

Online Resource 3: Model Inputs and Costs

A Cost-utility Analysis of Add-on Cannabidiol Versus Usual Care Alone for the Treatment of Seizures Associated With Tuberous Sclerosis Complex in England and Wales

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Declarations

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Conflicts of interest

All authors met the ICMJE authorship criteria and had full access to the relevant data. Neither honoraria nor payments were made for authorship. Colin Burke and Emma Tyas are employees of Lumanity, Inc.; Catriona Crossan, Matthew Hemstock, and Dawn Lee were employees of Lumanity, Inc., when the study was conducted and are currently employed by Putnam, Source Health Economics, and the University of Exeter, respectively. Sally Bowditch is an employee of Jazz Pharmaceuticals, Inc., and holds stock / stock options in Jazz Pharmaceuticals, Inc.

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Online Resource Table 5 Unit costs of drugs

ASM	Formulation	Pack size	Cost per pack (£)	Dose per pack	Cost per mg (£)	Prescription cost analysis quantity (2018)	Prescription share (%)	Average cost per mg (£)
Cannabidiol (list price) ^a	Oral solution	100 mL	850.29	100 mg/mL	0.0850	N/A	N/A	0.0850
Carbamazepine[1]	Tablet	84	2.07	100 mg	0.0002	36,311,425	42.78	0.0002
	Tablet	84	3.83	200 mg	0.0002	39,076,804	46.03	
	Tablet	56	5.02	400 mg	0.0002	9,497,449	11.19	
Clobazam[2]	Tablet	30	4.94	10 mg	0.0165	300,781	100.00	0.0165
Everolimus[3]	Dispersible tablet	30	960.00	2 mg	16.00	N/A	33.33	15.67
	Dispersible tablet	30	1440.00	3 mg	16.00		33.33	
	Dispersible tablet	30	2250.00	5 mg	15.00		33.33	
Lacosamide[4]	Tablet	14	10.81	50 mg	0.0154	2,515,572	34.34	0.0149
	Tablet	14	21.62	100 mg	0.0154	1,213,123	16.56	
	Tablet	56	86.50	100 mg	0.0154	1,213,123	16.56	
	Tablet	14	32.44	150 mg	0.0154	362,426	4.95	
	Tablet	56	129.74	150 mg	0.0154	362,426	4.95	
	Tablet	56	144.16	200 mg	0.0129	1,659,685	22.65	
Lamotrigine[5]	Tablet	56	23.53	25 mg	0.0168	32,622,603	25.99	0.0142
	Tablet	56	40.02	50 mg	0.0143	42,274,945	33.68	
	Tablet	56	69.04	100 mg	0.0123	50,572,588	40.30	
	Tablet	56	117.35	200 mg	0.0105	32,514	0.03	
Levetiracetam[6]	Tablet	60	2.16	250 mg	0.0001	38,855,011	21.95	0.0004
	Tablet	60	3.74	500 mg	0.0001	56,275,106	31.79	
	Tablet	60	4.60	750 mg	0.0001	10,698,589	6.04	
	Granule sachet	60	7.90	500 mg	0.0003	363,156	0.21	

ASM	Formulation	Pack size	Cost per pack (£)	Dose per pack	Cost per mg (£)	Prescription cost analysis quantity (2018)	Prescription share (%)	Average cost per mg (£)
	Solution for infusion	10 x 5 mL	18.36	500 mg/ 5 mL	0.0037	7621	0.00	
	Oral solution	1 x 150 mL	15.69	500 mg/ 5 mL	0.0010	57,615,150	32.54	
	Oral solution	1 x 300 mL	6.05	500 mg/ 5 mL	0.0002	13,224,600	7.47	
Oxcarbazepine[7]	Tablet	50	8.37	150 mg	0.0011	2,070,563	28.90	0.0009
	Tablet	50	8.04	300 mg	0.0005	3,656,975	51.04	
	Tablet	50	38.71	600 mg	0.0013	1,437,088	20.06	
Sodium valproate[6]	Gastro-resistant tablet	30	5.12	250 mg	0.0007	12,391,402	44.42	0.0007
	Gastro-resistant tablet	30	9.78	500 mg	0.0007	14,749,135	52.88	
	Gastro-resistant tablet	100	11.02	500 mg	0.0002	752,882	2.70	
Topiramate[6]	Tablet	60	1.79	25 mg	0.0012	23,435,960	44.23	0.0010
	Tablet	60	3.31	50 mg	0.0011	16,790,688	31.69	
	Tablet	60	3.01	100 mg	0.0005	10,751,252	20.29	
	Tablet	60	12.37	200 mg	0.0010	2,007,539	3.79	
Vigabatrin[8]	Tablet	100	44.41	500 mg	0.0009	686,516	44.47	0.0009
	Granules for oral solution	50	24.60	500 mg	0.0010	857,152	55.53	
Zonisamide[9]	Capsule[6]	56	10.44	100 mg	0.0019	6,149,006	59.91	0.0053
	Capsule[6]	14	0.85	25 mg	0.0024	1,452,045	14.15	
	Capsule[9]	56	41.97	50 mg	0.0150	2,662,284	25.94	

ASM, antiseizure medication; N/A, not available.

ASM costs were sourced from the Monthly Index of Medical Specialties and the electronic market information tool [6,10].

^aA confidential Patient Access Scheme price is used in the analysis.

Online Resource Table 6 ASM dosing (pediatric patients)

ASMs	Phase	Min age (years)	Weight/age	Minimum dose	Frequency	Maximum dose	Frequency	Dose used in the model	Frequency	Maximum dose
Cannabidiol[11]	Titration (Week 1)	2	N/A	5 mg/kg	Per day	25 mg/kg	Per day	5 mg/kg	Per day	N/A
	Titration (Week 2)	2	N/A	10 mg/kg	Per day	25 mg/kg	Per day	10 mg/kg	Per day	N/A
	Maintenance	2	N/A	10 mg/kg	Per day	25 mg/kg	Per day	12 mg/kg	Per day	N/A
Carbamazepine[12]	Maintenance	5	N/A	400 mg	Per day	600 mg	Per day	500 mg	Per day	N/A
	Maintenance	10	N/A	600 mg	Per day	1000 mg	Per day	800 mg	Per day	N/A
	Maintenance	15	N/A	800 mg	Per day	1200 mg	Per day	1000 mg	Per day	N/A
Clobazam[13]	Maintenance	6	N/A	0.3 mg/kg	Per day	1 mg/kg	Per day	0.65 mg/kg	Per day	N/A
Everolimus[14]	Titration (for 6 weeks)	2	<6 years	5 ng/mL	Per day	15 ng/mL	Per day	6 mg/m ²	Per day	N/A
	Maintenance ^a	2	<6 years	5 ng/mL	Per day	15 ng/mL	Per day	9 mg/m ²	Per day	N/A
	Titration (for 6 weeks)	2	≥6 years	5 ng/mL	Per day	15 ng/mL	Per day	5 mg/m ²	Per day	N/A
	Maintenance ^a	2	≥6 years	5 ng/mL	Per day	15 ng/mL	Per day	8 mg/m ²	Per day	N/A
Lacosamide[15]	Maintenance	4	<40 kg	4 mg/kg	Per day	12 mg/kg	Per day	8 mg/kg	Per day	N/A
	Maintenance	4	40–50 kg	4 mg/kg	Per day	10 mg/kg	Per day	7 mg/kg	Per day	N/A
Lamotrigine[16]	Maintenance	2	N/A	1 mg/kg	Per day	15 mg/kg	Per day	8 mg/kg	Per day	200 mg
Levetiracetam[17]	Maintenance	N/A	25–<50 kg	500 mg	Per day	1500 mg	Per day	1000 mg	Per day	N/A
			≥50 kg	1000 mg	Per day	3000 mg	Per day	1500 mg	Per day	N/A
Oxcarbazepine[18]	Maintenance	6	N/A	30 mg/kg	Per day	46 mg/kg	Per day	38 mg/kg	Per day	N/A

ASMs	Phase	Min age (years)	Weight/age	Minimum dose	Frequency	Maximum dose	Frequency	Dose used in the model	Frequency	Maximum dose
Topiramate[19]	Maintenance	2	N/A	N/A	N/A	N/A	N/A	100 mg	Per day	N/A
Valproic acid[20]	Maintenance	N/A	<20 kg	20 mg/kg	Per day	40 mg/kg/day	Per day	30 mg/kg	Per day	N/A
	Maintenance	N/A	>20 kg	20 mg/kg	Per day	35 mg/kg/day	Per day	27.5 mg/kg	Per day	N/A
Vigabatrin[21]	Maintenance	N/A	10–15 kg	500 mg	Per day	1000 mg	Per day	750 mg	Per day	N/A
	Maintenance	N/A	15–30 kg	1000 mg	Per day	1500 mg	Per day	1250 mg	Per day	N/A
	Maintenance	N/A	30–50 kg	1500 mg	Per day	3000 mg	Per day	2250 mg	Per day	N/A
	Maintenance	N/A	>50 kg	2000 mg	Per day	3000 mg	Per day	2500 mg	Per day	N/A
Zonisamide[22]	Maintenance	6	20–55 kg	6 mg/kg	Per day	8 mg/day	Per day	7 mg/kg	Per day	N/A
	Maintenance	6	>55 kg	300 mg	Per day	500 mg	Per day	400 mg	Per day	N/A

ASM, antiseizure medication; N/A, not available.

^aDoses are adjusted based on whole blood-trough concentrations assessed at least 1 week after treatment commencement within the range 5–15 ng/mL. Trough concentrations should be monitored every 3–6 months in patients with changing body surface area, or every 6–12 months in patients with stable body surface area, for the duration of treatment.

Online Resource Table 7 ASM dosing (adult patients)

ASMs	Phase	Recommended minimum dose (per day)	Recommended maximum dose (per day)	Dose used in the model (per day)
Cannabidiol[11]	Maintenance	10 mg/kg	25 mg/kg	12 mg/kg
Carbamazepine[12]	Maintenance	800 mg	2000 mg	1000 mg
Clobazam[13]	Maintenance	20 mg	60 mg	45 mg
Everolimus[14] ^a	Titration (for 6 weeks)	5 ng/mL	15 ng/mL	5 mg/m ²
	Maintenance	5 ng/mL	15 ng/mL	8 mg/m ²
Lacosamide[15]	Maintenance	100 mg	600 mg	150 mg
Lamotrigine[16]	Maintenance	100 mg	200 mg	150 mg
Levetiracetam[17]	Maintenance	1000 mg	3000 mg	2000 mg
Oxcarbazepine[18]	Maintenance	600 mg	2400 mg	1500 mg
Topiramate[19]	Maintenance	100 mg	500 mg	150 mg
Valproic acid[20]	Maintenance	1000 mg	2500 mg	1500 mg
Vigabatrin[21]	Maintenance	1000 mg	3000 mg	2000 mg
Zonisamide[22]	Maintenance	300 mg	500 mg	400 mg

ASM, antiseizure medication.

^aDoses are adjusted based on whole blood-trough concentrations assessed at least 1 week after treatment commencement within the range 5–15 ng/mL. Trough concentrations should be monitored every 3–6 months in patients with changing body surface area, or every 6–12 months in patients with stable body surface area, for the duration of treatment.

Online Resource Table 8 Healthcare resource use costs

Resource use		Unit costs (£)		Assumption	Source
Categories	Items	Pediatric	Adult		
Primary care	GP visit	39.00	39.00	GP visit (with qualifications): 10.3b general practitioner – page 111 – 9.22 minutes	PSSRU 2021[23]
Outpatient specialists	Physician visit (either neurologist/neurosurgeon or pediatric neurologist)	382.16	206.34	Outpatient attendances data 1) service code: 421 – pediatric neurology total cost; 2) service code: 400 – neurology total cost	NHS reference costs 2020–2021[24]
	Pediatrician visit	224.00	N/A	Services for children and their families: 6.1 NHS reference costs for children’s health services – pediatric consultant-led outpatient attendances – page 67	PSSRU 2021[23]
	Psychiatry or mental health service visit	361.19	266.77	Total outpatient attendances 1) 711 child and adolescent psychiatry; 2) 722 liaison psychiatry	NHS reference costs 2020–2021[24]
	Physiotherapy outpatient visit	114.00	53.00	1) 6.1 NHS reference costs for children’s health services: average cost per group session (1-to-1): physiotherapy or speech therapy services – page 67; 2) 12. Hospital-based scientific and professional staff: physiotherapy specialist or speech and language therapist specialist Band 6 – page 135	PSSRU 2021[23]
	Speech and language outpatient visit	114.00	53.00		
	Occupational therapy visit	160.00	53.00	1) 6.1 NHS reference costs for children’s health services: average cost per group session (1-to-1): occupational therapy – page 67; 2) Occupational therapist visit: 12. Hospital-based scientific and professional staff: occupational therapy specialist – Band 6 – page 135	
	Epilepsy nurse visit (hospital based [cost per hour])	51.00	51.00	Epilepsy nurse (hospital) visit: 13. Hospital-based nurses – Band 6 (nurse specialist/team leader) – page 138	

Resource use Categories	Items	Unit costs (£)		Assumption	Source
		Pediatric	Adult		
	Epilepsy nurse (phone calls)	75.00	75.00	10.5 Telephone triage – GP led and nurse led: cost per hour of face-to-face contact excluding other costs (including setup costs) – page 114	
Hospitalization ^a	A&E hospital admissions	235.48	235.48	Emergency medicine admitted – code [T01A > T04A] [VB01Z < > VB09Z]	NHS reference costs 2020–2021[24]
	Hospital admissions (cost per day)	1775.54	643.99	1) Non-elective long stay – cost per day: 1) code [PR02A/PR02B/PR02C] pediatric epilepsy syndrome with CC [score 0–6+]; 2) Non-elective long stay – cost per day: code [AA26C < > AA26H]; muscular. Balance. Cranial or peripheral nerve disorders. Epilepsy or head injury. With CC [score 0–2 < > Score 15+]	Length of stay data sourced from NHS reference costs 2017/2018[25]
	ICU admissions	3548.44	2254.87	Critical care: 1) CCU4 pediatric – code [XB01Z < > XB09Z]; 2) CCU05 neurosciences adult patients predominate – code [XC01Z < > XC07Z]	
Other frequently used or costly healthcare resource	MRI scan	195.18	195.18	Imaging: direct access – code [RD03Z < > RD07Z]	NHS reference costs 2020–2021[24]
Rescue medication	Rescue medication (buccal midazolam per event)	22.17	22.88	Buccolam 2.5 mg oromucosal solution	MIMS[26]
Institutionalization ^b	Residential care (per week)	N/A	1687.00	Residential care homes for adults requiring learning disability support (age 18–64 years): mean cost of £1687 per week – page 52	PSSRU 2021[23]
Additional support ^c	Educational support (per year)	475.14	N/A	The average annual cost to a council of a special needs placement in 2017/18 was £23,000 per pupil per year in a maintained special school. Inflated to 2021 values	Local Government Association 2020[27]
	Day care support (per week)	N/A	345.60	Home care worker: 4.1 Local authority own-provision day care for adults requiring learning disability support (age 18–64 years). £72 per	PSSRU 2021[23]

Resource use		Unit costs (£)		Assumption	Source
Categories	Items	Pediatric	Adult		
				client visit, assumed 4.8 visits per week – page 50	
	Additional homecare support (per hour)	25.00	25.00	Home care worker: 11.5 Home care worker – £25 per hour weekday – page 126	

A&E, Accident & Emergency; CC, clinical coding; GP, general practitioner; ICU, intensive care unit; MIMS, Monthly Index of Medical Specialties; MRI, magnetic resonance imaging; N/A, not applicable; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

^aThe Delphi panel discussed hospital admission data by frequency per year and the average length of stay [28,29]. 1) Refers to source/assumption for pediatric patients. 2) Refers to sources/assumptions for adult patients. To account for the average length of stay data, a cost per hospital admission day was applied in the model. Length of stay data are unavailable from NHS reference costs 2020–2021. Therefore, length of stay information from NHS reference costs 2017–2018 was used. ^bSocial and residential care costs apply to adults only, based on feedback from the Delphi panel study. ^cChildren who attend a school or a specialist school would alternatively receive educational support.

Online Resource Table 9 Summary of variables applied in the economic model

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Model setting						
Seizure type modeled		Generalized and focal with impairment of awareness seizures		Not tested		
Discount rate costs		3.5%		Not tested		
Discount rate QALYs		3.5%		Not tested		
Patient characteristics[30]						
Mean age, years	Age group (2–6 years)	4.46	1.36	Normal	1.79	7.13
	Age group (7–11 years)	9.37	1.51	Normal	6.41	12.33
	Age group (12–17 years)	14.90	1.66	Normal	11.65	18.15
	Age group (18+ years)	28.10	9.65	Normal	9.19	47.01
Baseline seizures mean pw		17.86	1.45	Normal	15.02	20.71
Baseline seizures variance pw		21.84	2.52	Normal	16.90	26.79
Efficacy[31]						
Seizure-free days						
Intercept		−0.922		Multivariate normal	−1.385	−0.458
Treatment (0 = CBD 25 mg/kg + UC, 1 = PBO + UC)		−0.518			−0.537	−0.500
log_cycle		0.536			0.390	0.681
Scaled baseline seizure frequency		−2.803			−3.466	−2.140
Treatment PBO + UC: log_cycle		−0.241			−0.229	−0.253
Seizure frequency						
Intercept		0.866		Multivariate normal	0.765	0.966
Treatment (0 = CBD 25 mg/kg + UC, 1 = PBO + UC)		−0.011			−0.007	−0.014
log_cycle		−0.062			−0.082	−0.042
Scaled baseline seizure frequency		0.494			0.452	0.535
Treatment PBO + UC: log_cycle		0.052			0.054	0.050
Mortality (per week)						
TSC-related excess mortality rate per week[32]		0.014%	0.021%	Gamma	0.000%	0.073%

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
SUDEP-related mortality rate per week[33]		0.003%	0.034%	Gamma	0.000%	0.015%
Treatment discontinuation (per week)[31]						
CBD						
Clinical trial period (up to Week 16)	Seizure free pw	0.67%	0.07%	Normal	0.54%	0.80%
	≤2 seizures pw	0.67%	0.07%	Normal	0.54%	0.80%
	>2–≤7 seizures pw	0.67%	0.07%	Normal	0.54%	0.80%
	>7 seizures pw	0.67%	0.07%	Normal	0.54%	0.80%
OLE trial period (up to Week 88)	Seizure free pw	0.04%	0.00%	Normal	0.03%	0.05%
	≤2 seizures pw	0.14%	0.01%	Normal	0.11%	0.16%
	>2–≤7 seizures pw	0.29%	0.03%	Normal	0.23%	0.34%
	>7 seizures pw	0.44%	0.04%	Normal	0.36%	0.53%
Long-term period (from Week 89)	Seizure free pw	0.04%	0.00%	Normal	0.03%	0.05%
	≤2 seizures pw[34]	0.77%	0.08%	Normal	0.62%	0.92%
	>2–≤7 seizures pw[34]	0.77%	0.08%	Normal	0.62%	0.92%
	>7 seizures pw[34]	0.77%	0.08%	Normal	0.62%	0.92%
Stopping rule[31]						
1st period	Reference week (once)	26		Not tested		
	Seizure free pw	0.00%	0.00%	Beta	0.00%	0.00%
	≤2 seizures pw	11.11%	2.62%	Beta	6.52%	16.73%
	>2–≤7 seizures pw	50.00%	16.67%	Beta	18.41%	81.59%
	>7 seizures pw	52.94%	17.65%	Beta	18.90%	85.41%
Subsequent periods	Reference week (every)	26		Not tested		
	Seizure free pw	0.00%	0.00%	Beta	0.00%	0.00%
	≤2 seizures pw	5.56%	1.24%	Beta	3.38%	8.23%
	>2–≤7 seizures pw	9.92%	4.05%	Beta	3.51%	19.14%
	>7 seizures pw	14.29%	5.40%	Beta	5.49%	26.36%
	Max (years)	2		Not tested		
TAND response rates (per week)[31]						
CBD						
Seizure free pw		100.00%	10.00%	Beta	0.00%	0.00%
≤2 seizures pw		77.78%	17.39%	Beta	35.79%	99.17%

Variable	Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
>2–≤7 seizures pw	43.75%	10.94%	Beta	23.18%	65.53%
>7 seizures pw	23.53%	5.71%	Beta	13.34%	35.57%
Usual care					
Seizure free pw	100.00%	10.00%	Beta	0.00%	0.00%
≤2 seizures pw	66.67%	16.67%	Beta	30.95%	93.53%
>2–≤7 seizures pw	45.45%	9.69%	Beta	26.97%	64.61%
>7 seizures pw	10.81%	1.78%	Beta	7.58%	14.53%
Utilities					
Patient utilities: vignette study [31]					
Seizure free[35]	0.73	0.07	Beta	0.57	0.85
Focal seizures 1 or 2	0.50	0.05	Beta	0.41	0.60
Focal seizures 3 or 4	0.28	0.03	Beta	0.23	0.34
Focal seizures 5 and 14	0.07	0.01	Beta	0.06	0.09
Generalized seizures 1	0.18	0.02	Beta	0.15	0.22
Generalized seizures 2	0.09	0.01	Beta	0.07	0.11
Generalized seizures 3 and 14	−0.11	0.01	Beta	−0.09	−0.14
Combined seizures 1 G and 1–4 F	0.12	0.01	Beta	0.10	0.15
Combined seizures 2 G and 1–4 F	0.03	0.00	Beta	0.02	0.03
Combined seizures 3–14 G and 1–2 F	−0.11	0.01	Beta	−0.09	−0.14
Combined seizures 3–14 G and 3–4 F	−0.17	0.02	Beta	−0.14	−0.21
Combined seizures 1 G and 5–14 F	0.06	0.01	Beta	0.05	0.07
Combined seizures 2 G and 5–14 F	−0.17	0.02	Beta	−0.14	−0.21
Combined seizures 3–14 G and 5–14 F	−0.23	0.02	Beta	−0.19	−0.28
Caregiver utilities: vignette study [31]					
Seizure free[35]	0.00	0.00	Beta	0.00	0.00
Focal seizures 1 or 2	−0.09	0.01	Beta	−0.07	−0.11
Focal seizures 3 or 4	−0.24	0.02	Beta	−0.20	−0.29
Focal seizures 5 and 14	−0.45	0.05	Beta	−0.36	−0.54
Generalized seizures 1	−0.34	0.03	Beta	−0.27	−0.40
Generalized seizures 2	−0.41	0.04	Beta	−0.33	−0.49
Generalized seizures 3 and 14	−0.56	0.06	Beta	−0.45	−0.67
Combined seizures 1 G and 1–4 F	−0.45	0.05	Beta	−0.37	−0.54
Combined seizures 2 G and 1–4 F	−0.45	0.05	Beta	−0.37	−0.54

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Combined seizures 3–14 G and 1–2 F		−0.56	0.06	Beta	−0.45	−0.67
Combined seizures 3–14 G and 3–4 F		−0.61	0.06	Beta	−0.49	−0.73
Combined seizures 1 G and 5–14 F		−0.43	0.04	Beta	−0.35	−0.52
Combined seizures 2 G and 5–14 F		−0.54	0.05	Beta	−0.43	−0.65
Combined seizures 3–14 G and 5–14 F		−0.66	0.07	Beta	−0.53	−0.78
Number of carers		1.80	0.18	Normal	1.45	2.15
Utilities adverse events		−0.06	0.01	Beta	−0.05	−0.07
Utilities TAND age group (2–6 years)		0.04	0.00	Beta	0.03	0.05
Utilities TAND age group (7–11 years)		0.10	0.01	Beta	0.08	0.12
Utilities TAND age group (12–17 years)		0.09	0.01	Beta	0.08	0.11
Utilities TAND age group (18+ years)		0.07	0.01	Beta	0.06	0.09
Costs (£)						
<i>Resource use cost – pediatrics</i>						
Primary care	GP visits[23]	39.00	3.90	Gamma	31.73	47.01
Outpatient	Physician visits[24]	382.16	38.22	Gamma	310.94	460.61
	Pediatrician[23]	224.00	22.40	Gamma	182.26	269.98
	Psychiatry or mental health service[24]	361.19	36.12	Gamma	293.88	435.34
	Physiotherapy[23]	114.00	11.40	Gamma	92.75	137.40
	Speech and language therapy[23]	114.00	11.40	Gamma	92.75	137.40
	Occupational therapy[23]	160.00	16.00	Gamma	130.18	192.85
	Epilepsy nurse[23]	51.00	5.10	Gamma	41.50	61.47
	Epilepsy nurse (phone calls)[23]	75.00	7.50	Gamma	61.02	90.40
Hospitalization	A&E hospital admissions[24]	235.48	23.55	Gamma	191.59	283.82
	Hospital admissions[24]	1775.54	177.55	Gamma	1444.65	2140.03
	ICU admissions[24]	3548.44	354.84	Gamma	2887.15	4276.90
Other	MRI scan[24]	195.18	19.52	Gamma	158.81	235.25
	Rescue medication[26]	22.17	2.22	Gamma	18.04	26.72

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Additional	Educational support[27]	475.14	47.51	Gamma	386.59	572.68
	Day care support[23]	N/A				
	Additional homecare support[23]	25.00	2.50	Gamma	20.34	30.13
Institutionalization	Residential care[23]	N/A				
Resource use cost – adult (£)						
Primary care	GP visits[23]	39.00	3.90	Gamma	31.73	47.01
Outpatient	Physician visits[24]	206.34	20.63	Gamma	167.89	248.70
	Psychiatry or mental health service[24]	266.77	26.68	Gamma	217.05	321.53
	Physiotherapy[23]	53.00	5.30	Gamma	43.12	63.88
	Speech and language therapy[23]	53.00	5.30	Gamma	43.12	63.88
	Occupational therapy[23]	53.00	5.30	Gamma	43.12	63.88
	Epilepsy nurse[23]	51.00	5.10	Gamma	41.50	61.47
	Epilepsy nurse (phone calls)[23]	75.00	7.50	Gamma	61.02	90.40
Hospitalization	A&E hospital admissions[24]	235.48	23.55	Gamma	191.59	283.82
	Hospital admissions[24]	643.99	64.40	Gamma	523.97	776.19
	ICU admissions[24]	2254.87	225.49	Gamma	1834.65	2717.77
Other	MRI scan[24]	195.18	19.52	Gamma	158.81	235.25
	Rescue medication[26]	22.88	2.29	Gamma	18.61	27.57
Additional	Educational support[27]	N/A				
	Day care support[23]	345.60	34.56	Gamma	281.19	416.55
	Additional homecare support[23]	25.00	2.50	Gamma	20.34	30.13
Institutionalization	Residential care[23]	1687.00	168.70	Gamma	1372.61	2033.32

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Resource use frequency – <i>pediatrics</i>[28]						
Primary care: GP visits (per year)	Seizure free pw	2.50	2.78	Normal	0.00	7.94
	≤2 seizures pw	5.25	4.37	Normal	0.00	13.81
	>2–≤7 seizures pw	6.69	6.15	Normal	0.00	18.73
	>7 seizures pw	8.44	7.32	Normal	0.00	22.78
Outpatient: physician visits (per year)	Seizure free pw	1.44	0.62	Normal	0.22	2.66
	≤2 seizures pw	3.06	1.52	Normal	0.08	6.05
	>2–≤7 seizures pw	4.25	1.67	Normal	0.98	7.52
	>7 seizures pw	5.00	1.51	Normal	2.04	7.96
Outpatient: pediatrician visits (per year)	Seizure free pw	1.42	0.45	Normal	0.54	2.30
	≤2 seizures pw	2.83	0.90	Normal	1.07	4.59
	>2–≤7 seizures pw	4.00	1.91	Normal	0.25	7.75
	>7 seizures pw	5.50	2.36	Normal	0.87	10.13
Outpatient: psychiatry or mental health service (per year)	Seizure free pw	0.44	0.73	Normal	0.00	1.87
	≤2 seizures pw	0.56	1.05	Normal	0.00	2.62
	>2–≤7 seizures pw	1.75	1.69	Normal	0.00	5.06
	>7 seizures pw	2.13	2.25	Normal	0.00	6.53
Outpatient: physiotherapy (per year)	Seizure free pw	0.69	0.88	Normal	0.00	2.42
	≤2 seizures pw	1.44	1.45	Normal	0.00	4.28
	>2–≤7 seizures pw	2.44	2.56	Normal	0.00	7.45
	>7 seizures pw	5.25	8.17	Normal	0.00	21.27
Outpatient: speech and language therapy (per year)	Seizure free pw	1.19	0.92	Normal	0.00	3.00
	≤2 seizures pw	2.13	1.55	Normal	0.00	5.17
	>2–≤7 seizures pw	2.75	1.75	Normal	0.00	6.18
	>7 seizures pw	3.75	2.76	Normal	0.00	9.17
Outpatient: occupational therapy (per year)	Seizure free pw	0.50	0.50	Normal	0.00	1.48
	≤2 seizures pw	1.17	0.69	Normal	0.00	2.51
	>2–≤7 seizures pw	3.00	1.41	Normal	0.23	5.77
	>7 seizures pw	5.17	3.02	Normal	0.00	11.09
Outpatient: epilepsy nurse (per year)	Seizure free pw	1.33	0.87	Normal	0.00	3.03
	≤2 seizures pw	2.89	1.05	Normal	0.82	4.95
	>2–≤7 seizures pw	4.56	1.88	Normal	0.87	8.24
	>7 seizures pw	7.67	3.54	Normal	0.74	14.60

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Outpatient: epilepsy nurse (phone calls) (per year)	Seizure free pw	2.33	0.94	Normal	0.49	4.18
	≤ 2 seizures pw	6.50	3.15	Normal	0.33	12.67
	$>2-\leq 7$ seizures pw	12.92	9.01	Normal	0.00	30.58
	>7 seizures pw	21.92	13.19	Normal	0.00	47.77
Hospitalization: A&E admissions (per year)	Seizure free pw	0.61	0.86	Normal	0.00	2.29
	≤ 2 seizures pw	1.83	1.70	Normal	0.00	5.16
	$>2-\leq 7$ seizures pw	3.33	2.82	Normal	0.00	8.86
	>7 seizures pw	6.25	3.16	Normal	0.05	12.45
Hospital other: hospital admissions per patient (per year)	Seizure free pw	0.34	0.52	Normal	0.00	1.68
	≤ 2 seizures pw	0.72	0.49	Normal	0.05	2.14
	$>2-\leq 7$ seizures pw	1.09	0.53	Normal	0.17	3.89
	>7 seizures pw	2.03	0.95	Normal	0.00	5.06
Hospital other: average length of stay (days)	Seizure free pw	1.14	2.00	Normal	0.00	5.85
	≤ 2 seizures pw	1.93	2.00	Normal	0.00	8.20
	$>2-\leq 7$ seizures pw	2.81	2.75	Normal	0.00	12.46
	>7 seizures pw	4.63	4.00	Normal	0.00	0.48
Hospital: other (%)	Proportion ICU	0.18	0.15	Normal	0.00	1.68
Hospitalization: hospital admissions (per year)	Seizure free pw	0.32	Not tested			
	≤ 2 seizures pw	1.14				
	$>2-\leq 7$ seizures pw	2.53				
	>7 seizures pw	7.72				
Hospitalization: ICU admissions (per year)	Seizure free pw	0.07	Not tested			
	≤ 2 seizures pw	0.25				
	$>2-\leq 7$ seizures pw	0.55				
	>7 seizures pw	1.67				
Other: MRI scan (per year)	Seizure free pw	0.35	0.34	Normal	0.00	1.02
	≤ 2 seizures pw	0.43	0.30	Normal	0.00	1.03
	$>2-\leq 7$ seizures pw	0.48	0.33	Normal	0.00	1.12
	>7 seizures pw	0.88	0.56	Normal	0.00	1.99
Other: rescue medication (per year)	Seizure free pw	0.00	21.21	Normal	0.00	0.00
	≤ 2 seizures pw	1.09	24.28	Normal	0.00	48.67
	$>2-\leq 7$ seizures pw	3.99	20.59	Normal	0.00	44.34
	>7 seizures pw	17.98	30.10	Normal	0.00	76.97

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Additional support: education (number of weeks per year)	Seizure free pw	22.52	Not included in base-case analysis			
	≤2 seizures pw	28.81				
	>2–≤7 seizures pw	37.49				
	>7 seizures pw	47.22				
Additional support: additional homecare (hours per year)	Seizure free pw	83.20	Not included in base-case analysis			
	≤2 seizures pw	135.20				
	>2–≤7 seizures pw	228.80				
	>7 seizures pw	832.00				
Resource use frequency – adult[28]						
Primary care: GP visits (per year)	Seizure free pw	4.29	3.59	Normal	0.00	11.33
	≤2 seizures pw	7.25	5.75	Normal	0.00	18.52
	>2–≤7 seizures pw	8.57	7.55	Normal	0.00	23.36
	>7 seizures pw	13.43	13.05	Normal	0.00	39.00
Outpatient: physician visits (per year)	Seizure free pw	1.00	1.41	Normal	0.00	3.77
	≤2 seizures pw	2.44	1.76	Normal	0.00	5.89
	>2–≤7 seizures pw	3.00	1.73	Normal	0.00	6.39
	>7 seizures pw	4.57	3.36	Normal	0.00	11.16
Outpatient: pediatrician visits (per year)	Seizure free pw	0.00	0.00	Normal	0.00	0.00
	≤2 seizures pw	0.00	0.00	Normal	0.00	0.00
	>2–≤7 seizures pw	0.00	0.00	Normal	0.00	0.00
	>7 seizures pw	0.00	0.00	Normal	0.00	0.00
Outpatient: psychiatry or mental health service (per year)	Seizure free pw	0.79	0.70	Normal	0.00	2.16
	≤2 seizures pw	1.38	1.38	Normal	0.00	4.08
	>2–≤7 seizures pw	1.93	1.69	Normal	0.00	5.25
	>7 seizures pw	1.86	1.75	Normal	0.00	5.29
Outpatient: physiotherapy (per year)	Seizure free pw	0.25	0.42	Normal	0.00	1.07
	≤2 seizures pw	0.60	0.65	Normal	0.00	1.88
	>2–≤7 seizures pw	0.60	0.65	Normal	0.00	1.88
	>7 seizures pw	1.60	1.19	Normal	0.00	3.94
Outpatient: speech and language therapy (per year)	Seizure free pw	0.30	0.45	Normal	0.00	1.18
	≤2 seizures pw	0.42	0.49	Normal	0.00	1.38
	>2–≤7 seizures pw	0.70	0.45	Normal	0.00	1.58
	>7 seizures pw	1.10	0.89	Normal	0.00	2.85

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Outpatient: occupational therapy (per year)	Seizure free pw	0.33	0.47	Normal	0.00	1.26
	≤ 2 seizures pw	0.58	0.73	Normal	0.00	2.02
	$>2-\leq 7$ seizures pw	1.58	1.24	Normal	0.00	4.01
	>7 seizures pw	2.67	1.80	Normal	0.00	6.18
Outpatient: epilepsy nurse (per year)	Seizure free pw	0.56	0.82	Normal	0.00	2.17
	≤ 2 seizures pw	2.19	0.37	Normal	1.46	2.92
	$>2-\leq 7$ seizures pw	3.29	0.76	Normal	1.80	4.77
	>7 seizures pw	4.71	1.70	Normal	1.37	8.05
Outpatient: epilepsy nurse (phone calls) (per year)	Seizure free pw	0.79	0.75	Normal	0.00	2.25
	≤ 2 seizures pw	4.86	3.23	Normal	0.00	11.18
	$>2-\leq 7$ seizures pw	6.71	2.86	Normal	1.10	12.33
	>7 seizures pw	9.57	3.02	Normal	3.66	15.48
Hospitalization: A&E admissions (per year)	Seizure free pw	0.50	0.76	Normal	0.00	2.00
	≤ 2 seizures pw	1.69	1.16	Normal	0.00	3.97
	$>2-\leq 7$ seizures pw	3.64	3.15	Normal	0.00	9.81
	>7 seizures pw	5.29	3.95	Normal	0.00	13.02
Hospital other: hospital admissions per patient (per year)	Seizure free pw	0.25	0.38	Normal	0.00	1.00
	≤ 2 seizures pw	0.53	0.39	Normal	0.00	1.29
	$>2-\leq 7$ seizures pw	1.25	0.32	Normal	0.62	1.88
	>7 seizures pw	2.25	1.07	Normal	0.15	4.35
Hospital other: average length of stay (days)	Seizure free pw	1.57	0.00	Normal	0.00	0.00
	≤ 2 seizures pw	2.56	1.25	Normal	0.11	5.01
	$>2-\leq 7$ seizures pw	3.86	3.00	Normal	0.00	9.74
	>7 seizures pw	6.00	5.00	Normal	0.00	15.80
Hospital: other (%)	Proportion ICU	0.18	0.15	Normal	0.00	0.48
Hospitalization: hospital admissions (per year)	Seizure free pw	0.32	Not tested			
	≤ 2 seizures pw	1.12				
	$>2-\leq 7$ seizures pw	3.96				
	>7 seizures pw	11.10				
Hospitalization: ICU admissions (per year)	Seizure free pw	0.07	Not tested			
	≤ 2 seizures pw	0.24				
	$>2-\leq 7$ seizures pw	0.86				
	>7 seizures pw	2.40				

Variable		Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Other: MRI scan (per year)	Seizure free pw	0.29	0.45	Normal	0.00	1.18
	≤2 seizures pw	0.43	0.49	Normal	0.00	1.40
	>2–≤7 seizures pw	0.65	0.58	Normal	0.00	1.79
	>7 seizures pw	1.30	0.73	Normal	0.00	2.72
Other: rescue medication (per year)	Seizure free pw	0.00	0.00	Normal	0.00	0.00
	≤2 seizures pw	0.39	16.24	Normal	0.00	32.23
	>2–≤7 seizures pw	2.56	26.90	Normal	0.00	55.28
	>7 seizures pw	8.93	27.14	Normal	0.00	62.12
Additional support: day care (number of weeks per year)	Seizure free pw	7.15	Not included in base-case analysis			
	≤2 seizures pw	14.27				
	>2–≤7 seizures pw	19.63				
	>7 seizures pw	29.71				
Additional support: additional homecare (hours per year)	Seizure free pw	147.16	Not included in base-case analysis			
	≤2 seizures pw	268.84				
	>2–≤7 seizures pw	949.00				
	>7 seizures pw	1386.84				
Institutionalization: residential care (weeks per year)	Seizure free pw	15.86	1.59	Normal	12.75	18.97
	≤2 seizures pw	15.86	1.59	Normal	12.75	18.97
	>2–≤7 seizures pw	15.86	1.59	Normal	12.75	18.97
	>7 seizures pw	15.86	1.59	Normal	12.75	18.97
Monitoring (£)[24]						
Liver function tests		2.10	0.21	Gamma	1.71	2.53
Adverse event costs (£)[24]						
Vomiting		959.10	95.91	Gamma	780.36	1155.99
Nausea		959.10	95.91	Gamma	780.36	1155.99
Fatigue		959.10	95.91	Gamma	780.36	1155.99
Malaise		959.10	95.91	Gamma	780.36	1155.99
Liver injury		51.00	5.10	Gamma	41.50	61.47
Type IV reaction		51.00	5.10	Gamma	41.50	61.47
Electrolyte imbalance		959.10	95.91	Gamma	780.36	1155.99
Rash erythematous		51.00	5.10	Gamma	41.50	61.47
TAND aspect costs (£)[36]^a						
Delayed development		4496.75	449.68	Gamma	3658.74	5419.89

Variable	Value	Standard deviation (for PSA)	Distribution	Lower bound (for DSA)	Upper bound (for DSA)
Behavioral issues	1818.60	181.86	Gamma	1479.68	2191.94
Intellectual disability	4496.75	449.68	Gamma	3658.74	5419.89
ASD	4496.75	449.68	Gamma	3658.74	5419.89
ADHD	4496.75	449.68	Gamma	3658.74	5419.89
Anxiety disorders (including panic, phobia, separation anxiety disorder)	1818.60	181.86	Gamma	1479.68	2191.94

A&E, accident and emergency; ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; CBD, cannabidiol; DSA, deterministic sensitivity analysis; GP, general practitioner; ICU, intensive care unit; MRI, magnetic resonance imaging; N/A, not applicable; OLE, open-label extension; PBO, placebo; PSA, probabilistic sensitivity analysis; pw, per week; QALY, quality-adjusted life year; SUDEP, sudden unexpected death in epilepsy; TAND, TSC-associated neuropsychiatric disorders; TSC, tuberous sclerosis complex; UC, usual care. ^aCosts presented in Euros (2011) and adjusted according to European Central Bank purchasing price parities using a nominal EU27 conversion rate and PSSRU inflation indices [23,37].

Online Resource Table 10 Adverse event, monitoring, and TAND management unit costs (£)

	Input	Unit costs (£)	Assumption	Source
Adverse events	Requires or prolongs hospitalization	959	Non-elective short-stay cost, index cost Applies to nausea, vomiting, fatigue, malaise, and electrolyte imbalance	NHS reference costs 2020–2021[24]
	Other medically important	51	Visit to an epilepsy specialist nurse (Band 6) Applied to liver injury, type IV hypersensitivity reaction, and erythematous rash	PSSRU 2021[23]
Monitoring	Liver function tests	2.10	One test per 3 months	NHS reference costs 2020–2021[24]
TAND	Child and adolescent disorders cost ^a	4496.75	Applied to delayed development, intellectual disability, ASD, and ADHD	Gustavsson 2011[36]
	Anxiety disorders cost ^a	1818.60	Applies to behavioral issues and anxiety disorders	

ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; NHS, National Health Service; PSSRU, Personal Social Services Research Unit; TAND, tuberous sclerosis complex-associated neuropsychiatric disorders.

^aCosts presented in Euros (2011) and adjusted according to European Central Bank purchasing price parities using a nominal EU27 conversion rate and PSSRU inflation indices [23,37].

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