Section A. Decision problem

A1. Thalidomide is identified as a comparator in the scope (P19) and is used in current treatment according to your 'Context' (P 35). However it is not considered an appropriate comparator for this appraisal for reasons given to do with the licence (P 108). However for the purpose of a NICE appraisal comparators do not require a marketing authorisation but should be treatments in routine use in the NHS. Please can you provide evidence that thalidomide is not currently in routine use in the NHS? The submission also states that 'comparable data do not exist …to enable a meaningful comparison' (P119). Has a systematic search been conducted to rule out the existence of such evidence? Please can you provide more detail to substantiate the claim that the available evidence is not suitable for use in the economic modelling?

Deciding which therapies require indirect comparison with Len/Dex is complicated by the lack of standardised treatment pathways. While acknowledging that thalidomide is used to treat multiple myeloma in the UK, the ERG responsible for reviewing the data on NICE appraisal of bortezomib for relapsed and refractory multiple myeloma appeared to support the manufacturer decision not to compare with thalidomide on the grounds that it was not licensed in the UK at that time and the optimum dose and duration of therapy was not clear. We used the same rationale for not undertaking an indirect comparison with thalidomide – it is not licensed for previously treated multiple myeloma and the optimum dose and duration for this indication is not clear. Since the NICE bortezomib appraisal, thalidomide has been licensed by the EMEA for first-line treatment of untreated multiple myeloma (which we understand will be the subject of a future NICE MTA as part of the 18th wave of referrals), but thalidomide has not been licensed for the treatment of previously treated multiple myeloma. In fact, the [redacted] the license application was withdrawn.

The systematic review detailed in our submission for lenalidomide was designed to identify RCTs of Len/Dex in the treatment of previously treated multiple myeloma compared with any of the treatments outline in the scope. No RCTs were identified that compared Len/Dex with thalidomide either alone or as combination treatment. In support of this finding, two systematic reviews of thalidomide as monotherapy (Glasmacher et al. 2006) and in combination with Dex (von Lilienfeld-Toal et al. 2008) for the treatment of previously treated multiple myeloma have been published. Only uncontrolled Phase II studies were identified. An indirect comparison with thalidomide using uncontrolled Phase II data would not have produced meaningful comparative clinical effectiveness or cost-effectiveness data for consideration. Since the indirect/mixed treatment comparison technique requires a "common reference" comparator across the two trials being compared. While there wasn't sufficient time available to conduct a detailed systematic review for this clarification letter, we conducted a combined search of Embase and Medline using Emtree terms and RCT limits available through EMBASE.com (see table below) and the only records of RCTs comparing thalidomide with Dex alone (i.e. the required "common reference" comparator required for a

indirect/mixed treatment comparison with Len/Dex MM-009/010 studies) are in first line treatment of newly diagnosed multiple myeloma, which is not the indication for Len/Dex under consideration in this submission (Rajkumar et al. 2008a, Rajkumar et al. 2008b, Greipp et al. 2003).

Bortezemib was considered a valid comparator to warrant a formal indirect/mixed treatment comparison as it is licensed and approved by NICE on the basis of RCT evidence for the treatment of patients who have had one prior therapy, and its RCT evidence uses the Dex “common reference” comparator (Richardson et al. 2005; Richardson et al. 2007).
.

References

Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, Orlopp K, Schmidt-Wolf I, Gorschlüter M. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006 Mar;132(5):584-93.

Greipp P.R. Eastern Cooperative Oncology Group E1A00: phase III randomized study of dexamethasone with or without thalidomide in patients with newly diagnosed multiple myeloma. 2003 1:3 (188 - 189).

Rajkumar S.V., Rosiñol L., Hussein M., Catalano J., Jedrzejczak W., Lucy L., Olesnyckyj M., Yu Z., Knight R., Zeldis J.B., Bladé J. Multicenter, randomized, double-blind, placebo-controlled study of thalidomide plus dexamethasone compared with dexamethasone as initial therapy for newly diagnosed multiple myeloma. J. Clin. Oncol. 2008 26:13 (2171 - 2177).

Rajkumar S.V., Blood E., Vesole D., Fonseca R., Greipp P.R.
Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the eastern cooperative oncology group
J. Clin. Oncol. 2006 24:3 (431 - 436).

Richardson PG, Sonneveld P, Schuster MW, Irwin D, Stadtmauer EA, Facon T, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005 Jun 16;352(24):2487-98.

Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, et al. Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. Blood 2007 Nov 15;110(10):3557-60.

von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, Hoffmann F, Naumann R, Bargou R, Cook G, Glasmacher A. A systematic review of phase ii trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. Eur J Haematol. 2008 Jul 10.

Embase and Medline search date 24/07/08

#	**8**	**#2** AND **#3** AND **#4** AND [randomized controlled trial]/lim AND [english]/lim AND [humans]/lim AND [article]/lim	**33**
#	**5**	**#2** AND **#3** AND **#4**	**1,171**
#	**4**	**'dexamethasone'**/exp AND [1998-2008]/py	**34,825**
#	**3**	**'thalidomide'**/exp AND [1998-2008]/py	**8,331**
#	**2**	**'multiple myeloma'**/exp AND [1998-2008]/py	**12,456**

A2. For the comparison of lenalidomide/dexamethasone with bortezomib the analysis should take account the stopping rules and response-based rebate scheme for bortezomib as recommended by NICE as per TA 129. Please provide analysis which takes these factors into account.

A comparison with the response-based rebate scheme for bortezomib would be very useful for decision-making. However, such a comparison is not possible for two key reasons. Firstly, the model submitted for this appraisal of lenalidomide would need to be modified to handle the specific requirements of the response-based rebate scheme. For example, time to response is not specifically modeled and this would be a crucial aspect for such a modification, since the rebate scheme is based on the timing of response (within 4 cycles). Secondly, such a comparison would required detailed audit data on both the extent to which the response-based rebate scheme is implemented in clinical practice and its effects on efficacy and safety. To our knowledge no such audit has been performed on this scheme. If NICE were able to provide us with these detailed audit data then the alterations to the model could be made and the analyses performed.

Section B. Clarification on effectiveness data

B1. P 44: QUOROM flowchart – we find it difficult to make the numbers presented tally. Please could they be verified?

Due to formatting issues, the top section of the flowchart was not visible in final submission document. We have gone back to the original Endnote files and Excel tables checked the data and re-drawn the QUOROM flowchart so it is easier to understand. A PDF version is shown below.

All potential hits for RCT identified and screened for retrieval = 1071

Database	Hits
Embase	464
Medline including (R) In-Process and Old Medline	215
The Cochrane Library - Clinical trials	25
ISI Science Citation Index web of knowledge	80
ISI Biosis Preview	81
ISI Proceedings	12
National Research Register	7
Current Controlled Trials	1
ClinicalTrials.gov	55
ASH	80
ASCO	11
Company literature	19
EHA	25

Total hits excluded based on Phase I review (title/abstract) = 924

Database	Include	Exclusion Reasons					
		PT	PP	SD	LB	DC	Total Excluded
Embase	11	219	78	2	23	131	453
Medline including (R) In-Process and Old Medline	9	97	46	10	29	24	206
The Cochrane Library - Clinicaltrials	20				1	4	5
ISI Science WOK	8	48	9	3	5	7	72
ISI Biosis Preview	18	14	9	3	19	18	63
ISI Proceedings	9	1			2		3
NRR	2		2	1		2	5
Current Controlled Trials	1						0
ClinicalTrials.gov	16		2	35		2	39
ASH	28	10	12	5	1	24	52
ASCO	3	1	1	2		4	8
Company literature	19						0
EHA	4	6	2	4	4	2	18

Total hits included for Phase II review (abstract/full text) = 148
After removing duplicate records =53

Reasons for Phase II exclusions:
DC =16
PP =10
SD =8

RCTs meeting the inclusion criteria = 2

- MM009
- MM010

Total publications relating to relevant RCTS =19

PT=Publication type
PP=Patient population or line of therapy
SD=Study design
LB=Lab based/basic science
DC=Drug class or combination

B2. P 60: It is stated that data on time to first skeletal-related event (SRE) and time to first decrease in ECOG performance status were collected for both RCTs, but these data are not presented amongst results. Could you please provide this information if it is available.

Time to first worsening of ECOG PS

Time to first worsening of ECOG PS was analysed as a secondary outcome (Table 1 below). The median time to first worsening of ECOG PS was significantly greater in the Len/dex arm of MM-009, versus placebo, [redacted].

Table 1: Studies MM-009 and MM-010 – time-to-first worsening of ECOG PS (ITT population)

		Study MM-009		Study MM-010	
	Statistic	**Len/Dex N=177**	**Dex N=176**	**Len/Dex N=176**	**Dex N=175**
Time to First Worsening	N n (%)	171	174	173	172
Worsened Censored	n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Overall Time to First Worsening (wk)	Median [95% CI]	[redacted]	[redacted]	[redacted]	[redacted]
	Mean SD Min, Max	[redacted]	[redacted]	[redacted]	[redacted]
Hazard Ratio [95% CI] Log-rank Test p-Value		[redacted]		[redacted]	

NE, not estimable

[redacted]

Time to first skeletal-related event (SRE)

Regarding the 'time to first skeletal-related event' endpoint, there have been too few events for both studies and no analysis can be done. In fact this does not seem a feasible endpoint so it has been removed from all the new multiple myeloma studies.

B3. P 89: The section headed "Pooled analysis at unblinding" provides pooled results for TTP and response up to unblinding, with data presented in Table 22. However, OS is only considered at longer follow-up. Please could you provide the equivalent data for pooled OS at unblinding? (We appreciate that median survival will be incalculable, but inter-arm HR should be available.)

In the document submitted to NICE, OS at follow-up was reported underneath Table 22 as follows:

"OS in the pooled studies at one year was 82% in patients treated with Len/Dex versus 75% in patients treated with Dex, after the start of treatment, with a median follow-up duration of 98.0 weeks (min: 0.3, max: 163.3). Despite 170 out of the 351 patients crossing-over from Dex to Len/Dex after the studies were un-blinded, the pooled analysis of OS demonstrated a statistically significant survival advantage in favour of Len/Dex (hazard/odds ratio: 0.75, 95% CI: [0.59, 0.95], p = 0.015)."

The complete results for the pooled OS at unblinding are presented below.

		Pooled Study MM-009 and MM-010	
	Statistic	**Len/Dex**	**Dex**
Overall survival	N	353	351
Died	n (%)	84 (23.8)	121 (34.5)
Censored	n (%)	269(76.2)	230 (65.5)
Overall Time to First Worsening (wk)	Median [95% CI] [b]	NE NE	93.4 [82.6, NE]
	Mean	**60.3**	**53.3**
	SD	**26.51**	**25.88**
	Min, Max	**1.1, 110.9**	**0.0, 110.9**
Hazard Ratio [95% CI] [c]		0.599 [0.453,0.791]	
Log-rank Test p-Value [d]		**< 0.001**	

Notes: This summary excludes any observations that occurred after 28Jun2005 for MM-009 and after 03Aug2005 for MM-010. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] For subjects who died during the follow-up phase and whose death dates are not available, the follow-up visit dates are used as the event date.
[b] 95% confidence intervals about the median survival time.
[c] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups (Placebo/Dex:CC-5013/Dex)
[d] The p-value is based on the one-tailed unstratified log rank test of survival curve differences between the treatment groups.

B4. App 6, pp. A17-A20: Please could you clarify that we are right to infer that the captions to Tables 29-33, instead of reading "… with at Least One Prior Therapy" should, in each case, specify "… with One Prior Therapy Only"?

The captions for Tables 29-33 should indeed be labelled for One Prior Therapy Only.

B5. Please could you provide the rapporteurs' report for the EMEA on the adequacy of M-protein levels as a surrogate for clinical outcome in thalidomide treatment?

B6. P100: The result of the indirect comparison states for TTP lenalidomide/dexamethasone had a 34 week advantage over bortezomib. Please could you clarify this result from the indirect comparison and explain its significance given that the results of the meta-analysis of the lenalidomide/dexamethasone trial (pg 95 but also the pooled estimates on pg 89) report a 28 week advantage of lenalidomide/dexamethasone over dexamethasone.

In the submission, different data were used to calculate the indirect/mixed treatment comparison of Len/Dex with bortezomib for TTP and the meta-analysis of the individual MM-009/010 trials. The indirect/mixed treatment comparison of Len/Dex with bortezomib was performed on those patients who had received one priory therapy only because NICE recommends bortezomib for patients who are at first relapse having received one prior therapy. The meta-analysis of individual Len/Dex MM-009/010 trials was performed on patients who had received at least one prior therapy (i.e. the entire cohort of patients included in the trials)

Source of data for the Indirect Comparison for TTP:

The following data were used to calculate the median TTP in the indirect comparison. Data were extracted from the clinical study reports for populations with one prior therapy only.

Table 2. Response Outcomes for Patients from the APEX Trial with One Prior Therapy Only Excluding Non-Evaluable Patients

	Bortezomib (Apex)±	Dex (Apex) ±	Len/Dex (MM09)	Dex (MM09)	Len/Dex (MM10)	Dex (MM10)
Median TTP (weeks)	30.3	24.3	61.4	21.1	61.4*	20.1
Standard Error	2.86§ 1.71¶	2.86§ 1.71¶	1.71**	1.71	2.86**	2.86

*Assumed same value as MM09 trial as MM10 median TTP was not estimable

**Assumed to be the same as the Dex arm.

±In the absence of published data, two standard errors were used for the Apex trials: one from the MM09 trial and one from the MM10 trial.

§Assumed to be the same as Dex arm in MM10

¶Assumed to be the same as Dex arm in MM09.

Source of this data:

Celgene Corporation, Protocol: CC-5013-MM-009 DB Ver: CUTOFF28JUN05, Table 14.2.1.1.9: Summary of Time to Progression (Per protocol Defined TTP) Intent-to-Treat Population (Had One Prior Anti-myeloma Therapy)

Celgene Corporation Protocol: CC-5013-MM-010 16JUN2008, Table 14.2.1.1.9, Summary of Time to Progression (Per protocol Defined TTP), Intent-to-Treat Population (Had One Prior Anti-myeloma Therapy)

Results of the indirect comparison using these data were 34 weeks difference in TTP between Len/Dex and bortezomib.

Source of data for the Meta-analysis:

The meta-analysis of the two Len/Dex trials used the following source data, which included all patients (i.e. those with only one prior therapy and those with at least two prior therapies) and found a difference in TTP of 28 weeks.

Table 3: Median TTP

Study	Treatment	N	Median TTP (weeks)	95% CI
MM09	DEX	176	20.1	16.7-23.1
	DEX + LEN	177	48.1	36.9-61.4
MM10	DEX	175	20.1	18.1-20.7
	DEX + LEN	176	48.7	40.9-72.1

Source: Dimopoulos (2007), Weber (2007) and Table 4 below:

Table 4. Analysis of the primary outcome – time-to-progression (TTP) – at study unblinding (intent-to-treat population), with data cut off to June (MM-009)/August (MM-010) 2005 (2007a;Dimopoulos, Spencer, Attal, Prince, Harousseau J-L, Dmoszynska, Miguel, & Hellmann 2007a;Weber D, Chen, Niesvizky, Wang, Belch, Stadtmauer, Siegel, & Borrello 2007a)

	Statistic	Study MM-009		Study MM-010	
		Len/Dex	Dex	Len/Dex	Dex
TTP	N	177	176	176	175
Progressed	n (%)	92 (52.0)	132 (75.0)	82 (46.6)	142 (81.1)
Censored	n (%)	85 (48.0)	44 (25.0)	94 (53.4)	33 (18.9)
Overall TTP (weeks)	Median [95% CI] [a]	48.1 [36.9, 61.4]	20.1 [16.7, 23.1]	48.7 [40.9, 72.1]	20.1 [18.1, 20.7]
Hazard Ratio [95% CI] [b]		2.822 [2.146, 3.701]		2.850 [2.159, 3.762]	
Log-rank Test p-Value [c]		< 0.001		< 0.001	

Notes: CI=Confidence interval. Percentages are based on the number of treated subjects. The median in this table is based on Kaplan-Meier estimate, and the mean is the univariate mean without adjusting for censoring.
[a] 95% confidence intervals about the median overall time to progression.
[b] Based on a proportional hazards model comparing the hazard functions associated with the treatment groups
(Len/Dex:/Dex)
[c] The p-value is based on the a one-tailed unstratified log rank test of survival curve differences between the treatment groups. Median follow up: 17.1 months for MM-009 (n=76), 16.7 months for MM-010 (n=74), 16.9 months for combined (n=150).

B7. Please can we be provided with WinBUGS code (including exact dataset used and initial values for MCMC) used for the mixed treatment comparison?

Windbugs code is in Appendix A.

B8. Can you please confirm that the dexamethasone dose and regimen used in the comparator arm of the clinical trials (MM-009 and MM-010) is consistent with best practice?

Dexamethasone was adopted as the control arm because it represents a standard antimyeloma therapy for the treatment of subjects with relapsed or refractory disease (Alexanian et al. 1986, Alexanian et al. 1992, Munshi et al. 2001). The use of single agent, high-dose dexamethasone as the control therapy allowed for a direct comparison with the lenalidomide plus high-dose dexamethasone experimental treatment in order to determine the contribution of lenalidomide to the efficacy and safety of the combination. The dose and schedule of dexamethasone administration used in this study represent a standard pulse high-dose regimen that is used to treat subjects with advanced multiple myeloma (Alexanian et al. 1992). Consistent with standard practice, the intensity of high-dose dexamethasone therapy was decreased after four cycles of therapy.

References

Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 1986 Jul;105(1):8-11.

Alexanian R, Dimopoulos MA, Delasalle K, Barlogie B. Primary dexamethasone treatment of multiple myeloma. Blood 1992 Aug 15;80(4):887-90.

Munshi NC, Tricot G, Barlogie B. Plasma cell neoplasms. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer Principles and Practice of Oncology. 6th ed. Philadelphia, PA 19106: Lippincott Williams & Wilkins; 2001. p. 2465-976.

Section C. Clarification on cost-effectiveness data

Important overriding considerations:

C1. We note that the model is heavily reliant on hard-coded random numbers. Please could you explain how these were generated, and on what rationale the particular simulation that is presented as base case was chosen? We note that, when we use a different set of random numbers, model outputs change substantially. The submission states that it is necessary to report the average of multiple replications (p. A40). Are we correct to conclude that the base case provided disregards this requirement? The submission also states that model replications "should be carried out manually" (p. A40). Is it suggested that these steps should be performed by the reviewers? If so, on what basis are the model outputs reported in the submission justified?

C2. We are unable to comment on the adequacy or otherwise of methods used for probabilistic sensitivity analysis, since the model provided is not equipped to perform the calculations described in Appendix 14. In order to investigate this important aspect of the submission, could you please provide us with access to a full, functioning version of the model.

As agreed, responses to C1 and 2 to be delivered by 8th August.

Specific queries:

C3. It is stated that "there are no well conducted studies using [repeat chemotherapy] in previously treated patients upon which to base a comparison [with lenalidomide/dexamethasone]." Could you please clarify on what basis this statement is made? Has a systematic search been conducted? Moreover, if there is no good evidence, could you please clarify how you can be sure that "none [of the chemotherapeutic regimens available] are superior to dexamethasone"?

Corticosteroids alone have produced responses in subjects with progressive myeloma after first-line therapy. Prednisolone, in doses of 60mg/m^2 daily for 5

days, has been associated with a response rate of 31% and with a median duration of response of 7 months (Alexanian et al. 1983). High-dose pulse dexamethasone (40 mg orally for 4 days beginning on Days 1, 9, and 17 of a 4- to 5-week schedule) has been observed to produce a response rate of 27% in subjects with primarily unresponsive disease and a response rate of 21% in subjects with relapsed (previously responsive) disease (Alexanian et al. 1986, Munshi et al. 2001). The addition of vincristine and doxorubicin to dexamethasone (i.e., the VAD regimen) did not improve the response rate (31%) over dexamethasone therapy alone in this primarily unresponsive group of subjects. In contrast, subjects who had previously responded to therapy and had then relapsed achieved a response rate of 65% with VAD treatments. The median duration of response was 9 months in both the dexamethasone alone- and VAD-treated subjects. In addition, median survival was similar for subjects in both treatment groups. Thus, compared with combination chemotherapy, single-agent dexamethasone therapy has been associated with 1) a similar response rate in subjects with primarily resistant (refractory) multiple myeloma, and 2) a similar duration of response and median overall survival time in both subjects with primarily resistant and relapsed disease.

The systematic review detailed in the submission for lenalidomide was designed to identify RCTs of Len/Dex in the treatment of previously treated multiple myeloma compared with any of the treatments outline in the scope section. No RCTs were identified that directly compared Len/Dex with the available chemotherapeutic regimens in previously treated multiple myeloma. Regular searches of the literature and examination of published guidelines by clinical staff have not revealed any studies of a comparable design, on which to base a comparison with the MM-009 and MM-010 trials. In addition, other than bortezomib, there remains no clear UK consensus on best practice for treatment of multiple myeloma with chemotherapy at first relapse. Therefore a formal systematic review of RCTs of chemotherapy vs. Dex was decided against in the timeframe of the STA.

For the purpose of this clarification letter, we conducted a combined search of Embase and Medline using Emtree terms and RCT limits available through EMBASE.com (see table below). We did not identify any RCTs that could be used for indirect/mixed treatment comparison with MM-009 and MM-010 data. (i.e. chemotherapy compared with Dex alone in previously treated multiple myeloma).

Embase and Medline combined search on 24/07/08

8	**#2** AND **#3** AND **#4** AND [randomized controlled trial]/lim AND [english]/lim AND [humans]/lim AND [article]/lim	**43**
5	**#2** AND **#3** AND **#4**	**1,750**
4	**'dexamethasone'**/exp AND [1998-2008]/py	**34,825**
3	**'mephalan'**/exp OR **'vincristine'**/exp OR **'cyclophosphamide'**/exp OR **'doxorubicin'**/exp AND [1998-2008]/py	**81,183**
2	**'multiple myeloma'**/exp AND [1998-2008]/py	**12,456**

References

Alexanian R, Yap BS, Bodey GP. Prednisone pulse therapy for refractory myeloma. Blood 1983 Sep 1;62(3):572-7.

\Munshi NC, Tricot G, Barlogie B. Plasma cell neoplasms. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer Principles and Practice of Oncology. 6th ed. Philadelphia, PA 19106: Lippincott Williams & Wilkins; 2001. p. 2465-976.

Alexanian R, Barlogie B, Dixon D. High-dose glucocorticoid treatment of resistant myeloma. Ann Intern Med 1986 Jul;105(1):8-11.

C4. P A41: "The model randomly selects patients from the appropriate patient file…" We need some way of verifying this process: is it possible to provide the raw source files? It would be helpful to know the number of trial patients on which each simulation was based, and their demographic and clinical characteristics (i.e. the pool from which each bootstrapping was performed). We also request details of the demographic and clinical characteristics of each simulated cohort.

C5. P A41: Patients are bootstrapped "based on the response distribution for each treatment. For example, if a total of 1,000 patients are to be simulated and 10% had a complete response with treatment A, then the model randomly picks 100 patients from the CR file and assigns them to treatment A." We note that, in the model, the numbers of simulated patients do not precisely reflect the proportions specified in the submission (and, as a further check, do not sum to 1000 per arm). Could you clarify the explanation for why this is the case?

As agreed, responses to C4 and 5 to be delivered by 8th August.

C6. P A42: "The model considers whether the patient dies immediately (i.e., whether it was death that signalled progression)". Could you clarify how this is implemented? In particular, what does column M in the "Patient File" worksheets of the model represent? Could you clarify on what basis the proportion of progression-related deaths is estimated?

The proportion of progressions that are signaled by death is entered on the treatment efficacy page. This proportion is compared to a random number for each patient and if the latter is lower then it is determined that that patient dies at the time of progression. Accordingly, the time of death is set equal to the time of progression. Column M on the Patient File worksheets is the recorded time of progression in the trials for each patient.

C7. P 139: "Utility decrements for adverse events and complications were not incorporated into the model due to lack of available published data." Could you clarify the basis on which this statement is made?

Could you provide us with details of any systematic search that has been undertaken?

Model Adverse Events	Published Health States	Assessment/ Utility Technique	Utility Scores	Comments	Reference
Anaemia	No anaemia	TTO	0.86	Erythropoeitin in chemotherapy related anaemia	Ossa et al, 2007
	Mild anaemia		0.78		
	Moderate anaemia		0.61		
	Severe anaemia		0.48		
Thrombocytopenia	No published studies				
Neutropenia	Febrile neutropenia	SG	0.57	A decrement of -0.15 from the value of 0.72 representing “Stable Metastatic Breast Cancer on treatment with no toxicity”	Lloyd A et al, 2006
Hypercalcaemia	Hypercalcemia	EQ-5D	–0.52	Hypercalcemia in advanced breast cancer	Milne RJ et al, 2006
Diarrhoea	Diarrhoea – moderate/severe	EQ-5D	0.59	Diarrhoea – moderate/severe in colon and rectal cancer patients	Wilson et al 2006
Constipation	Constipation – moderate/severe	EQ-5D	0.71	Constipation – moderate/severe in colon and rectal cancer patients	
Pneumonia	Ventilator dependence for 15 d	SG	0.66	Outcomes of surgery for chronic lung disease	Cykert et al, 2000
Peripheral Neuropathy	Painful diabetic peripheral neuropathy	EQ-5D	0.5	Diabetic Peripheral Neuropathy	Gore M et al, 2005
Deep-vein Thrombosis	Symptomatic DVT	TTO	0.84		Gould et al 1999

A literature search was performed (PubMed) in order to identify utility values for adverse events and complications. In the CE model utility values were required for the following grade 3 and 4 disease related complications (anaemia, hypercalcaemia and pneumonia) and treatment-related adverse events (thrombocytopenia, neutropenia, diarrhoea, constipation, peripheral neuropathy and deep-vein thrombosis). In order to estimate utility decrements due to AE and complications the search focused on obtaining first the utility scores for the AE health states. The literature search identified articles and utility scores shown in the table above.

The disutility due to an AE could have been obtained by subtracting the utility score of patients with multiple myeloma from the utility score of an AE. However we decided not to include any disutility due to AE in the model for the following reasons:

1) The utility scores identified from the literature search were estimated in patient populations (e.g. Breast, colon, rectal cancer) different from multiple myeloma patients. Thus we would have to assume that the AE of a patient suffering from a different disease would be the same as that of a patient with multiple myeloma.

2) Utility decrements for complications are included indirectly through progressive disease since this classification incorporates factors such as new lytic bone lesions or soft tissue plasmacytoma, increase in bone lesion size, and the development of hypercalcaemia.

References

Ossa DF, Briggs A, McIntosh E, Cowell W, Littlewood T, Sculpher M. Recombinant erythropoietin for chemotherapy-related anaemia: economic value and health-related quality-of-life assessment using direct utility elicitation and discrete choice experiment methodsPharmacoeconomics. 2007;25(3):223-37.

Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006 Sep 18;95(6):683-90

Milne RJ, Heaton-Brown KH, Hansen P, Thomas D, Harvey V, Cubitt A. Quality-of-life valuations of advanced breast cancer by New Zealand women. Pharmacoeconomics. 2006;24(4):415-6; author reply 416-7.

Wilson TR, Alexander DJ, Kind P. Measurement of health-related quality of life in the early follow-up of colon and
rectal cancer. Dis Colon Rectum. 2006 Nov;49(11):1692-702.

Cykert S, Kissling G, Hansen CJ. Patient preferences regarding possible outcomes of lung resection: what outcomes should preoperative evaluations target? Chest. 2000 Jun;117(6):1531-2.

Gore M, Brandenburg NA, Dukes E, Hoffman DL, Tai KS, Stacey B. Pain severity in diabetic peripheral neuropathy is associated with patient functioning, symptom levels of anxiety and depression, and sleep. J Pain Symptom Manage. 2005 Oct;30(4):374-85.

Gould MK, Dembitzer AD, Sanders GD, Garber AM (1999) Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A costeffectiveness analysis. Ann Intern Med 130:789–799

C8. Utility values were taken from a trial of intensive chemotherapy with and without myeloablative therapy with autologous stem cell transplant. Was utility data collected in the trials of lenalidomide and if so were they appropriate for use in the model? Was a systematic search undertaken to rule out the existence of utility values in multiple myeloma? Could you provide details of the primary condition/s for which chemotherapy/stem cell transplant was undertaken in the trial? Could you clarify how the utility values from the above mentioned condition(s) can be considered to apply to multiple myeloma? Could you please clarify how you can justify the assumption that utility value is the same regardless of the level of response?

No utility or quality of life data were collected in the MM-009 and MM-010 lenalidomide trials.

Patients entering the lenalidomide trials had 1 previous therapy (32%), 2 or more previous therapies (67-68%) and approximately 55% had received prior stem cell transplant. During the lenalidomide trials, patients did not undergo stem cell transplant.

Utility values were taken from van Agthoven et al. (2004) article, the same as were used in the NICE appraisal of bortezomib. The ERG for the NICE appraisal of bortezomib identified three potential studies with utility values for multiple myeloma patients and determined that the van Agthoven analysis, using the EQ-5D, was the most appropriate to use. Subsequently, for the lenalidomide submission, a literature search was conducted and no additional or new studies with utility values were identified.

Patients in the van Agthoven study were newly diagnosed with stage II or III multiple myeloma and the utility scores were obtained from a sample of the general UK population using the EQ-5D. In the current submission, we assumed no difference between levels of response, a conservative assumption (not favouring lenalidomide) and only differentiated between any response level and progressive disease. We had no data to differentiate utility by response, so selected the approach with fewest assumptions. A sensitivity analysis using differing rates by response was conducted and presented in our submission. The change in ICER was minimal.

Table 42 from submission: Utility Scores by Response Rate Used in Sensitivity Analysis

	Sensitivity		
Response	Linear relation between response rates	-10%	+10%
CR	0.81	0.73	0.89
PR	0.75	0.73	0.89
SD	0.70	0.73	0.89
PD	0.64	0.58	0.71

C9. P A47: Please provide more detail to support the assertion that there was no improvement in survival over time in the MRC dataset used to model post-progression survival.

[redacted]

[redacted]

[redacted]

	25th Percentile	50th Percentile	75th Percentile
1980-84	[redacted]	[redacted]	[redacted]
1985-89	[redacted]	[redacted]	[redacted]
1990-94	[redacted]	[redacted]	[redacted]
1995+	[redacted]	[redacted]	[redacted]

[redacted]

C10. Please provide a comparative analysis of the patient profiles in the MRC and MM-009 and MM-010 studies.

[redacted]

Characteristic at Start of Treatment	One Prior Group		Multiple Prior Group	
	MRC	MM 009/010	MRC	MM 009/010
Mean Age (yrs)	[redacted]	[redacted]	[redacted]	[redacted]
Sex				
Male	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]
Performance Status (Mapped ECOG)				
0	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]
2-3	[redacted]	[redacted]	[redacted]	[redacted]
Mean M-Protein (g/L)	[redacted]	[redacted]	[redacted]	[redacted]
Beta-2M > 2.5 mg/L	[redacted]	[redacted]	[redacted]	[redacted]
Disease Duration (Years)	[redacted]	[redacted]	[redacted]	[redacted]
Lytic Bone Lesions (at first-line treatment)	[redacted]	[redacted]	[redacted]	[redacted]
Durie-Salmon Stage (at first-line treatment)				
I	[redacted]	[redacted]	[redacted]	[redacted]
II	[redacted]	[redacted]	[redacted]	[redacted]
III	[redacted]	[redacted]	[redacted]	[redacted]

C11. Could you clarify if any adverse events simulated beyond 24 months for any treatment?

None of the adverse events is simulated beyond 24 months.

C12. Could you clarify assumptions (if any) regarding the use of G-CSF in the trials and the model, particularly given the importance of neutropenia as a cause for dose reduction and treatment discontinuation?

In the MM-009 and MM-010 trials G-CSF was administered only in response to Grade 3 or 4 myelosuppression. In the lenalidomide arm of MM-010 (the study conducted in Europe, Israel and Australia), 38 patients (21.6%) received G-CSF. Of these patients, 23 (60.5%) received G-CSF as the first step after having Grade 3 or 4 neutropenia to maintain the 25mg dose level. Among these 23 patients, 12 (52.2%) were able to continue with the 25mg dose level of lenalidomide from the time of the first episode of Grade 3 or 4 neutropenia until the last follow-up visit, as long as that period of time was at least 3 months (Dimopoulos et al. 2007). In MM-009 (the study conducted in the US), 60 patients (33.9%) received G-CSF, 28 (46.7%) of whom did so as the first dose reduction to maintain the 25mg dose level of lenalidomide. Among these 28 patients, 12 (42.9%) were able to continue with the 25-mg dose level of lenalidomide (Weber et al. 2007). Reflecting differences in the use of G-CSF in clinical practice in the US and Europe, use of G-CSF was more common in the US study (MM-009) than the European study (MM-010). G-CSF use in multiple myeloma in the UK is more commonly used in the treatment of febrile neutropenia and since Len/Dex is not a cytotoxic treatment the incidence of febrile Neutropenia was very low in both studies. Therefore, the level of administration of G-CSF in study MM-010 is likely to be an upper limit of the extent of use of G-CSF use in clinical practice for the treatment of neutropenia in the UK.

Table 45 of our submission reports model inputs for the proportion of patients with grade 3 or 4 disease related complications or adverse events (including neutropenia) who require any treatment and the location of care for the treatment. These model inputs are based on the results of interviews with fifteen haematologists who specialise in the treatment of multiple myeloma in the UK. Since G-CSF is administered as a SC injection, those patients with grade 3 or 4 neutropenia who receive G-CSF would most likely do so either in an inpatient or day case setting. Therefore, while G-CSF use is not explicitly included in the model, it is implicitly included in the cost of those inpatient and day case admissions for the treatment of grade 3 or 4 neutropenia.

References

Dimopoulos M, Spencer A, Attal M, Prince HM, Harousseau JL, Dmoszynska A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007 Nov 22;357(21):2123-32.

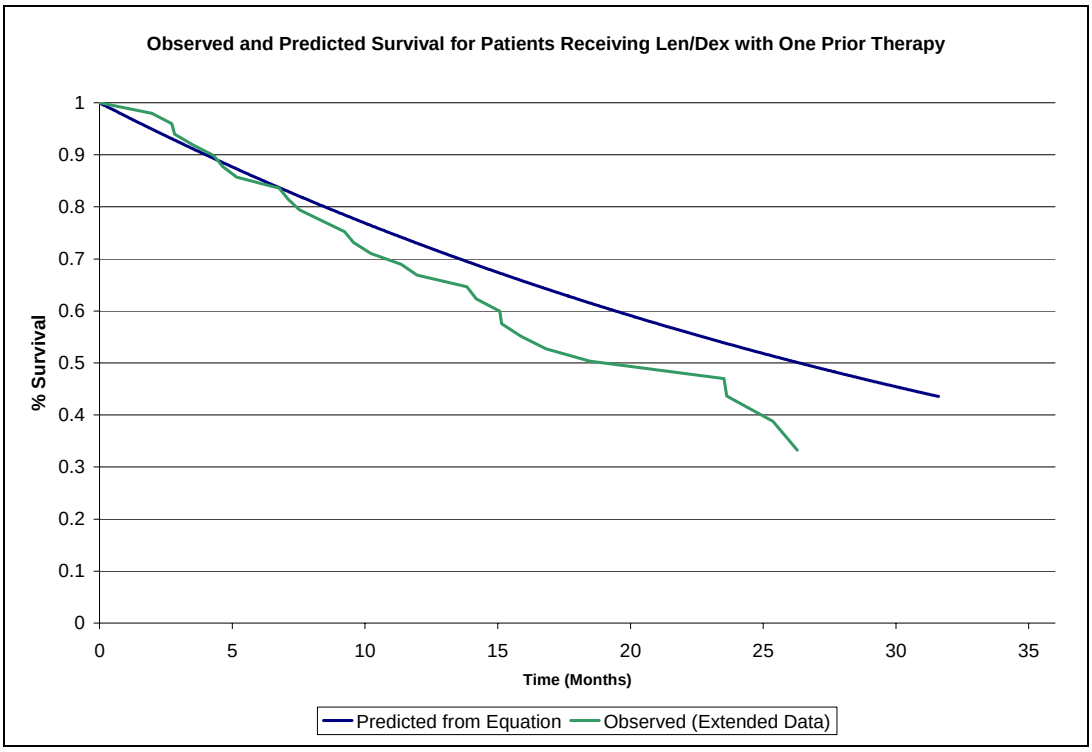
Weber DM, Chen C, Niesvizky R, Wang M, Belch A, Stadtmauer EA, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med 2007 Nov 22;357(21):2133-42.

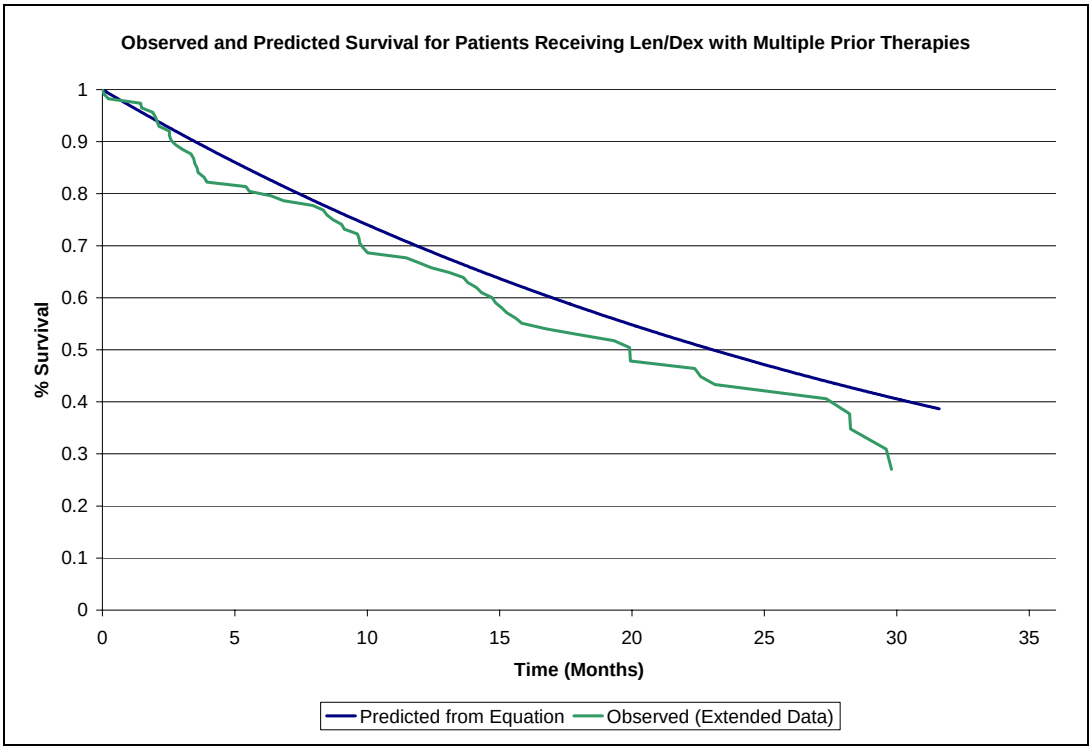
C13. Dose reductions and treatment interruptions (Appendix 12): Could you please clarify if the uncertainty in these dosages and profile of use were considered in the CEA? Could you please provide us with the dose reductions and treatment interruptions that were observed in the clinical trials?

Uncertainty in the doses is not considered in the CEA. The data on dose reductions and interruptions consists of the total number of cycles experienced by patients at each dose level. These data are used to compute the total actual cost of lenalidomide over 23 cycles. This is compared with the theoretical maximum cost of all dosing days (1-21 of each 28 day cycle) being experienced at the full starting dose of 25mg. This ratio is entered in the model and used to reduce proportionately the cost of lenalidomide. There are many sources of uncertainty in this estimate – 4 doses (25mg, 15mg, 10mg, 5mg) and treatment interruption state reported over 23 cycles. It is not clear how this uncertainty should be taken into account. The dose reductions and treatment interruptions that were observed in the trials were provided in section 6.2.1 (Figure 8) of our submission. It is appropriate to incorporate into the model the doses actually administered in the trials as these are the doses that were used to achieve the outcomes reported.

C14. Could you please provide more detail on the predictive performance of the equations used for post progression survival?

The plots below illustrate the observed and predicted post-progression survival (PPS) curves for patients receiving Len/Dex, by prior therapies. The predicted curves are evaluated by setting predictors in the PPS equation to the mean values for patients receiving Len/Dex with one or multiple prior therapies. The observed survival curve is derived from an updated data set that included extended follow-up on patients up to January 2007, which was not available at the time of developing the PPS equation.





In both cases, the observed median and first quartiles fell within the 95% confidence intervals around the corresponding predicted values. The table below summarizes these results.

	Observed	Predicted
One Prior Therapy		
First Quartile	9.2 months	10.9 (7.5 – 15.9)
Median	18.5 months	26.4 (18.2 – 38.2)
Multiple Priors Therapies		
First Quartile	8.7 months	9.6 (7.3 – 12.6)
Median	19.9 months	23.1 (17.5 – 30.3)

C15. We have tried to tally the class of best response with the "Response Levels at Clinical Evaluation Time Points (from trial)" in the "1st Patient calculation" worksheet. Could you please clarify the following apparent inconsistency? Patient ID 1104 is in the SD best response group, with response history of 3(SD), 4(PD). Patient IDs 213, 214 and 215 are all in the PD best response group, also with response histories of 3(SD), 4(PD).

Response levels were occasionally missing in the patient data set. These missing measurements of response were replaced by SD, to be able to assign a utility value. Patients 213, 214 and 215 are examples of patients for whom this replacement was made; the only non-missing response measurements these patients had were PD. Thus, these patients' best response was PD since the only SD records for these patients were replacements of missing records. The SD in the response history of patient 1104 is an actual observed SD during the trial, and thus the patient's best response is SD (despite PD in the history).

C16. In the economic analysis, for the group with preexisting peripheral neuropathy the 'analysis utilises the same efficacy data for the lenalidomide/dexamethasone treated patients as for the previous comparison' (P153). Does that mean it uses the same efficacy data as for patients who have received one prior therapy only? (P152). Could you please clarify how can this be justified when the comparators for each of these subgroups is different?

NICE recommends bortezomib for patients with multiple myeloma who are at first relapse having received one prior therapy. Bortezomib is known to induce peripheral neuropathy. In the APEX study, 36% of patients treated with bortezomib experienced any grade of peripheral neuropathy, with 27.6% (87 of 315) experiencing grade 2 or above peripheral neuropathy (Richardson et al. 2005). The high incidence of peripheral neuropathy associated with bortezomib is particularly important given that thalidomide is also known to induce peripheral neuropathy and thalidomide is commonly used in the first line treatment of untreated multiple myeloma. While NICE recommends bortezomib for patients who are at first relapse having received one prior therapy, patients who have received one prior therapy and have pre-existing peripheral neuropathy are unlikely to be considered suitable for treatment with bortezomib. Therefore, the appropriate comparator for this patient population is dexamethasone.

The economic analysis of the patient population with "one prior therapy and pre-existing peripheral neuropathy" utilises the same efficacy data for the Len/Dex treated patients with "one prior therapy only" because there were too

few patients in the trials with one prior therapy who had pre-existing peripheral neuropathy upon which to base such analyses and post-hoc analysis reported in our submission suggests the same outcomes can be expected for patients with pre-existing peripheral neuropathy.

C17. The submission goes on to say 'because post-hoc analysis suggests the same outcome can be expected for patients with pre-existing peripheral neuropathy' (P153). However the subgroup analysis (P10 of the appendix) refers to the difference in outcomes between patients with and without peripheral neuropathy in the pooled lenalidomide/dexamethasone arms only. Such an analysis breaks the randomisation of the trial. It can also not be used to justify the claim of a lack of differential effectiveness in patients with peripheral neuropathy between the lenalidomide/dexamethasone and dexamethasone arms of the trial. As the economic model is comparing lenalidomide/dexamethasone with dexamethasone in this subgroup of patients. Please can you clarify your approach using trial data that in this subgroup of patients there was no difference in the effectiveness between the pooled arms of the trials.

The analysis comparing TTP between patients with and without pre-existing peripheral neuropathy in the pooled Len/Dex arms of the studies, presented in the appendix of the submission was labelled as a post hoc analysis. It was intended to illustrate that those patients in the trial with pre-existing peripheral neuropathy who were treated with Len/Dex appeared to respond as well to treatment as those without pre-existing neuropathy.

In order to clarify the appropriateness of utilising the efficacy data for all the patients with "one prior therapy only" for our analysis of "one prior therapy and pre-existing peripheral neuropathy" it is necessary to show that the outcomes experienced by both Len/Dex and Dex patients with pre-existing peripheral neuropathy are no different to the outcomes experienced by Len/Dex and Dex patients without pre-existing peripheral neuropathy respectively and to show that the significant improvement in outcomes observed with Len/Dex compared with Dex remain in those patients with pre-existing peripheral neuropathy. The tables 1 and 2 below illustrate that there were no statistically significant differences in TTP for patient with our without pre-existing peripheral neuropathy when treated with Len/Dex (Table 1) and Dex (Table 2). Moreover, the median TTP and 95% confidence intervals for those with pre-existing peripheral neuropathy treated with Len/Dex (62.3 months: 95% CI - 39 - NE) and Dex (16.7 months: 95% CI - 12.1 - 25.0) demonstrate that statistically significant improvement in TTP for patients treated with Len/Dex compared with Dex occurred in patients with pre-existing peripheral neuropathy, despite the small sample sizes.

Table 1: Per protocol defined TTP in ITT population with and without pre-existing peripheral neuropathy – Len/Dex

	With pre-existing peripheral neuropathy	Without pre-existing peripheral neuropathy
N	[redacted]	[redacted]
Progressed (%)	[redacted]	[redacted]
Censored (%)	[redacted]	[redacted]
Median TTP (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio (RR) 95%CI	[redacted]	
95% CI	[redacted]	
P-value	[redacted]	

The P-value is based on the one-tailed log rank test of survival curve differences between the treatment groups.

Table 2: Per protocol defined TTP in ITT population with and without pre-existing peripheral neuropathy – Dex

	With pre-existing peripheral neuropathy	Without pre-existing peripheral neuropathy
N	[redacted]	[redacted]
Progressed (%)	[redacted]	[redacted]
Censored (%)	[redacted]	[redacted]
Median TTP (months)	[redacted]	[redacted]
95% CI	[redacted]	[redacted]
Hazard ratio (RR) 95%CI	[redacted]	
95% CI	[redacted]	
P-value	[redacted]	

The P-value is based on the one-tailed log rank test of survival curve differences between the treatment groups.

C18. The DES approach used in the analysis is justified (P126) as having the ‘flexibility to capture the variation in efficacy among individuals’ and further on the same page the events which are the milestones of disease course include ‘progression of disease’. However the submission also states that the TTP and OS do not depend on the individual experience of the patient but is estimated by an equation (P122). As this approach is unusual in NICE appraisals please can you provide further details and justify that though progression of disease

following from the ‘best response’ is ‘averaged’, the cost-incurring events for an individual patient during this time are individual to the patient.

All the times in the model are individualized – none of them are averaged. This individualization is carried out by solving each equation for time and replacing the cumulative failure proportion by a random number. This yields an individual time for each event for each patient. In the version of the model originally submitted the random numbers used in these calculations were fixed but in the model with Crystal Ball, they are allowed to change every time a calculation is performed.

C19. In the model subgroup of patients with one prior therapy the TTP for the comparator (bortezomib) is said to be 7 months and for lenalidomide/dexamethasone 14.3 months from the clinical trials (P152). However these figures do not match those of the indirect comparison (P 100) of 6.2 months and 11.1 (11.3) months (P100). The figures are taken from section 6.2.8 (P 136) which appear to be comparisons of lenalidomide/dexamethasone with dexamethasone and for best level of response. Please can you clarify what efficacy figures were used in the model for the comparison of lenalidomide/dexamethasone with bortezomib for the subgroup with one previous therapy?

The model uses equations derived from the pooled lenalidomide clinical trials in order to be able to compute for each individual the relevant times of progression and death. Derivation of these equations requires data at the individual patient level. As these were not available for bortezomib, the equations were calibrated to the published medians reported in the APEX study. Further explanation of how the bortezomib one prior therapy efficacy data used in the model were derived is provided in Appendix 6 section 6.1.1.1 of our submission. The indirect/mixed treatment comparison was undertaken in accordance with NICE methods guidance when comparing clinical effectiveness. As explained in section 5.6 of our submission, because of the uncertainty surrounding the validity of the indirect/mixed treatment comparison results, we did not employ the results of the indirect/mixed treatment comparison analysis in the economic model comparison of Len/Dex with bortezomib. Instead, the indirect/mixed treatment comparison results were used to ensure that the model estimates were in the same direction.

Appendix A

Winbugs code for response to question B7

1. TTP ANALYSIS

Code for drugs: 1=dex, 2=val, 3=rev

Fixed Effect Model for Median Time to Disease Progression

Assumes Apex Standard Error Same as MM10

Model

```
model {
for (i in 1:6) {
prec[i] <- 1/pow(se[i],3)
SCOR[i] ~ dnorm(dt[i],prec[i])
dt[i] <- mu[study[i]] + delta[i]*(1-equals(treat[i],b[i]))
delta[i] <- d[treat[i]] - d[b[i]]
}

# Priors for study-specific baselines
for (j in 1:3) {
mu[j] ~ dnorm(0.0,0.0001)  }

# Priors for difference in change from baseline
d[1] <- 0
for (k in 2:3) {
d[k] ~ dnorm(0.0,0.001)  }

# Effect of Treatment 1 based on 2 trials in which it was used
for (i in 1: 6){mu1[i] <- mu[study[i]]*equals(treat[i],1)}
m <- sum(mu1[])/3

# Calculate treatment effects
for (k in 1:3){ T[k] <- m + d[k] }

# Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- rank(T[],k)
                    best[k]<-equals(rk[k],1)  }

# Calculate pairwise contrasts & prob of superiority
for (c in 1:2){
        for (k in (c+1):3){ diff[c,k] <- d[k] - d[c]
        prob[c,k] <- 1 - step(diff[c,k])  # prob that treat k is superior to c
        }  }

}
```

Data

study[]	treat[]	SCOR[]	se[]	b[]
1	1	24.3	2.86	1
1	2	30.3	2.86	1
2	1	21.1	1.71	1
2	3	61.4	1.71	1
3	1	20.1	2.86	1
3	3	61.4	2.86	1

END

Initials

```
list(mu=c(0,0,0),
d=c(NA,0,0))
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
diff[1,2]	5.881	6.636	0.08056	-7.001	5.808	19.05	1001	20000
diff[1,3]	40.22	2.863	0.03832	34.61	40.21	45.91	1001	20000
diff[2,3]	34.34	7.253	0.09155	19.92	34.36	48.53	1001	20000

Assumes Apex SE Same as MM09

Model

```
model {
for (i in 1:6) {
prec[i] <- 1/pow(se[i],3)
SCOR[i] ~ dnorm(dt[i],prec[i])
dt[i] <- mu[study[i]] + delta[i]*(1-equals(treat[i],b[i]))
delta[i] <- d[treat[i]] - d[b[i]]
}

# Priors for study-specific baselines
for (j in 1:3) {
mu[j] ~ dnorm(0.0,0.0001)  }

# Priors for difference in change from baseline
d[1] <- 0
for (k in 2:3) {
d[k] ~ dnorm(0.0,0.001)  }

# Effect of Treatment 1 based on 2 trials in which it was used
for (i in 1: 6){mu1[i] <- mu[study[i]]*equals(treat[i],1)}
m <- sum(mu1[])/3

# Calculate treatment effects
for (k in 1:3){ T[k] <- m + d[k] }

# Rank the treatment effects (with 1=best) & record the best treatment
```

```
for(k in 1:3){ rk[k]<- rank(T[],k)
                    best[k]<-equals(rk[k],1)  }

# Calculate pairwise contrasts & prob of superiority
for (c in 1:2){
        for (k in (c+1):3){ diff[c,k] <- d[k] - d[c]
        prob[c,k] <- 1 - step(diff[c,k])  # prob that treat k is superior to c
        }   }

}
```

Data

study[]	treat[]	SCOR[]	se[]	b[]
1	1	24.3	1.71	1
1	2	30.3	1.71	1
2	1	21.1	1.71	1
2	3	61.4	1.71	1
3	1	20.1	2.86	1
3	3	61.4	2.86	1

END

Initials

```
list(mu=c(0,0,0),
d=c(NA,0,0))
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
diff[1,2]	5.998	3.125	0.03841	-0.07671	5.959	12.19	1001	20000
diff[1,3]	40.22	2.863	0.03832	34.61	40.21	45.91	1001	20000
diff[2,3]	34.22	4.259	0.05608	25.81	34.22	42.53	1001	20000

2. RESPONSE ANALYSIS

Code for drugs: 1=Dex, 2=Lenalidomide, 3=Bortezomib

Fixed Effect Model for One prior failure population, with Non Evaluable included

Fixed Effect Model for Overall Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	32	124	1
1	2	81	124	1
2	1	28	109	1
2	3	63	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	5.705	1.632	0.03312	3.137	5.498	9.493	1001	10000
or[1,3]	3.073	0.9095	0.01902	1.695	2.94	5.223	1001	10000
or[2,3]	0.5828	0.2435	0.004878	0.248	0.5315	1.177	1001	10000

4 June 2008

Fixed Effect Model for Complete Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
```

```
#Give priors for log-odds ratios
        d[1]<-0
        for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	3	124	1
1	2	23	124	1
2	1	1	109	1
2	3	13	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	13.12	11.02	0.4539	3.269	10.04	42.25	1001	10000
or[1,3]	46.16	121.1	6.209	2.678	15.98	312.0	1001	10000
or[2,3]	5.26	14.98	0.7157	0.1699	1.571	35.91	1001	10000

Fixed Effect Model for Partial Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	29	124	1
1	2	58	124	1
2	1	27	109	1
2	3	50	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1),mu=c(1,-1)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	3.013	0.8703	0.01891	1.674	2.887	5.036	1001	10000
or[1,3]	2.114	0.6325	0.01337	1.149	2.019	3.611	1001	10000
or[2,3]	0.7599	0.3208	0.006431	0.3187	0.6978	1.544	1001	10000

4 June 2008

Fixed Effect Model for Stable Disease

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
```

```
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	68	124	1
1	2	33	124	1
2	1	47	109	1
2	3	52	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.3064	0.08558	0.001469	0.1715	0.2954	0.5056	1001	10000
or[1,3]	0.9552	0.26	0.00477	0.5492	0.9229	1.56	1001	10000
or[2,3]	3.365	1.348	0.02364	1.487	3.118	6.606	1001	10000

4 June 2008

Fixed Effect Model for Progressive Disease

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	16	124	1
1	2	5	124	1
2	1	29	109	1
2	3	8	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.3014	0.1672	0.002201	0.08234	0.2667	0.7195	1001	10000
or[1,3]	0.1953	0.08412	0.001117	0.07269	0.1821	0.3953	1001	10000
or[2,3]	0.8751	0.7028	0.008661	0.177	0.6805	2.778	1001	10000

4 June 2008

Fixed Effect Model for Non Evaluable

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                r[i] ~ dbin(p[i],n[i])
                logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
        d[1]<-0
        for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
```

```
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	8	124	1
1	2	5	124	1
2	1	4	109	1
2	3	4	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.7001	0.4465	0.006322	0.1645	0.5973	1.867	1001	10000
or[1,3]	1.148	1.022	0.02098	0.1895	0.8672	3.877	1001	10000
or[2,3]	2.381	2.977	0.04979	0.2214	1.453	10.17	1001	10000

4 June 2008

2. Random Effects Model - One Prior Failure Population, NE Not Removed

Overall Response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
```

```
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	32	124	1
1	2	81	124	1
2	1	28	109	1
2	3	63	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	13.37	56.43	0.5846	0.4359	5.531	74.06	1001	10000
or[1,3]	7.167	39.28	0.4109	0.219	2.878	36.18	1001	10000
or[2,3]	4.033	93.11	0.9241	0.01466	0.5252	20.64	1001	10000

4 June 2008

Complete Response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
```

```
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	3	124	1
1	2	23	124	1
2	1	1	109	1
2	3	13	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	33.62	260.0	3.043	0.6704	10.59	180.9	1001	10000	
or[1,3]	190.9	1503.0	35.21	0.9314	17.57	1099.0	1001	10000	
or[2,3]	86.9	3570.0	38.52	0.02938	1.734	244.4	1001	10000	

4 June 2008

Partial response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	29	124	1
1	2	58	124	1
2	1	27	109	1

2 3 50 126 1

END

Initials

#initial 1
list(
d=c(NA,0,0),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0, -2,1,0,2,2, 1,-1,-2,0,0, -2,1,0,2,2, -2,-0.5,-3,0.5)
)

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	7.034	24.89	0.2941	0.2331	2.943	38.33	1001	10000
or[1,3]	4.86	24.1	0.2991	0.1568	1.963	25.49	1001	10000
or[2,3]	3.995	24.11	0.2573	0.01922	0.6792	25.58	1001	10000

4 June 2008

Stable Disease

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                r[i] ~ dbin(p[i],n[i])
                logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                delta[i] ~ dnorm(md[i],prec)
                md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
        d[1]<-0
```

```
        for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	68	124	1
1	2	33	124	1
2	1	47	109	1
2	3	52	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.6949	2.696	0.02729	0.02394	0.2963	3.613	1001	10000
or[1,3]	2.259	10.24	0.1048	0.0746	0.9156	11.9	1001	10000
or[2,3]	20.75	156.5	1.751	0.08557	3.088	109.2	1001	10000

4 June 2008

Progressive Disease

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	16	124	1
1	2	5	124	1
2	1	29	109	1
2	3	8	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.7384	3.335	0.03363	0.01755	0.2656	4.106	1001	10000
or[1,3]	0.4972	2.401	0.02404	0.01349	0.178	2.666	1001	10000
or[2,3]	6.751	96.52	0.9166	0.01559	0.6851	28.78	1001	10000

Non Evaluable

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
```

```
sd~dunif(0,2)
#Give priors for log-odds ratios
        d[1]<-0
        for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	8	124	1
1	2	5	124	1
2	1	4	109	1
2	3	4	126	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	1.543	5.737	0.06339	0.03797	0.5856	8.967	1001	10000
or[1,3]	2.954	19.06	0.2141	0.04891	0.8341	16.23	1001	10000
or[2,3]	19.98	310.7	3.097	0.02684	1.445	78.39	1001	10000

3. Fixed Effects Model - One Prior Failure Population, NE Removed

Fixed Effect Model for Overall Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	32	116	1
1	2	81	119	1

```
2	1	28	105	1
2	3	63	123	1
```

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	5.885	1.717	0.03072	3.195	5.669	9.892	1001	10000
or[1,3]	3.086	0.9305	0.01946	1.676	2.95	5.298	1001	10000
or[2,3]	0.5687	0.2411	0.004446	0.2386	0.5203	1.151	1001	10000

June 2008

Fixed Effect Model for Complete Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }
```

```
#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	3	116	1
1	2	23	119	1
2	1	1	105	1
2	3	13	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	13.2	11.26	0.4288	3.227	10.06	43.22	1001	10000
or[1,3]	73.74	384.2	19.67	2.752	17.29	421.5	1001	10000
or[2,3]	8.431	41.12	1.952	0.1727	1.711	53.69	1001	10000

June 2008

Fixed Effect Model for Partial Response

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	29	116	1
1	2	58	119	1
2	1	27	105	1
2	3	50	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1),mu=c(1,-1)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	2.99	0.8723	0.01759	1.631	2.873	5.004	1001	10000
or[1,3]	2.1	0.6336	0.0136	1.132	2.009	3.585	1001	10000
or[2,3]	0.7625	0.3273	0.006991	0.3167	0.6959	1.56	1001	10000

June 2008

Fixed Effect Model for Stable Disease

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}
```

```
#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	68	116	1
1	2	33	119	1
2	1	47	105	1
2	3	52	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)

#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.2771	0.07983	0.001488	0.1511	0.2668	0.4647	1001	10000
or[1,3]	0.9251	0.2503	0.004017	0.5246	0.8944	1.498	1001	10000
or[2,3]	3.619	1.465	0.02642	1.57	3.35	7.109	1001	10000

June 2008

Fixed Effect Model for Progressive Disease

Model

```
model{

#Model for log-odds of smoking cessation, for three types of trial indicated by
b[i]
```

```
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}

#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- sum(mu1[])/2 + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	16	116	1
1	2	5	119	1
2	1	29	105	1
2	3	8	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0),mu=c(0,0)
)
```

```
#initial 2
list(
d=c(NA,0.1,-1,-0.2,-.2),mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5,-.2)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.2913	0.1619	0.002118	0.07955	0.2576	0.6927	1001	10000
or[1,3]	0.1902	0.08218	0.001097	0.07052	0.1773	0.3859	1001	10000
or[2,3]	0.8826	0.7108	0.008573	0.1778	0.6852	2.788	1001	10000

June 2008

4. Random Effects Model - One Prior Failure Population, NE Removed

Overall Response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                r[i] ~ dbin(p[i],n[i])
                logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                delta[i] ~ dnorm(md[i],prec)
                md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
        d[1]<-0
        for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}
```

```
#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	32	116	1
1	2	81	119	1
2	1	28	105	1
2	3	63	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	12.79	46.64	0.4898	0.4745	5.767	67.11	1001	10000
or[1,3]	7.144	32.43	0.3581	0.2255	2.842	37.44	1001	10000
or[2,3]	4.417	83.13	0.8806	0.01411	0.5085	19.86	1001	10000

4 June 2008

Complete Response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
```

```
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	3	116	1
1	2	23	119	1
2	1	1	105	1
2	3	13	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	35.02	294.6	3.389	0.6762	10.61	180.7	1001	10000
or[1,3]	104.0	1111.0	23.41	0.7154	15.49	620.0	1001	10000
or[2,3]	33.5	1233.0	12.95	0.0226	1.455	139.0	1001	10000

4 June 2008

Partial Response

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
```

```
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	29	116	1
1	2	58	119	1
2	1	27	105	1
2	3	50	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	7.687	53.7	0.5319	0.2232	2.848	37.03	1001	10000
or[1,3]	4.969	19.61	0.2176	0.1513	1.976	27.2	1001	10000
or[2,3]	5.467	81.08	0.8099	0.0172	0.6989	27.29	1001	10000

4 June 2008

Stable Disease

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}

#All pairwise log odds ratios and odds ratios
for (c in 1:2){
          for (k in (c+1):3){
                    lor[c,k] <- d[k] - d[c]
                    log(or[c,k]) <- lor[c,k]
                    }
          }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	68	116	1
1	2	33	119	1
2	1	47	105	1

2 3 52 123 1

Initials

```
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))
```

Results

	node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.629	2.498	0.02534	0.02209	0.2692	3.246	1001	10000	
or[1,3]	2.193	9.977	0.1022	0.07535	0.8936	11.47	1001	10000	
or[2,3]	21.97	167.4	1.879	0.09293	3.32	114.7	1001	10000	

Progressive Disease

Model

```
model{

#Model for log-odds of ACR20,  types of trial indicated by b[i]
 for(i in 1:4){
                    r[i] ~ dbin(p[i],n[i])
                    logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))
#Random effects model for log-odds ratios
                    delta[i] ~ dnorm(md[i],prec)
                    md[i] <- d[t[i]] - d[b[i]]
#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))
                    }
sumdev <- sum(dev[])

#Fixed effect priors
for(j in 1:2){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)
#Give priors for log-odds ratios
          d[1]<-0
          for (k in 2:3){d[k] ~ dnorm(0,.001) }

#Absolute log odds on Treatment A based on 2 trials in which it was used
for (i in 1: 4){mu1[i] <- mu[s[i]]*equals(t[i],1)}
m<- sum(mu1[])/2
#Calculate treatment effects, T[k], on natural scale
for (k in 1:3){logit(T[k]) <- m + d[k]}

#Rank the treatment effects (with 1=best) & record the best treatment
for(k in 1:3){ rk[k]<- 4 - rank(T[],k)
                    best[k]<-equals(rk[k],1)}
```

```
#All pairwise log odds ratios and odds ratios
for (c in 1:2){
        for (k in (c+1):3){
                lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
                }
        }

}
```

Data

s[]	t[]	r[]	n[]	b[]
1	1	16	116	1
1	2	5	119	1
2	1	29	105	1
2	3	8	123	1

END

Initials

```
#initial 1
list(
d=c(NA,0,0 ),sd=1,mu=c(0,0), delta=c(0,0,0,0))

#initial 2
list(
d=c(NA,0.1,-1,-0.2),sd=.5,mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -
2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

Results

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
or[1,2]	0.7211	3.238	0.03282	0.01657	0.2585	4.082	1001	10000
or[1,3]	0.4824	2.327	0.02336	0.01298	0.1747	2.547	1001	10000
or[2,3]	7.317	108.0	1.014	0.01536	0.6933	29.42	1001	10000

Appendix B

[redacted]

[redacted]

[redacted]