Addendum
Model dated 24.08.2009.

Given the non-functionality of the most recent version of the model (dated 07.09.2009), the ERG have looked at the changes made by the manufacturer in the version dated 24.08.2009. We have not done a full appraisal of this version of the model, given the time constraints, but we feel that this approach should give the committee sufficient information on which to basis a decision. The most important issue surrounding the model and the results is the choice of model used for estimating survival data. This is covered in detail elsewhere in the report. In this section we examine whether or not the changes claimed by the manufacturer have been implemented, assess their reasons for not introducing certain changes requested previously and assess the internal validity of the model and the reliability of the results that were provided in the RACD.

Changes to costs:
In response to the ERG report, the manufacturers include in the revised model dated 24.08.2009 an increased pharmacy cost to take into account the continuous, seven day per week nature of the treatment. This increased cost takes into consideration the additional cost of preparation and administration costs at weekends and is applied to the average cost of pharmacy treatment per cycle. In the RACD the manufacturers assumed a two-fold increase in weekend costs, though no justification for this was provided. In the CRACD, further details of the increased costs were provided and are reproduced below, and the cost is applied in the model as stated.

From page 19 of the CRACD.

- The twofold increase in the total costs of preparation and administration of azacitidine during weekends was an assumption made due to the absence of any such cost data. The additional cost of weekend administration would be associated with pharmacy services which may operate an 'out-of-hours' weekend service to allow preparation of weekend doses.
- In the ACD response (and revised model submitted), a twofold increase in cost was assumed (and applied in the model) for all healthcare professionals associated with the preparation and administration of each cycle of chemotherapy. Hence, the total cost was inflated by a factor of 1.29 (equivalent to five days at the designated cost and two days at the 100% increased designated cost). This factor is applied to all the cost components (physician, nursing and pharmacy time). However, based on the current absence of provision of pharmacy services in some NHS organisations during weekends, this assumption more accurately represents an assumed 4.75-

fold increase in the cost of pharmacy preparation. This is because there would be no additional resources associated with physician or nursing time during weekends, as these are currently provided within the NHS. This is illustrated below in Table 4.1.

Table 4.1: Preparation and administration of treatment costs of azacitidine

Staff type	Mean time (mins)	Mean cost per cycle [initial assumption] (£)	Mean cost per cycle including increased weekend cost [revised base case] (£)
Consultant	12.3	21.74	21.74
Foundation house officer	5.0	2.63	2.63
Nurse	253.1	113.88	113.88
Pharmacy	107.7	50.26	104.12
Total	N/A	188.51	242.37*

* Total cost equivalent to 188.51 multiplied by weekend factor of 1.29

- Since each dose of azacitidine would cost £7.18 (or 15.39 minutes) in pharmacy preparation time, the weekend doses would be assumed to cost £34.11 (equivalent to 73.1 minutes) of pharmacy preparation time per dose.

Utility values

The manufacturers agree with the committee that the utility estimates used in the model are likely to be an underestimate of the true utility values of patients under treatment. However, the manufacturers repeat the claim that there is no better source of utility data than the mapped algorithm that they used. In the absence of any other source of utility data, mapped estimates of utility are acceptable under NICE methodology guidance.

In the model, the manufacturers appear to provide point estimates of the utility values, and then use these, along with an estimate of the standard deviation, to estimate distributions of utility data. Beta distributions are used, constraining the values between 0 and 1, and therefore precluding the possibility that negative utility values might be experienced for patients receiving these treatments. It is unclear what the source of the data is for the SD values that are used. In addition, this approach does not take into account the uncertainty inherent in the mapped estimate, as it uses a point estimate of the mapped data, and the full uncertainty may not have

been translated from the EORTC data into the utility estimate. The estimate is therefore presented with a greater degree of certainty than it possibly merits.

Economic model functionality and results.

As stated elsewhere by the ERG, the revised model provided by the manufacturers dated 07.09.2009 was not functional. Although the commands could be executed, an error in a model cell meant that no reliable results could be generated. In the model dated 24.08.2009 this error was not present and so this version of the model was tested for internal validity and to validate the results claimed by the manufacturer. Only deterministic results are considered here.

Although it is not explicitly stated in the RACD, the base case results presented appear to be based on the use of the log-normal curve fit for the survival data. The CRACD provides a range of results using different curve fits but these are not commented on in detail here as it is unclear which model version was used to generate the results. The lognormal curve fit is one of five potential curve fits that can be selected in the model, the others being Weibull, log-logistic, exponential and Gompertz. As there was no explicit mention of the choice of curve used in the RACD, it is also therefore unclear why the curve was chosen. Examining the deterministic results suggests (see results below) that the reason may be related to the fact that the lognormal produces the most favourable ICERS with respect to the presumed cost-effectiveness threshold of £30,000 per QALY. More detail on the choice of curve fit can be found in the main response to the RACD and CRACD.

Deterministic results using Weibull curve fit

Treatment option	Life Years	Costs incurred	QALYs gained	Marginal costs (vs azacitidine)	Life years gain on azacitidine	Marginal QALYs (vs azacitidine)	Cost per Life year gained (vs azacitidine)	Cost per QALY (vs azacitidine)
Azacitidine (BSC)	2.69	£94,934	2.04	-	-	-	**-**	**-**
BSC	1.50	£27,998	1.03	£66,937	1.19	1.01	**£56,021**	**£66,329**
Azacitidine (LDC)	3.18	£104,625	2.44	-	-	-	**-**	**-**
LDC	1.56	£35,684	1.10	£68,941	1.62	1.34	**£42,523**	**£51,471**
Azacitidine (SDC)	2.60	£94,747	1.91	-	-	-	**-**	**-**
SDC	1.39	£43,981	0.98	£50,766	1.21	0.93	**£41,859**	**£54,507**

Deterministic results using log-logistic curve fit

Treatment option	Life Years	Costs incurred	QALYs gained	Marginal costs (vs azacitidine)	Life years gain on azacitidine	Marginal QALYs (vs azacitidine)	Cost per Life year gained (vs azacitidine)	Cost per QALY (vs azacitidine)
Azacitidine (BSC)	3.64	£110,893	2.81	-	-	-	**-**	**-**
BSC	1.90	£35,435	1.32	£75,458	1.74	1.48	**£43,317**	**£50,929**
Azacitidine (LDC)	4.05	£119,230	3.14	-	-	-	**-**	**-**
LDC	2.14	£49,977	1.50	£69,254	1.91	1.64	**£36,230**	**£42,318**
Azacitidine (SDC)	3.66	£112,331	2.76	-	-	-	**-**	**-**
SDC	1.57	£49,109	1.13	£63,222	2.08	1.63	**£30,344**	**£38,834**

Deterministic results using exponential curve fit

Treatment option	Life Years	Costs incurred	QALYs gained	Marginal costs (vs azacitidine)	Life years gain on azacitidine	Marginal QALYs (vs azacitidine)	Cost per Life year gained (vs azacitidine)	Cost per QALY (vs azacitidine)
Azacitidine (BSC)	2.66	£94,379	2.01	-	-	-	**-**	**-**
BSC	1.58	£29,566	1.10	£64,813	1.07	0.92	**£60,397**	**£70,674**
Azacitidine (LDC)	2.83	£99,187	2.15	-	-	-	**-**	**-**
LDC	1.67	£38,341	1.17	£60,846	1.16	0.99	**£52,231**	**£61,759**
Azacitidine (SDC)	2.48	£92,912	1.81	-	-	-	**-**	**-**
SDC	1.57	£50,271	1.15	£42,642	0.90	0.66	**£47,292**	**£65,019**

Deterministic results using Gompertz curve fit

Treatment option	Life Years	Costs incurred	QALYs gained	Marginal costs (vs azacitidine)	Life years gain on azacitidine	Marginal QALYs (vs azacitidine)	Cost per Life year gained (vs azacitidine)	Cost per QALY (vs azacitidine)
Azacitidine (BSC)	3.30	£105,019	2.53	-	-	-	**-**	**-**
BSC	1.69	£31,580	1.18	£73,439	1.61	1.35	**£45,751**	**£54,255**
Azacitidine (LDC)	4.87	£132,943	3.79	-	-	-	**-**	**-**
LDC	1.69	£39,008	1.18	£93,935	3.17	2.60	**£29,588**	**£36,074**
Azacitidine (SDC)	3.07	£102,679	2.29	-	-	-	**-**	**-**
SDC	1.36	£43,640	0.96	£59,038	1.71	1.32	**£34,589**	**£44,572**

Deterministic results using log-normal curve fit

Treatment option	Life Years	Costs incurred	QALYs gained	Marginal costs (vs azacitidine)	Life years gain on azacitidine	Marginal QALYs (vs azacitidine)	Cost per Life year gained (vs azacitidine)	Cost per QALY (vs azacitidine)
Azacitidine (BSC)	3.86	£114,232	2.99	-	-	-	**-**	**-**
BSC	1.80	£33,587	1.26	£80,644	2.06	1.73	**£39,137**	**£46,632**
Azacitidine (LDC)	4.23	£122,023	3.28	-	-	-	**-**	**-**
LDC	1.79	£41,604	1.25	£80,419	2.44	2.02	**£33,022**	**£39,714**
Azacitidine (SDC)	3.88	£115,725	2.94	-	-	-	**-**	**-**
SDC	1.39	£44,410	0.99	£71,316	2.49	1.95	**£28,631**	**£36,591**