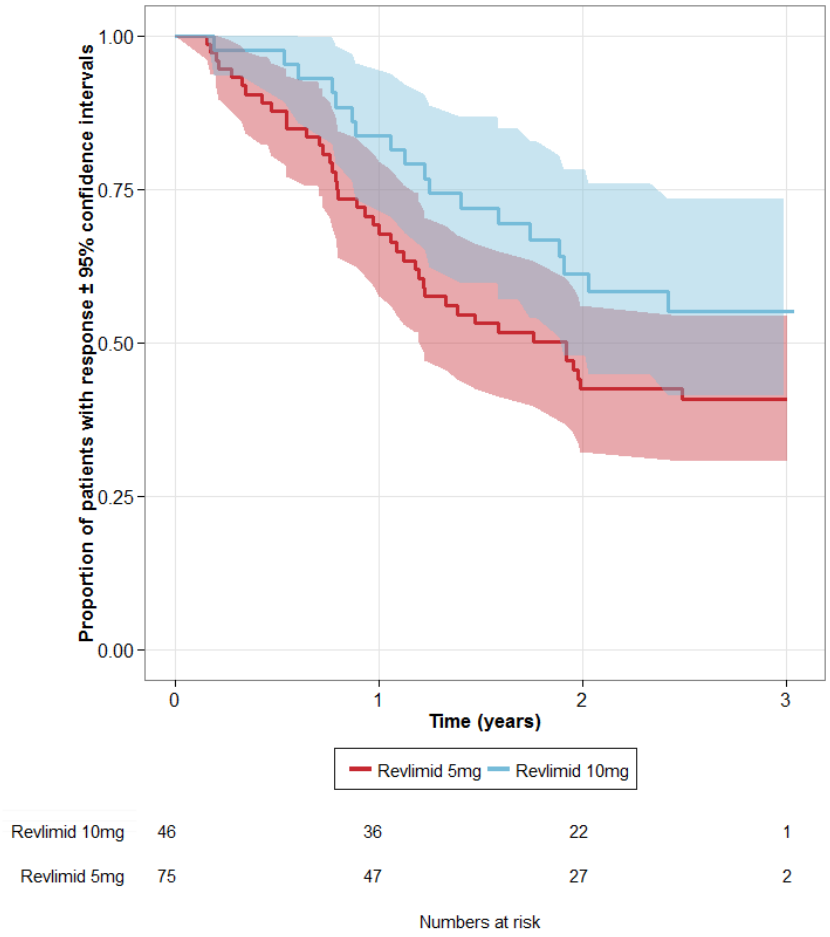
> *The excel sheet (Response KM), the KM curve shows (although based on only a few patients) a better response for placebo in the first 5 cycles than for 5mg and it actually appears closer to the 10 mg curve. In light of this, please justify why the 5 mg group may be used as a proxy for BSC.*

As this is based on five patients, only one of whom was not censored, very little should be read into this KM curve.

C13. *Page 109 (figure 13) of the MS shows the KM curve for responders in the lenalidomide 10 mg and 5 mg treatment arms. Please explain why there are 75 patients at risk if there were 69 in the ITT 10 mg group? Also, the KM curve of the 10 mg group seems similar to the 5 mg except for the plateau at the start. Do you have any explanation for this plateau?*

The numbers at risk have been printed the wrong way round in the figure which has caused the confusion. The 75 patients should refer to the 5 mg group. We have provided a corrected diagram below.

Figure 3: Corrected Kaplan Meier Curve showing responders in lenalidomide 10 mg and 5 mg treatment arms



Both the 10 mg and 5 mg samples include observations from the double blind phase and observations from crossover patients in the open label phase, in order to capture the largest amount of data, as crossover was determined not to impact treatment effect (see C10). Some patients are therefore counted twice.

Table 26: Total number of responders

	Number in clinical trial	Number of responders
Placebo	67	5
lenalidomide 5mg	69	33
lenalidomide 5mg after placebo	46	42
lenalidomide 10mg	69	42
lenalidomide 10mg after lenalidomide 5mg	27	4

As can be seen from the above the total responders over both phases include 75 patients on lenalidomide 5 mg and 46 patients on lenalidomide 10 mg.

The observed plateau is likely because of the treatment effect of lenalidomide which is building up and by cycle five it is observed that 95% of patients would have responded.

In addition, the excel sheet (Response KM) in the model looks very different from figure 13. Also, the patient numbers presented on that sheet do not match those in the trial arms. Please explain this discrepancy.

This is due to the inclusion of patients from the open label phase into the Kaplan Meier data presented in Figure 13. These patients are not included within the figures in the model.

C14. *Please clarify the rationale (page 113 of the MS) for assuming that there are no differences in blood transfusion rate between cardiac, diabetes, hepatic conditions as well as AML?*

Please also clarify the rationale for assuming that there are no differences in blood transfusions/platelets per cycle rate between cardiac, diabetes, HC as well as AML and also with disease progression?

There are differences especially in cardiac patients; however no evidence is available from either the trial (due to low numbers of these patients) or the literature to indicate what the difference in rates is. Patients with cardiac conditions will likely have higher transfusion rate. However the assumption within the model is conservative to lenalidomide. More patients with cardiac conditions are likely to be in the placebo arm than lenalidomide arm.

Blood transfusions are not included within the calculation in the model for patients in the AML state as these are included within the unit cost applied for treatment of AML and therefore including them separately would be double counting.

C15. *Page 114 of the MS details previous transfusion history. The MS states that patients who have had a total number of units greater than the threshold at which iron chelation is applied are excluded from this analysis as they are assumed to start the model in the iron chelation health state (8% of the UK patients). Please provide the treatment allocation of these patients.*

These UK patients were allocated to the 5 mg arm (1) and the placebo arm (1). Using the information from the entire trial patients who had received 25 or more units (and were therefore judged to already require chelation) were assigned as follows:

Table 27: Treatment allocation of patients who received 25 or more units in the 8 weeks prior to the trial

	All Trial Patients	UK Patients
Lenalidomide 10 mg QD	4	0
Lenalidomide 5 mg QD	5	1
Placebo	2	1

C16. ***Priority request:*** *Page 115 of the MS states that two different treatment choices for iron chelation are considered, based on the Prescription Cost Analysis: England 2010. However, that database also lists deferiprone as a prescribed treatment option. Please clarify why this drug was not considered in the model. Please also explain how the 71% for the Exjade was derived from the database, as the ERG obtain 74% based on Pxs and 80% based on Qty.*

The ERG are correct in that deferiprone should have been considered within the model. Please find below calculations updated using PCA 2011 based upon the Qty column.

Table 28: Prescipriont Cost Analysis 2011 split of drugs used for iron chelation

DRUG NAME	BNF CHEMICAL NAME	Qty (thousands)
Exjade_Disper Tab 125mg	Deferasirox	8.148
Exjade_Disper Tab 250mg	Deferasirox	18.361
Exjade_Disper Tab 500mg	Deferasirox	42.417
Ferriprox_Oral Soln 100mg/ml	Deferiprone	9.620
Ferriprox_Tab 1g	Deferiprone	0.645
Ferriprox_Tab 500mg	Deferiprone	78.732
Deferiprone_Cap 400mg	Deferiprone	1.344
Deferiprone_Liq Spec 400mg/5ml	Deferiprone	0.504
Desferal_Inj 2g Vl (Dry)	Desferrioxamine Mesilate	1.457
Desferal_Inj 500mg Vl (Dry)	Desferrioxamine Mesilate	7.797
Desferriox Mesil_Inj 2g Vl	Desferrioxamine Mesilate	0.118
Desferriox Mesil_Inj 500mg Vl	Desferrioxamine Mesilate	0.259
Market share Exjade		40.7%
Market share Ferriprox		52.5%
Market share Deferiprone		1.1%
Market share Desferal		5.5%
Market share Desferriox		0.2%

Using prices from the latest version of the BNF this leads to the following update of the cost of iron chelation:

Table 29: Updated cost for iron chelation

Treatment	Market share	Doses per week	Source	Unit Dose Price	Unit Dose Price + Carriage
DFO	6%	5	BNF	£25.66	£37.94
Deferiprone	54%	7	BNF	£28.43	£40.71
Exjade	41%	7	BNF	£46.37	£58.64
Total per cycle					**£1332.45**

The updated total cost per cycle is therefore £1,332.45 compared with the value of £1,383.39 used in the submission.

C17. *Please provide justification for the assumption of response to iron chelation in the first cycle (page 115 of the MS). Also please explain how different assumptions of time of response would impact the model outcomes.*

This assumption was made as no other information was available on the time taken to respond to chelation. If patients in fact take longer to respond to chelation this would reduce the ICER associated with lenalidomide as more patients require chelation on the standard care arm, due to reduced transfusion independence, meaning that if response takes longer more costs and disbenefits due to the this are accrued on the standard care arm of the model.

The MDS-004 trial had only a few patients who were on iron chelation at the study start and therefore no correlation was possible between response and iron chelation.

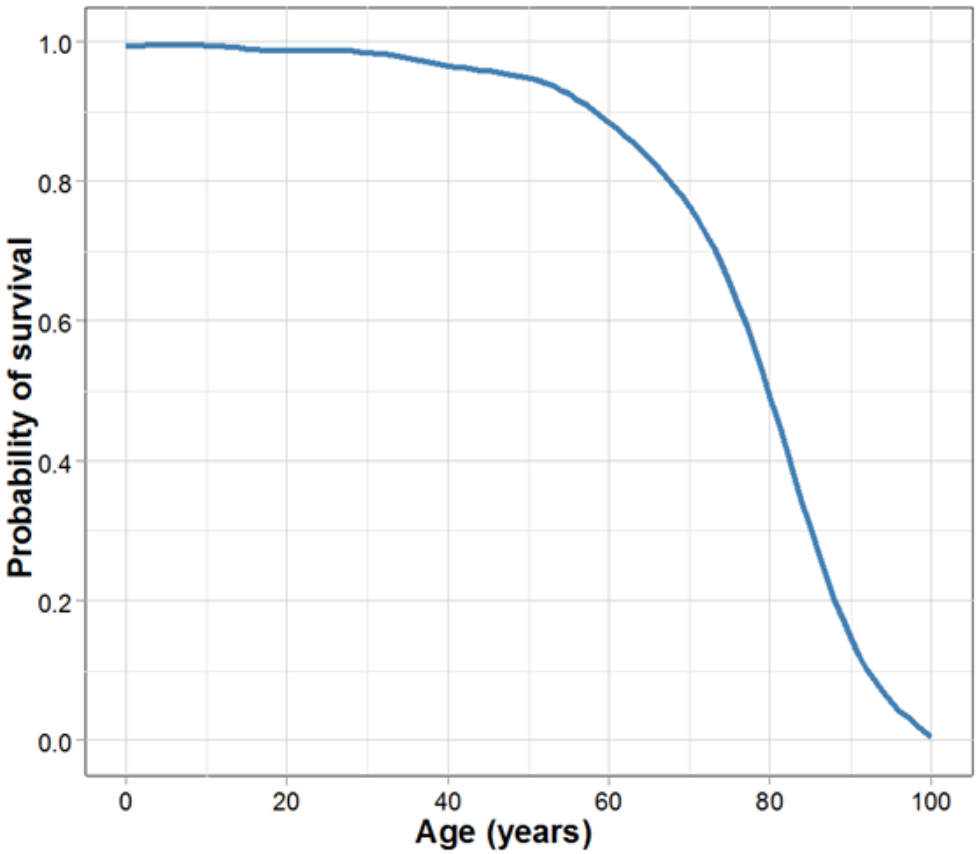
C18*.* *In the last paragraph of page 120 of the MS a description is given about the use of a GAM model to fit the ACM data. Please provide more details about this model. Also please explain how this relates to the curves in figure 21 of the MS, and how it relates to the calculations in the excel model.*

A generalised additive model (GAM) was used to predict the probability of survival for age using survival data from the office of national statistics for the UK baseline survival data (ONS, 2011).

For each patient in the sample the GAM was fitted using the patient's age to predict the survival from the start of treatment for the following 20 years to give the predicted survival assuming that the patient followed that from the UK average. This then gives a series of predictions for each patient. This gives a much more accurate estimation for baseline survival compared to simply assuming that all patients have the same age, since the method used takes into account the age distribution in the data and the fact that different ages give very different survival predictions depending upon where they start along the curve.

The chart below shows the predicted survival probability from the GAM. A penalised thin plate spline to fit the GAM. This is one of the most robust methods available since the user does have to specify the number of knots that make up the spline and the spline itself is penalised to avoid over-fitting.

Figure 4: Generalised additive model estimated of UK general population mortality



This was used to plot the black line (expected UK survival) in Figure 21. It was not used within the Excel calculations and was used solely as a validity check (i.e. that predicted survival was lower for MDS patients than general population mortality).

C19. ***Priority request:*** *Page 124 of the MS indicates that only two adverse events were included in the model. Please explain why only these two were included and why others, for example DVT/PE were not included?*

There was a low incidence of these adverse events in the trial and clinician opinion is that these can be routinely monitored without incurring many costs.

In the MDS-004 study, DVT occurred in 1 subject each in the 5-mg and placebo groups, in 4 (5.8%) subjects in the 10-mg group, and in 4 (7.1%) subjects who had crossed over from placebo to 5-mg. Pulmonary embolism was reported by the similar proportion of subjects (2 subjects; 2.9%) in the 5-mg group and (3 subjects; 4.3%) in the 10-mg group and by no subjects in the placebo group over the entire study.

C20. *Please justify why adverse effects of lenalidomide only occur in the first 4 cycles (page 125 of the MS).*

The majority of cases are experienced within the first 16 weeks (4 cycles). This is a marker of response/treatment effect of lenalidomide. Once treatment is initiated lenalidomide clears the abnormal blood picture and therefore you see a smaller count of normal cells after which then grow back to normal level. So if a patient takes lenalidomide, the counts goes down first before climbing up.

Table 30: Comparison of adverse event occurences within the first 16 weeks compared to the entire trial

	Within the first 16 weeks			**Within the entire double blind treatment phase**		
	Placebo	**5 mg**	**10 mg**	**Placebo**	**5 mg**	**10 mg**
Thrombocytopenia	2	29	31	2	30	34
Neutropenia	12	53	52	12	53	53

C21. *Please explain how from ref 86 the numbers for complications of iron overload in table 27 of the MS (page 125) were derived.*

Please see detailed calculations in the table below which has been relabelled in a more informative manner.

Table 31: Adverse events experienced over 16 weeks

Adverse event	**Placebo**	**lenalidomide 10 mg**	**% due to lenalidomide (Difference between the two)**	**Cycles risk applied over**	**Probability per cycle (applied for the first 4 cycles)**
Thrombocytopenia, Grade 3/4	2/67 = 3.0%	31/69 = 44.9%	44.9%-3.0% = 41.9%	4	1-(1-41.9%)^(1/4) = 12.69%
Neutropenia, Grade 3/4	12/67 = 17.9%	52/69 = 75.4%	75.4%-17.9% = 57.5%	4	=1-(1-57.5%)^(1/4) = 19.26%

C22*.* *Please provide further explanation of the generalizability of the results of Malcovati et al. (ref 76) to the current model (page 126 of the MS), especially regarding the population and the definition of transfusion dependency. Also please clarify how uncertainty around the estimated curve was estimated, since no patient-level data was available.*

As patient level data was not available and number at risk was not provided in the publication it was assumed that all patients who did not die within the trial were censored at the last time point provided when fitting the curves. Uncertainty was estimated based upon a multivariate normal distribution using the curve fit and variance covariance defined by the estimated patient level data produced using the assumption. As the curves provided a good visual fit and this parameter has only a small impact upon the model further investigation was not considered necessary. Cardiac complications account for <1% of total costs on both arms and the impact on the ICER if utility decrement is not included for cardiac disease is less than £100.

C23. *Utility values were obtained from Szende 2009 ref 99 (page 148 of the MS). The model is highly sensitive for the utility values per health state. Please explain if other options for utility estimation have been explored, such as the use of the CALGN 9221 study, in which EORTC score were collected which can be mapped to EQ-5D.*

We believe the study referred to above to be the CALGB 9221 – azacitadine – Int 2 and high risk patients. This indication is substantially different to the indication being appraised as this study is based solely upon more severe patients, it would be inappropriate to use utilities derived from this study.

C24. *Please provide further justification for why the utility estimate for AML was assumed to be the same as for patients who were transfusion dependent (page 148 of the MS).*

As no utility estimates were available for acute myeloid leukemia a conservative assumption was made that the utility of patients would be the same as for transfusion dependence. In reality the utility of patients with AML would be lower as these patients are transfusion dependent and experiencing additional symptoms associated with AML. However, this utility has little impact upon the model as numbers of patients progressing to AML are similar on both arms (as patients live longer on lenalidomide and therefore have longer in which to progress to AML but at a reduced probability each cycle compared to standard care). In fact setting the AML utility to zero alters the ICER by less than £200.

C25. *Please explain which tables and numbers where used from the Fryback (1993) publication to derive the AE utility decrement for cardiac disease and diabetes applied in the model (page 149 of the MS) and whether a systematic search was undertaken to obtain more contemporary estimates.*

The value was taken from Table 5 (TTO scores) and the % decrement for cardiac disease was calculated as 1 - 71/86.5 which is the change in utility for people with congestive heart failure compared to those who do not. The value for diabetes was calculated using diabetes non-insulin as 1-76.1/86.8.

A systematic search was not undertaken to obtain more contemporary estimates however this variable has little impact upon the model – removing either of these variables entirely changes the ICER by less than £100.

C26. *Please provide further justification for why no utility decrements were applied to the lenalidomide related SAE (i.e. neutropenia and thrombocytopenia). The effects are argued to be "typically transient and manageable and QoL is likely to be short term" (page 149 of the MS). However no evidence is provided for this. Can it be provided?*

Clinical opinion confirmed that these were fairly manageable and do not impact the quality of life.

Evidence from the lenalidomide submission in multiple myeloma, which is a more severe disease, indicates that both neutropenia and thrombocytopenia have a very small impact on patient quality of life with utility decrements lasting for seven days on average (Brown, 2012). The utility decrements used within this submission are negligible: 0.003 per patient experiencing neutropenia and 0.006 per patient experiencing thrombocytopenia.

C27*. It is currently assumed in the economic model that all monitoring of MDS is completed by a GP (page 156 of the MS). Please clarify how this assumption was derived and its justification.*

Haematology costs are included within the costs for adverse events and transfusions which are the main causes for haematologist visits. To avoid double counting haematology visits are therefore not included for regular monitoring which outside of the above is primarily conducted by GPs.

C28*. Please provide further justification for the assumption that all patients are assumed to have the same monitoring frequency (page 156 of the MS). Specifically comment on the assumption that non responders require the same amount of monitoring as responders.*

It is likely that monitoring costs would be higher for non-responders. As there are more of these on the standard care arm not assuming a higher rate is a conservative assumption which biases against lenalidomide.

C29. *Please explain why fixed cost estimates were used for chelation (page 156 of the MS), despite the fact that treatment is weight related, leading to variation in costs between patients?*

As a Markov model has been used, for simplicity the average patient weight from the trial (69kg) was used to calculate iron chelation costs. This conservatively assumes no wastage. Inclusion of wastage would reduce the ICER as more chelation therapy is used on the standard care arm of the model.

C30. *Please provide the document from which the UK costs of AML were retrieved and indicate on which page the cost estimate of £1,844 per 28 day cycle can be found (page 158 of the MS). The ERG were only able to find an estimate*

of £1,814 per 5-week cycle (page 100 of the MS for the STA of azacitidine). Please also clarify if any treatment costs for AML such as chemotherapy or stem cell transplantation are included in this cost estimate.

This value was updated during the azacitidine submission; however, as we cannot find the exact reference for the £1,844 we have updated to match the azacitidine submission. This leads to an updated per cycle cost of £1,451.42 ((£1814.27/(5*7))*28).

C31 ***Priority request:*** *Please explain why reference costs for SA08F (page 160 of the MS) were used even though there are specific codes for thrombocytopenia (SA12D with cc and SA12F w/o cc) and for febrile neutropenia (PA45Z)?*

Code PA45Z refers to febrile neutropenia with malignancy, this is considerably more severe than neutropenia which is what was seen in the lenalidomide trial. It is acknowledged that the costing currently provided is not realistic enough and in fact substantially overestimates the costs of these adverse events as in some cases the events either do not require treatment at all or can be treated as an outpatient appointment rather than requiring admission as an inpatient. Costs have therefore been updated to match those used for grade 4 AEs in the lenalidomide submission for multiple myeloma as published by Brown *et al* (2012).

These costs are as follows:

- Thrombocytopenia: £623
- Neutropenia: £560

The costs have been inflated to 2011/2012 prices using PSSRU to:

- Thrombocytopenia: £739
- Neutropenia: £664

As multiple myeloma is a more severe condition and only Grade 4 costs are used (as a breakdown of Grade 3 and 4 AEs was not available) these costs are likely to be overestimates.

C32*.* *Please justify why the number of monitoring visits for BSC and lenalidomide is not varied in the PSA (page 163 of the MS).*

For simplicity this was covered within the variation of the costs of monitoring rather than the number of visits. The new model provided has increased the variation to a standard error of 2 * the setting selected (see below) i.e. 20% of the mean in the base case to account for this dual purpose.

C33. *Please justify the use of a standard error of 10% of the mean for various parameters in the sensitivity analyses (page 162 of the MS). Please clarify why 10% was used rather than for example 20%? Also whether there was*

any data available that could inform the uncertainty around the mean estimates?

The use of a standard error of 10% of the mean in PSA when estimates of true uncertainty are not available is industry standard practice and has been used and accepted in many previous submissions. Functionality has been added to the model to allow the use of user-selectable proportions e.g. 20% and a PSA using this larger uncertainty estimate is provided.

C34. ***Priority request:*** *At section 7.7 (page 172 of the MS), in the response to question 7.7.1, no information is provided about the methods used to validate the model internally and externally and how technical validity was assured.*

Regarding the internal validity, some information is already provided in table 40, however, no discussion is provided on the degree of concurrence between trial results and model results, for example, the differences in the median overall survival for lenalidomide between the model and trial. Besides medians, please also provide restricted means as a measure to compare the trial with the model outcomes.

Regarding the external validity, please compare the model results to data sources outside the clinical trial. This is especially relevant for the BSC group.

The median overall survival as provided in Table 40 of the submission is similar to that within the model when looking at the results of both the MDS003 and MDS004 trials (which is the information used within the model). In fact the median is slightly higher for lenalidomide in the clinical trial as response to lenalidomide was slightly higher in MDS003. The median duration of response is similar for lenalidomide to that experienced in the clinical trial and the proportion of patients experiencing adverse events is consistent.

The median survival presented is also consistent with available external information: in the NICE scope it is stated that median survival with low risk and intermediate-1 risk MDS is 5.7 years and 3.5 years respectively. As the median duration of MDS prior to the trial is 2.4 years in the placebo arm of the trial the additional survival takes patients to a median of approximately 6.2 years, consistent with the survival estimates for low risk MDS and the healthier population which would be expected to be enrolled into a clinical trial.

Due to other commitments the company statisticians were not able to provide restricted mean estimates in time to respond to these questions. If this is still required we can provide this at a later date.

C35. *The proportion of patients achieving transfusion independence in the 10 mg lenalidomide arm is similar between the mITT (61%) and ITT (60.9) (page 175 of the MS). Please provide a similar comparison for the other treatment arms (i.e. 5 mg and placebo). Also please indicate how similar results are for overall survival in the different treatment arms.*

A comparison of response between the two populations for all arms is provided in Table 12 of the submission (reproduced below):

Table 32: Response rates by treatment arm for the ITT and mITT populations

	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

Using the data-cut of MDS-004 presented in the model overall survival is also similar between the mITT and ITT populations as presented in the table below.

Table 33: Overall survival from MDS-004 for the ITT and mITT populations

	Overall survival		
	Placebo	Lenalidomide 5 mg	Lenalidomide 10 mg
mITT population	n=51	n=47	n=41
% dead within trial	54.9%	62.0%	58.5%
Median overall survival (months)	42.2	48.7	35.6
ITT population	n=67	n=69	n=69
% dead within trial	62.7%	57.4%	50.7%
Median overall survival (months)	42.2	45.4	44.2

C36. *Section 7.9.1 (page 176 of the MS) asks about consistency of results to other economic analyses – the answer relates to analysis of sub groups. Please provide a response to this question about the extent to which the current HE outcomes are consistent with published economic literature.*

See answer to C1.

Issues regarding electronic model:

C37. Excel model sheet Transfusion: Please explain the variable “Increase in transfusion rates per cycle” 1%

This control was added during model development based upon a clinical theory that transfusions rates may increase over time as patients stay transfusion dependent. No evidence was found to support this theory therefore the control that would switch this on is not used either within the base case or sensitivity analyses. The control is located on the controls sheet (Range transfusion_rate_type) and is fixed as “Fixed Rate for Transfusions”.

C38. *Excel model sheet Sensitivity Analysis: Please explain why for the lower and upper bound of the parameters a 90% confidence interval was used rather than the 95% interval. For example for the response rate lenalidomide:*

- *Sensitivity Analysis sheet upper and lower bound 0.597 – 0.621;*
- *Response sheet CI 0.484 – 0.724*

The CI presented in the response sheet is the confidence interval relating to response for an individual. The formula used in the sensitivity analysis relates to the population and therefore uses the standard error. However, it is noted that a mistake has been made generally in applying confidence intervals using one tailed rather than two tailed (i.e. sampling using 0.05 rather than 0.025). This has now been corrected resulting in a CI of 0.594 - 0.624 for this particular variable.

C39. ***Priority request****: Please clarify how the uncertainty around the risk of cardiac disease in chelation was modelled. Table 28 indicates a multivariate normal distribution for the parameters of the Gompertz curve. However, on the sheets Parameters and PSA-parameters, these variables seem fixed.*

These calculations are carried out on the Complications sheet. The stochastic switch which indicates that the PSA parameters should be used is turned on as part of the PSA macro.

C40. *Please explain the role of the KM curves on the excel sheets Response KM, DeathnoAML KM and AML KM. Please indicate where are they used in the model calculations.*

These sheets are not used in the calculations, relate to the DB phase of the trial and were provided for information only.

C41. ***Priority request:*** *Excel model sheet Response: Here it states: "We assume that response to treatment occurs within the 1st 4 week cycle, so all patients spend the 1st cycle in the transfusion dependent state." However, on work sheet PF_revlimid this does not seem to be the case, in the first cycle already 60% of patients are in the transfusion independence health state. Please clarify the assumption made.*

The model currently assumed that patients who are going to respond do so immediately as a simplification. This has, however, been updated in response to the comments in C6.

C42. ***Priority request*** *Excel model sheet PF_SC: In column Y of this sheet the probability of response to GCSF is estimated multiplying p_percentESA (28%) and p_RespTIGCSF (2.4%). However, p_RespTIGCSF is defined on sheet Response as prop_ESA (28%) * m_RespTIEsa (8.4%). Thus, it appears that a correction for percentage of patients receiving ESA has been made twice by accident. Please explain whether this is indeed a programming error or if not, what the rationale is for weighting the response rate of GCSF twice.*

This is a programming error and has now been corrected.

C43. ***Priority request:*** *Table 23 on page 106 of the MS shows the response rate for the ITT population. The mean is 7.5% for the placebo group. To get the overall BSC response rate, this trial response rate is weighted with the ESA response rate (10.8%) in order to derive an overall BSC response rate of 8.4% [excel sheet Response cell I50]. However, in [excel sheet PF-SC G23] again a weighted average is calculated, this time of the 8.4% that was previously derived and the 7.5% of the placebo group. It appears that the weighting has been applied twice. Please explain whether this is a*

programming error or if not, the rationale for weighting the response rate twice.

This was also a programming error and has now been corrected through the application of the suggestion in C6.

C44*.* *Please explain why the dosage interruptions were modelled using a simple mean time to interruption that is applied to the whole cohort. Please justify why the patient level data on dosage interruption was not used to estimate a percentage interruption for cycle 1, 2, etc.to mimic reality better, where some patients have an interruption after 1 cycle and some after several cycles.*

In the interests of simplicity an overall mean was used. This is unlikely to affect results as interruptions are experienced prior to discounting and the number of cycles required for the PAS to be applied. We felt that it was more important to model accurately the time on treatment (and therefore cost of drug) within the cycles than to model the cycles during which discontinuation occurred. There are no competing risks or outcomes that are time dependent based upon whether patients are on treatment or experience a dose break therefore accuracy in modelling treatment cost is more important than mimicking reality.

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Appendix 1: Revised Model Results

As a variety of model amendments have been made on the basis of the ERG advice it has been necessary to update the model results submitted in the NICE STA template. Revised results are presented from Section 7.6.4 to 7.6.11 as this is where the results have been impacted.

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:

Table 1. Model outputs by clinical outcomes – lenalidomide

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Transfusion independent	1.64	1.29	£68,289.75
Transfusion dependent	3.69	2.01	£76,623.01
AML	0.32	0.17	£5,150.09
Total	**5.65**	**3.48**	**£150,062.85**
LY, life years; QALY, quality-adjusted life year			

Table 2. Model outputs by clinical outcomes – best supportive care

Outcome	LY (undiscounted)	QALY (discounted)	Cost (£) (discounted)
Transfusion independent	0.14	0.11	£2,343.38
Transfusion dependent	4.13	2.38	£96,226.44
AML	0.30	0.17	£5,010.74
Total	**4.58**	**2.66**	**£103,580.57**
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 3. Summary of QALY gain by health state (including discounting)

Health state	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
Transfusion Independent	1.29	0.11	1.18	1.18	69.32
Transfusion Dependent without Iron Chelation Therapy	0.18	0.10	0.07	0.07	4.34
Transfusion Dependent with Iron Chelation Therapy	1.05	1.48	-0.42	0.42	24.89
Transfusion Dependent with Chelation Failure	0.78	0.80	-0.02	0.02	1.21
AML	0.17	0.17	0.00	0.00	0.24
Total	**3.48**	**2.66**	**0.81**	**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 4. Summary of costs by health state

Health state	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Transfusion Independent	£68,289.75	£2,343.38	£65,946.37	£65,946.37	76.96%
Transfusion Dependent	£76,623.01	£96,226.44	-£19,603.43	£19,603.43	22.88%
AML	£5,150.09	£5,010.74	£139.35	£139.35	0.16%
Total	**£150,062.85**	**£103,580.57**	**£46,482.28**	**£85,689.15**	**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 5. Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Technology cost	£67,022.44	£2,324.58	£64,697.86	£64,697.86	75.39%
Complications: Thrombocytopenia and Neutropenia	£129.68	£0.00	£129.68	£129.68	0.15%
Iron Chelation Therapy	£28,553.86	£39,752.96	-£11,199.10	£11,199.10	13.05%
Complications:	£841.86	£777.96	£63.90	£63.90	0.07%

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Cardiac Disease, Diabetes Mellitus and Hepatic Complications					
Blood transfusions	£45,675.76	£53,710.17	-£8,034.42	£8,034.42	9.36%
AML	£5,150.09	£5,010.74	£139.35	£139.35	0.16%
General Monitoring	£1,137.64	£18.80	£1,118.84	£1,118.84	1.30%
Monitoring with Best Supportive Care	£1,524.97	£1,948.37	-£423.41	£423.41	0.49%
Monitoring with Iron Chelation Therapy	£26.55	£36.97	-£10.41	£10.41	0.01%
Total	**£150,062.85**	**£103,580.57**	**£46,482.28**	**£85,816.96**	**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 6. Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Best supportive care	£103,580.57	4.58	2.66	-	-	-	£38,895.33	-
Lenalidomide	£150,062.85	5.65	3.48	£46,482.28	1.07	0.81	£43,182.54	£57,242.63
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

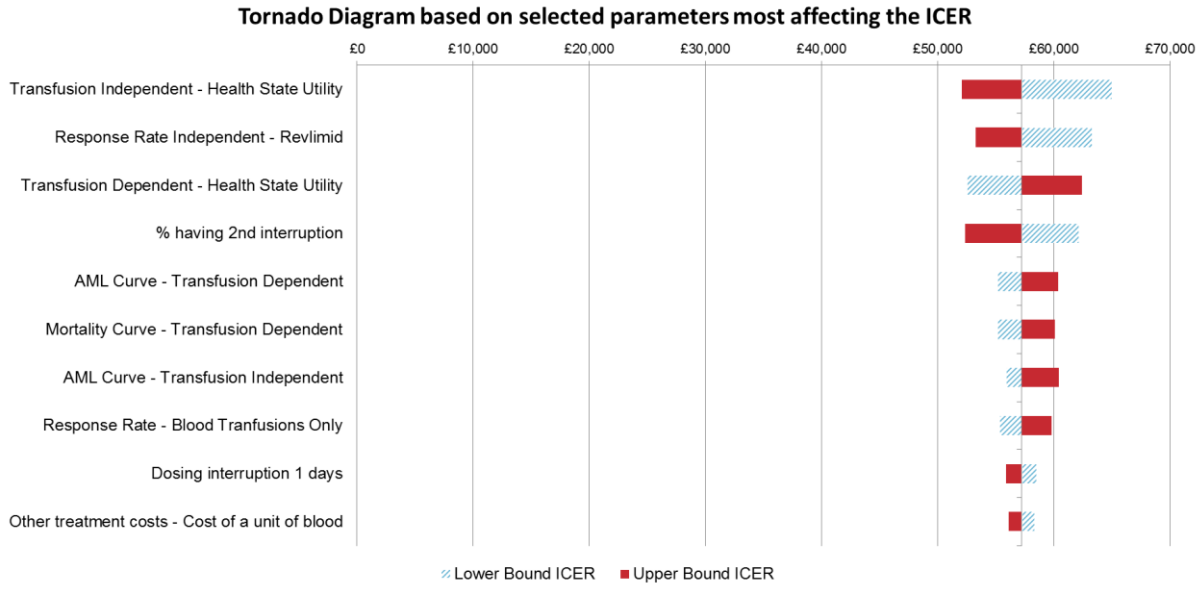
Sensitivity analyses

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

Figure 1 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 £52,067 and £64,941 under deterministic sensitivity analysis.

Figure 1. Tornado diagram – top 10 parameters affecting the ICER



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 7. Output from PSA

	Default Assumption Standard Error 10% of mean when uncertainty unknown	**Assumption Standard Error 20% of mean when uncertainty unknown**
Mean Incremental Costs	£46,982	£46,941
Mean Incremental QALYs	0.786	0.786
Mean ICER	£59,752	£59,690
% of observations cost-effective at £20,000 threshold	0%	0%
% of observations cost-effective at £30,000 threshold	0%	0%

Figure 2. Cost effectiveness scatter plot

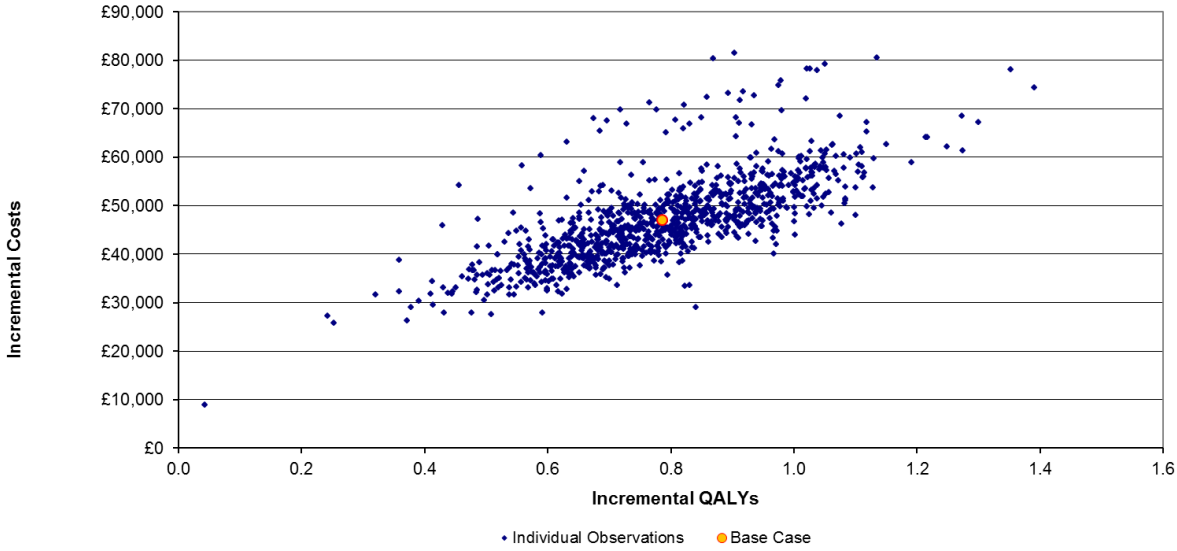
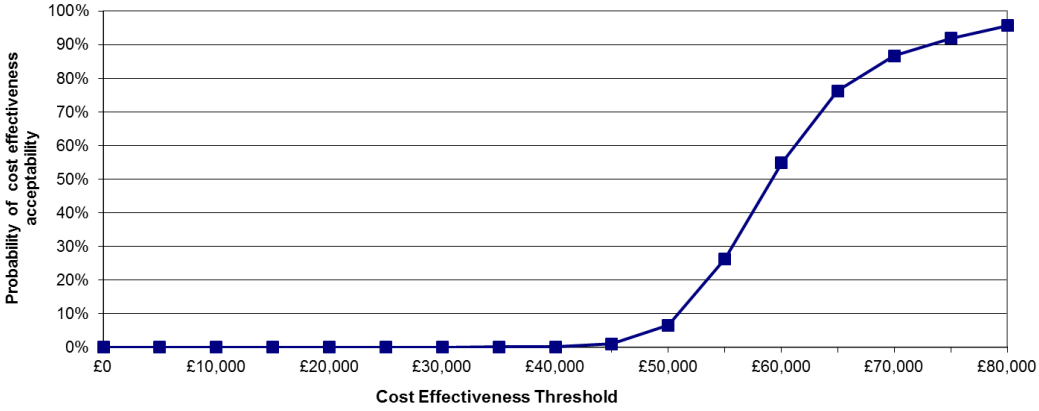


Figure 3. Cost effectiveness acceptability curve



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

Table 8 to Table 14 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 8. All trial patients rather than UK patients

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Best supportive care	£106,834	4.64	2.70	-	-	-	-
Lenalidomide	£154,050	5.65	3.48	£47,216	1.01	0.78	£60,731

Table 9. Comparator

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
All patients using ESA	Best supportive care	£112,595	4.77	2.77	-	-	-	-
	Lenalidomide	£150,063	5.65	3.48	£37,468	0.88	0.70	£53,286
All patients receiving only transfusions as required	Best supportive care	£100,570	4.51	2.62	-	-	-	-
	Lenalidomide	£150,063	5.65	3.48	£49,493	1.15	0.85	£58,093

Table 10. Iron chelation threshold

Threshold	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
20	Best supportive care	£102,652	4.58	2.66	-	-	-	-
	Lenalidomide	£150,364	5.65	3.47	£47,712	1.07	0.81	£58,730
30	Best supportive care	£103,358	4.58	2.66	-	-	-	-
	Lenalidomide	£153,439	5.65	3.48	£50,081	1.07	0.81	£61,501

Table 2. Source of utilities

Threshold	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Goss	Best supportive care	£103,581	4.58	2.08	-	-	-	-
	Lenalidomide	£150,063	5.65	3.06	£46,482	1.07	0.98	£47,452
Buckstein	Best supportive care	£103,581	4.58	2.70	-	-	-	-
	Lenalidomide	£150,063	5.65	3.48	£46,482	1.07	0.78	£59,693

Table 3. Curve selection – response duration

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive care	£103,561	4.58	2.66	-	-	-	-
	Lenalidomide	£149,708	5.65	3.47	£46,147	1.07	0.81	£57,133
Weibull	Best supportive care	£103,629	4.58	2.66	-	-	-	-
	Lenalidomide	£149,025	5.65	3.46	£45,395	1.07	0.80	£56,917
Log-logistic	Best supportive care	£103,599	4.58	2.66	-	-	-	-
	Lenalidomide	£149,712	5.65	3.47	£46,113	1.07	0.81	£57,132
Extreme Value	Best supportive care	£103,639	4.58	2.66	-	-	-	-
	Lenalidomide	£148,257	5.65	3.45	£44,618	1.07	0.79	£56,672

Table 4. Curve selection – AML progression

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive care	£107,022	4.76	2.74	-	-	-	-
	Lenalidomide	£154,651	5.91	3.58	£47,628	1.15	0.84	£56,778
Log-logistic	Best supportive care	£104,237	4.63	2.67	-	-	-	-
	Lenalidomide	£153,036	5.84	3.54	£48,799	1.21	0.87	£56,302
Lognormal	Best supportive care	£103,537	4.61	2.65	-	-	-	-
	Lenalidomide	£154,708	5.94	3.58	£51,171	1.33	0.92	£55,428
Extreme Value	Best supportive care	£102,886	4.53	2.65	-	-	-	-
	Lenalidomide	£147,172	5.48	3.41	£44,286	0.95	0.76	£58,212

Table 14. Curve selection – overall survival

Curve	Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER
Exponential	Best supportive care	£108,923	4.90	2.79	-	-	-	-
	Lenalidomide	£156,366	6.05	3.62	£47,443	1.15	0.84	£56,672
Log-logistic	Best supportive care	£105,965	4.71	2.72	-	-	-	-
	Lenalidomide	£156,250	5.96	3.62	£50,285	1.26	0.90	£55,691
Lognormal	Best supportive care	£108,068	4.82	2.77	-	-	-	-

	Lenalidomide	£159,474	6.13	3.70	£51,405	1.31	0.93	£55,296
Extreme Value	Best supportive care	£101,880	4.48	2.62	-	-	-	-
	Lenalidomide	£145,236	5.41	3.36	£43,356	0.92	0.74	£58,795

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, the response rate and duration for lenalidomide, dose interruption and the transfusion dependence health state utility assumed.

Table 8 to Table 14 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.

Appendix 2: Excluded studies

Table 1: List of references excluded due to “intervention not of interest” or “outcome not of interest”

Study author, date	Title	Reference	Primary reason for exclusion	Secondary reason(s) for exclusion
Abdulhaq et al. 2007	The role of azacitidine in the treatment of myelodysplastic syndromes	Expert Opin Invest Drugs; 16(12):1967-1975	Intervention not of interest (azacitidine)	Review
Aragon-Ching et al. 2007	Thalidomide analogues as anticancer drugs	Recent Pat Anticancer Drug Discov; 2(2):167-174	Intervention not of interest (thalidomide)	Review
Balducci, 2006	Transfusion independence in patients with myelodysplastic syndromes: impact on outcomes and quality of life	Cancer; 106(10):2087-2094	Outcome not of interest (impact of transfusion independence)	Review
Ballabio et al. 2010	Investigation of the molecular basis of lenalidomide treatment in lymphoma cell lines	Annals of Oncology; 21:viii355	Outcome not of interest (molecular basis of treatment effect)	In vitro study
Bouscary et al. 2005	A non-randomised dose-escalating phase II study of thalidomide for the treatment of patients with low-risk myelodysplastic syndromes: The Thal-SMD-2000 trial of the Groupe Francais des Myelodysplasies	Br J Haematol; 131(5):609-618	Intervention not of interest (thalidomide)	Non-randomised study; non-controlled study
Buchholz et al. 2009	Hematopoietic stem cell transplantation. Indications, foundations and perspective. [German]	Internist; 50(5):572-580	Stem cell transplantation	Review
Coutre, 2005	Thalidomide analogue has erythropoietic, cytogenetic activity in MDS	Oncology Report; Spring:101-102	Intervention not of interest (thalidomide)	Review
Giagounidis et al. 2005	Treatment of myelodysplastic syndrome with isolated del(5q) including bands q31-q33 with a combination of all-trans-retinoic acid and tocopherol-alpha: a phase II study	Annals of Hematology; 84(6):389-394	Intervention not of interest (all-trans retinoic acid + tocopherol-alpha)	Non-randomised study; non-controlled study

Study author, date	Title	Reference	Primary reason for exclusion	Secondary reason(s) for exclusion
Hellstrom-Lindberg et al. 1999	Spontaneous and cytokine-induced thrombocytopenia in myelodysplastic syndromes: serum thrombopoietin levels and bone marrow morphology	Br J Haematol; 105(4):966-973	Outcome not of interest (serum thrombopoietin levels)	Non-randomised study; non-controlled study
Hofmann et al. 1999	Treatment of patients with low-risk myelodysplastic syndromes using a combination of all-trans retinoic acid, interferon alpha, and granulocyte colony-stimulating factor	Annals of Hematology; 78(3):125-130	Intervention not of interest (all-trans retinoic acid + interferon alpha + granulocyte colony-stimulating factor)	Non-randomised study; non-controlled study
Itzykson et al. 2009	Is there a role for all-trans retinoic acid in combination with recombinant erythropoetin in myelodysplastic syndromes? A report on 59 cases	Leukemia; 23(4):673-678	Intervention not of interest (all-trans retinoic acid)	Case-study
Lacy et al. 2011	Pomalidomide therapy for multiple myeloma and myelofibrosis: an update	Leukemia & Lymphoma; 52(4):560-566	Intervention not of interest (pomalidomide)	Review
Lu et al. 2009	The anti-cancer drug lenalidomide inhibits angiogenesis and metastasis via multiple inhibitory effects on endothelial cell function in normoxic and hypoxic conditions	Microvascular Research; 77(2):78-86	Outcome not of interest (microvessel formation)	In vitro study
Lyons et al. 2009	Randomized phase II study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate risk myelodysplastic syndrome (MDS) receiving lenalidomide	Blood; 114(22)	Intervention not of interest (romiplostim)	-
Lyons et al. 2009	Hematologic Response to Three Alternative Dosing Schedules of Azacitidine in Patients With Myelodysplastic Syndromes	J Clin Oncol; 27(11):1850-1856	Intervention not of interest (azacitidine)	-
Mangi et al. 1998	Interleukin-3: Promises and perspectives	Hematology; 3(1):55-66	Intervention not of interest (interleukin 3)	Review

Study author, date	Title	Reference	Primary reason for exclusion	Secondary reason(s) for exclusion
Marcondes et al. 2008	Hematopoietic cell transplantation for patients with myelodysplastic syndromes (MDS): when, how and for whom?	Baillieres Best Pract Res Clin Haematol; 21(1):67-77	Intervention not of interest (stem cell transplantation)	Review
Metzgeroth et al. 2007	The soluble transferrin receptor in dysplastic erythropoiesis in myelodysplastic syndrome	Eur J Haematol; 79(1):8-16	Outcome not of interest (Transferrin receptor concentrations)	Non-randomised study; non-controlled study
Momot et al. 2007	Influence of lenalidomide treatment on the T-cell receptor repertoire in patients with 5q-myelodysplastic syndrome	Experimental Hematology; 35 (9):70	Outcome not of interest (T-cell receptor repertoire)	Non-randomised study
Musto et al. 2009	Thalidomide for the treatment of myelodysplastic syndromes: A systematic review and meta-analysis of the published studies	Haematologica; 94:105	Intervention not of interest (thalidomide)	Retrospective study
Musto et al. 2009	Efficacy, safety and feasibility of 5-azacitidine for the treatment of myelodysplastic syndromes in the clinical practice: Final results from a retrospective study in 177 patients enrolled in the italian patient named program	Haematologica; 94:32	Intervention not of interest (azacitidine)	Review
Oliva et al. 2010	Bone Marrow Immunological Changes During Treatment with Lenalidomide In Low and Intermediate-1 Risk Myelodysplastic Syndromes with Del(5Q)	Blood; 116(21):1205-1206	Outcome not of interest (cytokine transcription)	Non-randomised study; non-controlled study
Oliva et al. 2010	Increases In Mirna-145 and Mirna-146a Expression In Patients with IPSS Lower-Risk Myelodysplastic Syndromes and Del(5q) Treated with Lenalidomide	Blood; 116(21):1494-1495	Outcome not of interest (gene expression)	In vitro study
Oliva et al. 2010	Bone Marrow Cytokine Changes During Treatment with Lenalidomide in Low and Intermediate-1 Risk Myelodysplastic Syndromes with Del(5Q)	Haematologica; 95:381	Outcome not of interest (cytokine transcription)	Non-randomised study; non-controlled study

Study author, date	Title	Reference	Primary reason for exclusion	Secondary reason(s) for exclusion
Pellagatti et al. 2006	Lenalidomide up-regulates SPARC and inhibits in vitro growth of the malignant clone in myelodysplastic syndrome patients with 5q deletion	Blood; 108(11):256A-257A	Outcome not of interest (gene expression)	In vitro study
Rose, 2009	Azacitidine improves survival in myelodysplastic syndromes	Nat Rev Clin Oncol; 6(9):502-503	Intervention not of interest (azacitidine)	Review
Scharenberg et al.2009	Lenalidomide Abrogates the Clonal Advantage of Del(5Q) Mds Stem Cells Via Alteration of Niche Interactions	Haematologica; 94:98	Outcome not of interest (clonality)	
Schmetzer et al. 2000	Cytogenetic and Southern blot analysis to demonstrate clonality and to estimate prognosis in patients with myelodysplastic syndromes	Annals of Hematology; 79(1):20-29	Outcome not of interest (clonality)	Non-randomised study; non-controlled study
Sekeres et al. 2007	Correlation between occurrence of cytopenias and response to lenalidomide therapy in del 5q MDS patients	Haematologica; 92:83-84	Outcome not of interest (cytopenia impact on response)	Post-hoc analysis
Sekeres et al. 2007	Cytopenias correlate with response to lenalidomide in del 5q MDS patients	Leukemia Research; 31:S37-S38	Outcome not of interest (cytopenia impact on response)	Post-hoc analysis
Sekeres et al. 2008	Relationship of treatment-related cytopenias and response to lenalidomide in patients with lower-risk myelodysplastic syndromes	J Clin Oncol; 26(36):5943-5949	Outcome not of interest (cytopenia impact on response)	Post-hoc analysis
Strupp et al. 2002	Thalidomide for the treatment of patients with myelodysplastic syndromes	Leukemia; 16(1):1-6	Intervention not of interest (thalidomide)	Non-randomised study; non-controlled study
Weiss et al. 2009	Overview of venous thromboembolism (VTE) in nearly 100,000 patients treated with revlimid (lenalidomide)	Blood; 114(22):20	Outcome not of interest (VTE incidence)	Retrospective study
Xiao et al. 2011	Cyclosporin A and thalidomide in patients with myelodysplastic syndromes: Results of a pilot study	Leukemia Research; 35(1):61-65	Intervention not of interest (cyclosporin A & thalidomide)	Non-randomised study; non-controlled study

Study author, date	Title	Reference	Primary reason for exclusion	Secondary reason(s) for exclusion
Yang et al. 2009	Venous Thromboembolism in Myelodysplastic Syndrome Patients Receiving Lenalidomide Results from Postmarketing Surveillance and Data Mining Techniques	Clin Drug Invest; 29(3):161-171	Outcome not of interest (VTE incidence)	Retrospective study