Darvadstrocel for treating complex perianal fistula in Crohn's disease: A Single Technology Appraisal

Erratum in response to the Factual Accuracy Check

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Document 14 (comparing Akaike information criterion [AIC] and Bayesian information criterion [BIC], and by visual assessment).[36] An assessment of the proportional hazards assumption was carried out only for the time to relapse functions, because the remission time-to-event functions for the darvadstrocel and standard care groups were not extrapolated beyond the 1-year follow-up data (CS,[1] page 79).It should be noted that when patients received salvage therapy, the time to remission function was extrapolated. An assessment of other plausible assumptions (e.g. accelerated failure time) were not conducted. In all analyses a treatment effect covariate (either a constant HR or constant acceleration factor, depending on the model type) was included in the statistical models to estimate the treatment effect parameter (the difference between the time-to-event for patients receiving darvadstrocel versus those receiving standard care). Piecewise exponential models were also fitted to the data, however the ERG notes that, it is unclear how these functions were fitted and which goodness-of-fit tests, if any, were conducted in these cases. The Gompertz distributions for time to remission and time to relapse were presented to the company's clinical experts to assess the clinical plausibility of the extrapolation (CS,[1] page 79).

Table 1 presents the AIC and BIC statistics for each of the fitted parametric time-to-event functions. These indicate that when the CPC definition of remission is used, the generalised gamma distribution provides the best fit to the observed time to remission data and the Gompertz distribution provides the best fit to the observed time to relapse data (although there is very little to distinguish between the Gompertz and the log normal models).

Table 1: AIC and BIC statistics for time-to-event functions fitted to data on time to remission and relapse using the CPC definition of remission, excluding the piecewise exponential model (adapted from CS,[1] Tables 32 and 38)

	Remission		**Relapse**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	980.8393	987.4459	539.436	544.606
Weibull	965.6205	975.5305	528.702	536.457
Gompertz	946.2664	956.1763	***517.572***	***525.327***
Log normal	946.6324	956.5423	518.216	525.971
Log logistic	954.7821	964.6920	521.644	529.399
Generalised gamma	***931.1734***	***944.3866***	522.156[a]	532.496[a]

AIC – Akaike information criterion; BIC – Bayesian information criterion; a - the stacy parametrisation used for the generalised gamma rather than the default prentice parameterisation
Text in ***bold and italics*** indicates the lowest value out of the converged time-to-event functions in each column

The appropriateness of the proportional hazards assumption was assessed by examining the log cumulative hazard plot. The log cumulative hazard plot for CPC remission is presented in

for people who had non-active / mildly active luminal Crohn's disease that were not either mild or in remission. The company estimated the proportion of cases that were mild and severe by taking an average of the PDAI score of people with CSF. Patients with missing data or in remission were excluded from these calculations. It was assumed that these probabilities were constant with respect to time.

Probabilities that a proctectomy or defunctioning surgery are successful

The probability that a proctectomy was successful and the probability that a defunctioning surgery was successful were obtained from the St Mark's retrospective cohort study (CS,[1] Appendix Q). In this prospective study, data was collected from 78 consecutive patients who presented with a complex perianal fistula and Crohn's disease at St Marks hospital between from 1st January 2008 to July 1st 2017. Data were collected at baseline, routine visits and study termination (lost to follow up, transferred to another hospital, or patient death). In this data source, the probability that a proctectomy was successful was 0.80 and the probability that a defunctioning surgery was successful was 0.62.

Mortality

The age-dependent probability of death was taken from general population life tables for England and Wales in 2013-15.[26]

HRQoL

The ADMIRE-CD trial[1] did not include a preference-based measure of HRQoL. The CS states that there are no disease-specific measures of HRQoL available for patients with perianal fistula.[1] The only patient reported outcome measure included in ADMIRE-CD was the IBDQ. The company considered whether it was possible to map from the PDAI, CDAI or IBDQ scores obtained in the trial to the EQ-5D. The CS states that there is insufficient conceptual overlap between the content of the PDAI and CDAI, which are considered to be measures of disease activity, and the relevant components of HRQoL.[1] The company cites a mapping study by Buxton *et al.*(2007)[37] which they claim supports the poor performance of CDAI as a predictor of utility. The ERG notes that the mapping algorithms reported by Buxton *et al*[37] were derived and validated in studies that included patients with moderately to severely active Crohn's disease. The company does not consider mapping from IBDQ to be appropriate because IBDQ is focused on luminal disease and not complex perianal fistulae. The ERGs clinical advisors agreed that IBDQ was a Crohn's disease specific measure of health. The company conducted a systematic review of HRQoL studies, but concluded that none of the studies identified were suitable for informing utility values in the model.

The health state utility values (HSUVs) used in the company's model were taken from a vignette study reported by Fountain *et al*.[38] which was funded by Takeda (the full study report is provided in

Table 2: Health state resource use and associated costs used in the company's model (adapted from CS,[1] Tables 50, 58, and appendix Table 31)

	Unit cost		Resource use (number of visits / tests) per 4 weekly cycle								
Resource item	**Cost per item of resource use (£)**	**Source**	**Remission**	**CSF**		**Defunctioning**			**Proctectomy**		
				Mild	**Severe**	**Undergoing**	**S**	**U**	**Undergoing**	**S**	**U**
Healthcare professional resource use											
GP visits	37.00	PSSRU[29]	0.06	0.12	0.14	1.38	0.10	0.21	1.38	0.10	0.25
Gastroenterologist visits	149.76	NHS Reference costs[28]	0.13	0.17	0.31	2.00	0.10	0.31	2.00	0.12	0.31
Surgeon visits	127.09	NHS Reference costs[28]	0.04	0.10	0.22	2.25	0.10	0.29	3.25	0.12	0.48
Nurse appointments	51.15	NHS Reference costs[28]	0.06	0.16	0.27	1.75	0.12	0.35	2.75	0.15	0.56
Nutritionist visits	81.33	NHS Reference costs[28]	0.02	0.02	0.08	0.25	0.04	0.12	0.25	0.06	0.12
Total cost of health care professional visits per four weekly cycle			***£31.70***	***£52.04***	***£99.35***	***£746.38***	***£39.21***	***£117.66***	***£924.62***	***£48.06***	***£154.34***
Monitoring resource use											
Rectal MRI	162.23	NHS Reference costs[28]	0.01	0.06	0.13	1.00	0.02	0.10	1.25	0.04	0.13
Endoscopy	182.10	NHS Reference costs[28]	0.06	0.06	0.13	1.00	0.06	0.13	1.25	0.00	0.06
Stoma care*	1,961.00	NICE TA 329[30]	0.00	0.00	0.00	0.08	0.08	0.08	0.08	0.08	0.08
Computerised tomography	85.56	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Colonoscopy	334.76	NHS Reference costs[28]	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total cost of monitoring patients per four weekly cycle			***£12.07***	***£19.87***	***£44.60***	***£495.18***	***£164.47***	***£190.83***	***£581.26***	***£157.09***	***£183.19***
Laboratory resource use											
Blood count	1.69	NHS Reference costs[28]	0.15	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
C-reactive protein	1.13	NHS Reference costs[28]	0.17	0.13	0.27	2.25	0.15	0.31	2.50	0.15	0.37

Haemoglobin	3.06	NHS Reference costs[28]	0.17	0.12	0.23	2.25	0.15	0.28	2.50	0.15	0.35
Faecal calprotectin	22.79	NICE DG11[31]	0.13	0.13	0.27	1.50	0.10	0.15	1.75	0.12	0.15
Total cost of laboratory tests per four weekly cycle			***£3.77***	***£7.54***	***£4.05***	***£47.42***	***£3.10***	***£5.19***	***£54.58***	***£3.53***	***£5.56***
Total health state resource use costs per four weekly cycle			**£47.82**	**£75.67**	**£151.49**	**£1288.97**	**£206.78**	**£313.68**	**£1560.46**	**£208.68**	**£343.09**

CSF – chronic symptomatic fistula; S – successful; U – unsuccessful; GP – general practitioner; PSSRU - Personal Social Services Research Unit; NHS – National Health Service; MRI – magnetic resonance imaging; NICE – National Institute for Health and Care Excellence; TA – technology appraisal; DG – diagnostics guidance; * - the unit cost applied is an annual cost

Table 3: Percentage of patients receiving each treatment by health state and treatment group (adapted from CS,[1] Tables 52 and 53)

Treatment mix	Mild CSF			Severe CSF			Rem	Defunctioning		Proctectomy		Sources and assumptions
	DARV	Control	Salvage	DARV	Control	Salvage		S	U	S	U	
Darvadstrocel												
Darvadstrocel	100	0	0	100	0	0	0	0	0	0	0	
Antibiotics												
Ciprofloxacin	29.76	29.76	11.25	29.78	29.78	57.50	0	0	0	0	0	ADMIRE CD trial data
Metronidazole	38.05	38.05	55.28	38.05	38.05	58.75	11.20	18.56	57.81	1.09	32.66	
Immunosuppressants												
Azathioprine	46.23	46.23	46.37	46.23	46.23	47.50	51.32	58.99	46.88	45.01	52.50	ADMIRE CD trial data, clinical expert opinion
Methotrexate	0	0	9.05	0	0	0.5	7.29	0.00	5.84	11.66	0	
6-MP	0	0	7.50	0	0	26.75	10.00	11.88	11.88	0	0	
Biologics												
Adalimumab	33.59	33.59	30.65	33.59	33.59	19.17	31.76	21.32	27.03	12.86	25.47	ADMIRE CD trial data, clinical expert opinion
Infliximab	27.26	27.26	30.65	27.26	27.26	35.83	32.39	21.32	27.03	12.86	25.47	
Adalimumab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Infliximab dose escalation	0	0	5.94	0	0	7.5	4.92	3.38	10.21	0.75	8.75	
Vedolizumab	0	0	8.67	0	0	0	8.24	5.08	7.69	3.36	7.36	
Surgery												
Seton	95	95	20.56	95	95	48.5	5.21	11.54	11.96	0	2.50	ADMIRE CD trial data, clinical expert opinion
Fistulotomy	0	0	1.51	0	0	16.5	0	0	5.84	0	0	
Anal plug	0	0	12.50	0	0	11.25	0	0	0	0	0	
Fibrin glue	0	0	0	0	0	6.25	0	0	0	0	0	
Rectal flap	0	0	0	0	0	12.5	0	0	0	0	0	
EUA alone	0	0	43.09	0	0	0	11.12	6.59	37.38	0	26.43	
VAAFT	0	0	4.52	0	0	0	0	6.73	0	0	0	

CSF – chronic symptomatic fistulae; Rem – remission; DARV – darvadstrocel; Control – standard care; S – successful; U - unsuccessful; EUA, examination under anaesthesia; 6-MP, 6-mercaptopurine.

Table 4: Cost of pharmacological and surgical treatments given to each patient (adapted from CS,[1] Table 54)

Treatment	Unit cost	Doses per item	Source	Doses given in cycle 1	Doses given in subsequent cycles	Cost in cycle 1	Cost in subsequent cycles	Average Cycle cost across 13 model cycles
Darvadstrocel								
Darvadstrocel	[redacted]	1 unit	Takeda	4 units	0 units	[redacted]	£0	Not applicable
Antibiotics								
Ciprofloxacin	£0.089	500mg	BNF	56	56	£4.98	£4.98	£4.98
Metronidazole	£0.195	400mg	BNF	76.20	76.20	£14.88	£14.88	£14.88
Immunosuppressants								
Azathioprine	£0.039	50mg	BNF	91.44	91.44	£3.56	£3.56	£3.56
Methotrexate	£0.054	2.5mg	BNF	28	28	£1.51	£1.51	£1.51
6-MP	£1.966	50mg	BNF	50.80	50.80	£99.88	£99.88	£99.88
Biologics								
Adalimumab	£352.14	40mg	BNF	2	2	£704.28	£704.28	£704.28
Infliximab	£377.00	100mg	BNF	1.81	1.81	£684.01	£684.01	£684.01
Adalimumab dose escalation	£352.14	40mg	BNF	4	4	£1408.56	£1408.56	£1408.56
Infliximab dose escalation	£377.00	100mg	BNF	3.63	3.63	£1368.02	£1368.02	£1368.02
Vedolizumab	£2050	300mg	BNF	1.00	0	£1025	£1025	£78.85
Surgical procedures								
Seton	£0	1 set	Assumption	1	0	£0	£0	£0
Fistulotomy	£1,170.21	1 operation	NICE MIB 102	1	0	£1,170.21	£0	£90.02
Anal plug	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£90.02
Fibrin glue	£724.19	1 set	NICE MIB 105	1	0	£724.19	£0	£55.71
Rectal flap	£1,170.21	1 operation	Assumed equal to fisulotomy	1	0	£1,170.21	£0	£90.02
EUA	£1,170.21	1 operation	NHS reference costs[28]	1	0	£1,170.21	0	£90.02
VAAFT	£1,195.40	1 operation	NICE MIB 102	1	0	£1,195.40	0	£91.95

BNF – British National Formulary; 6–MP - 6-mercaptopurine; NICE – national institute for health and care excellence; MIB – Medtech Innovation Briefing; EUA – examination under anaesthesia; VAAFT - video-assisted anal fistula treatment

support differential discounting.[10] In scope analyses using discount rates of 3.5% for both costs and QALYs and 1.5% for both costs and QALYs were provided by the company at clarification.[2]

Table 5: Adherence of the company's model to the NICE Reference case

Element	Reference case	ERG comments
Defining the decision problem	The scope developed by NICE	The model reflects people with non-active / mildly active luminal Crohn's disease and complex perianal fistulae. However, a subgroup of the patient population whose complex perianal fistulae have more than two internal openings or more than three external openings are not considered within the company's analysis of the available evidence or the company's submitted model. It is unclear whether this missing population is included within the licence population for darvadstrocel (see Section **Error! Reference source not found.**)
Comparator(s)	As listed in the scope developed by NICE	The company's model compares darvadstrocel against standard care surgical interventions combined with associated medical management.
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	Health gains accrued by patients are modelled in terms of QALYs gained.
Perspective on costs	NHS and PSS	The model takes an NHS and PSS perspective
Type of economic evaluation	Cost-utility analysis with fully incremental analysis	The company's economic evaluation takes the form of a cost-utility analysis. The results of the analysis are presented in terms of the incremental cost per QALY gained for darvadstrocel versus standard care
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model adopts a 40-year time horizon. By this time point, only 31.7% of people have died in each group.
Synthesis of evidence on health effects	Based on systematic review	Based on the ADMIRE-CD study, which is the only study of the effectiveness of darvadstrocel in this population at the dose stated in the marketing authorisation.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	Health effects are expressed in QALYs. A vignette study, using time-trade off (TTO) valuations by members of the general public was used to inform HRQoL parameters in the model. EQ-5D data were not available from the ADMIRE-CD trial and mapping from the trial outcomes to the EQ-5D was not considered appropriate by the company.
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	No. The utility values used in the model were based on vignettes, not a description of HRQoL provided directly by patients. Patients did have input into the health state descriptions.

Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population	Yes. The vignette study used a representative sample of the UK population to value the health states using the time trade off method. Patient valuations of the vignettes using TTO methodology were considered in a scenario analysis
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No additional equity rating is applied to estimate QALY gains
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	Resource components include those relevant to the NHS and PSS. Whilst not explicitly stated in the CS, unit costs are valued in 2016/17 prices
Discount rate	The same annual rate for both costs and health effects (currently 3.5%)	The base case in the CS used 3.5% discounting for costs and 1.5% discounting for benefits, as the company claims that Section 6.2.19 of the NICE Methods Guide applies (see Section **Error! Reference source not found.**).[10] In response to clarification question B7, the company provided analyses where both health effects and costs are discounted at 3.5% and analyses where both the health effects and costs are discounted at 1.5%.

5.3.3 Model validation and face validity check

The ERG rebuilt the deterministic version of the company's base case model in order to verify its implementation. **Error! Reference source not found.** shows that the ERG's rebuilt model produces very similar estimates of undiscounted life years gained, health gains, costs and cost-effectiveness. This double-programming exercise led to the identification of three minor implementation errors:

i. When estimating the average risk of relapse and the average risk of remission across weeks 104 to 164, to inform the long-term relapse and remission rates, the company divides by 16 instead of 15 cycles.

ii. The per-cycle probability of all-cause mortality was subject to a minor error which led to a small over-prediction of the number of deaths throughout the model time horizon.

iii. The long-term remission rates in the salvage therapy arm were specific to the standard care arm time-to-event function, not the salvage therapy time-to-even function.

three of seven experts at the UK Advisory Board felt that the utility values for the CSF with mild symptoms state were underestimated (CS,[1] Appendix P); this issue was also noted by one of the ERG's clinical advisors. In addition, one of the clinical advisors to the ERG believed that the utility values for a successful outcome following surgery were underestimated; this would underestimate the benefits to patients of a successful surgical procedure.

The report by Fountain *et al*. (2017)[38] (which is provided in the CS,[1] Appendix R) assessed the external validity of the estimates derived from the vignettes by comparing them to values reported in the literature from 21 studies. Seventeen of these studies focussed on Crohn's disease and four studies focussed on IBD or UC but reported surgical states which are similar to the surgical states described in this study.[38] Seven of these studies reported values obtained from the EQ-5D (Richards 2001[43], Kuruvilla 2012[44], Casellas 2005[45], Stark 2010,[46] Benedini 2012[47], Casellas 2000[48], Casellas 2007[49]). Fountain *et al*. (2017)[38] conclude that *"all health states valued in [the vignette] study had lower utility estimates than other studies reporting utilities in Crohn's disease; however it is not possible to make direct comparisons due to the lack of data for many of the specific states and conditions included in [the vignette] study".* The ERG noted in particular, that many of the studies estimating the utility values in patients following surgical intervention gave higher utility estimates than the utilities for those patients with positive surgical outcomes estimated in the Fountain *et al*. vignette study. In particular, in the study by Casellas *et al.*(2000)[48], the EQ-5D estimates for patients in remission following surgery were much closer to those for patients in medically induced remission (median values of 0.87 vs 0.86, respectively in Casellas 2000). This suggests that the benefits to patients of defunctioning or proctectomy surgery may be underestimated in the company's model. However, the ERG accepts that any differences between the utility values obtained in the vignette study and those identified from the literature may be due to differences in the population studied, as few of the studies were specific to patients with mildly or inactive Crohn's disease and complex perianal fistulea. Fountain *et al*.[38] also state, "*Lower utility estimates could have been generated because of use of condition specific vignettes (as opposed to generic measure) that may cause a focussing effect, whereby attention is drawn to health problems that may not be considered as so severe when placed in the context of a broader description of health (Brazier and Tsuchiya, 2010).[50]*" This supports the ERG's concern regarding the use of a non-Reference Case method of measuring utility. The potential impact of this on the ICER is explored in the ERG's exploratory analyses (see Section **Error! Reference source not found.**)

5.3.4.11 Adoption of a 40-year time horizon

The ERG noted that in the company's submitted model only 31.7% of people in the model are in the death health state at the end of the model's 40-year time horizon. The ERG considers that it is possible that the company's base case model may not capture all important differences in costs and QALYs between darvadstrocel and standard care. The company did submit a scenario analysis in

Table 6: Comparison of three different annual transition probabilities, to four decimal places, used in the company's base case analysis and those used in exploratory analysis 2

Transition		Annual probabilities		
From health state	**To health state**	**Values used in the company's base case model**	**ERG calibrated values[a] (Exploratory analysis 2c)**	**St Mark's retrospective data (Exploratory analysis 2d)**
CSF severe	Defunctioning surgery	0.0375	0.2929	0.1975
CSF severe	Proctectomy	0.0385	0.0797	0.1555
Defunctioning surgery	Proctectomy	0.0385	0.0797	0.1706

ERG –evidence review group; CSF – chronic symptomatic fistulae
a – these values are from the calibration of the company's model to both the proctectomy and defunctioning surgery data. These values depend upon the health state occupancy of the CSF severe and defunctioning surgery health states, so the calibration used to calculate these values may produce slightly different results when other exploratory analyses are also implemented.

Exploratory analysis 3: Long-term remission rate for salvage therapy

The ERG had concerns that the long term rate used to extrapolate the company's curves had a treatment effect applied between the darvadstrocel and standard care groups but did not have a treatment effect applied between the standard care and salvage therapy groups (see Section **Error! Reference source not found.**). This resulted in the long term extrapolation rates being the same for the standard care and salvage therapy groups, whilst the rates differed for the darvadstrocel group. In this sensitivity analysis the ERG amended the long term rates so that the long term rates were based on the salvage therapy time to event functions and not on the standard care time to event functions.

Exploratory analysis 4: Setting the model time-horizon to 60 years

As the ERG believes that a longer-term (60 year) time-horizon is more appropriate than the shorter term time horizon applied in the company's base case (40 years). This analysis by the ERG replicates the company's analysis of the model time horizon presented in **Error! Reference source not found.**.

The ERG's preferred base case model

The ERG's preferred base case model combines ERG analyses 1, 2c, 3 and 4. Unless otherwise stated, all subsequent analyses start from the ERG preferred base case analysis and include discounting of 3.5% for both costs and QALYs.

Exploratory analysis 5: Exploration of the extent to which darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

The ERG has concerns about whether darvadstrocel meets two of the criteria set out in the NICE Methods Guide for the Committee to consider using discount rates of 1.5%. These are that over a long period of time (usually 30 years): (1) currently people will die or have a very severely impaired quality of life; and (2) the treatment restores these people to full or near full health.

Exploratory analysis 5: Analysis of the extent that darvadstrocel restores people with complex perianal fistulae and Crohn's disease to near full health

Table 7 shows that in the ERG's preferred model over a 30-year time horizon; patients in both treatment groups accrue 28.82 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

The equivalent values using the company's base case model show that over a 30-year time horizon; patients in both treatment groups accrue 28.76 life years; patients in the standard care group accrue [redacted] undiscounted QALYs, and; patients in the darvadstrocel group accrue [redacted] undiscounted QALYs. This results in darvadstrocel accruing an average utility of [redacted] per year and standard care accruing an average utility of [redacted] per year. These two values correspond to [redacted] and [redacted] of the utility value for the remission health state, respectively.

Table 7: Assessment of the proportion of health achieved in each model arm using the company's and the ERG's base case model over a 30-year time horizon and a 0% discount rate

Treatment	Undiscounted life years	Undiscounted QALYs	Mean utility accrued per year	Highest health state utility value	Percentage of maximum health achieved
Company's base case model					
Standard Care	28.76	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.76	[redacted]	[redacted]	0.865	[redacted]
ERG's base case model					
Standard Care	28.82	[redacted]	[redacted]	0.865	[redacted]
Darvadstrocel	28.82	[redacted]	[redacted]	0.865	[redacted]

QALYs – quality-adjusted life years

On the basis of these results the ERG believes that: (1) the average patient with complex perianal fistulae and Crohn's disease does not have a very severely impaired quality of life when treated with standard care and (2) that darvadstrocel does not restore the average patient with complex perianal fistulae and Crohn's disease to full or near full health. As such, the ERG considers that darvadstrocel does not meet the criteria described in Section 6.2.19 of the guide to the NICE Methods Guide.[10] Consequently, the ERG believes that costs and QALYs should be discounted at a rate of 3.5% for both costs and QALYs.

Exploratory analysis 2

1) For all parts of exploratory analysis 2, enable the solver add in to Excel, if you have not already done so.

2a) Proctectomy

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E128, change the formula to "='Patient flow-Control'!$E$2"
3) Go to Sheet "Clinical inputs" cell E127, change the formula to "='Patient flow-Control'!$E$2"
4) Go to Sheet "Clinical inputs" cell E125, change the formula to "='Patient flow-Control'!$E$2"
5) Go to the sheet Patient flow-Control'
6) Open solver and use the following settings:
    a. Set objective HL$84
    b. To: value of 0.2068965517 (18/87 to 10 dp)
    c. By changing variable cells: $E$2
    d. No constraints
    e. Solving method: GRG Nonlinear

2b) Defunctioning

1) Start with the Company's model
2) Go to Sheet "Clinical inputs" cell E111, change the formula to ='Patient flow-Control'!$F$2
3) Go to Sheet "Clinical inputs" cell E113, change the formula to ='Patient flow-Control'!$F$2
4) Go to Sheet "Patient flow-Control"
5) Go to cell G2 and input the following formula "=HK214"
6) Go to cell H2 and input the following formula: "=-(LN(1-G2))/16"
7) Go to cell I2 and input the following formula "=1-EXP(-H2*1)"
8) Set up solver with the following settings
    a. Set objective I2
    b. To: value of 0.03752771 (value given elsewhere in the model for the annual probability of undergoing a defunctioning surgery)
    c. By changing variable cells: $F$2
    d. Constraints: $F$2 ≤ 1
    e. Solving method: GRG Nonlinear

2c)

1) Start with the Company's model
2) Do steps 2 to 4 of exploratory analysis 2a
3) Do steps 2 to 7 of exploratory analysis 2b