

TOAST ONLINE APPENDIX

Table A1- Trial Resource Use Costs

TOAST TRIAL UNIT COSTS (2015 £)				
Cost ID	Cost Description	2015 (£)	Measure	Details
Int1	Oral Steroid	£ 5.04	1 dose	single 10mg dose of oral dexamethasone, BNF 2015
Int2	GP Visit	£ 44.00	11.7 minute consult	PSSRU 2015
Int3	Pharmacist	£ 6.00	5 minute consult	British National Formulary (BNF) 2015
Anti1	Penicillin	£ 0.04	per 250mg tab	BNF 2015
Anti2	Erythromycin	£ 0.04	per 250mg tab	BNF 2015
Anti3	Clarithromycin	£ 0.21	per 500mg tab	BNF 2015
Anti4	Amoxicillin	£ 0.08	per 500mg tab	BNF 2015
Anti5	Coamoxiclav	£ 0.20	per 500mg tab	BNF 2015
Anti6	Doxycycline	£ 0.14	per 500mg tab	BNF 2015
Otc1	Paracetamol	£ 0.24	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc2	Ibuprofen (NSAIDs)	£ 0.60	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc3	Anaesthetic spray	£ 1.25	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc4	Anaesthetic lozenges	£ 1.40	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc5	Decongestant	£ 1.00	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc6	Lozenges (non-analgesic)	£ 0.66	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Otc7	Other analgesia (cocodamol/ cough medicine, etc.)	£ 1.05	per recommended daily dose	Boots Pharmacy Generic Brand, 2015
Wage1	Cost of an adult working day	£ 119.37	median gross annual earnings	Office of National Statistics (UK)
Wage2	Minimum wage day rate	£ 53.60	October 2015 value	Office of National Statistics (UK)
Admin1	NHS prescription charge	£ 8.20		National Health Service (UK)-(NHS)
Res1	GP Nurse	£ 14.47	15.5 minute consult	PSSRU 2015
Res2	GP Telephone Call	£ 27.00	7.1 minute call	PSSRU 2015
Res3	Out-of-Hours GP Clinic	£ 69.53		NAO.org
Res4	111 Telephone Advice	£ 8.14		Micro-costing study, University of Sheffield
Res5	A&E	£ 140.59	Average weighted cost	NHS Ref Costs 2015
Res6	Hospital Bed Day – average	£ 613.63	Average weighted cost	NHS Ref Costs 2015
Pres1	Codeine (co-codamol 30/500)	£ 0.06	per tablet	BNF 2015
Pres2	Codeine Linctus	£ 0.16	15mg/ 5 ml	BNF 2015
Pres3	Benzydamine (Diffiam Oromucosal Spray)	£ 1.41	0.15% Spray/ 1 ml	BNF 2015
Pres4	Benzyl Penicillin & Metronidazole IV	£ 12.24	Daily dose (TBC)	BNF 2015

Table A2- Summary of Economic Analysis Scenarios

Options	Perspective	Details
Basecase	HSP	The basecase scenario included the net cost of the intervention i.e. the cost of the once-off medication, the cost of antibiotics used and the cost of resource use reported including serious adverse events. The adjusted QALY estimate was adopted as the outcome measure.
A	HSP	Basecase was adjusted to remove effects and costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
B	HSP	Basecase was adjusted to remove those over age 70 (seven in each arm removed) (n=551).
C	HSP	Basecase was restricted to only those who received a delayed prescription (n=223).
D	HSP	Basecase was restricted to those who did not receive a delayed prescription (n=342).
E	HSP	Basecase was restricted to only those reporting current smoker status (n=103).
F	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 24 hours were used as the outcome measure.
G	HSP	Basecase was adjusted and the imputed EQ-5D-5L differences from baseline at 48 hours were used as the outcome measure.
H	HSP	Basecase was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.
I	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 1 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 1 to 7.
J	SCP	Basecase was combined with costs associated with over-the-counter medications used , productivity losses due to missed days at work/ school for days 0 to 7 of the trial follow-up and costs associated with inability to carry out usual activities for days 0 to 7.
K	SCP	Option I was adjusted to remove costs of serious adverse events (one in each arm) and adverse events (one in the control group) (n=562).
L	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers/ students.
M	SCP	Option I was combined with antibiotic prescription charges that would be paid by workers only.
N	SCP	Option I was restricted to only those who received a delayed prescription (n=223).
O	SCP	Option I was restricted to those who did not receive a delayed prescription (n=342).
P	SCP	Option I was restricted to only those reporting current smoker status (n=103).
Q	SCP	Option I adopted the outcome measured at 24 hours
R	SCP	Option I adopted the outcome measured at 48 hours
S	SCP	Option I was adjusted and the imputed EQ-VAS averages from baseline to Day 7 were used as the outcome measure.

Table A3: Summary of multiple imputation analysis methods

The following variables were used in the multiple imputation dataset:

- EQ-5D-5L index values for day 0-7
- EQ-VAS scores for day 0-7
- Symptom resolution at 24 hours and 48 hours
- A treatment arm identifier
- A dichotomous variable to highlight patient experienced an SAE
- A dichotomous variable for delayed antibiotic prescription given
- Costs: intervention, antibiotics, OTC medication, resource use day 1-7, resource use day 8-28, missed work/ education, missed usual activities
- Patient characteristics: gender, age, employment status, location of care, current smoker, a dichotomous variable for those aged 71 and over.

The 'ICE' command in STATA was used for multiple imputation using chained equations was used. The data was multiply imputed generating 60 datasets using predictive mean matching and separately by treatment allocation based on the variation present in the complete data above. The 'seed' add-on sets a random number seed (this was set at 10), which is useful to improve consistency across imputations.

The following is the STATA code used:

```
"ice index_5L_day0 index_5L_day1 index_5L_day2 index_5L_day3 index_5L_day4 index_5L_day5  
index_5L_day6 index_5L_day7 VAS_day0 VAS_day1 VAS_day2 VAS_day3 VAS_day4 VAS_day5 VAS_day6  
VAS_day7 sae outlier resol48 cost_reportedantibiose totalcost_OTC resourceusediary_cost  
resourceuseFU_cost missed_days_costday1tounk cost_usualact1tounk trt delayed_script Male worker age  
current_smoker location age71andover, saving(MI_aggregated, replace) m(60) match genmiss(indmiss)  
by(trt) seed(10)"
```

Table A4: Quality of Life Analysis for ITT Impute Cohort (unadjusted)

EQ-5D-5L Imputed Full ITT				
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	0.746	0.766	0.0196	2.62%
Day 1	0.829	0.848	0.0189	2.28%
Day 2	0.861	0.871	0.0092	1.07%
Day 3	0.904	0.907	0.0023	0.25%
Day 4	0.918	0.931	0.0132	1.43%
Day 5	0.932	0.940	0.0074	0.79%
Day 6	0.939	0.950	0.0112	1.19%
Day 7	0.947	0.949	0.0028	0.30%
QAW¹	6.289	6.354	0.0652	1.04%
EQ-5D VAS Imputed Full ITT				
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	49.78	52.41	2.631	5.29%
Day 1	57.99	60.83	2.840	4.90%
Day 2	64.44	64.57	0.126	0.19%
Day 3	70.98	70.27	-0.714	-1.01%
Day 4	74.74	74.35	-0.389	-0.52%
Day 5	78.66	77.16	-1.497	-1.90%
Day 6	81.99	80.25	-1.733	-2.11%
Day 7	84.94	82.37	-2.571	-3.03%
aVAS²	70.44	70.27	-0.162	-0.23%
Delayed Prescription- Imputed ITT Cohort				
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	0.7431	0.7303	-0.0128	-1.72%
Day 1	0.8158	0.8404	0.0246	3.01%
Day 2	0.8384	0.8576	0.0193	2.30%
Day 3	0.9061	0.9180	0.0119	1.31%
Day 4	0.9180	0.9441	0.0261	2.85%
Day 5	0.9276	0.9579	0.0303	3.27%
Day 6	0.9390	0.9649	0.0259	2.76%
Day 7	0.9480	0.9663	0.0183	1.93%
QAW¹	6.2569	6.3943	0.1374	2.20%
No Delayed Prescription- Imputed ITT Cohort				
	Control	Intervention	Diff (I-C)	% Δ (I-C)
Baseline	0.7480	0.7892	0.0411	5.50%
Day 1	0.8381	0.8535	0.0154	1.84%
Day 2	0.8762	0.8793	0.0031	0.35%
Day 3	0.9035	0.8993	-0.0041	-0.46%
Day 4	0.9179	0.9225	0.0046	0.50%
Day 5	0.9351	0.9273	-0.0078	-0.83%
Day 6	0.9382	0.9396	0.0014	0.14%
Day 7	0.9457	0.9382	-0.0075	-0.79%
QAW¹	6.3099	6.3281	0.0182	0.29%

1. Quality-adjusted week estimated using area under the curve estimation.

2. Average VAS score estimated average across baseline to day 7.

Table A5: Quality of Life Analysis for Complete Cases (unadjusted)

EQ-5D-5L Analysis				
	Control	Intervention	Difference (I-C)	P value
	n=172	n=165		
Baseline	0.735	0.755	0.021	ns
Day 1	0.821	0.843	0.021	ns
Day 2	0.862	0.871	0.01	ns
Day 3	0.899	0.903	0.004	ns
Day 4	0.916	0.926	0.01	ns
Day 5	0.929	0.933	0.003	ns
Day 6	0.939	0.947	0.007	ns
Day 7	0.947	0.951	0.004	ns
Average (Day 1-7)	0.902	0.91	0.008	ns
Average Δ (%) from Baseline	0.167 (22.7)	0.155 (20.5)	-0.012	ns
Average Δ (%) from Baseline at 24 hrs	0.087 (11.8)	0.087 (11.5)	0	ns
Average Δ (%) from Baseline at 48 hrs	0.107 (14.6)	0.101 (13.4)	-0.005	ns

EQ-VAS Analysis				
	Control	Intervention	Difference (I-C)	P value
	n=166	n=161		
Baseline	49	52	3	ns
Day 1	57	61	4	ns
Day 2	64	65	1	ns
Day 3	70	70	0	ns
Day 4	75	74	-1	ns
Day 5	79	77	-2	ns
Day 6	82	80	-2	ns
Day 7	86	83	-3	ns
Average (Day 1-7)	73	73	0	ns
Average Δ (%) from Baseline	24 (49)	21 (40)	-3	ns
Average Δ (%) from Baseline at 24 hrs	8 (16)	9 (17)	1	ns
Average Δ (%) from Baseline at 48 hrs	15 (31)	13 (25)	-2	ns

EQ-5D-5L Sub-group Analysis				
	Delayed Script	No Delayed Script	Difference (Delayed-No Script)	P value
	n=121	n=216		
Baseline	0.709	0.765	-0.055	0.005
Day 1	0.813	0.842	-0.029	0.059
Day 2	0.878	0.846	-0.032	0.041
Day 3	0.903	0.9	0.003	ns
Day 4	0.925	0.919	0.006	ns
Day 5	0.935	0.929	0.006	ns
Day 6	0.948	0.94	0.008	ns
Day 7	0.959	0.943	0.016	ns
Average (Day 1-7)	0.904	0.907	-0.003	
Average Δ (%) from Baseline	0.195 (27.5)	0.143 (18.7)	0.052	0.001
Average Δ (%) from Baseline at 24 hrs	0.119 (20.7)	0.092 (14.1)	0.027	ns
Average Δ (%) from Baseline at 48 hrs	0.180 (31.3)	0.151 (23.3)	0.029	ns

Figure A1: Missingness assessment in EQ-5D-5L

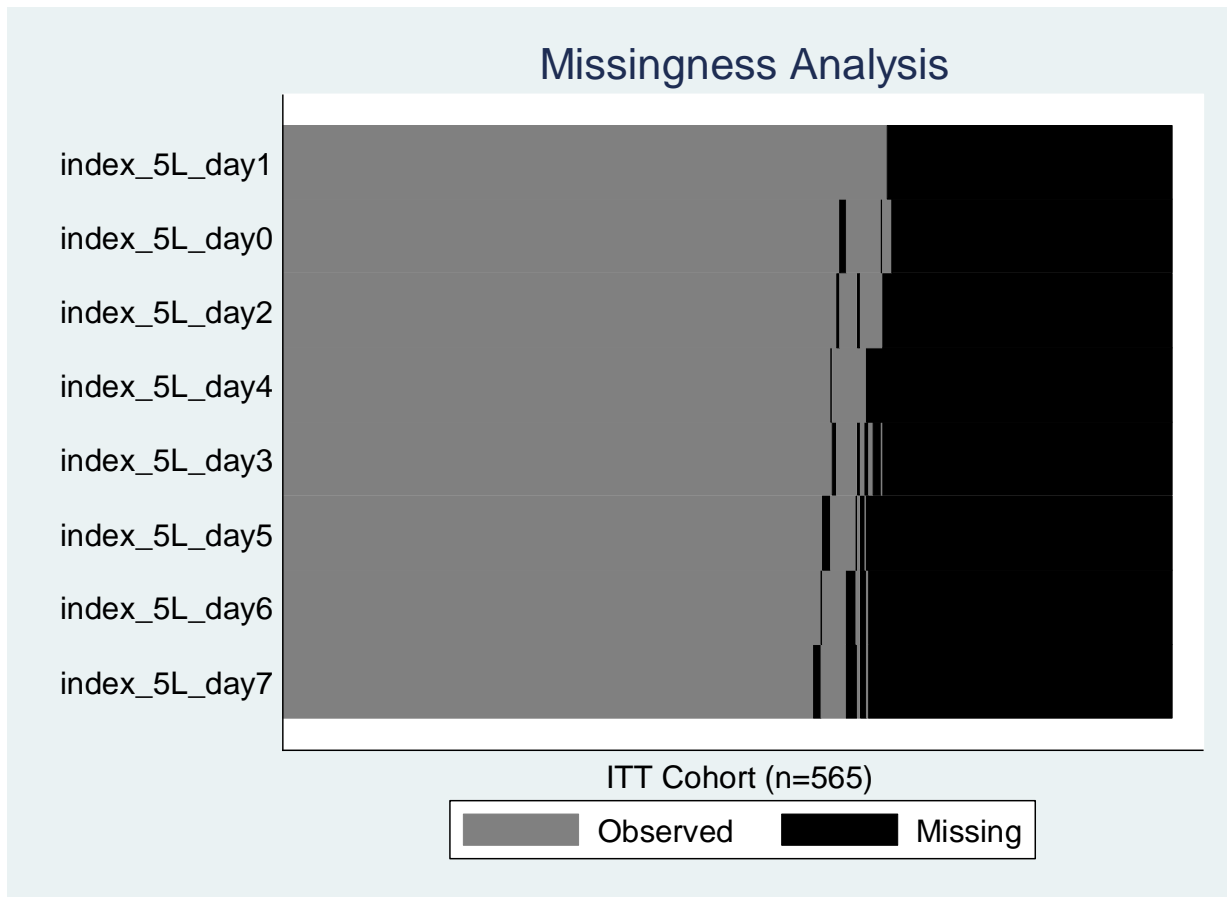


Figure A2: QALY distribution by treatment arm

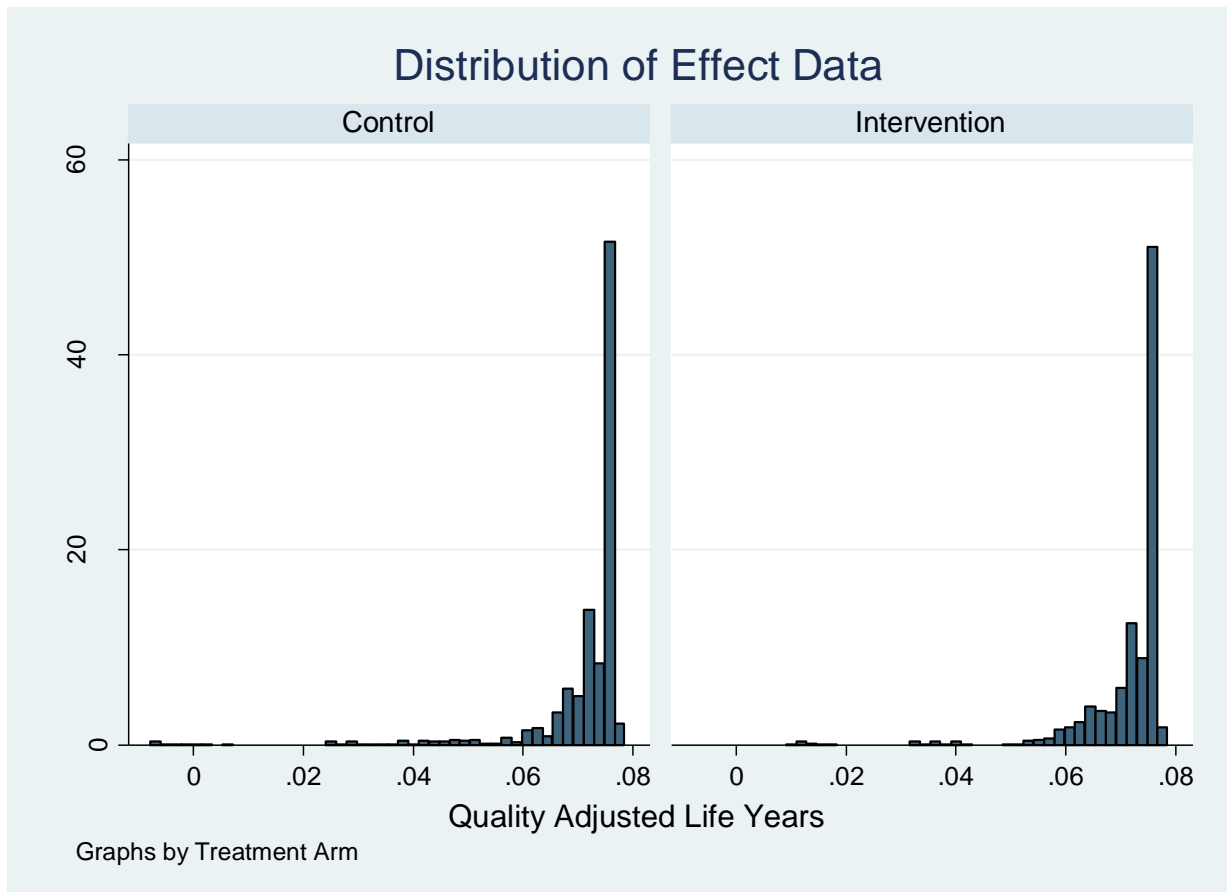


Figure A3: EQ-5D-5L Imputed Scores for ITT Cohort

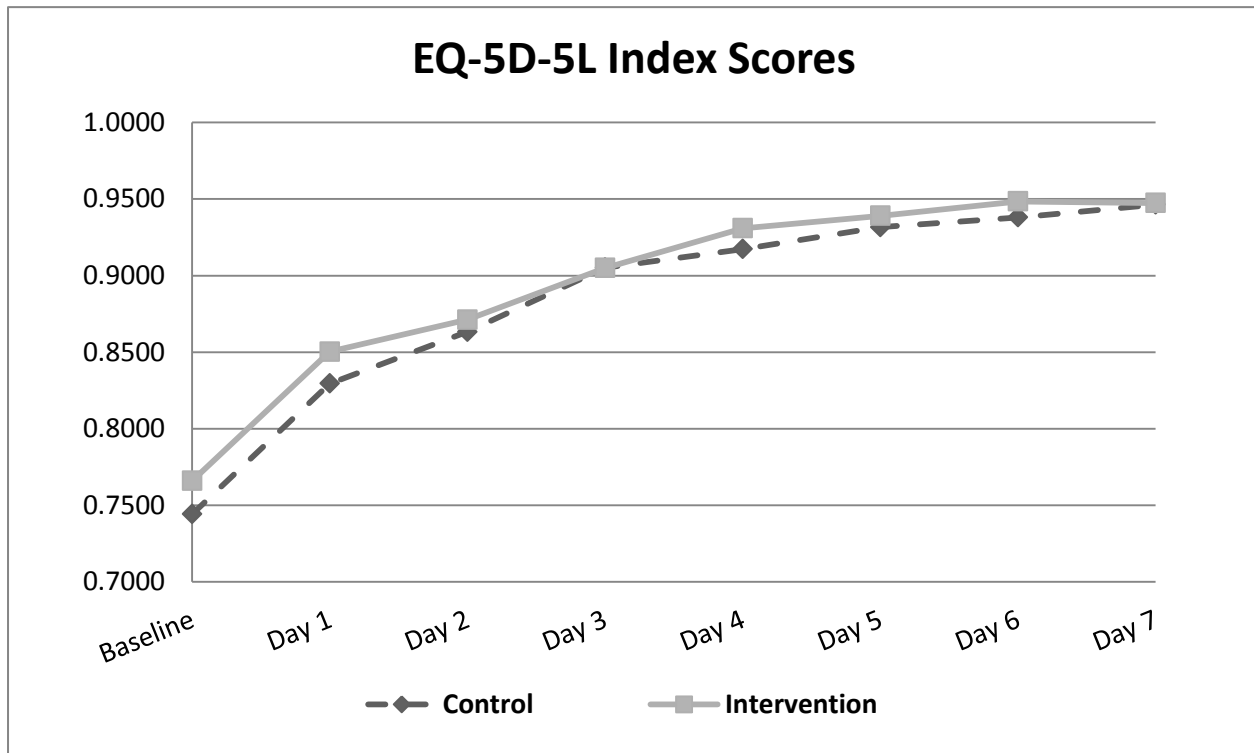


Figure A4: EQ-5D Visual Analogue Scale Imputed Scores for ITT Cohort

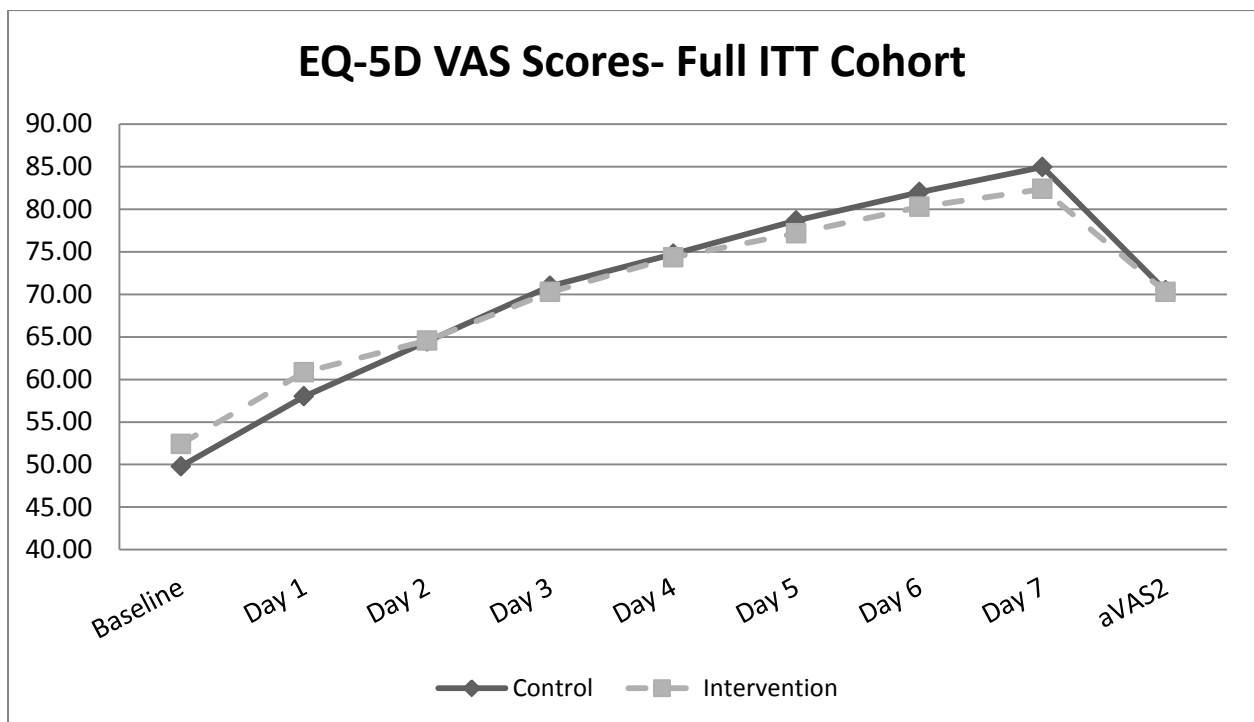


Figure A5: Cost-effectiveness Acceptability Curve

